JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

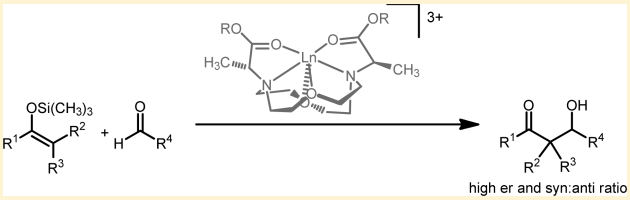
Study of the Lanthanide-Catalyzed, Aqueous, Asymmetric Mukaiyama Aldol Reaction

Yujiang Mei, Derek J. Averill, and Matthew J. Allen*

Department of Chemistry, Wayne State University, Detroit, Michigan 48202, United States

Supporting Information

ABSTRACT: The development of efficient methods for the asymmetric Mukaiyama aldol reaction in aqueous solution has received great attention. We have developed a new series of chiral lanthanide-containing complexes that produce Mukaiyama aldol products with outstanding enantioselectivities. In this paper, we describe an optimized ligand synthesis, trends in stereoselectivity that result from changing lanthanide ions, and an exploration of substrate scope that includes aromatic and aliphatic aldehydes and silyl enol ethers derived from aromatic and aliphatic ketones.



INTRODUCTION

Compounds that contain optically active β-hydroxy carbonyl moieties have received great attention from chemists and biologists because these molecules are building blocks for pharmaceuticals and natural products,[1−7] and the Mukaiyama aldol reaction is commonly used to synthesize the carbon−carbon bonds in β-hydroxy carbonyls.[2−27] To be stereoselective, this reaction requires a catalyst to induce stereochemistry. Various Lewis-acid-catalyzed[12−15] and organocatalyst-catalyzed[16] Mukaiyama aldol reactions have been reported for the enantioselective synthesis of β-hydroxy carbonyl compounds; however, the majority of these reactions require the use of aprotic anhydrous solvents because of the instability of precatalysts and reaction intermediates in the presence of water. In recent years, efforts have focused on the asymmetric Mukaiyama aldol reaction in aqueous media because of the environmental and financial benefits associated with water-tolerant reactants.[17] Examples of enantioselective catalysts that work in the presence of water include $Cu(OTf)_2$, $Pb(OTf)_2$, and $Ln(OTf)_3$ with chiral crown ethers;[18−22] $Ga(OTf)_3$ with Trost-type semicrowns;[23,24] and $Zn(OTf)_2$ and $FeCl_2$ with pybox-type ligands.[25−27] These systems produce a wide range of enantiometric ratios (er) that depend on the substrate identity.

Recently, two reports of outstanding stereoselectivities for a wide range of substrates in the presence of water were reported: $Fe(ClO_4)_2$ with Bolm's ligand[15] and our C_2-symmetric ligand set (**I**−**VI**, Figure 1) with $Eu(OTf)_3$.[14] The $Fe(ClO_4)_2$ system produced outstanding enantioselectivities (95:5−99:1 er),[15] but the ligand was synthesized in a moderate (54%) yield.[28] Our recent report of a new class of C_2-symmetric ligands (**I**−**VI**) with $Eu(OTf)_3$ described efficient precatalysts for lanthanide-catalyzed, enantioselective Mukaiyama aldol reactions in aqueous solution (Figure 1). This catalytic system works for aromatic aldehydes (95:5−97:3 er), aliphatic aldehydes (97:3−99:1 er), and a silyl enol ether derived from an aliphatic ketone (92:8 er). However, in our initial reports, the ligand synthesis yielded only moderate *syn*:*anti* ratios (4:1 and 5:1), and we only used Eu^{3+} to enable study of the system by luminescence-decay measurements.[14,29−31] We hypothesized that the choice of solvent led to the lower than desired *syn*:*anti* ratios in our ligand synthesis. Furthermore, because of the changes in size and Lewis acidity across the lanthanide series, we hypothesized that Eu^{3+} might not be the best metal to use with our best ligand **I**. We have tested both of these hypotheses, and here, we report (1) the optimization of the synthesis of chiral ligand **I**; (2) the influence of lanthanide ion on stereoselectivity; and (3) the exploration of the substrate scope.

