CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200800623

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

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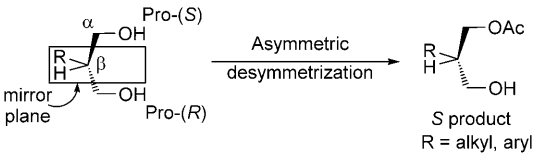
Abstract: The asymmetric acylation of *meso*-2-substituted-1,3-propanediols by using an amphoteric chiral dinuclear zinc catalyst is described. It is has been demonstrated that both 2-alkyl- and 2-aryl-1,3-propanediols can be desymmetrized in high yields and enantioselectivities by using the same family 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: asymmetric catalysis · chiral building blocks · desymmetrization · enantioselectivity · propanediol

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 through the enantiotopic acylation of *meso*-1,3-diols, stands out as a versatile entry into a wide range of chiral building blocks (Scheme 1). Although several



Scheme 1. Asymmetric desymmetrization of *meso*-1,3-propanediols.

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 for cases in which either enantiomer is accessible simply by reversing the chirality of the catalyst.

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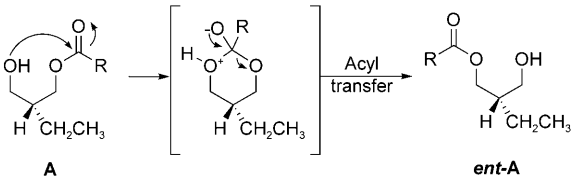
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200800623.

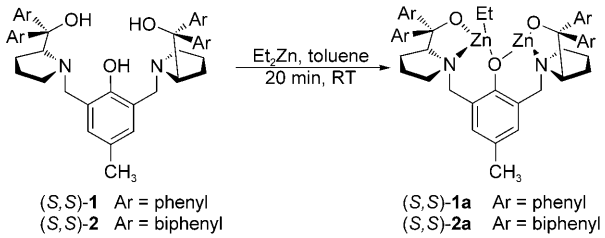
Differentiation of the enantiotopic alcohols in 2-substituted-1,3-propanediols is inherently difficult because the prostereogenic center is remotely situated β to the hydroxyl group (Scheme 1). To overcome this challenge, enzymes have traditionally been employed.[1] These enzymes have demonstrated broad 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 re-screening 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 by 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 by means of intramolecular acetyl migration (Scheme 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 start-



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



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

ing material by simply reversing the chirality of the desymmetrizing element.[10]

Fukumoto and co-workers 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 co-workers developed the first nonenzymatic 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, which 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 co-workers 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 co-workers 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*; *ee* = enatiomeric excess); however, when this method was applied to 2-alkyl-1,3-propanediols, lowered enantioselectivities were observed (56–67% *ee*).

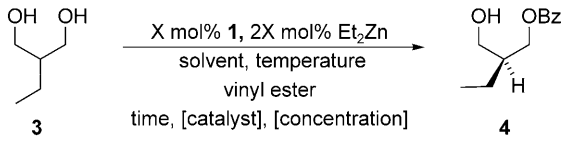
More recently, Miller and co-workers have developed a peptide-based catalyst that desymmetrizes glycerol derivatives in high enantioselectivities (86–97% *ee*) and modest yields (27–56% *ee*).[16] Nagao and co-workers have used a chiral sulfonamide zinc catalyst that is effective at desymmetrizing *N*-Boc-2-amino-2-alkyl-1,3-propanediols to provide chiral tertiary amines with high conversions (70–92%) and reasonable enantiomeric purity (70–88% *ee*).[17] Analogously, Kang and co-workers 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 Et_2Zn 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 (Scheme 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.[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 in which 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] 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 diol, 2-ethyl-1,3-propanediol (**3**; Scheme 4), the ester

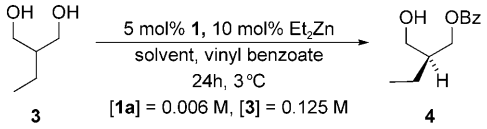


Scheme 4. Catalytic asymmetric desymmetrization study outline.

analogue of which 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 byproduct (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 (Scheme 2, R = Ph vs. R = CH_3).[22]

To examine the solvent dependence of the reaction, the desymmetrization of 1,3-propanediol **3** was attempted by 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]

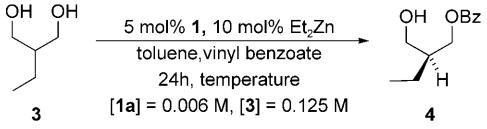
Table 1. The influence of solvent on the asymmetric benzoylation of **3**.



