JOC The Journal of Organic Chemistry

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Organocatalytic Direct Asymmetric Crossed-Aldol Reactions of Acetaldehyde in Aqueous Media

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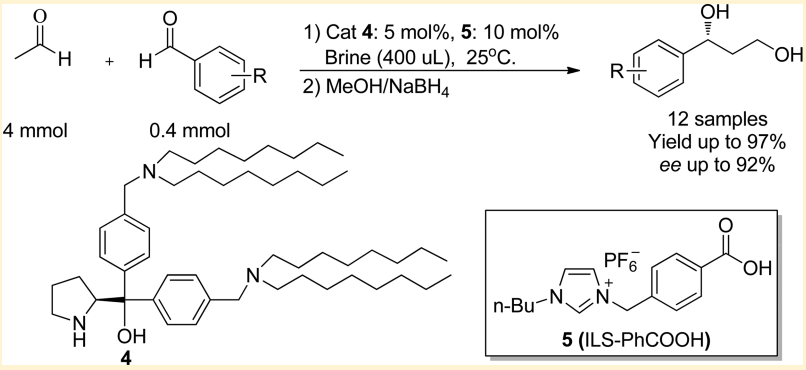
Supporting Information



ABSTRACT: A new type of diarylprolinol-based catalyst, which contains a dioctylamino group in the presence of a newly developed ionic liquid supported (ILS) benzoic acid as cocatalyst, is shown to be an effective catalytic system for the asymmetric direct crossed-aldol reaction of acetaldehyde in aqueous media using brine. For the reactions studied, the catalyst loading could be reduced to 5 mol %; high yields (up to 97%) and high enantioselectivities (up to 92% *ee*) were also achieved for a wide variety of aromatic aldehyde.

Owing to the unique properties of water, it is an ideal medium in which to perform reactions, especially organic reactions. Compared to organic solvents, water is cheap, safe, and environmentally benign; these combined properties make it a unique green solvent. In addition, water possesses other extraordinary properties, such as a high dielectric constant, hydrogen bonding capabilities, and high polarity;[1] these properties make water an ideal solvent for most reactions. There is still, however, a big challenge in carrying out reactions in water because it has the potential to inhibit catalytic activity and stereocontrol since it has the ability to disrupt hydrogen bonds and other polar interactions that are important for catalysis of some reactions.[2] In the 1930s the Diels–Alder reaction was reported in aqueous media,[3] but the full potential of water as a solvent for such reactions was not fully realized until in the 1980s, when it was discovered by Breslow[4] that the Diels–Alder reaction could be accelerated in aqueous media, compared to organic solvents. Since then, a revival of this chemistry was initiated at a breathtaking pace.

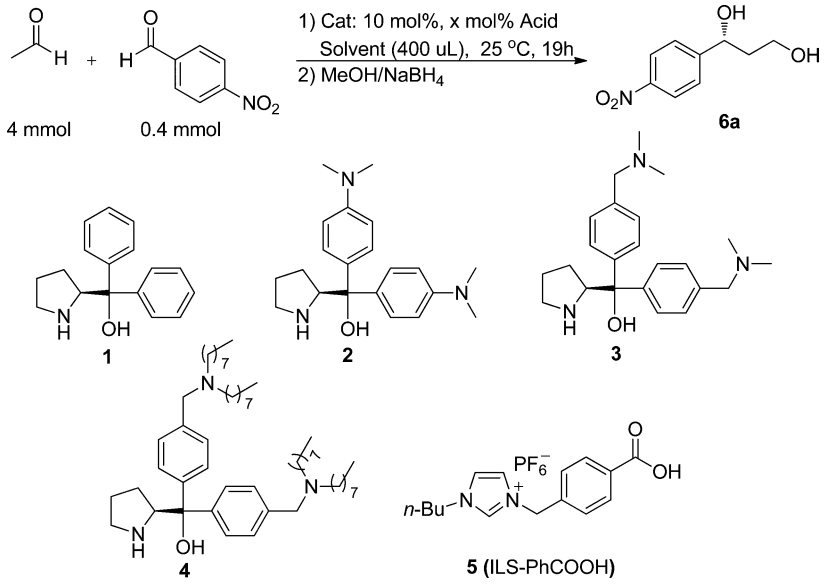
Recently, different types of organocatalysts have been developed for organic transformations.[5] A major challenge is the development of water-compatible catalysts that are also effective in aqueous media. Over the years, many types of catalysts were designed and synthesized and applied in synthesis carried out in aqueous media;[6] our research group has focused on the development of water-compatible organocatalysts for asymmetric reactions. The catalysts developed in our research group are unique in that they contain ionic liquid moieties, which make them extremely effective and versatile.[7]

