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Tetrahedron

Tetrahedron Vol. 60, No. 20, 2004

Tetrahedron Symposium-in-Print Number 103

Atropisomerism

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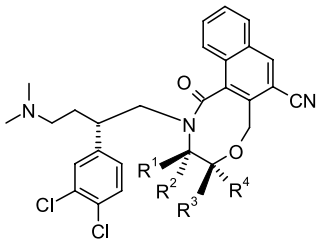
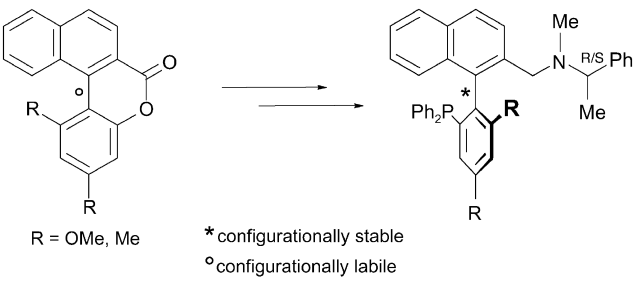
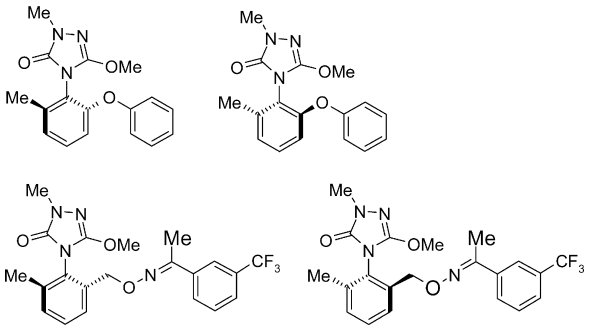
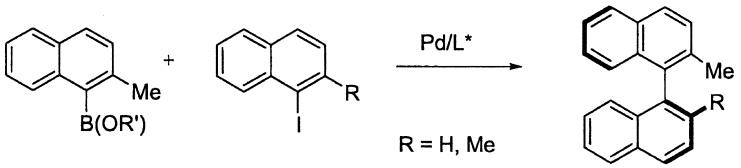
Contents

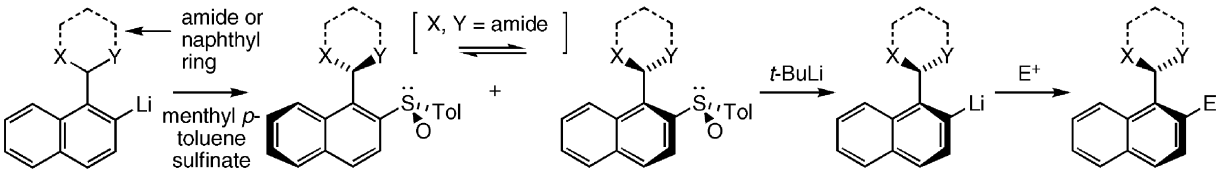


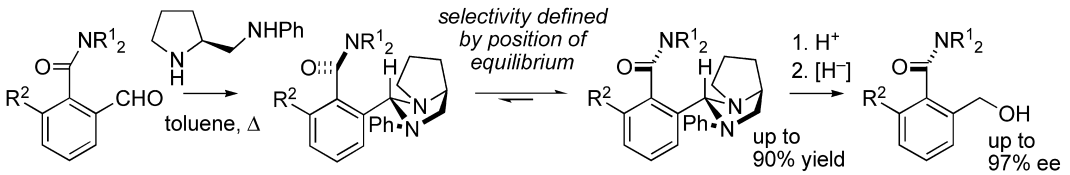
5: R^1, R^2, R^3, R^4 = H
6: R^1 = Me, R^2, R^3, R^4 = H
7: R^2 = Me, R^1, R^3, R^4 = H
8: R^3 = Me, R^1, R^2, R^4 = H
9: R^4 = Me, R^1, R^2, R^3 = H

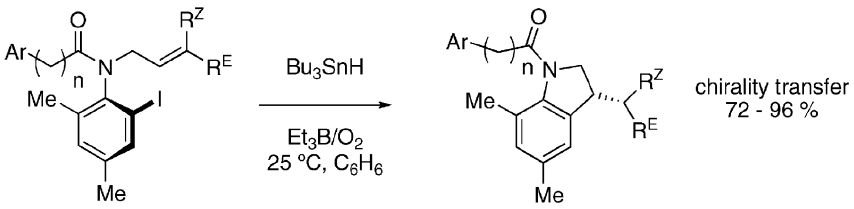


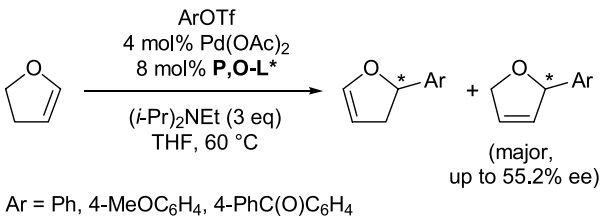


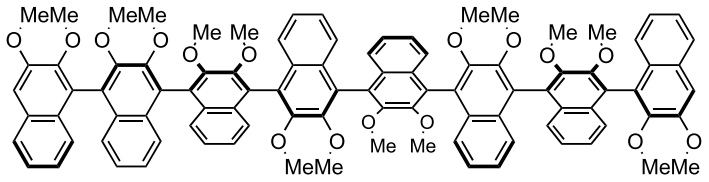


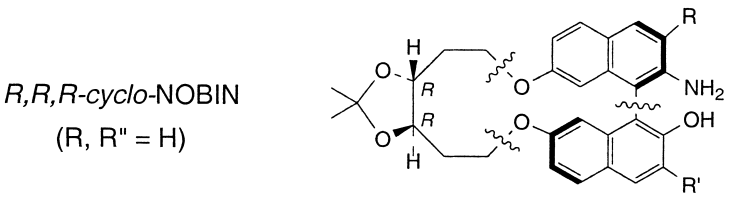


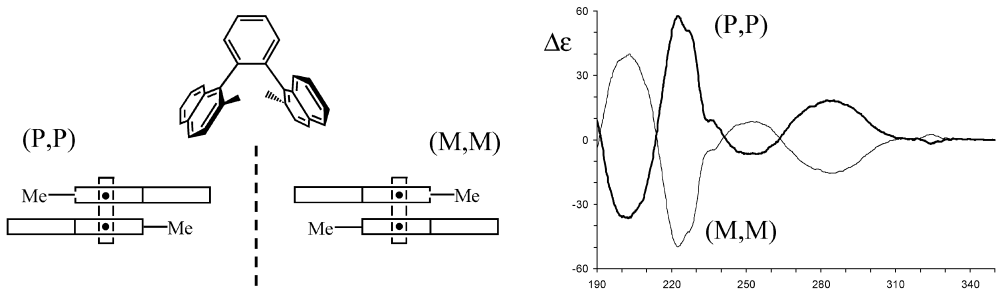


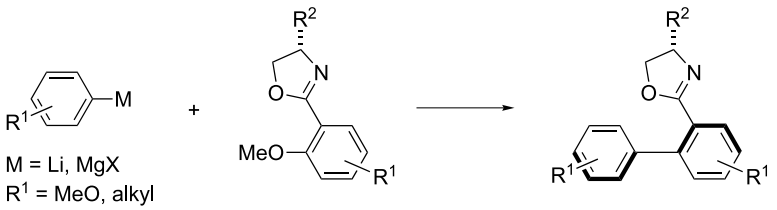


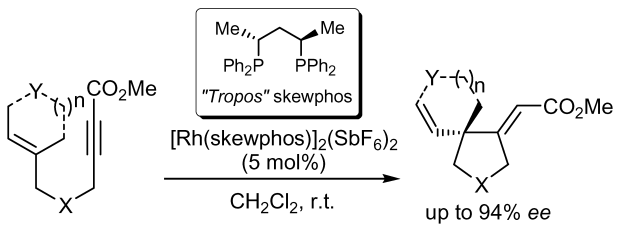


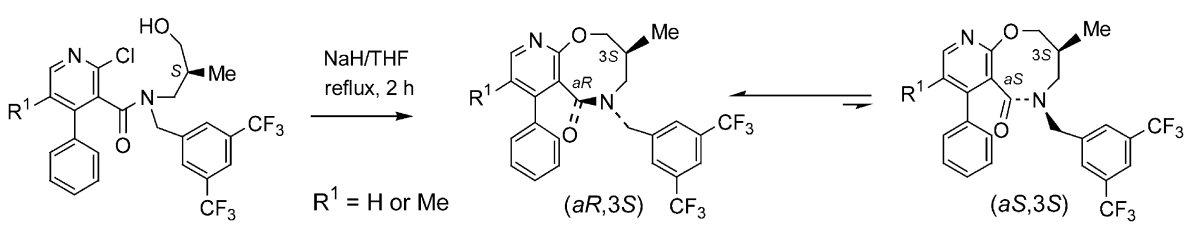


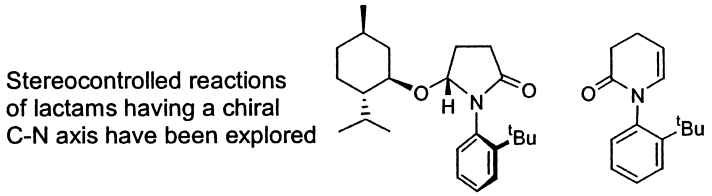


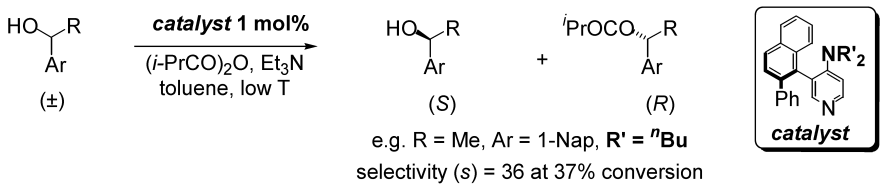


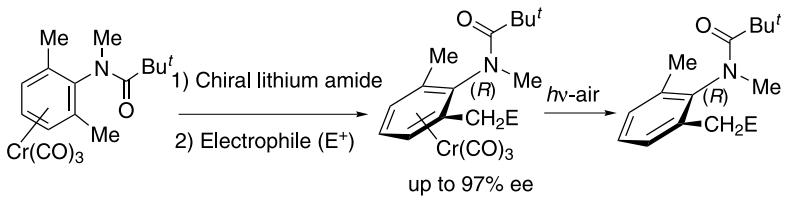


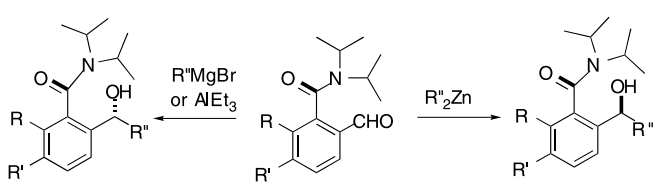


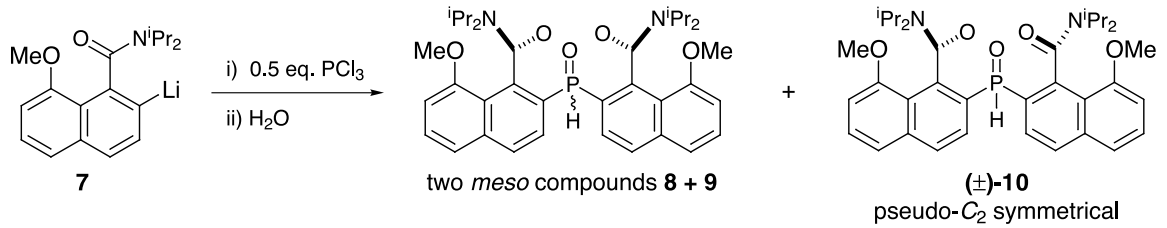












7 two *meso* compounds **8 + 9** **(±)-10** pseudo-C_2 symmetrical

OTHER CONTENTS

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COVER

The front cover shows a selection of the atropisomeric molecules described in this issue.

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts. Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei Compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch

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ISSN 0040-4020

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35. Recent developments in organocopper chemistry, Bruce H. Lipshutz, Ed. *Tetrahedron* **1989**, *45*, 349–578.
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43. Recent advances in bioorganic chemistry, Dale L. Boger, Ed. *Tetrahedron* **1991**, *47*, 2351–2682.
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45. Frontiers in natural products biosynthesis. Enzymological and molecular genetic advances, D. E. Cane, Ed. *Tetrahedron* **1991**, *47*, 5919–6078.
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49. Synthesis of optically active compounds—prospects for the 21st century, Kenji Koga and Takayuki Shioiri, Eds. *Tetrahedron* **1993**, *49*, 1711–1924.
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51. Transition metal organometallics in organic synthesis, Anthony J. Pearson, Ed. *Tetrahedron* **1993**, *49*, 5415–5682.
52. Palladium in organic synthesis, Jan-E. Bäckvall, Ed. *Tetrahedron* **1994**, *50*, 285–572.
53. Recent progress in the chemistry of enediyne antibiotics, Terrence W. Doyle and John F. Kadow, Eds. *Tetrahedron* **1994**, *50*, 1311–1538.
54. Catalytic asymmetric addition reactions, Stephen F. Martin, Ed. *Tetrahedron* **1994**, *50*, 4235–4574.
55. Mechanistic aspects of polar organometallic chemistry, Manfred Schlosser, Ed. *Tetrahedron* **1994**, *50*, 5845–6128.
56. Molecular recognition, Andrew D. Hamilton, Ed. *Tetrahedron* **1995**, *51*, 343–648.
57. Recent advances in the chemistry of zirconocene and related compounds, Ei-ichi Negishi, Ed. *Tetrahedron* **1995**, *51*, 4255–4570.
58. Fluoroorganic chemistry: synthetic challenges and biomedicinal rewards, Giuseppe Resnati and Vadim A. Soloshonok, Eds. *Tetrahedron* **1996**, *52*, 1–330.
59. Novel applications of heterocycles in synthesis, A. R. Katritzky, Ed. *Tetrahedron* **1996**, *52*, 3057–3374.
60. Fullerene chemistry, Amos B. Smith III, Ed. *Tetrahedron* **1996**, *52*, 4925–5262.
61. New synthetic methods—IV. Organometallics in organic chemistry, István E. Markó, Ed. *Tetrahedron* **1996**, *52*, 7201–7598.
62. Cascade reactions, Ron Grigg, Ed. *Tetrahedron* **1996**, *52*, 11385–11664.
63. Applications of solid-supported organic synthesis in combinatorial chemistry, James A. Bristol, Ed. *Tetrahedron* **1997**, *53*, 6573–6706.
64. Recent applications of synthetic organic chemistry, Stephen F. Martin, Ed. *Tetrahedron* **1997**, *53*, 8689–9006.
65. Chemical biology, Gregory L. Verdine and Julian Simon, Eds. *Tetrahedron* **1997**, *53*, 11937–12066.
66. Recent aspects of S, Se, and Te chemistry, Richard S. Glass and Renji Okazaki, Eds. *Tetrahedron* **1997**, *53*, 12067–12318.
67. Modern organic chemistry of polymerization, H. K. Hall Jr., Ed. *Tetrahedron* **1997**, *53*, 15157–15616.
68. New synthetic methods—V, John L. Wood, Ed. *Tetrahedron* **1997**, *53*, 16213–16606.
69. New developments in organonickel chemistry, Bruce H. Lipshutz and Tien-Yau Luh, Eds. *Tetrahedron* **1998**, *54*, 1021–1316.
70. Solution phase combinatorial chemistry, David L. Coffen, Ed. *Tetrahedron* **1998**, *54*, 3955–4150.
71. Heterocycles in asymmetric synthesis, Alexandre Alexakis, Ed. *Tetrahedron* **1998**, *54*, 10239–10554.
72. Recent advances of phase-transfer catalysis, Takayuki Shioiri, Ed. *Tetrahedron* **1999**, *55*, 6261–6402.
73. Olefin metathesis in organic synthesis, Marc L. Snapper and Amir H. Hoveyda, Eds. *Tetrahedron* **1999**, *55*, 8141–8262.
74. Stereoselective carbon–carbon bond forming reactions, Harry H. Wasserman, Stephen F. Martin and Yoshinori Yamamoto, Eds. *Tetrahedron* **1999**, *55*, 8589–9006.
75. Applications of combinatorial chemistry, Miles G. Siegel and Stephen W. Kaldor, Eds. *Tetrahedron* **1999**, *55*, 11609–11710.
76. Advances in carbon–phosphorus heterocyclic chemistry, François Mathey, Ed. *Tetrahedron* **2000**, *56*, 1–164.
77. Transition metal organometallics in organic synthesis, Kenneth M. Nicholas, Ed. *Tetrahedron* **2000**, *56*, 2103–2338.
78. Organocopper chemistry II, Norbert Krause, Ed. *Tetrahedron* **2000**, *56*, 2727–2904.
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80. Recent aspects of the chemistry of β-lactams—II, Marvin J. Miller, Ed. *Tetrahedron* **2000**, *56*, 5553–5742.
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84. New synthetic methods—VI, George A. Kraus, Ed. *Tetrahedron* **2000**, *56*, 10101–10282.
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87. Novel aromatic compounds, Lawrence T. Scott and Jay S. Siegel, Eds. *Tetrahedron* **2001**, *57*, 3507–3808.
88. Asymmetric synthesis of novel sterically constrained amino acids, Victor J. Hruby and Vadim A. Soloshonok, Eds. *Tetrahedron* **2001**, *57*, 6329–6650.
89. Recognition-mediated self-assembly of organic systems, Vincent M. Rotello, Ed. *Tetrahedron* **2002**, *58*, 621–844.
90. Synthesis of marine natural products containing polycyclic ethers, Masahiro Hirama and Jon D. Rainier, Eds. *Tetrahedron* **2002**, *58*, 1779–2040.

91. Fluorous chemistry, John A. Gladysz and Dennis P. Curran, Eds. *Tetrahedron* **2002**, *58*, 3823–4132.
92. Recent developments in chiral lithium amide base chemistry, Peter O'Brien, Ed. *Tetrahedron* **2002**, *58*, 4567–4734.
93. Beyond natural product synthesis (Tetrahedron Prize for Creativity in Organic Chemistry 2001 - Yoshito Kishi), Harry H. Wasserman and Stephen F. Martin, Eds. *Tetrahedron* **2002**, *58*, 6223–6602.
94. Strained heterocycles as intermediates in organic synthesis, Amy R. Howell, Ed. *Tetrahedron* **2002**, *58*, 6979–7194.
95. Molecular design of Lewis and Brønsted acid catalysts—the key to environmentally benign reagents (Tetrahedron Chair 2002), Hisashi Yamamoto, Ed. *Tetrahedron* **2002**, *58*, 8153–8364.
96. Recent developments in dendrimer chemistry, David K. Smith, Ed. *Tetrahedron* **2003**, *59*, 3787–4024.
97. Art, science and technology in total synthesis (Tetrahedron Prize for Creativity in Organic Chemistry 2002 - K. C. Nicolaou), Stephen F. Martin and Harry H. Wasserman, Eds. *Tetrahedron* **2003**, *59*, 6667–7070.
98. New synthetic methods—VII, Brian M. Stoltz, Ed. *Tetrahedron* **2003**, *59*, 8843–9030.
99. Oxiranyl and aziridinyl anions as reactive intermediates in synthetic organic chemistry, S. Florio, Ed. *Tetrahedron* **2003**, *59*, 9683–9864.
100. Recent advances in rare earth chemistry, Shū Kobayashi, Ed. *Tetrahedron* **2003**, *59*, 10339–10598.
101. Biocatalysts in synthetic organic chemistry, S. M. Roberts, Ed. *Tetrahedron* **2004**, *60*, 483–806.
102. Recent advances in the chemistry of zirconocenes, Keisuke Suzuki and Peter Wipf, Eds. *Tetrahedron* **2004**, *60*, 1257–1424.
103. Atropisomerism, Jonathan Clayden, Ed. *Tetrahedron* **2004**, *60*, 4325–4558.

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Preface

Atropisomerism

Atropisomerism, the phenomenon of chirality due to restricted rotation about a single bond, has been an intellectually intriguing and practically widely applicable area of stereochemistry from the first resolution of a chiral atropisomeric biaryl by Christie and Kenner in 1922 through the discovery of numerous naturally occurring atropisomeric molecules and the development of atropisomeric chiral ligands. A high point in the history of atropisomerism must be the central role played by the atropisomeric ligand BINAP in Professor Ryoji Noyori's share of the Nobel Prize for Chemistry in 2001.

This Symposium-in-Print contains 19 papers from both academic and industrial laboratories around the world covering a wide variety of aspects of the chemistry of atropisomers. The theme of catalysis is still strong, but many more of the papers address the main challenge in the area: the stereoselective synthesis of atropisomeric molecules, whether for use in catalysis, in synthesis more widely, or as biologically active compounds. Several papers address the issue of how to construct what will necessarily be a highly hindered single bond with control over its stereochemistry. A recent feature of research in atropisomerism has been the emergence of classes of atropisomeric compounds outside of the classical biaryl class, and in this issue over half of the papers discuss such types of molecules, in particular their biological activity, and the dependence of that activity on stereochemistry, their stereoselective synthesis, and the role of the atropisomeric axis in the stereoselectivity of their reactions. Another feature of atropisomers which appears in several papers in the issue is the question of enantiomeric stability and not only the problems which can arise with poor barriers to rotation but also the way in which dynamic processes can be used to exploit the interconversion of atropisomeric amides as a beneficial property.

Atropisomerism continues to intrigue chemists. It offers new ways of thinking about stereochemistry and about dynamic processes, and about the relationship between structure and activity in both the biological and stereoselective sense. The papers in this issue provide a snapshot of current thinking in the area and very much point forward to further advances in an exciting area of chemistry.

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0040–4020/$ - see front matter
doi:10.1016/j.tet.2004.03.002

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Design and optimization of cyclized NK_1 antagonists with controlled atropisomeric properties

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Received 10 October 2003; revised 12 March 2004; accepted 19 March 2004

Abstract—We have previously described a series of antagonists that showed high potency and selectivity for the NK_1 receptor. However, these compounds also had the undesirable property of existing as a mixture of four interconverting rotational isomers. Through biological and structural analysis of the atropisomers, a binding model was developed and used to guide the design of compounds, which were rigidified by installation of a cyclizing linkage. These compounds existed as a mixture of two atropisomers. Further elaboration of the ring system reinforced the desired conformation and eliminated atropisomeric properties. We found that the region distal to the 8-membered ring system could be modified while retaining NK_1 potency, and optimization led to further improvements in the in vivo activity.

1. Introduction

The tachykinins are a family of three mammalian neuropeptides: substance P (SP), neurokinin A (NKA), and neurokinin B (NKB). The preferred receptors for these are termed NK_1, NK_2 and NK_3, respectively. Substance P is widely distributed in the CNS and peripheral tissue and acts as a neurotransmitter or neuro-modulatory agent. The NK_1 receptor may be involved in several pathophysiological conditions including asthma, emesis, anxiety, depression, and pain.[1,2] The discovery of tachykinin antagonists has been extensively reviewed.[3–6]

Since the identification of the first non-peptidic tachykinin antagonist CP-96,345,[7] the area has received intense interest. This reflects the potential clinical importance that tachykinin antagonists are viewed to have. Prompted by the identification of the NK_2 antagonist SR-48,968,[8] our group initiated a program to identify NK_1 and NK_2 antagonists. These efforts led to the discovery of **1** (Fig. 1). As a result of the napthyl 2-substituent, this compound was more than two log units more potent as an NK_1 antagonist than as an NK_2 antagonist (pK_B 9.6 vs. 7.3, respectively). This compound was advanced for the treatment of depression.[9]

Compound **1** has two bonds with restricted rotation. The amide bond can exist in the *s-cis* or *s-trans* forms, and the carbonyl–aryl bond can exist in the *S*-axial or *R*-axial

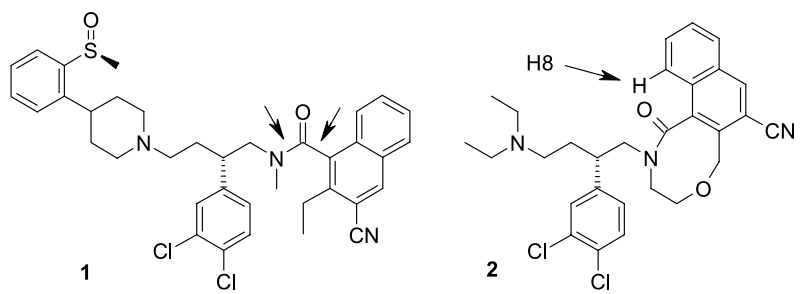

Figure 1. Left: structure of **1**, arrows indicate bonds with restricted rotation. Right: structure of **2**, arrow indicates the naphthalene H8.

Keywords: Tachykinin; Neurokinin; Atropisomer.
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0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.03.054

configurations. The barrier to rotation is sufficiently high such that four atropisomers (interconverting rotational isomers) can clearly be seen by HPLC (Fig. 2) and NMR spectroscopy.

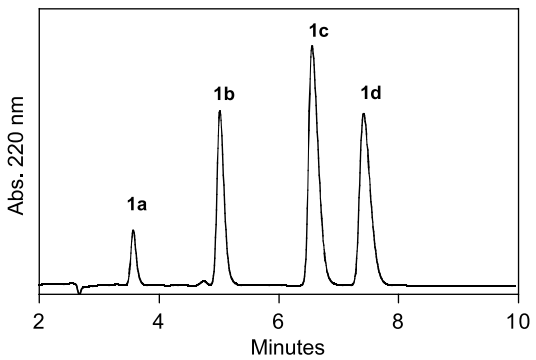


Figure 2. High pressure liquid chromatogram (HPLC) of **1** showing the resolution of the atropisomeric forms (**1a**–**1d**). Conditions: column; Phenomonex Luna C18(2) 3 μm, 4.6×75 mm; 60% methanol, 40% water (0.1% TFA), 1.5 mL/min. UV detection at 220 nM.

For a candidate drug, equilibrating atropisomeric properties would present possible safety concerns as well as very substantial complications for manufacturing and analytical development. To better understand the properties of **1**, we purified and independently studied each of the atropisomers (designated **1a**, **1b**, **1c**, and **1d**) by preparative HPLC. We observed that interconversion occurred primarily between atropisomers **1a/1d** and between **1b/1c**; interconversion between all other pairs (i.e. **1d/1b**, **1b/1a**, **1a/1c**, and **1c/1d**) was not seen.[10] Such behavior has been observed for related naphthamide systems.[11] In these cases, it is understood that the fastest interconversions are due to the simultaneous, paired rotation of the naphthamide–aryl and amide bonds.[11,12] This occurs because steric strain develops as the naphthamide or amide undergoes rotation; as a result, the rotations must occur together. This process is referred to as 'geared rotation.'[13]

The long rotational half-life (approximately 1.8 days at 37 °C) allowed us to individually test each component of **1**.[10] We found that most of the in vivo NK_1 activity was associated with the single atropisomer, **1d**. Using a combination of kinetic and spectroscopic studies, we assigned structures for each of the atropisomers as indicated in Figure 3.[10]

Based on the structural model for **1d**, we reasoned that we could enforce the single, desired conformation by introducing a tether to connect the methyl group of the amide with the naphthalene 2-position. Such a tether should stabilize the NK_1 binding conformation because the amide would be locked in the *trans* configuration. A similar approach has been demonstrated for a structurally unrelated series of NK_1 antagonists.[14]

We analyzed compounds with tethering ring systems containing 6, 7, and 8-membered rings and found that the 8-membered ring system was preferred.[15] Prior studies had shown that the piperidine substituent in **1** could be simplified[15] without significant loss of NK_1 receptor

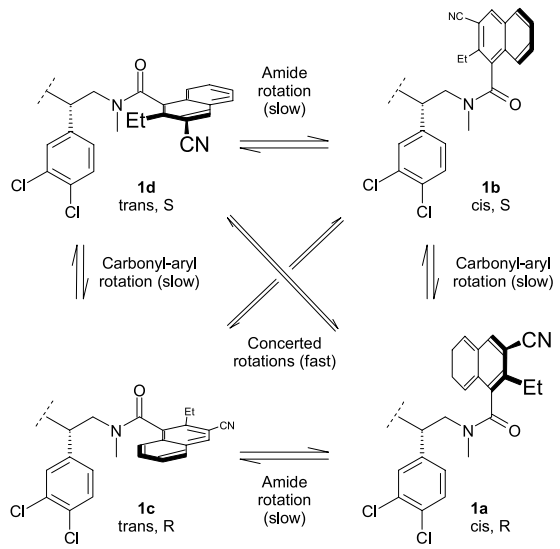


Figure 3. Model for the interconversion path and structural assignments for atropisomers **1a**–**1d**.

antagonist potency. Combining the 8-membered ring with the simplified piperidine led to the identification of **2**;[15] this compound maintained high NK_1 potency and selectivity (Table 1). As expected, conformational properties are simplified for compound **2** as a result of the cyclizing tether; it exists as a mixture of only two atropisomers which are presumably the *R*- and *S*-axial carbonyl-naphthalene isomers.

Table 1. NK_1 Receptor antagonist potency (pK_B) for **1** and **2**[a]

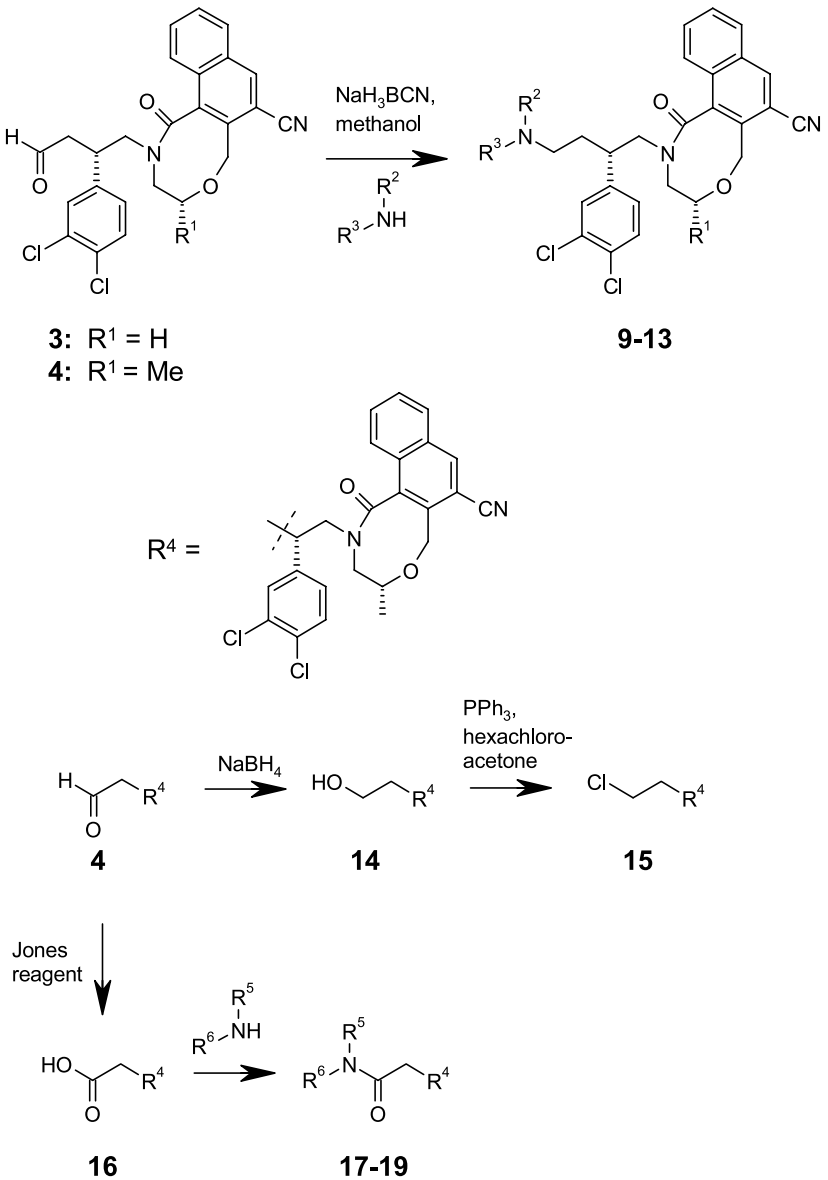
Compound	NK_1[b]	NK_2[c]
1	9.56±0.04	7.31±0.28
2	9.50±0.14	<7

[a] pK_B Determinations using rabbit pulmonary artery tissue (n=2–6).
[b] Agonist: Ac-(Arg[6], Sar[9], Met(O_2)[11]) SP_{6-11} (ASMSP).
[c] Agonist: BANK (β-ala[8]NKA(4-10)).

After demonstrating that we could reduce the number of isomers from four to two, our next goal became the stabilization of a single conformation. In this way, all potential concerns about atropisomerism would be eliminated. This paper describes the modeling and structural analysis of these 8-membered ring antagonists. In these studies, we have developed a series of novel NK_1 antagonists that exist in predominantly a single conformation. Furthermore, by comparing these compounds, we have constructed a detailed pharmacophore model for NK_1 receptor binding.

2. Synthesis

Secondary and tertiary amine compounds could be conveniently prepared from aldehyde **3**[15] or **4**[15] by reductive amination in the presence of sodium cyanoborohydride. Alcohol and carboxylic acid derived compounds were prepared by reduction or oxidation of **4** as indicated in the Scheme 1.



Scheme 1. For R^2, R^3, R^5, R^6 see Table 4.

3. Results

To better understand the factors responsible for the atropisomeric properties, molecular modeling studies were conducted for the cyclic analogs. With **2** as a starting point, and with knowledge of the rotational properties of related naphthamides, we sought to eliminate the atropisomeric properties. A detailed analysis of the ground state energetics was carried out for compounds in the cyclic series to explore this possibility.

3.1. Conformational analysis of the 8-membered ring system

To more fully understand the conformational properties of **2** and related compounds, we began by considering simpler model systems. Analysis of the possible conformations of the 8-membered ring was carried out by first considering 1,3-cyclo-octadiene (COD) (Fig. 4). As a first approximation, the *cis* double bonds in COD are expected to constrain the torsional angles in the 8-membered ring in a manner similar to that for the aryl and amide bonds in **2**. Thus, COD serves as a convenient starting point because its conformational properties have been extensively studied,[16–19] both theoretically and experimentally.

Previous studies indicate three relevant conformations for COD, a twist boat chair (TBC) conformation, and the two twist boats (TB1 and TB2) conformations (Fig. 5). We began by verifying that the conformational energetics calculated by our AESOP-Enigma program[20] were quantitatively consistent with empirical data and with energies determined by other theoretical methods. Next, we examined the energetics of these same conformations in the more elaborate cyanobenzamide and cyanonaphthamide-based ring systems (Fig. 5). The TBC conformers remained the most stable for both the cyanobenzamide and cyanonaphthamide adducts. Interestingly, both TB1 and TB2 conformers are substantially destabilized in these systems relative to COD. It is important to note that

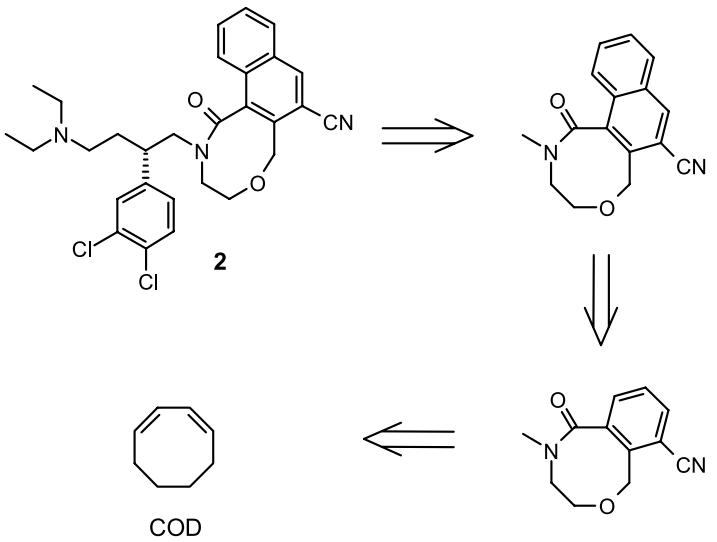


Figure 4. Progressive simplification from the 8-membered ring system in **2** to the simplified naphthalene analog, to the simplified benzamide analog, to COD.

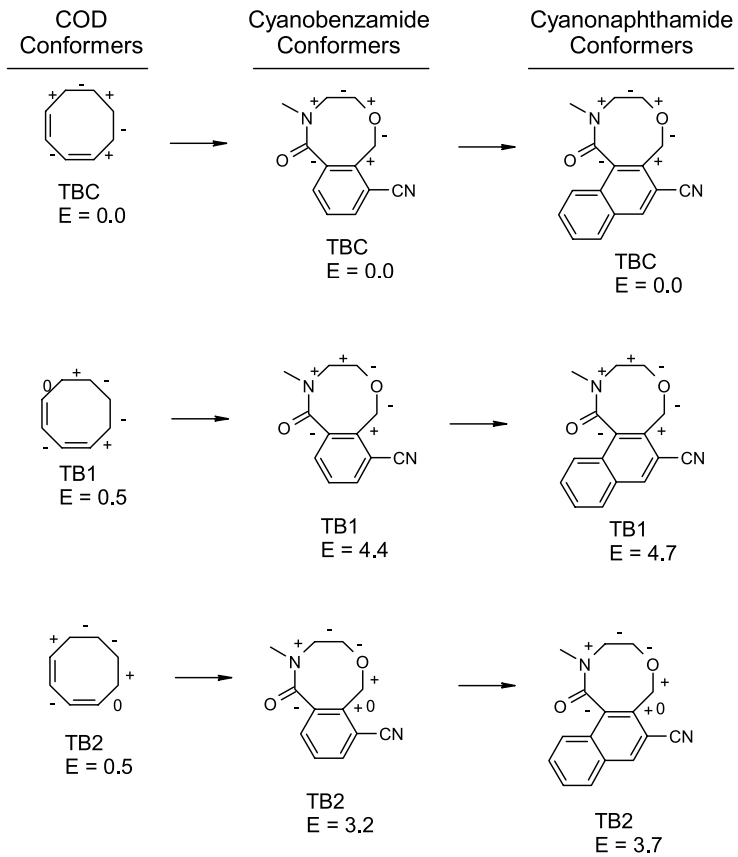


Figure 5. Relative conformational energies (kcal/mol) for COD, and cyanobenzamide and cyanonaphthamide model systems. The sign of the torsional angles for each bond in the 8-membered ring are indicated with (−) and (+).

all three conformations (TBC, TB1 and TB2) are chiral; a corresponding enantiomeric conformation exists for each of these conformations. (The enantiomeric conformation has an inversion of the sign of each of the torsional angles.) These pairs of enantiomeric conformations (denoted A and B below) are energetically equivalent in an achiral environment.

3.2. Conformational analysis including the pendant phenethyl side chain

As the next step in progressively elaborating from our simple starting model, a pendant phenethyl group (Fig. 6) was added to model the dichloroaryl region of compound **2**. Because the phenethyl group contains a chiral atom of

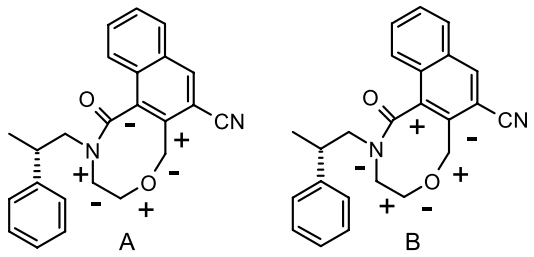


Figure 6. TBC conformations of the napthamide system with pendant chiral phenyl containing side chain used for computational analysis. The two structures differ by inversion of the torsion angles around each atom in the 8-membered ring; the sign of the torsional angles for each bond in the 8-membered ring are indicated with (−) and (+).

known fixed absolute stereochemistry, the (previously enantiomeric) conformers of the 8-membered ring become diastereomeric and thus both forms must be considered (Fig. 6). Prior studies had shown that NK_1 and NK_2 affinity are sensitive to the stereochemistry of the aryl methine carbon, with the *S*-enantiomer being preferred.[21] Therefore, all subsequent experimental and computational studies focused on this form.

For each ring conformation (2 TBC, 2 TB1 and 2 TB2) exhaustive conformational scanning of the pendant side chain was performed using Enigma-ConfScan.[20] The phenyl side chain does not appear to perturb the conformational preferences of the 8-membered ring; the conformations containing TB1 or TB2 ring conformations remained 3–4 kcal/mol higher in energy than those containing TBC conformations for the 8-membered ring system. Two conformers were found to be very close in energy; they are designated as A and B (Fig. 7). These conformers are based on TBC ring geometries of 'opposite' chirality as well as differing side chain geometries. The A conformer was favored by 0.7 kcal/mol over the B conformer. From this we conclude that the actual energies should be close to each other; the small predicted energy difference is within the uncertainty of the calculation.

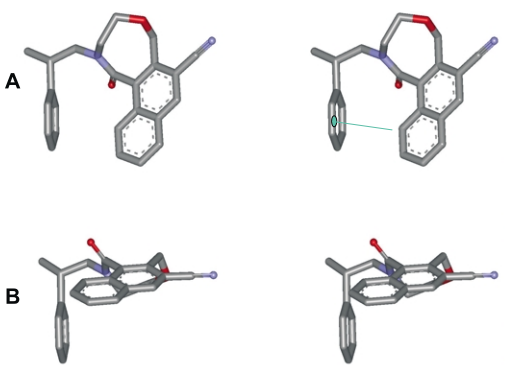


Figure 7. Relaxed-eye stereoview representation of the two low energy conformers of the model compounds from Figure 6. Conformation A shows an edge-to-face aryl–aryl stacking interaction (green line) which is hypothesized in the NK_1-active atropisomer. Conformation B cannot accommodate the stacking interaction and is hypothesized to be the less active atropisomer. Hydrogen atoms have been omitted for clarity.

3.3. Structural assignments of the 8-membered ring system

Experimentally, we observe two atropisomers for **2** with a population distribution of about 1:2 according to HPLC and ^{1}H NMR spectroscopy (Fig. 8). This implies that the conformational energies must be similar. For **2**, NMR spectra show that each of the two atropisomers are resolved for many of the protons. However, the separation of the corresponding signals is particularly striking for the naphthalene H8 proton. For the minor atropisomer, the naphthalene H8 proton is in the expected region at about 7.4 ppm. (It is obscured by overlapping signals but can be identified in two dimensional NMR experiments). For the major atropisomer, the naphthalene H8 proton is shifted upfield to about 6.4 ppm.

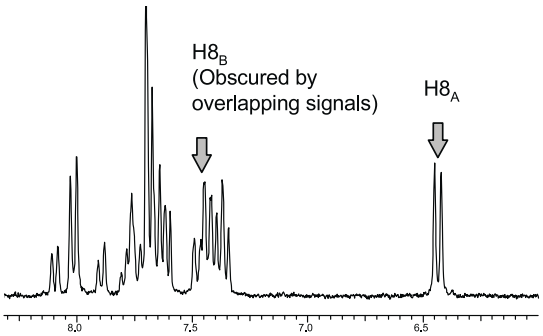


Figure 8. ^{1}H NMR spectrum of **2** in d_6-DMSO.

In ^{1}H NMR spectra of **2**, an upfield shift might be expected for the ring conformer A because the H8 proton is oriented into the shielding region of the phenyl ring (Fig. 7). For the B conformation, the H8 proton is distant from the phenyl ring, and no shift would be expected. The phenethyl side chain does not appear to perturb the conformational preferences of the 8-membered ring; conformational scanning indicated that for B, no stable conformation exists (<3 kcal/mol) for the pendant phenyl ring which would allow interaction of the naphthalene H8 proton. The atropiosmeric distribution and NMR spectroscopic properties of **2** are fully consistent with the structures and energies predicted by modeling. Based on this evidence, we assigned conformations to the atropisomers as indicated in Figure 7.

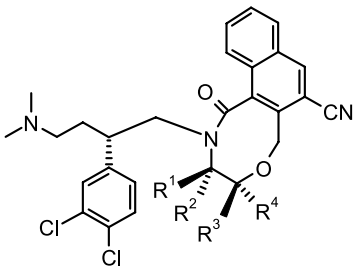
Prior studies on **1** demonstrated that it was atropisomer **1d** which was preferred for NK_1 antagonism[10] (Fig. 3). The conformation of **1d** overlays well with conformer A of the 8-membered system. In particular, they share the same orientation of the amide and naphthalene–carbonyl bonds, and they both have a potential aryl–aryl stacking interaction between the dichloroaryl ring and the naphthalene ring. For these reasons, we assign conformer A as the NK_1 preferring analogue.

3.4. Rigidification of the 8-membered ring by additional substitution

Despite the potent in vitro activity observed for **2** (Table 1) its existence as a mixture of two atropisomers limited further consideration of this compound for drug development. Kinetic analysis showed that the interconversion

half-life between the two atropisomers was 9.7 h (37 °C, 50% acetonitrile/water, 25 mM phosphate, pH 7.0; data not shown). This rate is fast enough that it would be impractical to isolate and administer the compound as a single atropisomer. We sought to eliminate the atropisomeric properties while further improving potency.

We speculated that addition of a methyl substituent in the 8-membered ring might perturb the energies enough to stabilize one conformer with respect to the other conformer.[14] Building upon the computational analysis described above, we analyzed the energies of each of the methyl substituted analogs in Figure 9. These modeling studies were used to aid conformational analysis; we have not attempted to extend the analysis for the interpretation of in vivo results which would require the addition of parameters to account for distribution, metabolism and other factors. In each of the examples, we found two predicted low energy conformers of the 8-membered ring system, which were analogous to the A and B conformations of the unsubstituted case. However, the predicted energy differences between the A and B conformers were small. Therefore, we could not reliably predict which position for substitution would most optimally stabilize the desired A-type conformation.



5: R^1, R^2, R^3, R^4 = H
6: R^1 = Me, R^2, R^3, R^4 = H
7: R^2 = Me, R^1, R^3, R^4 = H
8: R^3 = Me, R^1, R^2, R^4 = H
9: R^4 = Me, R^1, R^2, R^3 = H

Figure 9. Structures of **5**–**9**.

Each of the four methyl substituted analogs **6**–**9** were prepared and the atropisomeric distributions were analyzed by HPLC. As described above, the NK_1-preferential conformers of **1** and **2** showed a characteristic upfield shift in NMR spectra for the naphthalene H8 proton. We interpret this shift as resulting from an aryl–aryl interaction when the compound adopts a conformation like that shown in Figure 7(A). Therefore, we expected that the NK_1 preferred conformers in **6**–**9** would show a similar upfield shift for the naphthalene H8 proton. We determined which peaks in the HPLC chromatograms corresponded to the H8-shifted and non-shifted conformations by analysis of NMR integrations and comparison with HPLC integrations (Table 2). By extension of this, we assigned the one with the upfield shifted H8 resonance as the NK_1 preferred conformer. This assumption allowed us to expedite compound evaluation by avoiding the need to separate and test each atropisomer for each compound.

Table 2. Inhibition of ASMSP-induced foot tapping response in gerbil and receptor antagonist potency (pK_B) in rabbit pulmonary artery tissue

	pK_B[a]	% Inhibition of GFT response[b]	Isomer distribution; shifted/unshifted[c]
5	9.10±0.03	38±11	68:32
6	8.63±0.13	3±1	>98:2
7	8.64±0.09	8±3	10:90
8	8.29±0.15	23±13	31:68
9	8.34±0.24	63±23	>98:2

[a] pK_B Determinations using RPA tissue (n=2–6), agonist: ASMSP.
[b] Determined 4 h after oral dosing of antagonist at 5 μmol/kg and initiated by CNS administration of ASMSP (100 pmol).
[c] Isomer distribution determined by HPLC. Assignments ('shifted' and 'unshifted') refer to the position of the naphthalene H8 signal in NMR spectra.

For **5**–**9**, the distribution and assignment (H8-shifted and non-shifted) of the conformational forms are indicated in Table 2. It was evident that **7** and **8** existed as a mixture of atropisomers, and the conformational equilibrium favored the H8-nonshifted (and hence NK_1 non-preferred) conformation. In comparison, **6** and **9** existed predominantly as a single atropisomer in the H8 shifted conformation.

Detailed characterization of the four isomers will be presented separately, but key observations are summarized here. Central administration of ASMSP to gerbils induces a foot tapping (GFT) response which can be attenuated by prior dosing with an orally available CNS-penetrant, NK_1 receptor antagonist. This can provide a convenient way to assess potency of NK_1 receptor antagonists.[22] Gerbils were orally treated with antagonist at 5 μmol/kg at 4 or 6 h prior to administration of agonist. The CNS potency was then quantified by comparing the foot tapping response with control animals with vehicle only. Among the four isomers, compound **9** was the most potent in the GFT model (Table 2). Furthermore, it was more potent than the unsubstituted **5**. We were fortunate that this was one of the two compounds to exist as a single atropisomer; this could not have been predicted a priori.

Pharmacological activity was further assessed in vitro using pulmonary artery isolated from rabbit (RPA). Rabbit neurokinin receptors are homologous to human. It is noteworthy that while **9** is the most potent isomer in the in vivo model, it does not show the highest potency (pK_B) in the in vitro functional model. While each of the methyl-substituted isomers have similar RPA potencies (pK_B 8.3–8.6), the potency is clearly greater for **5** (pK_B 9.1). Obviously, receptor binding results from multiple interactions, and it is likely that addition of the methyl groups in **6**–**9** introduces some unfavorable interactions in addition to altering the atropisomeric distribution. The apparent discrepancy between the in vivo and in vitro potency for **5** and **9** cannot be attributed to overall drug exposure since gerbil dose-normalized exposure levels in brain are similar between **5** (1478 ng/g following 100 μmol/kg oral dose) and **9** (224 ng/g following 30 μmol/kg oral dose).[23] Possible explanations include differences between the rabbit and gerbil receptors, or differences in exposure levels at specific brain regions. Pharmacokinetic parameters for **9** are shown in Table 3.

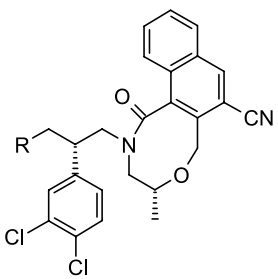
Table 3. Pharmacokinetic analysis of **9** in rat (n=2)

Pharmacokinetic parameter	Result
Oral dose (μmol/kg)	20
Formulation	75% PEG/Saline
Cmax (nM)	265
Tmax (h)	7
AUC-PO(0-i) (ng h/mL)	2370
Bioavailability (%)	25

3.5. Optimization of compounds based on the ring structure in 9

Compound **9** had excellent potency in the gerbil in vivo model and existed in predominantly a single conformational form. Based on this, we sought to further increase potency in compounds containing the same 8-membered ring system. We surveyed analogs of **9** in which the 'left side' dimethyl amine group was replaced with groups of varying properties (Table 4). We observed that antagonist potency (pK_B) was not greatly affected over the range of substituent groups, which included basic, acidic, hydrophobic, and polar functionality. Additionally, we found that antagonist in vitro potency (pK_B) did not directly correlate with in vivo potency in the GFT model; this most likely reflects substantial differences in distribution and metabolism. For example, **9** had much greater potency than **11** in the in vivo GFT model (63% vs 3% inhibition at 4 h); whereas **9** had weaker potency than **11** in the in vitro model (pK_B 8.2 vs 9.0). The most active compound identified was **13**. It showed excellent potency with a very long duration of action (81% inhibition of response after 6 h).

Table 4. In vitro potency (pK_B) in RPA and inhibition of ASMSP-induced foot tapping response in gerbil



	R	pK_B[a]	GFT, 4 h[b]	GFT, 6 h[b]
9	Me_2NCH_2–	8.3±0.1	63±23	52±24
10	MeNH–	9.3±0.1	5±8	9±8
11	(*N*-Piperidinyl)–CH_2–	9.0±0.1	3±1	3±2
12	Me_3CNCH_2–	7.8±0.1	1±0.6	38±31
13	$MeONHCH_2$–	8.2±0.1	73±6	81±19
14	$HOCH_2$–	8.6±0.3	15±7	6±3
15	$ClCH_2$–	7.9±0.1	35±5	63±13
16	HOC(O)–	8.2±0.2	1±0.3	1±0.8
17	$H_2NC(O)$–	8.8±0.1	4±2	3±1
18	MeNHC(O)–	9.0±0.3	4±2	4±2
19	$Me_2NC(O)$–	8.2±0.3	17±12	38±31

[a] pK_B Determinations using rabbit pulmonary artery (RPA) tissue (n=2–6), agonist: ASMSP.
[b] % Inhibition of gerbil foot tap (GFT) response determined after oral dosing of antagonist at 5 μmol/kg at 4 or 6 h (as indicated) prior to initiation by CNS administration of ASMSP (100 pmol).

3.6. Structural analysis and pharmacophore model for 13

Unfortunately, we were unable to crystallize **13**, however; we succeeded for the analog **17** (Fig. 10). Crystallographic analysis showed excellent correspondence with the assigned structure for the NK_1-preferential atropisomer **1d** (Fig. 3) and modeling of the 8-membered ring system (Fig. 7). In particular, the crystal structure shows the 8-membered ring adopting the TBC configuration with the naphthalene oriented such that the H8 proton is 3.1 Å from the dichloroaryl ring centroid. This close proximity is consistent with the upfield shift observed for this proton in NMR spectroscopy. Based on the potent in vivo activity and the structural information, we propose an NK_1 pharmacophore model involving an edge-to-face aryl–aryl stacking interaction and a polar group served by the amide carbonyl in the 8-membered ring system. The exocyclic methyl group may serve to stabilize the desired conformational form, but may also introduce penalizing interactions with the NK_1 receptor. Finally, we note that there is substantial tolerance to substitution at the left-side region in this series which could therefore be used to further optimize distribution and metabolic properties.

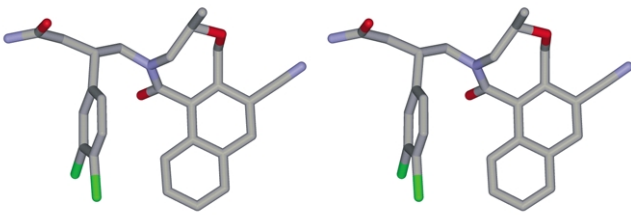


Figure 10. Crystal structure of **17**. The dichloroaryl ring exists both in the orientation shown, and with rotation such that 3-chloro group is on the 'alternate' 3-carbon. The structure is shown as a relaxed-eye stereoview with hydrogen atoms omitted for clarity.

4. Summary and conclusions

In earlier work, we developed a series of potent and selective NK_1 antagonists. However, this series had the undesirable property of existing as a mixture of four atropisomers. Structural analysis and comparisons of the activities of these atropisomers allowed us to construct an NK_1 pharmacophore model. This binding model was then used to design a new series in which the naphthalene amide system was constrained through a tether, thus forming an 8-membered ring. As a result of this constraint, the conformational features were simplified, and resulting compounds existed as a mixture of only two atropisomers. Through detailed computational analysis we constructed a model for both atropisomers and assigned a structure for the active conformer. In the conformational mixture, we found the NK_1 preferred component had a characteristic shift in the H8 naphthalene proton in NMR spectroscopy. The shift was suggestive of the orientation of the naphthalene, and it provided a convenient way to assign provisional conformations and population distributions to the mixture of atropisomers.

Our key goal was to eliminate atropisomeric properties completely. Thus, we modified the 8-membered ring system

of **5** by placing a methyl substituent on each of the four positions of the ethyl segment of the ring (**6**–**9**) and compared the atropisomeric distributions. As expected, the addition of the methyl group did influence the atropisomeric distribution, and two of the four isomers existed in predominantly a single conformational form. Among these two, **9** was the most potent in our in vivo model for CNS activity.

Starting from the ring system in **9**, we made alterations to the left side region in attempt to further improve activity. In this manner, we identified **13**, which showed excellent potency in the in vivo model and long duration of action. Crystallographic analysis of **17** (a close analogue of **13**) confirmed the structural features which had been predicted from structural analysis and modeling. Based on these results, we propose a binding conformation and NK_1 pharmacophore model which involves an edge-to-face aryl–aryl stacking interaction and a hydrogen bonding acceptor group.

5. Experimental

5.1. Molecular modeling

Molecular mechanics computations were performed in vacuo, using the AESOP[20] force field with full geometry optimization of all conformations examined and results were visualized using the in-house molecular graphics program ENIGMA.[24]

5.2. Biological studies

Isolated tissue response (pK_B), studies were carried out as previously described.[25] Inhibition of gerbil foot tapping (GFT) response studies were carried out as previously described.[22]

5.3. Drug exposure analysis

Studies were conducted in fed mongolian gerbils. The animals received 100 μmol/kg drug by oral administration in a dosing volume of 6 mL/kg in a 75% PEG400/saline solution. The gerbils were euthanized at 4 h after dosing by CO_2 inhalation and brain tissue samples were collected. Samples were stored at −20 °C or below until analysis. Brain homogenates were prepared in a tissue homogenizer using four milliliters of saline per gram of tissue. Samples were processed for analysis by the addition of acidified acetonitrile. The resulting extracts were analyzed by LC/MS.

5.4. Bioavailability analysis

Compounds were orally administered to rat (n=2) as a solution in 75% PEG400/saline solution. Blood samples were taken via surgically implanted cannula or by venipuncture over a 24 h period and plasma was analyzed for unchanged compound by LC/MS.

5.5. General chemistry methods

^{1}H NMR spectra were obtained at 300 MHz using a Bruker DPX 300 spectrometer and were referenced to TMS unless otherwise noted. Mass spectral data were obtained on a Micromass QTOF mass spectrometer. Silica gel chromatography was performed with ICN silica 32–63, 60 Å. Thin-layer chromatography was done on silica gel 60 F-254 (0.25 mm thickness) plates, and visualization was accomplished with UV light. Unless otherwise noted, all materials were obtained commercially and used without further purification. For compounds which exist as a mixture of atropisomers, ^{1}H NMR spectra and HPLC chromatograms are complex. In these cases, ^{1}H NMR integrations are not given. Mass spectra were acquired using atmospheric pressure chemical ionization. High resolution mass spectra were acquired using electrospray (ES). The synthesis of compounds **3**, **4**, **6**, **7**, **8**, and **9** are described separately.[15]

5.5.1. 2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-(diethylamino)-butyl]-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]-oxazocine-7-carbonitrile (2). Aldehyde **3**[26] (100 mg, 0.21 mmol) was dissolved in methanol (2 mL) under a nitrogen atmosphere. To this was added diethylamine hydrochloride (35 mg, 0.32 mmol) and triethylamine (34 μL, 0.25 mmol). Acetic acid was added dropwise until the pH was between 4 and 5. The mixture was stirred for 10 min, then 22 mg (0.36 mmol) sodium cyanoborohydride was added as a solution in methanol (approx. 1 mL). After stirring for 1.5 h the pH was adjusted to approximately 5.5 by addition of triethylamine and stirring was continued overnight. The mixture was then concentrated, diluted with ethyl acetate (20 mL), washed with water then brine (20 mL each), dried over magnesium sulfate, filtered and concentrated. The remaining residue was then purified via reverse phase HPLC (using a gradient of acetonitrile in water) to give the title compound (80 mg, 60%) as a gum, δ_H (300 MHz, d_6-DMSO) 9.09 (s), 8.68 (s), 8.62 (s), 8.10 (d, J=7.7 Hz), 8.02 (d, J=8.2 Hz), 7.90 (d, J=8.3 Hz), 7.70 (m), 7.42 (m), 6.44 (d, J=8.5 Hz), 4.81 (m), 4.34 (m), 4.00 (t, J=11.3 Hz), 3.45 (m), 2.71 (m), 2.08 (s), 1.13 (t, J=7.1 Hz); m/z (APCI) 524 MH^+.

5.5.2. 2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-(dimethyl-amino)butyl]-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (5). Aldehyde **3**[26] (150 mg, 0.32 mmol) was dissolved in methanol (3 mL) under a nitrogen atmosphere. To this was added dimethylamine hydrochloride (40 mg, 0.48 mmol) and triethylamine (50 μL, 0.35 mmol). Acetic acid was added dropwise until the pH was between 4 and 5. The mixture was stirred for 0.5 h, then 34 mg (0.54 mmol) sodium cyanoborohydride was added as a solution in methanol (approx. 1 mL). After stirring for 2 h the mixture was then concentrated, diluted with ethyl acetate (30 mL), washed with water then brine (30 mL each), dried over magnesium sulfate, filtered and concentrated. The remaining residue was then purified silica gel chromatrography (6–10% MeOH/CH_2Cl_2) to afford the title product (120 mg, 80%) a white solid, δ_H (300 MHz, d_6-DMSO) 8.68 (s), 8.62 (s), 8.09 (d, J=7.8 Hz), 8.01 (d, J=8.1 Hz), 7.90 (d, J=8.3 Hz), 7.82–7.59 (m), 7.40 (m), 6.43 (d, J=8.5 Hz), 4.87 (m), 4.71 (t, J=12.0 Hz), 4.32 (m), 3.99 (t, J=11.1 Hz), 3.89–3.64 (m), 3.42–2.94 (m), 2.83–2.55 (m), 2.10 (s); m/z (APCI) 496 MH^+.

5.5.3. (4*R*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-(methyl-amino)butyl]-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (10). Aldehyde

4[15] (70 mg, 0.145 mmol) was dissolved in 1 mL of THF and methylamine in THF (2 M, 87 μL, 0.174 mmol) was added. The mixture was diluted with methanol (2 mL), and then acetic acid (5 μL) was added and the mixture stirred for 10 min. A solution of sodium cyanoborohydride (1 M in THF, 0.5 mL, 0.500 mmol) was added and the reaction was stirred overnight at ambient temperature. The reaction mixture was evaporated and the residue purified by preparative HPLC using a Phenomenex LUNA C-18(2), 250×21.2 mm (10 μ) column eluting with acetonitrile–water gradient containing 0.1% TFA (40–70% acetonitrile over 20 min). Product containing fractions were pooled and partially concentrated to remove acetonitirile. The remaining aqueous solution was made basic by addition of 10% aqueous sodium carbonate, and the solution extracted with ethyl acetate (3 times, 20 mL). The organic extracts were dried (Na_2SO_4), filtered and evaporated to afford the title compound (40 mg, 55%) as a white foamy solid, δ_H (300 MHz, d_6-DMSO) 8.66 (s, 1H), 8.30 (1H, br), 8.05 (1H, d, *J*=8.3 Hz), 7.67 (3H, m), 7.42 (2H, m), 6.54 (1H, d, *J*=8.3 Hz), 4.95 (1H, d, *J*=13.8 Hz), 4.71 (1H, m), 4.51 (1H, d, *J*=13.8 Hz), 4.03 (1H, m), 3.24 (1H, m), 2.99–2.53 (6H, m), 2.37 (2H, m), 2.01 (2H, m), 1.10 (3H, d, *J*=6.1 Hz); *m/z* (APCI) 496 MH^+.

5.5.4. (4*R*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-piperidin-1-ylbutyl]-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (11). Aldehyde **4**[15] (70 mg, 0.145 mmol) was dissolved in THF (1 mL) and piperidine (15 mg, 0.176 mmol) was added. The mixture was diluted with methanol (2 mL), then acetic acid (5 μL) was added and the mixture stirred for 10 min. A solution of sodium cyanoborohydride (1 M in THF, 0.5 mL, 0.500 mmol) was added and the reaction was stirred overnight at ambient temperature. The reaction mixture was evaporated and the residue purified by preparative HPLC according to the procedure described for **10** to afford of the title compound as a white foamy solid (50 mg, 62%), δ_H (300 MHz, d_6-DMSO) 8.68 (1H, s), 8.39 (1H, br), 8.04 (1H, d, *J*=7.9 Hz), 7.68 (3H, m), 7.43 (2H, m), 6.55 (1H, d, *J*=8.3 Hz), 4.96 (1H, d, *J*=13.8 Hz), 4.72 (1H, m), 4.51 (1H, d, *J*=13.8 Hz), 4.04 (1H, m), 3.02–2.52 (8H, m), 2.05 (2H, m), 1.09 (3H, d, *J*=6.6 Hz), 0.96 (1H, m), 0.55 (2H. m), 0.30 (2H, m); *m/z* (APCI) 550 MH^+; HRMS (ES) M^+, found 550.2007. $C_{31}H_{33}Cl_2N_3O_2$ requires 550.2028.

5.5.5. (4*R*)-2-[(2*S*)-4-(*tert*-Butylamino)-2-(3,4-dichlorophenyl)butyl]-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (12). Aldehyde **4**[15] (70 mg, 0.145 mmol) was dissolved THF (1 mL) and *tert*-butylamine (13 mg, 0.177 mmol) was added. The mixture was diluted with methanol (2 mL), then acetic acid (5 μL) was added and the mixture stirred for 10 min. A solution of sodium cyanoborohydride (1 M in THF, 0.5 mL, 0.500 mmol) was added and the reaction was stirred overnight at ambient temperature. The reaction mixture was evaporated and the residue purified by preparative HPLC according to the procedure described for **10** to afford the title compound as a white foamy solid (50 mg, 64%), δ_H (300 MHz, d_6-DMSO) 8.67 (1H, s), 8.27 (1H, br), 8.05 (1H, d, *J*=8.3 Hz), 7.72–7.64 (3H, m), 7.43 (2H, m), 6.60 (1H, d, *J*=8.7 Hz), 4.96 (1H, d, *J*=14.0 Hz), 4.73 (1H, m), 4.52 (1H, d, *J*=14.0 Hz), 4.05 (1H, m), 2.94 (3H, m), 2.75–2.53 (3H, m), 2.02 (2H, m), 1.21 (9H, s), 1.10 (3H, d, *J*=6.5 Hz); *m/z* (APCI) 538 MH^+; HRMS (ES) M^+, found 538.2051. $C_{30}H_{33}Cl_2N_3O_2$ requires 538.2028.

5.5.6. (4*R*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-(methoxyamino)butyl]-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (13). Aldehyde **4**[15] (70 mg, 0.145 mmol) was dissolved THF (1 mL) and *O*-methylhydroxylamine hydrochloride (14 mg, 0.167 mmol) was added. The mixture was diluted with methanol (2 mL), then acetic acid (5 μL) was added and the mixture stirred for 10 min. A solution of sodium cyanoborohydride (1 M in THF, 0.5 mL, 0.500 mmol) was added and the reaction was stirred overnight at ambient temperature. The reaction mixture was evaporated and the residue purified by preparative HPLC according to the procedure described for **10** to afford the title compound as a white foamy solid (21 mg, 28%), δ_H (300 MHz, $CDCl_3$) 8.25 (1H, s), 8.81 (1H, d, *J*=7.4 Hz), 7.60–7.46 (3H, m), 7.39 (1H, d, *J*=1.7 Hz), 7.31–7.25 (1H, m), 6.68 (1H, d, *J*=8.3 Hz), 5.53 (1H, br), 5.14 (1H, d, *J*=13.6 Hz), 4.02 (1H, t, *J*=13.7 Hz), 4.56 (1H, d, *J*=13.7 Hz), 3.96 (1H, m), 3.52 (3H, s), 3.24–3.02 (4H. m), 2.80 (2H, m), 1.96 (2H, m), 1.17 (3H, d, *J*=6.6 Hz); *m/z* (APCI) 512 MH^+; HRMS (ES) M^+, found 512.1343. $C_{27}H_{27}Cl_2N_3O_3$ requires 512.1508.

5.5.7. (4*R*)-2-[(2*S*)-2-(3,4-Dichlorophenyl)-4-hydroxybutyl]-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (14). Aldehyde **4**[15] (250 mg, 0.52 mmol) was dissolved in methanol (5 mL) under a nitrogen atmosphere and cooled to 5 °C. Sodium borohydride (22 mg, 0.57 mmol) was then added, the cooling bath removed, and the reaction allowed to stir for 15 min. It was then concentrated, diluted with ethyl acetate, washed with water then brine, dried over magnesium sulfate, filtered and concentrated. The residue was then purified via silica gel chromatography (60–80% ethyl acetate/hexanes) to give the title compound as a foamy solid (200 mg, 80%), δ_H (300 MHz, $CDCl_3$) 8.25 (1H, s), 7.82 (1H, d, *J*=7.7 Hz), 7.54 (3H, m), 7.41 (1H, d, *J*=2.0 Hz), 7.29 (1H, m), 6.69 (1H, d, *J*=8.3 Hz), 5.15 (1H, d, *J*=13.8 Hz), 4.94 (1H, t, *J*=12.4 Hz), 4.57 (1H, d, *J*=13.8 Hz), 3.96 (1H, m), 3.70 (1H, m), 3.47 (1H, m), 3.29 (2H, m), 3.14 (3H, m), 1.98 (2H, m), 1.17 (3H, d, *J*=6.5 Hz); *m/z* (APCI) 438 MH^+; HRMS (ES) M^+, found 483.1223. $C_{26}H_{24}Cl_2N_2O_3$ requires 483.1242.

5.5.8. (4*R*)-2-[(2*S*)-4-Chloro-2-(3,4-dichlorophenyl)-butyl]-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocine-7-carbonitrile (15). Alcohol **14** (80 mg, 0.17 mmol) was dissolved in toluene (3.5 mL) under a nitrogen atmosphere and to this was added triphenylphosphine (48 mg, 0.18 mmol), then hexachloroacetone (264 mg, 0.42 mmol) over one min. as a solution in toluene. The reaction was allowed to stir for 1 h, heated briefly to 60 °C, cooled and allowed to stir overnight at room temperature. A second portion of triphenylphosphine (10 mg) and hexachloroacetone (2 drops) were added and reaction again heated briefly to 60 °C, cooled, then concentrated. The remaining residue was purified via silica gel chromatography (30–40% ethyl acetate/hexanes) to give the title compound as a foam solid (80 mg, 96%), δ_H (300 MHz, $CDCl_3$) 8.26 (1H, s), 7.83 (1H, d, *J*=7.8 Hz), 7.54 (3H, m), 7.43 (1H, d, *J*=2.0 Hz), 7.28 (1H, m), 6.73 (1H, d, *J*=8.4 Hz), 5.17 (1H, d,

J=13.8 Hz), 4.95 (1H, t, J=12.2 Hz), 4.58 (1H, d, J=13.8 Hz), 3.99 (1H, m), 3.60 (1H, m), 3.23 (5H, m), 2.18 (2H, m), 1.19 (3H, d, J=6.5 Hz); m/z (APCI) 501 MH^+; HRMS (ES) M^+, found 501.0905. $C_{26}H_{23}Cl_3N_2O_2$ requires 501.0903.

5.5.9. (3*S*)-4-[(4*R*)-7-Cyano-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocin-2-yl]-3-(3,4-dichlorophenyl)butanoic acid (16). Aldehyde **4**[15] (850 mg, 1.77 mmol) was dissolved in acetone (10 mL) under a nitrogen atmosphere and cooled to 0 °C. Jones reagent (2 M, 1.3 mL, 2.65 mmol) was added as a solution in acetone (4 mL) over 5 min. The reaction was stirred for 5 min, then 2-propanol (3 mL) was added and stirred for 5 min. The mixture was concentrated, diluted with ethyl acetate (15 mL), washed with water then brine (15 mL each), dried over magnesium sulfate, filtered and concentrated to give the title compound as a foamy solid (850 mg, 97%), δ_H (300 MHz, $CDCl_3$) 8.27 (1H, s), 7.84 (1H, d, J=7.8 Hz), 7.55 (3H, m), 7.42 (1H, d, J=2.0 Hz), 7.29 (1H, m), 6.67 (1H, d, J=8.4 Hz), 5.17 (1H, d, J=13.9 Hz), 4.94 (H, t, J=12.2 Hz), 4.56 (1H, d, J=13.9 Hz), 3.9 (1H, m), 3.51 (1H, m), 3.19 (3H, m), 2.83 (2H, d, J=7.2 Hz), 1.20 (3H, d, J=6.5 Hz); m/z (APCI) 497 MH^+; HRMS (ES) M^+, found 497.1027. $C_{26}H_{22}Cl_2N_2O_4$ requires 497.1035.

5.5.10. (3*S*)-4-[(4*R*)-7-Cyano-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocin-2-yl]-3-(3,4-dichlorophenyl)butanamide (17). Carboxylic acid **16** (80 mg, 0.16 mmol) was dissolved in dichloromethane (3 mL) under a nitrogen atmosphere; to this was added diisopropylethylamine (55 μL, 0.32 mmol), then fluoro-*N*,*N*,*N*′-tetramethylforamidinium hexafluorophosphate (51 mg, 0.19 mmol). After 1 h HOBt–NH_3[27] (43 mg, 0.32 mmol) was added and the mixture stirred for 2 h. Saturated aqueous sodium bicarbonate and ethyl acetate were added (15 mL each) and the mixture was washed with aqueous sodium bicarbonate, then brine (15 mL each), dried over magnesium sulfate and purified via silica gel chromatography (5–7% methanol/methylene chloride) to give the title compound as a foamy solid (60 mg, 76%), δ_H (300 MHz, $CDCl_3$) 8.25 (1H, s), 7.82 (1H, d, J=7.8 Hz), 7.52 (4H, m), 7.28 (1H, m), 6.68 (1H, d, J=8.3 Hz), 5.43 (2H, m), 5.16 (1H, d, J=13.9 Hz), 4.94 (1H, t, J=12.6 Hz), 4.56 (1H, d, J=13.9 Hz), 3.97 (1H, m), 3.60 (1H, m), 3.26 (1H, m), 3.15 (2H, d, J=7.1 Hz), 2.64 (2H, m), 1.19 (3H, d, J=6.5 Hz); m/z (APCI) 496 MH^+; HRMS (ES) M^+, found 496.1194. $C_{26}H_{23}Cl_2N_3O_3$ requires 496.1194. Crystals suitable for diffraction were prepared by dissolving the compound in ethyl acetate/methylene chloride (10:1) and allowing diethyl ether to diffuse into the solution in a closed vial, mp 168–170 °C, $[\alpha]_D^{20}=-130$ (c 0.5, methanol). Crystallographic data (excluding structure factors) for the structure in this paper was deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 230503. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

5.5.11. (3*S*)-4-[(4*R*)-7-Cyano-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocin-2-yl]-3-(3,4-dichlorophenyl)-*N*-methylbutanamide (18). Carboxylic acid **16** (80 mg, 0.16 mmol) was dissolved in dichloromethane (2 mL) under a nitrogen atmosphere; to this was added oxalyl chloride (28 μL, 0.32 mmol) and one drop of dimethylformamide. After stirring for 0.5 h, the mixture was concentrated, redissolved in dichloromethane (1 mL) and concentrated again. The residue was dissolved in dichloromethane (2 mL) and to this was added methylamine (2 M solution in THF, 120 μL, 0.24 mmol), and triethylamine (32 μL, 0.24 mmol). The mixture was stirred for 1 h, concentrated and purified using reverse phase HPLC to give the title compound as a white solid (60 mg, 60%), δ_H (300 MHz, $CDCl_3$) 8.26 (1H, s), 7.83 (1H, d, J=7.8 Hz), 7.53 (4H, m), 7.26 (1H, m), 6.67 (1H, d, J=8.4 Hz), 5.74 (1H, d, J=4.1 Hz), 5.16 (1H, m), 4.93 (1H, m), 4.56 (1H, m), 3.98 (1H, m), 3.65 (1H, m), 3.27 (1H, m), 3.12 (2H, m), 2.78 (d, J=4.8 Hz), 2.62 (2H, m), 1.18 (3H, d, J=6.5 Hz; m/z (APCI) 510 MH^+; HRMS (ES) M^+, found 510.1356. $C_{27}H_{25}Cl_2N_3O_3$ requires 510.1351.

5.5.12. (3*S*)-4-[(4*R*)-7-Cyano-4-methyl-1-oxo-1,3,4,6-tetrahydro-2*H*-naphtho[1,2-*f*][1,4]oxazocin-2-yl]-3-(3,4-dichlorophenyl)-*N*,*N*-dimethylbutanamide (19). Carboxylic acid **16** (80 mg, 0.16 mmol) was dissolved in dichloromethane (2 mL) under a nitrogen atmosphere; to this was added oxalyl chloride (28 μL, 0.32 mmol) and one small drop of dimethylforamide. After stirring for 0.5 h, the mixture was concentrated, redissolved in dichloromethane (1 mL) and concentrated again. The residue was dissolved in dichloromethane (2 mL) and to this was added dimethylamine (120 μL of 2 M solution in tetrahydrofuran, 0.24 mmol), and triethylamine (32 μL, 0.24 mmol). The mixture was stirred for 15 min, concentrated and purified using silica gel chromatography (2–3% methanol/dichloromethane) to give the title compound as a foamy solid (80 mg, 95%), δ_H (300 MHz, $CDCl_3$) 8.24 (1H, s), 7.81 (1H, d, J=7.8 Hz), 7.51 (4H, m), 7.30 (1H, m), 6.62 (1H, d, J=8.3 Hz), 5.15 (1H, d, J=13.8 Hz), 4.92 (1H, t, J=12.6 Hz), 4.56 (1H, d, J=13.8 Hz), 4.00 (1H, m), 3.64 (1H, m), 3.31 (2H, m), 3.11 (1H, m), 3.00 (3H, s), 2.95 (3H, s), 2.70 (2H, d, J=6.7 Hz), 1.22 (3H, d, J=6.5 Hz); m/z (APCI) 524 MH^+; HRMS (ES) M^+, found 524.1501. $C_{28}H_{27}Cl_2N_3O_3$ requires 524.1508.

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Tetrahedron 60 (2004) 4349–4360
Tetrahedron

The 'lactone method': enantioselective preparation of novel *P,N*-biaryl ligands and their use in the synthesis of the biarylic alkaloids, ancistrotanzanine B and ancistroealaine A☆

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Received 10 October 2003; revised 3 December 2003; accepted 8 December 2003

Abstract—The 'lactone method' is a versatile tool for the atroposelective synthesis of axially chiral biaryls. The potential and scope of the concept are highlighted, in particular with respect to its use in the preparation of natural products and chiral auxiliaries. As a new application, the synthesis of novel axially chiral phosphineamines in enantiopure form is described; these ligands were used in the asymmetric Suzuki cross coupling of the molecular portions of the biarylic natural products ancistrotanzanine B and ancistroealaine A.

1. Introduction

The importance of axially chiral biaryls has steadily grown during the past decades. One reason is that nature offers a large number of representatives of this class of compounds with, in many cases, interesting pharmacological activities.[2] Likewise intriguing is the broad structural variety reaching from simple bisphenols like **1**,[3] via the naphthylisoquinoline alkaloid ancistrotanzanine A [(*M*)-**2**],[4] a plant metabolite with promising antileishmanial activities, to complex glycopeptides like vancomycin (**3**),[5] a clinically used antibiotic from *Streptomyces orientalis*.[6] Moreover, the synthetic chemist has recognized axially chiral biaryls as versatile auxiliaries for asymmetric synthesis.[7] Just to mention two applications: the C_2-symmetric diphosphine (*M*)-**4** (BINAP) is the ligand of choice for enantioselective Ru-catalyzed hydrogenations of alkenes and ketones,[8] while the salen-type ligand **5**, which contains even two axially chiral subunits, is successfully employed in enantioselective Mn-catalyzed alkene epoxidations.[9]

In view of the increasing importance of atropisomerism, it is astonishing that synthetically useful methods for the atroposelective construction of axially chiral biaryls are still rare.[10] Many of the asymmetric biaryl coupling procedures published are applicable only to simple model systems and suffer from low chemical and optical yields when applied to 'real', more sophisticated and sterically congested systems, or even fail entirely. The main—mostly problematic—feature common to all these methods consists in the fact that the construction of the biaryl axis and the introduction of the stereochemical information have to be achieved simultaneously in the same step. An unprecedented approach that circumvents this problem and allows optimization of both partial tasks independently, by splitting them into two separate steps, is provided by the 'lactone method' as developed in our group.[11] As key intermediates, this method utilizes lactones of type **6**.[12] These bridged biaryls are not (yet) stereochemically fixed at the axis,[13] so that the asymmetric information can be introduced within the cleavage of the lactone bridge to give—atropo-enantio- or -diastereoselectively—the ring-opened products **7** in good to excellent chemical and optical yields (Fig. 1).

In our contribution to this special Tetrahedron issue, we wish to give a brief overview on the potential of the lactone method, here with particular focus on the synthesis of novel C_1-symmetric phosphineamines of type (*M*)-**8**. These can be used as chiral ligands in asymmetric Suzuki cross coupling of molecular 'halves' of the biaryl alkaloid ancistrotanzanine B and its atropo-diastereomer, ancistroealaine A Scheme 1.

2. Results and discussion

2.1. The lactone method

As mentioned previously, the two crucial goals of atroposelective biaryl synthesis, the formation of the aryl–

☆ See Ref. 1.

Keywords: Axially chiral biaryls; *P,N*-Ligands; Asymmetric Suzuki coupling; Natural product synthesis; Naphthylisoquinoline alkaloids.
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doi:10.1016/j.tet.2003.12.070

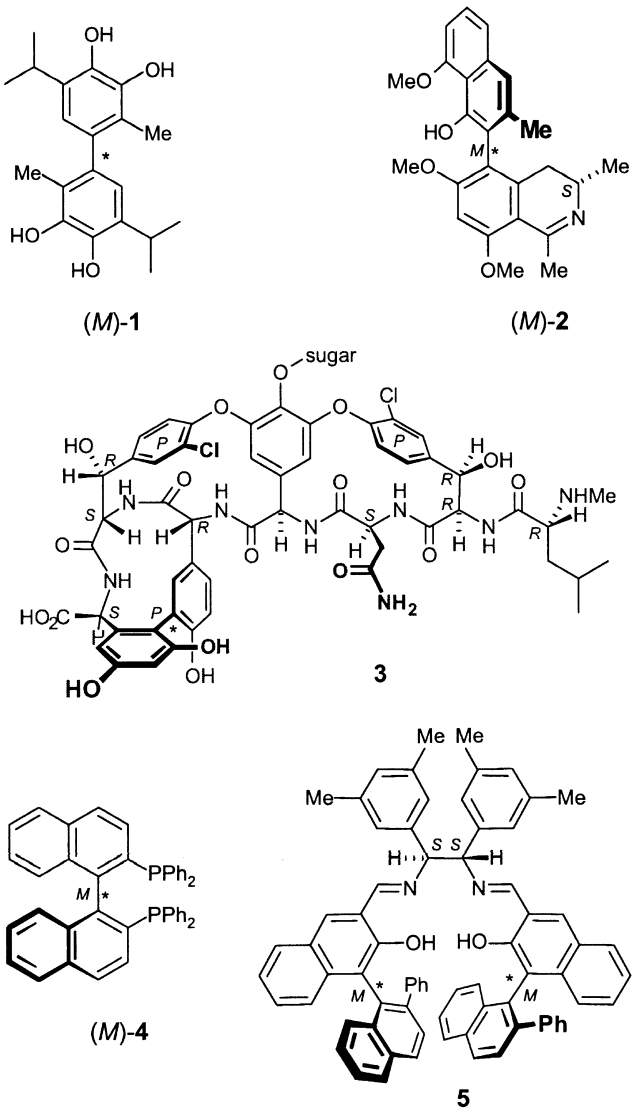
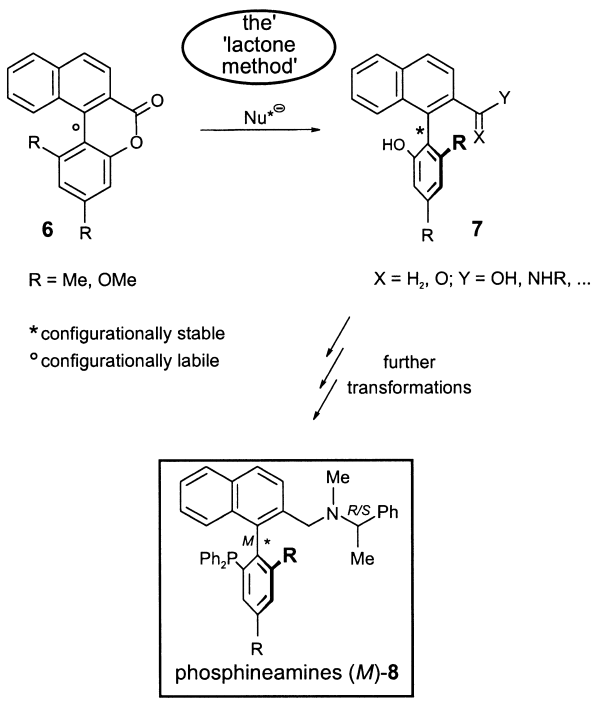


Figure 1. Selected axially chiral biaryl natural products (**1**-**3**) and ligands for asymmetric synthesis (**4**, **5**).

aryl linkage and the introduction of the asymmetric information at the newly created axis, are performed consecutively within the lactone method.[11] The basic principle, which is illustrated in Scheme 2 with the benzonaphthopyranones **6** as the model biaryl lactones, is quite generally applicable and offers several advantages: in the esters **9**, which are easily available in large quantities by standard procedures, the two aryl moieties are prefixed at a favorable distance to each other, thus allowing the cross coupling to proceed intramolecularly and thus with complete regiocontrol, dictated by the position of the bromine substituents and the likewise strict *ortho*-attack in the phenolic part. With $Pd(OAc)_2$ or, even better, with the more temperature-stable palladacycle **10**, the desired biaryl lactones **6** are obtained in high yields of up to 91%; even for sterically severely hindered systems with R=*i*Pr or *t*Bu, more than 80% are attained.[14] As a consequence of the steric repulsion between the *ortho*-substituent R and the *peri*-proton of the naphthalene ring, the lactones **6** are not flat, but helically distorted and thus chiral and can hence exist as a racemic pair of enantiomers, (*M*)-**6** and (*P*)-**6**.[13,15] On the other hand, the bridging lactone function drastically

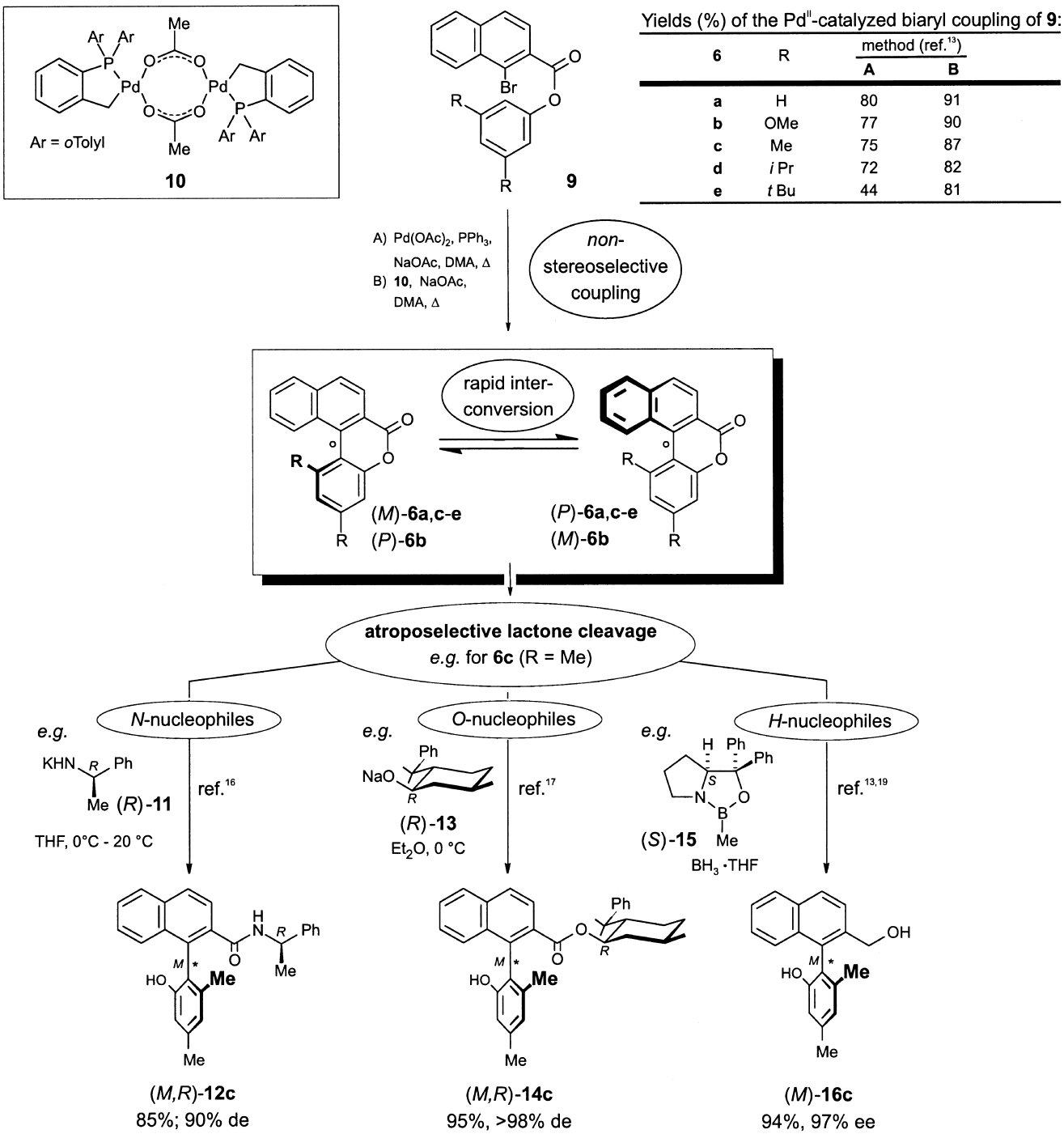


Scheme 1. The stereochemical key step of the lactone method and general structure of the new axially chiral phoshineamines (*M*)-**8** envisaged here.

lowers the atropisomerization barrier, so that the biaryl axis is configurationally unstable in most cases.[16] The resulting rapid interconversion[13] of the two enantiomers of **6** is a fundamental prerequisite for the following stereochemically decisive—and conceptionally most innovative—step of the lactone method, the cleavage of the lactone bridge of **6** with dynamic kinetic resolution. This is easily achieved by chiral *N*-,[17] *O*-,[18] or *H*-nucleophiles,[14,19] delivering the now configurationally stable, since ring-opened target biaryls in high chemical yields and good to excellent atropo-diastereomeric or -enantiomeric ratios.[11] As an example, reaction of **6c** (R=Me) with potassium (*R*)-1-phenylethyl-amide [(*R*)-**11**] gives the amide (*M*,*R*)-**12c** in 85% yield and with 90% de.[17] With the *O*-nucleophile sodium (1*R*)-8-phenylmenthoxide [(*R*)-**13c**], the ester (*M*,*R*)-**14c** is obtained in 95% yield and with an excellent de of >98%.[18] The atropo-enantioselective CBS-reduction[20] of **6c** delivers the diol (*M*)-**16c** in 94% yield and with 97% ee.[14,19]

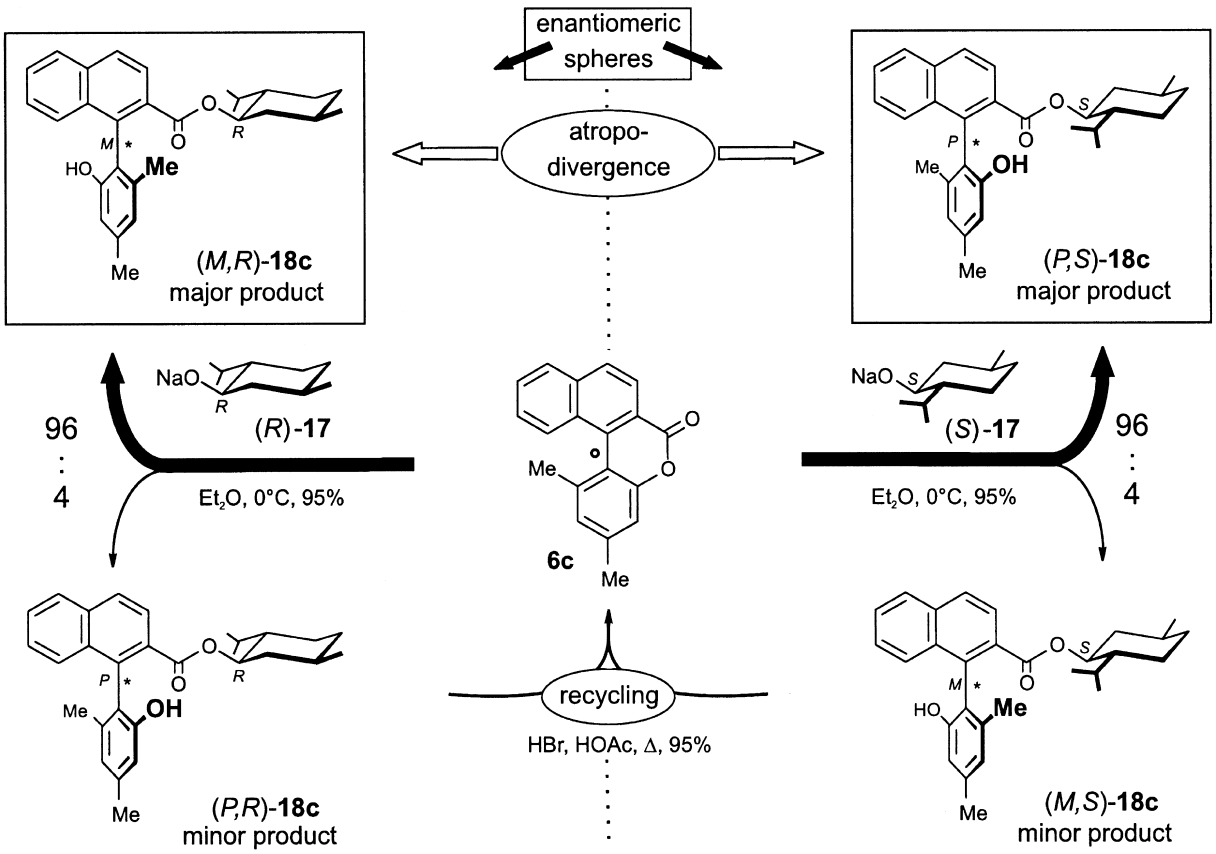
Due to the mild reaction conditions under which the lactone cleavage occurs, this protocol can be applied in the presence of various functional groups as found, for example, in bioactive target molecules. Moreover, in view of an application of the method in multi-step syntheses of, for example, natural products, there is sometimes no need to open the lactone ring immediately after the construction of the biaryl axis since this can likewise be achieved at any convenient later stage of the synthesis, with the lactone function meanwhile possibly even serving as a protecting group for the C_1 ($-CH_2OH$, $-CO_2H$) and oxygen functions involved.[21,22]

Since most of the chiral auxiliaries used for the ring opening of **6** are commercially available in both enantiomeric forms, another advantage of the method becomes obvious: from the



Scheme 2. Synthesis and atroposelective ring opening of the biaryl lactones **6c**.

very same lactone precursor, both atropisomeric products are available atropo-enantio- or -diastereodivergently, just by using the appropriate enantiomer of the nucleophile. This is a most valuable option which is provided only by very few other atroposelective coupling procedures;[23] usually, the decision of which atropisomer one wants to produce, has to be taken at an early stage of the synthesis, since often a chiral auxiliary of a given configuration is attached covalently to one of the precursor molecules and thus, by internal asymmetric induction,[10] will give only one particular product. Within the lactone method, by contrast, besides the atropo-divergence at a late stage of the synthesis, such a decision can even be 'corrected' by the unique option of recycling products with an undesired configuration (see below). As an example, cleavage of **6c** with sodium (1*R*)-menthoxide [(*R*)-**17**] delivers the ester (*M*,*R*)-**18c** in 95% yield and 88% de (Scheme 3), while the analogous ring opening with sodium (1*S*)-menthoxide [(*S*)-**17**]—predictably—leads to the enantiomer (*P*,*S*)-**18c**, as expected with the same optical and chemical yields.[18] The respective minor diastereomers (*P*,*R*)-**18c** and (*M*,*S*)-**18c**, which are easily separated by column chromatography, are not lost but can be recycled, just by acid-catalyzed cyclization back to the configurationally unstable lactone **6c** and renewed ring



Scheme 3. Two additional advantages of the lactone method: the possibility of a atropo-divergently opening the lactone ring to give one or, if desired, the other atropisomer, and the recycling of undesired stereoisomers (here, for example, the minor products), exemplarily illustrated for the alcoholysis of **6c** with menthoxides like **17**.

cleavage.[24] Even though not really necessary in this particular case, this option to recycle possibly precious material is another merit of the lactone concept and becomes extremely advantageous, for example, for precious substrates at a late stage of a multi-step natural product synthesis.[21]

An important touchstone for the practicability and usefulness of a method is its application in the synthesis of concrete, possibly complex, target molecules. Using the methodology described here, more than 25 axially chiral natural products[2,11] have meanwhile been prepared, in several cases this was possible only by the lactone method.[25] The structural diversity of these successfully attained target molecules is broad, reaching from naphthylisoquinoline alkaloids like korupensamine A [(*P*)-**19**, Fig. 2][26] to phenylanthraquinones such as knipholone [(*M*)-**20**].[27] Sterically less hindered biphenyls, which are on the verge of configurational stability at the biaryl axis, have also become accessible by the lactone method, for example, (*M*)-**21**, a synthetic precursor to the AB-fragment of vancomycin (**3**, see Fig. 1).[28] Furthermore, with large quantities of enantiopure model substances like **12**, **16** (see Scheme 2), and **18** (see Scheme 3) in hand, we have developed novel C_1-symmetric biaryls as catalysts, reagents, or ligands for asymmetric synthesis like the aminophenol (*M*)-**22c**, successfully used as a catalyst in enantioselective diethylzinc additions to aldehydes,[29] or the phosphine (*P*)-**23c**, applied in catalytic enantioselective hydrosilylations of styrenes.[30]

Further applications of the lactone method in the synthesis of natural products and chiral ligands are currently in progress. The latest results of our research in the preparation of novel axially chiral *P*,*N*-ligands will be discussed in the following sections.

2.2. Preparation of the enantiopure axially chiral phosphineamines (*M*)-8

Among the bifunctional C_1-symmetric ligands with a biaryl framework, phosphineamines (so-called *P*,*N*-ligands) have received considerable attention.[31] Derivatives such as (*P*)-**24** (Fig. 3), possessing elements of both axial and central chirality, were introduced by Wildhalm et al., giving excellent enantioselectivities in palladium catalyzed allylic substitution reactions.[32] We were interested in related *P*,*N*-ligands of type (*M*)-**8**, which carry a sterically crowded tertiary amine function and a phosphine moiety in a close proximity to each other. In view of the scheduled application of (*M*)-**8** as a chiral ligand in transition metal complexes, however, we considered an attachment of the PPh_2 group directly to the rigid chiral biaryl core—as also found in many highly stereo-differentiating diphosphines like, for example, BINAP [(*M*)-**4**, see Fig. 1)]—to be favorable. This should involve the element of axial chirality more strongly into the chirality transfer and, thus, give rise to good asymmetric induction, making phosphineamines like (*M*)-**8** rewarding synthetic targets.

The synthesis of the methyl-substituted derivatives

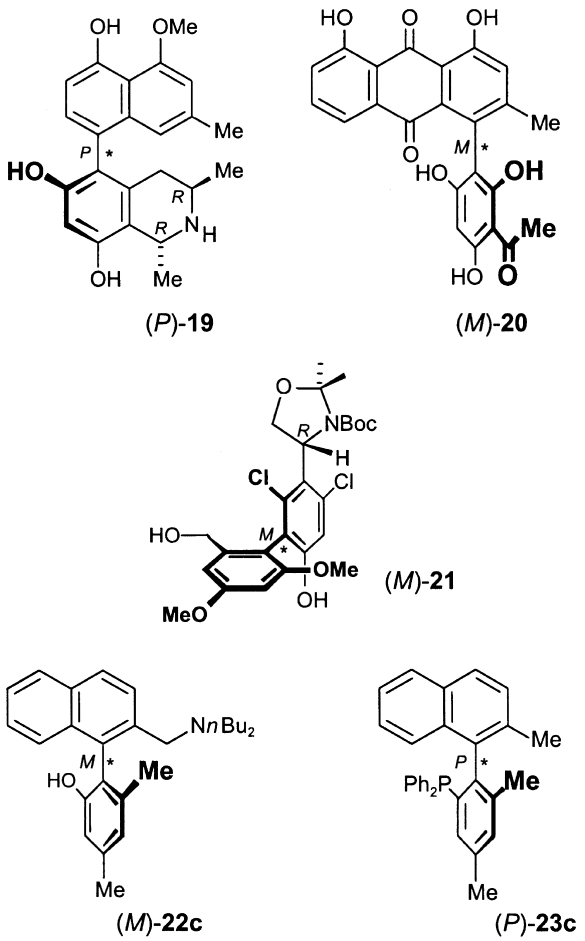


Figure 2. Selected axially chiral biarylic natural products [(*P*)-**19**, (*M*)-**21**], synthetic precursors [(*M*)-**21**], and ligands [(*M*)-**22**, (*P*)-**23**] prepared by the lactone method.

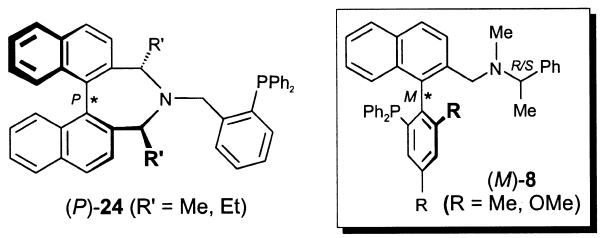


Figure 3. The known phosphineamines (*P*)-**24** and the target molecules **8**.

(*M*,*R*)-**8c** and (*M*,*S*)-**8c** (Scheme 4) started form the enantiopure biaryl diol (*M*)-**16c**,[14] which is easily accessible in large quantities by the lactone method (cf. Scheme 2). Protection of the phenolic OH function as a benzyl ether and of the benzylic alcohol as an ethyl ether, followed by BCl_3-mediated removal of the benzyl ether, delivered (*M*)-**25c**. Activation of the phenolic OH group as a triflate set the stage for a palladium-mediated phosphonylation,[33] which, after cleavage of the ethyl ether group using HBr, led to the bromophosphine oxide (*M*)-**26c**. The good crystallization properties of (*M*)-**26c** allowed us to perform an X-ray diffraction analysis, which fully confirmed the anticipated structure, including the absolute axial configuration [Fig. 4, Flack parameter[34] x=0.000 (11)]. Nucleophilic substitution of the bromine by (*R*)- and (*S*)-1-phenylethylamine, and subsequent *P*-deoxygenation gave the desired phosphineamines (*M*,*R*)-**8c** and (*M*,*S*)-**8c**, respectively.

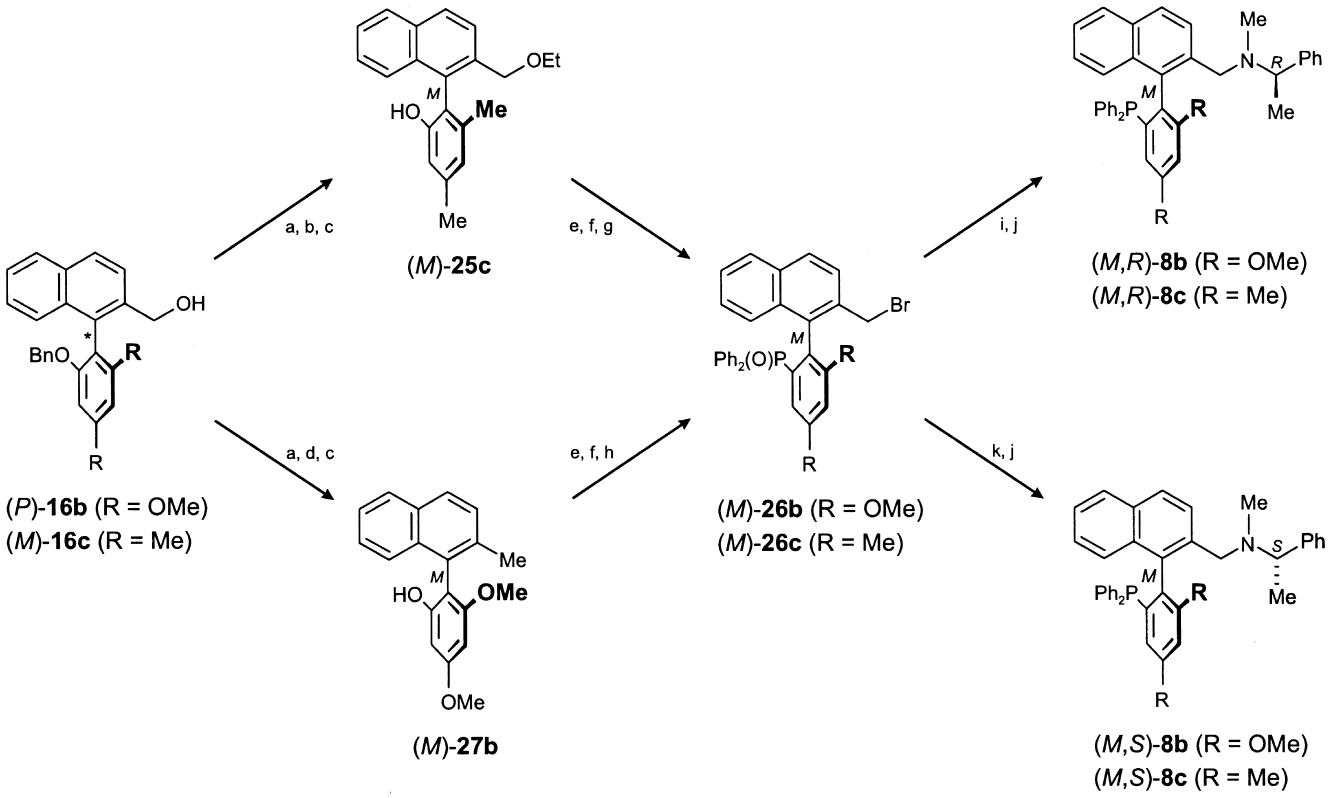
A slightly modified synthetic route was used for the preparation of the methoxy-substituted *P*,*N*-ligands (*M*,*R*)-**8b** and (*M*,*S*)-**8b**. Protection of the phenolic OH group of (*P*)-**16b**,[35] deoxygenation of the C_1-naphthalene sidechain, and removal of the protecting group delivered the biaryl alcohol (*M*)-**28b**. Introduction of the $Ph_2P(O)$ moiety after activation with triflic acid anhydride and radical bromination of the methyl group on the naphthalene ring gave the bromophosphineoxide (*M*)-**26b**, which was, in analogy to (*M*)-**26c**, converted into the diastereomeric phosphineamines (*M*,*R*)-**8b** and (*M*,*S*)-**8b**, by using the respective enantiomer of *N*-methyl-1-phenylethylamine.

2.3. Use of the phosphineamines as ligands in asymmetric Suzuki couplings

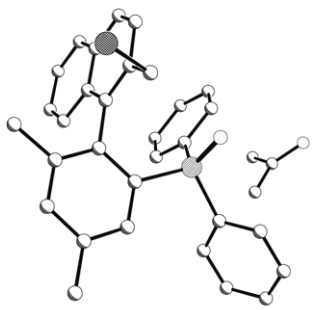
In our total synthesis[36] of the alkaloid ancistrotanzanine B [(*M*)-**30**][4] and its likewise naturally occurring atropo-diastereomer, ancistroealaine A [(*P*)-**30**][37] (Scheme 5), the biaryl axis was constructed by a Suzuki cross coupling of the boronic acid **28** with the iodinated isoquinoline **29**.[38] The existing stereogenic center in **29** had already been shown to possess no significant influence on the diastereoselectivity in the formation of the biaryl axis, as obvious from the low dr [(*M*)-**30**:(*P*)-**30**=55:45], for example, obtained with $Pd(PPh_3)_4$ as the catalyst (Table 1, entry 1). With commercially available chiral ligands like the ferrocene (S_p,*R*)-**31**[39] and (*M*)-BINAP [(*M*)-**4**], only moderate stereocontrol had previously been achieved [entries 2 and 3, best dr=75:25 for (*M*)-**4**], and the major problem, the low coupling yields (<52%), had remained unsolved,[36] making this reaction a rewarding test system for our new *P*,*N*-ligands of type (*M*)-**8**.[40] The Suzuki couplings of **28** and **29** in the presence of (*M*,*R*)-**8b**, (*M*,*S*)-**8b**, (*M*,*R*)-**8c**, and (*M*,*S*)-**8c** delivered ancistrotanzanine B (*M*)-**30** as the main diastereomer in each case, albeit with disappointingly low stereocontrol [entries 4–7, best dr=67:33 for (*M*,*R*)-**8c**]. The influence of the centrochiral *N*-1-phenylethyl side chain was only small, but, nevertheless, noticeable since the *M*,*R*-combination (matched case) led to higher diastereomeric ratios than *M*,*S* (mismatched case) (entries 4 vs 5 and 6 vs 7).

The electron density of the biarylic benzene ring had a significant effect on the amount of products formed: The more electron rich derivatives (*M*)-**8b** (R=OMe) gave higher yields, reaching, here for the first time, excellent 89% for (*M*,*S*)-**8b** (entry 5), while with (*M*)-**8c** (R=Me) and also with the two commercially available ligands (*M*)-**4** and (S_p,*R*)-**32**, only moderate yields of <60% were obtained.

In conclusion, we have established an enantioselective route to stereochemically homogeneous, both axially and centrally chiral *P*,*N*-ligands of type (*M*)-**8** using the lactone method. These phosphineamines were successfully applied as the chiral ligands in the asymmetric Suzuki coupling of the biaryl 'halves' of the natural products ancistrotanzanine B [(*M*)-**31**] and its atropo-diastereomer ancistroealaine A [(*P*)-**31**], in which excellent yields were achieved with the dimethoxy-substituted derivative, (*M*,*S*)-**8b**. In order to



Scheme 4. Synthesis of the enantio- and diastereomerically pure phosphineamines (*M*)-**8** from (*P*)-**16b** and (*M*)-**16c**.[34] (a) $(CCl_2Br)_2$, PPh_3; (b) NaOEt; (c) BCl_3; (d) LAH; (e) Tf_2O, DABCO; (f) $HP(O)Ph_2$, $Pd(OAc)_2$, dppb; (g) HBr; (h) AIBN, NBS; (i) (*R*)-*N*-methyl-1-phenylethylamine; (j) $HSiCl_3$; (k) (*S*)-*N*-methyl-1-phenylethylamine.



(*M*)-**26c**·acetone

Figure 4. Crystal structure of (*M*)-**26c** acetone (hydrogen atoms omitted for reasons of clarity).

improve the not yet satisfying levels of stereocontrol, further variations of the axially chiral biaryl and of the centrochiral N-substituent are in progress.

3. Experimental

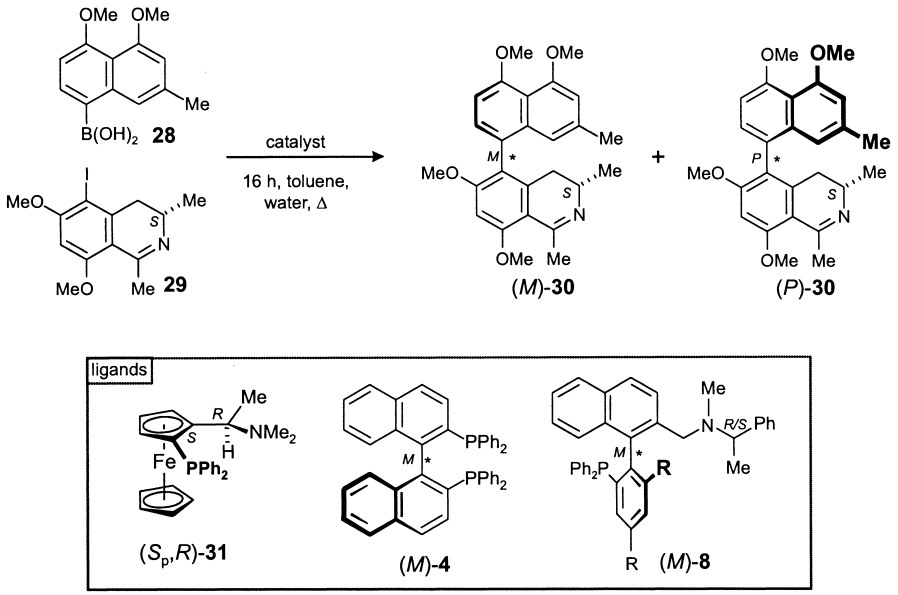
3.1. General

Melting points were determined with a Kofler melting point apparatus and are uncorrected. The optical rotations were measured with a Perkin–Elmer polarimeter. The IR spectra were scanned from KBr pellets or neat using a Perkin–Elmer spectrophotometer model 1420. The ^{2}H and ^{13}C NMR spectra were recorded with a Bruker AC 250 (250 MHz) or a Bruker Avance 400 (400 MHz) instrument using the deuterated solvent as an internal reference; *J* values are given in Hertz. The ^{31}P NMR spectra were recorded at 163 MHz. The chemical shifts δ refer to the signal of 85% H_3PO_4 (δ=0). Elemental analyses were performed in the Institute of Inorganic Chemistry of the University of Würzburg. Mass spectra were measured on a Finnigan MAT 2000 mass spectrometer at 70 eV. All reactions with moisture or air sensitive materials were carried out with flame-dried glassware using the Schlenk tube technique under inert argon atmosphere.

3.2. Crystallographic part

Crystal data for compound (*M*)-**26c**·acetone were collected from a shock cooled crystal on a BRUKER SMART-APEX diffractometer with a D8-goniometer (graphite Mo K_α radiation, λ=0.71073 Å) equipped with a low-temperature device[41] in Ω-scan mode at 143(2) K. The data were integrated with SAINT[42] and an empirical adsorption correction (SADABS)[43] was applied. The structure was solved by direct methods (SHELXS97)[44] and refined by full matrix least square calculations against F^2 (SHELXL97).[45] All non hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were assigned ideal positions using a riding model with U_{iso} constrained to 1.2 times U_{eq} value of the parent atom.

Crystallographic data (excluding structure factors) reported in this publication have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC 217292. Copies of the data can be obtained free



Scheme 5. The Suzuki cross coupling of **28** and **29**, and the chiral ligands (S_p, *R*)-**31**, (*M*)-**4**, and (*M*)-**8**.

Table 1. Yields and diastereomeric ratios obtained in the asymmetric Suzuki coupling of **28** and **29**

Entry	Catalyst	Yield (%)[a]	(*M*)-**30**:(*P*)-**30**[b]
1	$Pd(PPh_3)_4$	50[c]	55:45[c]
2	Pd_2dba_3/(*M*)-**4**	45[c]	61:39[c]
3	Pd_2dba_3/(S_p,*R*)-**31**	52[c]	75:25[c]
4	Pd_2dba_3/(*M*,*R*)-**8b**	65	63:37
5	Pd_2dba_3/(*M*,*S*)-**8b**	89	57:43
6	Pd_2dba_3/(*M*,*R*)-**8c**	44	67:33
7	Pd_2dba_3/(*M*,*S*)-**8c**	58	62:38

[a] Isolated yield after PLC.
[b] Determined by ^{1}H NMR.
[c] See Ref. 36.

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3.2.1. Synthesis of (*M*)-1-(2′-hydroxy-4′,6′-dimethylphenyl)-2-ethoxymethylnaphthalene [(*M*)-25c]. NaOEt (2 M in ethanol, 2.3 mL, 4.6 mmol) was added at 0 °C to a solution of (*M*)-2-bromomethyl-1-(2′-benzyloxy-4′,6′-dimethylphenyl)naphthalene[19c] (1.00 g, 2.30 mmol) in dry ethanol (50 mL). After 10 min, the reaction mixture was warmed to room temperature and heated for 10 h at 80 °C. The solvent was removed under reduced pressure, the residue suspended in diethyl ether, passed through a plug of celite, and purified by column chromatography (silica gel, petroleum ether/diethyl ether=10:1) to give (*M*)-1-(2′-benzyloxy-4′,6′-dimethylphenyl)-2-ethoxymethylnaphthalene (838 mg, 2.11 mmol, 92%) as a yellowish oil; $[\alpha]_D^{20}$=+19.1 (*c*1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.94–7.90 (m, 2H), 7.86–7.71 (m, 1H), 7.40 (m, 3H), 7.12 (m, 3H), 6.91–6.84 (m, 3H), 6.75 (s, 1H), 4.93 (d, *J*=12.6 Hz, 1H), 4.87 (d, *J*=12.6 Hz, 1H), 4.43 (d, *J*=12.5 Hz, 1H), 4.34 (d, *J*=12.5 Hz, 1H), 3.40 (dq, ^2J=7.0 Hz, ^3J=1.5 Hz, 2H), 2.42 (s, 3H), 1.86 (s, 3H), 1.15 (t, *J*=7.0 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 63 MHz): δ 156.3, 138.5, 138.3, 137.5, 134.7, 133.4, 133.0, 132.5, 128.1, 128.0, 127.4, 127.2, 126.3, 125.8, 125.7, 125.4, 125.3, 124.1, 123.6, 111.2, 70.5, 68.8, 65.7, 21.7, 19.2, 15.2 ppm. IR (neat): ν 3057, 2973, 2864, 1610, 1574, 1453, 1315, 1271, 1086, 816 cm^{-1}. MS: *m*/*z* 396 (M^+, 17), 305 (97), 91 (100). Anal. Calcd for $C_{28}H_{28}O_2$: C, 84.81; H, 7.12; found C, 84.58; H, 7.23.

(*M*)-1-(2′-Benzyloxy-4′,6′-dimethylphenyl)-2-ethoxymethylnaphthalene (911 mg, 2.30 mmol) as prepared above, was dissolved in dry methanol (20 mL), and Pd/C (10%, 20 mg) and NH_4CO_2 (750 mg, 11.9 mmol) were added. The reaction mixture was heated to reflux for 2 h. After cooling to room temperature, the catalyst was filtered off and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (20 mL) and washed three times with aq. sat. K_2CO_3 (20 mL). After removal of the solvent, the crude product was purified by column chromatography (silica gel, petroleum ether/diethyl ether=3:1) affording (*M*)-**25c** (600 mg, 1.96 mmol, 85%) as a colorless oil. $[\alpha]_D^{20}$=−43.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, *J*=8.6 Hz, 1H), 7.88 (d, *J*=8.4 Hz, 1H), 7.71 (d, *J*=8.6 Hz, 1H), 7.50–7.45 (m, 1H), 7.40–7.34 (m, 2H), 6.78 (s, 2H), 5.00 (s, br, 1H), 4.37 (d, *J*=11.2 Hz, 1H), 4.31 (d, *J*=11.2 Hz, 1H), 3.52–3.49 (m_c, 2H), 2.39 (s, 3H), 1.78 (s, 3H), 1.18 (t, *J*=7.1 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.6, 139.0, 137.8, 135.6, 133.6, 132.7, 131.8, 128.7, 128.1, 126.7, 126.6, 126.2, 125.5, 123.2, 121.6, 114.6, 71.1, 66.5, 21.3, 19.8, 15.0 ppm. IR (neat): ν 2980, 2920, 1610, 1580, 1300, 1100, 805, 695 cm^{-1}. MS: *m*/*z* 306 (M^+, 23), 260 (100), 245 (27), 230 (11). Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.31; H, 7.23; found C, 82.20; H, 7.25.

3.2.2. Preparation of (*M*)-2-bromomethyl-1-(4′,6′-dimethyl-2′-diphenylphosphanylphenyl)naphthalene [(*M*)-26c]. To a solution of (*M*)-**25c** (540 mg, 1.74 mmol) and DABCO (403 mg, 3.6 mmol) in dichloromethane (10 mL), Tf_2O (448 μL, 2.7 mmol) was added at 0 °C. After 6 h, the solvent was removed and the residue was

purified by column chromatography (silica gel, petroleum ether/diethyl ether=10:1) to give (*M*)-2-ethoxymethyl-1-(2′-trifluoromethanesulfonyloxy-4′,6′-dimethylphenyl)-naphthalene (610 mg, 1.39 mmol, 79%) as a colorless oil; $[\alpha]_D^{20}$=+36.1 (*c* 0.9, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (d, *J*=8.6 Hz, 1H), 7.83 (d, *J*=8.1 Hz, 1H), 7.69 (d, *J*=8.6 Hz, 1H), 7.43–7.39 (m, 1H), 7.34–7.29 (m, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 4.36 (d, *J*=12.4 Hz, 1H), 4.21 (d, *J*=12.4 Hz, 1H), 3.47–3.33 (m_c, 2H), 2.42 (s, 3H), 1.90 (s, 3H), 1.13 (t, *J*=7.0 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.6, 140.7, 139.8, 133.0, 131.9, 130.6, 129.7, 128.8, 128.2, 128.1, 126.3, 125.8, 125.3, 119.2, 118.0 (q, J_{C-F}=320 Hz), 70.5, 66.0, 21.2, 19.8, 15.1 ppm. IR (neat): ν 3058, 2976, 2868, 1622, 1419, 1223, 1140, 946, 821 cm^{-1}. MS: *m*/*z* 438 (M^+, 23), 409 (2), 392 (21), 259 (100). Anal. Calcd for $C_{22}H_{21}O_4SF_3$: C, 60.27; H, 4.82; S, 7.31; found C, 60.80; H, 4.96; S, 7.16. MS (EI) exact mass calcd for $C_{22}H_{21}O_4SF_3$: 438.11127; found 438.11133.

A mixture of the above prepared (*M*)-2-ethoxymethyl-1-(2′-trifluoromethanesulfonyloxy-4′,6′-dimethylphenyl)naphthalene (370 mg, 840 μmol), HP(O)Ph_2 (339 mg, 1.68 mmol), $Pd(OAc)_2$ (10 mg, 42 μmol), dppb (18 mg, 42 μmol) and (iPr)$_2$NEt (575 μL, 3.31 mmol) in DMSO (4 mL) was heated to 100 °C for 6 h, cooled to room temperature and concentrated in vacuo. After addition of ethyl acetate (10 mL), the precipitate was removed by filtration. The remaining organic layer was washed with H_2O (10 mL) and dried over $MgSO_4$. Chromatography (silica gel, petroleum ether / ethyl acetate=1:1) of the resulting red oil yielded (*M*)-2-ethoxymethyl-1-(4′,6′-dimethyl-2′-diphenylphosphanylphenyl)-naphthalene (340 mg, 694 μmol, 83%) as a colorless solid; mp 122 °C. $[\alpha]_D^{20}$=+22.4 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69–7.64 (m, 2H), 7.58 (d, *J*=8.3 Hz, 1H), 7.52–7.50 (m, 2H), 7.44–7.41 (m_c, 1H), 7.38–7.31 (m, 4H), 7.23–7.19 (m_c, 1H), 7.11–7.04 (m, 3H), 6.99–6.95 (m_c, 1H), 6.91 (d, *J*=8.4 Hz, 1H), 6.82–6.78 (m_c, 2H), 4.57 (d, *J*=12.1 Hz, 1H), 4.18 (d, *J*=12.1 Hz, 1H), 3.58–3.30 (m_c, 2H), 2.38 (s, 3H), 1.81 (s, 3H), 1.14 (t, *J*=7.0 Hz, 3H) ppm. ^{13}C NMR (acetone-d_6, 100 MHz): δ 139.4, 136.2, 135.2, 132.7, 132.6, 132.5, 132.4, 132.1, 132.0, 131.8, 131.6, 130.6, 130.5, 128.6, 128.2, 128.1, 127.8, 127.3, 127.2, 125.9, 125.6, 125.5, 124.9, 71.5, 66.3, 21.3, 20.0, 15.2 ppm. ^{31}P NMR (acetone-d_6, 163 MHz): δ 24.1 ppm. IR (neat): ν 3076, 2980, 2820, 1592, 1430, 1190, 1080, 975, 905, 850, 798, 560 cm^{-1}. MS: *m*/*z*490 (M^+, 19), 461 (100), 201 (65). Anal. Calcd for $C_{33}H_{33}O_2P{\cdot}C_3H_6O$: C, 78.81; H, 6.80; found C, 79.06; H, 7.02.

(*M*)-2-Ethoxymethyl-1-(4′,6′-dimethyl-2′-diphenylphosphanylphenyl)naphthalene (240 mg, 490 μmol) was dissolved in HBr (20 mL, 30% in HOAc). The deep yellow solution was heated to reflux overnight. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. Purification by column chromatography (silica gel, petroleum ether/ethyl acetate=1:1) gave (*M*)-**26c** (200 mg, 381 μmol, 78%) as white crystals; mp 127 °C. $[\alpha]_D^{20}$=+5.3 (*c* 0.9, $CHCl_3$). ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.84–7.78 (m, 2H), 7.70 (d, *J*=8.6 Hz, 1H), 7.60–7.48 (m, 6H), 7.29–7.19 (m_c, 1H), 7.19–7.10 (m, 4H), 6.96–6.82 (m, 2H), 6.82–6.78 (m, 2H), 4.71 (d, *J*=10.4 Hz, 1H), 4.52 (d, *J*=10.4 Hz, 1H), 2.35 (s, 3H), 1.89 (s, 3H) ppm. ^{13}C NMR (100 MHz, (acetone-d_6): δ 140.2, 139.0, 138.5, 136.2, 135.6, 133.8, 133.5, 132.9, 132.8, 132.7, 132.4, 131.1, 131.0, 129.8, 129.3, 129.1, 128.6, 128.2, 128.1, 128.0, 127.0, 126.4, 36.4, 21.3, 20.8 ppm. ^{31}P NMR (163 MHz, acetone-d_6): δ 24.0 ppm. IR (KBr): ν 3048, 2920, 1593, 1433, 1219, 1178, 1111, 860, 813, 748, 695, 554, 534 cm^{-1}. MS: *m*/*z* 526/524 (M^+, 13/13), 445 (100), 201 (81), 91 (18). Anal. Calcd for $C_{34}H_{32}O_2BrP{\cdot}C_3H_6O$: C, 69.99; H, 5.52; found C, 69.34; H, 5.49. Cell data for (*M*)-**9**: $C_{31}H_{26}OBrP{\cdot}C_3H_6O$, monoclinic, space group $P2_1$, a=1181.3 (8) pm, b=1014.2 (1) pm, c=1234.4 (1) pm, β=103.6430 (10).

3.2.3. Synthesis of (*M*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-2-methylnaphthalene [(*M*)-27b]. A suspension of (*M*)-**16b** (1.14 g, 3.68 mmol), benzyl bromide (871 μL, 8.65 mmol), and K_2CO_3 (1.02 g, 7.36 mmol) in acetone (20 mL) was stirred for 12 h at room temperature. After removal of excessive benzyl bromide in vacuo, the residue was chromatographed (silica gel, petroleum ether/ethyl ether=10:1→1:1) yielding (*M*)-1-(2′-benzyloxy-4′,6′-dimethoxyphenyl)-2-hydroxymethylnaphthalene (1.24 g, 3.10 mmol, 84%) as a colorless oil; $[\alpha]_D^{20}$=−12.6 (*c* 1.1 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.89 (d, *J*=8.2 Hz, 3H), 7.68 (d, *J*=8.6 Hz, 1H), 7.48–7.40 (m, 2H), 7.38–7.30 (m, 1H), 7.17–7.06 (m, 3H), 6.86–6.78 (m, 2H), 6.35 (d, *J*=2.3 Hz, 1H), 6.34 (d, *J*=2.3 Hz, 1H), 4.90 (d, *J*=12.2 Hz, 1H), 4.83 (d, *J*=12.2 Hz, 1H), 4.49 (s, 2H), 3.87 (s, 3H), 3.62 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.3, 158.9, 157.2, 137.3, 136.7, 133.2, 130.9, 128.3, 128.1, 128.0, 127.6, 127.1, 126.7, 126.3, 125.8, 125.5, 93.5, 92.1, 64.8, 70.8, 56.0, 55.4 ppm. IR (neat): ν 3185, 3028, 1584, 1562, 1400, 1250, 1205, 1102, 725. MS: *m*/*z* 400 (M^+, 40), 382 (13), 309 (33), 292 (44), 281 (30), 91 (100). Anal. Calcd for $C_{26}H_{24}O_4$: C, 77.93; H, 6.04; found C, 77.24; H, 6.04. MS (EI) exact mass calcd for $C_{26}H_{24}O_4$: 400.16746; found 400.16785.

(*M*)-1-(2′-Benzyloxy-4′,6′-dimethoxyphenyl)-2-hydroxymethylnaphthalene (460 mg, 1.15 mmol) as prepared above, PPh_3 (605 mg, 2.30 mmol), and $(CBrCl_2)_2$ (750 mg, 2.30 mmol) were dissolved in dichloromethane (40 mL) and stirred for 1 h at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, petroleum ether/diethyl ether=10:1) to give (*M*)-1-(2′-benzyloxy-4′,6′-dimethoxyphenyl)-2-bromomethylnaphthalene (440 mg, 0.95 mmol, 83%) as a yellow solid; mp 125 °C. $[\alpha]_D^{20}$=−1.3 (*c* 0.11, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90–7.83 (m, 2H), 7.65 (d, *J*=8.6 Hz, 1H), 7.48–7.44 (m, 2H), 7.34 (m_c, 1H), 7.15 (m, 3H), 6.91–6.89 (m, 2H), 6.32 (s, 2H), 4.95 (d, *J*=12.6 Hz, 1H), 4.91 (d, *J*=12.6 Hz, 1H), 4.48 (s, 2H), 3.87 (s, 3H), 3.64 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.5, 159.1, 157.9, 137.1, 133.9, 133.3, 133.2, 132.4, 128.2, 128.1, 127.9, 127.4, 127.3, 126.6, 126.4, 126.0, 125.9, 107.7, 92.7, 91.4, 70.1, 55.8, 55.4, 33.3 ppm. IR (KBr): ν 3005, 2910, 1589, 1615, 1499, 1435, 1403, 1211, 1108, 808 cm^{-1}. MS: *m*/*z* 464/462 (M^+, 13/13), 383 (13), 292 (100), 261 (6), 260 (6), 230 (1), 91 (49)). Anal. Calcd for $C_{26}H_{23}O_3Br$: C, 67.39; H, 5.00; found C, 66.93; H 5.06.

To a solution of (*M*)-1-(2′-benzyloxy-4′,6′-dimethoxyphenyl)-2-bromomethylnaphthalene (500 mg, 1.08 mmol) in diethyl ether (10 mL), LAH (82.0 mg, 2.16 mmol) was

added and the reaction was stirred for 1 h. After hydrolysis with 2 N HCl (20 mL), the aqueous phase was extracted with diethyl ether (20 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by chromatography on silica gel (petrolether/diethyl ether=5:1) afforded (*P*)-1-(2′-benzyloxy-4′,6′-dimethoxyphenyl)-2-methylnaphthalene (320 mg, 833 μmol, 77%); mp 87 °C. $[\alpha]_D^{20}$=+54.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.84 (d, *J*=7.6 Hz, 1H), 7.77 (d, *J*=8.4 Hz, 1H), 743–7.29 (m, 4H), 7.14–7.12 (m, 3H), 6.97–6.95 (m, 2H), 6.50 (d, *J*=2.0 Hz, 1H), 6.45 (d, *J*=2.0 Hz, 1H), 5.01 (d, *J*=12.6 Hz, 1H), 4.96 (d, *J*=12.6 Hz, 1H), 3.88 (s, 3H), 3.62 (s, 3H), 2.20 (s, 3H) ppm. ^{13}C NMR (acetone-d_6, 100 MHz): δ 162.2, 159.8, 158.5, 138.4, 135.5, 134.5, 133.2, 132.3, 129.2, 128.9, 128.6, 128.1, 127.6, 127.5, 126.7, 126.1, 125.1, 110.1, 93.6, 92.2, 70.6, 56.0, 55.7, 20.6 ppm. IR (KBr): ν 3020, 2980, 2930, 1600, 1590, 1500, 1475, 1380, 1220, 1190, 800 cm^{-1}. MS: *m*/*z* 384 (M^+, 100), 293 (32), 278 (30), 263 (16), 262 (10), 261 (9), 92 (89). Anal. Calcd for $C_{26}H_{24}O_3$: C, 81.22; H, 6.29; found C, 81.01; H, 6.35.

A solution of (*P*)-1-(2′-benzyloxy-4′,6′-dimethoxyphenyl)-2-methylnaphthalene (320 mg, 830 μmol) in dichloromethane (10 mL) was treated with BCl_3 (1.0 M in *n*-hexane, 1.25 mL, 1.25 mmol) at 0 °C. After 60 min, the reaction mixture was hydrolyzed cautiously with methanol (5 mL) and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, petroleum ether / diethyl ether=1:1) to give (*M*)-**27b** (240 mg, 815 μmol, 98%) as colorless needles; mp 157 °C. $[\alpha]_D^{20}$=+17.3 (*c* 0.8, $CHCl_3$). ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.83 (d, *J*=7.6 Hz, 1H), 7.76 (d, *J*=8.3 Hz, 1H), 7.42 (d, *J*=8.3 Hz, 1H), 7.39–7.29 (m, 3H), 6.30 (s, 2H), 3.85 (s, 3H), 3.58 (s, 3H), 2.07 (s, 3H) ppm. ^{13}C NMR (acetone-d_6, 100 MHz): δ 162.2, 160.0, 157.1, 136.5, 134.8, 133.4, 131.5, 129.5, 128.7, 128.0, 126.7, 126.3, 125.3, 107.9, 55.9, 55.6, 20.6 ppm. IR (KBr): ν 3495, 3005, 2920, 1610, 1590, 1500, 1350, 1205, 1150, 1100, 805 cm^{-1}. MS: *m*/*z* 294 (M^+, 100), 279 (12), 264 (7), 263 (7), 249 (6), 247 (5), 219 (6), 141 (10). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16; found C, 77.44; H, 6.17.

3.2.4. Preparation of (*M*)-2-bromomethyl-1-(4′,6′-dimethoxy-2′-diphenylphosphanoxyphenyl)naphthalene [(*M*)-26b]. DABCO (191 mg, 1.70 mmol) was added at 0 °C to a solution of (*M*)-**27b** (250 mg, 850 μmol) in dichloromethane (20 mL). The mixture was stirred for 30 min and Tf_2O (357 μL, 2.86 mmol) was added. After 6 h, the solvent was removed in vacuo and the crude product was purified by column chromatography (silica gel, petroleum ether/diethyl ether=5:1) affording (*P*)-1-(2′-trifluoromethanesulfonoxy-4′,6′-dimethoxyphenyl)-2-methylnaphthalene (329 mg, 688 μmmol, 81%) as an orange-colored oil; $[\alpha]_D^{20}$+13.3 (c 1.0, $CHCl_3$). ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.89–7.86 (m, 2H), 7.46 (d, *J*=8.6 Hz, 1H), 7.41–7.34 (m, 2H), 7.30–7.27 (m, 1H), 6.90 (d, *J*=2.0 Hz, 1H), 6.72 (d, *J*=2.0 Hz, 1H), 3.99 (s, 3H), 3.75 (s, 3H), 2.23 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.9, 159.4, 148.4, 135.6, 128.9, 128.4, 128.3, 128.2, 127.9, 126.0, 125.1, 124.7, 122.8, 115.6 (q, J_{C-F}=318 Hz), 112.9, 56.1, 55.8, 20.2 ppm. IR (neat): ν 3060, 3026, 2944, 1626, 1567, 1498, 1418, 1325, 1210, 1152, 1071, 967, 840, 805 cm^{-1}. MS: *m*/*z*: 426 (M^+, 100), 293 (32), 278 (88), 263 (24). MS (EI) exact mass calcd for $C_{20}H_{17}O_5SF_3$: 426.07488; found 426.07458.

A suspension of (*P*)-1-(2′-trifluoromethanesulfonoxy-4′,6′-dimethoxyphenyl)-2-methylnaphthalene (280 mg, 657 μmol), dppb (14 mg, 33 μmol), $Pd(OAC)_2$ (8 mg, 33 μmol), $HP(O)Ph_2$ (265, 1.31 mmol), and iPr_2EtN (450 μL, 2.59 mmol) was stirred at 100 °C for 12 h. The solvent was removed in vacuo, the resulting crude product suspended in ethyl acetate (30 mL) and filtered through a plug of Celite. The organic layer was washed with 2 N HCl (20 mL), dried over $MgSO_4$ and purified by column chromatography to give (*P*)-1-(4′,6′-dimethoxy-2′-diphenylphosphanoxyphenyl)-2-methylnaphthalene (270 mg, 565 μmol, 86%) as a white powder; mp 58 °C. $[\alpha]_D^{20}$=+51.9 (*c* 0.86 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 7.57–7.42 (m, 4H), 7.32 (d, *J*=7.6 Hz, 1H), 7.24–6.78 (m, 13H), 3.78 (s, 3H), 3.58 (s, 3H), 2.15 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$ 63 MHz): δ 136.2, 133.2, 131.8, 131.6, 131.3, 131.1, 130.9, 130.7, 130.4, 128.1, 127.9, 127.6, 127.4, 127.3, 127.1, 125.7, 125.0, 124.0, 110.0, 102.3, 56.1, 55.5, 21.1 ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ 28.8 ppm. IR (KBr): ν 3000, 2980, 1591, 1560, 1438, 1302, 1217, 1157, 857, 721. MS: *m*/*z* 478 (M^+, 15), 387 (100), 372 (5), 276 (21) cm^{-1}. Anal. Calcd for $C_{31}H_{27}O_3P$: C, 77.81; H, 5.69; found C, 77.06; H, 5.91.

(*P*)-1-(4′,6′-Dimethoxy-2′-diphenylphosphanoxyphenyl)-2-methylnaphthalene (326 mg, 681 μmol), dissolved in tetrachloromethane (15 mL), was treated with *N*-bromosuccinimide (372 mg, 2.09 mmol) and AIBN (32.3 mg, 227 μmol). The reaction mixture was heated to reflux for 2 h and the solvent removed in vacuo. The crude product was suspended in ethyl acetate/petroleum ether 1:1 (10 mL) and passed through a small plug of silica gel to afford (*M*)-**26b** (235 mg, 420 μmol, 63%) as a yellowish solid; mp 117 °C. $[\alpha]_D^{20}$=+91.3 (*c* 0.95 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84–7.78 (m, 2H), 7.64 (d, *J*=8.5 Hz, 1H), 7.59–7.46 (m, 5H), 7.25–7.07 (m, 4H), 7.03–6.81 (m, 5H), 6.61–6.57 (m, 1H), 4.63 (d, *J*=10.4 Hz, 1H), 4.58 (d, *J*=10.4 Hz, 1H), 3.62 (s, 3H), 3.79 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ 160.3, 136.1, 135.8, 132.8, 132.3, 132.0, 131.9, 131.7, 130.6, 130.4, 130.3, 129.1, 128.3, 128.2, 127.6, 127.4, 127.4, 127.3, 127.2, 126.5, 125.5, 125.3, 110.7, 110.6, 102.3, 56.1, 55.4, 34.8 ppm. ^{31}P NMR (acetone-d_6, 163 MHz): δ 25.9. IR (neat): ν 3055, 2933, 1709, 1653, 1592, 1565, 1456, 1277, 1044, 751 cm^{-1}. MS *m*/*z* 558/556 (M^+, 8/8), 477 (79), 275 (31), 201 (100). MS (EI) exact mass calcd for $C_{31}H_{26}O_3PBr$: 556.08029; found 556.08749.

3.3. General procedure for the preparation of the phosphineamines (*M*)-8b and (*M*)-8c

The bromides (*M*)-**26b** or (*M*)-**26c** (1.0 equiv.) were refluxed with (*R*)- or (*S*)-*N*-methylphenylethylamine (2.0 equiv.) and NaH (2.2 equiv.) in toluene [5 mL/mmol (*M*)-**26**] overnight. The solvent was removed in vacuo and the crude product passed through a plug of silica gel (petroleum ether/ethyl acetate=1:1). The residue was dissolved in *o*-xylene [5 mL/mmol (*M*)-**26**] and treated with $HSiCl_3$ (5 equiv.) and $(iPr)_2NEt$ (Hünig's base, 20 equiv.). The slightly yellow suspension was heated to

reflux for 16 h. After cooling to room temperature, the mixture was diluted with diethyl ether [5 mL/mmol (*M*)-**26**] and hydrolyzed with aq. sat. $NaHCO_3$ [2 mL/mmol (*M*)-**26**]. The precipitate was filtered off and washed with diethyl ether. The combined organic layers were concentrated and the crude product was chromatographed on silica gel to give (*M*)-**8b** or (*M*)-**8c**.

3.3.1. (*M*,*R*)-1-(4′,6′-Dimethyl-2′-diphenylphosphanophenyl)-2-[*N*-methyl-*N*-(1″-phenylethyl]aminomethylnaphthalene [(*M*,*R*)-8c]. Yield: 77%. $[\alpha]_D^{20}=+41.0$ (*c* 1.0, $CHCl_3$). CD (ethanol): $\Delta\varepsilon_{201}$ 27.3, $\Delta\varepsilon_{221}$ −29.3, $\Delta\varepsilon_{239}$ 19.0. ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.91–7.81 (m 3H), 7.33–6.96 (m, 16H), 6.96 (s, br., 1H), 6.89–6.85 (m, 3H), 3.37 (q, *J*=6.7 Hz, 1H), 3.32 (d, *J*=14.1 Hz, 1H), 3.15 (d, *J*=14.1 Hz, 1H), 2.75 (s, 3H), 2.31 (s, 3H), 1.81 (s, 3H), 1.20 (d, *J*=6.7 Hz, 3H) ppm. ^{13}C NMR (acetone-d_6, 100 MHz): δ 145.5, 142.6, 142.3, 138.9, 138.8, 138.4, 138.3, 138.0, 137.9, 137.8, 137.5, 136.6, 134.4, 134.3, 133.5, 133.4, 132.7, 129.2, 129.1, 129.0, 128.8, 128.7, 128.5, 128.2, 127.5, 127.4, 126.4, 126.2, 125.7, 63.4, 58.3, 39.3, 21.3, 20.4, 19.9 ppm. ^{31}P NMR (acetone-d_6, 163 MHz): δ −14.2 ppm. IR (neat): ν 3053, 2966, 2923, 1596, 1507, 1450, 1434, 1371, 1214, 1155, 1027, 814, 742 cm^1. MS *m*/*z* 563 (M^+, 1), 458 (100), 430 (27), 415 (100). Anal. Calcd for $C_{40}H_{38}NP$: C, 85.23; H, 6.79; N, 2.48; found C, 84.82; H, 7.04; N, 2.40.

3.3.2. (*M*,*S*)-1-(4′,6′-Dimethyl-2′-diphenylphosphanophenyl)-2-[*N*-methyl-*N*-(1″-phenylethyl]aminomethylnaphthalene [(*M*,*S*)-8c]. Yield: 64%. $[\alpha]_D^{20}=+12.6$ (*c*=1.0, $CHCl_3$). CD (ethanol): $\Delta\varepsilon_{203}$ 26.1, $\Delta\varepsilon_{222}$ −34.7, $\Delta\varepsilon_{239}$ 18.8. ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.91–7.80 (m, 2H), 7.33–7.28 (m, 8H), 7.26 (m, 1H), 7.22–7.01 (m, 8H), 6.96 (s, 1H), 6.89–6.84 (m, 3H), 3.38 (q, *J*=6.7 Hz, 1H, 3H), 3.32 (d, *J*=13.8 Hz, 1H), 3.15 (d, *J*=13.8 Hz, 1H), 2.31 (s, 3H), 2.00 (s, 3H), 1.81 (s, 3H), 1.20 (d, *J*=6.7 Hz, 3H) ppm. ^{13}C NMR (acetone-d_6, 100 MHz): δ 145.4, 142.7, 142.4, 138.8, 138.7, 138.6, 138.5, 138.1, 137.8, 137.6, 137.5, 136.9, 134.4, 134.3, 134.1, 133.6, 133.5, 132.7, 129.3, 129.2, 129.0, 128.9, 128.6, 128.2, 127.5, 127.4, 125.7, 126.3, 64.7, 57.5, 39.5, 21.3, 20.2, 18.5 ppm. ^{31}P NMR (acetone-d_6, 163 MHz): δ −14.3 ppm. IR (neat): ν 3052, 2958, 2923, 1597, 1507, 1452, 1434, 1217, 1155, 1092, 813, 697 cm^{-1}. MS: *m*/*z* 563 (M^+, 1), 458 (94), 430 (18), 415 (100), 201 (13). Anal. Calcd for $C_{40}H_{38}NP$: C, 85.23; H, 6.79; N, 2.48; found C, 85.16; H, 6.99; N, 2.35.

3.3.3. (*M*,*R*)-1-(4′,6′-Dimethoxy-2′-diphenylphosphanophenyl)-2-[*N*-methyl-*N*-(1″-phenylethyl]aminomethylnaphthalene [(*M*,*R*)-8b]. Yield: 77%. $[\alpha]_D^{20}=-21.1$ (*c* 1.0, $CHCl_3$). CD (ethanol): $\Delta\varepsilon_{200}$ 9.5, $\Delta\varepsilon_{223}$ −30.5, $\Delta\varepsilon_{238}$ 26.6. ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.85–7.78 (m, 3H), 7.34–7.27 (m, 8H), 7.23–7.12 (m, 4H), 7.06–7.11 (m, 4H), 6.96–6.92 (m_c, 2H), 6.78 (d, *J*=2.3 Hz, 1H), 6.40–6.39 (m_c, 1H), 3.71 (s, 3H), 3.54 (s, 3H), 3.37 (q, *J*=6.7 Hz, 1H), 3.22 (d, *J*=13.8 Hz, 1H), 2.99 (d, *J*=13.8 Hz, 1H), 1.96 (s, 3H), 1.25 (d, *J*=6.7 Hz, 3H) ppm. ^{13}C NMR (acetone-d_6, 100 MHz): δ 161.2, 159.2, 145.7, 141.5, 141.3, 138.3, 138.2, 138.1, 134.9, 134.4, 134.3, 134.0, 133.5, 129.4, 129.2, 129.1, 128.9, 128.4, 128.3, 128.0, 127.4, 127.0, 126.6, 125.9, 125.4, 111.8, 99.6, 65.4, 58.1, 55.8, 55.5, 39.0, 20.3 ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ −13.5 ppm. IR (neat): ν 3058, 2963, 2923, 1634, 1459, 1379, 1261, 1077, 807, 742, 699, 514 cm^{-1}. MS: *m*/*z* 595 (M^+, 1), 490 (27), 462 (7), 447 (100), 431 (2), 201 (3). Anal. Calcd for $C_{40}H_{38}NO_2P$: C, 80.65; H, 6.43; N, 2.35; found C, 79.92; H, 6.19; N, 2.47.

3.3.4. (*M*,*S*)-1-(4′,6′-Dimethoxy-2′-diphenylphosphanophenyl)-2-[*N*-methyl-*N*-(1″-phenylethyl]aminomethylnaphthalene [(*M*,*R*)-8b]. Yield: 68%. $[\alpha]_D^{20}=-14.7$ (*c* 1.0, $CHCl_3$). CD (ethanol): $\Delta\varepsilon_{194}$ −18.6, $\Delta\varepsilon_{206}$ −12.1, $\Delta\varepsilon_{225}$ −16.1, $\Delta\varepsilon_{248}$ 9.0, $\Delta\varepsilon_{290}$ −1.4. ^{1}H NMR (acetone-d_6, 400 MHz): δ 7.84 (d, *J*=8.6 Hz, 1H), 7.81–7.78 (m, 2H), 7.37–7.21 (m, 8H), 7.20–7.09 (m, 8H), 6.99–6.95 (m_c, 2H), 6.76 (d, *J*=8.4 Hz, 1H), 6.41 (m_c, 1H), 3.75 (s, 3H), 3.52 (s, 3H), 3.47 (q, *J*=6.6 Hz, 1H), 3.16 (d, *J*=14.0 Hz, 1H), 3.03 (d, *J*=14.0 Hz, 1H), 1.89 (s, 3H), 1.15 (d, *J*=6.6 Hz, 3H) ppm. ^{13}C NMR (acetone-d_6, 100 MHz): δ 161.2, 145.8, 138.2, 134.7, 134.5, 134.2, 134.0, 133.5, 129.5, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.4, 128.3, 128.1, 127.3, 126.9, 126.0, 125.5, 111.8, 99.6, 63.7, 57.0, 55.8, 55.5, 39.2, 17.4 ppm. ^{31}P NMR (acetone-d_6, 163 MHz): δ −14.0 ppm. IR (neat): ν 3054, 3005, 2932, 1590, 1563, 1457, 1435, 1300, 1214, 1150, 1040, 745, 699 cm^{-1}. MS: *m*/*z* 595 (M^+, 1), 490 (28), 462 (7), 447 (100), 431 (6), 201 (3). Anal. Calcd for $C_{40}H_{38}NO_2P$: C, 80.65; H, 6.43; N 2.35; found C, 79.86; H, 6.18; N, 2.38.

3.4. General procedure for the asymmetric Suzuki couplings using (*M*)-8

A flame-dried Schlenk tube charged with $Pd_2(dba)_3$ (0.1 equiv.) and the respective ligand (*M*)-**8** (0.2 equiv.) in toluene [1 mL/20 μmol $Pd_2(dba)_3$] was stirred for 2 h at room temperature. The solvent was removed in vacuo and the catalyst purified by filtration through a small plug of silica gel. A solution of **29** (1.0 equiv.) and **28** (1.5 equiv.) in toluene (13 mL/mmol **29**), and aq. sat. $NaHCO_3$ (5 mL/mmol **29**) were added. The mixture was stirred at 110 °C until **29** had been completely consumed as judged by TLC (approx. 12 h). After cooling to room temperature, the organic phase was separated and concentrated in vacuo. The crude material was purified by PLC (silica gel, CH_2Cl_2/MeOH=10:1).

Acknowledgements

This work has been supported by the Deutsche Forschungsgemeinschaft [SFB 630 'Erkennung, Gewinnung und funktionale Analyse von Wirkstoffen gegen Infektionskrankheiten' (research funds) and 'Emmy-Noether Programm' (fellowship for M. B. and research funds)], by the 'Fonds der Chemischen Industrie', and by the Freistaat Bayern (research fellowship for R.-M. P.). The authors gratefully acknowledge helpful suggestions by Dr. P. Keller (University of Wollongong, Australia) and Prof. Dr. D. Stalke (University of Würzburg, Germany).

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Tetrahedron 60 (2004) 4361–4375
Tetrahedron

Synthesis and properties of axially-chiral *N*-(2,6-disubstituted)phenyl triazolones

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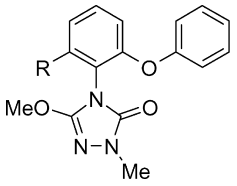
Received 20 November 2003; revised 18 March 2004; accepted 19 March 2004

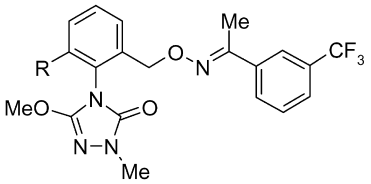
Abstract—Certain *ortho*-substituted phenyl triazolone compounds are fungicidal. When two *ortho*-substituents are present, stable atropisomers can be isolated. Several methods for resolving racemic intermediates into the enantiomers are described, including separations of diasteromeric ester derivatives and diasteromeric salts. The intermediates were converted into products in which the absolute configuration can be correlated to biological activity.

1. Introduction

For some time, we have been investigating phenyl triazolones such as **1** and **2** as agricultural fungicides.[1] These compounds are inhibitors of mitochondrial respiration by blocking electron transport of the cytochrome bc_1 complex. Like the commercial fungicides azoxystrobin[2] and kresoxim methyl,[3] they bind at the ubihydroquinone: cytochrome-c oxidoreductase site.[4]



1a R = H
1b R = CH_3



2a R = H
2b R = CH_3

The steric interaction between the triazolone ring and the large *o*-substituent disfavors co-planarity of the system. The resulting twist may contribute to the observed biological activity, since aryl triazolones and related respiration inhibitors without an *ortho*-group are inactive.[4b] As part of our exploration of structure–activity relationships, additional substituents on the phenyl ring were investigated. For example, a methyl group at the second *ortho*-position (as in compounds **1b** and **2b**) provided excellent in vitro respiration inhibition[4a] and in vivo fungicidal activity[5] (see Table 1).

Crystallographic studies of the 2,6-disubstituted compounds showed that the solid-state conformation has the triazolone nearly perpendicular to the phenyl ring. We reasoned that the buttressing of the second *ortho*-group might force the triazolone to remain in a conformation most suited for binding at the active site of the enzyme. We then wondered whether the rotational barrier in these molecules was sufficient to allow us to isolate stable enantiomers (atropisomers).[6,7] Small quantities of the atropisomers of **1a** were separated by preparative HPLC using a chiral stationary-phase column. However, complete racemization of the individual enantiomers occurred within hours. Racemic **1b** was also resolved chromatographically, but in this case the enantiomers proved to be completely stable at ambient temperature; after the fact, the rotational barrier was calculated to be about 40–50 kcal/mol.[8] As might be expected, one enantiomer is significantly more active than the other.[9] In both **1b** and **2b**, the (+)-enantiomer is the more active (see Table 1).

Since we believed that chromatographic separation would not be a practical strategy to pursue in our attempt to develop a non-racemic aryl triazolone as a commercial fungicide, we began an investigation of various synthetic approaches. Enantioselective or diastereoselective synthesis, though a proven strategy for other types of chiral non-racemic products, would probably be difficult to apply to our case of axial-chirality. Thus, we decided that we might be more successful in trying to find a suitable method to resolve a readily accessible racemic intermediate. This intermediate

Keywords: Atropisomers; Triazolones.
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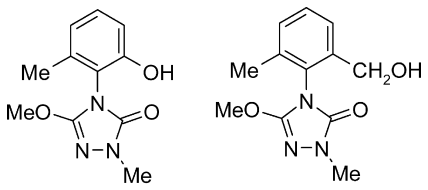
doi:10.1016/j.tet.2004.03.056

Table 1.

Compound	Enantiomeric excess	Wheat powdery mildew		Tomato late blight	
		Rate (ppm)	(% Control)	Rate (ppm)	(% Control)
1a	—	200	93	200	64
Racemic-**1b**	0	200	100	20	99
		2	53		
(+)-**1b**	84	2	100	200	100
				2	98
(−)-**1b**	99	10	28[a]	200	0
2a	—	200	100	200	93
		2	95	10	42
Racemic-**2b**	0	2	100	200	83
		0.4	52		
(+)-**2b**	83	40	99		
		2	95		
(−)-**2b**	96	2	0		

[a] Low levels of biological activity may be due to the presence of minor amounts of the active enantiomer.

would be required to have a rotational barrier around the chiral axis high enough to maintain its integrity during further processing to the final compound, but sufficiently low to allow thermal racemization for recycling to the process.[10] Because the atropic asymmetry does not arise unless the triazolone ring is completely formed, this also influenced the point when an asymmetric synthesis could be envisioned. Compound **3** can be used to prepare **1b** and compound **4** can be used to prepare **2b**. The phenol moiety in compound **3** and the benzylic alcohol moiety in compound **4** appeared to be useful groups for preparing covalent diastereomeric derivatives. We also considered that the phenol moiety in **3** also may be sufficiently acidic to prepare diastereomeric salts. Enzymatic kinetic resolutions of **3** or **4** also appeared to be potentially viable methods.[11] Therefore, we began to investigate methods of resolution of these key materials.



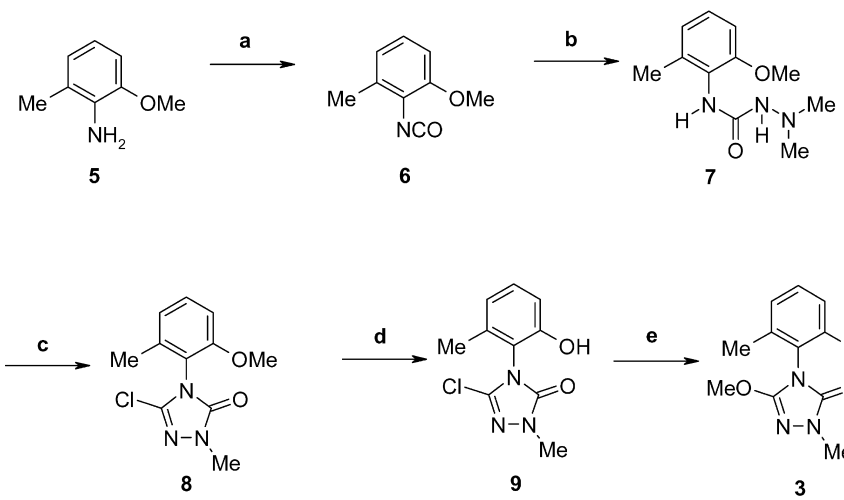
3 **4**

2. Results and discussion

2.1. Synthesis of racemic intermediates

Compound **3** may be readily prepared according to Scheme 1. Our synthesis began with commercially available **5**, which was treated with phosgene to provide the isocyanate **6**. The crude **6** was treated with dimethylhydrazine to provide the semicarbazide **7**. Cyclization with excess phosgene[12] provided chlorotriazolone **8**. To minimize undesirable side reactions, this reaction was best conducted by continuous addition of **7** to a hot solution of phosgene in ethyl acetate in order to maintain a large excess of phosgene relative to substrate. Deprotection of the phenol was accomplished with aluminum trichloride to yield **9**,[13] which was then treated with sodium methoxide to yield **3**.

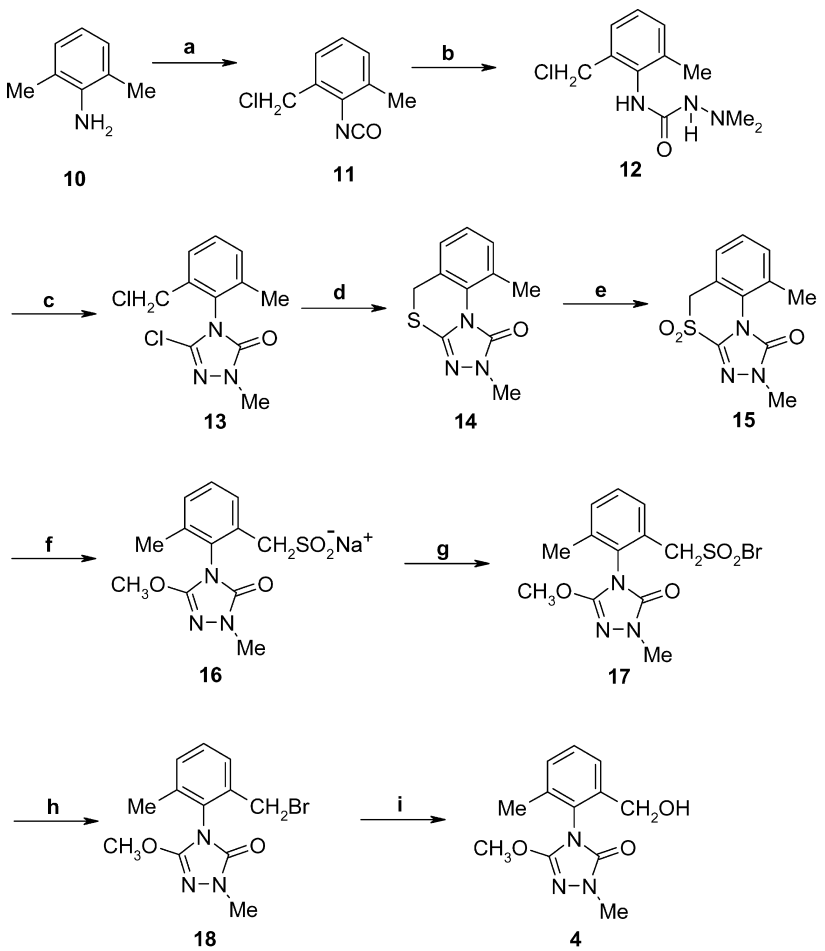
The synthesis of **4** (Scheme 2) began with the selective monochlorination of 2-isocyanato-1,3-dimethylbenzene. Reaction of **11** with dimethylhydrazine provided the semicarbazide **12** that was cyclized with phosgene as previously described. Direct introduction of the methoxy group to the triazolone was complicated by competing reaction with the benzylic chloride. An improved procedure was effected by preparation of the tricyclic sulfone **15**. Methanolysis of **15** resulted in clean introduction of the



5 **6** **7**

8 **9** **3**

Scheme 1. (a) $COCl_2$; (b) NH_2NMe_2; (a),(b) 98% overall; (c) $COCl_2$, 98%; (d) $AlCl_3$, 96%; (e) NaOMe, 57%.



Scheme 2. (a) i $COCl_2$, 92%; ii Cl_2, 84.5%; (b) NH_2NMe_2; (c) $COCl_2$; (b),(c) 66% overall; (d) Na_2S, 59%; (e) H_2O_2, 83%; (f) NaOMe; (g) Br_2; (f),(g) 84% overall; (h) tetrabutylammonium bromide, 78%; (i) H_2O, 86%.

methoxy group into the triazolone, providing the sulfinic acid salt **16**. This compound was converted into the benzylic bromide **18** by formation of the sulfonyl bromide followed by sulfur dioxide expulsion.[14] Finally, hydrolysis of **18** using calcium carbonate in aqueous dioxane[15] provided benzylic alcohol **4**.

2.2. Resolution methods

2.2.1. Separation of diastereomeric esters. Chemical separation of enantiomers by the preparation and separation of covalently bonded diastereomeric derivatives is perhaps the most commonly practised method for effecting resolutions of alcohols and phenols. Separation of the diastereomers can be accomplished by crystallization or chromatography.

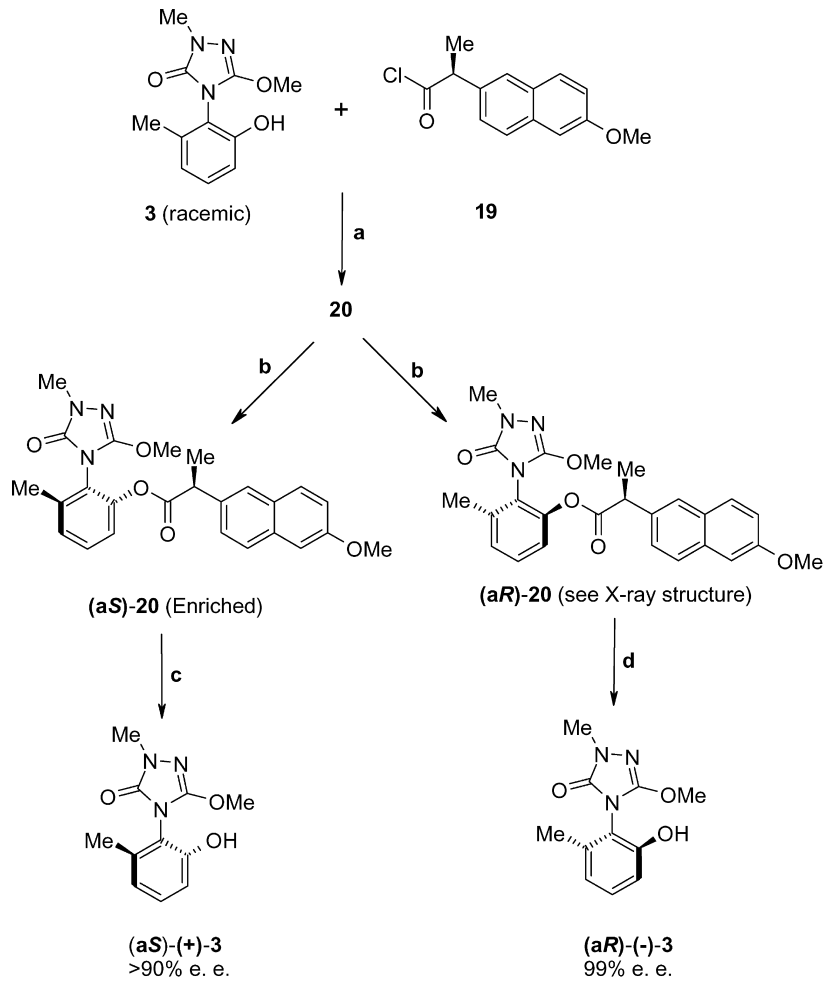
We began our efforts at resolving **3** by surveying several common resolving agents, including mandelate derivatives, (−)-menthyl chloroformate and *R*-(+)-α-methyl benzyliso-cyanate. We were unable to achieve efficient diastereomer separations with these resolving agents.

