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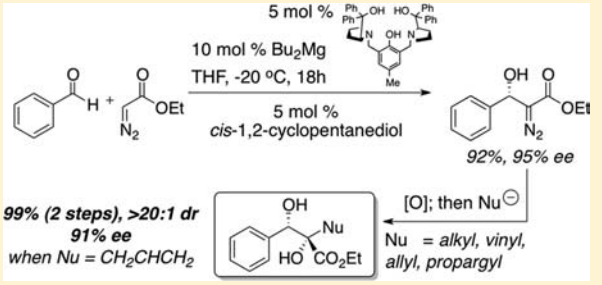
Development of the Enantioselective Addition of Ethyl Diazoacetate to Aldehydes: Asymmetric Synthesis of 1,2-Diols

Barry M. Trost,* Sushant Malhotra, Philipp Koschker, and Pascal Ellerbrock

Stanford University, Stanford, California 94305-5080, United States

Supporting Information

ABSTRACT: A novel synthetic strategy toward the asymmetric synthesis of vicinal diols bearing a tertiary center is presented. The method encompasses the dinuclear Mg-catalyzed asymmetric addition of ethyl diazoacetate into several aldehydes, oxidation of the diazo functionality, and diastereoselective alkyl transfer of various organometallics into the resulting chiral β-hydroxy-α-ketoesters to afford a diverse range of 1,2-diols in high yield, diastereoselectivity, and chirality transfer.

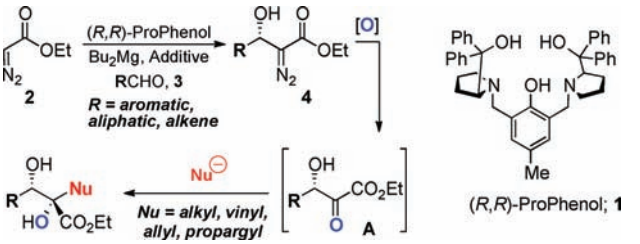


1. INTRODUCTION

Vicinal diols bearing a tertiary carbinol have played a vital role in the synthesis of natural products.[1] Several strategies toward the enantioselective synthesis of these structural motifs exist.[2] Asymmetric dihydroxylation and epoxidation/ring-opening reactions have found broad utility.[3] In these processes, product diastereoselectivity is highly dependent on the preparation of stereochemically defined trisubstituted olefins. Chemoselective control in these reactions may be attenuated by pendant olefins often present in complex molecules.[4a] Our work on the total synthesis of alternaric acid reveals the challenges of such a motif, wherein a seven-step sequence was required to assemble the vicinal diol fragment on the basis of an asymmetric dihydroxylation strategy.[4b] To address these limitations, Misaki, Sugimura, and Lu have recently reported an aldol-based approach toward vicinal diols via C−C bond formation by the development of direct asymmetric catalytic aldol reactions using α-oxycarbonyls.[5]

As a complementary strategy, we envisioned accessing a broad range of 1,2-diols bearing a tertiary carbinol employing the direct catalytic asymmetric addition of ethyl diazoacetate to aldehydes and manipulation of the diazo group to access a diverse range of vicinal diols via sequential oxidation and stereoselective alkyl transfer, as illustrated in Scheme 1.[6] At the outset, we recognized the conversion of β-hydroxy-α-diazo esters **4** to β-hydroxy-α-keto ester electrophiles **A** and the subsequent addition of carbon nucleophiles to such reactive intermediates with high chirality transfer could prove to be challenging due to the high propensity of these electrophiles to undergo competitive enolization or an α-ketol rearrangement.[7] Furthermore, the accessibility of the resulting 1,2-diols without recourse to protecting group manipulation would rely upon the identification of carbon nucleophiles that are compatible with a free alcohol. Despite these challenges, the flexibility of this approach to afford 1,2-diol motifs contained in numerous

Scheme 1. Strategy for the Asymmetric Synthesis of α,β-Dihydroxy-α-alkyl Esters



natural products led us to investigate the viability of such a protocol. Herein we provide a full account of our studies that led to the development of a highly enantioselective magnesium-catalyzed addition of ethyl diazoacetate to aldehydes. In this paper, we also report the ability of the resulting β-hydroxy-α-diazo esters to undergo the chemo- and diastereoselective synthesis of diverse 1,2-diols bearing a tertiary alcohol with high chirality transfer (see Scheme 1).[5a,8]

2. RESULTS AND DISCUSSION

2.1. Asymmetric Addition of Diazo Esters to Aldehydes. The catalytic asymmetric direct aldol reaction constitutes a powerful strategy toward the atom-economical synthesis of β-hydroxy carbonyl compounds.[5a] Although much progress has been made in the development of a direct ketone aldol, significantly fewer methods exist for the equivalent ester aldol reaction. The chemical reactivity of esters precludes their use in enamine

Received: August 1, 2011
Published: November 16, 2011

dx.doi.org/10.1021/ja206995s | J. Am. Chem. Soc. 2012, 134, 2075–2084

Scheme 2. Asymmetric Addition of Diazo Esters to Aldehydes

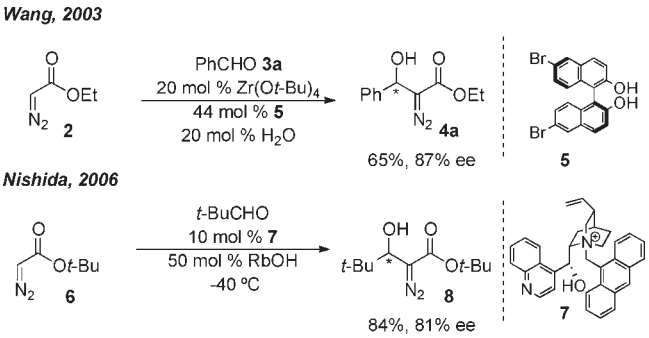
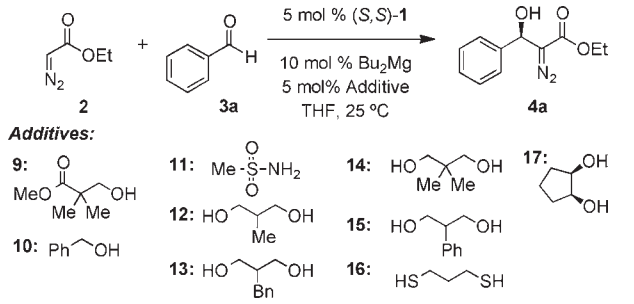


Table 1. Selected Optimization Studies



entry[a]	solvent	additive	ee (%)[b]
1	$PhCH_3$	–	9
2	Et_2O	–	8
3	dioxane	–	−11
4	DME	–	−16
5	THF	–	27
6	THF	**9**	37
7	THF	**10**	35
8	THF	**11**	27
9	THF	**12**	44
10	THF	**13**	38
11	THF	**14**	47
12	THF	**15**	51
13	THF	**16**	48
14	*THF*	***17***	*65*

[a] All reactions run on a 0.47 mmol scale at 1 M concentration in both donor **2** and acceptor **3a**. [b] Determined by chiral HPLC.

catalysis; the higher pK_a values of α-protons of esters relative to aldehydes or ketones also makes them less reactive substrates in direct aldol reactions. Furthermore, the thermal instability of simple ester enolates has limited the development of asymmetric aldol addition reaction of simple esters.