RESULTS AND DISCUSSION

The moderate *syn*:*anti* ratios of ligands **I**−**VI** (Figure 1) obtained during our ligand synthesis suggested that the (*S*)-methyl 2-bromopropanoate was undergoing racemization during the reaction with 1,7-diaza-12-crown-4 (Table 1). This moderate *syn*:*anti* ratio presents a problem because the undesirable *anti* ligands produce racemic aldol products. A possible mechanism for this racemization is solvolysis of the (*S*)-methyl 2-bromopropanoate; consequently, we hypothesized that screening a variety of solvents would lead to a minimization of racemization because solvolysis is faster in polar, protic solvents. To test our hypothesis, we prepared chiral ligand **I** from commercially available (*S*)-2-bromopropanoic acid (97.5:2.5 er) (Table 1). After esterification of (*S*)-2-bromopropanoic acid, the resulting (*S*)-methyl 2-bromopropanoate was used directly in the next step. Our previously reported synthesis in CH_3CN provided ligand **I** with a 4:1 *syn*:*anti* ratio and >99:1 er at ambient temperature.[14] To increase the *syn*:*anti* ratio, we screened solvents and monitored the *syn*:*anti* ratios of the resulting ligands for the reaction

Received: April 19, 2012
Published: June 14, 2012

dx.doi.org/10.1021/jo300800b | J. Org. Chem. 2012, 77, 5624−5632

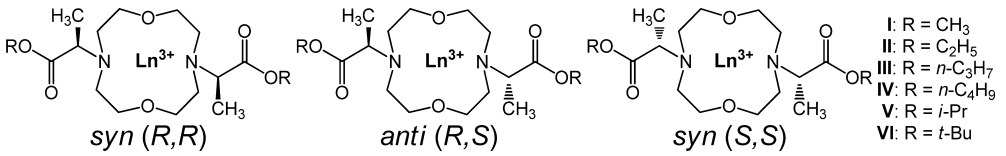
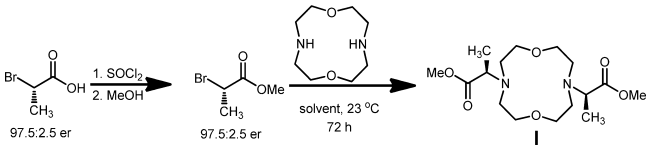


Figure 1. C_2-symmetric and racemic precatalysts (*anti* ligands form as a result of racemization of the bromide starting material during the ligand syntheses).[14]

Table 1. Solvent Effect on Synthesis of Chiral Ligand I



solvent	yield (%)	*syn*:*anti*[b]	er (*syn*)[b]
MeOH	77	1:1	59:41
CH_3CN	98	4:1	>99:1
THF[a]	98	6:1	>99:1
hexanes	40	7:1	>99:1
EtOAc	98	8:1	>99:1
$CHCl_3$	98	8:1	>99:1
CH_2Cl_2	98	16:1[c]	>99:1[c]

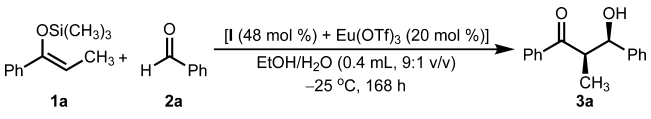
[a]Tetrahydrofuran. [b]Determined by chiral high-performance liquid chromatography (HPLC) analysis. [c]HPLC chromatogram in the Supporting Information.

between (*S*)-methyl 2-bromopropanoate and 1,7-diaza-12-crown-4 (Table 1). We found that the choice of solvent has a substantial influence on the selectivity and efficiency of this reaction: the protic solvent MeOH afforded ligand **I** with low yield, low *syn*:*anti* ratio (1:1), and poor er (59:41) of the *syn* product. This observation is expected because protic solvents promote solvolysis of α-bromo esters. Aprotic solvents afforded moderate to excellent *syn*:*anti* ratios (4:1−16:1) and excellent er (>99:1). Among these aprotic solvents, the reaction went to completion in CH_2Cl_2 providing **I** in the highest *syn*:*anti* ratio (*syn*:*anti* = 16:1).

Using our newly synthesized ligand **I** with $Eu(OTf)_3$, we established the relationship between enantioselectivity of catalysis and the *syn*:*anti* ratio of the ligand **I** (Table 2).[14] Ligand **I** with 16:1 *syn*:*anti* ratio was used to produce *syn* product **3a** with a 95:5 er. This value of er is higher than the value obtained with ligand **I** in a 4:1 or 5:1 *syn*:*anti* ratio, but not as high as with ligand in a *syn*:*anti* ratio of >99:1 that was achieved by purification by high-performance liquid chromatography (HPLC). However, if HPLC purification is needed, a starting point of 16:1 allows for much more pure *syn* isomer to be obtained relative to a starting point of 5:1. These experiments demonstrated that enantioselectivity is imparted to products by *syn* ligands but not *anti* ligands and supports our previously proposed mechanism for these precatalysts.[14]

With our improved ligand synthesis, we studied the effect of the choice of lanthanide ion on the stereoselectivity in the Mukaiyama aldol reaction. The screening of lanthanide ions was carried out using (*Z*)-trimethyl(1-phenylprop-1-enyloxy)-silane and benzaldehyde catalyzed by 24 mol % ligand **I** (*syn*:*anti* > 99:1) and 20 mol % lanthanide triflate (Table 3). We chose this metal-to-ligand ratio because higher ligand loadings led to outstanding stereoselectivities with many of the larger lanthanides, making it impossible to differentiate the influence of lanthanide ion selection on stereoselectivity. From these reactions, we found that diastereoselectivity and enantioselectivity are related to the ionic radius of the