Our first successful resolution of **3** used **19**, the acid chloride of the readily available (*S*)-(+)-6-methoxy-α-methyl-2-naphthaleneacetic acid (naproxen)[16] to prepare the corresponding esters (Scheme 3).

Selective fractional crystallization of a single diastereomer from methanol, followed by X-ray crystallographic analysis (see Fig. 1) allowed us to correlate the stereochemistry of the atropic axis with that of the known naproxen moiety. In this view, the α-methyl of the naproxen moiety and the methoxy group of the triazolone are oriented toward the viewer. The absolute configuration of the atropic axis is thus *aR*.[7] It is interesting to note that the triazolone and the naphthalene group are very nearly parallel and stacked together, indicating a possible π-stacking interaction between the two groups. The distance from the center of the triazolone ring to the mean plane of the naphthalene group is 3.93 Å.

The mother liquors contained a mixture of diastereomers enriched in the *aS* diastereomer. Following methanolysis of the enriched diastereomers to remove the naproxen moiety, recrystallization of the partially-enriched (*aS*)-**3** provided further enrichment by removal of additional racemic **3** from the mixture. This two-step process allowed us to obtain both enantiomers of **3** in high enantiomeric purity. We subsequently determined that the *aS* configuration provided the more fungicidally-active enantiomer (see below).

Enantiomerically enriched **3** can be readily racemized thermally by, for example, heating the neat solid above its melting point for a few minutes. After cooling, the resulting



Scheme 3. (a) Et_3N, 33%; (b) MeOH, Fractional Crystallisation; (c) NaOMe, 87%; (d) NaOMe, 85%.

solid was found to be completely racemic. Thus, we could recycle the undesired enantiomer to the process. On a manufacturing scale, the ability to use all of a late-stage intermediate such as **3** is very important for a cost-effective synthesis.

We also discovered that racemic **3** forms a dimer of the two enantiomers in the crystalline state. The dimer appears to have matched hydrogen bonds between the phenol of one enantiomer and the triazolone carbonyl of the other enantiomer (see Fig. 2). Enantiomerically pure **3** does not

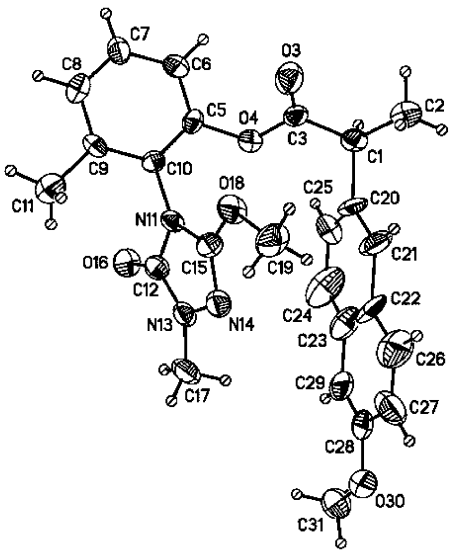


Figure 1. ORTEP drawing of (*aR*)-**20**. Thermal ellipsoids drawn to the 50% probability level.

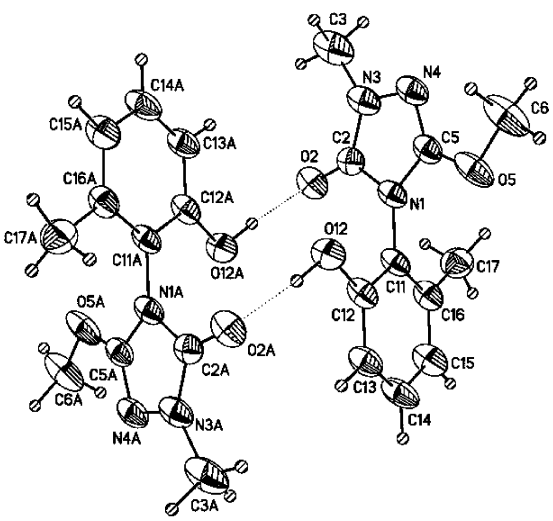


Figure 2. ORTEP drawing of racemic **3** showing hydrogen-bonded dimer. Thermal ellipsoids drawn to the 50% probability level.

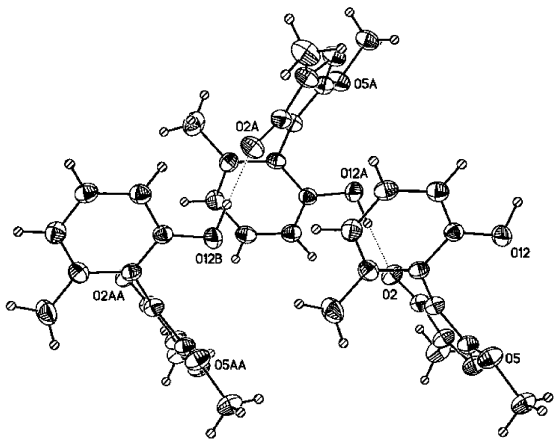


Figure 3. ORTEP drawing of (+)-**3** showing hydrogen-bonded chain. Thermal ellipsoids drawn to the 50% probability level.

form similar dimers, instead forming extended hydrogen-bonded chains (see Fig. 3).

We also observed that the aggregation behavior of racemic **3** and (+)-**3** differed in aprotic solvents (compare the partial ^{1}H NMR spectra of racemic **3** in Fig. 4(A) to that of (+)-**3** in Fig. 4(B)). It appears that formation of dimeric racemic pairs is preferred over more extensive chain aggregation in enantiomerically enriched samples, resulting in different NMR signals for the paired and unpaired molecules (Fig. 4(C)). The NMR signals shift depending on concentration and level of enrichment. Analysis of the spectra enabled us to calculate enantiomeric excesses of partially enriched **3** by comparing the integrations of the signals from the dimer to those from the enantiomer in excess. In protic solvents, the difference in NMR signals disappears (Fig. 4(D)), apparently due to solvent disruption of the hydrogen-bonded aggregation.

2.2.2. Separation of camphorsulfonate derivatives. Although resolution with naproxen can be used to prepare enantiomerically enriched triazolones, it is unsuitable for scale-up, since it required multiple recrystallizations to obtain high-purity diastereomers. Furthermore, the less soluble diasteromer provided the undesired enantiomer of **3**. As only one enantiomer of the 6-methoxy-α-methyl-2-naphthaleneacetic acid is commercially available, we were limited in our ability to switch to the opposite antipode to carry out a more efficient synthesis of the desired *aS*-**3**. Therefore, we wanted to investigate other resolving agents in order to find a system to resolve the preferred *aS* configuration more effectively. We settled upon 10-camphorsulfonyl chloride, both enantiomers of which are commercially available for a similar price. Thus, we would not be restricted by availability of the resolving agent, no matter which one proved more suitable for processing.

Compound **3** was coupled with 1*S*-(+)-10-camphorsulfonyl chloride to yield a mixture of diastereomers that we could not separate by fractional crystallization (Scheme 4). However, careful chromatography provided separation of the two diastereomers. Removal of the camphorsulfonate by methanolysis followed by comparison to the enantiomers of **3** showed that the diastereomer with the desired *aS* configuration at the atropic axis was the first eluting component. This allowed us to obtain the desired enantiomer of **3** in high enantiomeric excess. But, because of the need for chromatography, we still did not have a method suitable for large-scale preparations of (+)-**3**.

Following the successful resolution of **3** using the camphorsulfonate, we investigated the resolution of **4** by a similar strategy. In addition to the other advantages of the camphorsulfonates described above, the camphorsulfonate ester of **4** could itself act as a leaving group, thus

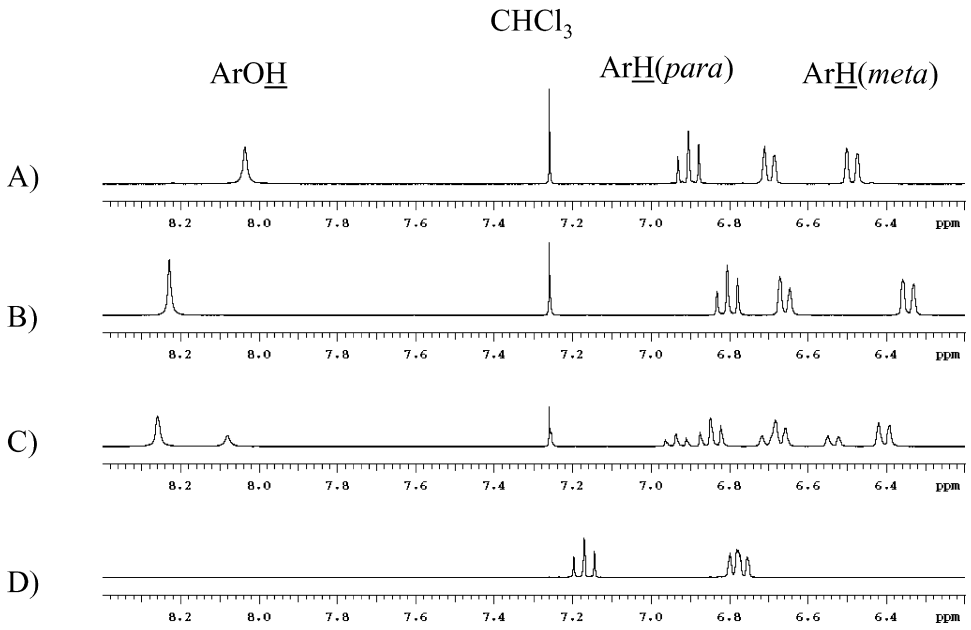
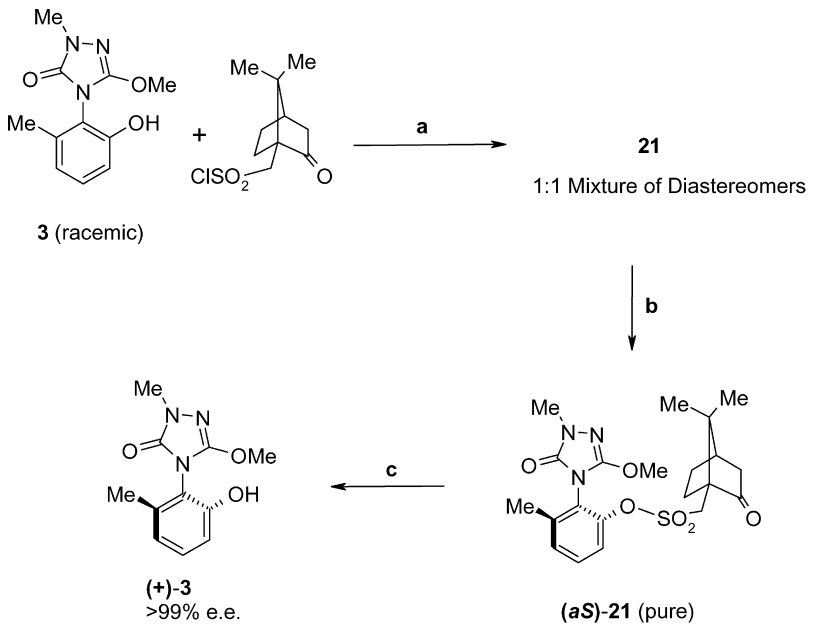


Figure 4. Partial ^{1}H NMR (300 MHz) spectra of **3**. (A) Racemic **3** in $CDCl_3$; (B) (−)-**3** (>95% ee, determined by HPLC) in $CDCl_3$; (C) **3** (40% ee, determined by HPLC) in $CDCl_3$; (D) **3** (40% ee) in CD_3OD.

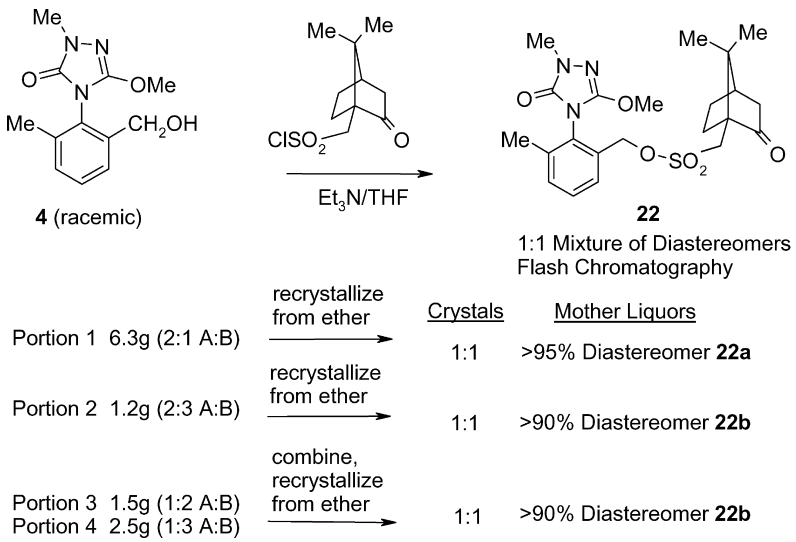


Scheme 4. (a) NaH, (*aS*)-**21** 34%, (*aR*)-**21** 28%; (b) Chromatography; (c) NaOMe, 75%.

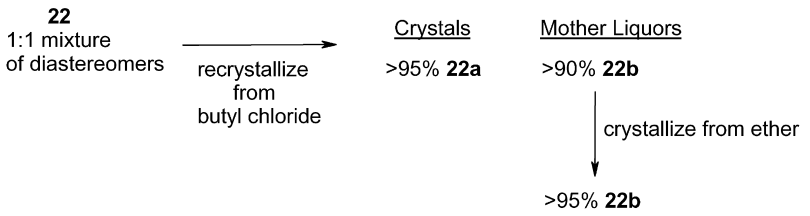
streamlining the synthesis of **2b**. Treatment of **4** with triethylamine and camphorsulfonyl chloride in tetrahydrofuran provided the camphorsulfonate in high yield and good purity (Scheme 5). With (1*S*)-(+)-10-camphorsulfonyl chloride, we obtained a 1:1 mixture of diastereomers **22** that did not appear to separate by thin-layer chromatography. Crystallization from ethereal solvents did not provide any diastereomeric enrichment. Flash chromatography with somewhat arbitrary breaks in the fractions gave four portions that were enriched, to varying degrees, in one or the other diastereomer. Each of those portions was then crystallized from ether. The crystalline material from the ether crystallizations proved to be a 1:1 mixture of both diastereomers, with the mother liquors >90% pure for the diastereomer which had been in excess! This selective co-crystallization of a 1:1 mixture of two different diastereomers was unexpected.

By this procedure, we had obtained a workable separation, albeit convoluted, of the two diastereomers. We expected that some refinement in chromatography to get better enrichment, followed by crystallization from ether to remove the minor diastereomer (in a 1:1 crystal with some of the major diastereomer) would allow us to generate reasonable amounts of quite pure diastereomers for further investigation.

However, the individual (nearly pure) diastereomers were non-crystalline following the ether crystallization, so we tried to crystallize them. Ether or ethyl acetate had not proven useful for fractional crystallization of the mixed diastereomers, so we looked at other solvents. We have found 1-chlorobutane to be a useful solvent for inducing crystallization of a number of varied compounds. 1-Chlorobutane has a Hildebrand solubility parameter [δ(H)][17] greater than ether or hexane and comparable to ethyl acetate, but is a less polar solvent than ethyl acetate. Chilling 1-chlorobutane solutions of the separated



Scheme 5.



Scheme 6.

diastereomers resulted in one diastereomer (diasteromer **22a**) precipitating out, while the other (diastereomer **22b**) remained in solution. This dramatic difference in solubility between the diastereomers was not anticipated, but certainly fortuitous. Therefore, we returned to the 1:1 mixture of diastereomers: a hot solution of the diastereomer mixture was seeded with a crystal of diastereomer **22a** and the resulting crystals collected by filtration. A single recrystallization of the 1:1 mixture of diastereomers from 1-chlorobutane provided separation of the two diastereomers in >90% efficiency (Scheme 6). Diastereomer **22b** could then be crystallized from ether. This separation method has been subsequently scaled up to several hundred grams.

We also found that the purified diastereomers could be interconverted thermally, to afford mixtures of about equal amounts of both diastereomers. Heating a solution of highly enriched **22a** in refluxing xylene for 48 h provided a 1:1 mixture of **22a** and **22b**.

Removal of the camphorsulfonate groups from the diastereomers **22a** and **22b** by hydrolysis provided the resolved enantiomers of benzyl alcohol **4**. Diastereomer **22a** provided (−)-**4** and **22b** provided (+)-**4**. However, for the purposes of preparing fungicidal derivatives, it was more desirable to use the camphorsulfonate as a leaving group in nucleophilic displacements (see below).

We did not observe any differences between the NMR spectra of racemic **4** and enantiomerically enriched **4**, as was observed for the phenolic triazolones **3**. This suggests that the hydrogen-bond-mediated aggregation is not as significant for the benzyl alcohol **4** as for the phenolic **3**.

2.2.3. Separation of diastereomeric salts. A more readily scaleable resolution of **3** was achieved by converting it to a hemisulfate salt. As noted above, we initially thought that phenol **3** would be sufficiently acidic to allow us to develop a resolution using a basic resolving agent. However, several attempts to prepare crystalline salts from alkaloid bases such as cinchonine were unsuccessful, apparently because of the low acidity of **3**. In order to increase the acidity of the triazolone, we converted it to the hemisulfate.

Thus treatment of **3** in dichloromethane with an excess of a sulfating agent such as DMF·SO_3 followed by the addition of (*R*)-(+)-α-methylbenzylamine afforded a 1:1 mixture of the diastereomeric hemisulfate salts **23** in high conversion (Scheme 7). Solvent exchange with toluene induced the preferential crystallization of the *aS*,*R* diastereomeric salt (*aS*,*R*)-**23a** which was then purified by trituration in toluene

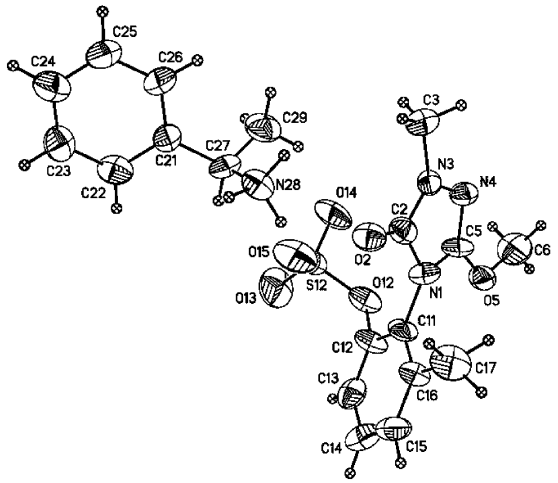
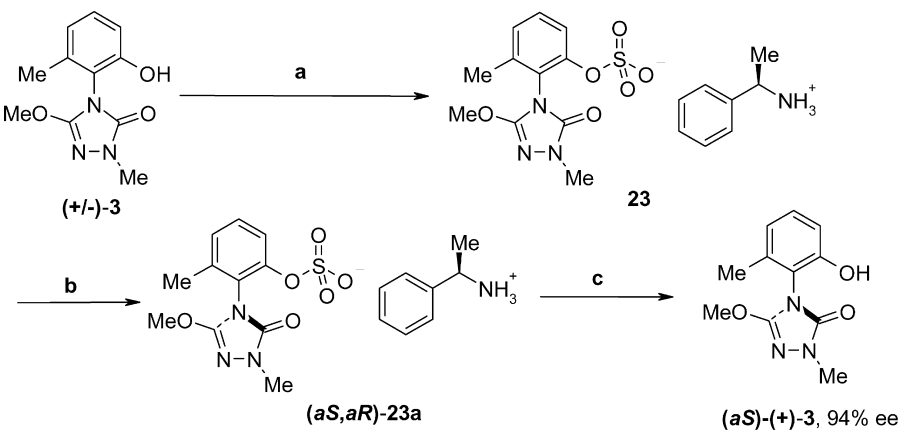
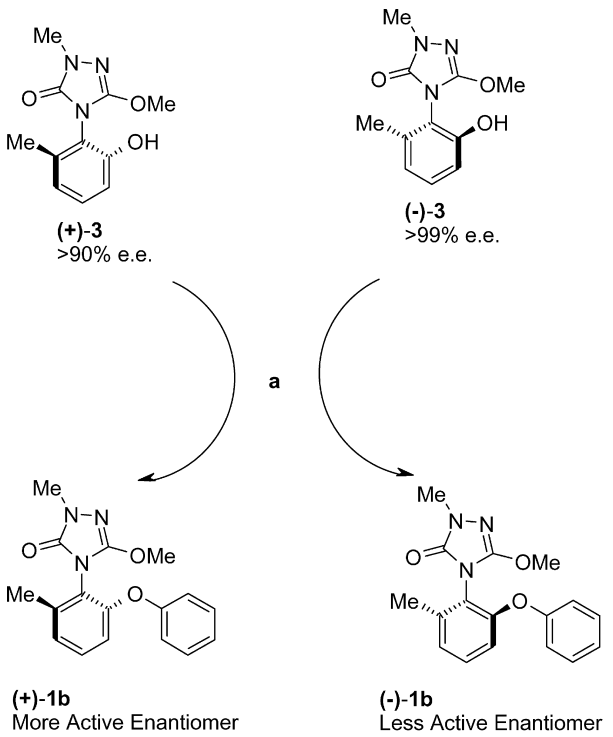


Figure 5. ORTEP drawing of (*aS*,*R*)-**23a**. Thermal ellipsoids drawn to the 50% probability level.



Scheme 7. (a) i DMF·SO_3, ii (*R*)-(+)-alpha-methylbenzylamine; (b) toluene extraction; (a),(b) 65% overall; (c) H_2SO_4, 99%.



Scheme 8. (a) Triphenylbismuthine, $Cu(OAc)_2$, Et_3N, (+)-**1b** 90%, (−)-**1b** 93%.

(2×). We confirmed the structure and absolute configuration of (*aS*,*R*)-**23a** by a single crystal X-ray diffraction analysis (see Fig. 5). Hydrolysis of (*aS*,*R*)-**23a** in aqueous sulfuric acid afforded the desired *aS*-enantiomer of **3** in 90–94% ee and 65–75% overall yield. In one case, 83% of the remaining *aR*-enriched **3** (68% ee) was recovered by acid hydrolysis of the toluene filtrate. With this procedure we were able to resolve up to 300 g of racemic **3**. Although this resolution is relatively straightforward, the use of excess $DMF{\cdot}SO_3$ must be minimized and all reagents and solvents used before the addition of toluene must be rigorously dried to reduce the formation of byproduct sulfate salts that interfere with the crystallization and purification of (*aS*,*R*)-**23a**.

2.3. Synthesis of fungicidal derivatives

With the successful production and separation of the enantiomers of **3** and **4**, we needed to correlate their absolute configuration with their biological activity.

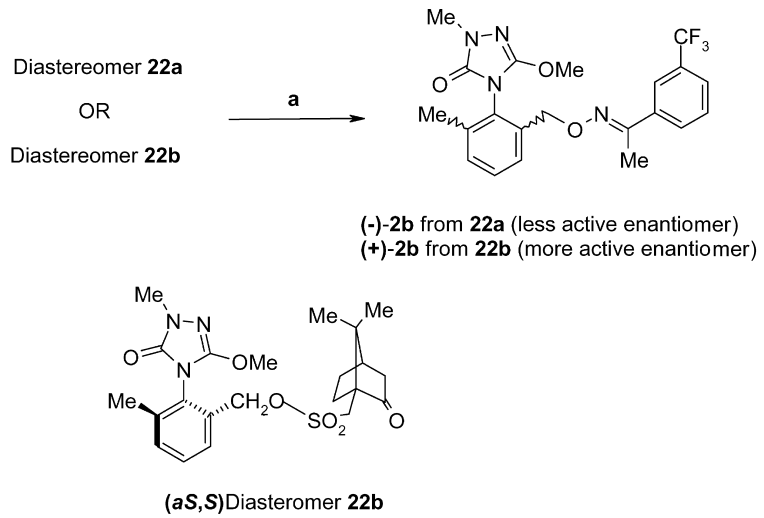
Samples of the enantiomerically enriched (*aR*)-**1b** and (*aS*)-**1b** were prepared from the phenols using a modification of Barton's copper mediated *O*-phenylation with triphenyl bismuth and triethylamine as a promoter[18] (Scheme 8). Biological testing and comparison to material previously separated by chiral-phase HPLC allowed us to assign the *aS* configuration to the more active enantiomer.

After the successful production and separation of the camphorsulfonate derivatives of **4**, we used the camphorsulfonate esters as the leaving group directly in displacement reactions with 1-[3-(trifluoromethyl)phenyl]ethanone oxime **24** (Scheme 9). As envisioned, displacements of the camphorsulfonate moiety went very well, leading to high conversions of both diastereomers to the enantiomers of **2b**. Biological testing of both enantiomers of **2b** indicated that diastereomer **22b** provided the more active enantiomer. Assuming that the chirality about the atropic axis was conserved for the fungicidally-active enantiomers with either *ortho* group, we hypothesised that the absolute configuration of diastereomer **22b** at the atropic axis was also *aS* as shown.

2.4. Biological activity

Biological activity was assayed by measuring plant disease control using the pathogen–host complex grown in greenhouse or growth chambers. Test compounds were applied at rates ranging from 0.4 to 200 parts per million (ppm) and an assessment of the prevention of disease was made by visually scoring the diseased area of the foliage relative to untreated checks.[19]

Test compounds were first dissolved in acetone in an amount equal to 3% of the final volume and then suspended at a concentration of 200 ppm in purified water containing 250 ppm of the surfactant Trem® 014 (polyhydric alcohol



Scheme 9. (a) NaH, 1-[3-(trifluoromethyl)phenyl]ethanone oxime, (−)-**2b** 70%, (+)-**2b** 65%.

esters). The resulting test suspensions were then used in the following tests, either at the 200 ppm rate or at lower rates after serial dilution. Spraying these 200 ppm test suspensions to the point of runoff on the test plants is the equivalent of a rate of 500 g/ha.

2.4.1. Wheat powdery mildew. The test suspension was sprayed to the point of run-off on wheat seedlings. The following day the seedlings were inoculated with a spore dust of *Erysiphe graminis f. sp. tritici*, (the causal agent of wheat powdery mildew) and incubated in a growth chamber at 20 °C for 7 days, after which disease ratings were made.

2.4.2. Tomato late blight. The test suspension was sprayed to the point of runoff on tomato seedlings. The following day the seedlings were inoculated with a spore suspension of *Phytophthora infestans* (the causal agent of potato and tomato late blight) and incubated in a saturated atmosphere at 20 °C for 24 h, and then moved to a growth chamber at 20 °C for 5 days, after which disease ratings were made.

In Table 1, a rating of 100 indicates 100% disease control and a rating of 0 indicates no disease control (relative to the checks).

3. Conclusions

Certain biologically active phenyl triazolones exhibit atropisomerism. We successfully investigated different approaches to resolving atropic phenyl triazolones having either phenolic or benzylic alcohol moieties, including separation of diasteromeric esters and sulfonates and selective crystallization of diasteromeric salts. The various methods were evaluated in terms of their suitability for manufacturing-scale synthesis. In the benzylic alcohol resolution, the separation of diastereomeric sulfonate derivatives was impacted by some dramatic differences in fractional crystallization using different solvents. We also briefly investigated thermal interconversions of the enriched materials. The results of these studies are highly efficient resolution/reaction sequences to prepare enantiomerically enriched fungicides from the racemic materials.

In addition, during these studies we discovered an interesting aspect of the phenolic triazolones. Racemic phenolic triazolones form dimers, while the corresponding enantiomerically enriched compounds form extended chains. These differences in aggregation behavior were observed in the crystalline states and in aprotic solvents.

4. Experimental

4.1. General

Percentages are by weight except for chromatographic solvent mixtures or where otherwise indicated. Parts and percentages for chromatographic solvent mixtures are by volume unless otherwise indicated. Melting points were obtained using a MEL-TEMP® capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained on a Varian Unity Plus at 300 MHz and are reported in ppm downfield from tetramethylsilane; s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets and br s=broad singlet.

Except where indicated, analyses of enantiomeric excesses (%ee) were carried out on an HP 1090 HPLC equipped with a 25 cm×4.6 mm (*R*,*R*) Whelk-O1 column (Regis Technologies Inc., Morton Grove, IL, USA), column temperature=40 °C, detector λ=230, 254 nm) using solvent mixtures, flow rates and elution times as indicated for each example.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC223076, CCDC223077, CCD223629 and CCD223630. 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].

4.1.1. *N*-(2-Methoxy-6-methylphenyl)-2,2-dimethylhydrazinecarboxamide (7). To a stirred solution of phosgene (108 g, 1.09 mol) in ethyl acetate (750 mL) at 0 °C was added dropwise 2-methoxy-6-methylaniline **5a** (125.0 g, 912 mmol) dissolved in ethyl acetate (250 mL) over 20 min. The reaction mixture was slowly warmed to room temperature and was then heated at reflux for 1 h. The solution was cooled to room temperature and was concentrated under reduced pressure to provide the crude isocyanate **6a** as a dark red liquid that was redissolved in ethyl acetate (1 L) and cooled to 0 °C. 1,1-Dimethylhydrazine (55.0 g, 911 mmol) was added dropwise over 30 min and then the mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was cooled and filtered, and the solid was washed with ethyl acetate and dried to provide 200.0 g (98% yield) of the title compound **7** as a white solid, mp 151–153 °C; δ_H (300 MHz, $CDCl_3$) 7.58 (1H, br s, N*H*), 7.10 (1H, t, *J*=8 Hz, Ar*H*), 6.84 (1H, d, *J*=8 Hz, Ar*H*), 6.74 (1H, d, *J*= 8 Hz, Ar*H*), 5.22 (1H, br s, N*H*), 3.80 (3H, s, OCH_3), 2.63 (6H, s, N(CH_3)$_2$), 2.31 (3H, s, ArCH_3).

4.1.2. 5-Chloro-2,4-dihydro-4-(2-methoxy-6-methylphenyl)-2-methyl-3*H*-1,2,4-triazol-3-one (8). The compound **7** (100.0 g, 448 mmol) was suspended in ethyl acetate (1 L) and added dropwise, via mechanical pump, over 3.5 h to a stirring solution of phosgene (177 g, 1.79 mol) in ethyl acetate (1.5 L) that was heated at reflux. After the addition was complete, the mixture was heated at reflux for a further 3 h, cooled to room temperature and stirred for 16 h. The solution was concentrated under reduced pressure and the residue was dissolved in ethyl acetate and water and extracted four times with ethyl acetate. The combined organic phases were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to afford 111.4 g (98% yield) of the title compound **8** as a pale yellow solid, mp 132–134 °C; δ_H (300 MHz, $CDCl_3$) 7.34 (1H, t, *J*=8 Hz, Ar*H*), 6.93 (1H, d, *J*=8 Hz, Ar*H*), 6.85 (1H, d, *J*=8 Hz, Ar*H*), 3.79 (3H, s, OCH_3), 3.54 (3H, s, NCH_3), 2.20 (3H, s, ArCH_3).

4.1.3. 5-Chloro-2,4-dihydro-4-(2-hydroxy-6-methylphenyl)-2-methyl-3*H*-1,2,4-triazol-3-one (9). To a stirring

solution of **8** (15.0 g, 59.3 mmol) in benzene (200 mL) at 0 °C was added aluminum chloride (23.7 g, 178 mmol) in small portions. The mixture was warmed to room temperature and stirred for 2 days. The mixture was poured over ice and water and then extracted four times with ethyl acetate. The combined organic phases were washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered and concentrated to an oil that was purified by flash chromatography on silica gel to provide 13.6 g (96% yield) of the title compound **9** as a pale orange solid, mp 175–178 °C; δ_H (300 MHz, $CDCl_3$) 8.11 (1H, s, ArO*H*), 6.92 (1H, t, *J*=8 Hz, Ar*H*), 6.71 (1H, d, *J*=8 Hz, Ar*H*), 6.41 (1H, d, *J*=8 Hz, Ar*H*), 3.56 (3H, s, NCH_3), 2.12 (3H, s, ArCH_3).

4.1.4. 2,4-Dihydro-4-(2-hydroxy-6-methylphenyl)-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one (3). To a stirred solution of **9** (133.5 g, 557.0 mmol), prepared as above, in tetrahydrofuran (1.5 L) was added dropwise sodium methoxide (25% by weight in methanol, 382 mL, 1.67 mol). The mixture was heated at reflux for 3 h, cooled to room temperature and then diluted with aqueous ammonium chloride and ethyl acetate. The aqueous layer was acidified (to pH 45) with 1 N HCl and extracted three times with ethyl acetate. The combined organic phases were washed with saturated aqueous NaCl, dried (MgSO4), filtered and concentrated to a dark brown solid that was triturated with ethyl acetate to afford 75.0 g (57% yield) of the racemic title compound **3** as a white solid, mp 194–196 °C; δ_H (300 MHz, DMSO-d_6) 9.91 (1H, s, ArO*H*), 7.17 (1H, t, Ar*H*), 6.78 (2H, m, Ar*H*), 3.84 (3H, s, OCH_3), 3.30 (3H, s, NCH_3), 2.03 (3H, s, ArCH_3).

4.1.5. [2-(1,5-Dihydro-3-methoxy-1-methyl-5-oxo-4*H*-1,2,4-triazol-4-yl)-3-methylphenyl] 6-methoxy-α-methyl-2-naphthaleneacetate (20). *S*-(+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid (23.03 g) was treated with 75 mL of oxalyl chloride at room temperature for 1 h. The excess oxalyl chloride was removed by rotary evaporation. The crude acid chloride was dissolved in 100 mL of tetrahydrofuran and added dropwise to a solution of **3** (23.5 g, 100 mmol) and triethylamine (14 mL) in 500 mL of tetrahydrofuran. After addition was complete, the mixture was allowed to stir at room temperature for 1 h. The precipitated triethylamine hydrochloride was removed by filtration and the filtrate was concentrated to yield orange oil. The crude material was purified by flash chromatography on silica gel (gradient from 1:1 ethyl acetate hexane to 100% ethyl acetate as eluant) to provide a mixture of two diastereomers in a 1:1 ratio as colorless oil. Trituration in ether provided a solid (15.4 g) that was enriched in one diastereomer. This material was fractionally crystallized from methanol (two recrystallizations) to provide a single diastereomer of the title compound (*aR*)-**20** as a white solid, mp 147 °C; δ_H (300 MHz, $CDCl_3$) 7.7 (3H, m, Ar*H*), 7.3 (2H, m, Ar*H*), 7.15 (4H, m, Ar*H*), 3.99 (1H, q, *J*=7.1 Hz, ArC*H*(CH_3)C=O), 3.93 (3H, s, OCH_3), 3.61 (3H, s, ArOCH_3), 3.10 (3H, s, NCH_3), 2.15 (3H, s, ArCH_3), 1.61 (3H, d, *J*=7.1 Hz, ArCH(CH_3)C=O).

The ether-soluble material (12 g) was enriched in the other diastereomer of the title compound (*aS*)-**20** (4:1 mixture of (*aS*)-**20**:(*aR*)-**20**). This material was fractionally crystallized from methanol to give 3.15 g of a white solid (4:1 mixture of (*aS*)-**20**:(*aR*)-**20**). The mother liquors were fractionally crystallized from ether to give 4.3 g of a white solid (8.4:1 mixture of (*aS*)-**20**:(*aR*)-**20**). This material was recrystallized from ethyl acetate/hexane to give 4.0 g (9% yield) of an 8.4:1 mixture of the diastereomers of the title compound (*aS*)-**20**:(*aR*)-**20**) as a white solid, mp 98–101 °C; δ_H (300 MHz, $CDCl_3$) (of the major diastereomer (*aS*)-**20**; signals from the minor diastereomer (*aR*)-**20** are not reported) 7.7 (3H, m, Ar*H*), 7.39 (1H, dd, *J*=1.9, 8 Hz, Ar*H*), 7.30 (1H, t, *J*=8 Hz, Ar*H*), 7.15 (3H, m, Ar*H*), 7.02 (1H, d, *J*=8 Hz, Ar*H*) 4.00 (1H, q, *J*=7 Hz, ArC*H*(CH_3)-C=O), 3.92 (3H, s, OCH_3), 3.75 (3H, s, ArOCH_3), 3.20 (3H, s, NCH_3), 2.19 (3H, s, ArCH_3), 1.60 (3H, d, *J*=7 Hz, ArCH(CH_3)C=O).

4.1.6. (*aS*)-2,4-Dihydro-4-(2-hydroxy-6-methylphenyl)-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one ((+)-3). To a suspension of 4.0 g (8.9 mmol) of the 8.4:1 mixture of diastereomers (*aS*)-**20**:(*aR*)-**20** in 40 mL of methanol was added 2.0 mL of 30% sodium methoxide in methanol. The mixture was stirred at room temperature for 30 min. The mixture was diluted with 40 mL of water and extracted with dichloromethane (3×40 mL). The aqueous phase was made acidic with 1 N hydrochloric acid and extracted again with dichloromethane (3×40 mL). These combined extracts were dried ($MgSO_4$), filtered and concentrated by rotary evaporation. The glassy residue was triturated in hexane to give a white solid that was collected by filtration to afford 1.82 g (87% yield) of the title compound (+)-**3**, mp 178–180 °C; δ_H (300 MHz, $CDCl_3$) 7.95 (1H, s, ArO*H*), 6.85 (1H, t, *J*=8 Hz, Ar*H*), 6.68 (1H, d, *J*=8 Hz, Ar*H*), 6.41 (1H, d, *J*=8 Hz, Ar*H*), 3.92 (3H, s, OCH_3), 3.48 (3H, s, NCH_3), 2.12 (3H, s, ArCH_3); $[\alpha]_D^{20}$=+113.1 (*c* 5.53, CH_2Cl_2). HPLC analysis [75% hexanes, 25% isopropyl alcohol, 0.1% acetic acid, 0.7 mL/min elution time 8.5 min] indicates 86% ee.

4.1.7. (*aR*)-2,4-Dihydro-4-(2-hydroxy-6-methylphenyl)-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one ((−)-3). To a suspension of 1.34 g (3 mmol) of (*aR*)-**20**, obtained as described above, in 10 mL of methanol was added 0.6 mL of 30% sodium methoxide in methanol. The mixture was stirred at room temperature for 30 min. The mixture was diluted with 10 mL of water and extracted with dichloromethane (3×15 mL). The aqueous phase was made acidic with 1 N hydrochloric acid and extracted again with dichloromethane (3×15 mL). These combined extracts were dried (Mg SO_4), filtered and concentrated by rotary evaporation. The glassy residue was triturated in hexane to give a white solid that was collected by filtration to provide 600 mg (85% yield) of the title compound (−)-**3**, mp 184 °C; δ_H (300 MHz, $CDCl_3$) 7.95 (1H, s, ArO*H*), 6.85 (1H, t, *J*=8 Hz, Ar*H*), 6.68 (1H, d, *J*=8 Hz, Ar*H*), 6.41 (1H, d, *J*=8 Hz, Ar*H*), 3.92 (3H, s, OCH_3), 3.48 (3H, s, NCH_3), 2.12 (3H, s, ArCH_3); $[\alpha]_D^{20}$=138.6 (*c* 5.53, CH_2Cl_2). HPLC analysis [75% hexanes, 25% isopropyl alcohol, 0.1% acetic acid, 0.7 mL/min, elution time 7.10 min] indicates >95% ee.

4.1.8. (*aS*)-2,4-Dihydro-5-methoxy-2-methyl-4-(2-methyl-6-phenoxyphenyl)-3*H*-1,2,4-triazol-3-one ((+)-1b). To a solution of (+)-**3**, prepared as above, (0.79 g, 3.4 mmol, 86% ee) in dichloromethane(16 mL) was added

triphenylbismuth (2.98 g, Aldrich Chemical Co.), anhydrous cupric acetate (0.61 g), and triethylamine (0.70 g). After stirring at room temperature for 70 h, the crude reaction mixture was directly subjected to flash chromatography purification (silica gel, 30–40% ethyl acetate in hexane) to give 0.95 g (90% yield) of the title compound (+)-**1b** as a white solid, mp 61–64 °C; δ_H (300 MHz, $CDCl_3$) 7.32–7.23 (3H, m, Ph*H* and Ar*H*), 7.10 (1H, tt, *J*=7.5, 1.0 Hz, Ph*H*), 7.04 (1H, d, *J*=7.0 Hz, Ar*H*), 6.99 (2H, m, Ph*H*), 6.80 (1H, d, *J*=7 Hz, Ar*H*), 3.86 (3H, s, OCH_3), 3.38 (3H, s, NCH_3), 2.27 (3H, s, ArCH_3). $[\alpha]_D^{20}$= +16.78 (*c* 2.55, CH_2Cl_2). HPLC analysis [20% isopropyl alcohol/80% hexane, 0.8 mL/min, elution time 12.04 min] indicates 84% ee.

4.1.9. (*aR*)-2,4-Dihydro-5-methoxy-2-methyl-4-(2-methyl-6-phenoxyphenyl)-3*H*-1,2,4-triazol-3-one ((−)-1b). To a solution of (−)-**3**, prepared as above, (0.38 g, 1.7 mmol, >95% ee) in dichloromethane(8 mL) was added triphenylbismuth (1.41 g, Aldrich Chemical Co.), anhydrous cupric acetate (0.29 g), and triethylamine (0.34 g). After stirring at room temperature for 94 h, an additional 0.2 g of triphenylbismuth was added. After a total of 160 h of stirring, the crude reaction mixture was directly subjected to flash chromatography purification (silica gel, 30% ethyl acetate in hexane) to give 0.46 g (93% yield) of the title compound (−)-**1b**, as a white solid, mp 69–71 °C; δ_H (300 MHz, $CDCl_3$) 7.32–7.23 (3H, m, Ph*H* and Ar*H*), 7.10 (1H, tt, *J*=7.5, 1.0 Hz, Ph*H*), 7.04 (1H, d, *J*=7.0 Hz, Ar*H*), 6.99 (2H, m, Ph*H*), 6.80 (1H, d, *J*=7 Hz, Ar*H*), 3.86 (3H, s, OCH_3), 3.38 (3H, s, NCH_3), 2.27 (3H, s, ArCH_3); $[\alpha]_D^{20}$= 19.33 (*c* 2.55, CH_2Cl_2). HPLC analysis [20% isopropyl alcohol/80% hexane, 0.8 mL/min, elution time 9.8 min] indicates approximately 99% ee.

4.2. Separation of enantiomers of 2,4-dihydro-5-methoxy-2-methyl-4-(2-methyl-6-phenoxyphenyl)-3*H*-1,2,4-triazol-3-one (1b)

A sample of racemic **1b** (650 g) (similarly prepared as above) was separated in portions on a Chiralcel OJ HPLC column, 50 cm×10 cm (inner diameter) [7:3 hexanes/ethanol, flow rate 200 mL/min, 25 °C, UV detection at 290 nm, sample concentration 40 mg/mL in 7:3 hexanes/ethanol, 100 mL injection volume] to separate the enantiomers of the title compound (+)-**1b**; elution time 21 min; and (−)-**1b**; elution time 27 min. Following solvent removal from the appropriate fractions, a total of 306 g (47% yield) of the (*aS*)-diastereomer of the title compound (+)-**1b** was isolated as a white solid, mp 78–80 °C; 95.6% chemical purity; 94% ee; and a total of 279 g (43% yield) of the (*aR*)-diastereomer of the title compound (−)-**1b** was isolated as a white solid, mp 82–84 °C; 99.2% chemical purity; 94% ee.

4.2.1. [*aS*-[2-(*R* *)]]-4-[2-[[[(7,7-Dimethyl-6-oxobicyclo-[2.2.1]heptan-1-yl)methyl]sulfonyl]oxy]-6-methylphenyl]-2,4-dihydro-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one (*aS*-21). To a solution of racemic **3** (similarly prepared as above) (20.0 g, 85 mmol) in 300 mL of tetrahydrofuran and 150 mL of dimethylformamide was added (1*S*)-(+)-10-camphorsulfonyl chloride (27.8 g). To this mixture was added 50% sodium hydride (5.12 g, washed with hexanes and slurried in tetrahydrofuran). The resulting mixture was stirred at ambient temperature for 16 h, becoming a thick paste. An additional 150 mL of tetrahydrofuran was added and the mixture was stirred for one week. The reaction mixture was cooled in an ice-water bath and quenched with 100 mL of water, then diluted with 500 mL of ethyl ether. The phases were separated and the organic phase washed with 100 mL water, 100 mL of saturated sodium carbonate solution, 100 mL of water, then 100 mL of saturated sodium chloride solution. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was triturated in ether and the solid collected by filtration to yield 35.5 g of a white solid. Flash chromatography on silica gel (9:1 ether/hexane as eluent), after concentrating the appropriate fractions, afforded 12.85 g (34% yield) of the first eluting component, which was recrystallized from ethyl acetate/hexane to yield the title compound *aS*-**21**, as a white solid; δ_H (300 MHz, $CDCl_3$) 7.4 (2H, m, Ar*H*), 7.25 (1H, m, Ar*H*), 3.96 (3H, s, OCH_3), 3.63 (1H, d, *J*=16 Hz, $SO_2CH_aH_b$), 3.45 (3H, s, NCH_3), 3.17 (1H, d, *J*=16 Hz, $SO_2CH_aCH_b$), 2.4 (2H, m), 2.26 (3H, s, ArCH_3), 2.0 (3H, m), 1.7 (1H, m), 1.45 (1H, m), 1.09 (3H, s, CCH_3CH_3'), 0.88 (3H, s, CCH_3CH_3').

Also, 10.6 g (28% yield) of the second eluting component, the enantiomer of the title compound *aR*-**21**, as a white solid; δ_H (300 MHz, $CDCl_3$) 7.4 (2H, m, Ar*H*), 7.3 (1H, m, Ar*H*), 3.94 (3H, s, OCH_3), 3.74 (1H, d, *J*=16 Hz, $SO_2CH_aH_b$), 3.45 (3H, s, NCH_3), 3.15 (1H, d, *J*=16 Hz, $SO_2CH_aH_b$), 2.4 (2H, m), 2.26 (3H, s, ArCH_3), 2.0 (3H, m), 1.7 (1H, m), 1.45 (1H, m), 1.11 (3H, s, CCH_3CH_3'), 0.89 (3H, s, CCH_3CH_3'). Some mixed fractions were discarded.

4.2.2. (*aS*)-2,4-Dihydro-4-(2-hydroxy-6-methylphenyl)-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one ((+)-3). Diastereomer *aS*-**21** (12.85 g, 29 mmol) was suspended in 100 mL of methanol and 14.6 mL of 30% sodium methoxide in methanol was added. The reaction mixture was stirred at ambient temperature for 4 h. The mixture was concentrated in vacuo to remove most of the methanol and the remainder was diluted with 200 mL of ethyl acetate and washed with 100 mL of 1 N hydrochloric acid, 50 mL of water, then 100 mL of saturated sodium chloride solution. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to yield 5.1 g (75% yield) of the title compound (+)-**3** as a white solid, mp 183 °C; δ_H (300 MHz, $CDCl_3$) 8.05 (1H, br s, ArO*H*), 6.85 (1H, t, *J*=8 Hz, Ar*H*), 6.7 (1H, d, *J*=8 Hz, Ar*H*), 6.4 (1H, d, *J*=8 Hz, Ar*H*), 3.9 (3H, s, OCH_3), 3.45 (3H, s, NCH_3), 2.1 (3H, s, ArCH_3). HPLC analysis indicates >95% ee.

4.2.3. (*aS*)-2,4-Dihydro-5-methoxy-2-methyl-4-[2-methyl-6-(sulfooxy)phenyl]-3*H*-1,2,4-triazol-3-one (*R*)-α-methylbenzenemethanamine ((*aS*,*R*)-23a). In a 500 mL round-bottomed flask, equipped with a condenser, addition funnel, thermometer and nitrogen inlet, sulfur trioxide·*N*,*N*-dimethylformamide complex (39.16 g, 255.6 mmol) was added as a solid to a slurry of racemic **3**, (50.00 g, 212.5 mmol) in 300 mL of dichloromethane (distilled from phosphorus pentoxide). The resulting homogeneous light brown solution was refluxed under nitrogen for 1 h. ^1H NMR analysis showed a 95:5 ratio of the sulfate to unreacted **3**, so an additional 1.63 g of sulfur trioxide·*N*,*N*-dimethylformamide complex (10.64 mmol, 0.05 equiv.)

was added to the reaction mixture. A solution of 41.30 g, 340.8 mmol) (*R*)-(+)-α-methylbenzylamine (98% purity, 96% ee, passed through a pad of neutral alumina prior to use), in 20 mL of dichloromethane was then added dropwise to the reaction mixture over about 20 min. This slightly exothermic reaction was maintained between 25–30 °C with an ice bath. After the addition was complete, the solution was refluxed for 15 min, whereupon a gray solid precipitated from the reaction mixture. The hot solution was filtered and the solids rinsed with 50 mL of dichloromethane. The filtrate was concentrated in vacuo until about 260 mL of dichloromethane had been removed and then 350 mL of toluene was added to the viscous residue. The resulting two-phase (liquid/liquid) mixture was heated to 60 °C whereupon white solids precipitated. The hot mixture was filtered and the solids washed with two 20 mL portions of toluene. ^{1}H NMR analysis of the solids showed a 95:5 ratio of the title compound (*aS*,*R*)-**23a** to the other diastereomeric sulfate (*aR*,*R*)-**23b**. The solids were triturated with an additional 250 mL of toluene at 60 °C, filtered, washed with 50 mL toluene followed by two 40 mL portions of hexanes, then dried in vacuo (0.2 Torr) for 16 h to provide 32.45 g (65% of theoretical based on a formulation of (*aS*,*R*)-**23a**·(toluene)$_{0.36}$, M_W=469.7 g/mol) of the title compound (*aS*,*R*)-**23a** as a white solid, mp 121–129 °C; [Found, C 54.41; H 5.75; N 11.51; S 6.94; $C_{11}H_{12}N_3O_6S{\cdot}C_8H_{12}N$, with 6% toluene by weight, requires C 54.60; H 5.73; N 12.07; S 6.91]; δ_H (300 MHz, CDC l_3) 7.42 (d, *J*=7.5 Hz, 1H, Ar*H*), 7.2–7.4 (m, Ar*H*), 7.15 (d, *J*=9.4 Hz, 1H, Ar*H*), 7.09 (d, *J*=7.7 Hz, 1H, Ar*H*), 3.92 (q, *J*=6.9 Hz, 1H, C*H*(CH_3)), 3.89 (s, 3H, OCH_3), 3.27 (s, 3H, NCH_3), 2.35 (s, CH_3(toluene)), 2.18 (s, 3H, ArCH_3), 1.43 (d, *J*=6.7 Hz, 3H, CH(CH_3)); the NH resonances were not clearly observed but may be broadened under the aromatic region; $[\alpha]_D^{20}$=+1.3 (*c* 10.2 g/100 mL $CHCl_3$). ^{1}H NMR analysis showed a 97:3 ratio of the diastereomers (*aS*,*R*)-**23a**:(*aR*,*R*)-**23b** and the presence of 0.36 equiv. of toluene. In $CDCl_3$, the ratio of diastereomers can be obtained via integration of their respective NMe singlets ((*aS*,*R*)-**23a** δ=3.27, (*aR*,*R*)-**23b**: δ=3.31).

4.2.4. (*aS*)-2,4-Dihydro-4-(2-hydroxy-6-methylphenyl)-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one ((+)-3). In a round-bottomed 300 mL flask equipped with a condenser, (+)-**23a** (containing 0.36 equiv. of toluene, 32.45 g, 69.1 mmol, 94% diastereomeric excess) was heated to 60 °C in 100 mL of 2 N sulfuric acid for 3 h. The initially thick slurry dissolved upon heating and then (+)-**3** slowly precipitated from the solution. The reaction mixture was cooled to room temperature and extracted with three 200 mL portions of dichloromethane. The organic extracts were extracted once with 30 mL of water, dried ($MgSO_4$), filtered and concentrated to dryness in vacuo. The solid was further dried in vacuo (0.2 Torr) for about 1 h to give 16.53 g (99% yield) of the title compound (+)-**3** as a white solid; δ_H (300 MHz, $CDCl_3$) 6.79 (t, *J*=7.9 Hz, 1H, Ar*H*), 6.65 (d, *J*=7.3 Hz, 1H, Ar*H*), 6.31 (d, *J*=8.0 Hz, 1H, Ar*H*), 3.91 (s, 3H, OCH_3), 3.46 (s, 3H, NCH_3), 2.11 (s, 3H, ArCH_3). ^{1}H NMR analysis showed the presence of 0.086 equiv. of toluene in addition to (+)-**3**. HPLC analysis (Chirobiotic T column purchased from Astec (i.e., Advanced Separations Technologies, Inc.), 80:20 hexanes/EtOH, 1.0 mL/min, 40 °C; 9.64 min for (+)-**3**, 11.3 min for (−)-**3**) showed 94% ee.

4.2.5. 1-(Chloromethyl)-2-isocyanato-3-methylbenzene (11). *Step A*. To 1.1 L of ethyl acetate, cooled in an ice-water bath under nitrogen atmosphere was added condensed phosgene (693 g, 7 mol). A solution of 2,6-dimethylaniline (**10**) (424.5 g, 3.5 mol) in 250 mL of ethyl acetate was added dropwise. A slight exotherm occurred and a precipitate formed during the addition. After addition was complete, the cooling bath was removed and the slurry heated to reflux, monitoring the reaction by IR. Heating was continued until a clear solution resulted. After 2 h, IR analysis showed a strong cyano band at 2270 cm^{-1}. The ethyl acetate was then removed by distillation at atmospheric pressure and the product was distilled (7 mm Hg, 80 °C) to yield 2,6-dimethyl phenylisocyanate as clear colorless oil, (472.9 g, 92% yield); ν_{max}(Nujol) 2270 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.9 (3H, m, Ar*H*), 2.3 (6H s, ArCH_3).

Step B. The isocyanate from Step A (424.4 g, 2.89 mol) and VAZO® 88 (1,1′-azobis(cyclohexanecarbonitrile) (4.0 g) were heated to 80 °C and chlorine (102.6 g, 1.45 mol), condensed with a dry ice condenser, was added over 2 h. After the addition was complete the reaction was held at 80 °C for 15 min, then distilled under reduced pressure to remove unreacted starting material (310 g, 79% pure). The crude product was collected from the pot residue and saved for further handling. The recovered starting material was recycled with 3.5 g VAZO® 88 and 61.4 g chlorine as above. After distillation, 213.2 g of starting material was recovered and the crude product was combined with the crude product from the first cycle and distilled (7 mm Hg, 127135 °C) to obtain 223.2 g of colorless oil (90% pure). Both fractions from this distillation were recombined and redistilled through a Vigreaux column (7 mm Hg, 130135 °C) to obtain the title compound **11** (237.1 g, 93% pure) as clear colorless oil, δ_H (300 MHz, $CDCl_3$) 7.0–7.25 (3H, m, Ar*H*), 4.6 (2H, s, ArCH_2Cl), 2.3 (3H, s, ArCH_3).

4.2.6. 5-Chloro-4-[2-(chloromethyl)-6-methylphenyl]-2,4-dihydro-2-methyl-3*H*-1,2,4-triazol-3-one (13). The distilled material **11** (237.6 g, 1.3 mol) was dissolved in 3 L of ethyl acetate. The solution was cooled to 10–15 °C and 1,1-dimethylhydrazine was added dropwise, resulting in a white suspension of crude **12**. The addition funnel was rinsed into the reaction vessel with 250 mL of ethyl acetate, the cooling bath was removed and the slurry held at room temperature until used in a second operation. To 1 L of ethyl acetate in a separate vessel was added 322 g (3.25 mol) of condensed phosgene. This phosgene solution was heated to reflux and the slurry described above was added via a Masterflex peristaltic pump over 1.5 h. After about 2/3 of the slurry was added, the remaining slurry was diluted with 1 L of ethyl acetate to facilitate the transfer. After all the slurry was added, the slurry vessel was rinsed into the reactor with 1 L of ethyl acetate. The reaction mixture was heated until a clear solution resulted (about 2 h). The reaction mixture was transferred into distillation vessel, followed by a rinse with 1 L of ethyl acetate. Atmospheric distillation removed about 5 L of ethyl acetate and the remaining solution was allowed to cool to room temperature for 16 h. The solution was diluted with 2 L of hexane and the resulting solid collected by filtration and washed with warm water (3×) then dried under nitrogen on the filter for 16 h to provide 220.9 g (66% yield from **11**) of the title

compound **13** as fluffy white solids; δ_H (300 MHz, $CDCl_3$) 7.4 (3H, m, Ar*H*), 4.45(2H, AB quartet), 3.5 (3H, s, NCH_3), 2.17 (3H, s, ArCH_3).

4.2.7. 2,9-Dimethyl-5*H*-[1,2,4]triazolo[4,3-*a*][3,1]benzothiazin-1(2*H*)-one (14). To a solution of **13** (2.18 g, 8 mmol), prepared similarly as above, in 20 mL of tetrahydrofuran and 5 mL of water was added sodium sulfide nonahydrate (1.92 g) and tetrabutylammonium bromide (9 g) and the resulting mixture was heated to reflux for 2 h. The mixture was cooled and diluted with 50 mL of water and 50 mL of ethyl acetate. The organic phase was separated, dried ($MgSO_4$), filtered and concentrated to give a dark semisolid. The crude material was triturated in ether/hexane to yield 1.1 g (59% yield) of **14** as a tan solid, mp 153–155 °C; δ_H (300 MHz, acetone-d_6) 7.3 (3H, m, Ar*H*), 4.13 (2H, br s, ArCH_2S), 3.43 (3H, s, NCH_3), 2.42 (3H, s, ArCH_3).

4.2.8. 2,9-Dimethyl-5*H*-[1,2,4]triazolo[4,3-*a*][3,1]benzothiazin-1(2*H*)-one (14). To a solution of **13** (832 g, 3.08 mol), prepared similarly as above, in 4 L of ethanol was added thiourea (281 g, 3.7 mol) and sodium bromide (9 g, 87 mmol) and the resulting mixture was heated to reflux for 16 h. To the refluxing mixture was added 50% sodium hydroxide (735 g, 9 mol) dropwise over 45 min, then the mixture was heated at reflux for an additional 1 h. The reaction mixture was cooled to room temperature then added to 4 L of ice/water and the mixture was stirred for 15 min. The resulting solids were collected by filtration and rinsed with water, then dried under vacuum in an inert atmosphere to yield the title compound (620 g, 83% yield) as a pale yellow solid, mp 155–157 °C; δ_H (300 MHz, $CDCl_3$) 7.3 (1H, d, J=7 Hz, Ar*H*), 7.2 (1H, t, J=7 Hz, Ar*H*), 7.13 (1H, d, J=7 Hz, Ar*H*), 3.9 (2H, br s, ArCH_2S), 3.52 (3H, s, NCH_3), 2.43 (3H, s, ArCH_3).

4.2.9. 2,9-Dimethyl-5*H*-[1,2,4]triazolo[4,3-*a*][3,1]benzothiazin-1(2*H*)-one 4,4-dioxide (15). To a suspension of **14** (400 g, 1.86 mol) in 1.6 L of acetic acid was added an aqueous solution of sodium tungstate (17.6 g, 60 mmol in 10 mL) and the mixture heated to 55 °C. Hydrogen peroxide (30%, 425 g) was added dropwise to the mixture over a 1-h period while maintaining a temperature of about 70 °C. Initial oxidation to the sulfoxide was rapid. The clear solution resulting after the addition of hydrogen peroxide was maintained at 7580 °C for 2.5 h. As the reaction progressed, the title compound precipitated as a white solid. The reaction mixture was cooled to 40 °C and was diluted with ice/water. The solids were removed by filtration, rinsed with water and dried under vacuum in an inert atmosphere to yield 443 g (83% yield) of the title compound **15** as a white solid, mp >240 °C; δ_H (300 MHz, $CDCl_3$) 7.41 (1H, d, J=7 Hz, Ar*H*), 7.32 (1H, t, J=7 Hz, Ar*H*), 7.2 (1H, d, J=7 Hz, Ar*H*), 4.2 (2H, br s, ArCH_2SO_2), 3.68 (3H, s, NCH_3), 2.5 (3H, s, ArCH_3).

4.2.10. 4-[2-[(Bromosulfonyl)methyl]-6-methylphenyl]-2,4-dihydro-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one (17). To a suspension of **15** (800 g, 3.0 mol), prepared similarly as above, in 2.4 L of methanol was added sodium methoxide (25% in methanol, 829 mL) dropwise over 25 min, resulting in an exotherm to 34 °C. The mixture was heated to 60 °C for 1 h, giving an orange solution. The majority of the methanol was removed by rotary evaporation to yield an orange semisolid (crude **16**), which was dissolved in1.7 L of water and brought to pH=5 with 48% HBr (approximately 100 mL). The aqueous solution was diluted with 1.7 L of dichloromethane and cooled in an ice/water bath. Bromine (150 mL was added dropwise over 45 min to provide a pale orange mixture, which was stirred for 45 min. The phases were separated and the organic phase was washed with water, dried ($MgSO_4$), filtered and concentrated. The residue was triturated in petroleum ether and the resulting solid collected by filtration to give 946 g (84% yield) of the title compound **17** as an off-white solid, mp 119–122 °C; δ_H (300 MHz, $CDCl_3$) 7.4–7.5 (3H, m, Ar*H*), 5.20(1H, J=14 Hz, 1/2AB quartet, C$H_aH_bSO_2$) 4.90(1H, J=14 Hz, 1/2AB quartet, $CH_aH_bSO_2$), 3.93 (3H, s, OCH_3), 3.49 (3H, s, NCH_3), 2.20 (3H, s, ArCH_3).

4.2.11. 4-[2-(Bromomethyl)-6-methylphenyl]-2,4-dihydro-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one (18). To a suspension of **17** (946 g, 2.52 mol) in 2.2 L of toluene was added tetrabutylammonium bromide (80 g). The mixture was heated to 60 °C for 16 h, resulting in an amber solution. The reaction mixture was cooled and added to 4 L of ice/water and the phases separated. The organic phase was washed with water, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by applying to 700 g of silica gel and eluting first with hexanes and then with 2:1 hexanes/ethyl acetate to recover the product. Removal of solvents gave 616 g (78% yield) of the title compound **18** as an off-white solid, mp 115–116 °C; δ_H (300 MHz, $CDCl_3$) 7.22–7.35 (3H, m, Ar*H*), 4.45(1H, J=10.7 Hz, 1/2AB quartet, CH_aH_bBr), 4.30(1H, J=10.7 Hz, 1/2AB quartet, CH_aH_bBr), 3.93 (3H, s, OCH_3), 3.49 (3H, s, NCH_3), 2.16 (3H, s, ArCH_3).

4.2.12. 2,4-Dihydro-4-[2-(hydroxymethyl)-6-methylphenyl]-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one (4). To a solution of **18**, prepared as above, (50 g, 160 mmol) in 500 mL of *p*-dioxane and 500 mL of water was added calcium carbonate (80.2 g), and the mixture was heated to reflux for 2 h. The dioxane was removed by rotary evaporation and the residue was diluted with 400 mL of 1 N hydrochloric acid. The pH was adjusted to **3** by the addition of concentrated hydrochloric acid and ice was added to cool. The aqueous mixture was extracted with dichloromethane (3×200 mL). The combined organic phases were washed with 500 mL of aqueous sodium bicarbonate, dried ($MgSO_4$), filtered and concentrated to yield a pale yellow solid. The crude product was triturated in hexanes and filtered to yield 34.1 g (86% yield) of the title compound **4** as a white solid, mp 132–134 °C; δ_H (300 MHz, $CDCl_3$) 7.35–7.43 (2H, m, Ar*H*), 7.3 (1H, m, Ar*H*), 4.48 (1H, 1/2ABX, J_{AB}=12.3 Hz, J_{AX}=2.5 Hz, CH_2OH), 4.40 (1H, 1/2ABX, J_{AB}=12.3 Hz, J_{AX}=9.0 Hz, CH_2OH), 3.94 (3H, s, OCH_3), 3.48 (3H, s, NCH_3), 3.27 (1H, dd, J=9.0, 2.5 Hz, CH_2OH), 2.15 (3H, s, ArCH_3).

4.2.13. [*aR*-[2-(*R* *)]]-4-[2-[[[[(7,7-Dimethyl-6-oxobicyclo-[2.2.1]heptan-1-yl)methyl]sulfonyl]oxy]methyl]-6-methylphenyl]-2,4-dihydro-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one (22a) and [*aS*-[2-(*R* *)]]-4-[2-[[[[(7,7-dimethyl-6-oxobicyclo[2.2.1]heptan-1-yl)methyl]sulfonyl]oxy]-methyl]-6-methylphenyl]-2,4-dihydro-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one (22b). To a solution of

62.0 g, (249 mmol) **4**, prepared as above, in 1000 mL of tetrahydrofuran was added 87.4 g of (1*S*)-(+)-camphorsulfonyl chloride and then 52 mL of triethylamine dropwise with ice-bath cooling. The resulting mixture was stirred at room temperature for 18 h. The solvents were removed by rotary evaporation and the residue was taken up in 500 mL of dichloromethane and washed with 500 mL of 1 N HCl, then 500 mL of water. The organic phase was dried ($MgSO_4$), filtered and concentrated to give 120.4 g of orange oil. Analysis by ^1H NMR showed a 1:1 ratio of diastereomers. The crude product was taken up in 500 mL of 1-chlorobutane and refrigerated for 72 h. The precipitated crystals were collected by filtration and dried under vacuum to yield 59.3 g of the title compound **22a** white crystals, mp 121–127 °C. NMR analysis showed a mixture of **22a** and **22b** in about 9:1 ratio with approximately 0.5 mol equiv. of 1-chlorobutane incorporated into the crystals (47% yield, after correction for the 1-chlorobutane present); δ_H (300 MHz, $CDCl_3$) 7.4 (3H, m, Ar*H*), 5.24 (1H, 1/2AB, J_{AB}=11.5 Hz, CH_2O), 5.18 (1H, 1/2AB, J_{AB}=11.5 Hz, CH_2O), 3.97 (3H, s, OCH_3), 3.47 (3H, s, NCH_3), 3.46 (1H, d, *J*=16 Hz, $SO_2CH_aC H_b$), 2.85 (1H, d, *J*=16 Hz, SO_2CH_a-CH_b), 2.4 (2H, m), 2.18 (3H, s, ArCH_3), 2.1 (2H, m), 1.93 (1H, d, *J*=18 Hz, C*H*), 1.6 (1H, m), 1.4 (1H, m), 1.07 (3H, s, CCH_3CH$'_3$), 0.81 (3H, s, CCH$_3$CH'_3). (Signals from **22b** and 1-chlorobutane are not reported.)

The mother liquors from the crystallization were concentrated to yield 63 g of orange oil. The oil was triturated in ether/hexanes to obtain 49.3 g (43% yield) of the title compound **22b** as a white solid, mp 104–110 °C; $[\alpha]_D^{20}$=+64.0 (*c* 5.62, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 7.4 (3H, m, Ar*H*), 5.26 (1H, 1/2AB, J_{AB}=11.8 Hz, CH_2O), 5.13 (1H, 1/2AB, J_{AB}=11.8 Hz, CH_2O), 3.95 (3H, s, OCH_3), 3.52 (1H, d, *J*=15 Hz, $SO_2CH_aC H_b$), 3.47 (3H, s, NCH_3), 2.94 (1H, d, *J*=15 Hz, $SO_2CH_aC H_b$), 2.4 (2H, m), 2.18 (3H, s, ArCH_3), 2.1 (2H, m), 1.93 (1H, d, *J*=19 Hz, C*H*), 1.6 (1H, m), 1.4 (1H, m), 1.08 (3H, s, CCH_3CH$'_3$), 0.86 (3H, s, CCH$_3$CH'_3). Analysis by ^1H NMR showed the oil to be >95% pure for a single diastereomer (**22b**).

4.2.14. (*aS*)-2,4-Dihydro-4-[2-(hydroxymethyl)-6-methylphenyl]-5-methoxy-2-methyl-3*H*-1,2,4-triazol-3-one ((+)-4). To a solution of **22b** (930 mg, 2 mmol), in 8 mL of 1,4dioxane and 8 mL of water was added 1.0 g of calcium carbonate. The mixture was heated for 5 h at reflux. The mixture was diluted with ethyl acetate and neutralized with 1 N hydrochloric acid. The phases were separated and the aqueous phase extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered and concentrated to provide colorless oil. The crude product was purified by flash chromatography (1:2 hexanes/ethyl acetate) to provide colorless oil which solidified on standing. Trituration in hexanes gave 230 mg (46% yield) of the title compound (+)-**4**as a white crystalline solid, mp 119–121 °C; $[\alpha]_D^{20}$=+100.3 (*c* 4.68, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 7.4 (2H, m, Ar*H*), 7.3 (1H, m, Ar*H*), 4.48 (1H, 1/2ABX, J_{AB}=12.3 Hz, J_{AX}=3.6 Hz, CH_2OH), 4.40 (1H, 1/2ABX, J_{AB}=12.3 Hz, J_{AX}=9.2 Hz, CH_2OH), 3.94 (3H, s, OCH_3), 3.48 (3H, s, NCH_3), 3.25 (1H, dd, *J*=9.2, 3.6 Hz, CH_2OH), 2.16 (3H, s, ArCH_3). HPLC analysis as described above using a Chiralpak AD column (25 cm×0.46 cm (inner diameter)) showed the material to be >98% ee [90% hexanes/10% ethanol, flow rate 0.8 mL/min, 40 °C, elution time 10.4 min]. (Under the same conditions the other enantiomer (−)-**4** eluted at 11.4 min).

4.2.15. 1-[3-(Trifluoromethyl)phenyl]ethanone oxime (24).[20] To 320 mL (1.08 mol) of 4 N sulfuric acid in a three-neck indented, Morton-style flask, equipped with a sidearm for thermometer, was added 40 mL (320 mmol) of 3-(trifluoromethyl)aniline. The resulting solution was cooled to about −5 °C using an acetone/ice bath to provide a slurry. To the slurry was added a solution of 28.0 g (406 mmol) of sodium nitrite in 80 mL of water. The rate of addition was carefully adjusted so the internal reaction temperature was maintained between −5 and 0 °C. The mixture was stirred at that temperature for 30 min to provide the diazonium salt derived from 3-(trifluoromethyl)aniline (which was not characterized) in a thin slurry. The slurry thickened when a solution of 15 g (183 mmol) of sodium acetate in 100 mL of water was added. Meanwhile, in another flask, 80 mL (1350 mmol) of acetaldoxime, 6.0 g (32 mmol) of copper (II) acetate, 2.0 g (16 mmol) of sodium sulfite, and 240 g (2.9 mol) of sodium acetate were combined and cooled to about 10 °C. To this solution was added via a cannula the mixture containing the diazonium salt. Immediate gas (N_2) evolution was observed, and a two-phase mixture (dark green oil and aqueous) was obtained. The mixture was stirred for 30 min at room temperature. The oil on the bottom was separated from the aqueous phase and transferred to another flask. Hydroxylamine (11.0 g, 320 mmol) and potassium carbonate (22.0 g, 320 mmol) were added together with 200 mL of water. The resulting mixture was subjected to a steam distillation. Over a period of 2 h, a total of 1700 mL of distillate was obtained. The product first existed as slightly yellow oil depositing on the bottom of the collecting flask. Upon chilling, product solidified. A total of 35.9 g (55% yield) of the title compound **24**, with an assay purity of 89.7%, was obtained as a white solid after filtration, mp 56–62 °C; δ_H (300 MHz, $CDCl_3$) 8.36 (1H, br s, =NOH), 7.89 (1H, d, *J*=0.5 Hz, Ar*H*), 7.81 (1H, d, *J*=8.0 Hz, Ar*H*), 7.63 (1H, d, *J*=8.0 Hz, Ar*H*), 7.53–7.49 (1H, m, ArH), 2.32 (3H, s, CH_3).

4.2.16. (*aR*)-2,4-Dihydro-5-methoxy-2-methyl-4-[2-methyl-6-[[[[1-[3-(trifluoromethyl)phenyl]ethylidene]-amino]oxy]methyl]phenyl]-3*H*-1,2,4-triazol-3-one ((*aR*)-2b). To a solution of 160 mg (0.79 mmol) of oxime **24**, prepared as above, in 10 mL of tetrahydrofuran was added 40 mg of sodium hydride (50% oil dispersion). Gas evolution was observed and the mixture was stirred at room temperature for 20 min. A solution of 366 mg (0.69 mmol) of **22a** (approximately 95% pure) in 10 mL of tetrahydrofuran was added and the mixture stirred at room temperature for 16 h. The mixture was diluted with water and extracted with ethyl acetate (2×25 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated to provide amber oil. The crude product was purified by flash chromatography (1:1 hexanes/ethyl acetate) to give 240 mg (70% yield) of the title compound (*aR*)-**2b** as a colorless oil; $[\alpha]_D^{20}$=−57.1 (*c* 4.98, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 7.86 (1H, s, Ar*H*), 7.8 (1H, d, *J*=8 Hz, Ar*H*), 7.6 (1H, d, *J*=8 Hz, Ar*H*), 7.45 (1H, t, *J*=8 Hz, Ar*H*), 7.38 (2H, m), 7.3(1H, m), 5.21 (1H, 1/2AB, J_{AB}=12.8 Hz, CH_2O), 5.14 (1H, 1/2AB, J_{AB}=12.8 Hz, CH_2O),

3.89 (3H, s, OCH_3), 3.41 (3H, s, NCH_3), 2.22 (3H, s, ON=CCH_3), 2.18 (3H, s, ArCH_3). HPLC analysis using a Chiralpak AD column (25 cm×0.46 cm (inner diameter)) showed the material to be 92% ee [4:1 hexanes/2-propanol, flow rate 0.8 mL/min, elution time 10.3 min].

4.2.17. (*aS*)-2,4-Dihydro-5-methoxy-2-methyl-4-[2-methyl-6-[[[[1-[3-(trifluoromethyl)phenyl]ethylidene]-amino]oxy]methyl]phenyl]-3*H*-1,2,4-triazol-3-one ((*aS*)-2b). By a procedure similar to that described for the preparation of (*aR*)-**2b**, 310 mg (0.67 mmol) of **22b** (approximately 90% pure) was converted to 190 mg (65% yield) of the title compound as colorless oil; $[\alpha]_D^{20}$=+53.0 (*c* 5.0, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$) 7.86 (1H, s), 7.79 (1H, d, *J*=8 Hz, Ar*H*), 7.59 (1H, d, *J*=8 Hz, Ar*H*), 7.45 (1H, t, *J*=8 Hz, Ar*H*), 7.38 (2H, m), 7.3(1H, m), 5.21 (1H, 1/2AB, J_{AB}=12.8 Hz, CH_2O), 5.14 (1H, 1/2AB, J_{AB}=12.8 Hz, CH_2O), 3.89 (3H, s, OCH_3), 3.41 (3H, s, NCH_3), 2.22 (3H, s, ON=CCH_3), 2.18 (3H, s, ArCH_3). HPLC analysis using a Chiralpak AD column (25 cm×0.46 cm (inner diameter)) showed the material to be 83% ee [4:1 hexanes/2-propanol, flow rate 0.8 mL/min, elution time 8.2 min].

Acknowledgements

The authors wish to thank all those who made significant contributions to this project, especially our co-workers involved in the synthesis, characterization, biological testing and mode of action studies of these compounds.

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Tetrahedron 60 (2004) 4377–4386
Tetrahedron

Synthesis of chiral binaphthalenes using the asymmetric Suzuki reaction

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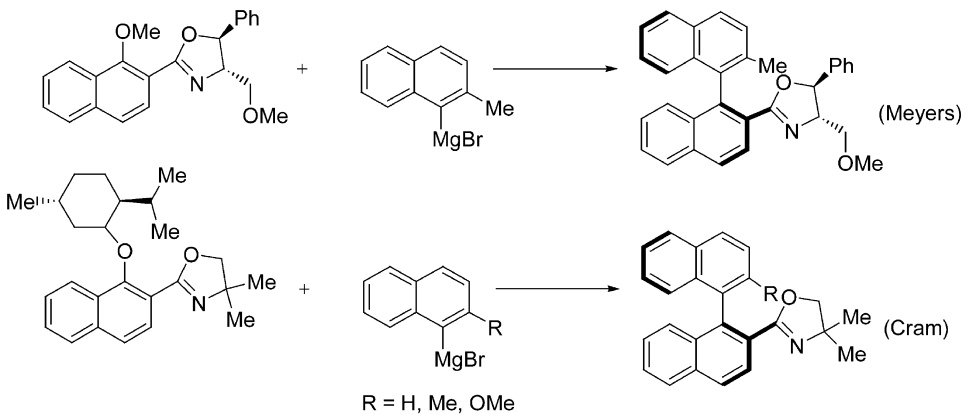
Received 10 October 2003; revised 25 November 2003; accepted 8 December 2003

Abstract—The synthesis of atropisomeric 1,1′-binaphthalenes can be achieved using an asymmetric Suzuki cross-coupling reaction. The Suzuki reaction leading to such hindered compounds is challenging and competing hydrolytic deboronation frequently dominates unless carefully chosen conditions are employed. The simple, standard mechanism is inadequate when describing the Suzuki coupling of hindered partners. Evidence suggests that the key step leading to asymmetry is transmetallation (delivery of the organometallic by the asymmetric ligand) and the reactions operate under kinetic control. Reductive elimination (itself likely to be triggered by oxidative addition of another molecule of halide) is fast compared with equilibration (epimerisation and/or *cis–trans* isomerisation).

1. Introduction

Chiral binaphthalenes are an important and extensively studied class of atropisomeric compounds. The parent compound, 1,1′-binaphthalene, has received attention because early observations indicated that the racemic material spontaneously resolves into higher melting crystals containing single enantiomer molecules.[1] The resolved material racemises with a half life of 14.5 min at 50 °C[2] in solution making direct substitution strategies inappropriate as a means for synthesising functionalised, optically active derivatives. Substituted, chiral binaphthalenes are among the most widely used and useful chiral ligands and auxiliaries employed in asymmetric synthesis[3] and a number of different strategies have been employed for their preparation.[4] By far the most widely used approach involves preparation of a racemic intermediate or target compound followed by resolution of the mixture (typically via co-crystallisation or derivatisation–crystallisation). To this end, convenient and reproducible procedures have been developed for simple derivatives (such as BINOL and BINAP).

Asymmetric syntheses of substituted chiral binaphthalenes are desirable in many cases and some elegant strategies have been demonstrated.[5] For example, Meyers has employed oxazoline chiral auxiliaries in S_NAr reactions leading to binaphthalenes (Scheme 1) and high diastereoselectivity



Scheme 1. Asymmetric S_NAr approaches to chiral binaphthalenes.

Keywords: Asymmetric Suzuki coupling; Palladium; Cross-coupling; Chiral binaphthalenes; Atropisomers.
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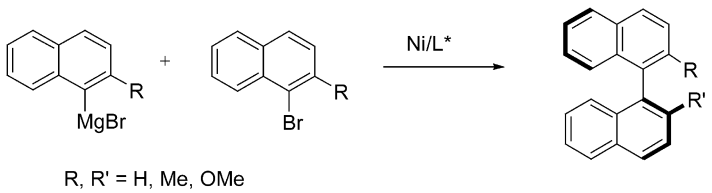
doi:10.1016/j.tet.2003.11.095



Scheme 2. Asymmetric Kumada coupling.

was achieved.[5b,c] In a somewhat complementary approach, Cram employed a chiral leaving group and also achieved high enantioselectivity.[5d,e] Although elegant, these procedures also suffer from the lack of generality and use of a stoichiometric chiral auxiliary.

An ideal procedure to binaphthalenes can be envisaged involving an asymmetric, catalytic cross-coupling reaction. Kumada reported the first such asymmetric cross-coupling reaction between 1-bromo-2-methylnaphthalene and its corresponding Grignard reagent using a nickel catalyst (Scheme 2) and modest selectivities were obtained (12.5%) using NAPHOS **2** (Fig. 1).[6] The procedure has been significantly improved by Hayashi who screened a series of chiral ligands and conditions.[7] Ees of up to 95% were achieved and the best ligand was found to be PFOMe **5**

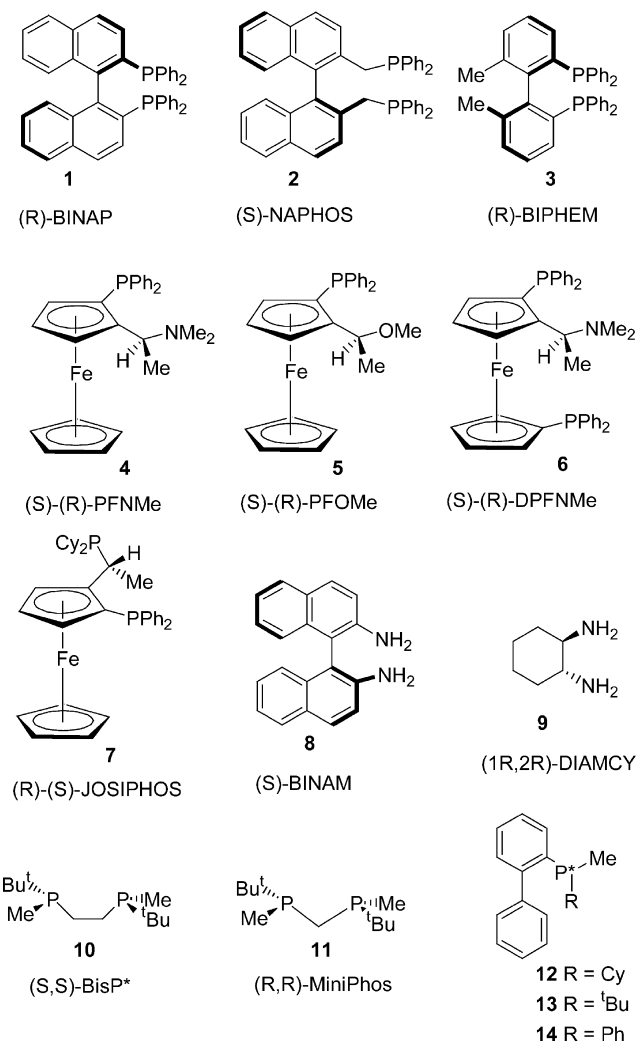


Figure 1. Chiral ligands **1**–**14**.

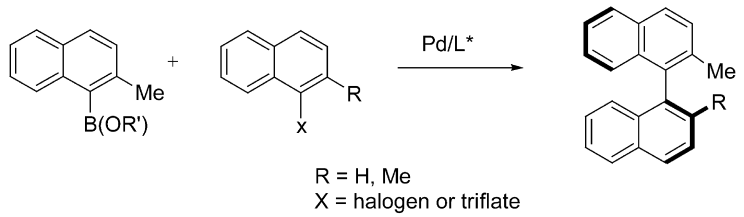
(Fig. 1). Although no definitive mechanism has been put forward, it was postulated that the methoxy group on the ligand serves to coordinate to the magnesium ion of the incoming Grignard reagent during transmetallation. The nickel catalyst in these reactions has, in some cases, been replaced by palladium. Mixed results have been obtained and the reactions give only modest ees.[8] Other approaches have involved the use of asymmetric desymmetrisation procedures.[9]

2. Results and discussion

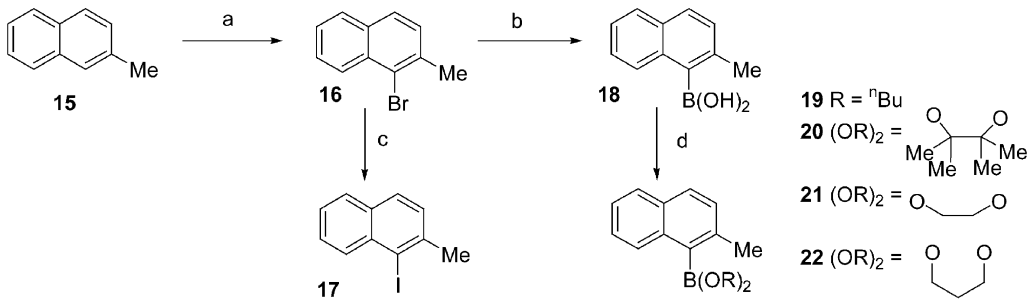
Our group was the first to describe the intermolecular asymmetric Suzuki cross-coupling reaction[10–12] and subsequent examples have been reported by others.[13] In this paper, we report details of our investigation of the synthesis of chiral biaryls (binaphthalenes) via the asymmetric Suzuki reaction. The Suzuki reaction[14] has many inherent advantages over related Ni and Pd-catalysed couplings and has become the method of choice for the synthesis of many biaryls and related products. Its advantages derive from the use of boronic acid derivatives as coupling partners (isolable compounds which are easily stored and handled). Furthermore, the Suzuki reaction (boronic acid derivatives) is compatible with a wide variety of functional groups (compared to Grignard reagents which cannot be used if one of the reactants bears an electrophile) and produces non-toxic by-products.

Simple binaphthalenes were chosen as targets for investigation of the asymmetric Suzuki reaction, not least because simple (lightly functionalised) targets represent significant challenges in asymmetric synthesis. The choice also permits direct comparison with previously reported procedures employing Grignard reagents as coupling partners and straightforward evaluation of optical purities by optical rotation (chiral HPLC is unsuitable for such lightly functionalised compounds). The general reaction is depicted in Scheme 3.

Pure 1-bromo-2-methylnaphthalene is not commercially available and its synthesis is complicated by production of an unwanted regioisomer (6-bromo) which cannot be easily removed.[15] This proved to be the case in our hands also and we were unable to isolate the pure compound. Alternative conditions were investigated and material of sufficient purity was obtained from direct bromination of 2-methylnaphthalene with NBS in acetonitrile.[16] Direct electrophilic iodination (iodine monochloride) of 2-methylnaphthalene failed to give the required iodide and the intermediate was most conveniently synthesised via metal–halogen exchange followed by iodine quench (Scheme 4).[17]



Scheme 3. General scheme for the asymmetric Suzuki reaction towards lightly functionalised binaphthalenes.

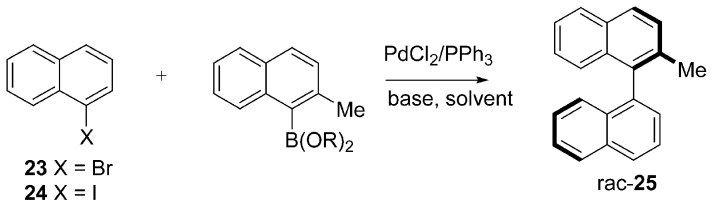


Scheme 4. Synthesis of coupling partners. Reagents: (a) NBS, acetonitrile (95%). (b) (i) Mg, THF; (ii) $BOMe_3$ (60%); (iii) H_3O^+. (c) (i) BuLi, THF, −78 °C; (ii) I_2, −78 °C–rt (74%). (d) see text.

Naphthyl boronic acids were conveniently prepared from the corresponding bromides via formation of the Grignard reagent and quenching with trimethyl borate at −78 °C. Subsequent hydrolysis and recrystallisation yielded the pure boronic acids. A series of boronate esters were prepared by treatment of the boronic acids with alcohol/diol and azeotropic removal of water (Scheme 4). It is interesting to note that attempts to prepare the boronate ester from 2-methylnaphth-1-yl boronic acid and propane diol under these conditions failed due to competing deboronation (see later).

2.1. Racemic coupling

The Suzuki coupling of sterically hindered partners remains a challenge.[14] Significant progress has been made over recent years but no general ligand/catalyst system exists.[18] Our investigation therefore started with assessment of the factors controlling successful coupling to give binaphthalenes (recognising that these 'standard' conditions would be used as the basis for subsequent modification for invention of an asymmetric version). Based on previous work on cross-coupling reactions[6c,7a,19] we chose the boronic acid



Scheme 5. Racemic Suzuki coupling to give **25**.

Table 1. Racemic Suzuki coupling to give **25**

Entry	Halide	Boron species[a]	Solvent (temperature)	Base	Time (h)	Yield (%) (conversion)
1	**23**	**18**	DME/H_2O (reflux)	$Ba(OH)_2$	17	44
2	**23**	**18**	DME (reflux)	CsF	17	72
3	**24**	**18**	Tol/EtOH/H_2O (reflux)	$Ba(OH)_2$	17	(>98)
4	**24**	**18**	DME/H_2O (reflux)	$Ba(OH)_2$	17	61
5	**24**	**18**	DME/H_2O (40 °C, ultrasound)	$Ba(OH)_2$	7	(>98)
6	**24**	**18**	DME/H_2O (50 °C)	$Ba(OH)_2$	5	(>98)
7	**24**	**18**	DME/H_2O (reflux)	$Ba(OH)_2$	5	(>98)
8	**24**	**18**	DME (reflux)	$Ba(OH)_2$	17	16
9	**24**	**18**	DME (reflux)	CsF	17	74
10	**24**	**18**	DME (reflux)	NaOH	17	36
11	**24**	**18**	Tol /crown ether (reflux)	KOH	17	19
12	**24**	**18**	Tol	K_2CO_3	17	3
13	**24**	**18**	DME/H_2O (reflux)	$Ba(OH)_2$	72	5[b]
14	**24**	**20**	DMF (reflux)	K_3PO_4	96	0
15	**24**	**20**	DME (reflux)	CsF	72	(>98)

[a] 1.1 equiv. of boron species except entries 5–7 where 2 equiv. used.
[b] Carried out with $PtCl_2$.

(derivative) as the most hindered partner for the synthesis of 2-methyl-1,1′-binaphthalene. Thus typical Suzuki coupling conditions were employed in the first instance and involved reaction of halonaphthalene with 2-methylnaphth-1-yl boronic acid or ester in the presence of 1.5–2.0 mol equiv. of base and 3 mol% $PdCl_2$/6 mol% PPh_3 in refluxing solvent. Total consumption of the boronic acid derivative was generally observed yielding a product mixture comprising target binaphthalene, halide starting material and 2-methylnaphthalene (from deboronation) (Scheme 5). Products were isolated and characterised but subsequent reaction analysis was performed by ^{1}H NMR spectroscopy of crude reaction mixtures to give an accurate assessment of product distribution. The results are summarised in Table 1. It is widely accepted that aryl iodides are superior to bromides in such coupling reactions and the same conclusion can be drawn in this case. Naphthyl iodide led to faster reaction and improved yields and was used in all subsequent experiments.

A series of experiments were then performed in both homogeneous and heterogeneous conditions to determine optimised conditions of solvent and base to minimise protonolysis of the boronic acid. Strong bases and homogeneous conditions have been reported to be effective in the coupling of sterically congested substrates and barium hydroxide is commonly employed.[20,21] We found the use of barium hydroxide in DME/water to be particularly effective in achieving the coupling but significant competing deboronation meant that 2 equiv. of boronic acid were required to achieve full conversion of the halide. Toluene/ethanol/water has been reported to be a good solvent mixture for such coupling reactions[22] and was found to give good conversions and reaction rates in our case also. The homogeneous reaction using CsF in DME gave reasonable conversions. Heterogeneous conditions employing the hindered boronic acid were, in contrast, far inferior. It is worth noting that use of platinum in place of palladium gave only a low conversion to biaryl.

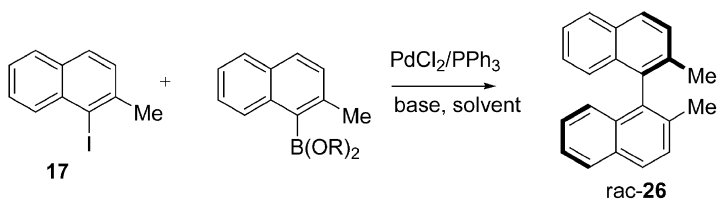
In many cases, the use of boronate esters (usually requiring anhydrous conditions) improves the Suzuki coupling of hindered substrates.[14] Pinacol boronate ester **20** coupled smoothly with iodonaphthalene to give a high conversion to the binaphthalene, albeit at a slower rate that the reaction employing the parent boronic acid.

Racemic Suzuki coupling toward 2,2′-dimethyl-1,1′-binaphthalene was performed in parallel to the above study (Scheme 6, Table 2). In this case, it was found that no coupled product was obtained when the parent boronic acid was employed (using the above optimised conditions) and complete deboronation was observed. Modest conversion (36%) of halide to binaphthalene was achieved when pinacol boronate ester **20** was employed (DME/CsF) but the reaction took 3 days to reach completion. The best results were obtained when the ethylene glycol ester was employed (69% after 6 days).

Like others, we found that efficient cross-coupling to give hindered biaryls was complicated by protonolysis (deboronation) which was frequently the dominating process. Deboronation is a slow process in the absence of palladium and is likely to occur via an Ar–Pd species.[23] In these reactions it can also be inferred that simple oxidative addition (of aryl halide to Pd(0)) is a relatively fast process independent of whether bromides or iodides are used.[23] The simple, standard mechanism for the Suzuki coupling is no longer adequate to describe such reactions and a more comprehensive mechanism is depicted in Figure 2. The key steps are transmetallation and reductive elimination. Fast reductive elimination (the process competing with hydrolysis/deboronation) is crucial to the success of the reaction and the observation that aryl iodides give faster, better reactions implies that reductive elimination is itself triggered by oxidative addition of another molecule of aryl halide.[23,24]

2.2. Asymmetric Suzuki coupling

Chiral ligands containing various features were employed in the investigation of the asymmetric Suzuki reaction and their structures are depicted in Figure 1. The general



Scheme 6. Racemic Suzuki coupling to give **26**.

Table 2. Racemic Suzuki coupling to give **26**

Entry	Halide	Boron species[a]	Solvent (reflux)	Base	Time (h)	Yield (%) (conversion)
1	**16**	**18**	DME/H_2O	Na_2CO_3	17	(Trace)
2	**16**	**18**	DME/H_2O	$Ba(OH)_2$	17	(Trace)
3	**17**	**18**	DME/H_2O	$Ba(OH)_2$	17	(Trace)
4	**17**	**18**	DME	CsF	17	(Trace)
5	**17**	**20**	DMF	K_3PO_4	96	(Trace)
6	**17**	**20**	DME	CsF	72	36
7	**17**	**19**	DME	CsF	17	0 (decomp)
8	**17**	**21**	DME	CsF	144	69

[a] 1.1 equiv. of boron species except entries 3, 4, 6–8 where 2 equiv. used.

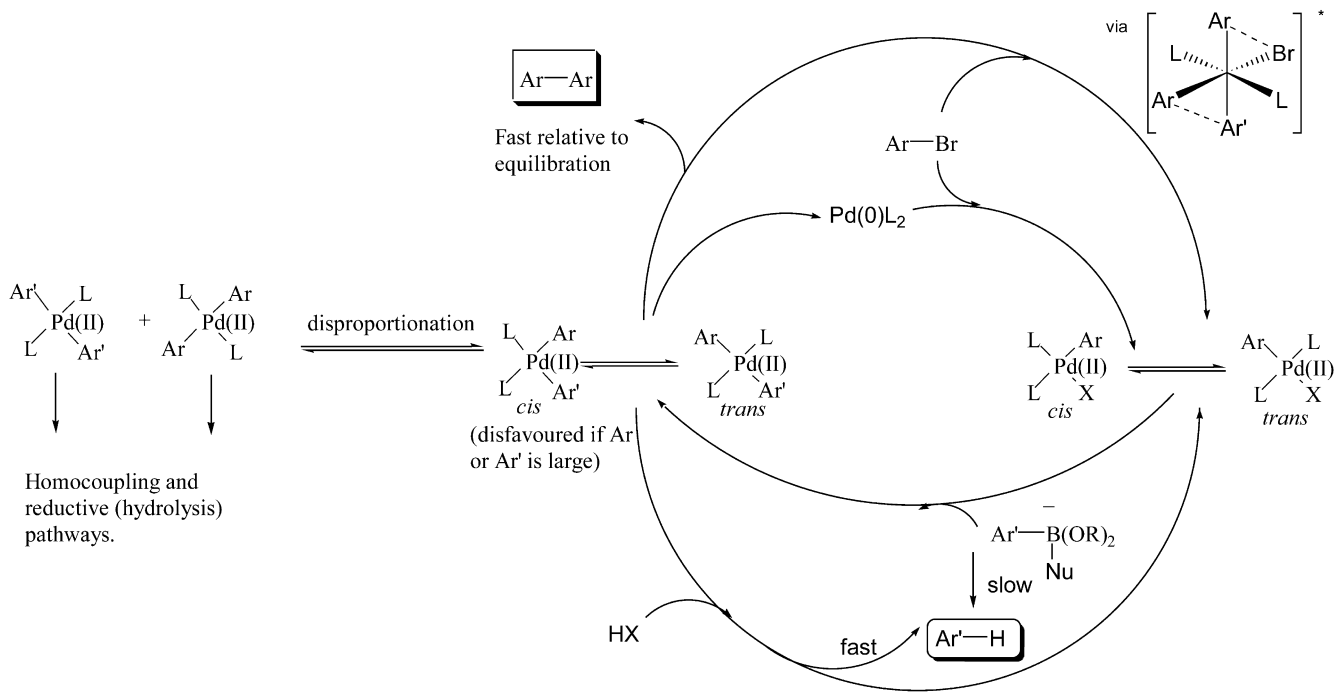
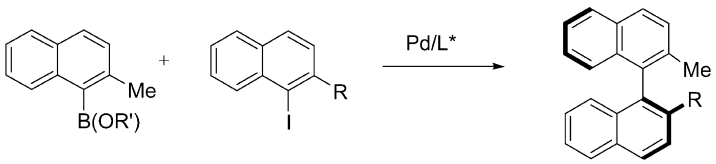


Figure 2. Mechanism for the Suzuki reaction of hindered coupling partners.

Table 3. Asymmetric Suzuki coupling to give **25** and **26**



Entry	Halide	Boron species[a]	L*[b]	Solvent (reflux)	Base	Product	Time (h)	Yield (%)	Opt. P'ty[c] (%)
1	**24**	**18**	**1**	DME/H_2O	$Ba(OH)_2$	(*S*)-(+)-**25**	17	55	25
2	**24**	**18**	**1**	DME	CsF	(*S*)-(+)-**25**	17	43	21
3	**24**	**18**	**1**	Tol/EtOH/H_2O	$Ba(OH)_2$	(*S*)-(+)-**25**	17	47	8
4	**24**	**18**	**4**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	44	63
5	**24**	**18**	**4**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	5	44	61
6	**24**	**18**	**4**	DME	CsF	(*R*)-(−)-**25**	17	44	55
7	**24**	**18**	**4**	Tol/EtOH/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	45	52
8	**24**	**18**	**5**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	2	82	2
9	**24**	**18**	**5**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	74	14
10	**24**	**18**	**6**	DME/H_2O	$Ba(OH)_2$	(*S*)-(+)-**25**	17	73	4
11	**24**	**18**	**7**	DME/H_2O	$Ba(OH)_2$	**25**	17	6	0
12	**24**	**18**	**10**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	7	4
13	**24**	**18**	**11**[d]	DME/H_2O	$Ba(OH)_2$	(*S*)-(+)-**25**	17	10	11
14	**24**	**18**	**12**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	54	4
15	**24**	**18**	**13**[c]	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	40	5
16	**24**	**18**	**13**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	83	10
17	**24**	**18**	**14**	DME/H_2O	$Ba(OH)_2$	(*R*)-(−)-**25**	17	73	24
18	**24**	**18**	**8**	DME/H_2O	$Ba(OH)_2$	**25**	17	9	0
19	**24**	**18**	**9**	DME/H_2O	$Ba(OH)_2$	—	17	0	—
20	**17**	**21**	**6**	DME	CsF	(*S*)-(+)-**26**	9 days	13	17
21	**17**	**21**	**4**	DME	CsF	(*R*)-(−)-**26**	6 days	60	85
22	**17**	**21**	**1**[e]	DME	CsF	(*S*)-(+)-**26**	5 days	21	14
23	**17**	**20**	**1**[e]	DME	CsF	(*R*)-(−)-**26**	4 days	17	10

[a] 1.1 equiv. of boron species except entries 7–9 where 2 equiv. used.
[b] Catalyst generated in situ using $PdCl_2$ and L* unless stated otherwise.
[c] Error estimated as $\leq \pm 3\%$.[25]
[d] Catalyst generated in situ using ($PdClC_3H_5$) and L*.
[e] Preformed complex.

conditions used for the asymmetric coupling were derived from the previous investigation of the corresponding racemic synthesis. The procedure involved treating 1-iodonaphthalene with 1.1–2.5 equiv. of 2-methylnaphth-1-yl boronic acid or boronate ester in refluxing solvent using 1.5–2 equiv. of base (homogeneous conditions) and 3 mol% $PdCl_2$/3 or 6 mol% chiral ligand. Binaphthalenes were isolated by column chromatography using carefully distilled hexane. Moreover, recrystallisation was not performed in order to avoid fractionation leading to erroneous results. Optical purities were determined by optical rotation (suitable conditions for chiral HPLC were not found).

In the first instance, the asymmetric Suzuki reaction leading to 2-methyl-1,1′-biphaphthalene was investigated and the results are summarised in Table 3. As expected, diamine ligands BINAM **8** and DIAMCY **9** (Fig. 1) gave only racemic product in poor yield. Modest selectivity (19–25% ee[25]) was observed when phosphine ligand BINAP **1** was employed. The selectivity drops when the solvent was changed from DME to toluene/ethanol/water.

Ligand PFOMe **5** proved to be excellent for the comparable asymmetric Kumada coupling employing the Grignard reagent in place of boronic acid.[7a] Poor selectivity was observed when this ligand was employed in the asymmetric Suzuki reaction (optical purity 2–14%). This observation is consistent with the suggestion that the methoxy group serves to deliver (in an asymmetric fashion) the organometallic during transmetallation.[7a] Such interactions are expected to be much stronger for the Grignard reagent. Ligand PFNMe **4** (in which the methoxy group of PFOMe **5** is replaced by NMe_2) was therefore used and found to improve selectivity in the reaction dramatically (giving optical purities up to 63%). It is interesting to note that this ligand is ineffective in the related Kumada coupling. Selectivity was significantly reduced when bisphosphine ligands JOSIPHOS **7** and DPFNMe **6** were used and this observation is consistent with the results obtained with Grignard reagents.

Selected syntheses of 2,2′-dimethyl-1,1′-binaphthalene were also investigated (using boronate esters). Once again, modest selectivities were observed when BINAP **1** and DPFNMe ligands were used. Ligand PFNMe again proved the best of all studied (in terms of both yield and selectivity) and gave the highest observed optical purity of 85%.

A selection of P-chiral ligands were also screened. BisP* **10**[26] and MiniPhos **11**[27] proved ineffective in the asymmetric Suzuki reaction giving both poor yields and optical purities. As expected the use of biphenylphosphine ligands **12**–**14**[28] led to good conversions but optical purities were again low. This observation reinforces the conclusion[10,13a] that P–N ligands provide the best combination for good yields and selectivity and it is reasonable to speculate that the amine nitrogen serves to deliver the boronate and the key step of the mechanism is transmetallation.

A closer inspection of our results hint at some surprising subtleties. Most striking is the observation that opposite enantiomers can result from (otherwise) identical reactions employing different boronates (the pinocol boronate ester **20** gives the opposite enantiomer to the ethylene glycol boronate **21**). The conclusion must be that the reaction is operating under kinetic control (thermodynamic control would lead to the same optical purity and stereochemistry independent of boronate) and again this suggests that the important step controlling asymmetry is the transmetallation. The Suzuki coupling leading to methoxybinaphthalenes has also been shown to give unexpected results and inversion of stereochemical outcome has been observed as a function of Pd/ligand ratio.[13b] The assumption is usually made that reductive elimination is slow (with respect to equilibration of the intermediate complex) when sterically hindered partners are used in the Suzuki coupling. However, it would appear that this is not the case and the intermediate complex undergoes reductive elimination faster than equilibration (epimerisation or via *cis*–*trans* isomerisation).

3. Conclusion

The asymmetric Suzuki coupling can be used to synthesise lightly functionalised binaphthalenes in reasonable yields and optical purities. As with many couplings involving sterically hindered partners, the reactions are complicated by competing protonolysis (deboronation). Indeed, in the most severe case (synthesis of 2,2′-dimethyl-1,1′-binaphthalene) successful coupling could only be achieved using homogeneous conditions and boronate esters. It is clear that the simple, standard mechanism is inadequate when describing the Suzuki coupling of hindered partners. There is strong evidence that the key step leading to asymmetry is transmetallation (delivery of the organometallic by the asymmetric ligand) and the reactions operate under kinetic control. Reductive elimination (itself likely to be triggered by oxidative addition of another molecule of halide) is fast compared with equilibration (epimerisation and/or *cis*–*trans* isomerisation).

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 270 MHz on a Jeol EX270 FT or at 300 MHz on a Varian 300 spectrometer in $CDCl_3$, unless otherwise stated. Signals are quoted in ppm as δ downfield from tetramethylsilane (δ 0.00) as internal standard. ^{13}C NMR spectra were recorded at 67.9 MHz or 75.4 MHz on the same spectrometers, respectively and in the same solvent. IR spectra were recorded on a Perkin–Elmer 1720X FT-IR spectrophotometer as neat liquid films or nujol mulls for solid materials.

Elemental analyses and low resolution electron impact mass spectra were performed by Mr. A. W. R. Saunders at the University of East Anglia on a Kratos model MS25 magnetic sector mass spectrometer using electron impact ionisation (EI, 70 eV). Analytical data are quoted to the nearest 0.01%. Additional mass spectra were obtained via the EPSRC National Mass Spectroscopy Service Centre at the University of Wales at Swansea. Melting points are

uncorrected and recorded using a Kofler hot-stage melting point apparatus with a digiton model 2751-K display.

Optical rotations were measured on a Perkin–Elmer model 141 polarimeter or on a Jasco DIP-370 digital polarimeter in the solvents stated (HPLC-grade), and $[\alpha]_D$ units are recorded in 10^{-1} deg cm^2 g^{-1} using the sodium lamp at 589 nm.

Reaction solvents were dried and distilled prior to use following standard procedures. Other solvents were SLR-grade and used without drying, unless stated otherwise. Temperatures quoted in the reaction conditions are the temperatures of the reaction mixture, and not the cooling or heating bath.

4.1.1. 2-Methylnaphth-1-yl boronic acid 18. The Grignard reagent of 1-bromo-2-methylnaphthalene **16** was prepared following the experimental procedure described by Miyano.[29] A solution of 1-bromo-2-methylnaphthalene **16** (10 g, 45.2 mmol) in dry THF (20 mL) was added in small portions to a suspension of dry magnesium turnings (1.1 g, 45.2 mmol) and a crystal of iodine in dry THF (10 mL) at room temperature under nitrogen. Once the reaction had started, the bromide was added at such a rate to maintain a gentle reflux. The mixture was heated under gentle reflux for 2 h then cooled to room temperature. The Grignard reagent was transferred in small portions to a solution of trimethyl borate (10.3 mL, 90.40 mmol) in dry THF (20 mL) at −78 °C. This mixture was gradually warmed to room temperature and stirred overnight. Dilute HCl (2 N, 40 mL) was added and the two layers were separated. The aqueous layer was extracted with diethyl ether (2×50 mL). The combined organic layers were washed with water (2×80 mL), dried, filtered and the solvent evaporated under reduced pressure. The cream powder (7.67 g, 91%) was recrystallised from toluene to give the title compound (5.19 g, 60% from 1-bromo-2-methylnaphthalene **16**) as a white powder, mp 90.0–92.5 °C (toluene). (Found: C, 71.11; H, 5.95. $C_{11}H_{11}BO_2$ requires: C, 71.02; H, 5.96%); ν_{max} (Nujol)/cm^{-1} 3302 (br, OH); δ_H (300 MHz; $CDCl_3$) 2.59 (3H, s), 4.85 (2H, s), 7.32 (1H, d, J=8.2 Hz), 7.42–7.48 (2H, m) and 7.76–7.87 (3H, m); δ_C (75.4 MHz) (*C*–B is not observed) 22.4, 125.0, 126.3, 127.4, 128.3, 128.3, 128.9, 131.3, 135.1 and 138.2; EIMS *m*/*z* 186 (M^+, 100%) and 141 ($M^+-B(OH)_2$, 53).

4.2. General procedure for the preparation of boronate esters 19–21

A solution of 2-methylnaphth-1-yl boronic acid **18**, diol (alcohol) and toluene was heated under reflux with azeotropic removal of water using a Dean–Stark type separator. The reaction was monitored by TLC and, when complete (typically 2–4 h), the solvent was removed under reduced pressure. Dichloromethane (20 mL) and water (20 mL) were added to the residue and the layers separated. The aqueous layer was extracted with dichloromethane (2×20 mL) and the combined organic layers washed with water (2×20 mL), dried, filtered and the solvent evaporated under reduced pressure to give the crude boronate.

4.2.1. 2-Methylnaphth-1-yl(butanol)boronate ester 19. 2-Methylnaphth-1-yl boronic acid **18** (0.5 g, 2.69 mmol), *n*-butanol (0.80 g, 5.38 mmol) and toluene (10 mL) were heated under reflux for 4 h with regular addition of butanol and worked up according to the general procedure to give the title compound as a colourless oil (0.75 g, 94%); δ_H (300 MHz; $CDCl_3$) 0.89 (6H, t, J=7.3 Hz), 1.38 (4H, m), 1.57 (4H, m), 2.50 (3H, s), 3.83 (4H, t, J=7.3 Hz), 7.31 (1H, d, J=8.3 Hz), 7.40–7.46 (2H, m), 7.65 (1H, d, J=8.1 Hz), 7.76 (1H, d, J=9.0 Hz) and 7.81 (1H, d, J=7.5 Hz). This compound was unstable over a short period of time at room temperature and was therefore used immediately.

4.2.2. 2-Methylnaphth-1-yl(pinacol)boronate ester 20. 2-Methylnaphth-1-yl boronic acid **18** (2.5 g, 13.45 mmol), pinacol (1.59 g, 13.45 mmol) and toluene (40 mL) were heated under reflux for 4 h and worked up according to the general procedure. The crude product was purified by column chromatography over silica gel (eluting with dichloromethane) to give the title compound as a colourless semi-solid (3.1 g, 86%). δ_H (300 MHz; $CDCl_3$) 1.49 (12H, s,), 2.63 (3H, s), 7.29 (1H, d, J=8.5 Hz), 7.37–7.45 (2H, m), 7.73–7.78 (2H, m) and 8.11 (1H, d, J=8.4 Hz); δ_C (75.4 MHz) (*C*–B is not observed) 22.6, 25.1 (4 C), 84.0 (2 C), 124.5, 125.9, 127.5, 128.1, 128.4, 129.5, 131.3, 136.6 and 141.3; EIMS *m*/*z* 268 (M^+, 83%) and 141 ($M^+-B(OC(CH_3)_2C(CH_3)_2O$, 24).

4.2.3. 2-Methylnaphth-1-yl(ethylene glycol)boronate ester 21. 2-Methylnaphth-1-yl boronic acid **18** (2 g, 10.76 mmol), ethylene glycol (760 mg, 11.84 mmol) and toluene (25 mL) were heated under reflux for 2 h and worked up according to the general procedure. The oil obtained crystallised after a few days to give the title compound (2.14 g, 94%) as a white solid, mp 50.2–52.2 °C. (Found: C, 73.65; H, 6.16. $C_{13}H_{13}O_2B$ Requires: C, 73.64; H, 6.18%); δ_H (300 MHz; $CDCl_3$) 2.64 (3H, s), 4.55 (4H, s), 7.34 (1H, d, J=8.4 Hz), 7.39–7.50 (2H, m), 7.81 (2H, d, J=8.1 Hz) and 8.16 (1H, d, J=8.3 Hz); δ_C (75.4 MHz) (*C*–B is not observed) 22.9, 65.8 (2 C), 124.8, 126.1, 127.9, 128.2, 128.6, 130.0, 131.4, 136.8 and 142.1; EIMS *m*/*z* 212 (M^+, 100%) and 141 ($M^+-B(OR)_2$, 21).

4.3. General procedure for Suzuki couplings

A round bottom flask containing solid materials, i.e. 2-methylnaphth-1-yl boronic acid or boronate ester, base (amount calculated with reference to the boronic acid), palladium chloride and ligand (both amounts calculated with reference to the halide derivative) was purged under nitrogen without any solvent for 10 min. A solution of naphthyl halide in solvent was injected and the mixture stirred for several hours under reflux and nitrogen (oil bath previously heated to obtain reflux as soon as all the reagents were mixed). The solvent was removed under reduced pressure and dichloromethane and water were added. The layers were separated and the aqueous layer extracted with dichloromethane. The combined organic layers were washed with water, dried, filtered and the solvent evaporated under reduced pressure. The crude product was typically purified by column chromatography over silica gel.

4.3.1. Racemic couplings

4.3.1.1. (±)-2-Methyl-1,1′-binaphthalene 25[29]—representative procedure (Table 1, entry 4). 2-Methylnaphth-1-yl

boronic acid **18** (0.8 g, 4.33 mmol), barium hydroxide octahydrate (1.86 g, 5.91 mmol), palladium chloride (20.9 mg, 0.12 mmol), triphenylphosphine (61.9 mg, 0.24 mmol), 1-iodonaphthalene **24** (1 g, 3.94 mmol), DME (25 mL) and water (4 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with petroleum ether) to give the title compound (645 mg, 61%) as a white solid, mp 82.8–87.1 °C (lit.,[29] 86–88 °C; δ_H (300 MHz; $CDCl_3$) 2.11 (3H, s), 7.13–7.65 (8H, m), 7.61 (1H, dd, J=7.0, 1.3 Hz), 7.88 (2H, d, J=8.4 Hz) and 7.96 (2H, d, J=8.4 Hz); δ_C (67.9 MHz) 20.4, 124.9, 125.7, 125.9, 126.0, 126.1, 126.2, 126.3, 127.6, 127.7, 127.8, 127.8, 128.3, 128.7, 132.1, 132.7, 133.556, 133.8, 134.5, 136.2 and 137.6.

4.3.1.2. (±)-2,2′-Dimethyl-1,1′-binaphthalene 26[30]—representative procedure (Table 2, entry 6). 2-Methylnaphth-1-yl(pinacol)boronate ester **20** (0.22 g, 0.82 mmol), cesium fluoride (0.25 g, 1.64 mmol), palladium chloride (2.2 mg, 0.01 mmol), triphenylphosphine (6.5 mg, 0.02 mmol), 1-iodo-2-methylnaphthalene **17** (0.15 g, 0.41 mmol) and DME (5 mL) were heated under reflux for 3 days and worked up according to the general procedure. The brown oil was purified by column chromatography over silica gel (eluting with petroleum ether) to give the title compound (86 mg, 36%) as a colourless oil; δ_H (300 MHz; $CDCl_3$) 1.96 (6H, s), 6.90 (2H, d, J=8.3 Hz), 7.13 (2H, m), 7.32 (2H, m), 7.44 (2H, d, J=8.4 Hz) and 7.82 (4H, dd, J=7.4, 4.1 Hz).

4.3.2. Asymmetric couplings. Optical purities were determined by optical rotation; 2-methyl-1,1′-binaphthalene **25** lit.,[7a] $[\alpha]_D^{22}=-43.9$ (c 1.0, $CHCl_3$); 2,2′-dimethyl-1,1′-binaphthalene **26** (lit.,[7a] $[\alpha]_D^{22}=-35.6$ (c 1.0, $CHCl_3$), lit.,[29] $[\alpha]_D^{22}=-19.0$ (c 1.3, ethanol)).

4.3.2.1. 2-Methyl-1,1′-binaphthalene 25—representative procedures.

(a) With (*R*)-(+)-BINAP 1.

Using $Ba(OH)_2{\cdot}8H_2O$/DME/H_2O (Table 3, entry 1). 2-Methylnaphth-1-yl boronic acid **18** (0.4 g, 2.17 mmol), barium hydroxide octahydrate (0.93 g, 2.96 mmol), [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]palladium(II) chloride **1** (47.3 mg, 0.06 mmol), 1-iodonaphthalene **24** (0.5 g, 1.97 mmol), DME (12 mL) and water (3 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil (0.56 g) was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (290 mg, 55%) as a white solid, $[\alpha]_D^{22}=+10.9$ (c 0.36, $CHCl_3$), optical purity 25%.

Using CsF/DME (Table 3, entry 2). 2-Methylnaphth-1-yl boronic acid **18** (0.18 g, 0.87 mmol), cesium fluoride (0.24 g, 1.57 mmol), [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]palladium(II) chloride **1** (18.9 mg, 0.02 mmol), 1-iodonaphthalene **24** (0.2 g, 0.79 mmol) and DME (5 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (90 mg, 43%) as a white solid, $[\alpha]_D^{22}=+9.1$ (c 0.22, $CHCl_3$), optical purity 21%.

Using $Ba(OH)_2{\cdot}8H_2O$/toluene/EtOH/H_2O (Table 3, entry 3). 2-Methylnaphth-1-yl boronic acid **18** (0.18 g, 0.87 mmol), barium hydroxide octahydrate (0.37 g, 1.19 mmol), [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]palladium(II) chloride **1** (18.9 mg, 0.02 mmol), 1-iodonaphthalene **24** (0.2 g, 0.79 mmol), toluene (3 mL), ethanol (3 mL) and water (1 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (100 mg, 47%) as a white solid, $[\alpha]_D^{22}=+3.4$ (c 0.37, $CHCl_3$), optical purity 8%.

(b) With (+)-(*S*)-(*R*)-PFNMe **4**.

Using $Ba(OH)_2{\cdot}8H_2O$/DME/H_2O (Table 3, entry 4). 2-Methylnaphth-1-yl boronic acid **18** (0.24 g, 1.3 mmol), barium hydroxide octahydrate (0.56 g, 1.77 mmol), palladium chloride (6.3 mg, 0.03 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-diphenylphosphino)ferrocenyl]ethylamine **4** (31.3 mg, 0.06 mmol), 1-iodonaphthalene **24** (0.3 g, 1.18 mmol), DME (7 mL) and water (2 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil (0.38 g) was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (144 mg, 44%) as a white solid, $[\alpha]_D^{22}=-27.7$ (c 0.39, $CHCl_3$), optical purity 63%.

Using CsF/DME (Table 3, entry 6). 2-Methylnaphth-1-yl boronic acid **18** (0.44 g, 2.36 mmol), cesium fluoride (0.72 g, 4.72 mmol), palladium chloride (6.3 mg, 0.04 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-diphenylphosphino)ferrocenyl]ethylamine **4** (31.3 mg, 0.07 mmol), 1-iodonaphthalene **24** (0.3 g, 1.18 mmol) and DME (7 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (138 mg, 44%) as a white solid, $[\alpha]_D^{22}=-24.2$ (c 0.38, $CHCl_3$), optical purity 55%.

Using $Ba(OH)_2{\cdot}8H_2O$/toluene/EtOH/H_2O (Table 3, entry 7). 2-Methylnaphth-1-yl boronic acid **18** (0.18 g, 0.87 mmol), barium hydroxide octahydrate (0.37 g, 1.18 mmol), palladium chloride (4.2 mg, 0.02 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-diphenylphosphino)ferrocenyl]ethylamine **4** (20.8 mg, 0.05 mmol), 1-iodonaphthalene **24** (0.2 g, 0.79 mmol) and toluene (3 mL), ethanol (3 mL) and water (1 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (94 mg, 45%) as a white solid, $[\alpha]_D^{22}=-22.8$ (c 0.35, $CHCl_3$), optical purity 52%.

(c) With (+)-(*S*)-(*R*)-PFOMe 5 (Table 3, entry 9).

2-Methylnaphth-1-yl boronic acid **18** (0.34 g, 1.82 mmol), barium hydroxide octahydrate (0.86 g, 2.72 mmol), palladium chloride (4.8 mg, 0.03 mmol), (+)-(*S*)-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethyl methyl ether **5** (23.3 mg, 0.06 mmol), 1-iodonaphthalene **24** (0.23 g,

0.91 mmol), DME (5 mL) and water (2 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil (0.32 g) was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (180 mg, 74%), $[\alpha]_D^{22}=-6.3$ (*c* 0.39, $CHCl_3$), optical purity 14%.

(d) With (+)-(*S*)-(*R*)-DPFNMe **6** (Table 3, entry 10).

2-Methylnaphth-1-yl boronic acid **18** (0.24 g, 1.30 mmol), barium hydroxide octahydrate (0.62 g, 1.95 mmol), palladium chloride (6.3 mg, 0.03 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine **6** (21.9 mg, 0.03 mmol), 1-iodonaphthalene **24** (0.3 g, 1.18 mmol), DME (7 mL) and water (2 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil (0.52 g) was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (230 mg, 73%) as a white solid, $[\alpha]_D^{22}=+1.9$ (*c* 0.42, $CHCl_3$), optical purity 4%.

(e) With (*S*)-(−)-BINAM **8** (Table 3, entry 18).

2-Methylnaphth-1-yl boronic acid **18** (0.24 g, 1.30 mmol), barium hydroxide octahydrate (0.62 g, 1.95 mmol), palladium chloride (6.3 mg, 0.04 mmol), (*S*)-(−)-diamino-1,1′-binaphthalene **8** (20.2 mg, 0.07 mmol), 1-iodonaphthalene **24** (0.3 g, 1.18 mmol), DME (7 mL) and water (2 mL) were heated under reflux overnight and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (30 mg, 9%) as a white solid, $[\alpha]_D^{22}=0$ (*c* 0.22, $CHCl_3$), optical purity 0%.

4.3.2.2. 2,2′-Dimethyl-1,1′-binaphthalene 26.

(a) With (+)-(*S*)-(*R*)-DPFNMe **6** (Table 3, entry 20).

2-Methylnaphth-1-yl(ethylene glycol)boronate ester **21** (0.45 g, 2.07 mmol), cesium fluoride (0.62 g, 4.14 mmol), palladium chloride (4.4 mg, 0.02 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine **6** (15 mg, 0.04 mmol), 1-iodo-2-methylnaphthalene **17** (0.3 g, 0.83 mmol) and DME (10 mL) were heated under reflux for 9 days (addition of chiral Pd-catalyst every 24 h) and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (60 mg, 13%) as a colourless solid, $[\alpha]_D^{22}=+5.9$ (*c* 0.22, $CHCl_3$), optical purity 17%.

(b) With (+)-(*S*)-(*R*)-PFNMe **4** (Table 3, entry 21).

2-Methylnaphth-1-yl(ethylene glycol)boronate ester **21** (0.45 g, 2.07 mmol), cesium fluoride (0.62 g, 4.14 mmol), palladium chloride (4.4 mg, 0.02 mmol), (+)-(*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-diphenylphosphino)ferrocenyl]ethylamine **4** (21 mg, 0.04 mmol), 1-iodo-2-methylnaphthalene **17** (0.30 g, 0.83 mmol) and DME (10 mL) were heated under reflux for 6 days (addition of chiral Pd-catalyst every 24 h) and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (140 mg, 60%) as a white solid, $[\alpha]_D^{22}=-16.1$ (*c* 0.31, ethanol), optical purity 85%.

(c) With (*R*)-(+)-BINAP **1**.

Using 2-methylnaphth-1-yl(ethylene glycol)boronate ester **21** (Table 3, entry 22). 2-Methylnaphth-1-yl(ethylene glycol)boronate ester **21** (0.45 g, 2.07 mmol), cesium fluoride (0.62 g, 4.14 mmol), [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]palladium(II) chloride **1** (19.2 mg, 0.02 mmol), 1-iodo-2-methylnaphthalene **17** (0.3 g, 0.83 mmol) and DME (10 mL) were heated under reflux for 5 days (addition of chiral Pd-catalyst every 24 h) and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (50 mg, 21%) as a colourless solid, $[\alpha]_D^{22}=+5.1$ (*c* 0.14, $CHCl_3$), optical purity 14%.

Using 2-methylnaphth-1-yl(pinacol)boronate ester **20** (Table 3, entry 23). 2-Methylnaphth-1-yl(pinacol)boronate ester **20** (0.40 g, 1.50 mmol), cesium fluoride (0.45 g, 3 mmol), [(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]palladium(II) chloride **1** (17.9 mg, 0.02 mol), 1-iodo-2-methylnaphthalene **17** (0.27 g, 0.75 mmol) and DME (7 mL) were heated under reflux for 4 days (addition of further aliquots of chiral Pd-catalyst every 24 h) and worked up according to the general procedure. The crude oil was purified by column chromatography over silica gel (eluting with distilled hexane) to give the title compound (35.3 mg, 17%) as a colourless solid, $[\alpha]_D^{22}=-3.68$ (*c* 0.35, $CHCl_3$), optical purity 10%.

Acknowledgements

Support for this work from UEA and (in part) the Ministry of Education, Sciences, Sports and Culture of Japan is gratefully acknowledged. We thank Professor T. Imamoto and Dr. H. Tsuruta for useful discussions, guidance on the synthesis of BisP* and MiniPhos and donation of ligands **12**–**14**. The service provided by the EPSRC mass spectrometry service centre (Swansea) is also gratefully acknowledged.

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Tetrahedron 60 (2004) 4387–4397

Sulfoxides as 'traceless' resolving agents for the synthesis of atropisomers by dynamic or classical resolution

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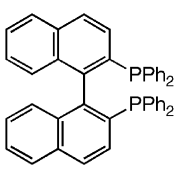
Received 19 November 2003; revised 19 January 2004; accepted 21 January 2004

Abstract—Reacting (−)-menthyl sulfinate with an atropisomeric but racemic aryllithium gives two atropdiastereoisomeric sulfoxides. Separation (by chromatography or crystallisation) and sulfoxide–lithium exchange of each diastereoisomer regenerates the aryllithium in enantiomerically pure form which can be quenched with a range of electrophiles with retention of stereochemical integrity. Overall the reaction sequence is a resolution but without the need for an acidic or basic substituent—a 'traceless' method. In certain instances, for example when the nucleophile is an ortholithiated *peri*-substituted 1-naphthamide, the diastereoisomeric sulfoxides may be interconverted thermally. This allows a dynamic resolution, under thermodynamic control, and hence in principle can give yields of the final products of greater than 50%. The utility of the method is demonstrated by the synthesis of a known atropisomeric phosphine ligand.

1. Introduction

Many of the most effective ligands for asymmetric catalysis by metals are atropisomeric.[1–3] Although there are an increasing number of asymmetric methods for the construction of atropisomeric biaryls by asymmetric coupling methods,[4,5] almost all practical syntheses of ligands rely on resolution.[6,7] The acidic or basic groups required for resolution are rarely present in the final target ligand, and this can place constraints on the choice of synthetic route and therefore the ability to vary a single route to provide a range of ligands. In the case of BINAP **1**, a resolution of the bis-phosphine oxide **2** is carried out—one enantiomer of this compound fortunately forms a much more crystalline 1:1 complex with di-*O*-benzoyl tartrate than the other.[6] The general asymmetric synthesis of chiral binaphthyls from a single precursor is made harder by the unfortunate fact that although the diamine **3** can be resolved, racemisation of the intermediates in its diazotisation–substitution reactions is rapid.[8]



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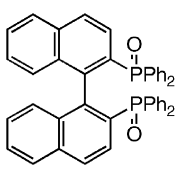

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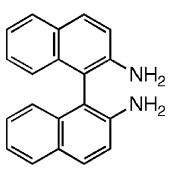

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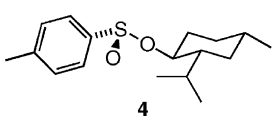

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We recently reported the use of sulfoxides as 'chiral equivalents' of anions in the asymmetric synthesis of some atropisomeric amides.[9] The sulfoxides have several features which make them amenable to use in this way: firstly, they may be constructed in enantiomerically pure form by any of a number of methods, the most important for our purposes being the Andersen substitution of (−)-menthyl sulfinate **4**.[10,11] Secondly, they have electronic properties which exaggerate the contrast between the physical properties of the two stereoisomeric atropisomers, mainly because of dipole orientation.[9] Thirdly, they may undergo sulfoxide–lithium exchange—nucleophilic substitution at sulfur—to regenerate a nucleophilic organometallic (organolithium) for use in further substitution reactions.[12–19]

In this paper we show that these properties are also applicable to the synthesis of some binaphthyl atropisomers, along with a known atropisomeric amidophosphine ligand. In one sequence, we aim to exploit the influence of the dipole of the intermediate binaphthylsulfoxide on the relative polarity of the atropisomeric diastereoisomers, allowing their chromatographic separation. In the other, the dipole governs the relative stability of a pair of diastereoisomeric atropisomers, and allows the quantitative

Keywords: Sulfoxides; Atropisomers; Resolution; Binaphthyls.
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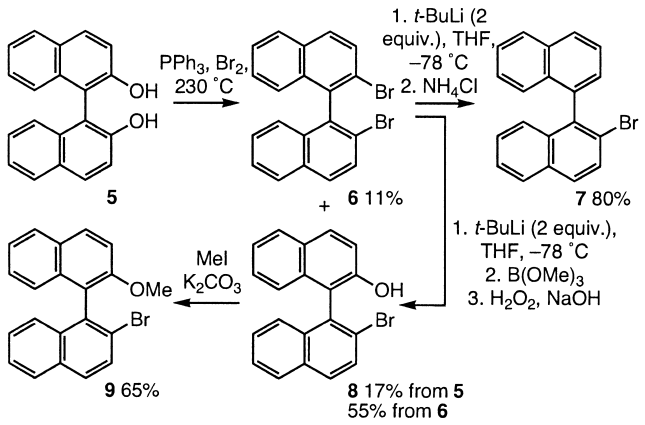
doi:10.1016/j.tet.2004.01.099

conversion of one diastereoisomer to the other. The resolution may therefore be dynamic in nature, and can yield significantly more than 50% of an enantiomerically pure product.

2. Results and discussion

2.1. Synthesis of atropisomeric binaphthyls by resolution via sulfoxides

Our plan was to use sulfoxide–lithium exchange[20] from an enantiomerically pure binaphthylsulfoxide **12** to generate a chiral, atropisomeric binaphthyllithium **10** which we hoped to quench with retention of stereochemistry, yielding enantiomerically enriched binaphthyls **11**. While the configurational stability about the chiral axis of biaryllithiums has not been studied in detail, it appears to depend on the nature of the substituent at the 2-position of the other ring. For example, 2-lithio-2′-phosphanyl-substituted binaphthyls are configurationally unstable while their borane adducts are configurationally stable.[21–23] 2,2′-Dilithio-1,1′-binaphthyl is known to be configurationally stable to −44 °C.[24]



Scheme 1. Synthesis of starting bromobinaphthalenes.

We found the reported synthesis of 2,2′-dibromobinaphthyl **6** from 2,2′dihydroxybinaphthyl (binaphthol) **5** to be a useful source of starting bromobinaphthalenes **7** and **9**:[6] in our hands **8** was always formed as a by-product during the vigorous conversion of **5** to **6**. The phenol **8** was methylated, giving **9** (Scheme 1).

Further supplies of the phenol **8** were obtained from the dibromobinaphthyl **6**. Clean monolithiation with 2 equiv. *t*-BuLi gave an organolithium, which was quenched with trimethyl borate and then oxidised to yield **8**. The same organolithium was hydrolysed to yield the bromide **7**.

The bromobinaphthyls **6**, **7** and **9** were used as starting materials for the synthesis of some sulfoxides **12**. *t*-BuLi gave the racemic organolithiums **10**, and reaction with (1*R*,2*S*,5*R*,S_S)-(−)-menthyl *p*-toluenesulfinate **4**[25] generated diastereoisomeric pairs of sulfoxides *M*- and *P*-**12a**–**c**. Reaction of **10** with achiral electrophiles MeI, NH_4Cl and *p*-Tol_2S_2 gave racemic standards **11a**, **11b** and **11c** for comparison with the enantiomerically pure samples produced later (see below).

The diastereoisomers **12b** were obtained, as expected, in a 1:1 ratio, and were readily separated by fractional crystallisation, which gave a 35% yield of *P*-**12b** and, by crystallisation from the mother liquors, a 31% yield of *M*-**12b**, both of which were identified by X-ray crystallography (Figs. 1 and 2).[26] Nucleophilic substitution with (−)-menthyl *p*-toluenesulfinate occasionally proceeds with incomplete stereospecificity:[15] later results, however, confirmed that both *M*-**12b** and *P*-**12b** obtained in this way were enantiomerically pure.

The diastereoisomers of sulfoxides **12a** and **12c** unfortunately turned out to be inseparable apart from by HPLC, which permitted the isolation of small amounts of each diastereoisomer of the two compounds, though in these cases we were unable to unequivocally assign stereochemistry to the products. The diastereoisomers of **12a** obtained in this way were compared with the racemic sulfoxides obtained when the racemic sulfide **11c** was oxidised with *m*-CPBA, and were >99% enantiomerically pure by HPLC.

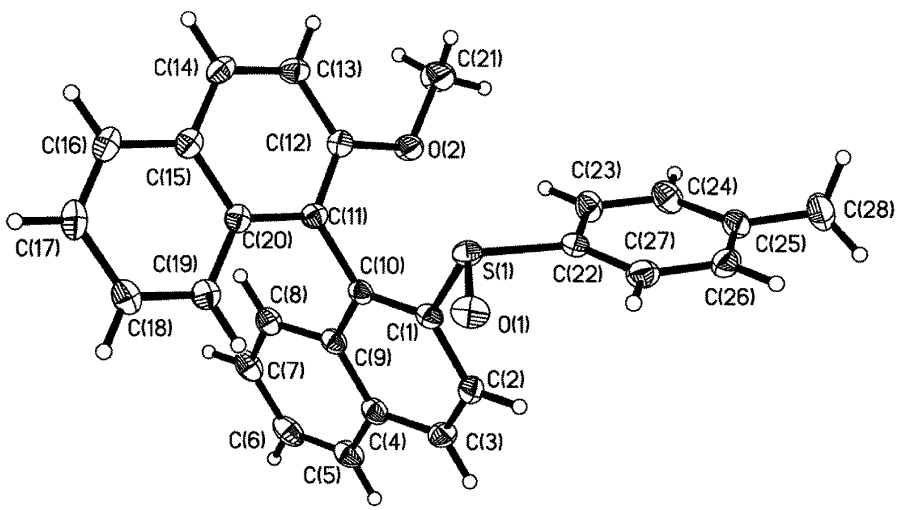


Figure 1. X-ray crystal structure of *P*-**12b**.

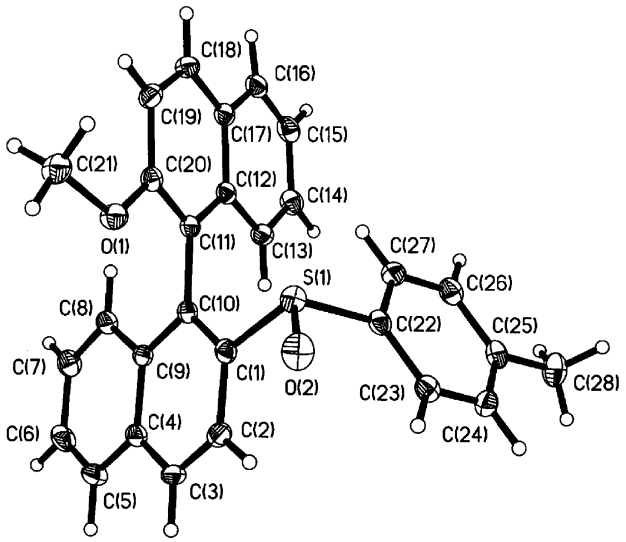
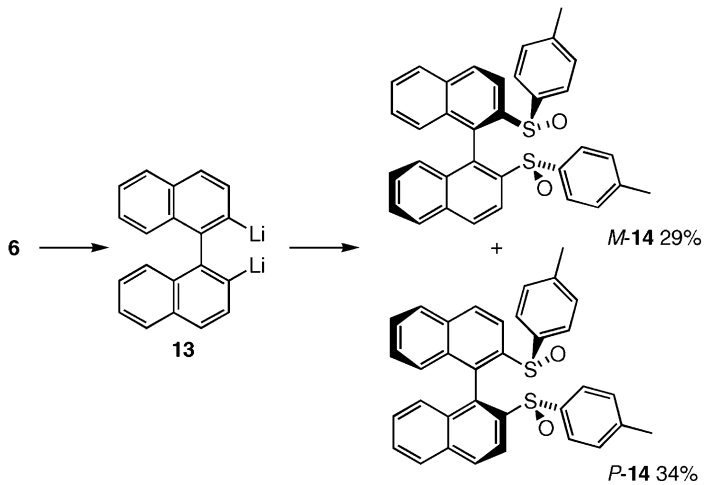


Figure 2. X-ray crystal structure of *M*-**12b**.

The oxidation of **11c** gave the diastereoisomers of **12a** in a 54:46 ratio.

Treatment of **6** with 4 equiv. of *t*-BuLi and 2 equiv. of sulfinate **4** yielded a much more readily separable pair of diastereoisomeric bis-sulfoxides **14**, whose identity was confirmed by X-ray crystal structure of the more crystalline of the pair (Fig. 3).

The separated diastereoisomers of the sulfoxides **12b** were subjected to sulfoxide–lithium exchange[9,18,20] by treatment with 2.1 equiv. *t*-BuLi to yield the enantiomerically pure binaphthyllithiums *M*- and *P*-**10b**. These organolithiums were evidently configurationally stable about the Ar–Ar axis over the period of the reaction, because methylation of each enantiomer yielded the enantiomerically pure binaphthyls *M*- and *P*-**11a** in good yield and with >99% ee in each case. Protonation yielded the enantiomerically enriched binaphthyls **11b** with some loss of enantiomeric excess (Scheme 2), which we attribute to partial racemisation of the product during isolation.



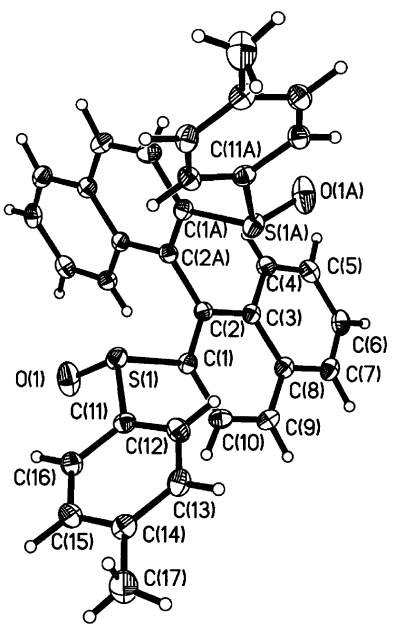
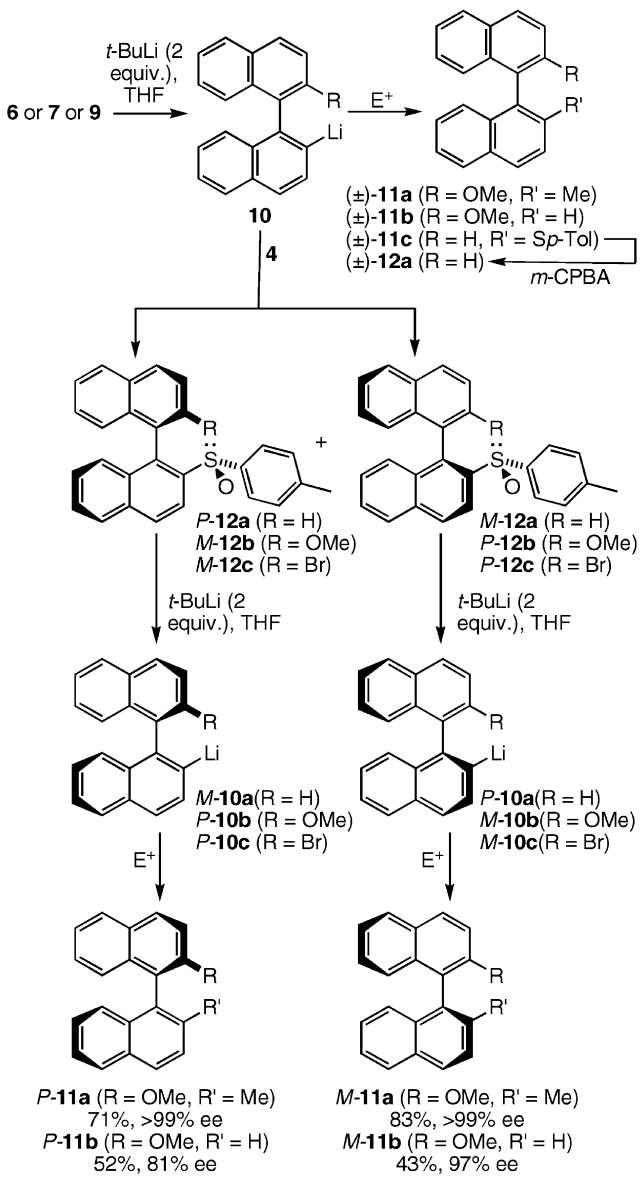


Figure 3. X-ray crystal structure of *P*-**14**.



Scheme 2. Resolution via binaphthylsulfoxides.

The asymmetric synthesis of **11a** and **11b**, although it is accomplished by resolution, is significant because of the lack of functionality in the final products of the sequence—the sulfoxide is 'traceless" as a resolving agent. In the model cases chosen here, extension of the method to further compounds was hampered by the unexpected inability to separate the sulfoxide diastereoisomers in some cases. However, the strategy clearly has potential for application to more valuable biaryl targets. We had furthermore hoped that heating mixtures of the diastereoisomers of **12a** or **12b** would allow enrichment of the mixture in the more stable of each diastereoisomeric pair, and thus allow us to convert the binaphthyl resolutions into dynamic resolutions under thermodynamic control.[9,27,28] However, in no case (heating either diastereoisomer separately or a mixture at temperatures up to 135 °C in xylene) did we see a change in the diastereoisomeric ratio. In Section 2.2, we describe the synthesis of a known ligand by a related sulfoxide-based method, which avoids the loss of 50% yield inherent in a classical resolution by incorporating just such an equilibration step into the resolution.

2.2. Synthesis of an atropisomeric amidophosphine by dynamic resolution

In 2002, Dai reported that the amidophosphine **18** (R=PPh_2) catalysed the asymmetric allylic alkylation of dimethylmalonate.[29] Secondary amidophosphines had previously been used as chiral ligands by Trost,[30] and we had shown that the chiral axis in tertiary amidophosphine ligands is the stereochemistry-controlling feature in some similar allylic alkylations.[31,32] Dai made phosphine **18**, whose configurational stability is ensured by the electronegative *peri* substituent,[33] by resolving the precursor phenol as a pair of diastereoisomeric camphanate esters.

For our asymmetric synthesis of **18**, which was under way before Dai's publication, we employed the sulfoxide-based strategy outlined above. We hoped that the known ability of the sulfoxide dipole to bias the conformation of an adjacent aromatic amide such that the C=O and S–O dipoles oppose

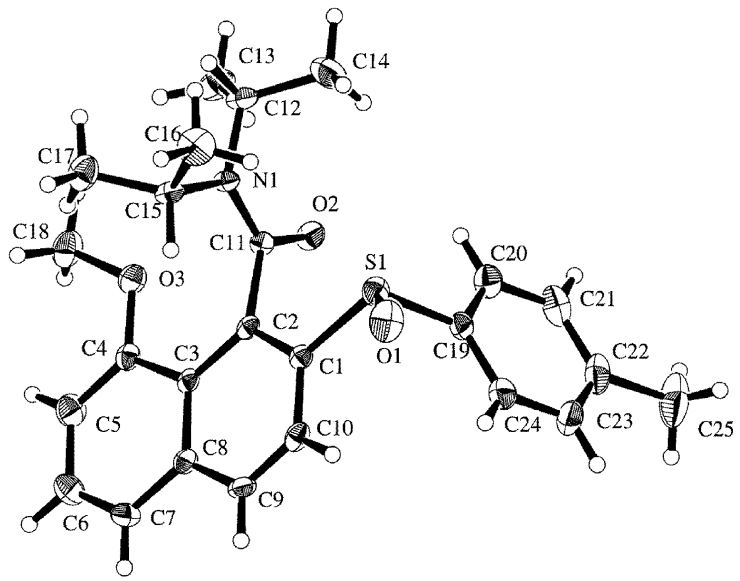


Figure 4. X-ray crystal structure of *P*-**17**.

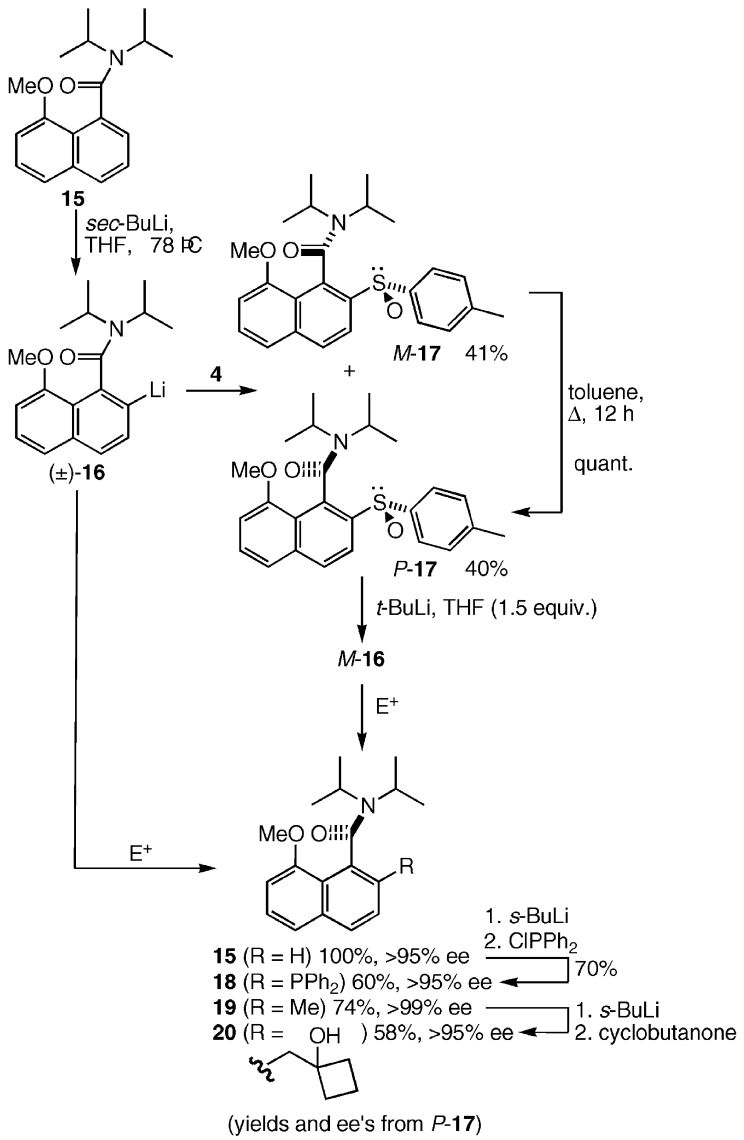
one another,[9] along with the relatively poor ability of second row elements (Si, P, S) to provide a steric barrier to amide bond rotation,[32,34] would allow us to make this ligand without recourse to a classical resolution, with the associated maximum 50% yield.

The 8-methoxynaphthamide **15** was made on a multigram scale by a published route[35] from 1,8-naphthalic anhydride. Ortholithiation with *sec*-BuLi in THF and reaction with (−)-menthyl sulfinate **4** gave the sulfoxides **17** in as a mixture of diastereoisomers. The diastereoisomers could be separated by flash chromatography, allowing the isolation of the diastereoisomers in 41 and 40% yield, respectively, and an X-ray crystal structure (Fig. 4) of one of them *P*-**17**) confirmed their relative and absolute stereochemistry.

In the light of previous studies of the preferred conformation of 2-sulfinyl amides,[9] we expected *M*-**17** to be the less stable of the two diastereoisomers. 8-Substituted naphthamides typically have very high barriers to Ar–CO rotation, especially when a non-hydrogen 2-substituent is present.[33] However, in the case of **17**, we found that heating to 100 °C for 12 h quantitatively converted *M*-**17** to *P*-**17**, while the same treatment of *P*-**17** left it unchanged. Clearly, under conditions where *M*- and *P*-**17** may interconvert, the equilibrium favours *P*-**17** to a very great extent. Application of the thermal equilibration step in the synthesis of the sulfoxides gave us a way of making, in a single transformation, the enantiomerically and diastereoisomerically pure sulfoxide *P*-**17** from the racemic amide **15** with an overall yield of >80%.

On treatment with *t*-BuLi (1.5 equiv.) in THF, the sulfoxide *P*-**17** underwent sulfoxide–lithium exchange to yield the enantiomerically pure organolithium *M*-**16**, which was quenched with the selection of electrophiles as shown in Scheme 3. Racemic standards of **18** and **19** were made by direct lithiation-electrophilic quench from **15**.

With chlorodiphenylphosphine, the ligand **18** (R=PPh_2) was formed in 60% yield (provided a non-aqueous work-up was employed[32]) and with >95% ee. Most of the remaining



Scheme 3. Asymmetric synthesis of atropisomeric amides by dynamic resolution employing amidosulfoxides.

material (30% isolated yield) was enantiomerically enriched (>95% ee) **15**, which was also easily synthesised in quantitative yield simply by protonation of *M*-**16**, a reaction which amounts to a direct dynamic thermodynamic resolution[28] of **15**. Use (or recycling) of this protonated material gives the phosphine in an improved 70% yield, but over two steps, and allows the overall yield of phosphine after a couple of recycling steps to approach 85–90%.

Methylation of *M*-**16** gave the amide **19** in 74% yield and >99% ee, which was laterally lithiated and quenched with cyclobutanone to return **20** in 58% yield and >95% ee.[36]

3. Conclusion

A sulfinyl substituent can bias the relative stability of a pair of diastereoisomeric *peri*-substituted atropisomeric amides such that one becomes much more stable than the other, allowing an efficient and high yield dynamic resolution to be achieved under thermodynamic control. The products of the resolution include an unusual amidophosphine ligand previously shown to be useful in allylic alkylation.

In the binaphthyl series, the barriers to rotation are too high for similar dynamic resolutions to be achieved, but in limited cases the sulfoxide can be used as a means of resolving the binaphthyls classically, and then replaced with any of a range of substituents, including H or Me. The products of such 'traceless' resolutions are rather more difficult to obtain by standard resolution methods. Whether sulfoxides will have a use in the asymmetric synthesis of less hindered biaryls under dynamic resolution conditions remains to be seen.[37]

4. Experimental

4.1. General methods have been published previously[32]

4.1.1. 2,2′-Dibromo-[1,1′]binaphthalenyl 6.[8] By the method of Miyashita and co-workers,[8] a 500 mL three-neck round bottom flask was equipped with mechanical stirrer, thermometer and dropping funnel. The flask was charged with triphenylphosphine (48 g, 0.183 mol) and acetonitrile (150 mL), previously distilled over calcium hydride under nitrogen; the solid was dissolved by warming the flask with hot water while stirring. The solution was then cooled by means of an ice bath, and bromine (10 mL, 0.194 mol) was added dropwise over a period of 30 in. The cold bath was removed and commercially available (±)-2,2′-hydroxy-1,1′-binaphthyl **5** (24 g, 0.084 mol) was added; the resulting slurry was heated with an oil bath at 60 °C while stirring for 30 min. Most of the solvent was removed by distillation under reduced pressure slowly increasing the temperature from 60 to 150 °C. The temperature was raised carefully to 230 °C with a sand bath, and an exothermic reaction occurred, with evolution of HBr. The reaction mixture was stirred at this temperature for 1 h. The temperature was increased and kept at 300 °C with a heating mantle for 30 min. The reaction mixture was allowed to cool to ca. 200 °C while stirring. Celite (200 mL) was added to the resulting thick black paste, and the flask was heated with an oil bath to facilitate stirring. The reaction mixture, cooled below 70 °C, was dissolved in 100 mL of hot toluene, and filtered through a sintered-glass funnel. The solid material was extracted with a boiling mixture of toluene and petrol, and the combined extracts were evaporated. The resulting brown oil was repeatedly purified by flash chromatography with a mixture petrol/EtOAc (4:1) as eluent to give the title compound **6** (3.81 g, 9.24 mmol, 11%) as white plates. δ_H (300 MHz, $CDCl_3$): 7.98 (2H, d, *J*=8.2 Hz), 7.92 (2H, d, *J*=8.8 Hz), 7.86 (2H, d, *J*=8.8 Hz), 7.54 (2H, dd, *J*=6.9, 8.1 Hz), 7.35 (2H, dd, *J*=6.9, 8.5 Hz), 7.13 (2H, d, *J*=8.5 Hz); δ_C (75 MHz, $CDCl_3$): 137.1, 133.3, 132.2, 129.9, 129.7, 128.2, 127.3, 126.3, 125.8, 122.7.

Also obtained was 2′-bromo-[1,1′]binaphthalenyl-2-ol **8** (4.98 g, 14.28 mmol, 17%).

4.1.2. 2-Bromo-[1,1′]binaphthalenyl 7.[38] *t*-BuLi (0.57 mL, 1.7 M solution in pentane, 2.00 equiv., 0.976 mmol) was added dropwise at −78 °C to a solution of 2,2′-dibromo-[1,1′]binaphthalenyl **6** (0.200 g, 0.488 mmol) in dry THF (5 mL) and stirred for 15 min under nitrogen. The reaction was then quenched with a saturated solution of NH_4Cl (10 mL) and allowed to warm to room temperature. The two layers were separated; the organic phase was washed with sat. NH_4Cl, dried over $MgSO_4$ and evaporated, to give a crude product which was purified by flash chromatography with eluent petrol/EtOAc (20:1); the title compound was obtained as yellow solid (0.1296 g, 0.390 mmol, 80%), R_f 0.53 (10% EtOAc in petrol). δ_H (300 MHz, $CDCl_3$): 8.07–8.01 (2H, m), 7.96 (1H, dd, *J*=8.4, 0.6 Hz), 7.90–7.80 (2H, m), 7.69 (1H, dd, *J*=8.1, 7.2 Hz) 7.57–7.50 (3H, m), 7.47 (1H, dd, *J*=7.2, 1.2 Hz), 7.40–7.23 (3H, m).

4.1.3. 2′-Bromo-[1,1′]binaphthalenyl-2-ol 8. *t*-BuLi (0.84 mL, 1.7 M solution in pentane, 1.95 equiv., 1.427 mmol) was added dropwise at −78 °C to a solution of 2,2′-dibromo-[1,1′]binaphthalenyl **6** (0.300 g, 0.732 mmol) in dry THF (10 mL) and stirred for 15 min under nitrogen. Dry trimethyl borate (0.10 mL, 1.20 equiv., 0.878 mmol) was added dropwise at −78 °C, and the cold bath was replaced by an ice bath. After 1 h the reaction was quenched with 2.5 M NaOH solution in 30% hydrogen peroxide (10 mL) and then allowed to warm to room temperature. The reaction mixture was acidified with 2 M HCl solution to pH <6 and the two layers were separated; the aqueous phase was extracted with EtOAc (2×20 mL) and the combined organic fractions were washed with brine (50 mL). The organic phase was dried over $MgSO_4$ and evaporated, to give a crude product, which was purified by flash chromatography eluting with petrol/EtOAc (20:1). The title compound was obtained as a yellow solid (0.1401 g, 0.403 mmol, 55%), R_f 0.38 (petrol/EtOAc 5:1), mp 166–169 °C;. ν_{max} ($CHCl_3$)/cm^{-1} 3583–3274 (OH), 1619, 1581, 1503, 811, 747; δ_H (300 MHz, $CDCl_3$): 8.02–7.86 (5H, m), 7.58 (1H, td, *J*=8.1, 1.6 Hz), 7.43–7.30 (5H, m), 7.05 (1H, d, *J*=8.4 Hz), 4.89 (1H, br, OH); δ_C (75 MHz, $CDCl_3$): 150.7, 134.2, 132.9, 132.7, 131.9, 130.5, 130.4, 130.3, 129.0, 128.3, 128.2, 127.8, 126.9, 126.8, 126.1, 124.8, 124.3, 123.6, 118.2, 117.7; *m/z* (EI) 350 ($M+^{81}Br$, 100%), 348 ($M+^{79}Br$, 79%), 269 (73%). Found M^+ 348.0148, $C_{20}H_{13}BrO$ requires M^+ 348.0150.

4.1.4. 2′-Bromo-2-methoxy-[1,1′]binaphthalenyl 9. Methyl iodide (0.51 mL, 10.00 equiv., 10.540 mmol) and potassium carbonate (0.7280 g, 5.00 equiv., 5.270 mmol) were added to a stirred solution of 2′-bromo-[1,1′]-binaphthalenyl-2-ol **8** (0.3681 g, 1.054 mmol) in acetone (7.50 mL) under nitrogen. The reaction mixture was heated under reflux for 24 h. After cooling, the mixture was filtered and the filtrate was evaporated to yield the title compound as a yellow solid (0.2480 g, 0.685 mmol, 65%), R_f 0.52 (30% EtOAc in petrol), mp 146–150 °C, *m/z* (EI) 364 ($M+^{81}Br$, 88%), 268 (100%), 239 (84%). Found M^+ 362.0308, $C_{21}H_{15}BrO$ requires M^+ 362.0307. ν_{max} ($CHCl_3$)/cm^{-1} 2930, 2838, 1620, 1588, 808, 745. δ_H (300 MHz, $CDCl_3$): 8.08 (1H, d, *J*=9.1 Hz), 7.96–7.88 (3H, m), 7.54–7.49 (2H, m), 7.42–7.22 (5H, m), 7.06 (1H, d, *J*=8.4 Hz), 3.85 (3H, s). δ_C (75 MHz, $CDCl_3$): 154.4, 134.8, 134.1, 133.0, 132.4, 130.0 (2CH), 129.1, 129.0, 128.0 (2CH), 126.8 (2CH), 126.3, 125.9, 124.6, 123.7, 123.3, 122.1, 113.8, 56.7.

4.1.5. (R_S,*P*) and (R_S,*M*)-2-Methoxy-2′-(toluene-4-sulfinyl)-[1,1′]binaphthalenyl 12b. *t*-BuLi (1.76 mL, 1.7 M solution in pentane, 2.10 equiv., 2.991 mmol) was added dropwise at −78 °C to a solution of 2′-bromo-2-methoxy-[1,1′]binaphthalenyl **9** (0.5157 g, 1.424 mmol) in dry THF (15 mL) and stirred for 15 min under nitrogen. The reaction was quenched with (−)-menthyl-(*S*)-*p*-toluene sulfinate (0.9647 g, 2.30 equiv., 3.276 mmol) dissolved in THF (10 mL). The mixture was left to warm to room temperature, and a saturated solution of NH_4Cl (10 mL) was added. The layers were separated, and the organic phase was washed with sat. NH_4Cl, dried over $MgSO_4$ and evaporated. The crude product was purified by flash chromatography with eluent petrol/EtOAc (4:1) to give a mixture of two diastereoisomers of the title compound; this mixture afforded separately the two diastereoisomers by repeated fractional crystallisation from EtOAc (Diastereoisomer A 0.4418 g, 35%; Diastereoisomer B 0.3913 g, 31%). Compounds **12b** show ν_{max} ($CHCl_3$)/cm^{-1} 2926, 2842, 1621, 1593, 1508, 1046 (S=O), 809, 747, 731; *m/z* (EI) 422 (M, 5%), 318 (49%), 268 (100%). Found M^+ 422.1335, $C_{28}H_{22}O_2S$ requires M^+ 422.13404.

Diastereoisomer A, colourless needles, shown by X-ray crystallography to be *P*-**12b**, mp 218–221 °C, R_f 0.30 (40% EtOAc in petrol); δ_H (300 MHz, $CDCl_3$): 8.07 (1H, d, *J*=8.8 Hz), 8.00 (1H, d, *J*=8.8 Hz), 7.93 (1H, d, *J*=9.1 Hz), 7.82 (1H, d, *J*=8.4 Hz), 7.78 (1H, d, *J*=8.2 Hz), 7.43–7.37 (1H, m), 7.27–7.17 (5H, m), 7.15 (1H, d, *J*=9.1 Hz), 7.12 (2H, d, *J*=8.0 Hz), 7.01 (2H, d, *J*=8.0 Hz), 3.28 (3H, s), 2.20 (3H, s); δ_C (75 MHz, $CDCl_3$): 154.8, 142.3, 142.0, 140.9, 134.6, 134.3, 133.5, 132.5, 131.0, 129.7, 129.3, 128.7, 128.3, 128.0, 127.6, 127.0, 126.4, 125.9, 124.5, 124.0, 120.6, 117.1, 112.0, 55.2, 21.3.

Diastereoisomer B, colourless needles, shown by X-ray crystallography to be *M*-**12b**, mp 208–212 °C, R_f 0.23 (40% EtOAc in petrol); δ_H (300 MHz, $CDCl_3$): 8.23 (1H, d, *J*=8.7 Hz), 8.07 (1H, d, *J*=8.8 Hz), 7.98 (1H, d, *J*=9.1 Hz), 7.86 (1H, d, *J*=8.1 Hz), 7.73 (1H, d, *J*=8.2 Hz), 7.43 (1H, d, *J*=9.1 Hz), 7.43 (1H, t, *J*=8.1 Hz), 7.21–7.10 (3H, m), 6.76–6.71 (1H, m), 6.64 (2H, d, *J*=8.2 Hz), 6.60 (2H, d, *J*=8.4 Hz), 6.16 (1H, d, *J*=8.5 Hz), 3.84 (3H, s), 2.04 (3H, s); δ_C (75 MHz, $CDCl_3$): 154.5, 141.2, 140.8, 134.5, 133.6, 132.8, 132.5, 130.9, 129.4, 129.0, 128.6, 128.3, 127.8, 127.3, 126.9, 126.4, 126.2, 125.4, 124.6, 123.2, 119.8, 117.0, 113.2, 56.5, 21.1.

4.1.6. 2-*p*-Toluenesulfanyl-[1,1′]binaphthalenyl 11c. *t*-BuLi (0.40 mL, 1.7 M solution in pentane, 2.10 equiv., 0.681 mmol) was added dropwise at −78 °C to a solution of 2-bromo-[1,1′]binaphthalenyl **7** (0.1076 g, 0.324 mmol) in dry THF (4 mL) and stirred for 15 min under nitrogen. The temperature was warmed to −20 °C to destroy the excess of *t*-BuLi, and then decreased again to −78 °C. The reaction was quenched with *p*-tolyl disulfide (0.1837 g, 2.30 equiv., 0.745 mmol). The mixture was then left to warm to room temperature, and a saturated solution of NH_4Cl (5 mL) was added. The two layers were separated; the organic phase was washed with NaOH (2 M), dried over $MgSO_4$ and evaporated. The product sulfide was employed without further purification.