Entry	Solvent	Yield [%]	*ee* [%]
1	CH_3CN	66	73
2	CH_2Cl_2	89	77
3	THF	80	80
4	$PhCH_3$	96	81

The influence of the temperature and the reaction time was investigated next. 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 1).

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



Entry	*T* [°C]	Yield [%]	*ee* [%]
1	−30	29	85
2	−20	84	86
3	3	93	81
4	RT	60	65

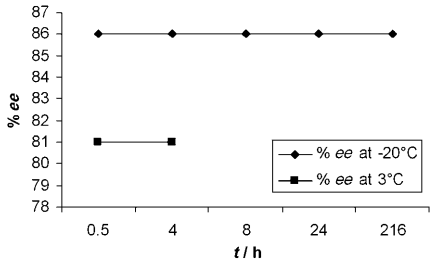
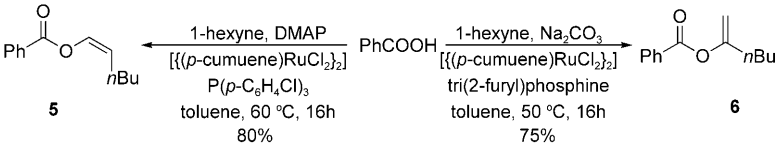


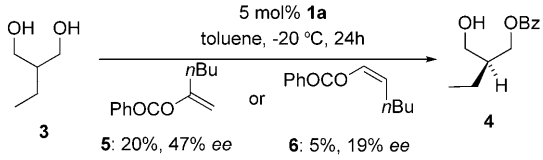
Figure 1. Enantioselectivity vs. time for the asymmetric desymmetrization of **3** at −20°C and 3°C.

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 by using a ruthenium-catalyzed addition of the corresponding carboxylic acids to alkynes (Scheme 5).[23] When the asymmetric desymmetrization reaction was conducted with such electrophiles, these structural changes had detrimental effects on both the yield and the enantioselectivity (Scheme 6).

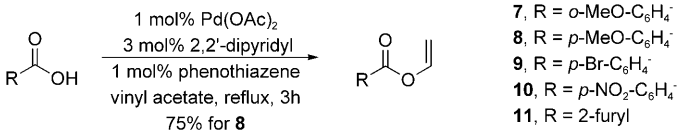
To alter the electronic nature of the benzoyl donor moiety, electrophiles **7**–**11** were synthesized by means of a Pd-catalyzed *trans*-vinylation reaction of vinyl acetate with the appropriate carboxylic acids (Scheme 7).[25] *O*-Methoxy vinylbenzoate **7** was synthesized to determine if incorporating a group capable of coordinating to the catalyst would influence the enantioselectivity.



Scheme 5. Synthesis of alkenyl benzoates **5** and **6**.



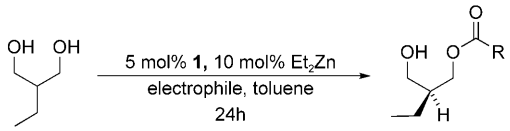
Scheme 6. Influence of electrophiles **5** and **6** on the asymmetric desymmetrization of **3**.



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

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

Table 3. The influence of electrophiles **7–11** on the desymmetrization of **3**.[a]



3 **12 - 16**

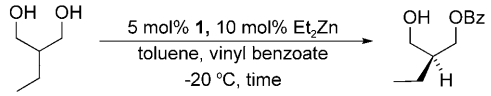
Entry	R	Electrophile/ Product	*T* [°C]	Yield [%]	*ee* [%]
1	*o*-$C_6H_4OCH_3$	**7/12**	3	88	82
2	*o*-$C_6H_4OCH_3$	**7/12**	RT	94	72
3	*p*-$C_6H_4OCH_3$	**8/13**	3	88	83
4	*p*-$C_6H_4OCH_3$	**8/13**	RT	90	76
5	*p*-C_6H_4Br	**9/14**	3	28	68
6	*p*-$C_6H_4NO_2$	**10/15**	3	0	NA
7	2-furyl	**11/16**	−20	82	68

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

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. 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 4–6 in Table 4) 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.