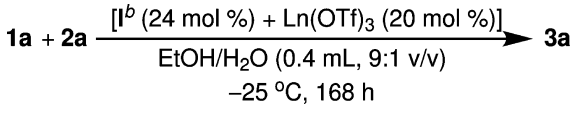
Table 2. Purification Improves Stereoselectivity[a]



ligand **I**	*syn*:*anti*[e] = 4:1[f]	*syn*:*anti*[e] = 5:1[f]	*syn*:*anti*[e] = 16:1	*syn*:*anti*[e] > 99:1[f]
yield (%)[b]	85	88	89	92
product *syn*:*anti*[c,d]	26:1	26:1	28:1	32:1
er (*syn*)[c]	93:7	94:6	95:5	97:3

[a]Reaction conditions: To a mixture of ligand **I** (48 mol %) and $Eu(OTf)_3$ (20 mol %), which was stirred at 50 °C for 2 h and then cooled to −25 °C, were added (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane (48.8 μmol, 1.5 equiv) and benzaldehyde (32.5 μmol, 1.0 equiv). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]*syn*:*anti* of **3a**. [e]*syn*:*anti* for ligand **I**. [f]From ref 14.

Table 3. Influence of Lanthanide Ion on the Mukaiyama Aldol Reaction of (*Z*)-Trimethyl(1-phenylprop-1-enyloxy)silane with Benzaldehyde[a]



lanthanide ion	Ln^{3+} radius (pm)[c]	*syn*:*anti*[d,e,f]	er (*syn*)[d,e,g]
La^{3+}	103.2	1.7:1	52:48
Ce^{3+}	102	1.8:1	60:40
Pr^{3+}	99	2.2:1	74:26
Nd^{3+}	98.3	3.0:1	82:18
Sm^{3+}	95.8	2.1:1	58:42
Eu^{3+}	94.7	2.4:1	75:25
Gd^{3+}	93.8	2.7:1	74:26
Tb^{3+}	92.3	2.5:1	72:28
Dy^{3+}	91.2	2.0:1	64:36
Ho^{3+}	90.1	1.9:1	59:41
Er^{3+}	89.0	1.8:1	58:42
Tm^{3+}	88.0	1.5:1	53:47
Yb^{3+}	86.8	1.3:1	50:50
Lu^{3+}	86.1	1.4:1	51:49

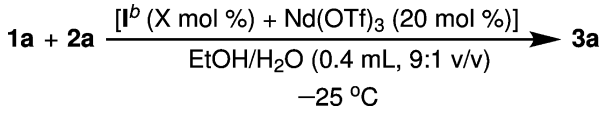
[a]Reaction conditions: To a mixture of ligand **I** (24 mol %) and $Ln(OTf)_3$ (20 mol %), which was stirred at 50 °C for 2 h and then cooled to −25 °C, were added (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane (48.8 μmol, 1.5 equiv) and benzaldehyde (32.5 μmol, 1.0 equiv); All isolated yields were 99%. [b]Ligand *syn*:*anti* > 99:1. [c]From ref 33. [d]Determined by chiral HPLC analysis. [e]Reactions were repeated three times and listed values represent the mean values of between 2 and 5 independent trials. [f]Standard error of the mean for all reactions was between 0 and 0.8 of the normalized *syn* value. [g]Standard error of the mean for the numerator of er (*syn*) was between 0.3 and 6.4.

dx.doi.org/10.1021/jo300800b | J. Org. Chem. 2012, 77, 5624−5632

lanthanide ion. From La^{3+} through Nd^{3+} (Pm^{3+} was skipped because it is radioactive), the decrease in ionic radius corresponded to an increase in the stereoselectivity of our system: the *syn*:*anti* ratio of product **3a** did not change with metal ion (Student's *t*-test, 95% confidence level), but the er values increased from 52:48 to 82:18. However, the continued decrease in ionic radius (from Nd^{3+} through Lu^{3+}) corresponded to a decrease in er values from 82:18 to 51:49 with no change in the *syn*:*anti* ratio of **3a** (Student's *t*-test, 95% confidence level). Under the nonoptimal conditions used for this comparison study, the most effective metal (Nd^{3+}) yielded product with a *syn*:*anti* ratio of 3.0:1 and an er of the *syn* isomer of 82:18. We hypothesize that coordination of Nd^{3+} by ligand **I** allows the most favorable steric environment for substrates during catalysis and, consequently, the best stereoselectivity.