4.1.7. (R_S,*P*) and (R_S,*M*)-2-(Toluene-4-sulfinyl)-[1,1′]binaphthalenyl 12a. (a) By lithiation of 2-bromo-[1,1′]binaphthalenyl **7** and reaction with (−)-menthyl-(*S*)-*p*-toluene sulfinate. *t*-BuLi (1.12 mL, 1.7 M solution in pentane, 2.10 equiv., 1.897 mmol) was added dropwise at −78 °C to a solution of 2-bromo-[1,1′]binaphthalenyl **7** (0.3000 g, 0.904 mmol) in dry THF (10 mL) and the mixture was stirred for 15 min under nitrogen. The reaction was quenched with (−)-menthyl-(*S*)-*p*-toluene sulfinate[11] (0.6119 g, 2.30 equiv., 2.079 mmol) dissolved in THF (10 mL). The mixture was allowed to warm to room temperature, and a saturated solution of NH_4Cl (20 mL) was added. The layers were separated, the organic phase was washed with sat. NH_4Cl, dried over $MgSO_4$ and evaporated. Purification by flash chromatography with eluent petrol/EtOAc (4:1) gave a mixture of two diastereoisomers of the title compound (0.0338 g, 0.086 mmol, 10%). Analytical HPLC was carried out with Sphereclone column, flow 0.5 mL/min, at room temperature in hexane/IPA (95:5), t_r 16.32 min (60.4%) and 17.01 min (39.6%). Small samples (ca. 2 mg) of each diastereoisomer were obtained by preparative HPLC.

(b) By oxidation of 2-*p*-tolylsulfanyl-[1,1′]binaphthalenyl (**7**) with *m*-CPBA. A 75% solution of *m*-chloroperoxybenzoic acid (0.1099 g, 1.00 equiv., 0.478 mmol) was added to a solution of 2-*p*-tolylsulfanyl-[1,1′]binaphthalenyl **11c** (0.1796 g, 0.478 mmol) in DCM (5 mL). The reaction mixture was stirred at room temperature for 2 h, washed with a solution of $NaHCO_3$, dried over $MgSO_4$ and evaporated. Purification by flash chromatography with eluent petrol/EtOAc (19:1) gave the title compound as a mixture of two diastereoisomers (0.0125 g, 0.032 mmol, 7%). Analytical HPLC was carried out with Sphereclone column, flow 0.5 mL/min, at room temperature in hexane/IPA (95:5), t_r 16.25 min (53.9%) and 16.99 min (46.1%). Compounds **12a** show R_f 0.24 (30% EtOAc in petrol), *m/z* (EI) 392 (M, 49%), 269 (100%), 49 (84%). Found M^+ 392.1235, $C_{27}H_{20}OS$ requires M^+ 392.1235. ν_{max} ($CHCl_3$)/cm^{-1} 2921, 2852, 1044 (S=O), 805, 781.

Diastereoisomer A. δ_H (300 MHz, $CDCl_3$): 8.29 (1H, d, *J*=8.7 Hz), 8.19 (1H, d, *J*=8.8 Hz), 8.06 (1H, dd, *J*=7.5, 1.7 Hz), 7.99 (1H, d, *J*=8.2 Hz), 7.92 (1H, d, *J*=8.2 Hz),

7.75–7.68 (2H, m), 7.59–7.53 (1H, m), 7.43–7.37 (1H, m), 7.34–7.28 (1H, m), 7.21 (1H, d, *J*=8.7 Hz), 6.95 (1H, ddd, *J*=8.2, 6.9, 1.2 Hz), 6.80 (2H, d, *J*=8.4 Hz), 6.75 (2H, d, *J*=8.1 Hz), 6.53 (1H, d, *J*=8.5 Hz), 2.16 (3H, s).

Diastereoisomer B. δ_H (300 MHz, $CDCl_3$): 8.29 (1H, d, *J*=8.7 Hz), 8.19 (1H, d, *J*=8.8 Hz), 8.07–7.98 (3H, m), 7.58–7.55 (3H, m), 7.50–7.27 (5H, m), 7.18 (2H, d, *J*=8.1 Hz), 7.03 (2H, dd, *J*=7.5, 1.1 Hz), 2.37 (3H, s).

4.1.8. (R_S,*P*) and (R_S,*M*)-2′-Bromo-2-(toluene-4-sulfinyl)-[1,1′]binaphthalenyl 12c. *t*-BuLi (0.63 mL, 1.7 M solution in pentane, 2.10 equiv., 1.076 mmol) was added dropwise at −78 °C to a solution of 2,2′-dibromo-[1,1′]-binaphthalenyl **6** (0.2100 g, 0.512 mmol) in dry THF (5 mL) and stirred for 15 min under nitrogen. (−)-Menthyl-(*S*)-*p*-toluene sulfinate[11] (0.3469 g, 2.30 equiv., 1.178 mmol) dissolved in THF (5 mL) was added. The mixture was left to warm to room temperature, and a saturated solution of NH_4Cl (10 mL) was added. The layers were separated, the organic phase was washed with sat. NH_4Cl, dried over $MgSO_4$ and evaporated. Purification by flash chromatography with eluent petrol/EtOAc (4:1) gave a mixture of two diastereoisomers of the title compound (0.0975 g, 0.207 mmol, 40%). Separation of the diastereoisomers of **12c** by flash chromatography failed, but analytical HPLC carried out with Sphereclone column, flow 0.5 mL/min, at room temperature in hexane/IPA (9:1) showed t_r 11.79 min (58%) and 13.04 min (42%). *m*/*z* (EI) 473 (MH^++^{81}Br, 33%), 268 (100%), 49 (87%). Found M^+ 470.0348, $C_{27}H_{19}BrOS$ requires M^+ 470.0340. νmax film/$CHCl_3$ (cm^{-1}) 2922 (CH_3), 1581, 1500 (two Ar C–C bands), 1044 (S=O), 809 (Ar C–H), 732 (C–Br); δ_H (300 MHz, $CDCl_3$): 8.42 (1H diast. A, d, *J*=8.7 Hz), 8.31–8.25 (1H diast. B, m), 8.22–6.71 (14H diast. A+15H diast. B, m), 6.28 (1H diast. A, d, *J*=8.4 Hz), 2.38 (3H diast. B, s), 2.16 (3H diast. A, s).

4.1.9. (R_S,R_S,*P*) and (R_S,R_S,*M*)-2,2′-Bis-(toluene-4-sulfinyl)-[1,1′]binaphthalenyl 14. *t*-BuLi (2.30 mL, 1.7 M solution in pentane, 4.00 equiv., 3.903 mmol) was added dropwise at −78 °C to a solution of 2,2′-dibromo-[1,1′]binaphthalenyl **9** (0.4000 g, 0.976 mmol) in dry THF (10 mL) and stirred for 15 min under nitrogen. The reaction mixture was then allowed to reach a temperature of about −20 °C, and added via cannula to a flask containing (−)-menthyl-(*S*)-*p*-toluene sulfinate[11] (0.7183 g, 2.50 equiv., 2.440 mmol) dissolved in THF (10 mL). The mixture was allowed to warm to room temperature, and a saturated solution of NH_4Cl (20 mL) was added. The layers were separated, the organic phase was washed with saturated NH_4Cl, dried over $MgSO_4$ and evaporated. Purification by flash chromatography with eluent petrol/EtOAc (4:1 to 1:1) gave the two diastereoisomers of the title compound: diastereoisomer A (0.1771 g, 0.334 mmol, 34%), and diastereoisomer B (0.1485 g, 0.280 mmol, 29%). *m*/*z* (EI) 531 (M, 3%), 268 (100%), 49 (64%). Found M^+ 531.1449, $C_{34}H_{26}O_2S_2$ requires M^+ 530.13741. ν_{max} ($CHCl_3$)/cm^{-1} 296, 2923 (two CH_3 bands), 1464 (CH_3), 1044 (S=O), 809 (Ar C–H).

Diastereoisomer A, identified by X-ray crystal structure as *P*-**14**: mp 248–252 °C, R_f 0.28 (petrol/EtOAc 2:3); δ_H (300 MHz, $CDCl_3$): 8.13 (2H, d, *J*=8.7 Hz), 7.99 (2H, d, *J*=8.1 Hz), 7.67–7.59 (4H, m), 7.49–7.44 (2H, m), 7.33 (2H, d, *J*=8.1 Hz), 7.24 (4H, d, *J*=8.4 Hz), 7.16 (4H, d, *J*=8.1 Hz), 2.36 (6H, s). δ_C (75 MHz, $CDCl_3$): 142.2, 141.3, 140.4, 136.7, 135.0, 133.0, 131.7, 130.4, 130.0, 129.7, 129.1, 128.5, 128.4, 127.8, 126.3, 126.0, 21.6.

Diastereoisomer B: mp 81–85 °C, R_f 0.15 (petrol/EtOAc 2:3); δ_H (300 MHz, $CDCl_3$): 8.48 (2H, d, *J*=8.8 Hz), 8.20 (2H, d, *J*=8.8 Hz), 7.80 (2H, d, *J*=8.2 Hz), 7.28 (2H, t, 7.2), 6.70–6.64 (2H, m), 6.54 (4H, d, *J*=8.2 Hz), 6.46 (4H, d, *J*=8.2 Hz), 6.06 (2H, d, *J*=8.5 Hz), 1.96 (6H, s). δ_C (75 MHz, $CDCl_3$): 142.8, 141.8, 140.7, 134.3, 132.5, 131.0, 130.3, 129.4, 128.4, 127.2, 127.1, 126.3, 125.9, 119.9, 21.4.

Also obtained were two diastereoisomers of bis-sulfoxide **14** as side products: diastereoisomer A (0.0351 g, 0.066 mmol, 13%) and diastereoisomer B (0.0239 g, 0.045 mmol, 9%).

4.1.10. (±)-2-Methoxy-2′-methyl-[1,1′]binaphthalenyl 11a.[39] *t*-BuLi (1.7 M solution in pentane, 0.34 mL, 0.580 mmol, 2.10 equiv.) was added dropwise at −78 °C to a solution of 2-bromo **7** (0.100 g, 0.276 mmol) in dry THF (5 mL) and stirred for 15 min under nitrogen. Iodomethane (0.09 mL, 1.381 mmol, 5.00 equiv.) was added at −78 °C and the mixture allowed to warm to room temperature. A saturated solution of NH_4Cl (5 mL) was added, and the two layers were separated; the organic phase was washed with sat. NH_4Cl, dried over $MgSO_4$ and evaporated under reduced pressure and without heating, to give the title compound (0.0409 g, 50%) as a yellow solid, *m*/*z* (EI) 298 (M, 100%), 268 (26%). Analytical HPLC was carried out with Chiralpak OT (+) column, flow 0.5 mL/min, at 5 °C in methanol, t_r 29.53 and 33.68 min. Spectroscopic data were consistent with the literature.[39] δ_H (300 MHz, $CDCl_3$): 8.04 (1H, d, *J*=9.1 Hz), 7.93 (2H, d, *J*=7.8 Hz), 7.91 (1H, d, *J*=9.0 Hz), 7.56 (1H, d, *J*=8.3 Hz), 7.51 (1H, d, *J*=9.1 Hz), 7.45–7.35 (2H, m), 7.30–7.23 (2H, m), 7.17 (1H, d, *J*=8.4 Hz), 7.05 (1H, d, *J*=8.5 Hz), 3.81 (3H, s), 2.15 (3H, s); δ_C (75 MHz, $CDCl_3$): 154.7, 135.3, 133.9, 133.5, 132.6, 132.4, 129.8, 129.6–122.3 (12 Ar C), 114.1, 56.9, 20.6.

4.1.11. (*M*)-2-Methoxy-2′-methyl-[1,1′]binaphthalenyl *M*-11a. In a similar way, *P*-**12b** (0.0864 g) gave *M*-**11a**, 0.0509 g, 83%, with >99% ee [Chiralpak OT (+)].

4.1.12. (*P*)-2-Methoxy-2′-methyl-[1,1′]binaphthalenyl *P*-11a. In a similar way, *M*-**12b** (0.0780 g) gave *P*-**11a**, 0.0390 g, 71%, with >99% ee [Chiralpak OT (+)].

4.1.13. (±)-2-Methoxy-[1,1′]binaphthalenyl (±)-11b.[40] In a similar way, but quenching with NH_4Cl instead of MeI, bromonaphthalene **7** (0.0894 g, 0.247 mmol) gave, after work up and evaporation under reduced pressure and without heating, the title compound as a yellow solid, 0.0542 g, 77%, R_f 0.30 (5% EtOAc in petrol). Analytical HPLC was carried out with Chiralpak OT (+) column, flow 0.7 mL/min, at 5 °C in methanol, t_r 25.63 and 29.61 min. Spectroscopic data were consistent with the literature.[40] δ_H (300 MHz, $CDCl_3$): 8.01 (2H, t, *J*=9.1 Hz), 7.99 (1H, d, *J*=9.2 Hz), 7.92 (1H, d, *J*=8.1 Hz), 7.66 (1H, dd, *J*=8.2,

7.0 Hz), 7.51–7.47 (3H, m), 7.38–7.21 (5H, m), 2.22 (3H, s).

4.1.14. (*M*)-2-Methoxy-[1,1′]binaphthalenyl *M*-11b (enantiomer A). In a similar way, *P*-**12b** (0.0383 g, 0.091 mmol) gave *M*-**11b**, 0.0111 g, 43%, 97% ee [Chiralpak OT (+)].

4.1.15. (*P*)-2-Methoxy-[1,1′]binaphthalenyl *P*-11b (enantiomer B). In a similar way, *M*-**12b** (0.0231 g, 0.055 mmol) gave *P*-**11b**, 0.0081 g, 52%, 81% ee [Chiralpak OT (+)].

4.1.16. (R_S,*P*) and (R_S,*M*)-8-Methoxy-2-(toluene-4-sulfinyl)-naphthalene-1-carboxylic acid diisopropylamide 17. *sec*-Butyllithium (1.3 equiv.) was added to naphthamide **15**[35] (0.7 g) dissolved in dry THF (10 mL) at −78 °C under nitrogen atmosphere. A light green colour appeared after 10 min, and after 2 h (−)-menthyl (*S*)-*p*-toluenesulfinate[11] (1.5 equiv.) was added. After 24 h at −78 °C the reaction mixture was allowed to warm slowly to room temperature and quenched with saturated NH_4Cl. The organic layer was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (EtOAc/petroleum ether (40–60 °C) 1:3 then 1:1 to obtain diastereoisomer A, then using EtOAc/DCM 1:1 in order to collect polar diastereoisomer B) gave two diastereoisomers in 1:1 ratio [0.43 g (41%) and 0.42 g (40%)].

Diastereoisomer A, shown by X-ray crystallography to be *P*-**17**: mp 117–119 °C; R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:1] 0.08; $[\alpha]_D^{23}$ −212.3 (*c*=1.25, $CDCl_3$); ν_{max} (film)/cm^{-1} 2970(CH), 1628 (C=O); δ_H (300 MHz, $CDCl_3$) 7.85 (1H, d, *J*=9 Hz, Ar*H*), 7.50 (5H, m, Ar*H*), 7.27 (2H, d, *J*=9 Hz, Ar*H*), 7.00 (1H, d, *J*=10 Hz, Ar*H*), 4.00 (3H, s, OCH_3), 3.59 [2H, 2 septets, *J*=7 Hz, NCH(CH_3)$_2$], 2.44 (3H, s, ArCH_3), 1.75 [6H, dd, *J*=7, 10 Hz, NCH(CH_3)$_2$], 1.08 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 0.94 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$]; δ_C ($CDCl_3$) 166.7 (C=O), 156.4, 141.6, 140.9, 138.7, 136.7, 136.5, 129.8, 129.6, 128.9 (×2), 126.3 (×2), 124.1, 121.0, 120.8, 107.3, 55.4, 50.7, 46.5, 21.3, 21.0, 20.4, 20.3, 19.6; *m*/*z* (CI) 424 (90%, $(M+H)^+$), (EI) 424 (15%, $M+H^+$); Found (EI): M^+, 423.1870, $C_{25}H_{29}NO_3S$ requires M, 423.1868.

Diastereoisomer B *M*-**17**): mp 200–201 °C; R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:1] 0.53; $[\alpha]_D^{23}$ −305.2 (*c*=0.85, $CDCl_3$); ν_{max} (film)/cm^{-1} 2972 (CH), 1629 (C=O); δ_H (300 MHz, $CDCl_3$) 7.80 (4H, m, Ar*H*), 7.45 (2H, m, Ar*H*), 7.25 (2H, d, *J*=8 Hz, Ar*H*), 6.98 (1H, d, *J*=8 Hz, Ar*H*), 4.02 (3H, s, OCH_3), 3.65 [2H, 2× septet, *J*=7 Hz, NCH(CH_3)$_2$], 2.37 (3H, s, ArCH_3), 1.80 [6H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.31 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.12 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$]; δ_C ($CDCl_3$) 168.0 (C=O), 156.1, 141.9, 140.7, 140.3, 136.1, 133.3, 130.0, 129.6, 128.5, 124.4, 121.3, 121.0, 120.2, 106.8, 55.2, 51.3, 46.3, 21.2, 20.8, 20.4, 20.2, 19.6; *m*/*z* (EI) 423 (5%, M^+); Found (EI): M^+, 423.1860, $C_{25}H_{29}NO_3S$ requires M, 423.1868.

Equilibration of the diastereoisomeric sulfoxides. Sulfoxide *M*-**17** (100 mg) was heated in toluene at 100 °C for 12 h. The solvent was evaporated under reduced pressure. Flash chromatography (EtOAc/petroleum ether (bp 40–60 °C) 1:3) gave the sulfoxide *P*-**17** as a white solid (95 mg, 95%).

4.1.17. (*M*)-8-Methoxynaphthalene-1-carboxylic acid diisopropylamide *M*-15. *t*-Butyllithium (1.5 equiv.) was added to sulfoxide *P*-**17** (40 mg, 0.1 mmol) in THF (5 mL) at −78 °C under nitrogen. After 24 h at this temperature, saturated ammonium chloride solution was added, and the mixture was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography [EtOAc/petroleum ether (bp 40–60 °C) 1:3] yielded *M*-**15** as a white solid (29 mg, 100%).[35] The enantiomeric excess was determined by HPLC on a chiral column (Whelk-O1) and was found to be greater than 99%.

4.1.18. (±)-2-Diphenylphosphanyl-8-methoxy-naphthalene-1-carboxylic acid diisopropylamide (±)-18 (R=PPh_2). Amide **15** (1 g, 3.51 mmol) was dissolved in 15 mL of degassed THF under nitrogen atmosphere at −78 °C. *sec*-Butyllithium (1.2 equiv.) was added dropwise to the reaction mixture. The brown-orange solution was stirred at −78 °C for 2 h. Chlorodiphenylphosphine (2 equiv., 7.02 mmol) was added dropwise to the solution, and after a further 24 h at −78 °C the mixture was allowed to warm to RT, poured through celite and concentrated under reduced pressure. Flash chromatography (EtOAc/petroleum ether (bp 40–60 °C) 1:7) gave the phosphine (±)-**18** (R=PPh_2) as a white solid (1.15 g, 70%); R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:1] 0.67; δ_H (300 MHz; $CDCl_3$) 7.70 (1H, d, *J*=8 Hz, Ar*H*), 7.40 (13H, m, Ar*H*), 6.92 (1H, d, *J*=7 Hz, Ar*H*), 3.96 (3H, s, OCH_3), 3.64 [2H, 2 septets, *J*=7 Hz, NCH(CH_3)$_2$], 1.82 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.76 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.15 [3H, d, *J*=6 Hz, NCH(CH_3)$_2$], 1.05 [3H, d, *J*=6 Hz, NCH(CH_3)$_2$]; *m*/*z* (CI) 470 (80%, $(M+H)^+$), (EI) 470 (5%, $(M+H)^+$); Found (EI): $(M+H)^+$, 470.2248, $C_{30}H_{32}NPO_4$ requires $(M+H)^+$ 470.2249.

4.1.19. (−)-2-Diphenylphosphanyl-8-methoxynaphthalene-1-carboxylic acid diisopropylamide (−)-18 (R=PPh_2).[29] (a) From *M*-**15**. By the method reported for (±)-**18**, *M*-**15** (100 mg, 3.51 mmol) gave phosphine (−)-**18** (115 mg, 70%) as a white solid, mp 207–209 °C (lit.[29] 209–211 °C) $[\alpha]_D^{23}$ −75.8 (*c*=0.25, $CHCl_3$); R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:1] 0.67; δ_H (300 MHz; $CDCl_3$) 7.70 (1H, d, *J*=8 Hz, Ar*H*), 7.40 (13H, m, Ar*H*), 6.92 (1H, d, *J*=7 Hz, Ar*H*), 3.96 (3H, s, OCH_3), 3.64 [2H, 2 septets, *J*=7 Hz, NCH(CH_3)$_2$], 1.82 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.76 [3H, d, *J*=7 Hz, NCH(CH_3)$_2$], 1.15 [3H, d, *J*=6 Hz, NCH(CH_3)$_2$], 1.05 [3H, d, *J*=6 Hz, NCH(CH_3)$_2$]; *m*/*z* (CI) 470 (80%, $(M+H)^+$), (EI) 470 (5%, $(M+H)^+$); Found (EI): $(M+H)^+$, 470.2248, $C_{30}H_{32}NPO_4$ requires $(M+H)^+$ 470.2249. Enantiomeric excess was determined by HPLC (Whelk-O1) and was found to be greater than 95%.

(b) By direct sulfoxide lithium exchange: *t*-Butyllithium (1.5 equiv.) was added to sulfoxide *P*-**17** (40 mg, 0.1 mmol) in degassed THF (5 mL) at −78 °C under nitrogen. After 10 min freshly distilled chlorodiphenylphosphine was added. The mixture was stirred for a further 24 h at −78 °C, allowed to warm to RT, poured through celite and evaporated under reduced pressure. Flash chromatography

(EtOAc/petroleum ether (bp 40–60 °C) 1:7) gave the phosphine (−)-**18** as a white solid (27 mg, 60%); $[\alpha]_D^{23}$ −77.6 (c=0.5, $CHCl_3$). The enantiomeric excess was determined by HPLC on a chiral column (Whelk-O1) and was found to be greater than 95%.

4.1.20. (±)-8-Methoxy-2-methyl-naphthalene-1-carboxylic acid diisopropylamide (±)-19. Amide **15** (1.00 g, 3.51 mmol) was dissolved in 15 mL of THF under nitrogen atmosphere at −78 °C. *sec*-Butyllithium (1.3 equiv.) was added dropwise to the reaction mixture. The brown-orange solution was stirred at −78 °C for 2 h and iodomethane (2 equiv., 7.02 mmol) was added dropwise. After a further 1.5 h, saturated NH_4Cl was added. The mixture was extracted with CH_2Cl_2 (30 mL). The extracts were washed with water, dried with $MgSO_4$ and evaporated under reduced pressure. Flash chromatography (EtOAc/petroleum ether (bp 40–60 °C) 1:3) gave the amide (±)-**18** (R=Me) as a white solid (1.00 g, 95%); mp 223–224 °C; R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:1] 0.36; ν_{max} (film)/cm^{-1} 2963 (CH), 1622 (C=O); δ_H (300 MHz; $CDCl_3$) 7.60 (1H, d, J=8 Hz, Ar*H*), 7.25 (3H, m, Ar*H*), 6.76 (1H, d, J=7 Hz, Ar*H*), 3.83 (3H, s, OCH_3), 3.45 [2H, 2 septets, J=7 Hz, NC*H*(CH$_3$)$_2$], 2.41 (3H, s, ArCH_3), 1.60 [6H, m, NCH(CH_3)$_2$], 0.94 [6H, m, NCH(CH_3)$_2$]; δ_C (75 MHz; $CDCl_3$) 171.0 (C=O), 155.2, 133.5, 131.7 (×2), 129.4, 127.4, 125.3, 122.0, 120.8, 105.8, 55.2, 50.7, 45.7, 20.6, 20.5, 20.4, 19.7, 19.3; *m/z* (CI) 300 (100%, (M+H)$^+$), (EI) 299 (35%, M$^+$); Found (EI): M$^+$, 299.1893, $C_{19}H_{25}NO_2$ requires M, 299.1885.

4.1.21. (−)-8-Methoxy-2-methylnaphthalene-1-carboxylic acid diisopropylamide (−)-19. *t*-Butyllithium (1.5 equiv.) was added to sulfoxide *P*-**17** (40 mg, 0.1 mmol) in THF (5 mL) at −78 °C under nitrogen. After 10 min, methyl iodide was added, and after a further 2 h at −78 °C the mixture was allowed to warm to room temperature. The product was extracted with DCM, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography [EtOAc/petroleum ether (bp 40–60 °C) 1:3] yielded a white solid (20 mg, 74%) $[\alpha]_D^{23}$ −106.6 (c=0.2, $CHCl_3$). The enantiomeric excess was determined by HPLC on a chiral stationary phase (Whelk-O1) and was found to be >99%.

4.1.22. (±)-2-(1-Hydroxycylobutylmethyl)-8-methoxynaphthamide-1-carboxylic acid diisopropylamide (±)-20. *sec*-Butyllithium (1.1 equiv.) was added to amide (±)-**19** (100 mg, 0.27 mmol) in THF (5 mL) at −78 °C under nitrogen atmosphere. The resulting purple solution was stirred at −78 °C for 20 min and cyclobutanone was added dropwise. After 3 h the reaction mixture was allowed to warm to RT and saturated NH_4Cl was added. The mixture was extracted with CH_2Cl_2 (10 mL). The extracts were washed with water, dried with $MgSO_4$ and evaporated under reduced pressure. Flash chromatography (EtOAc/petroleum ether (bp 40–60 °C) 1:3) gave the alcohol **20** as a white solid (72 mg, 58%). Mp 147–149 °C; R_f [EtOAc/petroleum ether (bp 40–60 °C), 1:5] 0.20; ν_{max} (film)/cm^{-1} 3311 (OH), 2972 (CH), 1603 (C=O); δ_H (300 MHz; $CDCl_3$) 7.80 (1H, d, J=8 Hz, Ar*H*), 7.40 (3H, m, Ar*H*), 6.90 (1H, d, J=7 Hz, Ar*H*), 5.10(1H, s, OH), 3.96 (3H, s, OCH_3), 3.60 [1H, septet, J=6 Hz, NC*H*(CH$_3$)$_2$], 3.35 [1H, septet, J=6 Hz, NC*H*(CH$_3$)$_2$], 3.12(1H, s, ArCH_2R), 3.10 (1H, s, ArCH_2R), 2.40 [1H, m, CH$_2$COH(CH_2)$_2$CH$_2$], 2.30 [1H, m, CH$_2$COH(CH_2)$_2$CH$_2$], 2.00 [2H, m, CH$_2$COH(CH_2)$_2$CH$_2$], 1.72 [8H, m, NCH(CH_3)$_2$ and CH$_2$COH(CH_2)$_2$CH$_2$], 1.00 [6H, m, NCH(CH_3)$_2$]; δ_C ($CDCl_3$) 173.3 (C=O), 155.2, 134.1, 133.2, 132.2, 129.4, 128.3, 126.7, 126.3, 121.7, 121.2, 106.2, 74.8, 55.6, 51.3, 45.5, 42.0, 39.1, 34.7, 20.9, 20.8, 20.6, 19.5; *m/z* (CI) 370 (100%, (M+H)$^+$), (EI) 470 (10%, (M+H)$^+$); Found (EI): (M)$^+$, 369.2290, $C_{23}H_{31}NO_3$ requires (M)$^+$ 369.2304.

4.1.23. (−)-2-(1-Hydroxy-cylobutylmethyl)-8-methoxynaphthamide-1-carboxylic acid diisopropylamide (−)-20. In a similar way, enantiomerically pure amide (−)-**19** (100 mg, 0.27 mmol) in THF (5 mL) gave, after flash chromatography (EtOAc/petroleum ether (bp 40–60 °C) 1:3) alcohol (−)-**20** as a white solid (72 mg, 58%). $[\alpha]_D^{23}$ −96 (c=0.2, $CHCl_3$). ee >95% [HPLC, Whelk-O1].

Acknowledgements

We are grateful to the EPSRC and AstraZeneca for funding (to P.M.K.), to Dr. Rudolf Schmid of Roche (Basel) for a generous donation of 2,2′-bisbromo-1,1′-binaphthyl **6**, and to Dr. Madeleine Helliwell for determining the X-ray crystal structures of *P*-**12b**, *M*-**12b**, *P*-**14** and *P*-**17**.

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Tetrahedron 60 (2004) 4399–4412
Tetrahedron

Dynamic resolution of atropisomeric amides using proline-derived imidazolines and ephedrine-derived oxazolidines

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Received 15 December 2003; revised 19 January 2004; accepted 21 January 2004

Abstract—Condensation of atropisomeric tertiary 2-formyl naphthamides or 2-formyl benzamides with some chiral diamines and amino alcohols leads, via a dynamic resolution process, to single atropisomers of tertiary amides bearing chiral imidazolidines or oxazolidines. Hydrolysis of the new heterocycle competes a dynamic thermodynamic resolution of the starting aldehyde, and rapid reduction allows the isolation of atropisomeric amides bearing 2-hydroxymethyl substituents in enantiomerically enriched form. Evidence that the reactions are under thermodynamic control is presented.

1. Introduction

Tertiary aromatic amides are now well known to have the potential for atropisomerism: We,[1] and others,[2–4] have demonstrated that they are resolvable[5] by chromatography on a chiral stationary phase. Given the wide utility of other more well known classes of atropisomers such as the biphenyls and binaphthyls in asymmetric catalysis[6,7] (principally because of the flexibility inherent in a stereogenic axis as opposed to a stereogenic centre[8]), we set out to develop a method for the resolution of tertiary aromatic amides on a practical scale which would open up the opportunity for their development as a new family of chiral ligands based on the aromatic amide structure. A small number of enantiomerically pure atropisomeric amides have already been used as effective chiral ligands, being made in enantiomerically pure form either by classical resolution[9] or by asymmetric synthesis.[10,11] Dynamic kinetic resolution[12,13] and enantioselective lithiation[14–17] have also been used to synthesise atropisomeric amides in enantiomerically form, and some of these compounds have also been used as chiral reagents[4] and auxiliaries[18] or are of biological interest.[19–25] Our studies into the resolution of aromatic amides via the condensation of amidoaldehydes with 1,2-diamines and 1,2-amino-alcohols to form imidazolidines and oxazolidines are described in full in this paper.[26–28] During the course of this work, we discovered a remarkable propensity of the atropisomers being resolved to equilibrate and thus facilitate a dynamic resolution, a reaction which appears to be a member of the relatively small class of dynamic thermodynamic resolutions.[29]

2. Results and discussion

2.1. Starting materials

The known[30,31] 2-formyl naphthamides **1** were made in good yield from the parent amides by a modification of the ortholithiation conditions described by Beak and Brown,[32,33] quenching with DMF as electrophile (Scheme 1). The benzamides **2a**-**d** were also made by ortholithiation, though the ethyl group of **2c** was protected as its 1-silyl derivative to prevent competing lateral lithiation.[34] Ortholithiation and formylation of **3**[35] gave **4** which was desilylated to yield **2c**. **2d** was made from benzamide **5** by two successive ortholithiation reactions. **2e** was made from the mesitamide **7**[17] by lateral lithiation and hydroxylation to yield **8** which was oxidised with the Dess Martin periodinane[36,37] to the aldehyde.

2.2. Condensation with a proline-derived diamine

The documented easy formation and cleavage of aminals derived from 1,2-diamines[38] prompted us to try, initially, the proline-derived diamine **9**[39] as a resolving agent for these aldehydes. We heated **9**, which is available in two[40] or four[39] steps from pyroglutamate or proline respectively, with aldehydes **1a** and **1b** in toluene at reflux for 24 h. The NMR spectrum of the crude reaction mixture showed, surprisingly, only a single diastereoisomer (>90:10 diastereoselectivity) of the imidazolines **10a** and **10b**, and purification by chromatography on neutral alumina (the

Keywords: Atropisomeric amides; Imidazolines; Oxazolidines; Ephedrine.
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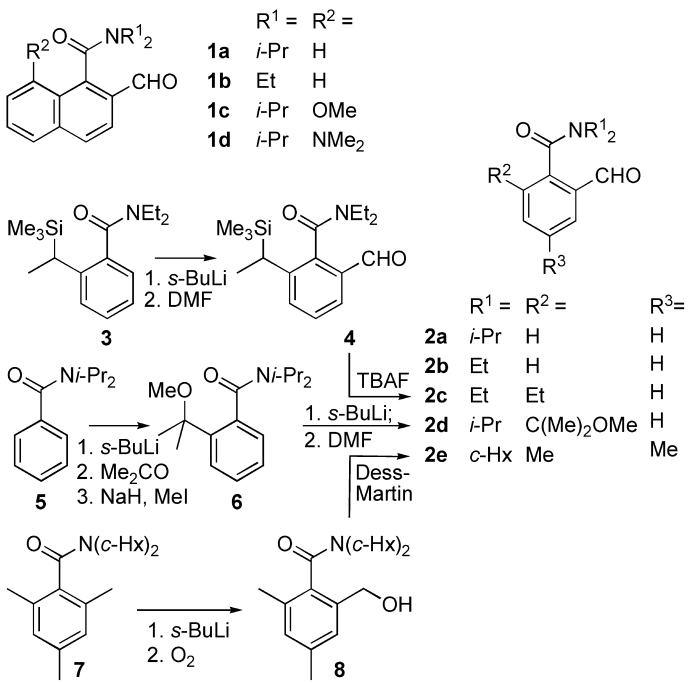
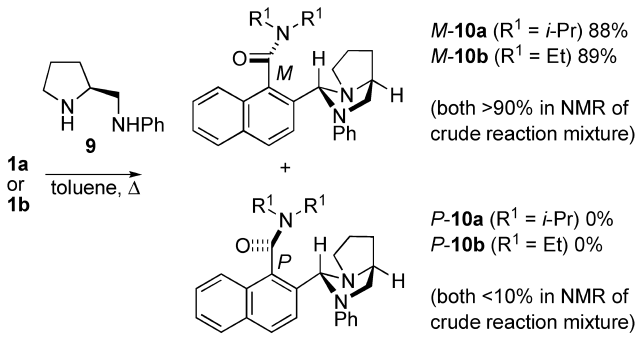
doi:10.1016/j.tet.2004.01.101



Scheme 1. The starting 2-formylnaphthamides.



Scheme 2. Synthesis of naphthamide-derived imidazolidines.

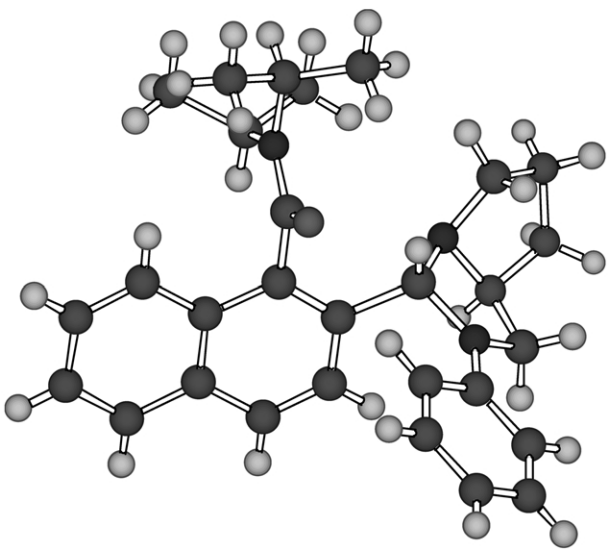
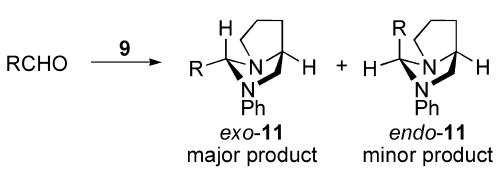


Figure 1. X-ray crystal structure of *M*-**10a**.

imidazolines are somewhat sensitive to chromatography on silica) allowed us to isolate these compounds in 88–89% yield (Scheme 2). X-ray crystallography (Fig. 1) proved the stereochemistry of *M*-**10a**.

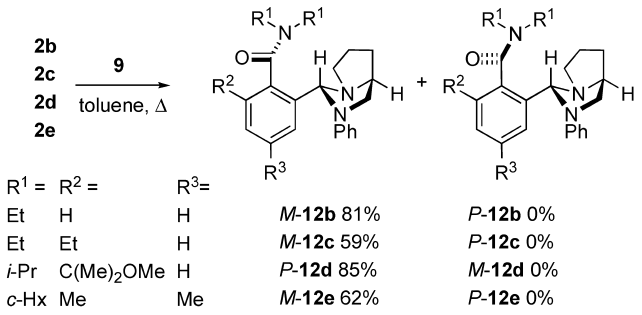
The formation of the imidazolines creates a new stereogenic centre at the aminal carbon, but based on previous results published by Mukaiyama[41] we expected this aspect of the reaction to be highly stereoselective: aldehydes RCHO tend to form imidazolidines *exo*-**11** rather than *endo*-**11**, which places R on the *endo* face of the bicyclic system (Scheme 3). However, the aldehydes **2** are chiral racemic compounds, so our initial expectation was that we would see the formation of *M*- and *P*-**10** in approximately equal quantities. The formation of a single isomer of **10a** and **10b** must indicate that rotation about the Ar–CO axis takes place under the conditions of the reaction, either before the formation of the imidazolidines, or both before and after their formation. In common with other atropisomers in which bond rotation is blocked by a trigonal carbon substituent,[42–44] the barrier to racemisation of aldehydes **1** and **2** is expected to be low relative to those bearing, say, a methyl group in the place of the formyl substituent: **1a** has a half-life of racemisation of only ca. 12 min at 20 °C,[43] which extrapolates to ca. 0.1 s at 110 °C, the temperature of the condensation. Naphthamides bearing branched substituents with a steric demand similar to the imidazolines of **10** have barriers to Ar–CO rotation of the order of 110 kJ mol^{-1},[43] which would suggest



Scheme 3. Typical stereoselectivity in the formation of proline-derived imidazolidines.

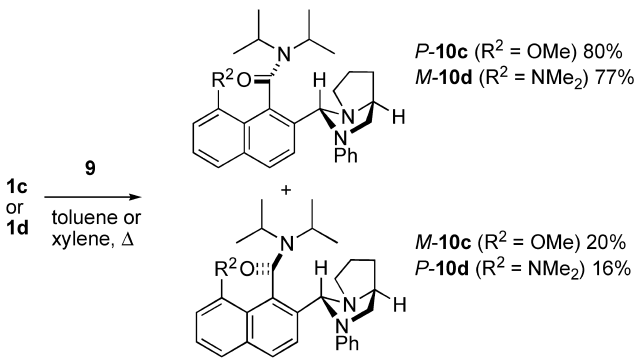
epimerisation of **10** should take place over a period of only minutes at 110 °C, easily within the timescale of the reaction. We shall return to the likely mechanism of the stereoselectivity later.

The same diamine **9** was condensed with 2-formyl benzamides **2b-e** and the reactions were similarly diastereoselective: ^{1}H NMR analysis of the crude reaction mixture indicated that the products were formed with at least >95% stereochemical purity (Scheme 4). Chromatography on alumina yielded pure imidazolines **12b-e** in good yield.



Scheme 4. Synthesis of benzamide-derived imidazolidines.

However, as previously reported,[18,45] diastereoselectivity in the condensation of the *peri*-substituted naphthamides **1c** and **1d** was rather poorer, with 20–25% of a minor epimer being evident in the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 5).



Scheme 5. Lower selectivity in more hindered *peri*-substituted naphthamides.

2.3. Condensation with chiral amino alcohols

Although condensation with the diamine **9** is a simple and versatile way of introducing chirality into the atropisomeric amides, **9** is rather expensive commercially and its synthesis, though not difficult, poses some practical problems on scale-up.[46] Moreover, we found that the imidazolidines were unstable to further lithiation reactions: attempted ortholithiation[33] of **12b** or lateral lithiation[47] of **12c** gave complex mixtures of products. We, therefore, sought a more readily available 'resolving agent', especially one which would be stable to lithiation conditions.

We chose readily available aminoalcohols (1*R*,2*S*)-(−)-ephedrine and (1*S*,2*S*)-(+)-pseudoephedrine as likely candidates. Both are known to condense with aldehydes to yield stable imidazolidines **15** with good, though not perfect, stereocontrol at the new stereogenic centre (Scheme 6).[48–51] Condensation of **1a** with ephedrine and with pseudoephedrine, and **1b** with ephedrine, gave essentially single diastereoisomers of the product imidazolines **16** and **17**, which were isolated after chromatography on silica (the oxazolidines are more stable to silica than the imidazolines) in good yield (Scheme 7). The stereochemistry of **16a** was proved by an X-ray crystal structure (Fig. 2), and is consistent with the expected 'all-*syn*' stereochemistry[51,50] which allows the four oxazolidine substituents in **16** to lie pseudoequatorial on the new five-membered ring.

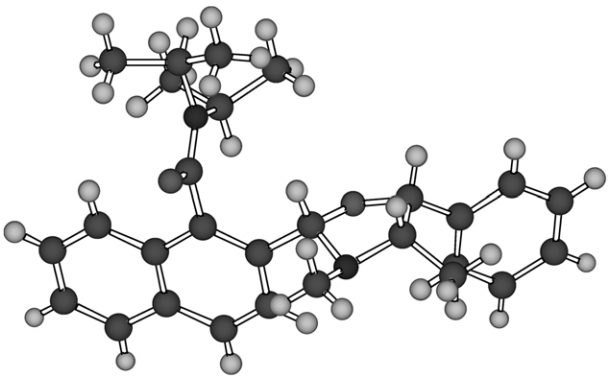
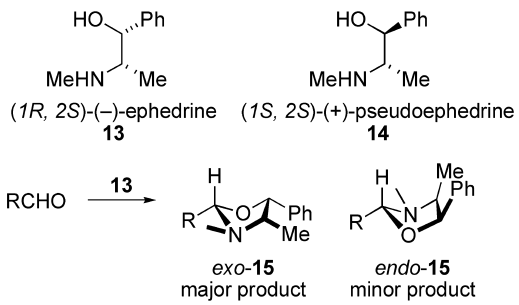
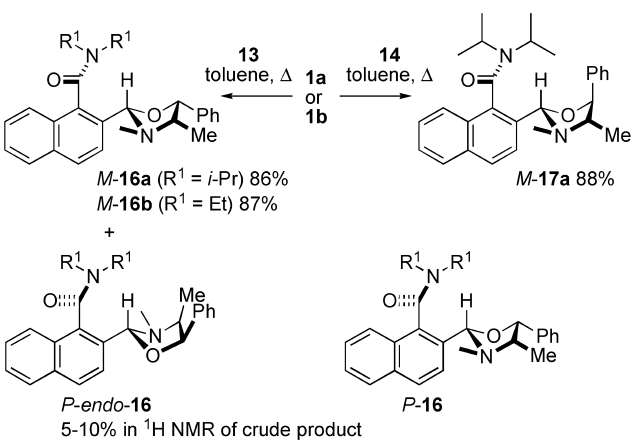


Figure 2. X-ray crystal structure of *M*-**16a**.

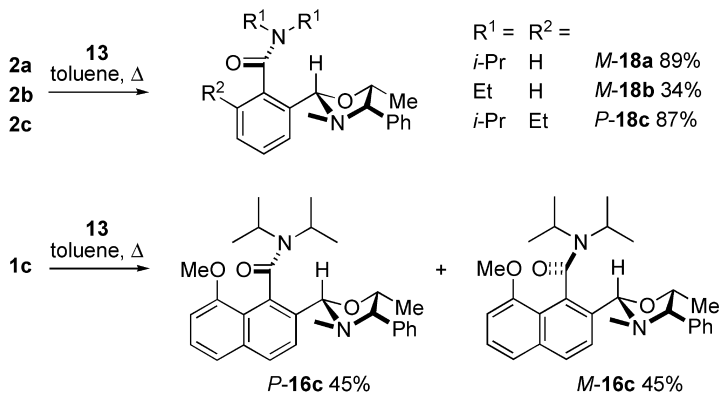
The ^{1}H NMR spectra of the crude products **16** showed consistently 5–10% of a minor diastereoisomer, unlike those of the crude products **10** which were essentially free of diastereoisomeric impurities. Although we were unable to isolate and fully characterise this diastereoisomer, it had a distinctive pattern of signals in the region of 5–6 ppm



Scheme 6. Oxazolidines from ephedrine.



Scheme 7. Synthesis of naphthamide-derived oxazolidines.



Scheme 8. Oxazolidines from benzamides and a *peri*-substituted naphthamide.

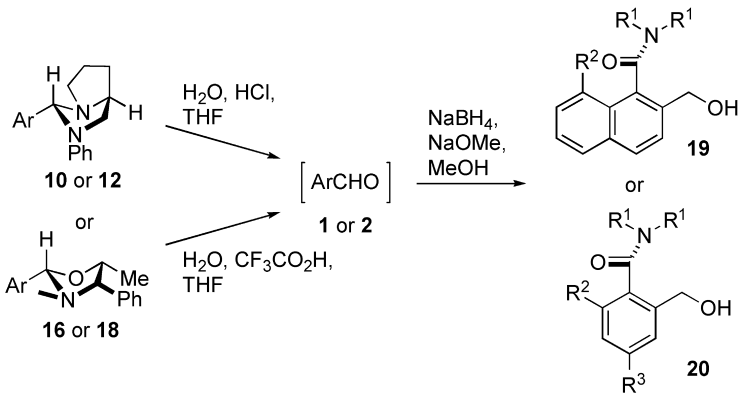
which we have found in other work[52] to be characteristic of ephedrine-derived oxazolidines with *endo* relative stereochemistry (Scheme 6). Indeed, condensations of aldehydes with ephedrine typically give varying amounts of the *endo* product, according to solvent and conditions,[51,50] and for this reason we assume this minor diastereoisomer is *P*-*endo*-**16** rather than the alternative *P*-**16**, of which we saw no sign (<5% by NMR). Nonetheless, it was a straightforward matter to remove this minor impurity during purification.

Condensation of the aldehydes **2a**-**2c** with (−)-ephedrine was similarly diastereoselective, with the oxazolidines **18a**-**18c** being formed with high diastereoselectivity, even if instability towards hydrolysis led to a low yield after purification in one case (Scheme 8). As with the diamine **9**, condensation of a hindered *peri*-substituted naphthamide with (−)-ephedrine gave much poorer selectivities, and **1c** gave a 1:1 mixture of the two diastereoisomers of **16c** in 90% yield.[45]

2.4. Completion of the resolution: hydrolysis of the imidazolidines and oxazolidines

Hydrolysis of the imidazolidines and oxazolidines back to the aldehydes **1** and **2** should complete a method for the dynamic resolution of **1** and **2**. However, as noted before, atropisomeric 2-formyl amides have low barriers to racemisation relative to structurally similar amides bearing tetrahedral 2-substituents.[43,53] The products of hydrolysis are, therefore, likely to racemise too fast for it to be possible to isolate them in enantiomerically enriched form. We, therefore, sought conditions which would allow us to remove the resolving agent (the diamine or aminoalcohol), preferably by hydrolysis at low temperature, and then rapidly reduce the formyl group to a methyl or hydroxymethyl substituent.

After a series of trial hydrolyses, we found that the imidazolidine **10a** was completely hydrolysed by 1 M aqueous HCl in THF at 0 °C over a period of 30 min.



Scheme 9. Deprotection and recovery of enantiomerically enriched amides.

Table 1. Completion of the resolution

Entry	S.M.	Conditions	Product	Yield	ee	Overall yield from **1** or **2**[a]
1	**10a**	1 M HCl	(−)-**19a**	94	89	83
2	**10b**	1 M HCl	(−)-**19b**	84	97	75
3	**12d**	1 M HCl	(−)-**20d**	90	77	77
4	**12e**	1 M HCl	(−)-**20e**=(−)-**8**	93	53	58
5	**16a**	CF_3CO_2H	(−)-**19a**	85	74	73
6	**16b**	CF_3CO_2H	(−)-**19b**	85	74	74

[a] Representing the efficiency of the resolution.

Hydrolysis of the ephedrine-derived oxazolidines was much slower, and remaining starting material was evident even after treatment with 6 M HCl in THF at 0 °C for 30 min. However, stirring with a excess of trifluoroacetic acid in wet THF at 0 °C for 30 min promoted complete hydrolysis of the oxazolidine to the aldehyde.

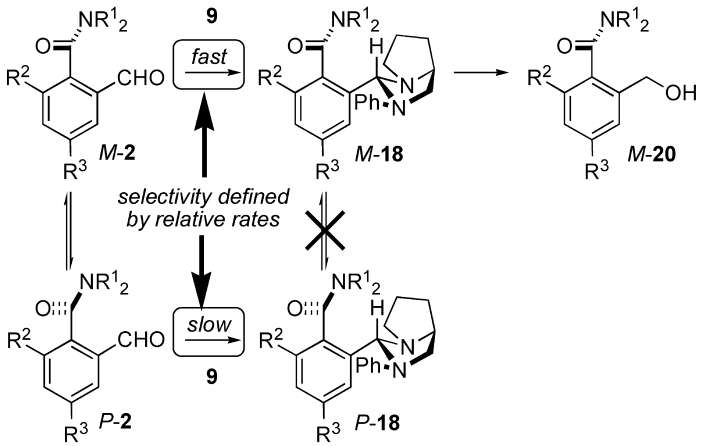
Reduction of the aldehyde to the alcohol was achieved by adding a large excess of sodium borohydride to the acidic solution containing the crude aldehydes. Because of the low pH, the borohydride rapidly decomposed somewhat exothermically under these conditions, and for reduction of the imidazolidine-derived aldehydes we added the sodium borohydride as a cold slurry in a solution of sodium methoxide in ethanol. A later improvement, which was used for reduction of the oxazolidine-derived aldehydes, was to add first an excess of methoxide to neutralise the trifluoroacetic acid and then to add the borohydride. Scheme 9 and Table 1 detail the application of these conditions for hydrolysis and reduction to the imidazolidines **10** and **12** and oxazolidines **16**. For determination of ee, where necessary, racemic alcohols **19** and **20** were also made by sodium borohydride reduction of the racemic aldehydes **1** and **2**.

In many cases, excellent enantiomeric excesses were observed in the atropisomeric hydroxymethyl amide products, and overall yields for the condensation–hydrolysis–reduction sequence which results in resolution of racemic aldehyde to enantiomerically pure alcohol were in most cases well over 50% (final column), demonstrating the very practical nature of this dynamic resolution process. In general, the ees obtained from the oxazolidines were lower, reflecting the harsher conditions necessary to force the hydrolysis to completion, and the imidazolidine method is to be preferred as a method for dynamic resolution.

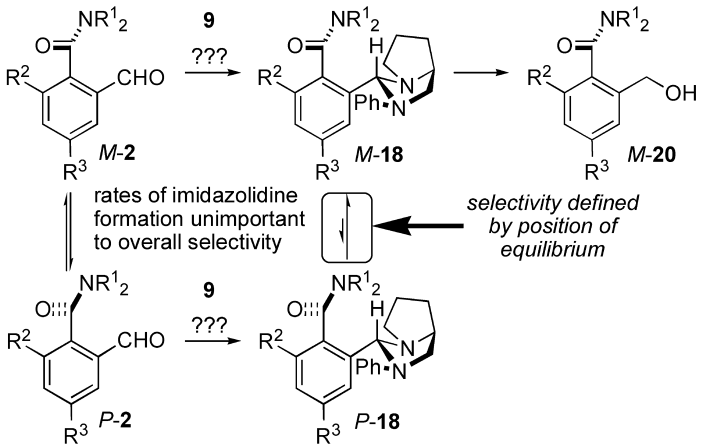
2.5. Mechanism of the resolution and origin of the stereoselectivity

When we set out to resolve racemic, atropisomeric aldehydes **1** and **2c-e**, we expected to obtain a 1:1 diastereoisomeric mixture of the imidazolidines **10** and **12** and the oxazolidines **16-18**. Formation of anything other than a 1:1 mixture of atropisomers of **10** and **12** can be explained only by dynamic resolution, involving Ar–CO bond rotation. As explained earlier, the conditions of the condensation reaction are such that for most of the aldehyde starting materials Ar–CO rotation is likely to be rapid prior to condensation and still possible over a period of minutes even after condensation.

Two distinct dynamic resolution mechanisms are possible, both of which may be operative at least to some extent. One



Scheme 10. Dynamic kinetic resolution of **2**.



Scheme 11. Dynamic Thermodynamic resolution of **2**.

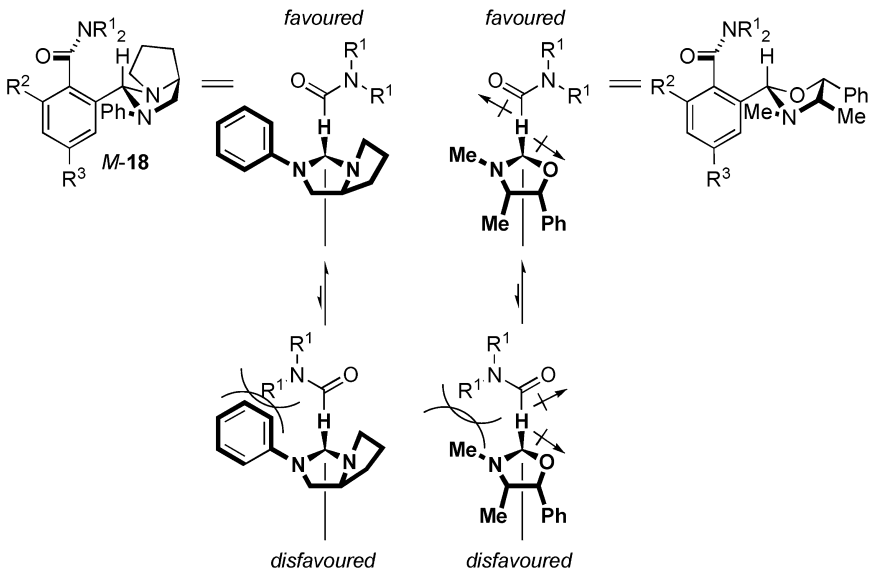
amounts to a dynamic resolution under kinetic control;[54–57] the other a dynamic resolution under thermodynamic control.[29] In the first, equilibration between stereoisomers by rotation about the Ar–CO bond occurs before formation of the imidazoline or oxazolidine; one enantiomer of the aldehyde reacts with the aldehyde faster than the other, and an excess of one product stereoisomer is formed (Scheme 10). In the second, stereochemistry is defined by equilibration after the formation of the imidazolines: whatever the initial ratio of products, the final product ratio is defined by their relative stability and not by their relative rate of formation (Scheme 11). We were unable to prove conclusively which mechanism operates, but we have strong evidence that the stereoselectivity of the reactions both with the diamine **9** and with ephedrine **13** is under thermodynamic control, that is, Scheme 11 best represents the mechanism of the resolution.

First, we repeated the condensation of **1a** with **9**, but allowed it to take place in an NMR tube in C_6D_6. NMR showed that as starting material disappeared at 20 °C, two products in a proportion of 3:1 were seen to increase in concentration. The minor product was the imidazolidine *M*-**10a** which we had previously isolated; the major product, however, appeared to be an epimer of **10a**, probably *P*-**10a**, although a structure related to *endo*-**11** cannot be ruled out. Attempts to characterise this epimer fully failed, though HPLC allowed us to obtain a small quantity which converted to *M*-**10a** on standing at ambient temperature for 20 min. Since *M*-**10a** is clearly not the kinetic product of the condensation, the stereoselectivity of the reaction must be due to control by an alternative, presumably thermodynamically controlled, mechanism. If the major epimer formed under kinetic control is indeed *P*-**10a** then interestingly a dynamic kinetic resolution appears to be operating inconsequentially in the opposite direction from the overall dynamic resolution.

Supporting evidence that a dynamic kinetic resolution is not the origin of the stereoselective formation of **10**, **12**, **16** or **18** is provided by two further observations. First, in the condensation of **1c** or **1d** with **9** or **13** (Schemes 5 and 8) to yield **10c**, **10d** and **16c**, a dynamic thermodynamic resolution is prevented by very high barriers to Ar–CO rotation in the *peri*-substituted products, though dynamic kinetic resolution should still be possible because of the lower barriers to Ar–CO rotation in the aldehydes **10c** and **10d**.[43,58] Yet selectivity is poor, suggesting that interconversion of the imidazolidine or oxazolidine products is necessary for good stereoselectivity.

Second, the imidazolidine **12a**, and the oxazolidines **18a** and **18b**, in which the Ar–CO bond is free to rotate (a typical tertiary amide bearing a single branched 2-substituent shows a half-life for Ar–CO rotation of the order of 0.01 s at 20 °C[43,35]) all exist as single conformers (>95:5 by NMR: Ar–CO rotation in such amides is slow on the NMR timescale). Evidently structures **12** and **18** display a thermodynamic preference for the stereochemistry of *M*-**18** (Scheme 11) when equilibration of the products is possible, a preference which is likely to persist in related structures **10**, **12**, **16** and **18**.

We therefore propose that the selectivity of all the condensation reactions arises because whatever the initial ratio of atropisomers formed in the condensation, interconversion of the products in refluxing toluene allows them to equilibrate to a ratio which is almost entirely the stereoisomer shown as, or analogous to, *M*-**18** in Scheme 11. Our proposed rationale for the favourability of this isomer, both for the imidazolidines and the oxazolidines, is illustrated in Scheme 12. In both series, we presume the benzylic stereogenic centre must arrange itself such that its smallest substituent, the C–H bond, more or less eclipses the amide group. For the imidazolidines, the favoured isomer allows the bulky *N*,*N*-dialkyl group of the amide to lie *anti* to the *N*-phenyl substituent. For the oxazolidines, the *N*,*N*-dialkyl group must choose between lying *syn* to N–Me or to smaller O, and presumably favours the latter, Moreover, an electronic factor presumably also favours the alignment of the amide C=O dipole and the oxazolidine C–O dipole *anti* to one another.



Scheme 12. Conformational preference in amidoimidazolidines and amidooxazolidines.

3. Conclusion

Condensation of 2-formyl benzamides and naphthamides with the proline-derived diamine **9** or with (−)-ephedrine **13** yields single atropisomers of imidazolidine or oxazolidine products by a process of dynamic thermodynamic resolution. Enantiomerically enriched products may be obtained by subsequent deprotection of these compounds by hydrolysis in aqueous acid, though for isolation of products in good ee it is necessary to 'fix' the stereochemistry of the aldehydes by immediate reduction to the corresponding alcohols.

Dynamic thermodynamic resolution protocols seem particularly well-suited for the synthesis of enantiomerically enriched atropisomers, in which epimerisation may be the result merely of thermally induced bond rotation. More recent developments of this work,[59] to be reported shortly in full, have employed sulfinyl substituents as versatile alternatives to the imidazolidinyl or oxazolidinyl groups described here.

4. Experimental

4.1. General

Aldehydes **1a**,[43] **1b**,[30] **2a**[60] and **2b**[61] were made by published methods.

X-ray crystal structures of *M*-**10a** and *M*-**16a** have been deposited with the Cambridge Crystallographic Database, Deposition numbers: *M*-**10a**: 228413; *M*-**16a**: 166016.

All commercially available solvents are distilled before use. Tetrahydrofuran (THF) was dried over sodium and distilled under dry nitrogen using benzophenone as an indicator. Dichloromethane was distilled from calcium hydride under an atmosphere of nitrogen. Toluene was distilled using a Dean–Stark apparatus and stored over 4 Å molecular sieves. 'Petrol' refers to petroleum ether (bp 40–60 °C); 'ether' refers to diethyl ether.

Thin layer chromatography (TLC) was performed using commercially available Macherey-Nagel 0.25 mm silica gel pre-coated aluminum sheets with fluorescent indicator UV_{254}. In the cases of the imidazolidines, TLC was performed on Merck neutral aluminum oxide pre-coated aluminum sheets. Flash chromatography refers to chromatography carried out on Merck silica gel 60H (40–63 m, 230–300 mesh) stationary phase by the method of Still, Kahn and Mitra.[62]

Analytical HPLC was carried out on a Chiralpak AD, 25 cm×4.6 mm ID or (*R*,*R*) Whelk-01, 25 cm×4.6 mm ID column at room temperature using a Merck Hitachi L-6200 Intelligent pump, typically eluting with 10% ethanol in hexane, flow rate 1 mL/min, 10 μL injection. Detection was carried out using a Merck L-300 Photo Diode Array System at UV absorbance at 280 nm.

^{1}H NMR spectra were recorded on a Varian XL 300 spectrometer at 300 MHz, a Bruker XC300 (300 MHz) or a Varian Unity 500 (500 MHz); ^{13}C NMR spectra were recorded on a Bruker XC300 (75 MHz) or a Varian Unity 500 (125 MHz). Chemical shifts are quoted in part per million downfield from tetramethylsilane. Coupling constants *J* are given in Hertz (Hz).

Infrared spectra were recorded on an ATI Genesis Series FTIR and only structurally significant peaks are listed. Mass spectra were recorded on a Fisons VG Trio 2000 (EI/CI and FAB) or a Concept IS (HRMS) Spectrometer.

Micronanalyses were performed using a Carlo-Erba combustion analyzer on C, H or N. Melting points are uncorrected and were carried out on a Gallenkamp melting point apparatus. Optical rotations were performed using an AA-100 polarimeter and are quoted in units of $^\circ\,g^{-1}\,mol\,dm^{-1}$.

4.1.1. *N*,*N*-Diethyl-2-formyl-6-(1-trimethylsilylethyl)-benzamide 4. *N*,*N*-Diethyl-2-(1-trimethylsilyl)ethylbenzamide **3**[35] (831 mg, 3.0 mmol) in THF (10 mL) was added dropwise to a stirred solution of *sec*-butyllithium (6 mL of a 1.5 M solution in cyclohexane, 3.0 equiv.) and TMEDA (1.35 mL, 9.0 mmol, 3.0 equiv.) in dry THF (40 mL) at −78 °C under an atmosphere of nitrogen. After 60 min, DMF (0.93 mL, 12.0 mmol, 4.0 equiv.) was added. The mixture was warmed to ambient temperature (colour change from dark yellow/orange to colourless) and stirred overnight. Water was added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3×30 mL). The organic fractions were combined and washed with brine (50 mL), water (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to afford the aldehyde **4** (871 mg, 95%) as a rapidly interconverting mixture of diastereoisomeric atropisomers/conformers, which were used without further purification. δ_H (300 MHz; $CDCl_3$) (Peaks for major atropisomer/conformer) 9.99 (1H, s, C*H*O), 7.70 (1H, dd, *J*=6, 3 Hz, Ar*H*), 7.48–7.41 (3H, m, Ar*H*), 3.71 (1H, dq, *J*=14, 7 Hz, NCH_2), 3.54 (1H, dq, *J*=14, 7 Hz, NCH_2), 3.08 (2H, m, NCH_2), 2.15 (1H, m, C*H*SiMe$_3$), 1.38 (3H, t, *J*=8 Hz, NCH$_2$CH_3), 1.31 (3H, t, *J*=7 Hz, NCH$_2$CH_3), 0.99 (3H, t, *J*=7 Hz, CH$_2$CH_3), 0.0 [12H, s, Si(CH$_3$)$_3$]; δ_C (75 MHz, $CDCl_3$) (Peaks for major atropisomer/conformer) 191.0 (C=O), 167.7 (C=O), 144.1, 137.6, 132.3, 128.4, 126.5, 125.5 (aromatics), 42.5 (NCH$_2$), 38.7 (NCH$_2$), 25.2 (*C*H$_2$CH$_3$), 16.2, 13.7 (NCH$_2$CH_3), 12.4 (CH$_2$CH_3), 3.0 (Si*Me*$_3$).

4.1.2. *N*,*N*-2-Triethyl-6-formylbenzamide 2c. *tetra-n*-Butylammonium fluoride (4.0 equiv. of a 1 M solution in THF) was added to a stirred solution of benzamide **4** (871.8 mg, 2.85 mmol) in THF (20 mL). The crude mixture was filtered though a pad of Celite® which was washed with THF (20 mL). The solvent was evaporated to give a crude product which was purified by chromatography eluting with petrol/EtOAc (5:1) to afford benzamide **2c** (168.2 mg, 24%) as an oil. δ_H (300 MHz; $CDCl_3$) 10.05 (1H, s, C*H*O), 7.82 (1H, dd, *J*=7, 1 Hz, Ar*H*), 7.59 (1H, dd, *J*=7, 1 Hz, Ar*H*), 7.52 (1H, t, *J*=8 Hz, Ar*H*), 3.76 (1H, dq, *J*=14, 7 Hz, NCH_2), 3.64 (1H, dq, *J*=14, 7 Hz, NCH_2), 3.12 (2H, t, *J*=7 Hz, NCH_2), 2.68 (2H, m, CH_2CH$_3$), 1.37 (3H, t, *J*=7 Hz, NCH$_2$CH_3), 1.31 (3H, t, *J*=8 Hz, CH$_2$CH_3), 1.04 (3H, t, *J*=7 Hz, NCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 190.09 (C=O),

167.9 (C=O), 141.0, 138.4, 132.2, 134.3, 128.8, 127.4 (aromatics), 42.7 (NCH_2), 38.6 (NCH_2), 25.2 (CH_2CH_3), 14.8, 13.5 (NCH_2CH_3), 12.4 (CH_2CH_3); ν_{max}(thin film)/cm^{-1} 1690 (aldehyde C=O), 1628 (amide C=O); *m/z* (CI) 234 (100%, $M+H^+$); *m/z* (EI) 234 (10.3%, $M+H^+$), 204 (100%, $M-CH_2CH_3$), 161 (73%, $M+H^+-CHO$ and NCH_2CH_3). (Found: $M+H^+$ 234.1487; $C_{14}H_{19}NO_2$ requires $M+H^+$ 234.1495).

4.1.3. *N*,*N*-Diisopropyl-2-(1-methoxy-1-methylethyl)-benzamide 6. *sec*-Butyllithium (13.6 mL of a 1.4 M solution in cyclohexane, 19 mmol, 1.3 equiv.) was added dropwise to a stirred solution of *N*,*N*-diisopropylbenzamide **5**[32] (3.0 mg, 14.6 mmol) in dry THF (40 mL) at −78 °C under an atmosphere of nitrogen. After 60 min at −78 °C, dry, distilled acetone (1.88 mL, 30 mmol, 2.0 equiv.) in THF (10 mL) was added dropwise to the reaction mixture. The mixture was warmed to ambient temperature (colour change from dark cloudy brown to clear) and water was added. Most of the THF was removed by evaporation under reduced pressure and the aqueous residue was extracted with diethyl ether (3×30 mL). The organic fractions were combined and washed with brine (50 mL), water (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to afford an oil, which was purified by flash chromatography, eluting with petrol/EtOAc (85:15, R_f 0.17) to yield the adduct (1.56 g, 40.6%) as a white crystalline solid, mp 82.3–83.1 °C; δ_H (300 MHz; $CDCl_3$), 7.40–7.29 (2H, m, Ar*H*), 7.25 (1H, td, *J*=7, 2 Hz, Ar*H*), 7.15 (1H, d, *J*=7 Hz, Ar*H*), 3.87–3.84 (1H, broad s, O*H*), 3.76 (1H, septet, *J*=7 Hz, NC*H*), 3.53 (1H, septet, *J*=7 Hz, NC*H*), 1.69 (3H, s, C(OH)CH_3CH$_3$), 1.6 (3H, d, *J*=7 Hz, NCHCH_3), 1.59 (3H, s, C(OH)CH$_3$CH_3), 1.57 (3H, d, *J*=7 Hz, NCHC*H*), 1.2 (6H, d, *J*=7 Hz, NCHCH_3CH_3); δ_C (75 MHz, $CDCl_3$), 174.2 (C=O), 145.9, 135.1, 128.3, 126.9, 126.2 (aromatics), 73.3 (*C*OH), 32.5, 31.0 (C*C*H$_3$), 20.3, 20.1, 19.7 (NCHCH$_3$CH$_3$); ν_{max}(thin film)/cm^{-1} 2886, 1609 (C=O); *m/z* (CI) 264 (100%, $M+H^+$), 246 (53.8%, $M+H^+-OH$); *m/z* (EI) 264 (100%, $M+H^+$), 246 (16.6%, $M+H^+-OH$). Found: *M* 263.1888; $C_{16}H_{25}NO_2$ requires *M* 263.1885. Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32. Found C, 73.07, H, 9.38, N, 5.22.

This alcohol (500 mg, 1.9 mmol) was dissolved in dimethylformamide (15 mL). Sodium hydride (0.17 g of a 60% suspension in mineral oil) was added at 0 °C. After 95 min, methyl iodide was added (0.5 mL, excess). The mixture was allowed to room temperature and stirred overnight. Water was added, and the mixture was extracted with ether (2×30 mL). The organic extracts were washed with brine (3×50 mL), dried ($MgSO_4$), filtered and concentrated to yield an oil which was purified by flash chromatography, eluting with 7:1 petrol/EtOAc) to afford the amide **6** (357.5 mg, 68%) as a white crystalline solid, mp 84.7–85.9 °C. δ_H (300 MHz; $CDCl_3$) 7.48 (1H, d, *J*=8 Hz, Ar*H*), 7.31 (1H, t, *J*=7 Hz, Ar*H*), 7.23 (1H, t, *J*=7 Hz, Ar*H*), 7.06 (1H, d, *J*=7 Hz, Ar*H*), 3.69 (1H, septet, *J*=7 Hz, NC*H*), 3.47 (1H, septet, *J*=7 Hz, NC*H*), 3.23 (3H, s, OCH_3), 1.55–1.42 (12H, m, NCHCH_3CH_3 and COCH$_3$(CH_3)$_2$), 1.14 (3H, d, *J*=7 Hz, NCHCH$_3$CH_3), 1.09 (3H, d, *J*=7 Hz, NCHCH_3CH$_3$); δ_C (75 MHz, $CDCl_3$), 171.9 (C=O), 143.8, 136.7, 127.8, 126.6, 126.4 (aromatics), 77.6 (*C*OCH$_3$), 51.0 (N*C*H), 49.6 (O*C*H$_3$), 45.2 (N*C*H), 27.4, 26.4 (C*C*H$_3$*C*H$_3$), 20.3, 20.3, 20.1, 19.7 (NCH*C*H$_3$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 2970, 2929, 1631 (C=O); *m/z* (CI) 278 (100%, $M+H^+$), 246 (55%, $M-OCH_3$); *m/z* (EI) 278 (4%, $M+H^+$), 145 (100% $M-OCH_3$, NCH(CH$_3$)$_2$CH(CH$_3$)$_2$). Found: *M* 277.2044; $C_{17}H_{27}NO_2$ requires *M* 277.2042.

4.1.4. *N*,*N*-Diisopropyl-2-formyl-6-(1-methoxy-1-methylethyl)benzamide 2d. By the method for the lithiation of **3** in the preparation of **4**, amide **6** (500 mg, 1.80 mmol) was treated with *sec*-BuLi and quenched with DMF (2 equiv.). The crude product was purified by flash chromatography, eluting with petrol/EtOAc (85:15, R_f=0.17) to yield aldehyde **2d** (165 mg, 30%) as a white crystalline solid, mp 88.3–91.7 °C. δ_H (300 MHz; $CDCl_3$) 10.1 (1H, s, CHO), 7.8 (1H, d, *J*=8 Hz, ArH), 7.59 (1H, d, *J*=8 Hz, ArH), 7.34 (1H, t, *J*=8 Hz, ArH), 3.56–3.3 (2H, m, NCH), 3.18 (3H, s, OCH$_3$), 1.55–1.48 (12H, m, NCHCH_3CH_3 and COCH$_3$(CH_3)$_2$), 1.07 (3H, d, *J*=7 Hz, NCHCH$_3$CH_3), 0.88 (3H, d, *J*=7 Hz, NCHCH_3CH$_3$); δ_C (75 MHz, $CDCl_3$), 191.7 (C=O), 145.0, 138.9, 132.9, 132.8, 128.0, 126.1 (aromatics), 78.0 (*C*OCH$_3$), 51.0 (NCH), 49.3 (OCH$_3$), 46.2 (NCH), 27.3, 26.3 (CCH$_3$), 20.4, 20.1, 20.0, 19.5 (NCH*Me*$_2$); ν_{max}(thin film)/cm^{-1} 1690 (aldehyde C=O), 1628 (amide C=O);; *m/z* (CI) 306 (100%, $M+H^+$); *m/z* (EI) 306 (100%, $M+H^+$). Found: $M+H^+$ 306.2065; $C_{18}H_{27}NO_3$ requires $M+H^+$ 306.2071. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.61, H, 9.03, N, 4.16.

4.1.5. *N*,*N*-Dicyclohexyl-2-hydroxymethyl-4,6-dimethylbenzamide 8. *sec*-Butylithium (1.4 mL of a 1.4 M solution in cyclohexane, 2 mmol) was added to a stirred solution of *N*,*N*-dicyclohexyl-2,4,6-trimethylbenzamide **7**[17] (500 mg, 1.53 mmol) in THF under argon at −78 °C. The resulting orange solution was stirred for 60 min. Oxygen was bubbled though the reaction solution for 20 min, when the mixture became colourless. (TLC, 1:1 petrol/EtOAc: starting material R_f 0.58, product alcohol R_f 0.39; traces of aldehyde also present at R_f 0.52). Water was added and the mixture was extracted with ether (3×30 mL). The combined organic extracts were washed with brine (3×30 mL), dried ($MgSO_4$) and concentrated to an oil which was purified by flash chromatography, eluting with petrol/EtOAc (4:1) to yield the alcohol **8** (330.1 mg, 63%) as a white crystalline solid, mp 142.7–144.6 °C. δ_H (300 MHz; $CDCl_3$) 7.06 (1H, s), 6.90 (1H, s), 4.54 (1H, d, *J*=13 Hz, CH_AH_BOH), 4.29 (1H, d, *J*=13 Hz, CH_AH_BOH). 3.97–3.71 (1H, broad s, O*H*), 3.21–2.99 (2H, m, NC*H*), 2.98–2.56 (2H, m, cyclohexyl-*H*), 2.95 (3H, s, CCH_3), 2.22 (3H, s, CCH_3), 1.96–0.72 (20H, m, cyclohexyl-*H*); δ_C (75 MHz, $CDCl_3$) 170.9 (C=O), 137.6, 136.9, 134.0, 132.6, 129.7, 126.8 (aromatics), 62.8 (*C*N), 60.0 (*C*H$_2$OH), 56.1 (*C*N), 31.3, 31.2, 29.7, 29.7, 26.5, 25.5, 25.5, 25.2, 25.0 (cyclohexyl carbons), 21.0, 18.7 (C*C*H$_3$); ν_{max}(thin film)/cm^{-1} 3339 (OH), 1609 (CO).

4.1.6. *N*,*N*-Dicyclohexyl-2-formyl-4,6-dimethylbenzamide 2e. A solution of *N*,*N*-dicyclohexyl-2-hydroxymethyl-4,6-dimethylbenzamide **8** (476.7 mg) in CH_2Cl_2 (20 mL) was added to a stirred solution of the Dess Martin reagent[36,37] (707.9 mg, 1.2 equiv.) in CH_2Cl_2 (20 mL). After 30 min, the mixture was diluted with ether (50 mL), and 1.3 M NaOH (100 mL) was added. After stirring for 20 min, the aqueous mixture was extracted with ether

(2×20 mL), and the extracts washed with 1.3 M HCl (2×20 mL), brine (2×30 mL) and dried ($MgSO_4$). Concentration under reduced pressure gave an oil which was purified by flash chromatography, eluting with petrol/EtOAc (9:1) to yield the aldehyde **2e** (291.9 mg, 62%) as a white crystalline solid, mp 149.9–151.2 °C; R_f=0.52 (1:1 petrol/EtOAc); δ_H (300 MHz; $CDCl_3$) 9.95 (1H, s, CHO), 7.48 (1H, s, C*H*CCH$_3$), 7.19 (1H, s, C*H*CCH$_3$), 3.08–2.88 (2H, m, NCH), 2.31 (3H, s, CH$_3$), 2.24 (3H, s, CH$_3$), 1.83–1.74 (2H, m, CH$_2$), 1.68–1.53 (8H, m, CH$_2$), 1.50–1.07 (10H, m, CH$_2$); δ_C (75 MHz, $CDCl_3$) 191.0 (*C*HO), 168.1 (C=O), 138.4, 137.9, 136.9, 134.4, 131.9, 126.5 (aromatics), 60.1 and 56.4 (N*C*H), 31.4, 30.9, 29.8, 29.6, 26.5, 25.6, 25.5, 25.2, 24.9 (cyclohexyl), 20.9 and 19.3 (*C*H$_3$); ν_{max}(thin film)/cm^{-1} 1696 (CHO), 1625 (CO); *m/z* (CI) 342 (100%, *M*+H$^+$); *m/z* (EI) 342 (3%, *M*+H$^+$−CH(CH$_3$)$_2$ CH(CH$_3$)$_2$). Found: *M* 341.2359; $C_{22}H_{31}NO_2$ requires *M* 341.2355. Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.38; H, 9.15, N, 4.10. Found C, 77.78, H, 9.15, N, 4.08.

4.1.7. (*M*,2′*R*,4′*S*)-*N*,*N*-Diisopropyl-2-[-2-phenylperhydropyrrolo-(1,2*c*)-imidazol-3-yl]-1-naphthamide 10a. Aldehyde **1a** (250 mg, 0.882 mmol) and (*S*)-2-(anilinomethyl)-pyrrolidine **9** (155.1 mg, 0.885 mmol) were heated at reflux in dry toluene (25 mL) for 16 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on alumina eluting with petrol/EtOAc (10:1) to afford the imidazolidine **10a** (282.4 mg 88%) as a pale yellow solid, mp 210.6–212.1 °C; $[\alpha]_D^{22}$=+0.84 (*c*=0.100, ethanol); R_f=0.75 (petrol/EtOAc 10:1); δ_H (300 MHz, $CDCl_3$) 7.85 (1H, dd, *J*=8, 1 Hz, Ar*H*), 7.69 (1H, dd, *J*=7, 3 Hz, Ar*H*), 7.59 (1H, d, *J*=9 Hz, Ar*H*), 7.43–7.33 (2H, m, Ar*H*), 7.18 (2H, d, *J*=9 Hz, Ar*H*), 7.05 (2H, t, *J*=7 Hz, Ar*H*), 6.56–5.45 (3H, m, Ar*H*), 5.88 (1H, s, C*H*N), 3.92 (1H, q, *J*=7 Hz, NC*H*CH$_2$), 3.70 (1H, t, *J*=8 Hz, PhNC*H*), 3.57 (1H, septet, *J*=7 Hz, NC*H*CH$_3$), 3.45 (1H, septet, *J*=7 Hz, NC*H*CH$_3$), 3.27–3.19 (2H, m, NC*H*HCH$_2$CH$_2$ and PhNCH*H*CHN), 2.65 (1H, m, NCH*H*CH$_2$CH$_2$), 2.02–1.81 (4H, m, PhNCH$_2$CHC*H*$_2$C*H*$_2$), 1.76 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.65 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.09 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 0.91 (3H, d, *J*=7 Hz, NCHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 169.5 (CO), 145.8, 138.0, 134.5, 134.5, 132.6, 129.7, 129.1, 127.9, 127.9, 126.0, 125.9, 125.2, 124.0 115.9, 112.0 (aromatics), 79.6 (*C*HN), 60.9 (PhNCH$_2$*C*H), 53.4 (PhN*C*H$_2$), 52.5 (N*C*H$_2$CH$_2$), 51.3 (N*C*H), 46.2 (N*C*H), 27.9 (*C*H$_2$), 23.5 (*C*H$_2$), 21.1 (*C*H$_3$), 20.5 (*C*H$_3$), 20.3 (*C*H$_3$), 19.98 (*C*H$_3$); ν_{max} (thin film)/cm^{-1} 2940, 1623 (C=O); *m/z* (CI) 442 (100%, *M*+H$^+$); *m/z* (EI) 442 (12.2%, *M*+H$^+$); 441 (9%, *M*), 356 (100%, *M*+H$^+$−C$_6$H$_{14}$). Found: *M* 441.2771. $C_{29}H_{35}N_3O$ requires *M*, 441.2781. Anal. Calcd for $C_{29}H_{35}N_3O$, C, 78.88, H, 7.59, N, 9.52. Found: C, 78.86, H, 7.86, N, 9.59.

4.1.8. (*M*,2′*R*,4′*S*,)-*N*,*N*-Diethyl-2-(2-phenylperhydropyrrolo-[1,2*c*]imidazol-3-yl)-1-naphthamide 10b. In the same way, aldehyde **1b** (987.1 mg) gave, after purification by flash chromatography on alumina eluting with petrol/EtOAc (11:1, R_f=0.77), the imidazolidine **10b** (1.42 g, 89%) as a yellow solid, mp 97.2–198.7 °C; $[\alpha]_D^{22}$=+107.2 (*c*=0.218, $CHCl_3$); δ_H (300 MHz, $CDCl_3$), 7.76–7.68 (2H, m, ArH), 7.64 (1H, d, *J*=9 Hz, ArH). 7.39 (2H, m, ArH), 7.26 (1H, d, *J*=8 Hz, ArH), 7.07 (2H, t, *J*=7 Hz, ArH), 6.60–6.48 (3H, m, ArH), 5.7 (1H, s, C*H*NN), 3.9 (1H, q, *J*=8 Hz, NC*H*CH$_2$CH$_2$), 3.71 (3H, m, NC*H*$_2$CH$_3$ and NC*H*HCHN), 3.27–3.09 (3H, m, NC*H*$_2$CH$_3$ and NCH*H*CHN), 2.98 (1H, dq, *J*=14, 7 Hz, NC*H*HCH$_2$), 2.72–2.61 (1H, m, NCH*H*CH$_2$), 2.02–1.7 (4H, m, PhNCH$_2$CHC*H*$_2$C*H*$_2$), 1.37 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$), 0.89 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 169.5 (CO), 145.8, 138.0, 134.5, 134.5, 132.6, 129.7, 129.1, 127.9, 127.9, 126.0, 125.9, 125.2, 124.0 115.9, 112.0 (aromatics), 80.6 (CNN), 61.0 (PhNCH$_2$*C*H), 53.8 (PhN*C*H$_2$), 52.9 (N*C*H$_2$CH$_2$), 43.5 (N*C*H$_2$CH$_3$), 38.9 (N*C*H$_2$CH$_3$), 29.6 (N*C*HCH$_2$), 28.3 (NCH$_2$*C*H$_2$CH$_2$), 24.0 (NCH$_2$CH$_2$*C*H$_2$), 13.4 (*C*H$_3$) and 13.3 (*C*H$_3$); ν_{max} (thin film)/cm^{-1} 2907, 1632 (C=O); *m/z* (CI)) 414 (100%, *M*+H$^+$), 226 (3.8%, *M*−C$_6$H$_{10}$N$_2$Ph); *m/z* (EI) 84 (100%, *M*+H$^+$−C$_6$H$_{10}$N$_2$Ph and C$_{10}$H$_6$). Found: *M* 413.2460. $C_{27}H_{31}N_3O$ requires *M*, 413.2467. Anal. Calcd for $C_{27}H_{31}N_3O$; C, 78.42, H, 7.56, N, 10.16: Found C, 78.64, H, 7.70, N, 9.90.

4.1.9. (*M*,2′*R*,4′*S*)-*N*,*N*-Diethyl-2-(2-phenylperhydropyrrolo-[1,2*c*]-imidazol-3-yl)benzamide 12b. In the same way, 2-formyl-*N*,*N*-diethyl-1-benzamide **2b** gave, after purification by flash chromatography on alumina eluting with petrol/EtOAc (8:1)+0.1% Et$_3$N, the imidazolidine **12b** (294.2 mg, 81%) as an oil; R_f=0.76 (petrol/EtOAc 8:1); $[\alpha]_D^{21}$=−0.11 (*c*=25., ethanol); δ_H (300 MHz, $CDCl_3$) 7.28–7.16 (6H, m, Ar*H*), 6.70 (1H, t, *J*=7 Hz, ArH), 6.60 (2H, d, *J*=8 Hz, ArH), 6.00 (1H, s, C*H*N), 3.90 (1H, quintet, *J*=7 Hz, PhNCH$_2$C*H*N), 3.70 (1H, q, *J*=8 Hz, PhNC*H*$_2$), 3.65 (1H, t, *J*=8 Hz, NC*H*), 3.6–3.49 (1H, quintet, *J*=7 Hz, NC*H*), 3.35–3.22 (2H, m, PhNC*H*$_2$ and NCH*H*CH$_2$), 2.75–2.63 (2H, m, NC*H*$_2$CH$_2$), 2.09–1.81 (4H, m, PhNCH$_2$ CHC*H*$_2$C*H*$_2$), 2.58 (1H, dq, *J*=14, 7 Hz, C*H*$_2$CH$_3$), 2.51 (1H, dq, *J*=14, 7 Hz, C*H*$_2$CH$_3$), 1.89–1.66 (4H, m, NCH$_2$C*H*$_2$C*H*$_2$CH), 1.24 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$), 1.09 (3H, t, *J*=8 Hz, CH$_2$C*H*$_3$), 1.02 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$); δ_C (75 MHz, $CDCl_3$) 171.2 (CO), 146.5, 139.0, 137.9, 129.1, 127.9, 126.7, 126.54, 125.55, 115.8, 111.9 (aromatics), 79.3 (*C*HN), 60.7 (PhNCH$_2$*C*H), 52.7 (PhN*C*H$_2$), 52.4 (N*C*H$_2$CH$_2$), 51.0 (N*C*H), 45.5 (N*C*HCH$_2$), 25.4 (*C*H$_2$CH$_3$), 23.9 (NCH$_2$CH$_2$*C*H$_2$), 14.7 (NCH$_2$*C*H$_3$), 13.1 (NCH$_2$*C*H$_3$), 13.0 (CH$_2$*C*H$_3$); ν_{max} (thin film)/cm^{-1} 1625 (C=O); *m/z* (CI)) 364 (100%, *M*+H$^+$), 363 (1.3%, *M*); *m/z* (EI) 363 (3.8%, *M*). Found: *M* 363.2620. $C_{23}H_{29}N_3O$ requires *M*, 363.2624.

4.1.10. (*M*,2′*R*,4′*S*)-*N*,*N*,2-Triethyl-6-(2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl)benzamide 12c. In the same way, *N*,*N*-2-triethyl-6-formylbenzamide **2c** (132.6 mg) gave, after purification by flash chromatography on alumina, eluting with petrol/EtOAc (11:1), the imidazolidine **12c** (130.9 mg, 59%) as an oil, $[\alpha]_D^{24}$=−11.7 (*c*=0.463, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.12–7.05 (.4H, m, Ar*H*), 6.91 (1H, t, *J*=5 Hz, Ar*H*), 6.56 (1H, t, *J*=7 Hz, ArH), 6.44 (2H, d, *J*=8 Hz, ArH), 5.55 (1H, s, C*H*NN), 3.81–3.69 (2H, m, NC*H*$_2$CH$_3$ and NC*H*CH$_2$CH$_2$), 3.59 (1H, t, *J*=8 Hz, PhNC*H*H), 3.39 (1H, dq, *J*=14, 7 Hz, NC*H*$_2$CH$_3$), 3.20 (1H, dq, *J*=14, 7 Hz, NC*H*$_2$CH$_3$), 3.11 (1H, dq, *J*=15, 7 Hz, NC*H*$_2$CH$_3$), 3.06–2.98 (2H, m, NC*H*$_2$CH$_2$ and PhNC*H*$_2$ CH$_2$), 2.58 (1H, dq, *J*=14, 7 Hz, C*H*$_2$CH$_3$), 2.51 (1H, dq, *J*=14, 7 Hz, C*H*$_2$CH$_3$), 1.89–1.66 (4H, m, NCH$_2$C*H*$_2$C*H*$_2$ CH), 1.24 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$), 1.09 (3H, t, *J*=8 Hz, CH$_2$C*H*$_3$), 1.02 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$); δ_C (75 MHz,

$CDCl_3$) 164.9 (C=O), 146.0 (NCC_5H_5), 104.0, 143.8, 136.0, 129.0, 128.0, 126.9, 123.4, 115.9, 112.1, 80.1 (*C*HNN), 60.6 (N*C*HCH$_2$), 53.2 (N*C*H$_2$CH$_2$), 52.5 (PhN*C*H$_2$), 43.2 (N*C*H$_2$CH$_3$), 38.4 (N*C*H$_2$CH$_3$), 28.0 (NCH$_2$*C*H$_2$), 25.4 (*C*H$_2$CH$_3$), 23.9 (NCH$_2$CH$_2$*C*H$_2$), 14.7 (NCH$_2$*C*H$_3$), 13.1 (NCH$_2$*C*H$_3$), 13.0 (CH$_2$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 2963–2931 (CH_3), 1627 (C=O); *m/z* (CI) 392 (100%, M+H$^+$); *m/z* (EI) 394 (8.9%, M+H$^+$). Found: M+H$^+$ 392.5641; $C_{25}H_{33}N_3O$ requires M+H$^+$ 392.5692.

4.1.11. (*P*,2′*R*,4′*S*)-*N*,*N*-Diisopropyl-2-(1-methoxy-1-methylethyl)-6-(2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl)benzamide 12d. In the same way, aldehyde **2d** gave the imidazolidine **12d** (96 mg, 85%) as an amorphous solid, $[\alpha]_D^{25}$=+34.8 (*c*=0.145, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.24–7.15 (3H, m, Ar*H*), 7.09 (2H, d, *J*=8 Hz, ArH), 6.74 (2H, d, *J*=8 Hz, ArH), 6.62 (1H, t, *J*=7 Hz, ArH), 5.68 (1H, s, C*H*N), 4.32–4.22 (1H, m, PhNCH$_2$ C*H*CH$_2$), 3.84–3.76 (1H, m, PhNC*H*$_2$), 3.74–3.69 (1H, m, PhNC*H*$_2$), 3.66–3.54 (2H, m, NCH), 3.37–3.26 (5H, m, NC*H*$_2$, NCH$_2$C*H*$_2$ and NCH$_2$CH$_2$C*H*$_2$), 2.74–2.62 (1H, m, NCH$_2$CH$_2$C*H*$_2$), 3.26 (3H, s, OCH_3), 1.70 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.66 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.64 (3H, s, CH_3), 1.55 (3H, s, CH_3), 0.99 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 0.95 (3H, d, *J*=7 Hz, NCHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 170.6 (C=O), 144.4 [N*C*(C_5H_5)], 142.8, 140.0, 135.6, 129.0, 127.7, 126.4, 125.4 (aromatics), 120.8, 115.6, 112.2 (aromatics), 79.4 (CHN), 60.4 (N*C*HCH$_2$), 53.7 (NCH), 52.6 (OCH_3), 50.8 (NCH), 49.2 (PhNCH$_2$), 45.9 (NCH$_2$), 29.0 (NCH$_2$CH$_2$), 27.9 (NCH$_2$CH$_2$*C*H$_2$), 25.7 (CCH_3), 23.3 (CH_3), 20.9, 20.6, 20.3, 19.6 (NCHC*H*$_3$); *m/z* (CI) 464 (100%, M+H$^+$), 388 (6.4%, M+H$^+$−C_4H_9O and CH_3); *m/z* (EI) 464 (23%, M+H$^+$), 463 (2%, *M*), 388 (100%, M+H$^+$−C_4H_9O and CH_3). Found: M+H$^+$ 464.3284; $C_{29}H_{41}N_3O_2$ requires M+H$^+$ 464.3278.

4.1.12. (*M*,2′*R*,4′*S*)-*N*,*N*-Dicylohexyl-2,4-dimethyl-6-(2-phenylperhydropyrrolo[1,2-*c*]imidazol-3-yl)benzamide 12e. In the same way, benzamide **2e** (88 mg) gave, after flash chromatography eluting with petrol/EtOAc (8:1; R_f=0.42), the imidazolidine **12e** (80.1 mg, 62%) as a white solid, mp 154.5–157.2 °C; $[\alpha]_D^{21}$=+42.1 (*c*=0.28, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.06 (2H, t, *J*=8 Hz, ArH), 6.78 (1H, s, Ar*H*), 6.64 (1H, s, Ar*H*), 6.53 (1H, t, *J*=7 Hz, ArH), 6.40 (2H, d, *J*=9 Hz, ArH), 5.60 (1H, s, C*H*N), 3.82–3.73 (1H, m, PhNCH$_2$C*H*CH$_2$), 3.56 (1H, t, *J*=8 Hz, PhNC*H*$_2$), 3.17–2.84 (5H, m, NCH, NCH, PhNC*H*$_2$ and NC*H*$_2$CH$_2$), 2.78–2.62 (3H, m, NC*H*$_2$CH$_2$ and NCH$_2$C*H*$_2$), 2.52–2.43 (2H, m, NCH$_2$CH$_2$C*H*$_2$), 2.24 (3H, s, ArC*H*$_3$), 2.11 (3H, s, ArC*H*$_3$), 2.06–0.65 (20H, m, cyclohexyl-*H*); δ_C (75 MHz, $CDCl_3$) 170.7 (C=O), 146.2, 136.7, 134.8, 133.2, 129.8, 129.0, 128.8, 124.3, 119.2, 115.6, 111.8 (aromatics), 79.6 (*C*HNN), 60.6 (N*C*HCH$_2$), 60.1 (N*C*H), 56.0 (N*C*H), 52.7 (PhN*C*H$_2$), 52.0 (N*C*H$_2$), 30.9 (NCH$_2$*C*H$_2$), 30.8 (NCH$_2$CH$_2$*C*H$_2$), 30.7, 29.3, 27.6, 26.7, 26.7, 25.8, 25.8, 25.4, 25.3, 23.4 (cyclohexyl), 21.4 (*C*H$_3$), 19.3 (*C*H$_3$); ν_{max}(thin film)/cm^{-1} 3005 (Ar–CH), 1609 (CO); *m/z* (CI) 500 (100%, M+H$^+$); *m/z* (EI) 499 (100%, *M*), 456 (34.6%, M−CH_3), 319 (28.2%, M−$C_{12}H_{22}N$), 303 (9%, M−ON(C_6H_{11})$_2$, 289 (52.6%, M+H$^+$−ON(C_6H_{11})$_2$ and CH_3), 187 (47.4%, M−$C_6H_2ON(C_6H_{11})_2$ and [CH_3]$_2$). Found: *M* 499.3560; $C_{22}H_{31}NO_2$ requires *M* 499.3562.

4.1.13. (*M*,2′*S*,4′*S*,5′*R*)-*N*,*N*-Diisopropyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-1-naphthamide 16a. 2-Formyl-*N*,*N*-diisopropyl-1-naphthamide **1a** (251 mg, 0.89 mmol) and (1*R*,2*S*)-ephedrine **13** (165 mg, 1.0 mmol, 1.1 equiv.) were heated to reflux in toluene (25 mL) for 16 h. The mixture was concentrated under reduced pressure and purified by flash chromatography on silica, eluting with petrol/EtOAc (11:1) to afford the oxazolidine **16a** (328.1 mg, 86%) as a white crystalline solid, mp 214.0–217.1 °C; $[\alpha]_D^{20}$=−157.1 (*c*=0.252, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 8.08 (1H, d, *J*=9 Hz, ArH), 7.95 (1H, d, *J*=9 Hz, ArH), 7.94–7.86 (2H, m, ArH), 7.57–7.52 (4H, m, ArH), 7.42 (2H, t, *J*=7 Hz, ArH), 7.35 (1H, d, *J*=7 Hz, ArH), 5.18 (1H, d, *J*=8 Hz, OC*H*Ph), 4.99 (1H, s, C*H*OCHPh), 3.68 (2H, septet, 2×NC*H*), 3.01 (1H, d quintet, *J*=2, 9 Hz, CHPhC*H*CH$_3$), 2.23 (3H, s, NCH_3), 1.82 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.75 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 1.15 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 0.99 (3H, d, *J*=7 Hz, NCHC*H*$_3$), 0.86 (3H, d, *J*=7 Hz, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 168.4 (C=O), 139.6, 137.3, 133.9, 130.8, 129.2, 128.4, 128.1, 127.9, 127.9, 127.6, 126.6, 126.5, 125.3, 125.0 (aromatics), 94.8 (*C*HNCH$_3$), 82.4 (O*C*HPh), 64.1 (CHPh*C*HCH$_3$), 51.3 (N*C*H), 46.2 (N*C*H), 35.8 (NCH$_3$), 20.9, 20.5, 20.3, 20.3 (CNHC*H*$_3$C*H*$_3$), 15.3 (CH*C*H$_3$); ν_{max}(thin film)/cm^{-1} 3062–2756 (CH_3), 1626 (C=O); *m/z* (CI) 431 (100%, M+H$^+$), 313 (7.7%, M+H$^+$−$C_6H_{14}ON$); *m/z* (EI) 431 (28%, M+H$^+$), 313 (7.7%, M+H$^+$−$C_6H_{14}ON$), 212 (100%, M+H$^+$−$C_{11}H_{14}NO$ and C_3H_7), 155 (9%, M+H$^+$−$C_{15}H_{14}NO$ and $C_6H_{14}N$), 127 (10.2%, $C_{15}H_{14}NO$ and $C_6H_{14}NOC$). Found: M+H$^+$ 431.2700; $C_{28}H_{34}N_2O_2$ requires M+H$^+$ 431.2699. Anal. Calcd for $C_{28}H_{34}N_2O_2$: C, 78.1; H, 7.96; N, 6.51. Found C, 77.73, H, 7.72, N, 6.31.

4.1.14. (*M*,2′*S*,4′*S*,5′*R*)-*N*,*N*-Diethyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-1-naphthamide 16b. In the same way, 2-formyl-*N*,*N*-diethyl-1-naphthamide **1b** gave the oxazolidine **16b** (196.2 mg, 87%) as white needles, mp 139.1–141.8 °C; $[\alpha]_D^{24}$=−93.6 (*c*=0.588, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 8.12 (1H, d, *J*=9 Hz, ArH), 7.95 (1H, d, *J*=9 Hz, ArH), 7.96–7.88 (1H, m, ArH), 7.86–7.79 (1H, m, ArH), 7.60–7.49 (5H, m, ArH), 7.41 (1H, dt, *J*=7, 1 Hz, ArH), 7.35 (1H, dd, *J*=7, 1 Hz, ArH), 5.2 (1H, d, *J*=9 Hz, OC*H*Ph), 4.98 (1H, s, C*H*OCHPh), 3.79 (2H, m, NC*H*$_2$), 3.16 (2H, m, NC*H*$_2$CH$_3$), 3.08 (1H, d quintet, *J*=2, 8 Hz, CHPhC*H*CH$_3$), 2.25 (3H, s, NC*H*$_3$), 1.46 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$), 0.97 (3H, t, *J*=7 Hz, NCH$_2$C*H*$_3$), 0.86 (3H, d, *J*=7 Hz, CHC*H*$_3$); δ_C (75 MHz, $CDCl_3$) 168.7 (C=O), 139.7, 136.2, 133.8, 131.4, 129.2, 128.9, 128.1, 127.9, 127.9, 127.6, 126.7, 126.7, 125.1, 124.9 (aromatics), 94.9 (*C*HNCH$_3$), 82.5 (O*C*HPh), 63.8 (CHPh*C*HCH$_3$), 43.3 (N*C*H$_2$), 38.8 (N*C*H$_2$), 35.6 (NCH$_3$), 15.2, 13.8 (CNCH$_2$-*C*H$_3$), 12.8 (CH*C*H$_3$); ν_{max}(thin film)/cm^{-1} 1629 (C=O); *m/z* (CI) 403 (100%, M+H$^+$), 212 (23%, M+H$^+$−$C_{11}H_{14}NO$ and CH_3); *m/z* (EI) 403 (19.2%, M+H$^+$), 254 (7.7%, M−$C_2H_{10}N$),212 (100%, M+H$^+$−$C_{11}H_{14}NO$ and CH_3), 127 (10.2%, M+H$^+$−$C_{11}H_{14}NO$ and $C_2H_{10}NO$). Found: M+H$^+$ 403.2388; $C_{26}H_{30}N_2O_2$ requires M+H$^+$ 403.2386.

4.1.15. (*M*,2′*S*,4′*S*,5′*S*)-*N*,*N*-Diisopropyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]-1-naphthamide 17. Similarly, 2-formyl-*N*,*N*-diisopropyl-1-naphthamide **1a** (124 mg, 0.44 mmol) and (1*S*,2*S*)-(−)-pseudoephedrine **14** (80 mg,

0.48 mmol, 1.1 equiv.) gave, after purification by flash chromatography eluting with petrol/EtOAc (11:1), the oxazolidine **17** (165.9 mg, 88%) as a white crystalline solid, mp 114.8–116.4 °C; $[\alpha]_D^{19}=-135.2$ (c=0.5, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.92–7.85 (4H, m, ArH), 7.58–7.52 (2H, m, ArH), 7.46–7.34 (5H, m, ArH), 5.23 (1H, s, C*H*OCHPh), 4.87 (1H, d, J=9 Hz, OC*H*Ph), 3.65 (2H, septet, J=7 Hz, 2×NC*H*), 2.62–2.53 (1H, m, CHPhC*H*CH_3), 2.27 (3H, s, NCH_3), 1.84 (3H, d, J=7 Hz, NCHCH_3), 1.81 (3H, d, J=7 Hz, NCHCH_3), 1.28 (3H, d, J=7 Hz, NCHCH_3), 1.18 (3H, d, J=7 Hz, NCHCH_3), 0.99 (3H, d, J=7 Hz, CHCH_3); δ_C (75 MHz, $CDCl_3$) 168.5 (C=O), 140.3, 136.5, 133.7, 132.4, 128.4, 128.2, 128.1, 127.9, 126.7, 126.6, 126.5, 125.2 (aromatics), 85.7 (*C*HNCH_3), 87.4 (O*C*HPh), 68.9 (CHPh*C*HCH_3), 51.3 (N*C*H), 46.2 (N*C*H), 35.2 (NCH_3), 20.9, 20.5, 20.4, 20.2 (CNHCH_3*C*H_3), 14.2 (CH*C*H_3); ν_{max}(thin film)/cm^{-1} 1620 (C=O); m/z (CI) 431 (100%, M+H^+), 313 (7.7%, M+H^+–$C_6H_{14}ON$); m/z (EI) 431 (28%, M+H^+),313 (7.7%, M+H^+–$C_6H_{14}ON$), 212 (100%, M+H^+–$C_{11}H_{14}NO$ and C_3H_7). Found: M+H^+ 431.2700; $C_{28}H_{34}N_2O_2$ requires M+H^+ 431.2699.

4.1.16. (*M*,2′*S*,4′*S*,5′*R*)-*N*,*N*-Diisopropyl-2-(3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl)benzamide 18a. In a similar way, aldehyde **2a** (2.0 g) and (1*R*,2*S*)-ephedrine **13** (1.42 g) gave, after purification by flash chromatography on silica, eluting with 11:1 petrol/EtOAc, the oxazolidine **18b** (2.89 g, 89%) as an oil which crystallised to a yellow wax upon standing, $[\alpha]_D^{20}=-39.4$ (c=0.28, $CHCl_3$). δ_H (300 MHz; $CDCl_3$) 8.01 (1H, d, J=8 Hz, C*H*CCHNO), 7.54–7.28 (8H, m, ArH), 7.15 (1H, d, J=8 Hz, ArH), 5.13 (1H, d, J=8 Hz, COC*H*Ph), 4.89 (1H, s, C*H*OCHPh), 3.76 (1H, septet, J=6 Hz, NC*H*CH_3), 3.56 (1H, septet, J=6 Hz, NC*H*CH_3), 2.93 (1H, m, C*H*CH_3), 2.2 (3H, s, CHNCH_3), 1.58 (6H, d, J=6 Hz, NCHCH_3CH_3), 1.08 (3H, t, J=6 Hz, NCHCH_3), 1.01 (3H, t, J=6 Hz, NCHCH_3), 0.77 (3H, d, J=6 Hz, NCHCH_3); δ_C (400 MHz, $CDCl_3$) 169.5 (C=O), 140.1–124.5 (aromatics), 94.3 (*C*HNO), 82.3 (O*C*HPh), 63.9 (N*C*CH_3), 51 (N*C*H_3), 45.7 (NCH$_3$*C*HCH_3), 35.8 (CH*C*H_3), 20.5–15.1 (COCN*C*H$_3$CH_3); ν_{max}(thin film)/cm^{-1} 1621 (C=O); m/z (CI) 381 (100%, M+H^+), 162 (11.3%, M+H^+–$C_{11}H_{14}NO$ and C_3H_7); m/z (EI) 381 (10%, M+H^+), 162 (100%, M+H^+–$C_{11}H_{14}NO$ and C_3H_7). Found: M+H^+ 381.2549; $C_{24}H_{32}N_2O_2$ requires M+H^+ 381.2543.

4.1.17. (*M*,2′*S*,4′*S*,5′*R*)-*N*,*N*-2-Diethyl-2-[3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl]benzamide 18b. In the same way, *N*,*N*-diethyl-2-formylbenzamide **2b** (125 mg) gave, after purification by flash chromatography eluting with petrol/EtOAc (11:1), the oxazolidine **18a** (80 mg, 34%) as an oil, $[\alpha]_D^{24}=-25.8$ (c=0.115, $CHCl_3$); δ_H (300 MHz; $CDCl_3$) 7.56 (1H, d, J=8 Hz, Ar*H*), 7.14 (2H, d, J=8 Hz, ArH), 7.1–6.98 (5H, m, Ar*H* and ArH), 4.79 (1H, d, J=8 Hz, OC*H*Ph), 4.23 (1H, s, C*H*OCHPh), 3.35 (1H, m, NCH_2CH$_3$), 2.63 (1H, d quintet, J=2, 7 Hz, CHPhC*H*CH_3), 2.43–2.23 (1H, m, NCH_2CH$_3$), 1.88 (3H, s, NCH_3), 0.99 (6H, d, J=7 Hz, NCH$_2$CH_3), 0.72 (3H, t, J=7 Hz, NCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$), 169.1 (C=O), 139.8, 139.0, 137.9, 133.9, 128.7–125.1 (aromatics), 94.8 (*C*HOCHPh), 82.3 (O*C*HPh), 63.7 (CHPHh*C*CH$_3$), 43.0 (N*C*H$_2$), 35.7 (N*C*H$_2$), 14.7, 13.4 (NCH$_2$*C*H$_3$×2), 12.6 (CH*C*H$_3$), 7.8 (CH$_2$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 1627 (C=O); m/z (CI) 352 (100%, M+H^+), 175 (6.7%, M−$C_{11}H_{14}NO$); m/z (EI) 367 (100%, M+H^+), 175 (4.7%, M−$C_{11}H_{14}NO$). Found: M+H^+ 352.4817; $C_{23}H_{30}N_2O_2$ requires M+H^+ 352.4807.

4.1.18. (*P*,2′*S*,4′*S*,5′*R*)-*N*,*N*-Diisopropyl-2-(3,4-dimethyl-5-phenyl-1,3-oxazolan-2-yl)-6-ethylbenzamide 18c. In the same way aldehyde **2c** (100.1 mg) and (1*R*,2*S*)-ephedrine **13** gave, after flash chromatography on alumina, eluting with petrol/EtOAc (11:1), the oxazolidine **13c** (136.8 mg, 87%) as an oil which formed a yellow wax on standing, $[\alpha]_D^{24}=-11.7$ (c=0.463, $CHCl_3$). δ_H (300 MHz; $CDCl_3$) 7.56 (1H, d, J=8 Hz, Ar*H*), 7.14 (2H, d, J=8 Hz, Ar*H*), 7.1–6.98 (5H, m, Ar), 4.79 (1H, d, J=8 Hz, OC*H*Ph), 4.23 (1H, s, C*H*OCHPh), 3.35 (1H, m, NCH_2CH$_3$), 2.63 (1H, d quintet, J=2, 7 Hz, CHPhC*H*CH_3), 2.43–2.23 (1H, m, NCH_2CH$_3$), 1.88 (3H, s, NCH_3), 0.99 (6H, t, J=7 Hz, NCH$_2$CH_3 and CH$_2$CH_3), 0.72 (3H, t, J=7 Hz, NCH$_2$CH_3), 0.49 (3H, t, J=7 Hz, CHCH_3); δ_C (75 MHz, $CDCl_3$), 169.1 (C=O), 139.8, 139.0, 137.9, 133.9, 128.7–125.1 (aromatics), 94.8 (*C*HOCHPh), 82.3 (O*C*HPh), 63.7 (CHPHh*C*CH$_3$), 43.0 (N*C*H$_2$), 38.1 (*C*H$_2$), 35.7 (N*C*H$_3$), 25.6 (*C*H$_2$CH$_3$), 14.7, 13.4 (NCH$_2$*C*H$_3$×2), 12.6 (CH*C*H$_3$), 7.8 (CH$_2$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 1627 (C=O); m/z (CI) 367 (100%, M+H^+), 190 (6.7%, M−$C_{11}H_{14}NO$); m/z (EI) 367 (100%, M+H^+), 190 (2.7%, M−$C_{11}H_{14}NO$). Found: M+H^+ 367.2380; $C_{23}H_{30}N_2O_2$ requires M+H^+ 367.2386.

4.1.19. (*M*)-(−)-2-Hydroxymethyl-*N*,*N*-diisopropyl-1-naphthamide 19a. (a) By hydrolysis-reduction of imidazolidine **10a**. A solution of 1 M HCl (2 mL, 2.5 equiv.) was added to a stirred solution of imidazolidine **10a** (331.6 mg, 0.79 mmol) in THF (20 mL) at 0 °C. After 35 min, a solution of sodium borohydride (2.7 equiv.) and sodium methoxide (1.0 equiv.) in methanol (20 mL) (a few droplets of ethanol was added to improved solubility) was added dropwise to the reaction mixture while keeping the temperature around 0 °C. The mixture was allowed to warm to room temperature over a period of 35 min. The mixture was concentrated under reduced pressure, without heating, to half of its original volume. It was extracted with diethyl ether (3×30 mL), and the combined extracts were washed with brine (2×30 mL), dried ($MgSO_4$) and evaporated under reduced pressure without heating. Purification by flash chromatography, eluting with petrol/EtOAc (5:1) gave enantiomerically enriched alcohol (−)-**19a** (202 mg, 94% yield) as a white solid, $[\alpha]_D^{20}=-105.7$ (c=0.5, $CHCl_3$); R_f=0.55 (petrol/EtOAc 7:1). Analytical HPLC on a chiral stationary phase (see below), eluting with 8% ethanol in hexane at 1 mL/min, indicated an ee of 89%.

(b) By hydrolysis-reduction of oxazolidine **16a**. A mixture of trifluroacetic acid (2.3 mL, 30 mmol, 20.0 equiv.) and water (0.5 mL, 3 mmol, 2.0 equiv.) was added dropwise to a solution of oxazolidine **16a** (346 mg, 1.51 mmol) in THF (30 mL) at 0 °C. After 60 min sodium methoxide (2.5 g, 33 equiv.) was added in small batches. The acidity of the solution reached pH 6. A slurry of sodium borohydride (10 equiv.) in ethanol (20 mL) was added at 0 °C. After 30 min, the mixture was allowed to warm to room temperature and evaporated under reduced pressure without applying heat until reduced to half its original volume. Cold water was added, and the mixture was extracted with diethyl

ether (3×30 mL). The combined organic extracts were washed with brine (2×30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure without applying any external heating. Purification by flash chromatography, as before, gave enantiomerically enriched alcohol (−)-**19a** (183 mg, 85%). HPLC on a chiral stationary phase (see below) indicated an enantiomeric excess of 74%.

4.1.20. (±)-2-Hydroxymethyl-*N*,*N*-diisopropyl-1-naphthamide (±)-19a. Sodium borohydride (80 mg, 2 equiv.) was added to a stirred solution of 2-formyl-*N*,*N*-diisopropyl-1-naphthamide **1a** (300 mg, 1.0 mmol) in ethanol (15 mL) at 0 °C. After 100 min, water (30 mL) was added. The mixture was extracted with ether (2×20 mL), and the combined extracts washed with brine (2×20 mL), dried ($MgSO_4$), evaporated under reduced pressure, and purified by flash column chromatography eluting with petrol/EtOAc (1:1) to afford alcohol (±)-**19a** (281.6 mg, 93%) as a white solid, mp 105–106.8 °C; R_f 0.25, petrol/EtOAc, 1:1); δ_H (300 MHz, $CDCl_3$) 7.80–7.70 (3H, m, ArH), 7.50–7.40 (3H, m, ArH), 4.77 (1H, dd, J=12, 3 Hz, CH_AH$_B$OH), 4.52 (1H, dd, J=12, 2 Hz, CH$_A$$H_B$OH), 3.56 (1H, septet, J=7 Hz, NCH), 3.51 (1H, septet, J=7 Hz, NCH), 3.10 (1H, br m, CH$_2$OH), 1.64 (3H, d, J=7 Hz, NCHCH_3), 1.62 (3H, d, J=7 Hz, NCHCH_3) 1.24 (3H, d, J=7 Hz, NCHCH_3) and 0.98 (3H, J=7 Hz, NCHCH_3); δ_C (75 MHz, $CDCl_3$) 170 (CHO), 134.3, 132.7, 129.2, 128.6, 128.2, 126.8, 126.3, 124.6 (aromatics), 63.4 (*C*H$_2$OH), 51.4 (N*C*H), 46.3 (N*C*H), 20.8 (*C*H$_3$), 20.5 (*C*H$_3$), 20.5 (*C*H$_3$); ν_{max}(thin film)/cm^{-1} 2941 (OH), 1610 (C=O); *m*/*z* CI 286 (100%, M+H$^+$), 254 (1.3%, M+H$^+$−CH$_2$OH); *m*/*z* (EI) 286 (100%, M+H$^+$), 285 (11.5% M), 254 (3.8%, M+H$^+$−CH$_2$OH), 168 (M+H$^+$−ONC$_6$H$_{14}$). Found: M+H$^+$ 286.1729; $C_{18}H_{23}NO_2$ requires M+H$^+$ 286.1708. Anal. Calcd for $C_{18}H_{23}NO_2$ C, 75.76; H, 8.12; N, 4.91%. Found C, 75.96; H, 8.05, N, 4.91%.

Analytical HPLC on a Chiralpak AD (250×4.6 mm) column, eluting with 10% EtOH in hexane at 1 mL/min, resolved two enantiomers at 6.49–6.59 min and 8.14–8.19 min.

4.1.21. (*M*)-(−)-2-Hydroxymethyl-*N*,*N*-diethyl-1-naphthamide (−)-19b. (a) By hydrolysis–reduction of imidazolidine **10b**. By the method used for hydrolysis-reduction of **10a**, imidazolidine **10b** (331.6 mg, 0.79 mmol) gave a product which was purified by flash column chromatography, eluting with petrol/EtOAc (3:1) to afford enantiomerically enriched alcohol (−)-**19b** (180.5 mg, 84%) as an oil, $[\alpha]_D^{18}$=−38.2 (c=0.5, $CHCl_3$). Analytical HPLC on a chiral stationary phase (see below), eluting with 16% ethanol in hexane at 1 mL/min, indicated an enantiomeric excess of 97%.

(b) By hydrolysis–reduction of oxazolidine **16b**. By the method used for oxazolidine **16a**, oxazolidine **16b** (331 mg) was reduced to give a crude alcohol which was purified by flash column chromatography, eluting with petrol/EtOAc (3:1), to afforded enantiomerically enriched alcohol (−)-**19b** (182.6 mg, 85%) as an oil. Analytical HPLC on a chiral stationary phase (see below) eluting with 6% ethanol in hexane at 1 mL/min indicated an enantiomeric excess of 74%.

4.1.22. (±)-2-Hydroxymethyl-*N*,*N*-diethyl-1-naphthamide 19b. By the method used for (±)-**19a**, 2-formyl-*N*,*N*-diethyl-1-naphthamide **1b** (250 mg) was reduced with sodium borohydride to give a crude product which was purified by flash chromatography, eluting with petrol/EtOAc (5:1), to give the corresponding alcohol (±)-**19b** as a oil (219.2 mg, 87% yield). δ_H (300 MHz; $CDCl_3$), 7.75 (1H, dd, J=2, 5 Hz, ArH), 7.72 (1H, d, J=8.9 Hz, ArH), 7.62 (1H, m, Ar*H*), 7.43 (3H, m, ArH), 4.65 (1H, d, J=13 Hz, CH$_A$$H_B$OH), 4.48 (1H, d, J=13 Hz, CH_AH$_B$OH), 3.74–3.52 (2H, m, NCH_2CH$_3$), 3.42 (1H, broad m, O*H*), 2.96 (2H, q, J=7 Hz, NCH_2CH$_3$), 1.30 (3H, t, J=7 Hz, NCH$_2$CH_3), 0.83 (3H, t, J=7 Hz, NCH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) 169.7 (C=O), 135.0, 132.7, 132.6, 129.2, 129.0, 128.2, 126.9, 126.4, 126.2, 124.5 (aromatics), 63.1 (*C*H$_2$OH), 43.2, 39.0 (N*C*H$_2$), 26.6, 13.8, 12.8 (NCH$_2$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 3386 (broad s), 2974–2849, 1611 (C=O); *m*/*z* (CI) 258 (100%, M+H$^+$), 227 (1.7%, M+H$^+$−CH$_2$OH); *m*/*z* (EI) 258 (3.6%, M+H$^+$), 257 (100% M), 227 (3.8%, M+H$^+$−CH$_2$OH). Found: M+H$^+$ 258.3387; $C_{16}H_{19}NO_2$ requires M+H$^+$ 258.3432.

4.1.23. (*P*)-(−)-*N*,*N*-Diisopropyl-2-(hydroxymethyl)-6-(1-methoxy-1-methylethyl)benzamide (−)-20d. By the method used for the hydrolysis and reduction of imidazolidine **10a**, imidazolidine **12d** was reduced to give a crude residue which was purified by flash chromatography, eluting with petrol/EtOAc (11:1), to give the enantiomerically enriched alcohol (−)-**20d** (56 mg, 90%), $[\alpha]_D^{20}$=−14.1 (c=0.5, $CHCl_3$). Formation of the Mosher's ester[63] of this compound and integration of the resulting ^{1}H NMR spectrum (in comparison with the ester of racemic material) indicated an enantiomeric excess of 77%.

4.1.24. (±)-*N*,*N*-Diisopropyl-2-(hydroxymethyl)-6-(1-methoxy-1-methylethyl)benzamide (±)-20d. By the method used to make (±)-**19a**, aldehyde **2d** (250 mg) was reduced by sodium borohydride to yield a crude product which was purified by flash chromatography, eluting with petrol/EtOAc (5:1), to give the corresponding racemic alcohol (±)-**20d** (218.9 mg, 87%) as a white solid, mp 94.2–95.8 °C. δ_H (300 MHz; $CDCl_3$) 7.35–7.29 (3H, Benz-*H*), 4.79 (1H, d, J=13 Hz, CH_AH$_B$OH), 4.37 (1H, d, J=13 Hz, CH$_A$$H_B$OH), 3.53 (1H, septet, J=7 Hz, NC*H*), 3.41 (1H, septet, J=7 Hz, NC*H*), 3.25 (3H, s, OCH$_3$), 1.63 (3H, d, J=7 Hz, NCHCH_3), 1.59 (3H, d, J=7 Hz, NCHCH_3), 1.58 (3H, s, COHCH$_3$CH$_3$CH_3), 1.52 (3H, s, COHCH$_3$CH$_3$ CH_3), 1.16 (3H, d, J=7 Hz, NCHCH_3), 0.97 (3H, d, J=7 Hz, NCHCH_3); δ_C (75 MHz, $CDCl_3$) 171.6 (C=O), 143.8, 138.0, 134.4, 128.1, 128.0, 126.2 (aromatics), 77.9 (*C*OHCH$_3$), 63.4 (*C*H$_2$OH), 50.7 and 45.8 (NCH), 28.0 and 26.1 (C*C*H$_3$), 20.4, 20.2, 20.0, 19.6 (4×NCH*C*H$_3$*C*H$_3$); ν_{max}(thin film)/cm^{-1} 3367 (OH), 1607 (amide C=O); *m*/*z* (CI) 308 (20%, M+H$^+$), 276 (100%, M−OCH$_3$); *m*/*z* (EI) 308 (2%, M+H$^+$), 86 (100%, M−CH$_2$OH, C$_4$H$_9$O, C$_6$H$_3$, NO). Found: M+H$^+$ 308.2225; $C_{18}H_{29}NO_3$ requires M+H$^+$ 308.2226. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found C, 70.94, H, 9.60, N, 4.43.

4.1.25. (*M*)-(−)-*N*,*N*-Dicyclohexyl-2-hydroxymethyl-4,6-dimethylbenzamide (−)-8. By the method used for the hydrolysis–reduction of imidazolidine **10a**, but at a temperature of −15 °C, imidazolidine **12e** (250 mg) gave

a crude residue which was purified by flash chromatography eluting with petrol/EtOAc (5:1), to afford the enantiomerically enriched alcohol (−)-**8** (158 mg, 93%) as a white solid $[\alpha]_D^{18}=-72.1$ (c=0.5, $CHCl_3$); R_f 5:1 (petrol/EtOAc, 5:1). Integration of the ^1H NMR spectrum of this material in the presence of Pirkle's chiral shift reagent (*R*)-TFAE,[64] in comparison with the racemic alcohol **8**, indicated an enantiomeric excess of 53%.

Acknowledgements

We are grateful to GlaxoSmithKline for support of this work, and to Dr. Andrew Craven for valuable discussions.

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Asymmetric radical cyclization reactions of axially chiral *N*-allyl-*o*-iodoanilides to form enantioenriched *N*-acyl dihydroindoles☆,☆☆

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Received 13 January 2004; revised 9 February 2004; accepted 23 February 2004

We dedicate this paper to Professor Leo Paquette on the occasion of his 70th birthday

Abstract—Radical cyclizations of enantiomerically enriched *N*-allyl-*o*-iodoanilides provide *N*-acyl-3-alkyl-2,3-dihydroindoles in good yields and with good to excellent levels of chirality transfer from the *N*–Ar axis to the new stereocenter. In competitive cyclizations of *N*-acryloyl-*N*-allyl-*o*-iodoanilides, the addition of an *o*-methyl group reverses the regioselectivity of the radical cyclization from the acryloyl group to the allyl group. Approximate rate constants for representative radical cyclizations have been measured to provide insight into the origin of these observations.

1. Introduction

Axially chiral benzamides, anilides and related imides have been known for several decades,[1] and work over the last 10 years has focused on asymmetric reactions of these species.[2–6] A recurring theme is the occurrence of an inter- or intramolecular reaction more rapidly than rotation of a C–N or C–C bond of an amide. Intermolecular reactions usually result in formation of a new stereocenter with retention of the chiral axis (asymmetric induction), while intramolecular reactions often result in formation of a new stereocenter with loss of the chiral axis (chirality transfer). Representative examples of intermolecular reactions are shown in Figure 1 and include the nitrile oxide cycloaddition reaction to *o-tert*-butylacrylanilide **1** (asymmetric induction by a C–N axis) to give **2**[2] and the addition of PhMgBr to *o*-formylnaphthamide **3** (asymmetric induction by a C–C axis) to give alcohol **4**.[7]

The radical cyclization of *N*-acryloyl anilide **5** to provide **6** (Fig. 2) is an example of an intramolecular reaction that occurs with faithful chirality transfer (enantiomer ratios >90/10).[2c] In this reaction, the intermediate aryl radical **7** must have a much lower barrier of rotation than its precursor **5**, but its barrier to cyclization to give **8** is even lower yet, so racemization of the intermediate radical is not a significant reaction.

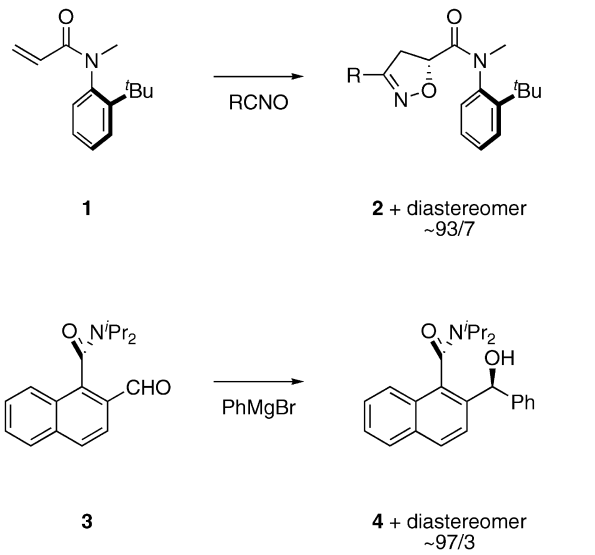

Figure 1. Examples of asymmetric induction with axially chiral anilides (top) and naphthamides (bottom).

Radical cyclizations of *o*-haloanilides lacking another *ortho* substituent to provide racemic products predate the above asymmetric cyclizations,[8–11] and these cyclizations occur whether the radical acceptor is present in the *N*-acyl group

☆ CDRI Communication No. 6414.

☆☆ Supplementary data associated with this article can be found, in the online version at doi: 10.1016/j.tet.2004.02.064

Keywords: Axially chiral *N*-allyl-*o*-iodoanilides; Intramolecular reaction; Radical cyclization.
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† Direct questions regarding the X-ray crystal structures to this author

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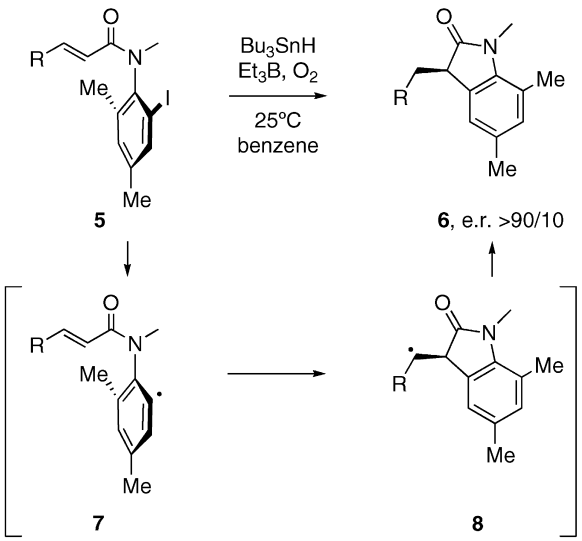


Figure 2. Chirality transfer in radical cyclizations of *o*-iodoacryanilides.

or the *N*-alkyl group (Fig. 3). For example, Bowman and coworkers[11a] have reported that cyclization of *N*-crotonoyl derivative **9** provided **10**, while Dittami[8a] and Toga[8b] observed that cyclization of *N*-allyl derivative **11** provided **12**. When the two types of cyclizations were pitted against each other by Jones and Storey in substrate **13**, then closure to the crotonoyl group dominated and **14** was the only observed product.[9a,12] Jones and McCarthy also reported attempted asymmetric cyclizations of chiral anilides like **15**, but the diastereomeric ratios of **16** were very poor.[13] These poor selectivities were interpreted in terms of a traditional chiral auxiliary model where a single radical passes through two diastereomeric transition states that are close in energy. However, our results[2c,d] suggest that an equally plausible model is that there are two diastereomeric iodides **15**, which in turn are precursors of two diastereomeric radicals, each of which cyclizes predominantly to a different isomer of **16**.

Following up on our previous studies on asymmetric cyclization reactions of enantioenriched *N*-acryloyl-*o*-iodoanilides,[2c] we now describe a complementary study of cyclization reactions of axially chiral *N*-allyl-*o*-iodoanilides **17** (Eq. 1). These reactions are general and good levels of chirality transfer to **18** are observed. The absolute configurations of the precursors and products are assigned, and a model is put forth to explain the observed chirality transfer. Finally, we have discovered that the presence of the

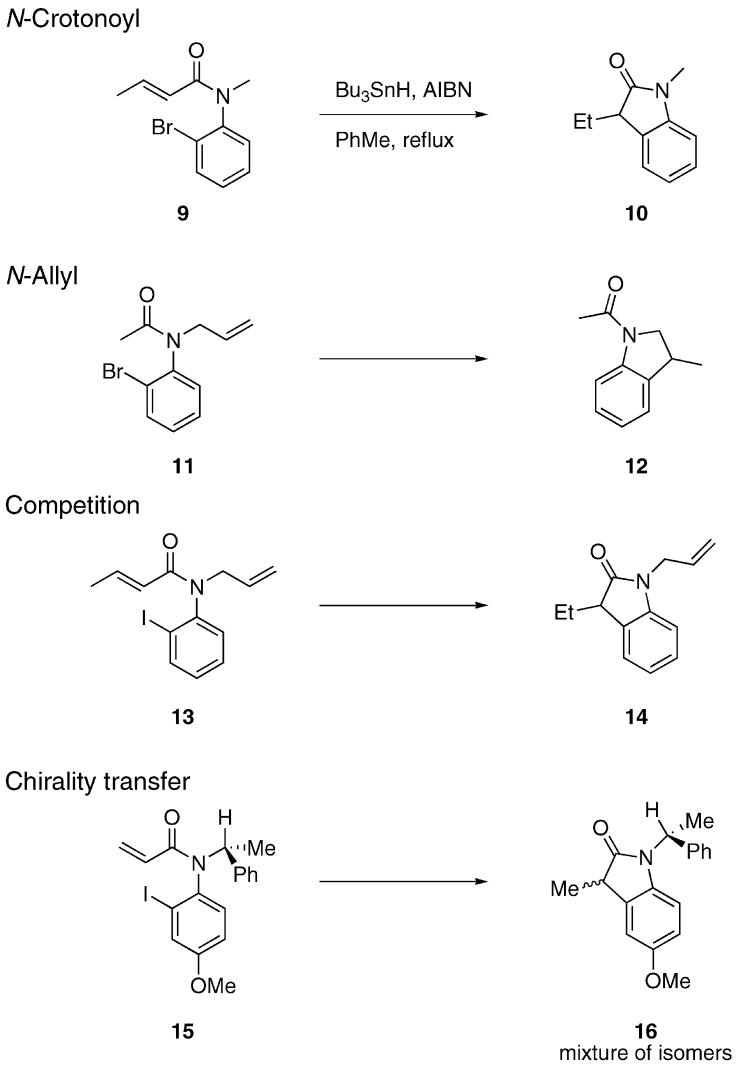
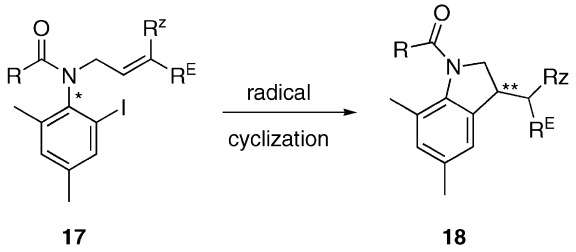


Figure 3. Radical cyclizations of iodo/bromoanilides lacking *ortho* substituents.

o-methyl group in these substrates reverses the regioselectivity in competitive cyclizations like that described by Jones (**13→14**), and we have measured approximate rate constants for representative cyclizations to help provide insight into the origin of this surprising observation.

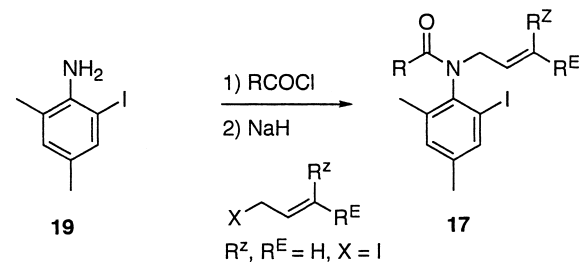


axial chirality (*) in **17** transfered to new stereocenter (**) in **18** (1)

2. Results and discussion

2.1. Precursor and product preparation, resolution and rotation barriers

All of the cyclization precursors **17a-i** used in this study were prepared as racemates from 2-iodo-4,6-dimethylaniline **19**[14] by a straightforward sequence of N-acylation followed by N-allylation, as shown in Eq. 2. Racemic standards of all the cyclization products **18** (see Eq. 1) were readily prepared from all these precursors by standard tin hydride mediated cyclizations. Section 4 contains representative procedures along with complete characterization data for the racemates.



	R	R^Z	R^E	% yield[a]
17a	Ph	H	H	35
17b	*p*-BrC_6H_4	Me	Me	54
17c	$PhCH_2$	H	H	50
17d	$PhCH_2$	H	Ph	47
17e	$PhCH_2$	H	Me	20
17f	$PhCH_2$	Me	Me	37
17g	$PhCH_2CH_2$	H	H	74
17h	*E*-CH_3CH=CH	H	H	20
17i	Me	H	H	69

a Overall isolated yield

(2)

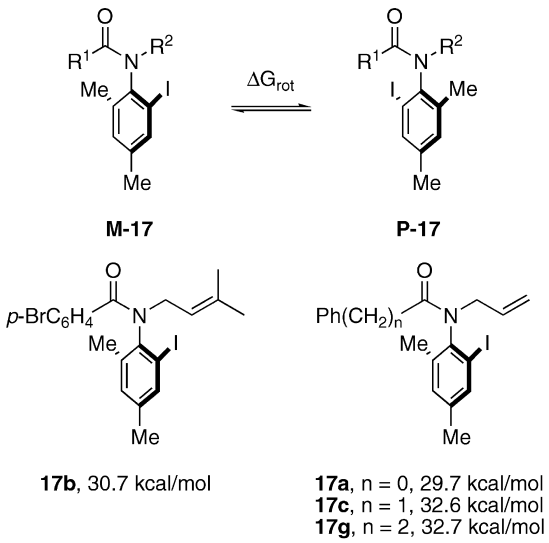


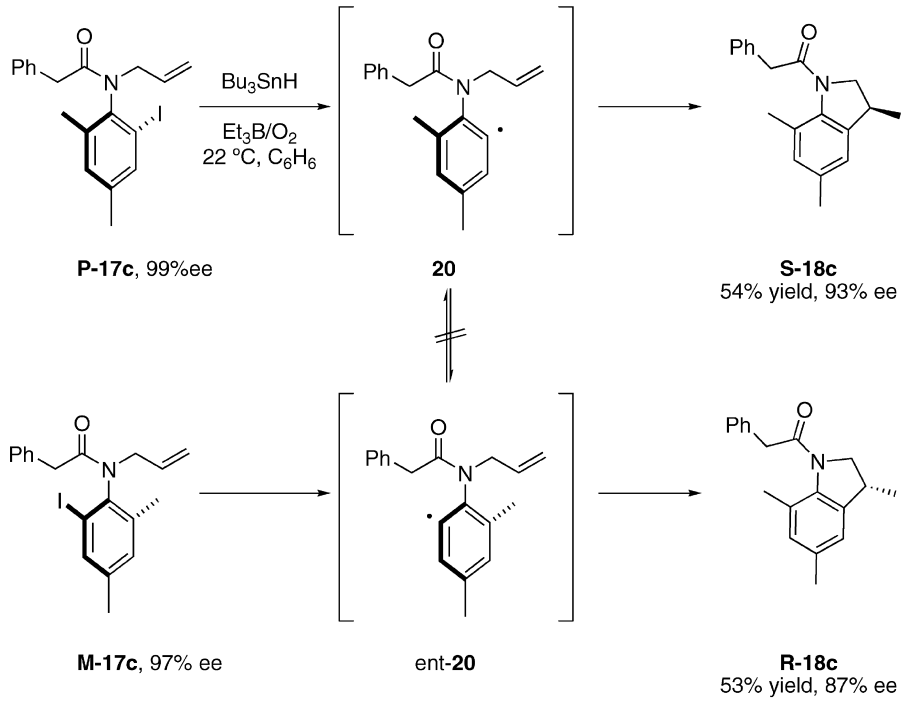
Figure 4. Rotation barriers for four axially chiral anilides.

Racemic precursors **17a-g** were resolved on a semi-preparative column ((*S*,*S*)-Whelk-O1, 25 cm×10.0 mm I.D., 10–40% *i*PrOH in hexanes, 8–10 mL/min).[15] Preparative injections ranged from 40 to 80 mg, depending on the effectiveness of the separation, and several hundred milligrams of most of the precursors were obtained in ees ranging from 96 to 99%. All the racemic products **18a-g** were injected into an analytical (*S*,*S*)-Whelk-O1 column and each pair of enantiomers was well resolved, thereby paving the way for a convenient quantitative analysis of chirality transfer experiments by chiral hplc.

Rotation barriers for four of the precursors were also measured (Fig. 4). In a typical experiment, phenmethyl-substituted anilide **17c** (>99% ee) was heated at 140 °C in 9:1 hexane:*i*PrOH, and the decrease in ee was measured as a function of time by chiral hplc analysis. A standard plot of this data (see Supplementary information) showed the expected first order racemization, and provided a rotation barrier of 32.6 kcal/mol. Phenethyl-substituted amide **17g** exhibited a similar rotation barrier of 32.7 kcal/mol, while benzamides **17a** and **17b** exhibited slightly lower rotation barriers of 30.7 and 29.7 kcal/mol, respectively. All of these barriers are well within the range to permit convenient handling of these compounds at room temperature. The lower barriers of benzamides have been observed previously,[14b] and presumably result because the phenyl ring of the benzamide group can twist out of plane with respect to the amide carbonyl group and thereby present a smaller substituent for the iodine or methyl group of the anilide to rotate past in the transition state.

2.2. Chirality transfer in radical cyclizations

With the enantioenriched radical precursors in hand, tin hydride cyclizations were conducted to measure the level of chirality transfer. The radical cyclization of substrate **17a** is typical of all the cyclizations and is summarized in Eq. 3. Triethylborane[16] (1.0 equiv.) was added to an aerated benzene solution of **17c** and Bu_3SnH (1.5 equiv., 0.01 M) to initiate the reaction, and progress was monitored by tlc. After about 30 min, the reaction was worked up and the

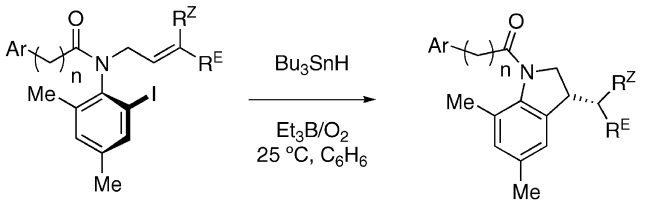


(3)

product was purified by flash chromatography and then analyzed by chiral hplc. Oxindole **S-18c** was produced in 54% yield and 93% ee starting from **P-17c** of 99% ee while **R-18c** was produced in 53% yield and 87% ee starting from **M-17c** of 97% ee. The levels of chirality transfer are 97 and 95%, and these levels are within experimental error, as expected for enantiomers. These results prove that the cyclization of intermediate radicals **20** and *ent*-**20** is much more rapid than their interconversion by *N*-aryl bond rotation.

Cyclizations of the other resolved precursors were conducted by similar procedures, and the data for this set of reactions are summarized in Table 1. These data reveal a number of trends. In all cases, the dextrorotatory (+) enantiomer of the precursor gave the dextrorotatory enantiomer of the product, and vice versa. In six of the

Table 1. Summary of radical cyclizations of **17a-g**



Entry	Precursor[a]	Ar	*n*	R^Z	R^E	Product	Yield[b]	%ee_{SM}[c]	%ee_P[d]	Chirality transfer[e] (%)
1	**P-17a**	Ph	0	H	H	**S-18a**	95	99	86	93
2	**M-17a**	Ph	0	H	H	**R-18a**	92	>99	87	93
3	**P-17b**	4-BrC_6H_4	0	Me	Me	**S-18b**	72	99	48	72
4	**M-17b**	4-BrC_6H_4	0	Me	Me	**R-18b**	95	98	47	72
5	**P-17c**	Ph	1	H	H	**S-18c**	54	>99	93	97
6	**M-17c**	Ph	1	H	H	**R-18c**	53	97	87	95
7	**P-17d**	Ph	1	H	Ph	**S-18d**	40	>99	74	87
8	**M-17d**	Ph	1	H	Ph	**R-18d**	50	98	76	88
9	**P-17e**	Ph	1	H	Me	**S-18e**	77	>99	79	89
10	**M-17e**	Ph	1	H	Me	**R-18e**	71	>99	83	91
11	**P-17f**	Ph	1	Me	Me	**S-18f**	79	>99	63	81
12	**M-17f**	Ph	1	Me	Me	**R-18f**	81	>99	57	78
13	**P-17g**	Ph	2	H	H	**S-18g**	67	96	85	94
14	**M-17g**	Ph	2	H	H	**R-18g**	74	>99	90	95

[a] The P configuration is assigned to the dextrorotatory enantiomers and M to levorotatory.
[b] Isolated yield after chromatography.
[c] ee of precursor.
[d] ee of product **18**.
[e] Yield (not excess) of the major enantiomer of **18** expected from an enantiopure sample of **17**.

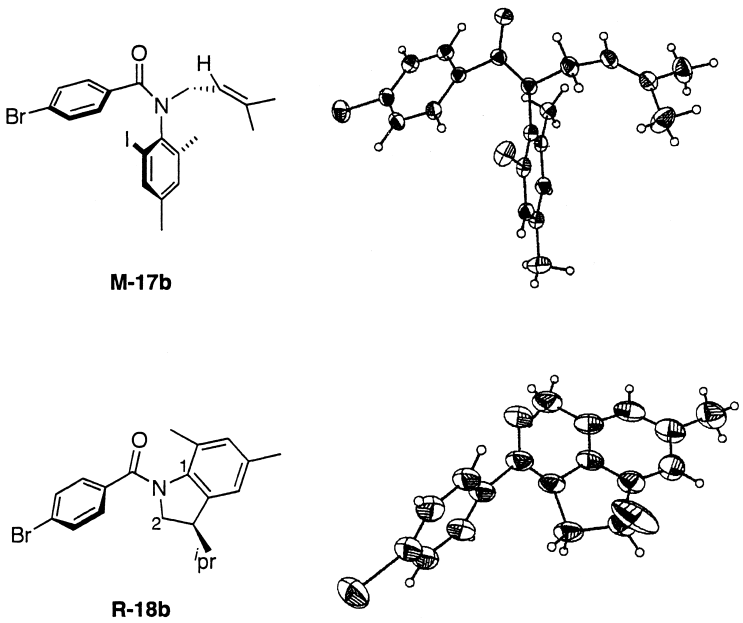


Figure 5. ORTEP representations of crystal structures of precursor **M-17b** (top) and product **R-18b** (bottom, the *iso*-propyl methyl groups are disordered and removed for clarity).

seven enantiomeric pairs, the first eluting enantiomer of the precursor gave the second eluting enantiomer of the product, and vice versa. The exception to this trend was **17a/18a**.

The last column of Table 1 records the level of chirality transfer, which corresponds to the yield of the major enantiomer of **18** expected from an enantiopure sample of **17**. This is an enantiomer ratio, not an enantiomeric excess. Levels of chirality transfer exhibited by enantiomeric pairs were comparable. All substrates with terminal or *E*-disubstituted acceptors cyclized with good to excellent levels of chirality transfer (87–97%, see entries 1/2, 5/6, 7/8, 9/10, 13/14), while acceptors with terminal *Z*-substituents exhibited somewhat lower selectivities (72–81%, entries 3/4, 11/12). These trends with the *N*-allyl acceptors are remarkably similar to those exhibited by the previously studied *N*-acryloyl class.[2c]

The absolute configurations of precursor **17b** (second eluting enantiomer) and its derived product **18b** (first eluting enantiomer) were determined by X-ray crystallography using the anomalous dispersion method, and the crystal structures of these compounds are shown in Figure 5.[17] The amide plane of precursor **17b** is nearly perpendicular to the N-Ar plane (117°), and the benzamide aryl plane is also significantly twisted (36°). The amide group is planar and the *N*-aryl group and the amide oxygen are trans, as expected. Product **18b** is strikingly different—the amide nitrogen is pyramidalized towards the viewer (sum of angles is 349°), with larger (O=C)NC^1 and (O=C)NC^2 angles (123 and 122°) not compensating for the small C^{1}NC^2 angle (104°). The *N*–Ar group is now more nearly cis to the carbonyl oxygen (angle 10°) while the N–CH$_2$ group is more nearly trans (angle 150°). This unusual geometry is a reflection of the severe strain that is imposed by the *o*-methyl group in standard planar geometries. Based on the trends observed in chirality transfer and rotation sign, we assigned the absolute configurations of all of the other compounds by analogy, and these assignments are shown in Table 1.

A model for chirality transfer that follows from these results is shown in Figure 6. To obtain a favorable geometry for cyclization, the aryl ring of perpendicular radical **21/22** must twist towards the allyl group. The alkene can twist its terminal CH$_2$ group either away from the radical to expose the back side of the alkene (as in **21→23**) or towards the radical to expose the front side (as in **22→24**). The formation of the product is consistent with twisting away from the radical (**21→23→25**). In striking contrast, the current model for cyclization of radicals derived from *N*-acryloyl anilides like **26** involves twisting of the acryloyl group towards the aryl radical as in **27** to give **28**.[2c] The only difference between the two classes of substrates is the location of the amide carbonyl group, which is either outside of (*N*-allyl) or within (*N*-acryloyl) the forming ring.

2.3. Regioselectivity, competitive cyclizations and rate constants

As a comparison to the Jones internal competition experiment in Figure 3, we also studied the cyclization of *rac*-**17h** (Eq. 4). This substrate has the same *N*-crotonoyl and *N*-allyl groups as Jones's compound **13**,[9a] but the aryl ring now has an *o*-methyl group in place of hydrogen. (There is also a *p*-methyl group in place of H, but this is presumably inconsequential) To our surprise, cyclization of *rac*-**17h** occurred to produce not the expected **30h** resulting from cyclization to the crotonoyl group, but instead produced exclusively **18h** resulting from cyclization to the *N*-allyl group. Dihydroindole **18h** was isolated in 65% yield by flash chromatography, and a careful analysis of the ^{1}H NMR spectrum of the crude product did not reveal any resonances attributable to the expected product **30h**. To ensure that the Jones structure assignment was correct, we

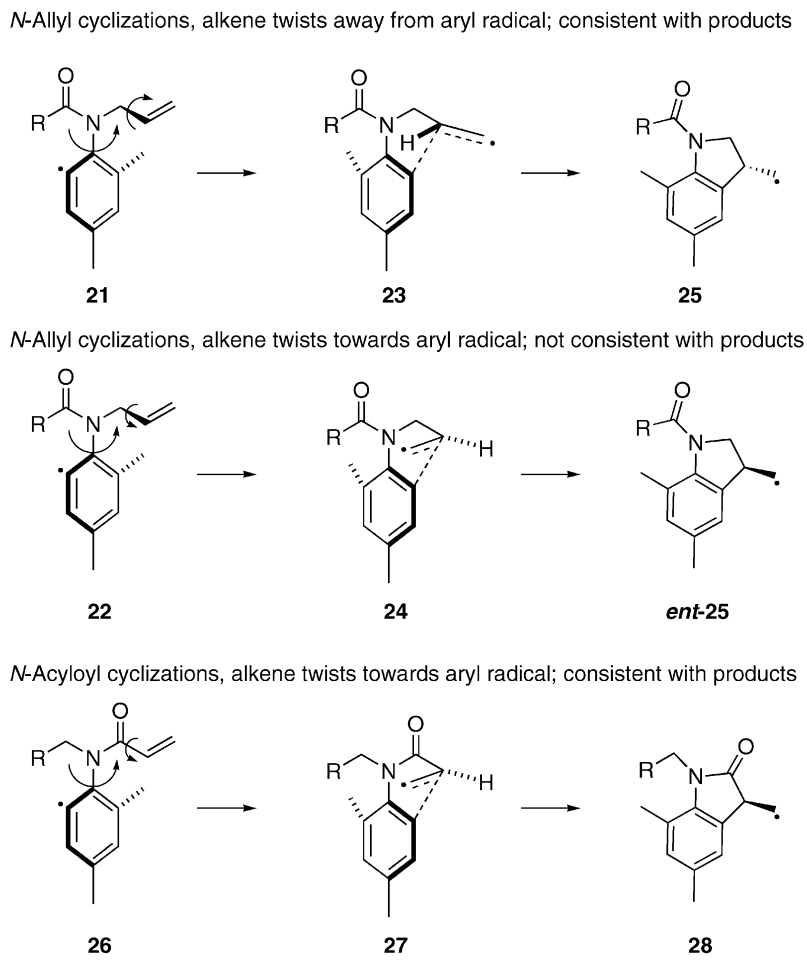
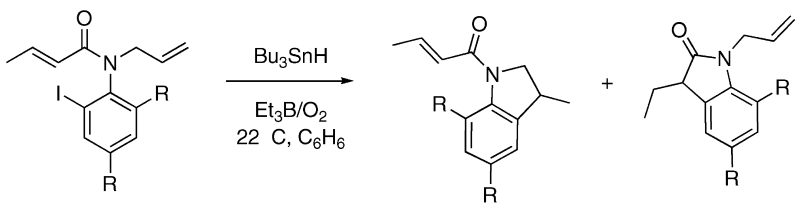


Figure 6. Transition state models for chiralitry transfer.

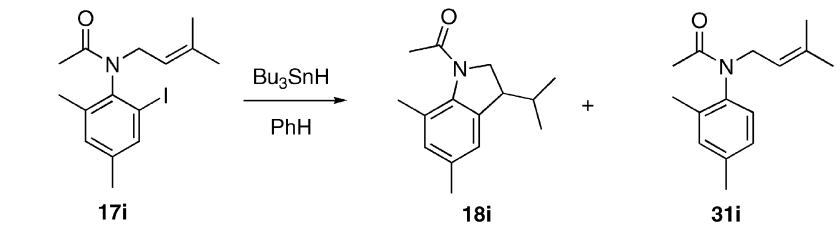
remade precursor **13** and, as billed,[9a] this provided exclusively **14**, and **29** was not detected. Accordingly, the regioselectivity in the cyclization of these anilide radicals is completely controlled by the presence or absence of an *ortho* methyl group.



(4)

To help understand the reversal in regioselectivity, we prepared racemic substrates *rac*-**17i** and **32** and measured their cyclization rate constants by standard competition kinetics with Bu_3SnH at 80 °C. Data for these experiments are summarized in Figure 7, and the calculated rate constants are summarized in Figure 8.[18] Consistent with the observed regioselectivity of **17h** (Eq. 4), the rate constant for cyclization of **35** (3.0×10^9 s^{-1}) was found to be about 40 times larger than the rate constant for cyclization of **39** (7.8×10^7 s^{-1}). We also attempted to measure the rate constant for cyclization of radical **37** derived from Jones substrate **13** at 80 °C; however, the cyclization of this radical was so fast that only traces of reduced product (<5%) were detected at the highest tin hydride concentrations (1–2 M). From this result, we can estimate a lower limit for cyclization of radical **37** at about 10^{10} s^{-1}.

These results show that cyclization to the *N*-acryloyl group (**37→38**) is inherently extremely fast, but is retarded by at least two orders of magnitude by introduction of an *o*-methyl group (**37→38**). This dramatic retardation allows the inherently less favorable cyclization to the *N*-allyl group (**35→36**) to intervene in the cyclization of **17h**. Figure 9 speculates on why cyclization to the acryloyl group is dramatically retarded by an *o*-methyl group while



[Bu_3SnH]	**18i/31i**	[Bu_3SnH]	**33/34**
0.01 M	29/1	0.02 M	5.2/1
0.37 M	6.6/1	0.03 M	3.5/1
1.0 M	2.7/1	0.05 M	2.2/1
3.6 M	0.8/1	0.1 M	1.1/1

Figure 7. Data from competition experiments with **17i** and **32**.

cyclization to the allyl group is not. Cyclization to the acryloyl group probably requires considerable twisting of the aryl radical and the alkene towards each other. When R°=Me, this results in a considerable steric interaction between this Me group and the CH_2 of the *N*-allyl group. In contrast, the *N*-allyl group is not constrained by amide resonance. The alkene can reach out to meet the aryl radical better (by rotation of the $N-CH_2$ bond) and less twisting of the aryl ring is required. This cyclization of the aryl radical to the *N*-allyl group does not result in a comparable steric interaction between the *o*-methyl group and the C=O on the other side. From the preparative standpoint, this analysis suggests that the regioselectivity of these reactions can be reversed by any medium or large *ortho*-substituent.

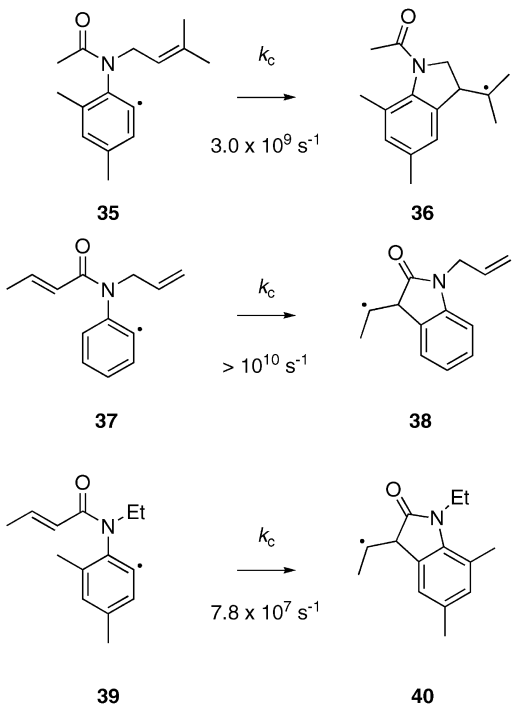


Figure 8. Competition experiments and rate constants.

3. Conclusions

In summary, radical cyclizations of axially chiral *N*-allyl-*o*-iodoanilides mirror their predecessor *N*-acryloyl-*o*-iodoanilides in both selectivity and trends, but give opposite enantiomeric products. Useful levels of chirality transfer are observed in many cases, and a straightforward model can be applied to predict the configuration of the major stereoisomer.

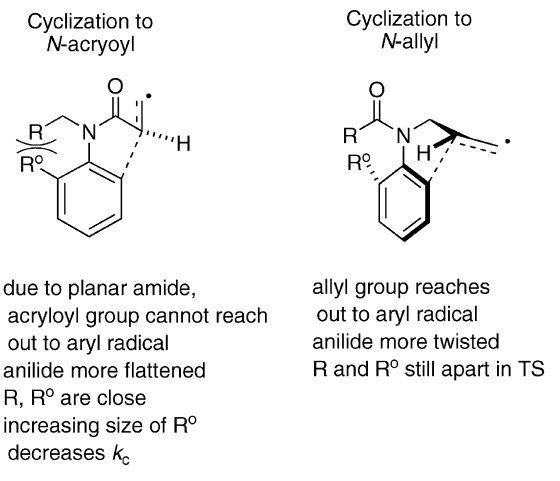


Figure 9. Twisting and effects of the *o*-methyl group on *N*-acryloyl (left) and *N*-allyl (right) cyclizations.

In all these reactions, the removal of the large iodine atom to generate a tiny radical is expected to dramatically reduce the barrier to rotation with attendant racemization, but the speed of the radical cyclization is so high that rotation cannot compete. Speed alone is not sufficient to ensure chirality transfer, yet one of two possible transition states is lower in energy, thereby ensuring selectivity. The presence of the *o*-substituent dictates not only stereoselectivity but also regioselectivity, in a surprising reversal from *N*-acryloyl cyclization to *N*-allyl cyclization. The detailed understanding of rotation barriers, regio- and stereoselectivity in this class of molecules sets the stage for future synthetic applications in asymmetric synthesis of oxindoles, dihydroindoles and related molecules.

4. Experimental

4.1. General procedure for acylation of 2-iodo-4,6-dimethylaniline (I)

To a CH_2Cl_2 (0.3 M) solution of 2-iodo-4,6-dimethylaniline (1.0 equiv.) was added triethylamine (1.1 equiv.). The reaction mixture was cooled to 0 °C and the respective acid chloride (1.1 equiv.) was added dropwise. The solution was warmed to room temperature. The reaction mixture was monitored by TLC and quenched accordingly with water upon completion. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic layers were washed with brine (1×) and dried with $MgSO_4$. Filtration and solvent evaporation in vacuo followed by purification by using flash chromatography on silica gel eluting with hexanes/ethyl acetate or recrystallization from hexanes provided the corresponding *o*-iodoanilide.

4.2. General procedure for N-allylation of anilides (II)

To a THF slurry of NaH (1.1 equiv.) at 0 °C was added the respective *o*-iodoanilide (1.0 equiv.) dissolved in THF (2 mL/mmol iodoanilide). The reaction mixture was stirred until the solution became clear and then the appropriate allyl bromide/iodide (1.3 equiv.) was added dropwise. The solution was warmed to room temperature. The reaction mixture was monitored by TLC and quenched with water upon completion. The resulting mixture was extracted with diethyl ether (3×, 25 mL/mmol of anilide). The combined organic layers were washed with brine (1×) and dried with $MgSO_4$. Filtration and solvent evaporation in vacuo followed by purification by flash chromatography on silica gel eluting with hexanes/diethyl ether (typically 9:1→7:3) provided the respective anilide.

4.3. General procedure for thermally initiated radical cyclization of anilides to make racemic cyclization products (III)

To a benzene solution of the respective *o*-iodoanilide (1.0 equiv.) was added Bu_3SnH (1.5 equiv., 0.01 M) and AIBN (0.2 equiv.). The reaction mixture was refluxed until the starting material was consumed by TLC (typically less than 1 h). The solvents were removed in vacuo and the crude was submitted to the DBU workup.[19] Purification of the remaining crude by flash column chromatography on silica gel eluting with hexanes/diethyl ether (9:1) provided the respective dihydroindole.

4.4. General procedure for Et_3B initiated radical cyclization of anilides (IV)

To a benzene solution of the respective *o*-iodoanilide (1.0 equiv. and Bu_3SnH (1.5 equiv., 0.01 M) was added a hexane solution (1.0 M) of Et_3B (1.0 equiv.). The reaction mixture was sealed and stirred at room temperature until the starting material was deemed consumed by TLC. The solvents were removed in vacuo and the crude was submitted the DBU workup.[18] Purification of the crude product by flash column chromatography on silica gel eluting with hexanes/diethyl ether (typically 100% hexanes→8:2) provided the respective dihydroindole.

4.4.1. *N*-(2-Iodo-4,6-dimethylphenyl)benzamide. This compound was prepared according to general procedure I. A white, crystalline solid (mp 175–176 °C) was obtained in quantitative yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1679, 1500, 1480, 1265, 1257; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 6H), 7.06 (s, 1H), 7.45–7.60 (m, 3H), 7.55 (s, 1H), 7.65 (s, 1H), 7.97 (d, J=7.1 Hz, 2H; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 20.5, 99.3, 127.4, 128.7, 131.8, 131.9, 134.2, 134.4, 137.2, 137.3, 139.1, 165.6; HRMS (EI) calcd for $C_{15}H_{14}INO$ 351.0120, found 351.0107; LRMS (EI) *m*/*z* 351 (M^+, 50), 259 (29), 246 (51), 224 (49), 105 (100), 77 (50).

4.4.2. *N*-(2-Iodo-4,6-dimethylphenyl)-2-phenylacetamide. This compound was prepared according to general procedure I. A white, crystalline solid (mp 161–162 °C) was obtained in 47% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3388, 3015, 2923, 1680, 1601, 1558, 1490, 1283, 1236, 852; ^1H NMR (300 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.24 (s, 3H), 3.80 (s, 2H), 6.70 (s, 1H), 6.99 (s, 1H), 7.45 (m, 5H), 7.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 20.4, 44.1, 99.0, 127.6, 129.2, 129.9, 131.7, 134.2, 134.6, 136.9, 137.0, 139.1, 169.1; HRMS (EI) calcd for $C_{16}H_{16}INO$ 365.0277, found 365.0289; LRMS (EI) *m*/*z* 365 (M^+, 3), 274 (3), 27 3 (4), 247 (66), 238 (100), 91 (71).

4.4.3. *N*-(2-Iodo-4,6-dimethylphenyl)-3-phenylpropionamide. This compound was prepared according to general procedure I. A white, crystalline solid (mp 156–157 °C) was obtained in 76% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1689, 1482, 1421, 1265; ^1H NMR (300 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.25 (s, 3H), 2.74 (t, J=8.1 Hz, 2H), 3.10 (t, J=8.1 Hz, 2H), 6.93 (s, 1H), 6.98 (s, 1H), 7.15–7.45 (m, 5H), 7.49 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 20.4, 31.5, 38.3, 99.4, 126.3, 128.5, 128.6, 131.7, 134.4, 137.0, 137.1, 139.0, 140.7, 170.5; HRMS (EI) calcd for $C_{17}H_{18}INO$ 379.0433, found 379.0439; LRMS (EI) *m*/*z* 379 (M^+, 37), 351 (88), 252 (68), 247 (53), 224 (99), 111 (80), 105 (100).

4.4.4. *N*-(2-Iodo-4,6-dimethylphenyl)-4-bromobenzamide. This compound was prepared according to general procedure I. A white, crystalline solid (mp 242–244 °C) was obtained in 82% yield. IR (thin film, $CH-_2Cl_2$, NaCl, cm^{-1}) 1681, 1477, 1421, 1271, 896; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 6H), 7.09 (s, 1H), 7.45 (bs, 1H), 7.57 (s, 1H), 7.65 (d, J=6.8 Hz, 2H), 7.68 (d, J=6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 20.5, 99.1, 126.8, 129.0,

132.0, 132.1, 133.0, 134.1, 137.1, 137.3, 139.4; HRMS (EI) calcd for $C_{15}H_{13}NOBrI$ 428.9225, found 428.9225; LRMS (EI) *m/z* 429 (M^+,23), 302 (87), 183 (100).

4.4.5. *N*-(2-Iodo-4,6-dimethylphenyl)acetamide. This compound was prepared according to general procedure I. A tan, crystalline solid (169–170 °C) was obtained in 82% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3416, 3377, 2924, 1687, 1486, 1369, 1245; ^1H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.29 (s, 3H), 2.31 (s, 3H), 6.95 (s, 1H), 7.01 (s, 1H), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.5, 20.4, 23.4, 99.5, 131.8, 134.5, 137.0, 137.8, 139.2, 168.6; HRMS (EI) calcd for $C_{10}H_{12}INO$ 288.9964, found 288.9974; LRMS (EI) *m/z* 289 (M^++H, 7), 247 (61), 224 (16), 162 (100), 120 (48), 91 (30).

4.4.6. *N*-(2-Iodo-4,6-dimethylphenyl)-*trans*-crotonamide. This compound was prepared according to general procedure I. A white, crystalline solid was obtained in 31% yield. IR 3396, 2913, 1620, 1478, 1286; ^1H NMR (300 MHz, $CDCl_3$) 1.95 (d, *J*=5.6 Hz, 3H), 2.17 (s, 3H), 2.22 (s, 3H), 6.06 (d, *J*=13.9 Hz, 1H), 6.89 (dq, *J*=13.9, 5.6 Hz, 1H), 6.94 (s,1H), 7.46 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) 19.4, 20.4, 41.6, 99.3, 120.3, 131.2, 131.6, 134.2, 138.7, 138.9, 141.4, 169.2; HRMS (EI) calcd for $C_{12}H_{14}INO$ 315.0120, found 315.0127; LRMS (EI) *m/z* 315 (M^+, 33), 247 (62), 188 (100), 69 (73).

