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Asymmetric Conjugate Reductions of Coumarins. A New Route to Tolterodine and Related Coumarin Derivatives

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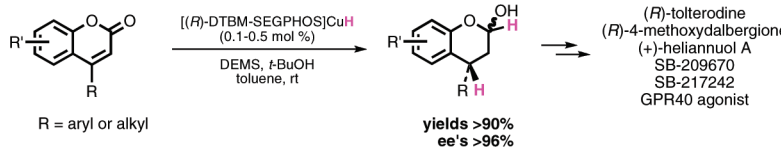
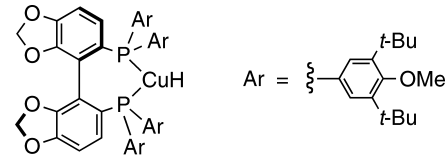
ABSTRACT



The combination of catalytic amounts of [(*R*)-DTBM-SEGPHOS]CuH in the presence of stoichiometric DEMS (diethoxymethylsilane) in toluene at room temperature leads to asymmetric reductions of 4-substituted coumarins. Several targets or their known precursors can be prepared in high yields and ee's, including the muscarine receptor antagonist (*R*)-tolterodine.

Conjugate reduction mediated by nonracemically ligated CuH has emerged as a powerful method for the induction of chirality β to a carbonyl.[1] Mild conditions, high chemo- and stereoselectivity, impressive substrate-to-catalyst ratios, widely available reagents, and simplicity of handling make asymmetric CuH chemistry an attractive alternative to catalytic hydrogenation. Several of the more recently introduced bisphosphine ligands have been shown to be particularly well-matched to CuH for this asymmetric transformation, including Solvias' PPF-P(t-Bu)$_2$,[2] Roche's 3,5-Xyl-MeO-BIPHEP,[3] and Takasago's DTBM-SEGPHOS.[4] In particular, ligation of CuH by DTBM-SEGPHOS, along with a silane such as PMHS (polymethylhydrosiloxane) generates a remarkably stable complex at room temperature when protected from the atmosphere.



[(*R*)-DTBM-SEGPHOS]CuH

Figure 1. Structure of [(*R*)-DTBM-SEGPHOS]CuH.

The species [(*R*)-DTBM-SEGPHOS]CuH (Figure 1), or "CuH in a Bottle", was introduced in 2005 as a highly

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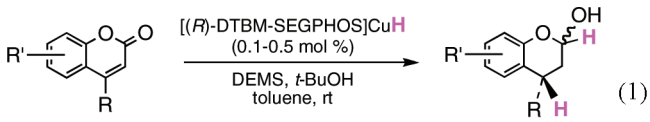
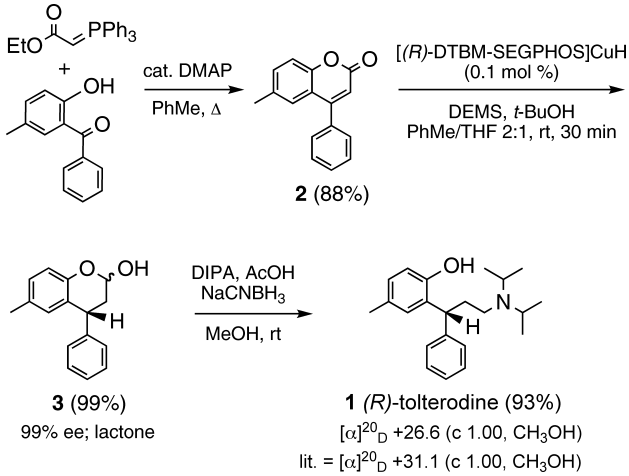
reactive, chemo- and stereoselective, storable reducing reagent.[5] To highlight the utility of DTBM-SEGPHOS]CuH in synthesis, 4-substituted coumarins were selected (eq 1), the conjugate reduction of which would lead to stereodefined intermediates of synthetic value. In this Letter we describe several new applications of [(*R*)-DTBM-SEGPHOS]CuH toward the synthesis of important bioactive, coumarin-derived targets.



