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Highly Effective Transition Structure Designed Catalyst for the Enantio- and Position-Selective Dihydroxylation of Polyisoprenoids

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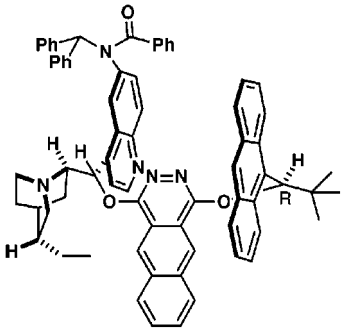
ABSTRACT



The chiral monocinchona derivative shown, synthesized in one step from two efficiently prepared chiral building blocks, was designed under mechanistic guidance as a catalyst for the enantio- and position-selective dihydroxylation of the terminal isopropylidene group of polyisoprenoids. Its efficacy as a synthetic reagent for this purpose was demonstrated for several different substrates.

The biscinchona alkaloid catalyzed dihydroxylation of olefins is remarkable because of its broad utility, fundamental mechanistic complexity, and uniqueness.[1,2] Despite the availability of extensive experimental evidence in favor of a highly organized [3 + 2] mechanistic pathway, as illustrated by pre-transition state assembly **1** for styrene and a bisdihydroquinidine catalyst,[3−7] and a rejection[6b,8] of the originally advanced[9,10] [2 + 2] pathway, there remains an impression of uncertainty regarding the asymmetric dihydroxylation that is not easily dispelled.[11,12] Perhaps the best measure of the value of a transition state model such as **1**

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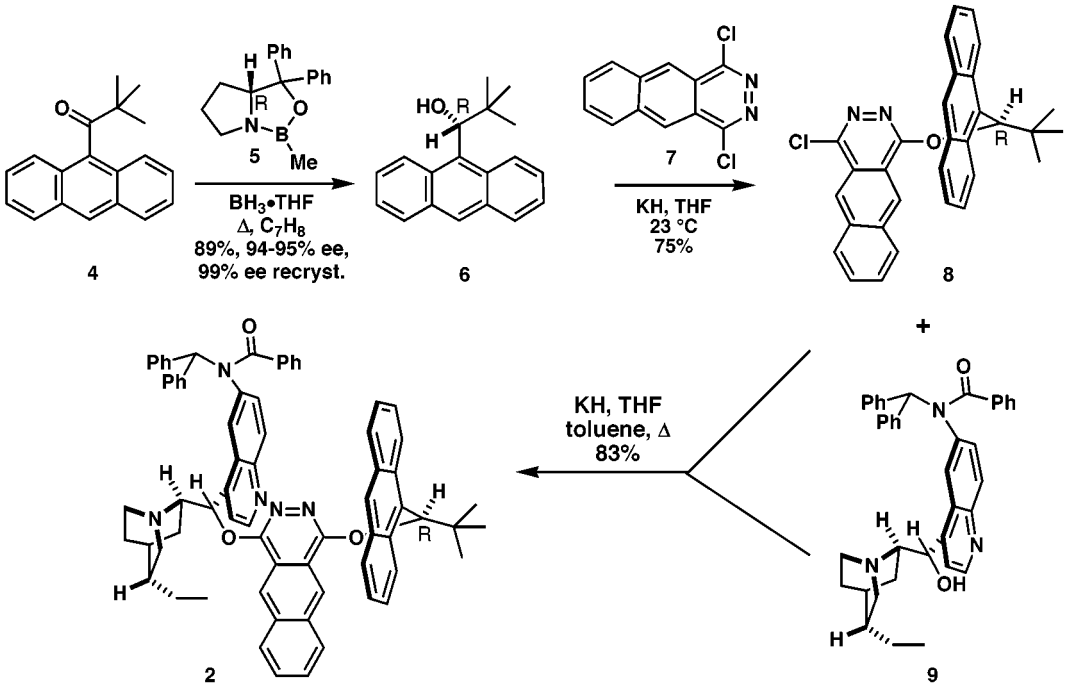
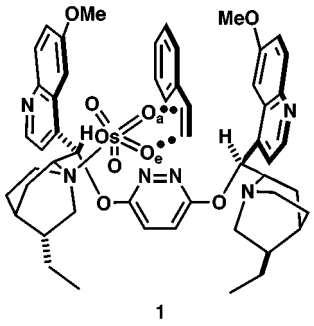
Scheme 1



(Criegee, Corey, Noe; CCN model[3]) is its predictive power. In this paper we describe the successful application of the CCN model[3] to the design of a new catalyst (**2**) for the enantio- and position-selective dihydroxylation of a variety of polyolefinic substrates of the isoprenoid type. Our expectation was that the reactive complex **2**·OsO_4 would react selectively with the terminal isopropylidine unit of a polyprenoid substrate via the pre-transition state assembly represented by **3** to form the corresponding terminal dihydroxylation product with >90% enantioselectivity. Presented herein is a full confirmation of this prediction and, in addition, evidence that catalyst **2** is an exceedingly useful and practical new reagent.

