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Dinuclear Zinc-Catalyzed Asymmetric Desymmetrization of Acyclic 2-Substituted-1,3-Propanediols: A Powerful Entry into Chiral Building Blocks

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Abstract

The asymmetric acylation of meso 2-substituted-1,3-propanediols using an amphoteric chiral dinuclear zinc catalyst is described. It has been demonstrated that both 2-alkyl- and 2-aryl-1,3-propanediols can be desymmetrized in high yields and enantioselectivities using the same family of ligands. Given that both antipodes of the chiral catalyst are available, both enantiomers of the desymmetrized product can be obtained from the same starting material.

The synthetic utility of the desymmetrized products has been demonstrated by the synthesis of several chiral building blocks with high enantiomeric purities.

Keywords

desymmetrization; 1,3-propanediol; asymmetric catalysis; enantioselective; chiral building block

Introduction

The ability to differentiate between two enantiotopic groups of a symmetrical molecule is a powerful strategy for the synthesis of chiral compounds. One such method, the asymmetric desymmetrization via the enantiotopic acylation of meso 1,3-diols, stands out as a versatile entry into a wide range of chiral building blocks (Figure 1). Although several efforts toward the desymmetrization of such diols have been described,[1] there remains a need for a general process that desymmetrizes a wide range of acyclic 2-substituted-1,3-propanediols, particularly where either enantiomer is accessible simply by reversing the chirality of the catalyst.

Differentiation of the enantiotopic alcohols in 2-substituted-1,3-propanediols is inherently difficult because the prostereogenic center is remotely situated β to the hydroxyl group (Figure 1). To overcome this challenge, enzymes have traditionally been employed.[1] These enzymes have demonstrated broad utility in the desymmetrization of such diols and, in many cases, provide high enantioselection.

The advantages of using enzymes in the desymmetrizations of 1,3-propanediols include their compatibility with a wide range of functional groups and the fact that they are environmentally benign. Despite these advantages, both enantiomers of an enzyme are not readily available, and rescreening an enzyme collection to obtain the other enantiomer is often required. Switching from the enantioselective acylation of the diol to the

enantioselective hydrolysis of the corresponding diester using the same enzyme is an alternative approach to accessing the desired enantiomer. Unfortunately, this strategy is often unreliable and requires an additional step. Furthermore, enzymes possess high substrate specificities and thus general methods to obtain high yields and enantioselectivities of both enantiomers of many substrates remain elusive.[2-8] Additionally, products obtained from enzymatic desymmetrization often contain an acetate group that can lead to product racemization via an intramolecular acetyl migration (Figure 2).[9]

Motivated by the limited generality of enzymatic desymmetrization processes, several efforts using non-enzymatic pathways have been undertaken to desymmetrize 2-substituted-1,3-propanediols. A significant advantage of using such synthetic processes is that both enantiomers of the desymmetrized product can be obtained from the same starting material by simply reversing the chirality of the desymmetrizing element.[10]

Fukumoto and coworkers developed the first synthetic method to obtain desymmetrized 2-substituted-1,3-propanediols in high enantiomeric purity by employing chiral auxiliaries.[11,12] Oriyama and coworkers developed the first non-enzymatic catalytic desymmetrization using a proline-derived diamine to desymmetrize meso 2-alkyl-1,3-propane diols.[13] In this reaction, the meso compound is first converted to the racemic monoacetate that then undergoes a kinetic resolution to afford the desymmetrized products (21 – 33% yields) along with a significant amount of the diester (50 – 67%). Inspired by the discovery that a chiral amine can be transiently acylated to generate a chiral acylating agent, Fujimoto and coworkers developed a quinidine-based bifunctional organocatalyst that can desymmetrize cyclic 1,3-diols; however, only racemic products are obtained with acyclic systems.[14]

Harada and coworkers developed a chiral oxazaborolidinone-catalyzed ring cleavage of 1,3-dioxane acetals as an entry into desymmetrized meso 1,3-diols.[15] This process provided several desymmetrized products containing monosubstituted 2-aryl-1,3-propanediols in excellent enantioselectivities (85 – 92% ee), however, when this method was applied to 2-alkyl-1,3-propanediols, lowered enantioselectivities were observed (56 – 67% ee).

More recently, Miller and co-workers have developed a peptide-based catalyst that desymmetrizes glycerol derivatives in high enantioselectivities (86 – 97% ee) and modest yields (27 – 56% ee).[16] Nagao and coworkers have used a chiral sulfonamide zinc catalyst that is effective at desymmetrizing N-Boc-2-amino-2-alkyl-1,3-propanediols to provide chiral tertiary amines with high conversions (70 – 92%) and reasonable enantiomeric purity (70 – 88% ee).[17] Analogously, Kang and coworkers have developed a copper-based system that catalyzes the asymmetric acylation of 2-substituted glycerols to give chiral tertiary alcohols in excellent yields (85 – 98%) and enantioselectivities (80 – 94% ee).[18]

Given the disadvantages of enzymatic desymmetrizations and the current limitations of synthetic catalysts, we set out to develop a general method that permits the synthesis of a range of chiral 2-monosubstituted alkyl, aryl, and alkoxy 1,3-propanediols. The underlying motivation for initially taking on this challenge lay in our finding that a dinuclear zinc catalyst derived from phenols **1** or **2** and Et₂Zn can activate carbonyl groups by providing a chiral environment with a basic zinc alkoxide species and a Lewis acidic zinc alkyl species that is highly amphoteric in nature (Figure 3).[19]