A tactic that has been employed in accessing β-hydroxy ester containing scaffolds involves the asymmetric addition of diazo esters to aldehydes. A summary of methods utilizing asymmetric catalysis are presented in Scheme 2. Wang and co-workers first demonstrated the utility of diazo esters as nucleophiles in an asymmetric aldol reaction.[9] A BINOL-derived zirconium catalyst afforded the desired products in 53−83% ee, where aromatic aldehydes gave higher levels of enantioinduction than did aliphatic aldehydes. Arai and co-workers employed a chiral phase transfer cinchonidium-derived catalyst that afforded the desired products in 0−81% ee and demonstrated the utility of the resulting products in accessing α-amino acids.[10] We became interested in obtaining a related product in high enantiocontrol to access a natural product fragment. This necessitated the development of a new method aimed at affording products with higher enantiocontrol. Herein we describe our efforts toward developing such a process, a portion of which has appeared in a preliminary communication, and the elaboration of such adducts for the asymmetric synthesis of vicinal diol motifs.[6]

In our work, initial evaluation of the catalyst derived from the treatment of 5 mol % ProPhenol (**1**) with 10 mol % diethylzinc using ethyl diazoacetate (**2**) as the nucleophile and benzaldehyde (**3a**) as the electrophile afforded the desired product **4a** in high yields but with low enantioinduction. Further optimization (Table 1) revealed that the replacement of diethylzinc with di-*n*-butylmagnesium afforded the desired product in up to 27% ee (entries 1−5). Previous work on the use of the catalyst derived from ProPhenol (**1**) and diethylzinc, wherein the remaining coordinative unsaturation had revealed that addition of complexing agents (additives) presumably to bind to the catalyst, provided a considerably more selective reaction pathway.[11] Exploration of this concept with a dinuclear magnesium complex derived from the treatment of 10 mol % di-*n*-butylmagnesium, 5 mol % ProPhenol (**1**), and 5 mol % of the β-hydroxy ester **9**, the preferred additive in a previous Zn-catalyzed process, enhanced the enantioselectivity to 37% ee (entry 6).

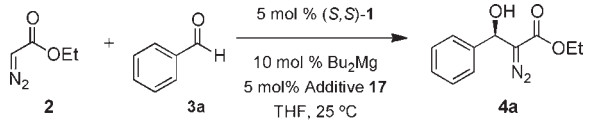
Coordinating groups possessing a mono alcohol such as **9** and **10** enhanced the enantiomeric excess to 37% ee (entries 6 and 7). The addition of methanesulfonamide (**11**) had no influence on the enantioinduction (entry 8). Replacement of mono alcohols with bis alcohols such as 2-substituted 1,3-propanediols **12**−**15** further enhanced the enantioselectivity up to 51% ee (entries 9−12). Although the use of dithiol **16** increased the enantioselectivity, markedly low conversion was observed (entry 13). Finally, the use of *meso-cis*-1,2-cyclopentanediol (**17**) resulted in the greatest increase in the enantiocontrol, affording **4a** in 65% ee (entry 14).

Having identified that the addition of complexing groups can markedly influence the enantioselectivity in the formation of diazo ester **4a**, we reinvestigated the effect of various solvents employing additive **17** (Table 2). These studies revealed the superiority of THF over other coordinating and noncoordinating solvents such as dimethoxyethane (DME), 2-methyltetrahydrofuran, toluene, and heptane. Comparison of the results presented in Tables 1 and 2 also reinforces the role of the additive **17** in achieving higher optical purity of product **4a** (compare experiments employing toluene, DME, and THF in Tables 1 and 2). Additionally, as a direct consequence of conducting the reaction on a larger scale, we observed that higher selectivity was achieved when ethyl diazoacetate (**2**) was added over a period of 2 min.

Next, we investigated the influence of varying the stoichiometric ratio between (*R,R*)-ProPhenol (**1**), di-*n*-butylmagnesium, and *meso-cis*-1,2-cyclopentanediol (**17**) (Table 3). Equalizing the molar ratio of magnesium and ligand **1** afforded only trace amounts of the desired product **4a** (entry 2). Increasing the molar ratio of magnesium and (*R,R*)-ProPhenol (**1**) to 4:1 resulted in the formation of unidentified byproducts and lowered the optical purity of diazo ester **4a** (compare entries 1 and 3). Presumably, the ad-

dx.doi.org/10.1021/ja206995s | J. Am. Chem. Soc. 2012, 134, 2075–2084

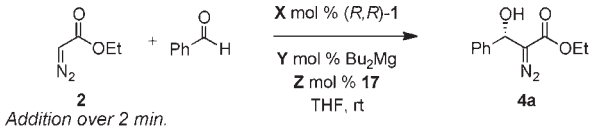
Table 2. Influence of Solvent with the Incorporation of Additive 17



entry[a]	amt of EDA (mmol)	Solvent	yield (%)	ee (%)[b]
1	0.47	THF	ND[c]	65
2[d]	*1.76*	*THF*	72	*−77*[e]
3[d]	1.76	DME	25	−47[e]
4[d]	1.76	2-MeTHF	67	−65[e]
5[d]	1.76	$PhCH_3$	47	−19[e]
6[d]	1.76	heptane	52	−51[e]

[a] All reactions run on a 0.47 mmol scale at 1 M concentration in both donor **2** and acceptor **3a**. [b] Determined by chiral HPLC. [c] ND = not determined. [d] Addition over 2 min. [e] (*R,R*)-ProPhenol (**1**) employed.

Table 3. Investigating the Ratio of (*R,R*)-1, Magnesium, and Additive 17



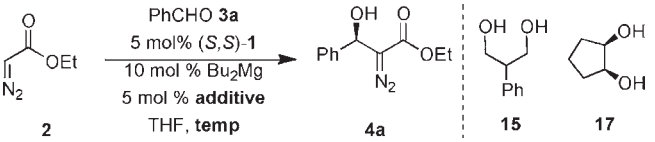
entry[a]	solvent	*X*	*Y*	*Z*	time (h)	yield (%)[b]	ee (%)[c]
1	*THF*	*5*	*10*	*5*	*20*	*72*	*77*
2	THF	5	5	5	20	trace	ND[d]
3	THF	5	20	5	20	52	47
4	THF	5	10	10	20	69	31
5	THF	5	10	30	20	66	72

[a] All reactions were conducted using 1.76 mmol of both ethyl diazoacetate (**2**) and benzaldehyde (**3a**) at a concentration of 1.0 M in THF unless otherwise noted. [b] Isolated yields. [c] Determined by chiral HPLC. [d] ND = not determined.

dition of adventitious base promotes the formation of product **4a** via the direct deprotonation of ethyl diazoacetate (**2**) with excess di-*n*-butylmagnesium. Furthermore, studies revealed that increasing the stoichometric ratio between *cis*-1,2-cyclopentanediol (**17**) and (*R,R*)-ProPhenol (**1**) also had a negative influence on the enantiocontrol (entries 4 and 5). Interestingly, a significant drop in optical purity was observed when the quantity of additive was increased from 5 to 10 mol %. Greater enantiocontrol could be regained using 30 mol % *meso-cis*-1,2-cyclopentanediol (**17**).