In pre-transition state assembly **3** there are four key domains of the ligand part, which are all important to catalyst function and are integrated in a conformationally organized way. The 1,4-dioxanaphthopyridazine domain in the center has several functions: (1) it serves as a distance-critical spacer for the domains on the left and right and as a binding surface for the R portion of the substrate, and (2) it maintains the attached domains to the left and right with fixed cisoid, coplanar C-O-pyridazine-O-C geometry at a proper distance for substrate intercalation. The dihydroquinidine domain serves as a conformationally fixed activating ligand for OsO_4, which holds it in a suitable position for reaction with the substrate in the binding pocket. The *N*-benzhydryl/benzoyl domain caps the top of the binding pocket and limits penetration of the substrate up into that region of the pocket while providing a upper binding surface. Finally, the (*R*)-*tert*-butyl-9-anthryl carbinol domain places the 9-anthryl



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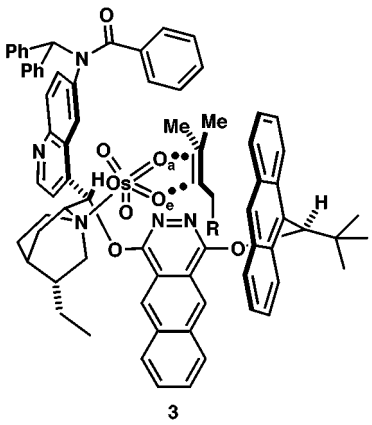

3

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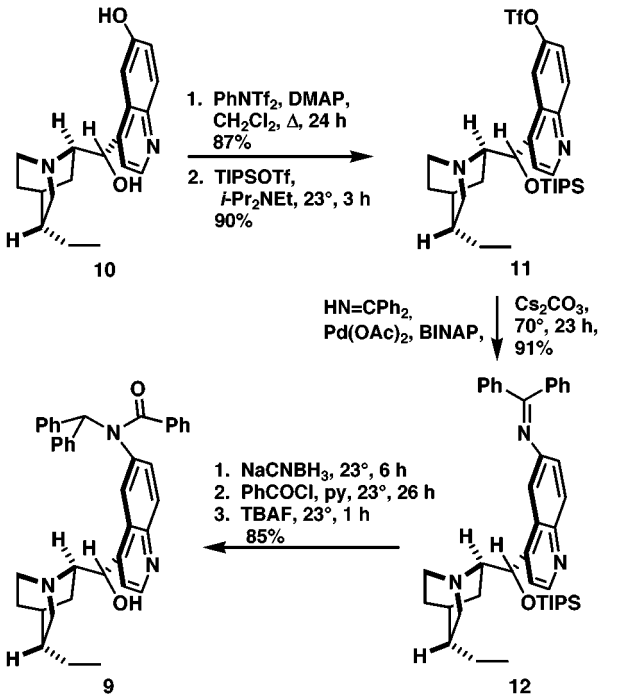
group in the vertical arrangement shown in **3** so that it functions as the right-hand wall of the binding pocket. In previous work 1-anthryl-[4c] and 9-anthrylmethyl[5c] groups have been used successfully as binding surfaces in structure-based catalyst design for enantioselective OsO_4-mediated dihydroxylation of olefins. However, these specific groups are not suited to the present application.

The synthetic pathway for the assembly of catalyst **2** is outlined in Scheme 1. Catalytic reduction of *tert*-butyl-9-anthryl ketone (**4**) by BH_3-THF in the presence of the chiral (*R*)-oxazaborolidine **5** (20 mol %) in toluene at reflux for 25 min (CBS method)[13] afforded the corresponding (*R*)-alcohol **6** (99% ee after one recrystallization). Conversion of **6** to the potassium alkoxide (KH, THF, 0.5 h) and reaction with 1,4-dichloronaphthopyridazine (**7**)[14] at 23 °C for 0.5 h produced the monoether **8**. Coupling of **8** with the potassium salt of the dihydroquinidine derivative **9** (110 °C, 0.5 h) gave catalyst **2** in good yield. The synthesis of **9** was accomplished by the straightforward reaction sequence shown in Scheme 2 starting with dihydrocupreidine (**10**), prepared by dem-