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



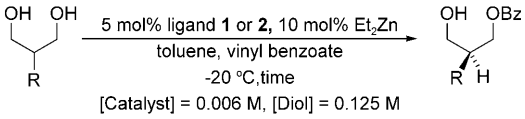
3 **4**

Entry	Catalyst [%]	[**3**][a]	[**1a**][a]	*t* [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

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).

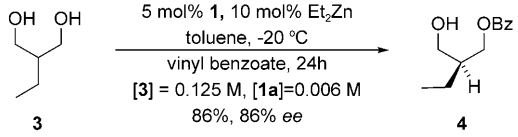
Table 5. The influence of catalyst on the asymmetric desymmetrization of **3** and **17**.



Entry	R	Substrate/ Product	Catalyst	*t* [h]	Yield [%]	*ee* [%]
1	CH_2CH_3	**3/4**	**1a**	24	86	86
2	CH_2CH_3	**3/4**	**2a**	24	66	86
3	CH_3	**17/18**	**1a**	24	88	90
4	CH_3	**17/18**	**2a**	20	89	82

Interestingly, higher enantioselectivities were obtained for 2-methyl-1,3-propanediol (**17**) by 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 Et_2Zn.

The studies outlined above demonstrate that the asymmetric desymmetrization of diol **3** can be achieved in impressive yields and in high enantiomeric selectivities when run with catalyst **1a** in toluene at −20 °C for 24 h (Scheme 8). 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 that contain functionality that could be further elaborated.

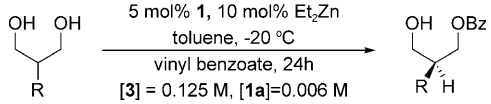


3 **4**

Scheme 8. Summary of optimized conditions for asymmetric desymmetrizations of diol **3**.

The desymmetrization of *meso*-2-alkyl and *meso*-2-alkoxy-1,3-propanediols: The optimized conditions shown in Scheme 5 were applied to a range of *meso*-2-alkyl and *meso*-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

Table 6. The desymmetrization of 2-alkyl-1,3-propanediols and 2-alkoxy-1,3-propanediols.[a]



Entry	R	Substrate/ Product	Yield [%]	*ee* [%]
1	R = CH_3	**17/18**	88	90
2	R = CH_2CH_3	**3/4**	86	86
3	R = CH_2CHCH_2	**19/20**	84	84
4	R = CH_2CCH	**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 8. [b] Yield based on recovered starting material.

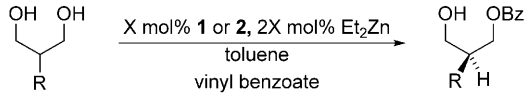
substrate **17** afforded benzoate **18** in 88% yield and 90% *ee* (Table 6, entry 1).

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% *ee* (Table 6, entry 5). A close analogue 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 atom 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 observed is due to the fact that 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

Table 7. The desymmetrization of 2-aryl-1,3-propanediols.[a]



29, 30: R = Ph **35, 36**: R = *p*-Cl-C_6H_4 **41, 42**: R = 2-naphthyl
31, 32: R = *p*-CH_3-C_6H_4 **37, 38**: R = *p*-biphenyl **43, 44**: R = 3-thienyl
33, 34: R = *p*-MeO-C_6H_4 **39, 40**: R = 1-naphthyl **45, 46**: R = 2-thienyl

Entry	Substrate/Product	Mol% cat.	*T* [°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**	*ent* 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 8.

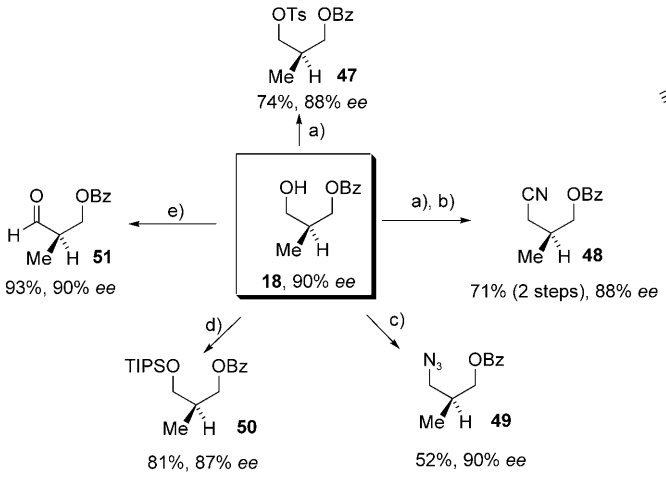
−15 °C also resulted in increased enantioselectivity (Table 7, entry 2 and 3).