The influence of temperature on the enantioinduction was investigated by employing the 1,3- and 1,2-diol additives **15** and **17**, respectively (Table 4). These studies reinforced the superiority of 1,2-diols over 1,3-diols. Presumably, the conformational bias present in diol **17** enhances its coordination ability to the dinuclear magnesium catalyst. Additionally, it was observed that the highest level of enantioinduction was achieved at a reaction temperature of −20 °C employing either additive **15** or **17**. The small decrease in selectivity by lowering the temperature to −40 °C could potentially be due to lowered reactivity leading to an increase in overall concentration of the diazo ester during

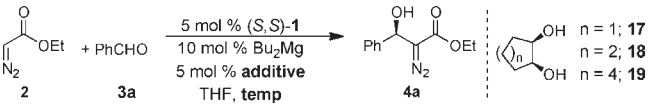
Table 4. Influence of Temperature on the Enantioinduction Employing Diols 15 and 17



entry[a]	additive	temp (°C)	ee (%)[b]
1	**15**	−40	74
2	**15**	−20	78
3	**15**	4	68
4	**15**	25	51
5	**17**	−40	72
6	*17*	*−20*	*82*
7	**17**	4	78
8	**17**	25	65

[a] All reactions conducted on a 0.47 mmol scale at 1 M concentration in both donor **2** and benzaldehyde acceptor **3a**. [b] Determined by chiral HPLC.

Table 5. Influence of Ring Size of Additive on Enantioinduction



entry[a]	*n*	temp (°C)	additive	ee (%)[b]
1	1	room temp	**17**	65
2	1	−20	**17**	82
3	*1*	*−20*	*17*	*95*[c]
4	2	−20	**18**	79
5	4	−20	**19**	80

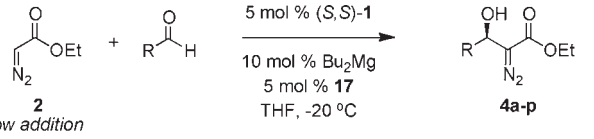
[a] All reactions run on a 0.47 mmol scale at 1 M concentration in both donor and acceptor. [b] Determined by chiral HPLC. [c] Diazo ester **2** added via slow addition using a syringe pump.

the slow addition that may result in the formation of a catalyst involving the coordination of multiple diazo esters. Another explanation invokes a shift of the relative energies of the diastereomeric transition states due to their differential temperature dependence. Experimental results support that the decrease in enantioselectivity is likely not due to a background reaction. The influence in the ratio of ligand to Bu_2Mg (Table 3, entries 1−3) suggests the presence of a background reaction only when a ProPhenol to magnesium ratio of 1:4 is employed. Subsequent control experiments (vide infra) further support that the temperature effect is not due to a background reaction. Regardless of the exact explanation, the effect is small.

Additionally, the evaluation of various ring sizes of commercially available 1,2-diols **17**−**19** revealed little influence of the ring size on enantioinduction (Table 5, entries 2, 4, and 5). The use of diol **17** offered a practical advantage, as it can be added to the catalyst via syringe without further dilution and was selected as the additive of choice for further evaluation of this reaction. Further, we wondered whether the diazo ester coordinated so strongly to the catalyst that multiple such units would be

dx.doi.org/10.1021/ja206995s | *J. Am. Chem. Soc.* 2012, 134, 2075–2084

Table 6. Expanded Reaction Scope for Asymmetric Catalytic Diazo Ester Aldols



entry[a]	R in RCHO	product	time (h)	yield (%)[b]	ee (%)[c]
1	Ph (**3a**)	**4a**	18	92	95
2[d]	Ph (**3a**)	**4a**	24	95	−95
3	*m*-$CH_3OC_6H_4$ (**3b**)	**4b**	18	83	90
4	*p*-$CH_3OC_6H_4$ (**3c**)	**4c**	18	70	87
5	*o*-ClC_6H_4 (**3d**)	**4d**	18	91	89
6	*m*-FC_6H_4 (**3e**)	**4e**	24	78	91
7[e]	*p*-FC_6H_4 (**3f**)	**4f**	24	87	94
8	*m*-ClC_6H_4 (**3g**)	**4g**	18	88	98
9[f]	*p*-ClC_6H_4 (**3h**)	**4h**	18	85	96
10[f]	2-furyl (**3i**)	**4i**	18	83	96
11[f]	*i*-Pr (**3j**)	**4j**	24	56	97
12	*n*-Bu (**3k**)	**4k**	24	50	97
13[g]	cyclohexyl (**3l**)	**4l**	24	49	91
14[h]	Et (**3m**)	**4m**	24	52	96
15	cyclopropane (**3n**)	**4n**	24	52	>99
16[h]	cyclopropane (**3n**)	**4n**	24	77	>99
17	*E*-BDMSCH=CH (**3o**)	**4o**	24	86	90
18[i]	PhCHCH (**3p**)	**4p**	18	50	94

[a] All reactions were conducted using 0.88 mmol of both ethyl diazoacetate (**2**) and the respective aldehyde **3a**−**p** at a concentration of 1.0 M in THF, unless otherwise noted. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Reaction conducted on a 1.76 mmol scale of benzaldehyde (**3a**) using (*R*,*R*)-**1**. [e] Ethyl diazoacetate (**2**) added at ∼12.5 μL/h. [f] Reactions conducted at 0.5 M. [g] Reaction conducted using 10 mol % of (*R*,*R*)-**1**, 20 mol % of Bu_2Mg, 10 mol % of **17**, and 2 equiv of diazo ester **2**. [h] Reactions conducted using 2 equiv of aldehyde with respect to ethyl diazoacetate (**2**). [i] See Mechanistic Discussion.

simultaneously involved which, in turn, would decrease the enantioselectivity. Interestingly, slow addition of ethyl diazoacetate (**2**) to the reaction mixture employing diol additive **17** afforded the desired product in the highest enantiomeric excess of 95% ee (Table 5, entry 3). Presumably when a low concentration of ethyl diazoacetate (**2**) is maintained during the reaction, competition between the additive **17** and the nucleophile **2** is minimized, thereby leading to greater enantiocontrol.

2.2. Scope. Evaluation of the reaction scope revealed that high levels of enantioinduction could be achieved for a broad range of aldehydes. Carbocyclic aromatic aldehydes possessing both electron-donating and -withdrawing groups (Table 6, entries 1−9) all afforded products **4a**−**f** with high levels of enantioinduction. The use of 2-furaldehyde (furfural) also afforded the aldol addition product **4g** in 83% yield and 96% ee (entry 10).[12] Aliphatic aldehydes such as those presented in entries 11−16 can be challenging substrates in metal-catalyzed direct aldol reactions, due to the presence of enolizable protons. Previous studies employing ProPhenol (**1**) for direct aldol reactions with unbranched aliphatic aldehydes required a 10-fold excess of the donor and resulted in the isolation of products in modest yields and enantioselectivity.[13] Employing aliphatic aldehydes in this process affords β-hydroxy diazo ester products in yields in the range 50−77% and in 90−98% ee using ethyl diazoacetate (**2**) and only up to 2 molar equiv of the respective aldehyde. With cyclopropylcarboxaldehyde (**3n**) the yield increased from 52% to 77% by increasing from 1 to 2 equiv of the aldehyde (Table 6, entry 15 vs 16). For cyclohexanecarboxaldehyde higher yields were obtained by increasing the catalyst loading to 10 mol % (Table 6, entry 13). Finally, of the two α,β-unsaturated aldehydes evaluated, cinnamyl aldehyde (**3p**; Table 6, entry 18) afforded the desired products with high enantioinduction. Further experiments revealed that the yield for this substrate was variable. Greater success was achieved with aldehyde **3o** (Table 6, entry 17).

