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Scalable synthesis of a new enantiomerically pure π-extended rigid amino indanol

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ABSTRACT

A convenient route to a benzo-fused amino indanol chiral controller is disclosed. The synthesis is based on a newly optimized entry to 3*H*-benz(e)indene that can be performed on decagram scale with no purification of intermediates. Subsequent oxidation, classical resolution, and Ritter steps give the target synthon in >98% ee. The resolution features (*S*)-naproxen as an inexpensive and highly crystalline resolving agent. Conversion of the amino alcohol to its bis(oxazolinyl)-propane is also reported. A solid state structure of the $CuCl_2$–box complex shows preservation of the distorted square planar geometry found in the parent $CuCl_2$(indanyl-box) despite greater steric crowding by the blocking groups.

Chiral vicinal amino alcohols, both natural and fully synthetic, represent an exceptionally important class of small molecules. Amino alcohols have long been utilized in asymmetric catalysis as ligands themselves[1] or as precursors to various ligand classes.[2] As chemists continue to expand the scope of available catalytic enantioselective transformations, the need for new and rationally designed synthetic amino alcohols is justified. The *cis*-substituted amino indanol **1** (Chart 1), for instance, was first developed as a subunit of the orally active HIV protease inhibitor *indinavir*[3] (Crixivan®). Davies, Senanayake, and others in process research at Merck went on to establish the derived oxazolidinone (**2**) and 2,2′-bis(oxazoline)alkanes[4] such as **3** as highly effective and tunable chiral controllers for catalytic Diels–Alder reactions.[5] The superiority of these systems relative to those based on (−)-phenyl-glycinol draws from the fact that the indane ring prevents free rotation about the C–Ph bond, enforcing conformational rigidity.[6] Herein, we report a practical synthesis of the π-extended amino indanol **4** and the solid state structure of its corresponding 2,2′-bis(oxazolinyl)propane bound to $CuCl_2$.

Scheme 1 shows a retrosynthesis for the new π-extended box ligand **5**. The required 3*H*-benz(e)indene (**6**) is a known material, but it forms in low yield as a byproduct of the pyrolysis of 2′-methylbiphenyl-2,3-dicarboxylic anhydride.[7] As such, it seemed appropriate to target **6** more efficiently by a simple reduction–elimination sequence on the known ketone **7**. In opening attempts to prepare **7** in one flask from acryloyl chloride and naphthalene by tandem $AlCl_3$-mediated Friedel–Crafts acylation and Nazarov cyclization,[8] tedious column chromatography was needed and the yield was only modest. Other literature procedures[9] called for expensive starting materials and did not scale well in our hands. Therefore, an alternative route was developed from inexpensive 2-methylnaph-

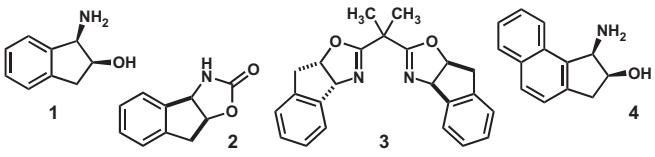
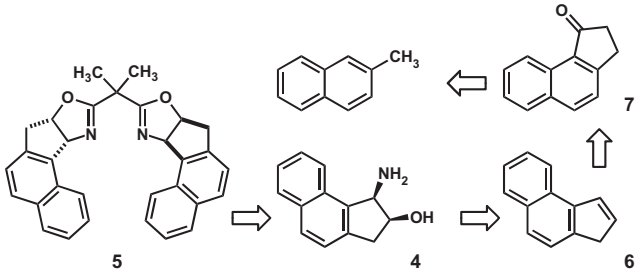


Chart 1.