We have previously reported the effectiveness of catalyst **2a** in desymmetrizing several 2-aryl-1,3-propanediols, 2-methyl-1,3-propanediol, and *cis*-1,2-bis(hydroxymethyl)cyclohexane using catalyst **2a**. [20] Despite promising results, improvements were necessary to enhance the substrate scope of 2-alkyl-1,3-propanediols and the enantioselectivities of 2-aryl-1,3-propanediols that had previously proven to be

problematic. Further, we wished to demonstrate that chiral building blocks with applications in complex molecule synthesis could be rapidly generated from the desymmetrized products. Our goal was thus to develop a process that (1) affords products in high enantioselectivities where the yields reflect a true desymmetrization event (theoretical yield of 100%), (2) is practical, experimentally simple, and robust, and (3) utilizes a commercially available ligand and acylating agent. Herein we describe our work on the desymmetrization of a wide range of meso 2-monosubstituted alkyl, aryl, and alkoxy 1,3-propanediols.

Results and Discussion

It has been shown that a desymmetrized 2-methyl-1,3-propanediol structural motif can be accessed from commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (Roche Ester).[10] In order to demonstrate our method as a general entry into other 2-substituted-1,3-propanediols we chose to optimize our desymmetrization protocol on the next simplest 2-ethyl-1,3-propanediol **3**, whose ester analog is not commercially available. Furthermore, the enzymatic desymmetrization of diol **3** has proven to be problematic.[7] For our initial studies, vinyl benzoate was the electrophile of choice, as the by-product (acetaldehyde) cannot participate in the reverse reaction. Further, it has been observed that the acyl transfer that led to product racemization is slower in the benzoyl, relative to the acetyl derivatives (Figure 2, R = Ph vs. R = CH₃).[22]

In order to examine the solvent dependence of the reaction, the desymmetrization of 1,3-propanediol **3** was attempted using 5 mol % catalyst **1a** and vinyl benzoate as the electrophile at 3 °C. These experiments (Table 1) show that toluene gave a combination of both the best yields and enantioselectivities.[23]

The influence of the temperature and the reaction time was next investigated. A temperature of -20 °C gave the highest yield and the greatest enantioselectivity (Table 2). Lowering the temperature below -20 °C had little effect on the enantioselectivity, but the isolated yield was significantly less due to low reaction conversion. We also found that the enantiomeric ratio remains constant during the course of the reaction and that catalyst **1a** does not promote the intramolecular benzoyl transfer at -20 °C and 3 °C (Figure 4).

To study the influence of the structure of the electrophile on the enantioselectivity of the reaction, we began by replacing the vinyl group with other alkenyl groups. Electrophiles **5** and **6** were synthesized from 1-hexyne and benzoic acid using a ruthenium-catalyzed addition of the corresponding carboxylic acids to alkynes (scheme 2).[23] When the asymmetric desymmetrization reaction was conducted using such electrophiles, these structural changes had detrimental effects on both the yield and the enantioselectivity (scheme 3).

To alter the electronic nature of the benzoyl donor moiety, electrophiles **7-11** were synthesized via a Pd-catalyzed transvinylolation of vinyl acetate with the appropriate carboxylic acids (scheme 4).[25] *O*-methoxy vinylbenzoate **7** was synthesized also to determine if incorporating a group capable of coordinating to the catalyst would influence the enantioselectivity.

Replacing vinyl benzoate with electrophiles **7** and **8** afforded esters **12** and **13**, respectively, in slightly higher enantioselectivities (Table 3). When electrophiles **9** and **11** were employed in the desymmetrization of 1,3-propanediol **3** to afford the desymmetrized products **14** and **16**, respectively, lower enantioselectivities were observed. Unfortunately, electrophile **10** failed to give any desired desymmetrized product **15**. Given that only a negligible improvement was achieved with electrophiles **7** and **8**, we continued our studies using commercially available vinyl benzoate.

Concentrations of both diol **3** and catalyst **1a** were also optimized. In order to understand the influence of the concentration of catalyst **1a** we maintained the concentration of the diol at 0.125 M and tested various catalyst concentrations (entries 1, 2, 4, and 5 in Table 4). Decreasing the catalyst loading to 2.5% reduced yields dramatically, though no change in enantiomeric excess was observed (entry 1 in Table 4). Increasing the catalyst loading past 5 mol % (entries 4, 5, and 6 in Table 3) resulted in no improvement in the enantioselectivity and reduced the yields for the transformation. As a result, a catalyst loading of 5 mol % was, to this point, the upper threshold for the desymmetrization process.

Given that a catalyst concentration of 0.006 M was optimal, we initiated experiments to lower the catalyst loading by maintaining [1a] = 0.006 M and doubling the concentration of diol **3**. Unfortunately, this resulted in both lowered yields and enantioselectivities (entry 3 in Table 4).

We have previously reported that catalyst **2a** gives an increase in the enantioselectivity for the asymmetric desymmetrization of 2-phenyl-1,3-propanediol compared to catalyst **1a**.^[20] This was, however, not the case for the 2-alkyl-1,3-propanediols **3** and **17** (Table 5). Both catalysts give similar enantioselectivities for diol **3** (Table 5, entries 1 and 2). Interestingly, higher enantioselectivities were obtained for 2-methyl-1,3-propanediol **17** using catalyst **1a** (Table 5, entries 3 and 4). Given that there was no advantage to switching to **2a**, we continued our studies with the catalyst derived from the commercially available ligand **1** and Et₂Zn.