Overal conversion using CuH-catalyzed asymmetric hydrosilylation

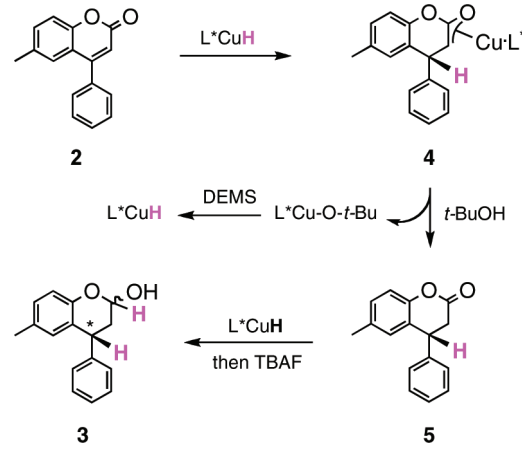
(*R*)-Tolterodine (1).[6] The tartrate salt of tolterodine ("Detrol-LA"; Scheme 1) is a competitive muscarine receptor antagonist widely used for the treatment of bladder disorders, such as urinary incontinence. Patented in 1998, the original synthetic route relies on chiral resolution to separate (*R*)-tolterodine from the racemate.[6a] Enormous demand for the drug has since inspired several catalytic asymmetric syntheses employing transition metals to establish chirality.[7] We envisioned educt **2** (6-methyl-4-phenylcoumarin, prepared by a Wittig-type reaction between 2-hydroxy-5-methylbenzophenone and carbethoxymethylenetriphenylphosphorane in refluxing toluene) as a good candidate for asymmetric CuH reduction. As such, conjugate reduction of coumarin **2** was complete in less than 30 min at room temperature in the presence of only 0.1 mol % [(*R*)-DTBM-SEGPHOS]CuH and excess DEMS (diethoxymethylsilane) and *t*-BuOH. Unexpectedly, however, lactol **3** rather than the corresponding lactone was isolated in near quantitative yield. Although such reduction of esters by CuH has not previously been reported, the resulting one-pot procedure fortuitously avoids a subsequent reduction by alternative means. Determination of ee by chiral HPLC analysis was made on a sample of lactol **3** that had been oxidized with PCC to the corresponding lactone, revealing a selectivity of 99% ee in the conjugate reduction step. Lactol **3** was then transformed into the target under reductive amination conditions using diisopropylamine (DIPA), yielding (*R*)-tolterodine (**1**) in 93% yield (optical rotation matched the literature value).[6] Overall, this three-step route compares very favorably with known, lengthier catalytic asymmetric syntheses that proceed through lactone **5**.[6]

Scheme 1. Synthesis of (*R*)-Tolterodine



Double reduction of coumarins by nonracemically ligated copper hydride yielding optically active lactols is a novel method[8] for the preparation of these versatile intermediates. This observation can be rationalized by an initial 1,4-reduction furnishing enolate **4** (Scheme 2), followed by protonation of the copper-bound enolate with *t*-BuOH, thus releasing lactone **5**. Unlike typical saturated alkyl esters and

Scheme 2. Proposed Sequence for Over-reduction



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(10) Shishido's intermediate is the lactone derived from **7**.
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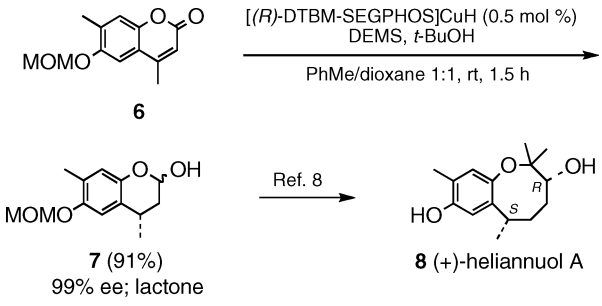
lactones that are stable to CuH, aryl lactones such as **5** are apparently activated toward 1,2-reduction. In this case, lactol **3** is realized from the initially formed silyl ether upon workup with TBAF.