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 excesses 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 excess 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 Scheme 2, either an acid- or base-catalyzed in-

tramolecular 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.

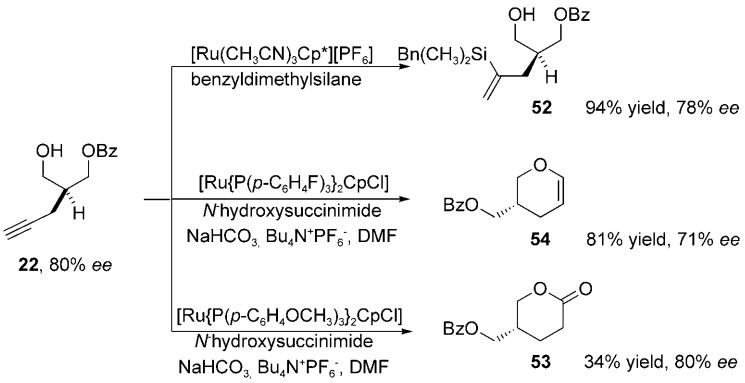
The formation of the *p*-toluenesulfonate **47** (path a) from substrate **18** using standard conditions gave a minimal erosion of the enantiomeric ratio (Scheme 9). This compound



Scheme 9. Synthesis of chiral building blocks from **18** as a representative example. a) TsCl, Et_3N, CH_2Cl_2, RT; b) NaCN, DMSO, 80 °C; c) [$Zn(N_3)_2$·Py], DIAD, PPh_3, $PhCH_3$; d) TIPSCl, imidazole, DMF; e) Ph-$(IOAc)_2$, TEMPO, CH_2Cl_2. Abbreviations: Py = pyridine, TsCl = tosyl chloride, DIAD = diisopropyl diazodicarboxylate, TIPSCl = triisopropylsilylchloride, TEMPO = 2,2,6,6-tetramethylpiperidine-*N*-oxide.

has been previously synthesized from the Roche ester in five 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** from 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 analogues that contain 2-substitution other than a methyl group, multistep 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 bisacetoxy iodosobenzene provided mild reaction conditions for the formation of aldehyde **51**, with no erosion of the enantiomeric selectivity. 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.

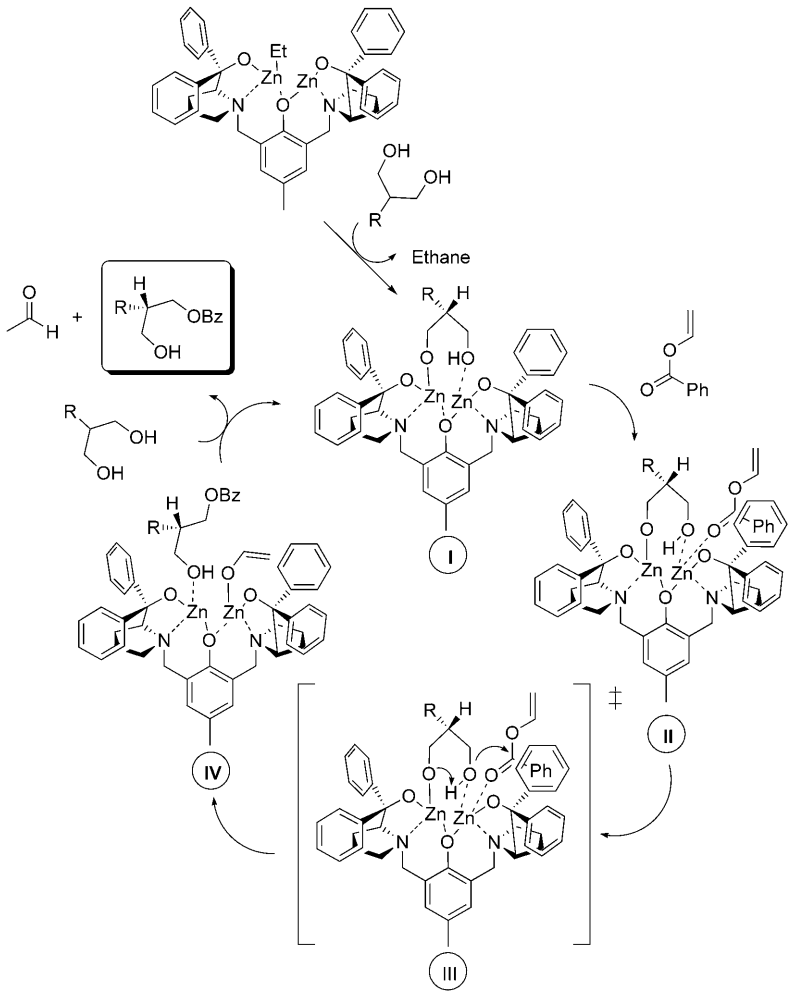
To further enhance the utility of our methodology, product **22** was transformed into structurally diverse chiral building blocks (Scheme 10). Ruthenium-catalyzed regioselective