The direct aldol reaction is considered to be one of the key transformations for carbon–carbon bond formation both in nature and in organic synthesis.[8] Within this category of reactions, the organocatalyzed direct crossed-aldol reactions are of special importance since they provide an efficient access to versatile synthetic building blocks for the synthesis of natural and unnatural compounds of biological interest.[8] During the past few years, various enamine-type catalysts have been developed, which have been successfully used for a wide range of asymmetric crossed aldol reactions.[9] However, limited success has been achieved so far for the asymmetric crossed-aldol reaction of acetaldehyde. Even though acetaldehyde is the simplest enolizable carbonyl compounds, the direct crossed-aldol reaction involving acetaldehyde has been known to be difficult due to the fact that various undesired side products of poly aldolization, dehydration, Tishchenko-type processes, oligomerization are formed.[10] Recently, Hayashi et al.[11] carried out a highly enantioselective direct crossed-aldol reaction of acetaldehyde in DMF catalyzed by a diarylprolinol-based catalyst. Later, Luo group[12] reported the primary amine catalyzed direct crossed-aldol reaction of acetaldehyde in neat condition, but 18 equiv of acetaldehyde were used to achieve

Received: November 8, 2012
Published: February 12, 2013

dx.doi.org/10.1021/jo302442g | J. Org. Chem. 2013, 78, 2693–2697

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	acid × mol %[b]	yield (%)[c]	*ee* (%)[d]
1	3	Brine	10	89	79
2	3	Brine	20	90	83
3	3	Brine	30	38	57
4	3	Brine	50	18	73
5	3	Brine	100	14	58
6	3	Brine	150	trace	
7	3	Brine	200	trace	
8	3	H_2O	20	50	85
9	3	DMF	20	8	83
10	3	NMP	20	trace	
11	3	H_2O:*i*PrOH=3:1	20	49	84
12	3	H_2O:*i*PrOH=4:1	20	37	84
13	1	Brine	20	58	74
14	2	Brine	20	13	60
15	4	Brine	20	89	85
16[e]	4	Brine	10	90	85
17[f]	**4**	**Brine**	**10**	**86**	**89**
18[f]	4		10	43	75
19[f]	1	Brine	10	10	75

[a]The reactions were carried out with 0.4 mmol of aromatic aldehyde, 4 mmol of acetaldehyde, indicated amount of acid and 0.04 mmol of catalyst in 400 μL of solvent at 25 °C. [b]Entries 1−16, PhCOOH; entries 17−19, ILS-benzoic acid **5**. [c]Isolated yield. [d]Determined by chiral HPLC. [e]Catalyst (5 mol %) was used, the reaction time was 28 h. [f]ILS-benzoic acid **5** was used, 5 mol % catalyst, the reaction time was 28 h.

high yield and enantioselectivities. While all of these reactions were carried out in organic solvents, there is current interest in carrying out such reactions in water. It is known that Class I aldolase enzymes and aldolase ctalytic antibodies that catalyze reactions through an enamine reaction mechanism are accomplished in water.[13] Hence, a mimic of such reactions in aqueous environment is desirable.