4.4.7. 3,5,7-Trimethyl-2,3-dihydroindole. This compound was prepared according to general procedure III. A clear, orange oil was obtained in 72% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 2964, 2927, 2872, 2857, 1660, 1605, 1486, 1463; ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, *J*=6.8 Hz, 3H), 2.22 (s, 3H), 2.37 (s, 3H), 3.19 (t, *J*=8.6 Hz, 1H), 3.38–3.50 (m, 1H), 3.78 (t, *J*=8.6 Hz, 1H), 6.82 (s, 1H), 6.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 18.6, 20.7, 36.9, 55.4, 118.8, 121.4, 128.1, 128.7, 133.9, 147.2; HRMS (EI) calcd for $C_{11}H_{15}N$– 161.1204, found 161.1211; LRMS (EI) *m/z* 161 (M^+, 67), 146 (100), 131 (67).

4.4.8. *rac*-*N*-Allyl-*N*-(2-iodophenyl)-*trans*-crotonamide (13).[9a] This compound was prepared according to general procedure I. A clear, yellow oil was obtained in 59% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1666, 1630, 1470, 1422, 1386, 1271; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (d, *J*= 7.0 Hz, 3H), 3.62 (dd, *J*=14.6, 7.6 Hz, 1H), 4.83 (dd, *J*= 14.6, 5.2 Hz, 1H), 4.98–5.11 (m, 2H), 5.44 (d, *J*=15.0 Hz, 1H), 5.80–5.98 (m, 1H), 6.94 (dq, *J*=14.6, 7.0 Hz, 1H), 7.06 (t, *J*=7.6 Hz, 1H), 7.13 (d, *J*=7.6 Hz, 1H), 7.36 (t, *J*=7.6 Hz, 1H), 7.91 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.9, 51.1, 100.7, 118.4, 122.3, 129.1, 129.6, 130.9, 132.6, 139.6, 142.1, 143.8, 165.2; HRMS (EI) calcd for $C_{13}H_{14}INO$ 327.0120, found 327.0123; LRMS (EI) *m/z* 327 (M^+, 3), 259 (21), 200 (99), 130 (33), 69 (100).

4.4.9. *rac*-*N*-Allyl-*N*-(2-iodo-4,6-dimethylphenyl)benzamide (17a). This compound was prepared according to general procedure II. A clear, colorless oil was obtained in 35% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2927, 1641, 1380, 1258; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.18 (s, 3H), 4.04 (dd, *J*=14.2, 7.9 Hz, 1H), 4.80 (dd, *J*= 14.2, 6.1 Hz, 1H), 5.05–5.20 (m, 2H), 6.08 (dddd, *J*=14.0, 9.9, 7.8, 6.2 Hz, 1H), 6.82 (s, 1H), 7.13 (t, *J*=7.6 Hz, 2H), 7.21 (d, *J*=7.6 Hz, 1H), 7.39 (d, *J*=7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 20.3, 53.1, 101.4, 119.0, 127.3, 127.9, 129.8, 132.0, 132.5, 135.8, 137.6, 138.3, 139.3, 140.7; HRMS (EI) calcd for $C_{18}H_{18}INO$ 391.0433, found 391.0432; LRMS (EI) *m/z* 391 (M^+, 27), 264 (70), 223 (31), 144 (32), 105 (100), 77 (58). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes: *i*PrOH; first eluting enantiomer (P) α_D^{23} +140, 87% ee (*c* 5.4 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} −191, 97% ee (*c* 2.4 mg/mL, $CHCl_3$).

4.4.10. *rac*-*N*-(2-Iodo-4,6-dimethylphenyl)-*N*-(3-methylbut-2-enyl)-4-bromobenzamide (17b). This compound was prepared according to general procedure II. A white, crystalline solid was obtained in 66% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2927, 1642, 1442, 1399, 1264, 1012; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.66 (s, 3H), 2.08 (s, 3H), 2.23 (s, 3H), 4.11 (dd, *J*=14.5, 8.6 Hz, 1H), 4.71 (dd, *J*=14.5, 6.8 Hz, 1H), 5.42 (app t, *J*=7.0 Hz, 1H), 6.85 (s, 1H), 7.28 (m, 4H), 7.52 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 19.6, 20.3, 25.7, 47.5, 101.2, 118.4, 124.3, 129.7, 130.6, 132.1, 134.9, 136.9, 137.7, 138.5, 139.5, 140.6, 168.8; HRMS (EI) calcd for $C_{20}H_{23}IBrNO$ 496.9851, found 496.9859; LRMS (EI) *m/z* 497 (M^+, 37), 454 (13), 429 (28), 302 (32), 191 (100). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes: *i*PrOH; first eluting enantiomer (M) α_D^{23} +156, 99% ee (*c* 1.4 mg/mL, $CHCl_3$); second eluting enantiomer (P) α_D^{23} −146, 98% ee (*c* 1.5 mg/mL, $CHCl_3$).

4.4.11. *rac*-*N*-Allyl-*N*-(2-iodo-4,6-dimethylphenyl)-2-phenylacetamide (17c). This compound was prepared according to general procedure II. A clear, colorless oil was obtained in 93% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3066, 3024, 3013, 2961, 2926, 2858, 1652, 1466, 1456, 1389, 1261, 990; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.33 (s, 3H), 3.22 (d, *J*=15.0 Hz, 1H), 3.40 (d, *J*= 15.0 Hz, 1H), 4.00 (dd, *J*=14.3, 7.5 Hz, 1H), 4.45 (dd, *J*= 14.3, 6.3 Hz, 1H), 5.05 (dd, *J*=10.0, 1.4 Hz, 1H), 5.09 (dd, *J*=17.3, 1.4 Hz, 1H), 5.96 (dddd, J=17.3, 10.0, 7.5, 6.3 Hz, 1H), 7.04 (s, 1H), 7.09 (d, *J*=6.2 Hz, 2H), 7.26 (m, 3H), 7.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 20.8, 41.8, 52.3, 102.3, 119.1, 119.2, 127.0, 128.5, 130.0, 132.5, 133.2, 134.9, 138.7, 140.4, 140.7, 171.0; HRMS (EI) calcd for $C_{19}H_{20}INO$ 405.0590, found 405.0601; LRMS (EI) *m/z* 405 (M^+, 43), 314 (19), 287 (26), 278 (100), 187 (58), 158 (52), 91 (97). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes:*i*PrOH; first eluting enantiomer (P) α_D^{23} −55, 97% ee (*c* 3.5 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} +59, >99% ee (*c* 1.4 mg/mL, $CHCl_3$).

4.4.12. *rac*-*N*-(2-Iodo-4,6-dimethylphenyl)-*N*-(3-phenylallyl)-2-phenylacetamide (17d). This compound was prepared according to general procedure II. A clear, yellow oil was obtained in 100% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3008, 2925, 1652, 1495, 1465, 1455, 1393, 1351, 1310, 1247, 968; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.32 (s, 3H), 3.23 (d, *J*=15.0 Hz, 1H), 3.43 (d, *J*=15.0 Hz, 1H), 4.19 (m, 1H), 4.57 (m, 1H), 6.37–6.40 (m,

2H), 7.02 (s, 1H), 7.07–7.12 (m, 2H), 7.18–7.30 (m, 8H), 7.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 20.4, 41.3, 51.3, 101.3, 124.1, 126.3, 126.6, 127.5, 128.1, 128.4, 129.5, 132.2, 133.4, 134.4, 136.5, 138.1, 138.3, 140.0, 140.1, 170.6; HRMS (EI) calcd for $C_{25}H_{24}INO$ 481.0903, found 481.0927; LRMS (EI) *m/z* 481 (M^+, 58), 390 (44), 363 (8), 236 (27), 158 (21), 117 (100), 91 (84). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes:*i*PrOH; first eluting enantiomer (P) α_D^{23} −17, 94% ee (*c* 6.3 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} +11, 98% ee (*c* 9.9 mg/mL, $CHCl_3$).

4.4.13. *rac*-*N*-But-2*E*-enyl-*N*-(2-iodo-4,6-dimethylphenyl)-2-phenylacetamide (17e). This compound was prepared according to general procedure II. A clear, yellow oil was obtained in 41% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3012, 2921, 2856, 1650, 1496, 1465, 1455, 1393, 1313, 1262, 1247, 1165, 970; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, *J*=5.9 Hz, 3H), 2.04 (s, 3H), 2.33 (s, 3H), 3.20 (d, *J*=15.0 Hz, 1H), 3.39 (d, *J*=15.0 Hz, 1H), 3.94 (dd, *J*=14.0, 7.1 Hz, 1H), 4.38 (dd, *J*=14.0, 6.3 Hz, 1H), 5.53 (m, 2H), 7.03 (s, 1H), 7.08 (m, 2H), 7.22 (m, 3H), 7.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 19.2, 20.3, 41.4, 50.9, 101.9, 125.5, 126.5, 128.0, 129.1, 129.5, 129.9, 132.0, 134.6, 138.2, 139.8, 140.3, 170.4; HRMS (EI) calcd for $C_{20}H_{22}INO$ 419.0746, found 419.0737; LRMS (EI) *m/z* 419 (M^+, 55), 292 (44), 238 (37), 174 (30), 158 (33), 91 (98), 55(100). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes:*i*PrOH; first eluting enantiomer (P) α_D^{23} −46, 99% ee (*c* 4.7 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} +41, 99% ee (*c* 11.4 mg/mL, $CHCl_3$).

4.4.14. *rac*-*N*-(2-Iodo-4,6-dimethylphenyl)-*N*-(3-methylbut-2-enyl)-2-phenylacetamide (17f). This compound was prepared according to general procedure II. A clear, yellow oil was obtained in 79% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3026, 3014, 2925, 2861, 1650, 1495, 1455, 1383, 1236, 1186, 1162, 1032; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.62 (s, 3H), 2.03 (s, 3H), 2.43 (s, 3H), 3.21 (d, *J*=15.0 Hz, 1H), 3.39 (d, *J*=15.0 Hz, 1H), 4.04 (dd, *J*=14.3, 8.0 Hz, 1H), 4.45 (dd, *J*=14.3, 7.1 Hz, 1H), 5.03 (dd, *J*=7.0, 7.0 Hz, 1H), 7.03 (s, 1H), 7.18 (m, 5H), 7.62 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 19.0, 20.3, 25.5, 41.1, 45.9, 53.8, 101.7, 118.7, 126.4, 127.9, 129.4, 131.9, 134.5, 136.2, 138.1, 139.7, 140.0, 170.4; HRMS (EI) calcd for $C_{21}H_{24}INO$ 433.0903, found 433.0901; LRMS (EI) *m/z* 433 (M^+, 100), 390 (9), 365 (27), 300 (21), 273 (14), 247 (17), 238 (41), 91 (93), 69 (66). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes:*i*PrOH; first eluting enantiomer (P) α_D^{23} −49, 99% ee (*c* 2.2 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} +43, 99% ee (*c* 4.5 mg/mL, $CHCl_3$).

4.4.15. *rac*-*N*-Allyl-*N*-(2-iodo-4,6-dimethylphenyl)-3-phenylpropionamide (17g). This compound was prepared according to general procedure II. A clear, yellow oil was obtained in 97% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 2926, 1649, 1395; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.28 (s, 3H), 2.95–3.05 (m, 2H), 3.96 (dd, *J*=14.3, 7.6 Hz, 1H), 4.54 (dd, *J*=14.3, 6.5 Hz, 1H), 5.04–5.15 (m, 2H), 5.97 (dddd, *J*=6.5, 7.5, 9.8, 13.7 Hz, 1H), 7.02 (s, 1H), 7.10–7.20 (m, 3H), 7.23 (d, *J*=6.7 Hz, 2H), 7.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 20.4, 31.2, 36.3, 51.6, 101.4, 118.7, 125.9, 128.3, 128.5, 132.1, 132.9, 137.7, 138.3, 139.9, 140.1, 141.4, 171.8; HRMS (EI) calcd for $C_{20}H_{22}INO$ 419.0746, found 419.0743; LRMS (EI) *m/z* 419 (M^+, 32), 292 (100), 160 (37), 158 (32), 155 (25), 131 (34), 105 (59). The racemate was submitted to preparative chiral HPLC separation (Regis Technologies (*S*,*S*)-Whelk-O1; 25 cm×10.0 mm I.D.; 10 mL/min hexanes:*i*PrOH; first eluting enantiomer (P) α_D^{23} −60, 99% ee (*c* 3.8 mg/mL, $CHCl_3$); second eluting enantiomer (M) α_D^{23} +58, 99% ee (*c* 4.3 mg/mL, $CHCl_3$).

4.4.16. *rac*-*N*-Allyl-*N*-(2-iodo-4,6-dimethylphenyl)-*trans*-crotonamide (17h). This compound was prepared according to general procedure I. A white, crystalline solid was obtained in 64% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2984, 2854, 1666, 1629, 1445, 1384, 1273; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (dd, *J*=6.9, 1.5 Hz, 3H), 2.18 (s, 3H), 2.31 (s, 3H), 3.94 (ddd, *J*=14.3, 7.1, 0.6 Hz, 1H), 4.58 (dd, *J*=14.3, 6.4 Hz, 1H), 5.02–5.11 (m, 2H), 5.48 (dd, *J*=15.0, 1.7 Hz, 1H), 5.97 (dddd, *J*=17.0, 10.0, 7.7, 6.5 Hz, 1H), 7.00 (dq, *J*=15.0, 6.9 Hz, 1H), 7.04 (s, 1H), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 19.7, 20.5 51.6, 101.6, 118.7, 121.9, 125.4, 132.0, 133.1, 138.2, 138.8, 139.9, 140.0, 142.4, 165.8; HRMS (EI) calcd for $C_{15}H_{18}INO$ 355.0433, found 355.0445; LRMS (EI) *m/z* 355 (M^+, 25), 340 (20), 313 (13), 287 (16), 228 (100), 18 (39), 158 (32), 69 (68).

4.4.17. *rac*-*N*-(2-Iodo-4,6-dimethylphenyl)-*N*-(3-methylbut-2*E*-enyl)acetamide (17i). This compound was prepared according to general procedure I. An orange-yellow oil was obtained in 84% yield. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 3005, 2926, 2858, 1643, 1553, 1467, 1440, 1396, 1289, 1034, 908; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.62 (s, 3H), 1.74 (s, 3H), 2.20 (s, 3H), 2.28 (s, 3H), 3.94 (dd, *J*=14.5, 8.2 Hz, 1H), 4.50 (dd, *J*=14.5, 7.1 Hz, 1H), 5.26 (m, 1H), 7.03 (s, 1H), 7.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 19.4, 20.5, 22.4, 25.7, 45.6, 101.2, 118.9, 132.0, 136.4, 137.9, 138.3, 139.8, 140.9, 170.3; HRMS (EI) calcd for $C_{15}H_{20}INO$ 357.0590, found 357.0603; LRMS (EI) *m/z* 357 (M^+, 95), 314 (37), 300 (46), 289 (83), 247 (56), 232 (46), 162 (87), 69 (100).

4.4.18. Phenyl-(3,5,7-trimethyl-2,3-dihydroindol-1-yl)methanone (18a). This compound was prepared according to general procedure IV. The atropisomer **M-17a** (>99% ee, second eluting enantiomer) yielded a white, crystalline solid in 92% yield (87% ee, −3, second eluting enantiomer). The atropisomer **P-17a** (99% ee, first eluting enantioimer) yielded a white, crystalline solid in 95% yield (86% ee, +3, first eluting enantiomer). A racemic standard of the title compound was prepared in 98% yield by radical cyclization of *rac*-**17a** according to general procedure III. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2966, 1649, 1371, 1264; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, *J*=7.0 Hz, 3H), 2.20 (s, 3H), 2.34 (s, 3H), 3.33 (sex, *J*=7.3 Hz, 1H), 3.65 (dd, *J*=10.4, 7.6 Hz, 1H), 4.22 (dd, *J*=10.4, 7.7 Hz, 1H), 6.88 (s, 1H), 6.91 (s, 1H), 7.40–7.55 (m, 3H), 7.74 (d, *J*=6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 19.9, 21.1, 36.9,

61.6, 121.2, 128.4, 128.5, 128.6, 130.3, 131.1, 135.2, 136.2, 139.2, 139.5, 169.6; HRMS (EI) calcd for $C_{18}H_{19}NO$ 265.1467, found 265.1462; LRMS (EI) *m/z* 265 (M^+, 39), 105 (100), 77 (35).

4.4.19. (4-Bromophenyl)-(3-isopropyl-5,7-dimethyl-2,3-dihydroinol-1-yl)methanone (18b). This compound was prepared according to general procedure IV. The atropisomer **P-17b** (99% ee, first eluting enantiomer) yielded a white, crystalline solid in 72% yield (48% ee, +16, second eluting enantiomer). The atropisomer **M-17b** (98% ee, second eluting enantiomer) yielded a white, crystalline solid in 95% yield (47% ee, −15, first eluting enantiomer). IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1649, 1421, 1267, 896; ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, *J*=6.8 Hz, 3H), 0.88 (d, *J*=7.2 Hz, 3), 1.92 (sex, *J*=6.7 Hz, 1H), 2.16 (s, 3H), 2.33 (s, 3H), 2.99 (m, 1H), 3.86 (dd, *J*=10.8, 3.3 Hz, 1H), 4.08 (dd, *J*=10.8, 8.1 Hz, 1H), 6.89 (s, 1H), 6.91 (s, 1H), 7.60 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 20.0, 20.3, 21.1, 30.8, 48.2, 56.2, 122.8, 125.7, 128.4, 130.2, 130.6, 131.7, 135.1, 134.2, 136.8, 139.6, 168.6; HRMS (EI) calcd for $C_{20}H_{22}N-OBr$ 371.0885, found 371.0870; LRMS (EI) *m/z* 371 (M^+, 33), 183 (87), 91 (100).

4.4.20. 1-(3-Methyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-2-phenylethanone (18c). This compound was prepared according to general procedure IV. The atropisomer **M-17c** (97% ee, first eluting enantiomer) yielded a clear oil in 53% yield (87% ee, −32, second eluting enantiomer). The atropisomer **P-17c** (>99% ee, second eluting enantiomer) yielded a clear oil in 54% yield (93% ee, +27, first eluting enantiomer). A racemic standard of the title compound was prepared in 74% yield by radical cyclization of *rac*-**17c** according to general procedure III. IR (thin film, $CHCl_3$, NaCl, cm^{-1}) 2965, 2928, 1649, 1388; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, *J*=6.8 Hz, 3H), 2.26 (s, 3H), 2.30 (s, 3H), 3.21 (sex, *J*=6.9 Hz, 1H), 3.52 (dd, *J*=10.3, 7.3 Hz, 1H), 3.88 (s, 2H), 4.17 (app t, *J*=8.5 Hz, 1H), 6.81 (s, 1H), 6.87 (s, 1H), 7.23–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 20.5, 20.9, 36.5, 43.4, 58.4, 121.0, 126.8, 127.1, 128.6, 128.7, 129.6, 130.4, 135.0, 135.1, 136.0, no carbonyl signal observed; IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1679, 1500, 1480, 1265, 1257; HRMS (EI) calcd for $C_{19}H_{21}NO$ 279.1623, found 279.1627; LRMS (EI) *m/z* 279 (M^+, 64), 188 (7), 161 (100), 146 (69), 91 (52).

4.4.21. 1-(3-Benzyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-2-phenylethanone (18d). This compound was prepared according to general procedure IV. The atropisomer **M-17d** (94% ee, first eluting eluting enantiomer) yielded a clear oil in 72% yield (75% ee, −29, second eluting enantiomer). The atropisomer **P-17d** (>99% ee, second eluting enantiomer) yielded a clear oil in 95% yield (75% ee, +24, first eluting enantiomer). A racemic standard of the title compound was prepared in 79% yield by radical cyclization of *rac*-**17d** according to general procedure III. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2927, 1660, 1377, 1268; ^1H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.29 (s, 3H), 2.53 (dd, *J*=13.9. 9.9 Hz, 1H), 2.96 (dd, *J*=13.9, 5.3 Hz, 1H), 3.35 (m, 1H), 3.76 (m, 1H), 3.82 (d, *J*=3.2 Hz, 2H), 3.94 (dd, *J*=10.6, 7.4 Hz, 1H), 6.75 (s, 1H), 6.91 (s, 1H), 7.30 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 21.0, 29.7, 39.6, 43.6, 55.9, 121.8, 126.4, 126.9, 128.6 (2C), 128.8 (6C), 130.9, 135.0, 135.1, 127.7, 137.7, 139.2; HRMS (EI) calcd for $C_{25}H_{25}NO$ 355.1936, found 355.1938; LRMS (EI) *m/z* 355 (M^+, 37), 146 (100), 131 (20), 105 (18), 91 (62).

4.4.22. 1-(3-Ethyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-2-phenylethanone (18e). This compound was prepared according to general procedure IV. The atropisomer **M-17e** (>99% ee, first eluting enantiomer) yielded a clear oil in 71% yield (83% ee, −38, second eluting enantiomer). The atropisomer **P-17e** (>99% ee, second eluting enantiomer) yielded a clear oil in 77% yield (79% ee, +34, first eluting enantiomer). A racemic standard of the title compound was prepared in 97% yield by radical cyclization of *rac*-**17e** according to general procedure III. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2927, 2876, 1656, 1598, 1379, 1268; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J*=7.4 Hz, 3H), 1.25–1.35 (m, 1H), 1.61–1.70 (m, 1H), 2.26 (s, 3H), 2.30 (s, 3H), 2.95 (m, 1H), 3.69 (dd, *J*=10.3, 5.4 Hz, 1H), 3.88 (s, 2H), 4.09 (app t, *J*=8.8 Hz, 1H), 6.82 (s, 1H), 6.87 (s, 1H), 7.20–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 20.5, 20.9, 26.2, 56.2, 64.7, 121.7, 126.8, 128.7, 128.8, 130.0, 130.6, 134.9, 135.2, 138.4, 139.1; HRMS (EI) calcd for $C_{20}H_{23}NO$ 293.1780, found 293.1779; LRMS (EI) *m/z* 293 (M^+, 64), 175 (86), 146 (100), 91 (56).

4.4.23. 1-(3-Isopropyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-2-phenylethanone (18f). This compound was prepared according to general procedure IV. The atropisomer **P-17f** (>99% ee, first eluting enantiomer) yielded a white, waxy solid in 79% yield (60% ee, +12, second eluting enantiomer). The atropisomer **M-17f** (>99% ee, second eluting enantiomer) yielded a white, waxy solid in 81% yield (58% ee, −11, first eluting enantiomer). A racemic standard of the title compound was prepared in 63% yield by radical cyclization of *rac*-**17f** according to general procedure III. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1656, 1602, 1378; ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (d, *J*=6.7 Hz, 3H), 0.88 (d, *J*=6.8 Hz, 3H), 1.77 (o, *J*=6.7 Hz, 1H), 2.24 (s, 3H), 2.29 (s, 3H), 2.83 (q, *J*=5.9 Hz, 1H), 3.86 (m, 2H), 3.92 (m, 2H), 6.81 (s, 1H), 6.87 (s, 1H), 7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 20.3, 20.7, 21.0, 30.5, 43.7, 48.1, 54.5, 122.8, 126.9, 128.7, 128.9, 130.7, 134.6, 135.0, 136.9, 136.9, 139.4, 168.9; LRMS (EI) *m/z* 307 (M^+, 22), 189 (19), 146 (100), 91 (47), 69 (16); HRMS (EI) calcd for $C_{19}H_{20}INO$ 307.1936, found 307.1931; LRMS (EI) *m/z* 307 (M^+, 27), 189 (22), 146 (100), 91 (37).

4.4.24. 1-(3-Methyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-3-phenylpropanone (18g). This compound was prepared according to general procedure IV. The atropisomer **M-17g** (>99% ee, first eluting enantiomer) yielded a clear oil in 74% yield (90% ee, −25, second eluting enantiomer). The atropisomer **P-17g** (96% ee, second eluting enantiomer) yielded a clear oil in 67% yield (85% ee, +24, first eluting enantiomer). A racemic standard of the title compound was prepared in 68% yield by radical cyclization of *rac*-**17g** according to general procedure III. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1641, 1421, 1264; ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, *J*=6.8 Hz, 3H), 2.20 (s, 3H), 2.30 (s, 3H), 2.8 (t, *J*=7.5 Hz, 2H), 3.09 (t, *J*=7.5 Hz, 2H), 3.08–3.20 (m, 1H), 3.46 (dd, *J*=10.1, 7.7 Hz, 1H), 4.10 (m, 1H), 6.81 (s, 1H), 6.86 (s, 1H), 7.15–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 21.0, 29.7, 31.8, 35.9, 41.4, 58.4,

118.1, 121.1, 126.0, 126.2, 127.6, 128.5, 129.0, 130.4, 132.0, 133.0, 134.9, 138.2, 138.9, 141.1, 172.1; HRMS (EI) calcd for $C_{20}H_{23}NO$ 293.1780, found 279.1792; LRMS (EI) *m/z* 293 (M^+, 34), 205 (9), 161 (100), 146 (38), 105 (25), 91 (44).

4.4.25. 1-(3-Methyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-but-2-enone (18h). IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 1666, 1630, 1470, 1423; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J=6.7 Hz, 3H), 1.92 (dd, J=6.9, 1.5 Hz, 3H), 2.22 (s, 3H), 2.31 (s, 3H), 3.32 (sex, J=7.1 Hz, 1H), 3.61 (dd, J=10.2, 7.6 Hz, 1H), 4.33 (app t, J=8.2 Hz, 1H), 6.17 (d, J=15.0 Hz, 1H), 6.85 (s, 1H), 6.87 (s, 1H), 7.00 (dt, J=15.0, 6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 18.2, 20.2, 21.0, 21.1, 36.5, 58.9, 121.3, 124.6, 130.4, 134.9, 138.9, 140.2, 141.7, 165.4; HRMS (EI) calcd for $C_{11}H_{15}N-$ 161.1204, found 161.1211; LRMS (EI) *m/z* 161 (M^+, 67), 146 (100), 131 (67).

4.4.26. 1-(3-Isopropyl-5,7-dimethyl-2,3-dihydroindol-1-yl)-methanone (18i). This compound was prepared according to general procedure III in 80% yield. IR (thin film, CH_2Cl_2, NaCl, cm^{-1}) 2957, 2925, 2872, 1667, 1477, 1386; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J=6.8 Hz, 3H), 0.98 (d, J=6.9 Hz, 3H), 1.89–2.03 (m, 1H), 2.22 (s, 6H), 2.30 (s, 3H), 2.85–3.00 (m, 1H), 3.80–4.05 (m, 2H), 6.85 (s, 1H0, 6.86 (s, 1H); HRMS (EI) calcd mass for $C_{15}H_{15}NO$ 231.1623, found 231.1619; LRMS (EI) *m/z* 231 (M^+, 19), 189 (8), 146 (100), 130 (22), 115 (6).

Acknowledgements

We thank the National Science Foundation for funding this work. We also thank Dr. Ali Ates for preparing sample **R-18b** for X-ray analysis.

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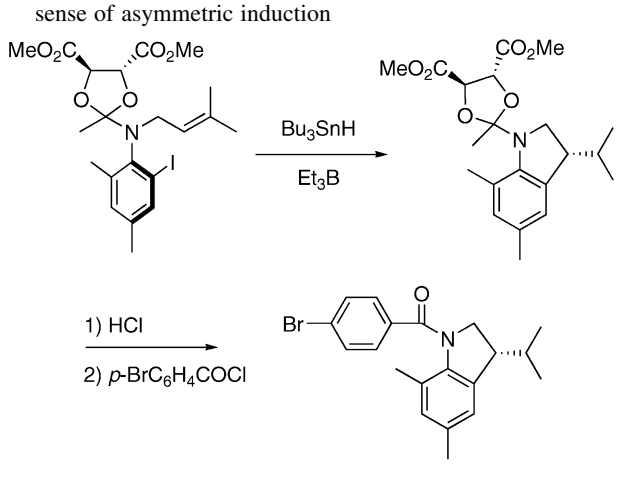
17. The sample for crystallography was prepared by the 'amide ketal' route summarized below (see Ref. 2d). These experiments also show that amides and amide ketals give the same sense of asymmetric induction



R-18b

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The first example of atropisomeric amide-derived P,O-ligands used for an asymmetric Heck reaction☆

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Received 13 January 2004; revised 10 February 2004; accepted 23 February 2004

Abstract—Atropisomeric *N*,*N*-diisopropyl 2-diphenylphosphino- and 2-di(*tert*-butyl)phosphino-1-naphthamides were used, for the first time, as bidentate P,O-ligands for intermolecular asymmetric Heck reactions of 2,3-dihydrofuran with aryl triflates. The reactions were carried out in the presence of 4 mol% $Pd(OAc)_2$, 8 mol% of the axially chiral ligand, and 3 equiv. of $(i\text{-Pr})_2NEt$ in THF at 60 °C for 3 days. Optically active 2-aryl-2,5-dihydrofurans were obtained as the major products along with the rearranged 2-aryl-2,3-dihydrofurans. Enantioselectivity up to 55.2% ee was obtained for the major product.

1. Introduction

In recent years, atropisomers arising from rotationally restricted amide scaffolds have received considerable attention in the area of asymmetric reactions and enantioselective catalysis.[1] A number of examples of axially chiral amides have been reported. These include anilides,[2] *N*-arylimides,[3] benzamides,[4] and 1-naphthamides.[5] Atropisomerism for C1 non-amide-substituted naphthalenes such as C1-vinylnaphthalenes[6] are also known. Related C1-arylsulfinylnaphthalenes[7] and *tert*-butyl-1-(2-methyl-1-naphthyl)phosphine oxide have been reported.[8] Curran,[2a–d,3a] Beak,[2e,5a] Simpkins,[2f–i] Taguchi,[2j–p] Uemura,[2r,4a–c] Clayden,[2s,4e,f,5b–j] and others have demonstrated applications of atropisomeric amides in stereocontrolled reactions. In particular, Clayden was the first to use axially chiral benzamides **1a**,**b** as bidentate P,O-ligands in the palladium-catalyzed asymmetric allylic alkylation (AAA) with up to 90% ee.[4e,f] In our previous studies, we prepared enantiomerically pure functionalized *N*,*N*-diisopropyl 1-naphthamides (−)-(a*R*)-*syn*-**2**,[5k] (+)-(a*S*)-**3**,[5n] (a*S*)-**4a**–**c**,[5m] and their antipodes (Fig. 1). These chiral amides have been used as 'chiral wall' templates in the desymmetrization of cyclic *meso* anhydrides with (−)-(a*R*)-*syn*-**2** (100% diastereoselectivity),[5k] in the SmI_2-mediated reductive coupling of aldehydes with (+)-(a*S*)-**3** (97.6% ee),[9] and in the Pd-catalyzed asymmetric allylic alkylation with (−)-(a*S*)-**4a** (94.7% ee),[5m] respectively. We report here on asymmetric Heck reactions[10,11] of 2,3-dihydrofuran[12] with aryl triflates by using the amide-based axially chiral P,O-ligands (−)-(a*S*)-**4a**,**c** and their antipodes. To the best of our knowledge, this is the first example that showcases enantioselective control of atropisomeric amides in an asymmetric Heck reaction.[11–14]

2. Results and discussion

Hayashi and co-workers first reported the intermolecular asymmetric Heck reaction of 2,3-dihydrofuran **5** with phenyl triflate **6a** using BINAP as the chiral ligand (Scheme 1).[12a] A kinetic resolution mechanism was proposed for the formation of the rearranged product **7a** as the major regioisomer in high enantioselectivity.[12a,b,15] Since then, a number of groups examined different chiral ligands for the prototype asymmetric Heck reaction of 2,3-dihydrofuran **5** with phenyl triflate **6a**.[12] These chiral ligands are grouped into the biaryl-derived P,P-ligands and the oxazoline- or ferrocene-based P,N-ligands. However, atropisomeric P,O-ligands have not been reported in asymmetric Heck reactions. In general, P,P-ligands afford a mixture of **7a** and **8a** with **7a** as the major regioisomer.[12a,d,e] For P,N-ligands, only **8a** was formed without isomerization into **7a**.[12f–k,14d,e] We are interested in exploration of the regio- and enantio-selectivity of the asymmetric Heck reaction of **5** with aryl triflates **6a**–**c** by using the naphthamide-derived atropisomeric P,O-ligands **4a**,**c** (Fig. 1).[5m]

The enantiomers of atropisomeric P,O-ligand **4a** were

☆ The Institute of Molecular Technology for Drug Discovery and Synthesis is supported by The Areas of Excellence Scheme (AoE/P-10/01) established under The University Grants Committee of Hong Kong SAR, China.

Keywords: Atropisomerism; P,O-ligand; Asymmetric Heck reaction; Dihydrofuran; Palladium.

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doi:10.1016/j.tet.2004.02.062

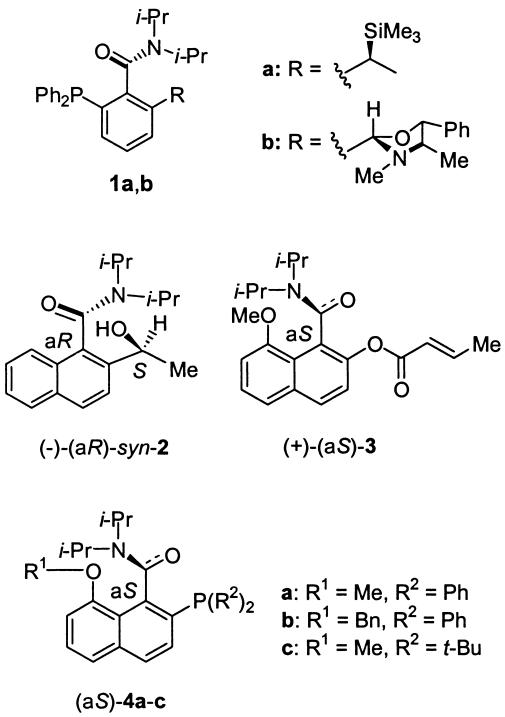


Figure 1. Structures of selected atropisomeric amides used for asymmetric reactions and catalysis.

previously prepared via a chemical resolution process.[5m] However, the same approach could not be applied to the synthesis of enantiomerically pure P,O-ligand **4c** due to poor separation of the diastereomers. Therefore, (a*S*)-(−)-**4c** and (a*R*)-(+)-**4c** were obtained by HPLC resolution over a chiral stationary phase. The racemic **4c** was synthesized from *N*,*N*-diisopropyl 8-methoxy-1-naphthamide **9** via the amide-directed *ortho*-lithiation and subsequent quenching with $ClP(t\text{-}Bu)_2$ (Scheme 2). The absolute stereochemistry of (a*S*)-(−)-**4c** was established by X-ray crystal structural analysis as given in Figure 2.

We examined two atropisomeric P,O-ligands **4a** and **4c** for the asymmetric Heck reactions of 2,3-dihydrofuran **5** with *para*-substituted phenyl triflates **6a**–**c** (Scheme 1). The results are summarized in Table 1. After a preliminary survey on the reaction conditions, including ligand/Pd ratio, solvent, base, and palladium precursor, we selected the following set of reaction conditions: 4 mol% $Pd(OAc)_2$ and 8 mol% P,O-ligand (Pd/L^*=1:2), 3 equiv. of $(i\text{-}Pr)_2NEt$ as the base, THF as the solvent, at 60 °C for 3 days. With P,O-ligand (a*S*)-(−)-**4a**, both products (−)-**7a** and (−)-**8a** were formed in a ratio of 20:80 in favor of 2-phenyl-2,5-dihydrofuran (−)-**8a**. Enantioselectivity of ca. 50% ee was obtained for both regioisomers (−)-**7a** and (−)-**8a** (entry 1). The absolute stereochemistry of (−)-**7a** and (−)-**8a** was assigned to be *R* and *S*, respectively, by comparison of the sign of optical rotation with the reported data.[12a] Unfortunately, when we applied the bulky P,O-ligand (a*S*)-(−)-**4c** for the same reaction, racemic products **7a** and **8a** were obtained in a ratio of 45:55 (entry 2). For the asymmetric Heck reaction of the *para*-methoxy-substituted phenyl triflate **6b** using the P,O-ligand (a*R*)-(+)-**4a**, the Heck products (+)-**7b** and (+)-**8b** were formed in a ratio of 19:81 and in ca. 40% ee for both (entry 3). The enantioselectivity of (+)-**8b** was improved to 55.2% ee along with a slight

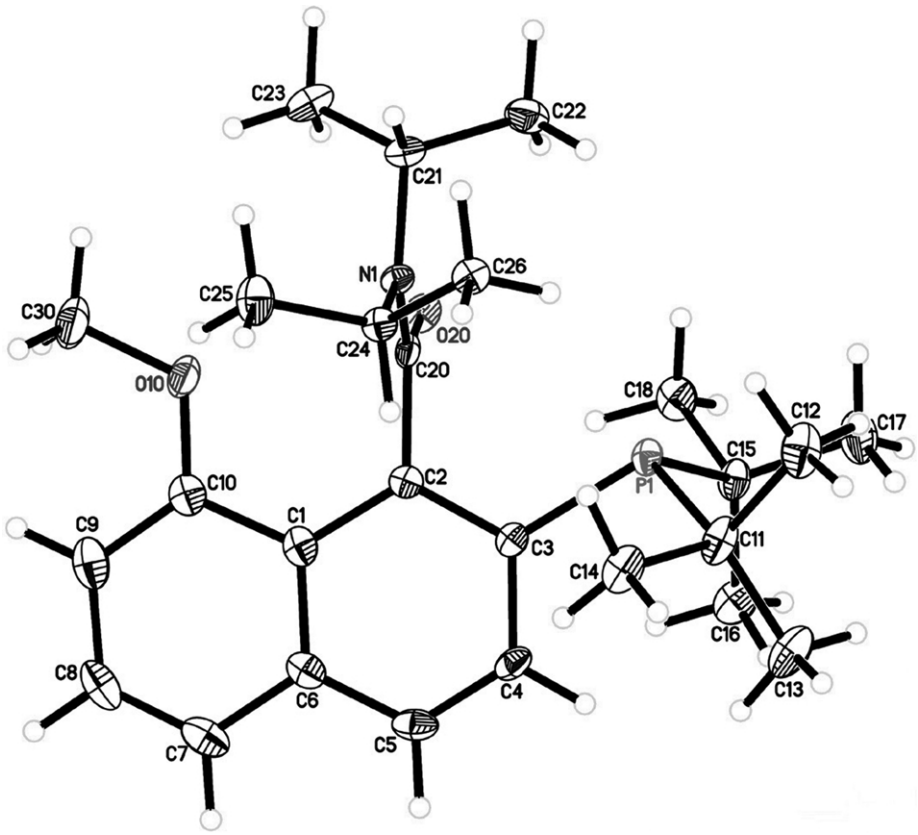
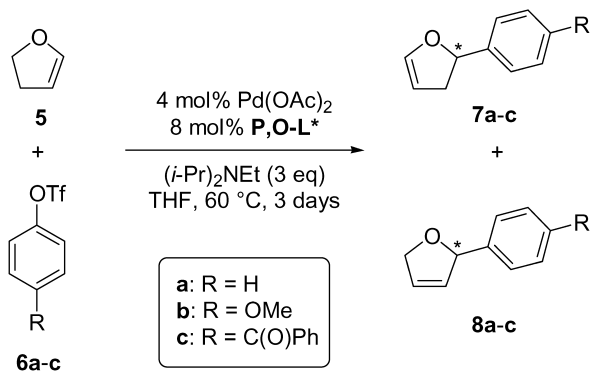


Figure 2. X-ray crystal structure of (a*S*)-(−)-**4c**.



Scheme 1. Asymmetric Heck reaction of 2,3-dihydrofuran **5**.

decrease in the ratio of (+)-**7b** to (+)-**8b** when the bulky P,O-ligand (a*R*)-(+)-**4c** was used. These results are different from those observed for the reactions of phenyl triflate **6a** (entry 2 vs. entry 4). We also tried the asymmetric Heck reaction of the *para*-phenylcarbonyl-substituted phenyl triflate **6c** by using both P,O-ligands (a*R*)-(+)-**4a** and (a*S*)-(−)-**4c**. Although the enantioselectivity in both cases is lower compared with the reactions of **6a**,**b**, an improvement in enantioselectivity up to 38.5% ee for the product (−)-**7c** was achieved by using the bulky P,O-ligand (a*S*)-(−)-**4c** (entries 5 and 6).

We investigated the asymmetric Heck reactions of 2,3-dihydrofuran **5** with a number of other *para*-substituted phenyl triflates, including 4-Br, 4-Cl, 4-Ph, 4-CN, and 4-CO_2Me. Unfortunately, all these reactions failed to form the Heck products. It seems that the amide-based atropisomeric P,O-ligands cannot promote the asymmetric Heck reactions of electron-deficient aryl triflates. It is different from the catalysis by using P,P- and P,N-ligands.[11–14] On the other hand, it is interesting to observe isomerization of the Heck product **8a** into **7a** in the order of P,P-ligands (**8a/7a**=9:91 for BINAP)[12a,d,e]>P,O-ligands (**8a/7a**=80:20–55:45 for **4a**,**c**)>P,N-ligands (**8a/7a**=100:0).[12f–k,14d,e]

3. Conclusion

As described above, for the first time, we have applied the amide-based atropisomeric P,O-ligands **4a**,**c** in the asymmetric Heck reactions of 2,3-dihydrofuran **5** with *para*-substituted phenyl triflates **6a**–**c**. Formation of both regioisomers **7a**–**c** and **8a**–**c** was observed in ratios ranging from 19:81 to 47:53. Enantioselectivity up to 55.2% ee was achieved for the major regioisomer, 2-(4-methoxy)phenyl-2,5-dihydrofuran **8b**. It seems that the atropisomeric P,O-ligands **4a**,**c** are sensitive to the electronic effect of the aryl triflates. The electron-donating group attached to the aryl triflate facilitates the asymmetric Heck reaction and affords higher enantioselectivity. We recently find that steric factor of the aryl triflates can also contribute to enantioselectivity of the asymmetric Heck reaction. The details will be disclosed in due course.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or acetone-d_6 (300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively) with $CHCl_3$ or acetone as the internal reference. IR spectra were taken on a FT-IR spectrophotometer. Mass spectra (MS) were measured by the +CI method. All reactions were carried out under a nitrogen atmosphere and monitored by thin-layer chromatography on 0.25-mm E. Merck silica gel plates (60 F-254) using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. 2,3-Dihydrofuran **5** was freshly distilled before use. Other reagents were obtained commercially and used as received.

4.1. Synthesis

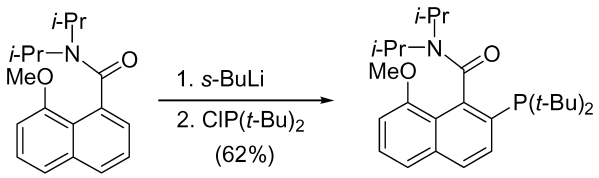
4.1.1. (a*R*)-(+)-*N*,*N*-Diisopropyl 2-di(*tert*-butyl)phosphino-8-methoxy-1-naphthamide (a*R*)-(+)-4c and (a*S*)-(−)-*N*,*N*-diisopropyl 2-di(*tert*-butyl)phosphino-8-methoxy-1-naphthamide (a*S*)-(−)-4c. To a solution of amide **9** (66.6 mg, 0.23 mmol) in THF (2.5 mL) cooled in a dry ice-acetone bath (−78 °C) was added *sec*-butyllithium (1.3 M in hexane, 0.26 mL, 0.34 mmol) followed by stirring at the same temperature for 1 h. To this mixture was added di(*tert*-butyl)chlorophosphine (50 μL, 0.25 mmol) followed by stirring at −78 °C for another 4 h. The reaction mixture was allowed to warm to room temperature and was filtered quickly though a plug of Celite. The filtrate was concentrated under reduced pressure to give a yellow solid, which was purified by flash column chromatography (silica gel, 30% EtOAc–hexane) to give the product *rac*-**4c** as a white solid (60.0 mg, 62%); R_f=0.63 (40% EtOAc–hexane). The

Table 1. Asymmetric Heck reactions of 2,3-dihydrofuran with aryl triflates by using atropisomeric P,O-ligands[a]

Entry	P,O-ligand	Aryl triflate	**7**: Yield (%);[b] ee (%);[c] config.[d]	**8**: Yield (%);[b] ee (%);[c] config.[d]	Ratio of **7/8**[e]
1	(a*S*)-(−)-**4a**	**6a**	(−)-**7a**: 17; 52.4; *R*	(−)-**8a**: 68; 49.8; *S*	20:80
2	(a*S*)-(−)-**4c**	**6a**	(±)-**7a**: 29; 0; —	(±)-**8a**: 36; 0; —	45:55
3	(a*R*)-(+)-**4a**	**6b**	(+)-**7b**: 13; 41.6; *S*	(+)-**8b**: 57; 42.0; *R*	19:81
4	(a*R*)-(+)-**4c**	**6b**	(+)-**7b**: 15; 29.5; *S*	(+)-**8b**: 36; 55.2; *R*	29:71
5	(a*R*)-(+)-**4a**	**6c**	(+)-**7c**: 17; 7.0; nd[f]	(+)-**8c**: 46; 14.0; nd[f]	27:73
6	(a*S*)-(−)-**4c**	**6c**	(−)-**7c**: 28; 38.5; nd[f]	(−)-**8c**: 32; 18.1; nd[f]	47:53

[a] The reaction was carried out at 60 °C for 3 days in THF in the presence of 4 mol% $Pd(OAc)_2$, 8 mol% of the chiral P,O-ligand, and 3 equiv. of (*i*-Pr)$_2$NEt.
[b] Isolated yield.
[c] ee was determined by HPLC or GC analysis over a chiral stationary phase. The details are found in Section 4.
[d] Absolute stereochemistry was assigned based on comparison of optical rotation data with reported values.
[e] Ratio was determined by ^{1}H NMR measurement of the crude reaction mixture before column chromatographic separation.
[f] Absolute stereochemistry is not determined.

enantiomerically pure isomers were obtained by HPLC separation over a Chiralpak AD column. The HPLC settings are as follows: a 13:87 ratio of *i*-PrOH–hexane at a flow rate of 6 mL min^{-1} with UV detection at 254 nm (Scheme 2).



9 *rac*-**4c**

Scheme 2. Synthesis of atropisomeric P,O-ligand *rac*-**4c**.

Compound (*aR*)-(+)-**4c**. A white solid; mp 201–202 °C (EtOAc–hexane); $[\alpha]_D^{20}$=+23.3 (*c* 1.02, $CHCl_3$); IR (CH_2Cl_2) 2967, 2929, 1634, 1449, 1299 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J*=8.4, 0.6 Hz, 1H), 7.68 (d, *J*=8.4 Hz, 1H), 7.40 (d, *J*=5.1 Hz, 1H), 7.40 (d, *J*=4.2 Hz, 1H), 6.88–6.82 (m, 1H), 3.90 (s, 3H), 3.66–3.48 (m, 2H), 1.71 (d, *J*=6.6 Hz, 6H), 1.30 (s, 9H), 1.27 (s, 9H), 1.26 (d, *J*=6.6 Hz, 3H), 1.25 (s, 9H), 1.21 (s, 9H), 0.93 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (d, J_{p-c}=4.5 Hz), 156.4, 143.0 (d, J_{p-c}=38.1 Hz), 136.0, 133.5, 133.2, 133.1, 127.5, 126.3, 121.3, 106.9, 55.9, 50.7, 46.7, 34.3 (d, J_{p-c}=23.9 Hz), 32.7 (d, J_{p-c}=27.4 Hz), 32.6 (×3, d, J_{p-c}=15.4 Hz), 31.3 (×3, d, J_{p-c}=14.1 Hz), 22.9 (d, J_{p-c}=3.2 Hz), 21.6 (d, J_{p-c}=1.3 Hz), 21.1 (d, J_{p-c}=3.2 Hz), 20.9; ^{31}P NMR (121 MHz, $CDCl_3$) δ 22.5; MS (+CI) *m/z* 430 ($M+H^+$, 100). Anal. Calcd for $C_{26}H_{40}NO_2P$: C, 72.69; H, 9.39; N, 3.26. Found: C, 72.35; H, 9.04; N, 3.21.

Compound (a*S*)-(−)-**4c**. A white solid; mp 203–204 °C (EtOAc–hexane); $[\alpha]_D^{20}$=−23.4 (*c* 0.98, $CHCl_3$). Other spectroscopic data are identical to those of (a*R*)-(+)-**4c**. The absolute stereochemistry of (a*S*)-(−)-**4c** was established by X-ray crystal structural analysis as given in Figure 2. The crystal data were deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 226917. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB12 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2. General procedure for asymmetric Heck reaction

A solution of $Pd(OAc)_2$ (1.3 mg, 4 mol%) and (a*R*)-(+)-**4c** (8 mol%) in THF (1.5 mL) was stirred at room temperature for 10 min. To the mixture were added the triflate **6b** (0.15 mmol), *N*,*N*-diisopropylethylamine (78 μL, 0.45 mmol), and 2,3-dihydrofuran **5** (57 μL, 0.75 mmol). The resultant mixture was stirred at 60 °C for 3 days. The reaction mixture was diluted with hexane (5 mL) and the resulting brown suspension was filtered off through a pad of silica gel with eluting by Et_2O. The combined filtrate was condensed under reduced pressure to give a residue, which was purified by preparative TLC to afford the products (entry 4, Table 1). The isomeric ratio of the product was determined by ^1H NMR of the crude product mixture before purification. The enantiomer ratio was determined by GC or HPLC analysis over a chiral stationary phase. GC analysis settings are: J & W Cyclosil β column; He gas flow rate of 2 mL min^{-1}; and oven temperature at 80 °C for 15 min and then increased to 170 °C. HPLC analysis settings are: one Chiralcel OD column connected with another Chiralcel OD-H column; solvent ratio of 99:1 (hexane-*i*-PrOH); flow rate of 0.2 mL min^{-1}; and UV detection at 254 nm.

4.2.1. (*R*)-(−)-2-Phenyl-2,3-dihydrofuran (*R*)-(−)-7a. Obtained from the reaction of phenyl triflate **6a** as the minor product (entry 1, Table 1). $[\alpha]_D^{20}$=−36.5 (*c* 1.20, $CHCl_3$, 52.4% ee by GC); lit. for (*R*)-(−)-**7a**, $[\alpha]_D$=−64.3 (*c* 1.2, $CHCl_3$, 93% ee by NMR)[12a,b] and $[\alpha]_D$=−61.5 (*c* 2.30, $CHCl_3$, 91% ee);[12d] IR (CH_2Cl_2) 1619, 1451, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 6.46–6.44 (m, 1H), 5.52 (dd, *J*=10.7, 8.4 Hz, 1H), 4.97–4.95 (m, 1H), 3.12–3.03 (m, 1H), 2.66–2.57 (m, 1H);[12b] ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 143.0, 128.5 (×2), 127.6, 125.6 (×2), 99.0, 82.3, 37.8; MS (+CI) *m/z* 147 ($M+H^+$, 100). The enantiomer excess was determined by GC analysis. Compound (*S*)-(+)-**7a** has retention time of 28.3 min and (*R*)-(−)-**7a** has retention time of 30.0 min.

4.2.2. (*S*)-(−)-2-Phenyl-2,5-dihydrofuran (*S*)-(−)-8a. Obtained from the reaction of phenyl triflate **6a** as the major product (entry 1, Table 1). $[\alpha]_D^{20}$=−138.1 (*c* 0.60, $CHCl_3$, 49.8% ee by GC); lit. for (*S*)-(−)-**8a**, $[\alpha]_D$=−175 (*c* 1.3, $CHCl_3$, 67% ee by NMR)[12a,b] and for (*R*)-(+)-**8a**, $[\alpha]_D$=+280 (*c* 1.06, $CHCl_3$, 97% ee);[13d] IR (CH_2Cl_2) 1454, 1063 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 6.05–6.02 (m, 1H), 5.91–5.87 (m, 1H), 5.82–5.78 (m, 1H), 4.92–4.85 (m, 1H), 4.81–4.75 (m, 1H);[12b] ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 129.9, 128.5 (×2), 127.8, 126.6, 126.4 (×2), 87.9, 75.8;[13d] MS (+CI) *m/z* 147 ($M+H^+$, 100). The enantiomer excess was determined by GC analysis. Compound (*R*)-(+)-**8a** has retention time of 30.1 min and (*S*)-(−)-**8a** has retention time of 31.0 min.

4.2.3. (*S*)-(+)-2-(4-Methoxyphenyl)-2,3-dihydrofuran (*S*)-(+)-7b. Obtained from the reaction of 4-methoxyphenyl triflate **6b** as the minor product (entry 4, Table 1). $[\alpha]_D^{20}$=+32.9 (*c* 0.81, $CHCl_3$, 29.5% ee by GC); lit. for (*R*)-(−)-**7b**, $[\alpha]_D$=−75.7 ($CHCl_3$, 73% ee by NMR)[12a] and $[\alpha]_D$=−92.7 (*c* 0.51, $CHCl_3$, 91.4% ee);[12l] ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 ($A'_2B'_2$, 2H), 6.94–6.85 ($A'_2B'_2$, 2H), 6.43 (q, *J*=2.1 Hz, 1H), 5.47 (dd, *J*=10.2, 8.4 Hz, 1H), 4.96 (q, *J*=2.7 Hz, 1H), 3.82 (s, 3H), 3.09–2.98 (m, 1H), 2.66–2.57 (m, 1H).[12l] The enantiomer excess was determined by GC analysis. Compound (*R*)-(−)-**7b** has retention time of 41.1 min and (*S*)-(+)-**7b** has retention time of 41.3 min.

4.2.4. (*R*)-(+)-2-(4-Methoxyphenyl)-2,5-dihydrofuran (*R*)-(+)-8b. Obtained from the reaction of 4-methoxyphenyl triflate **6b** as the major product (entry 4, Table 1). $[\alpha]_D^{20}$=+91.2 (*c* 1.25, $CHCl_3$, 55.2% ee by GC); lit.[12a] for (*S*)-(−)-**8b**, $[\alpha]_D$=−114 ($CHCl_3$, 66% ee by NMR); IR (CH_2Cl_2) 1602, 1514, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.19 ($A'_2B'_2$, 2H), 6.92–6.84 ($A'_2B'_2$, 2H), 6.05–6.02 (m, 1H), 5.88–5.84 (m, 1H), 5.76–5.74 (m, 1H), 4.88–4.81 (m, 1H), 4.77–4.71 (m, 1H), 3.80 (s, 3H);[12l] ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 134.0, 130.0, 127.7 (×2), 126.6, 113.8 (×2), 87.5, 75.5, 55.3;[12l] MS (+CI) *m/z* 177 ($M+H^+$, 100). The enantiomer excess was determined by

GC analysis. Compound (*S*)-(−)-**8b** has retention time of 42.7 min and (*R*)-(+)-**8b** has retention time of 42.9 min.

4.2.5. (−)-2-[4-(Phenylcarbonyl)phenyl]-2,3-dihydrofuran (−)-7c. Obtained from the reaction of 4-(phenylcarbonyl)phenyl triflate **6c** as the minor product (entry 6, Table 1). R_f=0.33 (17% EtOAc–hexane); $[\alpha]_D^{20}$=−16.8 (*c* 1.10, $CHCl_3$, 38.5% ee by HPLC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81–7.77 (m, 4H), 7.66–7.64 (m, 1H), 7.59–7.54 (m, 4H), 6.55 (q, *J*=2.7 Hz, 1H), 6.16 (dd, *J*=10.8, 8.2 Hz, 1H), 5.00 (q, *J*=2.3 Hz, 1H), 3.19 (dd, *J*=10.9, 2.4 Hz, 1H), 2.58 (dd, *J*=8.1, 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 148.2, 145.8, 138.1, 137.3, 132.9, 131.0 (×2), 130.5 (×2), 128.8 (×2), 125.9 (×2), 99.7, 82.3, 38.6; MS (+CI) *m*/*z* 251 ($M+H^+$, 100). The enantiomeric excess was determined by HPLC analysis. Compound (−)-**7c** has retention time of 104.7 min and (+)-**7c** has retention time of 107.6 min.

4.2.6. (−)-2-[4-(Phenylcarbonyl)phenyl]-2,5-dihydrofuran (−)-8c. Obtained from the reaction of 4-(phenylcarbonyl)phenyl triflate **6c** as the major product (entry 6, Table 1). R_f=0.20 (17% EtOAc–hexane); $[\alpha]_D^{20}$=−46.5 (*c* 1.20, $CHCl_3$, 18.1% ee by HPLC); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81–7.76 (m, 4H), 7.61–7.54 (m, 1H), 7.50–7.40 (m, 4H), 6.10–6.05 (m, 1H), 5.93–5.86 (m, 2H), 4.98–4.88 (m, 1H), 4.86–4.77 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.9, 147.3, 138.3, 137.6, 133.0, 131.0 (×2), 130.6 (×2), 130.0, 128.8 (×2), 127.7, 126.7 (×2), 88.1, 76.8; MS (+CI) *m*/*z* 251 ($M+H^+$, 100). The enantiomeric excess was determined by HPLC analysis. Compound (+)-**8c** has retention time of 140.7 min and (−)-**8c** has retention time of 148.1 min.

Acknowledgements

The work is financially supported by the Department of Chemistry, HKUST and the Research Grants Council (through a Direct Allocation Grant, DAG02/03.SC09) of the Hong Kong Special Administrative Region, China.

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Tetrahedron 60 (2004) 4431–4441
Tetrahedron

Configurationally defined sexi- and octinaphthalene derivatives: synthesis and optical properties☆

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Received 17 October 2003; revised 19 March 2004; accepted 19 March 2004

Abstract—The copper mediated oxidative coupling of optically active quaternaphthalenes having a 2-hydroxynaphthyl moiety gave configurationally defined optically active octinaphthalenes. The absolute configuration was determined by comparison with products of [6+2] coupling. The CD spectra of bi-, ter-, quater-, sexi- and octinaphthalenes suggested that the absolute configuration of the chiral axis could be deduced from the intensity of their Cotton effects.

1. Introduction

Monodisperse, nanometer sized molecules having a unique three-dimensional structure such as a helix have become of great interest due to the possibility for their use as a specific molecular device for material sciences as well as for the architectural beauty of their molecular shape. 2,2′-Difunctionalized 1,1′-binaphthalenes have been used not only as an excellent chiral inducer for asymmetric synthesis but also for chiral recognition in host–guest chemistry. These molecules possess a relatively rigid but flexible twisted conformation around the axis between its aromatic rings. Therefore, these molecules could be used as a key structural element for introduction of a twisted conformation as well as chirality into larger molecules. On the other hand, the development of novel monodisperse π-conjugated oligomers has recently attracted much attention due to their potential application in material sciences.[2] Among them, oligo(*p*-phenylene)s have received special attention and have been used as backbones for artificial proton channels[3] and β-barrels[4] and as rigid spacer units in an artificial receptor of cyclic dipeptides.[5] Oligo(*p*-phenylene)s are also important model compounds for poly(*p*-phenylene)s since some poly(*p*-phenylene)s are remarkable organic conductors upon doping[6] and are also used as laser materials.[7] The rod can contain 15 or even l6 phenyl rings.[8,9] However, little attention has been paid to rod-shaped naphthalenes connected at the 1,4-positions, in which the 1,1′-binaphthyl moieties are directly coupled each other, although the partial incorporation of a 2,2′-difunctionalized 1,1′-binaphthyl into a large molecule such as a polymer have been reported.[2a] One example of monodisperse oligonaphthalene reported so far was sexinaphthalene.[10,11] Recently, we reported the preparation of stereochemically defined ter-, quarter-[12a] and higher oligonaphthalenes[12b] and quarternaphthalene **1** showed unique function as an organic zeolite (Fig. 1).[12c] Moreover, it has been reported that the *meso*-ternaphthalene **2** tethered by two crown ethers plays an interesting role as a ditopic receptor for recognition of the length of

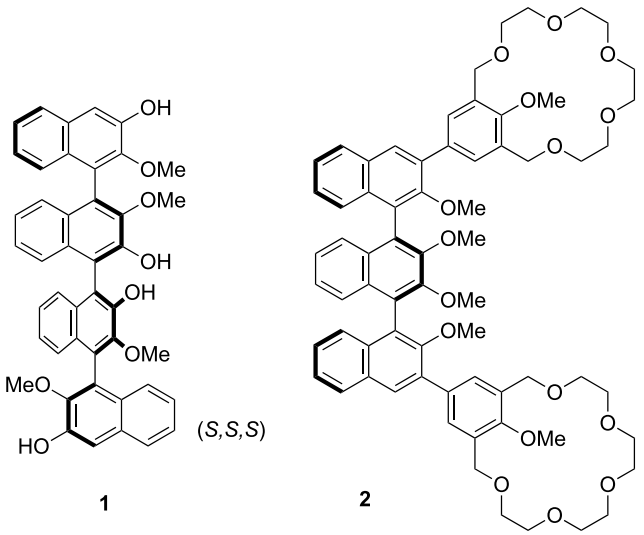

Figure 1. Ter- and quaternaphthalenes.

☆ See Ref. 1.

Keywords: Sexinaphthalene; Octinaphthalene; Atropisomerism; Oxidative coupling; CD spectra.

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0040–4020/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tet.2004.03.055

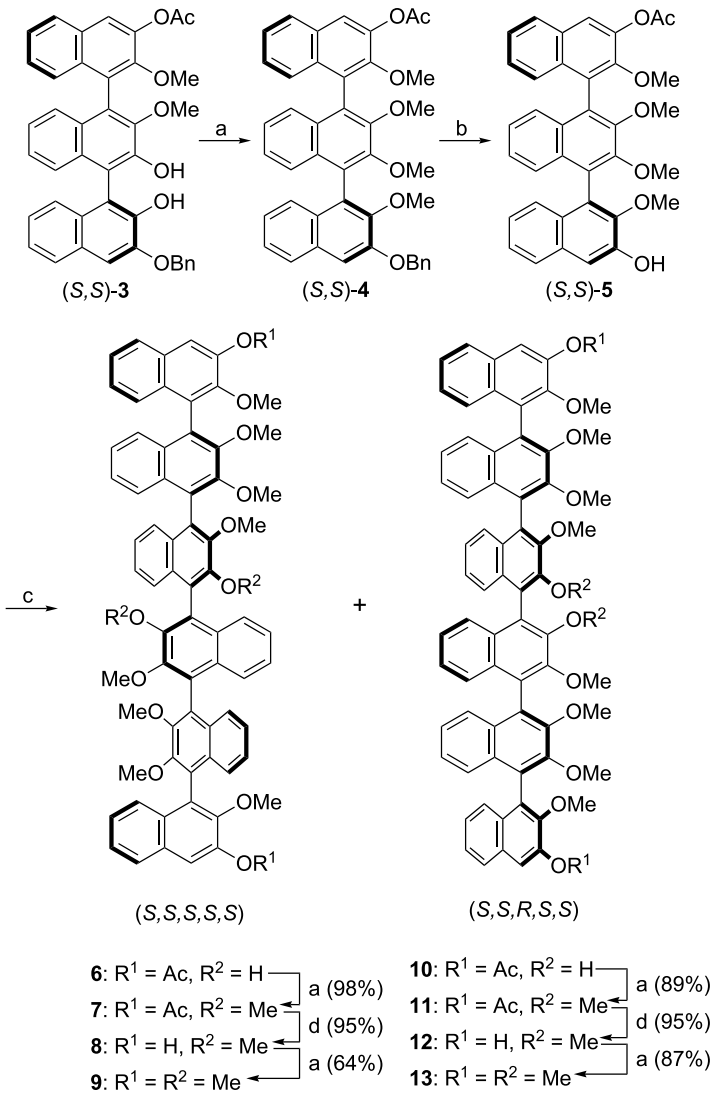
α,ω-diamines.[13] It would be interesting to determine whether higher oligonaphthalenes also show such specific characteristics. We report here the synthesis of optically active sexi- and octinaphthalenes as well as their CD spectra.[1]

2. Results and discussion

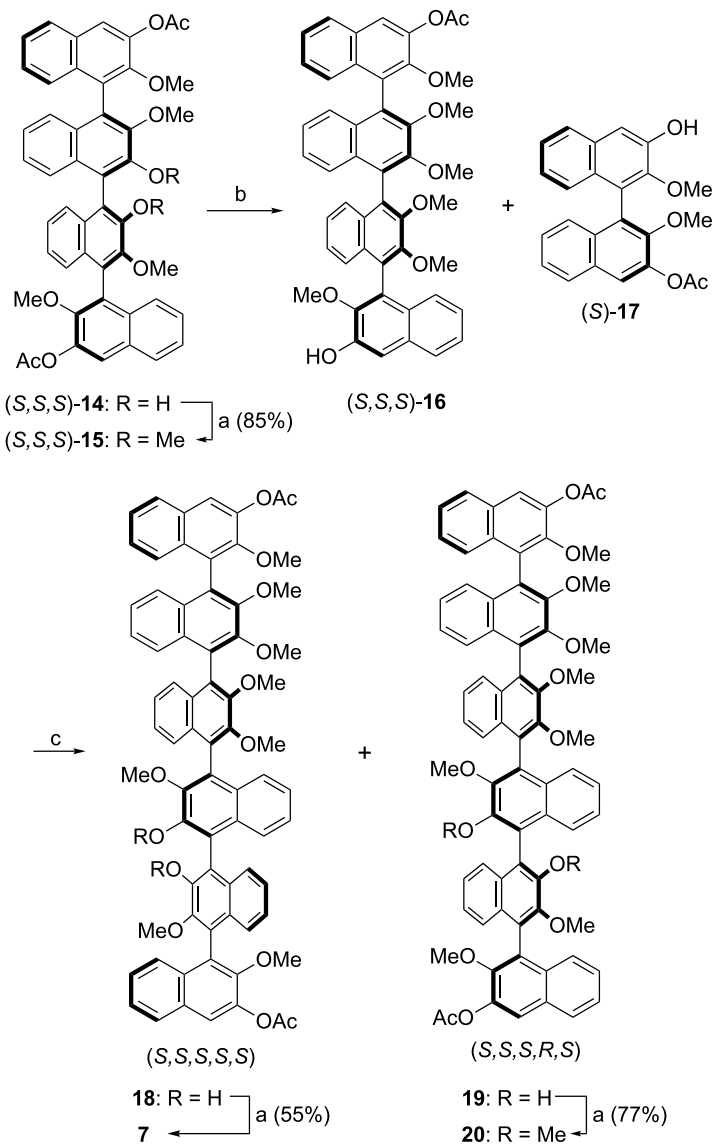
2.1. Synthesis of oligonaphthalenes and determination of their absolute configurations

The synthetic pathway to sexinaphthalenes, starting from the optically active ternaphthalene **3**,[12a] is shown in Scheme 1. Methylation of (*S*,*S*)-**3** afforded (*S*,*S*)-**4**, which was converted into monohydroxyternaphthalene (*S*,*S*)-**5** by hydrogenolysis, in 82% overall yield. Oxidative coupling[14] of **5** in the presence of $CuCl_2$ and racemic α-phenylethylamine afforded sexinaphthalenes (*S*,*S*,*S*,*S*,*S*)-**6** and its diastereomer (*S*,*S*,*R*,*S*,*S*)-**10** in 31 and 38% yield, respectively. Methylation of **6** and **10** gave diastereomers **7** and **11**, which were converted into the permethylated derivatives **9** and **13**, respectively. The only difference of coupling products between **6** and **10** is the absolute stereochemistry around the newly created central bond, which was unambiguously determined by synthesis via an alternative synthetic route that included the [4+2] construction of sexinaphthalenes (Scheme 2).

Thus, the known quaternaphthalene (*S*,*S*,*S*)-**14**[12a] was methylated to give (*S*,*S*,*S*)-**15**, partial hydrolysis of which afforded (*S*,*S*,*S*)-**16** in 40% yield. In order to avoid homocoupling of **16**, the oxidative coupling between **16** and (*S*)-**17**[12a] was carried out in the presence of excess amount of **17** to give sexinaphthalenes (*S*,*S*,*S*,*S*,*S*)-**18** and (*S*,*S*,*S*,*R*,*S*)-**19** in respective yields of 18 and l6%, along with (*S*,*S*,*S*)-**14** and its isomer with an *R* configuration at the central bond. Methylation of **18** gave **7**, which was identical to one of the products of the homocoupling of **5**, while methylation of **19** gave **20**, which is distinct from both **7** and **11**. These findings clearly support the absolute



Scheme 1. The [3+3] construction of sexinaphthalenes. Reagents: (a) CH_3I, K_2CO_3, 85%; (b) 10% Pd–C, H_2, 97%; (c) α-phenylethylamine, $CuCl_2$, **6** (31%), **10** (38%); (d) K_2CO_3, MeOH.



Scheme 2. The [4+2] construction of sexinaphthalenes. Reagents: (a) CH_3I, K_2CO_3; (b) K_2CO_3, MeOH, 40%; (c) α-phenylethylamine, $CuCl_2$, **18** (18%), **19** (16%).

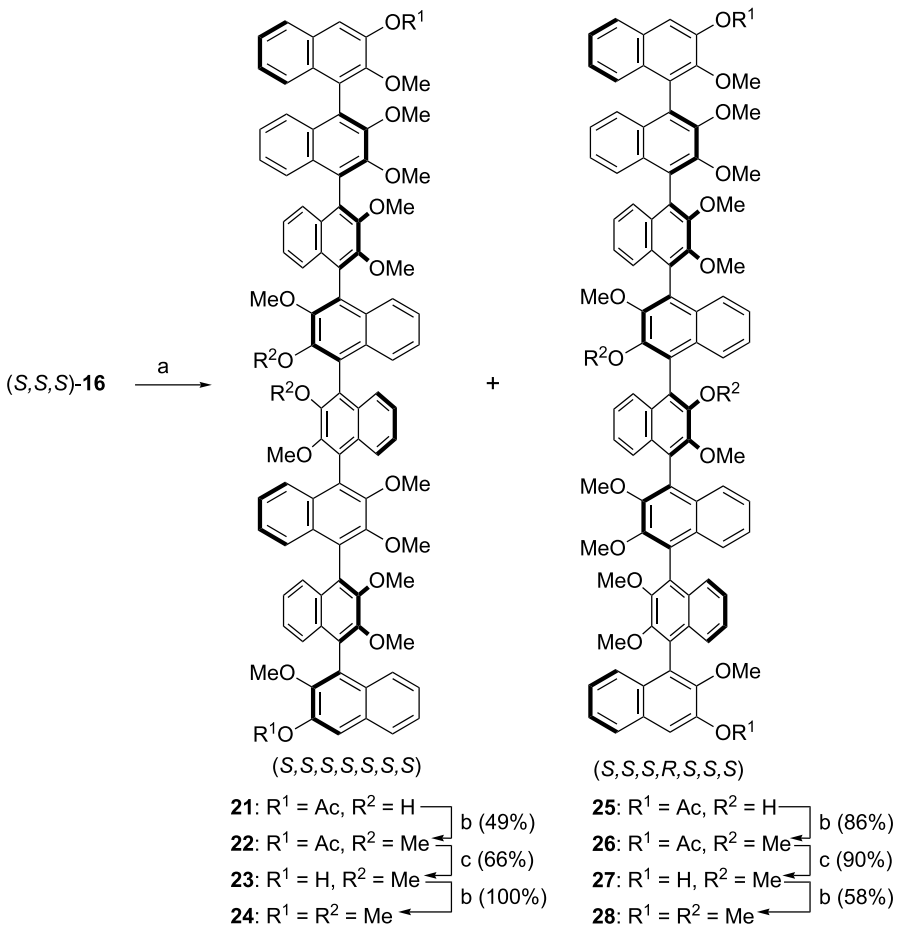
configurations of the coupling products **6**, **10**, **18** and **19** as depicted in Schemes 1 and 2.

A similar strategy to these transformations was used to synthesize octinaphthalenes as well as to determine their absolute stereochemistry (Schemes 3 and 4). Oxidative coupling of quaternaphthalene (*S*,*S*,*S*)-**16** gave (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**21** (22%) and (*S*,*S*,*S*,*R*,*S*,*S*,*S*)-**25** (30%). Methylation of **21** followed by hydrolysis gave **23**. Treatment of **23** with CH_3I/K_2CO_3 in acetone converted **23** into **24**, which has a methoxy group as a uniform substituent. The diastereomer **25** was transformed to **28** through the same sequence of reactions as those for **21** (Scheme 3). The [6+2] construction of octinaphthalenes is also shown in Scheme 4. Partial hydrolysis of (*S*,*S*,*S*,*S*,*S*)-**7** gave (*S*,*S*,*S*,*S*,*S*)-**29**, which was then subjected to the oxidative coupling in the presence of 5 equiv. of (*S*)-**17** to give (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**30** (13%) and (*S*,*S*,*S*,*S*,*S*,*R*,*S*)-**31** (22%). Methylation of **30** gave **22**, while that of **31** gave **32**, which resulted in determination of the absolute configuration of the products **30** and **31** as shown in Scheme 4.

For the CD study described below, (*S*)-tetramethoxybinaphthalene **33** was also prepared from binaphthalene **34**[12a] of known absolute configuration by methylation (Scheme 5).

2.2. Conformation of oligonaphthalenes

One of the most interesting aspects of oligonaphthalenes is their molecular shape, which is reminiscent of the banisters of a spiral staircase, and their π-system, which is totally different from that of helicenes.[15] An interesting question is how many naphthyl rings are required to complete a full turn of the helix. An X-ray crystal structural analysis of a quaternaphthalene **1** revealed that four naphthyl units are insufficient.[12a] Since none of the sexi- or octinaphthalenes gave fruitful crystals for X-ray analysis, the most stable



Scheme 3. The [4+4] construction of octinaphthalenes. Reagents: (a) α-phenylethylamine, $CuCl_2$, **21** (22%), **25** (30%); (b) CH_3I, K_2CO_3; (c) K_2CO_3, MeOH.

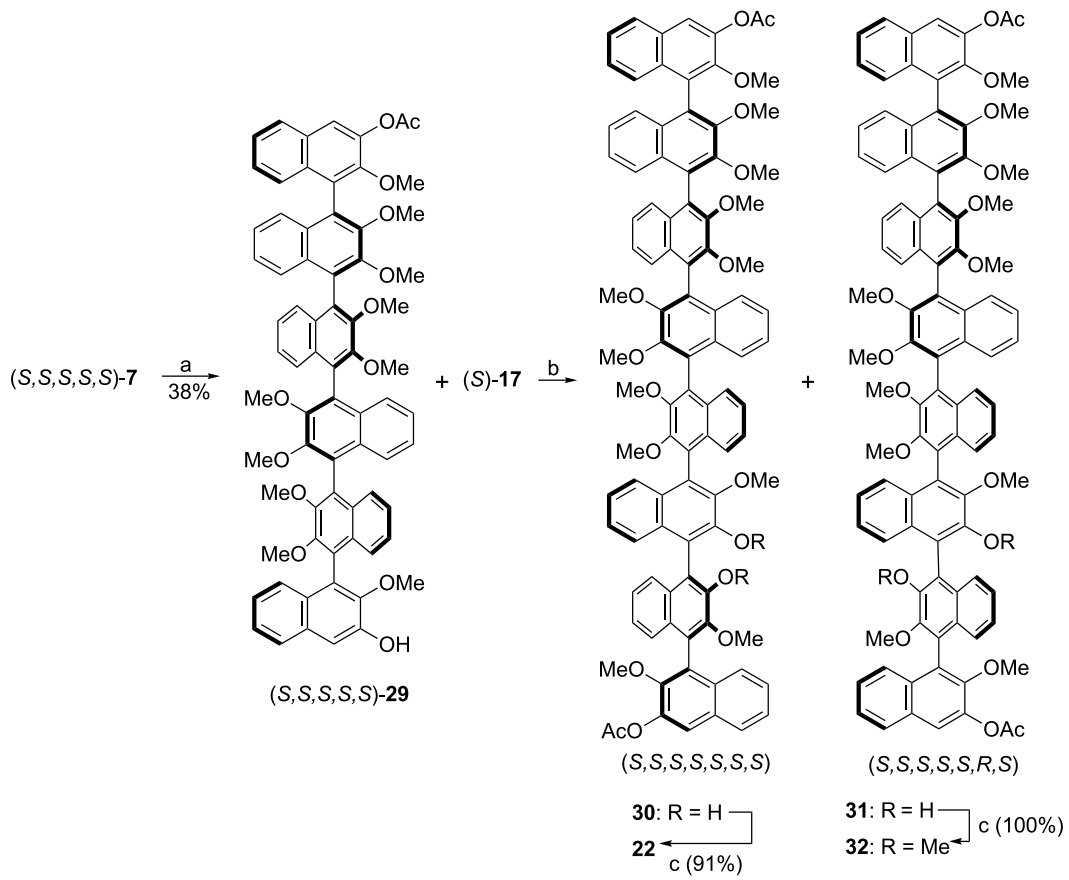
conformation of **24** was calculated by MacroModel/MM2 (version 6.0). The calculation results indicated that at least five to six naphthyls are necessary for a turn (Fig. 2a). The dihedral angles between each naphthyl unit are nearly 80° and the length of molecule including hydrogen atoms is 35 Å. These results are consistent with the X-ray analysis of quaternaphthalene **1**, in which the dihedral angles between each naphthalene are 74.7, 79.7 and 113.0°.[12a] The top view of **24** showed the cylindrical shape of molecule having around 9 Å diameter (Fig. 2b). The calculation for the corresponding 24-mer revealed that the helix repeated a full turn every five to six naphthyls (Fig. 2c). The central eight naphthalene units of the 24-mer were extracted and compared with octinaphthalene **24** (Fig. 2a and d). While the two conformations are quite similar, a slight lag was observed for a turn.

2.3. CD spectra of oligonaphthalenes

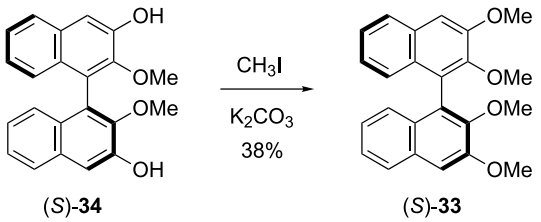
The CD spectra of permethylated, configurationally defined bi-, ter-, quater-, sexi- and octinaphthalenes **33**, **35**,[12a] **36**,[12a] **9** and **24**, possessing *aS* configuration around each axis, were taken (Fig. 3 and Table 1). All compounds showed strong split Cotton effects of positive exciton chirality.[16] The intensity of their Cotton effect around 240 nm are obviously increased in accordance with the increase of the number of naphthyl units, Δε 12.8, 68.8, 83.8, 102.7, 136.8 for **33**, **35**, **36**, **9** and **24**, respectively (Table 1). These results suggest an additivity relationship between the intensity of Cotton effect and the number of naphthalene chromophores.

Taking this hypothesis into account, the CD spectra of quater-, sexi-, and octinaphthalenes **37**,[12a] **13** and **28** possessing *aR* configuration at the central axis were measured and compared with the spectra of their diastereomers **36**, **9** and **24**, respectively. The quaternaphthalene **37** showed a smaller positive Cotton effect (Δε 27.7) at 233.7 nm than that of its isomer **36** (Fig. 4a). Also, the sexinaphthalene **13** exhibited a smaller positive Cotton effect (Δε 86.4) at 239.9 nm than that of **9** (Fig. 4b). The same tendency was observed in octinaphthalenes (Fig. 4c). Moreover, the intensity of Cotton effect of **13** around 240 nm is similar to that of **36**. This could be explained by the partial cancellation of Cotton effect owing to *R* axis of **13**. The same relationship was observed between **9** and **28**. These results clearly showed that the intensity of Cotton effect depends on the absolute configuration due to each axis. Therefore, it could be concluded that the intensity of Cotton effect could be useful informative source for the determination of the absolute configuration of such kinds of oligonaphthalenes.

The development of specific functions and the further study of optical properties of synthesized oligonaphthalenes are currently under investigation.



Scheme 4. The [6+2] construction of octinaphthalenes. Reagents: (a) K_2CO_3, MeOH; (b) α-phenylethylamine, $CuCl_2$, **30** (13%), **31** (22%); (c) CH_3I, K_2CO_3.



Scheme 5. Preparation of tetramethoxybinaphthalene.

3. Experimental

3.1. General

Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken in $CDC1_3$ at 200 or 400 MHz for ^1H NMR and at 50 MHz for ^{13}C NMR, with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard. FT-IR, UV and CD spectra were obtained

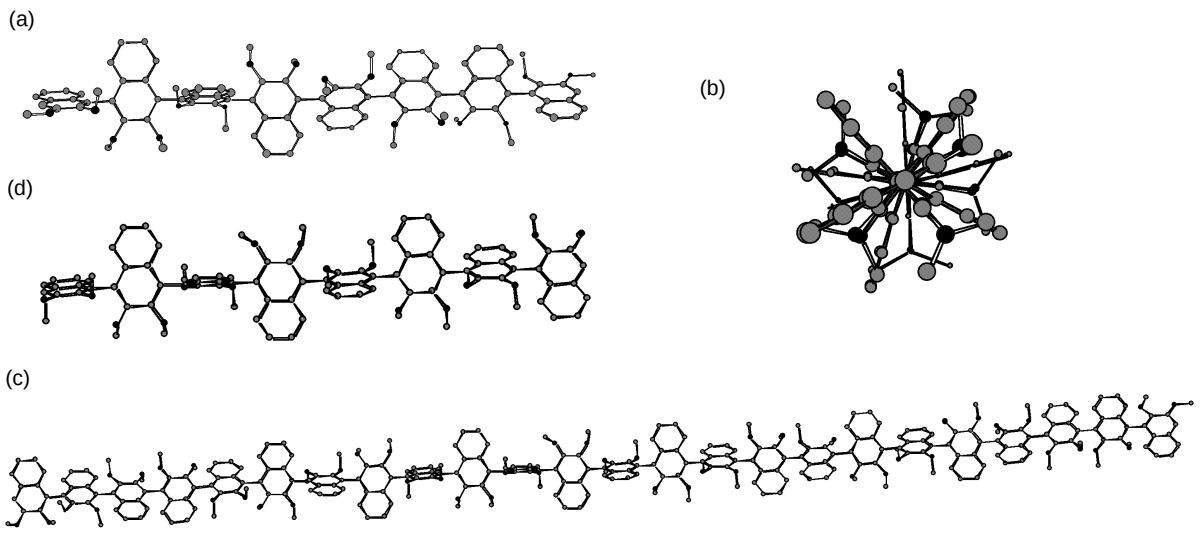


Figure 2. (a) The most stable conformation of octinaphthalene **24** calculated by MacroModel (version 6.0). (b) The top view of octinaphthalene **24**. (c) The most stable conformation of the 24-mer calculated by MacroModel (version 6.0). (d) The central eight naphthalenes of the 24-mer.

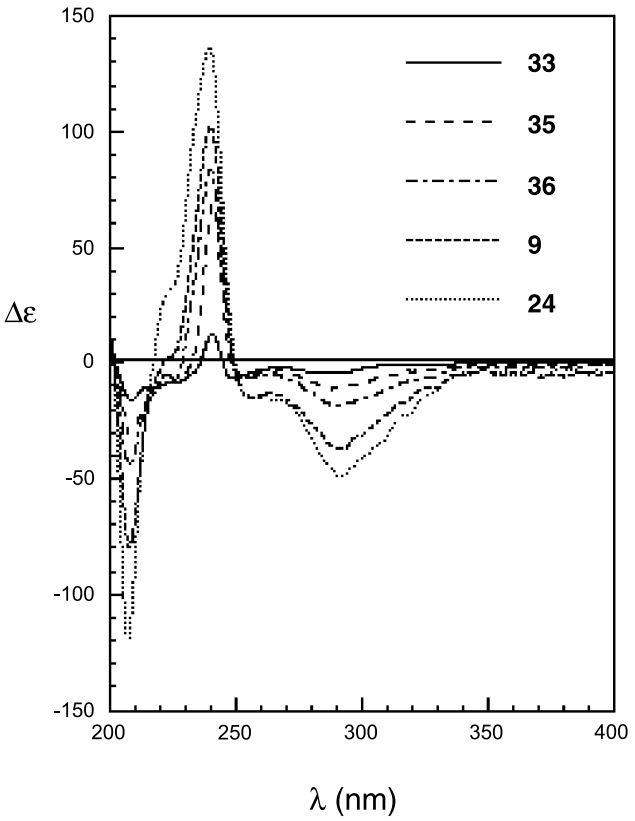
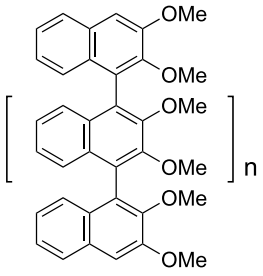


Figure 3. CD spectra of oligonaphthalenes in 0.4% dioxane–MeOH.

Table 1. CD Spectral data of oligonaphthalenes

Compound	λ_{ext} (nm) ($\Delta\varepsilon$)
33	286.1 (−4.4), 240.3 (12.8), 208.2 (−16.0)
35	286.3 (−11.3), 240.3 (68.8), 208.2 (−30.7)
36	288.9 (−18.3), 239.6 (83.8), 207.4 (−43.7)
9	291.9 (−36.8), 239.5 (102.7), 207.4 (−79.8)
24	291.6 (−48.8), 239.2 (136.8), 206.9 (−119.4)
37	285.7 (−6.9), 245.5 (−15.0), 233.7 (27.7), 209.3 (−27.9)
13	292.6 (−21.2), 239.9 (86.4), 207.7 (−63.4)
28	291.9 (−30.7), 239.5 (108.8), 207.1 (−84.0)



n = 0: **33** (*S*)
n = 1: **35** (*S,S*)
n = 2: **36** (*S,S,S*)
37 (*S,R,S*)
n = 4: **9** (*S,S,S,S,S*)
13 (*S,S,R,S,S*)
n = 6: **24** (*S,S,S,S,S,S,S*)
28 (*S,S,S,R,S,S,S*)

on a JASCO FT/IR-300, Shimadzu UV-2200 and JASCO J-720W, respectively. All extractive organic solutions were dried over anhydrous $MgSO_4$. Flash column chromatography was carried out with silica gel 60 spherical (150–325 mesh) and Kiesel gel 60 F_{254} plates (Merck) were used for preparative TLC (pTLC).

3.1.1. (*S,S*)-Ternaphthalene 4. To a mixture of (*S,S*)-**3** (500 mg, 0.79 mmol) and potassium carbonate (1.6 g, 12 mmol) in acetone (15 mL) was added dropwise methyl iodide (1.0 mL, 16 mmol) at room temperature. The mixture was refluxed for 2 h. After cooling, the reaction mixture was evaporated under reduced pressure, and the residue was added to a mixture of ethyl acetate and aq. 2 N HCl. The organic layer was separated, dried and then evaporated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2, *n*-hexane/EtOAc=2/1) to afford (*S,S*)-**4** as colorless powder (445 mg, 85%), which was recrystallized from CH_2Cl_2/EtOAc/pet. ether to give colorless prisms. Mp 206–208 °C; $[\alpha]_D^{20}=-113.7$ (*c* 2.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.0–7.1 (m, 19H), 5.37 (s, 2H), 3.79 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 3.60 (s, 3H), 2.42 (s, 3H); IR ($CHCl_3$): 3063, 3029, 3010, 2940, 1766, 1597, 1503, 1467, 1016 cm^{-1}; EI MS *m/z* 664 (M^+). Anal. Calcd for $C_{43}H_{36}O_7$: C, 77.69; H, 5.46. Found: C, 77.39; H, 5.45.

3.1.2. (*S,S*)-Ternaphthalene 5. To a suspension of palladium on carbon (10%, 296 mg) in $CHCl_3$, a solution of (*S,S*)-**4** (320 mg, 0.48 mmol) in $CHCl_3$ (15 mL) and AcOH (0.75 mL) was added. The mixture was stirred at room temperature for 29 h under hydrogen. After the catalyst was filtered off, the filtrate was evaporated under reduced pressure to give a residue, which was purified by the recrystallization from CH_2Cl_2/EtOAc/pet. ether to give (*S,S*)-**5** as colorless plates (268 mg, 97%). Mp 161–162 °C; $[\alpha]_D^{20}=-73.4$ (*c* 0.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.0–7.1 (m, 14H), 6.18 (s, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 3.62 (s, 3H), 3.60 (s, 3H), 2.43 (s, 3H); IR ($CHCl_3$): 3522, 3009, 3010, 2941, 1631, 1506, 1468, 1221 cm^{-1}; EI MS *m/z* 574 (M^+); HRMS *m/z* Calcd for $C_{36}H_{30}O_7$ (M^+) 574.1992. Found 574.2007.

3.1.3. Oxidative coupling to sexinaphthalenes (*S,S,S,S,S,S*)-6 and (*S,S,R,S,S*)-10. A mixture of $CuCl_2$ (126 mg, 0.94 mmol) and α-phenylethylamine (0.30 mL, 2.4 mmol) in MeOH (0.5 mL) was stirred for 20 min, to which was added a solution of (*S,S*)-**5** (268 mg, 0.47 mmol) in CH_2Cl_2 (20 mL). After being stirred for 23 h under nitrogen, the reaction mixture was acidified with conc. HCl, concentrated, and extracted with EtOAc. The organic layer was washed with water, dried, and evaporated to give a residue. The residue was purified by column chromatography (SiO_2, *n*-hexane/CH_2Cl_2/EtOAc=8/5/1) to afford (*S,S,S,S,S,S*)-**6** (83 mg, 31%) and (*S,S,R,S,S*)-**10** (102 mg, 38%).

Compound (*S,S,S,S,S,S*)-**6**. Mp >300 °C; colorless powder (from CH_2Cl_2/Et_2O/pet. ether); $[\alpha]_D^{20}=-190.6$ (*c* 0.4, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92 (d, 2H, *J*=8.4 Hz), 7.79 (s, 2H), 7.6–7.1 (m, 22H), 6.33 (s, 2H), 3.79 (s, 6H), 3.74 (s, 12H), 3.67 (s, 6H), 2.45 (s, 6H); IR ($CHCl_3$): 3511, 3009, 2941, 1767, 1507, 1453, 1391, 1237, 1201, 1014 cm^{-1}; FAB MS *m/z* 1147 $(M+H)^+$. Anal. Calcd for $C_{72}H_{58}O_{14}$: C, 75.38; H, 5.10. Found: C, 75.15; H, 5.05.

Compound (*S,S,R,S,S*)-**10**. Mp >300 °C; colorless prisms (from benzene); $[\alpha]_D^{20}=-117.0$ (*c* 0.3, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.93 (d, 2H, *J*=8.4 Hz), 7.79 (s, 2H), 7.6–7.1 (m, 22H), 6.23 (s, 2H), 3.78 (s, 6H), 3.76 (s, 6H), 3.72 (s, 6H), 3.68 (s, 6H), 2.45 (s, 6H); IR ($CHCl_3$): 3518, 3010, 2941, 1766, 1602, 1453, 1393, 1350, 1014 cm^{-1}; FAB MS *m/z* 1147 $(M+H)^+$. Anal. Calcd for $C_{72}H_{58}O_{14}\cdot 1/2H_2O$. Anal. Calcd for C, 74.79; H, 5.14. Found: C, 74.78; H, 5.09.

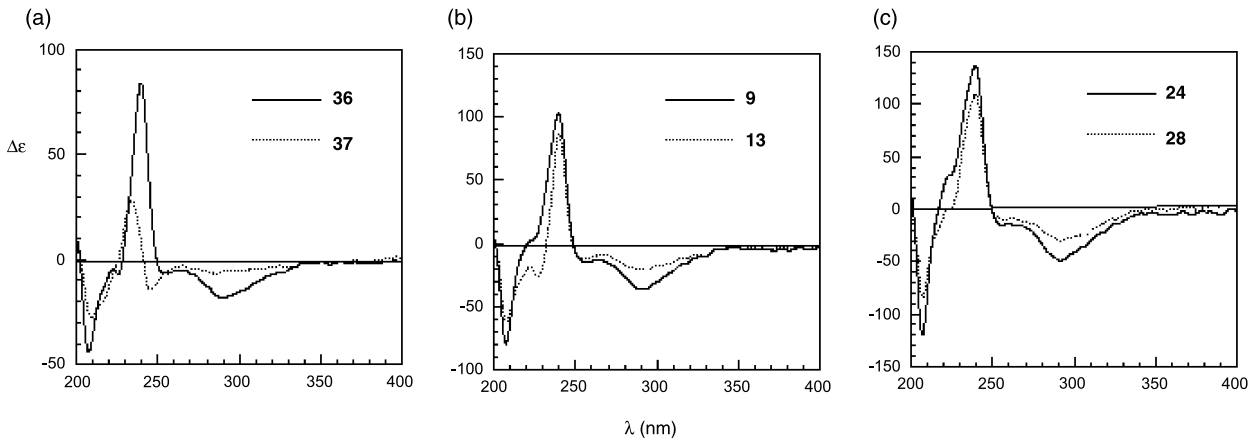


Figure 4. (a) CD spectra of quaternaphthalenes **36** and **37** in 0.4% dioxane–MeOH. (b) CD spectra of sexinaphthalenes **9** and **13** in 0.4% dioxane–MeOH. (c) CD spectra of octinaphthalenes **24** and **28** in 0.4% dioxane–MeOH.

3.1.4. (*S*,*S*,*S*,*S*,*S*)-Sexinaphthalene 7. Following the procedure for the preparation of **4**, (*S*,*S*,*S*,*S*,*S*)-**6** (73 mg, 64 μmol) was treated with potassium carbonate (128 mg, 0.93 mmol) and methyl iodide (82 μL, 1.3 mmol) in acetone (10 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (6/3/1) gave (*S*,*S*,*S*,*S*,*S*)-**7** (74 mg, 98%). Mp >300 °C; colorless powder (from CH_2Cl_2/Et_2O/pet. ether); $[\alpha]_D^{20}=-196.7$ (*c* 0.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.91 (d, 2H, *J*=8.1 Hz), 7.78 (s, 2H), 7.6–7.2 (m, 22H), 3.90 (s, 12H), 3.83 (s, 6H), 3.77 (s, 6H), 3.65 (s, 6H), 2.44 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.5, 151.0, 150.9, 150.8, 149.2, 143.6, 132.4, 131.2, 131.1, 131.0, 130.7, 127.9, 127.0, 126.7, 126.5, 126.3, 126.1, 125.9, 125.7, 125.6, 125.4, 120.9, 77.2, 61.1, 60.8, 60.7, 20.7; IR ($CHCl_3$): 3062, 3010, 2940, 2828, 1766, 1504, 1453, 1390, 1347, 1239, 1220, 1210, 1016 cm^{-1}; FAB MS *m*/*z* 1175 $(M+H)^+$. Anal. Calcd for $C_{74}H_{62}O_{14}$: C, 75.62; H, 5.32. Found: C, 75.75; H, 5.26.

3.1.5. (*S*,*S*,*S*,*S*,*S*)-Sexinaphthalene 8. To a mixture of (*S*,*S*,*S*,*S*,*S*)-**7** (43 mg, 37 μmol) and potassium carbonate (73 mg, 0.53 mmol) in CH_2Cl_2 (5 mL) was added MeOH (0.20 mL) at room temperature. After being stirred for 4 h, the reaction mixture was concentrated under reduced pressure, and then acidified with aq. 2 N HCl. The mixture was extracted with CH_2Cl_2, dried and evaporated in vacuo to give a residue. The residue was purified by column chromatography (SiO_2, *n*-hexane/CH_2Cl_2/EtOAc=6/3/1) to afford (*S*,*S*,*S*,*S*,*S*)-**8** (38 mg, 95%). Mp >300 °C; orange powder (from CH_2Cl_2/Et_2O/pet. ether); $[\alpha]_D^{20}=-146.5$ (*c* 1.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.84 (d, 2H, *J*=8.1 Hz), 7.54 (s, 2H), 7.56–7.2 (m, 22H), 6.22 (s, 2H), 3.911 (s, 6H), 3.907 (s, 6H), 3.82 (s, 6H), 3.75 (s, 6H), 3.64 (s, 6H); IR ($CHCl_3$): 3520, 3009, 2938, 2854, 1766, 1507, 1452, 1390, 1348, 1112, 1017 cm^{-1}; FAB MS *m*/*z* 1091 $(M+H)^+$; HRMS *m*/*z* Calcd for $C_{70}H_{59}O_{12}$ $(M+H)^+$ 1091.4007. Found 1091.3986.

3.1.6. (*S*,*S*,*S*,*S*,*S*)-Sexinaphthalene 9. Following the procedure for the preparation of **4**, (*S*,*S*,*S*,*S*,*S*)-**8** (29 mg, 26 μmol) was treated with potassium carbonate (52 mg, 0.37 mmol) and methyl iodide (63 μL, 1.0 mmol) in acetone (10 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (6/3/1) gave (*S*,*S*,*S*,*S*,*S*)-**9** (19 mg, 64%). Mp >300 °C; colorless powder (from CH_2Cl_2/Et_2O/pet. ether); $[\alpha]_D^{20}=-194.9$ (*c* 0.9, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.86 (d, 2H, *J*=8.1 Hz), 7.5–7.1 (m, 24H), 4.12 (s, 6H), 3.90 (s, 6H), 3.88 (s, 6H), 3.85 (s, 6H), 3.77 (s, 6H), 3.76 (s, 6H); IR ($CHCl_3$): 3062, 3010, 2939, 1463, 1390, 1346, 1019 cm^{-1}; CD (0.4% dioxane in MeOH): see Table 1; UV (0.4% dioxane in MeOH) λ_{max} 302.6 nm (ε 40187), 230.8 (301685); FAB MS *m*/*z* 1119 $(M+H)^+$. Anal. Calcd for $C_{72}H_{62}O_{12}$: C, 77.26; H, 5.58. Found: C, 77.14; H, 5.49.

3.1.7. (*S*,*S*,*R*,*S*,*S*)-Sexinaphthalene 11. Following the procedure for the preparation of **4**, (*S*,*S*,*R*,*S*,*S*)-**10** (92 mg, 81 μmol) was treated with potassium carbonate (158 mg, 1.1 mmol) and methyl iodide (0.1 mL, 1.6 mmol) in acetone (20 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (6/3/1) gave (*S*,*S*,*R*,*S*,*S*)-**11** (84 mg, 89%). Mp >300 °C; colorless prisms (recrystallized from *n*-hexane/CH_2Cl_2/EtOAc); $[\alpha]_D^{20}=-95.0$ (*c* 1.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.95 (d, 2H, *J*=8.2 Hz), 7.82 (s, 2H), 7.6–7.2 (m, 22H), 3.95 (s, 6H), 3.86 (s, 6H), 3.77 (s, 12H), 3.70 (s, 6H), 2.48 (s, 6H); IR ($CHCl_3$): 3063, 3013, 2940, 1766, 1453, 1390, 1015 cm^{-1}; FAB MS *m*/*z* 1175 $(M+H)^+$. Anal. Calcd for $C_{74}H_{62}O_{14}$: C, 75.62; H, 5.32. Found: C, 75.55; H, 5.31.

3.1.8. (*S*,*S*,*R*,*S*,*S*)-Sexinaphthalene 12. Following the procedure for the preparation of **8**, (*S*,*S*,*R*,*S*,*S*)-**11** (65 mg, 56 μmol) was treated with potassium carbonate (109 mg, 0.79 mmol) and MeOH (0.2 mL) in CH_2Cl_2 (5 mL) for 7 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/EtOAc (2/1) gave (*S*,*S*,*R*,*S*,*S*)-**12** (58 mg, 95%). Mp >300 °C; orange powder (from *n*-hexane/EtOAc); $[\alpha]_D^{20}=-63.8$ (*c* 1.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.83 (d, 2H, *J*=8.0 Hz), 7.6–7.1 (m, 24H), 6.22

(s, 2H), 3.92 (s, 6H), 3.82 (s, 6H), 3.72 (s, 12H), 3.65 (s, 6H); IR ($CHCl_3$): 3520, 3008, 2940, 2359, 1631, 1579, 1507, 1452, 1390, 1111, 1017, 908 cm^{-1}; FAB MS *m/z* 1091 $(M+H)^+$. Anal. Calcd for $C_{70}H_{58}O_{12}$: C, 77.05; H, 5.36. Found: C, 76.81; H, 5.09.

3.1.9. (*S*,*S*,*R*,*S*,*S*)-Sexinaphthalene 13. Following the procedure for the preparation of **4**, (*S*,*S*,*R*,*S*,*S*)-**12** (39 mg, 36 μmol) was treated with potassium carbonate (71 mg, 0.51 mmol) and methyl iodide (90 μL, 1.4 mmol) in acetone (20 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (6/3/1) gave (*S*,*S*,*R*,*S*,*S*)-**13** (35 mg, 87%). Mp >300 °C; colorless powder (from *n*-hexane/CH_2Cl_2/EtOAc); $[\alpha]_D^{20}=-89.3$ (*c* 0.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.86 (d, 2H, *J*=8.1 Hz), 7.6–7.1 (m, 24H), 4.13 (s, 6H), 3.89 (s, 6H), 3.82 (s, 6H), 3.78 (s, 6H), 3.75 (s, 6H), 3.73 (s, 6H); IR ($CHCl_3$): 3063, 3010, 2939, 1463, 1391, 1350, 1019 cm^{-1}; CD (0.4% dioxane in MeOH): see Table 1; UV (0.4% dioxane in MeOH) λ_{max} 302.6 nm (ε 42700), 230.8 (302330); FAB MS *m/z* 1119 $(M+H)^+$. Anal. Calcd for $C_{72}H_{62}O_{12}\cdot 1/2H_2O$: C, 76.65; H, 5.63. Found: C, 76.69; H, 5.61.

3.1.10. (*S*,*S*,*S*)-Quaternaphthalene 15. Following the procedure for the preparation of **4**, (*S*,*S*,*S*)-**14** (203 mg, 0.26 mmol) was treated with potassium carbonate (257 mg, 1.9 mmol) and methyl iodide (0.33 mL, 5.2 mmol) in acetone (7.0 mL) for 1.5 h. After extraction with EtOAc, the organic layer was dried and evaporated to give a residue. The residue was purified by recrystallization from *n*-hexane/CH_2Cl_2/Et_2O to give (*S*,*S*,*S*)-**15** as colorless plates (177 mg, 85%). Mp 298–300 °C; $[\alpha]_D^{20}=-131.0$ (*c* 0.8, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.91 (d, 2H, *J*=7.8 Hz), 7.77 (s, 2H), 7.6–7.1 (m, 14H), 3.80 (s, 6H), 3.75 (s, 6H), 3.62 (s, 6H), 2.44 (s, 6H); IR ($CHCl_3$): 3062, 3011, 2941, 1766, 1504, 1466, 1453, 1370, 1155, 1105, 1015 cm^{-1}; EI MS *m/z* 802 (M^+). Anal. Calcd for $C_{50}H_{42}O_{10}$: C, 74.80; H, 5.27. Found: C, 74.63; H, 5.16.

3.1.11. (*S*,*S*,*S*)-Quaternaphthalene 16. Following the procedure for the preparation of **8**, (*S*,*S*,*S*)-**15** (30 mg, 37 μmol) was treated with potassium carbonate (7.4 mg, 54 μmol) and MeOH (0.13 mL) in CH_2Cl_2 (5 mL) for 8 h. After extraction with EtOAc, the organic layer was dried and evaporated to give a residue, which was subjected to pTLC. Developing with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*)-**16** (11 mg, 40%). Mp 170–171 °C; colorless needles (recrystallized from CH_2Cl_2/EtOAc/Et_2O/pet. ether); $[\alpha]_D^{20}=-129.9$ (*c* 0.6, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 8.0–7.2 (m, 18H), 6.21 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.63 (s, 3H), 3.61 (s, 3H), 2.44 (s, 3H); IR ($CHCl_3$): 3522, 3010, 2940, 1767, 1602, 1467, 1453, 1390, 1155, 1110, 1016 cm^{-1}; EI MS *m/z* 760 (M^+). Anal. Calcd for $C_{48}H_{40}O_9$: C, 75.78; H, 5.30. Found: C, 75.61; H, 5.44.

3.1.12. Oxidative coupling to sexinaphthalenes (*S*,*S*,*S*,*S*,*S*)-18 and (*S*,*S*,*S*,*R*,*S*)-19. A mixture of $CuCl_2$ (210 mg, 1.6 mmol) and α-phenylethylamine (0.25 mL, 2.0 mmol) in MeOH (0.6 mL) was stirred for 20 min, to which was added a solution of (*S*,*S*,*S*)-**16** (96 mg, 0.13 mmol) and (*S*)-**17** (252 mg, 0.65 mmol) in CH_2Cl_2 (12 mL). After being stirred for 27 h under nitrogen, the reaction mixture was acidified with conc. HCl, concentrated, and extracted with EtOAc. The organic layer was washed with water, dried, and evaporated to give a residue, which was subjected to column chromatography. Elution with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*)-**14** (66 mg), its isomer possessing (*S*,*R*,*S*)-configuration (51 mg) and a separable mixture of **18** and **19**, from which **18** (27 mg, 18%) and **19** (24 mg, 16%) were afforded after pTLC with *n*-hexane/acetone (3/2).

Compound (*S*,*S*,*S*,*S*,*S*)-**18**. Amorphous; $[\alpha]_D^{20}=-144.1$ (*c* 1.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.92 (d, 2H, *J*=8.8 Hz), 7.80 (s, 1H), 7.78 (s, 1H), 7.6–7.1 (m, 22H), 6.34 (s, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.65 (s, 3H), 3.57 (s, 3H), 3.54 (s, 3H), 2.45 (s, 6H); IR ($CHCl_3$): 3508, 3063, 3009, 2940, 2854, 1766, 1506, 1454, 1392, 1348, 1014 cm^{-1}; FAB MS *m/z* 1147 $(M+H)^+$; HRMS *m/z* Calcd for $C_{72}H_{59}O_{14}$ $(M+H)^+$ 1147.3905. Found 1147.3885.

Compound (*S*,*S*,*S*,*R*,*S*)-**19**. Amorphous; $[\alpha]_D^{20}=-95.8$ (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.93 (d, 2H, *J*=7.0 Hz), 7.80 (s, 1H), 7.79 (s, 1H), 7.6–7.1 (m, 22H), 6.27 (s, 2H), 3.86 (s, 3H), 3.85 (s, 6H), 3.78 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H), 3.59 (s, 3H), 3.57 (s, 3H), 2.45 (s, 3H), 2.44 (s, 3H); IR ($CHCl_3$): 3517, 3063, 3026, 3009, 2941, 2855, 1766, 1731, 1504, 1453, 1391, 1014 cm^{-1}; FAB MS *m/z* 1147 $(M+H)^+$; HRMS *m/z* Calcd for $C_{72}H_{59}O_{14}$ $(M+H)^+$ 1147.3905. Found 1147.3915.

3.1.13. Methylation of (*S*,*S*,*S*,*S*,*S*)-18 to (*S*,*S*,*S*,*S*,*S*)-7. Following the procedure for the preparation of **4**, (*S*,*S*,*S*,*S*,*S*)-**18** (23 mg, 20 μmol) was treated with potassium carbonate (40 mg, 0.30 mmol) and methyl iodide (0.13 mL, 2.0 mmol) in acetone (15 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*,*S*,*S*)-**7** (13 mg, 55%), which was identical with the product obtained from the methylation of (*S*,*S*,*S*,*S*,*S*)-**6** in terms of the spectroscopic data as well as the retention time in HPLC analysis with chiral stationary phase (Chiralpak AS, 14% *i*-PrOH/*n*-hexane, 0.7 mL/min, t_R=23.9 min).

3.1.14. (*S*,*S*,*S*,*R*,*S*)-Sexinaphthalene 20. Following the procedure for the preparation of **4**, (*S*,*S*,*S*,*R*,*S*)-**19** (10 mg, 8.7 μmol) was treated with potassium carbonate (17 mg, 0.12 mmol) and methyl iodide (0.11 mL, 1.7 mmol) in acetone (10 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to pTLC. Developing with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*,*R*,*S*)-**20** (7.9 mg, 77%). Mp >300 °C; colorless powder (from CH_2Cl_2/benzene); $[\alpha]_D^{20}=-91.6$ (*c* 0.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.92 (d, 2H, *J*=8.0 Hz), 7.78 (s, 2H), 7.6–7.2 (m, 22H), 3.91 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.64 (s, 3H), 3.56 (s, 3H), 2.45 (s, 3H), 2.44 (s, 3H); IR ($CHCl_3$): 3063, 3009, 2940, 2854, 1766, 1729, 1577, 1502, 1466, 1453, 1390, 1016 cm^{-1}; FAB MS *m/z* 1175 $(M+H)^+$; HRMS *m/z*

Calcd for $C_{72}H_{63}O_{14}$ $(M+H)^+$ 1175.4218. Found 1175.4221.

3.1.15. Oxidative coupling to octinaphthalenes (*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*)-21 and (*S*,*S*,*S*,*R*,*S*,*S*,*S*,*S*)-25. A mixture of $CuCl_2$ (135 mg, 1.0 mmol) and α-phenylethylamine (0.16 mL, 1.3 mmol) in MeOH (0.4 mL) was stirred for 20 min, to which was added a solution of (*S*,*S*,*S*)-**16** (383 mg, 0.50 mmol) in CH_2Cl_2 (8 mL). After being stirred for 36 h under nitrogen, the reaction mixture was acidified with conc. HCl, concentrated, and extracted with EtOAc. The organic layer was washed with water, dried, and evaporated to give a residue. The residue was purified by column chromatography (SiO_2, *n*-hexane/CH_2Cl_2/EtOAc=4/5/1) to afford (*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**21** (84 mg, 22%) and (*S*,*S*,*S*,*R*,*S*,*S*,*S*,*S*)-**25** (114 mg, 30%).

Compound (*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**21**. Mp >300 °C; pale yellow powder (from CH_2Cl_2/Et_2O); $[\alpha]_D^{20}=-155.7$ (*c* 0.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.93 (d, 2H, *J*=7.9 Hz), 7.79 (s, 2H), 7.7–7.1 (m, 30H), 6.37 (s, 2H), 3.89 (s, 6H), 3.88 (s, 6H), 3.86 (s, 6H), 3.79 (s, 6H), 3.76 (s, 6H), 3.66 (s, 6H), 2.45 (s, 6H); IR ($CHCl_3$): 3510, 3063, 3009, 2940, 2854, 2360, 2341, 1766, 1155, 1111 cm^{-1}; FAB MS *m*/*z* 1519 $(M+H)^+$; HRMS *m*/*z* Calcd for $C_{96}H_{79}O_{18}$ $(M+H)^+$ 1519.5266. Found 1519.5240.

Compound (*S*,*S*,*S*,*R*,*S*,*S*,*S*)-**25**. Mp >300 °C; colorless powder (from toluene); $[\alpha]_D^{20}=-150.6$ (*c* 2.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.96 (d, 2H, *J*=8.0 Hz), 7.83 (s, 2H), 7.7–7.1 (m, 30H), 6.34 (s, 2H), 3.92 (s, 6H), 3.90 (s, 12H), 3.82 (s, 12H), 3.69 (s, 6H), 2.49 (s, 6H); IR ($CHCl_3$): 3519, 3009, 2940, 2854, 1766, 1155, 1110 cm^{-1}; FAB MS *m*/*z* 1519 $(M+H)^+$; HRMS *m*/*z* Calcd for $C_{96}H_{79}O_{18}$ $(M+H)^+$ 1519.5266. Found 1519.5259.

3.1.16. (*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*)-Octinaphthalene 22. Following the procedure for the preparation of **4**, (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**21** (6.0 mg, 4.0 μmol) was treated with potassium carbonate (16 mg, 0.12 mmol) and methyl iodide (0.10 mL, 1.6 mmol) in acetone (5 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**22** (3.0 mg, 49%). Mp >300 °C; colorless powder (from CH_2Cl_2/Et_2O/pet. ether); $[\alpha]_D^{20}=-215.7$ (*c* 0.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.92 (d, 2H, *J*=7.9 Hz), 7.79 (s, 2H), 7.6–7.1 (m, 30H), 3.93 (s, 12H), 3.92 (s, 12H), 3.84 (s, 6H), 3.78 (s, 6H), 3.66 (s, 6H), 2.45 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.6, 151.0, 150.9, 149.2, 143.6, 132.5, 131.3, 131.2, 131.1, 130.7, 127.9, 127.1, 126.8, 126.7, 126.6, 126.3, 126.1, 126.0, 125.7, 125.5, 121.0, 61.1, 60.9, 60.7, 20.8; IR ($CHCl_3$): 3063, 3009, 2938, 1765, 1453, 1389, 1222, 1017 cm^{-1}; FAB MS *m*/*z* 1547 $(M+H)^+$. Anal. Calcd for $C_{98}H_{82}O_{18}$: C, 76.05; H, 5.34. Found: C, 75.79; H, 5.24.

3.1.17. (*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*)-Octinaphthalene 23. Following the procedure for the preparation of **8**, (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**22** (16 mg, 10 μmol) was treated with potassium carbonate (60 mg, 0.43 mmol) and MeOH (0.4 mL) in CH_2Cl_2 (5 mL) for 3 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**23** (9.7 mg, 66%). Mp >300 °C; orange powder (from *n*-hexane/CH_2Cl_2/EtOAc); $[\alpha]_D^{20}=-190.3$ (*c* 0.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.84 (d, 2H, *J*=8.3 Hz), 7.6–7.1 (m, 32H), 6.23 (s, 2H), 3.94 (s, 6H), 3.92 (s, 18H), 3.83 (s, 6H), 3.76 (s, 6H), 3.65 (s, 6H); IR ($CHCl_3$): 3521, 3017, 2939, 2854, 1452, 1389, 1221, 1210 cm^{-1}; FAB MS *m*/*z* 1463 $(M+H)^+$; HRMS *m*/*z* Calcd for $C_{94}H_{79}O_{16}$ $(M+H)^+$ 1463.5368. Found 1463.5372.

3.1.18. (*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*)-Octinaphthalene 24. Following the procedure for the preparation of **4**, (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**23** (12 mg, 8.1 μmol) was treated with potassium carbonate (32 mg, 0.23 mmol) and methyl iodide (0.10 mL, 1.6 mmol) in acetone (5 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**24** (12 mg, 100%). Mp >300 °C; colorless powder (from CH_2Cl_2/Et_2O/pet. ether); $[\alpha]_D^{20}=-177.8$ (*c* 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, 2H, *J*=8.1 Hz), 7.5–7.1 (m, 32H), 4.13 (s, 6H), 3.92 (s, 6H), 3.914 (s, 6H), 3.912 (s, 6H), 3.88 (s, 6H), 3.85 (s, 6H), 3.77 (s, 6H), 3.76 (s, 6H); IR ($CHCl_3$): 3008, 2935, 2854, 1454, 1389, 1115, 1019 cm^{-1}; CD (0.4% dioxane in MeOH): see Table 1; UV (0.4% dioxane in MeOH) λ_{max} 305.4 nm (ε 72533), 229.8 (407143); FAB MS *m*/*z* 1491 $(M+H)^+$. Anal. Calcd for $C_{96}H_{82}O_{16}$: C, 77.30; H, 5.54. Found: C, 77.07; H, 5.43.

3.1.19. (*S*,*S*,*S*,*R*,*S*,*S*,*S*,*S*)-Octinaphthalene 26. Following the procedure for the preparation of **4**, (*S*,*S*,*S*,*R*,*S*,*S*,*S*)-**25** (14 mg, 9.2 μmol) was treated with potassium carbonate (37 mg, 0.26 mmol) and methyl iodide (0.23 mL, 3.7 mmol) in acetone (10 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to pTLC. Developing with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*,*R*,*S*,*S*,*S*)-**26** (12 mg, 86%). Mp >300 °C; colorless prisms (from *n*-hexane/CH_2Cl_2/EtOAc); $[\alpha]_D^{20}=-139.2$ (*c* 1.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.92 (d, 2H, *J*=8.1 Hz), 7.79 (s, 2H), 7.6–7.1 (m, 30H), 3.93 (s, 6H), 3.88 (s, 6H), 3.859 (s, 6H), 3.856 (s, 6H), 3.83 (s, 6H), 3.79 (s, 6H), 3.65 (s, 6H), 2.45 (s, 6H); IR ($CHCl_3$): 3063, 3010, 2940, 2854, 1766, 1577, 1504, 1453, 1390, 1017 cm^{-1}; FAB MS *m*/*z* 1547 $(M+H)^+$. Anal. Calcd for $C_{98}H_{82}O_{18}$: C, 76.05; H, 5.34. Found: C, 76.09; H, 5.41.

3.1.20. (*S*,*S*,*S*,*R*,*S*,*S*,*S*,*S*)-Octinaphthalene 27. Following the procedure for the preparation of **8**, (*S*,*S*,*S*,*R*,*S*,*S*,*S*)-**26** (36 mg, 23 μmol) was treated with potassium carbonate (91 mg, 0.66 mmol) and MeOH (0.4 mL) in CH_2Cl_2 (5 mL) for 25 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (6/3/1) gave (*S*,*S*,*S*,*R*,*S*,*S*,*S*,*S*)-**27** (30 mg, 90%). Mp >300 °C; orange powder (from CH_2Cl_2/EtOAc); $[\alpha]_D^{20}=-115.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.84 (d, 2H, *J*=8.1 Hz), 7.6–7.1 (m, 32H), 6.23 (s, 2H), 3.94 (s, 6H), 3.89 (s, 6H), 3.86 (s, 6H), 3.84 (s, 12H), 3.77 (s, 6H), 3.64 (s, 6H); IR ($CHCl_3$): 3521, 3063, 3009, 2940, 2853, 1507, 1467, 1452, 1389, 1111,

1071 cm^{-1}; FAB MS *m/z* 1463 $(M+H)^+$; HRMS *m/z* Calcd for $C_{94}H_{79}O_{16}$ $(M+H)^+$ 1463.5368. Found 1463.5370.

3.1.21. (*S*,*S*,*S*,*R*,*S*,*S*,*S*)-Octinaphthalene 28. Following the procedure for the preparation of **4**, (*S*,*S*,*S*,*R*,*S*,*S*,*S*)-**27** (20 mg, 14 μmol) was treated with potassium carbonate (55 mg, 0.40 mmol) and methyl iodide (0.17 mL, 2.8 mmol) in acetone (4 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*,*R*,*S*,*S*,*S*)-**28** (12 mg, 58%). Mp >300 °C; colorless powder (from CH_2Cl_2/EtOAc); $[\alpha]_D^{20}=-129.6$ (*c* 0.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, 2H, *J*=8.0 Hz), 7.6–7.1 (m, 32H), 4.13 (s, 6H), 3.93 (s, 6H), 3.87 (s, 6H), 3.85 (s, 12H), 3.82 (s, 6H), 3.772 (s, 6H), 3.768 (s, 6H); IR ($CHCl_3$): 3017, 2939, 1390, 1221 cm^{-1}; CD (0.4% dioxane in MeOH): see Table 1; UV (0.4% dioxane in MeOH) λ_{max} 305.2 nm (ε 72244), 230.6 (392756); FAB MS *m/z* 1491 $(M+H)^+$. Anal. Calcd for $C_{96}H_{82}O_{16}$: C, 77.30; H, 5.54. Found: C, 77.43; H, 5.52.

3.1.22. (*S*,*S*,*S*,*S*,*S*)-Sexinaphthalene 29. Following the procedure for the preparation of **8**, (*S*,*S*,*S*,*S*,*S*)-**7** (40 mg, 34 μmol) was treated with potassium carbonate (9.9 mg, 72 μmol) and MeOH (0.44 mL) in CH_2Cl_2 (5 mL) for 5 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to pTLC. Developing with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*,*S*,*S*)-**29** (15 mg, 38%). Amorphous; $[\alpha]_D^{20}=-191.6$ (*c* 0.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 8.0–7.8 (m, 3H), 7.6–7.2 (m, 23H), 6.27 (s, 1H), 3.94 (s, 12H), 3.93 (s, 12H), 3.86 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 2.48 (s, 3H); IR ($CHCl_3$): 3521, 3063, 3010, 2939, 2854, 1766, 1505, 1467, 1452, 1389, 1347, 1240, 1017 cm^{-1}; FAB MS *m/z* 1133 $(M+H)^+$; HRMS *m/z* Calcd for $C_{72}H_{61}O_{13}$ $(M+H)^+$ 1133.4112. Found 1133.4086.

3.1.23. Oxidative coupling to octinaphthalenes (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-30 and (*S*,*S*,*S*,*S*,*S*,*R*,*S*)-31. A mixture of $CuCl_2$ (51 mg, 0.38 mmol) and α-phenylethylamine (61 μL, 0.47 mmol) in MeOH (0.4 mL) was stirred for 20 min, to which was added a solution of (*S*,*S*,*S*,*S*,*S*)-**29** (35 mg, 31 μmol) and (*S*)-**17** (61 mg, 0.16 mmol) in CH_2Cl_2 (15 mL). After being stirred for 16 h under nitrogen, the reaction mixture was acidified with conc. HCl, concentrated, and extracted with EtOAc. The organic layer was washed with water, dried, and evaporated to give a residue, which was subjected to pTLC. Developing with *n*-hexane/acetone (3/2) afforded a mixture of **30** and **31** as a polar fraction and **14** and its isomer as less polar fraction. From a polar and less polar fractions, **30** (6.2 mg, 13%) and **31** (11 mg, 22%), and **14** (15 mg) and its isomer (18 mg) were isolated, respectively, after the second separation by pTLC with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1).

Compound (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**30**. Amorphous; $[\alpha]_D^{20}=-254.9$ (*c* 0.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.95 (d, 2H, *J*=8.8 Hz), 7.83 (s, 1H), 7.81 (s, 1H), 7.7–7.1 (m, 30H), 6.40 (s, 1H), 6.38 (s, 1H), 3.97 (s, 3H), 3.95 (s, 6H), 3.94 (s, 3H), 3.91 (s, 6H), 3.86 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 3.61 (s, 3H), 3.57 (s, 3H), 2.48 (s, 6H); IR ($CHCl_3$): 3693, 3510, 3063, 3026, 3009, 2940, 2854, 1766, 1505, 1453, 1390, 1347, 1016 cm^{-1}; FAB MS *m/z* 1519 $(M+H)^+$; HRMS *m/z* Calcd for $C_{96}H_{79}O_{18}$ $(M+H)^+$ 1519.5266. Found 1519.5251.

Compound (*S*,*S*,*S*,*S*,*S*,*R*,*S*)-**31**. Amorphous; $[\alpha]_D^{20}=-186.8$ (*c* 0.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.95 (d, 2H, *J*=8.5 Hz), 7.82 (s, 1H), 7.81 (s, 1H), 7.6–7.2 (m, 30H), 6.27 (brs, 2H), 3.97 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.79 (s, 6H), 3.67 (s, 3H), 3.62 (s, 3H), 3.60 (s, 3H), 2.47 (s, 3H), 2.46 (s, 3H); IR ($CHCl_3$): 3673, 3518, 3023, 3009, 2940, 1731, 1505, 1453, 1389, 1374, 1249, 1045, 1015 cm^{-1}; FAB MS *m/z* 1519 $(M+H)^+$; HRMS *m/z* Calcd for $C_{96}H_{79}O_{18}$ $(M+H)^+$ 1519.5266. Found 1519.5245.

3.1.24. Methylation of (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-30 to (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-22. Following the procedure for the preparation of **4**, (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**30** (5.1 mg, 3.4 μmol) was treated with potassium carbonate (14 mg, 0.10 mmol) and methyl iodide (85 μL, 1.4 mmol) in acetone (10 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**22** (4.8 mg, 91%), which was identical with the product obtained from the methylation of (*S*,*S*,*S*,*S*,*S*,*S*,*S*)-**21** in terms of the spectroscopic data as well as the retention time in HPLC analysis with chiral stationary phase (Chiralpak AS, 25% *i*-PrOH/*n*-hexane, 0.8 mL/min, t_R=32.0 min).

3.1.25. (*S*,*S*,*S*,*S*,*S*,*R*,*S*)-Octinaphthalene 32. Following the procedure for the preparation of **4**, (*S*,*S*,*S*,*S*,*S*,*R*,*S*)-**31** (5.0 mg, 3.3 μmol) was treated with potassium carbonate (13 mg, 94 μmol) and methyl iodide (81 μL, 1.3 mmol) in acetone (5 mL) for 2 h. After extraction with CH_2Cl_2, the organic layer was dried and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane/CH_2Cl_2/EtOAc (4/5/1) gave (*S*,*S*,*S*,*S*,*S*,*R*,*S*)-**32** (5.1 mg, 100%). Mp >300 °C; colorless powder (from CH_2Cl_2/benzene); $[\alpha]_D^{20}=-113.0$ (*c* 0.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.95 (d, 2H, *J*=8.0 Hz), 7.81 (s, 2H), 7.6–7.2 (m, 30H), 3.97 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 3.86 (s, 3H), 3.84 (s, 6H), 3.80 (s, 6H), 3.79 (s, 3H), 3.68 (s, 3H), 3.59 (s, 3H), 2.47 (s, 3H), 2.46 (s, 3H); IR ($CHCl_3$): 3062, 3007, 2939, 2854, 1766, 1728, 1577, 1503, 1453, 1390, 1349, 1239, 1017, 909 cm^{-1}; FAB MS *m/z* 1547 $(M+H)^+$; HRMS *m/z* Calcd for $C_{98}H_{83}O_{18}$ $(M+H)^+$ 1547.5579. Found 1547.5582.

3.1.26. (*S*)-2,3,2′,3′-Tetramethoxy-1,1′-binaphthalene (33). Following the procedure for the preparation of **4**, (*S*)-**34** (551 mg, 1.6 mmol) was treated with potassium carbonate (3.2 g, 23 mmol) and methyl iodide (2.0 mL, 32 mmol) in acetone (25 mL) for 1.5 h. After extraction with EtOAc, the organic layer was dried and evaporated to give a residue, which was purified by recrystallization from EtOAc to give (*S*)-**33** as colorless prisms (230 mg, 38%). Mp 204–206 °C; $[\alpha]_D^{20}=-52.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, 2H, *J*=8.3 Hz), 7.5–7.0 (m, 8H), 4.08 (s, 6H), 3.63 (s, 6H); IR ($CHCl_3$): 3011, 2940, 1597, 1464, 1420, 1251, 1117 cm^{-1}; CD (0.4% dioxane in

MeOH): see Table 1; UV (0.4% dioxane in MeOH) λ_{max} 325.6 nm (ε 5193), 290.6 (10559), 280.2 (11193), 232.0 (119248). Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.89; H, 5.89.

3.2. Molecular modeling of octinaphthalene 24 and corresponding 24-mer

The lowest energy conformations of octinaphthalene **24** and corresponding 24-mer were obtained by MacroModel (version. 6.0) using MM2 force field. The calculations were started from the structures **24** and 24-mer, in which the absolute configuration of each axis was prefixed as *aS*.

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A modular route to nonracemic *cyclo*-NOBINs. Preparation of the parent ligand for homo- and heterogeneous catalysis

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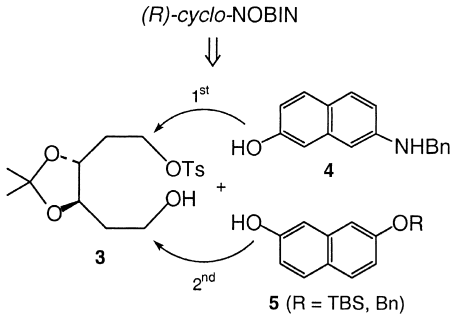
Received 22 January 2004; revised 17 February 2004; accepted 23 February 2004

Abstract—A sequence which combines a nonracemic tether, a naphthyl diol, and an aminonaphthol has been developed leading to the new ligand *cyclo*-NOBIN, which can easily be mounted onto polystyrene. Opportunities for extending the route to substituted *cyclo*-NOBINs are also discussed.

1. Introduction

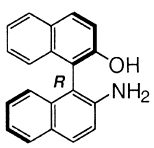
Since its introduction by Kocovsky in 1991,[1] the binaphthylic ligand NOBIN (**1**) has found increasing usage in synthesis.[2] Replacement of an OH residue in nonracemic BINOL with an NH_2 group, along with the inherent bias of the binaphthyl array, provide many opportunities for designing new organometallic complexes, in particular new catalysts for effecting selected asymmetric transformations. As in the case of BINOL, it is likely that substitution at the 3 and/or 3′-sites may on occasion increase significantly the level of steric discrimination and hence, improve enantioselectivities.[3] Although the basic NOBIN skeleton is readily available in nonracemic form,[4] such is not the case for substituted analogues. Moreover, we are unaware of any reports on the use of NOBIN in the context of heterogeneous catalysis, perhaps an obvious goal given the increasing importance of such processes.[5] In this contribution, we describe our preparation of the novel ligand *cyclo*-NOBIN **2** via a modular approach[6] which offers considerable flexibility for realizing both substituted derivatives[7] and a polymer-bound version.[3]



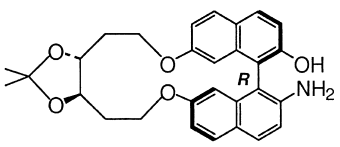
Scheme 1. Anticipated coupling sequence with modules **4** and **5**.

2. Results and discussion

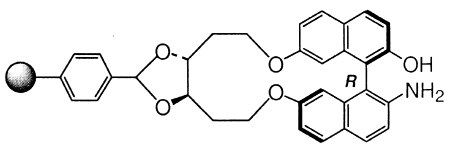
From previous work on the preparation of *cyclo*-BINOLs,[3,6] we anticipated that aminonaphthalene **4** could be attached via base-induced substitution to nonracemic tether **3**, followed by Mitsunobu coupling with **5**, thereby in two steps arriving at fully joined modules (Scheme 1). Amine **4** was envisioned as deriving from naphthol **5** by Pd-catalyzed amination of sulfonate **6** (Scheme 2).[8] Thus, **5** was



1 *(R)*-NOBIN



2 *(R)-cyclo*-NOBIN



polystyene-bound *(R)-cyclo*-NOBIN

Keywords: Binaphthyls; NOBINs; Ligands; Asymmetric catalysis; Heterogeneous catalysis.
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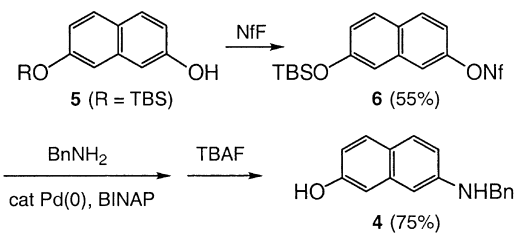
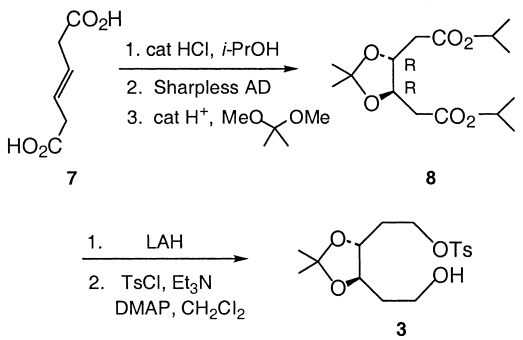
doi:10.1016/j.tet.2004.02.065



Scheme 2. Preparation of the amine-containing module **4**.

converted to nonaflate coupling partner **6** with perfluorobutanesulfonyl fluoride, NfF (NaH, THF, 0 °C; 55%), which in the presence of benzylamine underwent smooth Pd(0)-catalyzed coupling to give **4** in good overall yield (75%) after treatment of the crude product with TBAF in THF at room temperature.

A newly devised, streamlined route to gram quantities of tether **3** was also developed (Scheme 3). Employing the same *trans*-β-hydromuconic acid **7** as educt used previously, diesterification led to the olefinic diester (97%), which was subjected to Sharpless asymmetric dihydroxylation with AD-mix-β at 0 °C under buffered conditions. Selection of both the isopropyl esters as well as modified dihydroxylation conditions was crucial for this sequence. Use of methyl esters and unbuffered media encourages the initial diol to react further, leading to undesired hydroxybutyryl lactone formation. The desired diol (78%), obtained in virtually optically pure form (bis-Mosher ester) was

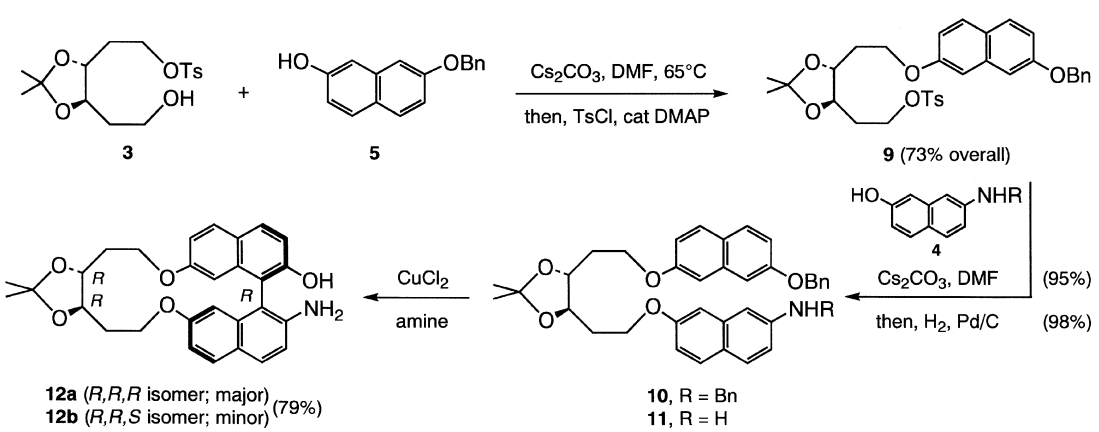


Scheme 3. A new, highly efficient route to tether **3**.

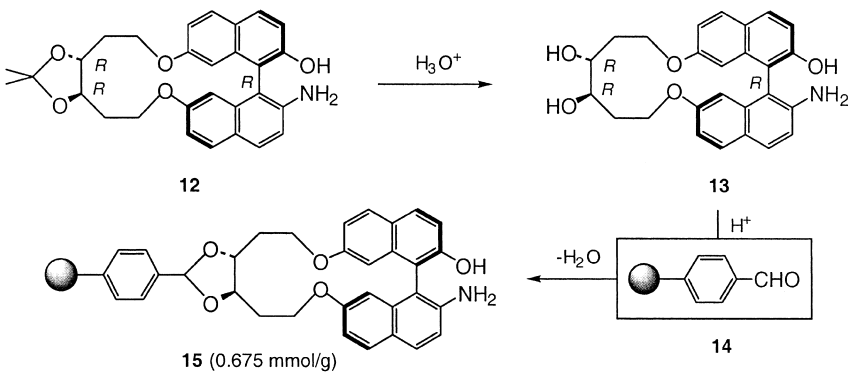
smoothly converted to its acetonide **8** (92%) prior to LAH reduction of the diester to the corresponding primary diol (95%). Monotosylation, as expected, was not selective (43%) to tether **3**, which nonetheless allows for recycling of unconsumed diol setting the stage for subsequent attachment of modules **4** and **5**. The 4-step sequence from the diester of **7** could be carried out without purification of intermediates in an overall yield of 33%.

Displacement of the tosylate in **3** with naphthol **5** gave the initial adduct which was directly treated crude with tosyl chloride in CH_2Cl_2/Et_3N containing catalytic DMAP (Scheme 4). Isolation afforded tosylate **9** after chromatography. All attempts according to the sequence in Scheme 1 involving a Mitsunobu coupling were low-yielding and thus were abandoned in favor of a second tosylate displacement. Naphthol **4** was then used to couple with intermediate **9**, which took place in high yield to give **10**. Simultaneous *O* and *N*-debenzylation with H_2 and Pd/C in warm (60 °C) THF led to the *cyclo*-NOBIN *seco* dinaphthyl **11**. Oxidation of **11** with excess $CuCl_2$ (4 equiv.) in MeOH at rt in the presence of racemic α-methylbenzylamine gave a mixture of diastereomers (5.9:1).[1,3,6,9] The ratio of diastereomers appeared to vary as a function of added amine in solution. For example, benzylamine afforded a 2.3:1 mix of *R*/*S* isomers (81% isolated). Ratios could be easily determined by 400 MHz proton NMR, Other amines, such as *t*-$BuNH_2$ and diphenylmethylamine were tested with $CuCl_2$ in alcoholic solvents and in mixtures of DMF and MeOH, but ratios were not as high as those observed using racemic α-methylbenzylamine in straight MeOH. Experiments employing pure enantiomers of this amine did not affect the de, nor yield, of the couplings. Similar results were achieved when scaling up the reaction from the 0.05 to 1.00 mmol level. Pure diastereomers could be obtained by traditional flash chromatography. The major isomer was unequivocally established as (*R*)-*cyclo*-NOBIN based on comparison of its CD spectrum with authentic (*R*)-NOBIN.[10]

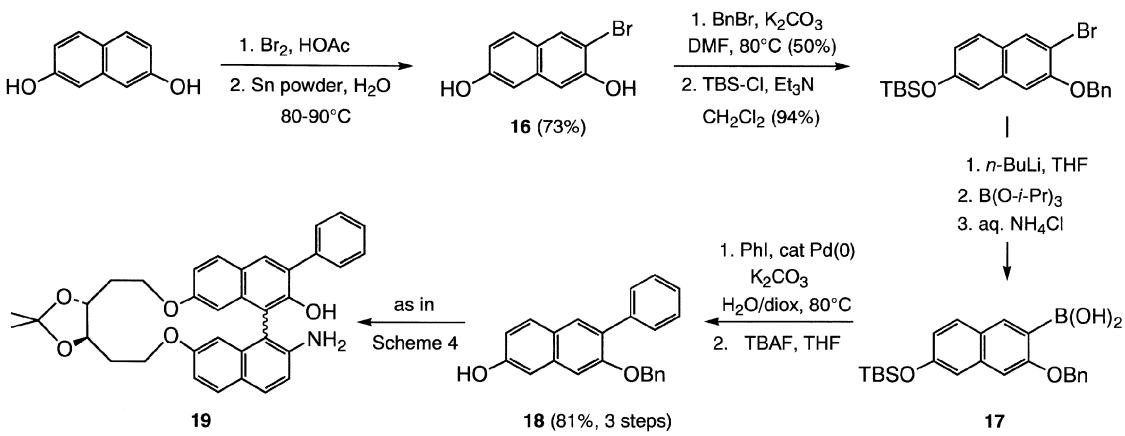
With ligands **12** in hand, attachment of **12a** to polystyrene (PS) was accomplished by initial hydrolysis of the acetonide to afford diol **13**. Direct acetalization of **13** with formylated 1% crosslinked polystyrene beads **14**[3] led to polystyrene-supported *R*-*cyclo*-NOBIN **15** (Scheme 5). Loadings in the 0.5–0.6 mmol/g range were typical.



Scheme 4. A modular sequence to the parent *cyclo*-NOBINs **12**.



Scheme 5. Mounting of the parent *cyclo*-NOBIN **12** onto polystyrene.



Scheme 6. A modular route to a 3-substituted *cyclo*-NOBIN **19**.

Lastly, we have tested the potential for this sequence to accommodate a substituted naphthyl module, ultimately aiming for a new series of 3- and/or 3′-mono- or disubstituted *cyclo*-NOBINs. As a first representative case, readily available naphthyl bromide **16**[9] was manipulated in the usual fashion to produce boronic acid **17**, which underwent Suzuki coupling with iodobenzene to give the corresponding biaryl (Scheme 6). Exposure of the crude product to TBAF gave naphthol **18** in 81% yield over the three steps. Using this module in the sequence in place of **5** (cf. Scheme 4), the unsymmetrically substituted *cyclo*-NOBIN **19** could be realized as a mix of diastereomers. Several additional examples of these ligands bearing a variety of substituents at the key sites *ortho* to oxygen (i.e., the 3-position) and/or nitrogen (i.e., the 3′-position), as well as selected examples for use in asymmetric catalysis (e.g., modified Carreira aldols)[11] will be reported in due course.

3. Summary and conclusions

The first example of a modified nonracemic NOBIN ligand, a *cyclo*-NOBIN, is reported. The route described is particularly flexible in that it allows for introduction of various substituents onto the individual modules at the key (3- and 3″-sites) that are to be built into the biaryl. The potential for attachment to a solid support, such as polystyrene has also been demonstrated for the parent system.

4. Experimental

4.1. General

Reactions were performed in either oven-dried or flame-dried glassware under an argon atmosphere with Teflon coated stir bars and dry septa. THF, Et_2O, and toluene were freshly distilled from Na/benzophenone ketyl prior to use. CH_2Cl_2 and DMF were freshly distilled from CaH_2 prior to use. All commercially available reagents were distilled from CaH_2, molecular sieves, or from themselves (under reduced pressure) before use. Column chromatography was performed using Davisil Grade 633 Type 60A silica gel. All columns were prepared and run with the eluent 'slurry' loading method. Columns that were 'doped' with NEt_3 were done so using 1-2% in the eluent 'slurry' and not the eluting solvent. TLC analysis was performed on commercial Kieselgel 60 F_{254} silica gel glass plates and visualized with a UV lamp. *p*-Anisaldehyde (PA) or ninhydrin were used to stain the plates and developed using a hot plate.

NMR spectra were obtained on Varian Inova systems using $CDCl_3$, D_2O, or deuterated acetone solvents with proton and carbon resonance at 400 and 100 MHz, respectively. All NMR spectra were referenced relative to TMS (δ 0.00) or the solvent used to obtain spectra (e.g., $CDCl_3$: δ 7.27 for ^1H; δ 77.23 for ^{13}C) and are reported in ppm.

FTIR spectra were obtained on an ATI Mattson Infinity series spectrometer or a Jasco FT/IR-430 series spectrometer neat on NaCl plates or KBr pellets, and are reported in cm^{-1}. Dr. James Pavlovich acquired low-resolution and high-resolution mass spectral data on a VF Autospec, PE Sciex QStar quadrapole/time-of-flight tandem mass spectrometer, or an analytical VG-70-250 HF instrument. A Fisher–Johns melting point apparatus Model 2572A was used to acquire all melting points that are all uncorrected. Optical rotations were taken on a Perkin–Elmer 241MC polarimeter (25 °C, 1 cm^3 cell) or a Perkin–Elmer 341 polarimeter (25 °C, 1 cm^3 cell cell). All reagents were purchased from Aldrich, Alfa Aesar, Lancaster, Acros, Fisher, or Strem and were purified prior to use where applicable. All alkyllithium reagents were obtained from Aldrich and titrated according to literature procedures prior to use.[12] All chromatography and general use solvents were purchased from Fisher in 4 L bottles or 20 L drums and used as received.

4.1.1. Diisopropyl 3-hexen-1,6-dioate. To a flame dried 500 mL RBF equipped with a magnetic stir bar was added 2-isopropanol (ca. 250 mL) and the flask was cooled to 0 °C. Acetyl chloride (25 mL, 346.9 mmol, 5 equiv.) was added slowly in portions (CAUTION: exotherm!) and the solution was allowed to stir at 0 °C for ca. 5 min. Then *trans*-β-hydromuconic acid (10 g, 69.4 mmol) was added as a solid as fast as possible and the reaction was heated, following attachment of a reflux condenser equipped with a $CaCl_2$ drying tube, overnight. The reaction was then cooled and concentrated in vacuo and diluted with ethyl acetate (250 mL) and washed with saturated aqueous $NaHCO_3$ (2×10 mL) and brine (10 mL), then dried over anhydrous $MgSO_4$. Concentration in vacuo produced the diester (15.5 g, 98%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (tt, J=4.6, 1.6 Hz, 2H), 5.00 (sept, J=6.2 Hz, 2H), 3.05 (dd, J=4.6, 1.6 Hz, 4H), 1.24 (d, J=6.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 126.1, 68.1, 38.4, 21.9.

4.1.2. Diisopropyl (3*R*,4*R*)-3,4-dihydroxyhexane-1,6-dioate. To a 1 L RBF equipped with a magnetic stir bar was added AD-mix-β (71.5 g, 1.4 g (mmol SM)$^{-1}$), methanesulfonamide (4.8 g, 50.8 mmol, 1 equiv.), and $NaHCO_3$ (12.8 g, 152.4 mmol, 3 equiv.) as solids. Then H_2O (340 mL) and *t*-BuOH (340 mL) were added and this mixture was allowed to stir at rt for 15 min. and was then cooled to 0 °C. Diisopropyl 3-hexen-1,6-dioate (11.6 g, 50.8 mmol) was then added as a solid and the reaction stirred overnight at 0 °C. Upon completion by TLC, Na_2SO_3 (77 g, 609.6 mmol, 12 equiv.) was added and allowed to stir for 10 min. at 0 °C then the reaction was warmed to rt and diluted with EtOAc (100 mL), H_2O (25 mL), and EtOH (3 mL) and stirred for 1 h. The organic layer was decanted off and washed with brine (10 mL). The aqueous layer was added back to the flask and the reaction mixture extracted with EtOAc (100 mL). The organic layer was washed with brine (10 mL). H_2O (ca. 150 mL) was added to dissolve the salts and was then extracted with EtOAc (4×100 mL). All organic layers were combined and dried over anhydrous Na_2SO_4. Flash chromatography (70% ether/hexanes). R_f=0.18 (50% ether/hexane, visualization with *p*-anisaldehyde stain), afforded the diol (8.53 g, 64%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (sept, J=6.4 Hz, 2H), 3.96 (m, 2H), 3.26 (d, J=5.2 Hz, 2H), 2.65–2.51 (m, 4H), 1.26 (d, J=6.4 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 70.1, 68.6, 38.4, 22.0.

4.1.3. Diisopropyl (3*R*,4*R*)-3,4-isopropylidene-hexane-1,6-dioate (8). To a flame dried 500 mL RBF was added $TsOH{\cdot}H_2O$ (309 mg, 1.62 mmol, 0.1 equiv.) as a solid and then 2,2-dimethoxypropane (ca. 160 mL) was added followed by addition of diisopropyl (3*R*,4*R*)-3,4-dihydroxyhexane-1,6-dioate (ca. 8.5 g, 32.4 mmol) as a solid. Hot oven-dried molecular sieves (excess) were added and the reaction was allowed to stand until all starting material was consumed by TLC. The reaction was then filtered through a pad of Celite and concentrated in vacuo yielding the corresponding acetal (9.8 g, >99%) as a yellow oil. R_f=0.81 (60% EtOAc/hexanes, visualization with *p*-anisaldehyde stain).[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (sept, J=6.2 Hz, 2H), 4.16 (m, 2H), 2.62 (m, 4H), 1.40 (s, 6H), 1.25 (dd, J=6.2, 2.9 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 109.2, 76.9, 68.3, 38.5, 27.3, 22.0. IR (neat): 3451, 2984, 2938, 1736, 1469, 1457, 1375, 1338, 1329, 1301, 1276, 1247, 1198, 1175, 1148, 1107, 1064, 961, 913, 848, 825 cm^{-1}; CIMS, *m/z* (rel int): 303(17), 245(70), 203(68), 189(11), 161(100), 143(49), 99(11), 59(78), 55(10), 45(14), 43(99); HRCIMS, *m/z* calcd for $C_{15}H_{26}O_6$+H)$^+$: 303.1808, found 303.1812.

4.1.4. (3*R*,4*R*)-*O*-Isopropylidenehexane-1,6-diol.[9] To a flame dried 500 mL RBF equipped with a magnetic stir bar was added lithium aluminum hydride (15 g, 330 mmol, 10 equiv.) as a grey solid. THF (50 mL) was added and the slurry was stirred at rt. Diisopropyl (3*R*,4*R*)-3,4-isopropylidenehexane-1,6-dioate (10 g, 33 mmol) was dissolved in THF (50 mL) and added to the RBF via cannula followed by rinsing with THF (10 mL). The reaction was heated to reflux and stirred overnight. Quenching was accomplished by cooling the reaction flask to 0 °C and addition of H_2O (12 mL) and 15% aq. NaOH (3 mL) followed by dilution with EtOAc (excess). The salts were then filtered through a pad of Celite and the solvent was concentrated in vacuo to afford the diol (4.9 g, 78%). R_f=0.08 (EtOAc), as a yellow oil (used without purification). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88–3.81 (m, 6H), 2.43 (br s, 2H), 1.90–1.73 (m, 4H), 1.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.0, 80.1, 60.8, 34.5, 27.4.

4.1.5. Toluene-4-sulfonic acid 2-[5-(2-hydroxyethyl)-2,2-dimethyl-[1,3]-dioxolan-4-yl] ethyl ester (3).[6] To a flame dried 250 mL RBF equipped with a magnetic stir bar was added tosyl chloride (1.77 g, 9.15 mmol, 1.05 equiv.), DMAP (135 mg, 0.87 mmol, 0.1 equiv.) as solids followed by (3*R*,4*R*)-*O*-isopropylidene-hexane-1,6-diol (1.68 g, 8.71 mmol) and CH_2Cl_2 (87 mL). The reaction vessel was cooled to 0 °C and NEt_3 (1.5 mL, 10.45 mmol, 1.2 equiv.) was added and the reaction was allowed to stir overnight. The reaction was followed by TLC and upon completion was concentrated in vacuo. After flash chromatography (50% EtOAc/hexanes) the corresponding mono-tosylated product (1.51 g, 50%) was isolated as a clear oil. R_f=0.27 (50% EtOAc/hexanes).[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (m, 2H), 7.36 (m, 2H), 4.25–4.12 (m, 2H), 3.79–3.67 (m, 4H), 2.65 (br s, 1H), 2.45 (s, 3H), 2.01–1.67 (m, 4H), 1.32 (s, 6H).

4.1.6. 7-Benzyloxy-2-naphthol (5). To a flame dried 1 L RBF equipped with a magnetic stir bar was added 2,7-dihydroxynaphthalene (11.2 g, 70.0 mmol), K_2CO_3 (12.1 g, 84 mmol, 1.2 equiv.), and DMF (ca. 350 mL). To the resulting reaction mixture was added benzyl chloride (8.4 mL, 73.5 mmol, 1.05 equiv.) at rt. The reaction vessel was then warmed to 65 °C and let stir overnight. Upon completion by TLC, the reaction was filtered through Celite to remove residual solids and the reaction solvent evaporated under reduced pressure. The resulting oil was recrystallized from MeOH and the solids were heated in boiling water and filtered hot. Recrystallizations from MeOH/H_2O gave the corresponding monobenzylated material (7.27 g, 42%) as a pink solid.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.66 (m, 2H), 7.49–7.47 (m, 2H), 7.42–7.39 (m, 2H), 7.36–7.32 (m, 1H), 7.09–7.06 (m, 2H), 7.04 (d, J=2.6 Hz, 1H), 6.94 (dd, J=8.8, 2.6 Hz, 1H), 5.16 (s, 2H), 4.86 (s, 1H).

4.1.7. 2-(1,1,2,2,3,3,4,4,4-Nonafluorobutane-1-oxysulfonyl)-7-(*tert*-butyldimethylsilyl)-naphthalene (6). To a flame dried 500 mL RBF equipped with a magnetic stir bar was added 7-(*tert*-butyldimethylsilyl)-2-naphthol (7.88 g, 28.7 mmol) in THF (50 mL) via cannula. The dissolved naphthol was cooled to 0 °C and NaH (1.6 g, 40.2 mmol, 1.4 equiv.) was added as a solid (CAUTION: gas evolution!) and allowed to stir for 30 min. Perfluorobutane sulfonyl fluoride (7.2 mL, 40.2 mmol, 1.4 equiv.) was added via syringe (CAUTION: foaming!) and the reaction was allowed to stir overnight. Upon completion by TLC the reaction was poured into brine (200 mL) and extracted with ether (3×250 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Flash chromatography (hexane/1% ether to 2% ether/hexane gradient) afforded the corresponding nonaflate (8.88 g, 55%) as a light yellow oil. R_f=0.62 (2% ether/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J=9.2 Hz, 1H), 7.76 (d, J=8.8 Hz, 1H), 7.60 (d, J=2.4 Hz, 1H), 7.23 (dd, J=9.2, 2.4 Hz, 1H), 7.20 (d, J=2.2 Hz, 1H), 7.14 (dd, J=8.8, 2.2 Hz, 1H), 1.02 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 148.1, 135.1, 130.5, 129.7, 128.3, 123.7, 118.2, 117.5, 115.2. 25.8, −4.1.

4.1.8. 7-Benzylamino-2-naphthol (4). To a flame dried 2 L RBF equipped with a magnetic stir bar was added $Pd(dba)_2$ (520 mg, 0.895 mmol, 0.03 equiv.), NaO-*t*-Bu (4.4 g, 44.75 mmol, 1.5 equiv.), and racemic BINAP (940 mg, 1.50 mmol, 0.05 equiv.) as solids in a glove box. Toluene (500 mL) was added and 2-(1,1,2,2,3,3,4,4,4-nonafluorobutane-1-oxysulfonyl)-7-(*tert*-butyldimethylsilyl)-naphthalene (16.6 g, 29.83 mmol), dissolved in toluene (500 mL) in a separate flame dried 1 L RBF, was transferred to the 2 L RBF via cannula. Benzylamine (5.0 mL, 44.75 mmol, 1.5 equiv.) was added via syringe and the reaction was heated to 95–100 °C and the dark wine-red colored homogeneous reaction mixture was allowed to stir overnight. Upon completion by TLC the wine-red heterogeneous reaction mixture was cooled to rt and filtered through a pad of Celite with copious EtOAc washings and the solvent was concentrated in vacuo. The crude material was redissolved in THF (ca. 300 mL) and TBAF (1.0 M in THF) (60 mL, 60 mmol, 2.0 equiv.) was added via syringe and the reaction was monitored by TLC. Upon completion, the reaction was poured into H_2O (100 mL) and the aqueous phase extracted with EtOAc (3×100 mL). The organic layer was dried over anhydrous Na_2SO_4. Flash chromatography (40% EtOAc/hexane, 1% NEt_3 dope) afforded the corresponding naphthol (5.55 g, 75%) as an orange solid. R_f=0.46 (40% EtOAc/hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J=8.6 Hz, 1H), 7.54 (d, J=8.6 Hz, 1H), 7.41–7.24 (m, 5H), 6.87 (d, J=2.6 Hz, 1H), 6.79 (dd, J=8.6, 2.6 Hz, 1H), 6.74 (dd, J=8.6, 2.0 Hz, 1H), 6.65 (d, J=2.0 Hz, 1H), 4.74 (br s, 1H), 4.40 (s, 2H), 4.16 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 146.5, 139.3, 136.7, 129.7, 129.1, 128.9, 127.8, 127.5, 123.1, 115.7, 113.9, 108.2, 103.6, 48.5.

4.1.9. Toluene-4-sulfonic acid 2-{5-[2-(7-benzyloxynaphthalen-2-yloxy)-ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl} ethyl ester (9). To a flame dried 10 mL RBF equipped with a magnetic stir bar was added toluene-4-sulfonic acid 2-[5-(2-hydroxyethyl)-2,2-dimethyl-[1,3]-dioxolan-4-yl] ethyl ester (353 mg, 1.0 mmol) as a neat oil, 7-benzyloxy-2-naphthol (274 mg, 1.09 mmol, 1.09 equiv.) as a solid, and Cs_2CO_3 (420 mg, 1.30 mmol, 1.3 equiv.) as a solid. DMF (2 mL) was then added and the heterogeneous reaction mixture was heated to ca. 65 °C and allowed to stir overnight. Upon completion by TLC (18 h) the reaction was diluted with EtOAc and filtered using a Buchner funnel. The solvent was concentrated in vacuo, redissolved in toluene (10 mL), and concentrated (repeat 3 times) in vacuo and put on the high vacuum for 2 h. Tosyl chloride (427 mg, 2.2 mmol, 2.2 equiv.) and DMAP (16 mg, 0.1 mmol, 0.1 equiv.) were added as solids and dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. NEt_3 (0.31 mL, 2.2 mmol, 2.2 equiv.) was added and the reaction was monitored by TLC. Upon completion (4 h) the reaction was concentrated in vacuo. Flash chromatography (20% EtOAc/hexanes) afforded the corresponding tosylated alcohol derivative (425.4 mg, 74%) as an orangish oil. R_f=0.24 (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (app d, J=8.0 Hz, 2H), 7.66 (d, J=9.0 Hz, 1H), 7.65 (d, J=8.8 Hz, 1H), 7.48 (app d, J=7.6 Hz, 2H), 7.42–7.27 (m, 5H), 7.12 (d, J=2.4 Hz, 1H), 7.08 (dd, J=8.8, 2.4 Hz, 1H), 7.04 (d, J=2.6 Hz, 1H), 6.98 (dd, J=9.0, 2.6 Hz, 1H), 5.16 (s, 2H), 4.25–4.11 (m, 4H), 3.87–3.75 (m, 2H), 2.40 (s, 3H), 2.06–1.78 (m, 4H), 1.34 (s, 3H), 1.33 (s, 3H). EIMS *m/z* (rel int): 576(14), 97(23), 91(100), 43(9); HREIMS, *m/z* calcd for $C_{33}H_{36}O_7S$: 576.2182, found 576.2164.

4.1.10. Benzyl-[7-(2-{5-[2-(7-benzyloxynaphthalen-2-yloxy)-ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-ethoxy)-naphthalen-2-yl]-amine (10). To a flame dried 25 mL RBF equipped with a magnetic stir bar was added toluene-4-sulfonic acid 2-{5-[2-(7-benzyloxynaphthalen-2-yloxy)-ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl} ethyl ester (2.93 g, 5.09 mmol), 7-benzylamino-2-naphthol (1.55 g, 6.11 mmol, 1.2 equiv.), and DMF (10 mL). Then Cs_2CO_3 (2.06 g, 6.11 mmol, 1.2 equiv.) was added as a solid as fast as possible. The resulting heterogeneous mixture was warmed to 65 °C and stirred until complete by TLC (24 h). The reaction was dumped into H_2O (100 mL) and extracted with EtOAc (5×50 mL). The organic layer was collected and concentrated in vacuo. Flash chromatography afforded the corresponding product (3.18 g, 95%) as a tan foam. R_f=0.49 (50% ether/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=8.8 Hz, 1H), 7.63 (d, J=9.2 Hz, 1H), 7.54 (d, J=8.8 Hz,

2H), 7.48–7.28 (m, 10H), 7.09–7.07 (m, 2H), 7.05 (d, J=2.4 Hz, 1H), 6.99 (dd, J=8.8, 2.4 Hz, 1H), 6.93 (d, J=2.4 Hz, 1H), 6.86 (dd, J=8.8, 2.4 Hz, 1H), 6.76 (dd, J=8.8, 2.4 Hz, 1H), 6.70 (d, J=2.4 Hz, 1H), 5.14 (s, 2H), 4.40 (s, 2H), 4.29–4.01 (m, 6H), 2.25–2.04 (m, 4H), 1.42 (s, 6H). EIMS, *m/z* (rel int) 654(21), 653(47), 97(15), 91(100); HREIMS, *m/z* calcd for $C_{43}H_{43}NO_5$: 653.3141, found 653.3162.

4.1.11. 7-(-2-{5-[2-(7-Aminonaphthalen-2-yloxy)-ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-ethoxy)-naphthalen-2-ol (11). To a flame dried 100 mL RBF equipped with a magnetic stir bar was added benzyl-[7-(2-{5-[2-(7-benzyloxynaphthalen-2-yloxy)-ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-ethoxy)-naphthalen-2-yl]-amine (3.17 g, 4.84 mmol) and 10%-Pd/C (1.3 g, 1.21 mmol, 25 mol% Pd) as solids. THF (50 mL) was added and the solution was purged well with H_2. The reaction flask was then equipped with a reflux condenser and was warmed to 70 °C (bath temperature, not reflux). Upon completion by TLC (52 h) the reaction was cooled to room temperature and purged with Ar for 15 min. The reaction was then filtered through a pad of Celite and washed with copious amounts of EtOAc (ca. 250 mL total volume of solvent). The solvent was then concentrated in vacuo and azeotropically dried with toluene (25 mL) followed by high vacuum overnight. The corresponding aminonaphthol (2.24 g, 98%) was isolated as an off-white solid. R_f=0.39 (40% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.66 (d, J=8.8 Hz, 1H), 7.65 (d, J=9.2 Hz, 1H), 7.53 (d, J=8.8 Hz, 1H), 7.51 (d, J=8.8 Hz, 1H), 7.11 (m, 2H), 6.98–6.93 (m, 3H), 6.85 (app s, 1H), 6.82 (m, 1H), 6.79 (d, J=2.4 Hz, 1H), 4.83 (s, 2H), 4.27–4.04 (m, 6H), 2.23–2.04 (m, 4H), 1.37 (s, 6H). EIMS, *m/z* (rel int): 473(10), 92(45), 91(100), 65(10), 56(14), 44(30), 43(27); HREIMS, *m/z* calcd for $C_{29}H_{31}NO_5$: 473.2202, found 473.2194.

4.1.12. (*R*)-*cyclo*-NOBIN (12/13). To a flame dried 50 mL RBF equipped with a magnetic stir bar was added $CuCl_2$ (197.4 mg, 1.44 mmol, 4.0 equiv.) as a solid. The flask was then charged with degassed MeOH (18 mL) and the green solution was cooled to 0 °C. The flask was then charged with racemic α-methylbenzylamine (0.74 mL, 5.76 mmol, 16.0 equiv.) and to the blue reaction mixture was then quickly added 7-(-2-{5-[2-(7-aminonaphthalen-2-yloxy)-ethyl]-2,2-dimethyl-[1,3]dioxolan-4-yl}-ethoxy)-naphthalen-2-ol (**11**; 170 mg, 0.36 mmol) as a solid. Upon completion by TLC (55 h) the reaction was poured into saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3×50 mL). The organic layer was dried over anhydrous Na_2SO_4. Flash chromatography (200:1 silica/theoretical yield (170 mg), 5% acetone/5% CH_2Cl_2/toluene, 1% NEt_3 dope) afforded (124 mg, 73%) of the (*R*)-diastereomer as an orange foam (106 mg) along with the minor isomer (18 mg). ^{1}H NMR (major isomer; 400 MHz, $CDCl_3$) δ 7.80 (d, J=8.8 Hz, 1H), 7.75 (d, J=8.8 Hz, 1H), 7.71 (d, J=8.8 Hz, 1H), 7.67 (d, J=8.8 Hz, 1H), 7.23 (d, J=8.8 Hz, 1H), 7.0 (app d, J=2.4 Hz, 1H), 6.97 (d, J=8.8 Hz, 1H), 6.91 (dd, J=8.8, 2.3 Hz, 1H), 6.36 (d, J=2.4 Hz, 1H), 6.25 (d, J=2.3 Hz, 1H), 5.71 (br s, 1H), 4.04–3.60 (m, 6H), 1.63–1.62 (m, 4H), 1.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 156.8, 152.6, 143.6, 135.1, 134.3, 130.55, 130.50, 130.49, 130.4, 124.9, 123.9, 117.5, 116.5, 116.0, 115.9, 113.7, 108.7, 105.9, 105.4, 76.5, 76.4, 63.8, 63.7, 32.6, 27.3. EIMS, *m/z* (rel int): 472(31), 471(100), 317(17), 97(15), 59(11), 43(31); HREIMS, *m/z* calcd for $C_{29}H_{29}NO_5$: 471.2046, found 471.2040.