2.3. Mechanistic Discussion. A catalytic cycle for the transformation supported by experimental evidence is illustrated in Figure 1a. Treatment of ProPhenol (**1**) with 2 equiv of di-*n*-butylmagnesium presumably affords species **II**. Although direct structural evidence for this complex **II** could not be ascertained by electrospray mass spectral analysis or X-ray crystallography, previous work by Ding and co-workers suggests the formation of a dinuclear complex (Figure 1b).[14] Experimental results underscore the importance of the 1:2 ratio between (*R*,*R*)-ProPhenol (**1**) and magnesium and reveal that minimal background reaction takes place in the presence of free di-*n*-butylmagnesium alone or free ProPhenol (**1**) alone (Table 7). In the presence of an equivalent ratio of ProPhenol (**1**) and magnesium, only trace amounts of the desired product are formed (Table 7, entry 1). A significant increase in yield is observed when the ratio between ProPhenol and magnesium is adjusted to 1:2. When the ratio is further increased to 1:4 (ProPhenol to magnesium), lowered yields and enantioselectivity are obtained. Initially we hypothesized that the lowered enantioselectivity was due to a competitive background reaction catalyzed either directly by free di-*n*-butylmagnesium, by a magnesium alkoxide dissociated from the chiral ligand (such as the magnesium alkoxide of the product), or from free ProPhenol serving as a tertiary amine base. Further experimentation revealed that, in the absence of ProPhenol or di-*n*-butylmagnesium, no reaction at room temperature was observed (Table 7, entry 4). The presence of 5 mol % of ProPhenol but no di-*n*-butylmagnesium afforded only trace amounts of product. Presumably the tertiary amine present in ProPhenol is promoting the formation of the trace product (Table 7, entry 5). Whether di-*n*-butylmagnesium itself could catalyze the reaction led us to evaluate the reaction in the absence of ProPhenol. Interestingly, with 10 mol % Bu_2Mg the desired product was obtained in 10% yield after 24 h at room temperature (Table 7, entry 6). Replacing benzaldehyde with valeraldehyde (**3k**) led to the formation of a complex mixture of products (Table 7, entry 7). In contrast, conducting the reaction in the presence of a catalyst derived from Bu_2Mg, ProPhenol (**1**), and diol **17** at −20 °C with valeraldehyde (**3k**) as the electrophile and with the slow addition of diazo ester **2** (optimized results presented in Table 6) afforded the desired product in 50% yield (Table 7, entry 8).

These results suggest that free Bu_2Mg promotes a detectable background reaction but only stoichiometrically to the amount of Bu_2Mg in the case of benzaldehyde. In the case of the enolizable aldehyde valeraldehyde (**3k**), a plethora of products are formed, and only a minor amount of the desired product is detected. Furthermore, the studies support that the dinuclear metal complex illustrated in Figure 1 is indeed the reactive form. The influence of the slow addition of ethyl diazoacetate in enhancing the optical purity of the desired product is less due to non-ProPhenol-catalyzed processes, but potentially because a higher concentration

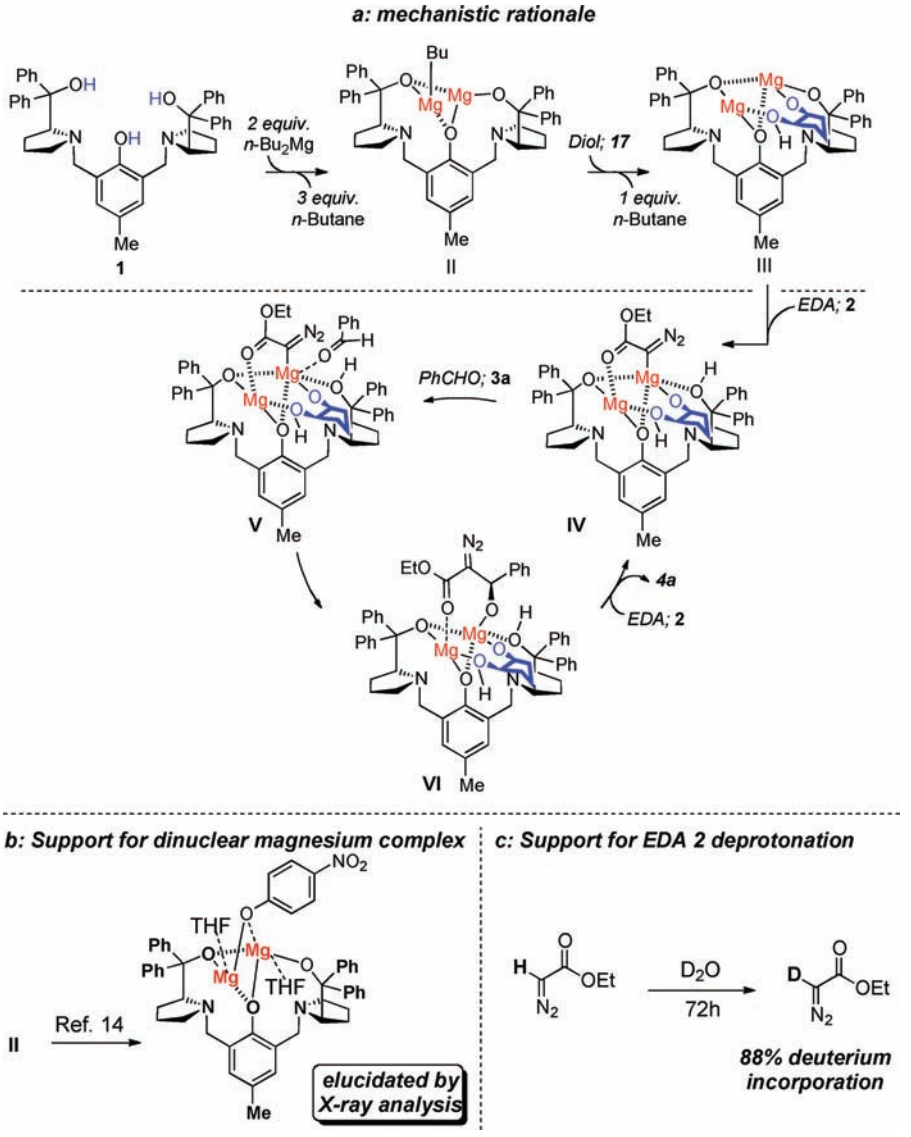


Figure 1. Proposed catalytic cycle for asymmetric addition of diazo ester **2** to aldehyde **3a**.

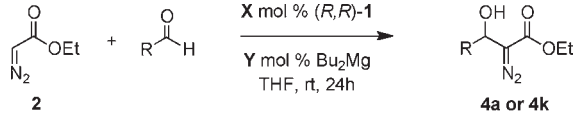
of ethyl diazoacetate leads to multiple coordination of diazo esters to the dinuclear complex, leading to ambiguity of which one adds to the carbonyl group. Presumably, one role of the addition of the bidentate additive (diol **17**) is that it minimizes the number of available coordination sites where nucleophile **2** can complex.