The studies outlined above demonstrate that the asymmetric desymmetrization of diol **3** can be achieved in impressive yields and in high enantiomeric ratios when run with catalyst **1a** in toluene at -20 °C for 24h (scheme 5). Although other vinyl benzoates may be employed, we determined that commercially available vinyl benzoate gave comparable results to *o*- and *p*-methoxy substituted vinyl benzoates. Further, it was determined that a catalyst loading of 5 mol% with concentrations of 0.125 M in diol and 0.006 M in catalyst were optimal. Having these conditions in hand the next step was to determine if the optimized conditions were suitable for the desymmetrization of other 2-substituted-1,3-propanediols which contained functionality that could be further elaborated.

The Desymmetrization of meso 2-alkyl and 2-alkoxy-1,3-propanediols

The optimized conditions shown in scheme 5 were applied to a range of meso 2-alkyl and 2-alkoxy-1,3-propanediols that can serve as synthetically useful precursors. The optimized conditions proved to be a general and robust method to enantioselectively desymmetrize 2-alkyl-1,3-propanediols with high yields and enantioselectivities (Table 6). For example, the desymmetrization of substrate **17** afforded benzoate **18** in 88% yield and 90 % ee (Table 6, entry 1).

Previous work on the addition of terminal alkynes to aldehydes demonstrated that catalyst **1a** has the ability to deprotonate and bind to alkynes.^[19g] Yet diol **21**, which contains a terminal alkyne, did not poison the catalyst or react with the acetaldehyde that is generated during the course of the reaction, instead affording product **22** in 90% yield and 80% ee (Table 6, entry 4). Further, substrate **23** afforded the desymmetrized product **24** in 85% yield and 90% enantioselectivity (Table 6, entry 5). A close analog of product **24**, which contains a benzyl ether instead of the benzoyl ester, has recently been synthesized in three steps and 55% yield using a chiral auxiliary.^[26] The auxiliary approach has been employed in the synthesis of *E*-alkene peptide isosteres.^[27] The method presented here, therefore, provides a more direct route to such structures.

Although excellent results were achieved with 2-alkyl-1,3-propanediols, the desymmetrization of 2-alkoxy-1,3-propanediols **25** and **27** gave both lowered isolated yields and enantioselectivities (Table 6, entries 6 and 7). These 1,3-propanediols are unique in that they contain an electron withdrawing group on the β carbon that lowers the nucleophilicity of the primary alcohols compared to the 2-alkyl-1,3-propanediols discussed above. It is conceivable that the lowered enantioselectivity and yield was observed because this class of 1,3-diols are intrinsically poorer ligands for the zinc catalyst and possess a reduced propensity to undergo acylation by the vinyl benzoate.

The Desymmetrization of meso 2-aryl-1,3-propanediols

Given the prevalence of aromatic functionality in both natural products and pharmaceuticals, a general method that would provide either enantiomer of the desymmetrized 2-aryl-1,3-propanediols would also be of significant value. Although the dinuclear zinc catalyst **1a** desymmetrized meso 2-aryl-1,3-propanediols in yields and enantioselectivities comparable to the 2-alkyl-1,3-propanediols, extending the chiral pocket by using a larger biphenyl based catalyst **2a** enhanced the enantioselectivities for 1,3-propanediol **29** (Table 7, entry 1 and 2). Similar to observations made with diol **3**, lowering the temperature for reactions with meso 2-phenyl-1,3-propanediol **29** from room temperature to -15 °C also resulted in increased enantioselectivity (Table 7, entry 2 and 3).

The results presented in Table 7 show that the catalyst **2a** desymmetrizes both 2-aryl (Table 7, entries 1-9) and 2-thienyl-1,3-propanediols (Table 7, entries 10 and 11), giving enantiomeric ratios ranging from 80% to 93%. The 1-naphthyl substrate **39** is structurally unique because it contains an additional benzene ring in close proximity to the pronucleophile. Enzymatic catalysis affords the desymmetrized product **40** in 40 % ee,[28] however, the desymmetrized product can be obtained in 67% ee with catalyst **2a** and in 80% ee with catalyst **1a**. Additionally, changing the positioning of the 1,3-propanediol to the 2-naphthyl substrate gave an enantiomeric ratio of 93% using catalyst **2a**. The results presented in Table 7 demonstrate that either catalyst effects the desymmetrization of 2-aryl-1,3-propanediols in high enantioselectivities. An added advantage to this process is that either enantiomer of the desymmetrized product can be accessed by switching to the other enantiomer of the chiral catalyst.

Synthetic Utility: The rapid generation of chiral building blocks

The asymmetric desymmetrization of 2-substituted-1,3-propanediols provides several chiral building blocks that can be potentially employed in total synthesis. There are two challenges that needed to be addressed in order to demonstrate a broad applicability of this methodology. First, as described in Figure 2, either an acid or base catalyzed intramolecular acyl transfer that may lead to erosion in enantiomeric excess must be avoided. Second, in the oxidation of the desymmetrized alcohol to an aldehyde or carboxylic acid, the β -elimination of the benzoate must be minimized. The latter issue was specifically relevant to an ongoing project involving the total synthesis of a marine macrolide for which the aldehyde was required.