(−)-Heliannuol A (*ent*-8). (−)-Heliannuol A is a naturally occurring sesquiterpenoid that exhibits strong allelopathic activity. The unique sturctural features (eight-membered ring) combined with impressive phytotoxic properties make (−)-heliannuol A an attractive target for synthesis. This feat has recently been accomplished by Shishido and co-workers using a porcine pancreatic lipase (PPL)-mediated transesterification to impart chirality (78% ee).[9] Coumarin **6**, prepared via Pechmann condensation, was found to be compatible with asymmetric DTBM-ligated CuH, leading to known intermediate **7** in Shishido's synthesis.[10] Reduction took place at room temperature in 91% yield (Scheme 3).

Scheme 3. Formal Synthesis of (+)-Heliannuol A

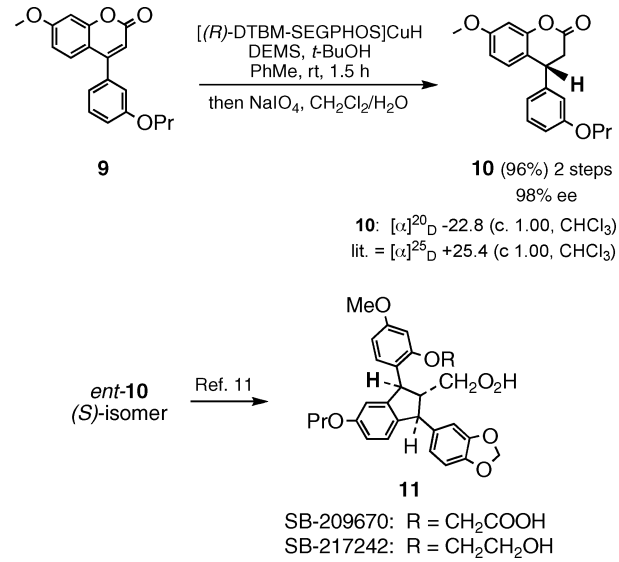


Lactol **7** was generated upon workup in 99% ee as determined by HPLC after oxidation to the corresponding lactone. By analogy to lactol **3**, [(*R*)-DTBM-SEGPHOS]CuH delivers hydride to the same face of each coumarin; hence, the absolute stereochemistry at the 4-position of **7** should be *S*. Product **7** will ultimately lead to the unnatural isomer, (+)-heliannuol A (**8**); a switch to [(*S*)-DTBM-SEGPHOS]CuH would produce the natural (*R*)-enantiomer.[11]

SB-217242. SB-209670 and SB-217242 (**11**) are potent endothelin antagonists currently under development.[12] The known syntheses employ nonracemic dihydrocoumarin **10** as an intermediate, arrived at via asymmetric hydrogenation.[13] The process requires high pH, high pressures of H_2, expensive rhodium salts, and heat. Hydrosilylation of coumarin **9** could be readily accomplished using [(*R*)-DTBM-SEGPHOS]CuH catalysis. Under similar conditions applied to both tolterodine and heliannuol A (vide supra), educt **9** was reduced to the derived lactol at room temperature. Oxidation of the crude material by $NaIO_4$ yielded lactone **10** (96% yield, 98% ee, over 2 steps; Scheme 4). The optical rotation of **10** indicates that the unnatural (*R*)-enantiomer was formed.