Despite the difficulties encountered in the use of acetaldehyde as a reactant, we report in the research our success for the highly water-compatible organocatalytic direct crossed-aldol reactions of acetaldehyde in aqueous media without any organic cosolvent afforded the desired products in moderate to high yields and high enantioselectivities. The direct crossed-aldol reaction of acetaldehyde and *p*-nitrobenzyaldehyde was selected as the model reaction. Diarylprolinol-based catalyst **3** was first investigated, as shown in Table 1. For the majority of reactions studied, Brønsted acids have been used extensively as additives for the amine-catalyzed organic reactions of carbonyl groups due to their ability to activate the carbonyl group and the amine catalyst through the formation of iminium and enamine intermediates; as a result, improved stereoselectivity of the products is observed. Another major function of the acid in this catalytic system is to protonate the amine functionality of the organocatalyst. These organocatalysts that contain the amine functionality exhibit unique properties upon protonation since they result in ammonium salts.

The first Brønsted acid selected was benzoic acid and various acid concentrations were first evaluated. Initially, the aldol reaction was conducted in brine with 10 mol % of catalyst **3** and 10 mol % of benzoic acid as additive, 89% yield and 79% enantioselectivity were obtained in 19 h at room temperature (Table 1, entry 1). When the amount of benzoic acid was increased to 20 mol %, the reaction yields were slightly

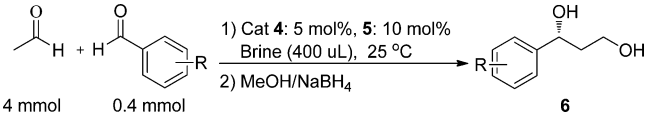
dx.doi.org/10.1021/jo302442g | *J. Org. Chem.* 2013, 78, 2693−2697

increased to 90% with 83% *ee* (Table 1, entry 2). Unfortunately, the reaction rate was greatly reduced when the amount of the benzoic acid was increased from 30 mol % to 200 mol % (Table 1, entries 3−7). With the best loading of acid in hand, different solvents were then examined. The activity of the reaction was found to be highly solvent-dependent, when water was used as the reaction medium, 50% yield and 85% *ee* were observed (Table 1, entry 8). Organic solvents such as DMF, NMP were ineffective, only trace products were obtained (Table 1, entries 9, 10). The mixtures of the solvents were also tested to further increase the activity of the catalytic system, but no solvent was more efficient than brine, only moderate yields were obtained, while the enantioselectivities remained the same (Table 1, entries 11, 12). Next, different types of organocatalysts were examined using the best reaction conditions. When diarylprolinol catalyst **1** was used as the catalyst, only 58% yield and 74% *ee* were obtained (Table 1, entry 13). When the water-compatible catalyst **2** was used for the screening, it gave the final product in even lower yield, 13%, and moderate enantioselectivity 60% *ee* (Table 1, entry 14). Catalyst **4**, which contains long alkyl chains, was used for this reaction, the desired product was produced in 89% yield and a slightly higher enantioselectivity 85% *ee* observed (Table 1, entry 15). Moreover, when the catalyst loading was decreased to 5 mol %, in 28h, the yield of the desired product was increased to 90% while the enantioselectivity was maintained (Table 1, entry 16). These results may be due to the fact that the catalytic system forms a hydrophobic active site that diminishes contact between bulk water and the reaction transition states.[14] Surprisingly, when the cocatalyst was changed to the ionic liquid supported (ILS) benzoic acid **5**, comparable yield and a slightly higher enantioselectivity (89% *ee*) were obtained (Table 1, entry 17). It is interesting to note that without brine, the yield was dramatically reduced to 43%, indicating the great effect that brine has on the reaction in the presence of this newly developed catalytic system (Table 1, entry 18). When diphenylprolinol catalyst **1** in combination with the ionic liquid supported (ILS) benzoic acid **5** was used, only 10% yield was obtained with 75% *ee* (Table 1, entry 19).