The formation of the *p*-toluenesulfonate **47** (path a) from substrate **18** using standard conditions gave a minimal erosion of the enantiomeric ratio (scheme 6). This compound has been previously synthesized from the Roche ester in 5 steps (compared to two steps from inexpensive commercially available diol **17**) and served as an essential intermediate in determining the absolute stereochemistry of benzoate **18**.^[29] Building block **47** proved to be a useful intermediate for the formation of nitrile **48** (path b).^[29] Azide **49** (path c) can be accessed directly from the desymmetrized product **18** via a Mitsunobu reaction.^[30] The desbenzoyl derivatives for both substrates **48** and **49** have been accessed from commercially

available chiral 3-bromo-2-methyl-1-propanol[31] and have been employed in the total synthesis of natural products.[32] However, to access analogs that contain 2-substitution other than a methyl group, multi-step sequences have been employed.[32c] The orthogonally protected asymmetric 1,3-propanediol (path d) **50** provides another potentially useful chiral building block. Initial attempts to oxidize primary alcohol **18** to aldehyde **51** proved problematic due to subsequent elimination of the benzoyl group. Gratifyingly, TEMPO and bisacetoxyl iodobenzene provided mild reaction conditions for the formation of aldehyde **51** with no erosion of the enantiomeric ratio. Although these examples represent entries into 2-methyl substituted derivatives, this methodology provides a general entry into other 2-alkyl and 2-aryl derivatives, for which the chiral precursors are not commercially available.

To further enhance the utility of our methodology, product **22** was transformed into structurally diverse chiral building blocks (scheme 7). Ruthenium-catalyzed regioselective hydrosilylation[33] transformed alkyne **22** into vinyl silane **52** in high yields and with minimal degradation in the enantiomeric ratio. Vinyl silanes have shown great utility in the formation of C – H,[43] C – C,[35] and C – O[36] bonds and provide a route to more elaborated chiral building blocks. The desymmetrized alkyne **22** can also undergo ruthenium-catalyzed oxidative cyclizations and cycloisomerizations to afford lactone **53** and dihydropyran **54**. The acetate derivative of lactone **53** has been used for the enantioselective total synthesis of the natural product tacamonic,[37] and this method provides a more efficient way to access this intermediate. Interestingly, no degradation of enantiomeric excess is observed when electron rich phosphines are used to access lactone **53**. However, with electron deficient phosphines, the electrophilicity of the metal is enhanced, and this may account for the degradation of the enantiomeric excess from 80% to 71% during the formation of dihydropyran **54**.

Proposed Mechanism and Stereochemical Proof

In the proposed mechanism, the reaction between a 1,3-propanediol and the zinc catalyst **1a** furnishes the zinc alkoxide (Figure 5, I). Coordination of the vinyl benzoate can occur from either face of the C₂ symmetric ligand, away from the two phenyl groups that are almost perpendicular to the plane of the catalyst. This mode of binding activates the carbonyl carbon to give intermediate **II**. Catalyst-directed benzoylation could then proceed via transition state **III**, where a proton transfer is followed by acylation by the activated ester within the coordination sphere of the catalyst. Ligand exchange on **IV** with another molecule of diol decomplexes the desymmetrized product and then protonates the zinc-enolate, releasing acetaldehyde.

The absolute stereochemistry was assigned by comparison of the optical rotation of desymmetrized products **18**[5] and **47**[29] with known literature values. It was found that the (*S,S*)-**1** ligand gives products with (*S*)-stereochemistry for 2-alkyl, 2-alkoxy, and 2-(hetero)aryl-1,3-propanediols. The stereochemical outcome can be rationalized based on transition state **III** depicted in Figure 5, where the prochiral alcohol proximal to the vinyl benzoate is benzoylated.

Conclusion

In summary, we have developed an efficient method to desymmetrize 2-alkyl- and 2-aryl-1,3-propanediols in excellent yields and enantiomeric ratios. The underlying rationale for the success of a catalyst system such as **1a** and **2a** is that it provides an amphoteric environment in which one zinc generates an alkoxide of a 1,3-propanediol and the other acts as a Lewis acid by activating the vinyl benzoate. The result of this coordination is an enantioselective benzoylation that affords a wide range of desymmetrized 2-alkyl and 2-aryl-1,3-propanediols.

In comparison to enzymatic desymmetrizations, this process does not require the screening of enzymes and it incorporates a benzoyl group that is less prone to intramolecular acyl transfer.[38] Usually enzymatic acylation and enzymatic hydrolysis are complementary and give opposite enantiomers, but this is not always the case. For example, the desymmetrization of 1,3-propanediol **3** to product **4** gave superior enantioselectivities compared to enzymatic acylation, which affords the (*R*) configured product in 72 % yield and 46% ee.[7] Although the enzymatic hydrolysis of the diacetylated product derived from diol **3** gives higher enantioselectivities (94% ee), only the (*R*) enantiomer can be directly accessed by this method.[7] With our asymmetric desymmetrizations, both antipodes of the desymmetrized product are accessible in high enantioselectivities by switching the chirality of the ligand.[7] The substrate scope of these reactions extends to both 2-alkyl- and 2-aryl-1,3-propanediols. The reactions are operationally simple and the product can be obtained in excellent purities by directly loading the crude reaction mixture onto silica gel. An added benefit of this procedure is that both ligand **1** and vinyl benzoate are commercially available.