4.1.13. Polymer supported (*R*)-*cyclo*-NOBIN (15). To a 5 mL CV was added (*R*)-*cyclo*-NOBIN (331 mg, 0.7 mmol). THF (1.8 mL), H_2O (1.8 mL), and conc. HCl (ca. 10 drops) were added and the CV was fitted with a yellow-cap and allowed to stir overnight. Upon completion by TLC (40% EtOAc/hexanes; ca. 14.5 h), the reaction was poured into sat. aq. $NaHCO_3$ (ca. 10 mL) and extracted with EtOAc (5×10 mL). The organic layer was collected and concentrated in vacuo followed by azeotropically drying with toluene (3×20 mL) and high vacuum overnight. Polystyrene-1% cross-linked divinylbenzene supported aldehyde (505.8 mg, 1 mmol/g) and *p*-toluenesulfonic acid monohydrate (26.9 mg, 0.14 mmol) were added as solids followed by toluene (10 mL). The reaction was set up with a Dean Stark trap and heated to 130–135 °C where it was allowed to stir for 24 h. After cooling to rt, addition of sat. aq. $NaHCO_3$ (ca. 10 drops) and filtration through a Buchner funnel with solvent washes (EtOAc, CH_2Cl_2, ether, THF, H_2O, EtOH; ca. 20 mL each) afforded polymer-bound *cyclo*-NOBIN (new polymer weight=632.9 mg corresponds to 0.675 mmol/g), after drying under high vacuum overnight; IR (KBr pellet) 3491, 3387, 3024, 2917, 2347, 1944, 1872, 1809, 1715, 1607, 1499, 1446, 1208, 1061, 756 cm^{-1}.

Acknowledgements

We warmly thank the NIH (GM 40287) and AstraZeneca (sabbatical leave for C.O.) for financial support. We are also grateful to Mr. John Unger (UCSB) for outstanding assistance with this project.

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Conformational studies by dynamic NMR spectroscopy. Part 96: Stereomutations of highly hindered naphthylphenyl atropisomers in solution and in the solids☆

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Received 10 October 2003; revised 19 January 2004; accepted 21 January 2004

Abstract—When a benzene ring bears two 2-methyl-1-naphthyl moieties in the *para*, *meta* or *ortho* positions as in 1,4-bis(2-methyl-1-naphthyl)benzene, **1**, 1,3-bis(2-methyl-1-naphthyl)benzene, **2** and 1,2-bis(2-methyl-1-naphthyl)benzene **3**, two rotational isomers (atropisomers) are generated, with the two naphthyl substituents in a *syn* or *anti* relationship. In the case of the *para* and *meta* derivatives (**1** and **2**, respectively) these atropisomers could not be separated but were detected by NMR spectroscopy, that also allowed the determination of their *syn*–*anti* interconversion barriers in solution (19.5 and 20.4 kcal mol^{-1}, respectively) and, in the case of **2**, also in the solid state (26.7 kcal mol^{-1}). In the more hindered *ortho* derivative **3**, the *syn* (*meso*) and *anti* (racemic) atropisomers interconvert in solution with a barrier (31.2 kcal mol^{-1}) sufficiently high to allow their physical separation. The racemic form could also be separated (by enantioselective HPLC) into the PP and MM enantiomers. Analysis of the corresponding CD spectra allowed the assignment of the absolute configuration. When three such naphthyl substituents are bonded to the phenyl in a *meta* relationship, two atropisomers in statistical proportions were observed: the *anti* (C_s symmetry) and the *syn* (C_{3v} symmetry) display a 3:1 ratio at the equilibrium in solution. This ratio is different in the solid state, as is the interconversion barrier (22.1 and 32.1 kcal mol^{-1} in solution and in the solid, respectively).

1. Introduction

Aromatic derivatives bearing two or three aryl substituents exist as conformational or configurational stereoisomers (atropisomers), depending on the extent of the steric effects involved.[2–7] The presence of such stereoisomers, generated by the restricted rotation about the aryl–aryl bond, can usually be detected by NMR spectroscopy either at ambient or at an appropriate low temperature. In a number of cases these stereoisomers could even be physically separated.[2,3] A benzene ring substituted by two bulky 2-methyl-1-naphthyl moieties is thus expected to yield stereolabile isomers (conformational rotamers) when these substituents are in a *para* or in a *meta* relationship, but to yield stable stereoisomers (configurational rotamers or atropisomers) when in an *ortho* relationship. In order to verify such a prediction, derivatives **1**–**4** were synthesized and the related stereomutation processes occurring in solution and in the solid state were investigated by NMR spectroscopy techniques (Chart 1).

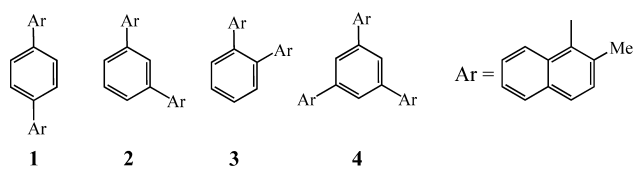

Chart 1.

2. Results and discussion

The ^{1}H NMR spectrum of **1** in $CDCl_3$ displays, at ambient temperature, two equally intense lines for the methyl groups, thus indicating the presence of two rotational stereoisomers (rotamers or atropisomers) in a 1:1 proportion. The ratio is independent of the polarity of the solvent, since the same result was observed in toluene-d_8 and DMSO.

These stereoisomers are the consequence of the two possible situations where the naphthyl rings, orthogonal to the plane of benzene, are either in an *anti* (C_{2h} symmetry) or in a *syn* (C_{2v} symmetry) relationship: the corresponding structures (resulting from ab initio computations[8] at the RHF 6-31G* level) are displayed in Figure 1 (traces b and c, respectively). These calculations, and Molecular Mechanics

☆ See Ref. 1.

Keywords: Dynamic NMR spectroscopy; NOE; Enantioseparation; Absolute configuration; X-ray diffraction.
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doi:10.1016/j.tet.2004.01.094

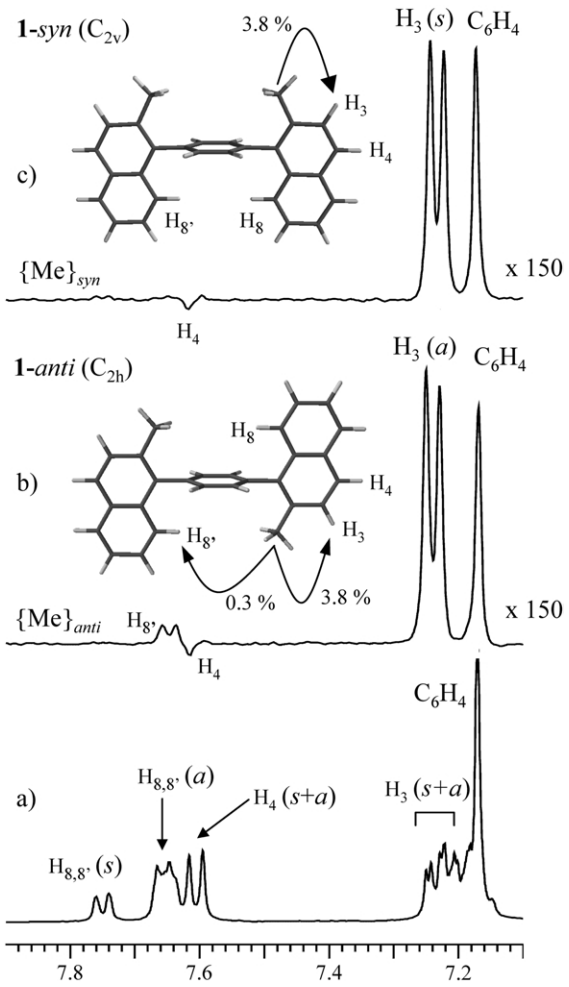


Figure 1. (a) ^{1}H NMR spectrum (400 MHz in toluene-d_8) of the aromatic region of **1** showing the partially overlapped signals of the *anti* (*a*) and *syn* (*s*) conformers in a 1:1 ratio. (b) The NOE trace (150-fold amplified) of the same region, obtained by irradiation of the downfield (2.25 ppm) methyl line (*anti*), displays three enhanced signals:[11] that of the four equivalent phenyl hydrogens (C_6H_4), that of the H-3 hydrogen in the same naphthyl ring (3.8%) and that of the *peri* hydrogen (H-8′) in the other naphthyl ring (0.3%). (c) The NOE trace (150-fold amplified), obtained by irradiation of the upfield (2.19 ppm) methyl line (*syn*), does not display the enhancement of the H-8′ signal.

(MMFF force field[9]) as well, indicate the *anti* isomer to be only slightly more stable than the *syn* isomer (0.1 and 0.2 kcal mol^{-1}, respectively), in fair agreement with the experimental observation of an essentially equal proportion of the two atropisomers.

In order to identify the NMR signals of each isomer, a NOE experiment (DPFGSE-NOE sequence[10]) was performed by irradiating the downfield (2.25 ppm as in Figure 1, trace b) and the upfield (2.19 ppm as in Figure 1, trace c) methyl singlet. In the latter case NOE effects were observed for the singlet of the four equivalent phenyl hydrogens (C_6H_4) and for the doublet due to the hydrogen in position 3 of the naphthyl ring (H-3).[11] Irradiation of the downfield methyl singlet (Fig. 1, trace b) produces the same effects mentioned above and, in addition, a not negligible enhancement (0.3%) for the upfield doublet due to the *peri* hydrogen of the other naphthyl ring (H-8′). The latter observation implies that we are dealing with the atropisomer *anti*, in which the methyl group of one naphthyl ring is close enough to the hydrogen in the *peri* position of the other ring (i.e., H-8′) as to yield a measurable NOE effect. Indeed the ab initio[8] computed average distance of the methyl hydrogens from H-3 is 3.25 Å, that from H-8′ is 4.88 Å:[12] the ratio of these distances (0.66) matches the ratio (0.65) of the corresponding NOE enhancements (3.8 and 0.3%, respectively) elevated to the $-1/6$ power.[13] It can be, thus concluded that the *anti* rotamer is the one having the methyl line downfield with respect to the corresponding signal of the *syn* rotamer.

On raising the temperature of a DMSO solution of **1**, the NMR methyl singlet of the *syn* isomer and of the *anti* isomer broaden and coalesce, eventually yielding a single line, owing to the rapid interconversion of the two conformers at high temperature (Fig. 2). The rate constants for this process were determined by computer line shape simulation,[14] from which the corresponding free energy of activation ($\Delta G^{\neq}=19.5_5\pm0.15$ kcal mol^{-1}, as in Table 1) was derived. A transmission coefficient of 1/2 was employed here since the process may occur by two degenerate pathways, in that rotation of either of the two naphthyl rings interconverts one rotamer into the other, as discussed for similar situations.[5b,15] As often observed in this type of conformational processes, the $\Delta S^{\neq}$ value was found negligible within the experimental errors.[16]

It should be also noticed that if derivative **1** is melted (at +233 °C) and subsequently allowed to cool to ambient temperature, a 1:1 ratio is constantly observed in the resulting vitreous solid phase. The proportion of the atropisomer in this solid solution is therefore equal to that detected in the fluid solution.[17] This was demonstrated by dissolving such a solid in $CDCl_3$, cooled below −30 °C, and observing that the NMR spectrum, recorded without ever raising the temperature, displays a 1:1 ratio. On the basis of the previously measured barrier of 19.5_5 kcal mol^{-1}, this procedure guarantees that the interconversion rate in solution is negligible at this temperature (at −30 °C the half-life time of these forms is about two weeks). As a consequence the ratio measured in this way corresponds to that occurring in the examined solid phase. In the latter state compound **1** does not undergo interconversion processes: even when left overnight at +150 °C, the ratio of the atropisomers in the solids was still found equal to 1:1, indicating that the lattice imposes a significant constraint upon the internal rotation of **1**.

As in the case of **1**, the *meta* derivative **2** also shows, at ambient temperature, two different NMR solution spectra for the two possible forms in a ratio (1:1) which is independent of the dielectric constant of the solvent employed (e.g., toluene-d_8, $CDCl_3$, DMSO-d_6). The atropisomer *syn* (C_s symmetry) corresponds to a *meso* and the *anti* (C_2 symmetry) to a racemic conformer, as shown, for a very similar case, in Scheme 2 of Ref. 5b. Ab initio calculations (at the RHF 6-31G* level)[8] predict that these conformers have quite similar energies (the *anti* being more stable only by 0.3 kcal mol^{-1}) and this accounts for the observation of essentially equal proportion in solution since both species have the same two-fold degeneracy (two

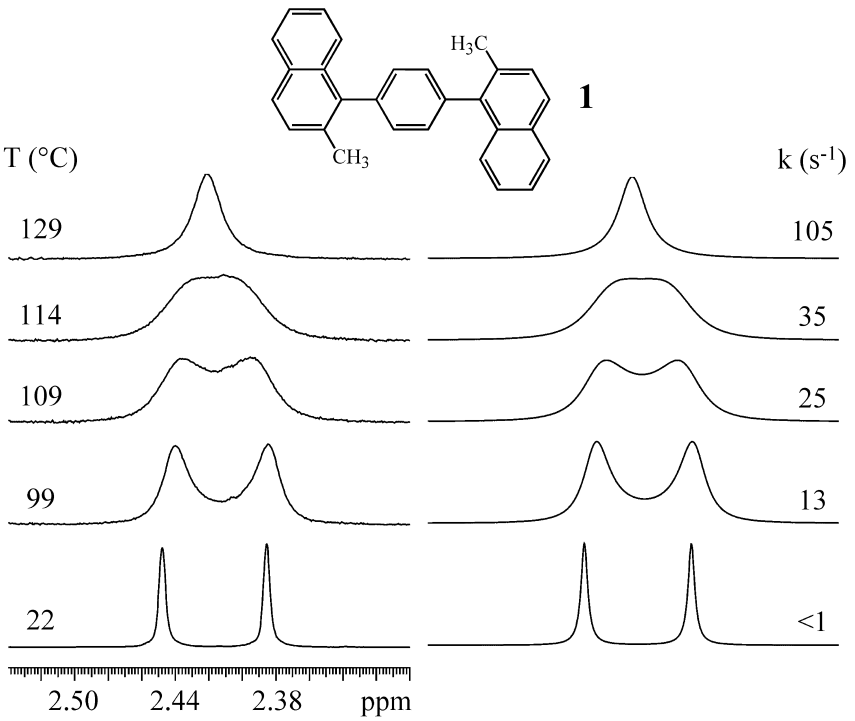


Figure 2. Left: temperature dependence of the ^{1}H NMR (300 MHz) methyl signals of **1** in DMSO. Right: computer line shape simulation obtained with the rate constants indicated.

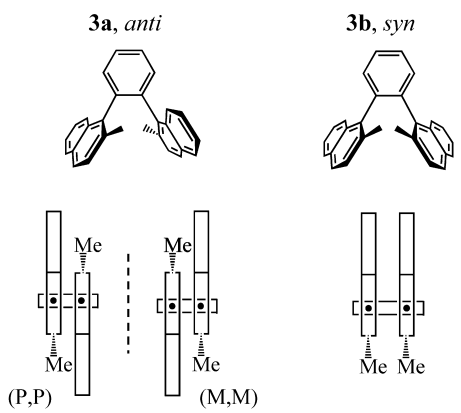
Table 1. Barriers ($\Delta G^{\neq}\pm0.15$ kcal mol^{-1}) for the *anti* to *syn* interconversion in compounds **1**–**4**

Compound	Solution (DMSO)	Solid state
1	19.5_5	—
2	20.4	26.7
3	31.2	—
4	22.1	32.1

topomers for the *meso* and two enantiomers for the racemic[5b]). The same type of NOE experiment described for **1** was carried out in the case of **2**, and this allowed us to identify the conformer *anti* as that displaying the methyl line at lower field with respect to the *syn*.[18]

The NMR signals of **2** broaden and coalesce on raising the temperature: line shape simulation provided a set of rate constants from which the free energy of activation ($\Delta G^{\neq}$=20.4 kcal mol^{-1} in DMSO as solvent) could be derived (the 1/2 transmission coefficient was likewise employed). The interconversion barrier is 0.85 kcal mol^{-1} higher for **2** than for **1**, owing to the higher steric hindrance experienced by the rotational transition state of the *meta* with respect to that of the *para* isomer, since the two bulky 2-methylnaphthyl rings are closer to each other in the former than in the latter.

Also compound **2**, when melted (at +116 °C) and subsequently allowed to solidify, initially displays in the solid phase[19] the same 1:1 ratio as found in solution (the measurements were performed with the same method mentioned for **1**). Here, however, a rotation process does occur also in the solid state, leading, at the equilibrium, to an *anti*–*syn* ratio (4:1) substantially different from that of the initial conditions. The kinetics[20] of the interconversion process in the solids was examined at the constant temperature of +80 °C, by measuring the time dependent ratio of the conformers (the low temperature NMR method described for **1** was employed). The rate constant for this rotation process in the solid phase was found equal to 2×10^{-4} s^{-1}, corresponding to a $\Delta G^{\neq}$ of 26.7 kcal mol^{-1}, a value which is 6.3 kcal mol^{-1} higher than in solution, on the assumption of a time independent free energy of activation.[16] The constraints imposed by the lattice to the internal rotation of the naphthyl substituents are much lower here than in the case of **1**: the difference between the two barriers observed for **2** is quite in line with those reported for analogous processes occurring in solution and in the solid state.[21]



Scheme 1.

Due to the much higher steric hindrance, the *ortho* derivative **3** yields rotational isomers that are configurationally stable and could, therefore, be separated at ambient temperature. The *syn* isomer has a C_s symmetry and is, therefore, a *meso* compound, whereas the symmetry of the *anti* is C_2, which implies that this atropisomer comprises MM and PP enantiomers, as shown in Scheme 1.

NOE experiments allowed the *anti* (racemic) and the *syn* (*meso*) configurations of **3** (**3a** and **3b**, respectively) to be unambiguously obtained. Irradiation of the methyl hydrogens of isomer **3a** (mp 163 °C) enhances the hydrogens in position 3 (H-3) of the same naphthyl ring (8%), the *ortho* hydrogens of the phenyl ring (2%) and the hydrogen (H-8′) in position *peri* of the other naphthyl ring (7.5%), as displayed in Figure 3.

The same NOE experiment, carried out on the atropisomer **3b** (mp 180 °C) shows enhancement only for the H-3 and H-*ortho* signals (7 and 2.5%, respectively) but not for the H-8′ signal (Fig. 4). Thus **3a** must have the *anti* (racemic) structure because the methyl group of one naphthyl ring is close to the H-8′ hydrogen of the other naphthyl ring and **3b** must have the *syn* (*meso*) structure because the methyl and H-8′ hydrogens are quite far apart.

These assignments were subsequently confirmed by X-ray diffraction: the crystal cell of the **3a** atropisomer comprises,

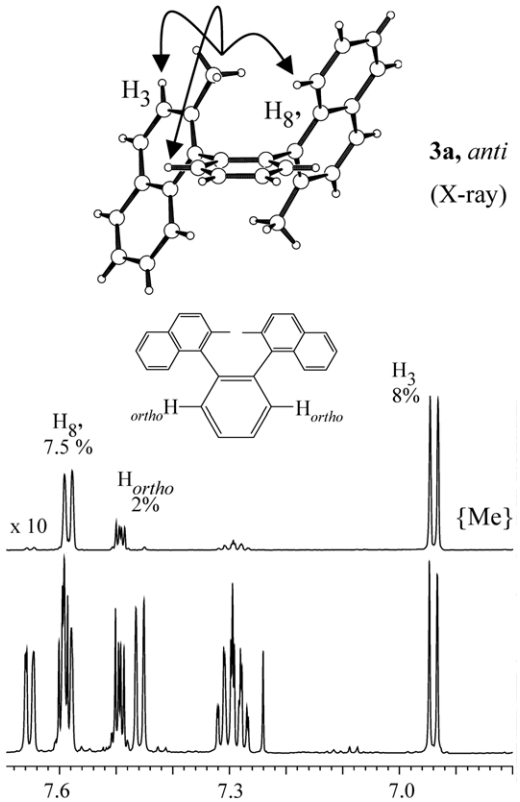


Figure 3. Top: X-ray structure of derivative **3a** (*anti* configuration). Bottom: 600 MHz NOE trace (10-fold amplified with respect to the corresponding ^{1}H spectrum in $CDCl_3$ reported underneath) of the aromatic region obtained by irradiation of the methyl signal. Enhancements were observed for the *ortho* hydrogens of the phenyl ring (2%), the hydrogen (H-3) in position 3 of the same naphthyl ring (8%) and the hydrogen in position *peri* (H-8′) of the other naphthyl ring (7.5%).

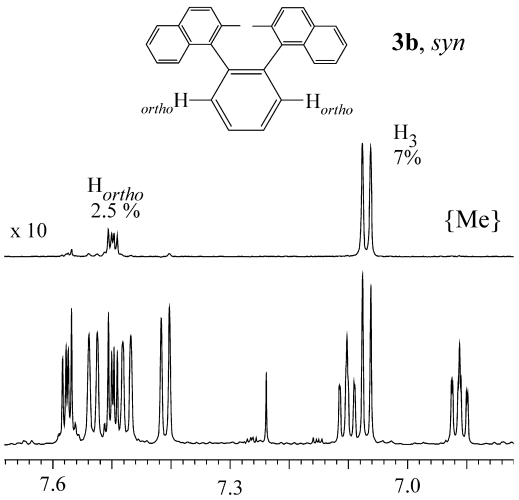


Figure 4. 600 MHz NOE trace (10-fold amplified with respect to the corresponding ^{1}H spectrum in $CDCl_3$ shown underneath) of the aromatic region of **3b** obtained by irradiation of the methyl signal. Enhancements were observed for the *ortho* hydrogens of the phenyl ring (2.5%) and the hydrogen (H-3) in position 3 of the same naphthyl ring (7%) but not for hydrogen in position *peri* (H-8′) of the other naphthyl ring.

in fact, two *anti* molecules in enantiomeric relationship (see Section 3), one of them being displayed in Figure 3.

Although, as mentioned, the *anti* (**3a**) and *syn* (**3b**) atropisomers could be physically separated at ambient temperature, the rotation rate of their naphthyl substituents is not completely negligible. For, when DMSO solutions of either **3a** or **3b** are kept overnight at +150 °C, an equilibrium is reached showing, in both cases, the presence of the same *anti*–*syn* ratio (1.1:1). The kinetic process leading to this equilibrium condition was followed starting from individual **3b**, whereby a rate constant of 4.7×10^{-5} s^{-1} was obtained at a temperature of +130 °C. This corresponds to a free energy of activation[5b,15] of 31.2 kcal mol^{-1}, which implies a half life of about 274 years at ambient temperature, on the reasonable assumption[16] of a temperature independent value of $\Delta G^{\neq}$. Such a lifetime should also correspond to the lifetimes of the individual MM and PP enantiomers of racemic **3a** (see Scheme 1) because MM will not interconvert directly into the PP enantiomer by simultaneous rotation of both the naphthyl rings, but would rather accomplish this process stepwise, by rotating first one of the two rings to yield the *meso* form MP which would subsequently yield the enantiomer PP by rotating the second ring. As a consequence it should be possible, in principle, to achieve the physical separation of these antipodes at ambient temperature.

By making use of an enantioselective HPLC column (see Section 3) the two enantiomers were actually isolated (Fig. 5, top), as proved by the corresponding CD spectra that show oppositely phased trend, the bold trace being that of the first eluted enantiomer (Fig. 5, bottom). An attempt was also made to assign the absolute configuration by taking advantage of the observation that the CD spectrum is dominated by the exciton[1c,22] band at about 220 nm, corresponding to the long-axis polarized ^1B_b transition of naphthalene. The dihedral angle between the naphthalene and the phenyl ring is not precisely 90°, but deviates from orthogonality being measured as 114° in the solid state

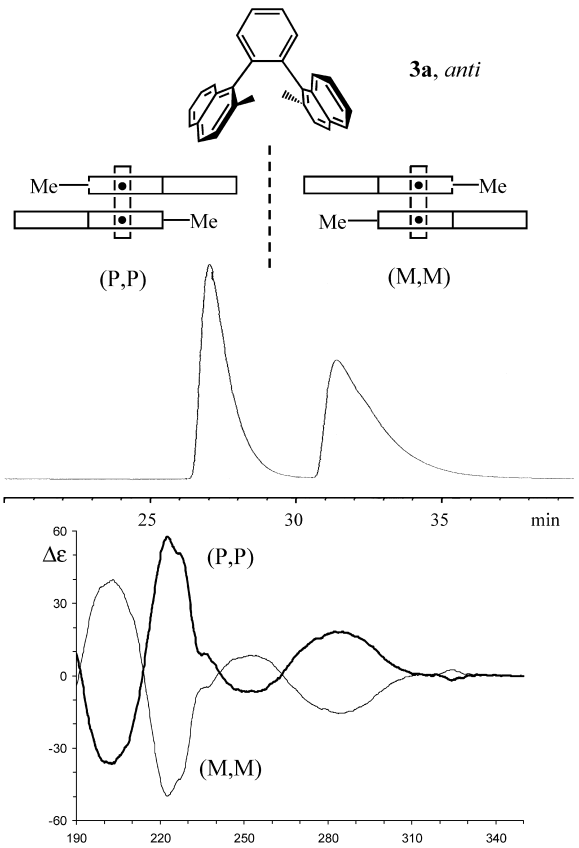


Figure 5. Top: HPLC trace showing the separation of the PP and MM enantiomers of the atropisomers *anti* **3a**. Bottom: CD spectra of the first eluted (bold trace) and of the second eluted enantiomer (weaker trace), displaying opposite phased trends (abscissa in nm).

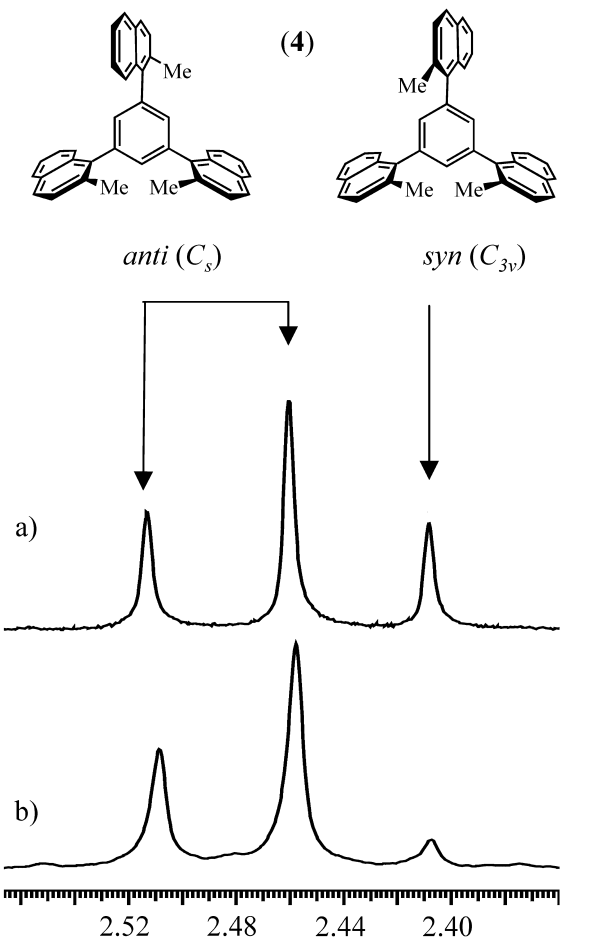


Figure 6. (a) ^{1}H NMR (300 MHz) methyl signals observed by dissolving the solid of **4** in $CDCl_3$ at −30 °C and recording the spectrum without ever rising the temperature. (b) Spectrum obtained with the same method after having kept the solid of **4** at +80 °C for 96 h, in such a way as to reach the equilibrium between the two conformers in the solid phase.

(X-ray) or predicted to be 106° in the isolated molecule (ab initio computations[8]). Accordingly, the long axes of the two naphthalene moieties are not exactly parallel to each other and in the enantiomer PP their dipole moments display a positive helicity, which corresponds to the strong positive–negative exciton, that is, to the bold trace of Figure 5. Thus the PP configuration should be attributed to the first eluted enantiomer: to the second eluted enantiomer, exhibiting the weaker CD trace of Figure 5, should be consequently assigned the MM configuration.

When three such aryl substituents (i.e., Ar=2-methylnaphth-1-yl) are bonded to the benzene ring in a *meta* relationship, the resulting 1,3,5-tris(2-methylnaphth-1-yl)benzene, **4** comprises two atropisomers having the naphthyl substituents either antiparallel (C_s symmetry) or parallel (C_{3v} symmetry) to each other, as shown in Figure 6. The pathway by which they interconvert has been described in detail in the case of analogous, albeit less hindered, hydrocarbons.[5a,b]

Owing to the bulkiness of the substituents, the NMR solution (DMSO) spectrum of **4** displays, even at ambient temperature, two sets of signals for the two atropisomers, with an *anti*–*syn* ratio (3:1) that reflects the statistic distribution of the substituent orientation.[5] In particular the *anti* conformer yields a pair of methyl signals with a 1:2 intensity ratio (the C_s symmetry implies that one methyl has a chemical shift different from that of other two) whereas the conformer *syn* yields a single line for the three homotopic methyl groups, as expected for a C_{3v} symmetry. On raising the temperature these signals broaden and coalesce: from the rate constants derived by line shape simulation a $\Delta G^{\neq}$ value of 22.1 kcal mol^{-1} is obtained for the interconversion process (as discussed in Ref. 5b a unitary transmission coefficient has to be used for this type of pathway). The explanation for the higher barrier observed in the three-substituted compound **4** with respect to the analogous di-substituted compound **2** has been already proposed for an analogous situation.[5b]

By making use of the same technique previously mentioned for the cases of **1** and **2**, it was possible to measure the *anti*–*syn* ratio of **4** in the solid phase (obtained by melting and subsequently cooling the compound to ambient temperature). Initially the ratio was found equal to 3:1 as in solution[23] (see Fig. 6(a)) but when the equilibrium conditions were reached (by keeping the solid at +80 °C for 96 h) the ratio became 9:1 (Fig. 6(b)). The kinetic process[20] was monitored by the same method described for **2**, and from the rate constant (1.1×10^{-6} s^{-1} at+100 °C for the interconversion of the more stable *anti* into the less stable *syn* rotamer of **4**), the barrier in the solids ($\Delta G^{\neq}$=32.1 kcal mol^{-1}) turned out to be significantly

higher than the corresponding value measured in solution (see Table 1), as observed in the case of compound **2**.

3. Experimental

3.1. Synthesis

3.1.1. 1,4-Bis(2-methyl-1-naphthyl)benzene (1). The titled compound was prepared from 1,4-dibromobenzene according to the procedure of Suzuki.[24] To a solution of 1,4-dibromobenzene (235 mg, 1 mmol, in 6 mL of benzene), K_2CO_3 (2 M solution, 1.25 mL), 2-methyl-1-naphthylboronic acid[25] (465 mg, 2.5 mmol, suspension in 4 mL of ethanol), and $Pd(PPh_3)_4$ (230 mg, 0.2 mmol, solid) were added at room temperature. The stirred solution was refluxed for 24 h, the reaction being monitored by TLC (eluent petroleum ether–Et_2O 200:1). To the cooled solution a second amount of 2-methyl-1-naphthylboronic acid (465 mg, 2.5 mmol, suspension in 4 mL of ethanol), K_2CO_3 (2 M solution, 1.25 mL) and $Pd(PPh_3)_4$ (230 mg, 0.2 mmol, solid) was added. After refluxing for 24 h, $CHCl_3$ and H_2O were added and the extracted organic layer dried (Na_2SO_4) and evaporated. The crude was purified by chromatography on silica gel (eluent petroleum ether) to yield 220 mg (0.65 mmol, 65%). White powder, mp 233–234 °C; ^{1}H NMR ($CDCl_3$, 600 MHz), δ: 2.34 and 2.40 (s, 6H, Me), 7.39 (m, 2H), 7.42(s, 8H Ph), 7.44–7.48 (m, 10H), 7.54 (d, 2H, J=8.3 Hz), 7.63 (m, 2H), 7.84 (d, 4H, J=8.4 Hz), 7.86–7.89 (m, 4H); ^{13}C NMR ($CDCl_3$, 150.7 MHz) δ: 20.85(Me) 20.99(Me), 124.79(CH), 124.82(CH), 125.87(CH), 129.92(CH), 126.10(CH), 126.21(CH), 127.28(CH), 127.81(CH), 128.64(CH), 128.66(CH), 130.17 (CH), 132.02(C), 133.00(C), 133.03(C), 133.28(C), 133.29(C), 138.05(C), 138.06(C), 138.44 (C). Anal. Calcd for $C_{28}H_{22}$: C, 93.81; H, 6.19. Found: C, 93.78; H, 6.22.

3.1.2. 1,3-Bis(2-methyl-1-naphthyl)benzene (2). The titled compound was prepared starting from 1,3-dibromobenzene using the same procedure described above. Yield 185 mg (0.57 mmol, 57%). White powder, mp 113–114 °C, ^{1}H NMR ($CDCl_3$, 600 MHz), δ 2.31(s, Me), 2.34(s, Me), 7.20 (m, 2H), 7.32–7.40 (m, 16H), 7.54 (d, 2H, J=8.3 Hz), 7.62(m, 4H), 7.75(d, 4H, J=8.4 Hz), 7.81(m, 4H); ^{13}C NMR ($CDCl_3$, 150.7 MHz): of the expected 2 Me, 18 CH and 10 quaternary signals, 2 Me, 18 CH and 8 Cq were observed. δ: 20.89(Me), 20.94(Me), 124.69(CH), 124.73(CH), 125.81(CH), 125.86(CH), 125.99(CH), 126.09(CH), 127.23(CH), 127.24(CH), 127.76(CH), 127.79(CH), 128.43(CH), 128.46(CH), 128.57(CH), 128.61(CH), 128.85(CH), 128.88(CH), 131.97(CH), 131.99(CH), 132.86(C), 132.96(C), 133.07(C), 133.09(C), 137.95(C), 137.97(C), 139.90(C), 139.93 (C). Anal. Calcd for $C_{28}H_{22}$: C, 93.81; H, 6.19. Found: C, 93.79; H, 6.21.

3.1.3. 1,2-Bis(2-methyl-1-naphthyl)benzene (3). The titled compound was prepared according to a modified Suzuki reaction.[26] To a solution of 1,2-diiodobenzene and 2-methyl-1-naphthylboronic acid[25] (respectively, 990 mg, 3 mmol and 2.20 g, 7 mmol in 12 mL of H_2O and 15 mL of acetone), K_2CO_3 (1.04 g, 7.5 mmol, solid) and $Pd(OAc)_2$ (68 mg, 0.3 mmol, solid) were added at room temperature. The stirred solution was refluxed for 24 h, then a second amount of and $Pd(OAc)_2$ (68 mg, 0.3 mmol) was added, and the solution was again refluxed for 24 h. The reaction was monitored by TLC (eluent petroleum ether–Et_2O 1:1). The cooled solution was treated with $CHCl_3$ and H_2O, then the extracted organic layer was dried (Na_2SO_4) and evaporated. The crude was pre-purified by chromatography on silica gel (eluent petroleum ether–Et_2O 10:1) to yield 210 mg (0.65 mmol, 22%). Separation of *syn* and *anti* atropisomers was obtained by preparative TLC on silica-gel (eluent petroleum ether–Et_2O 1:1). Crystals of the *anti* atropisomer, suitable for X-ray diffraction, were obtained from absolute ethanol by slow evaporation (7 months).

syn Atropisomer (**3b**): white powder, mp 179–180 °C; ^{1}H NMR ($CDCl_3$, 600 MHz), δ:2.18 (s, 6H, Me), 6.91 (ddd, 2H, J=8.3, 6.8, 1.4 Hz), 7.05 (d, 2H, J=8.40 Hz), 7.08 (ddd, 2H, J=7.9, 6.8, 1.2 Hz), 7.39 (d, 2H, J=8.4 Hz), 7.46(d, 2H, J=8.2 Hz), 7.48 (m, 2H), 7.52 (d, 2H, J=8.3 Hz), 7.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 150.7 MHz) δ: 21.20(Me), 124.16(CH), 124.53(CH), 126.92(CH), 126.93(CH), 127.05(CH), 127.16(CH), 128.09(CH), 131.37(C), 132.35(C), 132.67(CH), 133.35(C), 136.61(C), 139.64(C). Anal. Calcd for $C_{28}H_{22}$: C, 93.81; H, 6.19. Found: C, 93.82; H, 6.18.

anti Atropisomer (**3a**): white powder, mp 162–163 °C ^{1}H NMR ($CDCl_3$, 600 MHz), δ:1.95 (s, 3H, Me), 6.92 (d, 2H, J=8.40 Hz), 7.27 (m, 4H),), 7.44 (d, 2H, J=8.40 Hz), 7.47(m, 2H), 7.57(m, 4H), 7.63(d, 2H, J=8 Hz); ^{13}C NMR ($CDCl_3$, 150.7 MHz) δ: 21.72(Me), 124.25(CH), 124.74(CH), 126.85(CH), 127.03(CH), 127.04(CH), 127.60(CH), 128.26(CH), 131.61(C), 132.66(CH), 134.15(C), 136.41(C), 139.88(C). Anal. Calcd for $C_{28}H_{22}$: C, 93.81; H, 6.19. Found: C, 93.85; H, 6.15.

3.1.4. 1,3,5-Tris(2-methyl-1-naphthyl)benzene (4). The titled compound was prepared according to the procedure of Suzuki.[24] To a solution of 1,3,5-tribromobenzene (315 mg, 1 mmol in 5 mL of benzene), K_2CO_3 (1 M solution, 3 mL), 2-methyl-1-naphthylboronic acid[25] (930 mg, 5 mmol, suspension in 7 mL of ethanol), and $Pd(PPh_3)_4$ (230 mg, 0.2 mmol, solid) were added at room temperature. The stirred solution was refluxed for 8 h, the reaction being monitored by TLC (eluent petroleum ether–Et_2O 200:1). To the cooled solution a second amount of 2-methyl-1-naphthylboronic acid (930 mg, 5 mmol in 7 mL of ethanol), K_2CO_3 (1 M solution, 3 mL) and $Pd(PPh_3)_4$ (460 mg, 0.4 mmol, solid) was added. After refluxing for 8 h, $CHCl_3$ and H_2O were added and the extracted organic layer dried (Na_2SO_4) and evaporated. The crude was purified by chromatography on silica gel (eluent petroleum ether–Et_2O 200:1) to yield 115 mg (0.24 mmol, 24%). White powder, mp 230–231 °C; ^{1}H NMR ($CDCl_3$, 600 MHz), δ 2.39(s, Me), 2.45(s, Me) and 2.50(s, Me), 7.28–7.31 (m), 7.40–7.50 (m), 7.67 (m), 7.74–7.78 (m), 7.82–7.86 (m). ^{13}C NMR ($CDCl_3$, 150.7 MHz) δ: of the expected 3 Me, 21 CH and 15 quaternary signals, 3 Me, 19 CH and 11 Cq were observed: 21.07 (Me), 21.14 (Me), 21.22 (Me), 124.66(CH), 124.70(CH), 124.74(CH), 125.75(CH), 125.85(CH), 125.87(CH), 125.93(CH), 125.95(CH), 125.99(CH), 127.26(CH), 127.80(CH),

127.82(CH), 127.84(CH), 128.57(CH), 128.59(CH), 128.61(CH), 130.67(CH), 130.71(CH), 130.74(CH), 131.85(C), 132.61(C), 132.71(C), 132.81(C), 133.10(C), 133.11(C), 133.12(C), 137.67(C), 137.68(C), 139.81(C), 139.86(C). Anal. Calcd for $C_{39}H_{30}$: C, 93.94; H, 6.06. Found: C, 93.97; H, 6.03.

3.2. NMR measurements

NMR spectra were recorded at 400 or 600 MHz for ^{1}H and 100.6 or 150.8 MHz for ^{13}C. The assignments of the ^{13}C signals were supported by DEPT and 2D experiments. DPFGSE-NOE spectra were acquired using a 'rsnob' selective pulse (typically 92.5 ms), and a mixing time of 2.0 or 2.5 s. Since with this sequence it is intrinsically difficult to obtain the NOE percentage enhancement,[10] the standard NOE difference sequence was used to measure the largest NOE effect and the other values were scaled accordingly.[27] The temperature was calibrated before the VT experiments by means of a thermocouple which has an uncertainty not exceeding ±1 °C. The line shape computer simulations were performed by a computer program based on DNMR6 routines[14] and the best fit was visually judged by overlapping the experimental and calculated traces. The intrinsic line width was measured from the spectra taken at temperatures where the motion is 'frozen'. We also checked that uncertainty on such a width as large as ±50% affected the rate constants by less than ±15%, hence the $\Delta G^{\neq}$ by ±0.05 kcal mol^{-1}. On the other hand, when the combined errors on the line width and on the temperature have to be taken into account, the uncertainty on the absolute value of $\Delta G^{\neq}$ becomes ±0.15 kcal mol^{-1}.

HPLC separation of the enantiomers of **3a** was performed at +20 °C on a enantioselective Chiralcel OD-H column (5 μm), 250 mm×4.6 mm ID, UV detected at 254 nm, flow rate 0.5 mL min^{-1} (hexane–iPr$_2$O 85:15). Retention times: 27.00 and 31.38 min. The necessary amount of the two separated enantiomers was obtained by collecting 16 elutions (50 μL of a 1.00 mg mL^{-1} solution each one).

CD-spectra of the two enantiomers of **3a** were recorded at +25 °C on a Jasco J-600 dicrograph in a 0.01 cm cell in the range 190–350 nm. Concentration were 0.32 mg mL^{-1} (8.94×10^{-4} M in *n*-hexane) for the first eluted enantiomer, and 0.48 mg mL^{-1} (1.34×10^{-3} M in *n*-hexane) for the second eluted one. An ε=53.000 was calculated at 223 nm from the UV spectrum.

3.3. X-ray diffraction: crystal data of *anti* 1,2-bis(2-methyl-napth-1-yl)-benzene (3a)

$C_{28}H_{22}$ (358.46), Triclinic, Space group P-1, Z=2, a=8.9569(3), b=9.3302(3), c=12.3044(4) Å, α=90.9450(10), β=97.9040(10), γ=99.2240(10) V=1004.55(6) Å^3, D_c=1.185 g cm^{-3}, $F(000)$=380, μ_{Mo}=0.067 mm^{-1}, T=293 K; Crystal size 0.6×0.5×0.5 mm. Data were collected using a graphite monochromated Mo-Kα X-radiation (λ=0.71073 Å) in the range 1.67° $<\theta<$30.06°. Of 13197 reflections collected, 5866 were found to be independent (R_{int}=0.0118), 4413 of which were considered as observed [$I>2\sigma(I)$], and used in the refinement of 255 parameters leading to a final R_1 of 0.0532 and a R_{all} of 0.0675. The structure was solved by direct method and refined by full-matrix least squares on F^2, using SHELXTL 5.1 program packages. In refinements were used weights according to the scheme $w=[\sigma^2(F_o^2)+(0.0954P)^2+0.0908P]^{-1}$ where $P=(F_o^2)+2F_c^2)/3$. The hydrogen atoms were located by geometrical calculations and refined using a 'riding' method. wR_2 was equal to 0.1530. The goodness of fit parameters S was 1.031. Largest difference between peak and hole was 0.245 and −0.229 eÅ^{-3}. Crystallographic data (excluding structure factors and including selected torsion angles) have been deposited with the Cambridge Crystallographic Data Centre, CCDC number 215142.

Acknowledgements

Thanks are due to Professors G. Gottarelli and G. P. Spada of our Department for very helpful discussions on the interpretation of the CD spectra. One of the authors (M.P.) thanks CINMPIS for a fellowship. Financial support was received from the University of Bologna (Funds for selected research topics 2001–2002 and RFO) and from MIUR-COFIN 2001, Rome (national project 'Stereoselection in Organic Synthesis').

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11. The indirect negative effect of the H-4 signal is a consequence of a relayed NOE.[10c] The occurrence of *J* coupled spins makes only one line of the H-4 doublet to be visible in the negative NOE.[10c]
12. The computed averaged distance between the methyl hydrogens and the hydrogen in position *peri* of the same naphthalene ring (H_8) is much too high (5.53 Å) to yield an observable NOE effect. This explains why no enhancement was observed for this hydrogen signal in the spectrum of the rotamer reported in trace c, to which structure *syn* must thus be assigned.
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17. When compound **1** is obtained by crystallization from solvents, different ratios were observed (using the same technique) depending, in a non-reproducible way, on the conditions employed. For instance the *anti*–*syn* ratios were in the range 2:1 to 3:1 when $CDCl_3$ was used and in the range 3.5:1 to 5:1 when toluene-d_8 was employed. Unfortunately we were unable to grow crystals suited for X-ray diffraction. We might speculate that the architecture of a single crystal would favor the *anti* conformer but, not having such a crystal available, the different ratios probably reflect the variable compositions of a disordered crystalline state. The erratic ratios obtained in these crystalline phases are at variance with that detected in the solid solution (obtained by melting) where the ratio was constantly 1:1.
18. In this case the experiment had to be carried out in toluene-d_8 at 600 MHz in order to have a sufficiently large separation between the *anti* and *syn* methyl signals to be irradiated (30.3 Hz).
19. When rapidly crystallized from solvents, compound **2** exhibits, initially, the same 1:1 ratio for the two conformers. Here too it was impossible to grow single crystals suited for X-ray diffraction.
20. The first order equation for an equilibrium process between A and B [$k_1/k_2=B/A$] has been used: $\ln(x_e-x)=\ln x_e-(k_1+k_2)t$.
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23. The same initial 3:1 ratio was also obtained when solid **4** was rapidly crystallized from a solution.
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Tetrahedron 60 (2004) 4459–4473
Tetrahedron

Chiral oxazoline route to enantiomerically pure biphenyls: magnesio and copper mediated asymmetric hetero- and homo-coupling reactions

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Received 17 October 2003; revised 16 January 2004; accepted 21 January 2004

Abstract—A series of chiral biphenyls were prepared via asymmetric reactions involving chiral oxazolines. One series of chiral biphenyls was reached by the magnesium mediated coupling of aryl bromides (via their Grignard reagents) with *o*-methoxyaryl oxazolines. In this case only the *o*-methoxy group was replaced by the ArMgBr. The initially formed biphenyl adducts were obtained in de's as high as 92:8. These adducts could be manipulated to various other chiral biphenyls. Another series of chiral biphenyls were obtained via an asymmetric Ullmann reaction, which was shown to be thermodynamically controlled. The de's of this copper mediated process were also in the range of 90% and could be utilized to reach various derivatives. Racemization, thermal stability, and atropisomerization characteristics were also studied.

1. Introduction

It has been 30 years, since we first introduced chiral oxazolines as valuable auxiliaries in asymmetric C–C bond forming reactions.[1] Since then there has been a large number of advances using oxazolines, and these have been summarized for chiral nucleophiles,[2,3] chiral electrophiles,[2,3] and chiral ligands.[3b,4]

Within the context of this special issue, we will describe our results leading to chiral, configurationally stable, biphenyls wherein the oxazoline has been a key component in the success leading to these goals. Although much of these studies were reported between 1992 and 1996 as short communications, further details, including atropisomerization and experimental procedures, are presented herein.

In 1975, we reported[5] that Grignard reagents displaced *o*-methoxy groups from aryl oxazolines **1** at or near room temperature (Scheme 1). When the Grignard reagent was derived from an aryl halide, good yields of the biphenyl **2** were obtained containing a variety of substituents.[6] This readily accessible route to biphenyl derivatives inspired us to examine the use of chiral oxazolines that may lead to chiral biphenyls **3**. In 1985, we reported[7] our first attempts to prepare non-racemic biphenyls (+)-**3**. Although they were obtained in generally good yields (60–95%), the de's varied widely between 0 and 92%. Nevertheless, much was learned regarding the nature and position of the aryl substituents. In 1990, we reported[8] the asymmetric total synthesis of (−)-schizandrin **5** (Scheme 2), a dibenzocyclooctane lignin utilizing the chiral 4-methoxymethyl-5-phenyloxazoline **6**. When this was coupled with the Grignard reagent derived from arylbromide **7**, methoxy displacement occurred giving the appropriate biphenyl in >97% de. This was ultimately taken on to the biphenyl lignin, (−)-**5**.

In a related study, we also earlier reported,[10] in brief form, the copper mediated Ullmann coupling of *o*-bromoaryloxazolines **8** to give symmetrically substituted biphenyls, **9**. This route to chiral biphenyls also proved to be both thermodynamically controlled as well as efficient (Scheme 3).

The two routes described above will be discussed in the following sections.

Keywords: Chiral biphenyls; Atropisomerism; Chiral oxazolines; Ullmann coupling; Grignard reagents.
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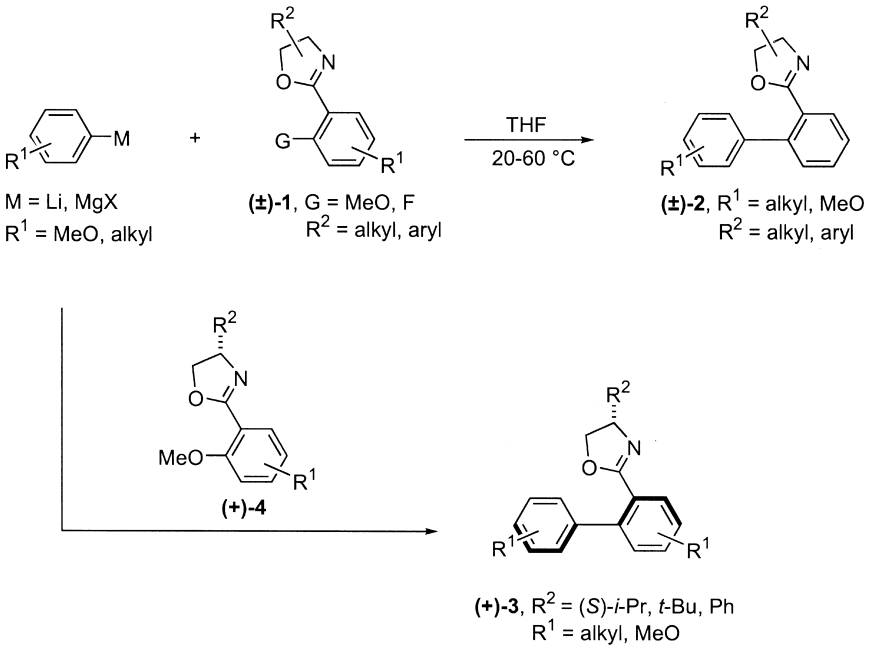
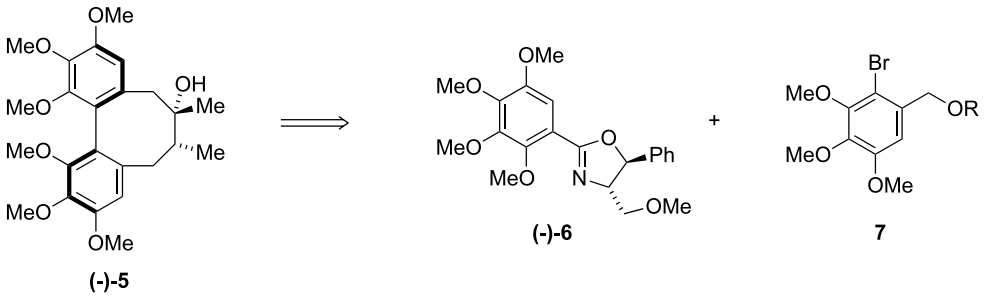
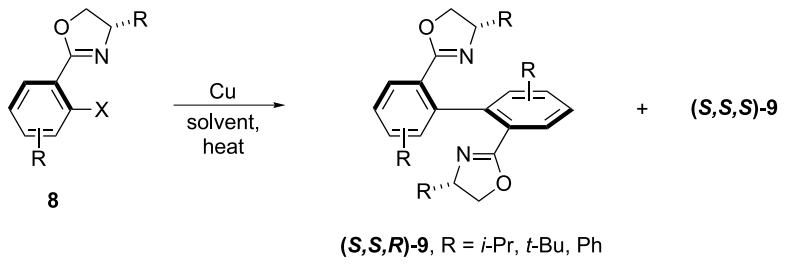
doi:10.1016/j.tet.2004.01.095



Scheme 1.



Scheme 2.



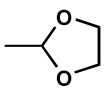
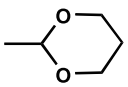
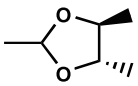
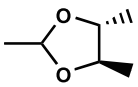
Scheme 3.

2. Magnesio-mediated couplings

As mentioned above in the Section 1, the aromatic nucleophilic displacement of MeO or F groups, *ortho* to the oxazoline group, produced high yields of biphenyls. In the asymmetric variant[7] of this reaction, we subsequently employed a less substituted chiral oxazoline, readily accessible from inexpensive amino acids, for example, valine. The latter was reduced[9] to valinol and transformed into the aryl oxazoline **10**. The aryl bromides **11**, prepared via known methods[11] from *m*-anisaldehyde, were converted into their respective magnesio derivatives using the entrainment method ($BrCH_2CH_2Br$)[12] and the oxazoline **10**, in THF, was added. At room temperature the nucleophilic substitution leading to **12** was very slow (6% after 21 h). At 65 °C, the methoxy displacement proceeded much faster, and the biphenyls were formed in 67–90% yields, with diastereomeric ratios of varying amounts (Table 1). Furthermore, a number of different substituents on the aryl bromide **11** gave, as expected, different ratios of diastereomeric biphenyls. Examining Table 1, it is immediately clear that, although the coupling yields are generally independent of the nature of R^1, the de's varied significantly (Scheme 4).

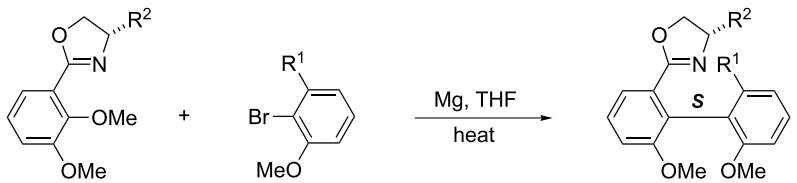
This effect by the substituent R^1 in **11** appeared to be dependent on the availability of the oxygen or oxygens to act as a ligand or a donor to the intermediate magnesium

Table 1. Variation of substituent on aryl Grignard 11 and the effect of stereoselectivity on **12**

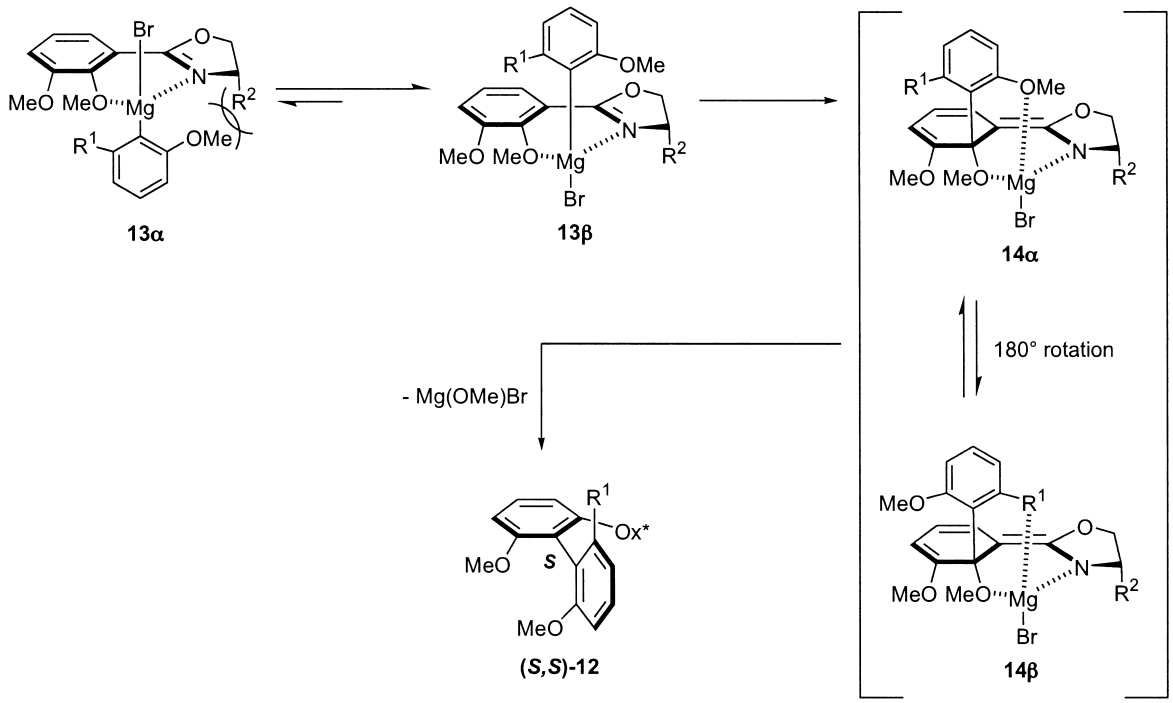
Entry	R^1 (**11**)	R^2	Biphenyl **12**	Yield (%)	Diastereomeric ratio (*S*: *R*)-**12**[a]
1		*i*-Pr	**12a**	90	20:80
2		*i*-Pr	**12b**	78	60:40
3		*i*-Pr	**12c**	79	32:68
4		*i*-Pr	**12d**	77	34:66
5	$CH_2OCH_2C_6H_5$	*i*-Pr	**12e**	80	42:58
6	CH_2OCH_3	*i*-Pr	**12f**	75	40:60
7	CH_3	*i*-Pr	**12g**	79	90:10
8	$CH_2OTBDMS$	*i*-Pr	**12h**	73	93:7
9	$CH_2OTBDMS$	*t*-Bu	**12i**	67	92:8
10	CH_2OTIPS	*t*-Bu	**12j**	70	93:7

[a] Refers only to axial configuration.

species **14A**, **14B** (Scheme 5). Thus, complexation by the oxygen atoms may control the stereochemistry of the biphenyl products, **12**. Since nucleophilic entry from the α-face (**13**α) may be hindered by the steric bulk of the pendant *i*-propyl or *t*-butyl (R^2) on the oxazoline ring, entry should occur predominantly from the β-face (**13B**). Free rotation around the newly formed σ intermediates (**14A**, **14B**), prior to elimination of the magnesium salt, may therefore be responsible for the *S* axial stereochemistry observed in the biphenyl **12**. It is, at this stage of the reaction, that steric and electronic effects of the substituents *ortho* to the magnesium come into the picture. If the σ intermediate **14A** rearomatizes with the *ortho*-methoxy group complexed to the magnesium (in place of solvent), the axial (*S*)-biphenyl will form. However, if the R^1 substituent also contains oxygen lone pairs, then **14B** may also be present at this stage of the reaction, and elimination of magnesium salt from **14B** will lead to the axial (*R*)-biphenyl. With this assumption in place, we found it readily explains the variations of de's with R^1 substituents in Table 1. The poor selectivities are seen in all cases (entries 1–6) where the oxygen lone pairs are accessible for complexing with the magnesium in **14B**, thus competing with **14A** for dominance in the formation of the σ intermediates. When R^1=Me, there is no possibility that **14B** will be present to any meaningful extent, thus the observed diastereomeric ratios are rather good (90:10)



Scheme 4.



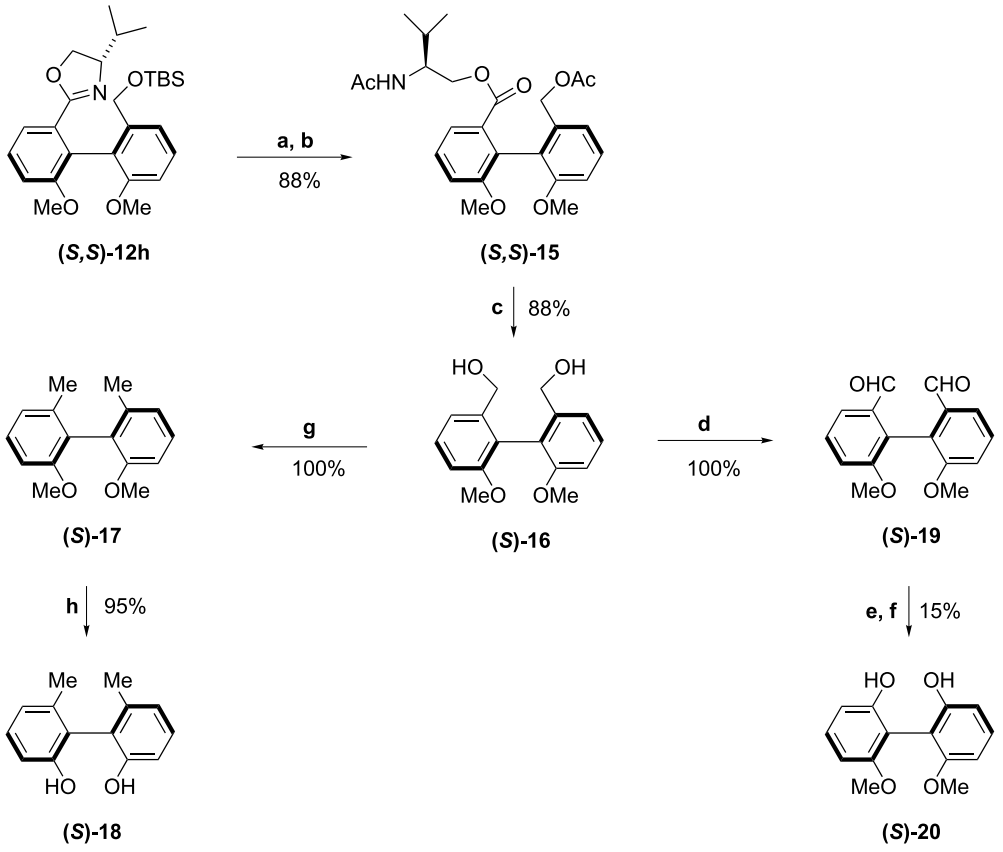
Scheme 5.

favoring axial (*S*)-**12**. The *S*,*S*-notation in **12** (Scheme 5) refers to oxazoline as well as axial stereochemistry. Additionally, in entries 8–10, the oxygen donating ability is diminished by the silicon atom, thus again favoring **14A** as the σ intermediate. Although the bulky siloxy substituents were originally introduced for steric effects in the transition state, it was found that the smaller methyl group (entry 7) was almost as effective in providing good axially chiral biphenyl ratios. Thus, the electronic effects (availability of lone pair on oxygen) in the magnesio-assisted couplings appear to be more important than the size of the substituent.

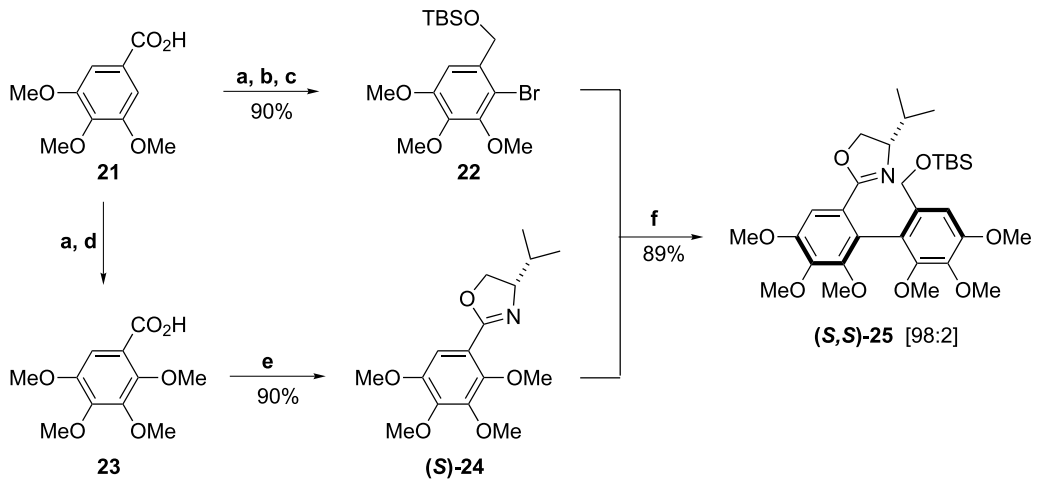
These results, using oxazolines derived from valinol or *t*-leucinol, **10** (R^2=*i*-Pr, *t*-Bu) agreed well with an earlier study[13] using a more substituted chiral oxazoline containing a methoxymethyl group (−)-**6**. Thus, the chelating methoxy group on the oxazoline ring appeared not to have any significant effect, that is, only the alkoxy groups on the aromatic ring (**14A**, **14B**) appeared to be important. Others[14] have drawn the same conclusion for the factors controlling the stereochemistry in these magnesium mediated couplings. The synthesis of these biphenyl oxazolines should contribute to the growing interest in various chiral C_2-symmetric and non-symmetric biphenyls that have more recently appeared in the literature.[3b,4]

In order to demonstrate the synthetic value of these biphenyl oxazolines **12**, a study was initiated to transform them into biphenyls containing other functional groups. It is important to note that by having four *ortho* substituents in **12**, the chances were high they could be synthetically manipulated without atropisomeric destruction of their stereochemical integrity. The transformation of (*S*,*S*)-**12h**, one of the better results presented in Table 1, was used as a typical example as shown in Scheme 6. Thus, the biphenyl (*S*,*S*)-**12h**, purified by radial chromatography[15] to remove the 6–7% of the *SR* diastereomer (Table 1), was converted into the stable diester amide (*S*,*S*)-**15** with aqueous trifluoroacetic acid followed by acetylation of the intermediate ammonium salt with acetic anhydride. Reduction of **15** with lithium aluminum hydride furnished the biscarbinol (*S*)-**16** as a single enantiomer. This was confirmed by the ^{1}H NMR spectrum of the Mosher ester and compared with the spectrum of the racemic Mosher ester.[16]

It is noteworthy that (*S*)-**16** was totally stable toward atropisomerization (racemization) showing no change in $[\alpha]_D$ after 5 days at room temperature. This is undoubtedly due to the two sp^3 carbons in the *ortho* positions. Oxidation[17] of the biscarbinol **16** gave the dialdehyde (*S*)-**19** in quantitative yield. This material was unstable to racemization and, after heating at 90 °C for 24–30 h, lost all of its $[\alpha]_D$ value. However, it was quite stable to racemization under milder conditions (room temperature). The transformation to the bisphenol (*S*)-**20** was accomplished in moderate yield (15%) via Baeyer–Villiger oxidation. The racemization of the dimethoxy bisphenol **20** was also examined and appeared to be stable at room temperature, but racemized readily at 64 °C (THF) after 48 h. The poor conversion in the Baeyer–Villiger oxidation of (*S*)-**19** to (*S*)-**20** may be due to the poor migratory



Scheme 6. (a) Na_2SO_4, TFA, THF, H_2O; (b) Ac_2O, pyridine, DCM; (c) LAH, THF; (d) CrO_3, pyridine, DCM; (e) MCPBA, $NaHCO_3$, DCM; (f) K_2CO_3, MeOH, H_2O; (g) Pd/C (10%). H_2, TFA, MeOH; (h) BBr_3, DCM.



Scheme 7. (a) Br_2 (Ref. 19); (b) $NaBH_4$, $ZrCl_4$; (c) TBSCI, TEA; (d) NaOMe, Cu (Ref. 19); (e) $COCl_2$, (*S*)-valinol; $SOCl_2$; K_2CO_3; (f) Mg, $BrCH_2CH_2Br$, heat.

aptitude of the *m*-methoxyphenyl unit. The lack of sufficient electron-density at the migrating center allows the hydrogen to shift preferentially. This result is quite consistent with earlier reports[25] of benzaldehyde derivatives where the aryl ring is a poor competitor to the H in Baeyer–Villiger reactions.

To overcome the poor yield of bisphenol **20** which would make a potentially useful new chiral ligand, we found that the benzylic hydroxy groups in (*S*)-**16** were readily hydrogenolyzed. Using Pd-charcoal in 2–5% TFA in ethanol, the hydrogenolysis proceeds under a balloon of hydrogen to afford the dimethylbiphenyl (*S*)-**17** in quantitative yield. The desired bisphenol (*S*)-**18** was obtained in 95% yield after methoxyl cleavage of (*S*)-**17** with BBr_3. The latter was stable at room temperature toward racemization. Upon heating (*S*)-**18** at 110 °C (toluene) for 9 h, no racemization was observed. However, heating to 140 °C (xylene) for 24 h caused the loss of half the optical activity.

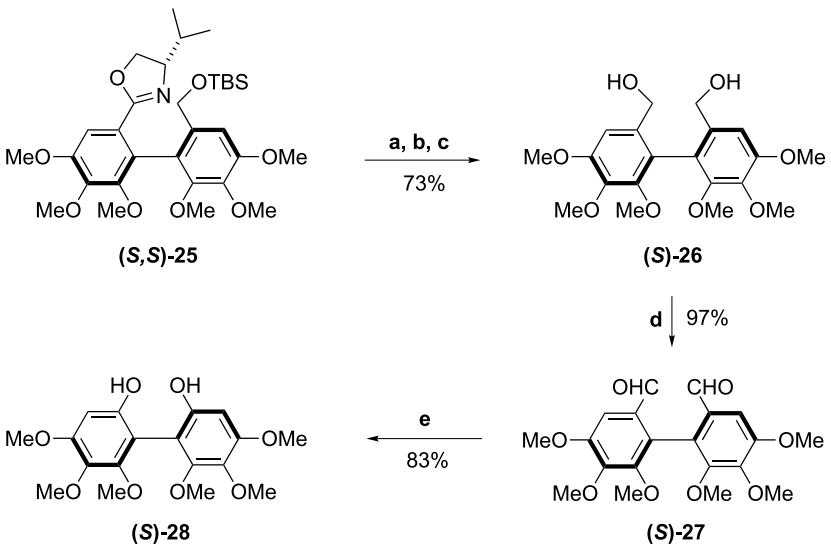
Since (*S*)-**18** has been previously reported[18] via classical resolution, we were able to assign absolute configuration of **18** as *S*, which was expected based on our assumed mechanism in Scheme 5. It should be noted that no axial racemization was detectable during the sequence from **12** to **18**. Based on the above, the major diastereomer formed via the magnesium coupling to **12** must be *S* for the oxazoline stereocenter and *S* for the axial portion of the molecule. Furthermore, we were able to prepare multigram quantities of (*S*)-**18**, enantiomerically pure, and in 50–55% overall yield from **10**. This compares with the 15% overall yield for **18** reported earlier[18] using a combination of Ullmann coupling and resolution.

Another closely related series of chiral, non-racemic biphenyls were also reached by a sequence similar to that described above. In the event, the trimethoxy benzene **22** was coupled via its Grignard reagent to the tetramethoxyphenyloxazoline (*S*)-**24**[19] to give an excellent ratio of axially diastereomeric biphenyls (*S*,*S*)-**25** and (*S*,*R*)-**25** as a 98:2 mixture in 89% yield[20] (Scheme 7).

In a similar fashion, the synthesis of the C_2-symmetric hexamethoxy bisphenol (*S*)-**28** was prepared (Scheme 8). Thus, the biphenyl oxazoline (*S*,*S*)-**25** was transformed into the bisbenzyl alcohol (*S*)-**26**, which proceeded via oxidation with oxalyl chloride/DMSO to the bisbiphenylaldehyde, **27**. Studies were initiated on the atropisomerization of both the dibenzyl alcohol **26**[8] and the biphenyl diol **28**. The latter was smoothly prepared by a Baeyer–Villiger oxidation of the aldehyde **27** in 83%, a significant improvement over the aldehyde oxidation to the diol, (*S*)-**20**. The reason for the hexamethoxy biphenylaldehyde **27** proceeding much more efficiently than the earlier described dimethoxy derivative **19** may be due to the higher electron density in the trimethoxybenzene, which would make the aryl group the preferred migratory group over the weakly nucleophilic *m*-methoxy phenyl moiety (in **19**).

The atropisomerization of both the biscarbinol **26** and the bisphenol **28** were examined and the rates of racemization determined by heating and plotting changes in the $[\alpha]_D$ values. As expected, **26** was stable for months at room temperature as indicated by no change in the $[\alpha]_D$ value. When heated in tetrahydrofuran (66 °C) for 72 h, there was also no measurable change in $[\alpha]_D$. Once again, the two *o*-substituents containing sp^3 carbons was considered to be the factor responsible for this stability. However, when **28** was heated to reflux (66 °C) in THF, racemization appeared to begin after several minutes. The original $[\alpha]_D$ of 48.9 (2.3 $CHCl_3$) began to linearly decrease in value until after 60 h of heating, the $[\alpha]_D$ had decreased to 24–25 (2.3 $CHCl_3$). Thus, half of the enantiomeric purity dropped in 60 h. When **28** was heated at 110 °C (toluene), half of its $[\alpha]_D$ had dropped after only 1 h. At room temperature, however, **28** was found to be stable for at least three months.

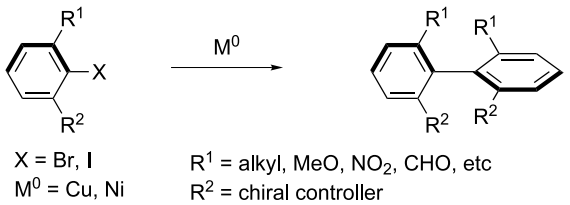
Finally, it should be stated that the use of valinol to convert the benzoic acid **23** into the oxazoline (*S*)-**24** (Scheme 7) appeared to possess optimal characteristics. First of all, the use of *tert*-leucinol, which would have provided the 4-*t*-butyl group in place of the 4-isopropyl group, was found to be insignificantly more efficient in the magnesio coupling step to **25** (98:2 for *t*-Bu vs 97:3 for *i*-Pr, Table 1, entries 9 and 10). Secondly, the very high cost of *tert*-leucine, as the precursor to *t*-leucinol, did not justify its use for the relatively small difference in the observed diastereoselectivity.



Scheme 8. (a) TFA, Na_2SO_4, THF, H_2O; (b) Ac_2O, pyridine, DCM; (c) LAH, THF; (d) oxalyl chloride, DMSO, Et_3N; (e) MCPBA, $NaHCO_3$, DCM.

3. Ullmann couplings

The Ullmann reaction, known[21] since 1901, has attracted the attention of many investigators trying to prepare chiral biphenyls. The requirement for maintaining enantiomeric integrity involves having at least 3 groups in the *ortho* positions adjacent to the aryl–aryl bond.[22a,b] These would be necessary to inhibit rotation of the aryl–aryl bond and allow atropisomers to be isolated. The degree of stability in these systems would, of course, depend on the nature of the *ortho* substituents when this asymmetric Ullman coupling, shown in Scheme 9,[23] was carried out.

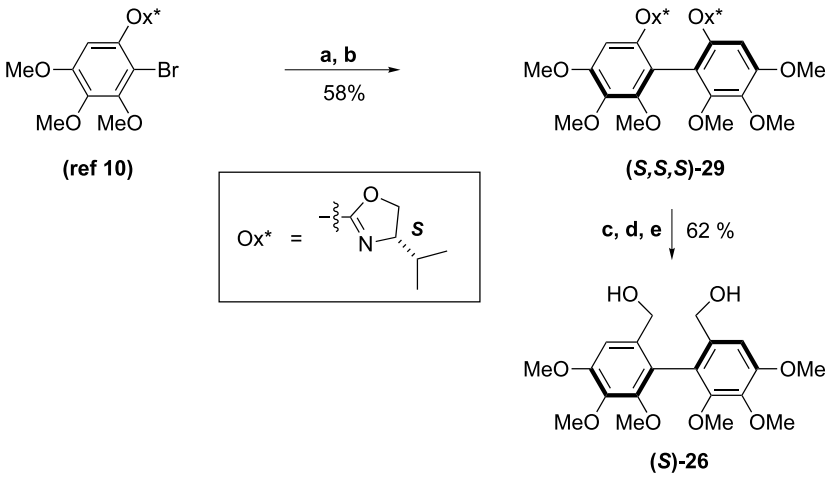


Scheme 9.

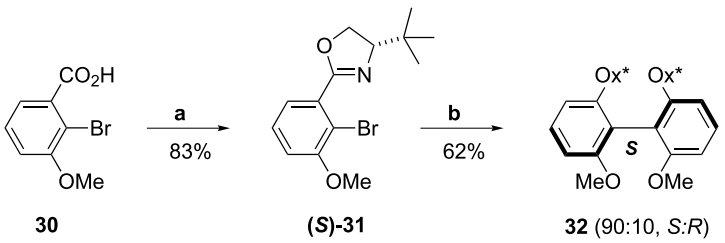
Using a chiral oxazoline as the chiral control element, there had been only one other report of an asymmetric Ullmann in the literature.[24] We performed the Ullmann reaction of an aryl oxazoline[10] involving the copper mediated coupling in DMF for 24 h at 110 °C. The biphenyl, **29**,[10] obtained in 58–60% yield, showed an axial diastereomeric ratio of *SSS* to *SSR* of 94:6 (Scheme 10).

After isolation of the biphenyl (*SSS*)-**29**, the product was transformed into the previously prepared bisbenzyl alcohol (*S*)-**26** and then to the previously prepared bisaldehyde **27** and bisphenol **28** (Scheme 8). In all cases, the compounds prepared from the Ullmann route were identical to those prepared by the magnesium mediated coupling in Scheme 8.

There has, in the past few years, been a number of reports utilizing the above chiral Ullmann couplings, and the stereochemical results obtained by these investigators were variable leading some to separate the oxazoline biphenyls into single diastereomers.[26] Further studies will need to be performed to asses the effects of the substituents on the de observed in the biphenyl. A study done in this laboratory



Scheme 10. Cu, DMF, heat; (b) trituration from Et_2O/hexanes; (c) TFA, Na_2SO_4, THF, H_2O; (d) Ac_2O, pyridine, DCM; (e) LAH, THF.



Scheme 11. (a) Oxalyl chloride, DMF, *t*-leucinol, $SOCl_2$; (b) Cu powder, DMF, 72 h, reflux.

involving only one methoxy group (Scheme 11), rather than the three seen in Scheme 10, gave the biphenyl **32** as a 95:5 mixture of diastereomers in 62% yield. The *S*-axial-diastereomer was again the major product. It should be noted that the copper coupling in Scheme 11 was carried out on the 4-*t*-butyloxazoline (*S*)-**31** derived from *t*-leucinol and 2-bromo-3-methoxybenzoic acid **30**. The added bulk on the oxazoline chiral controlling group, may also have had an effect on the de of the product. This is perhaps due to the intermediate copper species forcing the two aromatic rings into close proximity. In this case, *t*-butyl may be more selective than *i*-propyl. A similar result was previously observed[27] in the coupling of naphthalene oxazolines.

The most interesting aspect of the Ullmann coupling involving chiral aryloxazoline halides is the course of the reaction. In Scheme 10, the coupling of (*S*)-2-bromo-3,4,5-trimethoxyphenyloxazoline to *S*-**29** was time dependant with regard to the % de observed (Fig. 1). In order to demonstrate that a thermodynamically controlled resolution was responsible for the observed final diastereoselectivity of **29** (93:7),[10] the diastereomeric ratio of the two atropisomers was monitored over 160 h.

Thus, a mixture containing bromotrimethoxyoxazoline,[10] dry DMF, and copper powder[28] was heated to reflux and aliquots of the mixture were examined at different time periods. After work-up, NMR examination of the diastereotopic isopropyl resonances in **29**[10] afforded a measure (±3%) of the diastereoselectivity for the process. For a more accurate measure of diastereoselectivity, the crude bisoxazoline mixtures were transformed in a three-step process (Scheme 10) to the dicarbinol **26**, which was assayed by chiral high performance liquid chromatography (HPLC).[29] Comparison of the de of **29** (via NMR spectroscopy) and HPLC of **26** showed them to be virtually identical. It can be seen from Figure 1 that after 1 h, the de of **29** was poor (62:38), indicating that there is a slight preference for the (*SSS*)-stereochemistry, even in the early stages. Continuing the heating of the DMF–Cu mixture containing the bromooxazoline afforded higher ratios of atropisomers with increasing time, until, after 60 h, the mixture (*SSS*)93:(*SSR*)7, remained constant.

The equilibrium noted above may accurately referred be to as a first-order asymmetric transformation[30a] or a dynamic resolution.[30b] This involves establishing an equilibrium between the two diastereomers (*SSS*-**29**, *SSR*-**29**) such that the undesired one would be converted into the other under specified reaction conditions. In this manner, rather than obtain a 50% yield of enantiomerically pure product from classical or kinetic resolution, the theoretical yield would be

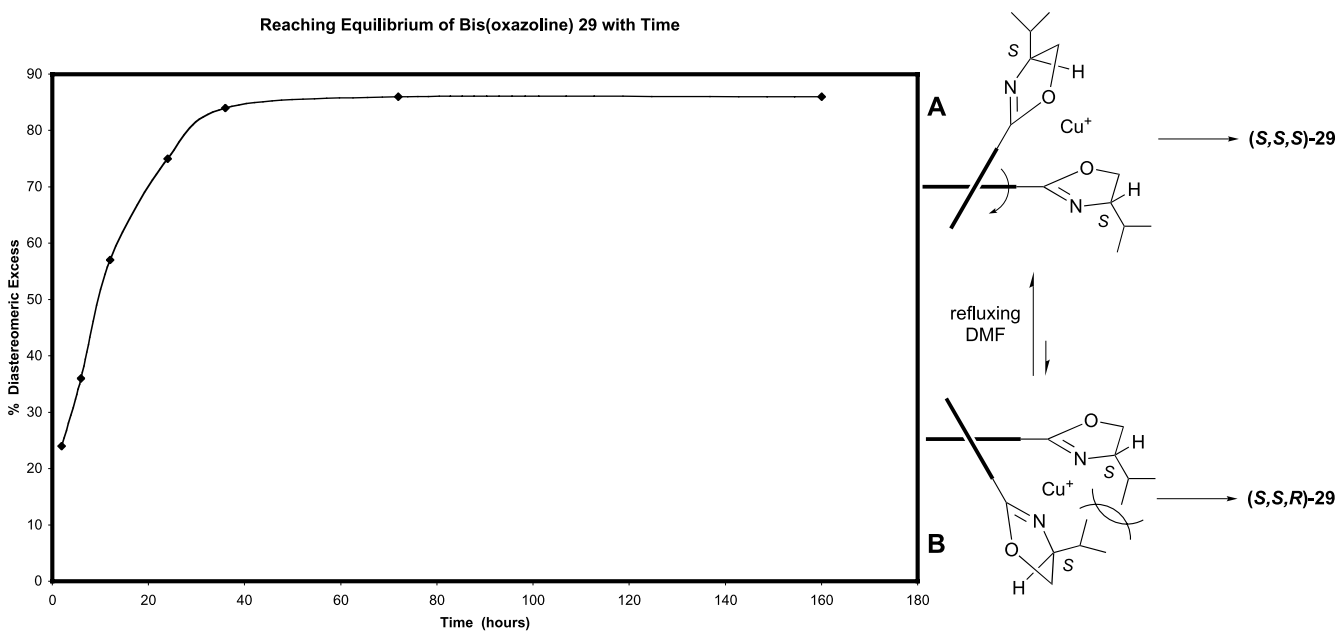


Figure 1.

100%. In other words, a 1:1 mixture would be potentially converted to a diastereomerically enriched or pure product under the equilibrating conditions. The results of heating the bisoxazoline **29** such that it changed from a 2:1 ratio to the final 13:1 ratio of *SSS* over *SSR* is clearly an example of this behavior.

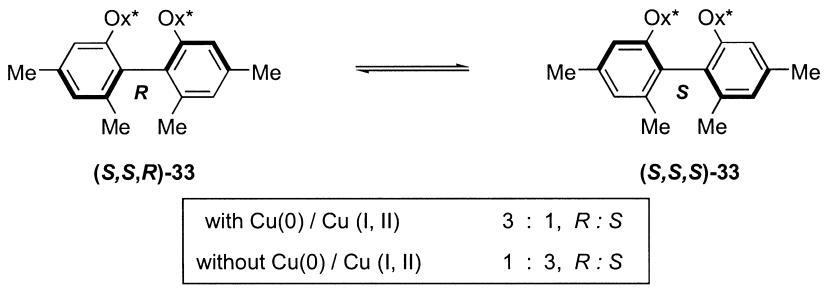
The factors responsible for this reasonably effective first order asymmetric synthesis can be presented with some degree of confidence. First, although the biaryl **29** is tetrasubstituted about the chiral axis, under the heated reaction conditions (refluxing DMF), rotation is still possible about the biaryl axis. Second, the final diastereomeric ratio may be the result of chelation control utilizing a Cu(I),[31] Cu(II),[32] or Cu(III)[26b] species **A**, **B** (Fig. 1) under equilibrating conditions. Thus, although only a small diastereomeric excess was initially observed, the ratio increased steadily until equilibrium for this process was established. The diastereomeric Cu complexes **A**, **B** indicate how the copper might be complexed between the two oxazoline moieties. Severe non-bonded interactions between the isopropyl groups in **B** result in the equilibrium being favored to lie towards **A**, which then led to (*SSS*)-**29**.

In a further attempt to assess the role of the copper species in this equilibration behavior, a 3:1 mixture of biphenyl oxazolines **33** (75% *SSR*, 25% *SSS*) was obtained from the corresponding bromooxazolines.[33] The mixture was heated in DMF (160 °C) for 2 days in the absence of any copper catalyst and slowly changed to the diastereomer (*SSR*:*SSS*, 3:1). On the other hand, when Cu(I) and (II) were added to the above 3:1 mixture and heated for 2 days, no change from the *SSR*:*SSS*, 3:1 starting mixture occurred. (The absolute configuration assignments at the biphenyl axis have changed due to priority of the methyl groups in **33** vs the methoxyl in **29**.) These results clearly support the Cu chelation shown in Figure 1 (Scheme 12). In the absence of Cu, there is transformation to the thermodynamically more favored biaryl-*S* axis, albeit by 3:1. However, when Cu(I, II, or III) is involved, it can bring together, in close proximity, the two oxazoline rings (**B**), which would otherwise be further apart with minimum non-bonded interactions. Thus, there is, under the conditions given, a 6:1 turnaround in the stereochemistry of **33** in the presence or absence of a chelated metal.[34] Recently, Wulff,[35] Andrus,[36] and Ikeda[37] have noted the importance of Cu species in affecting the stereochemical ratios of biphenyl oxazolines with regard to the deracemization, stereochemical integrity, and catalytic efficiency.

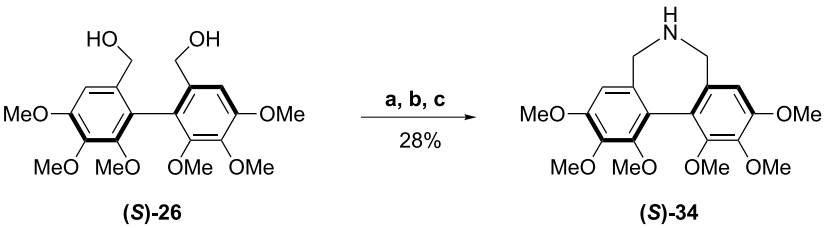
To further demonstrate how acquisition of chiral biphenyl oxazolines could serve as precursors to other axially chiral biphenyl derivatives, we examined some routes to the dibenzoazepine, **34** (Scheme 13). The latter systems have been prepared earlier by Hawkins.[38] By using the previously prepared bisbenzyl alcohol (*S*)-**26**, we utilized the Hawkins route to prepare dibenzoazepine **34**. The product was formed, albeit in 28% yield. More significantly, however, was the fact that there was no observable atropisomerization (racemization) of **34** after refluxing in THF for 12 h.

This was performed by periodically monitoring the optical rotation ($[\alpha]_D=-46.3$[2.0 CH_2Cl_2]), which held constant. The secondary amine **34** could also be converted, by known means to the tertiary amine **35** ($R^1=R^2=OMe$) or the latter could be directly prepared from the bisaldehyde **27** (Scheme 14) by reductive amination in excellent yield.[39] Similarly, the bisaldehyde **19** was transformed into the corresponding dibenzoazepine **35** ($R^1=R^2=H$). The above sequence is another example of the products from the asymmetric coupling being obtained in high enantiomeric purity when the coupling is carried out under substrate dependent conditions.[40]

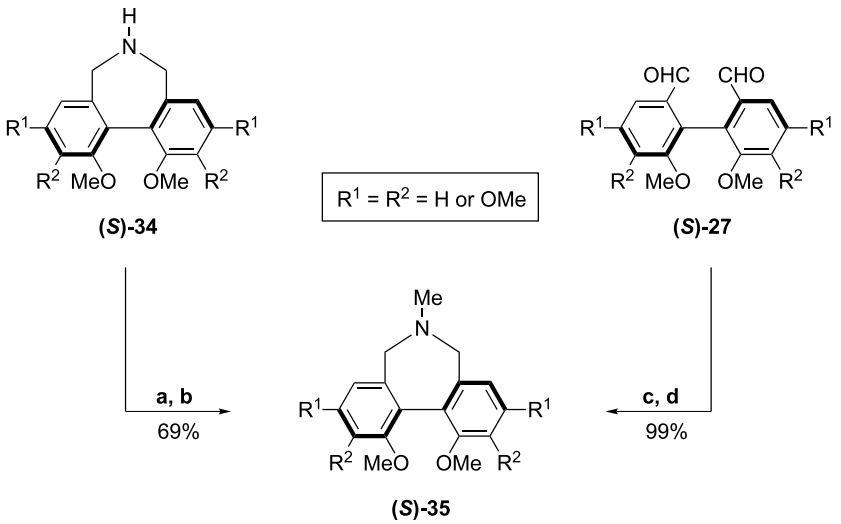
Finally, it should be stated that the chiral bisphenol **28** has been shown to be a rather useful ligand for $LiAlH_4$ reductions of various ketones.[41] Furthermore, bisphenol **18** prepared in high enantiomeric purity via the magnesio-mediated coupling (Scheme 6) has already been reported by



Scheme 12.



Scheme 13. (a) PBr_3; (b) trifluoroacetamide; (c) K_2CO_3.



Scheme 14. (a) Ethyl formate; (b) LAH; (c) $MeNH_2$·HCl; (d) $NaBH_3CN$.

Suda[42] to also serve as an efficient chiral ligand for hydride reductions of prochiral ketones. The bisphenol used in the latter work was prepared by resolution of the racemic 2,2′-dihydroxy-6,6′-dimethyl biphenyl.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 300 or 400 MHz and data were reported as follows: chemical shifts, in parts per million referenced to the internal chloroform ($CHCl_3$). ^{13}C NMR spectra were recorded at 75 or 100 MHz, with chemical shifts referenced to the central peak of the $CDCl_3$ triplet (77.0 ppm). Infrared absorption spectra were recorded on a Perkin–Elmer model PE 1600 spectrophotometer. Low resolution mass spectra (GC-MS) were obtained with a Hewlett–Packard model 5890 instrument equipped with a Hewlett–Packard 5970B mass selective detector (ionization potential 70 eV). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, Georgia. Optical rotations were determined with a Rudolph Research Autopol III instrument and were referenced to the sodium D line (598 nm). Melting points were measured in open Pyrex capillary tubes and are uncorrected. High performance liquid chromatography (HPLC) was performed with Regis Pirkle Covalent and Characil OD chiral columns. Thin layer chromatography (TLC) and flash chromatography were performed with E. Merck or Amicon Matrix silica gel (230–400 mesh), (60 Å). TLCs of compounds were visualized by UV light (254 nm), or by using potassium permanganate or vanillin stain.

All nonaqueous reactions were conducted under an argon atmosphere in a flame dried apparatus. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Concentrations were performed under reduced pressure with a rotary evaporator.

Solvents were dried according to established protocols by distillation under argon from an appropriate drying agent. Dichloromethane, benzene, toluene, triethylamine, diisopropylamine, and acetonitrile were dried via distillation from calcium hydride and maintained under an inert atmosphere (Ar or N_2). Tetrahydrofuran and diethyl ether were dried via distillation from sodium benzophenone ketyl, and maintained under an inert atmosphere. Pyridine was distilled from calcium hydride and stored over 4 Å molecular sieves. Dimethylsulfide, packaged under nitrogen in 1 L Sure/Seal bottles, was purchased from Aldrich.

4.2. 2-(2,3-Dimethoxyphenyl)-4-i-propyloxazoline (10) R^2=i-Pr)

Oxalyl chloride (1.91 g, 15 mmol) was added to a solution of 2,3-dimethoxybenzoic acid (1.82 g, 10 mmol) in CH_2Cl_2 (25 mL) at room temperature. Five drops of DMF were added, causing effervescence. After stirring for 3 h, the volatiles were removed in vacuo. The crude yellow acid chloride was dissolved in CH_2Cl_2 (20 mL) and added to a stirred solution of (*S*)-valinol (1.13 g, 11 mmol) and triethylamine (1.21 g, 12 mmol) in CH_2Cl_2 (20 mL) at 0 °C over 30 min. Stirring was continued for another 8 h, and the reaction was quenched with 1 N HCl and extracted from the mixture with CH_2Cl_2 (3×50 mL). The organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude intermediate amide was dissolved in CH_2Cl_2 (30 mL) and $SOCl_2$ (2.9 mL, 40 mmol) was added dropwise. Stirring was continued until effervescence ceased, and the mixture was poured into a 2 N NaOH solution. Extraction with CH_2Cl_2, drying (Na_2SO_4), and concentration under reduced pressure, gave the oxazoline **10** as a yellow oil (2.1 g, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, 3H, J=6.8 Hz), 1.29 (d, 3H, J=6.8 Hz) 2.15 (octet, 1H, J=6.8 Hz), 4.13 (s, 3H), 4.25 (s, 3H), 4.30–4.41 (m, 2H), 4.60–4.75 (m, 1H), 7.25–7.36 (m, 2H), 7.65 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 16.8, 17.2, 31.8, 54.5, 59.8, 68.5, 71.2, 112.5, 120.4, 121.9, 122.9, 147.2, 151.9, 160.7.

4.2.1. 2-Bromo-3-methoxybenzaldehyde (11) (R^1=CHO).

n-BuLi (31 mmol, 1.6 N solution in hexanes)

was added to a solution of *N*,*N*′, *N*′-trimethylenediamine[11] (4.2 mL, 33 mmol) in toluene (60 mL) at 0 °C. After 15 min at room temperature, *m*-anisaldehyde (3.7 mL, 30 mmol) was added. The mixture was stirred at room temperature for 15 min and phenyllithium (50 mL of a 1.8 M solution in cyclohexane/ether, (Aldrich) 90 mmol) was added while maintaining room temperature. The solution was stirred at room temperature for 8 h. While cooling the mixture to −78 °C, THF (60 mL) was added. 1,2-Dibromotetrafluoroethane (22 mL, 180 mmol) was added dropwise at −78 °C. The mixture was allowed to warm to room temperature and poured into a cold 10% HCl solution (150 mL) and extracted with toluene (2×100 mL). The combined organic layers were dried over $MgSO_4$. Concentration of the organic layer under reduced pressure, gave a yellow oil, which was purified by column chromatography to afford **11** as a crystalline compound (6.2 g, 96%). Mp: 67.5–68.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.95 (s, 3H), 7.13 (dd, 1H), 7.38 (m, 1H), 7.53 (dd, 1H), 10.4 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 56.91, 117.16, 117.38, 121.67, 128.58, 135.04, 156.52, 192.52.

4.3. General procedure biphenyl 12a–12j (Table 1)

A mixture of aryl bromide **11a**–**11j**[11] (1 mmol) and Mg turnings (2 mmol) in THF (5 mL) was heated at reflux and treated dropwise with a solution of 1,2-dibromoethane (1.3 mmol) in THF (1 mL). A vigorous reaction was observed. The mixture was heated for 1–2 h (the formation of the Grignard reagent was followed by GC) and cooled to room temperature. A solution of oxazoline **10a** (R^2=*i*-Pr 0.6 mmol) in THF (4 mL) was added. The reaction mixture was heated at reflux for 5–18 h and quenched with saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with ether (2×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford biphenyl **12a**–**12j** as a mixture of diastereomers. The crude biphenyl was purified by radial chromatography (SiO_2; hexanes/EtOAc). A typical example is described below.

4.3.1. Biphenyl (*S*,*S*)-12h. A mixture of aryl bromide **11h** (3.0 g, 9.1 mmol) and Mg turnings (0.44 g, 18 mmol) in THF (25 mL) was heated at reflux and treated dropwise with a solution of 1,2-dibromoethane (1.0 mL, 11.8 mmol) in THF (4 mL) over 30 min. A vigorous reaction was observed. The mixture was heated at reflux for 1 h after which all Mg had reacted. The solution was cooled to room temperature, and a solution of oxazoline **10a** (R=*i*-Pr, 1.37 g, 5.5 mmol) in THF (10 mL) was added. The reaction mixture was stirred overnight at room temperature, poured into an aqueous saturated NH_4Cl solution (40 mL) and extracted with ether (2×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford a yellow oil. The crude product, consisting of a mixture of diastereomers (93:7) was purified by radial chromatography to remove a trace of the minor isomer (SiO_2; hexanes/EtOAc 9:1 to 4:1). Biphenyl (*S*,*S*)-**12h** was isolated as a colorless oil (1.89 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.05 (s, 6H), 0.71 (d, *J*=6.7 Hz, 3H), 0.75 (d, *J*=6.7 Hz, 3H), 0.86 (s, 9H), 1.50 (septet, *J*=6.7 Hz, 1H), 3.62 (s, 3H), 3.69 (s, 3H), 3.61–3.99 (m, 3H), 4.36 (dd, *J*=14 Hz, 2H), 6.77 (d, *J*=8.0 Hz, 1H), 7.02 (d, *J*=8.1 Hz, 1H), 7.18–7.43 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.85, −5.47, 18.18, 18.31, 18.54, 25.91, 32.69, 55.76, 62.74, 70.03, 72.49, 108.93, 112.72, 117.56, 121.82, 122.93, 125.15, 127.96, 128.36, 130.32, 141.55, 156.45, 156.82, 163.68.

4.3.2. Diester amide (*S*,*S*)-15. A solution of biphenyl oxazoline (*S*,*S*)-**12h** (1.77 g, 3.77 mmol) in THF (40 mL) was treated with Na_2SO_4 (27 g, 0.19 mol), water (3.4 mL, 19 mmol) and trifluoroacetic acid (1.46 mL, 19 mmol). The suspension was stirred at room temperature for 18 h. Anhydrous Na_2SO_4 (7.5 g) was then added. The solids were filtered and washed with THF (30 mL). The filtrate was concentrated in vacuo at a bath temperature not to exceed 25 °C. The remaining ammonium salt was dissolved in CH_2Cl_2 (70 mL) and cooled to 0 °C. Acetic anhydride (12.9 mL, 0.14 mmol) and pyridine (20.2 mL, 0.25 mol) were added, and the solution was allowed to warm to room temperature. The mixture was washed with cold 3 N HCl (3×100 mL), followed by a saturated aqueous $NaHCO_3$ solution (100 mL). After drying over Na_2SO_4, the solvent was removed in vacuo, and the residue was purified by radial chromatography (SiO_2; hexanes/EtOAc 9:1 to 1:1) to afford the diester amide **15** as a colorless oil (1.52 g, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.72 (d, *J*=6.8 Hz, 3H), 0.77 (d, *J*=6.8 Hz, 3H), 0.99 (m, *J*=6.8 Hz, 1H), 1.88 (s, 3H), 1.92 (s, 3H), 3.68 (s, 3H), 3.61–3.71 (m, 1H), 3.71 (s, 3H), 3.92 (dd, *J*=3.0 Hz, *J*=11.7 Hz, 1H), 4.22 (dd, *J*=3.0 Hz, *J*=11.7 Hz, 1H), 4.73 (dd, *J*=12.7 Hz, 2H), 5.19 (d, *J*=9.3 Hz, 1H), 6.91 (d, *J*=8.2 Hz, 1H), 7.04–7.11 (m, 2H), 7.30–7.42 (m, 3H), 7.64 (d, *J*=7.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.20, 19.53, 20.73, 23.09, 27.77, 53.04, 55.60, 56.05, 64.45, 65.55, 110.46, 114.60, 119.96, 123.21, 124.54, 126.19, 128.24, 128.00, 132.42, 132.62, 156.83, 156.89, 167.80, 169.60, 170.63.

4.3.3. (*S*)-2,2′-(Dihydroxymethyl)-6,6′-dimethoxy-1,1′-biphenyl (16). A solution of diester amide (*S*,*S*)-**15** (1.56 g, 3.41 mmol) in THF (60 mL) was cooled to 0 °C, and a solution of $LiAlH_4$ in THF (10.2 mL of a 1.0 M solution) was added. The mixture was allowed to warm to room temperature and stirred for 2 h. To the mixture was added was Na_2SO_4, $10H_2O$ (2.0 g), 1.0 mL of an aqueous 40% NaOH solution, anhydrous Na_2SO_4 (4.0 g), and the mixture was stirred for 6 h. The salts were filtered and washed with THF, and the filtrate was concentrated in vacuo to afford an oil that crystallized on standing. The product was purified by radial chromatography (SiO_2; hexanes/EtOAc 9:1) to yield **16** as a colorless crystalline compound (0.82 g, 88%). $[\alpha]_D$=−96.5 (*c*=1.00, $CHCl_3$). Mp 136–136.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64 (s, 2H), 3.67 (s, 6H), 4.19 (dd, *J*=11.7 Hz, 2H), 6.93 (dd, *J*=8.2 Hz, 2H), 7.13 (d, *J*=7.5 Hz), 7.37 (t, *J*=7.9 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.87, 63.27, 110.63, 121.79, 124.23, 129.12, 140.91, 156.63.

4.3.4. (*S*)-2,2′-(Dimethyl)-6,6′-dimethoxy-1,1′-biphenyl (17). A suspension of biscarbinol (*S*)-**16** (0.18 g, 0.65 mmol), $Pd(OH)_2$ (20 mg) and trifluoro-acetic acid (5 drops) in EtOH (abs. 10 mL) was stirred under an atmosphere of hydrogen (balloon). After stirring for 36 h, the catalyst was removed by filtration, and the solvent was removed in vacuo. The crude product was purified using

radial chromatography (SiO_2; hexanes/EtOAc 6:1) to yield **17** as a colorless solid in quantitative yield (0.157 g). $[\alpha]_D$=7−53.0 (c=1.00, $CHCl_3$). Mp 85.9–86.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95 (s, 6H), 3.70 (s, 6H), 6.82 (d, J=8.2 Hz, 2H), 6.91 (d, J=7.5 Hz, 2H), 7.24 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.56, 55.77, 108.31, 122.19, 126.19, 127.87, 138.18, 156.93.

4.3.5. 2,2′-(Dihydroxyl)-6,6′-dimethyl-1,1′-biphenyl (18). A solution of dimethoxybiphenyl (*S*)-**17** (0.245 g, 1.01 mmol) in CH_2Cl_2 (4–6 mL) was cooled to −78 °C, and BBr_3 (0.57 g, 2.26 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was carefully poured into ice water, stirred for 30 min, saturated with NaCl and extracted with CH_2Cl_2. Drying (Na_2SO_4) and evaporation of the solvent in vacuo yielded the bisphenol **18** as a colorless crystalline compound (0.206 g, 95%. $[\alpha]_D$=−60.5 (c=1.00, $CHCl_3$). Mp 159–160 °C (lit. 159–160 °C).[18] ^{1}H NMR (300 MHz, $CDCL_3$): δ 1.99 (s, 6H), 4.66 (s, 2H), 6.86–6.92 (m, 4H), 7.21–7.27 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.49, 113.16, 119.49, 122.62, 130.15, 138.94, 154.81.

4.3.6. (*S*)-2,2′-(Diformyl)-6,6′-dimethoxy-1,1′-biphenyl (19). Chromium trioxide (0.54 g, 5.4 mmol) was added to a solution of pyridine (0.85 g, 10.8 mmol) in CH_2Cl_2 (15 mL). The solution was stirred for 15 min, and a solution of biscarbinol (*S*)-**16** in CH_2Cl_2 (10 mL) was added. A black deposit formed. After stirring for 15 min, the solution was decanted from the deposit that was washed twice with CH_2Cl_2. The combined organic layers were washed with 5% NaOH solution (3×100 mL), 5% HCl solution (3×100 mL), 5% $NaHCO_3$ solution (100 mL), and brine (100 mL). Drying (Na_2SO_4) and evaporation of the solvent in vacuo yielded the crude product as a slightly yellow oil, which was purified by radial chromatography (SiO_2; hexanes/EtOAc, 9:1) to give dialdehyde **19** as a colorless oil in quantitative yield (0.97 g). $[\alpha]_D$=−291 (c=1.30, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.71 (s, 6H), 7.18–7.66 (m, 6H), 9.64 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 56.59, 115.85, 119.71, 124.54, 129.81, 136.14, 143.32, 191.64.

4.3.7. 2,2′-(Dihydroxy)-6,6′-dimethoxy-1,1′-biphenyl (20). To a solution of dialdehyde **19** (0.45 g, 1.67 mmol) in CH_2Cl_2 (25 mL) was added $NaHCO_3$ (2.2 g, 26.6 mmol) and *m*-chloroperbenzoic acid (80%, 2.3 g, 13.3 mmol). The mixture was stirred at room temperature for 3 days. Aqueous 10% $Na_2S_2O_3$ solution (30 mL) was added, and stirring was continued for another 30 min. The solution was diluted with CH_2Cl_2 and saturated with NaCl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. Drying (Na_2SO_4) and evaporation of the solvent in vacuo gave a yellow oil. ^{1}H NMR indicated formation of the desired formate. To the mixture was added a suspension of K_2CO_3 (6.2 g) in MeOH (27 mL) and water (13 mL) that had been degassed in an ultrasonic bath for 1 h. The mixture was stirred for 1 h, quenched with 1 N HCl, and extracted with CH_2Cl_2. Drying (Na_2SO_4) and evaporation of the solvent in vacuo yielded a yellow oil. TLC indicated the presence of other compounds that were not identified. The crude oil was purified by radial chromatography (SiO_2; hexanes/EtOAc, 9:1 to 5:1) to give bisphenol **20** (60 mg, 15%). $[\alpha]_D$=−144 (c=0.77, $CHCl_3$).[8] ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (s, 6H), 5.00 (s, 2H), 6.55 (d, J=8.0 Hz, 2H), 6.55 (d, J=7.9 Hz, 2H), 7.24 (t, J=8.1 Hz, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 55.99, 103.46, 106.97, 109.14, 130.51, 155.21, 157.95.

4.4. 2-Bromo-1-[(*tert*-butyldimethylsiloxy)methyl]-3,4,5-trimethoxybenzene (22) (According to literature procedure)[8]

Alternatively, the silylating system of TBDMSOTf/Et_3N was substituted with TBDMSCl/Et_3N/4-DMAP to afford silyl ether **22** in a similar fashion. For a more convenient and efficient reduction of acid **21**, the following was employed.

4.4.1. 2-Bromo-3,4,5-trimethoxybenzyl alcohol. To a solution of 3.00 g (12.9 mmol, 1.25 equiv.) or zirconium tetrachloride in 46 mL of anhydrous THF at 25 °C under Ar was added 1.95 g (51.5 mmol, 5.0 equiv.) of sodium borohydride with immediate evolution of gas. After 10 min, to this cream-colored mixture was added a solution of 3.00 g (10.3 mmol) of acid **21** in 10 mL of anhydrous THF via cannula. (The flask was rinsed with 4.0 mL of THF, and this was also added via cannula.) After stirring for 12 h, the reaction was cooled to 0 °C and slowly quenched with 25 mL of H_2O. The mixture was then extracted with CH_2Cl_2 (1×250 mL, 1×200 mL), and the combined organic portions were dried over $MgSO_4$. Filtration and removal of the solvent afforded 2.86 g (10.3 mmol, 100%) of an off colorless solid that was homogeneous by GC and whose physical characteristics were identical with the previously reported data.[8]

4.4.2. Phenyl oxazoline (*S*)-24. To a solution of 7.05 g (29.1 mmol) of acid **23**[8] in 70 mL of anhydrous CH_2Cl_2 was added 5.2 mL (59.6 mmol) of oxalyl chloride and then 5 drops of DMF. The reaction mixture was stirred overnight under Ar at 25 °C. The CH_2Cl_2, DMF, and excess oxalyl chloride were removed in vacuo to afford the acid chloride as a light yellow solid. This was then dissolved in 30 mL of anhydrous CH_2Cl_2 and added over 15 min to a solution of 4.00 g (38.8 mmol) of S-valinol and 9.0 mL of Et_3N in 50 mL anhydrous CH_2Cl_2 cooled to 0 °C. The mixture was then stirred at room temperature for 6 h at which time the solvent was evaporated, and the yellow, oily residue was dissolved in 50 mL of ethyl acetate. The precipitated trimethylamine hydrochloride was filtered away, and concentration of the filtrate gave the amide as a yellow oil. This was dissolved in 120 mL of anhydrous CH_2Cl_2, and 11 mL of thionyl chloride were added. After stirring at 25 °C, the dark mixture was cooled to 0 °C and carefully quenched with 40 mL of H_2O and then 40 mL of 4 aq. NaOH. After separation, the aqueous layer was extracted with CH_2Cl_2 (2×150 mL), the organic portions combined, dried over $MgSO_4$, filtered, and the solvent removed. On occasion, this was contaminated with the aliphatic chloride; therefore, to induce ring closure, this mixture was refluxed with K_2CO_3 in (10:1, CH_3CN–H_2O) (monitored by TLC), cooled, the CH_3CN removed, and the aqueous portion extracted with CH_2Cl_2. This additional process did not affect the overall yield of oxazoline **24**. Purification by flash chromatography (SiO_2, 33% ethyl acetate/hexane) afforded 6.56 g (21.2 mmol, 73%) of oxazoline **24** as a light brown oil: $[\alpha]_D^{26}$=−31.5 (c=1.06, THF). ^{1}H NMR (300 MHz,

$CDCl_3$): δ 0.92 (d, J=9.1 Hz, 3H), 1.01 (d, J=9.1 Hz, 3H), 1.82–1.89 (m, 1H), 3.82 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 4.07–4.12 (m, 2H), 4.32–4.40 (m, 1H), 7.03 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.01, 18.77, 32.70, 56.11, 61.11, 61.24, 61.65, 69.76, 72.44, 105.36, 107.85, 116.85, 147.53, 147.64, 149.03, 161.75; IR (thin film) 2958, 2938, 2872, 1651, 1493, 1464, 1409, 1231, 1213, 1170, 1119, 1069, 1027, 1009 cm^{-1}. Anal. Calcd for $C_{16}H_{23}O_5N$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.45; H, 7.44; N, 4.13.

4.4.3. Biaryl oxazoline (*S*,*S*)-25. To a solution of 7.31 g (18.7 mmol) of aryl bromide **22**[8] in 40 mL of anhydrous THF was added 0.91 g (37.4 mmol) of Mg turnings, and then the reaction was brought to reflux under Ar. A solution of 3.52 g (18.7 mmol) of 1,2-dibromoethane in 5 mL of THF was added in portions over 1 h. Refluxing was continued until there was complete disappearance of bromide **22** as monitored by GC (ca. 2 h). To this refluxing solution, a solution of 2.70 g (9.3 mmol) of oxazoline **24** in 20 mL of THF was added, and reflux was maintained until oxazoline **24** was completely consumed, as monitored by GC analysis (ca. 5–15 h). The reaction was cooled to room temperature, quenched with 30 mL of sat. NH_4Cl, separated, the organic portion was washed with brine (2×30 mL), dried over $MgSO_4$, and concentrated to obtain a crude brown oil. An aliquot of this oil was quickly passed through a plug of silica gel to remove material other than the two coupled biaryl diastereomers. The diastereomeric ratio, as determined by analytical HPLC (3% *i*-propanol/hexane, flow rate 2 mL/min), was determined to be 98:2 (retention times=5.24 and 4.08 min, respectively). The crude oil was purified by flash chromatography (SiO_2, 20–70% EtOAc) to afford 4.73 g (8.0 mmol, 86%) of biaryl (*S*)-**25** as analytically homogeneous light yellow viscous oil, which could be crystallized from Et_2O/hexane to give a colorless solid: $[\alpha]_D^{26}$=−15.9 (c=2.52, CH_2Cl_2). Mp 83–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.04 (s, 3H), −0.03 (s, 3H), 0.74 (d, J=6.7 Hz, 3H), 0.78 (d, J=6.7 Hz, 3H), 0.88 (s, 9H), 1.53–1.67 (m, 1H), 2.61 (s, 3H), 3.65 (s, 3H), 2.66–3.80 (m, 2H), 3.82 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 4.03 (dd, J=8.0, 9.4 Hz, 1H), 4.27 (AB quartet, J_{AB}=14 Hz, 1H), 4.37 (d, J=14 Hz, 1H), 6.94 (s, 1H), 7.18 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ −5.37, 18.23, 18.29, 18.75, 25.90, 29.67, 32.78, 55.73, 56.00, 60.48, 60.63, 62.67, 170.19, 72.49, 76.58, 77.00, 77.43, 104.22, 108.63, 120.27, 123.44, 124.30, 136.09, 139.90, 144.20, 150.92, 151.54, 152.43, 152.54, 163.56. Anal. Calcd for $C_{31}H_{45}O_8NSi$: C, 63.13; H, 8.03; N, 2.37. Found: C, 62.97; H, 7.98; N, 2.33.

4.4.4. (*S*)-Biscarbinol (26). A 3-L round-bottomed flask was charged with 44.49 g (75.4 mmol) of biaryl **25**, 1.2 L of THF, 40 mL of TFA, 101 mL of H_2O, and 736 g of Na_2SO_4. This was stirred with a mechanical overhead stirrer for 13.5 h. An additional 250 g of Na_2SO_4 was added and then filtered. The sulfate was rinsed with THF (3×250 mL) and the solvent removed in vacuo, affording a yellow oil. This oil was dissolved in 400 mL of CH_2Cl_2, and to this was added 120 mL of pyridine and immediately placed in an ice bath. To this, 100 mL of Ac_2O was added and the mixture stirred for 5.5 h, diluted with 350 mL of CH_2Cl_2 washed with cold 1 N HCl (1×100 mL, 2×200 mL), washed with sat. aq. $NaHCO_3$ (1×300 mL), dried over $MgSO_4$, filtered, and the solvent removed in vacuo. The crude acylamide was dissolved in 1 L THF and cooled to 0 °C and 19 g of $LiAlH_4$ was added in portions and then stirred at 0 °C for 4 h and then at 25 °C for 14 h. The mixture was again cooled to 0 °C and slowly quenched with 3 N aq. NaOH, dried with 750 g of Na_2SO_4, filtered, and the solvent removed. The residue was dissolved in 350 mL of CH_2CL_2 and washed with N HCl (2×100 mL), the organic portions combined, dried over $MgSO_4$, and the solvent evaporated. This was purified by flash column chromatography (SiO_2, 10–70% EtOAc/hexane) to afford 20.8 g (52.8 mmol, 70%) of biscarbinol (*S*)-**26** as a colorless solid. The physical characteristics were identical with the previously reported data.[8]

4.4.5. (*S*)-Dialdehyde (27). To a solution of 0.40 mL (4.40 mmol) of oxalyl chloride in 10 mL of anhydrous CH_2Cl_2, cooled to −55 °C under Ar, was added a solution of 0.65 mL (8.40 mmol) of DMSO in 2.5 mL of anhydrous CH_2Cl_2. After stirring for 2 min, a solution of 500 mg (1.26 mmol) of biscarbinol (*S*)-**26** in 5 mL of CH_2Cl_2 was added dropwise. After 25 min of stirring at −55 °C, 2.65 mL (19.1 mmol) of triethylamine was added; stirring continued at −55 °C for 5 min, and then the reaction mixture was warmed to 25 °C. The solution was quenched with 18 mL of H_2O and then diluted with 100 mL of CH_2Cl_2. This was washed with 50 mL of H_2O, the aqueous layer extracted with CH_2Cl_2 (2×50 mL), the combined organic layers were dried over $MgSO_4$, and the solvent evaporated. Purification by flash chromatography (SiO_2, 33% EtOAc/hexane) afforded 470 mg (1.21 mmol) of dialdehyde (*S*)-**27** as a colorless oil: $[\alpha]_D^{26}$=−81.7 (c=1.17, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.60 (s, 6H), 3.96 (s, 6H), 3.97 (s, 6H), 7.38 (s, 2H), 9.57 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 56.14, 60.69, 61.07, 105.69, 124.41, 130.47, 147.27, 151.60, 153.88, 190.13; IR (thin film) 2941, 1689, 1587. Anal. Calcd for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.31; H, 5.73.

4.4.6. (*S*)-2,2′-Dihydroxy-4,5,6,4′,5′,6′-hexamethoxybiphenyl (28). A round-bottomed flask was charged with 0.365 g (0.94 mmol) of dialdehyde **27**, 0.472 g (5.62 mmol) of $NaHCO_3$, 0.607 g (2.81 mmol) of *m*-chloroperbenzoic acid (ca. 80%), and 50 mL of dry CH_2Cl_2. After stirring at room temperature for 7 h, the reaction was quenched with 30 mL of 10% sodium thiosulfate, and stirring was continued for 30 min. The reaction mixture was diluted with 100 mL of CH_2Cl_2 and then washed with brine (2×50 mL). The aqueous layer was re-extracted with CH_2Cl_2 (2×70 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed in vacuo to obtain the bisformate ester as a colorless oil. In another flask, potassium carbonate (3.5 g) was dissolved in a mixture of 15 mL MeOH and 7 mL H_2O. The solution was degassed in an ultrasonic bath for 1 h. This was then added to the crude bisformate, and the mixture was stirred for 10 min, after which 30 mL of 1 N aq. HCl was added and the mixture extracted with CH_2Cl_2 (3×80 mL). After drying over $MgSO_4$, the solvent was removed, and the crude product purified by silica gel chromatography (50% EtOAc/hexane) afforded 0.278 g (0.76 mmol, 83%) of diol (*S*)-**28** as a colorless solid (Mp 155–156 °C. $[\alpha]_D^{26}$=−48.9 (c=2.27, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 6H), 3.80 (s, 6H), 3.82 (s, 6H), 5.40 (s, 2OH), 6.45 (s, 2H). ^{13}C NMR

(75.5 MHz, $CDCl_3$): δ 55.80, 61.17, 96.94, 105.10, 136.21, 150.61, 151.64, 154.34; IR (thin film) 3600–3000, 2940, 1604; Anal. Calcd for $C_{18}H_{22}O_8$: C, 59.01; H, 5.98. Found: C, 59.01; H, 5.85.

4.4.7. 2-Bromo-3-methoxy benzoic acid (30). A round-bottomed flask was charged with 8.38 g of 2-bromo-3-methoxybenzaldehyde **11** (R=CHO) (38.9 mmol) and 20.4 g of $KMnO_4$ (0.13 mol) in 65 mL of acetone and 5 mL of H_2O and equipped with a reflux condenser. The mixture was heated at 55 °C overnight (during this time, the reaction became exothermic and briefly refluxed). An additional 10 mL of H_2O and 11.2 g of $KMnO_4$ was added and heated at 55 °C overnight. After cooling, the mixture was filtered through a plug of silica gel with a solution of MeOH/EtOAc/CH_2Cl_2 and acetone. The solvent was removed in vacuo, and the crude acid was used without further purification.

4.4.8. 2-Bromo-3-methoxyphenyl oxazoline (31). To the crude acid above was added 100 mL of CH_2Cl_2, 20 mL of oxalyl chloride and 4 drops of DMF and stirred under Ar at room temperature overnight. The solvent was removed in vacuo and then added to 200 mL of CH_2Cl_2. This mixture was added to a solution of 5.02 g of (*S*)-*tert*-leucinol (Degussa) and 27 mL of Et_3N in 50 mL of CH_2Cl_2 and stirred overnight at room temperature. To this, a solution of 8.5 mL of $SOCl_2$ in 20 mL of CH_2Cl_2 was added, and the reaction was stirred for 30 min, cooled in an ice bath, quenched with H_2O and made basic with 4 N NaOH. The two-phase system was separated, the organic portion was washed with H_2O, dried ($MgSO_4$), and the solvent removed. The residue was dissolved in 100 mL of toluene and 10 mL of Et_3N and heated at reflux overnight. The solvent was removed in vacuo and filtered through silica gel with EtOAc to give 7.86 g of the oxazoline **31** (32.3 mmol, 83%) as a light yellow oil that solidified upon standing. Mp 76.5–78.5 °C. This material was used without further purification.

4.5. (*S*,*S*,*S*)-Dimethoxybiphenyl oxazoline (32)

In a round-bottomed flask, the bromo oxazoline **31** (7.86 g, 32.3 mmol) was azeotropically dried twice with benzene and then held under high vacuum overnight. This was dissolved in 10 mL of dry DMF, and then 4.7 g of freshly activated Cu powder was added. The flask was equipped with a reflux condenser under Ar and then placed in a preheated (105 °C) sand bath for 2 h. The reaction was then refluxed overnight. An additional 15 mL of DMF was added, and the mixture was refluxed an additional 3 days. After cooling, the mixture was diluted with CH_2Cl_2 and then washed with NH_4OH until all the copper was removed, washed with H_2O, dried over $MgSO_4$, filtered, and the solvent removed in vacuo. Purification by silica gel chromatography (hexane to 1:1 EtOAc/hexane) afforded two separate fractions of the bis(oxazoline) **32**. The diastereomeric ratios of each were determined by direct conversion to the biscarbinol (*S*)-**16** (described above) followed by bis(Mosher ester) formation and integration of the appropriate resonances. The biscarbinol (*S*)-**16** was obtained in 2 fractions.

Fraction 1: 2.35 g (31.3%), diastereomeric ratio (100: 0).

Fraction 2:2.28 g (30.4%) diastereomeric ratio (94.5:5.5). The minor diastereomer (*SSR*)-**32** was also isolated (0.32 g, 4.3%). The total yield of **32** was 62.7% and, if combined, had a ratio of diastereomers of approximately 95:5. Further characterization of **32** is not reported since the biscarbinol **16** derived from it was identical to **16** obtained in Scheme 6.

4.6. Amine (*S*)-35 from (S)-34 (R^1=R^2=OMe)

A round-bottomed flask was charged with 59.1 mg (0.157 mmol) of the amine (*S*)-**34**[38] and 5.0 mL of ethyl formate. This solution was then heated to reflux for 3 h, cooled, and the solvent removed in vacuo. The residue was dissolved in 3 mL of THF followed by the addition of 0.460 mL of 1 M $LiAlH_4$ (in THF). After stirring overnight at room temperature, the mixture was quenched with a few drops of 4 N NaOH, diluted with THF and dried over Na_2SO_4. Purification by radial chromatography (1 mm SiO_2, 20% EtOAc/hexane to pure EtOAc to 50% EtOAc/MeOH) afforded 42.7 mg (0.11 mmol, 69%) of the *N*-methyl amine (*S*)-**35** as a yellow oil. The physical data for this compound is reported in the following experimental procedure.

4.6.1. Amine (*S*)-35 from dialdehyde (*S*)-27 (R^1=R^2=OMe). A flame-dried round-bottomed flask was charged with 202 mg (0.514 mmol) of dialdehyde (*S*)-**27**, 287 mg (4.25 mmol, 8.3 equiv.) of methylamine hydrochloride, 5 mL of MeOH, and 3 Å molecular sieves. After stirring for 4.5 h at room temperature, the yellow reaction mixture was cooled to 0 °C, and 213 mg (3.34 mmol) of $NaBH_3CN$ in 2.0 mL MeOH was added over 2 min. The cream-colored mixture was stirred at room temperature for 16 h, and then the solvent was removed in vacuo. The residue was acidified with 20 mL of 0.3 N aq. HCl, stirred for 1 h and then made basic with NaOH pellets. This was extracted with CH_2Cl_2 (4×75 mL), concentrated, passed through a plug of silica gel with EtOAc/MeOH, and the solvent removed leaving a yellow foam. The product, **35**, was purified by radial chromatography (2 mm SiO_2, EtOAc to 50% MeOH/EtOAc) to give 198.9 mg (0.511 mmol, 99%) of the *N*-methyl amine (*S*)-**35** (R^1=R^2=OMe) as a yellow oil/foam $[\alpha]_D$=−60.9 (c=1.28, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.05 (AB quarlet, J_{AB}=12.3 Hz, 2H), 3.32 (AB quarlet, J_{AB}=12.3 Hz, 2H), 3.67 (s, 6H), 3.87 (s, 6H), 3.88 (s, 6H), 6.62 (s, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 43.09, 56.07, 57.24, 60.70, 61.02, 108.10, 122.70, 130.36, 141.64, 151.41, 152.77).

4.6.2. Amine (*S*)-35 from (*S*)-19 (R^1=R^2=H). A solution of dialdehyde (*S*)-**19** (86 mg, 0.32 mmol) and methylamine hydrochloride (172 mg, 2.55 mmol) in MeOH (3 mL) was stirred at room temperature for 5 h in the presence of 3 Å sieves. The solution was cooled to 0 °C, and a solution of $NaCNBH_3$ (130 mg, 2.07 mmol) in MeOH (1 mL) was added. The resulting mixture was stirred at room temperature for 15 h. The solvent was removed in vacuo, and the residue was acidified with 10 mL of 0.3 N HCl. After stirring for 1 h, NaOH (0.11 g, 2.75 mmol) was added. Extraction with CH_2Cl_2 (3×10 mL), drying (Na_2SO_4) followed by evaporation of the solvent afforded *N*-methyl amine (*S*)-**35** (R^1=R^2=H) as a slightly yellow oil. Purification using radial chromatography (SiO_2; EtOAc to

EtOAc/MeOH 1:1) yielded the product as a colorless oil (77 mg, 90%). $[\alpha]_D$=+70.9 (c=0.57, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 2.62 (s, 3H), 3.41 (d, J=12.2 Hz, 2H), 3.75 (d, J=12.2 Hz), 4.09 (s, 6H), 7.21–7.27 (m, 4H), 7.56–7.61 (m, 2H). ^{13}C NMR (75.5 MHZ, $CDCl_3$): δ 42.84, 55.70, 56.73, 110.78, 121.78, 125.18, 128.60, 135.61, 161.60.

Acknowledgements

The authors are grateful to the National Institutes of Health for financial support. A DFG fellowship (to A.M.) is also gratefully acknowledged.

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Tetrahedron 60 (2004) 4475–4480
Tetrahedron

Enantioselective spiro ene-carbocyclization of 1,6-enynes catalyzed by tropos rhodium(I) complex with skewphos ligand

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Received 13 January 2004; revised 6 February 2004; accepted 24 February 2004

Abstract—A tropos rhodium(I) complex having skewphos ligand is shown to be a highly enantioselective catalyst for asymmetric ene-type carbocyclization of 1,6-enynes with tri-substituted olefins to control quaternary stereogenic centers or spiro-rings.

1. Introduction

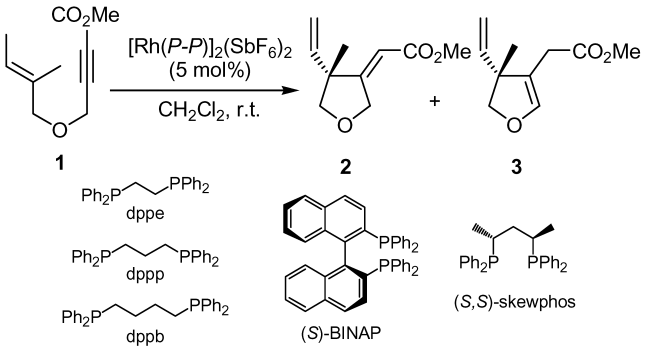
Transition metal catalysed ene-type cyclization of 1,6-enynes[1–3] is a useful synthetic method, particularly for five-membered ring formation. However, previous examples for enantioselective catalysis with chiral metal complexes are limited to palladium[4,5] and rhodium[6,7] complexes, despite its synthetic potential leading not only to carbocycles but also to heterocycles.[8] Recently, an excellent example[9] has been reported where a chiral rhodium complex is advantageous in terms of the facile cyclization even at room temperature but this was only applicable to disubstituted *cis*-olefin substrates. Herein, we report the efficient catalysis of ene-type cyclization including tri-substituted 1,6-enynes by chiral cationic rhodium(I) complexes[10] bearing a skewphos ligand.[11] The chirally dynamic (tropos: 'turn' in Greek)[12] skewphos complex provides a deep insight into the key transition state for C–C bond formation.

2. Results and discussions

2.1. Ene-carbocyclization catalyzed by cationic rhodium(I) complexes with achiral ligands

The feasibility of the ene-type carbocyclization was first investigated for a tri-substituted olefinic ether substrate **1** using 5 mol% of cationic Rh(I) catalyst including a variety of achiral bidentate PP-ligands in dichloromethane at room temperature (Table 1). Since the cationic Rh(I)(PP-ligand) dimer complexes[11,13] are usually unstable to isolate or have some difficulty for storage in solution for a long time even at low temperature, 'in situ preparation'[14] is adopted in our reactions: a CH_2Cl_2 solution of [Rh(PP-ligand)(nbd)]SbF_6 was frozen for deaeration and then stirred under hydrogen gas (1 atm) to remove norbornadiene (nbd) as hydrogenated norbornane.

Table 1. Ene-type cyclizations of 1,6-enynes catalysed by cationic Rh(I)/PP-ligand complex



Entry	PP-ligand	Reaction time (h)	Yield (%) (ee (%))	
			2	**3**
1	dppe	7	47 (−)	33 (−)
2	dppp	6	84 (−)	2 (−)
3[a]	dppb	4	66 (−)	13 (−)
4	(*S*)-BINAP	3	90 (28, *S*)	10 (18, *S*)
5	(*S*,*S*)-Skewphos	7	59 (**93**, *R*)	6 (>**95**, *R*)
6[a]	(*S*,*S*)-Skewphos	84	59 (**94**, *R*)	1 (>**95**, *R*)

[a] Temperature is 0 °C.

Keywords: Asymmetric catalysis; Cyclization; Rhodium; Tropos.
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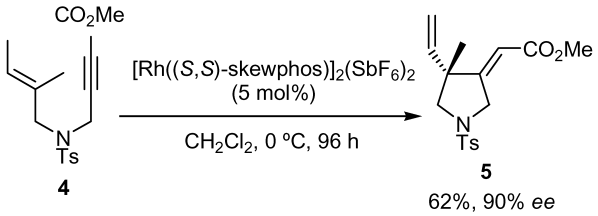
doi:10.1016/j.tet.2004.02.063

Interestingly enough, the normal ene-type cyclization proceeded[15] even with such a sterically congested tri-substituted olefinic substrate, but was accompanied with the unexpectedly isomerized *endo*-olefinic secondary products **3** with dppe (1,2-bis(diphenylphosphino)ethane) (Table 1, entry 1). By contrast, dppp (1,3-bis(diphenylphosphino)-propane) and dppb (1,4-bis(diphenylphosphino)butane) gave the desired ene-type cyclization products **2** with high regioselectivity (entries 2 and 3).

2.2. Asymmetric ene-carbocyclization catalyzed by a cationic rhodium(I) complex with chiral ligands

We next examined the chiral PP-ligands such as (*S*)-BINAP and (*S*,*S*)-skewphos ((2*S*,4*S*)-2,4-bis(diphenylphosphino)-pentane, (*S*,*S*)-BDPP)[13] corresponding to dppp and dppb skeletons, respectively (Table 1, entries 4–6). The key to the success in increasing the enantioselectivity and olefinic regioselectivity in carbocyclization is the use of skewphos rather than BINAP: a solution of [Rh{(*S*,*S*)-skewphos}(nbd)]SbF_6 complex in dry CH_2Cl_2 was frozen for degas and charged with hydrogen gas (1 atm balloon), then stirred for 30 min at room temperature. ^{31}P NMR spectroscopy taken under Ar atmosphere in CH_2Cl_2 is exemplified below to show its dimeric nature:[10,11] each Rh complex in this mixture has certainly no symmetrical two phosphorus coupled by J_{P-P} and J_{Rh-P} (Fig. 1). The Rh(I)/(*S*,*S*)-skewphos complex gave higher enantioselectivity (93% ee) and olefinic regioselectivity (90%) (entry 5) than those obtained with the BINAP counterpart (entry 4) at room temperature. Even at 0 °C, the reaction with (*S*,*S*)-skewphos proceeded slowly, and moreover olefinic regioselectivity increased up to 98% maintaining chemical yield and enantioselectivity of the major product **2** (entry 6).

Furthermore, catalytic asymmetric cyclization of the sulfonamide substrate **4** using the Rh(I)/(*S*,*S*)-skewphos complex proceeded in moderate yield but without olefin migration, to afford **5** with quarternary carbon center as the sole product (Eq. 1).

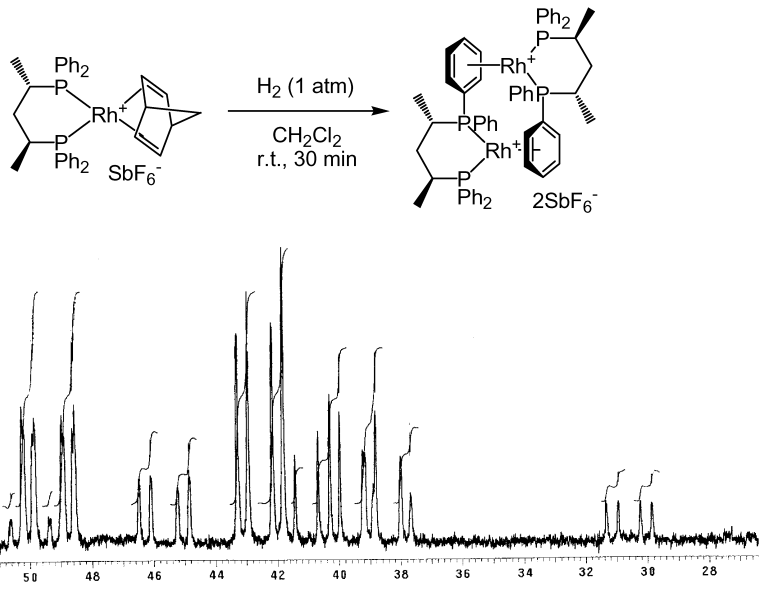


(1)

2.3. Asymmetric spiro ene-carbocyclization catalyzed by a chiral but tropos skewphos rhodium(I) complex

Encouraged by these interesting results with tri-substituted substrates, we next tried spiro-cyclization of ether compounds **6** catalyzed by a chiral cationic Rh(I)/(*S*,*S*)-skewphos complex (Table 2). Cyclization of **6a** with a six-membered ring was investigated at room temperature for 46 h to give **7a** in 53% yield and 88% ee, accompanied by olefin-migration product **8a** with high enantiomeric excess (97% ee)[16] (entry 1).

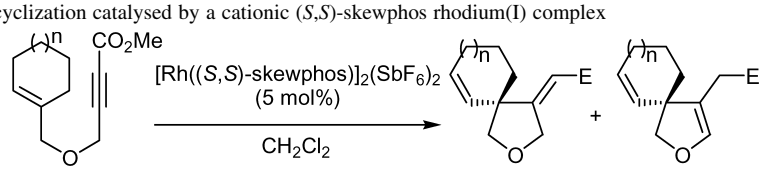
The reactivity increased dramatically at 80 °C and the cyclization of **6a** was completed within only 40 min but **8a** was mainly obtained in high enantioselectivity (44%, 91% ee) (entry 2). For **6b** involving an eight-membered medium sized ring, the major product was also **8b** at either 40 or



Chemical shift of the dimer complexes (mixture of major A, B and C)
A: 42.5 ppm (dd, J_{Rh-P}= 182 Hz, J_{P-P}= 57.0 Hz), 49.4 ppm (dd, J_{Rh-P}= 209 Hz, J_{P-P}= 54.6 Hz).
B: 38.4 ppm (dd, J_{Rh-P}= 231 Hz, J_{P-P}= 59.9 Hz), 45.6 ppm (dd, J_{Rh-P}= 201 Hz, J_{P-P}= 62.2 Hz).
C: 30.5 ppm (dd, J_{Rh-P}= 179 Hz, J_{P-P}= 57.7 Hz), 50.0 ppm (dd, J_{Rh-P}= 195 Hz, J_{P-P}= 58.3 Hz).

Figure 1. Preparation of (*S*,*S*)-skewphos–Rh(I) dimer catalyst and its ^{31}P NMR spectrum.

Table 2. Enantioselective spiro cyclization catalysed by a cationic (*S*,*S*)-skewphos rhodium(I) complex



6 **7** **8**

Entry	Substrate (*n*)	*T* (°C)	Reaction time	Yield (%) (ee (%))	
				7	**8**
1	**6a** (1)	rt	46 h	53 (88)	16 (97)
2	**6a** (1)	80	40 min	4 (67)	44 (91)
3	**6b** (3)	80	40 min	6 (79)	55 (79)
4	**6b** (3)	40	17 h	12 (88)	51 (88)

80 °C, although the enantioselectivity was high (88% ee and 79% ee, respectively) (entries 3 and 4).

To increase the synthetic usefulness, spiro-cyclization[17] of pyran sulfonamide compound **9** was examined (Eq. 2). Spiro cyclization proceeded smoothly at room temperature to afford the desired spiro amide-pyran **10** with extremely high enantioselectivity (94% ee) without any accompanying olefin-migration product.

9 **10**
72%, 94% *ee*

(2)

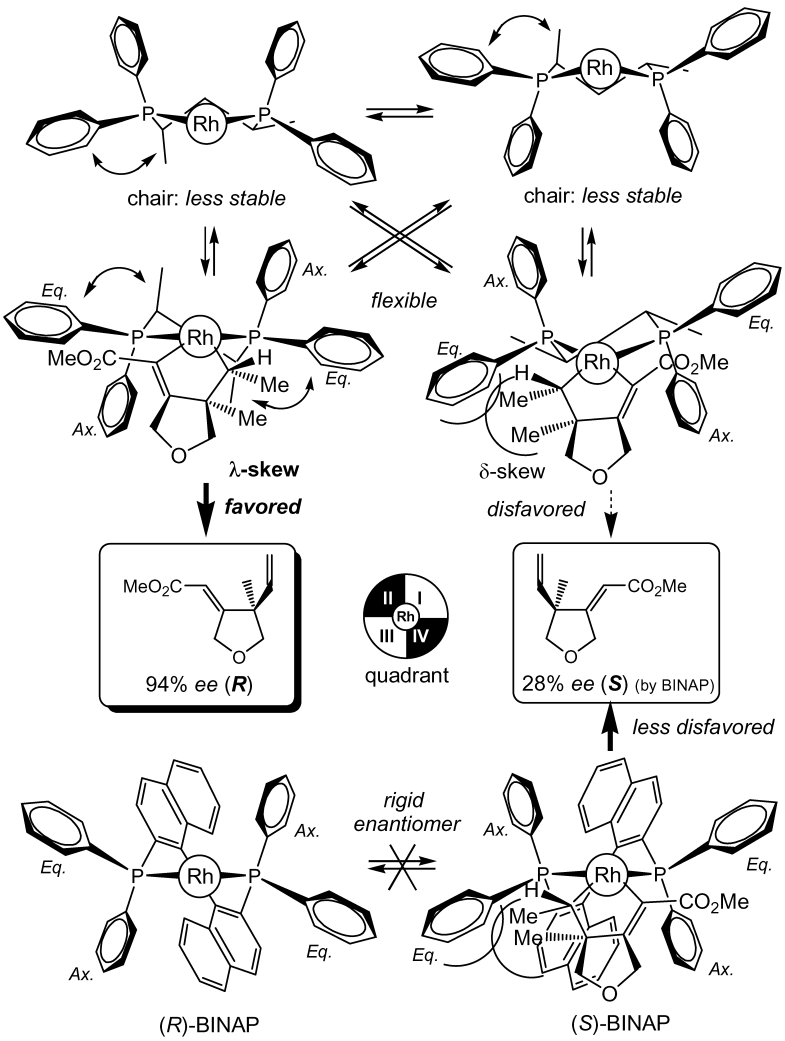


Figure 2. Tropos skew-conformation of skewphos–Rh versus atropos BINAP–Rh complexes.

2.4. Tropos nature of cationic rhodium(I) skewphos complex

It should be noted here that the transition states for carbocyclization[9c] indicate the chirally dynamic (tropos) nature of the skewphos complex. Skewphos is known to have both chair and skew forms in equilibrium[18] (Fig. 2). As its name shows, skewphos is stable in favourable skew conformation (λ- over δ-skew forms).[17,18] In fact, due to the incontrollable nature, examples of asymmetric catalysis using skewphos analogue are so limited although some chiral skewphos analogues have been devised.[19–21] Undoubtedly, BINAP is of rigid (atropos: 'not turn' in Greek)[12] binaphthyl skeleton and not easy to epimerize. (*S*)-Enriched cyclized product **2** was obtained by optically pure and atropos (*S*)-BINAP,[22] which has (I,III)-equatorial phenyl groups in Rh-quadrant (Table 1, entry 4). On the other hand, we obtained (*R*)-enriched cyclized product **2** by (*S*,*S*)-skewphos, in sharp contrast to the (*R*)-product obtained with (*S*)-BINAP (Table 1, entries 5 and 6). In our ene-type cyclization, (*S*,*S*)-skewphos should possess the less stable δ-skew form in (I,III)-equatorial conformation as does (*S*)-BINAP. Therefore, it is indicated that our cationic Rh(I)-catalyzed ene-type cyclization should proceed via the less favourable λ-skew form. In the λ-skew form, the (II,IV)-equatorial phenyl groups are in horizon because of the repulsion between two axial-Me groups of skewphos and these Ph groups. In the quadrant II and IV in the δ-skew form, a vacant space is available for the bulky alkyl group of the substrate, leading to (*R*)-enriched product **2** without conspicuous repulsions.

In summary, we have developed highly enantioselective ene-type cyclization of 1,6-enynes with tri-substituted olefin catalysed by tropos rhodium(I) complex with skewphos ligand. This is the first example of spiro-construction by Rh(I) catalysis via ene-type cyclization.

3. Experimental

3.1. General

^{1}H, ^{13}C and ^{31}P NMR spectra are measured on Varian Gemini 300 (300 MHz) and Varian Gemini 400 (400 MHz) spectrometers. Chemical shifts of ^{1}H NMR spectra are expressed in parts per million downfield from tetramethylsilane as an internal standard (δ=0) in $CDCl_3$. Chemical shifts of ^{13}C NMR spectra are expressed in parts per million downfield from $CDCl_3$ as an internal standard (δ=77.0) in $CDCl_3$. Chemical shifts of ^{31}P NMR spectra are expressed in parts per million downfield from 85% H_3PO_4 as an internal standard (δ=0) in $CDCl_3$. IR spectra were measured on a JASCO FT/IR-5000 spectrometer. Optical rotations were measured on a JASCO DIP-370. High performance liquid chromatography (HPLC) was conducted on JASCO PU-980, LG-980-02, DG-980-50, AS-950 and CO-966 instrument equipped with model UV-975 spectrometers as an ultra violet light. Peak area was calculated by JASCO-BORWIN (Windows NT) as an automatic integrator. Capillary gas chromatographic analyses (GC) were conducted on Shimadzu GC-14B instrument equipped with FID detector and capillary column coated with CP-Cyclodextrin-β-2,3,6-M-19 and CP-Chirasil-Dex CB (GL Science Inc.) by using He as a carrier gas. Peak area were calculated by Shimadzu C-R6A as an automatic integrator. Analytical thin layer chromatography (TLC) was performed on a glass plates and/or aluminum sheets pre-coated with silica gel (Merck Kieselgal 60 F_{254}, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$ and phosphomolybdic acid. Column chromatography was performed on Merck Kieselgel 60 and KANTO Silica Gel 60N (spherical, neutral), employing hexane ethyl acetate mixture as an eluent unless otherwise noted. All experiments were carried out under argon atmosphere otherwise noted. Dehydrated solvents (ethyl acetate, dichloroethane, diethyl ether, dichloromethane, hexane, 2-propanol and tetrahydrofuran) were purchased from Kanto chemical Co., Inc. $[Rh(nbd)Cl]_2$ was purchased from Strem Chemicals. Silver hexafluoroantimonate was purchased from Aldrich.

3.2. General procedure for Rh-catalyzed ene-type cyclization

To [Rh(PP-ligand)(nbd)]SbF_6 (0.02 mmol) in a 10 mL Schlenk tube was added dry CH_2Cl_2 or $(CH_2Cl)_2$ (0.8 mL) under Ar atmosphere. The solution was frozen for degas and charged by hydrogen gas with balloon (1 atm), and then gently warmed up to room temperature for 15 min. Continuously, a solution was stirred for 30 min at room temperature. After exchange with Ar again, CH_2Cl_2 or $(CH_2Cl)_2$ (1.2 mL) and substrate (0.20 mmol) was added. The mixture was stirred at desired temperature under Ar atmosphere and the reactions was monitored by TLC. The crude mixture was purified by neutral silica-gel column chromatography (5–10% Et_2O/pentane eluent) to give the cyclization product.

3.2.1. [Rh{(*S*,*S*)-skewphos}(nbd)]SbF_6. A Schlenk tube was charged under Ar with $[Rh(nbd)Cl]_2$ (138.3 mg, 0.30 mmol) and THF (3 mL) was added. Then, a solution of $AgSbF_6$ (275.0 mg, 0.80 mmol) in THF (2 mL), previously prepared in another Schlenk tube, was added via cannula. After stirring for an additional 30 min, the AgCl precipitate was removed by filtration through a bed of celite under Ar. To the turbid filtrates THF (5.0 mL) solution of (*S*,*S*)-skewphos (264.3 mg, 0.60 mmol) was slowly added via cannula. After stirring for 1 h, solvent was removed in vacuo, then CH_2Cl_2 (8 mL) was added. This solution was allowed to settle at 0 °C for 12 h. The clear red supernatant was then transferred via syringe to another schlenk tube (or Celite filtration under Ar atmosphere). The titled compound was isolated quantitatively as orange powder by concentrating the mixture, addition of little amount of Et_2O, removal of supernatant liquid via syringe, washing with Et_2O, and drying in vacuo.

δ_H (300 MHz, $CDCl_3$) 1.15 (6H, m, 2*Me*), 1.60 (2H, brs, CH_2 nbd), 1.86 (2H, m, CH_2 of skewphos), 2.80 (2H, m, 2C*H* skewphos), 3.94 (2H, m, 2C*H* nbd), 4.34 (2H, s, C*H*=), 4.88 (2H, m, C*H*=), 7.40–7.76 (20H, m, Ph). δ_P (162 MHz, $CDCl_3$) 27.8 (d, J=149.5 Hz).

3.2.2. (*S*,*S*)-Skewphos–Rh(I) dimer catalyst. To [Rh{(*S*,*S*)-skewphos}(nbd)]SbF_6 complex (17.4 mg, 0.02 mmol) in a

10 mL schlenk tube was added dry CH_2Cl_2 (0.8 mL) under Ar atmosphere. The solution was frozen and charged with hydrogen gas with balloon (1 atm) and then gently warmed up to room temperature for 15 min. Corresponding solution was stirred for additional 30 min at room temperature. After exchange with Ar again, CH_2Cl_2 (1.2 mL) was added. This Rh-solution was directly used as catalyst.

δ_P (162 MHz, $CDCl_3$) 42.5 (dd, J_{Rh-P}=182 Hz, J_{P-P}=57.0 Hz), 49.4 (dd, J_{Rh-P}=209 Hz, J_{P-P}=54.6 Hz), 38.4 (dd, J_{Rh-P}=231 Hz, J_{P-P}=59.9 Hz), 45.6 ppm (dd, J_{Rh-P}=201 Hz, J_{P-P}=62.2 Hz), 30.5 (dd, J_{Rh-P}=179 Hz, J_{P-P}=57.7 Hz), 50.0 (dd, J_{Rh-P}=195 Hz, J_{P-P}=58.3 Hz). (see Fig. 1).

3.2.3. (4-Methyl-4-vinyl-dihydrofuran-3-ylidene)-acetic acid methyl ester (2).[5a] δ_H (300 MHz, $CDCl_3$) 1.26 (3H, m, *Me*), 3.62 (1H, d, *J*=8.7 Hz, OC*H*$_a$H$_b$), 3.69 (3H, s, CO_2*Me*), 3.72 (1H, d, *J*=8.7 Hz, OCH$_a$*H*$_b$), 4.77 (1H, dd, *J*=17.7, 2.4 Hz, OC*H*$_a$H$_b$C=), 4.91 (1H, dd, *J*=17.7, 2.4 Hz, OCH$_a$*H*$_b$C=), 5.16 (1H, d, *J*=11.1 Hz, CH=C*H*$_a$H$_b$), 5.17 (1H, d, *J*=17.7 Hz, CH=CH$_a$*H*$_b$), 5.63 (1H, t, *J*=2.4 Hz, =C*H*CO_2Me), 5.79 (1H, dd, *J*=17.7, 10.5 Hz, CH_2=C*H*). δ_C (75 MHz, $CDCl_3$) 22.2, 50.7, 51.4, 72.2, 78.3, 111.0, 114.9, 140.7, 166.8, 169.4. IR (neat) 2934, 2848, 1717, 1667, 1437, 1354, 1224, 1168, 1065, 1021, 930 cm^{-1}. GC (column, CP-Cyclodextrin-β-2,3,6-M-19, i.d. 0.25 mm× 25 m, CHROMPACK; carrier gas, nitrogen 75 kPa; column, 105 °C; injection and detection temperature, 135 °C; split ratio, 100:1), t_R of *R*-isomer 40.2 min, t_R of *S*-isomer 42.5 min. $[\alpha]^{29}$ (Na 589 nm) =−38.0 (*c*=0.586 in $CHCl_3$, 94% ee (*R*)).

3.2.4. (4-Methyl-4-vinyl-4,5-dihydrofuran-3-yl)-acetic acid methyl ester (3). δ_H (300 MHz, $CDCl_3$) 1.20 (3H, s, *Me*), 2.90 (2H, m, C*H*$_2$$CO_2$Me), 3.67 (3H, s, CO_2*Me*), 4.02 (1H, dd, *J*=8.7, 0.9 Hz, OC*H*$_a$H$_b$), 4.15 (1H, d, *J*=8.7 Hz, 1H, OCH$_a$*H*$_b$), 5.04 (1H, d, *J*=17.4 Hz, CH=C*H*$_a$H$_b$), 5.08 (1H, d, *J*=10.5 Hz, CH=CH$_a$*H*$_b$), 5.82 (1H, dd, *J*=17.4, 10.5 Hz, CH_2=C*H*), 6.36 (1H, t, *J*=1.5 Hz, OC*H*=). GC (column, CP-Cyclodextrin-β-2,3,6-M-19, i.d. 0.25 mm× 25 m, CHROMPACK; carrier gas, nitrogen 75 kPa; column, 105 °C; injection and detection temperature, 135 °C; split ratio, 100:1), t_R of *S*-isomer 29.9 min, t_R of *R*-isomer 30.6 min.

3.2.5. [4-Methyl-1-(toluene-4-sulfonyl)-4-vinyl-pyrrolidin-3-ylidene]-acetic acid methyl ester (5).[5d] δ_H (300 MHz, $CDCl_3$) 1.27 (3H, s, *Me*), 2.43 (3H, s, SO_2*Me*), 3.09 (1H, d, *J*=9.0 Hz, OC*H*$_a$H$_b$), 3.14 (1H, d, *J*=9.0 Hz, OCH$_a$*H*$_b$), 3.68 (3H, s, CO_2*Me*), 4.19 (1H, dd, *J*=18.0, 2.7 Hz, OC*H*$_a$H$_b$C=), 4.41 (1H, dd, *J*=18.0, 2.7 Hz, OCH$_a$*H*$_b$C=), 5.15 (1H, d, *J*=10.8 Hz, CH=C*H*$_a$H$_b$), 5.16 (1H, d, *J*=17.4 Hz, CH=CH$_a$*H*$_b$), 5.60 (1H, t, *J*=2.7 Hz, =C*H*CO_2Me), 5.69 (1H, dd, *J*=17.4, 10.8 Hz, CH_2=C*H*), 7.33 (2H, d, *J*=8.1 Hz, Ph), 7.72 (2H, d, *J*=8.1 Hz, Ph). δ_C (75 MHz, $CDCl_3$) 21.6, 23.1, 49.8, 51.5, 52.2, 58.3, 112.9, 115.4, 128.0, 129.8, 140.2, 143.9, 164.3, 166.3. IR (neat) 2928, 2856, 1715, 1667, 1601, 1437, 1340 cm^{-1}. HPLC (column, CHIRALCEL OD-H, hexane/2-propanol, 95:5, flow rate 0.6 mL/min, 15 °C, detection UV 254 nm) t_R of *R*-isomer 21.7 min, t_R of *S*-isomer 24.0 min. $[\alpha]^{25}$ (Na 589 nm) =−16.0 (*c*=0.865 in $CHCl_3$, 90% ee (*R*)).

3.2.6. (2-Oxa-spiro[4.5]dec-6-en-4-ylidene)-acetic acid methyl ester (7a).[5b] δ_H (300 MHz, $CDCl_3$) 1.40–2.22 (6H, C*H*$_2$ cyclohexene ring), 3.50 (1H, d, *J*=8.4 Hz, OC*H*$_a$H$_b$), 3.71 (3H, s, CO_2*Me*), 3.82 (1H, d, *J*=8.4 Hz, OCH$_a$*H*$_b$), 4.70 (1H, dd, *J*=17.7, 2.7 Hz, OC*H*$_a$H$_b$C=), 4.98 (1H, dd, *J*=17.7, 2.7 Hz, OCH$_a$*H*$_b$C=), 5.30 (1H, dm, *J*=10.2 Hz, CH_2C*H*=CH), 5.67 (1H, t, *J*=2.7 Hz, =C*H*CO_2Me), 5.99 (1H, dt, *J*=10.2, 3.6 Hz, CH_2CH=C*H*). GC (Chiral Capillary Column, CP-Chirasil-Dex CB, 135 °C, INJ/DET 165 °C) t_R of *S*-isomer 22.7 min, t_R of *R*-isomer 24.4 min.

3.2.7. (2-Oxa-spiro[4.7]dodec-6-en-4-ylidene)-acetic acid methyl ester (7b).[5b] δ_H (300 MHz, $CDCl_3$) 0.70–2.60 (10H, C*H*$_2$ cyclooctene ring), 3.53 (1H, d, *J*=8.7 Hz, OC*H*$_a$H$_b$), 3.70 (3H, s, CO_2*Me*), 3.98 (1H, d, *J*=8.7 Hz, OCH$_a$*H*$_b$), 4.69 (1H, dd, *J*=17.7, 2.4 Hz, OC*H*$_a$H$_b$C=), 4.91 (1H, dd, *J*=17.7, 2.4 Hz, OCH$_a$*H*$_b$C=), 5.37 (1H, d, *J*=12.0 Hz, CH_2C*H*=CH), 5.60 (1H, dd, *J*=12.0, 8.4 Hz, CH_2CH=C*H*), 5.71 (1H, t, *J*=2.4 Hz, =C*H*CO_2Me). δ_C (75 MHz, $CDCl_3$) 23.4, 24.5, 25.3, 26.4, 51.2, 71.5, 76.3, 111.1, 129.1, 133.2. IR (neat) 2932, 2856, 1717, 1663, 1582, 1437, 1352, 1265, 1214, 1131, 1073 cm^{-1}. GC (Chiral Capillary Column, CP-Chirasil-Dex CB, 145 °C, INJ/DET 180 °C), t_R of *S*-isomer 42.5 min, t_R of *R*-isomer 45.2 min.

3.2.8. (2-Oxa-spiro[4.5]deca-3,6-dien-4-yl)-acetic acid methyl ester (8a). δ_H (300 MHz, $CDCl_3$) 1.40–2.22 (6H, C*H*$_2$ cyclohexene ring), 2.93 (2H, m, C*H*$_2$$CO_2$Me), 3.67 (3H, s, CO_2*Me*), 3.98 (1H, d, *J*=9.0 Hz, OC*H*$_a$H$_b$), 4.11 (1H, d, *J*=9.0 Hz, OCH$_a$*H*$_b$), 5.43 (1H, dm, *J*=9.9 Hz, CH_2C*H*=CH), 5.83 (1H, dt, *J*=9.9, 3.6 Hz, CH_2CH=C*H*), 6.34 (1H, m, OC*H*=). GC (Chiral Capillary Column, CP-Chirasil-Dex CB, 125 °C, INJ/DET 155 °C) t_R of *S*-isomer 31.8 min, t_R of *R*-isomer 32.6 min.

3.2.9. (2-Oxa-spiro[4.7]dodeca-3,6-dien-4-yl)-acetic acid methyl ester (8b). δ_H (300 MHz, $CDCl_3$) 0.70–2.60 (10H, C*H*$_2$ cyclooctene ring), 2.96 (2H, m, C*H*$_2$$CO_2$Me), 3.67 (3H, s, CO_2*Me*), 4.14 (1H, dd, *J*=8.7, 1.2 Hz, OC*H*$_a$H$_b$), 4.25 (1H, d, *J*=8.7 Hz, OCH$_a$*H*$_b$), 5.46 (m, 2H, C*H*=C*H*), 6.28 (1H, t, *J*=1.5 Hz, 1H, OC*H*=). GC (Chiral Capillary Column, CP-Chirasil-Dex CB, 135 °C, INJ/DET 165 °C), t_R of *S*-isomer 60.2 min, t_R of *R*-isomer 61.6 min.

3.2.10. [2-(Toluene-4-sulfonyl)-8-oxa-2-aza-spiro[4.5]-dec-6-en-4-ylidene]-acetic acid methyl ester (10).[5d] δ_H (300 MHz, $CDCl_3$) 1.72 (1H, m, OCH$_2$C*H*$_a$H$_b$), 2.05 (1H, m, OCH$_2$CH$_a$*H*$_b$), 2.43 (3H, s, SO_2*Me*), 2.69 (1H, d, *J*=9.6 Hz, NTsC*H*$_a$H$_b$), 3.46 (1H, d, *J*=9.6 Hz, NTsCH$_a$*H*$_b$), 3.68 (3H, s, CO_2*Me*), 3.85–4.10 (2H, OC*H*$_2$), 3.98 (1H, dd, *J*=18.3, 2.4 Hz, NTsC*H*$_a$H$_b$C=), 4.23 (1H, d, *J*=6.3 Hz, OCH=C*H*), 4.59 (1H, dd, *J*=18.3, 2.4 Hz, NTsCH$_a$*H*$_b$C=), 5.73 (1H, t, *J*=3.0 Hz, =C*H*CO_2Me), 6.57 (1H, d, *J*=6.3 Hz, OC*H*=CH), 7.34 (2H, d, *J*=8.1 Hz, Ph), 7.72 (2H, d, *J*=7.8 Hz, Ph). δ_C (75 MHz, $CDCl_3$) 21.6, 34.0, 44.6, 51.5, 51.8, 58.3, 62.8, 101.1, 113.6, 128.0, 129.9, 132.1, 144.0, 147.6, 165.0, 166.3. IR (neat) 2930, 1717, 1644, 1352, 1247, 1166 cm^{-1}. HPLC (column, CHIRALCEL AD-H, hexane/2-propanol, 85:15, flow rate 1.0 mL/min, 28 °C, detection UV 254 nm) t_R of *S*-isomer 16.0 min, t_R of *R*-isomer 23.5 min. $[\alpha]^{29}$ (Na 589 nm) =−76.8 (*c*=0.850 in $CHCl_3$, 94% ee (*R*)).

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Tetrahedron 60 (2004) 4481–4490

Amide-based atropisomers in tachykinin NK_1-receptor antagonists: synthesis and antagonistic activity of axially chiral *N*-benzylcarboxamide derivatives of 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one

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Received 17 October 2003; revised 22 December 2003; accepted 5 January 2004

Abstract—A series of novel *N*-benzylcarboxamide derivatives of bicyclic compounds, 3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one and 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one, were synthesized by cyclization of *N*-benzyl-2-chloro-*N*-(2-hydroxyethyl)-[and -(3-hydroxypropyl)-] nicotinamides, respectively. Atropisomerism was observed in 5-[3,5-bis(trifluoromethyl)benzyl]-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-ones due to steric hindrance of the carboxamide moiety and restriction of its rotation. Cyclization of *N*-[3,5-bis(trifluoromethyl)benzyl]-2-chloro-*N*-[(2*S*)-3-hydroxy-2-methylpropyl]-5-methyl-4-phenylnicotinamide gave (3*S*)-5-[3,5-bis(trifluoromethyl)benzyl]-3,8-dimethyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3*b*][1,5]oxazocin-6-one, which exists predominantly in the thermodynamically stable *aR*-conformer in $CDCl_3$. This compound showed excellent NK_1-antagonistic activity with IC_{50} value (in vitro inhibition of [^{125}I]-Bolton–Hunter-substance P binding in human IM-9 cells) of 0.47 nM, which is ca. 200-fold more potent than that of its enantiomer, indicating that the atropisomer chirality affects NK_1-receptor recognition.

1. Introduction

In our previous papers,[1–4] we described the synthesis of the axially chiral 1,7-naphthyridine-6-carboxamide derivatives, represented by **1** (Scheme 1)[1,2] and TAK-637 (Scheme 2),[3,4] as orally active tachykinin NK_1-receptor antagonists. Because the carboxamide moiety of these compounds exists at the sterically hindered position, rotation around the $-C_{(6)[or\ (5a)]}-C(=O)-$ bond is restricted, yielding separable and stable atropisomers.

Compound **1**, which has a *trans*-amide form,[5] was separated into *aR*- and *aS*-atropisomers by preparative high-performance liquid chromatography (HPLC) using a chiral column. They have significant stability in solution, e.g., they were not interconverted in dimethyl sulfoxide (DMSO) at 37 °C for 16 h and underwent racemization only after storage at 50 °C for 6 days. The enantiomeric atropisomers differed in activity at the tachykinin NK_1-receptor, with *aR* isomer being more active (i.e., eutomer) [IC_{50}, nM: *aR*, 0.24; *aS*, 1.4] (Scheme 1).[2]

TAK-637 [(*aR*,9*R*)-**3**], which is an 8-membered cyclic analogue of **1** with *aR* stereochemistry, was formed atropodiastereoselectively by cyclization of the chiral (*R*) methyl intermediate *R*-**2** in preference to the *aS*-isomer [(*aS*,9*R*)-**3**] in a ratio of ca. 98:2. The diastereomerically pure *aR*-form (TAK-637) was obtained by a single recrystallization of the crude product, and the minor *aS*-isomer was isolated from the mother liquor by repeated preparative HPLC (Scheme 2).