Scheme 1. Synthetic strategy

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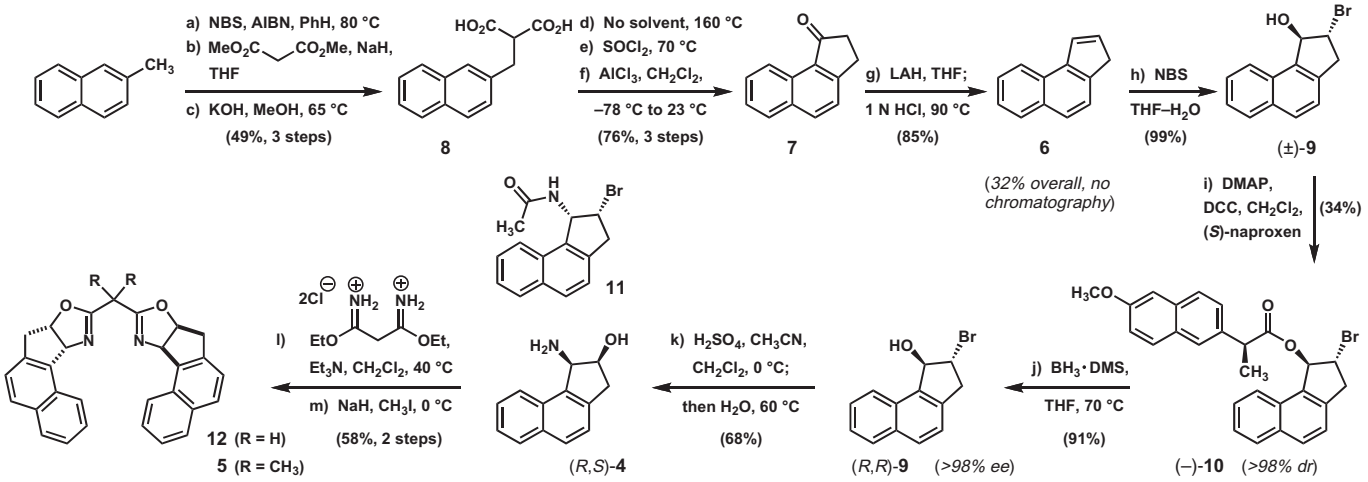


Scheme 2.

thalene. As we demonstrate below, a convenient and scalable seven-step preparation of **6** precedes its conversion to enantiopure **4** by the resolution of a naproxen ester and subsequent Ritter reaction. Conversion to bis(oxazoline) **5** then proceeds via its des(dimethyl) variant following standard procedures.

The path of synthesis is illustrated in Scheme 2. Radical monobromination, displacement of the crude bromide with the sodium salt of dimethyl malonate, and basic hydrolysis affords the homobenzylic diacid **8** in a 49% yield.[10] Cationic cyclization[9c] to give **7** is possible in one step using molten H_3PO_4/P_2O_5, but the yield is variable (30–76%) due to competitive oligomerization. In practice, we found it preferable to accomplish the transformation by the sequence: (1) thermal decarboxylation, (2) chlorination, and (3) Friedel–Crafts ring closure (**8** → **7**, 76% yield). In just six steps requiring no purification of intermediates, ketone **7** can be obtained on decagram scale in an overall 37% yield and >95% purity as judged by ^{1}H NMR analysis. Reduction and acid-mediated elimination in the same vessel provides the target hydrocarbon (3*H*-benz(e)indene, **6**) in an 85% yield as a white crystalline solid after simple filtration through a pad of silica gel.

An initial plan to use the Jacobsen epoxidation[11] for the control of absolute stereochemistry was complicated by the propensity for racemic epoxide (from *m*-CPBA/$NaHCO_3$ or DMDO) to undergo spontaneous ring opening/1,2-rearrangement to the homobenzylic cyclopentanone (not shown). Alternative strategies based on catalytic enantioselective dihydroxylation[12] or diboration[13] could be applicable, but experimentation with racemic material quickly established chiral esters of bromohydrin **9** as highly crystalline. Thus, indene oxidation with NBS in THF-water (quantitative) and coupling with (*S*)-naproxen under standard conditions gives a mixture of diasteromeric esters from which (–)-**10** crystallizes in a 34% yield as a single diastereomer. Naproxen was selected as a resolving agent because of the trivial means by which multigram quantities of enantiopure material can be obtained from over-the-counter pain relief tablets.[14] Absolute configuration in (–)-**10** has been unequivocally assigned by X-ray diffraction (Fig. 1).