The derivatization of alcohols **18** and **22** demonstrates the potential of this methodology to provide rapid access to a range of chiral building blocks. The desymmetrized 2-methyl-1,3-propanediol structural motif has been previously synthesized from commercially available Roche ester. This work presents a new way to access this common chiral starting material in either fewer or a comparable number of inexpensive synthetic steps from commercially available starting material. Additionally, for compounds that contain a substituent other than a methyl group, this method provides a direct entry into such desymmetrized structural motifs.

Experimental Section

General Information

All reactions were carried out in flame-dried glassware under a N₂ atmosphere. Anhydrous acetonitrile, dichloromethane, tetrahydrofuran, and toluene were obtained from a Seca solvent purification system by Glass Contour. Solvents and reagents were transferred via a syringe, which had been oven dried and cooled in a dessicator.

Analytical thin-layer chromatography was performed on precoated 250 μ m layer thickness silica gel 60 F₂₅₄ plates (EMD Chemicals Inc.). Visualization was performed by ultraviolet light and/or by staining with either ceric ammonium molybdate or potassium permanganate. Flash column chromatography was performed using 32-63 μ m silica gel (Sorbent Technologies) using compressed air. The eluents employed for flash chromatography are reported as volume: volume percentages.

Proton and carbon nuclear magnetic resonance (¹H NMR and ¹³C NMR, respectively) spectra were acquired using Varian Inova 500 MHz, Mercury 400 MHz, and Gemini 300 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and are calibrated to residual solvent peaks: proton (CDCl₃ 7.26 ppm) and carbon (CDCl₃ 77.0 ppm). Coupling constants (*J*) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. ¹³C NMR spectra were recorded using a Varian Unity INOVA spectrometer at 125 MHz or a Varian Gemini at 75 MHz.

Infrared spectroscopic data was recorded on NaCl plates as thin films on a Perkin-Elmer Paragon 500 FT-IR spectrophotometer using 0.1 mm path length. The absorbance frequencies are recorded in wavenumbers (cm⁻¹). Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. High resolution mass spectra were obtained from the

Mass Spectrometry Resource, School of Pharmacy, University of California-San Francisco, supported by the NIH Division of Research Resource, and are reported as *m/e* (relative ratio). Accurate masses are reported for the molecular ion (M^+) or a suitable fragment ion. Chiral HPLC analysis were performed on Daicel Chiralpack columns (AD, AS, OB-H, OC, OD, or OJ) using heptane/2-propanol mixtures. The respective ratio of the eluent mixture, flow rate, detection wavelength, and column are indicated within the experimental details. Retention times (*Tr*) are reported in minutes (min). Optical rotations were determined using a JASCO DIP-1000 digital polarimeter in 50-mm cells and the sodium D line (589 nm) at the temperature, solvent, and concentration indicated.

Representative procedure for Asymmetric Desymmetrizations

Preparation of the dinuclear zinc catalyst—Diethyl zinc (47 μ L, 0.0312 mmol, 0.67 M in toluene) was added dropwise to a solution of (*S,S*)-Pro-phenol ligand 1 (9.96 mg, 0.0156 mmol) in anhydrous toluene (553 μ L) while stirring under nitrogen. The light yellow catalyst solution (0.026 M) was stirred for 30 min at room temperature and then transferred to the appropriate reaction using a syringe.

Asymmetric Desymmetrization—To a flame dried tube containing 2-ethylpropane-1,3-diol (32.5 mg, 0.312 mmol) and vinyl benzoate (231 mg, 1.56 mmol) at room temperature, was added anhydrous toluene (1.9 mL). To this solution was added a stock solution of catalyst (0.026 M, 0.6 mL, 0.0156 mmol) at -70 °C under a positive flow of nitrogen. The reaction was sealed and stirred at -20 °C for 24h (stirring was essential to the yield of the reaction as the reaction is heterogeneous at this temperature, when the reaction was conducted at -20 °C without stirring, similar enantioselectivities were obtained, however, significantly lowered yields were observed). The crude product was directly applied to a silica gel column, and eluted with 20% → 50% ethyl acetate/hexanes to give the desired product (54.7 mg, 84% yield). R_f = 0.44 (50% ethyl acetate/hexanes); $[\alpha]_D^{25}$ -1.89 (86% ee, *c.* 1.0, CH_2Cl_2); 1H NMR (500 MHz, $CDCl_3$): δ 8.07 (dd, J = 8.4, 1.4 Hz, 2H), 7.60 (tt, J = 7.4, 1.4 Hz, 1H), 7.48 (dt, J = 8.4, 7.4 Hz, 2H), 4.51 (dd, J = 11.2, 4.3 Hz, 1H), 4.39 (dd, J = 11.2, 6.3 Hz, 1H), 3.71 (m, 1H), 3.63 (m, 1H), 2.05 (t, J = 6.3 Hz, 1H), 1.90 (m, 1H), 1.50 (m, 2H), 1.02 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 133.4, 130.3, 129.9, 128.7, 64.9, 62.6, 42.7, 21.1, 11.8; IR (neat): ν_{max} 3332, 2963, 2932, 2879, 1719, 1464, 1381, 1044, 1008, 969, 767 cm^{-1} . t_r = 31.4 and 37.6 min (major) (Chiralcel® OBH Chiral HPLC, λ = 254 nm, heptane : *i*-PrOH = 99:1, 0.8 mL/min); ee = 86%. Elemental Analysis Theoretical C69.21, H7.74 Found C69.19, H7.60.