The *aR* stereochemistry of TAK-637 was determined by single-crystal X-ray structural analysis,[3,4] which also revealed the *trans*-conformation of the amide bond and a stacking conformation between the $C_{(5)}$-phenyl and the $N_{(7)}$-benzylic phenyl groups. The relative spatial orientation of the $C_{(9)}$-methyl group and the *N*-benzyl group in TAK-637 (*aR*,9*R*) is important for high atropodiastereoselectivity; these two groups are disposed in opposite directions, both in the crystalline form (as observed in the X-ray analysis) and in solution (i.e., the NOE was observed between the $C_{(9)}$-proton and a benzylic methylene proton by NMR spectroscopic studies), whereas the same groups in the minor

Keywords: Atropisomer; Stereoselective synthesis; Tachykinin NK_1 antagonist; Pyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one; Pyrido[2,3-*b*][1,5]oxazocin-6-one.
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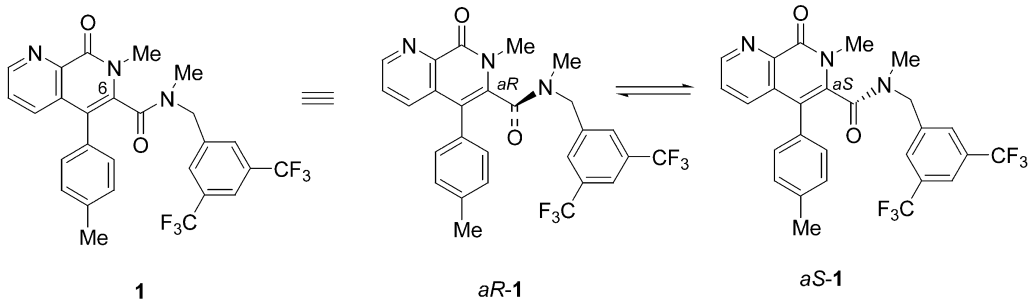
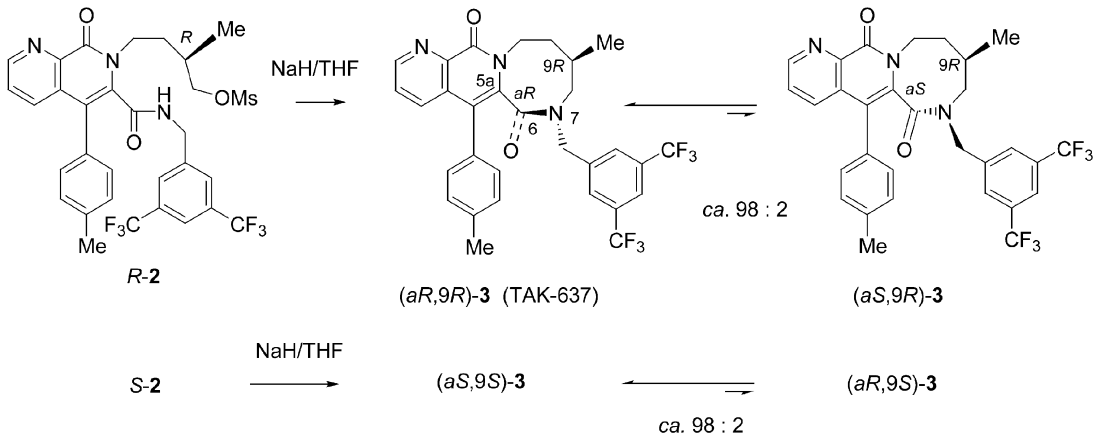
doi:10.1016/j.tet.2004.01.097



Scheme 1. Atropisomers of **1**.



Scheme 2. Atropodiastereoselective formation of **3** from the chiral intermediates (*R*-**2** and *S*-**2**).

isomer [(*aS*,9*R*)-**3**] are shown to be disposed in the same orientation in solution as observed by the NOE between the $C_{(9)}$-methyl protons and a benzylic methylene proton.[4] The repulsion of these groups in (*aS*,9*R*)-**3** may cause steric instability, leading to the preferential formation of the thermodynamically stable atropisomer (*aR*,9*R*)-**3** in the cyclization of the chiral intermediate *R*-**2**. The enantiomers [(*aS*,9*S*)-**3** and (*aR*,9*S*)-**3**] were similarly obtained starting from the enantiomeric *S*-methyl intermediate (*S*-**2**).

The NK_1-antagonistic activity of these stereoisomers [IC_{50}, nM: (*aR*,9*R*)-**3**, 0.45; (*aS*,9*R*)-**3**, 20; (*aS*,9*S*)-**3**, 340; (*aR*,9*S*)-**3**, 8.6] and X-ray analysis of (*aR*,9*R*)-**3** indicate that the pharmacophore of this class antagonists is **A** (Fig. 1), in which the *aR* stereochemistry and the stacking conformation between the two phenyl groups are important for NK_1-receptor binding.[4]

In this paper, we describe the amide-based atropisomerism in the *N*-benzylcarboxamide derivatives of bicyclic 3,4-dihydropyrido[3,2-*f*][1,4] oxazepin-5(2*H*)-one (**4**), 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (**5**) and its chiral derivatives (**6**) using the chemistry developed in our previous studies. Those NK_1-antagonistic activities are also examined to obtain more simplified, bicyclic analogues of TAK-637.

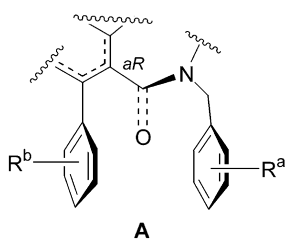
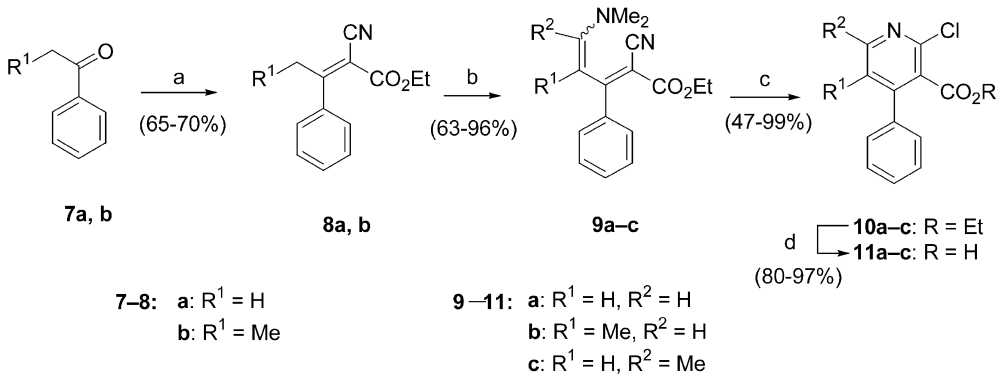


Figure 1. Pharmacophore structure (**A**) required for NK_1-receptor recognition.

2. Synthetic chemistry

The synthesis of bicyclic compounds (**4**–**6**) is outlined in Schemes 3 and 4. Key components are 2-chloro-4-phenyl-3-pyridine carboxylic acids (**11a**–**c**), which were prepared according to a procedure similar to that previously reported.[6] Thus, commercially available acetophenones (**7a** and **7b**) were condensed with ethyl cyanoacetate, followed by reaction with dimethylformamide dimethyl acetals to afford the enamines (**9a**–**c**). Formation of the pyridine ring was achieved by reacting the enamines with anhydrous hydrogen chloride to afford ethyl 2-chloro-4-phenylpyridine-3-carboxylates (**10a**–**c**), which were hydrolyzed to give acids (**11a**–**c**). Other components (Schemes 3), *N*-3,5-bis(trifluoromethyl) benzylamino-alkanols (**15i**–**iv**), were prepared from 3,5-bis(trifluoromethyl) benzyl alcohol (**12**) by mesylation, followed by displacement with amino-alkanols (**14i**–**iv**).[7]Amidation of pyridine carboxylic acids (**11a**–**c**) (via the acid chloride) with *N*-benzylamino-alkanols (**15i**–**iv**) followed by intramolecular cyclization using sodium hydride in tetrahydrofuran (THF) under reflux afforded the desired 7- and 8-membered cyclic compounds (**4**–**6**). The stereochemical features of the bicyclic compounds are described in Section 4.



Scheme 3. Preparation of 2-chloro-3-phenyl-2-carboxylic acids **11a**–**c**. Reagents: (a) $NCCH_2CO_2Et$, AcONa/AcOH/PhH (azeotropic); (b) for **9a** and **9b**: $Me_2NCH(OMe)_2$, rt, for **9c**: $Me_2NCMe(OMe)_2$, rt; (c) 4 N-HCL in AcOEt; (d) 4 N-NaOH(aq)/EtOH.

3. Biology

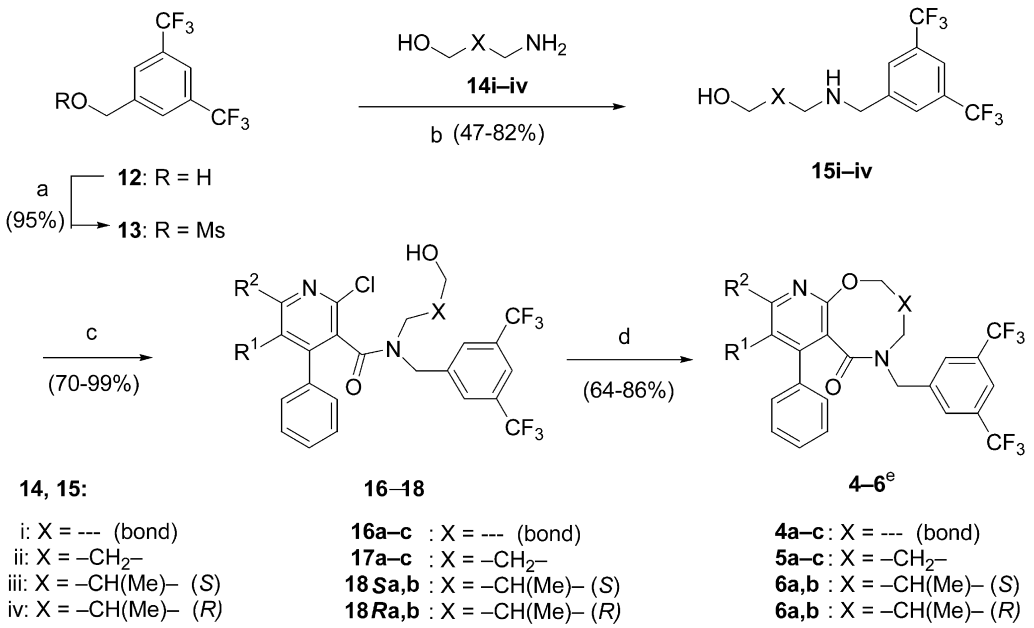
The compounds prepared were evaluated in vitro for inhibition of [^{125}I]-Bolton–Hunter (BH)-substance P binding in human IM-9 cells.[1,8]

4. Results and discussion

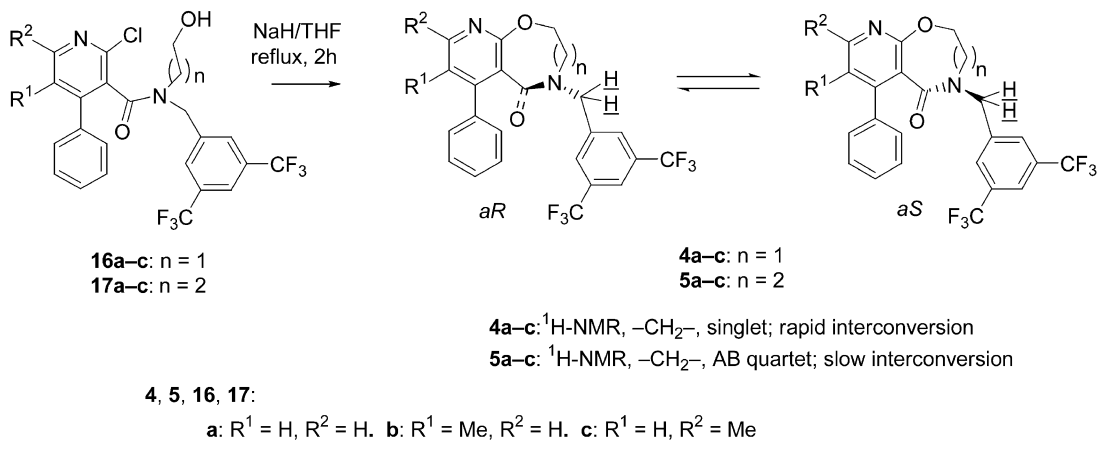
4.1. Atropisomerism

Since the carboxamide moiety of the compounds **4**–**6** exists at a sterically hindered position, the presence of stable atropisomers (*aR*- and *aS*-forms) was anticipated, as was observed in **1** and TAK-637. First, the *N*-benzylcarboxamide derivatives of bicyclic 3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one (**4**) and 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (**5**), which do not have a methyl substituent on the 7- and 8-membered ring, were synthesized (Scheme 5), and those structures were analyzed by ^{1}H NMR spectroscopy since the pattern of *N*-benzylic methylene protons in the NMR spectrum is diagnostic for the detection of the atropisomers. In compounds with a 7-membered ring (**4a**–**c**), the methylene protons appeared as a singlet,[9] whereas those of the compounds with an 8-membered ring (**5a**–**c**) appeared as an AB pattern (J=15.2–15.6 Hz) (Table 1). These data indicate that the conformers (atropisomers) of **4** are rapidly interconverted[9] even on the NMR timescale at room temperature, whereas those of **5** are slowly interconverted, with the methylene protons being diastereotopic.[2,4] Thus, although the separation of the atropisomers of **5** has not been attempted, we presume that compounds **5** exist as racemates.

Based on these data, we next synthesized the *N*-benzylcarboxamide derivatives of 7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (**6**), which bear a chiral methyl group on the 8-membered ring, expecting the



Scheme 4. Preparation of bicyclic compounds. Reagents: (a) MsCl, Et_3N/THF; (b) **14i**–**iv**, THF; (c) acid chlorides of **11a** or **11b**, Et_3N/THF; (d) NaH, THF, reflux, 2 h; (e) for specification of the reside X in **4**–**6** including stereochemistry originating from atropisomerism, see Schemes 5 and 6.



Scheme 5. Cyclization of the intermediates (**16** and **17**) and interconversion between a*R*- and a*S*-isomers in the products (**4** and **5**).

enantioselective formation of the axial chirality induced by the chirality at $C_{(3)}$, as was observed in the synthesis of TAK-637 (Scheme 6).

Heating a THF solution of the chiral intermediates with the *S*-methyl group (**18*S*a** and **18*S*b**) under reflux for 2 h in the presence of sodium hydride gave the cyclized compounds (3*S*)-**6a**[10] and (3*S*)-**6b**[10] as colorless crystalline substances, respectively. Similarly, the enantiomeric intermediates with the *R*-methyl group, **18*R*a** and **18*R*b**, afforded (3*R*)-**6a** and (3*R*)-**6b**, respectively, in satisfactory yields (Table 2, Scheme 6).

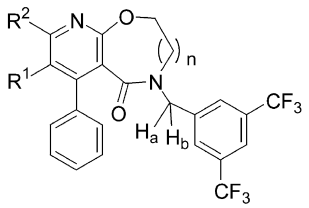
The ^{1}H NMR spectra (in $CDCl_3$) revealed that all of these compounds showed signals due to two diastereomers in a ratio of ca. 98:2[11] as determined by the peak area of the methyl group(s) at $C_{(3)}$ [for (3*S*)-**6b**; δ, major 0.83 (d, J=6.6 Hz) and minor 1.31 (d, J=7.3 Hz)] and/or $C_{(8)}$ [for (3*S*)-**6b**; δ, major 2.07 (s) and minor 1.98 (s)]. The ratio (ca. 98:2) was not altered by repeated crystallization of (3*S*)-**6b** or by heating (3*S*)-**6b** in toluene under reflux for 2 h. From these data, we assumed that (3*S*)-**6b** is a single isomer in the solid state and exists as two conformers in solution.[12]

The stereochemistry was deduced by detailed NMR spectroscopic analysis in $CDCl_3$ using (3*S*)-**6b**: the signals of the major isomer were in good agreement with those of TAK-637,[4] revealing (*aR*,3*S*)[10] stereochemistry [i.e., the NOE observed between the $C_{(3)}$-proton (H-3) and a benzylic methylene proton (H-1′a) (Fig. 2) indicates that the axial chirality is *aR*, and the chemical shifts and coupling constants of the 8-membered ring protons (–$C_{(3)}$HMe–$C_{(4)}H_2$–) together with long range coupling between a $C_{(4)}$-proton (H-4b) and a benzylic methylene proton (H-1′b) (J=1.4 Hz) also support the (*aR*,3*S*) structure]. On the other hand, the signals of the minor isomer (see Section 6) correspond well to those of the minor *aS*-isomer of TAK-637, indicating that the minor peaks observed in the NMR spectrum are those of the (*aS*,3*S*)-isomer.

In the NOESY spectrum of (3*S*)-**6b**, intersite exchange peaks were observed between the two isomers at the positions of CH_3-3, CH_3-8, H-4b, H-2a and H-2b, demonstrating that these isomers are interconverted in solution.[13]

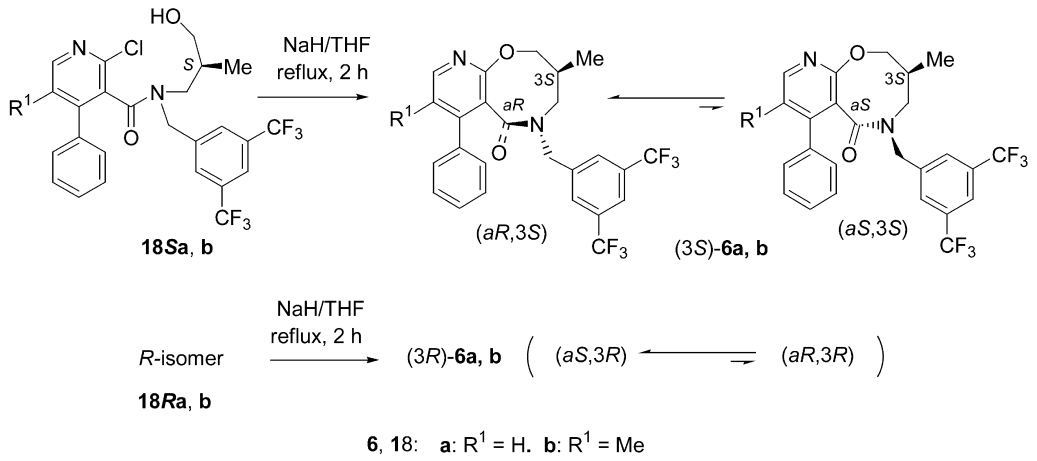
Taking all this evidence into consideration, the structure of (3*S*)-**6b** could reasonably be explained as (*aR*,3*S*) in the

Table 1. Physicochemical properties and NK_1-antagonistic activity of 3,4-dihydrophyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-ones (**4a–c**) and 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-ones (**5a–c**)



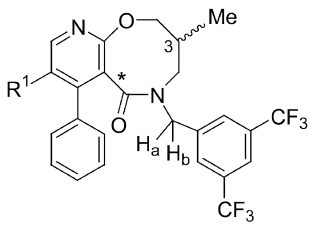
Compound no.	R^1	R^2	*n*	Yield (%)	Mp (°C)	^{1}H NMR[a] ppm, δ (Hz) (–CH_aH_b–)	NK_1-antagonistic activity[b] IC_{50} (nM)
4a	H	H	1	86	200–201	4.88 (2H, s)	4.3
4b	Me	H	1	80	179–181	4.80 (2H, s)	1.1
4c	H	Me	1	83	151–153	4.87 (2H, s)	3.3
5a	H	H	2	82	188–189	4.17, 5.50 (each 1H, d, J=15.2 Hz)	7.1
5b	Me	H	2	64	180–182	4.05, 5.45 (each 1H, d, J=15.6 Hz)	1.6
5c	H	Me	2	77	164–165	4.14, 5.49 (each 1H, d, J=15.2 Hz)	2.5

TAK-637 showed IC_{50} value of 0.45 nM in this assay.
[a] In $CDCl_3$: s=singlet, d=doublet.
[b] Inhibition of [^{125}I]-BH-SP binding in human 1M-9 cells (lymphoblast cells).



Scheme 6. Cyclization of the intermediates with *S*-Me and *R*-Me (**18*S*** and **18*R***).

Table 2. Physicochemical properties and NK_1-antagonistic activity of chiral 2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-ones (**6**)



Compound no.	R^1	Chirality		Yield (%)	Mp (°C)	$[\alpha]_D$ (in $CHCl_3$)	^1H NMR[a] ppm,δ (Hz) ($-CH_aH_b-$)[b]	NK_1-antagonistic activity[a] IC_{50} (nM)
		At $C_{(3)}$	At axial (*)[c]					
(3*S*)-**6a**	H	*S*	*R*	82	142–143	−75.1	4.19, 5.49 (each 1H, d, *J*=15.6 Hz)	1.4
(3*S*)-**6b**	Me	*S*	*R*	65	147–148	−106.8	4.06, 5.44 (each 1H, d, *J*=15.3 Hz)	0.47
(3*R*)-**6c**	H	*R*	*S*	74	142–143	+75.2	4.19, 5.49 (each 1H, d, *J*=15.6 Hz)	69
(3*R*)-**6b**	Me	*R*	*S*	68	147–149	+102.5	4.06, 5.44	96

[a] See corresponding footnotes of Table 1.
[b] The peaks for the major atropisomer are described.
[c] In solution ($CDCl_3$), ca. 2% of the atropisomer exists as determined by ^1H NMR.

solid state, and to be in an equilibrium state between the (*aR*,3*S*)- and (*aS*,3*S*)-isomers in a ratio of ca. 98:2 in solution,[11] which may result from the low free energy of activation.

The predominantly formed (*aR*,3*S*) structure determined for (3*S*)-**6b** is also established for (3*S*)-**6a**. Consequently, the enantiomers (3*R*)-**6a** and (3*R*)-**6b** should have an (*aS*,3*R*) stereochemistry. The conformational preference at the axial chirality is well explained by the thermodynamically stable conformation in these isomers, i.e., the $C_{(3)}$-methyl group and the *N*-[3,5-bis(trifluoromethyl)-benzyl] group are disposed in opposite direction as observed in TAK-637 (see Fig. 2).

4.2. NK_1-Antagonistic activity

The NK_1-antagonistic activity of the bicyclic compounds without a methyl substituent on the 7- and 8-membered ring (**4a**–**c** and **5a**–**c**) are shown in Table 1. The in vitro potency is similar for both series of compounds. It is noteworthy that the compounds with a methyl group on the benzene ring at 7- or 8-position (**4b** and **5b**) showed improved affinity compared with compounds without a methyl group (**4a**, **4c**, **5a** and **5c**), which presumably reflects the stacking conformation desirable for receptor recognition, i.e., the methyl group in **4b** and **5b** constricts the two phenyl rings so as to take that conformation, as shown in Figure 3.[14]

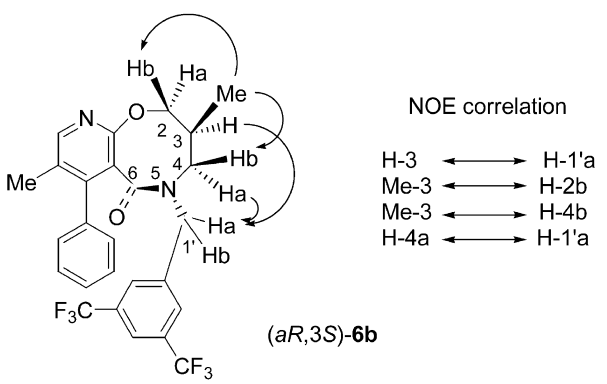
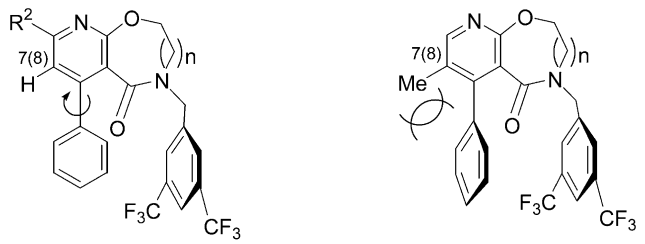


Figure 2. NOE correlation in (a*R*,3*S*)-**6b**.



4a: R^2 = H, n = 1
4c: R^2 = Me, n = 1
5a: R^2 = H, n = 2
5c: R^2 = Me, n = 2

4b: n = 1
5b: n = 2

Figure 3. Stacking conformation in **4b** and **5b** (right) caused by the 7- or 8-methyl group.

Table 2 shows the NK_1-antagonistic activity of the optically active compounds with an 8-membered ring (**6**). It was clearly shown that the enantiomers differ in activity, i.e., the (3*S*)-isomers which have a predominantly *aR* stereochemistry showed ca. 50–200-fold higher potency than the (3*R*)-enantiomers, indicating that the axial chirality is recognized by the NK_1 receptor. The methyl substituent on the benzene ring again improved the affinity by ca. 3-fold [(3*S*)-**6a** versus (3*S*)-**6b**].[13]

5. Conclusion

This study demonstrated that cyclization of the chiral intermediates (**18*S*** and**18*R***) gave thermodynamically stable conformers at the amide-based axial bond, the chirality of which was induced by the $C_{(3)}$ chirality. As observed in 1,7-naphthyridine-6-carboxamide derivatives (TAK-637 and **1**), in these compounds the *aR* axial chirality and the stacking conformation of the two phenyl rings are also important for NK_1-receptor recognition. Synthesis of NK_1 antagonists having other heterocycles based on the chemistry described in this study will be the subject of the forthcoming paper.

6. Experimental

6.1. Chemistry

Melting points were determined on a Yanagimoto micro melting point apparatus and were uncorrected. ^{1}H NMR spectra were taken on Varian Gemini 200 (200 MHz) spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts were given in ppm with tetramethylsilane as the internal standard and coupling constants (*J*) are given in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra were obtained on a JEOL JMS-AX505W spectrometer. Optical rotations were determined with a JASCO DIP-370 digital polarimeter. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd. Extracted solutions were dried over anhydrous $MgSO_4$ or anhydrous Na_2SO_4. The yields reported are not optimized.

6.1.1. Ethyl 2-cyano-3-phenylbut-2-enoate (8a). This compound was prepared according to the published method.[6]

6.1.2. Ethyl 2-cyano-3-phenylpent-2-enoate (8b). A mixture of **7b** (33.6 g, 250 mmol), ethyl cyanoacetate (28.3 g, 250 mmol), ammonium acetate (3.85 g, 50 mmol), acetic acid (12 g), and benzene (50 mL) was refluxed for 10 h, while water was removed azeotropically using Dean–Stark apparatus. After evaporation of the solvent, Et_2O (100 mL) was added to the residue. The mixture was washed with H_2O, 0.5 N HCl, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine successively. The organic layer was dried and concentrated. The residue was distilled under reduced pressure (3 mm Hg, 160 °C) to afford **8b** as a pale yellow oil (37.0 g, 65%): ^{1}H NMR 1.00–1.15 (3H+3H×1/2, m), 1.38 (3H×1/2, t, *J*=7.2 Hz), 2.87 (2H×1/2, q, *J*=7.6 Hz), 3.11 (2H×1/2, q, *J*=7.4 Hz), 4.08 (2H×1/2, q, *J*=7.4 Hz), 4.35 (2H×1/2, q, *J*=7.2 Hz), 7.05–7.20 (1H, m), 7.30–7.55 (4H, m).

6.1.3. Ethyl 2-cyano-5-(dimethylamino)-3-phenylpenta-2,4-dienoate (9a). This compound was prepared according to the published method.[6]

6.1.4. Ethyl 2-cyano-5-(dimethylamino)-4-methyl-3-phenylpenta-2,4-dienoate (9b). *N*,*N*-Dimethylformamide dimethyl acetal (9.40 mL, 70.2 mmol) was added dropwise to **8a** (13.4 g, 58.4 mmol) at 0 °C. After stirring at room temperature for 2 h, the mixture was concentrated under reduced pressure to afford **9b** as a red oil (16.0 g, 96%). The oil was used for next reaction without preparation and further purification.

6.1.5. Ethyl 2-cyano-5-(dimethylamino)-3-phenylhexa-2,4-dienoate (9c). *N*,*N*-Dimetylacetamide dimethyl acetal (containing 5–10% MeOH) (26.7 g, 180 mmol) was added dropwise to **8a** (30.0 g, 131 mmol) at 0 °C. After stirring at room temperature for 2 h, the mixture was concentrated under reduced pressure. The resulting solid was washed with Et_2O–AcOEt (1:1) to afford **9c** as yellow crystals (23.3 g, 63%); ^{1}H NMR 1.12 (3H×1/5, t, *J*=7.0 Hz), 1.33 (3H×4/5, t, *J*=7.0 Hz), 1.39 (3H×4/5, s), 1.51 (3H×1/5, s), 3.12 (6H×1/5, s), 3.15 (6H×4/5, s), 4.00 (2H×1/5, q, *J*=7.0 Hz), 4.25 (2H×4/5, q, *J*=7.0 Hz), 5.78 (1H×1/5, s), 7.12 (1H×4/5, s), 7.15–7.48 (5H, m).

6.1.6. Ethyl 2-chloro-4-phenylnicotinate (10a). This compound was prepared according to the published method.[6]

6.1.7. Ethyl 2-chloro-5-methyl-4-phenylnicotinate (10b). A solution of 4 N HCl in AcOEt (150 mL) was added to **9b** (17.9 g, 62.9 mmol), and the mixture was stirred at room temperature for 30 h. After evaporation of the solvent, AcOEt was added to the residue. The mixture was washed successively with H_2O, 1 N HCl, H_2O, saturated aqueous $NaHCO_3$, H_2O, and brine. The organic layer was dried and concentrated. The residue was subjected to chromatography on silica gel using hexane–AcOEt (4:1) as eluant to afford **10b** as colorless oil (8.23 g, 47%). Recrystallization from AcOEt–hexane gave colorless crystals: mp 89–90°C; ^{1}H NMR 0.98 (3H, t, *J*=7.2 Hz), 2.11 (3H, s), 4.06 (2H, q,

J=7.2 Hz), 7.15–7.30 (2H, m), 7.37–7.50 (3H, m), 8.33 (1H, s).

6.1.8. Ethyl 2-chloro-6-methyl-4-phenylnicotinate (10c). Compound **9c** (6.61 g, 81.9 mmol) was treated according to a procedure similar to that described for the preparation of **10b** to afford **10c** as a pale yellow oil (15.4 g, 68%); ^{1}H NMR 1.08 (3H, t, J=7.0 Hz), 2.60 (3H, s), 4.18 (2H, q, J=7.0 Hz), 7.13 (1H, s), 7.30–7.50 (5H, m).

6.1.9. 2-Chloro-4-phenylnicotinic acid (11a). This compound was prepared according to the published method.[6]

6.1.10. 2-Chloro-5-methyl-4-phenylnicotinic acid (11b). A mixture of **10b** (8.20 g, 29.7 mmol), EtOH (10 mL) and 4 N aqueous NaOH solution (10 mL) was refluxed for 4 h, and then concentrated under reduced pressure. The residue was acidified with concentrated HCl, and the mixture was extracted with AcOEt. The extract was washed with brine, dried and evaporated to afford **11b** as colorless crystals (5.97 g, 81%). Recrystallization from AcOEt–isopropyl ether (IPE) gave colorless crystals: mp 204–206 °C; ^{1}H NMR 2.18 (3H, s), 7.15–7.30 (2H, m), 7.37–7.60 (3H, m), 8.33 (1H, s). Anal. Calcd $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.02; H, 4.09; N, 5.69.

6.1.11. 2-Chloro-6-methyl-4-phenylnicotinic acid (11c). Compound **10c** (6.60 g, 25.2 mmol) was treated according to a procedure similar to that described for the preparation of **11b** to afford **11c** as colorless crystals (4.70 g, 80%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 191–194 °C; ^{1}H NMR 2.59 (3H, s), 7.16 (1H, s), 7.45 (5H, s), 9.53 (1H, br.s). Anal. Calcd $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.06; H, 4.06; N, 5.65.

6.1.12. 3,5-Bis(trifluoromethyl)benzyl methanesulfonate (13). Methanesulfonyl chloride (1.74 mL, 22.5 mmol) was added dropwise to a solution of 3,5-bis(trifluoromethyl)-benzyl alcohol **12** (5.00 g, 20.5 mmol) and triethylamine (3.14 mL, 22.5 mmol) in THF (50 mL) at 0°C. After stirring at room temperature for 30 min, the mixture was concentrated. The residue was diluted with AcOEt (50 mL) and washed with brine. The organic layer was dried and concentrated to afford **13** as colorless crystals (6.28 g, 95%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 61–62°C; ^{1}H NMR 3.09 (3H, s), 5.33 (2H, s), 7.87 (2H, s), 7.91 (1H, s). Anal. Calcd $C_{10}H_8F_6O_3S$: C, 37.27; H, 2.50. Found: C, 37.25; H, 2.72.

6.1.13. 2-{[3,5-Bis(trifluoromethyl)benzyl]amino}alkanols (15i–iv). A typical procedure is described for 2-{[3,5-bis(trifluoromethyl)benzyl]amino}ethanol **15i**: A solution of **13** (1.89 g, 5.86 mmol) in THF (10 mL) was added dropwise to a solution of 2-aminoethanol **14i** (3.6 mL, 59.6 mmol) in THF (30 mL) at 0 °C. After stirring at room temperature for 1 h, the mixture was concentrated. The residue was diluted with AcOEt (50 mL), and washed with H_2O and brine. The organic layer was dried and concentrated to give **15i** as colorless crystals (1.38 g, 82%). Recrystallization from EtOH–Et_2O gave colorless crystals: mp 107–108°C; ^{1}H NMR 1.38 (2H, s), 2.83 (2H, t, J=5.4 Hz), 3.72 (2H, t, J=5.4 Hz), 3.96 (2H, s), 7.78 (1H, s), 7.82 (2H, s). Anal. Calcd $C_{11}H_{11}F_6NO$: C, 46.00; H, 3.86; N, 4.88. Found: C, 46.01; H, 3.86; N, 4.89.

Similarly, compounds **15ii–iv** were prepared from **13** and the corresponding amino-alkanols **14ii–iv**.

6.1.14. 3-{[3,5-Bis(trifluoromethyl)benzyl]amino}propan-1-ol (15ii). From **13** (6.65 g, 20.6 mmol) and 3-aminopropanol **14ii** (15.7 mL, 205 mmol). Colorless crystals (4.10 g, 66%). Recrystallization from Et_2O–hexane gave colorless crystals: mp 57–58 °C; ^{1}H NMR 1.77 (2H, quintet, J=5.8 Hz), 2.20–2.80 (2H, br), 2.89 (2H, t, J=5.8 Hz), 3.82 (2H, t, J=5.8 Hz), 3.93 (2H, s), 7.89 (3H, s). Anal. Calcd $C_{12}H_{13}F_6NO$: C, 47.85; H, 4.35; N, 4.65. Found: C, 47.76; H, 4.32; N, 4.65.

6.1.15. (2*S*)-3-{[3,5-Bis(trifluoromethyl)benzyl]amino}-2-methylpropan-1-ol (15iii). From **13** (1.20 g, 3.72 mmol) and (2*S*)-3-amino-2-methylpropan-1-ol **14iii**[7] (500 mg, 5.61 mmol). A colorless oil (635 mg, 56%); ^{1}H NMR 0.86 (3H, d, J=6.8 Hz), 1.98 (1H, m), 2.63 (1H, dd, J=11.8, 9.4 Hz), 2.70–2.90 (2H, m), 2.86 (1H, ddd, J=11.8, 4.0, 1.4 Hz), 3.56 (1H, dd, J=10.6, 9.4 Hz), 3.71 (1H, ddd, J=10.6, 4.0, 1.4 Hz), 3.87 (1H, d, J=13.8 Hz), 3.98 (1H, d, J=13.8 Hz), 7.79 (3H, s).

6.1.16. (2*R*)-3-{[3,5-Bis(trifluoromethyl)benzyl]amino}-2-methylpropan-1-ol (15iv). From **13** (2.40 g, 7.45 mmol) and (2*R*)-3-amino-2-methylpropan-1-ol **14iv**[7] (1.00 g, 11.2 mmol). A colorless oil (1.10 g, 47%); ^{1}H NMR spectrum was identical with that of **15iii**.

6.1.17. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(2-hydroxyalkyl)-4-phenylnicotinamides (16, 17, 18*S* and 18*R*). A typical procedure is described for *N*-[3,5-bis(trifluoromethyl)benzyl]-2-chloro-*N*-(2-hydroxyethyl)-4-phenylnicotinamide **16a**: Thionyl chloride (0.70 mL, 9.6 mmol) was added dropwise to a solution of **11a** (318 mg, 1.36 mmol) and DMF (catalytic amount) in THF (10 mL), and the mixture was refluxed for 4 h. The mixture was concentrated, and dissolved in THF (5 mL). The solution was added dropwise to a mixture of **15i** (391 mg, 1.36 mmol), triethylamine (0.57 mL, 4.1 mmol) and THF (5 mL) at 0 °C. After stirring at room temperature for 2 h, the mixture was concentrated. The residue was diluted with AcOEt, and washed with H_2O and brine. The organic layer was dried and concentrated. The residue was subjected to chromatography on silica gel using hexane–AcOEt (1:1) as eluant to give **16a** as a colorless oil (551 mg, 81%, the ratio of *cis*–*trans* amide isomer: ca. 2:1); ^{1}H NMR 2.00–2.40 (1H, m), 2.82–3.92 (4H, m), 4.16 (1H×1/3, d, J=16.0 Hz), 4.41 (1H×1/3, d, J=16.0 Hz), 4.73 (1H×2/3, d, J=15.0 Hz), 4.87 (1H×2/3, d, J=15.0 Hz), 7.20–8.85 (9H, m), 8.43 (1H, m).

Similarly, compounds **16b**,**c**, **17a–c**, **18*S*a**,**b** and **18*R*a**,**b** were prepared from corresponding 3-pyridine carboxylic acids **11a–c** and 2-{[3,5-bis(trifluoromethyl)benzyl]amino}alkanols **15i–iv**.

6.1.18. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(2-hydroxyethyl)-5-methyl-4-phenylnicotinamide (16b). From **11b** (300 mg, 1.21 mmol) and **15i** (430 mg, 1.33 mmol). Colorless crystals (435 mg, 70%). Recrystallization

from AcOEt–IPE gave colorless crystals: mp 146–148 °C; ^{1}H NMR 1.60–1.70 (1H, m), 2.09 (3H, s), 3.02 (1H, dt, *J*=15.0, 5.6 Hz), 3.25 (1H, dt, *J*=15.0, 5.6 Hz), 3.60 (2H, m), 4.57 (1H, d, *J*=15.2 Hz), 4.79 (1H, d, *J*=15.2 Hz), 7.05–7.50 (5H, m), 7.62 (2H, s), 7.76 (1H, s), 8.33 (1H, s). Anal. Calcd $C_{24}H_{19}ClF_6N_2O_2$: C, 55.77; H, 3.71; N, 5.42. Found: C, 55.79; H, 3.73; N, 5.41.

6.1.19. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(2-hydroxyethyl)-6-methyl-4-phenylnicotinamide (16c). From **11c** (2.00 g, 8.07 mmol) and **15i** (2.86 g, 8.88 mmol). A colorless oil (4.07 g, 98%); the ratio of *cis*–*trans* amide isomer, ca. 3:2; ^{1}H NMR 1.95–3.80 (5H, m), 2.58 (3H, s), 4.15 (1H×2/5, d, *J*=16.2 Hz), 4.41 (1H×2/5, d, *J*=16.2 Hz), 4.75 (1H×3/5, d, *J*=15.0 Hz), 4.85 (1H×3/5, d, *J*=15.0 Hz), 7.15 (1H×3/5, s), 7.17 (1H×2/5, d, *J*=15.0 Hz), 7.23–7.58 (5H, m), 7.74 (2H, s), 7.78 (1H, s).

6.1.20. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(3-hydroxypropyl)-4-phenylnicotinamide (17a). From **11a** (830 mg, 3.55 mmol) and **15ii** (1.07 g, 3.55 mmol). Colorless crystals (1.55 g, 84%, the ratio of *cis*–*trans* amide isomer: ca. 3:1). Recrystallization from AcOEt–IPE gave colorless crystals: mp 121–122 °C; ^{1}H NMR 1.00–1.70 (2H, m), 2.75–3.20 (2H, m), 3.35–3.55 (3H, m), 4.06 (1H×1/4, d, *J*=16.2 Hz), 4.31 (1H×1/4, d, *J*=16.2 Hz), 4.65 (1H×3/4, d, *J*=15.2 Hz), 4.76 (1H×3/4, d, *J*=15.2 Hz), 7.20–7.55 (6H, m), 7.72 (2H, s), 7.80 (1H, s), 8.47 (1H, d, *J*=5.2 Hz). Anal. Calcd $C_{24}H_{19}ClF_6N_2O_2$: C, 55.77; H, 3.71; N, 5.42. Found: C, 55.65; H, 3.70; N, 5.57.

6.1.21. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(3-hydroxypropyl)-5-methyl-4-phenylnicotinamide (17b). From **11b** (300 mg, 1.21 mmol) and **15ii** (400 mg, 1.33 mmol). A colorless oil (626 mg, 97%, the ratio of *cis*–*trans* amide isomer: ca. 1:1); ^{1}H NMR 1.10–1.80 (2H, m), 1.85–2.00 (1H, m), 2.06 (3H×1/2, s), 2.08 (3H×1/2, s), 2.80–3.30 (3H, m), 3.35–3.70 (1H, m), 4.08 (1H×1/2, d, *J*=16.4 Hz), 4.39 (1H×1/2, d, *J*=15.0 Hz), 4.47 (1H×1/2, d, *J*=16.4 Hz), 4.70 (1H×1/2, d, *J*=15.0 Hz), 6.90–7.62 (7H, m), 7.72 (1H×1/2, s), 7.77 (1H×1/2, s), 8.28 (1H×1/2, s), 8.31 (1H×1/2, s).

6.1.22. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-(3-hydroxypropyl)-6-methyl-4-phenylnicotinamide (17c). From **11c** (938 mg, 4.02 mmol) and **15ii** (1.33 g, 4.42 mmol). A colorless oil (1.95 g, 96%, the ratio of *cis*–*trans* amide isomer: ca. 3:2); ^{1}H NMR 1.15–1.65 (2H, m), 2.59 (3H, s), 2.75–3.20 (2H, m), 3.25–3.55 (3H, m), 4.06 (1H×2/5, d, *J*=15.4 Hz), 4.31 (1H×2/5, d, *J*=15.4 Hz), 4.65 (1H×3/5, d, *J*=15.2 Hz), 4.74 (1H×3/5, d, *J*=15.2 Hz), 7.16 (1H, s), 7.20–7.60 (5H, m), 7.72 (2H, s), 7.78 (1H, s).

6.1.23. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-[(2*S*)-3-hydroxy-2-methylpropyl]-4-phenylnicotinamide (18*S*a). From **11a** (850 mg, 3.64 mmol) and **15iii** (1.37 g, 4.35 mmol). A colorless oil (1.40 g, 74%, the ratio of *cis*–*trans* amide isomer: ca. 1:1); ^{1}H NMR 0.53 (3H×1/4, d, *J*=7.0 Hz), 0.63 (3H×1/4, d, *J*=7.0 Hz), 0.75 (3H×1/4, d, *J*=6.8 Hz), 0.81 (3H×1/4, d, *J*=6.8 Hz), 1.50–1.90 (1H, m), 2.42–3.80 (5H, m), 4.00–4.95 (2H, m), 7.10–7.90 (9H, m), 8.42 (1H, m).

6.1.24. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-[(2*S*)-3-hydroxy-2-methylpropyl]-5-methyl-4-phenylnicotinamide (18*S*b). From **11b** (513 mg, 2.07 mmol) and **15iii** (653 mg, 2.07 mmol). A colorless oil (1.06 g, 94%); ^{1}H NMR 0.60–0.82 (3H, m), 1.50–2.00 (2H, m), 2.00–2.15 (3H, m), 2.15–3.92 (4H, m), 4.05–4.92 (2H, m), 7.00–7.85 (8H, m), 8.34 (1H, m).

6.1.25. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-[(2*R*)-3-hydroxy-2-methylpropyl]-4-phenylnicotinamide (18*R*a). From **11a** (1.14 g, 4.88 mmol) and **15iv** (1.84 g, 5.83 mmol). A colorless oil (2.14 g, 85%, the ratio of *cis*–*trans* amide isomer: ca. 1:1); ^{1}H NMR spectrum was identical with that of **18*S*a**.

6.1.26. *N*-[3,5-Bis(trifluoromethyl)benzyl]-2-chloro-*N*-[(2*R*)-3-hydroxy-2-methylpropyl]-5-methyl-4-phenylnicotinamide (18*R*b). From **11b** (824 mg, 3.49 mmol) and **15iv** (1.10 g, 3.49 mmol). A colorless oil (1.73 g, 100%.); ^{1}H NMR spectrum was identical with that of **18*S*b**.

6.1.27. 4-[3,5-Bis(trifluoromethyl)benzyl]-6-phenyl-3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-ones (4a–c) and 5-[3,5-bis(trifluoromethyl)benzyl]-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-ones (5a–c). A typical procedure is described for 4-[3,5-bis(trifluoromethyl)benzyl]-6-phenyl-3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one **4a**: NaH (60% in oil) (60 mg, 1.5 mmol) was added to a solution of **16a** (348 mg, 0.69 mmol) in THF (15 mL), and the mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and diluted with AcOEt, washed successively with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried and concentrated to afford **4a** as colorless crystals (278 mg, 86%). Recrystallization from EtOH–hexane gave colorless crystals: mp 200–201 °C; ^{1}H NMR 3.70 (2H, t, *J*=5.8 Hz), 4.47 (2H, t, *J*=5.8 Hz), 4.88 (2H, s), 7.24 (1H, d, *J*=5.2 Hz), 7.25–7.55 (5H, m), 7.80 (2H, s), 7.86 (1H, s), 8.44 (1H, d, *J*=5.2 Hz). MS (electron impact) *m*/*z* 466 (M^+) $[(C_{23}H_{16}F_6N_2O_2)^+]$.

Similarly, **4b**, **4c** and **5a**–**c** were prepared from **16b**, **16c** and **17a**–**c**, respectively.

6.1.28. 4-[3,5-Bis(trifluoromethyl)benzyl]-7-methyl-6-phenyl-3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one (4b). From **16b** (100 mg, 0.19 mmol). Colorless crystals (74 mg, 80%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 179–181 °C; ^{1}H NMR 2.13 (3H, s), 3.57 (2H, t, *J*=5.8 Hz), 4.42 (2H, t, *J*=5.8 Hz), 4.80 (2H, s), 7.16 (2H, m), 7.47 (3H, m), 7.65 (2H, s), 7.81 (1H, s), 8.32 (1H, s).

6.1.29. 4-[3,5-Bis(trifluoromethyl)benzyl]-8-methyl-6-phenyl-3,4-dihydropyrido[3,2-*f*][1,4]oxazepin-5(2*H*)-one (4c). From **16c** (2.16 g, 4.18 mmol). Colorless crystals (1.66 g, 83%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 151–153 °C; ^{1}H NMR 2.58 (3H, s), 3.69 (2H, t, *J*=5.4 Hz), 4.47 (2H, t, *J*=5.4 Hz), 4.87 (2H, s), 7.11 (1H, s), 7.17–7.56 (5H, m), 7.80 (2H, s), 7.86 (1H, s). Anal. Calcd $C_{24}H_{18}F_6N_2O_2 \cdot 1/4H_2O$: C, 59.44; H, 3.85; N, 5.78. Found: C, 59.42; H, 3.82; N, 5.84.

6.1.30. 5-[3,5-Bis(trifluoromethyl)benzyl]-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (5a). From **17a** (1.00 g, 1.93 mmol). Colorless crystals (763 mg, 82%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 188–189 °C; ^{1}H NMR 1.65–1.88 (1H, m), 2.18–2.45 (1H, m), 3.36 (1H, dd, *J*=15.2, 3.8 Hz), 3.73 (1H, m), 4.17 (1H, d, *J*=15.2 Hz), 4.32 (1H, dt, *J*=12.6, 3.6 Hz), 4.67 (1H, ddd, *J*=12.6, 5.6, 3.6 Hz), 5.50 (1H, d, *J*=15.2 Hz), 7.16 (1H, d, *J*=5.2 Hz), 7.20–7.45 (5H, m), 7.71 (2H, s), 7.83 (1H, s), 8.41 (1H, d, *J*=5.2 Hz). Anal. Calcd $C_{24}H_{18}F_6N_2O_2$: C, 60.00; H, 3.78; N, 5.83. Found: C, 59.92; H, 3.76; N, 5.89.

6.1.31. 5-[3,5-Bis(trifluoromethyl)benzyl]-8-methyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (5b). From **17b** (550 mg, 1.03 mmol). Colorless crystals (324 mg, 64%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 180–182 °C; ^{1}H NMR 1.71 (1H, m), 2.07 (3H, m), 2.28 (1H, m), 3.24 (1H, dd, *J*=15.2, 3.8 Hz), 3.64 (1H, dd, *J*=15.2, 12.0 Hz), 4.05 (1H, d, *J*=15.6 Hz), 4.27 (1H, dt, *J*=12.6, 3.8 Hz), 4.63 (1H, ddd, *J*=12.6, 5.4, 2.0 Hz), 5.45 (1H, d, *J*=15.6 Hz), 6.6–7.4 (2H, m), 7.37 (3H, br.s), 7.54 (2H, s), 7.78 (1H, s), 8.29 (1H, s). Anal. Calcd $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.67. Found: C, 60.69; H, 4.05; N, 5.63.

6.1.32. 5-[3,5-Bis(trifluoromethyl)benzyl]-9-methyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one (5c). From **17c** (1.95 g, 3.67 mmol). Colorless crystals (1.40 g, 77%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 164–165 °C; ^{1}H NMR 1.79 (1H, m), 2.30 (1H, m), 2.56 (3H, s), 3.35 (1H, m), 3.77 (1H, m), 4.14 (1H, d, *J*=15.2 Hz), 4.31 (1H, m), 4.65 (1H, m), 5.49 (1H, d, *J*=15.2 Hz), 7.02 (1H, s), 7.20–7.50 (5H, m), 7.72 (2H, s), 7.83 (1H, s). Anal. Calcd $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.67. Found: C, 60.43; H, 4.04; N, 5.74.

6.1.33. (3*S*)-5-[3,5-Bis(trifluoromethyl)benzyl]-3,8-dimethyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one [(3*S*)-6b]. NaH (60% in oil) (61 mg, 1.53 mmol) was added to a solution of **18*S*b** (417 mg, 0.76 mmol) in THF (40 mL), and the mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and diluted with AcOEt, washed successively with 1 N HCl, H_2O, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried and concentrated to afford (3*S*)-**6b** as colorless crystals (251 mg, 65%). Recrystallization from AcOEt–hexane gave colorless crystals: mp 147–148 °C; $[\alpha]_D^{20}=-106.8°$ (*c*=0.257, $CHCl_3$). Anal. Calcd $C_{26}H_{22}F_6N_2O_2$: C, 61.49; H, 4.36; N, 5.51. Found: C, 61.30; H, 4.52; N, 5.70. In the ^{1}H NMR spectrum ($CDCl_3$) taken on Varian Mercury 300 (300 MHz), a set of major and minor peaks were observed in a ratio of ca. 98:2, which was calculated from the peak area of CH_3-3 and CH_3-8. The major isomer assigned as (*aR*,3*S*)-**6b** showed the following peaks, which are corresponding well to those of TAK-637:[3,4] 0.83 (3H, d, *J*=6.6 Hz, CH_3-3), 2.07 (3H, s, CH_3-8), 2.40 (1H, m, H-3), 2.97 (1H, d, *J*=15.5 Hz, H-4a), 3.48 (1H, dd, *J*=15.5, 10.5 Hz, H-4b), 3.87 (1H, dd, *J*=12.6, 10.5 Hz, H-2a), 4.06 (1H, d, *J*=15.3 Hz, –C*H*aHb-Ar), 4.59 (1H, dd, *J*=12.6, 5.1 Hz, H-2b), 5.44 (1H, d, *J*=15.3 Hz, –CHa*H*b-Ar), 6.6–7.4 (2H, m, Ar), 7.37 (3H, br.s, Ar), 7.53 (2H, s, Ar), 7.78 (1H, s, Ar), 8.29 (1H, s, H-9); NOEs taken on a Bruker DPX 300 (300 MHz) spectrometer in $CDCl_3$, were observed between a benzylic methylene-Ha and H-3, CH_3-3 and H-2a, CH_3-3 and H-4b, and H-4a and a benzylic methylene-Ha (Fig. 2); long range couplings between H-4b and a benzylic methylene-Hb (*J*=1.4 Hz), and H-2b and H-4a (*J*=1.0 Hz) were also observed. The minor isomer assigned as (*aS*,3*S*)-**6b** showed the following peaks in the ^{1}H NMR spectrum, which are corresponding well to those of the minor isomer of TAK-637:[3,4] 1.31 (3H, d, *J*=7.3 Hz, CH_3-3), 1.98 (3H, s, CH_3-8), 3.35 (1H, dd, *J*=15.0, 4.5 Hz, H-4a), 3.65 (1H, dd, *J*=15.0, 6.0 Hz, H-4b), 4.23 (1H, dd, *J*=13.5, 4.5 Hz, H-2b), 4.35 (1H, dd, *J*=13.5, 4.5 Hz, H-2a), 8.23 (1H, s, H-9). Other peaks of the minor isomer could not be assigned because of overlapping with those of the major isomer. In the NOESY spectrum of (3*S*)-**6b**, intersite exchange peaks were observed between the two isomers at the positions of CH_3-3, CH_3-8, H-4b, H-2a and H-2b.

6.1.34. (3*S*)-5-[3,5-Bis(trifluoromethyl)benzyl]-3-methyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one [(3*S*)-6a]. Compound **18*S*a** (1.40 g, 2.63 mmol) was treated according to a procedure similar to that described for the preparation of (3*S*)-**6b** to afford (3*S*)-**6a** as colorless crystals (1.06 g, 82%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 142–143 °C; $[\alpha]_D^{20}=-75.1°$ (*c*=0.381, $CHCl_3$). Anal. Calcd $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.77. Found: C, 60.60; H, 4.00; N, 5.77; ^{1}H NMR (taken on Varian Mercury 300) [(*aR*,3*S*):(*aS*,3*S*)=ca. 98:2]; for (*aR*,3*S*), 0.87 (3H, d, *J*=6.9 Hz), 2.45 (1H, m), 3.10 (1H, d, *J*=15.3 Hz), 3.58 (1H, dd, *J*=15.3, 10.5 Hz), 3.91 (1H, dd, *J*=12.7, 10.5 Hz), 4.19 (1H, d, *J*=15.6 Hz), 4.63 (1H, dd, *J*=12.7, 5.1 Hz), 5.49 (1H, d, *J*=15.6 Hz), 7.17 (1H, d, *J*=5.0 Hz), 7.20–7.50 (5H, m), 7.71 (2H, s), 7.83 (1H, s), 8.42 (1H, d, *J*=5.0 Hz), and for (*aS*,3*S*), following peaks were assigned;1.36 (3H, d, *J*=7.8 Hz, CH_3-3), 3.64 (1H, dd, *J*=15.0, 6.6 Hz, H-4b), 4.34 (1H, dd, *J*=13.5, 4.5 Hz, H-2a), 7.06 (1H, d, *J*=5.0 Hz, H-8), 8.36 (1H, d, *J*=5.0 Hz, H-9).

6.1.35. (3*R*)-5-[3,5-Bis(trifluoromethyl)benzyl]-3-methyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one [(3*R*)-6a]. Compound **18*R*a** (2.14 g, 4.14 mmol) was treated according to a procedure similar to that described for the preparation of (3*S*)-**6b** to afford (3*R*)-**6a** as colorless crystals (1.52 g, 74%). Recrystallization from AcOEt–IPE gave colorless crystals: mp 142–143 °C; ^{1}H NMR spectrum was identical with that of (3*S*)-**6a**. $[\alpha]_D^{20}=+75.2°$(*c*=0.724, $CHCl_3$). Anal. Calcd $C_{25}H_{20}F_6N_2O_2$: C, 60.73; H, 4.08; N, 5.67. Found: C, 60.60; H, 3.86; N, 5.77.

6.1.36. (3*R*)-5-[3,5-Bis(trifluoromethyl)benzyl]-3,8-dimethyl-7-phenyl-2,3,4,5-tetrahydro-6*H*-pyrido[2,3-*b*][1,5]oxazocin-6-one [(3*R*)-6b]. Compound **18*R*b** (843 mg, 1.55 mmol) was treated according to a procedure similar to that described for the preparation of (3*S*)-**6b** to afford (3*R*)-**6b** as colorless crystals (533 mg, 68%). Recrystallization from AcOEt–hexane gave colorless crystals: mp 147–149 °C; ^{1}H NMR spectrum was identical with that of (3*S*)-**6b**. $[\alpha]_D^{20}=+102.5°$ (*c*=0.573, $CHCl_3$). Anal. Calcd $C_{26}H_{22}F_6N_2O_2$: C, 61.49; H, 4.36; N, 5.51. Found: C, 61.26; H, 4.33; N, 5.69.

6.2. [^{125}I]-BH-substance P binding in human IM-9 cells

The binding activity was determined according to the protocol previously reported.[1,8]

Acknowledgements

We thank Dr. Takenori Ishimaru for in vitro screening, and Ms. Fumiko Kasahara and Ms. Mika Murabayashi for NMR analysis.

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5. Compound **1** (*trans*-amide) reached an equilibrium state of *trans*- and *cis*-amide (=ca. 7:1) in solution (e.g., $CDCl_3$) in about ca. 6 h at room temperature. The *cis*-form of **1**, which was separated and isolated in a crystalline form by column chromatography, has weaker NK_1-antagonistic activity (IC_{50}=7.0 nM) than **1**. The presence of atropisomers in the *cis*-form was also shown by HPLC analysis using a chiral column.[1,2]
6. (a) Prager, R. H.; Were, S. T. *Aust. J. Chem.* **1983**, *36*, 1441–1453. (b) Miyazaki, M.; Matsuzawa, M. Jpn. Kokai Tokkyo Koho. H6-41116 (February 15, 1994).
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9. It should be noted that the *N*-benzylic methylene protons of 7-membered ring analogues of TAK-637 appeared as an AB pattern in the NMR spectrum,[4] suggesting that the conformation of the 7-membered ring in compounds **4a–c** changes more rapidly than that in TAK-637 derivatives.
10. For the stereochemistry at $C_{(3)}$ of **6**, note that the sequence of priority is different from that of TAK-637; the methyl group exists in β-configuration for both compounds.
11. The ratio in the NMR spectrum changed slightly depending on the solvent used; i.e., in CD_3OD, it was ca. 96:4, in DMSO-d_6, ca. 97:3, and in pyridine-d_5, ca. 97:3.
12. Coexistence of the two conformers (ca. 98:2) in the solid state of (3*S*)-**6b** may not be ruled out.
13. For a recent NOESY (EXSY) experiment in atropisomers, see: Gibson, K. R.; Hitzel, L.; Mortishire-Smith, R. J.; Gerhard, U.; Jelley, R. A.; Reeve, A. J.; Rowley, M.; Nadin, A.; Owens, A. P. *J. Org. Chem.* **2002**, *67*, 9354–9360.
14. In the ^{1}H NMR spectra, the $C_{(7)}$-phenyl protons of **5b**, (3*S*)-**6b** and (3*R*)-**6b** were observed as a broad signal (2H at 6.6–7.4 ppm) and a broad singlet (3H at 7.37 ppm), whereas those of **5a**, **5c**, (3*S*)-**6a** and (3*R*)-**6a** were observed as multiplets with sharp peaks, suggesting that rotation of the phenyl ring is moderately restricted for **5b**, (3*S*)-**6b** and (3*R*)-**6b**.

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Tetrahedron 60 (2004) 4491–4511

Stereoselectivity in reactions of atropisomeric lactams and imides

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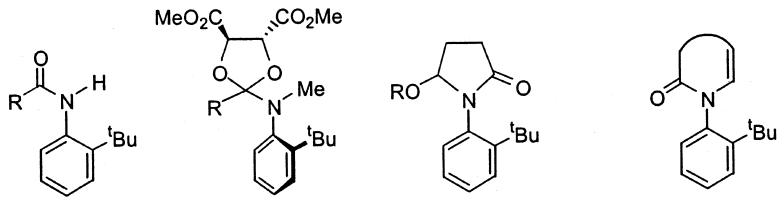
Received 5 December 2003; revised 16 January 2004; accepted 21 January 2004

Abstract—A range of reactions of cyclic lactam systems is described in which an atropisomeric C–N axis controls the stereochemical outcome of ring substitution or addition. In the case of enantiopure menthol adducts, substitution via *N*-acyliminium intermediates occurred with essentially complete control. However, the range of nucleophiles that participate in the reaction is very limited and at present the removal of the *N*-aryl substituent is problematic. A six-membered enamide is of moderate configurational stability and the axis exerts synthetically useful levels of control over enolate alkylations of the system. A novel Lewis acid mediated enamide arylation process was identified.

1. Introduction

The seminal contribution by Curran and co-workers in 1994 showed that anilides having a bulky *ortho*-substituent showed significant promise in stereocontrolled reactions in which an atropisomeric C–N axis controls the formation of new stereogenic centre(s).[1] Since that time a number of groups, including our own, have further developed this chemistry with various amide, lactam and imide systems.[2–6] Although some of this work has focused on the atroposelective reactions of racemic systems, access to non-racemic derivatives of known absolute configuration has emerged as a key issue. Some non-racemic anilides have been obtained, either by the chiral pool approach, by asymmetric *N*-allylation of N–H amides such as **1**, or by selective crystallisation of tartrate anilides **2**.[7–10]

Our own studies have turned to the chemistry of cyclic systems bearing the *N-ortho-tert*-butylphenyl motif, and we previously described some aspects of the *N*-acyliminium chemistry of menthol-derived lactams of general structure **3**.[11] In attempting to progress this work, we also became interested in the atroposelective reactions of cyclic enamides represented by structure **4**, and have now explored the chemistry of the six-membered variant in some detail, including enolate alkylations, alkene reactivity and modification of the aromatic portion. The purpose of this paper is to describe these new results, in addition to providing full details of our earlier work.



1 **2** **3** R=menthyl **4**

2. Results and discussion

2.1. *N*-Acyliminium chemistry of a 5-membered lactam

Our initial explorations were focussed on the development of a chiral auxiliary approach for *N*-acyliminium chemistry

Keywords: Lactams; Imides; Enolate; *N*-Acyliminium; Atropisomerism; Allylation.
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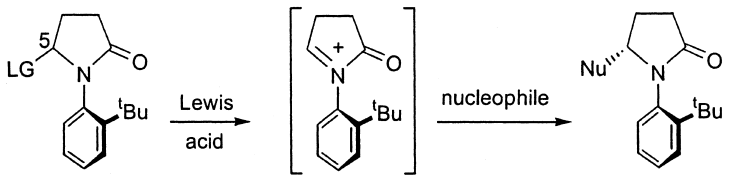
doi:10.1016/j.tet.2004.01.100



5 6 7

Scheme 1.

of lactams of general structure **5**, having a leaving group (LG) derived from a readily available chiral pool material, Scheme 1.

The idea was to generate a stereoisomerically pure lactam **5**, in which stereocentres in the auxiliary LG would fix the chiral C–N axis (and presumably the stereochemistry at C-5), allowing us to generate a chiral *N*-acyliminium intermediate **6**, the C–N axis in which would be responsible for the eventual stereochemical outcome, leading to **7**.[12]

Molecular modelling studies of the parent lactam (**5** LG=H) showed a relatively low energy barrier for rotation around the aryl C–N bond, which did not augur well for the configurational stability of the intermediate **6**.[13] Also, even if this intermediate was configurationally stable there was no guarantee that the C–N axis would exert a high level of control in the subsequent nucleophilic attack. Nevertheless, we considered this sequence potentially viable and we rapidly focussed on the idea of using readily available L-menthol as the leaving group.

Reduction of the readily available imide **8** with DIBAL gave the hydroxy lactam **9** in excellent yield. Condensation of this material with L-menthol under mildly acidic conditions then resulted in the formation of the two solid diastereomeric adducts **10** and **11**, Scheme 2.

Both of the isolated compounds were assigned as having the *ortho-tert*-butyl substituent on the opposite face of the lactam ring to the bulky menthyl substituent. The structure of the minor isomer **10** was readily secured by X-ray crystallography, as shown in Figure 1. The structure shown for **11** is based upon the fact that both **10** and **11** were shown to equilibrate with another isomer on brief warming in $CDCl_3$, but not with each other. In addition, isomers **10** and **11** gave enantiocomplementary results in substitution chemistry, vide infra. Both **10** and **11** proved to be reasonably stable as single atropisomers if stored as solids in the freezer.

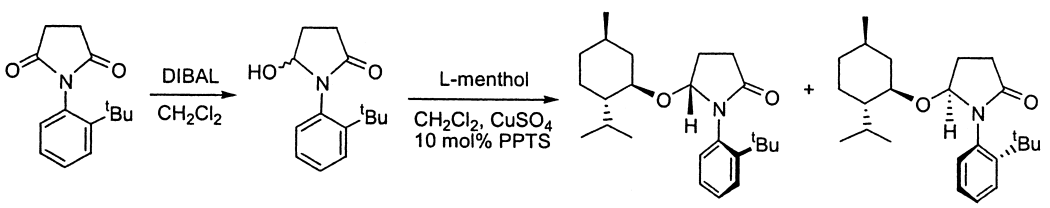
Initial attempts at *N*-acyliminium chemistry using Lewis acids such as $TiCl_4$ or $BF_3{-}OEt_2$ were not fruitful, and useful results were found only when we turned to the use of Me_3SiOTf. Under the influence of this catalyst, we were able to carry out efficient allylation or propargylation of **10** as shown in Scheme 3.

A temperature of about −40 °C was found to be important, since low temperatures (−78 °C) gave little or no reaction, whereas reaction at 0 °C was shown to give products of eroded ee. The products **12** and **13** were both found to be less stable with respect to the C–N axis than the menthol-containing precursors and they rapidly equilibrated to a diastereomeric mixture. As mentioned above, the use of the other available starting lactam **11** gave the enantiomeric product to **12** under the allylating conditions.

For ease of product analysis we chose to hydrogenate both the allyl and allenyl compounds to give the corresponding saturated propyl lactam **14**, Scheme 4.

Analysis of this compound by HPLC allowed separation of all four possible stereoisomers (one enantiomeric pair for each atropisomer), enabling us to determine that the substitution products **12** and **13** had been formed in essentially enantiomerically pure form (≥99% ee). We also needed to assign the configurations of the substitution products, and we chose to correlate allenyl adduct **13** (generated from **10**) with the known methoxymethyl lactam **15**, which had been described by Taguchi and co-workers, Scheme 5.[7e]

We assigned the stereochemistry shown on the basis of HPLC data, namely that the sequence shown gives the lactam with the longer elution time on analysis with a Chiralpak AD column, under conditions described by Taguchi. We have been unable to determine reliable specific rotation values for samples of this compound, and in fact the anomalously low $[\alpha]_D$ value that we reported initially prompted a re-examination of the sign of the value for **15**,



8 **9** 92% **10** less polar 25% **11** more polar 41%

Scheme 2.

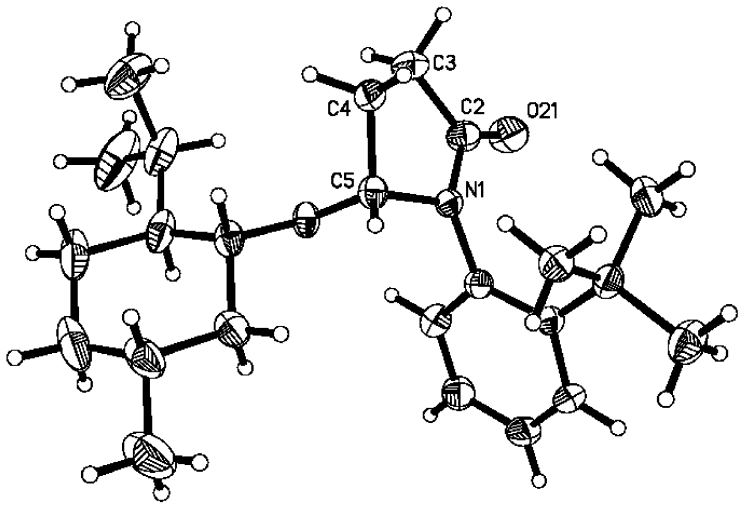
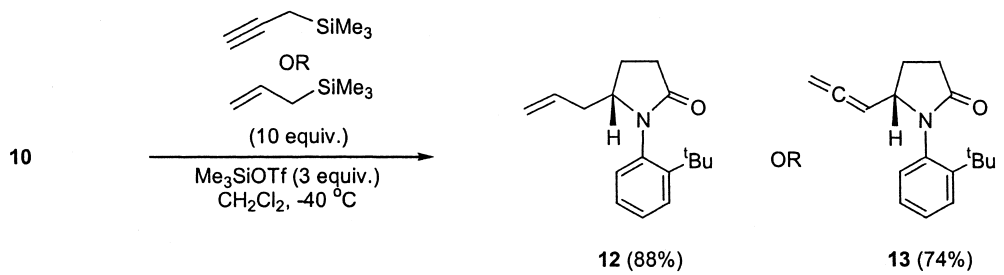
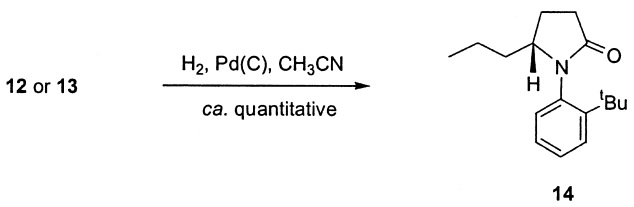


Figure 1. X-ray structure of lactam **10** (displacement elipsoids are drawn at the 50% probability level).



Scheme 3.



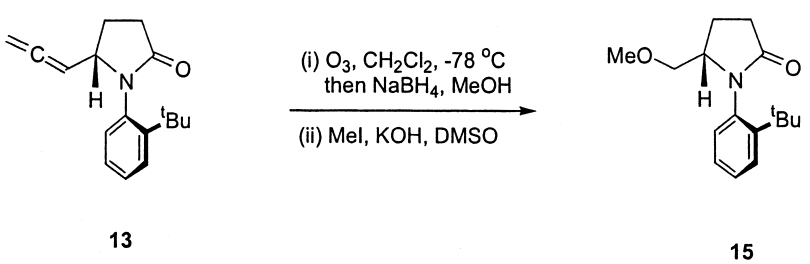
Scheme 4.

leading to a revision.[14] Fortunately none of the stereochemical assignments are affected.

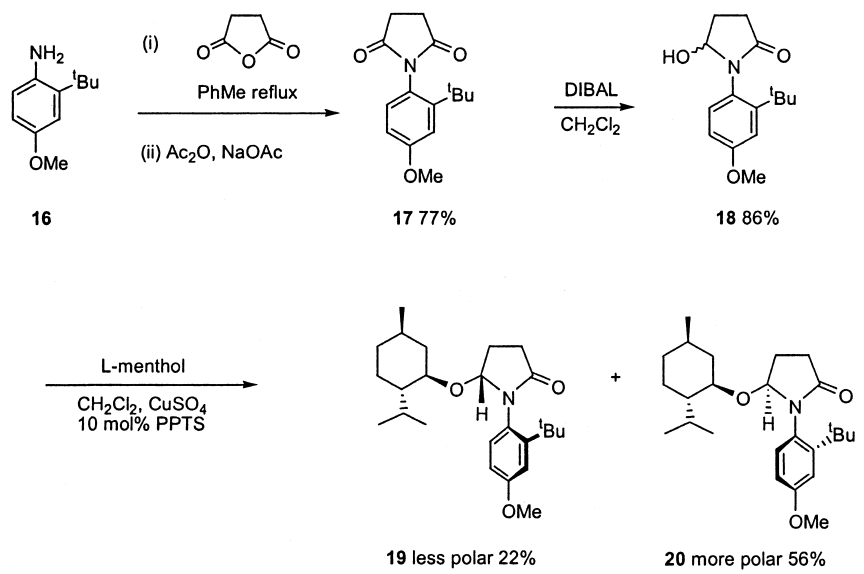
Overall, this work had established that substitution of the menthol adducts along the lines indicated in Scheme 1 was indeed possible, and we propose that this is due to stereochemical control exerted by the chiral C–N axis of the intermediate *N*-acyliminium ion. Unfortunately, we were unable to broaden the scope of the substitution process in that attempted reactions using Me_3SiCN or the enol silane from acetophenone as nucleophiles did not give the desired products.

In a final phase of this work, we also examined analogous transformations of lactams bearing an additional methoxy substituent on the *N*-aryl group. Imide **17** was prepared from the readily available aniline **16**, and subsequent DIBAL reduction and menthol condensation were carried out as described previously, Scheme 6.

This outcome of the menthol condensation was subject to an initial mis-assignment by us in the original communication.[11] Thus, we initially assigned the more polar isomer as **19**, based on erroneous specific rotation measurements of a subsequent product, vide infra. In retrospect, the analogy between Schemes 2 and 6 is very clear. Both systems produce mainly two isomers, each of which have a *trans* disposition of the menthol and *tert*-butyl groups, and in each case the less polar isomer is the minor one. That the less



Scheme 5.



Scheme 6.

polar one has structure **19** is very strongly suggested by the very close matching of the upfield region of the ^{1}H NMR spectrum for **19** with that of **10**, whilst the spectra for **11** and **20** also match well, but are very distinct to the other pair. Specific rotation data (all measured in $CHCl_3$ at the same concentration) also strongly suggest that **19** ($[\alpha]_D=-113$) is analogous to **10** ($[\alpha]_D=-101$), and that **20** ($[\alpha]_D=-18$) is analogous to **11** ($[\alpha]_D=-19$).

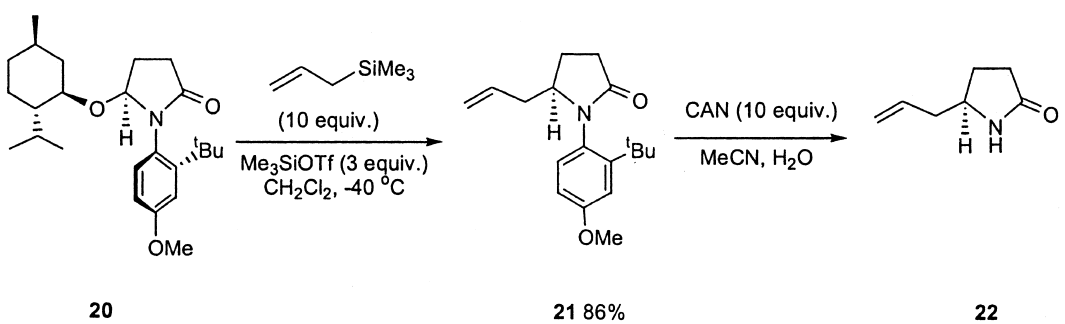
The more polar isomer **20** was allylated under our typical conditions to give product **21**, which was then subjected to reaction with excess of CAN, in an effort to remove the *N*-aryl substituent, Scheme 7.

Reaction of **20** with allylsilane gave **21**, the ee of which was shown by HPLC to be ca. 98% ee, which again demonstrates the high level of fidelity possible in this type of *N*-acyliminium ion reaction. Unfortunately, subsequent conversion into the known lactam **22** proved highly problematic, both in terms of chemical yields, which were mainly in the 30% region, and also that we obtained inconsistent measurements of the $[\alpha]_D$ value of the product.[15] The enantiomer of **22** shown in Scheme 7 is well established to be the (−)-isomer, but the enantiomerically pure compound has a low specific rotation of only $[\alpha]_D=4$ (*c* 0.65, CH_2Cl_2).[15d] Our product showed very low positive values of $[\alpha]_D$, leading us to believe that we had made the enantiomer of **22**, and leading to a mis-assignment of **20** and **21**. Although we are now confident of the assignment in Scheme 7 it rests solely on analogy with the earlier series, since we have been unable to convincingly correlate with lactam **22**.

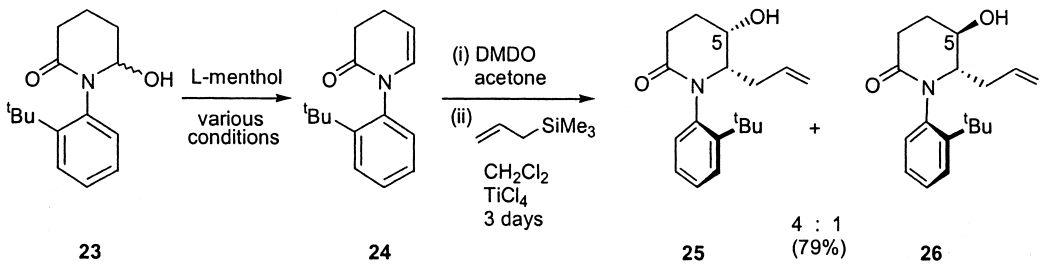
A natural extension of this work would have involved probing the homologous six-membered ring family of compounds. This did not prove possible since attempted formation of menthol adducts from hydroxylactam **23** always led to the enamide **24**, the product of elimination, Scheme 8.

It seemed to us that the double bond present in enamide **24** might enable useful substitution of the ring by sequential treatment with a powerful electrophile, followed by a nucleophile. To this end, we reacted enamide **24** with DMDO (osmylation conditions gave a similar result) and then exposed the crude product to reaction with allylsilane.[16] As shown, we obtained two products **25** and **26** in good overall yield, the stereochemistries of which were both determined by X-ray crystallography, Figures 2 and 3.

This allylation reaction is much more sluggish than those described with the five-membered menthol derived systems and the extended reaction time and relatively elevated temperature do not appear suitable for asymmetric synthesis using enantiomerically pure derivatives (racemisation by C–N rotation or reversible ring-opening of the intermediates would be expected). Also, the level of selectivity in the



Scheme 7.



Scheme 8.

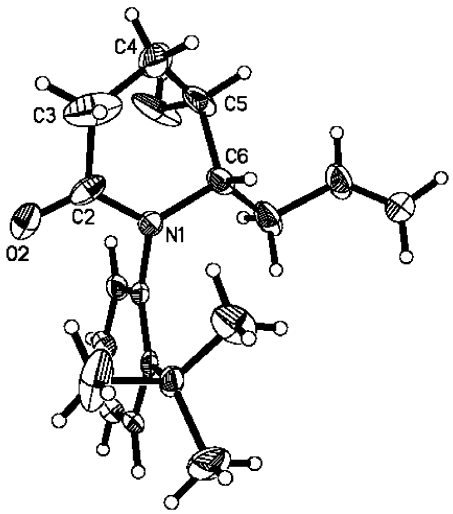


Figure 2. X-ray structure of lactam **25** (displacement elipsoids are drawn at the 30% probability level).

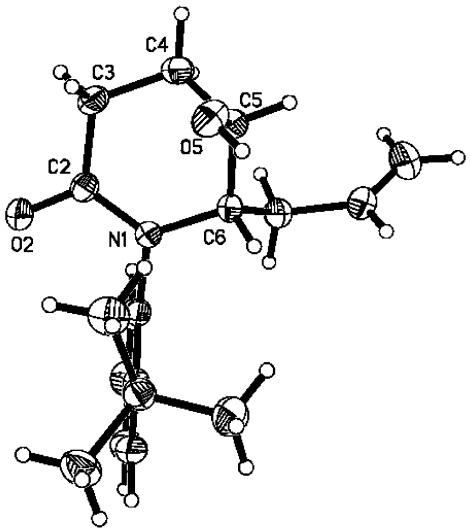


Figure 3. X-ray structure of lactam **26** (displacement elipsoids are drawn at the 50% probability level). Only one of two independent molecules is shown.

initial oxidation appears modest, judging by the ratio of C−5 epimers. Although in both product isomers the allyl group is arranged *anti* to the *ortho-tert*-butyl group, the relative ease of C−N rotation for most compounds with a saturated C−6 position means that this could be a thermodynamic effect (as in **15**). We also noted that these types of piperidinone, bearing stereodefined C-5 hydroxyl and C-6 allyl groups have recently been used as key intermediates in the synthesis of antimalarial alkaloids of the febrifugine group.[17]

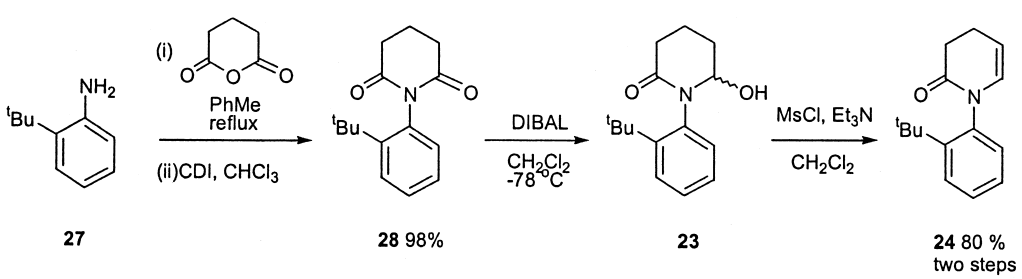
Although we did not pursue this line of investigation the ready availability of enamide **24** made it an interesting system for further study.

2.2. Synthesis and enolate chemistry of enamide 24

In order to conduct an extended study of the chemistry of enamide **24**, we optimised the supply of this material by means of the route shown in Scheme 9.

The synthesis of the imide **28** proved very straightforward and, following reduction to **23**, elimination was best done via mesylation, rather than simple acid catalysed dehydration. This simple sequence easily gave access to multigram quantities of the desired enamide **24**.

We had previously studied the levels of diastereocontol in enolate reactions of certain types of acyclic anilides having the *ortho-tert*-butyl motif.[3] Although we achieved some potentially useful levels of control the product analysis was hampered by the complicated conformational behaviour of these systems, and the products also proved recalcitrant to further transformation, especially hydrolysis. By contrast



Scheme 9.

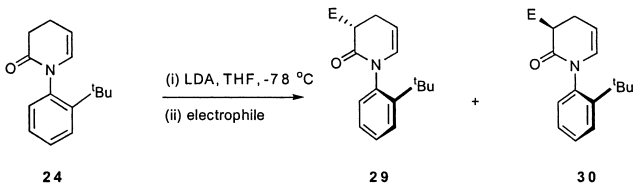


Table 1. Alkylation of enamide **24**

Entry	Electrophile	Product (%)	Ratio 29:30[a]
1	MeI	**29a** 81	6:1
2	$H_2C{=}CHCH_2Br$	**29b** 66	12:1
3	$PhCH_2Br$	**29c** 79	13:1
4	$HC{\equiv}CCH_2Br$	**29d** 62	12:1
5	$^nC_5H_{11}Br$	**29e** 88	7:1
6	EtI	**29f** 61	10:1
7	PhSSPh	**29 g** 81	12:1
8	$Me_3SiC{\equiv}CCH_2Br$	**29 h** 66	15:1

[a] Estimated from ^1H NMR spectra of crude reaction mixture.

enamide **24** is conformationally much simpler, and the presence of two potentially reactive functions in the ring might enable more facile removal of the aniline when desired.[18]

We started our investigation of the enolate chemistry of enamide **24** by carrying out a range of alkylations, under typical conditions, using LDA as the base, Table 1.

Enolate alkylation occurred cleanly at −78 °C to give the products in very good yields, and with good to excellent levels of selectivity. Atropisomer ratios were measured immediately after the alkylation, since we observed partial equilibration in samples stored at room temperature over a period of a few weeks. Although this gave us a rough idea of the conformational stability of these systems we did not quantify the energy barrier to rotation around the C–N axis for these products, and a more detailed study was reserved for the parent system, vide infra.

In all cases we assumed that the alkylation was controlled by the bulky *ortho-tert*-butyl substituent, leading to a predominance of the *anti* isomer **29** in the product, although we have no proof of this except in the case of sulfide **29g**, which proved amenable to X-ray crystallographic study, as shown in Figure 4.

We also tested the enolate reactions of enamide **24** with a range of aliphatic and aromatic aldehydes, but found that the aldol reactions are poorly controlled, giving rise to at least three major stereoisomeric products in each case. Therefore, we did not pursue this area further.

2.3. Kinetic resolution, absolute configuration and rotational energy barrier of enamide 24

In our previous work in this area we had used a chiral lithium amide base to achieve kinetic resolution of an acyclic atropisomeric amide, albeit with modest levels of selectivity,[3] and it was decided to conduct a related study with enamide **24** in order to obtain a sample of non-racemic compound. This would then enable us to establish a rotational energy barrier for the C–N axis through studying the rate of racemisation, and we might also be able to assign the absolute stereochemistry for this compound.

Partial alkylation of enamide **24** was, therefore, carried out, by initial deprotonation with a deficiency of the chiral base shown, followed by reaction with benzyl bromide, Scheme 10.

In reactions that were allowed to proceed to 53–74% conversion we were able to recover quantities of (−)-**24** (44–24%), along with the alkylated product **29c**. We analysed recovered enamide **24** from both a 74% and a 53% conversion reaction and found it to be of 74 and 62% ee, by HPLC, respectively. As in the related kinetic resolution reactions of acyclic amides the selectivity appears to be quite low, but the supply of small quantities of moderately enriched material was adequate for our purposes.

We next warmed a solution of **24** of 62% ee in $CHCl_3$ at 60 °C and monitored the ensuing racemisation by HPLC. A

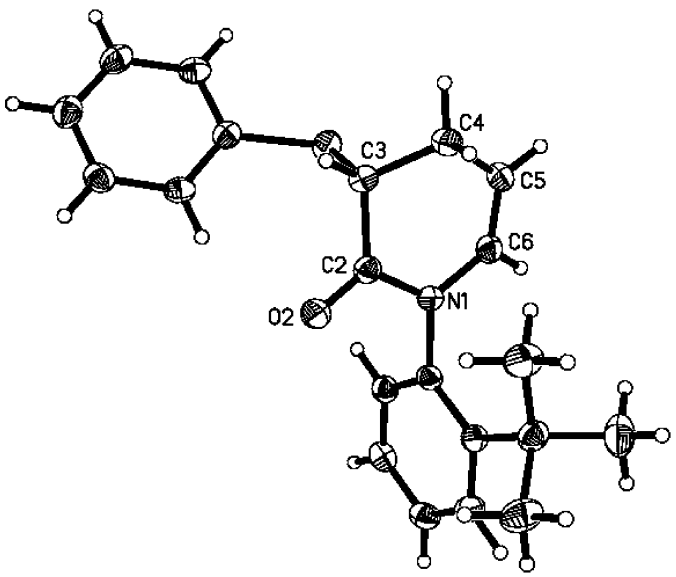
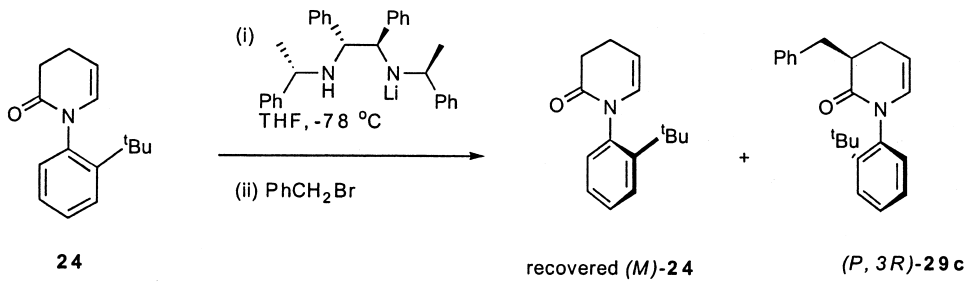


Figure 4. X-ray structure of enamide **29g** (displacement elipsoids are drawn at the 50% probability level).



24 recovered *(M)*-**24** *(P, 3R)*-**29c**

Scheme 10.

graph of the logarithm of the relative ee values of **24** as a function of time for the thermal racemisation indicates a very good linear relationship, Figure 5.[19]

The energy barrier to rotation around the C–N axis ($\Delta G^{\neq}$=+26.95 kcal mol^{-1}) was calculated using the slope of the graph ($-2k_{rot}$=-2.6×10^{-3} s^{-1}) and Eyring's equation, and the half-life for racemisation at 25 °C estimated to be 2.03×10^{6} s (ca 3 weeks). Therefore the enamide system is significantly less stable than most of the documented, 'Curran type', amide and imide systems incorporating this motif, but still rather more stable than the lactams having a saturated carbon at C-6 in the ring (like **25** and **26**).

The stereochemical assignment for **24** shown in Scheme 10 was determined by correlation with commercially available diacid **31**, as indicated in Scheme 11.

Thus, conversion of the diacid (*R*)-**31** into the known glutaric anhydride (+)-**32**, was followed by conversion into the isomeric mixture of imides **33**, which were easily separated.[20] An X-ray crystallographic structure determination of the minor product identified it as *syn*-**33** (or *P*,3*R*), as shown in Figure 6. We were then able to take the major product (which was clearly *anti*-**33**), which was at this stage of 72% ee, and subject it to our reduction–elimination sequence, to give a mixture of the new compound **34**,

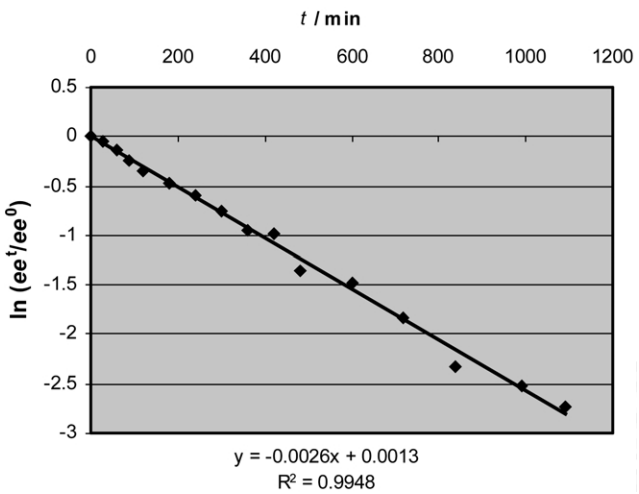


Figure 5. Plot of the logarithm of the relative ee value of **24** (ln ee^{t}/ee^{0}) vs time (t) for thermal racemisation of **24**. ee^{0}=the ee value obtained for recovered **24** from the kinetic resolution. ee^{t}=the ee value of **24** obtained after heating at 60 °C in $CHCl_3$ for the time indicated.

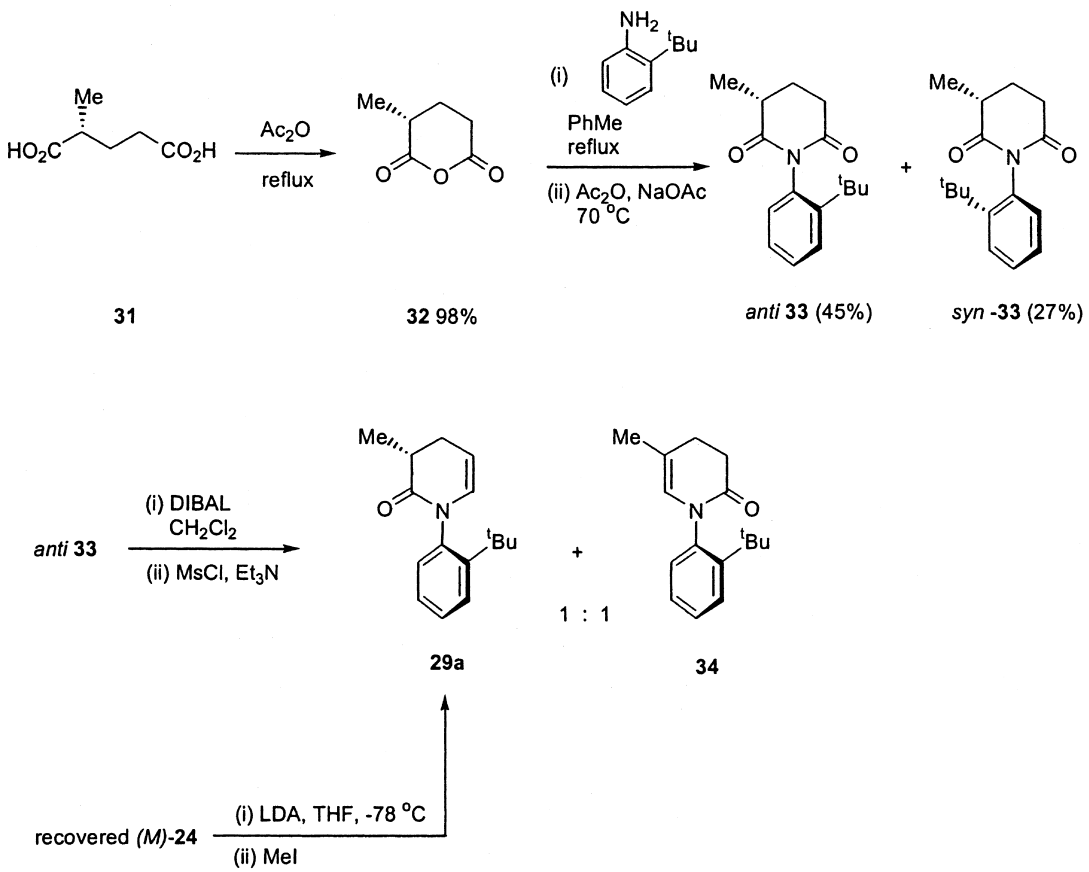
alongside enamide **29a**, which was a compound that we had prepared before in racemic form. To complete the correlation it remained for us to take enantiomerically enriched (73% ee) **24** from the kinetic resolution (recovered (*M*)-**24** in the Scheme) and methylate it to give **29a**. At this point both samples of **29a** showed substantial (+)-rotations but the sample from the enolate alkylation had a ca. 7:1 *anti*:*syn* ratio, whereas the sample from the reduction–elimination had a lower ratio (ca. 2:1). Therefore, in order to make a better comparison each sample of **29a** was equilibrated in refluxing $CDCl_3$ until each had the same, almost 1:1 ratio of rotamers. At this point both samples showed a specific rotation of $[\alpha]_D$=+55−56. That the values should match is a consequence of partial racemisation in the sequence leading to imide **33**, bringing it to a level (72% ee) almost matching our enamide recovered from the kinetic resolution.

At this point we had established the key aspects of the stereochemistry of enamide **24**, and decided to explore one final aspect of the reactivity of the system, namely reactions of the C=C bond.

2.4. Exploring the C=C reactivity of enamide 24

Initial studies showed that the C=C bond present in **24** was extremely reluctant to participate in a variety of C–C bond forming reactions, including [4+2] cycloaddition with either electron rich or poor diene partners, [2+2] type reactions with ketenes, or Heck reactions under a range of conditions. This was very disappointing since a number of common alkaloid systems might otherwise have been accessed via this approach.

However, during the course of an investigation into cleavage of the *tert*-butyl group from the *N*-aryl group of enamide **24**, we were surprised to discover some unexpected reactivity of the C=C bond. The $AlCl_3$ catalysed *trans-tert*-butylation of aromatics is well known, and has been used for the synthesis of substituted fluorenes.[21] Treatment of enamide **24** with $AlCl_3$ in benzene resulted in the anticipated loss of the *tert*-butyl group, but gave a product in which the enamide C=C was no longer present. Spectroscopic analysis revealed the product to be lactam **35a**, in which the enamide function has undergone a Friedel–Crafts alkylation reaction. Analogous reactions using toluene, bromobenzene or iodobenzene as reaction partners also gave arylated lactams **35b–d** in good yield, the products **35b** and **35c** being mixtures of *ortho*/*para* regioisomers, Scheme 12.



Scheme 11.

This type of enamide arylation appears novel in intermolecular mode, although we are aware of intramolecular varaints involving an activated, tethered aromatic ring, for example, Scheme 13.[22]

Attempts to employ anisole in this process led to none of the product lactam of structure **35**, and instead gave only recovered enamide and phenol. Since anisole appeared incompatible with $AlCl_3$ under these reaction conditions, we switched the Lewis acid to $TiCl_4$, and two novel lactam products **38** and **39** were obtained in which arylation occurred but the *tert*-butyl group remained intact, Scheme 14.

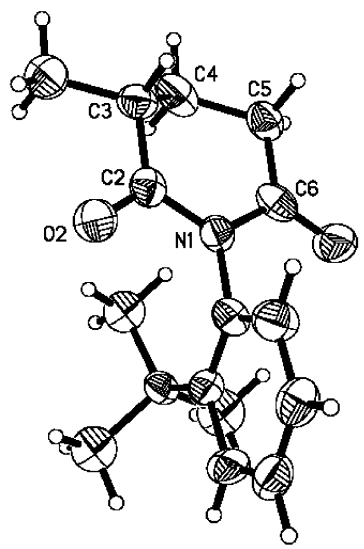
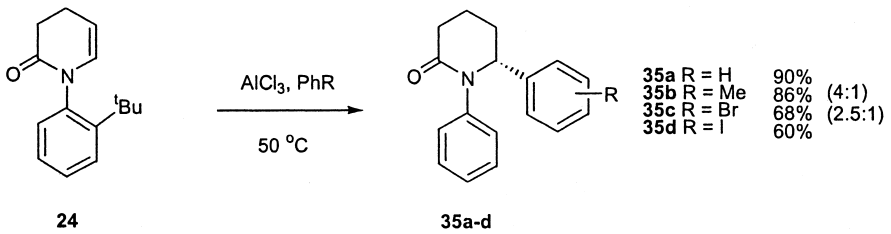


Figure 6. X-ray structure of imide *syn*-**33** (displacement elipsoids are drawn at the 50% probability level). One of the disordered *tert*-butyl components is omitted for clarity.

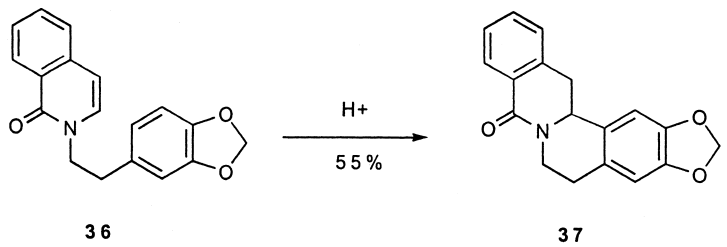
The NMR spectra for the major product **38** appeared broad and ill-resolved, presumbly due to conformational complications arising due to the highly congested nature of the system. Definitive proof of structure was obtained through an X-ray crystallographic structure determination, Figure 7.

This result seemed to indicate that addition to the enamide C=C is faster than the *trans-tert*-butylation, at least for anisole, which might enable the chiral axis to control the formation of the new stereogenic centre at C-6. In the interest of probing this possibility the reaction of enamide **24** of 63% ee with $AlCl_3$ in benzene was carried out and resulted in the recovery of the product **35a** of identical ee. The analogous reaction with bromobenzene did result in some erosion of ee, as the product **35c** from a reaction with enamide **24** of 73% ee had a lower ee value of 57%. This probably reflects a slower rate of alkylation for bromobenzene compared with benzene, allowing partial racemisation of **24** via C–N bond rotation, thus resulting in erosion of the product ee.

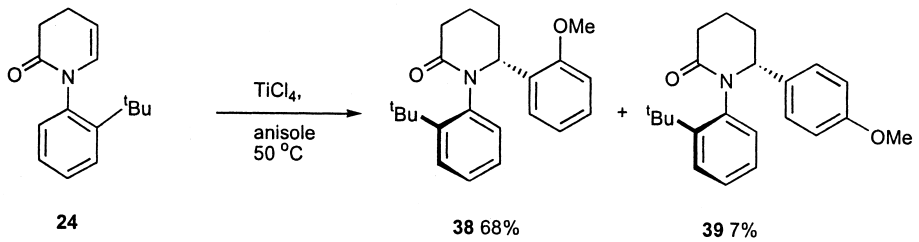
On the basis of the above results it appears that the Friedel–Crafts alkylation reaction occurs prior to cleavage of the



Scheme 12.



Scheme 13.



Scheme 14.

tert-butyl group and that the change from an sp^2 carbon in the C=C bond to an sp^3 carbon may be a requirement for the second step, cleavage of the *tert*-butyl group.

3. Summary and conclusion

We have described a range of reactions of cyclic lactam systems in which an atropisomeric C–N axis can control the stereochemical outcome of ring substitution or addition reactions. In the case of enantiopure menthol adducts **10**, **11** or **20**, substitution via *N*-acyliminium intermediates occurred with essentially complete control. However, the range of nucleophiles that participate in the reaction is very limited and at present the removal of the *N*-aryl substituent is problematic.

The six-membered enamide **24** is of moderate configurational stability and the axis exerts synthetically useful levels of control over the enolate alkylations of the system. A novel Lewis acid mediated enamide arylation process was also identified, which may have further applications in synthesis.

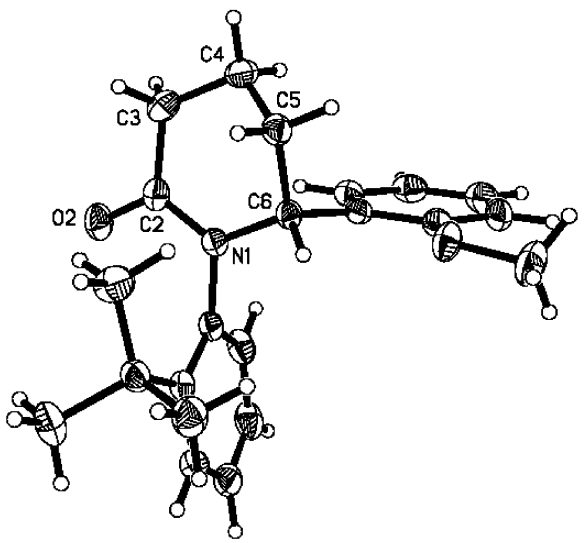


Figure 7. X-ray structure of lactam **38** (displacement elipsoids are drawn at the 50% probability level).

4. Experimental

4.1. General details

General experimental details can be found in our recent paper.[23]

In the present work, some high resolution mass spectra were also acquired on a PerSeptive Biosystems Mariner TOF instrument (TOF), with a resolution of 5000 ppm, calibrated using internal standards. In addition, where stated, purification was carried out using pre-packed Biotage 40 flash columns (KP-Sil, 60 Å, 32–63 μM).

The precursor chiral diamine base to the lithiated base shown in Scheme 10 was prepared from (*R*)-α-methylbenzylamine, according to a literature procedure.[24] Aniline **16** was prepared by methylation of the corresponding hydroxy aniline, which was in turn prepared according to the literature procedure.[25]

All ^{13}C NMR spectra of compounds in which atropisomers were observed are quoted for the major isomer only.

4.1.1. 1-(2-*tert*-Butylphenyl)-pyrrolidine-2,5-dione 8.[26] To solution of 2-*tert*-butylaniline (1.00 g, 6.70 mmol) in toluene (25 mL) was added succinic anhydride (0.81 g, 8.09 mmol) and the reaction mixture refluxed overnight, cooled, and filtered to give crude succinamic acid. A solution of this acid, sodium acetate (3.08 g, 37.5 mmol) in acetic anhydride (25 mL) was stirred at 70–80 °C overnight. The reaction mixture was poured onto H_2O (50 mL), extracted with $CHCl_3$ (3×50 mL), the combined organic extracts were washed with 2 N sodium hydroxide (3×50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting white solid was recrystallised from EtOH to yield **8** as a crystalline white solid (1.43 g, 6.18 mmol, 92%), mp 139–141 °C, (lit.[26] 131–132 °C); ν_{max} ($CHCl_3$)/cm^{-1} 2969, 1714, 1382; δ_H (400 MHz; $CDCl_3$) 1.30 (9H, s, C(CH_3)$_3$), 2.88 (4H, s, 3-H), 6.85 (1H, dd, *J*=7.5, 1.6 Hz, Ar-*H*), 7.29 (1H, ddd, *J*=7.5, 7.3, 1.5 Hz, Ar-*H*), 7.40 (1H, ddd, *J*=8.1, 7.3, 1.6 Hz, Ar-*H*), 7.59 (1H, dd, *J*=8.1, 1.5 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 28.6 (CH_2), 31.5 (CH_3), 34.4 (C), 127.3 (CH), 128.8 (CH), 129.7 (CH), 130.3 (C), 130.5 (CH), 147.8 (C), 177.3 (C=O); *m*/*z* (EI) 231 (M^+, 40%), 216 (100), 174 (26) (Found M^+, 231.1254. $C_{14}H_{17}NO_2$ requires *M*, 231.1259). Anal. Calcd for $C_{14}H_{17}NO_2$. C, 72.69; H, 7.41; N, 6.06%. Found: C, 72.56; H, 7.53; N, 6.11%

4.1.2. 1-(2-*tert*-Butylphenyl)-5-hydroxypyrrolidin-2-one 9. DIBAL (6.90 mL of a 1 M solution in CH_2Cl_2) was added dropwise to a stirred solution of imide **8** (0.80 g, 3.46 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After 10 min stirring at −78 °C, H_2O (10 mL), and 2 N NaOH (2 mL) were cautiously added and the reaction mixture extracted with $CHCl_3$ (3×20 mL). The organic extracts were then washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield a white solid. The crude mixture was then purified by flash column chromatography (100% EtOAc) to yield the title compound **9** (15:1 ratio of isomers) as white crystals (0.74 g, 0.32 mmol, 92%), mp 136–138 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3590, 3367, 2949, 2868, 1714; δ_H (400 MHz, $CDCl_3$) 1.29 (9H major, s, C(CH_3)$_3$), 1.37 (9H minor, C(CH_3)$_3$), 1.97 (1H major+1H minor, m, 4-H_A), 2.25 (2H major+2H minor, m, 4-H_B+3-H_A), 2.58 (1H major+1H minor, m, 3-H_B), 4.24 (1H major+1H minor, d, *J*=5.5 Hz, O*H*), 5.18 (1H major+1H minor, t, *J*=5.3 Hz, 5-H), 7.03 (1H major+1H minor, dd, *J*=7.7, 1.6 Hz, Ar-*H*), 7.17 (1H major+1H minor, ddd, *J*=7.7, 7.4, 1.4 Hz, Ar-*H*), 7.27 (1H major+1H minor, ddd, *J*=8.0, 7.4, 1.6 Hz, Ar-*H*), 7.48 (1H major+1H minor, dd, *J*=8.0, 1.6 Hz, Ar-*H*); δ_C ($CDCl_3$, 68 MHz) 27.8 (CH_2), 28.3 (CH_2), 31.6 (CH_3), 35.4 (C), 86.2 (CH), 126.6 (CH), 128.0 (CH), 128.4 (CH), 132.8 (CH), 134.5 (C), 147.9 (C), 176.8 (C=O); *m*/*z* (EI) 233 (M^+, 52%), 216 (100), 174 (33) (Found M^+, 233.1409. $C_{14}H_{19}NO_2$ requires *M*, 233.1416). Anal. Calcd for $C_{14}H_{19}NO_2$. C, 72.06; H, 8.21; N, 5.80%. Found: C, 71.88; H, 8.26; N, 6.01%.

4.1.3. (*P*,5*R*)-1-(2-*tert*-Butylphenyl)-5-(2*S*-*iso*-propyl-5*R*-methylcyclohexyl-1*R*-oxy)-pyrrolidin-2-one (−)-10 and (*M*,5*S*)-1-(2-*tert*-butylphenyl)-5-(2*S*-*iso*-propyl-5*R*-methylcyclohexyl-1*R*-oxy)-pyrrolidin-2-one (−)-11. (−)-Menthol **8** (3.70 g, 23.7 mmol) and PPTS (0.56 g, 2.23 mmol) were added to a stirred solution of hydroxylactam **9** (5.25 g, 22.5 mmol) and anhydrous copper sulphate (10.0 g, 62.7 mmol) in CH_2Cl_2 (100 mL) and stirred at room temperature overnight. The reaction mixture was poured onto H_2O (100 mL) and extracted with $CHCl_3$ (3×100 mL), the combined organic extracts were then dried ($MgSO_4$) and evaporated under reduced pressure. The resultant solid was then purified by flash column chromatography (25–50% EtOAc7–petroleum ether) to give firstly the minor diastereoisomer (−)-**10** as white crystals (1.84 g, 4.95 mmol, 25%), $[\alpha]_D^{23}$=−101 (*c* 1.00, $CHCl_3$); mp 89–90 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2956, 2921, 2871, 1698, 1061; δ_H (400 MHz; $CDCl_3$) 0.43 (1H, ddd, *J*=12.3, 12.3, 10.8 Hz, 6′-H_A), 0.69 (3H, d, *J*=6.6 Hz, 2″-Me_A), 0.73–0.79 (4H, m with d at 0.78, *J*=7.0 Hz, 5′-Me+3′-H_A), 0.86–0.93 (4H, m with d at 0.92, *J*=7.0 Hz, 2″-Me_B+4′-H_A), 1.17 (2H, m, 2′-H+5′-H), 1.34–1.38 (10H, m with s at 1.36, C(CH_3)$_3$+6′-H_B), 1.58 (2H, m, 3′-H_B+4′-H_B), 2.24 (3H, m, 4-H+1″-H), 2.44 (1H, ddd, *J*=17.0, 9.3, 1.6 Hz, 3-H_A), 2.73 (1H, ddd, *J*=17.0, 9.9, 8.8 Hz, 3-H_B), 3.03 (1H, dt, *J*=10.8, 10.3, 4.0 Hz, 1′-H), 5.07 (1H, d, *J*=4.8 Hz, 5-H), 7.19 (2H, m, Ar-*H*), 7.27 (1H, m, Ar-*H*), 7.48 (1H, m, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 15.8 (CH_3), 21.0 (CH_3), 21.9 (CH_3), 22.8 (CH_2), 25.0 (CH), 26.2 (CH_2), 28.3 (CH_2), 31.0 (CH), 31.6 (CH_3), 34.0 (CH_2), 35.3 (C), 40.0 (CH_2), 47.8 (CH), 76.4 (CH), 90.4 (CH), 126.3 (CH), 127.3 (CH), 128.2 (CH), 133.6 (CH), 134.9 (C), 147.6 (C), 176.7 (C=O); *m*/*z* (EI) 371 (M^+, 2%), 216 (61), 176 (25) (Found M^+, 371.2824. $C_{24}H_{37}NO_2$ requires *M*, 371.2826), followed by the major diastereoisomer (−)-**11** as fine white needles (4.68 g, 12.6 mmol, 41%), $[\alpha]_D^{23}$=−19 (*c* 1.05, $CHCl_3$); mp 63–65 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2955, 2925, 2870, 1698, 1065; δ_H (400 MHz; $CDCl_3$) 0.29 (3H, d, *J*=6.9 Hz, 2″-Me_A), 0.68 (3H, d, *J*=7.0 Hz, 2″-Me_B), 0.80 (2H, m, 3′-H_A+4′-H_A), 0.90 (3H, d, *J*=6.5 Hz, 5′-Me), 0.99 (1H, ddd, *J*=12.6, 12.1, 10.6 Hz, 6′-H_A), 1.13 (1H, m, 5′-H), 1.29–1.35 (10H, m with s at 1.35, C(CH_3)$_3$+2′-H), 1.55 (2H, m, 3′-H_B+4′-H_B), 1.75 (1H, m, 1″-H), 1.92 (1H, m, 6′-H_B), 2.12 (1H, m, 4-H_A), 2.39 (2H, m, 4-H_B+3-H_A), 2.72 (1H, m, 3-H_B), 3.00 (1H, ddd, *J*=10.6, 10.4, 4.3 Hz, 4′-H), 5.09 (1H, d, *J*=4.8 Hz, 5-H), 7.17 (2H, d, *J*=3.7 Hz, Ar-*H*), 7.26 (1H, m, Ar-*H*), 7.47 (1H, d, *J*=7.8 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 15.3 (CH_3), 21.0 (CH_3), 22.2 (CH_3), 22.3 (CH_2), 24.1 (CH), 28.2 (CH_2), 28.4 (CH_2), 31.4 (CH), 31.7 (CH_3), 34.0 (CH_2), 35.5 (C), 42.8 (CH_2), 48.6 (CH), 78.3 (CH), 92.7 (CH), 126.4 (CH), 127.7 (CH), 128.2 (CH), 133.9 (CH), 134.5 (C), 147.3 (C), 176.4 (C=O); *m*/*z* (EI) 371 (M^+, 0.7%), 215 (68), 158 (74) (Found M^+, 371.2828. $C_{24}H_{37}NO_2$ requires *M*, 371.2826)

4.1.4. (*P*,5*S*)-5-Allyl-1-(2-*tert*-butylphenyl)-pyrrolidin-2-one (−)-12. To a stirred solution of pyrrolidin-2-one (−)-**10** (1.00 g, 2.69 mmol) and allyl trimethylsilane (4.20 mL, 26.8 mmol) in CH_2Cl_2 (10 mL) at −40 °C, was added dropwise trimethylsilyltrifluoromethanesulphonate (1.50 mL,

8.29 mmol). The reaction mixture was stirred at −40 °C for 8 h before H_2O (10 mL) was cautiously added. The reaction mixture was extracted with $CHCl_3$ (3×20 mL), the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (50% EtOAc–petroleum ether) to yield the title compound (−)-**12** (6:1 ratio of isomers) as a pale yellow oil (612 mg, 2.40 mmol, 88%), $[\alpha]_D^{23}=-35$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2874, 1682; δ_H (400 MHz; $CDCl_3$) 1.39 (9H major, s, C(C*H*$_3$)$_3$), 1.41 (9H minor, C(C*H*$_3$)$_3$), 1.99 (1H major+1H minor, m, 4-H$_A$), 2.15 (1H major+1H minor, m, 4-H$_B$), 2.44 (4H major+4H minor, m, 3-H+1′-H), 3.93 (1H major+1H minor, m, 5-H), 5.07 (2H minor, m, 3′-H), 5.10 (2H major, m, 3′-H), 5.67 (1H major+1H minor, m, 2′-H), 6.97 (1H major, dd, *J*=7.7, 1.6 Hz, Ar-*H*), 6.98 (1H minor, dd, *J*=7.7, 1.6 Hz, Ar-*H*), 7.27 (2H major+2H minor, m, Ar-*H*), 7.56 (1H major+1H minor, m, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 23.7 (CH_2), 29.7 (CH_2), 31.7 (CH_3), 35.7 (C), 37.8 (CH_2), 61.5 (CH), 118.5 (CH_2), 126.7 (CH), 128.4 (CH), 128.9 (CH), 132.8 (CH), 133.2 (CH), 134.6 (C), 148.2 (C), 175.5 (C=O); *m/z* (EI) 257 (M^+, 0.2%), 216 (100) (Found M^+, 257.1785. $C_{17}H_{23}NO$ requires *M*, 257.1780).

4.1.5. (*P*,5*S*)-1-(2-*tert*-Butylphenyl)-5-propa-1,2-dienylpyrrolidin-2-one (−)-13. To a stirred solution of pyrrolidin-2-one (−)-**10** (300 mg, 0.81 mmol) and propargyltrimethylsilane (1.20 mL, 8.05 mmol) in CH_2Cl_2 (5 mL) at −40 °C was added dropwise trimethylsilyltrifluoromethanesulphonate (0.43 mL, 2.38 mmol). The reaction mixture was stirred at −40 °C for 8 h before H_2O (5 mL) was cautiously added. The reaction mixture was extracted with $CHCl_3$ (3×10 mL), the combined organic extracts were then dried ($MgSO_4$) and evaporated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (50% EtOAc–petroleum ether) to yield the title compound (−)-**13** (3:1 ratio of isomers) as a colourless oil (152 mg, 0.60 mmol, 74%), $[\alpha]_D^{23}=-61$ (*c* 1.10, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2968, 1954, 1682; δ_H (400 MHz, $CDCl_3$) 1.28 (9H major, s, C(C*H*$_3$)$_3$), 1.29 (9H minor, C(C*H*$_3$)$_3$), 2.08 (1H major+1H minor, m, 4-H$_A$), 2.48 (3H major+3H minor, m, 4-H$_B$+3-H), 4.36 (1H major+1H minor, m, 5-H), 4.68 (2H major+2H minor, m, 3′-H), 5.01 (1H minor, 1′-H), 5.10 (1H major, dt, *J*=7.5, 6.6 Hz, m, 1′-H), 6.90 (1H major+1H minor, m, Ar-*H*), 7.19 (2H major+2H minor, m, Ar-*H*), 7.47 (1H major+1H minor, m, Ar-*H*); δ_C (67.5 MHz, $CDCl_3$) 25.9 (CH_2), 30.1 (CH_2), 32.0 (CH_3), 35.9 (C), 62.2 (CH), 77.4 (CH_2), 90.6 (CH), 126.9 (CH), 128.6 (CH), 128.8 (CH), 133.3 (CH), 135.2 (C), 148.6 (C), 175.7 (C=O), 208.6 (C=*C*=C); *m/z* (EI) 255 (M^+, 1%), 216 (100), 198 (66) (Found M^+, 255.1627. $C_{17}H_{21}NO$ requires *M*, 255.1623).

4.1.6. (5*R*)-1-(2-*tert*-Butylphenyl)-5-propylpyrrolidin-2-one (−)-14. A solution of pyrrolidin-2-one (−)-**12** (610 mg, 2.37 mmol) and 10% palladium on carbon (50.0 mg, 0.05 mmol) in MeCN (25 mL) was shaken under an atmosphere of hydrogen overnight. The reaction mixture was then filtered through celite and evaporated under reduced pressure to yield the title compound (−)-**14** (3:1 ratio of isomers) as a colourless oil (610 mg, 2.35 mmol, 99%), $[\alpha]_D^{23}=-22$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2934, 2875, 1682; δ_H (400 MHz; $CDCl_3$) 0.84 (3H minor, 3′-H), 0.86 (3H major, t, *J*=7.2 Hz, 3′-H), 1.19 (2H major+2H minor, m, 2′-H), 1.30–1.41 (10H major+10H minor, m with major s at 1.38 and minor s at 1.41, C(C*H*$_3$)$_3$+1′-H$_A$), 1.49–1.56 (1H major+1H minor, m, 1′-H$_B$), 1.99 (1H major+1H minor, m, 4-H$_A$), 2.44 (3H major+3H minor, m, 4-H$_B$+3H), 3.89 (1H major+1H minor, m, 5-H), 6.92 (1H major, dd, *J*=7.7, 1.5 Hz, Ar-*H*), 6.96 (1H minor, dd, *J*=7.7, 1.5 Hz, Ar-*H*), 7.24 (2H major+2H minor, m, Ar-*H*), 7.55 (1H major+1H minor, m, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 13.7 (CH_3), 18.4 (CH_2), 24.7 (CH_2), 30.0 (CH_2), 31.5 (CH_3), 35.4 (CH_2), 35.5 (C), 61.9 (CH), 126.4 (CH), 128.1 (CH), 128.6 (CH), 132.8 (CH), 134.6 (C), 148.0 (C), 175.3 (C=O); *m/z* (EI) 259 (M^+, 2%), 216 (58) 202 (100) (Found M^+, 259.1934. $C_{17}H_{25}NO$ requires *M*, 259.1936).

Similar reactions starting with allene **13** gave the same results.

All four isomers of **14** were separated by HPLC using a Chiralcel OD column [25 cm×0.46 cm i.d.; 2% *i*-PrOH in hexane; flow rate, 1.0 mL/min]. Samples of **14** originating with **10** gave two atropisomers eluting at 21.2 and 29.0 min, whereas samples originating with **11** gave two atropisomers eluting at 22.8 and 24.8 min. Each sample proved to be essentially enantiomerically pure (≥99% ee).

4.1.7. (*P*,5*S*)-1-(2-*tert*-Butylphenyl)-5-methoxymethylpyrrolidin-2-one 15.[7e,14] *Ozonolysis*. Ozone was bubbled through a solution of pyrrolidin-2-one (−)-**13** (150 mg, 0.59 mmol) in CH_2Cl_2 (5 mL) and MeOH (5 mL) at −78 °C, for 30 min, before sodium borohydride (75.0 mg, 1.98 mmol) was added and the reaction mixture stirred at room temperature overnight. The reaction mixture was then poured onto H_2O (10 mL) and extracted with $CHCl_3$ (3×10 mL), the combined organic extracts were then washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil. The crude oil was then purified by flash column chromatography (100% EtOAc) to yield an intermediate hydroxymethyl compound as a white solid (94.0 mg, 0.38 mmol, 65%), $[\alpha]_D^{23}=-23$ (*c* 1.00, $CHCl_3$); mp 132–133 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3652, 3400, 2958, 2878, 1682; δ_H (400 MHz; $CDCl_3$) 1.35 (9H, s, C(C*H*$_3$)$_3$), 2.25 (3H, m, 4-H+3-H$_A$), 2.64 (1H, dt, *J*=16.5, 9.3 Hz, 3-H$_B$), 3.43 (1H, dd, *J*=11.3, 1.8 Hz, 1′-H$_A$), 3.55 (1H, dd, *J*=11.3, 3.4 Hz, 1′-H$_B$), 3.74 (2H, m, 5-H+O*H*), 7.07 (1H, dd, *J*=7.7, 1.4 Hz, Ar-*H*), 7.18 (1H, ddd, *J*=7.7, 7.3, 1.5 Hz, Ar-*H*), 7.27 (1H, ddd, *J*=8.0, 7.3, 1.4 Hz, Ar-*H*), 7.50 (1H, dd, *J*=8.0, 1.5 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 22.0 (CH_2), 30.6 (CH_2), 31.8 (CH_3), 35.7 (C), 62.0 (CH_2), 63.7 (CH), 127.0 (CH), 128.4 (CH), 128.6 (CH), 132.4 (CH), 134.8 (C), 148.1 (C), 177.3 (C=O); *m/z* (FAB) 248 (MH^+, 8%), 154 (100), 136 (66) (Found MH^+, 248.1651. $C_{15}H_{22}NO_2$ requires *M*, 248.1651).

Methylation. To a solution of the primary alcohol product (90.0 mg, 0.36 mmol) and KOH (82.0 mg, 1.46 mmol) in DMSO (2.5 mL) was added MeI (0.50 mL, 8.03 mmol) and the reaction mixture stirred at room temperature overnight. The reaction mixture was then poured onto H_2O (10 mL) and extracted with $CHCl_3$ (3×10 mL), the combined organic extracts were then washed with brine (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield

a yellow oil. The crude oil was then purified by column chromatography (60% EtOAc–petroleum ether) to yield the lactam **15** as a white solid (72 mg, 0.28 mmol, 76%), mp 94–95 °C (lit.[7e,14] 93–94.5 °C); ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2881, 1682, 1121; δ_H (400 MHz; $CDCl_3$) 1.38 (9H, s, $C(CH_3)_3$), 2.16 (1H, m, 4-H_A), 2.37 (2H, m, 4-H_B +3-H_A), 2.66 (1H, m, 3-H_B), 3.31 (1H, dd, J=9.9, 2.3 Hz, 1′-H_A), 3.36 (3H, s, 1′-OMe), 3.44 (1H, dd, J=9.9, 3.5 Hz, 1′-H_B), 3.89 (1H, m, 5-H), 7.00 (1H, dd, J=7.7, 1.6 Hz, Ar-*H*), 7.27 (2H, m, Ar-*H*), 7.53 (1H, dd, J=8.0, 1.5 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 22.7 (CH_2), 30.5 (CH_2), 31.8 (CH_3), 35.7 (C), 58.9 (CH_2), 62.0 (CH), 72.5 (CH_3), 127.0 (CH), 128.4 (CH), 128.7 (CH), 132.3 (CH), 135.1 (C), 148.4 (C), 176.9 (C); *m*/*z* (EI) 261 (M^+, 2%), 216 (100), 204 (24) (Found M^+, 261.1722. $C_{16}H_{23}NO_2$ requires *M*, 261.1729).

The enantiomers of **15** were separated by HPLC using a Chiralpak AD column [25 cm×0.46 cm i.d.; 10% *i*-PrOH in hexane; flow rate, 1.0 mL/min; t_R=7.3 min and 8.2 min]. Samples of **15** originating with **10** gave mainly the enantiomer with the longer retention time, allowing us to assign the stereochemistry as (*P*,5*S*).[7e]

4.1.8. 2-*tert*-Butyl-4-aminoanisole 16. To a stirred solution of 1-amino-2-*tert*-butylphenol (16.5 g, 100 mmol) in DMSO (250 mL) was added potassium *tert*-butoxide (12.2 g, 100 mmol) and the reaction mixture stirred for 2 h. Dimethyl sulphate (10.0 mL, 106 mmol) was added in one portion, the reaction mixture stirred for 5 min, poured onto H_2O (500 mL) and extracted with EtOAc (3×250 mL). The organic extracts were then washed with H_2O (3×250 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resultant black oil was then purified by distillation (165 °C/10 mmHg) followed by flash column chromatography (40% Et_2O–hexanes) to yield the title compound as a yellow oil (14.2 g, 80.1 mmol, 80%), ν_{max} ($CHCl_3$)/cm^{-1} 3471, 3390, 2954, 2911, 2834, 1622, 1054; δ_H (400 MHz, $CDCl_3$) 1.41 (9H, s, $C(CH_3)_3$), 3.54 (2H, br.s, NH_2), 3.74 (3H, s, OCH_3), 6.59 (2H, m, Ar-*H*) 6.86 (1H, d, J=2.5 Hz, Ar-*H*); δ_C (67.5 MHz, $CDCl_3$) 29.8 (CH_3), 34.7 (C), 55.8 (CH_3), 111.3 (CH), 114.0 (CH), 119.0 (CH), 136.1 (C), 138.6 (C), 152.9 (C); *m*/*z* (EI) 179 (M^+, 62%), 164 (100) (Found M^+, 179.1307. $C_{11}H_{17}NO$ requires *M*, 179.1310).

4.1.9. 1-(2-*tert*-Butyl-4-methoxyphenyl)-pyrrolidine-2,5-dione 17. Succinic anhydride (4.70 g, 47.0 mmol) was added to a solution of 3-*tert*butyl-4-aminoanisole **16** (7.00 g, 39.1 mmol) in toluene (50 mL) and heated to reflux overnight, cooled, and filtered to give a beige solid. This crude succinamic acid was added to solution of sodium acetate (1.60 g, 19.5 mmol) and acetic anhydride (50 mL) and was heated to 70 °C for 6 h. The reaction mixture was then poured onto H_2O, extracted with $CHCl_3$, washed with 2 N sodium hydroxide, dried over magnesium sulphate and evaporated under reduced pressure to yield a brown solid. The crude solid was purified by flash column chromatography (40% EtOAc–petroleum ether) to yield the title compound **17** as a white solid (7.81 g, 29.9 mmol, 77%), mp 130–131 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3475, 2908, 2253, 1732; δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, $C(CH_3)_3$), 2.82 (4H, s, 3-H), 3.79 (3H, s, OMe), 6.79 (2H, m, Ar-*H*), 7.09 (1H, d, J=2.5 Hz, Ar-*H*); δ_C (67.5 MHz, $CDCl_3$) 28.8 (CH_2), 31.5 (CH_3), 35.7 (C), 55.7 (CH_3), 111.7 (CH), 115.3 (CH), 123.3 (C), 132.0 (CH), 149.6 (C), 160.2 (C), 177.9 (C=O); *m*/*z* (EI) 261 (M^+, 100%), 246 (88) (Found M^+, 261.1373. $C_{15}H_{19}NO_3$ requires *M*, 261.1365).

4.1.10. 1-(2-*tert*-Butyl-4-methoxyphenyl)-5-hydroxypyrrolidin-2-one 18. DIBAL (56.0 mL of a 1 M solution in CH_2Cl_2) was added dropwise to a stirred solution of imide **17** (7.30 g, 27.9 mmol) in CH_2Cl_2 (50 mL) at −78 °C. After 10 min stirring at −78 °C, H_2O (50 mL), and 2 N NaOH (10 mL) were cautiously added and the reaction mixture extracted with $CHCl_3$ (3×50 mL). The organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield a white solid. The crude solid was then purified by flash column chromatography (100% EtOAc) to yield the title compound **18** (17:1 ratio of isomers) as a white solid (6.32 g, 24.0 mmol, 86%), mp 136–138 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3597, 2960, 2837, 1694, 1052; δ_H (400 MHz, $CDCl_3$) 1.32 (9H major, s, $C(CH_3)_3$), 1.41 (9H minor, $C(CH_3)_3$), 2.09 (1H major+1H minor, m, 4-H_A), 2.37 (2H major+2H minor, m, 4-H_B+3-H_A), 2.66 (1H major+1H minor, m, 3-H_B), 3.53 (1H major+1H minor, d, J=4.6 Hz, O*H*), 3.81 (3H major+3H minor, s, OMe), 5.29 (1H major+1H minor, t, J=5.0 Hz, 5-H), 6.77 (1H major+1H minor, dd, J=5.8, 2.9 Hz, Ar-*H*), 7.04 (2H major+2H minor, m, Ar-*H*); δ_C (67.5 MHz, $CDCl_3$) 27.5 (CH_2), 28.4 (CH_2), 31.5 (CH_3), 35.6 (C), 55.3 (CH_3), 86.3 (CH), 110.8 (CH), 115.1 (CH), 127.3 (CH), 133.6 (CH), 149.7 (C), 159.2 (C), 176.9 (C=O); *m*/*z* (EI) 263 (M^+, 18%), 245 (50), 170 (36), 70 (100) (Found M^+, 263.1509. $C_{15}H_{21}NO_3$ requires *M*, 263.1521).

4.1.11. (*P*,5*R*)-1-(2-*tert*-Butylphenyl)-5-(2*S*-*iso*-propyl-5*R*-methylcyclohexyl-1*R*-oxy)-pyrrolidin-2-one (−)-19 and (*M*,5*S*)-1-(2-*tert*-butylphenyl)-5-(2*S*-*iso*-propyl-5*R*-methylcyclohexyl-1*R*-oxy)-pyrrolidin-2-one (−)-20. (−)-Menthol (3.70 g, 23.7 mmol) and PPTS (0.56 g, 2.23 mmol) were added to a stirred solution of pyrrolidin-2-one **18** (5.25 g, 22.5 mmol) and anhydrous copper sulphate (10.0 g, 62.7 mmol) in CH_2Cl_2 (100 mL) and stirred at room temperature overnight. The reaction mixture was poured onto H_2O (100 mL) and extracted with $CHCl_3$ (3×100 mL), the combined organic extracts were then dried ($MgSO_4$) and evaporated under reduced pressure. The resultant solid was then purified by flash column chromatography (25–50% EtOAc–petroleum ether) to give firstly the minor diastereoisomer (−)-**19** as a yellow oil (1.44 g, 3.59 mmol, 22%), $[\alpha]_D^{23}$=−113 (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2956, 2926, 2870, 1697, 1052; δ_H (400 MHz; $CDCl_3$) 0.49 (1H, ddd, J=12.3, 12.3, 10.5 Hz, 6′-H_A), 0.73 (3H, d, J=6.6 Hz, 2″-Me_A), 0.78 (4H, m with d at 0.78, J=7.0 Hz, 5′-Me+3′-H_A), 0.92 (4H, m with d at 0.92, J=7.1 Hz, 2″-Me_B+4′-H_A), 1.22 (2H, m, 2′-H+5′H), 1.34 (9H, s, $C(CH_3)_3$), 1.45 (1H, m, 6′-H_B), 1.60 (2H, m, 3′-H_B+4′-H_B), 2.10 (1H, m, 1″-H), 2.21 (2H, m, 4-H), 2.43 (1H, dd, J=17.0, 9.3 Hz, 3-H_A), 2.68 (1H, ddd, J=17.0, 9.8, 9.4 Hz, 3-H_B), 3.05 (1H, dt, J=10.5, 4.0 Hz, 1′-H), 3.79 (3H, s, OMe), 5.05 (1H, d, J=4.5 Hz, 5-H), 6.74 (1H, dd, J=8.6, 2.9 Hz, Ar-*H*), 7.01 (1H, d, J=2.9 Hz, Ar-*H*), 7.12 (1H, d, J=8.6 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 15.8 (CH_3), 21.1 (CH_3), 22.0 (CH_3), 22.9 (CH_2), 25.1 (CH), 26.1 (CH_2), 28.3 (CH_2), 30.4 (CH), 31.4 (CH_3), 33.9 (CH_2), 35.4

(C), 40.1 (CH_2), 48.0 (CH), 55.1 (CH_3), 76.1 (CH), 90.4 (CH), 110.4 (CH), 114.2 (CH), 127.8 (CH), 134.5 (CH), 149.1 (C), 158.9 (C), 177.1 (C=O); *m/z* (EI) 401 (M^+, 9%), 259 (16), 245 (100) (Found M^+, 401.2942. $C_{25}H_{39}NO_3$ requires *M*, 401.2930), followed by the major diastereoisomer (−)-**20** as a white solid (3.67 g, 9.14 mmol, 56%), $[\alpha]_D^{23}=-18$ (*c* 1.00, $CHCl_3$); mp 85–88 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2955, 2925, 2870, 1698, 1065, 1051; δ_H (400 MHz; $CDCl_3$) 0.34 (3H, d, *J*=6.9 Hz, 2″-Me_A), 0.71 (3H, d, *J*=7.0 Hz, 2″-Me_B), 0.81 (2H, m, 3′-H_A+4′-H_A), 0.91 (3H, d, *J*=6.5 Hz, 5′-Me), 0.99 (1H, ddd, *J*=12.0, 11.8, 10.4 Hz, 6′-H_A), 1.14 (1H, m, 5′-H), 1.32–1.33 (10H, m with s at 1.33, C(CH_3)$_3$+2′-H), 1.53 (2H, m, 3′-H_B+4′-H_B), 1.80 (1H, m, 1″-H), 1.92 (1H, m, 6′-H_B), 2.12 (1H, m, 4-H_A), 2.37 (2H, m, 4-H_B+3-H_A), 2.70 (1H, m, 3-H_B), 3.02 (1H, ddd, *J*=10.5, 10.4, 4.1 Hz, 1′-H), 3.79 (3H, s, OMe), 5.05 (1H, d, *J*=4.4 Hz, 5-H), 6.71 (1H, dd, *J*=8.6, 1.5 Hz, Ar-*H*), 7.00 (1H, d, *J*=1.5 Hz, Ar-*H*), 7.11 (1H, d, *J*=8.6 Hz, Ar-*H*); δ_C (67.5 MHz; $CDCl_3$) 15.5 (CH_3), 21.2 (CH_3), 22.3 (CH_3), 22.5 (CH_2), 24.4 (CH), 28.3 (CH_2), 28.5 (CH_2), 31.6 (CH), 31.7 (CH_3), 34.2 (CH_2), 35.5 (C), 43.0 (CH_2), 48.9 (CH), 55.3 (CH_3), 78.4 (CH), 92.9 (CH), 110.6 (CH), 114.6 (CH), 128.4 (CH), 135.0 (CH), 149.1 (C), 158.7 (C), 177.6 (C=O); *m/z* (EI) 401 (M^+, 0.8%), 246 (19), 245 (100) (Found M^+, 401.2915. $C_{25}H_{39}NO_3$ requires *M*, 401.2930).

4.1.12. (*M*,5*R*)-5-Allyl-1-(2-*tert*-butyl-4-methoxyphenyl)-pyrrolidin-2-one (+)-21. To a stirred solution of pyrrolidin-2-one (−)-**20** (200 mg, 0.50 mmol) and allyltrimethylsilane (1.10 mL, 6.92 mmol) in CH_2Cl_2 (5 mL) at −40 °C, was added dropwise trimethylsilyltrifluoromethanesulphonate (0.35 mL, 1.94 mmol). The reaction mixture was stirred at −40 °C for 8 h before H_2O (5 mL) was cautiously added. The reaction mixture was extracted with $CHCl_3$ (3×10 mL), the combined organic extracts were then dried ($MgSO_4$) and evaporated under reduced pressure. The resulting yellow oil was purified by flash column chromatography (60% EtOAc–petroleum ether) to yield the title compound (+)-**21** (6:1 ratio of isomers) as a colourless oil (177 mg, 0.62 mmol, 90%), $[\alpha]_D^{23}=11$ (*c* 1.00, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2959, 2838, 1682, 1051; δ_H (400 MHz, $CDCl_3$) 1.28 (9H major, s, C(CH_3)$_3$), 1.31 (9H minor, C(CH_3)$_3$), 1.88 (1H major+1H minor, m, 4-H_A), 2.05 (1H major+1H minor, m, 4-H_B), 2.36 (4H major+4H minor, m, 3-H+1′-H), 3.69 (3H minor, s, OMe), 3.70 (3H major, s, OMe), 3.82 (1H major+1H minor, m, 5-H), 4.95 (2H minor, m, 3′-H), 5.03 (2H major, m, 3′-H), 5.60 (1H major+1H minor, m, 2′-H), 6.68 (1H major+1H minor, dd, *J*=8.6, 2.9 Hz, Ar-*H*), 6.81 (1H major+1H minor, m, Ar-*H*), 6.99 (1H major+1H minor, d, *J*=2.8 Hz, Ar-*H*); δ_C (67.5 MHz, $CDCl_3$) 23.5 (CH_2), 29.3 (CH_2), 31.4 (CH_3), 35.6 (C), 37.7 (CH_2), 55.0 (CH_3), 61.4 (CH), 110.7 (CH), 115.2 (CH), 118.4 (CH), 127.2 (C), 133.3 (CH_2), 133.6 (CH), 158.9 (C), 149.5 (C), 175.9 (C=O); *m/z* (EI) 287 (M^+, 8%), 246 (100) (Found M^+, 287.1882. $C_{18}H_{25}NO_2$ requires *M*, 287.1885).

All four isomers of **21** were separated by HPLC using a Chiralcel OD column [25 cm×0.46 cm i.d.; 2% *i*-PrOH in hexane; flow rate, 1.0 mL/min]. Two atropisomers eluted at 32.9 and 48.2 min, and a further pair at 38.7 and 44.9 min. Samples of **21** originating with **20** gave the first pair of peaks as by far the major, allowing estimation of the ee as ca. 98%.

4.1.13. (*R*)-5-Allylpyrrolidin-2-one 22. To a solution of pyrrolidin-2-one (+)-**21** (175 mg, 0.61 mmol) in MeCN (12.5 mL), at 0 °C was added a solution of ceric ammonium nitrate (3.30 g, 6.02 mmol) in water (12.5 mL). The reaction mixture was then stirred at 0 °C for 5 h, before pouring onto H_2O (100 mL) and extracting with $CHCl_3$ (5×100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield a yellow oil. The crude oil was then purified by flash column chromatography (100% EtOAc) to yield **22** as a yellow oil (21 mg, 0.17 mmol, 28%), ν_{max} ($CHCl_3$)/cm^{-1} 3432, 2927, 1693; δ_H (400 MHz, $CDCl_3$) 1.78 (2H, m, 4-H), 2.22 (4H, m, 3-H+1′-H), 3.71 (1H, app. quin, *J*=6.4 Hz, 5-H), 5.14 (2H, m, 3′-H), 5.75 (1H, m, 2′-H), 5.93 (1H, br. s, N*H*); δ_C (126 MHz, $CDCl_3$) 26.6 (CH_2), 29.9 (CH_2), 40.9 (CH_2), 53.3 (CH), 118.4 (CH_2), 133.5 (CH), 177.7 (C=O); *m/z* (EI) 125 (M^+, 0.2%), 84 (100) (Found M^+, 125.0834. $C_7H_{11}NO$ requires *M*, 125.0841).

4.1.14. 1-(2-*tert*-Butyl-phenyl)-piperidin-2,6-dione 28. *Amide bond formation*. To a solution of 2-*tert*-butylaniline **27** (77.6 mL, 48.6 mmol) in toluene (50 mL) was added glutaric anhydride (6.55 g, 57.4 mmol) and the reaction mixture was heated at reflux for 1 h, cooled, and filtered to give the crude butyric acid. The solid was washed with petroleum ether, to give the butyric acid (2:1 ratio of rotamers) as a white solid (12.5 g, 48.4 mmol, 98%), mp 120–123 °C (recrystallised from petroleum ether/EtOAc); ν_{max} ($CHCl_3$)/cm^{-1} 3516, 2969, 1710, 1578; δ_H (400 MHz, $CDCl_3$) 1.40 (9H major+9H minor, s, C(CH_3)$_3$), 1.95 (2H minor, 4-H), 2.12 (2H major, apparent quin, *J*=7.1 Hz, 4-H), 2.17 (2H minor, 5-H/3-H), 2.38 (2H minor, 3-H/5-H), 2.51 (4H major, apparent q, *J*=6.9 Hz, 5-H+3-H), 7.07 (1H minor, Ar-*H*), 7.15–7.30 (2H major+2H minor, m, Ar-*H*), 7.30 (1H major, d, *J*=7.0 Hz, Ar-*H*), 7.46 (1H minor, Ar-*H*); 7.51 (1H major, d, *J*=7.5 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 20.6 (CH_2), 30.8 (CH_3), 33.1 (CH_2), 34.7 (C), 36.3 (CH_2), 126.7 (CH), 126.9 (CH), 127.2 (CH), 128.4 (CH), 134.9 (C), 143.0 (C), 170.9 (C=O), 178.2 (C=O); *m/z* (FAB) 264 (MH^+, 60%), 246 (10) 154 (100) (Found MH^+, 264.1603. $C_{15}H_{22}NO_3$ requires *M*, 264.1600). Anal. Calcd for $C_{15}H_{21}NO_3$. C, 68.44; H, 7.98; N, 5.32%. Found: C, 68.22; H, 7.95; N, 5.41%.

Imide formation. To a solution of the butyric acid (26.9 g, 0.10 mol) in $CHCl_3$ (500 mL) was added 1,1′-carbonyldiimidazole (17.8 g, 0.11 mol) and the reaction mixture heated at 70 °C overnight, and cooled. The reaction mixture was washed with H_2O (2×600 mL), and the aqueous re-extracted with $CHCl_3$ (2×200 mL). The combined organics were then washed with 2 N HCl (300 mL), then with water until washings were neutral, washed with brine (200 mL), dried ($MgSO_4$), and evaporated under reduced pressure to yield the title compound as a white solid (23.9 g, 0.10 mol, 98%), mp 116–118 °C (recrystallised from petroleum ether/EtOAc); ν_{max} ($CHCl_3$)/cm^{-1} 2966, 2908, 1734, 1682; δ_H (400 MHz, $CDCl_3$) 1.31 (9H, s, C(CH_3)$_3$), 2.10 (2H, apparent quin, *J*=6.6 Hz, 4-H), 2.81 (4H, apparent t, *J*=6.6 Hz, 3-H), 6.83 (1H, dd, *J*=7.7 Hz, 1.5, Ar-*H*), 7.28 (1H, ddd, *J*=7.7, 7.4, 1.5 Hz, Ar-*H*); 7.38 (1H, ddd, *J*=8.0,

7.4, 1.5 Hz, Ar-*H*), 7.58 (1H, dd, *J*=8.0, 1.5 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 17.1 (CH_2), 31.7 (CH_3), 33.5 (CH_2), 35.9 (C), 127.3 (CH), 129.1 (CH), 131.0 (2×CH), 133.3 (C), 146.8 (C), 173.3 (C=O); *m/z* (EI) 245 (M^+, 0.8%), 188 (100) (Found M^+, 245.1410. $C_{15}H_{19}NO_2$ requires *M*, 245.1416). Anal. Calcd for $C_{15}H_{19}NO_2$. C, 73.47; H, 7.76; N, 5.71%. Found: C, 73.33; H, 7.78; N, 5.70%.

4.1.15. 1-(2-*tert*-Butyl-phenyl)-6-hydroxy-piperidin-2-one 23. DIBAL (166 mL of a 1 M solution in CH_2Cl_2) was added dropwise to a stirred solution of imide **28** (22.5 g, 91.7 mmol) in CH_2Cl_2 (300 mL) at −78 °C. After 15 min stirring at −78 °C, H_2O (160 mL), followed by 2 N NaOH (50 mL) were cautiously added and the reaction mixture poured into a saturated solution of Rochelles salt (1.20 L). The mixture was then extracted with CH_2Cl_2 (4×350 mL). The combined extracts were then washed with brine (350 mL), dried ($MgSO_4$), and evaporated under reduced pressure to yield a yellow oil. The crude mixture was then purified by flash column chromatography (50% EtOAc–petroleum ether) to give a yellow oil, which was triturated with petroleum ether/EtOAc to yield the title compound **23** (3:1 ratio of isomers) as a white solid (14.5 g, 58.8 mmol, 64%), mp 104–106 °C; ν_{max} ($CHCl_3$)/cm^{-1} 3667, 3592, 3405, 3124, 2961, 1722, 1698, 1650, 1573; δ_H (400 MHz, $CDCl_3$) 1.31 (9H major, s, $C(CH_3)_3$), 1.38 (9H minor, $C(CH_3)_3$), 1.77 (1H major+1H minor, m, 4-H_A), 1.96–2.04 (2H major+2H minor, m, 4-H_B+5-H_A), 2.22–2.39 (2H major+2H minor, m, 5-H_B+3-H_A), 2.50–2.55 (1H major+1H minor, m, 3-H_B), 3.69 (1H major+1H minor, br.s, O*H*), 4.96 (1H major, m, 6-H), 5.26 (1H minor, 6-H), 6.96 (1H minor, Ar-*H*), 7.10 (1H major, dd, *J*=7.6, 1.6 Hz, Ar-*H*), 7.18 (1H major+1H minor, ddd, *J*=7.6, 7.3, 1.6 Hz, Ar-*H*); 7.27 (1H major+1H minor, ddd, *J*=8.0, 7.3, 1.6 Hz, Ar-*H*), 7.51 (1H major, dd, *J*=8.0, 1.6 Hz, Ar-*H*) 7.56 (1H minor, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 16.0 (CH_2), 29.4 (CH_2), 31.7 (CH_3), 33.1 (CH_2), 35.7 (C), 82.3 (CH), 126.8 (CH), 128.2 (CH), 128.9 (CH), 132.6 (CH), 139.0 (C), 146.6(C), 172.3 (C=O); *m/z* (TOF) 270 $(M+Na)^+$ (Found $M+Na^+$, 270.1476. $C_{15}H_{21}NO_2$+Na requires *M*, 270.1470). Anal. Calcd for $C_{15}H_{21}NO_2$. C, 72.87; H, 8.50; N, 5.67%. Found: C, 72.67; H, 8.53; N, 5.65%.

4.1.16. 1-(2-*tert*-Butyl-phenyl)-3,4-dihydro-1*H*-pyridin-2-one 24. To a solution of piperidine-2-one **23** (14.0 g, 56.8 mmol) in CH_2Cl_2 (500 mL) at 0 °C, was added Et_3N (24.0 mL, 172 mmol), then MsCl (6.66 mL, 86.1 mmol). The reaction mixture was stirred at room temperature for 2 h, then washed with H_2O (500 mL), a saturated solution of $NaHCO_3$ (500 mL), and brine (500 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting orange oil was purified by flash column chromatography (20% EtOAc–petroleum ether), to give the title compound as a white solid (10.6 g, 46.4 mmol, 81%), mp 91–93 °C (recrystallised from petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 2960, 2775, 2577, 2465, 2263, 2144, 1723, 1698, 1672, 1573; δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, $C(CH_3)_3$), 2.44–2.49 (2H, m, 4-H), 2.66–2.70 (2H, m, 3-H), 5.24 (1H, dt, *J*=7.7, 4.4 Hz, 5-H), 6.07 (1H, dt, *J*=7.7, 1.6 Hz, 6-H), 7.01 (1H, dd, *J*=7.6, 1.7 Hz, Ar-*H*), 7.26 (1H, ddd, *J*=7.6, 7.3, 1.6 Hz, Ar-*H*), 7.32 (1H, ddd, *J*=8.0, 7.3, 1.7 Hz, Ar-*H*), 7.54 (1H, dd, *J*=8.0, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 20.5 (CH_2), 31.7 (CH_3), 32.2 (CH_2), 35.7 (C), 105.0 (CH), 127.6 (CH), 128.6 (CH), 128.7 (CH), 130.9 (CH), 132.9 (CH), 139.5 (C), 147.6 (C), 170.3 (C=O); *m/z* (TOF) 252 $(M+Na)^+$ (Found $M+Na^+$, 252.1364. $C_{15}H_{19}NO$+Na requires *M*, 252.1364). Anal. Calcd for $C_{15}H_{19}NO$. C, 78.60; H, 8.30; N, 6.11%. Found: C, 78.28; H, 8.36; N, 6.16%.

4.1.17. (5*S*,6*S*)-6-Allyl-1-(2-*tert*-butyl-phenyl)-5-hydroxy-piperidin-2-one 25 and (5*R*,6*S*)-6-allyl-1-(2-*tert*-butyl-phenyl)-5-hydroxy-piperidin-2-one 26. To a solution of **24** (1.20 g, 5.22 mmol) in dry acetone (30 mL) at 0 °C, was added DMDO (100 mL of an approx. 0.10 M solution). The reaction mixed was stirred at 0 °C for 1 h then concentrated and redissolved in CH_2Cl_2 (30 mL). To this solution, was added allyl trimethylsilane (4.14 mL, 26.1 mmol) and $TiCl_4$ (2.86 mL, 26.1 mmol) slowly. The reaction mixture was stirred at room temperature for 3 days, then diluted with CH_2Cl_2 (60 mL), washed with H_2O (50 mL), a saturated solution of $NaHCO_3$ (50 mL), and brine (50 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting crude mixture was purified by flash column chromatography (20% EtOAc–petroleum ether), to give: firstly the minor isomer **26** (R_f 0.4, 70:30 petroleum ether–EtOAc) as a white solid (170 mg, 0.60 mmol, 11%), δ_H (500 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 1.94–2.05 (1H, m, 4-H_A), 2.09 (1H, m, 1′-H_A), 2.18 (1H, dddd, *J*=15.5, 9.9, 6.2, 4.0 Hz, 4-H_B), 2.51 (1H, ddd, *J*=17.6, 5.9, 4.0 Hz, 3-H_A), 2.65 (1H, dddd, *J*=16.1, 5.6, 3.8, 1.7 Hz, 1′-H_B), 2.74 (1H, ddd, *J*=17.6, 11.0, 6.2 Hz, 3-H_B), 3.78 (1H, ddd, *J*=9.9, 3.3, 3.2 Hz, 5-H), 4.23 (1H, m, 6-H), 5.09 (2H, m, 3′-H), 5.62 (1H, dddd, *J*=18.9, 10.5, 6.8, 5.6 Hz, 2′-H), 6.91 (1H, dd, *J*=7.7, 1.7 Hz, Ar-*H*), 7.20 (1H, ddd, *J*=7.7, 7.3, 1.5 Hz, Ar-*H*), 7.29 (1H, ddd, *J*=8.2, 7.3, 1.7 Hz, Ar-*H*), 7.58 (1H, dd, *J*=8.2, 1.5 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 25.3 (CH_2), 28.2 (CH_2), 31.9 (CH_3), 36.1 (C), 37.8 (CH_2), 65.4 (CH), 66.9 (CH), 118.4 (CH_2), 126.3 (CH), 128.1 (CH), 129.8 (CH), 134.1 (2×CH), 138.2 (C), 147.0 (C), 171.2 (C=O); *m/z* (FAB) 288 (MH^+, 35%), 230 (12) (Found MH^+, 288.1962. $C_{18}H_{25}NO_2$ requires *M*, 288.1964); followed by the major isomer **25** (R_f 0.3, 70:30 petroleum ether–EtOAc) as a white solid (950 mg, 3.03 mmol, 63%), mp 140–142 °C (recrystallised from petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3622, 2960, 1643, 1597; δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, $C(CH_3)_3$), 1.93–2.00 (1H, m, 1′-H_A), 2.05–2.11 (2H, m, 4-H), 2.31 (1H, ddd, *J*=14.2, 10.5, 8.5 Hz, 1′-H_B), 2.50 (1H, ddd, *J*=17.7, 7.6, 5.7 Hz, 3-H_A), 2.71 (1H, dt, *J*=17.7, 8.0 Hz, 3-H_B), 3.76 (1H, ddd, *J*=10.7, 4.0, 2.9 Hz, 5-H), 4.48 (1H, m, 6-H), 5.07 (2H, m, 3′-H), 5.65 (1H, dddd, *J*=18.9, 10.5, 6.3, 5.7 Hz, 2′-H), 7.01 (1H, dd, *J*=7.8, 1.6 Hz, Ar-*H*), 7.19 (1H, ddd, *J*=7.8, 7.2, 1.7 Hz, Ar-*H*), 7.27 (1H, ddd, *J*=8.0, 7.2, 1.6 Hz, Ar-*H*), 7.53 (1H, dd, *J*=8.0, 1.7 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 27.0 (CH_2), 28.4 (CH_2), 31.8 (CH_3), 34.6 (CH_2), 35.9 (C), 63.4 (CH), 64.2 (CH), 118.0 (CH_2), 126.4 (CH), 127.9 (CH), 129.0 (CH), 133.2 (CH), 134.5 (CH), 137.2 (C), 147.0 (C), 171.6 (C=O); *m/z* (FAB) 288 (MH^+, 100%), 230 (24) (Found MH^+, 288.1980. $C_{18}H_{25}NO_2$ requires *M*, 288.1964). Anal. Calcd for $C_{18}H_{25}NO_2$. C, 75.26; H, 8.71; N, 4.88%. Found: C, 75.53; H, 8.81; N, 4.94%.

4.1.18. 3-Alkyl-1-(2-*tert*-butyl-phenyl)-3,4-dihydro-1*H*-pyridin-2-one 29a–f. General procedure for alkylation of

24. To a stirred solution of di*iso*propylamine (0.14 mL, 1.00 mmol) in THF (5 mL) at −78 °C was added ^{n}BuLi (0.68 mL of a 1.60 M solution in hexanes), and the mixture then warmed to room temperature for 15 min before cooling to −78 °C. To the resulting solution of LDA, a solution of pyridin-2-one **24** (200 mg, 0.87 mmol) in THF (5 mL) was added. After 1.5 h the electrophile (8.70 mmol) was added and the reaction mixture stirred at −78 °C for 1 h. Saturated NH_4Cl solution (5 mL) was then added and the reaction mixture was allowed to warm to room temperature. The mixture was extracted with EtOAc (4×30 mL), the combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude product was purified by flash column chromatography.

4.1.19. (3*R*)-1-(2-*tert*-Butyl-phenyl)-3-methyl-3,4-dihydro-1*H*-pyridin-2-one 29a. From **24** (200 mg, 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (20% EtOAc–petroleum ether) to yield the title compound (6:1 ratio of isomers) as an oily solid (171 mg, 0.70 mmol, 81%), ν_{max} ($CHCl_3$)/cm^{-1} 2966, 2359, 1711, 1667; δ_H (400 MHz, $CDCl_3$) 1.30 (3H major, d, *J*=6.9 Hz, 3-Me), 1.33 (3H minor, 3-Me), 1.36 (9H major, s, C(CH_3)$_3$), 1.37 (9H minor, C(CH_3)$_3$), 2.24 (1H major+1H minor, dddd, *J*=16.9, 10.8, 4.0, 1.8 Hz, 4-H_A), 2.51 (1H major+1H minor, dddd, *J*=16.9, 14.1, 3.7, 1.2 Hz, 4-H_B), 2.72 (1H major+1H minor, ddq, *J*=14.1, 10.8, 6.9 Hz, 3-H), 5.17 (1H, ddd, *J*=7.7, 4.0, 3.7 Hz, 5-H), 5.25 (1H minor, 5-H), 6.04 (1H, ddd, *J*=7.7, 1.8, 1.2 Hz, 6-H), 6.07 (1H minor, 6-H), 6.98 (1H major+1H minor, dd, *J*=7.6, 1.6 Hz, Ar-*H*), 7.24 (1H major+1H minor, ddd, *J*=7.6, 7.3, 1.6 Hz, Ar-*H*), 7.31 (1H major+1H minor, ddd, *J*=8.0, 7.3, 1.6 Hz, Ar-*H*), 7.52 (1H major+1H minor, dd, *J*=8.0, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 15.7 (CH_3), 28.6 (CH_2), 31.7 (CH_3), 35.7 (C), 36.2 (CH), 104.0 (CH), 127.4 (CH), 128.5 (CH), 128.7 (CH), 131.1 (CH), 132.6 (CH), 139.6 (C), 147.4 (C), 173.1 (C=O); *m*/*z* (FAB) 244 (MH^+, 100%), 186 (92) (Found MH^+, 244.1716. $C_{16}H_{22}NO$ requires *M*, 244.1701).

4.1.20. (3*R*)-3-Allyl-1-(2-*tert*-butyl-phenyl)-3,4-dihydro-1*H*-pyridin-2-one 29b. From **24** (200 mg, 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (10% EtOAc–petroleum ether) to yield the title compound (12:1 ratio of isomers) as a yellow oil (155 mg, 0.58 mmol, 66%), ν_{max} ($CHCl_3$)/cm^{-1} 2963, 1710, 1668; δ_H (400 MHz, $CDCl_3$) 1.37 (9H major+9H minor, s, C(CH_3)$_3$), 2.29–2.35 (2H major+2H minor, m, 4-H), 2.52 (1H major+1H minor, dddd, *J*=16.7, 6.0, 3.9, 1.2 Hz, 1′-H_A), 2.62–2.72 (2H major+2H minor, m, 1′-H_B+3-H), 5.08–5.19 (3H major+2H minor, m, 3′-H+5-H), 5.25 (1H minor, 5-H), 5.81–5.88 (1H major+1 H minor, m, 2′-H), 6.04 (1H major+1H minor, dt, *J*=7.8, 1.5 Hz, 6-H), 6.96 (1H major+1H minor, dd, *J*=7.6, 1.7 Hz, Ar-*H*), 7.25 (1H major+1H minor, ddd, *J*=7.6, 7.3, 1.6 Hz, Ar-*H*); 7.31 (1H major+1H minor, ddd, *J*=8.0, 7.3, 1.7 Hz, Ar-*H*), 7.53 (1H major+1H minor, dd, *J*=8.0, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 25.2 (CH_2), 31.7 (CH_3), 34.2 (CH_2), 35.7 (C), 40.8(CH), 103.9 (CH), 117.2 (CH_2), 127.5 (CH), 128.5 (CH), 128.7 (CH), 131.1 (CH), 132.5 (CH), 136.0 (CH), 139.5 (C), 147.5 (C), 172.0 (C=O); *m*/*z* (FAB) 270 (MH^+, 100%), 212 (80) (Found MH^+, 270.1851. $C_{18}H_{24}NO$ requires *M*, 270.1858).

4.1.21. (3*S*)-3-Benzyl-1-(2-*tert*-butyl-phenyl)-3,4-dihydro-1*H*-pyridin-2-one 29c. From **24** (200 mg, 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (10% EtOAc–petroleum ether) to yield the title compound (13:1 ratio of isomers) as a yellow oil (218 mg, 0.68 mmol, 79%), ν_{max} ($CHCl_3$)/cm^{-1} 2959, 2358, 1668; δ_H (400 MHz, $CDCl_3$) 1.40 (9H major+9H minor, s, C(CH_3)$_3$), 2.19 (1H major+1H minor, dddd, *J*=17.1, 8.7, 4.3, 1.6 Hz, 4-H_A), 2.36 (1H major+1H minor, dddd, *J*=17.1, 6.6, 4.6, 1.6 Hz, 4-H_B), 2.78–2.88 (2H major+2H minor, m, 3-H+1′-H_A), 3.37 (1H major, dd, *J*=12.6, 3.2 Hz, 1′-H_B), 3.46 (1H minor, d, *J*=10.2 Hz, 1′H_B), 5.16 (1H major, dt, *J*=7.5, 4.5 Hz, 5-H), 5.21 (1H minor, 5-H), 6.09 (1H major+1H minor, dt, *J*=7.5, 1.6 Hz, 6-H), 7.00 (1H major+1H minor, dd, *J*=7.6, 1.6 Hz, Ar-*H*), 7.01 (1H minor, dd, *J*=7.4, 1.5 Hz, Ar-*H*), 7.24–7.30 (4H major+4H minor, m, Ar-*H*); 7.31–7.37 (3H major+3H minor, m, Ar-*H*), 7.56 (1H major+1H minor, dd, *J*=8.0, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 24.6 (CH_2), 31.8 (CH_3), 35.6 (CH_2), 35.8 (C), 43.0 (CH), 103.8 (CH), 126.4 (CH), 127.5 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.4 (CH), 131.1 (CH), 132.6 (CH), 139.4 (C), 139.5 (C), 147.5 (C), 172.1 (C=O); *m*/*z* (FAB) 320 (MH^+, 100%), 262 (77) (Found MH^+, 320.2039. $C_{22}H_{26}NO$ requires *M*, 320.2014).

4.1.22. (3*S*)-1-(2-*tert*-Butyl-phenyl)-3-prop-2-ynyl-3,4-dihydro-1*H*-pyridin-2-one 29d. From **29** (200 mg. 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (10% EtOAc–petroleum ether) to yield the title compound (12:1 ratio of isomers) as a solid (144 mg, 0.22 mmol, 62%), mp 105–108 °C (recrystallised from petroleum ether); ν_{max} ($CHCl_3$)/cm^{-1} 3307, 2963, 2337, 1673, 1607; δ_H (400 MHz, $CDCl_3$) 1.35 (9H major, s, C(CH_3)$_3$), 1.37 (9H minor, s, C(CH_3)$_3$), 2.01 (1H minor, apparent t, *J*=2.7 Hz, 3′-H), 2.03 (1H major, apparent t, *J*=2.7 Hz, 3′-H), 2.42–2.51 (2H major+2H minor, m, 1′-H_A+4-H_A), 2.71–2.84 (2H major+2H minor, m, 4-H_B+3-H), 2.91 (1H major+1H minor, ddd, *J*=17.0, 3.9, 2.7 Hz, 1′-H_B), 5.24 (1H major, dt, *J*=6.6, 3.3 Hz, 5-H), 5.32 (1H minor, 5-H), 6.05 (1H major+1H minor, dt, *J*=6.6, 1.8, 6-H), 6.99 (1H major+1H minor, dd, *J*=7.7, 1.5 Hz, Ar-*H*), 7.24 (1H major+1H minor, ddd, *J*=7.7, 7.3, 1.6 Hz, Ar-*H*); 7.32 (1H major+1H minor, ddd, *J*=8.1, 7.3, 1.5 Hz, Ar-*H*), 7.53 (1H major+1H minor, dd, *J*=8.1, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 19.4 (CH_2), 25.6 (CH_2), 31.7 (CH_3), 35.7 (C), 40.4 (CH), 70.0 (CH), 82.0 (C), 104.2 (CH), 127.5 (CH), 128.7 (CH), 128.8 (CH), 131.1 (CH), 132.5 (CH), 139.1 (C), 147.2 (C), 170.4 (C=O); *m*/*z* (FAB) 268 (MH^+, 64%), 210 (48) (Found MH^+, 268.1718. $C_{18}H_{22}NO$ requires *M*, 268.1701).

4.1.23. (3*R*)-1-(2-*tert*-Butyl-phenyl)-3-pentyl-3,4-dihydro-1*H*-pyridin-2-one 29e. From **29** (200 mg, 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (4% EtOAc–petroleum ether) to yield the title compound (7:1 ratio of isomers) as an oil (229 mg, 0.77 mmol, 88%), ν_{max} ($CHCl_3$)/cm^{-1} 2929, 2860, 1667, 1572; δ_H (400 MHz, $CDCl_3$) 0.91 (3H major+3H minor, t, *J*=7.0 Hz, 5′-H) 1.27–1.55 (16H major+16H minor, m, C(CH_3)$_3$ +1′-H_A+2′-H +3′H+4′-H), 1.90–1.93 (1H major+1H minor, m, 1′-H_B), 2.25 (1H major+1H minor, dddd, *J*=19.1, 10.6, 4.4, 1.5 Hz, 4-H_A), 2.52–2.58 (2H

major+2H minor, m, 3-H+4-H_B), 5.16 (1H major, dt, J=7.7, 4.4 Hz, 5-H), 5.23 (1H minor, 5-H), 6.03 (1H major+1H minor, dt, J=7.7, 1.5 Hz, 6-H), 6.95 (1H major+1H minor, dd, J=7.6, 1.7 Hz, Ar-*H*), 7.28 (1H major+1H minor, ddd, J=7.6, 7.3, 1.6 Hz, Ar-*H*), 7.34 (1H major+1H minor, ddd, J=8.0, 7.3, 1.7 Hz, Ar-*H*), 7.52 (1H major+1H minor, dd, J=8.0, 1.6 Hz, Ar-*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 26.9 (CH_2), 29.7 (CH_2), 31.7 (CH_3), 31.9 (CH_2), 35.7 (C), 41.2 (CH), 103.8 (CH), 127.5 (CH), 128.4 (CH), 128.7 (CH), 131.1 (CH), 132.4 (CH), 139.7 (C), 147.6 (C), 172.8 (C=O); *m*/*z* (FAB) 300 (MH^+, 54%), 242 (64) (Found MH^+, 300.2339. $C_{20}H_{30}NO$ requires *M*, 300.2327).