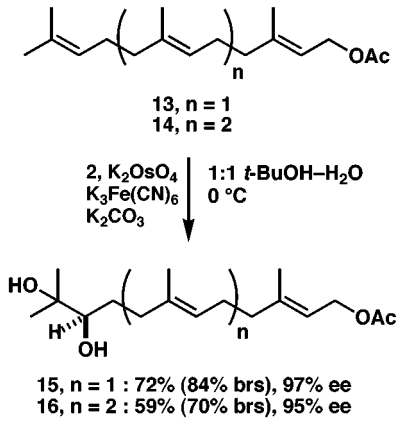
Scheme 2



ethylation of dihydroquinidine in aqueous HBr.[15] Conversion of **10** to the phenolic triflate[16] followed by silylation to **11** and amination[17] gave **12**. The transformation of **12** to **9** was accomplished in three steps without purification of intermediates in 85% overall yield.

Farnesyl and geranylgeranyl acetates (**13** and **14**) are known to undergo oxidation by OsO_4 and the standard Sharpless $(DHQD)_2$-PYDZ ligand with poor selectivity with respect to dihydroxylation at the terminal isopropylidene group vs the internal olefinic linkage(s).[5d,18] In contrast, as shown in Scheme 3 catalyst **2** (1 mol %) affords the highest

Scheme 3



selectivity observed thus far in dihydroxylation of **13** and **14**. In the case of **13** the (*R*)-terminal diol **15** of 97% ee can be isolated in 72% yield (84% based on recovered starting material (brs)) with only ca. 4% of internal diol being formed.[19] To investigate the minor internal dihydroxylation pathway further, the dihydroxylation of farnesyl 4-methoxybenzoate was studied with catalyst **2**. In addition to the major terminal isopropylidene oxidized diol (86% yield brs, 95% ee) ca. 4% of internal diol was obtained of 57% ee as determined by HPLC analysis using a Chiral Technologies AS column. The low ee of the minor product indicates that it is probably formed by dihydroxylation modes not involving (i.e., outside of) the binding pocket. The dihydroxylation of geranylgeranyl acetate (**14**) at the terminal isopropylidene unit also proceeded selectively with catalyst **2** to give (*R*)-diol **16** (95% ee, 70% brs). The yields of **15** and **16** obtained with **2** are higher than those obtained with the Noe-Lin catalyst,[5d] a biscinchona type, in side by side experiments, and also the reactions of **2** are considerably faster, i.e., more strongly accelerated. It should be emphasized that the product diols **15** and **16** possess the (*R*) configuration as expected. Also, catalyst **2** could be recovered from these reactions for reuse with at least 90% efficiency.[20,21]

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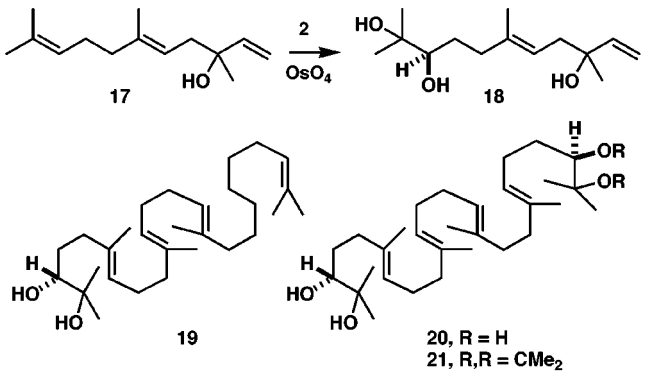
(19) Enantiomeric purities, unless indicated otherwise, were determined by 500 MHz ^{1}H NMR analysis of the mono-(*S*)-MTPA (Mosher) ester using racemic mono Mosher ester as standard.
(20) The diols **15** and **16** are readily converted via the corresponding secondary mesylates ($MeSO_2Cl$-py, then base) to the corresponding (*S*)-epoxides, which are useful for the enantioselective synthesis of many polycyclic natural products. See, for example: (a) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999. (b) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765. (c) Corey, E. J.; Luo, G.; Lin, S. *J. Am. Chem. Soc.* **1997**, *119*, 9927. (d) Corey, E. J.; Lee, J. *J. Am. Chem. Soc.* **1993**, *115*, 8873. (e) Corey, E. J.; Lee, J.; Liu, D. R. *Tetrahedron Lett.* **1994**, *35*, 9149.



As anticipated the dihydroxylation of (*E*)-nerolidol (**17**) using **2** as catalyst (1 mol %) gave the (*R*)-dihydroxylation product **18** with 94% π-facial selectivity and high position selectivity for the terminal isopropylidine group (isolated yield 78%; 96% brs).