On the basis of these results, we postulate that upon initial addition of di-*n*-butylmagnesium three of the alkyl groups are consumed by the three protons on the ligand. The fourth alkyl group serves as the base to remove a proton from the 1,2-diol **17** to afford the desired complex **III**. Previous results on the incubation of diazo ester **2** with D_2O lead to significant H/D exchange at ambient temperature without the incorporation of an extraneous base, thereby suggesting that the pK_a of ethyl diazoacetate is suitably low for it to be deprotonated by the putative magnesium alkoxide in **III** (Figure 1c).[23] The deprotonation would be expected to dramatically increase the rate of addition of ethyl diazoacetate to the aldehyde substrate. Thus, the deprotonation of ethyl diazoacetate (EDA; **2**) employing magnesium alkoxide **III** affords complex **IV**. Coordination of benzaldehyde **3a** then affords species **V**, which undergoes an intramolecular aldol reaction to afford the magnesium alkoxide complex **VI**. Protonation of this alkoxide in complex **VI** with ethyl diazoacetate (**2**) reveals the desired product and recycles to the catalytic species **IV**.

2.4. Synthesis of 1,2-Diols. Treatment of readily accessible (*S*)-**4a** (95% ee) with dimethyldioxirane[15] and concentration followed by the addition of alkyl Grignard reagents at low temperatures resulted in complete conversion of the starting material: however, with disappointingly low yields and diastereocontrol of the tertiary alcohol products. We then turned our attention to less basic organoindium and organozinc reagents. Allylindium reagents readily undergo 1,2-addition with both aldehydes and ketones.[16] These reagents, generated in situ, are efficacious in protic media. Paquette and co-workers have demonstrated the addition of allylindium reagents to achiral α-hydroxy carbonyl compounds.[17] The transfer in chirality upon the addition of such nucleophiles to enantiomerically enriched β-hydroxy-α-keto esters remained unknown. Gratifyingly, the addition of In(0) and allyl iodide in DMF to the crude reaction mixture afforded

dx.doi.org/10.1021/ja206995s |*J. Am. Chem. Soc.* 2012, 134, 2075–2084

Table 7. Evaluation of a Background Reaction



entry[a]	R	X	Y	yield (%)[b]
1	Ph	5	5	trace
2[c]	Ph	5	10	72
3	Ph	5	20	52
4	Ph	0	0	0
5	Ph	5	0	trace
6[d]	Ph	0	10	10
7[d]	*n*-Bu	0	10	complex mixture
8[c,e]	*n*-Bu	5	10	50

[a] All reactions were conducted using 1.76 mmol of both ethyl diazoacetate (**2**) and benzaldehyde (**3a**) at a concentration of 1.0 M in THF unless otherwise noted. [b] Isolated yields. [c] Reaction conducted in the presence of 5 mol % diol **17**. [d] 10 mol % Bu_2Mg added to a solution of ethyl diazoacetate prior to the addition of the respective aldehyde. [e] Reaction conducted under optimized conditions at −20 °C with slow addition of diazo ester **2**.

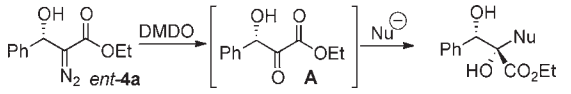
1,2-diol **20** in 99% yield, 91% ee, and >20:1 dr over two steps (Table 8, entry 1).

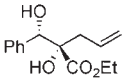
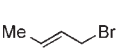
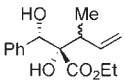
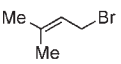
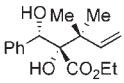
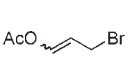
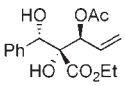
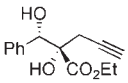
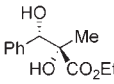
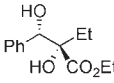
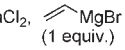
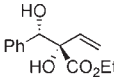
Exploration of the nucleophiles that can be employed is presented in Table 8. Using crotyl bromide, high levels of diastereocontrol at the carbinol centers was accomplished; however, a 1:1.3 ratio of products **21** and **22** epimeric at the methyl-bearing stereocenter was obtained, potentially due to the rapid *E*/*Z* isomerization of the crotyl indium intermediate, as has been previously observed by Paquette and co-workers (entry 2).[18] Reverse prenylation of the keto ester derived from **4a** led to the exclusive formation of **23** in 95% ee (entry 3). Stereotriad **24** was accessed from In(0) and 3-bromo-1-acetoxypropene to generate a formal 1-hydroxyallyl anion equivalent.[19] The desired product was obtained with a 5:1 dr with respect to the acetoxy-bearing stereocenter and 92% ee (entry 4). Using 3-bromoprop-1-yne led to propargyl alcohol **26** in 95% ee (entry 5). Organozinc reagents are also effective nucleophiles for the transfer of nonallyl groups. Commercially available Et_2Zn and Me_2Zn afforded 1,2-diols **27** and **28** both in >20:1 dr and in 95% ee (entries 6 and 7).[20] The addition of vinylzinc chloride, an sp^2-hybridized nucleophile, afforded the desired diol **29** in 8:1 dr and 85% ee (entry 8). In contrast to these results, ethylmagnesium bromide afforded diol **28** in 24% and 4:1 dr and vinylmagnesium bromide afforded diol **29** in 24% and 1.9:1 dr in the absence of zinc chloride.

Next, we turned our attention to the diastereo- and enantioselective allyl transfer to β-hydroxy α-keto esters where R ≠ Ph. Replacement of the phenyl group in diazo ester **4a** with other aromatic, aliphatic, and olefinic groups also affords vicinal diols **30**−**34** with high dr and chirality transfer (Table 9).

To further demonstrate the synthetic utility of this method toward the streamlined synthesis of biologically active targets, we rapidly assembled the western fragment of several macrolide antibiotics, including azithromycin, which is pivotal in the containment of human bacterial infections. Magnesium−ProPhenol-catalyzed diazo ester aldol with propionaldehyde affords **3m** in 96% ee. Oxidation followed by the addition of Me_2Zn initially afforded a complex mixture with trace quantities of the desired

Table 8. Diastereoselective Addition of Carbon Nucleophiles to β-Hydroxy α-Keto Esters A



Entry[a]	Conditions	Product		% yield[b]	dr[c]	ct (%)[d]
1	In, 		**20**	99	>20:1[e]	96
2	In, 		**21:22**	72	>20:1 (1:1.3[f])	99,95
3	In, 		**23**	62	>20:1	>99
4	In, 		**24:25**	85	>20:1[e] (5:1[f])	97,95
5	In, 		**26**	60[g]	>20:1[e]	>99
6	Me_2Zn		**27**	71	>20:1[h]	99
7	Et_2Zn		**28**	80	>20:1	>99
8	$ZnCl_2$,  (1 equiv.)		**29**	69	8:1	88

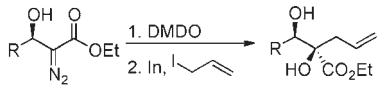
[a] Conditions: (i) DMDO, concentrate; (ii) In (1.1 equiv), allyl halide (2.0 equiv) (entries 1−5), Me_2Zn/Et_2Zn/vinylzinc bromide (entries 6−8). [b] Combined isolated yield (over two steps). [c] Determined by crude NMR. [d] ct (chirality transfer, %) = (ee product (%))/(ee (*S*)-**4a** (%)) (HPLC). [e] Assigned by NOE on acetonide. [f] Diastereoselectivity at allylic position. [g] Isolated as a 5:1 mixture of homopropargyl alcohol and allenyl alcohol. [h] See the Supporting Information for assignment.

product. Interestingly, we found that the addition of racemic ProPhenol (**1**) promoted the alkyl transfer, thereby affording the requisite 1,2-diol. The ability of ProPhenol to facilitate alkyl transfer to such easily enolizable substrates may prove to be a useful additional application of this catalytic zinc complex. Chemoselective acylation afforded western fragment **35** in 95% ee (Scheme 3).