4.1.24. (3*R*)-1-(2-*tert*-Butyl-phenyl)-3-ethyl-3,4-dihydro-1*H*-pyridin-2-one 29f. From **24** (200 mg, 0.87 mmol), the resulting yellow oil was purified by flash column chromatography (10% EtOAc–petroleum ether) to yield the title compound (10:1 ratio of isomers) as an oil (153 mg, 0.60 mmol, 61%), ν_{max} ($CHCl_3$)/cm^{-1} 2966, 2877, 1687; δ_H (400 MHz, $CDCl_3$) 1.03 (3H major+3H minor, t, J=7.5 Hz, 2′-H) 1.37 (9H major+9H minor, s, C(CH_3)$_3$), 1.55–1.64 (1H major+1H minor, m, 1′-H_A), 1.98 (1H major+1H minor, dqd, J=13.4, 7.5, 5.6 Hz, 1′-H_B), 2.28 (1H major+1 H minor, dddd, J=16.6, 8.2, 4.4, 1.3 Hz, 4-H_A), 2.45–2.58 (2H major+2H minor, m, 4-H_B+3-H), 5.17 (1H major, dt, J=7.8, 4.4 Hz, 5-H), 5.23 (1H minor, 5-H), 6.03 (1H major+1H minor, dt, J=7.8, 1.3 Hz, 6-H), 6.95 (1H major+1H minor, dd, J=7.6, 1.8 Hz, Ar-*H*), 7.22–7.51 (2H major+2H minor, m, Ar-*H*), 7.52 (1H major+1H minor, dd, J=8.0, 1.6 Hz, Ar-*H*), δ_C (100 MHz, $CDCl_3$) 11.7 (CH_3), 22.9 (CH_2), 25.3 (CH_2), 31.7 (CH_3), 35.7 (C), 42.7 (CH), 103.8 (CH), 127.6 (CH), 128.4 (CH), 128.7 (CH), 131.1 (CH), 132.4 (CH), 139.7 (C), 147.5 (C), 172.6 (C=O); *m*/*z* (TOF) 280 (M+Na)$^+$ (Found M+Na^+, 280.1682. $C_{17}H_{23}NO$+Na requires *M*, 280.1677).

4.1.25. (3*R*)-1-(2-*tert*-Butyl-phenyl)-3-phenylsulfanyl-3,4-dihydro-1*H*-pyridin-2-one *anti*-29g, (3*S*)-1-(2-*tert*-butyl-phenyl)-3-phenylsulfanyl-3,4-dihydro-1*H*-pyridin-2-one *syn*-29g. To a stirred solution of di*iso*propylamine (0.12 mL, 0.87 mmol) in THF (5 mL) at −78 °C was added ^{n}BuLi (0.56 mL of a 1.60 M solution in hexanes), followed by warming to room temperature for 15 min, then recooling to −78 °C. To the resulting LDA solution was added a solution of enamide **24** (200 mg, 0.87 mmol) in THF (5 mL). After 1 h at −78 °C, phenyl disulfide (1.90 g, 8.70 mmol) in a solution of THF (4 mL) was added and the reaction mixture stirred at −78 °C for 1 h. A solution of saturated NH_4Cl solution (5 mL) was then added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (2×40 mL), the combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude product was purified by biotage chromatography (2–20% EtOAc–petroleum ether) to give firstly the *anti*-adduct of **29g** (R_f 0.8, 70:30 petroleum ether–EtOAc) (10:1 ratio of *anti*:bis products) as a white solid (200 mg, 0.59 mmol, 68%), mp 85–90 °C; ν_{max} ($CHCl_3$/cm^{-1} 2962, 1672, 1488, 1467, 1440, 1396, 1356, 1299, 1145; δ_H (500 MHz, $CDCl_3$) 1.37 (9H, s, C(CH_3)$_3$), 2.69 (1H, ddd, J=17.4, 6.3, 3.4 Hz, 4-H_A), 2.96 (1H, dddd, J=17.4, 5.6, 2.9, 2.8 Hz, 4-H_B), 3.99 (1H, dd, J=5.6, 3.4 Hz, 3-H), 5.23 (1H, ddd, J=7.6, 6.3, 2.8 Hz, 5-H), 6.14 (1H, dd, J=7.6, 2.9 Hz, 6-H), 7.06 (1H, dd, J=7.6, 1.2 Hz, Ar-*H*), 7.25–7.34 (5H, m, Ar-*H*), 7.52 (1H, dd, J=7.8, 1.2 Hz, Ar-*H*), 7.61 (2H, d, J=7.6 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 27.4 (CH_2), 31.8 (CH_3), 35.8 (C), 48.7 (CH), 102.2 (CH), 127.8 (2×CH), 128.6 (CH), 128.8 (CH), 129.0 (2×CH), 130.3 (CH), 132.8 (2×CH), 133.3 (CH), 136.7 (C), 139.4 (C), 147.8 (C), 168.0 (C=O); *m*/*z* (EI) (Found M^+, 337.1490. $C_{21}H_{23}NOS$ requires *M*, 337.1500); followed by the *syn*-adduct of **29g** (R_f 0.75, 30:70 petroleum ether–EtOAc) as an oil (30.0 mg, 0.09 mmol, 15%), ν_{max} ($CHCl_3$)/cm^{-1} 2962, 2873, 1672, 1587, 1485, 1440, 1398, 1358, 1303, 1146; δ_H (500 MHz, $CDCl_3$) 1.35 (9H, s, C(CH_3)$_3$), 2.63 (1H, ddd, J=17.8, 5.3, 5.2 Hz, 4-H_A), 2.97 (1H, ddd, J=17.8, 6.2, 3.4, 2.2 Hz, 4-H_B), 4.10 (1H, dd, J=6.3, 6.2 Hz, 3-H), 5.21 (1H, ddd, J=7.6, 5.2, 3.4 Hz, 5-H), 6.10 (1H, dd, J=7.6, 2.2 Hz, 6-H), 7.01 (1H, dd, J=7.6, 1.2 Hz, Ar-*H*), 7.21–7.33 (5H, m, Ar-*H*), 7.51 (1H, dd, J=7.9, 1.2 Hz, Ar-*H*), 7.57 (2H, dd, J=7.6, 1.3 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 28.1 (CH_2), 31.6 (CH_3), 35.7 (C), 48.4 (CH), 103.4 (CH), 127.3 (CH), 127.5 (CH), 128.5 (CH), 128.8 (CH), 129.0 (2×CH), 131.3 (CH), 131.8 (2×CH), 133.0 (CH), 134.2 (C), 139.4 (C), 147.7 (C), 167.6 (C=O); *m*/*z* (EI) (Found M^+, 337.1486. $C_{21}H_{23}NOS$ requires *M*, 337.1500).

4.1.26. 1-(2-*tert*-Butyl-phenyl)-3-(3-trimethylsilanyl-prop-2-ynyl)-3,4-dihydro-1*H*-pyridin-2-one 29h. To a stirred solution of di*iso*propylamine (0.03 mL, 0.22 mmol) in THF (2 mL) at −78 °C was added ^{n}BuLi (0.14 mL of a 1.60 M solution in hexanes), followed by warming to room temperature for 15 min, then recooled to −78 °C. To the resulting LDA, a solution of pyridin-2-one **24** (50.0 mg, 0.22 mmol) in THF (2 mL) was added. After 1 h TMS-propargyl bromide (0.31 mL, 2.20 mmol) was added and the reaction mixture stirred at −78 °C for 1 h, saturated NH_4Cl solution (5 mL) was then added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (2×20 mL), the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude product was purified by biotage chromatography (5% EtOAC–petroleum ether) to yield the title compound (15:1 ratio of isomers) as a yellow oil (50.0 mg, 0.15 mmol, 68%), ν_{max} ($CHCl_3$)/cm^{-1} 2961, 2908, 1673, 1488, 1440, 1399, 1364, 1286, 1151; δ_H (500 MHz, $CDCl_3$) 0.18 (9H major+9H minor, s, Si(CH_3)$_3$), 1.35 (9H+9H minor, s, C(CH_3)$_3$), 2.38–2.51 (2H major+2H minor, m with dd at 2.47, J=17.1, 10.2 Hz, 7-H and 4-H_A), 2.72–2.82 (2H major+2H minor, m, 4-H_B and 3-H), 2.96 (1H major+1H minor, dd, J=17.1, 3.7 Hz, 7-H_B), 5.24 (1H major, ddd, J=7.7, 5.0, 3.5 Hz, 5-H), 5.27 (1H minor, 5-H), 6.05 (1H major+1H minor, dd, J=7.7, 1.9 Hz, 6-H), 6.98 (1H major+1H minor, dd, J=7.7, 1.4 Hz, Ar-*H*), 7.24 (1H major+1H minor, ddd, J=7.7, 7.5, 1.2 Hz, Ar-*H*), 7.31 (1H major+1H minor, ddd, J=8.2, 7.5, 1.4 Hz, Ar-*H*), 7.52 (1H major+1H minor, dd, J=8.2, 1.2 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 0.18 (CH_3), 20.9 (CH_2), 25.6 (CH_2), 31.7 (CH_3), 35.7 (C), 40.5 (CH), 86.4 (C), 104.3 (CH), 104.7 (C), 127.4 (CH), 128.6 (CH), 128.7 (CH), 131.1 (CH), 132.5 (CH), 139.2 (C), 147.2 (C), 170.5 (C=O); *m*/*z* (EI) (Found M^+, 339.2026. $C_{21}H_{29}NOSi$ requires *M*, 339.2018).

4.1.27. Kinetic resolution of 1-(2-*tert*-butyl-phenyl)-3,4-dihydro-1*H*-pyridin-2-one 24. To a stirred solution of chiral diamine[24] (273 mg, 0.65 mmol) in THF (5 mL) at −78 °C was added ^{n}BuLi (0.42 mL of a 1.60 M solution in hexanes), followed by warming to room temperature for 15 min, then recooled to −78 °C. To the resulting chiral base, a solution of pyridin-2-one **24** (200 mg, 0.87 mmol) in THF (5 mL) was added. After 1 h benzyl bromide (1.03 mL, 8.70 mmol) was added and the reaction mixture stirred at −78 °C for 1 h, saturated NH_4Cl solution (5 mL) was then added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (2×40 mL), the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude NMR indicated the reaction had proceeded to 74% conversion. The ee of the remaining starting material (73%) was determined by HPLC analysis using a Chirapak AD-H column [25 cm ×0.46 cm i.d.; 3% *i*-PrOH in hexane; flow rate, 0.4 mL/min; (−)-**24**; t_R=25.7 min, (+)-**24**; t_R=29.0 min].

The reaction was also carried using 0.25 equiv. of chiral base [chiral amine (92.0 mg, 0.22 mmol) and ^{n}BuLi (0.14 mL of a 1.60 M solution in hexanes)] to give enamide **24** of 15% ee; and 0.5 equiv. of chiral base [chiral amine (184 mg, 0.44 mmol) and ^{n}BuLi (0.27 mL of a 1.60 M solution in hexanes)] to give enamide **24** of 62% ee.

4.1.28. (3*R*)-(+)-Methylglutaric anhydride 32. A solution of (*R*)-(−)-2-methylglutaric acid **31** (2.00 g, 14.0 mmol) in Ac_2O (50 mL) was refluxed for 24 h. Removal of excess Ac_2O by azeotropic codistillation with dry toluene (27×40 mL) yielded a brown solid **32** (1.75 g, 13.7 mmol, 98%), which was used without further purification, mp 48–50 °C (lit.[20] 35–36 °C); $[\alpha]_D^{23}$=+38.9 (*c* 1.50, $CHCl_3$) (lit.[20] $[\alpha]_D$=+44.4 (neat); ν_{max} ($CHCl_3$)/cm^{-1} 2978, 2941, 2883, 1814, 1770, 1460, 1384, 1352, 1326; δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J*=6.9 Hz, 3-Me), 1.78 (1H, dddd, *J*=13.8, 12.1, 12.0, 5.1 Hz, 4-H_A), 2.07 (1H, dddd, *J*=12.0, 8.0, 5.3, 3.5 Hz, 4-H_B), 2.66 (1H, dqd, *J*=13.8, 6.9, 5.3 Hz, 3-H), 2.73 (1H, ddd, *J*, 18.2, 12.1, 5.9 Hz, 5-H_A), 2.93 (1H, ddd, *J*=18.2, 5.1, 3.5 Hz, 5-H_B); δ_C (125 MHz, $CDCl_3$) 15.8 (CH_3), 24.4 (CH_2), 30.2 (CH_2), 35.8 (CH), 166.9 (C═O), 169.7 (C═O); *m*/*z* (EI) (Found M$^+$, 128.0479. $C_6H_8O_3$ requires *M*, 128.0474).

The above procedure was also carried out using racemic 2-methylglutaric acid and yielded the racemic anhydride (1.80 g, 14.0 mmol, 100%).

4.1.29. (*M*,3*R*)-1-(2-*tert*-Butyl-phenyl)-3-methyl-piperidine-2,6-dione *anti*-33 and (*P*,3*R*)-1-(2-*tert*-butyl-phenyl)-3-methyl-piperidine-2,6-dione *syn*-33. A solution of 2-*tert*-butylaniline **27** (1.69 mL, 10.8 mmol) and (*R*)-(+)-2-methylglutaric anhydride **32** (1.67 g, 13.0 mmol) in toluene (50 mL) was refluxed for 15 h, evaporated and subsequently heated at 80 °C with NaOAc (5.32 g, 64.8 mmol) in Ac_2O (50 mL) for 15 h then poured into H_2O (150 mL), extracted with $CHCl_3$ (4×60 mL), washed with 2 N NaOH (60 mL), brine (60 mL), dried ($MgSO_4$) and concentrated to yield the crude product, which was purified by biotage chromatography (10–60% EtOAc–petroleum ether) to give firstly the least polar diastereoisomer *anti*-**33** (R_f 0.9, 1:1 petroleum ether–EtOAc) as an oil which slowly solidified (1.20 g, 4.60 mmol, 43%), mp 48–52 °C; $[\alpha]_D^{25}$=+20.6 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2962, 1732, 1682, 1488, 1460, 1355, 1311, 1284; δ_H (500 MHz, $CDCl_3$) 1.29 (9H, s, C(CH_3)$_3$), 1.39 (3H, d, *J*=6.9 Hz, 3-Me), 1.89 (1H, dddd, *J*=13.7, 11.8, 11.4, 4.6 Hz, 4-H_A), 2.17 (1H, dddd, *J*=13.7, 5.2, 5.0, 4.7 Hz, 4-H_B), 2.72 (1H, m, 3-H), 2.76 (1H, ddd, *J*=17.2, 11.9, 5.2 Hz, 5-H_A), 2.95 (1H, ddd, *J*=17.2, 4.7, 4.6 Hz, 5-H_B), 6.78 (1H, dd, *J*=7.7, 1.3 Hz, Ar-*H*), 7.25 (1H, ddd, *J*=7.7, 7.5 Hz, 1.4, Ar-*H*), 7.35 (1H, ddd, *J*=7.9, 7.5, 1.3 Hz, Ar-*H*), 7.57 (1H, dd, *J*=7.9, 1.4 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 16.0 (CH_3), 25.5 (CH_2), 31.7 (CH_3), 33.0 (CH_2), 35.9 (C), 37.9 (CH), 127.2 (CH), 128.9 (CH), 129.1 (CH), 131.0 (CH), 133.5 (C), 146.7 (C), 173.5 (C═O), 176.1 (C═O); *m*/*z* (EI) (Found M$^+$, 259.1568. $C_{16}H_{21}NO_2$ requires *M*, 259.1572). The ee of *anti*-**33** (72% ee) was determined by HPLC analysis using a Chirapak AD-H column [25 cm×0.46 cm i.d.; 3% *i*-PrOH in hexane; flow rate, 0.4 mL/min; (−)-*anti*-**33**; t_R=34.2 min, (+)-*anti*-**33**; t_R=38.7 min]; followed by the most polar diastereoisomer *syn*-**33** (R_f 0.8, 1:1 petroleum ether–EtOAc) as a white solid (0.75 g, 3.00 mmol, 27%), mp 172–177 °C; $[\alpha]_D^{25}$=+19.0 (*c* 0.93, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2970, 1732, 1682, 1602, 1460, 1356, 1310, 1171; δ_H (500 MHz, $CDCl_3$) 1.29 (9H, s, C(CH_3)$_3$), 1.40 (3H, d, *J*=7.0 Hz, 3-Me), 1.92 (1H, dddd, *J*=14.2, 12.3, 12.2, 4.7 Hz, 4-H_A), 2.14 (1H, dddd, *J*=14.2, 5.3, 4.5, 4.4 Hz, 4-H_B), 2.74 (1H, m, 3-H), 2.78 (1H, ddd, *J*=17.8, 12.3, 5.3 Hz, 5-H_A), 2.96 (1H, ddd, *J*=17.8, 4.7, 4.4 Hz, 5-H_B), 6.80 (1H, dd, *J*=7.6, 1.2 Hz, Ar-*H*), 7.27 (1H, ddd, *J*=7.6, 7.3, 1.2 Hz, Ar-*H*), 7.35 (1H, ddd, *J*=7.8, 7.3, 1.2 Hz, Ar-*H*), 7.56 (1H, dd, *J*=7.8, 1.2 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 16.5 (CH_3), 24.8 (CH_2), 31.8 (CH_3), 32.9 (CH_2), 35.9 (C), 38.0 (CH), 127.3 (CH), 128.8 (CH), 128.9 (CH), 131.1 (CH), 134.0 (C), 146.7 (C), 173.2 (C═O), 175.8 (C═O); *m*/*z* (EI) (Found M$^+$, 259.1563. $C_{16}H_{21}NO_2$ requires *M*, 259.1572). The ee of *syn*-**33** (78% ee) was determined by HPLC analysis using a Chirapak AD-H column [25 cm×0.46 cm i.d.; 3% *i*-PrOH in hexane; flow rate, 0.4 mL/min; (+)-*syn*-**33**; t_R=42.4 min, (−)-*syn*-**33**; t_R=47.3 min].

The above procedure was also carried out using racemic 2-methylglutaric anhydride and yielded the racemic diastereoisomers *anti*-**33** (1.30 g, 5.00 mmol, 40%) and *syn*-**33** (0.42 g, 1.62 mmol, 14%).

4.1.30. (*M*,3*R*)-1-(2-*tert*-Butyl-phenyl)-3-methyl-3,4-dihydro-1*H*-pyridin-2-one 29a and (*P*)-1-(2-*tert*-butyl-phenyl)-5-methyl-3,4-dihydro-1*H*-pyridin-2-one 34. DIBAL (3.47 mL of a 1 M solution in CH_2Cl_2) was added dropwise to a stirred solution of imide *anti*-**33** (500 mg, 1.93 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After 45 min stirring at −78 °C, H_2O (4 mL), followed by 2 N NaOH (2 mL) were added and the reaction mixture poured into a saturated solution of Rochelles salt (25 mL). The mixture was then extracted with CH_2Cl_2 (2×15 mL). The combined extracts were then washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give an oil which was dissolved in CH_2Cl_2 (15 mL). To this solution, at 0 °C, was added Et_3N (0.81 mL, 5.79 mmol), then MsCl (0.22 mL, 2.90 mmol). The reaction mixture was

stirred at room temperature for 1 h, then washed with H_2O (25 mL), a saturated solution of $NaHCO_3$ (25 mL), and brine (25 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The resulting oil was purified by biotage chromatography (5–30% EtOAc–petroleum ether), to give firstly **29a** (2:1 ratio of isomers) (R_f 0.75, 1:1 petroleum ether–EtOAc) as an oily solid (110 mg, 0.45 mmol, 23%), $[\alpha]_D^{27}$=+46.6 (*c* 0.86, $CHCl_3$). All remaining data was in agreement with that previously reported for **29a**; followed by **34** (R_f 0.5, 1:1 petroleum ether–EtOAc) as an oily solid (110 mg, 0.45 mmol, 23%): $[\alpha]_D^{27}$=+10.3 (*c* 0.86, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2967, 2936, 1666, 1488, 1393, 1364, 1285; δ_H (500 MHz, $CDCl_3$) 1.37 (9H, s, $C(CH_3)_3$), 1.77 (3H, s, 5-Me), 2.39 (2H, m, 4-H), 2.67 (2H, m, 3-H), 5.83 (1H, d, *J*=1.2 Hz, 6-H), 7.00 (1H, dd, *J*=7.5, 1.4 Hz, Ar-*H*), 7.25 (1H, ddd, *J*=7.7, 7.5, 1.5 Hz, Ar-*H*), 7.31 (1H, ddd, *J*=8.0, 7.7, 1.4 Hz, Ar-*H*), 7.52 (1H, dd, *J*=8.0, 1.5 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 19.5 (CH_3), 26.1 (CH_2), 31.7 (CH_3), 31.9 (CH_2), 35.7 (C), 114.6 (C), 127.5 (CH), 127.6 (CH), 128.5 (CH), 128.7 (CH), 131.0 (CH), 139.7 (C), 147.5 (C), 169.6 (C=O); *m*/*z* (EI) (Found M^+, 243.1624. $C_{16}H_{21}NO$ requires *M*, 243.1623).

4.1.31. (*M*,3*R*)-1-(2-*tert*-Butyl-phenyl)-3-methyl-3,4-dihydro-1*H*-pyridin-2-one 29a. To a stirred solution of di*iso*propylamine (0.07 mL, 0.53 mmol) in THF (3 mL) at −78 °C was added ^{n}BuLi (0.33 mL of a 1.60 M solution in hexanes), followed by warming to room temperature for 15 min, then recooled to −78 °C. To the resulting LDA, a solution of *M*-pyridin-2-one **24** (73% ee) (100 mg, 0.44 mmol) in THF (3 mL) was added. After 1 h MeI (0.27 mL, 4.40 mmol) was added and the reaction mixture stirred at −78 °C for 1 h, saturated NH_4Cl solution (3 mL) was then added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (2×20 mL), the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude product was purified by biotage chromatography (10% EtOAc–petroleum ether) to yield the title compound (7:1 ratio of isomers) as an oily solid (75 mg, 0.03 mmol, 70%), $[\alpha]_D^{27}$=+22.6 (*c* 0.69, $CHCl_3$). All remaining data was in agreement with that previously reported for **29a**.

For a direct comparison of the samples of (*M*,3*R*)-1-(2-*tert*-butyl-phenyl)-3-methyl-3,4-dihydro-1*H*-pyridin-2-one **29a**, synthesised from the chiral diacid precursor (R)-(−)-**31** and from the enantioenriched enamide *M*-**24**, both samples were thermally equilibrated to a ratio of 1.1:1 (from 2:1 and 7:1, respectively) and the resulting optical rotations measured as: $[\alpha]_D^{26}$=+54.8 (*c* 0.54, $CHCl_3$) and $[\alpha]_D^{27}$=+55.4 (*c* 0.24, $CHCl_3$), respectively.

4.1.32. 1,6-Diphenyl-piperidin-2-one 35a. A solution of enamide **24** (50.0 mg, 0.22 mmol) and $AlCl_3$ (294 mg, 2.20 mmol) in benzene (20 mL) was heated at 50 °C for 12 h. After cooling, the reaction mixture was poured into H_2O (20 mL) and extracted with $CHCl_3$ (3×20 mL). Combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (20–70% EtOAc–petroleum ether) to give the title compound as a pale orange solid (50.0 mg, 0.20 mmol, 90%), mp 125–127 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2953, 1639, 1596, 1494, 1456, 1404, 1344, 1301; δ_H (400 MHz, $CDCl_3$) 1.83 (1H, m, 4-H_A), 1.93 (1H, m, 4-H_B), 2.03 (1H, m, 5-H_A), 2.36 (1H, dddd, *J*=13.5, 10.4, 5.3, 3.6 Hz, 5-H_B), 2.68 (1H, ddd, *J*=18.1, 8.3, 6.7 Hz, 3-H_A), 2.76 (1H, dt, *J*=18.1, 6.1 Hz, 3-H_B), 5.03 (1H, t, *J*=5.1 Hz, 6-H), 7.12–7.16 (3H, m, Ar-*H*), 7.22–7.26 (5H, m, Ar-*H*), 7.27–7.34 (2H, m, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.5 (CH_2), 32.2 (CH_2), 32.5 (CH_2), 65.0 (CH), 126.6 (CH), 126.9 (2×CH), 127.2 (2×CH), 127.4 (CH), 128.4 (2×CH), 128.7 (2×CH), 141.3 (C), 142.3 (C), 170.7 (C=O); *m*/*z* (EI) (Found M^+, 251.1308. $C_{17}H_{17}NO$ requires *M*, 251.1310).

The above reaction was also carried out using enantioenriched (63% ee) enamide **24** (50.0 mg, 0.22 mmol) to yield the product **35a** described above (40.0 mg, 0.16 mmol, 72%, showing no erosion of ee (63% ee). The ee was determined by HPLC analysis using a Chirapak AD-H column [25 cm×0.46 cm i.d.; 5% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (+)-**35a**; t_R=35.9 min, (−)-**35a**; t_R=30.9 min]; $[\alpha]_D^{25}$=+66.2 (*c* 0.52, $CHCl_3$).

4.1.33. 1-Phenyl-6-tolyl-piperidin-2-one 35b. A solution of enamide **24** (50.0 mg, 0.22 mmol) and $AlCl_3$ (294 mg, 2.20 mmol) in toluene (20 mL) was heated at 50 °C for 12 h. After cooling, the reaction mixture was poured into H_2O (20 mL) and extracted with $CHCl_3$ (3×20 mL). Combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (CH_2Cl_2, then 10–60% EtOAc–petroleum ether) to give the title compound (4:1 ratio of isomers) as pale brown solid (50.0 mg, 0.19 mmol, 86%), mp 112–115 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2953, 1638, 1596, 1494, 1455, 1402, 1335, 1306; δ_H (500 MHz, $CDCl_3$) 1.75–1.82 (1H major+1H minor, m, 4-H_A), 1.87–2.00 (2H major+2H minor, m, 5-H_A+4-H_B), 2.20 (3H minor, Ar-Me), 2.26–2.34 (4H major, m with s at 2.29, 5-H_B +Ar-Me and 1H minor, 5-H_B), 2.64 (1H major+1H minor, ddd, *J*=18.1, 8.6, 6.8 Hz, 3-H_A), 2.73 (1H major+1H minor, dt, *J*=18.1, 6.0 Hz, 3-H_B), 4.98 (1H major, t, *J*=5.1 Hz, 6-H), 5.25 (1H minor, 6-H), 7.02–7.08 (3H minor, m, Ar-*H*), 7.09–7.15 (7H major, m, Ar-*H* and 2H minor, m, Ar-*H*), 7.20–7.26 (2H major, m, Ar-*H* and 3H minor, m, Ar-*H*), 7.39 (1H minor, d, *J*=7.5 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.6 (CH_2), 21.1 (CH_3), 32.3 (CH_2), 32.6 (CH_2), 64.8 (CH), 126.5 (CH), 126.7 (2×CH), 127.2 (2×CH), 128.7 (2×CH), 129.0 (2×CH), 137.0 (C), 138.3 (C), 142.4 (C), 170.8 (C=O); *m*/*z* (EI) (Found M^+, 265.1469. $C_{18}H_{19}NO$ requires *M*, 265.1467).

4.1.34. 6-(4-Bromo-phenyl)-1-phenyl-piperidin-2-one 35c. A solution of enamide **24** (50.0 mg, 0.22 mmol) and $AlCl_3$ (294 mg, 2.20 mmol) in bromobenzene (15 mL) was heated at 50 °C for 12 h. After cooling, the reaction mixture was poured into H_2O (15 mL) and extracted with $CHCl_3$ (3×20 mL). Combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (CH_2Cl_2, then 10–70% EtOAc–petroleum ether) to give firstly the major isomer (R_f 0.3, 70:30 petroleum ether–EtOAc) as a pale brown

solid (35.0 mg, 0.11 mmol, 48%), mp 117–120 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2954, 1642, 1596, 1494, 1465, 1406, 1340; δ_H (500 MHz, $CDCl_3$) 1.83–1.90 (2H, m, 4-H_A and 4-H_B), 2.07–2.18 (1H, m, 5-H_A), 2.29–2.36 (1H, m, 5-H_B), 2.68 (1H, dt, J=18.1, 7.9 Hz, 3-H_B), 2.77 (1H, dt, 18.1, 5.6, 3-H_A), 5.48 (1H, t, J=5.1 Hz, 6-H), 7.08–7.18 (4H, m, Ar-*H*), 7.24–7.28 (2H, m, Ar-*H*), 7.32 (1H, t, J=7.5 Hz, Ar-*H*), 7.44 (1H, d, J=7.6 Hz, Ar-*H*), 7.47 (1H, d, J=8.2 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.5 (CH_2), 29.6 (CH_2), 32.7 (CH_2), 63.9 (CH), 122.5 (C), 126.8 (CH), 127.0 (2×CH), 127.3 (CH), 128.9 (3×CH), 129.1 (CH), 133.4 (CH), 139.7 (C), 142.0 (C), 171.0 (C=O); *m/z* (EI) (Found M^+, 329.0421 and 331.0346. $C_{17}H_{16}{}^{79}BrNO$ requires *M*, 329.0415 and $C_{17}H_{16}{}^{81}BrNO$ requires *M*, 331.0395); and secondly, a minor regioisomer (R_f 0.3, 70:30 petroleum ether–EtOAc) (8:1 mixture of atropisomers) as a brown oil (15.0 mg, 0.05 mmol, 20%), ν_{max} ($CHCl_3$)/cm^{-1} 2954, 1643, 1595, 1491, 1455, 1396, 1333, 1298; δ_H (500 MHz, $CDCl_3$) 1.81–2.00 (3H major+3H minor, m, 4-H_A and 4-H_B and 5-H_A), 2.31–2.37 (1H major+1H minor, m, 5-H_B), 2.66 (1H major+1H minor, ddd, J=17.9, 8.1, 7.0 Hz, 3-H_A), 2.73 (1H major+1H minor, dt, J=17.9, 6.3 Hz, 3-H_B), 4.99 (1H major, t, J=5.2 Hz, 6-H), 5.02 (1H minor, 6-H), 7.10–7.18 (4H major+4H minor, m with d at 7.11, J=8.1 Hz, Ar-*H*), 7.23–7.32 (4H major+4H minor, m, Ar-*H*), 7.43 (1H major+1H minor, d, J=8.3 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.6 (CH_2), 32.3 (CH_2), 32.6 (CH_2), 64.6 (CH), 121.4 (C), 126.9 (CH), 127.3 (2×CH), 128.7 (2×CH), 129.0 (2×CH), 131.7 (2×CH), 140.6 (C), 142.1 (C), 170.7 (C=O); *m/z* (EI) (Found M^+, 329.0410. $C_{17}H_{16}^{79}BrNO$ requires *M*, 329.0415).

The above reaction was also carried out using enantioenriched (73% ee) enamide **24** (50.0 mg, 0.22 mmol) to yield the product **35c** described above (20.0 mg, 0.06 mmol, 28%, showing some erosion of ee (57% ee). The ee was determined by HPLC analysis using a Chirapak AD-H column [25 cm×0.46 cm i.d.; 5% *i*-PrOH in hexane; flow rate, 1.0 mL/min; (+)-**35c**; t_R=32.9 min, (−)-**35c**; t_R=29.5 min]; $[\alpha]_D^{25}$=+21.1 (*c* 0.36, $CHCl_3$).

4.1.35. 6-(4-Iodo-phenyl)-1-phenyl-piperidin-2-one 35d. A solution of enamide **24** (50.0 mg, 0.22 mmol) and $AlCl_3$ (294 mg, 2.20 mmol) in iodobenzene (15 mL) was heated at 50 °C for 12 h. After cooling, the reaction mixture was poured into H_2O (15 mL) and extracted with $CHCl_3$ (3×20 mL). Combined extracts were washed with brine (20 mL), dried ($MgSO_4$), and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (CH_2Cl_2, then 20–70% EtOAc–petroleum ether) to give the title compound as a pale brown solid (50.0 mg, 0.13 mmol, 60%), mp 115–119 °C; ν_{max} ($CHCl_3$)/cm^{-1} 2954, 1640, 1596, 1494, 1456, 1405, 1344; δ_H (500 MHz, $CDCl_3$) 1.83 (1H, m, 4-H_A), 1.93 (1H, m, 4-H_B), 2.09 (1H, m, 5-H_A), 2.35 (1H, dddd, J=14.2, 9.9, 5.2, 3.7 Hz, 5-H_B), 2.67 (1H, ddd, J=18.1, 8.3, 7.0 Hz, 3-H_A), 2.74 (1H, dt, J=18.1, 6.0 Hz, 3-H_B), 5.01 (1H, t, J=5.1 Hz, 6-H), 7.12–7.14 (3H, m, Ar-*H*), 7.22–7.32 (6H, m, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.6 (CH_2), 32.4 (CH_2), 32.7 (CH_2), 65.1 (CH), 126.8 (CH), 127.0 (2×CH), 127.3 (2×CH), 127.5 (C), 128.5 (2×CH), 128.9 (2×CH), 140.5 (C), 141.4 (C), 170.9 (C=O); *m/z* (EI) (Found M^+, 377.0268. $C_{17}H_{16}INO$ requires *M*, 377.0277).

4.1.36. 1-(2-*tert*-Butyl-phenyl)-6-(2-methoxy-phenyl)-piperidin-2-one 38 and 1-(2-*tert*-butyl-phenyl)-6-(4-methoxy-phenyl)-piperidin-2-one 39. A solution of enamide **24** (50.0 mg, 0.22 mmol) and $TiCl_4$ (0.24 mL, 2.20 mmol) in anisole (15 mL) was heated at 50 °C for 12 h. After cooling, the reaction mixture was poured into H_2O (20 mL) and extracted with $CHCl_3$ (3×20 mL). Combined extracts were washed with brine (20 mL), dried ($MgSO_4$), treated with decolourising charcoal, and evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (30–90% EtOAc–petroleum ether) to give firstly the major isomer **38** (R_f 0.20, 1:1 petroleum ether–EtOAc) as a white solid (50.0 mg, 0.15 mmol, 68%), mp 145–147 °C (recrystallised from petroleum ether/CH_2Cl_2); ν_{max} ($CHCl_3$)/cm^{-1} 2960, 1633, 1599, 1489, 1463, 1409, 1364, 1332, 1294, 1107, 1056; δ_H (500 MHz, $CDCl_3$, 50 °C) 1.49 (9H, s, $C(CH_3)_3$), 1.84 (1H, br m, 4-H_A), 1.96 (1H, br m, 5-H_A), 2.05 (1H, br m, 4-H_B), 2.40 (1H, dddd, J=12.8, 12.4, 5.7, 3.9 Hz, 5-H_B), 2.59 (1H, ddd, J=18.0, 10.2, 7.0 Hz, 3-H_A), 2.76 (1H, ddd, J=18.0, 5.5, 3.5 Hz, 3-H_B), 3.70 (3H, br.s, OMe), 5.29 (1H, br.s, 6-H), 6.76–6.89 (3H, m, Ar-*H*), 7.00 (1H, m, Ar-*H*), 7.11 (1H, dd, J=7.6, 7.2 Hz, Ar-*H*), 7.25 (2H, m, Ar-*H*), 7.48 (1H, d, J=8.0 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 17.0 (CH_2), 28.2 (CH_2), 32.1 (CH_3), 32.7 (CH_2), 36.0 (C), 55.3 (CH_3), 58.6 (CH), 110.9 (CH), 119.7 (CH), 126.3 (CH), 127.6 (CH), 128.6 (CH), 128.9 (CH), 129.1 (CH), 131.5 (CH+C), 140.4 (C), 146.4 (C), 153.2 (C), 172.2 (C=O); *m/z* (FAB) (Found MH^+, 338.2120 $C_{22}H_{28}NO_2$ requires *M*, 338.2120). Anal. Calcd for $C_{22}H_{27}NO_2$. C, 78.34; H, 8.01; N, 4.15%. Found: C, 78.00; H, 7.93; N, 4.07%; followed by the minor isomer **39** (R_f 0.15, 1:1 petroleum ether–EtOAc) as an oil (15.0 mg, 0.04 mmol, 7%), ν_{max} ($CHCl_3$)/cm^{-1} 2958, 2838, 1729, 1633, 1612, 1510, 1487, 1463, 1406, 1364, 1295, 1167, 1136; δ_H (500 MHz, $CDCl_3$) 1.47 (9H, s, $C(CH_3)_3$), 1.82–1.88 (2H, m, 5-H_A and 4-H_A), 2.13–2.19 (1H, m, 4-H_B), 2.42–2.50 (1H, m, 5-H_B), 2.63 (1H, ddd, J=17.9, 10.9, 6.9 Hz, 3-H_A), 2.81 (1H, br dd, J=17.9, 5.0 Hz, 3-H_B), 3.80 (3H, s, OMe), 4.72 (1H, dd, J=4.8, 3.4 Hz, 6-H), 6.63 (1H, d, J=8.0 Hz, Ar-*H*), 6.86–6.89 (3H, m, Ar-*H*), 7.12–7.15 (3H, m, Ar-*H*), 7.49 (1H, d, J=8.1 Hz, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 16.8 (CH_2), 30.5 (CH_2), 32.1 (CH_3), 32.6 (CH_2), 35.9 (C), 55.3 (CH_3), 65.6 (CH), 113.7 (2×CH), 126.3 (CH), 127.7 (CH), 128.9 (2×CH), 129.1 (CH), 131.9 (CH), 133.3 (C), 140.0 (C), 146.2 (C), 159.1 (C), 171.5 (C=O); *m/z* (EI) (Found M^+, 337.2039 $C_{22}H_{27}NO_2$ requires *M*, 337.2042).

4.2. X-ray crystallographic data

The structures of **10**, **25**, **26**, **29g**, **33** and **38** were determined by single-crystal X-ray diffraction studies. Crystal data and other details are given in Table 2. Data were collected on a Bruker SMART CCD area detector diffractometer in all cases except that of **10**, for which a Stoe Stadi-4 diffractometer was used, using Mo K_α X-radiation (λ= 0.71073 Å). In all cases the diffractometers were equipped with an Oxford Cryosystem open-flow nitrogen cryostat and data were collected at 150 K. The structures were solved by direct methods (SHELXS-97) and refined using full matrix least squares refinement against F^2, all non-H atoms were refined with anisotropic atomic displacement parameters (adps) and H atoms placed in geometrically calculated

Table 2. Crystallographic data and structure refinement details

Compound	**10**	**25**	**26**	**29g**	**33**	**38**
Chemical formula	$C_{24}H_{37}NO_2$	$C_{18}H_{25}NO_2$	$C_{18}H_{25}NO_2$	$C_{21}H_{23}NOS$	$C_{16}H_{21}NO_2$	$C_{22}H_{27}NO_2$
Mr	371.55	287.39	287.39	337.46	259.34	337.45
Crystal system	Monoclinic	Orthorhombic	Triclinic	Monoclinic	Orthorhombic	Triclinic
Space group	$P2_1$	$P2(1)2(1)2(1)$	P-1	$P2_1/c$	$P2_12_12_1$	P-1
a (Å)	10.787 (3)	9.226 (2)	10.1547 (8)	11.9803 (10)	8.510 (3)	8.2002 (8)
b (Å)	7.747 (3)	11.873 (3)	11.8289 (9)	11.8217 (10)	9.914 (3)	9.8021(10)
c (Å)	13.402 (5)	14.639 (4)	14.3724(11)	13.1329 (11	16.963 (5)	11.9046(12)
α (°)			83.764 (2)			103.989 (2)
β (°)	98.34 (3)		77.925 (2)	106.460 (2)		92.632 (2)
γ (°)			81.422 (2)			100.153 (2)
V (Å^3)	1108.1 (7)	1603.6 (12)	1664.0 (2)	1783.8 (4)	1431.1 (8)	910.0 (3)
Z	2	4	4	4	4	2
T (K)	150	150	150	150	150	150
Crystal form, colour	Block, colourless	Column, colourless	Block, colourless	Tablet, colourless	Column, colourless	Column, colourless
Crystal size (mm)	0.41×0.27×0.19	0.28×0.09×0.09	0.50×0.41×0.33	0.54×0.49×0.21	0.40×0.12×0.12	0.43×0.25×0.16
No. of measured reflections	2429	9977	19321	15736	6762	7994
Unique, obsd ($I>2\sigma(I)$) reflections	2110, 1722	1627, 1154	7432, 5943	4097, 3631	1478, 843	4091, 3420
R_{int}	0.023	0.040	0.022	0.029	0.121	0.030
$R[F^2>2\sigma(F^2)]$, $wR(F^2)$, S	0.048, 0.104, 1.18	0.079, 0.212, 1.06	0.041, 0.118, 1.07	0.038, 0.108, 1.06	0.056, 0.146, 0.95	0.042, 0.124, 1.07
No. of parameters	245	190	381	217	177	226
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.18, −0.22	0.53, −0.53	0.31, −0.18	0.42, −0.19	0.16, −0.22	0.30, −0.18

positions and refined as part of a riding model, unless otherwise stated. The hydroxyl H-atom in **26** was located from a difference Fourier map and refined as a rigid rotor, as were the methyl H-atoms in **33**. There was also disorder present in the t-butyl group of **33**, which was modeled over 2 half occupied sites with isotropic adps.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 221091–221096. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

We thank the University of Nottingham, Syngenta Agrochemicals, and Organon Laboratories for studentship support for P. L. P. and M. D. W.

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New atropisomeric biaryl derivatives of 4-aminopyridine—identification of an improved nucleophilic catalyst for asymmetric acylation of *sec*-alcohols

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Received 6 November 2003; revised 12 December 2003; accepted 5 January 2004

Abstract—The synthesis, CSP-HPLC resolution, and absolute configuration assignment of a series of 4-dialkylaminopyridine-based atropisomeric biaryls are described. Screening of these enantiomerically pure catalysts, which differ only in the nature of the 4-dialkylamino substituent, for the kinetic resolution of 1-(1-naphthyl)ethanol reveals the importance of this group on the selectivity of catalysis. The di-*n*-butylamino derivative displays the most favourable catalytic profile. The utility of this catalyst for the kinetic resolution of a selection of *sec*-alcohols, including a precursor for the synthesis of the antidepressant fluoxetine hydrochloride (Prozac®) are reported. The possible role of the dialkylamino group in chirality transfer is discussed.

1. Introduction

Enantiopure *sec*-alcohols are important building blocks for the synthesis of natural products, chiral ligands, auxiliaries, catalysts and biologically active compounds.[1] One method for their preparation that has been widely used on both laboratory and plant scales is the kinetic resolution (KR) of racemic alcohols by acylation (or by deacylation of the corresponding ester derivatives) catalysed by hydrolytic enzymes, particularly lipases.[2] Although enzymatic KR has proved highly efficient for numerous substrates,[3,4] the high cost of purified enzymes, the availability of enzymes in just one enantiomeric form, the need for stringent operating parameters, and batch to batch irreproducibility can compromise the attractiveness of this approach. Intensive efforts have been made recently to develop analogous processes using low molecular weight chiral nucleophilic catalysts that circumvent these limitations and provide wider substrate scope (e.g. to include *tert*-alcohols.[5])[6,7] A number of chiral nucleophilic phosphines,[8–10] diamines,[11–14] *N*-alkylimidazoles[15–17] and 4-aminopyridines[18–30] have been developed that can deliver levels of enantioselectivity comparable with those of enzymes in catalytic acylative KR of *sec*-alcohols. Of these, the 4-aminopyridine-based systems, which can be considered as chiral derivatives of the well known achiral acylation catalyst 4-dimethylaminopyridine (DMAP),[31,32] have been particularly widely investigated. The challenge in developing catalytically active and selective chiral DMAPs is to engineer derivatives that retain the nucleophilicity of DMAP and yet provide a highly asymmetric environment for the acyl carbonyl function of derived acyl pyridinium salts (i.e. the active intermediates in the catalytic cycle).[20] This has been achieved, with varying degrees of success, by relaying stereochemical information from remote stereocentres appended to the 4-amino group (catalyst families **I**–**V**, Fig. 1)[18–25] or a 3-amino group (catalyst **VI**, Fig. 1),[26] by rendering the pyridine planar chiral by fusing it to a ferrocenyl unit (catalyst family **VII**, Fig. 1),[27,28] and by positioning an axis of chirality at the pyridyl 3-position (catalyst families **VIII** and **IX**, Scheme 1).[29,30]

The work on axially chiral atropisomeric catalyst families **VIII** and **IX** (Fig. 1) has been carried out in our laboratories and has resulted in the development of 4-diethylaminopyridine derivative (−)-(S_a)-**6c** (Scheme 1, cf. **IX**, Ar=Ph, Fig. 1) as an easily accessible and efficient chiral catalyst for the acylative KR of various *sec*-alcohols using isobutyric anhydride in toluene at low temperature.[29,30]

Here we describe the synthesis, CSP-HPLC resolution, and absolute configuration assignment by circular dichroism (CD) correlation of a series of seven atropisomeric biaryls related to catalyst (−)-(S_a)-**6c** but incorporating alternative 4-dialkylamino groups. Screening of these catalysts for

Keywords: Nucleophilic catalysis; Asymmetric catalysis; Atropisomerism; Esterification; Acylation; *sec*-Alcohols.
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doi:10.1016/j.tet.2004.01.098

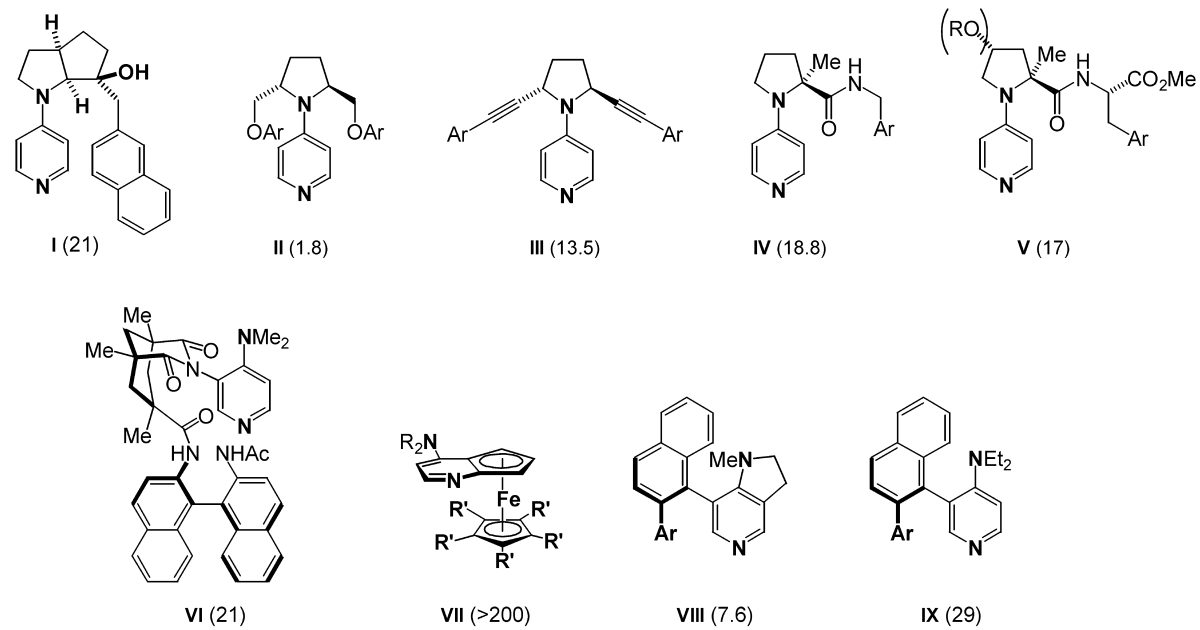
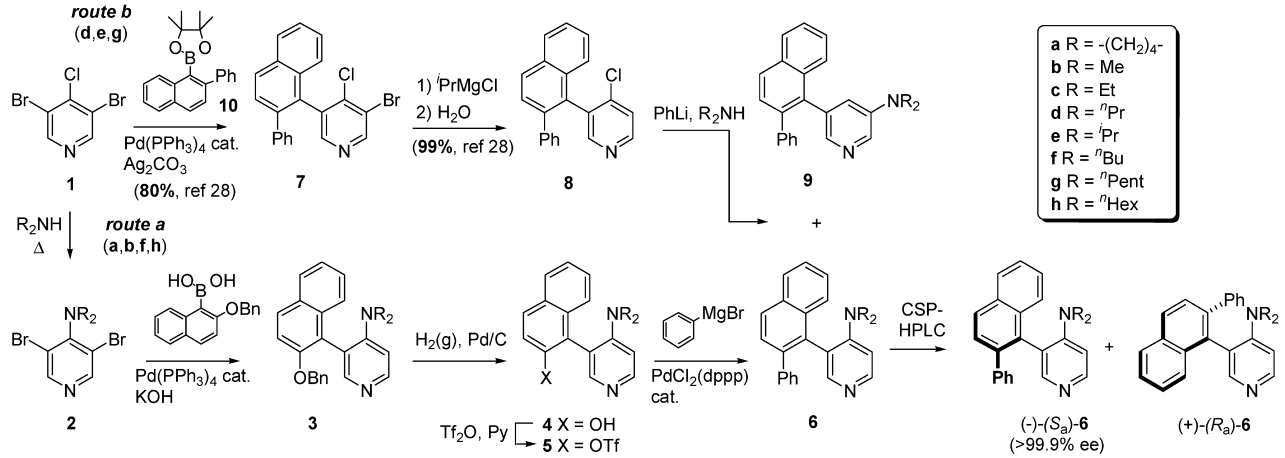


Figure 1. Families of chiral 4-aminopyridine catalysts for asymmetric acylation of *sec*-alcohols. The values in parenthesis by each structure are the maximum selectivity (*s*)[33,34] reported for a *sec*-alcohol KR using a member of that catalyst family.



Scheme 1. The synthesis and resolution of catalyst candidates **6a**–**h**.

the KR of 1-(1-naphthyl)ethanol reveals a significant but irregular influence of the 4-dialkylamino group on the selectivity of catalysis. In particular, the di-*n*-butylamino derivative (−)-(S_a)-**6f** (Scheme 1) is found to be the fastest and most selective catalyst of this class. The utility of this catalyst for the KR of a selection of *sec*-alcohols, including a precursor for the synthesis of the anti-depressant fluoxetine hydrochloride (Prozac®) are reported. The possible role of the dialkylamino group in chirality transfer is also discussed.

2. Results and discussion

The original inspiration to incorporate an atropisomeric axis as the element of chirality in our chiral DMAP design arose from the venerable track record of axially chiral biaryls, e.g. BINOL, in providing highly dissymmetric scaffolds for numerous functionally diverse chiral auxiliaries, ligands and catalysts.[35] In many of these systems, particularly chiral ligands for transition metals, chirality transfer from the atropisomeric axis to the metal centre is relayed by induced chirality in intervening structural motifs such as the diarylmethylene group.[36] The aryl groups are forced to adopt specific chiral conformations as the result of non-bonding interactions and so provide a chiral 'pocket' for the metal.[37] More recently, the tactic of exploiting the reversed situation; i.e. using a chiral centre such as that contained in α-methylbenzylamine to induce chirality in a labile ('tropos')[38] biaryl axis, again via non-bonded interactions, has also been exploited for asymmetric catalysis.[38–40]

In the light of the above, we hypothesised that one factor possibly responsible for the significantly higher selectivity values (*s*)[33,34] displayed by 4-diethylaminopyridine-based biaryl catalysts **VIII** (Fig. 1) as compared to the corresponding 5-azaindoline-based biaryl catalysts **IX** (Fig. 1) in the KR of aryl alkyl *sec*-alcohols[30] could be the ability of the diethylamino group in the former to adopt a chiral conformation induced by the adjacent chiral axis which in

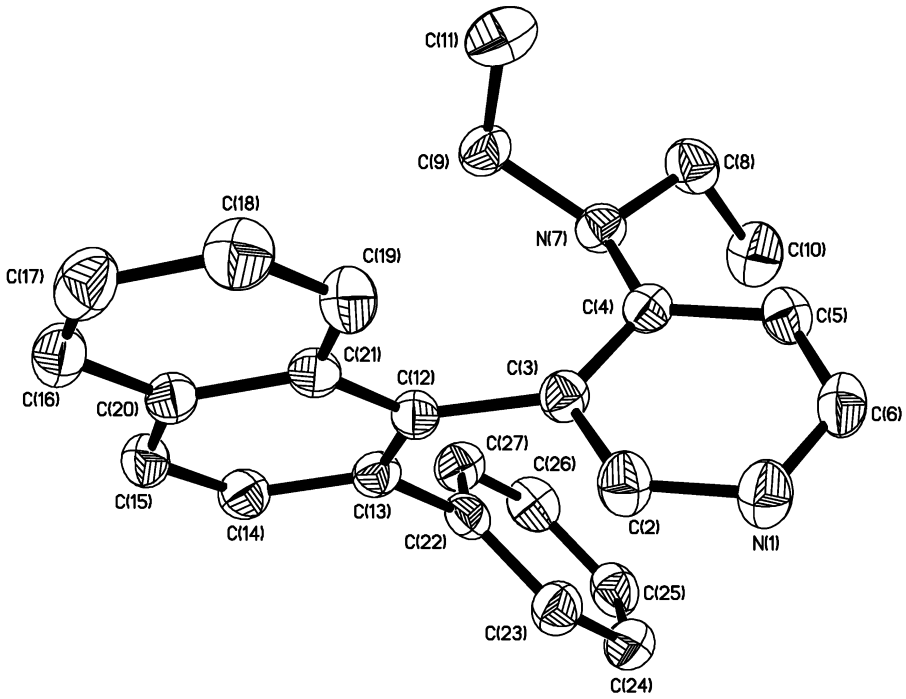


Figure 2. An ORTEP plot of the single crystal X-ray structure of biaryl (±)-**6c** showing induced chrality of the diethylamino group.

turn might influence the position of the counter ion in the derived acyl pyridinium salt.[41] Such a conformation is present in the X-ray crystal structure of 4-diethylaminopyridine (±)-**6c** (Fig. 2):[30] the ethyl group proximal to the axis is angled away from the phenyl substituent and the ethyl group distal to the axis is angled towards the phenyl substituent giving the diethylamino group a pseudo C_2-symmetry axis.

If this conformation were to be replicated for derived acyl pyridinium salts in solution[42] then it could be anticipated that varying the 4-dialkylamino substituents should strongly impact on the selectivity values (*s*) displayed by biaryls like **VIII** (Fig. 1) as asymmetric acylation catalysts. To test this hypothesis we prepared a series of seven atropisomeric biaryl analogues of 4-diethylaminopyridine catalyst (−)-(S_a)-**6c** incorporating pyrrolidino (**6a**), dimethylamino (**6b**), di-*n*-propylamino (**6d**), diisopropylamino (**6e**), di-*n*-butylamino (**6f**), di-*n*-pentylamino (**6g**) and di-*n*-hexylamino (**6h**) groups at the pyridyl 4-position (Scheme 1).

Two routes were employed for the preparation of the biaryl catalyst candidates in racemic form. The first (*route a*, Scheme 1), which was used to prepare biaryls **6a**, **6b**, **6f** and **6h**, followed a 4-step synthetic sequence from 3,5-dibromo-4-chloropyridine **1** as developed during our early work on the 4-diethylaminopyridine biaryl **6c**.[30] This route involves introduction of the dialkylamino group in the first step by an S_NAr reaction and then two sequential cross-coupling reactions to set up the tri-*ortho*-substituted biaryl axis. Yields over the four steps were between 13 and 28% (see Section 4). This route proved unsuitable for the preparation of the 4-diisopropylaminopyridine biaryl **6e** as we were unable to obtain any product from the reaction of diisopropylamine with trihalopyridine **1** even after 48 h at 170 °C in DMF in a sealed tube, presumably due to steric constraints. Consequently, we adopted an alternative approach for the synthesis of this biaryl and also biaryls **6d** and **6g**. (*route b*, Scheme 1). This second route involves introduction of the dialkylamino group by treatment of 4-chloropyridine biaryl **8** with phenyl lithium and an excess of the dialkylamine in refluxing THF. This reaction provides a mixture of desired 4-dialkylaminopyridine biaryl **6** and undesired 3-dialkylaminopyridine biaryl **9** (which are readily separated by chromatography), presumably via a 3,4-pyridyne intermediate. 4-Chloropyridine biaryl **8** is prepared by cross-coupling of trihalopyridine **1** with naphthyl boronic ester **10** using a Suzuki-type reaction developed by Chaumeil[43] to give chlorobromopyridine **7** (80% yield) and then debromination via a Grignard intermediate (99% yield). These reactions were developed by us previously as an improved route to diethylaminopyridine biaryl **6c**.[29] The ratio of the isomeric products from the pyridyne addition reaction varies depending on the dialkylamine used. Ratios from the crude ^{1}H NMR spectra are as follows: $HNEt_2$ **6c**:**9c**,[44] 1:2.0;[29] HN^nPr_2 **6d**:**9d**, 1:5.0; HN^iPr_2 **6e**:**9e**, 1:4.5; and HN^{n}Pent, **6g**:**9g**, 1:2.0. The predominance of the 3-substituted products in all cases presumably reflects unfavourable steric interactions between the dialkylamino group and the naphthyl substituent in the transition state leading to the 4-substituted product although the precise ratios are not easily rationalised. We noted that these reactions fail unless an excess of dialkylamine is employed and that the ratio of 4- to 3-substituted products increases slightly as the concentration of amine increases. This suggests that lithium dialkylamide–dialkylamine aggregates may be involved[45,46] and that a competitive S_NAr pathway may also operate in these reactions. Yields of the desired 4-dialkylaminobiaryls **6d**, **6e** and **6g** over the three steps were 9%, 8% and 20% respectively (see Section 4).

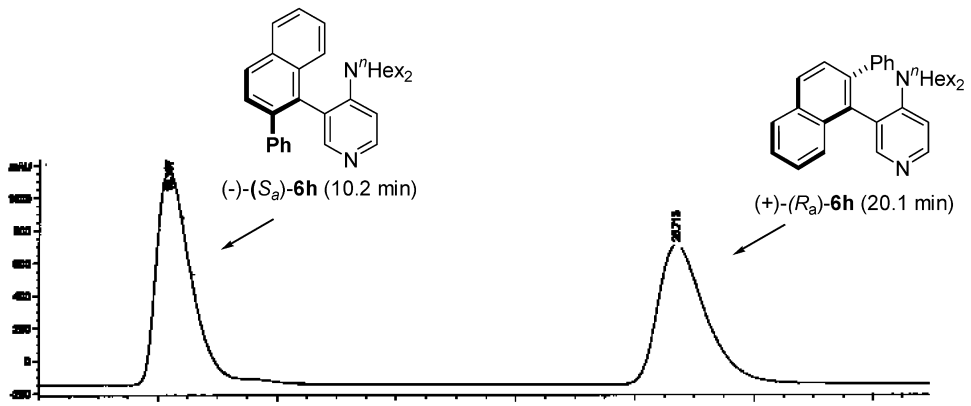


Figure 3. CSP-HPLC trace for the separation of (−)- and (+)-biaryl **6h**.

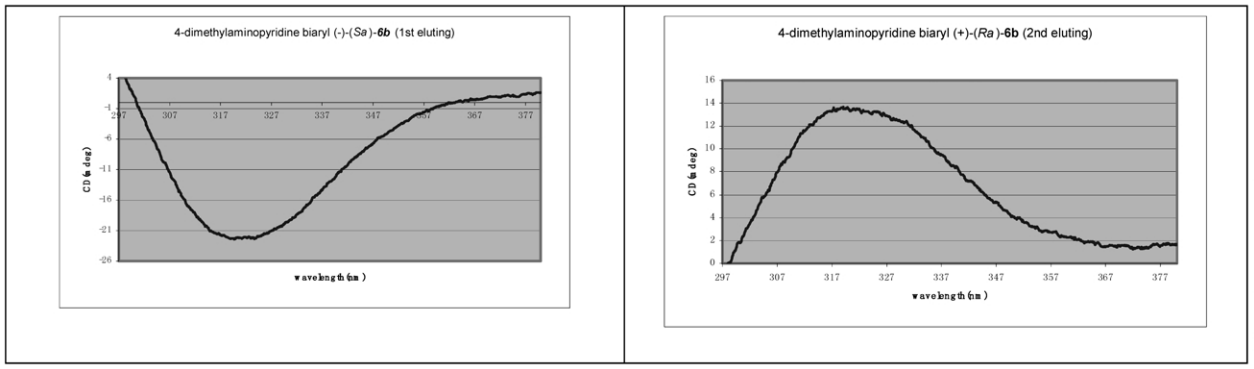
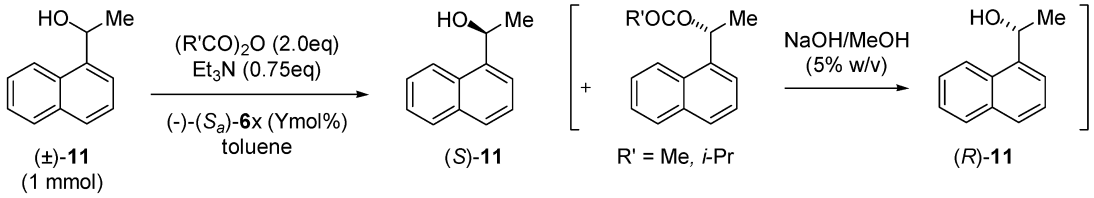


Figure 4. CD spectra of (−)- and (+)-biaryls **6b**.

Table 1. KR of (±)-1-(1-naphthyl)ethanol **11** using enantiomerically pure biaryls **6a**–**h**



x (NR_2)	R′	Time (h)	Temperature (°C)	Y	ee_A[a] (%)	ee_E[b] (%)	C[c] (%)	*s*[d]
a (pyrrolidino)	Me	9.0	−78	1.0	25.5	31.5	45	2.5
	^{i}Pr	9.0	−78	1.0	67.5	28.5	70	3.5
b (NMe_2)	Me	9.0	−78	1.0	11.6	54.9	23	4
	^{i}Pr	9.0	−78	1.0	59.8	69.2	46	10
c[30] (NEt_2)	Me	7.3	−78	1.0	17.5	77.4	18.5	9.5
	^{i}Pr	9.0	−78	1.0	69.2	84.1	45	24
d (N^nPr_2)[e,f]	^{i}Pr	9.0	−78	0.5	81.3	81.6	50	25
e (N^iPr_2)[e]	^{i}Pr	9.0	−78	0.5	74.1	74.0	50	15
f (N^nBu_2)	Me	9.0	−78	1.0	41.2	78.7	34	13
	^{i}Pr	9.0	−78	1.0	99.9	69.1	59	31
	^{i}Pr	14.2	−93	1.0	53.6	90.8	37	36
g (N^nPent_2)[e,f]	^{i}Pr	9.0	−78	0.5	93.2	79.8	54	30
h (N^nHex_2)	Me	14.2	−93	1.0	29.7	55.0	35	5
	^{i}Pr	14.2	−93	1.0	53.5	91.6	37	9

[a] ee of recovered alcohol, established by CSP HPLC.
[b] ee of ester, established by CSP HPLC on derived alcohol following saponification.
[c] Conversion $C=100\times ee_A/(ee_A+ee_E)$.
[d] Selectivity factor, see Refs. 33 and 34.
[e] Reactions performed on 0.5 mmol scale.
[f] The dextrotatory enantiomer of catalyst was employed giving enantiomeric products to those shown.

All seven new biaryls were readily separated into their atropisomers using semi-preparative CSP-HPLC (see Section 4). In all cases the first eluting atropisomers were the levorotatory enantiomers. These were used in the subsequent catalytic studies and were purified to >99.9% ee. A representative CSP-HPLC chromatogram, that of biaryl **6h**, is shown (Fig. 3).

Assignment of the absolute configuration of the biaryl axes[47] in these enantiomerically pure biaryls follows from correlation of the sign of the Cotton-effect peaks in their CD spectra at ~320 nm with that of biaryl (−)-**6c** which has a negative peak at this wavelength and has the S_a absolute configuration as established by an X-ray determination on its salt with *N*-Boc-*O*-benzyl-(*S*)-tyrosine.[29] The profiles of all the CD spectra were essentially superimposable and those of the enantiomers of biaryl **6b** are representative (Fig. 4).

Using the enantiomerically pure biaryls **6a**–**6h** a series of KR experiments were performed using (±)-1-(1-naphthyl)-ethanol **11** as the substrate and isobutyric and acetic anhydride as acyl donors (Table 1).

Inspection of Table 1 reveals that the 4-dialkylamino substituent clearly has an important influence on the level of selectivity of these catalysts although in all cases the sense of induction is the same and conforms to our simple transition state model.[29] The selectivities (*s*) observed using isobutyric anhydride at −78 °C range from 3.5 for 4-pyrrolidinopyridine biaryl **6a** to 31 for 4-di-*n*-butylamino biaryl **6f**. That the pyrrolidino-substituted biaryl is the least selective catalyst in this series is consistent with our hypothesis that induced chirality in the 4-dialkylamino group could be an important factor in determining the levels of selectivity attained as the pyrrolidine ring in this derivative cannot adopt an 'overtly' chiral conformation. However, no clear trend emerges from the selectivities displayed by the other derivatives that can convincingly be interpreted as strongly supporting the hypothesis as there is no clear correlation with steric bulk or chain length. Isobutyric anhydride consistently provides higher levels of selectivity than acetic anhydride. The 4-di-*n*-butylaminopyridine biaryl **6f** is also clearly the most selective catalyst for substrate (±)-**11**, more so than the 4-diethylaminopyridine biaryl **6c** we reported previously, giving a selectivity value (*s*) of 36 at −93 °C and 37% conversion. Only Fu's ferrocenyl DMAP catalyst **VII** (Fig. 1, R=Me, R′=Ph), has been reported to be more efficient for this substrate, giving a selectivity value (*s*) of 65 at 0 °C and 53% conversion.[48] The levels of conversion (C) also do not appear to follow a clear trend and it is likely that solubility plays an important role in determining the extent of conversion as many of the solutions became cloudy during the course of these KR reactions.

In order to determine whether the 4-di-*n*-butylaminopyridine biaryl catalyst (−)-(S_a)-**6f** was also an efficient catalyst for other *sec*-alcohols, five additional substrates were selected for KR (Fig. 5).

Aryl alkyl *sec*-alcohols **12**, **13** and **14** were selected for purposes of direct comparison with KR results obtained previously using 4-diethylaminopyridine biaryl catalyst (−)-(S_a)-**6c**[30] (Table 2).

From Table 2 it is evident that biaryl (−)-(S_a)-**6f** catalyses

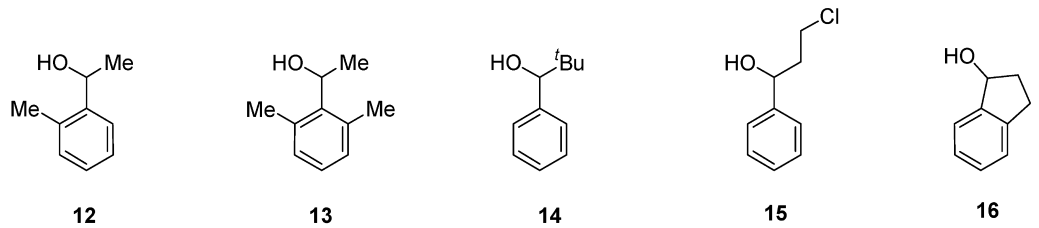
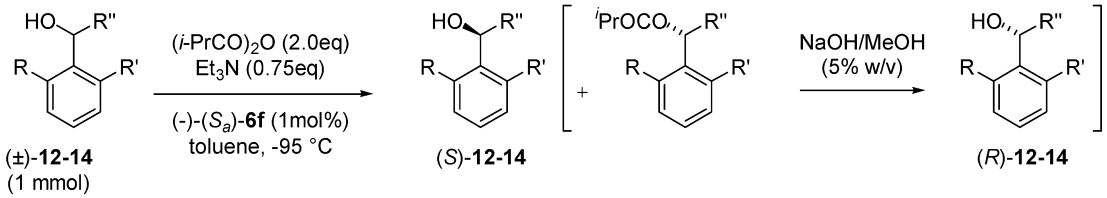


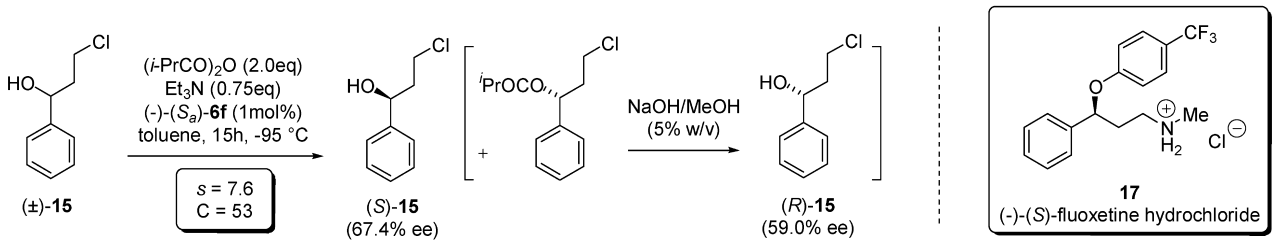
Figure 5. Alcohol substrates **14**–**18**.

Table 2. KR of alcohols **12**–**14** using biaryl (−)-(S_a)-**6f**



Alcohol	R	R′	R″	Time (h)	ee_A[a] (%)	ee_E[b] (%)	C[c] (%)	*s*[d]
12	H	Me	Me	15.0	93.6	76.5	55	26 (25)
13	Me	Me	Me	15.0	98.7	71.8	58	29 (25)
14	H	H	tBu	9.0	17.5	91.1	16	26 (20)

[a] ee of recovered alcohol, established by CSP HPLC.
[b] ee of ester, established by CSP HPLC on derived alcohol following saponification.
[c] Conversion $C=100\times ee_A/(ee_A+ee_E)$.
[d] Selectivity factor, see Refs. 33 and 34, values in parenthesis are those obtained when using the 4-diethylaminopyridine biaryl catalyst (−)-(S_a)-**6c** at −78 °C, see Ref. 30.



Scheme 2. KR of 3-chloro-1-phenylpropan-1-ol **15** using biaryl (−)-(S_a)-**6f**.

the KR of alcohols **12**, **13** and **14** highly efficiently, giving selectivity values (*s*) greater than 25 in all cases. This level of selectivity allows the recovery of unreacted alcohol in >99% ee at ~60% conversion, i.e. allowing isolation of a 40% yield (of a possible 50% maximum yield). The selectivities attained exceed those obtained using 4-diethylaminopyridine biaryl catalyst (−)-(S_a)-**6c** in all three cases although it should be noted that the previous reactions were run at −78 °C (cf. −95 °C here).

3-Chloro-1-phenylpropan-1-ol **15** is a synthetic precursor to the well-known selective serotonin reuptake inhibitor (SSRI) fluoxetine hydrochloride **17** (Prozac®) and related aryloxyphenylpropylamines[49] indicated for treatment of depression.[50] Enantiomerically pure (−)-(*S*)-**15** and (+)-(*R*)-**15** have been prepared previously by CBS reduction of 3-chloropropiophenone[51] and by enzymatic KR of (±)-**15**.[49,52] We were interested to see how biaryl (−)-(S_a)-**6f** would perform in the KR of this substrate (Scheme 2).

In the event, a surprisingly modest selectivity value (*s*) of 7.6 at 53% conversion was obtained under the standard conditions. This was somewhat unexpected as the 4-diethylaminopyridine biaryl catalyst (−)-(S_a)-**6c** shows good tolerance for different alkyl substituents in aryl alkyl *sec*-alcohols.[30] It appears that the chlorine atom has an adverse effect on the selectivity of the 4-di-*n*-butylaminopyridine biaryl catalyst (−)-(S_a)-**6f** in this instance.

Finally, the KR of indan-1-ol **16** was attempted because previous work by Vedejs[53] has shown that this is a challenging substrate for non-enzymatic acylative KR (Scheme 3).

Disappointingly, biaryl (−)-(S_a)-**6f** also proved ineffective for the KR of this substrate giving a selectivity value (*s*) of just 2.5 at 32% conversion (cf. Vedejs: $s=<1.5$ using a PBO chiral phosphine catalyst.[53]) Presumably this substrate is unable to adopt a conformation that favours enantiodiscrimination for either of these non-enzymatic catalysts.

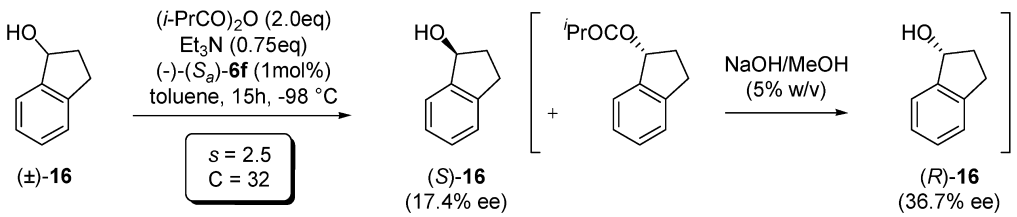
3. Conclusions

In summary, a series of 4-dialkylaminopyridine-based atropisomeric biaryls have been prepared, resolved by CSP-HPLC and screened as chiral nucleophilic catalysts for the acylative KR of 1-(1-naphthyl)ethanol. The levels of selectivity displayed by the various biaryl catalysts, which differed only in the nature of the 4-dialkylamino group, varied from $s=3.5$ (for the pyrrolidino substituted biaryl **6a**) to 36 (for the di-*n*-butylamino substituted biaryl **6f**) when employing isobutyric anhydride as the acylating agent. Although it is not yet clear why the selectivity is so dependent on the nature of this group the di-*n*-butylamino derivative has also been shown to be a useful catalyst for the acylative KR of four other aryl alkyl *sec*-alcohols including a precursor for the synthesis of the antidepressant fluoxetine hydrochloride. Work is ongoing to identify more selective catalysts and to further understand chirality transfer in these reactions.

4. Experimental

4.1. General procedures

All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in ovendried glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials. Reagents were used as obtained from commercial sources or purified according to known procedures.[54] Flash chromatography was carried out using Merck Kiesegel 60 F_{254} (230400 mesh) silica gel. Only distilled solvents were used as eluents. Thin layer chromatography (TLC) was performed on Merck DCAlufolien or glass plates precoated with silica gel 60 F_{254} which were visualised either by quenching of ultraviolet fluorescence (λ_{max}=254 nm) or by charring with 10% $KMnO_4$ in 0.1 M NaOH. All reaction solvents were distilled before use and stored over activated 4 Å molecular sieves, unless otherwise indicated. Anhydrous CH_2Cl_2 was obtained by refluxing over calcium hydride. Petrol refers to the fraction of light petroleum boiling between 40–60 °C. High



Scheme 3. KR of indan-1-ol **16** using biaryl (−)-(S_a)-**6f**.

Resolution Mass Spectrometry (HRMS) measurements are valid to ±5 ppm. CSP-HPLC was performed on a Hewlett Packard Series 1100 instrument using Diacel Chiralcel OD (1 cm×25 cm and 0.46 cm×25 cm) columns for biaryls **6a–h** and alcohols **11–16**. CD spectra were recorded between 280 and 380 nm in CH_3CN (~1 mg/5 mL) with a Jasco J600 spectropolarimeter using 10 mm quartz cuvettes at 20 °C.

4.1.1. 3,5-Dibromo-4-pyrrolidin-1-ylpyridine 2a. 3,5-Dibromo-4-chloropyridine **1**[30] (2.02 g, 7.45 mmol), pyrrolidine (1.87 mL, 22.34 mmol) and *N*-formylpyrrolidine (5 mL) were heated together in a sealed reaction vessel at 100 °C for 20 h. After cooling the mixture was dissolved in EtOAc then washed with 1 M K_2CO_3 and water. The organic extracts were then dried using $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with EtOAc/petrol (1/9) gave dibromide **2a** (2.06 g, 6.73 mmol, 90%) as a yellow oil. R_f 0.50 (CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$) 3047, 2971, 1550, 1440, 1350; δ_H ($CDCl_3$, 250 MHz) 1.99 (4H, m), 3.49 (4H, m), 8.48 (2H, s); δ_C (63 MHz) 26.0 (2×CH_2), 49.8 (2×CH_2), 120.2 (2×C_q), 152.0 (2×CH), 152.2 (C_q); *m*/*z* (EI^+) (rel intensity) 308, 306, 304 (1:2:1, 100, M^+), 225, 227 (1:1, 35); HRMS calculated for $C_9H_{10}N_2Br_2^{79}$ 303.921, found 303.920.

4.1.2. 3-(2-Benzyloxynaphthalen-1-yl)-4-pyrrolidin-1-yl pyridine 3a. To a solution of dibromide **2a** (1.00 g, 3.08 mmol) in toluene (25 mL) and ethanol (1 mL) was added 2 M KOH (6 mL) followed by $Pd(PPh_3)_4$ (189 mg, 0.16 mmol) and 2-benzyloxy-1-naphthaleneboronic acid[30] (1.183 g, 4.26 mmol). The mixture was heated at 100 °C for 20 h with vigorous stirring, then cooled to RT and diluted with water (50 mL). The phases were separated and the aqueous layer extracted further with CH_2Cl_2. The organic extracts were dried using $MgSO_4$, filtered, then concentrated in vacuo. Purification by flash chromatography eluting with CH_2Cl_2→EtOAc gave the following compounds:

Benzyl ether **3a** (490 mg, 1.29 mmol, 40%) as a yellow oil. R_f 0.70 (NH_3 sat. MeOH/EtOAc, 1/19); ν_{max}/cm^{-1} ($CHCl_3$) 3062, 2968, 1586, 1504, 1271; δ_H ($CDCl_3$, 250 MHz) 1.61 (4H, m), 2.71–2.78 (2H), 2.94–3.03 (2H), 5.15 (2H, s), 6.59 (1H, d, *J*=6.0 Hz), 7.23–7.54 (8H), 7.68 (1H, m), 7.78–7.85 (2H), 8.02 (1H, s), 8.27 (1H, d, *J*=6.0 Hz); δ_C (63 MHz) 25.4 (2×CH_2), 48.8 (2×CH_2), 70.9 (CH_2), 108.0 (CH), 114.8 (CH), 115.9 (C_q), 123.8 (CH), 123.8 (C_q), 125.9 (CH), 126.7 (CH), 126.9 (2×CH), 127.7 (CH), 127.9 (CH), 128.4 (2×CH), 128.8 (C_q), 129.4 (CH), 134.6 (C_q), 137.4 (C_q), 148.6 (CH), 152.3 (C_q), 152.9 (CH), 153.8 (C_q); *m*/*z* (EI^+) (rel intensity) 380 (70, M^+), 363 (65), 289 (100); HRMS calculated for $C_{26}H_{24}N_2O$ 380.189, found 380.189.

3-(2-Benzyloxynaphthalen-1-yl)-5-bromo-4-pyrrolidin-1-yl pyridine (268 mg, 0.59 mmol, 18%) as a yellow oil. R_f 0.80 (CH_2Cl_2/EtOAc, 1/1); ν_{max}/cm^{-1} ($CHCl_3$) 3032, 2964, 1451, 1332; δ_H ($CDCl_3$, 250 MHz) 1.48 (4H, m), 2.87–2.96 (2H), 3.03–3.11 (2H), 5.15 (2H, s), 7.20–7.41 (9H), 7.79–7.88 (2H), 8.00 (1H, s), 8.56 (1H, s); δ_C (63 MHz) 25.4 (2×CH_2), 50.1 (2×CH_2), 71.0 (CH_2), 113.8 (C_q), 114.8 (CH), 122.3 (C_q), 124.0 (CH), 125.1 (C_q), 125.1 (CH), 126.9 (2×CH), 126.9 (CH), 127.9 (CH), 128.0 (CH), 128.5 (2×CH), 129.0 (C_q), 129.9 (CH), 133.7 (C_q), 137.0 (C_q), 152.0 (CH), 152.7 (CH), 153.1 (C_q), 153.3 (C_q); *m*/*z* (EI^+) (rel intensity) 458, 460 (1:1, 15, M^+), 367, 369 (1:1, 100); HRMS calculated for $C_{26}H_{23}N_2OBr^{79}$ 458.099, found 458.100.

4.1.3. 1-(4-Pyrrolidin-1-ylpyridin-3-yl)naphthalene-2-ol 4a. To a solution of benzyl ether **3a** (431 mg, 1.14 mmol) in ethanol (30 mL) was added 10% Pd/C (135 mg). The resulting mixture was stirred under H_2 at atmospheric pressure and RT for 18 h. The mixture was then passed through a pad of Celite® and concentrated in vacuo to give naphthol **4a** (288 mg, 0.99 mmol, 82%) as a white foam. R_f 0.20 (MeOH/EtOAc, 9/1); ν_{max}/cm^{-1} ($CHCl_3$) 3356, 3054, 2918, 1507, 1500, 1338; δ_H ($CDCl_3$, 250 MHz) 1.66 (4H, m), 1.94 (1H, s), 2.80 (2H, m). 3.10 (2H, m), 6.72 (1H, d, *J*=6.0 Hz), 7.15–7.36 (4H), 7.78–7.80 (3H), 8.10 (1H, d, *J*=6.0 Hz); δ_C (63 MHz) 26.3 (2×CH_2), 49.9 (2×CH_2), 109.6 (CH), 117.5 (C_q), 118.8 (CH), 120.0 (C_q), 123.9 (CH), 125.5 (CH), 127.7 (CH), 129.2 (CH), 129.5 (C_q), 130.7 (CH), 136.27 (C_q), 148.0 (CH), 152.5 (CH), 154.1 (C_q), 154.5 (C_q); *m*/*z* (EI^+) (rel intensity) 290 (100, M^+), 273 (35), 219 (60); HRMS calculated for $C_{19}H_{18}N_2O$ 290.142, found 290.141.

4.1.4. Trifluoromethanesulfonic acid 1-(4-pyrrolidin-1-ylpyridin-3-yl)napthalen-2-yl ester 5a. To a solution of naphthol **4a** (361 mg, 1.25 mmol) in pyridine (7 mL) at 0 °C was slowly added triflic anhydride (250 μL, 1.49 mmol). The resulting mixture was stirred at 0 °C for 4 h then concentrated in vacuo. The residue was then partitioned between CH_2Cl_2 and water, the organic extracts were then dried using $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with petrol/EtOAc (1/1) gave triflate **5a** (367 mg, 0.87 mmol, 70%) as an orange oil. R_f 0.17 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3057, 2921, 1586, 1420, 1212, 1136; δ_H ($CDCl_3$, 250 MHz) 1.67 (4H, m), 2.77 (2H, m), 2.95 (2H, m), 6.63 (1H, d, *J*=6.1 Hz), 7.44 (1H, d, *J*=9.2 Hz), 7.53–7.58 (2H), 7.75–7.79 (1H), 7.91–7.97 (2H), 8.04 (1H, s), 8.30 (1H, d, *J*=6.1 Hz); δ_C (63 MHz) 25.4 (2×CH_2), 49.1 (2×CH_2), 108.5 (CH), 112.6 (C_q), 118.3 (CF_3, q, *J*=320 Hz), 119.0 (CH), 127.1 (CH), 127.2 (CH), 127.9 (CH), 128.2 (CH), 130.0 (C_q), 130.3 (CH), 132.2 (C_q), 134.3 (C_q), 145.6 (C_q), 149.6 (CH), 152.2 (C_q), 152.8 (CH); *m*/*z* (EI^+) (rel intensity) 422 (40, M^+), 289 (85), 273 (100); HRMS calculated for $C_{20}H_{17}N_2O_3F_3S$ 422.091, found 422.090.

4.1.5. (±)-3-(2-Phenylnaphthalen-1-yl)-4-pyrrolidin-1-yl pyridine 6a. To a solution of triflate **5a** (70 mg, 0.17 mmol) in Et_2O (1.0 mL), was added $PdCl_2$(dppp) (5 mg, 0.01 mmol) followed by a solution of PhMgBr in hexanes (2.5 M, 166 μL, 0.42 mmol). The resulting mixture was heated at 40 °C for 20 h, then cooled to RT, diluted with water and extracted with CH_2Cl_2. The organic extracts were then dried using $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with EtOAc/CH_2Cl_2 (1/1)→MeOH/EtOAc (1/9) gave (±)-biaryl **6a** (37 mg, 0.11 mmol, 64%) as a yellow oil. R_f 0.43 (MeOH/EtOAc, 1/9); ν_{max}/cm^{-1} ($CHCl_3$) 3049, 2964, 1584, 1502, 1370; δ_H ($CDCl_3$, 250 MHz) 1.41–1.71 (4H), 2.46–2.54 (2H), 2.77–2.87 (2H), 6.22 (1H, d, *J*=6.0 Hz), 7.06–7.18 (5H), 7.44–7.54 (3H), 7.82–7.94 (3H), 8.07 (1H, s), 8.12 (1H, d, *J*=6.0 Hz); δ_C (100 MHz) 25.5 (2×CH_2), 48.8

(2×CH_2), 108.1 (CH), 118.7 (C_q), 125.8 (CH), 126.5 (CH), 126.6 (CH), 127.3 (CH), 127.5 (2×CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 129.2 (2×CH),132.6 (C_q), 133.5 (C_q), 134.4 (C_q), 139.6 (C_q), 141.6 (C_q), 148.3 (CH), 152.0 (C_q), 153.3 (CH); *m/z* (EI^+) (rel intensity) 350 (100, M^+), 146 (20); HRMS calculated for $C_{25}H_{22}N_2$ 350.178, found 350.178.

4.2. General procedure for the optical resolution of biaryls (±)-6

The enantiomers of biaryl **6** were separated using semi-preparative CSP HPLC by repeated injection of ~2 mg of the racemate in 30 μL of CH_2Cl_2. In all cases the levorotatory enantiomer (−)-**6** eluted first and the dextrorotatory enantiomer (+)-**6** eluted second. Analytical CSP HPLC revealed >99.9% ee for both the levorotatory and the dextrorotatory enantiomers. Assignment of the absolute configuration of the biaryl axes in these enantiomerically pure biaryls follows from correlation of the sign of the Cotton-effect peaks in their CD spectra at ~320 nm with that of biaryl (−)-**6c** (see main text).

4.2.1. (−)-(S_a) and (+)-(R_a)-3-(2-Phenylnaphthalen-1-yl)-4-pyrrolidin-1-yl pyridine 6a. CSP-HPLC conditions: Chiralcel OD (1 cm×25 cm); hexanes/EtOAc/Et_2NH, 80/19.2/0.8; 4 mL min^{-1}; 30 °C; UV detection at 254 nm, reference at 525 nm. Biaryl (−)-(S_a)-**6a**, colourless oil. Spectroscopic data as above; retention time 14.7 min; $[\alpha]_D^{25}=-80$ (*c* 0.09, CH_2Cl_2); CD λ_{max}/nm 320 (−ive). Biaryl (+)-(R_a)-**6a**, colourless oil. Spectroscopic data as above; retention time 29.4 min; $[\alpha]_D^{25}=+86$ (*c* 0.13, CH_2Cl_2).

4.2.2. 3,5-Dibromo(pyridine-4-yl)dimethylamine 2b. 3,5-Dibromo-4-chloropyridine **1**[30] (201 mg, 1.85 mmol) and dimethylamine (40% aq solution, 5 mL, 4.07 mmol), were heated together in a sealed reaction vessel at 115 °C for 20 h. After cooling the mixture was dissolved in EtOAc, then washed with 1 M K_2CO_3 and water. The organic extracts were then dried using $MgSO_4$, filtered, and concentrated in vacuo to give dibromide **2b** (452 mg, 1.61 mmol, 87%) as yellow needles without any further purification. Mp 44.5–45.8 °C. R_f 0.53 (CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$) 2922, 1560, 1419, 1169; δ_H ($CDCl_3$, 250 MHz) 2.98 (6H, s), 8.48 (2H, s); δ_C (63 MHz) 42.5 (2×CH_3), 119.7 (2×C_q), 152.1 (2×CH), 155.2 (C_q); *m/z* (EI^+) (rel intensity) 278, 280, 282 (1:2:1, 35, M^+); HRMS calculated for $C_7H_8N_2Br_2^{79}$ 277.905, found 277.904.

4.2.3. [3-(2-Benzyloxynaphthalen-1-yl)pyridine-4-yl]dimethylamine 3b. To a solution of dibromide **2b** (863 mg, 3.08 mmol) in toluene (17 mL) and ethanol (900 μL) was added 2 M KOH (5.4 mL) followed by $Pd(PPh_3)_4$ (176 mg, 0.15 mmol) and 2-benzyloxy-1-naphthaleneboronic acid[30] (689 mg, 4.01 mmol). The mixture was heated at 100 °C for 20 h with vigorous stirring, then cooled to RT and diluted with water. The phases were separated and the aqueous layer extracted further with CH_2Cl_2.The organic extracts were dried using $MgSO_4$, filtered then concentrated in vacuo. Purification by flash chromatography eluting with CH_2Cl_2→EtOAc gave benzyl ether **3b** (432 mg, 1.22 mmol, 40%) as a yellow oil. R_f 0.30 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3057, 2921, 1586, 1508; δ_H ($CDCl_3$, 250 MHz) 2.55 (6H, s), 5.16 (2H, s), 6.73 (1H, d, *J*=6.0 Hz), 7.21–7.41 (6H), 7.45–7.55 (2H), 7.62–7.70 (1H), 7.78–7.80 (1H), 7.84 (1H, d, *J*=9.1 Hz), 8.08 (1H, s), 8.33 (1H, d, *J*=6.0 Hz); δ_C (100 MHz) 41.1 (2×CH_3), 70.9 (CH_2), 109.4 (CH), 115.0 (CH), 118.4 (C_q), 123.4 (C_q), 123.9 (CH), 125.4 (CH), 126.7 (CH), 126.8 (CH), 127.7 (CH), 127.9 (CH), 128.4 (CH), 129.1 (C_q), 129.4 (CH), 132.0 (CH), 132.1 (CH), 133.5 (C_q), 137.2 (C_q), 148.7 (CH), 153.1 (C_q), 153.2 (CH), 156.1 (C_q); *m/z* (EI^+) (rel intensity) 355 (25, MH^+), 354 (100), 338 (20), 278 (20); HRMS calculated for $C_{24}H_{22}N_2O$ 354.173, found 354.173.

4.2.4. 1-(4-Dimethylaminopyridin-3-yl)naphthalene-2-ol 4b. To a solution of benzyl ether **3b** (432 mg, 1.22 mmol) in ethanol (30 mL) was added 10% Pd/C (125 mg). The resulting mixture was stirred under H_2 at atmospheric pressure and RT for 18 h. The mixture was then passed through a pad of Celite® and concentrated in vacuo to give naphthol **4b** (261 mg, 0.99 mmol, 81%) as a white foam. R_f 0.25 (MeOH/EtOAc, 9/1); ν_{max}/cm^{-1} ($CHCl_3$) 3405, 3015, 2926, 1594, 1342; δ_H ($CDCl_3$, 250 MHz) 2.63 (6H, s), 6.90 (1H, d, *J*=6.0 Hz), 7.19–7.36 (4H), 7.79 (2H, d, *J*=8.5 Hz), 7.88 (1H, s), 8.18 (1H, d, *J*=6.0 Hz), (OH absent); δ_C (100 MHz) 41.2 (2×CH_3), 110.9 (CH), 119.0 (CH), 119.9 (C_q), 119.9 (C_q), 124.1 (CH), 125.3 (CH), 127.7 (CH) 129.2 (CH), 129.9 (C_q), 130.8 (CH), 135.0 (C_q),148.2 (CH), 152.9 (CH), 153.0 (C_q), 158.3 (C_q); *m/z* (EI^+) (rel intensity) 265 (20, MH^+), 219 (100); HRMS calculated for $C_{17}H_{16}N_2O$ 264.126, found 264.125.

4.2.5. Trifluoromethanesulfonic acid-1-(4-dimethylamino-pyridin-3-yl)napthalen-2-yl ester 5b. To a solution of naphthol **4b** (48 mg, 0.18 mmol) in pyridine (1 mL) at 0 °C was slowly added triflic anhydride (46 μL, 0.27 mmol). The resulting mixture was stirred at 0 °C for 4 h then concentrated in vacuo. The residue was then partitioned between CH_2Cl_2 and water, the organic extracts were then dried using $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography eluting with CH_2Cl_2→EtOAc gave triflate **5b** (61 mg, 0.16 mmol, 85%) as an orange oil. R_f 0.10 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3066, 2930, 1585, 1421, 1213, 1140; δ_H ($CDCl_3$, 250 MHz) 2.57 (6H, s), 6.80 (1H, d, *J*=6.0 Hz), 7.47 (1H, d, *J*=9.1 Hz), 7.58 (2H, m), 7.80 (1H, m), 7.94 (1H, m), 7.98 (1H, s), 8.12 (1H, s), 8.38 (1H, d, *J*=6.0 Hz); δ_C (63 MHz) 41.2 (2×CH3), 110.2 (CH), 115.6 (C_q), 118.3 (CF_3, q, *J*=314 Hz), 119.3 (CH), 126.6 (CH), 127.2 (CH), 128.0 (CH), 128.4 (CH), 129.5 (C_q), 130.4 (CH), 132.6 (C_q), 133.2 (C_q), 145.0 (C_q), 149.9 (CH), 153.0 (CH), 156.3 (C_q); *m/z* (EI^+) (rel intensity) 396 (15, M^+), 247 (100); HRMS calculated for $C_{18}H_{15}N_2O_3F_3S$ 396.076, found 396.077.

4.2.6. (±)-Dimethyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine 6b. To a solution of triflate **5b** (61 mg, 0.15 mmol) in Et_2O (1.5 mL), was added $PdCl_2$(dppp) (5 mg, 0.01 mmol) followed by a solution of PhMgBr in hexanes (1.17 M, 329 μL, 0.39 mmol). The resulting mixture was heated at 40 °C for 20 h, then cooled to RT, diluted with water and extracted with CH_2Cl_2.The organic extracts were then dried using $MgSO_4$, filtered then concentrated in vacuo. Purification by flash chromatography eluting with EtOAc/CH_2Cl_2 (1/1)→MeOH/EtOAc (1/9) gave (±)-Biaryl **6b** (30 mg, 0.09 mmol, 60%) as a yellow

oil. R_f 0.46 (MeOH/EtOAc, 1/9); ν_{max}/cm^{-1} ($CHCl_3$) 3057, 2923, 1585, 1512; δ_H ($CDCl_3$, 250 MHz) 2.29 (6H, s), 6.39 (1H, d, J=6.1 Hz), 7.05–7.10 (2H) 7.16–7.18 (3H), 7.45–7.55 (3H), 7.86–7.95 (3H), 8.16 (1H, s), 8.18 (1H, d, J=6.1 Hz); δ_C (100 MHz) 40.5 (2×CH_3), 109.9 (CH), 121.0 (C_q), 125.9 (CH), 126.4 (CH), 126.7 (CH), 127.4 (2×CH), 128.1 (2×CH), 128.1 (CH), 128.1 (CH), 129.0 (2×CH), 132.4 (C_q), 133.0 (C_q), 135.1 (C_q), 139.0 (C_q), 141.7 (C_q), 148.5 (CH), 153.7 (CH), 155.8 (C_q); m/z (EI^+) (rel intensity) 324 (100, M^+), 233 (65); HRMS calculated for $C_{23}H_{20}N_2$ 324.163, found 324.164.

4.2.7. (−)-(S_a) and (+)-(R_a)-Dimethyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine 6b. CSP-HPLC conditions: Chiralcel OD (1 cm×25 cm); hexanes/EtOAc/Et_2NH, 80/19.2/0.8; 4 mL min^{-1}; 30 °C; UV detection at 254 nm, reference at 525 nm. Biaryl (−)-(S_a)-**6b**, colourless oil. Spectroscopic data as above; retention time 11.3 min; $[\alpha]_D^{25}$=−90 (c 0.74, $CHCl_3$); CD λ_{max}/nm 320 (−ive). Biaryl (+)-(R_a)-**6b**, colourless oil. Spectroscopic data as above; retention time 20.5 min; $[\alpha]_D^{25}$=+91 (c 0.73, CH_2Cl_2); CD λ_{max}/nm 320 (+ive).

4.2.8. (±)-Di-*n*-propyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine 6d. To a solution of 4-chloro-3-(2-phenylnaphthalen-1-yl)pyridine **8**[29] (91 mg, 0.3 mmol) in THF (2.0 mL) was added di-*n*-propylamine (417 μL, 3.0 mmol) and a solution of PhLi in cyclohexane/Et_2O (7:3)(2 M, 360 μL, 0.72 mmol). The mixture was heated at reflux for 30 h then the solvent removed in vacuo. Purification by flash chromatography eluting with EtOAc gave:

Di-*n*-propyl-[5-(2-phenylnaphthalen-1-yl)pyridin-3-yl]-amine **9d** (50 mg, 46%) as a yellow oil. R_f 0.60 (EtOAc/petrol, 6/4); ν_{max}/cm^{-1} (neat) 2959, 2362, 1584; δ_H ($CDCl_3$, 400 MHz) δ 0.80 (6H, t, J=8.4 Hz), 1.24–1.52 (4H), 2.96–3.22 (4H), 6.58 (1H, s), 7.10–7.24 (5H), 7.42–7.54 (3H), 7.60 (1H, d, J=4.3 Hz), 7.78 (1H, d, J=8.4 Hz), 7.94 (3H, t, J=9.2 Hz); δ_C (100 MHz) 11.3 (2×CH_3), 20.0 (2×CH_2), 52.5 (2×CH_2), 115.6 (CH), 125.9 (CH), 126.4 (2×CH), 126.5 (CH), 127.8 (2×CH), 128.0 (2×CH), 128.1 (CH), 128.3 (2×CH), 129.8 (2×C_q), 130.0 (C_q), 130.2 (C_q), 132.5 (C_q), 132.7 (CH), 137.6 (C_q), 139.0 (CH), 141.6 (C_q); m/z (EI^+) (rel intensity) 380 (38, M^+), 323 (68), 365 (100), 366 (35), 280 (11), 252 (12); HRMS calculated for $C_{27}H_{28}N_2$ 380.225, found 380.224.

(±)-Di-*n*-propyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine **6d** (12.2 mg, 11%) as a yellow oil. R_f 0.25 (EtOAc/petrol, 6/4); ν_{max}/cm^{-1} (neat) 2928, 1630, 1503; δ_H ($CDCl_3$, 300 MHz) δ 0.40 (6H, m), 0.78–1.18 (4H), 2.50–2.87 (4H), 6.40–6.58 (1H), 7.08–7.30 (5H), 7.40–7.70 (3H), 7.80–8.04 (3H) 8.10–8.37 (2H); δ_C (100 MHz) 20.2 (2×CH_3), 21.3 (2×CH_2), 47.4 (2×CH_2), 111.4 (CH), 121.3 (C_q), 125.4 (CH), 126.8 (2×CH), 127.5 (CH), 127.9 (2×CH), 128.6 (2×CH), 128.7 (CH), 129.5 (2×CH), 129.7 (C_q), 131.0 (C_q), 131.4 (C_q), 132.9 (C_q), 138.3 (C_q), 139.9 (CH), 143.8 (CH), 157.9 (C_q); m/z (EI^+) (rel intensity) 380 (27, M^+), 309 (18), 351 (100), 352 (38), 231 (9), 73 (10); HRMS calculated for $C_{27}H_{28}N_2$ 380.225, found 380.225.

4.2.9. (−)-(S_a) and (+)-(R_a)-Di-*n*-propyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine 6d. CSP-HPLC conditions: Chiralcel OD (1 cm×25 cm); hexanes/*i*-PrOH, 97/3; 4 mL min^{-1}; 30 °C; UV detection at 211 nm, reference at 525 nm. Biaryl (−)-(S_a)-**6d**, colourless oil. Spectroscopic data as above; retention time 9.9 min; $[\alpha]_D^{25}$=−120 (c 0.21, MeCN); CD λ_{max}/nm 320 (−ive). Biaryl (+)-(R_a)-**6d**, colourless oil. Spectroscopic data as above; retention time 18.5 min; $[\alpha]_D^{25}$=+121 (c 0.21, MeCN).

4.2.10. (±)-Diisopropyl-[3-(2-phenylnaphthalen-1-yl)-pyridin-4-yl]amine 6e. To a solution of 4-chloro-3-(2-phenyl-naphthalen-1-yl)pyridine **8**[29] (62 mg, 0.2 mmol) in THF (1.0 mL) was added diisopropylamine (288 μL, 2.0 mmol) and a solution of PhLi in cyclohexane/Et_2O (7:3) (2 M, 120 μL, 0.24 mmol). The mixture was heated at reflux for 20 h then the solvent removed in vacuo. Purification by flash chromatography eluting with EtOAc gave:

Diisopropyl-[5-(2-phenylnaphthalen-1-yl)pyridin-3-yl]-amine **9e** (28 mg, 37%) as a yellow oil. R_f 0.65 (EtOAc/petrol, 6/4); ν_{max}/cm^{-1} (neat) 3053, 2970, 1581; δ_H ($CDCl_3$, 400 MHz) δ 1.04 (12H, d, J=7.2 Hz), 3.62 (2H, m), 6.89 (1H, s), 7.11–7.28 (5H), 7.50 (2H, m), 7.61 (1H, d, J=8.3 Hz), 7.77 (1H, d, J=8.4 Hz), 7.92–8.06 (3H), 8.18 (1H, s); δ_C (100 MHz) 21.1 (4×CH_3), 47.6 (2×CH_2), 115.7 (CH), 125.9 (CH), 126.5 (2×CH), 126.6 (CH), 127.9 (2×CH), 128.0 (2×CH), 128.1 (CH), 128.3 (2×CH), 128.6 (2×C_q), 130.1 (C_q), 132.5 (C_q), 132.7 (C_q), 139.0 (CH), 139.2 (C_q), 141.2 (CH), 141.6 (C_q); m/z (EI^+) (rel intensity) 380 (38, M^+), 323 (68), 365 (100), 366 (35), 280 (11), 252 (12); HRMS calculated for $C_{27}H_{28}N_2$ 380.225, found 380.224.

(±)-Diisopropyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine **6e** (7.4 mg, 10%) as a yellow oil. R_f 0.25 (EtOAc/petrol, 6/4); ν_{max}/cm^{-1} (neat) ν_{max} 3053, 2970, 1581; δ_H ($CDCl_3$, 270 MHz) δ 0.65 (6H, d, J=6.7 Hz), 0.85 (6H, d, J=6.7 Hz), 3.43 (2H, m), 6.80 (1H, d, J=6.2 Hz), 7.11–7.28 (5H), 7.50 (2H, m), 7.57 (1H, d, J=8.7 Hz), 7.71 (1H, d, J=8.2 Hz), 7.87–7.97 (2H), 8.11 (1H, s), 8.17 (1H, d, J=6.0 Hz); δ_C (68 MHz) 21.1 (2×CH_3), 21.8 (2×CH_3), 48.7 (2×CH), 110.0 (CH), 114.1 (C_q), 121.9 (CH), 124.0 (2×CH), 126.0 (CH), 126.6 (2×CH), 126.8 (2×CH), 128.0 (CH), 128.1 (2×CH), 128.9 (2×C_q), 129.9 (C_q), 135.0 (C_q), 136.0 (C_q), 147.4 (CH), 150.2 (CH), 155.0 (C_q); m/z (EI^+) (rel intensity) 380 (26, M^+), 323 (60), 365 (100), 366 (30), 134 (13), 308 (7); HRMS calculated for $C_{27}H_{28}N_2$ 380.225, found 380.225.

4.2.11. (−)-(S_a) and (+)-(R_a)-Diisopropyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine 6e. CSP-HPLC conditions: Chiralcel OD (0.46 cm×25 cm); hexanes/*i*-PrOH, 99/1; 1 mL min^{-1}; 25 °C; UV detection at 211 nm, reference at 525 nm. Biaryl (−)-(S_a)-**6e**, colourless oil. Spectroscopic data as above; retention time 20.0 min; $[\alpha]_D^{25}$=−93 (c 0.21, MeCN); CD λ_{max}/nm 325 (−ive). Biaryl (+)-(R_a)-**6e**, colourless oil. Spectroscopic data as above; retention time 32.0 min; $[\alpha]_D^{25}$=+92 (c 0.21, MeCN); CD λ_{max}/nm 325 (+ive).

4.2.12. 3,5-Dibromo(pyridin-4-yl)di-*n*-butylamine 2f. 3,5-Dibromo-4-chloropyridine **1**[30] (819 mg, 6.58 mmol), di-*n*-butylamine (1.53 mL, 9.06 mmol), and DMF (3 mL) were heated together in a sealed reaction vessel at 170 °C

for 24 h. After cooling the mixture was dissolved in EtOAc then washed with 1 M K_2CO_3 and water. The organic extracts were then dried using $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with petrol/CH_2Cl_2 (6/4)→CH_2Cl_2 gave:

3,5-Dibromo(pyridine-4-yl)di-n-butylamine **2f** (550 mg, 1.51 mmol, 50%) as a yellow oil. R_f 0.38 (CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$) 2957, 1547, 1454; δ_H ($CDCl_3$, 400 MHz) 0.83 (6H, t, J=7.0 Hz), 1.16–1.46 (8H), 3.21 (4H, t, J=7.0 Hz), 8.47 (2H, s); δ_C (100 MHz) 13.9 (2×CH_3), 20.2 (2×CH_2), 30.8 (2×CH_2), 52.0 (2×CH_2), 121.9 (2×C_q), 152.1 (2×CH), 154.5 (C_q); m/z (EI^+) (rel intensity) 362, 364, 366 (1:2:1, 10, M^+), 321 (100), 265 (55); HRMS calculated for $C_{13}H_{20}N_2Br_2^{79}$ 361.999, found 362.000.

3,5-Dibromo(pyridine-4-yl)-*n*-butylamine (101 mg, 0.33 mmol, 11%) as a yellow oil. R_f 0.14 (CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$) 2958, 1561, 1496; δ_H ($CDCl_3$, 250 MHz) 0.94 (3H, t, J=7.0 Hz), 1.40 (2H, m), 1.58 (2H, m), 3.65 (2H, q, J=7.0 Hz), 4.70 (1H, s), 8.28 (2H, s); δ_C (63 MHz) 13.7 (CH_3), 19.8 (CH_2), 33.0 (CH_2), 46.1 (CH_2), 108.2 (2×C_q), 149.0 (C_q), 151.2 (2×CH); m/z (EI^+) (rel intensity) 306, 308, 310 (1:2:1, 35, M^+), 265 (100); HRMS calculated for $C_9H_{12}N_2Br_2^{79}$ 305.937, found 305.938.

4.2.13. [3-(2-Benzyloxynaphthalen-1-yl)pyridine-4-yl]di-*n*-butylamine 3f. To a solution of dibromide **2f** (443 mg, 1.22 mmol) in toluene (12 mL) and ethanol (750 μL) was added 2 M KOH (3 mL) followed by $Pd(PPh_3)_4$ (70 mg, 0.06 mmol) and 2-benzyloxy-1-naphthaleneboronic acid[30] (406 mg, 1.46 mmol). The mixture was heated at 100 °C for 20 h with vigorous stirring, then cooled to RT and diluted with water (25 mL). The phases were separated and the aqueous phases extracted further with CH_2Cl_2. The combined organic extracts were dried using $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with CH_2Cl_2→CH_2Cl_2/EtOAc (1/1) gave benzyl ether **3f** (263 mg, 0.6 mmol, 50%) as a brown oil. R_f 0.22 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 2956, 1582, 1497, 1267; δ_H ($CDCl_3$, 250 MHz) 0.62 (6H, t, J=7.2 Hz), 0.82 (4H, m), 0.95–1.09 (2H), 1.16–1.31 (2H), 2.87 (4H, m), 5.16 (2H, s), 6.77 (1H, d, J=6.0 Hz), 7.23–7.42 (8H), 7.43–7.47 (1H), 7.77–7.86 (2H), 8.11 (1H, s), 8.34 (1H, d, J=6.0 Hz); δ_C (63 MHz) 13.7 (2×CH_3), 20.0 (2×CH_2), 29.5 (2×CH_2), 51.4 (2×CH_2), 70.8 (CH_2), 110.7 (CH), 114.9 (CH), 119.8 (C_q), 123.5 (C_q), 123.9 (CH), 125.6 (CH), 126.5 (CH), 126.8 (2×CH), 127.6 (CH), 127.9 (CH), 128.4 (2×CH), 129.3 (C_q), 129.4 (CH), 133.3 (C_q), 137.3 (C_q), 148.8 (CH), 153.1 (C_q), 153.7 (CH), 155.3 (C_q); m/z (EI^+) (rel intensity) 439 (100, M^+); HRMS calculated for $C_{30}H_{55}N_2O$ 439.275, found 439.274.

4.2.14. 1-(4-Di-*n*-butylaminopyridin-3-yl)naphthalene-2-ol 4f. To a solution of benzyl ether **3f** (263 mg, 0.60 mmol) in ethanol (20 mL) was added 10% Pd/C (80 mg). The reaction mixture was stirred under H_2 at atmospheric pressure and RT for 18 h. The mixture was then passed through a pad of Celite® and concentrated in vacuo to give naphthol **4f** (159 mg, 0.46 mmol, 78%) as a white foam. R_f 0.20 (MeOH/EtOAc, 9/1); ν_{max}/cm^{-1} ($CHCl_3$) 3049, 3957, 1593, 1504, 1345; δ_H ($CDCl_3$, 250 MHz) 0.66 (6H, t, J=7.8 Hz), 0.91 (4H, m), 1.24 (4H, m), 2.94 (4H, t, J=7.8 Hz), 6.73 (1H, d, J=6.0 Hz), 7.24–7.38 (4H), 7.72–7.77 (2H), 8.07 (1H, s), 8.13 (1H, d, J=6.0 Hz), 9.34 (1H, s); δ_C (63 MHz) 13.7 (2×CH_3), 20.1 (2×CH_2), 29.3 (2×CH_2), 51.4 (2×CH_2), 111.2 (CH), 118.6 (C_q), 119.5 (CH), 120.3 (C_q), 123.0 (CH), 124.7 (CH), 126.3 (CH), 128.0 (CH), 128.8 (C_q), 129.6 (CH), 133.4 (C_q), 148.0 (CH), 152.8 (C_q), 154.0 (CH), 155.2 (C_q); m/z (EI^+) (rel intensity) 348 (30, M^+), 305 (100); HRMS calculated for $C_{23}H_{28}N_2O$ 348.220, found 348.220.

4.2.15. Trifluoromethanesulfonic acid-1-(4-di-*n*-butylaminopyridin-3-yl)napthalen-2-yl ester 5f. To a solution of naphthol **4f** (160 mg, 0.46 mmol) in pyridine (4 mL) at 0 °C was slowly added triflic anhydride (93 μL, 0.55 mmol). The reaction mixture was stirred at 0 °C for 4 h and then concentrated in vacuo. The residue was then partitioned between CH_2Cl_2 and water, the organic extracts were then dried using $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with CH_2Cl_2/EtOAc (6/4) gave triflate **5f** (209 mg, 0.44 mmol, 95%) as an orange oil. R_f 0.61 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 2960, 1582, 1421, 1215, 1142; δ_H ($CDCl_3$, 250 MHz) 0.62 (6H, t, J=7.2 Hz), 0.81 (4H, m), 1.12 (4H, m), 2.80 (4H, m), 6.82 (1H, d, J=6.0 Hz), 7.45–7.60 (3H), 7.79 (1H, d, J=7.6 Hz), 7.94 (2H, t, J=8.2 Hz), 8.13 (1H, s), 8.37 (1H, d, J=6.0 Hz); δ_C (63 MHz) 13.5 (2×CH_3), 19.9 (2×CH_2), 29.4 (2×CH_2), 51.5 (2×CH_2), 111.7 (CH), 117.1 (C_q), 118.3 (CF_3, q, J=315 Hz), 119.5 (CH), 126.6 (CH), 127.2 (CH), 127.8 (CH), 128.3 (CH), 129.6 (C_q), 130.3 (CH), 132.8 (C_q), 132.9 (C_q), 144.9 (C_q), 150.0 (CH), 153.6 (CH), 155.7 (C_q); m/z (EI^+) (rel intensity) 480 (20, M^+), 437 (60), 287 (100); HRMS calculated for $C_{24}H_{27}N_2O_3F_3S$ 480.170, found 480.170.

4.2.16. (±)-Di-*n*-butyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine 6f. To a solution of triflate **5f** (100 mg, 0.21 mmol) in Et_2O (2 mL) was added $PdCl_2$(dppp) (6 mg, 0.01 mmol) followed by a solution of PhMgBr in hexanes (1.65 M, 315 μL, 0.52 mmol). The resulting mixture was heated at 40 °C for 20 h, then cooled to RT, diluted with water, and extracted with CH_2Cl_2. The organic extracts were then dried using $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with EtOAc/CH_2Cl_2 (1/1)→MeOH/EtOAc (1/9) gave (±)-biaryl **6f** (65 mg, 0.16 mmol, 77%) as a white solid. Mp 92–94 °C. R_f 0.40 (MeOH/EtOAc, 1/9); ν_{max}/cm^{-1} ($CHCl_3$) 3054, 2957, 1583, 1494; δ_H ($CDCl_3$, 250 MHz) 0.55 (6H, t, J=6.9 Hz), 0.61–0.77 (4H), 0.79–0.99 (4H), 2.48–2.60 (2H), 2.67–2.79 (2H), 6.45 (1H, d, J=6.0 Hz), 7.08–7.20 (5H), 7.41–7.54 (2H), 7.56 (1H, s), 7.82–7.95 (3H), 8.16 (1H, s), 8.19 (1H, d, J=6.0 Hz); δ_C (63 MHz) 13.5 (2×CH_3), 19.9 (2×CH_2), 29.2 (2×CH_2), 51.2 (2×CH_2), 111.1 (CH), 121.7 (C_q), 126.0 (CH), 126.5 (2×CH), 126.8 (CH), 127.6 (2×CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 129.6 (2×CH), 132.3 (C_q), 133.2 (C_q), 134.1 (C_q), 138.9 (C_q), 141.5 (C_q), 148.4 (CH), 154.0 (CH), 154.7 (C_q); m/z (EI^+) (rel intensity) 408 (25, M^+), 365 (100); HRMS calculated for $C_{29}H_{32}N_2$ 408.257, found 408.256.

4.2.17. (−)-(S_a) and (+)-(R_a)-Di-*n*-butyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine 6f. CSP-HPLC conditions: Chiralcel OD (1 cm×25 cm); hexanes/EtOAc/Et_2NH, 85/14.4/0.6; 3 mL min^{-1}; 25 °C; UV detection at

250 nm, reference at 360 nm. Biaryl (−)-(S_a)-**6f**, colourless oil. Spectroscopic data as above; retention time 9.3 min; $[\alpha]_D^{25}=-140$ (*c* 0.84, CH_2Cl_2). Biaryl (+)-(R_a)-**6f**, colourless oil. Spectroscopic data as above; retention time 17.6 min; $[\alpha]_D^{25}=+135$ (*c* 0.80, CH_2Cl_2); CD λ_{max}/nm 320 (+ive).

4.2.18. (±)-Di-*n*-pentyl-[3-(2-phenylnaphthalen-1-yl)-pyridin-4-yl]amine 6g. To a solution of *4-chloro-3-(2-phenyl-naphthalen-1-yl)-pyridine* **8**[29] (91 mg, 0.3 mmol) in THF (2.0 mL) was added di-*n*-pentylamine (613 μL, 3.0 mmol) and a solution of PhLi in cyclohexane/Et_2O (7:3)(2 M, 360 μL, 0.72 mmol). The mixture was heated at reflux for 36 h then the solvent removed in vacuo. Purification by flash chromatography eluting with EtOAc gave:

Di-*n*-pentyl-[5-(2-phenylnaphthalen-1-yl)pyridin-3-yl]-amine **9g** (30.9 mg, 25%) as a yellow oil. R_f 0.60 (EtOAc/CH_2Cl_2, 6/4); ν_{max}/cm^{-1} (neat) 3051, 2928, 1584; δ_H ($CDCl_3$, 270 MHz) δ 0.88 (6H, t, *J*=8.4 Hz), 1.10–1.45 (12H), 2.95–3.24 (4H), 6.60 (1H, s), 6.95–7.28 (5H), 7.38–7.54 (2H), 7.58 (1H, d, *J*=8.3 Hz), 7.78 (1H, d, *J*=8.4 Hz), 7.75 (1H, d, *J*=8.4 Hz), 7.82 (1H, s), 7.92 (3H, t, *J*=8.3 Hz); δ_C (125 MHz) 14.1 (2×CH_3), 22.5 (2×CH_2), 26.6 (2×CH_2), 29.2 (2×CH_2), 50.8 (2×CH_2), 115.5 (CH), 121.5 (CH), 125.9 (2×CH), 126.5 (CH), 126.6 (2×CH), 127.8 (2×CH), 128.0 (CH), 128.3 (2×CH), 129.6 (2×C_q), 130.0 (C_q), 132.6 (C_q), 132.8 (C_q), 134.6 (CH), 138.5 (C_q,), 139.0 (CH), 141.6 (C_q); *m*/*z* (EI^+) (rel intensity) 436 (38, M^+), 323 (34), 379 (100), 309 (25), 278 (19), 89 (27); HRMS calculated for $C_{31}H_{36}N_2$ 436.288, found 436.286.

(±)-Di-*n*-pentyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine **6g** (10.2 mg, 8%) as a yellow oil. R_f 0.25 (EtOAc/CH_2Cl_2, 6/4); (neat) ν_{max}/cm^{-1} 2926, 1583, 1497; δ_H ($CDCl_3$, 300 MHz) δ 0.52–0.82 (12H), 0.84–1.12 (6H), 2.48–2.65 (2H), 2.66–2.85 (2H), 6.64 (1H, d, *J*=6.0 Hz), 7.06–7.26 (5H), 7.42–7.65 (3H), 7.85–8.40 (3H), 8.21 (2H, t, *J*=6.6 Hz); δ_C (125 MHz) 13.9 (2×CH_3), 22.2 (2×CH_2), 26.9 (2×CH_2), 28.9 (2×CH_2), 51.4 (2×CH_2), 111.0 (CH), 125.9 (C_q), 126.5 (CH), 126.8 (2×CH), 127.6 (CH), 127.9 (2×CH), 128.1 (2×CH), 128.4 (CH), 129.6 (2×CH), 132.4 (2×C_q), 133.2 (C_q), 134.2 (C_q), 138.9 (C_q), 141.6 (CH), 148.5 (CH), 154.2 (C_q); *m*/*z* (EI^+) (rel intensity) 436 (21, M^+), 323 (34), 379 (100), 309 (19), 323 (7), 231 (7); HRMS calculated for $C_{31}H_{36}N_2$ 436.288, found 436.286.

4.2.19. (−)-(S_a) and (+)-(R_a)-Di-*n*-pentyl-[3-(2-phenyl-naphthalen-1-yl)pyridin-4-yl]amine 6g. CSP-HPLC conditions: Chiralcel OD (0.46 cm×25 cm); hexanes/*i*-PrOH, 86/4; 1 mL min^{-1}; 30 °C; UV detection at 211 nm, reference at 525 nm. Biaryl (−)-(S_a)-6 g, colourless oil. Spectroscopic data as above; retention time 6.1 min; $[\alpha]_D^{25}=-136$ (*c* 0.21, MeCN); CD λ_{max}/nm 320 (−ive). Biaryl (+)-(R_a)-**6g**, colourless oil. Spectroscopic data as above; retention time 9.6 min; $[\alpha]_D^{25}=+138$ (*c* 0.21, MeCN); CD λ_{max}/nm 320 (+ive).

4.2.20. 3,5-Dibromo(pyridine-4-yl)di-*n*-hexylamine 2h. 3,5-Dibromo-4-chloropyridine **1**[30] (3.50 g, 12.90 mmol), di-*n*-hexylamine (4.46 mL, 19.35 mmol) and DMF (12 mL) were heated together in a sealed reaction vessel at 170 °C for 48 h. After cooling the mixture was dissolved in EtOAc then washed with 1 M K_2CO_3 and water. The organic extracts were then dried using $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with petrol/CH_2Cl_2 (4/1) gave dibromide **2h** (3.52 g, 8.39 mmol, 65%) as a pale yellow oil. R_f 0.55 (CH_2Cl_2); ν_{max}/cm^{-1} ($CHCl_3$) 2928, 1567, 1423, 1174; δ_H ($CDCl_3$, 250 MHz) 0.55 (6H, t, *J*=7.0 Hz), 0.93–1.00 (12H), 1.12 (4H, m), 2.93 (4H, t, *J*=7.0 Hz), 8.20 (2H, s); δ_C (63 MHz) 14.0 (2×CH_3), 22.6 (2×CH_2), 26.7 (2×CH_2), 28.6 (2×CH_2), 31.6 (2×CH_2), 52.3 (2×CH_2), 121.8 (2×C_q), 152.1 (2×CH), 154.5 (C_q); *m*/*z* (EI^+) (rel intensity) 418, 420, 422 (1;2:1, 15, M^+), 349 (100); HRMS calculated for $C_{17}H_{28}N_2Br_2^{79}$ 418.062, found 418.061.

4.2.21. [3-(2-Benzyloxynaphthalen-1-yl)pyridine-4-yl]di-*n*-hexylamine 3h. To a solution of dibromide **2h** (500 mg, 1.19 mmol) in toluene (12 mL) and ethanol (750 μL) was added 2 M KOH (3 mL) followed by $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and 2-benzyloxy-1-naphthaleneboronic acid[30] (397 mg, 1.43 mmol). The mixture was heated at 100 °C for 20 h with vigorous stirring, then cooled to RT and diluted with water (25 mL). The phases were separated and the aqueous layer extracted further with CH_2Cl_2. The organic extracts were dried using $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with CH_2Cl_2→MeOH/EtOAc (1/9) gave benzyl ether **3h** (152 mg, 0.31 mmol, 26%) as a brown oil. R_f 0.59 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3052, 2975, 1587, 1472; δ_H ($CDCl_3$, 250 MHz) 0.52–1.30 (22H), 2.87 (4H, m), 5.15 (2H, s), 6.75 (1H, d, *J*=6.0 Hz), 7.21–7.47 (9H), 7.76–7.82 (1H), 7.86 (1H, s), 8.07 (1H, s), 8.31 (1H, d, *J*=6.0 Hz); δ_C (63 MHz) 14.1 (2×CH_3), 22.6 (2×CH_2), 26.5 (2×CH_2), 27.4 (2×CH_2), 31.5 (2×CH_2), 51.7 (2×CH_2), 70.8 (CH_2), 110.6 (CH), 114.9 (CH), 119.7 (C_q), 123.40 (C_q), 123.9 (CH), 125.5 (CH), 126.5 (CH), 126.8 (2×CH), 127.6 (CH), 128.0 (CH), 128.4 (2×CH), 129.2 (C_q), 129.5 (CH), 133.3 (C_q), 137.2 (C_q), 148.6 (CH), 153.1 (C_q), 153.6 (CH), 155.3 (C_q); *m*/*z* (EI^+) (rel intensity) 494 (25, M^+), 423 (100); HRMS calculated for $C_{34}H_{42}N_2O$ 494.330, found 494.330.

4.2.22. 1-(4-Di-*n*-hexylaminopyridin-3-yl)naphthalen-2-ol 4h. To a solution of benzyl ether **3h** (152 mg, 0.31 mmol) in ethanol (10 mL) was added 10% Pd/C (50 mg). The resulting mixture was stirred under H_2 at atmospheric pressure and RT for 20 h. The mixture was then passed through a pad of Celite® and concentrated in vacuo to give naphthol **157** (120 mg, 0.30 mmol, 97%) as a yellow oil. R_f 0.20 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3037, 2968, 1572, 1371; δ_H ($CDCl_3$, 250 MHz) 0.72–1.36 (22H), 3.00 (4H, m), 6.76 (1H, d, *J*=6.7 Hz), 7.18–7.33 (3H), 7.48 (1H, d, *J*=9.2 Hz), 7.66 (2H, d, *J*=8.7 Hz), 7.76 (1H, s), 8.07 (1H, d, *J*=6.7 Hz), (OH absent); δ_C (63 MHz) 13.9 (2×CH_3), 22.5 (2×CH_2), 26.3 (2×CH_2), 27.0 (2×CH_2), 31.3 (2×CH_2), 51.2 (2×CH_2), 110.0 (CH), 114.6 (C_q), 118.9 (CH), 119.0 (C_q), 123.1 (CH), 123.8 (CH), 126.8 (CH), 128.5 (CH), 128.6 (C_q), 130.3 (CH), 133.0 (C_q), 141.8 (CH), 147.7 (CH), 152.8 (C_q), 156.4 (C_q); *m*/*z* (EI^+) (rel intensity) 404 (25, M^+), 334 (25), 333 (100); HRMS calculated for $C_{27}H_{36}N_2O$ 404.283, found 404.283.

4.2.23. Trifluoromethanesulfonic acid-1-(4-di-*n*-hexyl-aminopyridin-3-yl)napthalen-2-yl ester 5h. To a solution

of naphthol **4h** (120 mg, 0.30 mmol) in pyridine (5 mL) at 0 °C was slowly added triflic anhydride (60 μL, 0.36 mmol). The resulting mixture was stirred at 0 °C for 4 h and then concentrated in vacuo. The residue was then partitioned between CH_2Cl_2 and water, the organic extracts were then dried using $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with CH_2Cl_2/EtOAc (6/4) gave triflate **5h** (122 mg, 0.23 mmol, 77%) as an orange oil. R_f 0.76 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3056, 2979, 1592, 1413; δ_H ($CDCl_3$, 250 MHz) 0.74–1.32 (22H), 2.69–2.93 (4H), 6.82 (1H, d, J=6.0 Hz), 7.45–7.61 (3H), 7.79 (1H, d, J=8.0 Hz), 7.94 (2H, t, J=8.0 Hz), 8.13 (1H, s), 8.37 (1H, d, J=6.0 Hz); δ_C (63 MHz) 13.9 (2×CH_3), 22.5 (2×CH_2), 26.4 (2×CH_2), 27.2 (2×CH_2), 31.3 (2×CH_2), 51.7 (2×CH_2), 111.6 (CH), 117.0 (C_q), 118.5 (CF_3, t, J= 309 Hz), 119.5 (CH),126.6 (CH), 127.2 (CH), 127.8 (CH), 128.3 (CH), 129.6 (C_q), 130.3 (CH), 132.8 (C_q), 132.9 (C_q), 144.9 (C_q), 149.9 (CH), 153.4 (CH), 155.7 (C_q); m/z (EI^+) (rel intensity) 536 (25, M^+), 465 (90), 315 (100); HRMS calculated for $C_{28}H_{35}N_2O_3F_3S$ 536.232, found 536.230.

4.2.24. (±)-Di-*n*-hexyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine 6h. To a solution of triflate **5h** (60 mg, 0.11 mmol) in Et_2O (2 mL) was added $PdCl_2$(dppp) (4 mg, 0.01 mmol) followed by a solution of PhMgBr in hexanes (1.65 M, 170 μL, 0.28 mmol).The resulting mixture was heated at 40 °C for 20 h, then cooled to RT, diluted with water and extracted with CH_2Cl_2. The organic extracts were then dried using $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography eluting with CH_2Cl_2→ EtOAc gave (±)-biaryl **6h** (36 mg, 0.08 mmol, 69%) as a yellow oil. R_f 0.50 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3051, 2974, 1576, 1492; δ_H ($CDCl_3$, 250 MHz) 0.59–1.24 (22H), 2.47–2.59 (2H), 2.67–2.85 (2H), 6.44 (1H, d, J=6.0 Hz), 7.01–7.18 (5H), 7.41–7.55 (3H), 7.81–7.95 (3H), 8.15 (1H, s), 8.18 (1H, d, J=6.0 Hz); δ_C (100 MHz) 14.4 (2×CH_3), 22.9 (2×CH_2), 26.8 (2×CH_2), 27.5 (2×CH_2), 31.7 (2×CH_2), 51.9 (2×CH_2), 111.3 (CH), 122.0 (C_q), 126.4 (CH), 126.9 (CH), 127.0 (CH), 127.1 (CH), 128.0 (2×CH), 128.7 (CH), 128.7 (CH), 128.8 (CH), 130.0 (2×CH), 132.7 (C_q), 133.6 (C_q), 134.4 (C_q), 139.4 (C_q), 141.9 (C_q), 148.3 (CH), 153.9 (CH), 155.2 (C_q); m/z (EI^+) (rel intensity) 465 (100, MH^+), 393 (30); HRMS calculated for $C_{33}H_{41}N_2$ 465.327, found 465.328.

4.2.25. (−)-(S_a) and (+)-(R_a)-Di-*n*-hexyl-[3-(2-phenylnaphthalen-1-yl)pyridin-4-yl]amine 6h. CSP-HPLC conditions: Chiralcel OD (1 cm×25 cm); hexanes/EtOAc/Et_2NH, 90/9.6/0.4; 4 mL min^{-1}; 30 °C; UV detection at 270 nm, reference at 360 nm. Biaryl (−)-(S_a)-6 h, colourless oil. Spectroscopic data as above; retention time 10.2 min; $[\alpha]_D^{25}$=−60 (c 0.61, CH_2Cl_2). Biaryl (+)-(R_a)-**6h**, colourless oil. Spectroscopic data as above; retention time 20.1 min; $[\alpha]_D^{25}$=+61 (c 0.60, CH_2Cl_2).

4.3. General procedure for catalytic acylative kinetic resolution (Tables 1 and 2, Schemes 2 and 3)

A solution of (±)-alcohol (1.00 mmol), Et_3N (104 μL, 0.75 mmol) and biaryl (−)-(S_a)-**6** (0.01 mmol, >99.9% ee) in toluene (2 mL) was cooled to −78 °C. (i-PrCO)$_2$O (2.00 mmol, 331 μL) was then added dropwise with vigorous stirring. After 9 h at −78 °C the reaction was quenched by the dropwise addition of MeOH (3 mL), the reaction mixture was allowed to warm to RT over 15 min, and the solvents were evaporated in vacuo. The alcohol and its *iso*-butyric ester were separated by flash chromatography (petrol/CH_2Cl_2 (2/1)→CH_2Cl_2). The ester was hydrolysed by heating at reflux in a solution of 5% NaOH/MeOH (2 mL) for 5 min. After removal of the solvent the residue was passed through a small plug of flash silica eluting with EtOAc. The enantiomeric excesses for the unreacted alcohol and alcohol obtained from hydrolysis of the ester were established by CSP HPLC.

4.4. CSP-HPLC analysis of chiral alcohols (Tables 1 and 2, Schemes 2 and 3)

4.4.1. 1-(1-Naphthyl)ethanol 11. Chiralcel OD (0.46 cm×25 cm); hexanes/i-PrOH, 90/10; 1 mL min^{-1}; 30 °C; UV detection at 220 nm, reference at 525 nm. Retention times: 9.5 min (S), 14.2 min (R).[55]

4.4.2. 1-*o*-Tolyl-ethanol 12. Chiralcel OD (1 cm×25 cm); hexanes/i-PrOH, 99/1; 3 mL min^{-1}; 30 °C; UV detection at 220 nm, reference at 360 nm. Retention times: 6.1 min (S), 26.4 min (R).[56]

4.4.3. 1-(2,6-Dimethyl-phenyl)-ethanol 13. Chiralcel OD (1 cm×25 cm); hexanes/i-PrOH, 93/7; 3 mL min^{-1}; 30 °C; UV detection at 210 nm, reference at 360 nm. Retention times: 8.6 min (R), 10.3 min (S).[55]

4.4.4. 2,2-Dimethyl-1-phenyl-propan-1-ol 14. Chiralcel OD (1 cm×25 cm); hexanes/i-PrOH, 93/7; 3 mL min^{-1}; 30 °C; UV detection at 210 nm, reference at 380 nm. Retention times: 6.3 min (S), 8.3 min (R).[55]

4.4.5. 3-Chloro-1-phenyl-propan-1-ol 15. Chiralcel OD (0.46 cm×25 cm); hexanes/i-PrOH, 92/8; 1 mL min^{-1}; 30 °C; UV detection at 220 nm, reference at 525 nm. Retention times: 7.9 min (S), 8.9 min (R).[52]

4.4.6. Indan-1-ol 16. Chiralcel OD (0.46 cm×25 cm); hexanes/i-PrOH, 98/2; 1 mL min^{-1}; 30 °C; UV detection at 220 nm, reference at 525 nm. Retention times: 18.6 min (S), 21.9 min (R).[57]

Acknowledgements

Grateful acknowledgement is made to the BBSRC (studentship to D.P.L.), GlaxoSmithKline, the University of Sheffield and Imperial College London for financial support of this work. We thank Professor Christopher S. Frampton (Southampton University) for performing the X-ray structure determination of pyridine **9c**.

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Tetrahedron 60 (2004) 4527–4541
Tetrahedron

Asymmetric synthesis of axially chiral benzamides and anilides utilizing planar chiral arene chromium complexes

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Received 17 October 2003; revised 10 December 2003; accepted 5 January 2004

Abstract—Optically active axially chiral 2,6-disubstituted benzamides and anilides were stereoselectively prepared by utilizing planar chiral (arene)chromium complexes. Nucleophilic addition to enantiomerically pure planar chiral tricarbonyl(*N*,*N*-diethyl-2-methyl-6-formyl- (or 6-acyl)benzamide)chromium complex gave axially chiral 2-methyl-6-substituted *N*,*N*-diethyl benzamide chromium complexes with high selectivity. An alternative method for the preparation of axial chiral benzamides or anilides is an enantiotopic lithiation at the benzylic methyl of prochiral tricarbonylchromium complexes of *N*,*N*-diethyl-2,6-dimethylbenzamide and *N*-methyl-*N*-acyl-2,6-dimethylaniline with a chiral lithium amide followed by electrophilic substitution. The resulting axially chiral chromium-complexed benzamides and anilides were oxidized in air to give chromium-free axially chiral benzamides and anilides in enantiomerically enriched form without axial bond rotation at room temperature.

1. Introduction

Axially chiral non-biaryl and biaryl compounds are attractive molecules. *N*,*N*-Dialkyl aromatic carboxamides[1] or *N*-alkyl anilide[2] derivatives possessing a sterically bulky *ortho* substituent exist as atropisomers due to the high rotational barrier about the C(aryl)–C(carbonyl) or C(aryl)–N bond. Chromatographic separation of racemates to optically active aromatic carboxamides and anilides has been achieved using HPLC on a chiral stationary phase.[3] Some axially chiral benzamides and anilides could be employed as a chiral ligand or auxiliary in asymmetric reactions, e.g. cycloaddition, alkylation, radical-mediated cyclization, and catalytic allylic alkylation.[1,2,4] Therefore, enantiopure axially chiral benzamides or anilides are significant for asymmetric reactions and possibly biological activity. There are relatively few reports on the asymmetric synthesis of axially chiral benzamides and anilides. An asymmetric deprotonation of *N*,*N*-dialkyl 1-naphthamides with a combination of butyl lithium/(−)-sparteine was reported for preparation of axially chiral *N*,*N*-dialkyl 2-alkyl-1-naphthamides.[5] However, the optical purity of the axial aromatic carboxamides obtained by this asymmetric deprotonation was moderate. Simpkins et al. attempted to prepare an optically enriched anilide by a kinetic resolution of racemic *N*-propionyl-*o*-*tert*-butylanilide by treatment with a chiral lithium amide. However, the yield of the optically enriched chiral anilide was low.[6] In addition, the absolute configuration of the axial anilide could not be determined. Axially chiral anilides with highly enantiomeric purity have been prepared by separation of diastereomers derived from (*S*)-*O*-acetyl lactic acid, and these anilides were used in asymmetric reactions.[7] Axially chiral cyclic *N*-*o*-*tert*-butylphenyl pyrrolidinone[8a,b] or atropisomeric quinazolinone derivatives having a diphenylphosphino group[8c,d] were obtained by using chiral auxiliary or optical resolution with a chiral palladium(II) reagent, respectively. Recently, Clayden et al. reported that axially chiral 2-substituted naphthamides were obtained with highly optical purity by reaction with proline-derived aniline through a dynamic resolution.[9] Consequently, a new synthetic strategy for enantiopure axially chiral non-biaryl compounds is still required. As part of our asymmetric synthetic exploration of planar chiral (arene)chromium complexes, we report herein the asymmetric synthesis of axially chiral *N*,*N*-diethyl 2,6-disubstituted benzamides and *N*-methyl-*N*-acyl 2,6-disubstituted anilides.[10]

Keywords: Amides; Anilides; Asymmetric reactions; Atropisomerism; Chromium and compounds.
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doi:10.1016/j.tet.2004.01.096

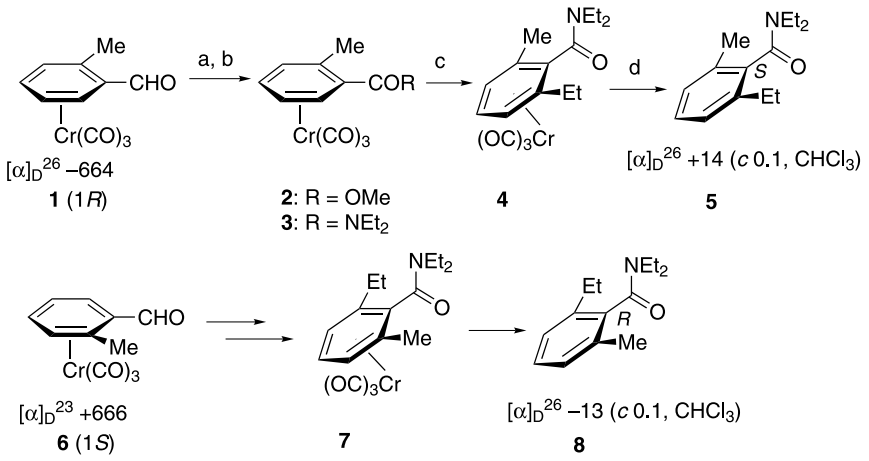
2. Results and discussion

2.1. Asymmetric synthesis of axially chiral benzamide chromium complexes

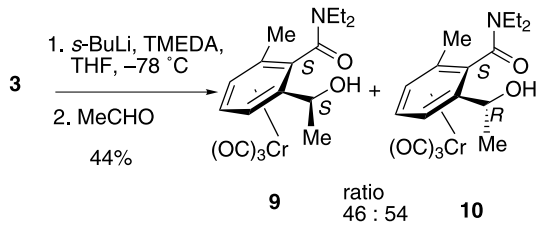
(η^6-Arene)chromium complexes exist in two enantiomeric forms due to planar chirality, when the arene ring is substituted at *ortho*- or *meta*-positions with different substituents. This fact, coupled with steric effect of the tricarbonylchromium function to effectively block one face of the arene ring, has led to a rapid increase in the use of (arene)chromium complexes as synthetic intermediates and as catalysts for the asymmetric reactions.[11] Herein, we report[12] the synthesis of axially chiral benzamides starting from resolved[13] (2-methyl benzaldehyde)$Cr(CO)_3$. (−)-(1*R*)-(2-Methyl benzaldehyde)$Cr(CO)_3$ (**1**) was oxidized with active MnO_2 and NaCN in MeOH and AcOH to give the corresponding methyl ester **2** ($[\alpha]_D^{26}$ −100.0) in 85% yield. Methyl ester chromium complex **2** was converted to enantiopure (*N*,*N*-diethyl-2-methylbenzamide)$Cr(CO)_3$ (**3**) ($[\alpha]_D^{25}$=+8.0 (*c* 0.4, $CHCl_3$)) by treatment with lithium diethylamide. *Ortho* lithiation of **3** with *t*-BuLi followed by quenching with ethyl iodide afforded axially chiral (R_p,S_{ax})-tricarbonyl(*N*,*N*-diethyl 2-ethyl-6-methylbenzamide)chromium (**4**) ($[\alpha]_D^{25}$=−33.0) in 36% yield along with 15% yield of tricarbonyl(*N*,*N*-diethyl 2-propylbenzamide)chromium via lithiation at the benzylic position. The formation of (*S*)-axial benzamide **4** as a single diastereomer may be attributed to a stereoelectronic effect between the tricarbonylchromium and the diethylamine fragment. The corresponding (*R*)-axial isomer was not observed in this directed *ortho* lithiation. *N*,*N*-Diethyl 2-ethyl-6-methylbenzamide complex (**4**) was found to be >99% ee by HPLC with Chiralcel OD-H. The (*S*)-axial stereochemistry of **4** was determined by X-ray crystallography,[14] in which the diethylamino group oriented an *anti*-conformation to the tricarbonylchromium fragment, and the amide carbonyl oxygen a *syn*-orientation. Oxidative demetallation of the axially chiral benzamide chromium complex (−)-**4** by exposure to sunlight in ether at 0 °C gave chromium-free *N*,*N*-diethyl 2-ethyl-6-methylbenzamide (**5**) ($[\alpha]_D^{26}$=+14.0) with (*S*)-axial chirality. Similarly, the axially chiral antipode (*R*)-(−)-*N*,*N*-diethyl 6-ethyl-2-methylbenzamide (**8**) was obtained from antipode (+)-(1*S*)-tricarbonyl(2-methyl benzaldehyde)chromium (**6**) by the same reaction sequence (Scheme 1).

The ee of freshly obtained chromium-free axially chiral *N*,*N*-diethyl-2-ethyl-6-methylbenzamides **5** and **8** was determined as ~94% ee by ^1H NMR spectroscopy in the presence of chiral shift reagent, $Eu(tfc)_3$. However, the ee of these chromium-free axial benzamides decreased slowly on standing at room temperature. Thus, the enantiomeric excess of axially chiral benzamide **5** decreased to 86% ee after 6 h at room temperature and to 70% ee after 24 h. Since *N*,*N*-diethyl-2-ethyl-6-methylbenzamide undergoes racemization at room temperature, sterically bulky *ortho* substituents should be introduced for an inhibitation of the axial isomerization. The *ortho*-lithiated intermediate generated from **3** was treated with MeCHO to give 1:1 diastereomeric mixture of secondary benzyl alcohol chromium complexes **9** and **10** (Scheme 2). Both chromium complexes have (*S*)-axial chirality. However, the diastereoselectivity was low, and we next studied nucleophilic addition of *ortho* formyl or alkyl ketone group of (*N*,*N*-diethyl-2-methyl-6-formyl (or acyl)benzamide)$Cr(CO)_3$ for transformation to sterically bulky substituents.

Reaction of methylmagnesium bromide with *o*-formyl chromium complex **11** ($[\alpha]_D^{26}$=−454.0 (*c* 0.1, $CHCl_3$)) in THF at −78 °C gave easily separable diastereomeric mixture **14** and **15** in a ratio of 98:2 (Table 1, entry 1).[15] The stereochemistry of the major product **14** (R=Me) ($[\alpha]_D^{26}$=−30.5 (*c* 0.2, $CHCl_3$)) was assigned as (S_p,S_{ax},*R*)-configuration by X-ray crystallography (Fig. 1).[16] On the other hand, reaction with MeLi gave the diastereomeric complex **15** (R=Me; $[\alpha]_D^{27}$=−49.0 (*c* 0.5, $CHCl_3$)) with the (*S*)-benzylic alcohol as the major product (entry 2). Reaction with $MeCeCl_2$ resulted in a moderate predominance of **14**. Similarly, ethyl lithium afforded the corresponding complex **15** as a major product, while EtMgBr gave a reduced compound, tricarbonyl(*N*,*N*-diethyl 2-methyl-6-hydroxymethylbenzamide)chromium, without formation of any addition products. Reduction of the alkyl ketone of (*N*,*N*-diethyl-2-methyl-6-acylbenzamide)$Cr(CO)_3$ complexes **12** and **13** with $NaBH_4$ gave predominantly (*R*)-configured



Scheme 1. Synthesis of axially chiral *N*,*N*-diethyl 2-ethyl-6-methylbenzamide. Reagents and conditions: (a) MnO_2, NaCN, AcOH, MeOH, 85%; (b) $LiNEt_2$, THF, −78 °C, 80%; (c) *t*-BuLi, TMEDA, THF, −78 °C, then Etl, 36%; (d) *hν*, air, ether, 0 °C, 90%.



Scheme 2.

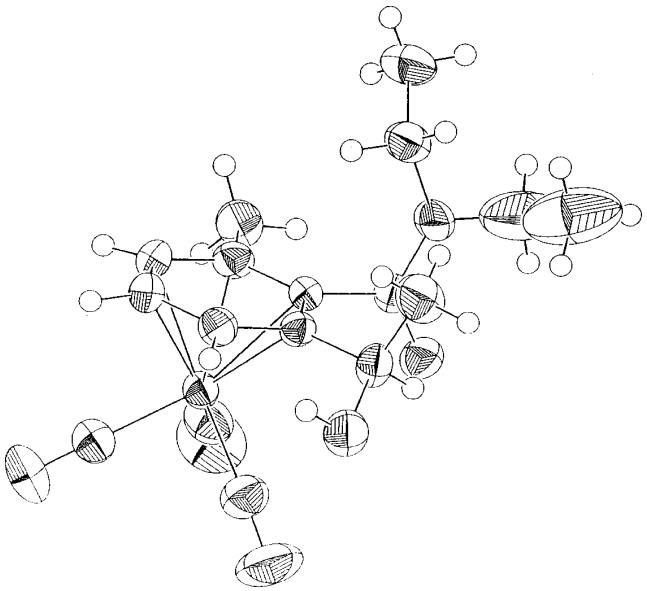


Figure 1. Crystal Structure of **14** (R=Me).

secondary benzyl alcohol chromium complexes **14** with high diastereoselectivity (entries 8, 11). However, reduction with diisobutylaluminium hydride afforded diastereomeric (*S*)-benzyl alcohol chromium complexes **15** (entries 10, 13).

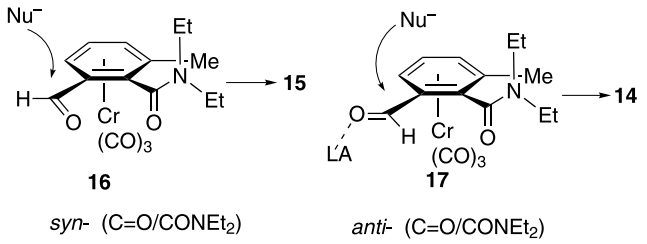
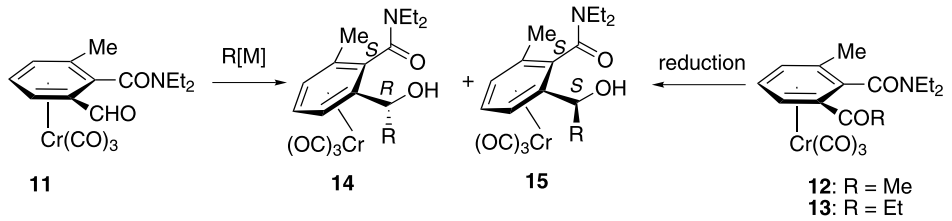


Figure 2. Proposed transition state.

The corresponding (*R*)-axially chiral benzamide chromium complexes with secondary benzyl alcohols were prepared starting from the enantiomeric (+)-(1*S*)-tricarbonyl(*o*-methylbenzaldehyde)chromium complex under same reaction sequence.

The observed diastereoselectivity at the benzylic position in the nucleophilic additions to the arene chromium complexes could be explained as follows (Fig. 2). It is well known that diastereoselectivity in nucleophilic addition to *o*-substituted benzaldehyde chromium complexes depends on the carbonyl oxygen conformation.[11] With *o*-alkoxy- and *o*-methylbenzaldehyde chromium complexes, the carbonyl oxygen exhibits predominantly an *anti*-conformation to the *ortho* substituents, in which nucleophiles attack from an opposite face of the $Cr(CO)_3$ fragment giving a single diastereomer.[11] However, the *o*-formyl complex **11** was found to be *syn*-conformer **16** by X-ray crystallography (Fig. 3),[17] in which the plane of H–C=O is nearly coplanar and N–C=O plane is perpendicular to the arene ring, respectively. Consequently, (*S*)-benzyl alcohol chromium complex **15** was predominantly obtained by reaction with alkyllithiums. In the reaction with Grignard reagent, the *syn*-conformer **16** lies to the *anti*-conformer **17** via a coordination of the carbonyl oxygen with the Grignard reagent giving (*R*)-benzyl alcohol chromium complex **14**.[18] To confirm this mechanism, $MgBr_2{\cdot}OEt_2$ was added to the reaction mixture

Table 1. Addition of nucleophiles to planar chiral benzamide chromium complexes



Entry	Complex	Nucleophile (RM or H^-)	Yield (%)	Ratio of **14**:**15**
1	**11**	MeMgBr	83	98:2
2	**11**	MeLi	70	29:71
3	**11**	MeLi, $MgBr_2{\cdot}OEt_2$	76	55:45
4	**11**	$MeCeCl_2$	78	61:39
5	**11**	EtMgBr	0	—
6	**11**	EtLi	65	25:75
7	**11**	$EtCeCl_2$	75	48:52
8	**12**	$NaBH_4$	96	96:4
9	**12**	$LiAlH_4$	99	90:10
10	**12**	DIBAL-H	91	9:91
11	**13**	$NaBH_4$	98	93:7
12	**13**	$LiAlH_4$	98	91:9
13	**13**	DIBAL-H	88	10:90

Reactions were performed at −78 °C in THF. A reduced product, tricarbonyl(*N*,*N*-diethyl-2-methyl-6-hydroxymethylbenzamide)chromium was obtained in 57% yield. Reduction with $NaBH_4$ was performed at 0 °C in MeOH.

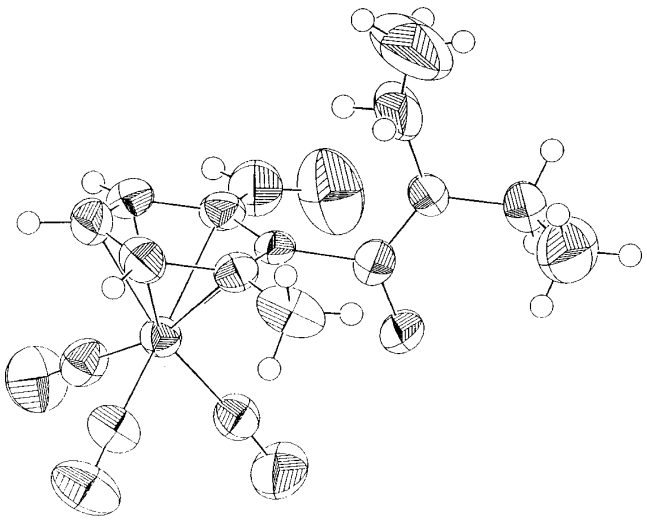


Figure 3. Crystal structure of **11**.

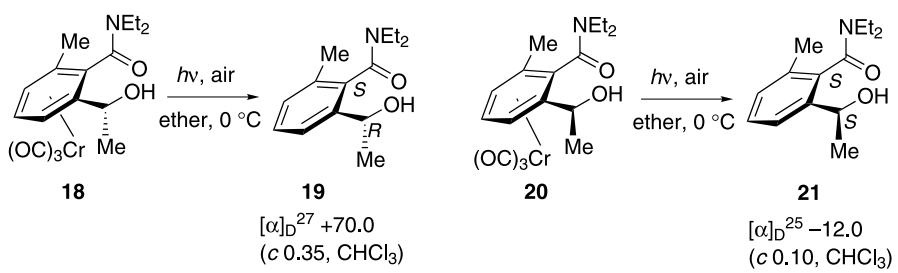
of **11** and MeLi (entry 3). The diastereoselectivity of nucleophilic addition decreased, thus supporting our hypothesis. The transition state for hydride reduction of the acyl chromium complexes **12** and **13** would be analogous. $NaBH_4$ and $LiAlH_4$ attack the *syn*-oriented carbonyl, while diisobutylaluminium hydride approaches the *anti*-carbonyl. In this manner, the nucleophiles attack from the *exo*-side of the $Cr(CO)_3$ fragment to the carbonyl in a preferable conformer depending on the nature of reagents, while diastereoselectivity in the nucleophilic addition to chromium-free benzamides was induced by the stereogenic axis of rotationally restricted carboxamides.[19]

Oxidative demetallation of (−)-**18** by exposure to sunlight in ether at 0 °C gave the chromium-free (S_{ax},*R*)-*N*,*N*-diethyl-2-methyl-6-(hydroxyethyl)benzamide (**19**) ($[\alpha]_D^{27}$=+70.0) with >99% ee in a quantitative yield, and the diastereomeric benzamide chromium complex (−)-**20** afforded enantiomerically pure (S_{ax},*S*)-benzamide **21** ($[\alpha]_D^{25}$=−12.0) (Scheme 3). These chromium-free axially chiral benzamides were stable to axial bond rotation at room temperature for 24 h. Thus, axially chiral benzamides with stereogenic center at the benzylic position have been prepared in optically active form by diastereoselective nucleophilic addition to planar chiral (arene)chromium complexes. However, this procedure for the preparation of axially chiral benzamides involves resolution of racemic *o*-methylbenzaldehyde chromium complex as starting material, and we next studied the asymmetric synthesis of axially chiral non-biaryls by enantiotopic lithiation of prochiral arene chromium complexes.

Since introduction of sterically bulky *ortho* substituents to planar chiral *N*,*N*-dialkyl 2-substituted benzamide chromium complexes could induce the axial chirality as mentioned above, we next focused on enantiotopic deprotonation of prochiral arene chromium complexes. Enantiotopic *ortho* lithiation of *N*,*N*-dialkyl benzamide chromium complex with chiral lithium amide bases[20] is a promising method for synthesis of planar chiral 2-substituted *N*,*N*-dialkyl benzamide chromium complexes. Simpkins et al. reported[21] that treatment of (*N*,*N*-diisopropyl benzamide)$Cr(CO)_3$ with lithium (*R*,*R*)-bis-α-phenylethylamide in the presence of Me_3SiCl gave (−)-(*o*-trimethylsilyl benzamide)$Cr(CO)_3$ in 87% yield. However, the enantiomeric excess was unfortunately moderate (48% ee). Therefore, we next turned our attention to a discriminating lithiation between two enantiotopic benzyl methyls of prochiral tricarbonyl(*N*,*N*-diethyl 2,6-dimethylbenzamide)chromium (**22**).[22] The reaction results are summarized in Table 2.

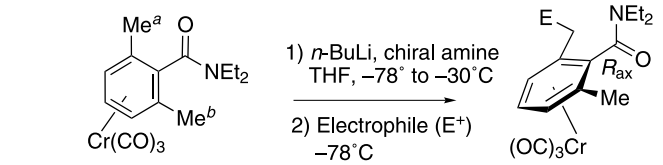
Among the various chiral monoamines or diamines examined,[23] chiral versions of LDA gave a reasonable result with respect to enantioselectivity, while *N*,*N*,*N*′,*N*-tetraalkyl diamines led to unsatisfactory results. Particularly, a chiral lithium amide derived from bis-(*R*,*R*)-α-phenylethylamine (**24**) resulted in high ee. Thus, the lithiation of prochiral benzamide chromium complex **22** with the chiral lithium amide of **24** followed by quenching with methyl iodide gave (+)-tricarbonyl(*N*,*N*-diethyl-2-ethyl-6-methylbenzamide)chromium (**23**) (E=Me) with 86% ee in 85% yield (entry 1). The effects of other solvents and the presence of an additive, e.g. LiCl, were not observed to enhance the enantiomeric excess. The axial configuration of **23** (E=Me) was assigned as (*R*)-configuration by comparison with the optical rotation of an authentic compound.[12] With other electrophiles, e.g., benzyl bromide or allyl bromide, the corresponding (*R*)-axial benzamide chromium complexes were obtained with comparable ee (entries 10 and 11). In this way, the enantiotopic deprotonation at the benzylic methyl of prochiral *N*,*N*-diethyl-2,6-dimethylbenzamide chromium complex (**22**) afforded the axially chiral benzamides with high ee.

We further investigated enantiotopic lithiation of prochiral 2,6-diethyl benzamide chromium complex **35**. Treatment of **35** with the lithium amide of **24** followed by quenching with electrophile gave axially chiral benzamide chromium complexes **36** (Scheme 4). Although the reaction products **36** were obtained as a single diastereomer, the chemical yield was low. Furthermore, the ee of **36** was moderate.[24] The absolute stereochemistry at the newly created benzylic position was not determined.

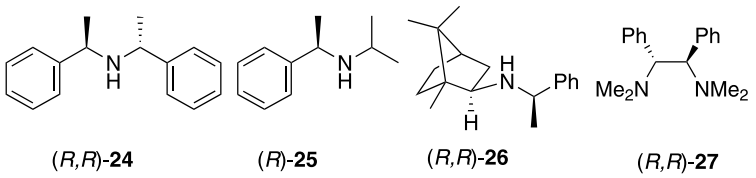


Scheme 3. Photo-oxidative demetallation.

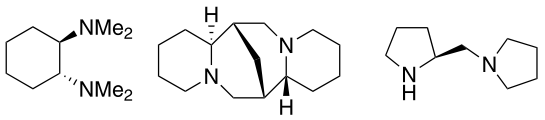
Table 2. Enantiotopic lithiation of prochiral benzamide chromium complex



22 **23**



(*R*,*R*)-**24** (*R*)-**25** (*R*,*R*)-**26** (*R*,*R*)-**27**

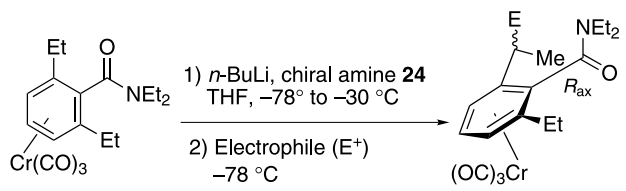


(*R*,*R*)-**28** **29** (–)-sparteine (*S*)-**30**

Entry	Chiral amine	Electrophile (E^+)	Yield (%)	% ee of **23**
1	**24**	MeI	85	86
2	**25**	MeI	82	51
3	**26**	MeI	15	21
4	**27**	MeI	43	3
5	**28**	MeI	40	5
6	**29**	MeI	40	17
7	**30**	MeI	18	27
8	**32**	MeI	41	6
9	**33**	MeI	10	44
10	**24**	$PhCh_2Br$	41	83
11	**24**	$CH_2{=}CHCH_2Br$	52	83

2.2. Asymmetric synthesis of axially chiral anilide chromium complexes

We further developed kinetically discriminated lithiation for asymmetric synthesis of axially chiral *N*-methyl 2,6-disubstituted anilides.[10,22b] By analogy with enantiotopic lithiation of prochiral benzamide chromium complex **22**, the chiral versions of LDA could discriminate the enantiotopic benzyl methyls of *N*-methyl *N*-pivaloyl 2,6-dimethylaniline chromium complex (**37**). However, the chiral lithium amides of monoamines resulted in moderate ee (Table 3, entries 1–3). Therefore, bidentate chiral lithium amides, which could exist as five-membered chelated structure, were next used in enantioselective lithiation. The chiral lithium amide derived from (*S*)-2-(1-pyrrolidinylmethyl)pyrrolidine



35 **36**

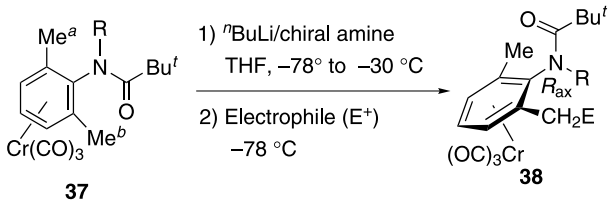
E^+ ; $CH_2{=}CHCH_2Br$ (19%), 74% ee
$PhCH_2Br$ (13%), 66% ee

Scheme 4.

(**30**) resulted in an increase of ee, although the chemical yield was moderate (entry 7). 1-Phenyl-2-piperidinoethylamine derivatives **31** and **32** resulted in higher yields (entries 8 and 9). Fortunately, 4-methylpiperazinylethylamine derivative **34** with an additional nitrogen atom increased both enantioselectivity and chemical yield. Thus, treatment of prochiral anilide chromium complex **37** with the chiral lithium amide prepared from amine **34** in THF at −78 °C followed by quenching with MeI gave axially chiral anilide complex **38a** (E=Me) in 90% yield with 95% ee (entry 10). The absolute stereochemistry of (−)-**38a** (E=Me) was determined to be (S_p,R_{ax})-configuration by X-ray crystallography (Scheme 4).[25] The pivaloyl group is *exo* to the $Cr(CO)_3$ fragment and the *N*-methyl is *trans* to the amido oxygen. Other electrophiles such as allyl-, benzyl bromides or carbonyl compounds gave the corresponding (*R*)-axially chiral anilide chromium complexes **38** via lithiation at the Me^b group between two benzyl methyls with high selectivity (entries 13–19). Interestingly, the lithiated position of prochiral anilide **37** is different to that of benzamide chromium complexes **22** with an identical chiral lithium amide. Thus, the chiral lithium amides derived from (*R*,*R*)-**24**, (*R*)-**25** or (*S*)-**30** took place deprotonation at Me^b of prochiral anilide complex **37**, while prochiral benzamide chromium complex **22** was lithiated at Me^a position with the same lithium amide (Fig. 4).

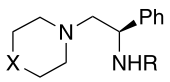
The highly enantiotopic deprotonation at different benzyl

Table 3. Enantiotopic lithiation of prochiral anilide chromium complex



37 **38**

a: R = Me, **b:** R = Et, **c:** R = CH_2OMe



(*R*)-**31**; X=CH_2, R=$CHMe_2$
(*R*)-**32**; X=CH_2, R=CH_2Bu^t
(*R*)-**33;** X=CH_2, R=$CH_2OCH_2CH_2OMe$
(*R*)-**34**; X=NMe, R=CH_2Bu^t

Entry	Complex	Chiral amine	Electrophile (E^+)	Yield (%)	% ee **38**
1	**37a**	**24**	MeI	50	44
2	**37a**	**25**	MeI	51	72
3	**37a**	**26**	MeI	86	42
4	**37a**	**27**	MeI	35	0
5	**37a**	**28**	MeI	24	0
6	**37a**	**29**	MeI	50	0
7	**37a**	**30**	MeI	44	78
8	**37a**	**31**	MeI	60	65
9	**37a**	**32**	MeI	80	79
10	**37a**	**34**	MeI	90	95
11	**37a**	**32**	$C_6H_5CH_2Br$	78	80
12	**37a**	**33**	$C_6H_5CH_2Br$	48	89
13	**37a**	**34**	$C_6H_5CH_2Br$	90	97
14	**37a**	**34**	$CH_2{=}CHCH_2Br$	81	92
15	**37a**	**34**	$MeC{\equiv}CCH_2Br$	86	96
16	**37a**	**34**	$PhC{\equiv}CCH_2Br$	84	96
17	**37a**	**34**	Benzophenone	73	96
18	**37a**	**34**	Cyclohexanone	58	96
19	**37a**	**34**	PhCOCl	31	97
20	**37b**	**34**	MeI	83	98
21	**37b**	**34**	$C_6H_5CH_2Br$	71	99
22	**37c**	**34**	MeI	73	96
23	**37c**	**34**	$C_6H_5CH_2Br$	78	94

methyl groups of prochiral benzamide and anilide chromium complexes with the same chiral lithium amide could be contributed to the conformation of the C(=O)–NR to the tricarbonylchromium fragment. In the anilide chromium complex **37**, the pivaloyl group is oriented *anti* to the tricarbonylchromium fragment due to a steric effect, and the amido carbonyl oxygen is *trans* to *N*-Me. Predominant existence of the *trans* rotamer between *N*-methyl and amido carbonyl oxygen of **37a** was also observed by ^{1}H NMR spectra.[26] The predominant *trans* rotamer of chromium-complexed anilide is in sharp contrast to chromim-free *N*-methyl anilides.[27] On the other hand, the amido carbonyl oxygen of *N*,*N*-diethyl-2,6-dimetyl benzamido chromium complex (**22**) was found to be *syn* to the tricarbonylchromium fragment. Lithiation would be initiated by a coordination of the lithium with the amido carbonyl, and consequently, different benzylic positions would be lithiated.