Among several different hydrolytic conditions tested, cleavage of the resolving agent was best achieved by borane reduction to give the desired (*R*,*R*) bromohydrin **9** in a 91% yield with >98% ee by chiral SFC (supercritical fluid chromatography). This material was then subjected to a Ritter reaction[15] to afford (*R*,*S*)-**4** cleanly in a 68% yield after an acid/base extraction procedure. The modest yield is accounted for by the recovery of *cis*-acetamide **11** (in a >2:1 ratio in favor of amino alcohol **4**). Noteworthy is that acetamide hydrolysis does not occur in the absence of the vicinal hydroxyl

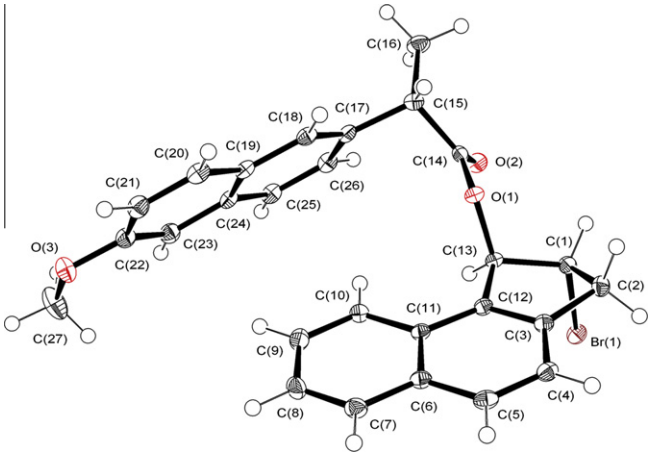
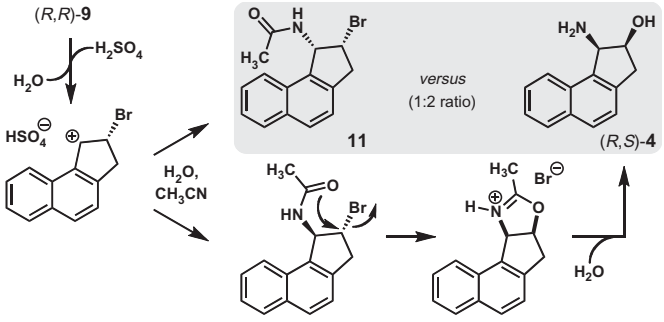


Figure 1. X-ray crystal structure of naproxen ester (–)-**10**.



Scheme 3. Ritter reaction mechanism and co-production of amide **11**.

functionality. As illustrated below in Scheme 3, the byproduct likely forms as a result of non-stereospecific trapping of the benzylic cation by acetonitrile and subsequent failure to undergo intramolecular closure to the intermediate oxazoline. The added stability gained by transient bromonium ion formation – a key feature for stereocontrol in this reaction – is offset by enhanced delocalization of the cation within the naphthalene ring. Co-production of acetamide **11**, together with the aforementioned facile rearrangement of epoxy-**6**, lends support to this hypothesis.

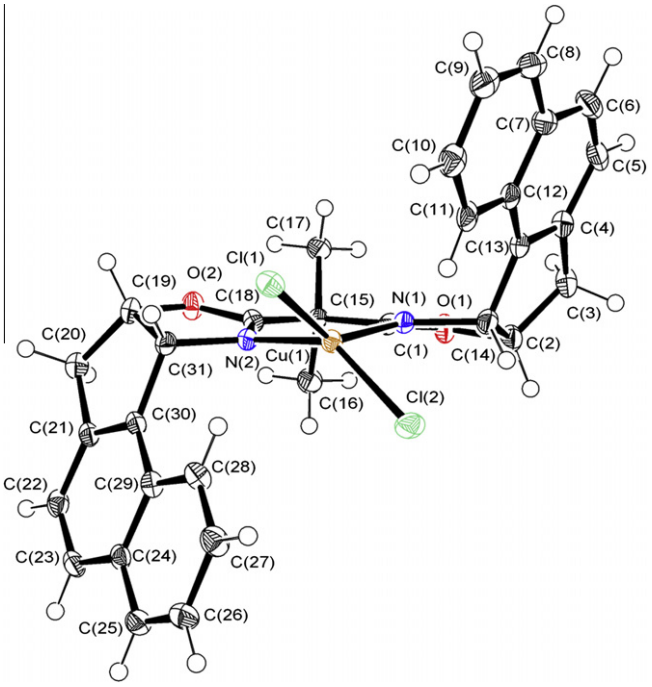


Figure 2. ORTEP of the complex between $CuCl_2$ and box ligand **5**.