2.5. Determination of Relative and Absolute Configuration. The relative and absolute stereochemistry were established by a combination of ^{1}H NMR and X-ray techniques. In order to determine the absolute configuration of the stereogenic center created in the initial addition, we initially turned to the *O*-methyl-mandelate method,[21] which we applied to the more elaborated diol **31** derived from adduct (−)-**4a** (Scheme 4).

While this method establishes the absolute stereochemistry of the benzylic alcohol stereocenter, it does not establish the relative stereochemistry of the adjacent tertiary stereocenter. To address this deficiency, we turned to X-ray crystallographic analysis of acetonide **38**, derived from initial adduct (*S*)-**4a**. As shown in Scheme 5a, conversion of diazo ester **4a** to diol **24**, protection as the

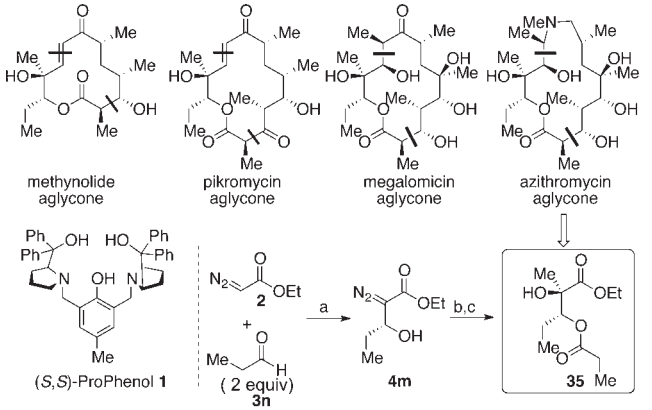
Table 9. Reaction Scope with In-Mediated Allyl Transfer



entry[a]	R	product	yield (%)[b]	dr[c]	ct (%)[d]
1	*p*-MeOC$_6$H$_4$	**30**	89	>20:1	98
2	*p*-ClC$_6$H$_4$	**31**	90	>20:1	>99
3	cyclopropane	**32**	86	13:1	>99
4	*n*-Bu	**33**	91	>20:1	>99
5	PhCHCH	**34**	33	6:1	94

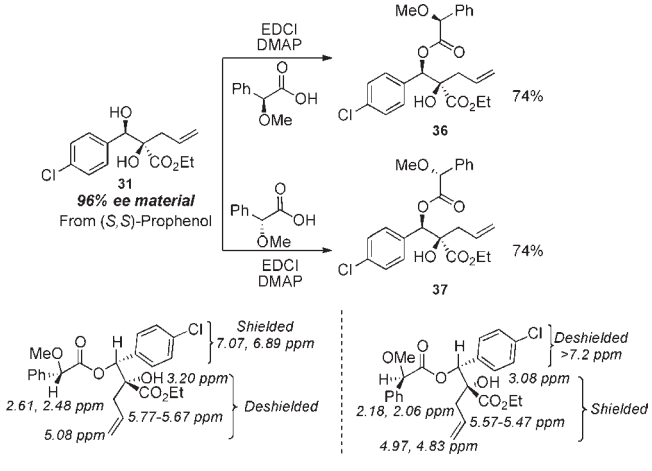
[a] Substrates prepared from (*S*,*S*)-ProPhenol. [b] Isolated yield (over two steps). [c] Determined by crude NMR. [d] ct (chirality transfer, %) = (ee product (%))/(ee starting material (%)) (HPLC).

Scheme 3. Synthesis of Polyketide Fragment



Conditions: (a) 5 mol % (*S*,*S*)-ProPhenol **1**, 10 mol % Bu_2Mg, *cis*-1,2-cyclopentanediol **17**, 52%, 96% ee. (b) (i) DMDO; (ii) Me_2Zn, 25 mol% (±)-ProPhenol **1** (10:1 dr). (c) Propionic anhydride, DMAP, Et_3N, 45%, 99% ct (3 steps).

Scheme 4. Synthesis of Mandelate Esters 36 and 37



acetonide, and acylation of the allylic alcohol with *p*-bromobenzoyl chloride afforded crystalline product **38**. To determine whether the relative configuration was influenced by the functional nature of the allylating agent leading to adduct **24**, the relative stereochemistry of two more diols, **20** and **26**, was determined via ^{1}H NMR analysis of their corresponding acetonides **39** and **40** (Scheme 5b). Thus, the relative stereochemistry for all three acetonides **38**−**40** is the same. The rationale for the diastereocontrol is based upon a chelation-controlled Zimmerman−Traxler transition state[18] with preferential *si*-face attack (Scheme 5c).

3. CONCLUSIONS

We have developed a highly general catalyst system for the addition of commercially available ethyl diazoacetate to several aliphatic and aromatic aldehydes to access diverse β-hydroxy α-diazo esters. Initial results employing a catalyst derived from the treatment of 5 mol % ProPhenol and 10 mol % Et_2Zn or Bu_2Mg furnished a catalyst capable of promoting the addition reaction in up to 37% ee. The incorporation of 5 mol % of several additives that putatively complex with the metal afforded the desired products in higher enantiocontrol. Further development of the reaction led to the identification of a catalyst system that afforded the desired products in up to 98% ee, employing *cis*-1,2-cyclopentanediol as the additive at −20 °C with the slow addition of ethyl diazoacetate. We hypothesize that the combination of the additive and the slow addition minimizes the coordination of ethyl diazoacetate to the catalyst, thereby enhancing the enantioselectivity in the formation of β-hydroxy diazo esters.

Given our long-standing interest in accessing natural products containing vicinal diols, we envisioned the use of these enantiomerically enriched products to access 1,2-diols bearing a tertiary alcohol in high enantio- and diastereomeric purities using atom-economical means. We envision that these motifs could be accessed via a sequence involving the oxidation of β-hydroxy α-diazo esters to β-hydroxy α-keto esters followed by an alkyl transfer using a carbanion equivalent. The validity of this concept hinged upon the ability to identify carbon nucleophiles that would maintain the configurational stability of highly enolizable β-hydroxy α-keto esters without promoting α-ketol rearrangement and at the same time afford products in high diastereocontrol without recourse to protecting groups. Although initial efforts employing alkylmagnesium reagents led to limited yields and diastereoselectivity, it was determined that less reactive allyl and propargyl indium species could be employed to access several diols and a triol in high optical purity. Furthermore, the addition of alkyl and vinyl nucleophiles was accomplished using vinyl- and alkylzinc reagents, also affording products in high diastereoselectivity and chirality transfer. This strategy complements traditional asymmetric oxidations when chemoselectivity difficulties would preclude their use for the formation of products **20**−**26** and **29**. Further, the ability to access numerous α-hydroxy β-diazo esters via a direct diazo ester aldol coupled with the range of nucleophiles that can be employed in the sequential alkyl transfer to the corresponding β-hydroxy α-keto ester reinforces the utility of the method in the rapid generation of molecular complexity.