We further investigated the enantiotopic lithiation at the benzyl position of prochiral 2,6-diethyl anilide chromium complex **39**. Although prochiral 2,6-diethyl benzamide chromium complex **35** resulted in low yields by enantiotopic lithiation with chiral lithium amides (Scheme 4), the corresponding anilide complex **39** gave the reaction products in good yields (Scheme 5). Thus, treatment of **39** with chiral lithium amide of **34** followed by quenching with alkyl halide gave axially chiral anilide complexes **40** as a single diastereomer. The newly created benzylic stereocenter **40** (R=CH_2Ph) was determined as (*R*)-configuration by X-ray crystallography (Fig. 5).[28] We further examined

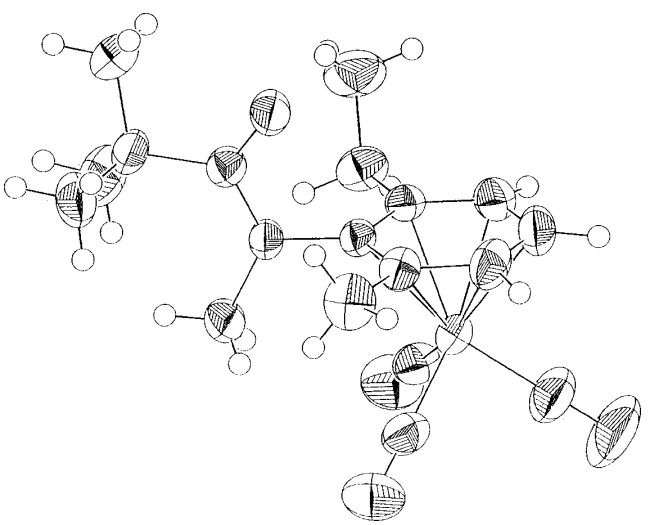
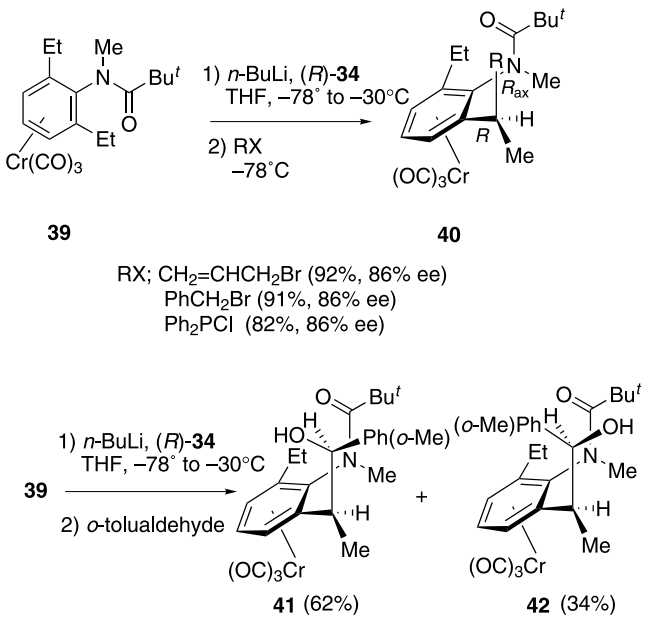


Figure 4. Crystal structure of **38a** (E=Me).



Scheme 5. Enantiotopic lithiation of prochiral anilide **39**.

the stereoselectivity by quenching the lithiated intermediate with benzaldehyde. Two products **41** and **42** were obtained by reaction with *o*-methylbenzaldehyde in 62 and 34% yields, respectively. The stereochemistry at the benzylic and homobenzylic positions of a major compound **41** was found to be (*R*,*R*)-configuration X-ray crystallography (Fig. 6).[29] Although *syn* and *anti*-diastereoselectivity of the reaction products is not so high, both isomers were easily separated by column chromatography. Further synthetic applications are in progress.

The formation of **40** as a single diastereomer by the reaction of 2,6-diethyl anilide complex **39** with chiral lithium amide and subsequent quenching with alkyl halides is explained as follows (Scheme 6). The chiral lithium amide deprotonates a proton H^a in the sterically favored conformation **43** to generate a configurationally stable carbanion intermediate with *exo* cyclic double dond character **44** due to an overlap of the p-orbital of the benzylic carbon with the d-orbital of the chromium.[11] Therefore, isomerization at the benzylic position of **44** is inhibited, and electrophiles attack from the *exo* side giving **40** as a single diastereomer. The axially chiral anilide complex **40** (R=PPh_2; 86% ee) with a phosphine group was used as a chiral ligand for palladium-catalyzed allylic alkylation (Scheme 7). Unfortunately, palladium-catalyzed reaction of 1,3-diphenyl 2-propenylacetate with sodium malonate in the presence of axially chiral anilide ligand **40** (R=PPh_3) resulted in low ee of the allylic alkylation product.

The obtained axially chiral *N*-methyl *N*-pivaloylaniline

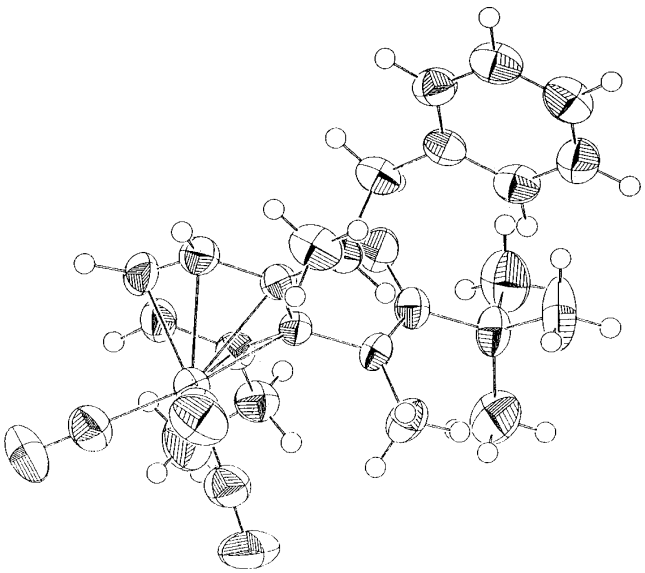


Figure 5. Crystal structure of **40** (R=CH_2Ph).

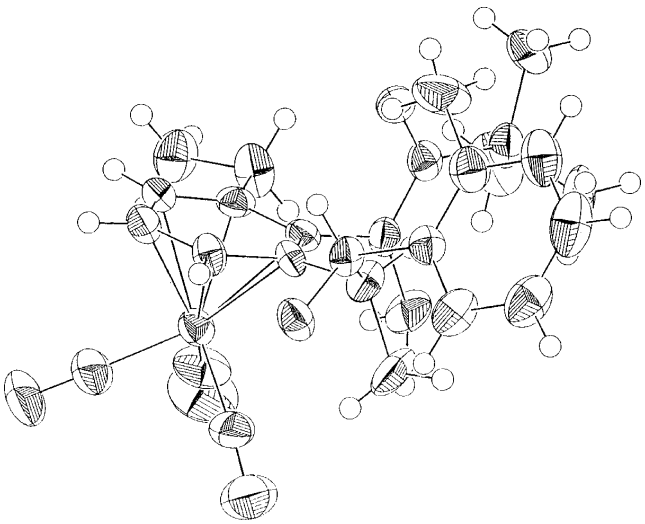
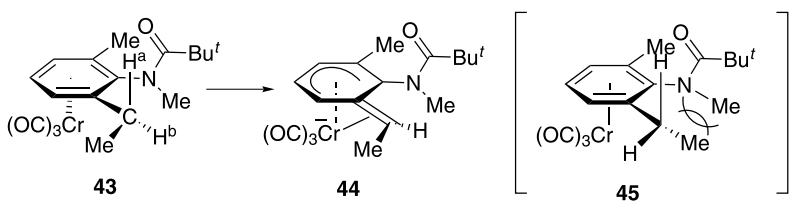
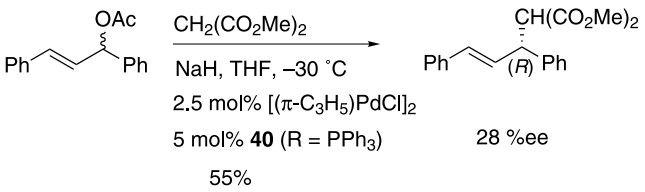


Figure 6. Crystal structure of **41**.

chromium complexes are useful compounds for further transformation to other axially chiral *N*-acyl aniline chromium complexes as follows (Scheme 8). Reduction of **46** ($[\alpha]_D^{24}$ −19.5, 97% ee) with $LiAlH_4$ in THF at room temperature for 3 h gave planar chiral *N*-methyl aniline chromium complex **47**. *N*-Acylation of **47** with acyl chloride in the presence of base gave single axially chiral anilide complexes **48** in good yields. These axially chiral anilide chromium complexes would be expected to be useful for further development in asymmetric reaction as chiral auxiliary or ligand.



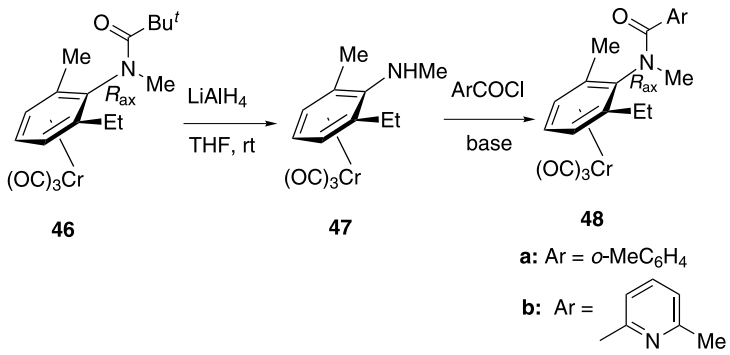
Scheme 6. Proposed reaction mechanism.



Scheme 7.

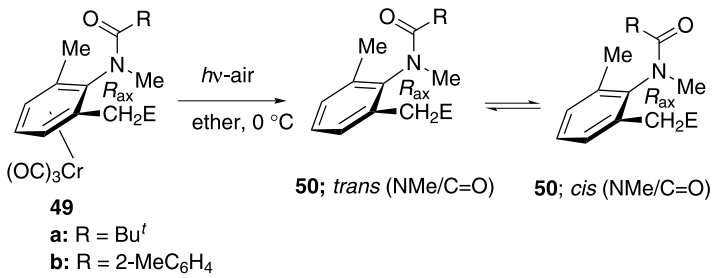
2.3. Chromium-free axially chiral anilides

Since we have prepared the tricarbonylchromium-complexed axially chiral anilides in high ee, our attention was next focused on chromium-free axially chiral non-biaryl compounds (Table 4). An ether solution of the axially chiral *N*-methyl anilide chromium complexes **49** was exposed to sunlight to give chromium-free anilide derivatives **50** in good yields. No axial bond rotation of the chromium-free chiral anilides was observed by 1H NMR spectroscopy in the presence of $Eu(tfc)_3$ after standing at room temperature for 24 h. The chromium-free axially chiral *N*-methyl-*N*-acyl anilines **50** exist as an equilibration of *trans* and *cis* rotamers between the *N*-methyl and amido carbonyl oxygen group in $CDCl_3$ solution as shown in equation in Table 4. The *cis* rotamer preference is well known in both crystalline and solution states for *N*-methyl anilides.[25] The *N*-methyl signal for the major rotamer of **50a** (E=Me) appeared at 3.11 ppm, while the corresponding signal for the minor rotamer was observed at 3.34 ppm. Since the downfield *N*-Me singlet of the *N*-methyl-*N*-acyl anilides was assigned to the *trans*-rotamers,[3e] the major rotamer of **50** could be assigned to the *cis*-conformer. Furthermore, the major *cis*-rotamers of **50a** (E=CH_2Ph, CH_2CCMe, CH_2CCPh) were also observed by 0.40–0.45 ppm high field shifts of *t*-butyl group compared with those of the corresponding minor rotamer. These shifts are attributed to the *cis*-conformation, where the *t*-butyl group is located closely facing the phenyl ring plane. Similarly, the axially chiral *N*-methyl-*N*-*o*-methylbenzoyl anilines **50b** were found to exist predominantly as the *cis*-rotamer. However, the *trans*-rotamer is the predominant conformer for the axially chiral anilides **50b** possessing a hydroxy group on the side chain, probably due to an intramolecular hydrogen bond with the amido carbonyl (entries 6 and 7).



Scheme 8.

Table 4. Photo-oxidative demetallation



Entry	Anilide complex	Yield (%)	% ee[a]	*cis*/*trans* (**50**)
1	**49a** (E=Me)	98	95	6/1
2	**49a** (E=CH_2Ph)	95	97[b]	6/1
3	**49a** (E=$CH_2CH{=}CH_2$)	96	92	4/1
4	**49a** (E=$CH_2C{=}CMe$)	95	96	5/1
5	**49a** (E=$CH_2C{=}CPh$)	95	96	4/1
6	**49a** (E=$C(OH)Ph_2$)	96	96	1/2.5
7	**49a** (E=1-cyclohexanol)	96	96	1/1.5
8	**49a** (E=COPh)	94	97	2/1
9	**49a** (E=Me)	97	97	2/1
10	**49a** (E=CH_2Ph)	98	98	2.5/1
11	**49a** (E=1-cyclohexanol)	96	96	6/1

[a] Ee was determined by ^1H NMR in the presence of $Eu(tfc)_3$ unless otherwise noted.
[b] Ee was determined by HPLC with chiralpak AS.

3. Conclusion

We have developed new asymmetric syntheses of the axially chiral *N*,*N*-diethyl benzamides and *N*-methyl anilides by using arene chromium complexes. One method for the preparation of axially chiral benzamides is an introduction of sterically bulky substitutent at 6-position of enantiomerically pure *N*,*N*-diethyl 2-methylbenzamide chromium complex. An alternative procedure is desymmetrization of prochiral tricarbonylchromium complexes of *N*,*N*-diethyl 2,6-dimethylbenzamide and *N*-methyl-*N*-acyl 2,6-dimethylanilide via enantioselective deprotonation using chiral lithium amide bases at the benzylic methyls.

4. Experimental

4.1. General

All manipulations involving organometallics were carried out under an atmosphere of nitrogen or argon and using an inert gas/vacuum double manifold techniques. All melting points were determined on a Yanagimoto MPJ-2 micro-melting point apparatus and were uncorrected. ^{1}H NMR spectra were measured on Hitachi R-90, JEOL GX-400, EX-270 instrument, and all NMR spectra were recorded in $CDCl_3$ solvent with tetramethylsilane as an internal reference. IR spectra were determined in $CHCl_3$ solution on a JASCO A-100 spectrometer. Elemental analyses were performed on a Perkin-Elmer Model 240 automatic analyzer. Mass spectra were determined on a JEOL JMS-AM 500 with EI mode (70 eV). Optical rotations were obtained on a JASCO DIP-370 automatic polarimeter at wavelength 589 nm (sodium D line) using a 1.0 dm cell with a total volume of 3 mL. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl immediately before use.

4.1.1. Preparation of (−)-(1*R*)-tricarbonyl(methyl *o*-methylbenzoate)chromium (2). To a mixture of enantiomerically pure (−)-(1*R*)-tricarbonyl(*o*-methylbenzaldehyde)chromium (**1**) (1.3 g, 5.0 mmol), NaCN (1.4 g, 28 mmol) and freshly prepared MnO_2 (12.8 g, 147 mmol) in dry MeOH (100 mL) was added acetic acid (0.6 g, 10.0 mmol) with stirring at room temperature, and the reaction mixture was vigorously stirred for 1 h. After filtration and evaporation of methanol, the residue was extracted with ether (20 mL×2), and the extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, concentrated in vacuo. The residue was purified by silica gel column chromatography with *n*-hexane/ether to afford 1.2 g (85% yield) of crystals **2**. Recrystallization with hexane/ether; orange crystals; mp 83 °C; $[\alpha]_D^{26}=-100.0$ (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H), 3.88 (s, 3H), 5.06 (d, *J*=6.3 Hz, 1H), 5.14 (t, *J*=6.3 Hz, 1H), 5.58 (t, *J*=6.3 Hz, 1H), 6.18 (d, *J*=6.3 Hz, 1H). antipode of **2**; $[\alpha]_D^{26}=+101.0$ (*c* 0.20, $CHCl_3$).

4.1.2. (+)-(1*R*)-Tricarbonyl(*N*,*N*-diethyl-2-methylbenzamide)chromium (3). To a solution of diethylamine (439 mg, 6.0 mmol) in THF (7 mL) was added *n*-BuLi (1.6 M in hexane, 3.8 mL, 6.0 mmol) at −78 °C under argon, and the mixture was stirred for 30 min. A solution of (−)-**2** (572 mg, 2.0 mmol) in THF (8 mL) was added to the above mixture at −78 °C by a syringe and the reaction mixture was warmed to room temperature over 3 h, and quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted with ether (10 mL×2) and the extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure. The residue was purified by silica gel column chromatography with *n*-hexane/ether to afford 572 mg (80%) of yellow crystals **3**. Recrystallization with hexane/ether; mp 104 °C; $[\alpha]_D^{25}=+8.0$ (*c* 0.40, $CHCl_3$); IR ($CHCl_3$) 1970, 1890, 1630, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (t, *J*=6.6 Hz, 3H), 1.20 (t, *J*=6.6 Hz, 3H), 2.20 (s, 3H), 3.22–3.80 (m, 4H), 5.06 (d, *J*=6.3 Hz, 1H), 5.08 (t, *J*=6.3 Hz, 1H), 5.36 (t, *J*=6.3 Hz, 1H), 5.51 (d, *J*=6.3 Hz, 1H); Anal. Calcd for $C_{15}H_{17}NO_4Cr$: C, 55.05; H, 5.24; N, 4.28. Found: C, 54.88, H, 5.20, N, 4.22. antipode of **3**; $[\alpha]_D^{25}=-8.0$ (*c* 0.40, $CHCl_3$).

4.1.3. (−)-(S)$_{ax}$-Tricarbonyl(*N*,*N*-diethyl-2-ethyl-6-methylbenzamide)chromium (4). To a solution of (+)-**3** (164 mg, 0.50 mmol) and TMEDA (87.2 mg, 0.75 mmol) in dry THF (5 mL) was added *t*-BuLi (1.7 M in pentane, 0.44 mL, 0.75 mmol) at −78 °C under argon by syringe, and the reaction mixture was stirred for 1 h. A solution of methyl iodide (39.0 mg, 2.5 mmol) in THF (1 mL) was added to the reaction mixture and warmed to −10 °C over 2 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with ether (10 mL×2) and washed with brine, dried over $MgSO_4$. The extract was reduced in vacuo, and the residue was purified by silica gel column chromatography with *n*-hexane/ether to afford 64.2 mg (36%) of **4** and 27 mg (15%) of laterally lithiated product, tricarbonyl(*N*,*N*-diethyl *o*-propylbenzamide)chromium. **4**; yellow crystals; mp 100 °C; $[\alpha]_D^{26}=-33.0$ (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 1970, 1890, 1630, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, *J*=7.3 Hz, 3H), 1.21 (t, *J*=7.3 Hz, 3H), 1.22 (t, *J*=7.3 Hz, 3H), 2.20 (s, 3H), 2.46–2.64 (m, 2H), 3.22–3.29 (m, 2H), 3.50–3.59 (m, 2H), 4.96 (d, *J*=6.3 Hz, 1H), 5.02 (d, *J*=6.3 Hz, 1H), 5.37 (t, *J*=6.3 Hz, 1H); Anal. Calcd for $C_{17}H_{21}NO_4Cr$: C, 57.46; H, 5.96; N, 3.94. Found: C, 57.30, H, 5.92, N, 3.93. antipode of **4**; $[\alpha]_D^{25}=+33.0$ (*c* 0.20, $CHCl_3$).

4.1.4. (−)-Tricarbonyl(*N*,*N*-diethyl-2-formyl-6-methylbenzamide)chromium (11). To a solution of (+)-**3** (982 mg, 3.0 mmol) and TMEDA (523 mg, 4.5 mmol) in THF (20 mL) was added *s*-BuLi (1.04 M in cyclohexane, 4.4 mL, 4.5 mmol) at −78 °C under argon by syringe, and the reaction mixture was stirred for 1 h. A solution of dimethylformamide (1.1 g, 15 mmol) in THF (3 mL) was added to the reaction mixture and warmed to 0 °C over 3 h. Usual work up produced 460 mg (43%) of orange crystals. mp 150 °C; $[\alpha]_D^{26}=-454.0$ (*c* 0.10, $CHCl_3$); IR ($CHCl_3$) 1980, 1910, 1620 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.04 (t, *J*=7.3 Hz, 3H), 1.26 (t, *J*=7.3 Hz, 3H), 2.20 (s, 3H), 3.17 (q, *J*=7.3 Hz, 1H), 3.18 (q, *J*=7.3 Hz, 1H), 3.45–3.56 (m, 1H), 3.60–3.70 (m, 1H), 5.30 (t, *J*=6.3 Hz, 1H), 5.49 (d, *J*=6.3 Hz, 1H) 5.76 (d, *J*=6.3 Hz, 1H), 9.59 (s, 1H); Anal. Calcd for $C_{16}H_{17}NO_5Cr$: C, 54.09; H, 4.82; N, 3.94. Found: C, 53.91, H, 4.82, N, 3.94.

4.1.5. Reaction of (−)-tricarbonyl(*N*,*N*-diethyl-2-formyl-6-methylbenzamide)chromium (11) with MeMgBr. To a solution of (−)-**11** (533 mg, 1.5 mmol) in THF (15 mL) was

added MeMgBr solution (0.86 M in THF, 2.1 mL, 1.8 mmol) at −78 °C under argon. The mixture was stirred for 1 h and quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted with ether (10 mL×2), and the extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure. The residue was purified by chromatography to give the (*R*)-complex **14** (453 mg) and (*S*)-complex **15** (9 mg). **14** (R=Me); yellow crystals; mp 124 °C; $[\alpha]_D^{26}=-30.5$ (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 1970, 1890, 1620, 1440 cm^{-1}; ^1H NMR (270 MHz) δ 1.17 (t, *J*=7.3 Hz, 3H), 1.22 (t, *J*=7.3 Hz, 3H), 1.41 (d, *J*=6.3 Hz, 3H), 2.20 (s, 3H), 2.34 (d, *J*=3.0 Hz, 1H), 3.18–3.31 (m, 2H), 3.47–3.65 (m, 2H), 4.79 (dq, *J*=3.0, 6.3 Hz, 1H), 5.09 (d, *J*=6.3 Hz, 1H), 5.40 (t, *J*=6.3 Hz, 1H), 5.44 (d, *J*=6.3 Hz, 1H); Anal. Calcd for $C_{17}H_{21}NO_5Cr$: C, 55.00; H, 5.70; N, 3.77. Found: C, 54.78, H, 5.67, N, 3.73.

4.1.6. Reduction of (+)-tricarbonyl(*N*,*N*-diethyl-2-acetyl-6-methylbenzamide)chromium (12) with DIBAL-H. To a solution of acetyl chromium complex **12** (R=Me) (185 mg, 0.5 mmol) in THF (5 mL) was added a Dibal-H (0.95 M in hexane, 0.63 mL, 0.6 mmol) at −78 °C under argon and the resulting mixture was stirred at −78 °C for 30 min. The mixture was quenched with saturated aqueous NH_4Cl and extracted with ether (10 mL×2). The extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure. The residue was purified by chromatography to give the (*R*)-complex **14** (R=Me) (15 mg) and the (*S*)-complex **15** (R=Me) (154 mg). **15** (R=Me); yellow crystals; mp 148~149 °C (dec.); $[\alpha]_D^{27}=-49.0$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 3300, 1970, 1890, 1620, 1440 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.14 (t, *J*=7.3 Hz, 3H), 1.22 (t, *J*=7.3 Hz, 3H), 1.57 (d, *J*=6.3 Hz, 3H), 2.10 (d, *J*=4.6 Hz, 1H), 2.19 (s, 3H), 3.21~3.36 (m, 2H), 3.52 (q, *J*=7.3 Hz, 1H), 3.55 (q, *J*=7.3 Hz, 1H), 4.86 (qd, *J*=6.3, 4.6 Hz, 1H), 5.11 (d, *J*=6.3 Hz, 1H), 5.22 (d, *J*=6.3 Hz, 1H), 5.34 (t, *J*=6.3 Hz, 1H); Anal. calcd for $C_{17}H_{21}NO_5Cr$: C, 55.00; H, 5.70; N, 3.77. Found; C, 54.80; H, 5.68; N, 3.71.

4.1.7. Lithiation of 3 followed by reaction with acetaldehyde to give 9 and 10. A solution of (+)-tricarbony (*N*,*N*-diethyl-2-methylbenzamide)chromium (3) (327 mg, 1.0 mmol) in THF (10 mL) was added *s*-BuLi (1.04 M in cyclohexane, 1.4 mL, 1.5 mmol) at −78 °C under argon by syringe, and the reaction mixture was stirred for 1 h. A solution of acetaldehyde (220 mg, 10 mmol) in THF (2 mL) was added to the above mixture at −78 °C, and the resulting mixture was warmed to 0 °C over 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether (20 mL x 2). The extract was washed with brine, dried over $MgSO_4$, evaporated under reduced pressure. The residue was purified by chromatography to give **9** (75 mg) and **10** (88 mg). The compound **9** is identical with **15** (R=Me) and the compound **10** is equal with **14** (R=Me).

4.1.8. Preparation of tricarbonyl(*N*-methyl-*N*-pivaloyl-2,6-dimethylaniline)chromium (37). To a solution of tricarbonyl(*N*-methyl 2,6-dimethylaniline)chromium (1.0 g, 3.7 mmol) in dry THF (30 mL) was added *n*-BuLi (1.6 M in hexane, 3.5 mL, 5.52 mmol) at −78 °C under argon and the resulting mixture was stirred for 1 h. Pivaloylchloride (7.4 mmol, 0.9 g) was added to the reaction mixture at −78 °C and the mixture was warmed to room temperature over 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate; 3/1) to give 1.0 g (76%) of **37**. Yellow crystals; mp 178 °C; ^1H NMR ($CDCl_3$) δ 1.37 (s, 9H), 2.09 (s, 6H), 3.55 (s, 3H), 4.95 (d, 2H, *J*=6.3 Hz), 5.54 (t, 1H, *J*=6.3 Hz); IR ($CHCl_3$) 1970, 1880, 1630 cm^{-1}; Anal. Calcd. for $C_{17}H_{21}NO_4Cr$: C, 57.46; H, 5.96; N, 3.94. Found: C, 57.72; H, 5.89; N, 3.97.

4.1.9. Asymmetric lithiation of prochiral arene chromium complexes with chiral lithium amide. Typical procedure is as follows. To a solution of (*R*,*R*)-bis-α-phenylethylamine (**24**) (101 mg, 0.45 mmol) in dry THF (1.5 mL) was added *n*-BuLi (1.6 M in hexane, 0.23 mL, 0.36 mmol) at −78 °C under argon, and the mixture was stirred for 30 min. To the mixture was added a solution of *N*,*N*-diethyl 2,6-dimethylbenzamide chromium complex (**22**) (102 mg, 0.30 mmol) in THF (1.5 mL) at −78 °C and the mixture was warmed to −30 °C over 1 h. The reaction mixture was again cooled to −78 °C and then, a solution of MeI (90 mg, 0.60 mmol) in THF (0.5 mL) was added to the reaction mixture. The mixture was warmed to −30 °C and quenched with saturated aqueous NH_4Cl, extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give 90 mg (85%) of (+)-*N*,*N*-diethyl 2-ethyl-6-methylbenzamide chromium complex **23** (R=Me). Yellow crystals; mp 99 °C; $[\alpha]_D^{26}=+27.0$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H, *J*=7.3 Hz), 1.21 (t, 3H, *J*=7.3 Hz), 1.22 (t, 3H, *J*=7.3 Hz), 2.20 (s, 3H), 2.46–2.64 (m, 2H), 3.22–3.29 (m, 2H), 3.50–3.59 (m, 2H), 4.96 (d, 1H, *J*=6.3 Hz), 5.02 (d, 1H, *J*=6.3 Hz), 5.37 (t, 1H, *J*=6.3 Hz); IR ($CHCl_3$) 1970, 1890, 1630 cm^{-1}; Anal. Calcd. for $C_{17}H_{21}NO_4Cr$: C, 57.46; H, 5.96; N, 3.94. Found: C, 57.30; H, 5.92; N, 3.93. The optical purity was determined as 86% ee by chiral HPLC with Chiralcel OJ-H eluted with hexane/2-propanol (1/1); flow rate, 0.5 mL/min; column temperature, 40 °C; UV detector, 254 nm. Retention time; 13.5 and 17.2 min.

23: (E=CH_2Ph). Yellow crystals; mp 144 °C; $[\alpha]_D^{27}=+24.0$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (t, 3H, *J*=7.3 Hz), 1.20 (t, 3H, *J*=7.3 Hz), 2.21 (s, 3H), 2.75–2.93 (m, 4H), 3.18–3.35 (m, 2H), 3.54 (q, 2H, *J*=7.3 Hz), 4.98 (d, 2H, *J*=6.3 Hz), 5.34 (t, 1H, *J*=6.3 Hz), 7.16–7.32 (m, 5H); IR ($CHCl_3$) 1970, 1890, 1630, 1435 cm^{-1}; Anal. Calcd. for $C_{23}H_{25}NO_4Cr$: C, 64.03; H, 5.84; N, 3.25. Found: C, 64.26; H, 5.66; N, 3.06. Retention time; 13.4 and 16.8 min.

23 (E=$CH_2CH=CH_2$). Yellow crystals; mp 88 °C; $[\alpha]_D^{30}=+26.7$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (t, 3H, *J*=7.3 Hz), 1.21 (t, 3H, *J*=7.3 Hz), 2.20 (s, 3H), 2.29–2.37 (m, 2H), 2.57–2.62 (m, 2H), 3.18–3.33 (m, 2H), 3.41–3.69 (m, 2H), 4.97 (d, 1H, *J*=6.3 Hz), 5.02 (d, 1H, *J*=6.3 Hz), 5.03–5.13 (m, 2H), 5.36 (t, 1H, *J*=6.3 Hz), 5.75–5.90 (m, 1H); IR ($CHCl_3$) 1970, 1890, 1630, 1435 cm^{-1}; Anal. Calcd. for $C_{19}H_{23}NO_4Cr$: C, 59.83; H,

6.08; N, 3.67. Found: C, 60.12; H, 6.00; N, 3.77. Retention time; 12.3 and 18.1 min.

4.1.10. Asymmetric lithiation of anilide chromium complexes 37 with chiral lithium amide. Asymmetric lithiation of **37** was performed in THF by using lithium amide base derived from chiral amine **34** under the same conditions with asymmetric lithiation of benzamide chromium complex **22**.

38: (R=E=Me). Yellow crystals; mp 108 °C; $[\alpha]_D^{30}=-29.4$ (*c* 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.16 (t, 3H, *J*=7.6 Hz), 1.36 (s, 9H), 2.07 (s, 3H), 2.41 (dq, 1H, *J*=15.0, 7.6 Hz), 2.44 (dq, 1H, *J*=15.0, 7.6 Hz), 3.55 (s, 3H), 4.97 (d, 1H, *J*=6.3 Hz), 4.98 (d, 1H, *J*=6.3 Hz), 5.58 (t, 1H, *J*=6.3 Hz); IR ($CHCl_3$) 1970, 1890, 1640 cm^{-1}; Anal. Calcd. for $C_{18}H_{23}NO_4Cr$: C, 58.53; H, 6.28; N, 3.79. Found: C, 58.81; H, 6.37; N, 3.77. The ee was determined by chiral HPLC with Chiralpak AS eluted with hexane/2-propanol (20/1); flow rate, 1 mL/min; column temperature, 40 °C; UV detector, 254 nm. Retention time; 7.6 and 8.8 min.

38: (R=Me, E=CH_2Ph). Yellow crystals; mp 118 °C; $[\alpha]_D^{31}=-19.5$ (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.37 (s, 9H), 2.09 (s, 3H), 2.48–2.91 (m, 4H), 3.57 (s, 3H), 4.75 (d, 1H, *J*=6.3 Hz), 4.96 (d, 1H, *J*=6.3 Hz), 5.50 (t, 1H, *J*=6.3 Hz), 7.15–7.31 (m, 5H); IR ($CHCl_3$) 1970, 1890, 1640 cm^{-1}; Anal. Calcd. for $C_{24}H_{27}NO_4Cr$: C, 64.71; H, 6.11; N, 3.14. Found: C, 64.68; H, 6.14; N, 3.10. The enantiomeric excess was determined by chiral HPLC with Chiralpak AS eluted with hexane/2-propanol (20/1); flow rate, 1 mL/min; column temperature, 40 °C; UV detector, 254 nm. Retention time; 8.0 and 10.9 min.

38: (R=Me, E=$CH_2CH{=}CH_2$). Yellow crystals; mp 90 °C; $[\alpha]_D^{29}=-25.9$ (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.36 (s, 9H), 2.07 (s, 3H), 2.16–2.54 (m, 4H), 3.52 (s, 3H), 4.96 (d, 2H, *J*=6.3 Hz), 5.01–5.09 (m, 2H), 5.56 (t, 1H, *J*=6.3 Hz), 5.74–5.89 (m, 1H); IR ($CHCl_3$) 1970, 1880, 1630 cm^{-1}; Anal. Calcd. for $C_{20}H_{25}NO_4Cr$: C, 60.75; H, 6.37; N, 3.54. Found: C, 60.48; H, 6.09; N, 3.57. Retention time; 6.7 and 8.0 min.

38: (R=Me, E=CH_2CCMe). Yellow crystals; mp 126 °C; $[\alpha]_D^{23}=-38.5$ (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.36 (s, 9H), 1.77 (t, 3H, *J*=2.3 Hz), 2.06 (s, 3H), 2.24–2.63 (m, 4H), 3.56 (s, 3H), 4.97 (d, 1H, *J*=6.3 Hz), 5.07 (d, 1H, *J*=6.3 Hz), 5.57 (t, 1H, *J*=6.3 Hz); IR ($CHCl_3$) 2330, 1960, 1880, 1630 cm^{-1}; Anal. Calcd. for $C_{21}H_{25}NO_4Cr$: C, 62.20; H, 6.22; N, 3.44. Found: C, 62.50; H, 6.02; N, 3.40. Retention time; 7.6 and 10.2 min.

38: (R=Me, E=CH_2CCPh). Yellow crystals; mp 108 °C; $[\alpha]_D^{23}=-51.1$ (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.08 (s, 3H), 2.52–2.71 (m, 4H), 3.59 (s, 3H), 4.99 (d, 1H, *J*=6.3 Hz), 5.13 (d, 1H, *J*=6.3 Hz), 5.89 (t, 1H, *J*=6.3 Hz), 7.27–7.40 (m, 5H); IR ($CHCl_3$) 2340, 1980, 1880, 1640 cm^{-1}; Anal. Calcd. for $C_{26}H_{27}NO_4Cr$: C, 66.52; H, 5.80; N, 2.98. Found: C, 66.40; H, 5.78; N, 2.92. Retention time; 8.3 and 14.6 min.

38: (R=Me, E=$C(OH)Ph_2$). Yellow crystals; mp 178 °C; $[\alpha]_D^{31}=-75.7$ (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.23 (s, 9H), 2.07 (s, 3H), 3.21 (d, 1H, *J*=13.8 Hz), 3.59 (s, 3H), 3.65 (d, 1H, *J*=13.8 Hz), 4.09 (s, 1H), 4.28 (d, 1H, *J*=6.3 Hz), 4.89 (d, 1H, *J*=6.3 Hz), 5.28 (t, 1H, *J*=6.3 Hz), 7.21–7.53 (m, 10H); IR ($CHCl_3$) 3300, 1970, 1890, 1620 cm^{-1}; Anal. Calcd. for $C_{30}H_{31}NO_5Cr$: C, 67.03; H, 5.81; N, 2.61. Found: C, 67.28; H, 5.77; N, 2.88. Retention time; 7.2 and 13.4 min.

38: (R=Me, E=*c*-C_6H_{10}(OH)). Yellow crystals; mp 123 °C; $[\alpha]_D^{30}=-77.3$ (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.12–1.83 (m, 10H), 1.36 (s, 9H), 2.07 (s, 3H), 2.08 (s, 1H), 2.48 (d, 1H, *J*=18.5 Hz), 2.53 (d, 1H, *J*=18.5 Hz), 3.85 (s, 3H), 4.95 (d, 1H, *J*=6.3 Hz), 5.10 (d, 1H, *J*=6.3 Hz), 5.57 (t, 1H, *J*=6.3 Hz); IR ($CHCl_3$) 3400, 1960, 1880, 1620 cm^{-1}; Anal. Calcd. for $C_{23}H_{31}NO_5Cr$: C, 60.92; H, 6.89; N, 3.09. Found: C, 60.71; H, 6.64; N, 3.06. Retention time; 11.9 and 21.9 min.

38: (R=Me, E=COPh). Yellow crystals; mp 103 °C; $[\alpha]_D^{22}=-15.0$ (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.15 (s, 9H), 2.08 (s, 3H), 3.57 (s, 3H), 3.70 (d, 1H, *J*=16.0 Hz), 4.21 (d, 1H, *J*=16.0 Hz), 5.03 (d, 1H, *J*=6.3 Hz), 5.16 (d, 1H, *J*=6.3 Hz), 5.63 (t, 1H, *J*=6.3 Hz), 7.45–7.94 (m, 5H); IR ($CHCl_3$) 1980, 1890, 1680, 1640 cm^{-1}; Anal. Calcd. for $C_{24}H_{25}NO_5Cr$: C, 62.74; H, 5.48; N, 3.05. Found: C, 62.50; H, 5.28; N, 3.12. Retention time; 17.5 and 20.3 min.

38: (R=Et, E=Me). Yellow crystals; mp 114 °C; $[\alpha]_D^{25}=-25.0$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.14 (t, 3H, *J*=7.3 Hz), 1.37 (s, 9H), 1.50 (t, 3H, *J*=7.3 Hz), 2.06 (s, 3H), 2.29–2.47 (m, 2H), 3.79–4.00 (m, 2H), 5.00 (d, 1H, *J*=6.3 Hz), 5.02 (d, 1H, *J*=6.3 Hz), 5.62 (t, 1H, *J*=6.3 Hz); IR ($CHCl_3$) 1970, 1880, 1640 cm^{-1}; Anal. Calcd. for $C_{19}H_{25}NO_4Cr$: C, 59.52; H, 6.57; N, 3.65. Found: C, 59.76; H, 6.29; N, 3.40. The ee was determined by chiral HPLC with Chiralpak AS eluted with hexane/2-propanol (40/1); flow rate, 0.5 mL/min; column temperature, 40 °C; UV detector, 254 nm. Retention time; 15.7 and 17.1 min.

38: (R=Et, E=CH_2Ph). Yellow crystals; $[\alpha]_D^{21}=-27.0$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H), 1.50 (t, 3H, *J*=7.0 Hz), 2.06 (s, 3H), 2.46–2.91 (m, 4H), 3.93 (q, 2H, *J*=7.0 Hz), 4.83 (d, 1H, *J*=6.2 Hz), 5.01 (d, 1H, *J*=6.2 Hz), 5.54 (t, 1H, *J*=6.2 Hz), 7.14 (d, 2H, *J*=6.9 Hz), 7.22 (d, 1H, *J*=6.9 Hz), 7.29 (t, 2H, *J*=6.9 Hz); IR ($CHCl_3$) 1970, 1880, 1640 cm^{-1}; MS (relative intensity) *m*/*z* 459 (M^+, 15), 375 (100), 323 (14), 266 (32); HRMS calcd for $C_{25}H_{29}NO_4Cr$: 459.1654, found 459.1647. Retention time; 7.7 and 10.5 min.

38: (R=CH_2OMe, E=Me). Yellow liquid; $[\alpha]_D^{22}=-18.2$ (*c* 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H, *J*=7.7 Hz), 1.38 (s, 9H), 2.13 (s, 3H), 2.36–2.58 (m, 2H), 3.39 (s, 3H), 3.61–3.74 (m, 4H), 4.94 (d, 2H, *J*=6.3 Hz), 5.09 (d, 1H, *J*=9.9 Hz), 5.24 (d, 1H, *J*=9.9 Hz), 5.63 (t, 1H, *J*=6.3 Hz); IR ($CHCl_3$) 1970, 1880, 1640 cm^{-1}; MS (relative intensity) *m*/*z* 443 (M^+, 14), 359 (100), 301 (31), 285 (36); HRMS calcd for $C_{21}H_{29}NO_6Cr$: 443.1400, found 443.1405. Retention time; 5.2 and 5.8 min.

38: (R=CH_2OMe, E=CH_2Ph). Yellow liquid; $[\alpha]_D^{27}=-13.7$ (*c* 2.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.14 (s, 3H), 2.46–2.56 (m, 1H), 2.62–2.72 (m, 1H), 2.78–2.87 (m,

1H), 2.94–3.03 (m, 1H), 3.36 (s, 3H), 3.59–3.71 (m, 4H), 4.72 (d, 1H, *J*=6.2 Hz), 4.93 (d, 1H, *J*=6.2 Hz), 5.15 (d, 1H, *J*=9.5 Hz), 5.21 (d, 1H, *J*=9.5 Hz), 5.48 (t, 1H, *J*=6.2 Hz), 7.15 (d, 2H, *J*=7.0 Hz), 7.21 (d, 1H, *J*=7.0 Hz), 7.28 (t, 2H, *J*=7.0 Hz); IR ($CHCl_3$) 1970, 1880, 1640 cm^{-1}; MS (relative intensity) *m/z* 519 (M^+, 12), 435 (100), 360 (19), 276 (16); HRMS calcd for $C_{27}H_{33}NO_6Cr$: 519.1713, found 519.1706.

40: (R=CH_2Ph). Yellow crystals; mp 154 °C; $[\alpha]_D^{24}$ -9.9 (*c* 2.2, EtOH); ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, *J*=7.3 Hz), 1.24 (d, 3H, *J*=6.9 Hz), 1.40 (s, 9H), 2.38–2.51 (m, 3H), 2.82–3.00 (m, 2H), 3.60 (s, 3H), 4.86 (d, 1H, *J*=6.3 Hz), 5.10 (d, 1H, *J*=6.3 Hz), 5.55 (t, 1H, *J*=6.3 Hz), 7.05–7.27 (m, 5H); IR ($CHCl_3$) 1960, 1870, 1640 cm^{-1}; Anal. Calcd. for $C_{26}H_{31}NO_4Cr$: C, 65.95; H, 6.60; N, 2.96. Found: C, 66.15; H, 6.52; N, 3.01. Retention time; 5.2 and 6.2 min.

40: (R=$CH_2CH{=}CH_2$). Yellow crystals; mp 133 °C; $[\alpha]_D^{22}$ −0.5 (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, *J*=7.3 Hz), 1.31 (d, 2H, *J*=6.9 Hz), 1.36 (s, 9H), 1.84–1.95 (m, 1H), 2.39 (q, 2H, *J*=7.3 Hz), 2.40–2.42 (m, 1H), 2.54–2.61 (m, 1H), 3.56 (s, 3H), 4.98–5.09 (m, 2H), 5.03 (d, 2H, *J*=6.3 Hz), 5.61 (t, 1H, *J*=6.3 Hz), 5.58–5.77 (m, 1H); IR ($CHCl_3$) 1960, 1870, 1640, 1410 cm^{-1}; Anal. Calcd. for $C_{22}H_{29}NO_4Cr$: C, 62.40; H, 6.90; N, 3.31. Found: C, 62.56; H, 6.92; N, 3.38. Retention time; 5.0 and 5.6 min.

40: (R=PPh_2). Yellow liquid; $[\alpha]_D^{26}$=+43.0 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24 (d, 3H, *J*=7.3 Hz), 1.26 (m, 9H), 1.27–1.37 (m, 3H), 2.41–2.49 (m, 2H), 3.41 (q, 1H, *J*=7.3 Hz), 3.66 (s, 3H), 4.37 (d, 1H, *J*=5.7 Hz), 5.08 (d, 1H, *J*=5.7 Hz), 5.37 (t, 1H, *J*=5.7 Hz), 7.29–7.41 (m, 10H); IR ($CHCl_3$) 1960, 1890, 1645 cm^{-1}; MS (relative intensity) *m/z* 567 (M^+, 1), 279 (32), 247 (25), 218 (43), 190 (66), 167 (96), 149 (100).

41 Yellow crystals; mp 149 °C; $[\alpha]_D^{26}$=+17.5 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, *J*=7.8 Hz), 1.22 (t, 3H, *J*=7.6 Hz), 1.30 (s, 9H), 2.34 (s, 3H), 2.41 (q, 2H, *J*=7.8 Hz), 2.59 (d, 1H, *J*=6.9 Hz), 3.19 (dd, 1H, *J*=3.0, 6.9 Hz), 3.62 (s, 3H), 5.05 dd, 1H, *J*=3.0, 6.9 Hz), 5.12 (d, 1H, *J*=6.4 Hz), 5.16 (d, 1H, *J*=6.4 Hz), 5.49 (t, 1H, *J*=6.4 Hz), 7.15–7.32 (m, 4H); IR ($CHCl_3$) 3200 (br), 1980, 1900, 1630 cm^{-1}; Anal. Calcd. for $C_{29}H_{33}NO_5Cr$: C, 64.40; H, 6.61; N, 2.78. Found: C, 64.44; H, 6.77; N, 3.00.

4.1.11. Conversion of 46 to 48b. To a suspension of $LiAlH_4$ (57.0 mg, 1.5 mmol) in THF (3 mL) was added a solution of **46** (185 mg, 0.50 mmol) in THF (7 mL) at room temperature and stirred for 3 h. The reaction mixture was quenched with aqueous 2 M NaOH (0.07 mL). After filtration and washing with ether, the organic layer was dried over $MgSO_4$ and evaporated in a vacuo. The resulting yellow oil (91 mg) was dissolved in THF (3 mL) and cooled to −78 °C. To the above solution *n*-BuLi (1.6 M in hexane, 0.30 mL, 0.48 mmol) was added under nitrogen. And then, a solution of α-picolyl chloride (100 mg, 0.64 mmol) in THF (2 mL) was added to the above solution, and the reaction mixture was stirred at room temperature for 1 h. Usual work up and purification with SiO_2 column chromatography gave 104.0 mg of **48b**. Yellow crystals; mp 142–143 °C; $[\alpha]_D^{28}$=−32.8 (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) for major *trans* rotamer δ 1.14 (t, 3H, *J*=7.3 Hz), 2.11 (s, 3H), 2.17 (s, 3H), 2.46–2.70 (m, 2H), 3.54 (s, 3H), 4.85 (d, 1H, *J*=6.2 Hz), 4.96 (d, 1H, *J*=6.2 Hz), 5.50 (t, 1H, *J*=6.3 Hz), 7.06 (d, 1H, *J*=7.7 Hz), 7.61 (d, 1H, *J*=7.7 Hz), 7.74 (t, 1H, *J*=7.7 Hz); for minor *cis* rotamer δ 1.26 (t, 3H, *J*=7.3 Hz), 2.27 (s, 3H), 2.61 (s, 3H), 2.46–2.70 (m, 2H), 3.47 (s, 3H), 5.05 (d, 2H, *J*=6.2 Hz), 5.64 (t, 1H, *J*=6.2 Hz), 6.93 (d, 1H, *J*=7.7 Hz), 7.45 (d, 1H, *J*=7.7 Hz), 7.70 (t, 1H, *J*=7.7 Hz); IR ($CHCl_3$) 1970, 1890, 1640, 1430 cm^{-1}; Anal. Calcd. for $C_{20}H_{20}N_2O_4Cr$: C, 59.40; H, 4.98; N, 6.93. Found: C, 59.19; H, 4.92; N, 6.66.

4.1.12. Preparation of chromium-free axially chiral benamide and anilides by photo-oxidative demetalation. Typical reaction is as follows. A solution of **49a** (E=Me) (260 mg, 0.71 mmol) in ether (5 mL) was exposed to sunlight at 0 °C until a yellow color was disappeared. A precipitate was filtered and washed with ether. The ether layer was evaporated under reduced pressure to give 161 mg (98%) of **50a** (E=Me) as colorless crystals. The ee was determined by ^1H NMR spectrum in the presence of $Eu(tfc)_3$. mp 33 °C; $[\alpha]_D^{24}$=−4.9 (*c* 3.0 $CHCl_3$); ^1H NMR ($CDCl_3$) for major *cis*-rotamer δ 0.97 (s, 9H), 1.23 (t, 3H, *J*=7.6 Hz), 2.24 (s, 3H), 2.58 (q, 2H, *J*=7.6 Hz), 3.11 (s, 3H), 7.05–7.22 (m, 3H); for minor *trans*-rotamer δ 1.20 (t, 3H, *J*=7.6 Hz), 1.42 (s, 9H), 2.15 (s, 3H), 2.58 (q, 2H, *J*=7.6 Hz), 3.34 (s, 3H), 7.05–7.22 (m, 3H); IR ($CHCl_3$) 1610, 1420 cm^{-1}; Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.31; H, 10.10; N, 5.79.

50a: (E=CH_2Ph). Colorless crystals; mp 43 °C; $[\alpha]_D^{30}$=−11.9 (*c* 1.3 $CHCl_3$) ^1H NMR ($CDCl_3$) for major *cis*-rotamer δ 0.96 (s, 9H), 2.23 (s, 3H), 2.86–2.93 (m, 4H), 3.00 (s, 3H), 7.10–7.30 (m, 8H); for minor *trans*-rotamer δ 1.41 (s, 9H), 2.16 (s, 3H), 2.86–2.93 (m, 4H), 3.25 (s, 3H), 7.10–7.30 (m, 8H); IR ($CHCl_3$) 1620, 1460 cm^{-1}; Anal. Calcd. for $C_{21}H_{27}NO$: C, 81.51; H, 8.79; N, 4.53. Found: C, 81.80; H, 9.07; N, 4.42.

50a: (E=$CH_2CH{=}CH_2$). Colorless liquid; $[\alpha]_D^{21}$=−9.4 (*c* 2.6 $CHCl_3$); ^1H NMR ($CDCl_3$) for major *cis*-rotamer δ 0.90 (s, 9H), 2.16 (s, 3H), 2.24–2.60 (m, 4H), 3.03 (s, 3H), 4.88–5.00 (m, 2H), 5.69–5.84 (m, 1H), 6.99–7.20 (m, 3H); for minor *trans*-rotamer δ 1.33 (s, 9H), 2.07 (s, 3H), 2.24–2.60 (m, 4H), 3.26 (s, 3H), 4.88–5.00 (m, 2H), 5.69–5.84 (m, 1H), 6.99–7.20 (m, 3H); IR ($CHCl_3$) 1610, 1440 cm^{-1}; MS (relative intensity) *m/z* 259 (M^+, 64), 202 (47), 174 (26), 160 (22), 98 (100); HRMS calcd for $C_{17}H_{25}NO$: 259.1942, found 259.1939.

50a: (E=CH_2CCMe). Colorless liquid; $[\alpha]_D^{22}$=−27.3 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) for major *cis*-rotamer δ 0.98 (s, 9H), 1.75 (t, 3H, *J*=2.6 Hz), 2.24 (s, 3H), 2.34–2.47 (m, 2H), 2.62–2.82 (m, 2H), 3.31 (s, 3H), 7.09–7.23 (m, 3H); for minor *trans*-rotamer δ 1.42 (s, 9H), 1.76 (t, 3H, *J*=2.6 Hz), 2.15 (s, 3H), 2.34–2.47 (m, 2H), 2.62–2.82 (m, 2H), 3.35 (s, 3H), 7.09–7.23 (m, 3H); IR ($CHCl_3$) 2320, 1610, 1420 cm^{-1}; MS (relative intensity) *m/z* 271 (M^+, 45), 256 (11), 214 (100), 98 (73); HRMS calcd for $C_{18}H_{25}NO$: 271.1916, found 271.1927.

50a: (E=CH_2CCPh). Colorless liquid; $[\alpha]_D^{22}$=−47.1 (*c* 1.3, $CHCl_3$); $_1H$ NMR ($CDCl_3$) for major *cis*-rotamer δ 0.99 (s,

9H), 2.25 (s, 3H), 2.60–2.95 (m, 4H), 3.16 (s, 3H), 7.10–7.36 (m, 8H); for minor *trans*-rotamer δ 1.44 (s, 9H), 2.16 (s, 3H), 2.60–2.95 (m, 4H), 3.37 (s, 3H), 7.10–7.36 (m, 8H); IR ($CHCl_3$) 2320, 1610, 1420 cm^{-1}; MS (relative intensity) *m/z* 333 (M^+, 50), 318 (17), 276 (100), 215 (89); HRMS calcd for $C_{23}H_{27}NO$: 333.2100, found 333.2096.

50a: (E=C(OH)Ph_2). Colorless crystals; mp 183 °C; $[\alpha]_D^{22}$=+78.1 (*c* 3.7, $CHCl_3$); ^1H NMR ($CDCl_3$) for major *trans*-rotamer δ 1.30 (s, 9H), 2.14 (s, 3H), 3.31 (s, 3H), 3.48 (d, 1H, *J*=14.0 Hz), 3.74 (d, 1H, *J*=14.0 Hz), 4.26 (s, 1H), 6.36–7.58 (m, 13H); for minor *cis*-rotamer δ 0.98 (s, 9H), 2.19 (s, 3H), 2.96 (s, 3H), 3.40 (d, 1H, *J*=14.0 Hz), 3.64 (s, 1H), 3.68 (d, 1H, *J*=14.0 Hz), 6.36–7.58 (m, 13H); IR ($CHCl_3$) 3320, 1610, 1460 cm^{-1}; Anal. Calcd. for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.76; N, 3.49. Found: C, 80.98; H, 7.71; N, 3.39.

50a: (E=*c*-C_6H_{10}(OH)). Colorless crystals; mp 82 °C; $[\alpha]_D^{23}$=+9.0 (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) for major *trans*-rotamer δ 1.24–1.65 (m, 10H), 1.42 (s, 9H), 2.14 (s, 3H), 2.32 (s, 1H), 2.67 (d, 1H, *J*=14.0 Hz), 2.76 (d, *J*=14.0 Hz), 3.34 (s, 3H), 7.12–7.43 (m, 3H); for minor *cis*-rotamer δ 0.94 (s, 9H), 1.24–1.65 (m, 10H), 2.24 (s, 3H), 2.32 (s, 1H), 2.67 (d, 1H, *J*=14.0 Hz), 2.76 (d, 1H, *J*=14.0 Hz), 3.16 (s, 3H), 7.12–7.43 (m, 3H); IR ($CHCl_3$) 3390, 1640, 1460 cm^{-1}; Anal. Calcd. for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.64; H, 9.73; N, 4.34.

50a: (E=COPh). Colorless liquid; $[\alpha]_D^{20}$=−40.9 (*c* 1.3, $CHCl_3$); 1H NMR ($CDCl_3$) for major *cis*-rotamer δ 1.02 (s, 9H), 2.27 (s, 3H), 3.03 (s, 3H), 4.20 (d, 1H *J*=16.0 Hz), 4.38 (d, 1H *J*=16.0 Hz), 7.05–8.02 (m, 8H); for minor *trans*-rotamer δ 1.31 (s, 9H), 2.19 (s, 3H), 3.25 (s, 3H), 4.12 (d, 1H *J*=16.0 Hz), 4.21 (d, 1H *J*=16.0 Hz), 7.05–8.02 (m, 8H); IR ($CHCl_3$) 1680, 1640, 1430 cm^{-1}; MS (relative intensity) *m/z* 323 (M^+, 89), 308 (13), 266 (40), 222 (100); HRMS calcd for $C_{21}H_{25}NO_2$: 323.1878, found 323.1882.

50b: (E=Me). Colorless liquid; $[\alpha]_D^{21}$=+2.3 (*c* 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$) for major *cis*-rotamer δ 1.31 (t, 3H, *J*=7.6 Hz), 2.36 (s, 3H), 2.48 (s, 3H), 2.58–2.81 (m, 2H), 3.02 (s, 3H), 6.70–7.35 (m, 7H); for minor *trans*-rotamer δ 1.18 (t, 3H, *J*=7.6 Hz), 2.25 (s, 3H), 2.49 (s, 3H), 2.58–2.81 (m, 2H), 3.33 (s, 3H), 6.70–7.35 (m, 7H); IR ($CHCl_3$) 1630, 1420 cm^{-1}; MS (relative intensity) *m/z* 267 (M^+, 100), 238 (28), 148 (33), 132 (41), 119 (89); HRMS calcd for $C_{18}H_{21}NO$: 267.1609, found 267.1616.

50b: (E=CH_2Ph). Colorless liquid; $[\alpha]_D^{20}$=+10.8 (*c* 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) for major *cis*-rotamer δ 2.37 (s, 3H), 2.44 (s, 3H), 2.87–3.09 (m, 4H), 2.95 (s, 3H), 6.68–7.32 (m, 12H); for minor *trans*-rotamer δ 2.26 (s, 3H), 2.43 (s, 3H), 2.87–3.09 (m, 4H), 3.21 (s, 3H), 6.70–7.35 (m, 12H); IR ($CHCl_3$) 1640, 1430 cm^{-1}; MS (relative intensity) *m/z* 343 (M^+, 100), 252 (17), 238 (18), 224 (32), 132 (33), 119 (80); HRMS calcd for $C_{24}H_{25}NO$: 343.1954, found 343.1945.

50b: (E=*c*-C_6H_{10}(OH)). Colorless liquid; $[\alpha]_D^{21}$=+16.8 (*c* 3.2, $CHCl_3$); ^1H NMR ($CDCl_3$) for major *cis*-rotamer δ 1.23–1.74 (m, 10H), 2.13 (s, 1H), 2.37 (s, 3H), 2.35 (s, 3H), 2.75–2.88 (m, 2H), 3.04 (s, 3H), 6.60–7.44 (m, 7H); for minor *trans*-rotamer δ 1.23–1.74 (m, 10H), 2.27 (s, 1H), 2.38 (s, 3H), 2.50 (s, 3H), 2.75–2.88 (m, 2H), 3.39 (s, 3H), 6.60–7.44 (m, 7H); IR ($CHCl_3$) 3420, 1630, 1440 cm^{-1}; MS (relative intensity) *m/z* 351 (M^+, 2), 333 (10), 253 (100), 238 (16), 119 (79); HRMS calcd for $C_{23}H_{29}NO_2$: 351.2195, found 351.2198.

Acknowledgements

This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan.

References and notes

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17. CCDC number for **11**: 225222; Crystal data: empirical formula; $C_{16}H_{17}O_5NCr$, M=355.31, red prismatic, orthorhombic, space group, Pbca (#61), a=15.918(4), b=15.626(4), c=13.301(3)Å, V=3308(2)Å^3, Z=8, D_c=1.427 g/cm^3, F(000)=1472.00, μ (Mo Kα)=7.15 cm^{-1}. The carbonyl oxygen is oriented upper side to the chromium-complexed arene with 4° incline, and the angle between N–C=O plane and the ring is 91°.
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26. 5.7% of NOE between *N*-Me and Me of Bu^t groups in *N*-pivaloyl aniline chromium complex **37a** was observed. The ratio of *trans*- and *cis* rotamers was >12:1. The *N*-methyl singlet and three methyls of *t*-butyl group of trans rotamer

were observed at lower field than those of *cis*-rotamer: *trans* rotamer δ 1.37 (CMe_3), 3.55 (NMe) ppm; *cis* rotamer δ 1.06, 3.33 ppm.

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28. CCDC number for **40** (R=CH_2Ph): 170561.
29. CCDC number 224584 for **41**: 224584; Crystal data: empirical formula; $C_{27}H_{33}O_5NCr$, M=503.56, yellow block, orthorhombic, space group, $P2_12_12_1$ (#19), a=10.672(6), b=12.507(8), c=18.45(1) Å, V=2462.7(3) Å^3, Z=4, D_c=1.358 g/cm^3, F(000)=1064.00, μ (Mo Kα)=5.03 cm^{-1}.

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Tetrahedron 60 (2004) 4543–4548
Tetrahedron

Rapid, highly diastereoselective addition of dialkylzinc reagents to atropisomeric 2-formyl arylamides

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Received 10 October 2003; revised 3 December 2003; accepted 8 December 2003

Abstract—We have observed that dialkylzinc reagents add to atropisomeric 2-formyl arylamides many times faster than they react with other substituted benzaldehyde derivatives. Additionally, with diethylzinc the products were formed with very high diastereoselectivity, affording the *syn* product (d.r. greater than 95:5), except in one case where epimerization of the product is rapid. In contrast, Grignard and trialkylaluminum reagents afforded the *anti* diastereomers, with diminished stereoselectivity and formation of reduction products.

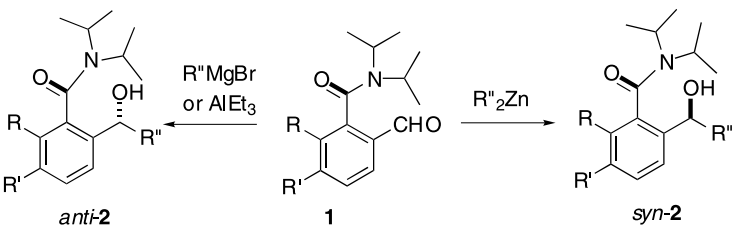
1. Introduction

Atropisomeric amides, imides, and anilides are known to control a variety of stereoselective reactions[1] such as cycloadditions,[2,3] radical additions,[2] lateral lithiations,[4–9] and *ortho*-lithiations,[10,11] among others.[12–16] Atropisomeric *N*,*N*-diisopropyl amides have recently been used to control stereochemistry over long distances, as demonstrated by Clayden in the highly diastereoselective addition of phenylmagnesium chloride to a remote carboxaldehyde.[17,18] Atropisomeric 1-naphthamides have also been shown to influence diastereoselectivity in the addition of organomagnesium and organolithium reagents to 2-formyl groups.[18]

In our continuing studies of atropisomeric amides,[19] we have examined the addition of organometallic reagents to 2-formylaryl amides. We herein report surprising rate enhancements and excellent control of diastereoselectivity in the alkyl group addition to a series of racemic 2-formyl arylamides. We are not aware of related observations in this system in the literature, despite the fact that substrate controlled diastereoselective reactions are well known.[20,21] Dialkylzinc reagents were found to afford the *syn* products on addition to 2-formyl arylamides, whereas Grignard and trialkylaluminum compounds yielded the *anti* products as the major diastereomer under our reaction conditions (Scheme 1).

2. Results and discussion

During a study directed toward the dynamic kinetic resolution of atropisomeric amides, we found that diethylzinc added to amides **1** with excellent control over diastereoselectivity (Table 1). Surprisingly, the reaction took place equally as fast in the presence or absence of amino alcohols, finishing after 1 h at room temperature. These results were unexpected because it is known that diethylzinc reacts with benzaldehyde slowly in the absence of amino alcohols.[22] Therefore, we propose that a mechanism involving activation of the diethylzinc by the



Scheme 1. Reagent controlled diastereoselection in the addition to 2-formyl arylamides.

Keywords: Dialkylzinc reagents; Atropisomeric amides; Stereochemistry; 1,2-Addition reactions.
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0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.12.071

Table 1. Addition of organometallic reagents to 2-formyl arylamides

Entry	Substrate	R	R′	MR″	Product	Yield	d.r. (*syn*/*anti*)
1	**1a**	NMe_2	H	$ZnEt_2$	**2a**	99	>98:2
2	**1b**	CF_3	H	$ZnEt_2$	**2b**	96	95:5
3	**1c**	Ph	H	$ZnEt_2$	**2c**	80	>98:2
4	**1c**	Ph	H	EtMgBr	**2c**	94	50:50
5	**1c**	Ph	H	$AlEt_3$	**2c**	75[a]	11:89
6	**1d**	OMe	H	$ZnEt_2$	**2d**	95	>98:2
7	**1d**	OMe	H	EtMgBr	**2d**	83	33:67
8	**1d**	OMe	H	$AlEt_3$	**2d**	39[b]	14:86
9	**1d**	OMe	H	$ZnMe_2$	**3d**	64[c]	85:15
10	**1d**	OMe	H	MeMgBr	**3d**	97	33:67
11	**1e**	1-Naph[d]		$ZnEt_2$	**2e**	68	>98:2
12	**1e**	1-Naph[d]		EtMgBr	**2e**	90	25:75
13	**1e**	1-Naph[d]		$ZnMe_2$	**3e**	60[c]	91:9
14	**1e**	1-Naph[d]		MeMgBr	**3e**	80	25:75
15	**1f**	$SiMe_3$	H	$ZnEt_2$	**2f**	57	33:67
16	**1f**	$SiMe_3$	H	EtMgBr	**2f**	92	33:67

[a] 19% of reduction product.
[b] 44% of reduction product.
[c] After 2 days.
[d] *N*,*N*-Diisopropyl-2-formyl-1-naphthamide.

amide carbonyl is responsible for both the increase in reaction rate and the high diastereoselectivity, as outlined below. Dialkylzinc reagents can give excellent diastereoselectivity if a Lewis-basic functional group is in close proximity to the reaction center.[23,24]

We applied this reaction to a series of atropisomeric aldehydes, achieving excellent diastereocontrol, as determined by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy (Table 1, entries 1–3, 6 and 11). Only the addition to **1f** afforded poor diastereoselectivity as discussed below (entry 15). Dimethylzinc additions required longer reaction times (approximately 2 d) and gave somewhat lower diastereoselectivities (Table 1, entries 9 and 13). It is well known that dimethylzinc is significantly less reactive than diethylzinc. For example, Noyori reported that dimethylzinc reacted 20 times slower with benzaldehyde than diethylzinc in the presence of catalyst formed from the amino alcohol ligand DAIB.[25] We attribute the decrease in the diastereoselectivity in the dimethylzinc additions to the prolonged reaction times, which permit the epimerization of the product through rotation about the Ar-carbonyl bond. Experimental support for this hypothesis is presented below.

To examine the diastereoselectivity with Grignard reagents, we carried out the addition of ethylmagnesium bromide to aldehydes **1c**–**f** (Table 1, entries 4, 7, 12, and 16) and methylmagnesium bromide to **1d** and **1e** (entries 10 and 14). Surprisingly, in contrast to the formation of the *syn* product with dialkylzinc reagents, the *anti* diastereomer predominated in these addition reactions. Under our conditions, where the Grignard reagent was used as a diethyl ether solution at 0 °C, we observed formation of the *anti* diastereomer. In contrast, Clayden and co-workers employed Grignard reagent in THF at low temperature and reported formation of the *syn* diastereomer.[18] We repeated the experiment of the Clayden group and obtained the *syn* diastereomer under these conditions, in agreement with their report.[26] It is likely that the change in diastereoselectivity of the addition in diethyl ether and THF is related the higher affinity of magnesium for THF. The specific cause, however, remains unclear at this time.

Only in the additions to **1f** (entries 15 and 16), which has a trimethylsilyl group *ortho* to the amide, was the same mixture of diastereomers isolated with the zinc and magnesium reagents. There are two possible explanations for this observation. The increased length of the carbon–silicon bond could result in a decrease in the barrier to rotation of the amide. Alternatively, the trimethysilyl group could facilitate rotation about the aryl–amide bond by coordination of the carbonyl oxygen to the silicon in the transition state as illustrated in Eq. 1.[19] Coordination of Lewis bases by trialkylsilyl in an intramolecular fashion has been proposed in many systems.[27] Similar *ortho* silyl effects have been observed previously by Clayden[28] and our group.[19]

To examine the aldehyde conformation in the solid state, an X-ray structure determination of **1d** was performed.[29] An ORTEP drawing is shwon in Figure 1 where the perpendicular architecture of the atropisomeric amide can be seen.

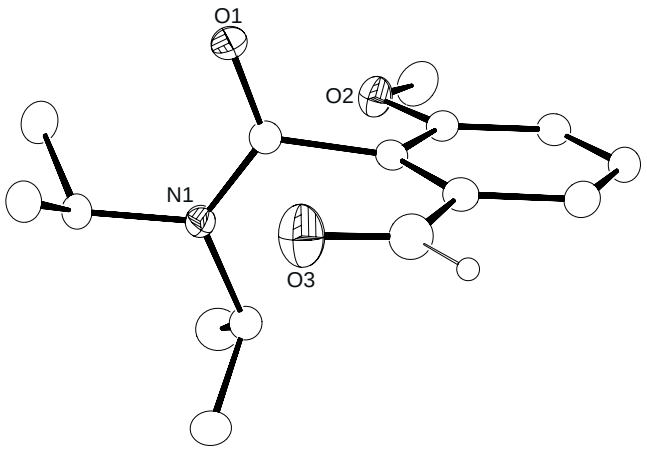
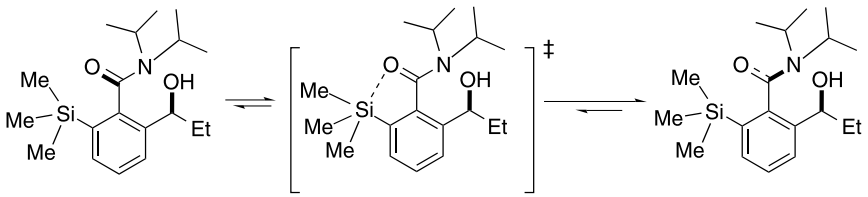


Figure 1. ORTEP drawing of **1d**.

In order to assign the relative stereochemistry of each diastereomer, crystals of the *syn*/*anti* mixtures of **2d**, **2e**, and **3d** were grown,[29] and their structures determined by X-ray diffraction. Only the *anti* diastereomers crystallized under our conditions. ^1H NMR spectroscopy of those crystals



(1)

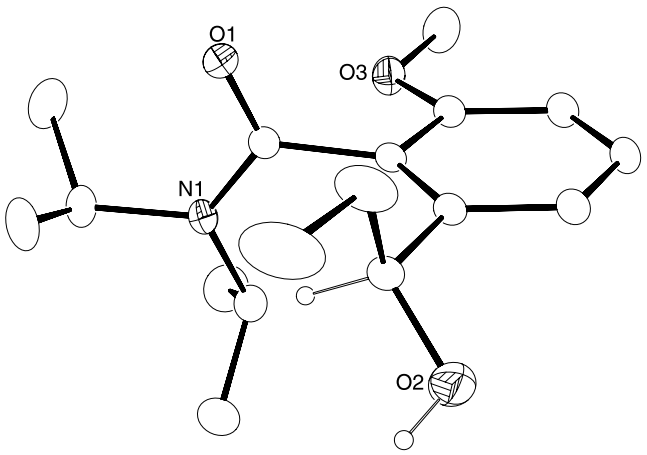


Figure 2. ORTEP drawing of *anti*-**2d**.

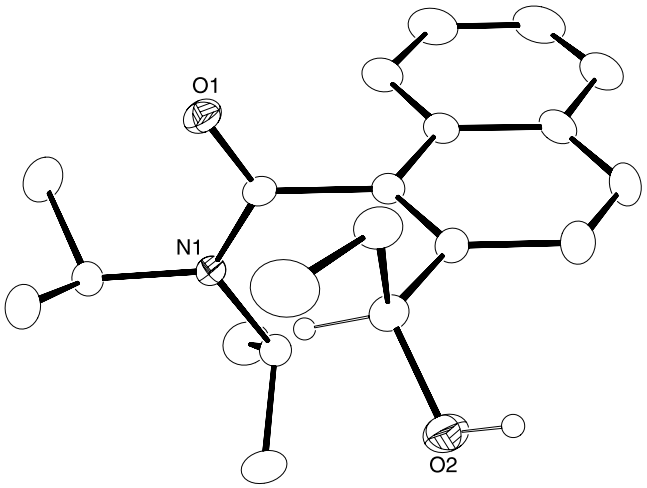


Figure 3. ORTEP drawing of *anti*-**2e**.

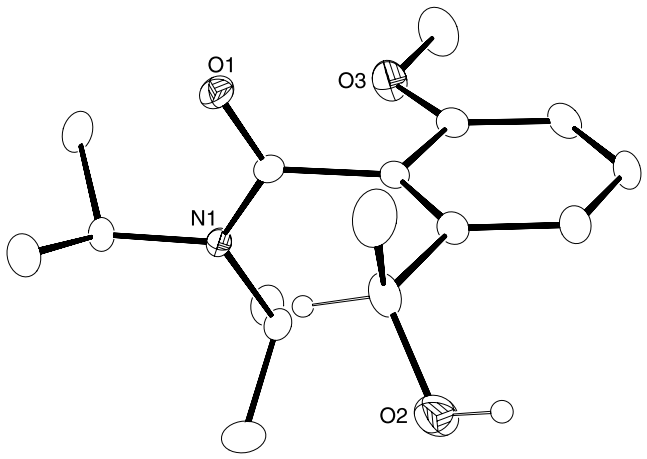


Figure 4. ORTEP drawing of *anti*-**3d**.

showed that they were the major diastereomer in the reactions with the Grignard reagents. Therefore, the *syn* diastereomer was formed in the dialkylzinc additions. Figures 2–4 show ORTEP drawings of **2d**, **2e**, and **3d** where the *anti* arrangement can be clearly seen.

To examine the rates of epimerization of the atropisomeric amide products a 90:10 mixture of *anti*-**3d**:*syn*-**3d** was

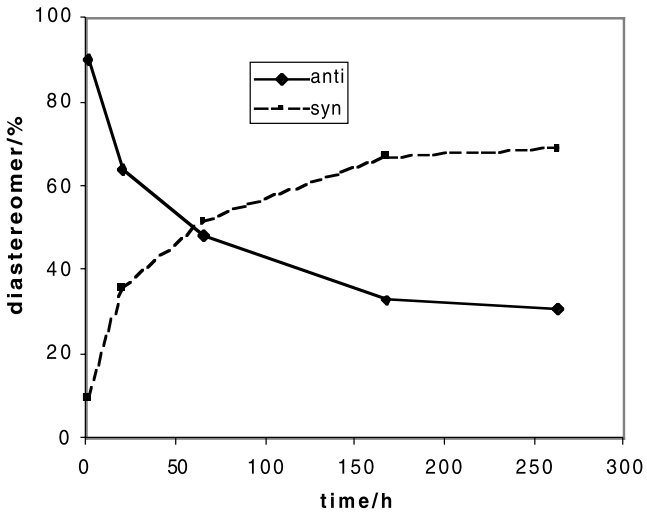


Figure 5. Epimerization of *anti*-**3d**. Plot of the diastereomer % vs time.

monitored at room temperature by ^{1}H NMR spectroscopy. From Figure 5 it is clear that the equilibration of the *syn* and *anti* diastereomers occurs slowly at room temperature eventually leading to the thermodynamic ratio (30:70 *anti*:*syn*).[9,28] However, the epimerization rate is sufficiently fast to result in a decrease in the diastereoselectivities in the addition of dimethylzinc to aldehydes.

The diastereoselectivity in the Grignard addition reactions was only moderate, and thus we decided to explore other reagents in order to improve the *anti* selectivity. We were pleased to find that triethylaluminum added to **1c** and **1d** with much better diastereoselection, affording predominantly the *anti* diastereomer (Table 1, entries 5 and 8). However, variable amounts of reduction products were also isolated.

Next we compared the rates of reaction of diethylzinc with 2-formylatropisomeric amides and 2-substituted benzaldehyde derivatives. The reactions with **1d** and **1e** were complete after 3 h at room temperature, whereas reactions with 2-anisaldehyde, 2-tolualdehyde, and 2-trifluoromethylbenzaldehyde exhibited no conversion after 3 h by ^{1}H NMR spectroscopy. The results of these studies allow us to propose a mechanism for the addition of dialkylzinc reagents to 2-formylatropisomeric amides that explains the high level of diastereoselectivity observed. The rapid addition of diethylzinc to the amides **1d** and **1e** suggests that the zinc is activated by coordination to the amide carbonyl oxygen. It has been proposed that the alkyl groups in coordinated zinc complexes of the type $LZnR_2$ (where L is a Lewis-basic group) are significantly more reactive than those of ZnR_2.[25,30] Thus, the activated ZnR_2 can deliver the alkyl group as shown in Figure 6. The proposed conformation of the formyl group is that found in the crystal structure of **1d** in Figure 1. A model for the addition of Grignard reagents to 2-formylatropisomeric amides is also proposed in Figure 6. Activation of the aldehyde by the magnesium center is proposed to cause a conformational change of the aldehyde carbonyl–aryl bond as a result of steric interactions of the magnesium assembly with the substrate. Thus, the addition reaction takes place on the opposite face of the aldehyde.

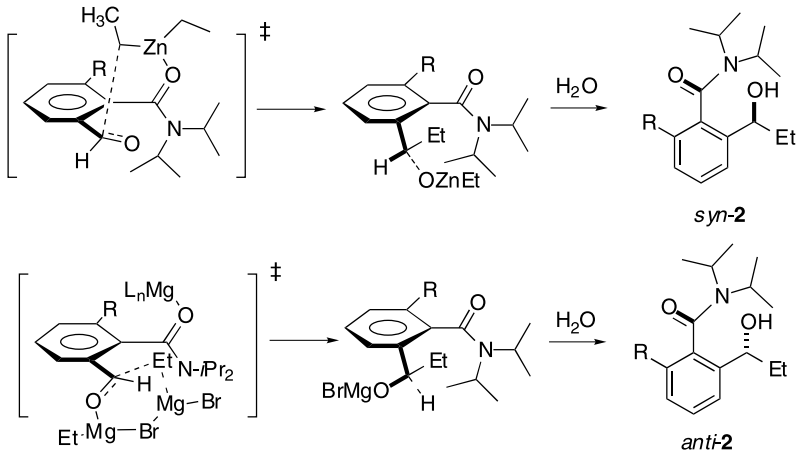


Figure 6. Proposed models for the diethylzinc and the Grignard additions to 2-formylarylamides. Solvent molecules coordinated to magnesium are not shown.

3. Conclusions

In summary, we report that dialkylzinc reagents react rapidly with atropisomeric 2-formyl arylamides relative to 2-substituted benzaldehyde derivatives. It is proposed that this large difference in reactivity is due to an internal activation of the organozinc reagent by the amide carbonyl. Furthermore, the alkyl zinc reagents add in a highly diastereoselective fashion, affording the *syn* adducts in high yields and diastereoselectivities. The *anti* diastereomers have also been synthesized through the addition of Grignard reagents to the same starting material. A promising alternative to this latter reaction is the use of trialkylaluminum compounds, which provides the *anti* diastereomer with high diastereoselectivity. We are currently examining the possibility of using other reactions to achieve the dynamic kinetic resolution of these interesting substrates.

4. Experimental

4.1. General experimental section

^{1}H NMR spectra were obtained on a 500 MHz Fourier transform NMR spectrometer at the University of Pennsylvania NMR facility. ^{1}H NMR spectra were recorded relative to tetramethylsilane. ^{13}C{^{1}H} NMR spectra were obtained at 125 MHz on the 500 MHz instrument, and chemical shifts were recorded relative to the solvent resonance. Chemical shifts are reported in units of parts per million downfield from tetramethylsilane and all coupling constants are reported in Hz. IR spectra were obtained on a Perkin–Elmer 1600 series spectrometer. Unless otherwise specified, all reagents were either purchased from Aldrich Chemical Co. or Acros Organics, and used without further purification. TMEDA was distilled over CaH_2 prior to use. Aldehyde precursors to compounds **2** and **3** were synthesized by the literature methods.

4.2. Procedure A. Addition of dialkylzinc reagents to compounds 1a–f

The aldehyde (0.4 mmol) was weighed into a dry, round bottom flask and dissolved in 2 mL of dry toluene under nitrogen. 1 M solutions of either diethyl- or dimethylzinc in hexanes (0.8 mmol, 0.8 mL) were added dropwise. The reaction was quenched with aq. sat. NH_4Cl after 1 h when diethylzinc was used, and after 2 d when dimethylzinc was used. The mixture was extracted with diethyl ether (×3), dried ($MgSO_4$), and solvents removed in vacuo. The crude reaction product was purified by column chromatography on silica gel when necessary using ethyl acetate and hexanes. The d.r. was determined prior and after purification by ^{1}H NMR spectroscopy.

4.3. Procedure B. Addition of Grignard reagents to compounds 1c–f

The aldehyde (0.4 mmol) was weighed into a dry, round bottom flask and dissolved in 2 mL of dry diethyl ether under nitrogen. The solution was cooled to 0 °C and 3 M solutions of either ethyl- or methylmagnesium bromide in diethyl ether (0.8 mmol, 0.27 mL) were added dropwise. The mixture was allowed to warm to room temperature. After 4 h, the reaction was quenched with aq. sat. NH_4Cl, extracted with diethyl ether (×3), dried ($MgSO_4$), and solvents removed in vacuo. The crude reaction product was purified by column chromatography on silica gel when necessary using ethyl acetate and hexanes. The d.r. was determined prior and after purification by ^{1}H NMR spectroscopy.

4.4. Procedure C. Addition of triethylaluminum to aldehydes 1c–d

The aldehyde (0.4 mmol) was weighed into a dry, clean, round bottom flask, and dissolved in 2 mL of dry toluene under nitrogen. A 1 M solution of triethylaluminum in hexanes (0.8 mmol, 0.8 mL) was added dropwise. The reaction was quenched with aq. sat. NH_4Cl after 12 h, extracted with diethyl ether (×3), dried ($MgSO_4$), and solvents removed in vacuo. The crude product was purified by column chromatography on silica gel. The d.r. was determined after purification by ^{1}H NMR spectroscopy.

4.4.1. *syn N,N*-Diisopropyl 1-(dimethylamino)-3-(1-hydroxypropyl)-2-benzamide, *syn*-2a. Prepared according

to general procedure A. *syn*-**2a** was isolated as a clear oil in 99% yield (120 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, J=8 Hz, 1H), 7.01 (d, J=8 Hz, 1H), 6.86 (d, J=8 Hz), 4.38 (m, 1H), 3.79 (broad s, 1H), 3.53 (m, 1H), 3.45 (m, 1H), 2.67 (s, 6H), 1.92 (m, 1H), 1.82 (m, 1H), 1.55 (d, J=7 Hz, 3H), 1.50 (d, J=7 Hz, 3H), 1.12 (d, J=7 Hz, 3H), 0.93–0.89 (m, 6H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.0, 149.8, 141.6, 132.9, 129.1, 119.3, 117.4, 72.0, 51.2, 45.8, 44.1, 26.5, 20.6, 20.5, 20.1, 20.0 11.1 ppm; IR (film) 3420, 3065, 2963, 1600, 1466, 1336 cm^{-1}; HRMS (ES+) m/z 329.2218 (calcd for [$C_{18}H_{30}N_2O_2$+Na]=329.2205).

4.4.2. *syn N,N*-Diisopropyl 1-(trifluoromethyl)-3-(1-hydroxypropyl)-2-benzamide, *syn*-2b. Prepared according to general procedure A. *syn*-**2b** was isolated in 96% yield as a clear oil (115 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J=8 Hz, 1H), 7.52 (d, J=8 Hz, 1H), 7.45 (t, J=8 Hz, 1H), 4.54 (m, 1H), 3.48 (m, 2H), 3.10 (broad s, 1H), 2.00 (m, 1H), 1.75 (m, 1H), 1.56 (d, J=7 Hz, 3H), 1.47 (d, J=7 Hz, 3H), 1.09 (d, J=7 Hz, 3H), 1.01 (m, 3H), 0.99 (d, J=7 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 167.9, 141.7, 135.2, 129.8, 129.1, 128.4, 126.1, 71.2, 51.2, 46.4, 26.9, 20.7, 20.2, 19.6, 19.4, 11.1 ppm; IR (film) 3420, 3080, 2969, 1614, 1440, 1372, 1319 cm^{-1}; HRMS (ES+) m/z 354.1671 (calcd for [$C_{17}H_{24}F_3NO_2$+Na]=354.1657).

4.4.3. *syn N,N*-Diisopropyl 1-phenyl-3-(1-hydroxypropyl)-2-benzamide, *syn*-2c. Prepared according to general procedure A. *syn*-**2c** was isolated as a white solid (105 mg) in 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47–7.24 (m, 8H), 4.48 (m, 1H), 3.39 (m, 1H), 3.32 (m, 1H), 1.99 (m, 1H), 1.84 (m, 1H), 1.49 (d, J=7 Hz, 3H), 1.23 (d, J=7 Hz, 3H), 0.95 (t, J=7 Hz, 3H), 0.79 (d, J=7 Hz, 3H), 0.14 (d, J=7 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 170.5, 140.9, 139.9, 137.9, 136.8, 129.4, 128.8, 128.7, 128.3, 127.6, 124.7, 72.1, 50.8, 46.0, 26.7, 20.5, 20.4, 19.3, 19.2, 11.1 ppm; IR (film) 3407, 3057, 2964, 1603, 1444, 1370, 1335 cm^{-1}; HRMS (ES+) m/z 362.2083 (calcd for [$C_{22}H_{29}NO_2$+Na]=362.2096).

4.4.4. *syn N,N*-Diisopropyl 1-methoxy-3-(1-hydroxypropyl)-2-benzamide, *syn*-2d. Prepared according to general procedure A. *syn*-**2d** was isolated in 95% yield as a clear oil (98 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, J=8 Hz, 1H), 6.99 (d, J=8 Hz, 1H), 6.73 (d, J=8 Hz, 1H), 4.41 (m, 1H), 3.73 (s, 3H), 3.63 (m, 1H), 3.45 (m, 1H), 3.40 (broad s, 1H), 1.89 (m, 1H), 1.78 (m, 1H), 1.52 (d, J=7 Hz, 3H), 1.50 (d, J=7 Hz, 3H), 1.12 (d, J=7 Hz, 3H), 0.97 (d, J=7 Hz, 3H), 0.91 (t, J=7 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.5, 154.9, 142.1, 129.5, 127.6, 118.0, 109.5, 72.1, 55.3, 51.2, 46.0, 27.2, 20.8, 20.6, 20.3, 20.2, 10.9 ppm; IR (film) 3396, 3055, 2964, 1608, 1469, 1440, 1337, 1262 cm^{-1}; HRMS (ES+) m/z 316.1877 (calcd for [$C_{17}H_{27}NO_3$+Na]=316.1889).

4.4.5. *syn N,N*-Diisopropyl 1-methoxy-3-(1-hydroxyethyl)-2-benzamide, *syn*-3d. Prepared according to general procedure A. *syn*-**3d** was isolated in 64% yield (99 mg) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (t, J=8 Hz, 1H), 7.04 (d, J=8 Hz, 1H), 6.73 (d, J=8 Hz, 1H), 4.73 (q, J=6 Hz, 1H), 3.72 (s, 3H), 3.60 (m, 1H), 3.44 (m, 1H), 1.51 (d, J=7 Hz, 3H), 1.49 (d, J=7 Hz, 3H), 1.45 (d, J=6 Hz, 3H), 1.10 (d, J=7 Hz, 3H), 0.96 (d, J=7 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 168.6, 154.7, 143.1, 129.5, 126.8, 117.6, 109.6, 66.0, 55.3, 51.2, 46.0, 20.8, 20.6, 20.5, 20.2, 20.1 ppm; HRMS (CI+) m/z 279.1835 (calcd for [$C_{16}H_{25}NO_3$+Na]=279.1834).

4.4.6. *anti N,N*-Diisopropyl 1-methoxy-3-(1-hydroxyethyl)-2-benzamide, *anti*-3d. Prepared according to procedure C and isolated as a white solid in 39% yield (42 mg). Sample characterized from the crystals used for X-ray diffraction. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, J=8 Hz, 1H), 7.02 (d, J=8 Hz, 1H), 6.72 (d, J=8 Hz, 1H), 4.78 (q, J=6 Hz, 1H), 3.71 (s, 3H), 3.62 (m, 1H), 3.44 (m, 1H), 1.50 (m, 6H), 1.46 (d, J=6 Hz, 3H), 1.08 (d, J=7 Hz, 3H), 1.02 (d, J=7 Hz, 3H).

4.4.7. *syn N,N*-Diisopropyl 2-(1-hydroxypropyl)-1-naphthamide, *syn*-2e. Spectroscopic data identical to that reported in the literature.[28]

4.4.8. *anti N,N*-Diisopropyl 2-(1-hydroxypropyl)-1-naphthamide, *anti*-2e. Spectroscopic data identical to that reported in the literature.[28]

4.4.9. *syn N,N*-Diisopropyl 2-(1-hydroxyethyl)-1-naphthamide, *syn*-3e. Spectroscopic data identical to that reported in the literature.[28]

Acknowledgements

We thank the Petroleum Research Fund (ACS-PRF 38021), administered by the American Chemical Society, and the University of Pennsylvania for support of this work.

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Synthesis and properties of atropisomeric phosphinous acids

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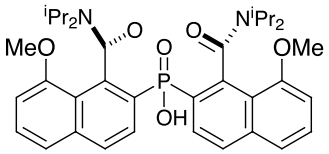
Received 10 October 2003; revised 22 December 2003; accepted 5 January 2004

Abstract—In this paper we describe two groups of atropisomeric phosphinous acids—bis-[(*N*,*N*-diisopropyl-1-naphthamide)-2-]-phosphinous acids (**2** to **4**) and their 8-methoxy- substituted relations (**8** to **10**). The first group of acids interconvert at room temperature and the second group do not. The interconversion and properties are illustrated by two dimensional TLC and some NMR spectra. The *peri* substituent turns out to be important.

1. Introduction

Axial chirality and, in particular, atropisomerism in aromatic amides, is now well established as a powerful way to transfer chiral information with atropisomeric amides being used as chiral substrates,[1] and chiral ligands.[2,3] The rate of rotation about the aromatic-carbonyl bond can be greatly influenced by neighbouring *peri* and *ortho* substituents. With a view to making C_2 symmetric phosphinic acids[4] with two axes of chirality based upon aromatic amides, we prepared the phosphinous acids described below.



C_2 symmetric phosphinic acid

Whether the compounds (either phosphinous or subsequent phosphinic acids) could be isolated at all or, potentially, be prepared in enantiomerically pure form would depend upon the rate of rotation about the aromatic-carbonyl bond.

2. Results and discussion

2.1. Interconverting phosphinous acids

Naphthamide **1** was prepared by known methods from 1-naphthoic acid.[5] Naphthamide **1** was lithiated and reacted with PCl_3 in the hope that double addition of the lithiated species would occur. This would lead to three possible diastereoisomers. When the two chiral axes are of the same relative configuration,[†] then the product is pseudo C_2 symmetric (**4**) and the phosphorus atom is non-stereogenic. However, when the two axes are of opposite configuration then the phosphorus becomes pseudoasymmetric[6] (stereogenic and achirotopic) and so there are a further two diastereomers possible here (**2** and **3**). If these diastereomers were formed by chance alone then we would expect the ratio of products **2**:**3**:**4** to be 1:1:2. Two equivalents of lithiated naphthamide **1** did indeed add to PCl_3 which, on workup, gave the phosphinous acids (**2** to **4**) (Scheme 1).

Although different products could clearly be identified by TLC (Fig. 1) they could not be isolated by flash column chromatography. The coelution of compounds with TLC spots that were distinct and well separated led us to suspect that the compounds might be interconverting. Inspection of a two dimensional[‡] TLC indicated that this was indeed the case. Since there are three diastereomers we could expect to see three spots on the standard TLC and a total of nine spots by two dimensional TLC.

As well as the diagonal spots to be expected of materials that do not interconvert and do not decompose, both non-diagonal spots can be seen for a given two compounds (Fig. 1) which indicates interconversion rather than mere decomposition. Most of the nine possible spots are visible.

Keywords: Atropisomeric phosphinous acids; Two dimensional TLC; *peri* Substituent.
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† The distinction between configuration and conformation is, of course, blurred in the realm of restricted rotation.
‡ The TLC plate was run in the verticle direction first, dried and left to stand for about 50 min before being run again in the perpendicular direction (right as the plate appears in Fig. 1).

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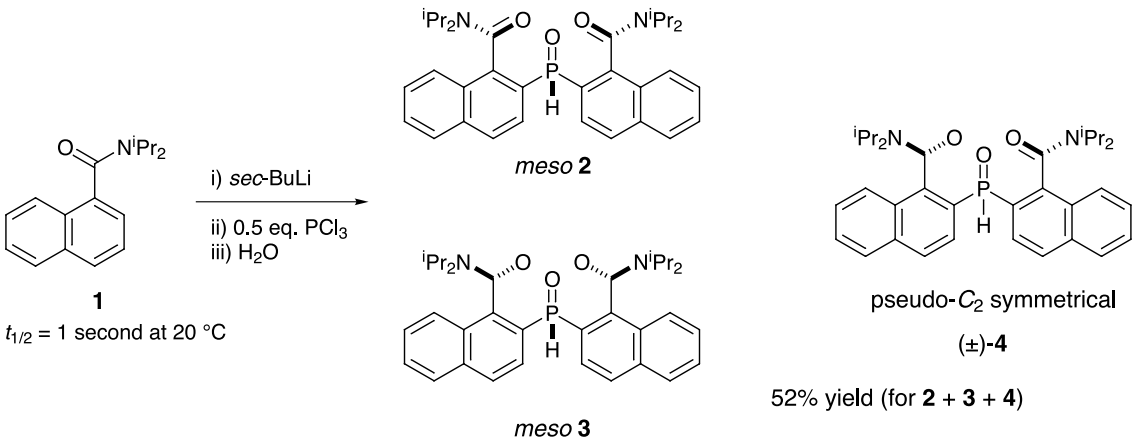
doi:10.1016/j.tet.2004.01.093



Scheme 1. Formation of configurationally unstable phosphinous acids.

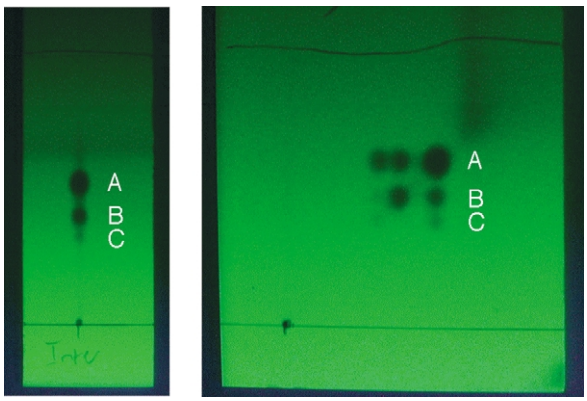


Figure 1. Standard and 2D TLC of phosphinous acids **2**, **3** and **4**.

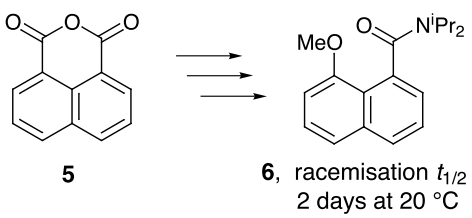
One or two are either not present or too faint to observe. It would appear from the TLC that the top spot (A) interconverts into both B and C but the direct interconversion of B and C is less significant or not present. It seems likely that configuration change will happen by rotation of one chiral axis at a time. If this were the case then the two achiral diastereomers (**2** and **3**) could interconvert only via the chiral diastereomer **4** (but a small amount of **2** might have time to convert into **4** and on to **3** before the second TLC run was performed—thus giving a faint spot). We thus speculated that this top spot (A) represented the racemate (±)-**4**. This was supported by the NMR spectroscopic data.

By ^{31}P NMR spectroscopy, only two of the three species are visible and, assuming similar chromophores, it is therefore the compound represented by spot C which cannot be seen by NMR spectroscopy. Both detectable compounds show the characteristic large coupling constant between phosphorus and hydrogen (484 and 500 Hz). The weaker ^{31}P signal is further split into a triplet by the two protons on the *ortho* positions of the rings (not unlike Fig. 5) while the stronger signal is split into a double doublet (masquerading as an imperfect triplet not unlike Fig. 6). The *ortho* protons in the *meso* compounds are enantiotopic and would give rise to a triplet whereas those in (±)-**4** are diastereotopic and would be expected to give rise to a double doublet. Similar spectra from compounds showing similar properties are reproduced in the next section. We could also see from ^{31}P NMR spectroscopy that the ratio of products was far from 1:1:2 for **2**:**3**:**4** but closer to <0.1:1:4 (or 1:<0.1:4). Since the compounds interconvert we know this is the thermodynamic ratio of compounds. Clearly, the racemic compound is favoured. We speculate that one of the *meso* compounds is destabilised by its larger dipole moment resulting from alignment of two C═O bonds and one P═O bond.

The interconversion rate for these compounds falls in a narrow window: it is sufficiently slow for the compounds to be clearly distinguished by TLC (which had a run time of about 7 min) but sufficiently fast for them to interconvert substantially in less than an hour. Without doing any measurements or calculations, we thus estimated we had diastereomers with half lives of around 30 min.

2.2. Configurationally stable phosphinous acids

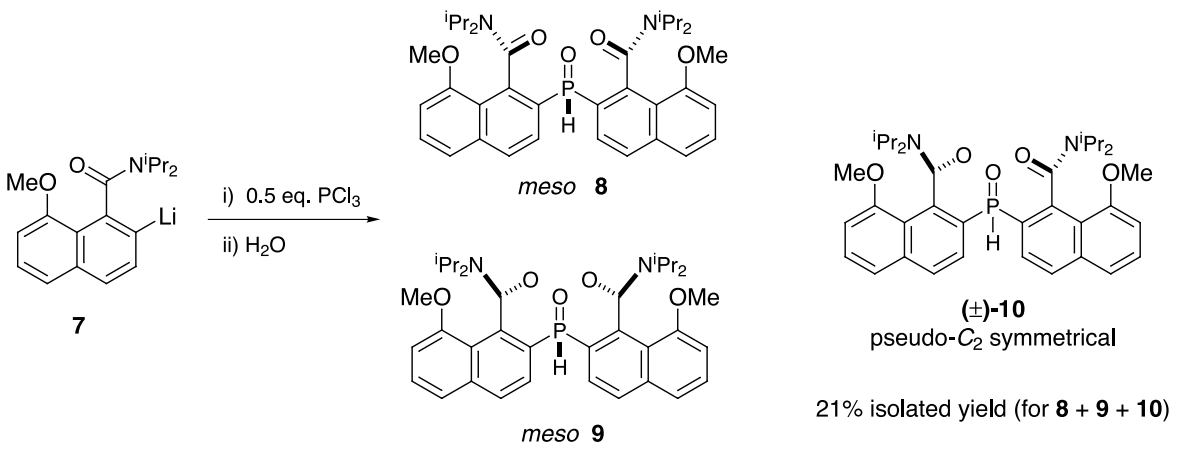
In order to inhibit the interconversion of the diastereomers we set about making the rotation about the chiral axis more difficult. The half-life of naphthamide **1** is one second at 20 °C whereas the half life of naphthamide **6** is 12 days at 20 °C. Starting from anhydride **5**, naphthamide **6** was prepared by known routes (Scheme 2).[7–9]



Scheme 2.

Lithiation of naphthamide **7** proceeds *ortho* to the amide rather than *ortho* to the methoxy group.[9] Reaction of 2 equivalents of lithiated naphthamide **7** with PCl_3 gave phosphinous acids **8** to **10** on workup (Scheme 3).

This time, the two dimensional TLC had all the spots on the diagonal—there was no interconversion (Fig. 2). The three diastereomers fluoresce under UV illumination.



Scheme 3. Formation of configurationally stable phosphinous acids.

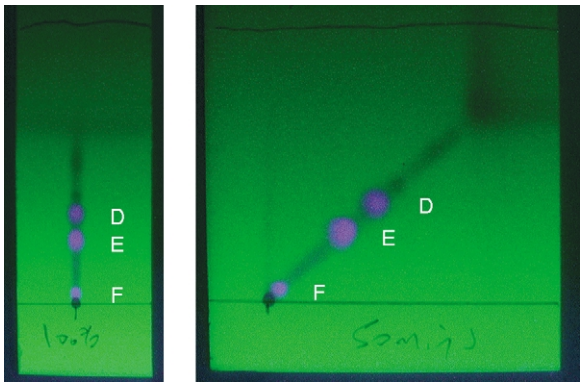


Figure 2. Standard and 2D TLC of phosphinic acids **8**, **9** and **10**.

The ^{31}P NMR spectrum of the crude reaction mixture clearly showed all three signals and demonstrated that the products had been made in a 1:3:5 ratio. Because the compounds do not interconvert, this ratio is the kinetic product ratio instead of the thermodynamic ratio previously observed. The less favoured diastereomer is unable to equilibrate away. And this time, because the compounds could be separated and purified, some of the more interesting aspects of the ^{1}H NMR spectra could also be seen. The two *meso* compounds **8** and **9** should have four diastereotopic sets of methyl groups. Each set contains two methyl groups which are enantiotopic—one of the pair on one naphthamide unit and the other on the other. These four doublets are observed (Fig. 3). However, in the racemic compound, with no symmetry to relate the methyl groups, all eight are diastereotopic and eight sets of doublets are clearly visible (Fig. 4).

The symmetry is reflected in the ^{31}P NMR spectra too. The signal from **8** (or **9**) is a double triplet (Fig. 5) whereas the less symmetrical **10** sports a double double doublet (Fig. 6).

Phosphinous acids usually oxidize all too easily to phosphinic acids. The phosphinic acids were of particular interest because the two *meso* compounds would react to form the same compound and the pseudo C_2 symmetrical **10** would become symmetrical. Disappointingly, reaction of the phosphinous acids with H_2O_2 was slow and we were not able to isolate any phosphinic acid.

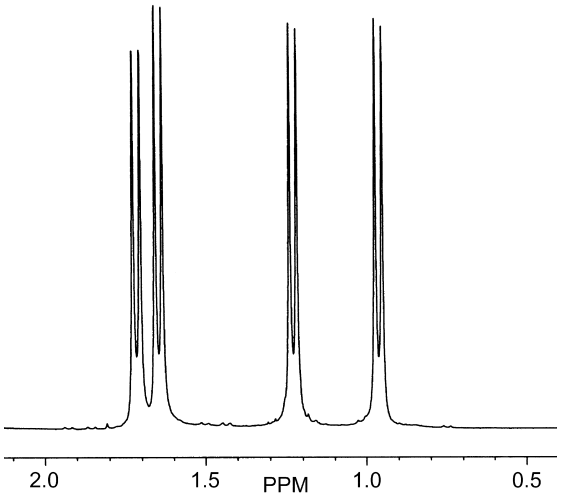


Figure 3. ^{1}H NMR. Four diastereotopic methyl groups in the four ^{i}Pr groups of **8** (or **9**).

2.3. Studies towards the resolution of naphthamide 6

Since phosphinous acids prepared from naphthamide **6** are configurationally stable, preparation from a single enantiomer would lead only to a single enantiomer of diastereomer **10** and we therefore looked into the resolution of **6**. Resolution *after* an electrophile has been introduced has been achieved by Dai et al.[2] In that instance the enantiomers were resolved as diastereomeric camphanic

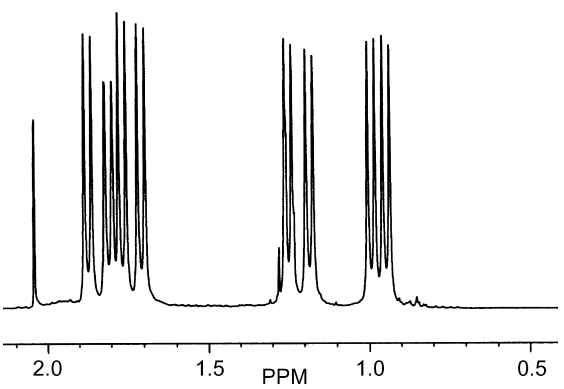


Figure 4. ^{1}H NMR. Eight diastereotopic methyl groups in the four ^{i}Pr groups of (±)-**10**.

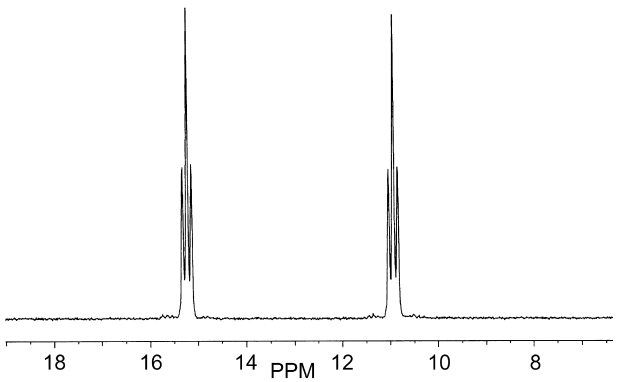


Figure 5. ^{31}P NMR of **8** (or **9**).

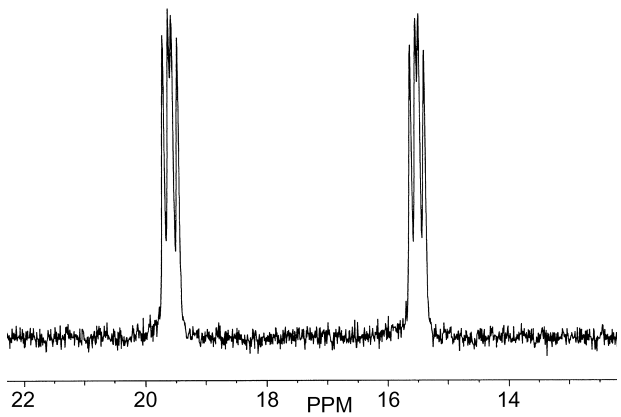
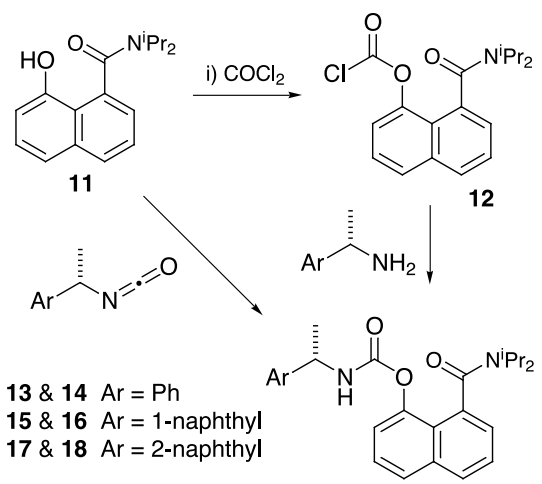


Figure 6. ^{31}P NMR of (±)-**10**.

esters. We decided that the resolution of the intermediate phenol **11** was a good strategy as the phenolic OH provided a means of attaching a resolving agent. The resolving agents were α-methylbenzylamine, and the two related chiral amines with naphthyl rings, which were connected to the phenol by a carbamate linkage. The phenol **11** was reacted with phosgene to give the chloroformate **12** before reaction with one of these three optically pure amines. Carbamates of this kind have been used to resolve alcohols and they are readily removed with trichlorosilane.[10] We also prepared these carbamates by reaction of phenol **11** with isocyanates (Scheme 4).



Scheme 4. Preparation of carbamates.

Although kinetic resolution (and even dynamic kinetic resolution) is conceivable in these reactions, none was observed. Separation of the diastereomers was not possible by column chromatography and our suspicion that they were interconverting was investigated as follows. A sample of the diastereomers **15** and **16** was injected onto a chiral column. Although in principle an achiral phase will separate diastereomers, we achieved much better separation using an OD chiral column. The two diastereomers eluted as shown in Figure 7. Next, we injected another sample but elution was terminated before the first diastereomer emerged from the column. The samples were then left on the column for 15 h thus giving them the opportunity to epimerise. Elution was then restarted (stop–start elution) and the resulting chromatogram contained four peaks. The two new peaks come from the interconversion of the original diastereomers.

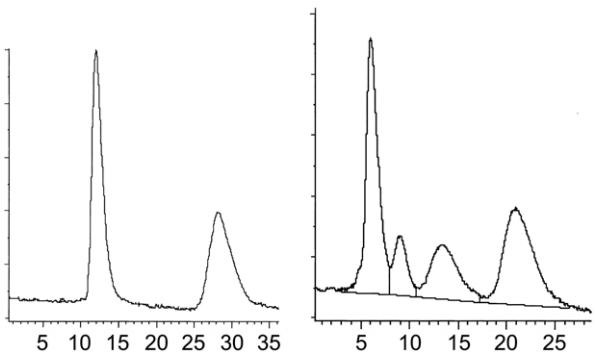
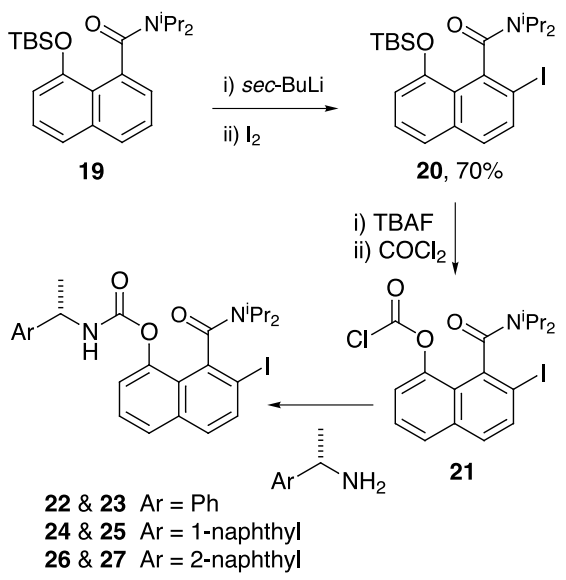


Figure 7. Normal and stop-start elution of carbamates **15** and **16**.

Similar results were seen with the other sets of diastereomers **13** and **14** and **17** and **18**. The rate of interconversion is clearly far too high to be useful. This seemed strange given that methoxynaphthamide **7** has a half-life of 12 days at 20 °C but Clayden has shown the conformational stability of 8-substituted 1-naphthamides depends more on whether the *peri* substituent has a lone pair available to donate into the amide than on substituent size.[11]



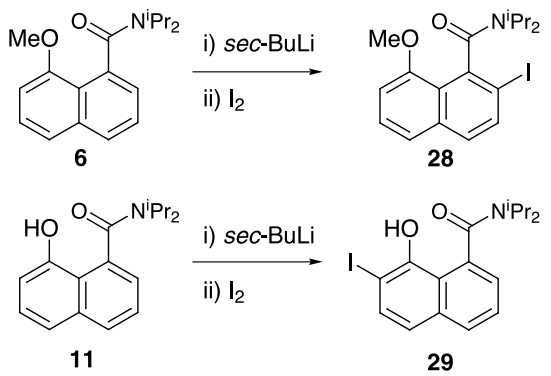
Scheme 5. Preparation of iodinated carbamates.

The oxygen atom of a carbamate is expected to be less effective than that of an ether.

We thus set about making it more difficult for the naphthamide to rotate by introducing a substituent on the other (*ortho*) side and an iodine atom seemed the ideal choice. Not only is iodine big, it could be exchanged for lithium when we were ready to react it with a phosphorus electrophile. Other atropisomers containing iodine have previously been separated[12] and iodine has been reported to have good blocking (or 'buttressing') ability.[13] Phenol **11** was protected as its silyl ether **19** and then reacted with *sec*-BuLi followed by iodine to give iodide **20** (Scheme 5).

Iodination occurred in a 70% yield while bromination was less good (41%). TBAF revealed the phenol, which was then treated with phosgene followed by optically pure amines as before. The HPLC analysis described above was repeated. To our vexation, these diastereomers interconverted too. Unlike the situation with other compounds, iodine was no help on this occasion.

In related experiments, naphthamide **6** could be brominated or iodinated whereas iodination of the unmethylated phenol **11** led to regioisomeric iodination (Scheme 6).



Scheme 6. Iodination of naphthamides **6** and **11**.

3. Conclusion

Although we failed to resolve optically pure naphthamide **6**, the configurational stability of naphthamide **6** and of phosphinous acid **10** suggests that the strategy (using optically pure **6**) is still sound for the stereoselective preparation a single diastereomer and enantiomer of phosphinous acid **10**. It is clear that one of the three diastereomers (with both sets of diastereomers) is not favoured. In both cases it is one of the *meso* diastereomers and when the diastereomers can interconvert (acids **2** to **4**) there becomes so little it is difficult to observe.

4. Experimental

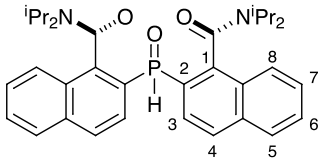
4.1. General

All reactions, unless otherwise stated, were run under an atmosphere of nitrogen in glassware that had been dried overnight in an oven at 150 °C. Anyhdrous solvents were obtained by passing HPLC grade solvents through a modified Grubbs system[14] manufactured by anhydrous engineering. De-oxygenated solvents were prepared by passing a stream of N_2 through the solvent of choice at room temperature via a fine capillary for 2 h prior to use.

Reactions were monitored by TLC using glass-backed silica gel F_{254} plates (Merck) and visualised using $UV_{254\ nm}$ or anisaldehyde solution as appropriate. Flash column chromatography[15] was carried out routinely using 60 Å silica gel (Fluorochem). Reagents were used without further purification from commercial sources unless otherwise stated. Petrol refers to petroleum ether fraction of 40–60 °C boiling point range.

NMR spectra were recorded on a Joel Delta/GX 270, 400, a Lambda 300 or an Eclipse 300 MHz spectrometer. All mass spectra were recorded on a Fisons Autospec mass spectrometer and were determined by electron impact (EI) or chemical impact (CI). IR spectra were recorded on a Perkin–Elmer 881 IR spectrometer in the solid state or as a liquid film. $[\alpha]_D$ Values were recorded on a Perkin–Elmer 241 MC polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer as solids or KBr discs.

High Performance Liquid Chromatography was carried out using a Chiralcel OD column (25 cm×4.6 mm), Gilson model 303 and 305 pumps, dynamic mixer 811C, manomeric module 806, a Gilson 506C system interface module, a Dynamax Rainin absorbance detector at 235 nm operating with a Gilson 712 HPLC system controller software. The compounds were eluted with mixtures of HPLC grade 2-propanol and heptane. Medium Pressure Liquid Chromatography was carried out using a pre-packed column size C (440–37) LiChroprep Si 60 (40–63 μm) liquid chromatography column and a FMI LAB pump model PR-SY.



4.1.1. Bis-[(*N*,*N*-diisopropyl-1-naphthamide)-2-] phosphinous acid 2, 3 and (±)-4. The naphthamide **1** (1.328 g, 5.208 mmol) was dissolved in THF (130 mL) and cooled to −78 °C. TMEDA (0.825 mL, 5.47 mmol) and *sec*-BuLi (4.60 mL of a 1.19 M solution, 5.47 mmol) were added and the reaction was left to stir for 1 h. Phosphorus trichloride (0.25 mL, 2.9 mmol) was added to the yellow solution. The reaction was left to warm to room temperature overnight. Water (1 mL) was added and the reaction was then concentrated under reduced pressure to give a yellow foam. The foam was dissolved in dichloromethane (30 mL) and water (30 mL) was added. The layers were separated and the product was further extracted with dichloromethane (2×30 mL). The organic fractions were combined, dried with anhydrous magnesium sulfate and concentrated under reduced pressure giving a yellow foam. The product was purified by flash chromatography, eluting with 1:1 ethyl

acetate–petroluem ether (40–60 °C), to give the acids (0.76 g, 52%) as a white foam; R_f (ethyl acetate) three diastereomers: 0.52, 0.39 and 0.32; ν_{max} (solid)/cm^{-1} 2227 (P–H), 1622 (C=O), 12078 (P=O), 953 (P–OH); δ_H (300 MHz; $CDCl_3$) 8.57 (1H, d, J_{HP}=499.7 Hz, *meso*, PH), 8.47 (1H, d, J_{HP}=484.0 Hz, racemate, PH), 8.36–7.51 (24H, m, ArH), 3.77–3.52 (8H, m, 8×NCH), 1.87–1.80 (12H, m, racemate, $Me_{A\text{-}D}$), 1.76 (6H, d, J=6.9 Hz, *meso*, 2×Me_A), 1.70 (6H, d, J=6.9 Hz, *meso*, 2×Me_B), 1.35 (6H, d, J=6.6 Hz, *meso*, 2×Me_C), 1.29 (3H, J=6.6 Hz, racemate, Me_E), 1.27 (3H, d, J=6.6 Hz, racemate, Me_F), 1.05 (6H, d, J=6.6 Hz, *meso*, 2×Me_D), 1.04 (3H, d, J=6.6 Hz, racemate, Me_G) and 0.99 (3H, d, J=6.6 Hz, racemate Me_H); δ_C (100 MHz; $CDCl_3$) 167.83 (d, J_{CP}=7.7 Hz, racemate C=O), 167.73 (d, J_{CP}=5.4 Hz, racemate C=O), 167.37 (d, J_{CP}=6.2 Hz, *meso* C=O), 141.53, 141.49, 141.42, 138.75, 138.62, 134.91, 134.89, 134.85, 134.82, 134.79, 134.78, 129.64, 129.52, 129.20, 129.12, 129.09, 129.00, 128.55, 128.52, 128.50, 128.40, 128.36, 128.34, 128.30, 128.25, 127.41, 127.28, 127.21, 127.16, 127.12, 126.58, 126.46, 126.12, 125.76, 125.63, 125.57, 125.47, 125.38, 125.00 and 124.39 (Ar), 51.81 (racemic NCH), 51.66 (racemic NCH and *meso*NCH), 46.71 (racemic NCH), 46.56 (*meso*NCH), 46.37 (racemic NCH), 21.24, 20.69, 20.67, 20.64, 20.58, 20.54, 20.51, 20.46, 20.29, 20.25 and 19.86 (12×Me); δ_P {^{1}H}(121 MHz; $CDCl_3$) 17.12 racemate and 13.80 *meso*; δ_P (121 MHz; $CDCl_3$) 17.12 (ddd [appears as a 'dt' with thickened central line] J_{PH}=483.8, 13.1 Hz) and 13.80 (dt, J_{PH}=499.63 Hz, J_{PH}=12.09 Hz); *m/z* (CI) 557 (12%, M+H$^+$) (Found: M+H$^+$ 557.2933. $C_{34}H_{41}N_2O_3P$ requires M+H$^+$ 557.2927).

4.1.2. (*R*,*s*,*S*)-Bis-[(*N*,*N*-diisopropyl-8-methoxy-1-naphthamide)-2-]phosphinous acid 9, (*R*,*r*,*S*)-bis-[(*N*,*N*-diisopropyl-8-methoxy-1-naphthamide)-2-]phosphinous acid 8, (*R,*R**)-bis-[(*N*,*N*-diisopropyl-8-methoxy-1-naphthamide)-2-]phosphinous acid 10.** The naphthamide **6**[9] (2.28 g, 8.00 mmol) was dissolved in THF (60 mL) cooled to −78 °C and *sec*-BuLi (6.62 mL of a 1.24 M solution, 8.2 mmol) was added to give a green solution. The reaction was left to stir for 80 min and neat phosphorus trichloride (0.350 mL, 3.87 mmol) added. The solution turned yellow and then black. The reaction was left to warm to room temperature overnight. Water (45 mL) was added and the reaction was extracted with dichloromethane (3×40 mL). The organic extracts were combined, dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give a yellow foam. The low running *meso* phosphinous acid was purified by flash chromatography, eluting with ethyl acetate to give a white solid. The solid was crystallised from ethyl acetate to give the *meso* phosphinous acid (46.7 mg, 2%) as off white plates; R_f (ethyl acetate–methanol 9:1) 0.35; ν_{max} (KBr)/cm^{-1} 2975 (MeO stretch), 1628 (C=O), 1211 (P=O), 951 (P–OH); δ_H (300 MHz; $CDCl_3$) 8.49 (1H, d, J_{HP}=499.0 Hz, PH), 7.95 (2H, dd, J_{HP}=14.8, 8.5 Hz, 2×Ar3-H), 7.78 (2H, dd, J=8.5, 2.0 Hz, 2×Ar4-H), 7.48 (2H, t, J=8.0 Hz, 2×Ar6-H), 7.40 (2H, dd, J=8.0, 1.0 Hz, 2×Ar5-H), 6.89 (2H, dd, J=8.0, 1.0 Hz, 2×Ar7-H), 3.91 (6H, s, 2×OMe), 3.58 (2H, septet, J=7.0 Hz, 2×NCH), 3.26 (2H, septet, J=7.0 Hz, 2×NCH), 1.69 (6H, d, J=7.0 Hz, 2×Me_A), 1.63 (6H, d, J=7.0 Hz, 2×Me_B), 1.00 (6H, d, J=7.0 Hz, 2×Me_C) and 0.87 (6H, d, J=7.0 Hz, 2×Me_D); δ_C (100 MHz; $CDCl_3$) 168.15 (d, J_{CP}=5.0 Hz, 2×C=O), 156.51, 138.68 (d, J_{CP}=9.0 Hz), 136.48 (d, J_{CP}=2.0 Hz), 128.48, 128.36, (d, J_{CP}=6.0 Hz), 128.22 (d, J_{CP}=5.0 Hz), 127.24 (d, J_{CP}=101.0 Hz), 121.59, (d, J_{CP}=11.0 Hz), 120.95, 106.85 (Ar), 55.60 (2×OMe), 50.77, 46.48 (2×NCH), 21.16, 20.69, 20.42 and 19.61 (4×Me); δ_P {^{1}H}(121 MHz; $CDCl_3$) 19.69; δ_P (300 MHz; $CDCl_3$) 19.69 (dt, J_{PH}=499.0 Hz, $J_{P3\text{-}H}$=15.0 Hz); *m/z* (EI) 617 (38%, M) (Found: M 616.3056. $C_{36}H_{45}N_2O_5P$ requires M 616.3066).

The high running *meso* phosphinous acid was purified by MPLC, eluting with 6:3:1 petroleum ether (40–60 °C)–ethyl acetate–methanol, to give a white solid (353.4 mg, 14%) which was crystallised from ethyl acetate to give the *meso* phosphinous acid as white needles, mp 233–239 °C (from ethyl acetate); R_f (ethyl acetate) 0.28; ν_{max} (KBr)/cm^{-1} 2973 (MeO stretch), 2223 (P–H), 1631 (C=O), 1212 (P=O) and 935 (P–OH); δ_H (300 MHz; $CDCl_3$) 8.69 (1H, d, J_{HP}=521.0 Hz, PH), 7.77 (2H, dd, J=8.0, 2.0 Hz, 2×ArH), 7.48 (6H, m, 2×Ar3-H), 6.90 (2H, dd, J=8.0, 1.0 Hz, 2×ArH), 3.92 (6H, s, 2×OMe), 3.62 (2H, septet, J=7.0 Hz, 2×NCH), 3.43 (2H, septet, J=7.0 Hz, 2×NCH) 1.72 (6H, d, J=7.0 Hz, 2×Me_A), 1.65 (6H, d, J=7.0 Hz, 2×Me_B), 1.23 (6H, d, J=7.0 Hz, 2×Me_C) and 0.96 (6H, d, J=7.0 Hz, 2×Me_D); δ_C (100 MHz; $CDCl_3$) 168.02 (d, J_{CP}=5.0 Hz, 2×C=O), 156.36, 138.68 (d, J_{CP}=12.0 Hz), 136.57 (d, J_{CP}=2.0 Hz), 128.52, 128.15, (d, J_{CP}=7.0 Hz), 128.04, (d, J_{CP}=8.0 Hz), 126.09 (d, J_{CP}=102.0 Hz), 121.07, (d, J_{CP}=11.0 Hz), 120.94, 106.43 (Ar), 55.24 (2×OMe), 51.01, 46.43 (2×NCH), 20.48, 20.47, 20.42 and 19.66 (4×Me); δ_P {^{1}H}(121 MHz; $CDCl_3$) 13.08; δ_P (121 MHz; $CDCl_3$) 13.08 (dt, J_{PH}=521.0 Hz, $J_{P3\text{-}H}$=11.0 Hz); *m/z* (EI) 617 (40%, M) (Found: M 616.3060. $C_{36}H_{45}N_2O_5P$ requires M 616.3066).

The racemate **10** was purified by MPLC, eluting with 6:3:1 petroleum ether (40–60 °C)–ethyl acetate–methanol, to give the phosphinous acid (114.6 mg, 5%) as an off-white solid; R_f (ethyl acetate) 0.37; ν_{max} (KBr)/cm^{-1} 2973 (Me-O stretch), 2381 (P–H), 1628 (C=O), 1212 (P=O), 954 (P–OH); δ_H (300 MHz; $CDCl_3$) 8.56 (1H, dd, J=11.0, 9.0 Hz, ArH), 8.15 (1H, d, J_{HP}=495.0 Hz, PH), 7.95 (1H, dd, J=18.0, 9.0 Hz, ArH), 7.79 (1H, dd, J=9.0, 2.0 Hz, ArH), 7.69 (1H, dd, J=9.0, 2.0 Hz, ArH), 7.47–7.33 (4H, m, 4×ArH), 6.90–6.86 (2H, m, 2×ArH), 3.95 (6H, s, 2×OMe), 3.72–3.38 (4H, m, 4×NCH), 1.87 (3H, d, J=7.0 Hz, Me_A), 1.81 (3H, d, J=7.0 Hz, Me_B), 1.77 (3H, d, J=7.0 Hz, Me_C), 1.71 (3H, d, J=7.0 Hz, Me_D, 1.28–1.17 (6H, m, Me_E and Me_F), 0.99 (3H, d, J=7.0 Hz, Me_G), 0.95 (3H, d, J=7.0 Hz, Me_H); δ_C (100 MHz; $CDCl_3$) 169.14 (d, J_{CP}=7.0 Hz, C=O), 168.40 (d, J_{CP}=5.0 Hz, C=O), 156.55, 156.15, 138.95 (d, J_{CP}=8.0 Hz), 136.50 (d, J_{CP}=2.0 Hz), 136.40 (d, J_{CP}=2.0 Hz), 135.44 (d, J_{CP}=14.0 Hz), 129.27 (d, J_{CP}=12.0 Hz), 128.35, 128.24, 128.23 (d, J_{CP}=7.0 Hz), 127.26 (d, J_{CP}=22.0 Hz), 125.62 (d, J_{CP}=100.0 Hz), 121.48 (d, J_{CP}=12.0 Hz), 121.25, 120.97, 120.23, 106.59, 106.38 (Ar), 55.34 (OMe), 55.27 (OMe), 51.39, 51.05 46.56, 46.29 (2×NCH), 21.28, 20.82, 20.76, 20.72, 20.29, 20.08, 19.75 and 19.38 (8×Me); δ_P {^{1}H}(121 MHz; $CDCl_3$) 17.52; δ_P (121 MHz; $CDCl_3$) 17.52 (ddd, J_{PH}=495.0 Hz, J_{PH}=18.0, 11.0 Hz); *m/z* (EI) 616 (60%, M) (Found: M 616.3069. $C_{36}H_{45}N_2O_5P$ requires M 616.3066).

4.1.3. *N*,*N*-Diisopropyl-8-chloroformyl-1-naphthamide 12. Phosgene (3.9 mL of a 20% wt solution in toluene, 7.4 mmol) was dissolved in dry toluene (6.2 mL). The alcohol **11** (510 mg, 1.88 mmol) was dissolved in toluene (20 mL) and pyridine (0.17 mL, 2.1 mmol) was added. The alcohol solution was added dropwise to the phosgene solution at −10 °C to give a yellow suspension. The cooling bath was removed and the reaction was left to stir at room temperature for 2 h. The chloroformate was concentrated under reduced pressure at 40 °C to give a yellow solid and dissolved in dry dichloromethane (10 mL) and used without further purification.

4.1.4. *N*,*N*-Diisopropyl-8-[(*R*)-1-(2-naphthyl) ethyl carbamoyl]-1-naphthamides 17 and 18. A solution of chloroformate **12** in dichloromethane (5.0 mL, 0.94 mmol) was added to a solution of (*R*)-(+)-1-(2-naphthyl)ethylamine (0.16 g, 0.96 mmol) and pyridine (0.17 mL, 2.1 mmol) in dichloromethane (4 mL). The reaction was left to stir for 25 h. The reaction was diluted with dichloromethane (10 mL) and washed with 1 M HCl (2×25 mL) and water (25 mL). The organic extract was dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give a pale green foam. The product was purified by flash chromatography, eluting with 7:2:1 petroleum ether (40–60 °C)–ethyl acetate–methanol to give the carbamates **17** and **18** (234 mg, 53.2%) as a white foam; R_f (petroleum ether (40–60 °C): ethyl acetate–methanol 7:2:1) two diastereomers: 0.32 and 0.27; ν_{max} (KBr)/cm^{-1} 1740 (ROC═ON), 1619 (C═O), 1507 (NH); δ_H (300 MHz; $CDCl_3$) 7.8–7.2 (26H, m, 26×ArH), 6.43 (1H, d, *J*=7.7 Hz, NH), 6.36 (1H, d, *J*=7.0 Hz, NH), 5.12–5.00 (2H, m, 2×MeC*H*N), 3.64–3.29 (4H, m, 4×Me_2CNH), 1.69 (3H, d, *J*=7.5 Hz, Me), 1.64 (3H, d, *J*=6.0 Hz, Me), 1.62 (6H, d, *J*=6.0 Hz, 2×*Me*CHN), 1.53 (3H, d, *J*=7.0 Hz, Me), 1.43 (3H, d, *J*=7.5 Hz, Me), 1.10 (3H, d, *J*=7.5 Hz, Me),1.00 (3H, d, *J*=6.6 Hz, Me), 0.95 (3H, d, *J*=6.2 Hz, Me) and 0.92 (3H, d, *J*=6.2 Hz, Me); δ_C (100 MHz; $CDCl_3$) 172.10 (C═O), 153.58, 153.38, 147.41, 147.35, 140.53, 140.22, 135.22, 135.16, 133.35, 133.32, 132.79, 132.71, 128.53, 128.48, 128.35, 127.99, 127.94, 127.58, 127.54, 126.09, 126.02, 125.79, 125.70, 125.52, 125.04, 124.83, 124.50, 124.35, 124.32, 124.25, 122.84, 122.54, 118.12, 117.47 (Ar), 51.50, 51.40, 51.06, 50.95, 45.68, 45.59 (6×NCH), 22.43, 21.94, 21.75, 21.64, 20.33, 20.24, 20.20, 19.93 and 19.80 (10×Me) *m*/*z* (EI) 468 (44%, M+H$^+$) (Found: M 468.2398. $C_{30}H_{32}N_2O_3$ requires M 468.2413).

4.1.5. *N*,*N*-Diisopropyl-8-[(*R*)-1-(1-naphthyl) ethyl carbamoyl]-1-naphthamides 15 and 16. A solution of chloroformate **12** in dichloromethane (5.0 mL, 0.94 mmol) was added to a solution of (*R*)-(+)-1-(1-naphthyl)ethylamine (0.15 mL, 0.93 mmol) and pyridine (0.17 mL, 2.1 mmol) in dichloromethane (4 mL). The reaction was left to stir for 25 h. The reaction was diluted with dichloromethane (10 mL) and washed with HCl 1 M (2×25 mL) and water (25 mL). The organic extract was dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give a pale brown foam. The product was purified by flash chromatography, eluting with 7:2:1 petroleum ether (40–60 °C)–ethyl acetate–methanol to give the carbamates **15** and **16** (119 mg, 27.3%) as a white foam; R_f (petroleum ether (40–60 °C)–ethyl acetate–methanol 7:2:1) two diastereomers: 0.32, 0.27; ν_{max} (KBr)/cm^{-1} 1740 (ROC═ON), 1620 (C═O), 1507 (NH); δ_H (300 MHz; $CDCl_3$) 7.8–7.2 (26H, m, ArH), 6.43 (1H, d, *J*=7.7 Hz, NH), 6.36 (1H, d, *J*=7.0 Hz, NH), 5.12–5.00 (2H, m, MeC*H*N), 3.64–3.29 (4H, m, Me_2CNH), 1.69 (3H, d, *J*=7.5 Hz, Me), 1.64 (3H, d, *J*=6.0 Hz, Me), 1.62 (6H, d, *J*=6.0 Hz, 2×*Me*CHN), 1.53 (3H, d, Me), 1.43 (3H, d, *J*=7.5 Hz, Me), 1.1 (3H, d, *J*=7.5 Hz, Me), 1.0 (3H, d, *J*=6.6 Hz, Me), 0.95 (3H, d, *J*=6.2 Hz, Me) and 0.92 (3H, d, *J*=6.2 Hz, Me); δ_C (75 MHz; $CDCl_3$) 172.16, 172.12 (C═O), 153.59, 153.41, 147.62, 147.43, 138.70, 138.20, 135.25, 135.15, 133.92, 133.87, 133.44, 133.41, 131.01, 130.60, 128.81, 128.73, 128.48, 128.20, 127.95, 126.38, 126.28, 126.08, 125.69, 125.61, 125.54, 125.49, 125.31, 125.08, 124.81, 124.34, 124.20, 123.36, 123.04, 122.84, 122.80, 122.50, 122.16, 118.07, 117.34 (Ar), 51.40, 50.83, 47.30, 46.70, 45.64, 45.46 (6×NCH), 21.91, 21.66, 21.20, 20.38, 20.34, 20.28, 20.11, 19.96 and 19.71 (10×Me) *m*/*z* (EI) 469 (56%, M+H$^+$) (Found: M 468.2439. $C_{30}H_{32}N_2O_3$ requires M 468.2413).

4.1.6. *N*,*N*-Diisopropyl-8-[(*R*)-α-methylbenzyl carbamoyl]-1-naphthamides 13 and 14. *Method 1*. Phosgene (2.0 mL of a 20% wt solution in toluene, 3.8 mmol) was added to toluene (3 mL). The alcohol **11** (251 mg, 0.921 mmol) and pyridine (0.1 mL, 1 mmol) was dissolved in toluene (10 mL). The alcohol **11** solution was added dropwise to the phosgene solution at −10 °C to give a yellow suspension. The cooling bath was removed and the reaction was left to stir at room temperature for 2 h. The chloroformate was concentrated under reduce pressure at 40 °C to give a yellow solid and dissolved in dichloromethane (10 mL). The chloroformate was added to a solution of (*R*)-(+)-α-methylbenzylamine (0.12 mL, 0.93 mmol) and pyridine (0.1 mL, 1 mmol) in dichloromethane (4 mL). The residual chloroformate was dissolved in dichloromethane (2.4 mL) and added to the mixture. The reaction was left to stir for 13 h. The reaction was diluted with dichloromethane (10 mL) and washed with HCl 1 M (2×25 mL) and water (25 mL). The organic extract was dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give a pale green foam. The product was purified by flash chromatography, eluting with 7:2:1 petroleum ether (40–60 °C)–ethyl acetate–methanol to give the carbamates **13** and **14** (190 mg, 49%) as a white foam.

Method 2. The alcohol **11** (103 mg, 0.38 mmol) and DMAP (1.8 mg, 0.015 mmol) was dissolved in dichloromethane (1.7 mL). Triethylamine (0.05 mL, 0.36 mmol) was added followed by (*S*)-(−)-α-methylbenzylisocyanate (70 μL, 0.50 mmol). The reaction was left to stir for 3 days. It was diluted with dichloromethane (10 mL) and washed with HCl 1 M (2×10 mL) and the aqueous layer was extracted with dichloromethane (2×10 mL). The organic extracts were combined and dried with anhydrous magnesium sulfate. It was concentrated under reduced pressure to give a white foam. The product was purified by flash chromatography, eluting with 7:2:1 petroleum ether (40–60 °C)–ethyl acetate–methanol to give the carbamates **13** and **14** (77 mg, 49%) as a white foam; R_f (petroleum ether (40–60 °C): ethyl acetate–methanol 7:2:1) two diastereomers: 0.30 and 0.25; ν_{max} (KBr)/cm^{-1} 1740 (ROC═ON), 1619

(C═O), 1507 (NH); δ_H (300 MHz; $CDCl_3$) 7.83 (1H, d, J=8.4 Hz, ArH), 7.82 (1H, d, J=8.1 Hz, ArH), 7.70–7.56 (2H, m, ArH), 7.50–7.20 (18H, m, ArH), 6.35 (1H, d, J=7.3 Hz, NH), 6.21 (1H, d, J=7.0 Hz, NH), 4.94–4.82 (2H, m, MeC*H*N), 3.63–3.32 (4H, m, Me_2CN*H*), 1.67 (3H, d, J=7.0 Hz, Me), 1.61 (3H, d, J=6.6 Hz, Me), 1.57–1.52 (9H, m, 3×Me), 1.53 (3H, d, J=7.0 Hz, Me), 1.09 (3H, d, J=6.6 Hz, Me) and 1.02–0.92 (9H, m, 3×Me); δ_C (75 MHz; $CDCl_3$) 171.97 (C═O), 153.51, 153.38, 147.40, 147.29, 143.24, 142.77, 135.19, 135.15, 133.36, 133.35, 128.56, 128.52, 128.49, 128.48, 127.39, 127.14, 126.50, 126.07, 126.03, 125.91, 125.48, 125.47, 124.96, 124.71, 124.28, 124.19, 122.81, 122.53, 118.12, 117.48 (Ar), 51.39, 51.30, 50.98, 50.89, 45.64, 45.57 (6×NCH), 22.51, 21.87, 21.69, 21.53, 20.32, 20.31, 20.24, 20.21, 19.93 and 19.82 (10×Me); *m*/*z* (CI) (30%, $M+H^+$) (Found: $M+H^+$ 419.2335. CHNO requires $M+H^+$ 419.2335).

4.1.7. *N*,*N*-Diisopropyl-8-[*tert*-butyl(dimethyl) silyloxy]-1-naphthamide 19. Sodium hydride 60% wt (0.337 g, 8.42 mmol) was suspended in THF (10 mL) and the alcohol **11** (2.0 g, 7.4 mmol) was dissolved in THF (15 mL). The sodium hydride suspension was cooled to −10 °C and the alcohol solution was slowly added to form an orange solution. The solution was left to stir at this temperature for 30 min and then warmed to room temperature and left to stir at this temperature for 30 min. It was then cooled to −10 °C and TBSCl (1.232 g, 8.170 mmol) in THF (5 mL) was added. The bright orange solution was left to stir for 17 h. The solution was diluted with water (50 mL) and the organic layer separated. The aqueous layer was extracted with diethyl ether (2×50 mL). The organic extracts were combined and washed with brine (50 mL), dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give a crude brown solid. The crude was crystallised from diethyl ether to give the silyl ether **19** (1.65 g, 58.1%) as grey cubes, mp 115–120 °C (from diethyl ether); R_f (Ethyl acetate–petroleum ether (40–60 °C) 1:5) 0.55; ν_{max} (KBr)/cm^{-1} 1640 (NC═O), 1265 ($SiMe_2$) and 854 ($SiMe_2$); δ_H (300 MHz; $CDCl_3$) 7.76 (1H, dd, J=8.0, 1.1 Hz, Ar2-H), 7.44 (1H, t, J=8.0 Hz, ArH), 7.40 (1H, d, J=8.3 Hz, ArH), 7.31 (1H, t, J=8.0 Hz, ArH), 7.18 (1H, dd, J=7.1, 1.3 Hz, ArH), 6.97 (1H, dd, J=7.4, 1.1 Hz, Ar7-H), 3.64 (1H, septet, J=6.8 Hz, NCH), 3.25 (1H, septet, J=6.7 Hz, NCH), 1.65 (3H, d, J=7.1 Hz, Me), 1.55 (3H, d, J=6.9 Hz, Me), 1.06 (3H, d, J=6.6 Hz, Me), 1.01 (9H, s, *tert*-BuSi), 0.85 (3H, d, J=6.6 Hz, Me), 0.46 (3H, s, $SiMe_AMe_B$) and 0.20 (3H, s, $SiMe_AMe_B$); δ_C (75 MHz; $CDCl_3$) 171.7 (C═O), 152.2, 135.5, 135.1, 128.4, 125.9, 125.5, 125.0, 124.0, 121.6, 114.9 (Ar), 50.3, 45.6 (2×NCH), 27.2 ($SiCMe_3$), 22.7 ($SiCMe_3$), 21.0, 20.2, 19.9, 19.8 (4×Me), −2.3 and −3.5 (2×SiMe); *m*/*z* (EI) 385 (24%, M) (Found: M 385.2426. $C_{23}H_{35}NO_2Si$ requires M 385.2437).

4.1.8. *N*,*N*-Diisopropyl-8-[*tert*-butyl (dimethyl) silyloxy]-2-iodo-1-naphthamide 20. The silyl ether **19** (0.90 g, 2.3 mmol) was dissolved in THF (50 mL) and cooled to −78 °C. *sec*-BuLi (2.15 mL, 2.60 mmol) was added dropwise to give an orange solution. The reaction was left to stir for 40 min. Iodine (0.929 g, 3.66 mmol) was dissolved in THF (6 mL) and added to the lithiated ether to give a red solution. The reaction was left to warm to room temperature. After 20 h aqueous sodium thiosulfate solution (40 mL, 1 M) was added and the organic fraction drained. The aqueous layer was extracted with diethyl ether (3×40 mL). The organic extracts were combined, dried with anhydrous magnesium sulfate and concentrated under reduce pressure to give a black solid. The crude was crystallised from diethyl ether to give the iodo silyl ether **20** (834 mg, 70%) as white needles, mp 143–144 °C; R_f (diethyl ether–petroleum ether (40–60 °C) 1:5) 0.31; ν_{max} (solid)/cm^{-1} 1636 (NC═O), 1264 ($SiMe_2$), 830 ($SiMe_2$); δ_H (300 MHz; $CDCl_3$) 7.86 (1H, d, J=8.8 Hz, Ar3-H), 7.43 (1H, d, J=8.8 Hz, Ar4-H), 7.41 (1H, dd J=7.5, 1.5 Hz, Ar5-H), 7.35 (1H, t, J=7.7 Hz, Ar6-H), 7.00 (1H, dd J=7.3, 1.5 Hz, Ar7-H), 3.86 (1H, septet, J=6.9 Hz, NCH), 3.04 (1H, septet, J=6.8 Hz, NCH), 1.68 (3H, d, J=7.0 Hz, Me), 1.64 (3H, d, J=6.6 Hz, Me), 1.04 (3H, d, J=7.0 Hz), 0.99 (9H, s, ^{t}BuSi), 0.95 (3H, d, J=7.0 Hz), 0.47 (3H, s, $SiMe_AMe_B$) and 0.09 (3H, s, $SiMe_AMe_B$); δ_C (75 MHz; $CDCl_3$) 170.0 (C═O), 151.6, 138.2, 137.0, 134.6, 129.4, 126.6, 121.6, 121.8, 116.5, 94.2 (Ar), 50.9, 46.3 (2×NCH), 27.4 ($SiCMe_3$), 22.7 ($SiCMe_3$), 21.1, 20.9, 20.7, 19.6 (4×Me), −2.4 and −3.9 (2×SiMe); *m*/*z* (EI) 511 (16%, M) (Found: M 511.1385. $C_{23}H_{34}NO_2SiI$ requires M 511.1404).

4.1.9. *N*,*N*-Diisopropyl-2-bromo-8-[*tert*-butyl (dimethyl) silyloxy]-1-naphthamide. The silyl ether **19** (526 mg, 1.36 mmol) was dissolved in THF (25 mL). It was cooled to −78 °C and *sec*-BuLi (1.30 mL, 1.69 mmol) was added dropwise to give an orange solution. The reaction was left to stir for 30 min. Bromine (0.1 mL, 2 mmol) was dissolved in THF (23 mL) and was added dropwise to the lithiated ether to give a green solution. The reaction was left to warm to room temperature. After 20 h aqueous sodium thiosulfate (22 mL of a 1 M solution) was added and the layers separated. The aqueous layer was extracted with ether (3×25 mL). The organic extracts were combined, dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give a crude white solid. The product was purified by flash chromatography, eluting with 1:9 diethyl ether–petroleum ether (40–60 °C) to give the bromo silyl ether (0.26 g, 41%) as a white solid, mp 144–151 °C (from diethyl ether); R_f (ethyl acetate–petroleum ether (40–60 °C) 1:1) 0.73; ν_{max} (KBr)/cm^{-1} 1638 (NC═O), 1266 ($SiMe_2$), 853 ($SiMe_2$), 786 (ArBr); δ_H (75 MHz; $CDCl_3$) 7.59 (1H, d, J=8.8 Hz, Ar3-H), 7.59 (1H, d, J=8.8 Hz, Ar4-H), 7.42 (1H, dd J=8.0, 1.5 Hz, Ar5-H), 7.34 (1H, t, J=7.7 Hz, Ar6-H), 7.00 (1H, dd J=7.5, 1.3 Hz, Ar7-H), 3.84 (1H, septet, J=6.9 Hz, NCH), 3.12 (1H, septet, J=6.7 Hz, NCH), 1.66 (3H, d, J=6.9 Hz, Me), 1.60 (3H, d, J=7.0 Hz, Me), 1.02 (3H, d, J=6.6 Hz, Me), 1.01 (9H, s, ^{t}BuSi), 0.98 (3H, d, J=6.6 Hz, Me), 0.46 (3H, s, $SiMe_AMe_B$) and 0.01 (3H, s, $SiMe_AMe_B$); δ_C (300 MHz; $CDCl_3$) 168.3 (C═O), 151.8, 134.2, 133.9, 130.9, 129.5, 126.4, 125.4, 121.8, 119.4, (Ar), 50.8, 43.3 (2×NCH), 27.3 ($SiCMe_3$), 22.8 ($SiCMe_3$), 21.5, 20.5, 20.3, 19.6 (4×Me), −2.5 and −3.8 (2×SiMe); *m*/*z* (EI) 464 (18%, $M+H^+$) (Found: M 463.1529. $C_{23}H_{34}NO_2Si^{79}Br$ requires M 463.1542).

4.1.10. *N*,*N*-Diisopropyl-8-hydroxy-2-iodo-1-naphthamide. The iodo silyl ether **20** (300 mg, 0.590 mmol) was dissolved in THF (4.8 mL) and the flask was covered in foil. To this TBAF (0.59 mL of a 1 M solution in THF, 0.59 mmol) was added and the reaction was left to stir for 16 h. It was concentrated under reduced pressure and

purified by flash chromatography, eluting with 2:5 ethyl acetate–petroleum ether (40–60 °C) to give the iodo alcohol (235.8 mg, 100%) as off-white cubes, mp 227–230 °C (from ethyl acetate); R_f (ethyl acetate–petroleum ether (40–60 °C) 1:5) 0.27; ν_{max} (solid)/cm^{-1} 3416 (OH); 1605 (NC=O); δ_H (300 MHz; $CDCl_3$) 8.82 (1H, s, OH), 7.71 (1H, d, J=8.8 Hz, Ar3-H), 7.20 (1H, d, J=8.8 Hz, Ar4-H), 6.82 (1H, d, J=7.3 Hz, Ar5-H), 6.66 (1H, t, J=7.9 Hz, Ar6-H), 6.36 (1H, d, J=6.6 Hz, Ar7-H), 3.57 (1H, septet, J=6.9 Hz, NCH), 3.36 (1H, septet, J=6.7 Hz, NCH), 1.7 (3H, d, J=7.0 Hz, Me), 1.68 (3H, d, J=7.0 Hz, Me), 1.19 (3H, d, J=6.6 Hz, Me) and 0.98 (3H, d, J=7.0 Hz, Me); δ_C (75 MHz; $CDCl_3$) 173.03 (C=O), 151.27, 137.32, 135.29, 133.96, 129.38, 126.58, 123.35, 119.45, 113.29, 91.19 (Ar), 52.01, 46.70 (2×NCH), 20.47, 20.37, 19.59 and 19.51 (4×Me); *m/z* (EI) 397 (40%, M) (Found: M 397.0539. $C_{23}H_{34}NO_2SiI$ requires M 397.0539).

4.1.11. *N*,*N*-Diisopropyl-2-iodo-8-[(*R*)-1-(2-naphthyl) ethyl carbamoyl]-1-naphthamides 26 and 27. Phosgene (0.45 mL of a 20% wt solution in toluene, 0.85 mmol) was added to toluene (0.55 mL). *N*,*N*-Diisopropyl-8-hydroxy-2-iodo-1-naphthamide (70 mg, 0.26 mmol), DMAP (10.1 mg, 0.0827 mmol) and pyridine (0.020 mL, 0.25 mmol) were dissolved in toluene (3.2 mL). The solution of the naphthol was added dropwise to the phosgene solution at −10 °C to give a yellow suspension. The cooling bath was removed and the flask was covered in foil and the reaction was left to stir at room temperature for 6 h. The chloroformate **21** was concentrated under reduced pressure at 40 °C to give a yellow solid and dissolved in dichloromethane (1 mL). A solution of (*R*)-(+)-1-(2-naphthyl)ethylamine (37.1 mg, 0.21 mmol) and pyridine (0.020 mL, 0.25 mmol) in dichloromethane (0.9 mL) was added to the chloroformate **21** solution which turned dark green. The reaction was covered with foil and left to stir overnight. The reaction was diluted with dichloromethane (40 mL) and washed with HCl 1 M (2×20 mL) and water (20 mL). The aqueous fractions were collected and washed with dichloromethane (2×10 mL). The organic extracts were combined, dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give a yellow solid. The product was purified by flash chromatography, eluting with 7:2:1 petroleum ether (40–60 °C)–ethyl acetate–methanol to give the carbamates **26** and **27** (14 mg, 13%) as a white foam; R_f (petroleum ether (40–60 °C)–ethyl acetate–methanol 7:2:1) two diastereomers; 0.42 and 0.34; ν_{max} (solid)/cm^{-1} 1738 (ROC=ON), 1615 (C=O), 1561 (NH); δ_H (300 MHz; $CDCl_3$) 7.90–7.40 (24H, m, ArH), 6.71 (1H, d, J=7.3 Hz, NH), 6.58 (1H, d, J=7.0 Hz, NH), 5.06–4.92 (2H, m, 2×MeC*H*N), 3.66–3.50 (2H, m, 2×Me_2CN*H*), 3.25–3.06 (2H, m, 2×Me_2CN*H*), 1.72–1.56 (18H, m, 6×Me), 1.16 (3H, d, J=6.6 Hz, Me), 1.11 (3H, d, J=6.6 Hz, Me), 0.99 (3H, d, J=6.8 Hz, Me) and 0.91 (3H, d, J=6.8 Hz, Me); δ_C (75 MHz; $CDCl_3$) 171.27 (C=O), 153.42, 149.44, 147.00, 146.62, 136.94, 136.90, 136.87, 134.27, 134.16, 133.39, 133.34, 132.81, 132.74, 129.49, 129.43, 129.00, 128.46, 128.40, 128.01, 127.98, 127.61, 127.54, 126.90, 126.86, 126.11, 126.00, 125.79, 125.70, 125.26, 124.95, 124.89, 124.72, 124.63, 124.59, 124.50, 119.25, 117.86, 94.05 (Ar), 51.65, 51.62, 51.57, 51.51, 46.53, 46.50 (6×NCH), 22.35, 22.14, 22.11, 21.87, 20.58, 20.38, 20.31, 20.27 and 20.25 (10×Me); *m/z* (CI) 595 (50%, M+H$^+$).

4.1.12. *N*,*N*-Diisopropyl-2-iodo-8-[(*R*)-1-(1-naphthyl) ethyl carbamoyl]-1-naphthamides 24 and 25. Phosgene (0.90 mL of a 20% wt solution in toluene, 1.7 mmol) was added to toluene (1 mL). *N*,*N*-Diisopropyl-8-hydroxy-2-iodo-1-naphthamide (153 mg, 0.564 mmol), DMAP (12 mg, 0.098 mmol) and pyridine (0.050 mL, 0.57 mmol) were dissolved in toluene (5.6 mL). The solution of the naphthol was added dropwise to the phosgene solution at 0 °C to give a yellow suspension. The cooling bath was removed and the reaction flask was covered in foil. The reaction was left to stir at room temperature for 4.3 h. The chloroformate **21** was concentrated under reduced pressure at 40 °C to give a yellow solid which was dissolved in dichloromethane (3 mL). A solution of (*R*)-(+)-1-(1-naphthyl)ethylamine (0.10 mL, 0.62 mmol) and pyridine (0.050 mL, 0.57 mmol) in dichloromethane (1.9 mL) was added to the chloroformate **21** solution which turned instantly brown. The reaction was covered with foil and left to stir for 24 h. The reaction was diluted with dichloromethane (40 mL) and washed with HCl 1 M (2×20 mL) and water (20 mL). The aqueous fractions were collected and washed with dichloromethane (2×10 mL). The organic extracts were combined, dried with anhydrous magnesium sulfate and concentrated under reduced pressure to give a yellow solid. The product was purified by flash chromatography, eluting with 7:2:1 petroleum ether (40–60 °C)–ethyl acetate–methanol to give the carbamates **24** and **25** (36 mg, 17%) as a dark green solid; R_f (petroleum ether (40–60 °C)–ethyl acetate–methanol 7:2:1) two diastereomers: 0.47, 0.38; ν_{max} (solid)/cm^{-1} 1738 (ROC=ON), 1615 (C=O), 1513 (NH); δ_H (300 MHz; $CDCl_3$) 8.19 (1H, d, J=8.4 Hz, ArH), 8.15 (1H, d, J=8.1 Hz, ArH), 7.90–7.37 (22H, m, ArH), 6.88 (1H, d, J=7.3 Hz, NH), 6.46 (1H, d, J=7.7 Hz, NH), 5.74–5.64 (2H, m, 2×MeC*H*N), 3.62 (1H, septet, J=7.0 Hz, Me_2CN*H*), 3.44 (1H, septet, J=7.7 Hz, Me_2CN*H*), 3.24 (1H, septet, J=6.6 Hz, Me_2CN*H*), 3.09 (1H, septet, J=6.6 Hz, Me_2CN*H*), 1.73–1.67 (9H, m, 3×Me), 1.59 (3H, d, J=6.6 Hz, Me), 1.30–1.20 (6H, m, 2×Me), 1.17 (3H, d, J=6.6 Hz, Me), 1.07 (3H, d, J=6.6 Hz, Me), 1.01 (3H, d, J=6.6 Hz, Me) and 0.86 (3H, d, J=6.6 Hz, Me); δ_C (75 MHz; $CDCl_3$) 171.29, 171.13 (C=O), 153.36, 152.95, 147.12, 146.58, 138.59, 138.35, 137.03, 136.93, 136.89, 134.27, 134.17, 133.92, 133.84, 130.97, 130.54, 129.46, 129.42, 128.79, 128.77, 128.16, 127.90, 126.89, 125.86, 126.84, 126.35, 126.25, 125.66, 125.65, 125.56, 125.38, 125.30, 124.74, 124.63, 123.91, 123.29, 123.04, 122.76, 122.39, 119.26, 117.39, 94.09, 93.86 (Ar), 51.70, 51.49, 47.44, 46.99, 46.56, 46.40 (6×NCH), 21.94, 21.71, 21.68, 21.35, 20.55, 20.42, 20.27, 20.22, 20.20 and 20.19 (10×Me); *m/z* (CI) 595 (50%, M+H$^+$).

4.1.13. *N*,*N*-Diisopropyl-2-iodo-8-[(*R*)-α-methylbenzyl carbamoyl]-1-naphthamides 22 and 23. Phosgene (0.30 mL of a 20% wt solution in toluene, 0.57 mmol) was added to toluene (0.4 mL). *N*,*N*-Diisopropyl-8-hydroxy-2-iodo-1-naphthamide (52.7 mg, 0.194 mmol), DMAP (2 mg, 0.02 mmol) and pyridine (0.015 mL, 0.20 mmol) were dissolved in toluene (2.2 mL). The solution of the naphthol was added dropwise to the phosgene solution at −10 °C to give a yellow suspension. The cooling bath was removed and the flask was covered in foil and the reaction was left to stir at room temperature for

3.5 h. The chloroformate **21** was concentrated under reduced pressure at 40 °C to give a yellow solid that was dissolved in dichloromethane (1 mL). A solution of (*R*)-(+)-α-methylbenzylamine (0.03 mL, 0.2 mmol) and pyridine (0.015 mL, 0.20 mmol) in dichloromethane (0.3 mL) was added to the chloroformate **21** solution which turned maroon. The reaction was covered with foil and left to stir for 18 h. The reaction was diluted with dichloromethane (10 mL) and washed with HCl 1 M (2×10 mL) and water (10 mL). The aqueous fractions were collected and washed with dichloromethane (2×10 mL). The organic extracts were combined, dried with anhydrous magnesium sulfate and concentrated under reduce pressure to give a yellow solid. The product was purified by flash chromatography, eluting with 7:2:1 petroleum ether (40–60 °C)–ethyl acetate–methanol to give the carbamates **22** and **23** (15.8 mg, 22%) as a white foam; R_f (petroleum ether 40–60 °C–ethyl acetate–methanol 7:2:1) two diastereomers; 0.45 and 0.38; ν_{max} (KBr)/cm^{-1} 1739 (ROC═ON), 1616 (C═O), 1520 (NH); δ_H (300 MHz; $CDCl_3$) 7.89 (2H, d, *J*=8.4 Hz, 2×ArH), 7.82–7.20 (18H, m, ArH), 6.59 (1H, d, *J*=7.7 Hz, NH), 6.44 (1H, d, *J*=7.1 Hz, NH), 4.87–4.78 (2H, m, 2×MeC*H*N), 3.65–3.50 (2H, m, 2×Me$_2$*H*CN), 3.24–3.06 (2H, m, 2×Me$_2$*H*CN), 1.71 (3H, d, *J*=6.8 Hz, Me), 1.67 (6H, d, *J*=6.8 Hz, 2×Me), 1.57–1.53 (9H, m, 3×*Me*CHN), 1.15 (3H, d, *J*=6.6 Hz, Me), 1.11 (3H, d, *J*=6.8 Hz, Me), 0.98 (3H, d, *J*=6.8 Hz, Me) and 0.91 (3H, d, *J*=6.6 Hz, Me); δ_C (75 MHz; $CDCl_3$) 171.24 (C═O), 153.02, 146.97, 146.60, 142.98, 142.92, 137.05, 136.94, 136.88, 136.85, 134.24, 134.16, 129.46, 129.40, 128.65, 128.61, 128.59, 128.38, 127.24, 126.89, 126.83, 126.37, 126.09, 126.06, 125.75, 125.18, 124.80, 124.04, 122.36, 119.15, 117.71, 94.03, 93.89 (Ar), 51.73, 51.62, 51.53, 51.39, 46.51, 46.47 (6×NCH), 22.41, 22.07, 22.05, 21.85, 20.55, 20.37, 20.31, 20.29, 20.27, 20.25 (10×Me); *m/z* (CI) 545 (60%, M+H$^+$).

4.1.14. *N*,*N*-Diisopropyl-2-iodo-8-methoxy-1-naphthamide 28. The naphthamide **6** (205 mg, 0.720 mmol) was dissolved in THF (20 mL) and the solution cooled to −78 °C. To this *sec*-BuLi (0.65 mL, 0.78 mmol) was added dropwise to give a green solution. The reaction was left to stir for 45 min. Iodine (270 mg, 1.06 mmol) was dissolved in THF (3 mL) and added to the lithiated solution. A brown solution formed that left to warm to room temperature overnight. The reaction was washed with aqueous sodium thiosulphate (20 mL, 1 M). The aqueous layer was extracted with diethyl ether (2×20 mL). The organic extracts were combined, dried with anhydrous magnesium sulphate and concentrated under reduced pressure to give a white solid which was crystallised from ethyl acetate to give the iodo ether **28** (187 mg, 63.1%) as white needles, mp 212–218 °C (from ethyl acetate); R_f (ethyl acetate–petroleum ether 40–60 °C, 1:1) 0.39; ν_{max} (KBr)/cm^{-1} 2953 (MeO stretch), 1627 (NC═O); δ_H (300 MHz; $CDCl_3$) 7.87 (1H, d, *J*=8.4 Hz, Ar3-H), 7.44–7.36 (3H, m, ArH), 7.00 (1H, dd, *J*=6.5, 2.2 Hz, Ar7-H), 3.90 (3H, s, OMe), 3.57 (1H, septet, *J*=6.9 Hz, NCH), 3.44 (1H, septet, *J*=6.7 Hz, NCH), 1.72 (3H, d, *J*=6.9 Hz, Me), 1.69 (3H, d, *J*=6.9 Hz, Me), 1.22 (3H, d, *J*=6.6 Hz, Me) and 0.93 (3H, d, *J*=6.6 Hz, Me); δ_C (75 MHz; $CDCl_3$) 170.5 (C═O), 154.7, 138.4, 137.2, 134.6, 129.0, 127.1, 123.1, 121.1, 106.7, 93.2 (Ar), 55.6 (OMe), 51.3, 46.3 (2×NCH), 20.8, 20.7, 20.5 and 19.9 (4×Me); *m/z* (CI) 411 (100%, M+H$^+$) (Found: M+H$^+$ 412.0774. $C_{18}H_{23}NO_2I$ requires M+H$^+$ 412.0762).

4.1.15. *N*,*N*-Diisopropyl-2-bromo-8-methoxy-1-naphthamide. The naphthamide **6** (203 mg, 0.711 mmol) was dissolved in THF (20 mL) and the solution cooled to −78 °C. To this *sec*-BuLi (0.65 mL, 0.78 mmol) was added dropwise to give a green solution. This was left to stir for 30 min. Bromine (0.07 mL, 1 mmol) was added neat to the lithiated solution. A yellow solution formed that was left to warm to room temperature overnight. The reaction was washed with aqueous sodium thiosulphate (20 mL of a 1 M solution). The aqueous layer was extracted with diethyl ether (2×20 mL). The organic extracts were combined, dried with anhydrous magnesium sulphate and concentrated under reduced pressure to give a yellow solid which was crystallised from ethyl acetate to give the bromo ether (121 mg, 46.7%) as pale brown needles, mp 217–223 °C (from ethyl acetate); R_f (ethyl acetate–petroleum ether (40–60 °C), 1:1) 0.39; ν_{max} (KBr)/cm^{-1} 2966 (MeO stretch), 1627 (NC═O), 827 (ArBr); δ_H (300 MHz; $CDCl_3$) 7.60–6.85 (5H, m, ArH), 3.92 (3H, s, OMe), 3.57 (1H, septet, *J*=7.0 Hz, NCH), 3.51 (1H, septet, *J*=6.6 Hz, NCH), 1.68 (6H, d, *J*=6.8 Hz, 2×Me), 1.18 (3H, d, *J*=6.6 Hz, Me) and 0.98 (3H, d, *J*=6.6 Hz, Me); δ_C (75 MHz; $CDCl_3$) 168.53 (C═O), 154.91, 134.06, 130.98, 129.01, 126.79, 123.00, 120.92, 118.44, 106.73 (Ar), 55.40 (OMe), 51.18, 46.12 (2×NCH), 20.61, 20.53, 20.19 and 19.93 (4×Me); *m/z* (CI) 364 (90%, M) (Found: M 364.0922. $C_{18}H_{23}NO_2^{79}Br$ requires M 364.0912).

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