Scheme 10. Synthesis of complex chiral building blocks from **22**.

hydrosilylation[33] transformed alkyne **22** into vinyl silane **52** in high yields and with minimal degradation in the enantiomeric excess. Vinyl silanes have shown great utility in the formation of C–H,[33] 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 tacamonie,[37] and this method provides a more efficient way to access this intermediate. Interestingly, no degradation of enantiomeric excess is observed when electron-rich phosphanes are used to access lactone **53**. However, with electron-deficient phosphanes, 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 (Scheme 11, **I**). Coordination of the vinyl benzoate can occur from either face of the C_2 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 atom to give intermediate **II**. Catalyst-directed benzoylation could then proceed via transition state **III**, for which 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, leading to the release of acetaldehyde.



Scheme 11. Proposed catalytic cycle for the desymmetrization of *meso*-2-substituted-1,3-propanediols.

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 Scheme 11, in which 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 selectivites. 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 atom 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 materials. 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 N_2 atmosphere. Anhydrous acetonitrile, dichloromethane, tetrahydrofuran, and toluene were obtained from a Seca solvent purifica-

tion system by Glass Contour. Solvents and reagents were transferred by means of a syringe, which had been oven dried and cooled in a dessicator.

Analytical thin-layer chromatography was preformed on precoated 250 μm layer thickness silica gel 60 F_{254} 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 over 32–63 μm silica gel (Sorbent Technologies) and by using compressed air. The eluents employed for flash chromatography are reported as volume: volume percentages.

^{1}H NMR 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 ($CDCl_3$ 7.26 ppm) and carbon ($CDCl_3$ 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. ^{13}C NMR spectra were recorded using a Varian Unity INOVA spectrometer at 125 MHz or a Varian Gemini at 75 MHz.

IR 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/z (relative ratio). Accurate masses are reported for the molecular ion $[M^+]$ or a suitable fragment ion. Chiral HPLC analyses 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 μL, 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 μL) 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: Anhydrous toluene (1.9 mL) was added to a flame-dried tube containing 2-ethyl-propane-1,3-diol (32.5 mg, 0.312 mmol) and vinyl benzoate (231 mg, 1.56 mmol) at room temperature. A stock solution of catalyst (0.026 M, 0.6 mL, 0.0156 mmol) was added at −70 °C under a positive flow of nitrogen. The reaction was sealed and stirred at −20 °C for 24 h (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 in CH_2Cl_2); ^{1}H 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 ppm (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 ppm; IR (neat): $\tilde{\nu}_{max}$ = 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^{-1}); *ee* = 86 %; elemental analysis calcd (%): C 69.21, H 7.74; found: C 69.19, H 7.60.

(*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 to 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 15 h, 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 with ethyl acetate/hexane mixtures gave compound **47** (0.27 g, 74 %, 88 % *ee*) as a white solid. R_f = 0.45 (20 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = −4.80 (88 % *ee*, c = 0.99 in 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^{-1}). The product **47** has been reported previously[29] was identified by comparison of ^{1}H NMR and IR data.