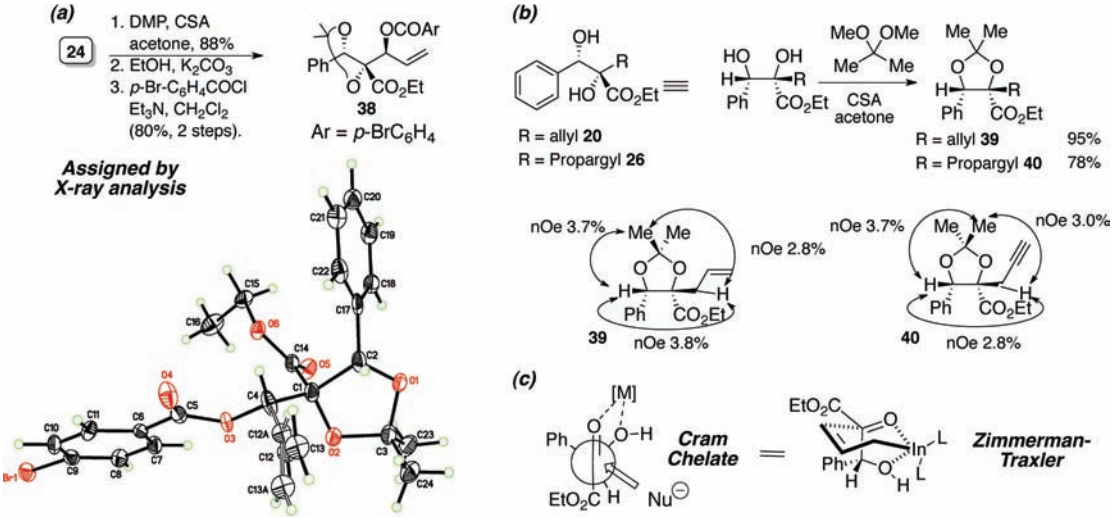
4. EXPERIMENTAL SECTION

4.1. General Information. All magnesium−ProPhenol-catalyzed asymmetric additions of ethyl diazoacetate to aldehydes were performed in flame-dried glassware with magnetic stirring under an atmosphere of nitrogen in a −20 °C cryostat. All indium-mediated reactions were performed using "open-flask" conditions. All organozinc-mediated couplings were performed under an atmosphere of nitrogen.

Anhydrous DMF, dichloromethane, chloroform, tetrahydrofuran, acetone, acetonitrile, and toluene were obtained from a Seca solvent puri-

dx.doi.org/10.1021/ja206995s |*J. Am. Chem. Soc.* 2012, 134, 2075–2084

Scheme 5. Determination of Relative and Absolute Configuration



fication system by Glass Contour. Solvents and reagents were transferred via a syringe which had been oven-dried and cooled in a desiccator. Microliter syringes were dried under high vacuum for 1 h prior to use. Aldehydes for the asymmetric addition were freshly distilled prior to use. All other reagents were purchased from Aldrich Chemical Co. and were used without further purification.

Analytical thin-layer chromatography was preformed on precoated 250 μm layer thickness silica gel 60 F254 plates (EMD Chemicals Inc.). Visualization was performed by ultraviolet light and staining with ceric ammonium molybdate, potassium permanganate, or *p*-anisaldehyde. Organic solutions were concentrated by rotary evaporation at ambient temperature (essential for all diazo compounds). Flash column chromatography was performed using 40−63 μm silica gel (Silicycle silica gel) using compressed air. The eluents employed for flash chromatography are reported as v/v percentages.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were acquired using Varian Inova 400, 500, and 600 MHz and Mercury 400 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). Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; br s, broad 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 Mercury instrument at 100 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and are calibrated to residual solvent peaks: carbon ($CDCl_3$ 77.0 ppm).

Infrared spectroscopic data were recorded on NaCl plates as thin films on a Thermo Scientific Nicolet IR100 FT-IR spectrometer. The absorbance frequencies are recorded in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were acquired by the Vincent Coates Foundation Mass Spectrometry Laboratory, Stanford University Mass Spectrometry (http://mass-spec.stanford.edu) on a Micromass Q-Tof API-US mass spectrometer (Waters Corp., Milford, MA). Chiral HPLC analysis was 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 (T_r) are reported in minutes (min). Optical rotations were measured 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.

4.2. Representative Procedure for the Asymmetric Addition of Ethyl Diazoacetate to Aldehydes. *4.2.1. (S)-Ethyl 2-Diazo-3-hydroxy-3-phenylpropanoate (**4a**).* To a solution of (*R*,*R*)-ProPhenol (**1**; 56 mg, 0.088 mmol, 0.05 equiv) in anhydrous THF (1.65 mL) was added a solution of di-*n*-butylmagnesium (176 μL of a 1 M solution in heptane, 0.10 equiv). After the mixture was stirred for 30 min, *cis*-1,2-cyclopentanediol (9 μL, 0.088 mmol, 0.05 equiv) was added and the reaction mixture was stirred for an additional 45 min. To the reaction mixture was added benzaldehyde (177 μL, 1.76 mmol, 1.0 equiv). After it was stirred for 5 min at room temperature, the reaction mixture was cooled to −20 °C and ethyl diazoacetate (201 mg, 1.76 mmol, 1.0 equiv) was added over 8 h (25 μL/h). Upon completion, the reaction mixture was quenched with pH 7 buffer and extracted with Et_2O (5 × 5 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated. Silica gel chromatography using a gradient of 15−20% EtOAc in petroleum ether afforded 370 mg (95%, 95% ee) of the desired product as a yellow oil. This oil can be stored for several weeks in the freezer; however, it transforms into the corresponding β-keto ester when stored at room temperature. TLC: R_f = 0.50 (20% EtOAc in petroleum ether). $[\alpha]_D^{25}$ = −31.8° (95% ee, *c* 11.5 mg/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44−7.31 (m, 5H), 5.91 (d, J = 3.0 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 2.97 (br s, 1H), 1.29 (t, J = 7.2 Hz, 3H). HPLC: T_r = 26.5 (minor) and 27.9 min (major) (Chiracel OJ, λ 254 nm, isocratic elution, heptane:*i*PrOH = 97:3, flow rate 0.8 mL/min). The spectroscopic data were consistent with values reported in the literature.[6]