(*S*)-2,3-Oxidosqualene, a very important precursor in the biosynthesis of triterpenoids and sterols, is readily prepared from inexpensive commercial squalene using **2** as catalyst via diol **19**. In this case, because squalene is only very slightly soluble in aqueous *t*-BuOH, the dihydroxylation is slow at 0 °C. However, we have discovered that the reaction is accelerated by the use of 0.5 equiv of *n*-Bu_4NOH as surfactant (relative to squalene). Thus, using **2** (1 mol %), K_2OsO_4 (1 mol %), $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, and Bu_4NOH in 1:1:0.3 *t*-BuOH/H_2O/methylcyclohexane at 0 °C for 20 h, the terminal diol (*R*)-**19** was obtained of 90% ee in 38% yield (53% brs, 90% recovery of **2**), the major byproduct being tetraol **20**. By doubling the amount of oxidant mixture (to 7 equiv) of $K_2Fe(CN)_6$ and eliminating methylcyclohexane as cosolvent, squalene could also be converted into the (*R*)-tetraol **20** after 3 h at 0 °C in 40% isolated yield after silica gel chromatography (99% ee and 92% de as measured by HPLC analysis with a Chiral Technologies AS column). Similarly the acetonide of (*R*)-2,3-squalene diol could be dihydroxylated to the (*R,R*)-tetraol monoacetonide **21** of 98% ee, 95% de in 50% yield (60% brs, 92% recovery of **2**) after 3 h at 0 °C. These syntheses of **19**, **20** and **21**, which in our judgment are the most efficient and convenient to date, emphasize the effectiveness of catalyst **2**.

In summary, the design, synthesis, and testing of catalyst **2**, as described above, provides additional strong support for the CCN transition state model for chiral ligand-catalyzed dihydroxylation of olefins. In addition, the facile synthesis of **2**, its efficacy as a catalytic ligand at 1 mol % levels, and its efficient recovery for reuse (90% or better) underscore the value and practicality of **2** as a synthetic reagent. Further, the elaborate binding pocket and design elements of **2** lend confidence that organic chemistry can advance the frontier of molecular catalysis toward enzyme-like performance with greater versatility and much lower complexity. Also, we have discovered an excellent new way of accelerating the dihydroxylation of water insoluble substrates in *t*-Bu_4NOH as a surfactant. Finally, the utility of reagent **2** in multistep synthesis has been demonstrated by a synthesis of serrantenediol (as described in the paper that follows).

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Supporting Information Available: Procedures for the synthesis of **2** and for its use as a catalyst for enantio- and position-selective dihydroxylation of selected substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) **Procedure for Synthesis of 15.** A mixture of ligand **2** (32.0 mg, 31.3 μmol), $K_2OsO_4 \cdot 2H_2O$ (5.9 mg, 15.7 μmol), $K_3Fe(CN)_6$ (3.10 g, 9.42 mmol), K_2CO_3 (1.30 g, 9.42 mmol), $CH_3SO_2NH_2$ (299 mg, 3.14 mmol), and 2,6-(*E*,*E*)-farnesyl acetate (829 mg, 3.14 mmol) in 32 mL of 1:1 *t*-BuOH/H_2O was stirred at 0 °C for 4 h. The reaction mixture was treated with 10 mL of saturated aqueous Na_2SO_3 and 10 mL of saturated $Na_2S_2O_3$ at 0 °C, allowed to warm to 23 °C, and stirred for 45 min. After removal of *t*-BuOH under reduced pressure, the reaction mixture was extracted four times with 50 mL of ethyl acetate. The combined extracts were washed with 15 mL of 1 N NaOH, followed by 20 mL of brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography (20−40% EtOAc in hexanes) to give 124 mg of unreacted farnesyl acetate (15%), 37.4 mg of 6,7-dihydroxy-6,7-dihydrofarnesylacete (4%), and 674 mg of (10*R*)-10,11-dihydroxy-10,11-dihydrofarnesyl acetate (84%, 72% uncorrected for recovered farnesyl acetate). Elution with 20% EtOH in EtOAc provided 38.0 mg (4%) of tetraol and 29.5 mg (92%) of recovered ligand **2**. The spectroscopic data of the terminal diol agreed with those reported. The ee of (10*R*)-10,11-dihydroxy-10,11-dihydrofarnesyl acetate was determined as 97% by ^1H NMR analysis of its corresponding mono-(*S*)-MTPA ester: ^1H NMR (500 MHz, C_6D_6) δ 3.54 (s, 3H) for the *R* enantiomer; δ 3.47 (s, 3H) for the *S* enantiomer, corresponding to the α-methoxy group of the ester.