Our experience with the synthesis of bis(oxazolinyl)methanes shows that the diethoxyimidate methodology of Davies et al.[5c] allows expedient access to the unsubstituted box framework. Coupling of amino alcohol **4** with commercially available diethyl malonimidate dihydrochloride furnishes box ligand **12** in a 63% yield as a white flocculent solid after washing with hexanes and methanol. Deprotonation with sodium hydride and subsequent trapping with methyl iodide leads to the target *gem*-dimethylated ligand **5** in a 92% yield after a hexanes wash.

For further proof of structure and to confirm that **5** can act as a viable chiral ligand, we turned to copper(II) salts. Suitable single crystals of $CuCl_2$·**5** were obtained by vapor diffusion of pentane into a saturated dichloromethane solution. As shown in Figure 2, X-ray diffraction reveals a four-co-ordinate, 17-electron complex flanked by sizeable naphthalene units and distorted square planar geometry. Importantly, there is considerable homology between this structure and the analogous $CuCl_2$(indanyl-box) catalyst with regard to the disposition of groups around the copper(II) center.[16] Some comparative structural data for each complex are provided in Table 1. One striking similarity is the extent of distortion from an ideal square plane, which in the solid state corresponds to a 0° angle between the Cl(1)–Cu–Cl(2) and bis(oxazoline)–Cu planes. Jørgensen[16] has taken the value [90°–(the C(17)–C(15)–Cu–Cl(1) dihedral angle)] (or its symmetry equivalent, see final column of Table 1) as a measure of this distortion; in both structures it lies between 41° and 46°. It therefore appears that the larger blocking groups have a negligible effect on the local bonding arrangement at copper. There is, however, noticeable distortion more proximal to their site of attachment. In particular, the planes defined by C(18)–N(2)–C(31) and C(1)–N(1)–C(14) are offset by −9.65° and 10.66°, respectively, from a central plane of reference chosen as N(2)–Cu–N(1). This likely reflects the modest ability of the two oxazoline rings to relax into conformations that help to relieve steric hindrance and situate the benzo(indane) subunits farther from the metal center. Whether or not these features can translate into improved enantioselectivities or nonconventional modes of substrate approach for various copper-catalyzed transformations is an interesting prospect for future study. The application of box ligand **5** to our Sc-catalyzed asymmetric α-arylation method[17] is currently under investigation and results will be forthcoming.

In summary, we have described an efficient and scalable entry to the (*R*,*S*) enantiomer of π-extended amino indanol **4** and its conversion to bis(oxazolinyl)propane **5**. Such C_2-symmetric box ligands continue to attract interest as mainstream chiral ligands for asymmetric catalysis.[18] Noteworthy features of our strategy include a minimal use of chromatography, the application of (*S*)-naproxen found in commercial pain relief tablets as an inexpensive and highly crystalline resolving agent, and improved synthetic access to the key benzo(indane) intermediate **6**, which could be of use in preparing other ligand constructs. We hope that this new amino alcohol will find use in asymmetric synthesis or potentially in other broader areas of chemistry.

Acknowledgments

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Supplementary data

Crystallographic data (excluding structure factors) for the two structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 844999 and 845000. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.144.

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Table 1
Select structural data for chiral $CuCl_2$ complexes of **5** and **3**

	Cu–N1 (Å)	Cu–N2 (Å)	Cu–Cl1 (Å)	Cu–Cl2 (Å)	C17–C15–Cu–Cl1[a] (°)	C16–C15–Cu–Cl2[a] (°)
$CuCl_2$·**5**	1.977	1.975	2.224	2.235	41.9	41.8
$CuCl_2$(indanyl-box)[b]	1.997	1.992	2.234	2.223	45.9	41.0

[a] Compiled as 90° – dihedral angle to ensure a 0° value in the square planar case.
[b] Reproduced from Ref. 16.

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