(−)-3-Cyano-2-methylpropyl benzoate (48): Sodium cyanide (12.7 mg, 0.260 mmol) was added to a solution of (*R*)-2-methyl-3-(tosyloxy)propyl benzoate (45 mg, 0.129 mmol) in [D_6]DMSO (0.8 mL). The reaction mixture was heated to 80 °C for 2.5 h. Upon completion (monitored by ^{1}H NMR spectroscopy), the reaction was diluted with diethyl ether (40 mL), washed five 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 compound **48** (25 mg, 96 %) as a clear oil. R_f = 0.2 (20 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ = −14.65 (88 % *ee*, c = 0.39 in CH_2Cl_2); ^{1}H 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 ppm (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 ppm; IR (neat): $\tilde{\nu}_{max}$ = 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, λ = 254 nm, heptane/*i*PrOH = 4000:1, 0.8 mL min^{-1}); HRMS (ESI): m/z calcd for $C_{12}H_{14}NNaO_2$ $[M+Na+H]^+$: 227.0971; found: 227.0369.

(−)-2-Methyl-3-oxopropyl benzoate (51): (Diacetoxyiodo)benzene (930 mg, 2.89 mmol) and TEMPO (41 mg, 0.26 mmol) was added to a solution of (*S*)-3-hydroxy-2-methylpropyl benzoate (500 mg, 2.63 mmol, 90 % *ee*) in dichloromethane (2.63 mL). The reaction mixture was stirred for 1.5 h 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 with 20 % ethyl acetate/hexanes afforded compound **51** (470 mg, 93 %, 90 % *ee*) 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 in $CHCl_3$); ^{1}H 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 ppm (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 ppm; IR (neat): $\tilde{\nu}_{max}$ = 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, λ = 254 nm, heptane/*i*PrOH = 95:5, 1.0 mL min^{-1}). This compound has been previously reported.[40]

(−)-4-(Benzyldimethylsilyl)-2-(hydroxymethyl)pent-4-enyl benzoate (52): $[Ru(CH_3CN)_3Cp^*][PF_6]$ (1 mg, 0.0018 mmol) was added to a solution of (*S*)-2-(hydroxymethyl)pent-4-yn-1-yl benzoate (20 mg, 0.092 mmol) and benzyldimethyl silane (16 mg, 0.11 mmol) in acetone (1 mL). The reaction was stirred at room temperature for 2 h, concentrated, and subjected to chromatography (15 % ethyl acetate/hexanes) to give compound **52** (32 mg, 94 %, 78 % *ee*) as a clear oil. R_f = 0.35 (15 % ethyl acetate/hexanes); $[\alpha]_D^{25}$ −12.86 (78 % *ee*, c = 0.3 in CH_2Cl_2); ^{1}H 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 ppm (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 ppm; IR (neat): $\tilde{\nu}_{max}$ = 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, λ = 220 nm, heptane/*i*PrOH = 98:2, 0.8 mL min^{-1}); HRMS ESI: m/z calcd for $C_{22}H_{29}O_3Si$ $[M+H]^+$: 369.1886; found: 369.1891.

(−)-(3,4-Dihydro-2*H*-pyran-3-yl)methyl benzoate (54): (*S*)-2-(Hydroxymethyl)pent-4-yn-1-yl benzoate (52.4 mg, 0.24 mmol), RuCp(*p*-fluorotriphenylphoshine)$_2$Cl (15 mg, 0.018 mmol), *p*-fluorotriphenylphoshine

(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 for 24 h under nitrogen. The reaction was then cooled to room temperature, diluted with diethyl ether, and washed with water (×3). 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 compound **54** (42 mg, 81%, 71% *ee*) as a yellow oil. R_f=0.52 (5% diethyl ether/hexanes); $[\alpha]_D^{25}=-4.5$ (71% *ee*, $c=0.34$ in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=8.04$ (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 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=166.4$, 143.9, 133.0, 130.0, 129.5, 128.4, 99.2, 66.9, 65.2, 32.2, 22.5 ppm; IR (neat): $\tilde{\nu}_{max}=$ 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}; $t_r=36.51$ min (major) and 39.82 min (Chiralcel AD Chiral HPLC, $\lambda=$ 220 nm, heptane*i*PrOH = 99.1:0.1 mL min^{-1}); HRMS ESI: *m*/*z* calcd for $C_{13}H_{15}O_3$ $[M+H]^+$: 219.1016; found: 219.1025.

Acknowledgements

We thank the National Science Foundation and the National Institutes of Health (GM-33049) for their generous financial support. S.M. thanks Eli Lilly & Company for a graduate fellowship. Mass spectra were provided by the Mass Spectrometry Facility, University of San Francisco, supported by the NIH division or Research Resources.

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Received: April 3, 2008
Published online: July 24, 2008