4.3. Representative Procedure for the Conversion of β-Hydroxy-α-diazo Esters to Vicinal Diols. *4.3.1. Indium Based Method: (S)-Ethyl 2-Hydroxy-2-((S)-hydroxy(phenyl)methyl)pent-4-enoate (**20**).* To a solution of (*S*)-ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (40 mg, 0.18 mmol, 1.0 equiv) in acetone (2 mL) was added DMDO (~0.1 M solution in acetone, 3.7 mL, 0.37 mmol, 1.7 equiv) at −35 °C. Upon completion of the reaction (determined by TLC, ~1 h), the reaction mixture was warmed to room temperature and concentrated under reduced pressure. Methylene chloride was added, the solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in DMF (1.6 mL), and indium powder (23 mg, 0.2 mmol, 1.1 equiv) and allyl iodide (33 μL, 0.36 mmol, 2.0 equiv) were added sequentially. The reaction mixture was stirred 12 h and quenched with saturated aqueous $NaHCO_3$. After extraction with CH_2Cl_2 (4 × 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel chromatography using a 20−33% EtOAc in petroleum ether gradient

dx.doi.org/10.1021/ja206995s | *J. Am. Chem. Soc.* 2012, 134, 2075–2084

afforded 45 mg (>99%, 91% ee) of the desired product as a white solid. R_f = 0.25 (20% EtOAc in petroleum ether, $KMnO_4$ stain). Mp: 49−51 °C. $[\alpha]_D^{25}$ = −34.2° (91% ee, *c* 9.3 mg/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.28 (m, 5H), 5.78 (dddd, *J* = 17.0, 10.3, 8.2, 6.5 Hz, 1H), 5.13 (m, 1H), 4.77 (d, *J* = 8.0 Hz, 1H), 4.10 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.99 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.36 (s, 1H), 3.06 (d, *J* = 8.0 Hz, 1H), 2.86 (ddt, *J* = 14.0, 6.9, 1.2, 0.6 Hz, 1H), 2.63 (ddd, *J* = 14.0, 7.4, 0.6 Hz, 1H), 1.17 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 139.4, 132.5, 128.5, 128.3, 127.4, 119.4, 80.7, 77.7, 62.3, 40.7, 14.3 ppm. IR (neat): ν_{max} 3649, 3503, 1733, 1717, 1699, 1558, 1541, 1507, 1456 1223, 1150 cm^{-1}. HPLC: T_r = 13.1 (minor) and 14.6 (major) (Chiracel AD Chiral HPLC, λ 220 nm, heptane:*i*PrOH = 90:10, 1.0 mL/min). HRMS (ES$^+$) *m*/*z* calcd for $C_{14}H_{18}NaO_4$ $[M + Na]^+$ 273.1103, found 273.1100.

*4.3.2. (S)-Ethyl 2-Hydroxy-2-((S)-hydroxy(phenyl)methyl)-3,3-dimethylpent-4-enoate (**23**).* To a solution of (*S*)-ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (40 mg, 0.18 mmol, 1.0 equiv) in acetone (2 mL) was added DMDO (~0.1 M solution in acetone, 6 mL, 0.6 mmol, 3.3 equiv) at −35 °C. Upon completion of the reaction (checked by TLC, approximately 1 h) the reaction mixture was warmed to room temperature and concentrated. CH_2Cl_2 was added, and the solution was dried over Na_2SO_4 and concentrated. The residue was dissolved in DMF (1.6 mL), and indium powder (23 mg, 0.2 mmol, 1.1 equiv) and 3,3-dimethylallyl bromide (90% pure, 46.6 μL, 0.36 mmol, 2.0 equiv) were added. After 16 h additional 3,3-dimethylallyl bromide (90% pure, 53.4 μL, 0.44 mmol, 2.0 equiv) was added and the reaction mixture stirred for 2 h at 35 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. After extraction with Et_2O (4 × 10 mL) the organic layers were combined, washed with H_2O (50 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography (gradient 20−33% EtOAc in petroleum ether) and afforded the title compound (20.7 mg, 62%, 95% ee) as a white solid. R_f = 0.40 (20% EtOAc in petroleum ether). Mp: 97−99 °C. $[\alpha]_D^{25}$ = +24.0° (95% ee, *c* 3.3 mg/mL, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.24 (m, 5H), 6.29 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.19−5.09 (m, 3H), 4.00 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.81 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.55 (s, 1H), 2.90 (d, *J* = 8.2 Hz, 1H), 1.31 (s, 3H), 1.27 (s, 3H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 144.7, 140.2, 128.1, 127.9, 127.6, 113.1, 83.1, 74.9, 62.0, 43.7, 23.5, 23.2, 13.8 ppm. IR (neat): ν_{max} 3465, 2979, 1715, 1261, 1105 cm^{-1}. HPLC: T_r = 7.3 (minor) and 9.1 (major) (Chiracel IA Chiral HPLC, *l* = 220 nm, heptane:*i*PrOH = 90:10, 1.0 mL/min). ee = 95%. HRMS (ES+): *m*/*z* calcd for $C_{16}H_{22}NaO_4$ $[M + Na]^+$ 301.1416, found 301.1408.

*4.3.3. Zinc Based Method: (2S,3S)-Ethyl 2,3-Dihydroxy-2-methyl-3-phenylpropanoate (**27**).* To a solution of (*S*)-ethyl 2-diazo-3-hydroxy-3-phenylpropanoate (50 mg, 0.22 mmol, 1.0 equiv) in acetone (2 mL) was added DMDO (~0.1 M solution in acetone, 6 mL, 0.6 mmol, 2.7 equiv) at −35 °C. Upon completion of the reaction (checked by TLC, approximately 1 h) the reaction mixture was warmed to room temperature and concentrated. CH_2Cl_2 was added and the solution dried over Na_2SO_4 and concentrated. The residue was dissolved in THF (1 mL) and cooled to −78 °C. Dimethylzinc (1.2 M solution in toluene, 0.6 mL, 0.66 mmol, 3.0 equiv) was added dropwise, and the reaction mixture was warmed gently to room temperature. After 40 h the reaction mixture was quenched with pH 7 buffer and extracted with diethyl ether (4 × 10 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography using a gradient of 15−33% EtOAc in petroleum ether to afford 35 mg (71%, 94% ee) of the desired product as a light yellow oil. R_f = 0.15 (20% EtOAc in petroleum ether). $[\alpha]_D^{25}$ = +10.0° (94% ee, *c* 10.0 mg/mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.27 (m, 5H), 4.74 (d, *J* = 7.4 Hz, 1H), 4.11 (dq, *J* = 10.4, 7.0 Hz, 1H), 4.03 (dq, *J* = 10.4, 7.0 Hz, 1H), 3.34 (s, 1H), 3.01 (d, *J* = 7.4 Hz, 1H), 1.56 (s, 3H), 1.18 (dd, *J* = 7.0, 7.0 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.5, 139.1, 128.2, 128.0, 127.0, 77.9, 775, 62.0, 22.6, 13.9 ppm. IR (neat): ν_{max} 3473, 2984, 2939, 1730, 1453, 1243, 1160, 1049, 1026, 702 cm^{-1}. HPLC: T_r = 16.5 (minor) and 18.0 (major) (Chiracel AD Chiral HPLC, *l* = 220 nm, heptane:*i*PrOH = 90:10, 0.8 mL/min).

■ ASSOCIATED CONTENT

Supporting Information. Text and figures giving experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) and tables and a CIF files giving crystal data for **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: bmtrost@stanford.edu.

■ ACKNOWLEDGMENT

This work has been supported by the National Institutes of Health (No. GM33049) and the National Science Foundation. S.M. acknowledges Stanford University for a graduate fellowship. P.K. acknowledges Landesstiftung BW for the Baden-Württemberg-Stipendium undergraduate scholarship. P.E. acknowledges the DAAD and the Bayer Fellowship Program.

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