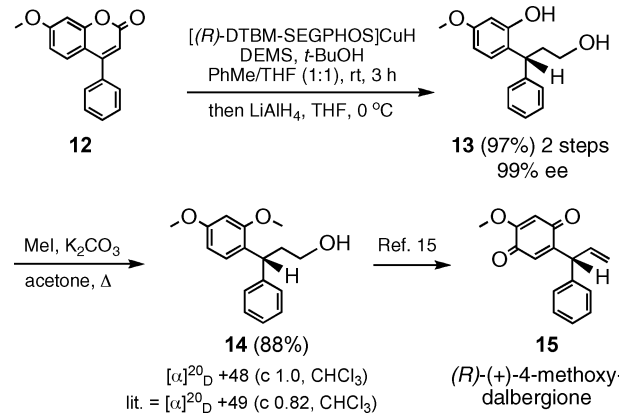
(*R*)-4-Methoxydalbergione (15). This natural product, isolated from tropical woods,[14] belongs to a family of optically active quinones (dalbergiones) known to be responsible for inducing allergic contact dermatitis (ACD). Compound **15** was recently synthesized by Lepoittevin

Scheme 4. Formal Synthesis of SB-209670



and co-workers via asymmetric hydrogenation of coumarin **12**, a process subject to similar issues as seen with educt **9**, above.[15] Not surprisingly, coumarin **12** was smoothly reduced in the presence of catalytic [(*R*)-DTBM-SEGPHOS]CuH at room temperature, and following exposure of the crude lactol to $LiAlH_4$, diol **13** was isolated in 97% yield and 99% ee (Scheme 5). Selective alkylation of the

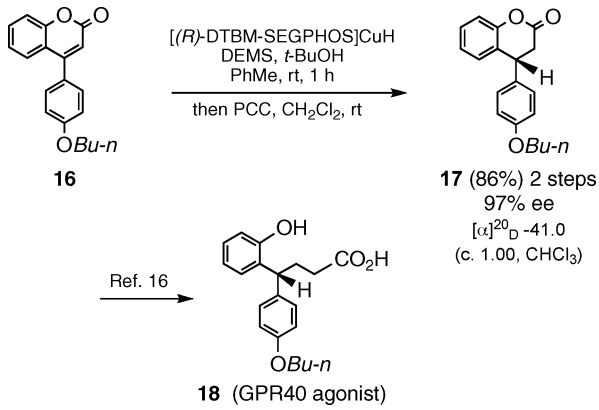
Scheme 5. Formal Synthesis of (*R*)-(+)-4-Methoxydalbergione



phenolic hydroxyl was achieved using K_2CO_3 and iodomethane to afford chiral alcohol **14**, a precursor to 4-methoxydalbergione. The optical rotation of **14** was consistent with the known data for the (*R*)-enantiomer.[15]

GPR40. A formal synthesis of GPR40 agonist, **18**,[16] was performed by hydrosilylation involving catalytic [(*R*)-DTBM-SEGPHOS]CuH and coumarin **16**. Asymmetric reduction at room temperature followed by PCC oxidation of the resultant lactol yielded lactone **17** in a 86% overall yield and 97% ee

Scheme 6. Formal Synthesis of a GPR40 Agonist



(Scheme 6). The absolute stereochemistry of **17** was assigned as *R* by analogy to the facial selectivity of prior reductions herein. Saponification (LiOH) of **17** is known to produce GPR40 agonist **18** in enantiopure form.[16]

In summary, several examples of functionalized coumarins have been reduced in asymmetric fashion using copper hydride catalysis. Each case leads to an intermediate useful for subsequent conversion to a known physiologically active compound. Of particular note is the total synthesis of (*R*)-tolterodine ("Detrol-LA") that is especially competitive with existing routes to this widely prescribed drug. In general, the conditions for these hydrosilylations are mild, employ 200−1000:1 substrate-to-catalyst ratios at room temperature, and rely on an inexpensive silane as the stoichiometric source of hydride. Exceptional yields and ee's are observed in all cases studied, thus comparing favorably with established techniques that oftentimes rely on asymmetric catalytic hydrogenation.

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Supporting Information Available: Detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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