To further demonstrate the potentials of the catalytic system, the scope of the reaction with different substituted aromatic aldehydes were examined using catalyst **4** in brine. As shown in Table 2, the reaction proceeded very well with aromatic aldehydes with electron-withdrawing substituents, and the aldol products could be generated in moderate to excellent yields and high enantioselectivities (Table 2, entries 1−10), demonstrating the high efficiency of the catalytic system. The reaction of nonactivated aldehydes, such as benzaldehyde and 2-naphthaldehyde, also proceeded smoothly with moderate yield and high *ee* (Table 2, entries 11, 12). The absolute stereochemistry of the aldol products were determined by comparing its optical rotation with literature values.[11,12] The high enantioselectivities of the products resulting from reactions with catalyst **4** can be explained by related transition state models discussed previously by using (*S*)-diphenylprolinol as catalyst.[11]

In summary, we have developed a highly efficient organocatalytic system for the direct asymmetric crossed-aldol reaction of acetaldehyde that can be performed in brine without addition of any organic solvents. Furthermore, the catalyst loading could be lowered to 5 mol %, even though the diarylprolinol-based catalytic system demonstrated high reactivity and enantioselectivity for a broad range of aromatic aldehydes.

Table 2. Substrate Scope of Organocatalytic Direct Crossed-Aldol Reactions of Acetaldehyde[a]



4 mmol 0.4 mmol **6**

entry	R	time (h)	yield (%)[b]	*ee* (%)[c]
1	4-NO_2	28	**6a**/86	89
2	2-NO_2	28	**6b**/97	90
3	3-NO_2	45	**6c**/77	86
4	4-CF_3	45	**6d**/94	86
5	2-CF_3	48	**6e**/74	85
6	4-CN	45	**6f**/84	86
7	2-Br	96	**6g**/81	80
8	4-Br	96	**6h**/55	82
9	3-Br	120	**6i**/62	82
10	2-Cl	96	**6j**/45	92
11	H	96	**6k**/35	83
12	Naph	96	**6l**/30	82

[a]Reactions were carried out with 0.4 mmol of aromatic aldehyde, 4 mmol of acetaldehyde, 0.02 mmol of catalyst **4** and 0.04 mmol of **5** (ILS-PhCOOH) in 400 μL of Brine at 25 °C. [b]Isolated yield. [c]Determined by chiral HPLC.

EXPERIMENTAL SECTION

General Information. Commercially available chemicals were used as received. Catalyst 2, 3, 4 were prepared according to previously reported procedures.[7b] ^{1}H and ^{13}C NMR spectra were recorded on the Varian-400. Chemical shifts in NMR were reported in ppm (δ), relative to the internal standard of tetramethylsilane (TMS). The signals observed were described as s (singlet), d (doublet), t (triplet), dd(double doublet), m (multiplets), br (board). The number of protons (n) for a given resonance is indicated as nH. Coupling constants are reported as *J* in hertz. The high resolution mass spectra were analyzed by using ESI-TOF high-acc from the Scripps Research Institute. All the compounds synthesized (shown in Table 1 and 2) in the manuscript are known compounds.[11,12] Their relative and absolute configurations of the products were determined by comparison with known optical rotation values. Optical rotations were measured using a 1 mL cell with a 1 dm path length and reported as follows: $[\alpha]^{25}_D$ (*c* in g per 100 mL of solvent). HPLC analysis was performed using ChiralPak columns.

(*S*)-bis(4-(Dimethylamino)phenyl)(pyrrolidin-2-yl)methanol (2). Purified by flash chromatography using Ethyl acetate/triethylamine = 200/1−100/1 to give compound **2** as white solid(0.653g, yield 62% (for 2 steps)). $[\alpha]^{25}_D$ = −71.6 (c = 0.52, MeOH), ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 12 Hz, 2H), 6.68 (d, *J* = 8 Hz, 2H), 6.65 (d, *J* = 8 Hz, 2H), 4.15 (d, *J* = 8 Hz, 1H), 3.02 (s, 4H), 2.90 (s, 6H), 2.89 (s, 6H), 1.72−1.58 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =149.0, 148.9, 136.9, 134.5, 126.5, 126.2, 112.4, 112.1, 76.5, 64.7, 46.7, 40.6, 26.2, 25.5. HRMS (ESI-TOF high-acc) *m*/*z* calcd for $C_{21}H_{29}N_3O$ (MH^+): 340.2383, found: 340.2388.