(*R*)-2-methyl-3-(tosyloxy)propyl benzoate (47)

A solution of (*S*)-3-hydroxy-2-methylpropyl benzoate (204 mg, 1.05 mmol, 91% ee) in dichloromethane (3 mL) was added in Et_3N (1.06 g, 10.5 mmol) and *p*-toluenesulfonyl chloride (0.40 g, 2.10 mmol). The reaction was stirred at room temperature for 15h, diluted with diethyl ether and washed with saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated. Silica gel chromatography using ethyl acetate/hexane mixtures gave 0.27 g (74%, 88% ee) of the title compound as a white solid. R_f = 0.45 (20% ethyl acetate/hexanes); $[\alpha]_D^{25}$ -4.80 (88% ee, *c.* 0.99, CH_2Cl_2); t_r = 18.57 (major) and 20.83 min (Chiralcel® OD Chiral HPLC, λ = 254 nm, heptane : *i*-PrOH = 95:5, 0.8 mL/min). The product **47** has been reported previously[29] was identified by comparison of 1H NMR and IR data.

(-)-3-cyano-2-methylpropyl benzoate (48)

To a solution of (*R*)-2-methyl-3-(tosyloxy)propyl benzoate (45 mg, 0.129 mmol) in DMSO- d_6 (0.8 mL) was added sodium cyanide (12.7 mg, 0.260 mmol). The reaction mixture was

heated to 80°C for 2.5 h. Upon completion (monitored by ^1H NMR), the reaction was diluted with diethyl ether (40 mL), washed 5 times with water, dried (MgSO_4), filtered, and concentrated. The crude product was purified by silica gel column chromatography (20% ethyl acetate/hexanes) to afford 25 mg (96%) of the title compound as a clear oil. $R_f = 0.2$ (20% ethyl acetate/hexanes); $[\alpha]_D^{25} -14.65$ (88% ee, c . 0.39, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3): δ 8.04 (dd, $J = 8.0, 1.0$ Hz, 2H), 7.57 (tt, $J = 8.0, 1.0$ Hz, 1H), 7.45 (dd, $J = 8.0, 8.0$ Hz, 2H), 4.28 (dd, $J = 11.0, 5.6$ Hz, 1H), 4.23 (dd, $J = 11.0, 6.5$ Hz, 1H), 3.43 (dd, $J = 11.9, 5.8$, 1H), 3.36 (dd, $J = 11.9, 6.3$ Hz, 1H), 2.28 – 2.16 (m, 1H), 1.1 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 166.2, 133.2, 129.6, 129.6, 128.5, 118.1, 66.4, 30.4, 21.7, 16.3; IR (neat): ν_{max} 2967, 2935, 2101, 1721, 1460, 1452, 1272, 1111, 1071, 211 cm^{-1} ; $t_r = 39.82$ (major) and 41.23 min (Chiralcel® OD Chiral HPLC, $\lambda = 254$ nm, heptane : i -PrOH = 4000:1, 0.8 mL/min). HRMS (ESI, $[\text{MC}_{12}\text{H}_{13}\text{NO}_2 + \text{Na} + \text{H}]$) Calc'd for $\text{C}_{12}\text{H}_{14}\text{NNaO}_2$ 227.0971 Found 227.0369.

(-)-2-methyl-3-oxopropyl benzoate (51)

To a solution of (*S*)-3-hydroxy-2-methylpropyl benzoate (500 mg, 2.63 mmol, 90% ee) in dichloromethane (2.63 mL) was added (diacetoxyiodo)benzene (930 mg, 2.89 mmol) and TEMPO (41 mg, 0.26 mmol). The reaction mixture was stirred for 1.5 hours at room temperature, quenched with saturated aqueous NaHCO_3 , and extracted into diethyl ether. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Silica gel chromatography using 20% ethyl acetate/hexanes afforded 470 mg (93%, 90% ee) of the title compound as a yellow oil. It is important to store this oil at -20 °C away from light. $R_f = 0.24$ (35% diethyl ether/hexanes); $[\alpha]_D^{25} -12.38$ (90% ee, c . 2.34, CHCl_3); ^1H NMR (500 MHz, CDCl_3): δ 9.8 (d, $J = 1.0$ Hz, 1H), 8.03 (dd, $J = 8.4, 1$ Hz, 2H), 7.59 (td, $J = 8.4, 1.0$ Hz, 1H), 7.45 (dd, $J = 8.4, 8.4$ Hz, 2H), 4.58 (m, 2H), 2.89 (m, 1H), 1.28 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 201.8, 165.9, 132.9, 129.3, 128.2, 63.7, 45.6, 10.4; IR (neat): ν_{max} 3064, 2968, 2894, 1721, 1602, 1452, 1389, 1377, 1337, 1314, 1272, 1177, 1114, 1070, 1026, 982, 934, 850, 806, 711 cm^{-1} . $t_r = 18.94$ and 19.74 min (major) (Chiralcel® OJ Chiral HPLC, $\lambda = 254$ nm, heptane : i -PrOH = 95:5, 1.0 mL/min). This compound has been previously reported.[40]