(*S*)-bis(4-((Dimethylamino)methyl)phenyl)(pyrrolidin-2-yl)-methanol (3). Purified by flash chromatography using Ethyl acetate/triethylamine = 200/1−50/1 to give compound **3** as an oil(0.8964g, yield 59% (for 2 steps)), $[\alpha]^{25}_D$ = −34.7 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51(d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.21 (t, *J* = 8 Hz, 4H), 4.22 (t, *J* = 7.6 Hz, 1H), 3.35 (s, 4H), 3.05−2.92 (m, 2H), 2.20 (s, 6H), 2.19 (s, 6H), 1.74−1.52 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =147.2, 144.5, 137.2, 137.0, 129.1, 128.9, 126.0, 125.6, 77.2, 64.8, 64.3, 64.2, 46.9, 45.7, 45.6, 26.5, 25.7; HRMS (ESI-TOF high-acc) *m*/*z* calcd for $C_{23}H_{33}N_3O$ (MH^+): 368.2696, found: 368.2692.

dx.doi.org/10.1021/jo302442g | J. Org. Chem. 2013, 78, 2693−2697

(*S*)-bis(4-((Dioctylamino)methyl)phenyl)(pyrrolidin-2-yl)-methanol 4. Purified by flash chromatography using Ethyl acetate/triethylamine = 200/1 to give compound **4** as an oil (0.9245g, yield 51% (for 2 steps)), $[\alpha]_D^{25}$ = −43.1 (*c* 0.5, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, *J* = 8 Hz, 2H), 7.40 (d, *J* = 8 Hz, 2H), 7.21 (t, *J* = 8.4 Hz, 4H), 4.52 (s, 1H), 4.20 (t, *J* = 7.2 Hz, 1H), 3.47 (s, 4H), 3.04−2.92 (m, 2H), 2.37−2.33 (m, 8H), 1.74−1.62 (m, 5H), 1.42 (s, 8H), 1.31−1.23 (m, 40H), 0.88 (t, *J* = 7.2 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ =146.5, 143.8, 138.3, 138.1, 128.5, 128.3, 125.5, 125.2, 76.9, 64.7, 58.3, 58.1, 53.8, 53.7, 46.7, 31.8, 29.5, 29.5, 29.3, 27.4, 27.0, 26.2, 25.4, 22.6, 14.1; HRMS (ESI-TOF high-acc) *m*/*z* calcd for $C_{51}H_{89}N_3O$ (MH^+): 760.7078, found: 760.7073.

Typical Procedure for the Aldol Reactions. Acetaldehyde (4 mmol) was added to a mixture of aromatic aldehyde (0.4 mmol), Catalyst **4** (0.02 mmol) and ILS-$PhCO_2H$ **5** (0.04 mmol) in brine (0.4 mL) at room temperature. The resulting mixture was stirred for the time indicated in Table 2 and then quenched with 1 M HCl. The organic materials were extracted three times with dichloromethane. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. $NaBH_4$ (2 mmol) was added to the mixture in methanol (3 mL) at 0 °C and the mixture was stirred for additional 30 min before quenching with water. The products were extracted three times with dichloromethane, and the combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuo. The residue was purified by flash chromatograph on silica gel to afford the desired products **6a**−**l**.