(-)-4-(benzyltrimethylsilyl)-2-(hydroxymethyl)pent-4-enyl benzoate (52)

To a solution of (*S*)-2-(hydroxymethyl)pent-4-en-1-yl benzoate (20 mg, 0.092 mmol) and benzyltrimethyl silane (16 mg, 0.11 mmol) in acetone (1 mL) was added $\text{Cp}^*\text{Ru}(\text{CH}_3\text{CN})_3\text{PF}_6$ (1 mg, 0.0018 mmol). The reaction was stirred at room temperature for 2h, concentrated, and chromatographed (15% ethyl acetate/hexanes) to give 32 mg (94%, 78% ee) of the title compound as a clear oil. $R_f = 0.35$ (15% ethyl acetate/hexanes); $[\alpha]_D^{25} -12.86$ (78% ee, c . 0.3, CH_2Cl_2); ^1H NMR (125 MHz, CDCl_3): δ 8.05 (m, 2H), 7.58 (tt, $J = 8.0, 1.5$ Hz, 1H), 7.45 (m, 2H), 7.20 (m, 2H), 7.06 (m, 1H), 7.0 (d, $J = 7.0$ Hz, 2H), 5.72 (m, 1H), 5.59 (d, $J = 2.5$ Hz, 1H), 4.45 (dd, $J = 11.2, 4.3$ Hz, 1H), 4.29 (dd, $J = 11.2, 6.2$ Hz, 1H), 3.60 (ddd, $J = 8.1, 5.1, 3.5$ Hz, 2H), 2.3 – 2.0 (m, 5H), 0.11 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ 167.1, 147.6, 139.6, 133.1, 129.9, 129.6, 128.4, 128.2, 128.1, 127.9, 124.1, 64.3, 62.3, 39.5, 34.7, 25.5, -3.3; IR (neat): ν_{max} 3449, 3051, 3030, 2958, 2916, 2855, 1716, 1602, 1493, 1451, 1384, 1317, 1280, 1202, 1182, 1156, 1119, 1052, 1031, 927, 829, 756, 715, 699 cm^{-1} ; $t_r = 70.23$ min (major) and 73.73 min (Chiralcel® OD Chiral HPLC, $\lambda = 220$ nm, heptane : i -PrOH = 98:2, 0.8 mL/min). HRMS (ESI, $[\text{C}_{22}\text{H}_{29}\text{O}_3\text{Si} + \text{H}]$) Calc'd for $\text{C}_{22}\text{H}_{29}\text{O}_3\text{Si}$ 369.1886 Found 369.1891.

(-)-(3,4-dihydro-2H-pyran-3-yl)methyl benzoate (54)

To an oven dried flask was added (*S*)-2-(hydroxymethyl)pent-4-en-1-yl benzoate (52.4 mg, 0.24 mmol), $\text{RuCp}(p\text{-fluorotriphenylphosphine})_2\text{Cl}$ (15 mg, 0.018 mmol), p -fluorotriphenylphosphine (22.8 mg, 0.072 mmol), N -hydroxysuccinimide (28 mg, 0.24

mmol), and tetrabutylammonium hexafluorophosphate (21 mg, 0.055 mmol) were combined in a flame-dried vial cooled under nitrogen. To this was added DMF (0.6 mL) that had been degassed with argon (essential for high yielding reaction). The mixture was placed in a pre-heated oil bath (85 °C) and was stirred 24 hr under nitrogen. The reaction was then cooled to room temperature, diluted with diethyl ether, and washed with water 3 times. The aqueous layer was re-extracted with diethyl ether and the combined organic layers were dried with sodium sulfate, filtered, and concentrated to dryness. Silica gel that was pretreated with 5% diethyl ether/hexanes and 1% triethylamine was used for column chromatography by eluting with the same solvent system to afford 42 mg (81%, 71% ee) of the title compound as a yellow oil. $R_f = 0.52$ (5 % diethyl ether/hexanes). $[\alpha]_D^{25} -4.5$ (71% ee, *c.* 0.34, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃): δ 8.04 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.57 (tt, *J* = 1.0 Hz, 1H), 7.45 (m, 2H), 6.40 (td, *J* = 6.1, 2.0 Hz, 1H), 4.72 (ddd, *J* = 6.2, 4.2, 3.3 Hz, 1H), 4.36 (dd, *J* = 11.0, 5.8 Hz, 1H), 4.25 (dd, *J* = 11.0 Hz, 1H), 4.15 (ddd, *J* = 10.5, 3.0, 1.5 Hz, 1H), 3.85 (dd, *J* = 10.5, 8 Hz, 1H), 2.4 (m, 1H), 2.2 (m, 1H), 1.9 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 166.4, 143.9, 133.0, 130.0, 129.5, 128.4, 99.2, 66.9, 65.2, 32.2, 22.5; IR (neat): $\nu_{\max}$ 3063, 2926, 1722, 1651, 1602, 1584, 1451, 1392, 1379, 1344, 1315, 1274, 1245, 1196, 1177, 1118, 1071, 1027, 976, 921, 894, 878, 806, 736, 711 cm⁻¹; tr = 36.51 min (major) and 39.82 min (Chiralcel® AD Chiral HPLC, λ = 220 nm, heptane : *i*-PrOH = 99.1:0.1 mL/min). HRMS (ESI, [C₁₃H₁₄O₃+H]) Calc'd for C₁₃H₁₅O₃ 219.1016 Found 219.1025.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Asymmetric desymmetrization of meso 1,3-propanediols.

Figure 2.
Mechanism for racemization of **A** to **ent-A**.

Figure 3.
Generation of the desymmetrization catalysts **1a** and **2a**.

Figure 4. Enantioselectivity vs. time for the asymmetric desymmetrization of **3** at -20 °C and 3 °C.

Figure 5.
Proposed catalytic cycle for the desymmetrization of meso 2-substituted-1,3-propanediols

Scheme 1.

Catalytic asymmetric desymmetrization study outline.

Scheme 2.
Synthesis of alkenyl benzoates **5**, **6**.

Scheme 3. Influence of electrophiles **5** and **6** on the asymmetric desymmetrization of **3**.

Scheme 4.
Synthesis of alkenyl benzoates **7** – **11**.

Scheme 5.

Summary of optimized conditions for asymmetric desymmetrizations of diol **3**.

Scheme 6.

Synthesis of chiral building blocks from **18** as a representative example. a) TsCl, Et₃N, CH₂Cl₂, rt; b) NaCN, DMSO, 80 °C; c) Zn(N₃)₂.Py, DIAD, PPh₃, PhCH₃; d) TIPSCl, Imidazole, DMF; e) Ph(IOAc)₂, TEMPO, CH₂Cl₂

Scheme 7.
Synthesis of complex chiral building blocks from **22**.

Table 1The influence of solvent on the asymmetric benzylation of **3**.

Entry	Solvent	Yield [%]	ee [%]
1	CH ₃ CN	66	73
2	CH ₂ Cl ₂	89	77
3	THF	80	80
4	PhCH ₃	96	81

Table 2The influence of temperature on the asymmetric desymmetrization of **3**.

Entry	Temp. [°C]	Yield [%]	ee [%]
1	-30	29	85
2	-20	84	86
3	3	93	81
4	rt	60	65

Table 3

The influence of electrophiles **7** – **11** on the desymmetrization of **3**.^a

Entry	R	Electrophile/Product	Temp [°C]	Yield [%]	ee [%]
1	<i>o</i> -C ₆ H ₄ OCH ₃	7/12	3	88	82
2	<i>o</i> -C ₆ H ₄ OCH ₃	7/12	rt	94	72
3	<i>p</i> -C ₆ H ₄ OCH ₃	8/13	3	88	83
4	<i>p</i> -C ₆ H ₄ OCH ₃	8/13	rt	90	76
5	<i>p</i> -C ₆ H ₄ Br	9/14	3	28	68
6	<i>p</i> -C ₆ H ₄ NO ₂	10/15	3	0	NA
7	2-Furyl	11/16	-20	82	68

^a All reactions were run in toluene at the specified temperature using 0.31 mmol of **3** for 24 hours with [**3**] = 0.125 M and [**1a**] = 0.006 M.

Table 4Influence of concentration of **3** and **1a** on the asymmetric desymmetrization of **3**.

Entry	Catalyst [%]	[3] ^a	[1a] ^a	Time [h]	Yield [%]	ee [%]
1	2.5	0.125	0.002	24	26	81
2	5	0.125	0.006	24	84	86
3	2.5	0.25	0.006	72	51	75
4	7.5	0.125	0.009	24	70	84
5	10	0.125	0.012	24	53	84
6	10	0.25	0.012	24	55	87

Table 5

The influence of catalyst on the asymmetric desymmetrization of **3** and **17**.

Entry	R	Substrate/Product	Catalyst	Time	Yield [%]	ee [%]
1	CH ₂ CH ₃	3/4	1a	24h	86	86
2	CH ₂ CH ₃	3/4	2a	24h	66	86
3	CH ₃	17/18	1a	24h	88	90
4	CH ₃	17/18	2a	20h	89	82

Table 6

The Desymmetrization of 2-alkyl-1,3-propanediols and 2-alkoxy-1,3-propanediols.

Entry	R	Substrate/Product	Yield [%]	ee [%]
1	R = CH ₃	17/18	88	90
2	R = CH ₂ CH ₃	3/4	86	86
3	R = CH ₂ CHCH ₂	19/20	84	84
4	R = CH ₂ CCH	21/22	90	80
5	R = Bn	23/24	85	90
6	R = OBn	25/26	36	40
7	R = OTIPS	27/28	22(54) ^b	60

^a All reactions conducted using optimized conditions shown in scheme 5.^b Yield based on recovered starting material.

Table 7

Entry	Substrate/Product	Mol % cat.	Temp. [°C]	Yield [%]	ee [%]
1	29/30	5% 1a	rt	85	74
2	29/30	5% 2a	rt	98	83
3	29/30	5% 2a	-15	94	91
4	31/32	5% 2a	-15	94	91
5	33/34	5% 2a	-15	99	93
6	35/36	10% 2a	-15	89	90
7	37/38	10% 2a	-15	83	86
8	39/40	5% 1a	-20	56(95) ^b	80 ^c
9	39/40	<i>ent</i> 5% 2a	-20	80	-67 ^c
10	41/42	10% 2a	-15	97	93
10	43/44	10% 2a	-15	88	74
11	45/46	5% 2a	-15	78	70

^a Reactions were performed at 0.1 M except as indicated elsewhere

^b Yield based on recovered starting material

^c Reaction performed with optimized conditions shown in scheme 5.