(*R*)-1-(4-Nitrophenyl)propane-1,3-diol (6a). Silica gel column chromatography (Ethyl acetate/Hexane = 1/1−2/1) gave **6a** (67.8 mg, 86%, 0.4 mmol scale) as a colorless oil. $[\alpha]_D^{25}$ = 19.1 (c = 0.86, MeOH). Lit.[11,12] $[\alpha]_D^{25}$ = 21.6 (c = 0.87, MeOH), $[\alpha]_D^{20}$ = 20.2 (c = 0.5, MeOH). Enantiomeric excess 89%, HPLC analysis Chiralpak IC, *i*-propanol/hexane = 5/95, 1.0 mL/min, 254 nm, t_R (minor) = 36.63 min, t_R (major) = 41.18 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 5.12−5.09 (m, 1H), 3.92 (t, *J* = 4.8 Hz, 2H), 3.52 (d, *J* = 2.8 Hz, 1H), 2.21 (s, 1H), 2.00−1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.7, 147.2, 126.4, 123.7, 73.3, 61.3, 40.2.

(*R*)-1-(2-Nitrophenyl)propane-1,3-diol (6b). Silica gel column chromatography (Ethyl acetate/Hexane = 1/1) gave **6b** (76.5 mg, 97%, 0.4 mmol scale) as a colorless oil. $[\alpha]_D^{25}$ = −57.1 (c = 0.92, MeOH). Enantiomeric excess 90%, HPLC analysis Chiralpak IC, *i*-propanol/hexane = 5/95, 1.0 mL/min, 254 nm, t_R (major) = 48.49 min, t_R (minor) = 80.28 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92−7.88 (m, 2H), 7.68−7.64 (m, 1H), 7.44−7.40 (m, 1H), 5.49 (d, *J* = 8.8 Hz, 1H), 3.97−3.90 (m, 2H), 2.84 (s, 1H), 2.11−1.90 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.3, 139.8, 133.6, 128.1, 128.1, 124.3, 69.6, 61.7, 39.5.

(*R*)-1-(3-Nitrophenyl)propane-1,3-diol (6c). Silica gel column chromatography (Ethyl acetate/Hexane = 1/1−2/1) gave **6c** (60.7 mg, 77%, 0.4 mmol scale) as a colorless oil. $[\alpha]_D^{25}$ = 29.2 (c = 0.79, MeOH). Enantiomeric excess 86%, HPLC analysis Chiralpak IC, *i*-propanol/hexane = 5/95, 1.0 mL/min, 254 nm, t_R (minor) = 62.15 min, t_R (major) = 71.94 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.25(s, 1H), 8.14−8.11 (m, 1H), 7.71 (d, *J* = 8 Hz, 1H), 7.53 (t, *J* = 8 Hz, 1H), 5.10 (t, *J* = 6.4 Hz, 1H), 3.92 (t, *J* = 5.6 Hz, 2H), 3.73 (s, 1H), 2.45 (s, 1H), 2.01−1.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.3, 146.5, 131.8, 129.4, 122.4, 120.6, 73.2, 61.3, 40.2.

(*R*)-1-(4-(Trifluoromethyl)phenyl)propane-1,3-diol (6d). Silica gel column chromatography (Ethyl acetate/Hexane = 1/1) gave **6d** (82.8 mg, 94%, 0.4 mmol scale) as a colorless oil. $[\alpha]_D^{25}$ = 25.0 (*c* = 0.35, MeOH). enantiomeric excess 86%, HPLC analysis Chiralpak IC, *i*-propanol/hexane = 5/95, 1.0 mL/min, 254 nm, t_R (minor) = 10.52 min, t_R (major) = 11.90 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, *J* = 8 Hz, 2H), 7.47 (d, *J* = 8 Hz, 2H), 5.01 (d, *J* = 2.8 Hz, 1H), 3.88−3.85 (m, 2H), 3.59 (s, 1H), 2.63 (s, 1H), 1.98−1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.3, 129.5, 125.9, 125.4, 125.3, 73.6, 61.2, 40.3.

(*R*)-1-(2-(Trifluoromethyl)phenyl)propane-1,3-diol (6e). Silica gel column chromatography (Ethyl acetate/Hexane = 1/2) gave **6e** (65.2 mg, 74%, 0.4 mmol scale) as a colorless oil. $[\alpha]_D^{25}$ = 42.4 (*c* = 1.4, MeOH). enantiomeric excess 85%, HPLC analysis Chiralpak OJ-H, *i*-propanol/hexane = 10/90, 1.0 mL/min, 254 nm, t_R (minor) = 5.44 min, t_R (major) = 5.94 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (d, *J* = 8 Hz, 1H), 7.63−7.58 (m, 2H), 7.40−7.36 (m, 1H), 5.36 (d, *J* = 9.2 Hz, 1H), 3.96−3.86 (m, 2H), 3.50 (s, 1H), 2.76 (s, 1H), 2.00−1.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.4, 132.3, 127.7, 127.4, 125.4, 125.4, 125.3, 70.1, 61.9, 40.6.

(*R*)-4-(1,3-Dihydroxypropyl)benzonitrile (6f). Silica gel column chromatography (Ethyl acetate/Hexane = 2/1) gave **6f** (59.5 mg, 84%, 0.4 mmol scale) as a colorless oil. $[\alpha]_D^{25}$ = 15.8 (*c* = 0.22, MeOH). enantiomeric excess 86%, HPLC analysis Chiralpak IC, *i*-propanol/hexane = 5/95, 1.0 mL/min, 254 nm, t_R (minor) = 59.42 min, t_R (major) = 68.56 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 8 Hz, 2H), 7.50 (d, *J* = 8 Hz, 2H), 5.05 (t, *J* = 6 Hz, 2H), 2.17 (s, 2H), 1.97−1.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.7, 132.3, 126.3, 118.8, 111.1, 73.5, 61.3, 40.2.

(*R*)-1-(2-Bromophenyl)propane-1,3-diol (6g). Silica gel column chromatography (Ethyl acetate/Hexane = 1/2) gave **6g** (74.9 mg, 81%, 0.4 mmol scale) as a colorless oil. $[\alpha]_D^{25}$ = 44.9 (*c* = 0.54, MeOH). enantiomeric excess 80%, HPLC analysis Chiralpak IC, *i*-propanol/hexane = 5/95, 1.0 mL/min, 254 nm, t_R (minor) = 18.73 min, t_R (major) = 21.51 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (d, *J* = 9.6 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.37−7.26 (m, 1H), 7.15−7.11(m, 1H), 5.30−5.28(m, 1H), 3.95−3.88 (m, 2H), 3.49 (s, 1H), 2.70 (s, 1H), 2.08−2.02 (m, 1H), 1.92−1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.0, 132.5, 128.7, 127.7, 127.3, 121.4, 73.1, 61.5, 38.4.

(*R*)-1-(4-Bromophenyl)propane-1,3-diol (6h). Silica gel column chromatography (Ethyl acetate/Hexane = 1/1) gave **6h** (50.8 mg, 55%, 0.4 mmol scale) as a colorless oil. $[\alpha]_D^{25}$ = 14.4 (*c* = 0.20, MeOH). enantiomeric excess 82%, HPLC analysis Chiralpak IC, *i*-propanol/hexane = 5/95, 1.0 mL/min, 254 nm, t_R (minor) = 18.18 min, t_R (major) = 20.97 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 (d, *J* = 6.8 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.95−4.92 (dd, *J* = 3.6 Hz, 8.4 Hz, 1H), 3.87−3.84 (m, 2H), 3.20 (s, 1H), 2.40 (s, 1H), 1.97−1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.3, 131.5, 127.4, 121.2, 73.6, 61.3, 40.4.

(*R*)-1-(3-Bromophenyl)propane-1,3-diol (6i). Silica gel column chromatography (Ethyl acetate/Hexane = 1/1) gave **6i** (57.3 mg, 62%, 0.4 mmol scale) as a colorless oil. $[\alpha]_D^{25}$ = 22.5 (*c* = 0.95, MeOH). enantiomeric excess 82%, HPLC analysis Chiralpak OJ-H, *i*-propanol/hexane = 10/90, 1.0 mL/min, 254 nm, t_R (minor) = 8.55 min, t_R (major) = 9.23 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (s, 1H), 7.41−7.38 (m, 2H), 7.27−7.21 (m, 1H), 4.92−4.89 (m, 1H), 3.83 (d, *J* = 3.2 Hz, 2H), 3.56 (s, 1H), 2.76 (s, 1H), 1.99−1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.6, 130.5, 130.0, 128.7, 124.2, 122.6, 73.4, 61.2, 40.2.

(*R*)-1-(2-Chlorophenyl)propane-1,3-diol (6j). Silica gel column chromatography (Ethyl acetate/Hexane = 1/2) gave **6j** (33.6 mg, 45%, 0.4 mmol scale) as a colorless oil. $[\alpha]_D^{25}$ = 54.3 (*c* = 1.90, MeOH). enantiomeric excess 92%, HPLC analysis Chiralpak IC, *i*-propanol/hexane = 5/95, 1.0 mL/min, 254 nm, t_R (major) = 10.67 min, t_R (minor) = 11.91 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 8.8 Hz, 1H), 7.36−7.22 (m, 3H), 5.40−5.37 (dd, *J* = 3.2 Hz, 8.8 Hz, 1H), 3.97−3.88 (m, 2H), 3.52 (s, 1H), 2.74 (s, 1H), 2.12−2.05 (m, 1H), 1.95−1.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.6, 131.3, 129.3, 128.4, 127.1, 127.0, 71.0, 61.7, 38.4.

(*R*)-1-Phenylpropane-1,3-diol (6k). Silica gel column chromatography (Ethyl acetate/Hexane = 1/1) gave **6k** (21.3 mg, 35%, 0.4 mmol scale) as a colorless oil. $[\alpha]_D^{25}$ = 23.5 (*c* = 0.17, MeOH). enantiomeric excess 83%, HPLC analysis Chiralpak IC, *i*-propanol/hexane = 5/95, 1.0 mL/min, 254 nm, t_R (major) = 19.47 min, t_R (minor) = 20.79 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38−7.26 (m, 5H), 4.99−4.96 (dd, *J* = 3.6 Hz, 8.4 Hz, 1H), 3.87 (t, *J* = 5.6 Hz, 2H), 2.96 (s, 1H), 2.44 (s, 1H), 2.05−1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.3, 128.5, 127.6, 125.6, 74.4, 61.5, 40.5.

(*R*)-1-(Naphthalen-2-yl)propane-1,3-diol (6l). Silica gel column chromatography (Ethyl acetate/Hexane = 1.5/1) gave **6l** (24.3 mg, 30%, 0.4 mmol scale) as a white solid. $[\alpha]_D^{25}$ = 21.5 (*c* = 0.52, MeOH). enantiomeric excess 82%, HPLC analysis Chiralpak IC, *i*-

dx.doi.org/10.1021/jo302442g | J. Org. Chem. 2013, 78, 2693−2697

propanol/hexane = 5/95, 1.0 mL/min, 254 nm, t_R (minor) = 33.52 min, t_R (major) = 45.90 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84−7.82 (m, 4H), 7.50−7.46 (m, 3H), 5.14−5.11 (m, 1H), 3.89 (t, J = 5.2 Hz, 2H), 3.07 (s, 1H), 2.45 (s, 1H), 2.11−1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.6, 133.2, 132.9, 128.3, 127.9, 127.7, 126.2, 125.9, 124.2, 123.8, 74.4, 61.5, 40.3.

■ ASSOCIATED CONTENT

Supporting Information

Full optimization details, ^{1}H and ^{13}C NMR spectra, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Science Foundation for financial support of this research (CHE-1213287).

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