Because Nd^{3+} afforded a higher er than the other lanthanide ions (Student's *t*-test, 95% confidence), we selected this ion to examine the influence of ligand **I** loading on enantioselectivity. With 20 mol % Nd^{3+} and 42 mol % **I**, the *syn* product was observed with 96:4 er (Table 4, entry 3). However, the er

Table 4. Influence of Ligand Loading on the Mukaiyama Aldol Reaction of (*Z*)-Trimethyl(1-phenylprop-1-enyloxy)silane with Benzaldehyde[a]



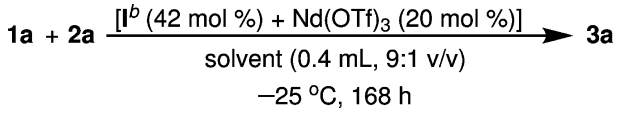
entry	X	reaction time (h)	yield (%)[c]	*syn*:*anti*[d]	er (*syn*)[d]
1	24	24	99	3.0:1	82:18
2	36	72	97	22:1	95:5
3	42	168	93	36:1	96:4

[a]Reaction conditions: To a mixture of ligand **I** (X mol %) and $Nd(OTf)_3$ (20 mol %), which was stirred at 50 °C for 2 h and then cooled to −25 °C, were added (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane (48.8 μmol, 1.5 equiv) and benzaldehyde (32.5 μmol, 1.0 equiv). [b]Ligand *syn*:*anti* > 99:1. [c]Isolated yield. [d]Determined by chiral HPLC analysis.

decreased to 95:5 when 36 mol % ligand **I** was used (Table 4, entry 2) and 82:18 when 24 mol % of ligand **I** was used (Table 4, entry 1). These results suggest that 42 mol % of ligand **I** corresponds to the amount of ligand required for Nd^{3+}–ligand complexes to predominate over free Nd^{3+}. The minimization of unchelated Nd^{3+} is important because unchelated Nd^{3+} can catalyze racemic Mukaiyama aldol reactions. Using the xylenol orange test for free metal, we determined that increasing concentrations of ligand **I** correspond to lower concentrations of free Nd^{3+},[32] which supports our hypothesis for the need of larger amounts of ligand relative to Nd^{3+}.

To further optimize the reaction conditions, we examined the effect of solvent composition on the yield and stereoselectivity of the Mukaiyama aldol reaction using $Nd(OTf)_3$ and ligand **I**. Similar to previous studies, low yields, diastereoselectivities, and enantioselectivities were observed when the Mukaiyama aldol reaction was carried out in aqueous aprotic solvents such as dimethylformamide (DMF), CH_3CN, or THF (Table 5, entries 1–3).[17,21] Protic solvents such as *i*-PrOH and EtOH (Table 5, entries 4 and 5) with 10% water resulted in improved yields and stereoselectivities relative to aprotic solvents (Table 5, entries 1–3). However, larger amounts of water resulted in lower yields and stereoselectivities (Table 5, entries 5–9) likely due

Table 5. Influence of Solvent on the Mukaiyama Aldol Reaction of (*Z*)-Trimethyl(1-phenylprop-1-enyloxy)silane with Benzaldehyde[a]



entry	solvent	yield (%)[c]	*syn*:*anti*[d]	er (*syn*)[d]
1	90:10 DMF/H_2O	7	3:1	55:45
2	90:10 THF/H_2O	11	11:1	74:26
3	90:10 CH_3CN/H_2O	12	7:1	86:14
4	90:10 *i*-PrOH/H_2O	80	13:1	94:6
5	90:10 EtOH/H_2O	93	36:1	96:4
6	85:15 EtOH/H_2O	90	15:1	95:5
7	70:30 EtOH/H_2O	81	5:1	88:12
8	60:40 EtOH/H_2O	62	4:1	87:13
9	50:50 EtOH/H_2O	5	1:1	85:15

[a]Reaction conditions: To a mixture of ligand **I** (42 mol %) and $Nd(OTf)_3$ (20 mol %), which was stirred at 50 °C for 2 h and then cooled to −25 °C, were added (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane (48.8 μmol, 1.5 equiv) and benzaldehyde (32.5 μmol, 1.0 equiv). [b]Ligand *syn*:*anti* > 99:1. [c]Isolated yield. [d]Determined by chiral HPLC analysis.

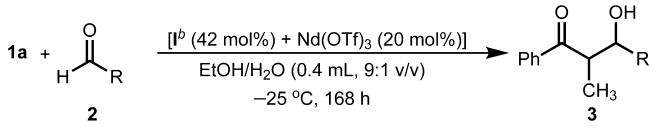
to the poor aqueous solubility of (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane and the competing hydrolysis reaction of (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane, as others have observed.[22]

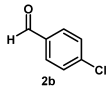
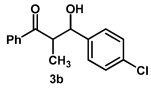
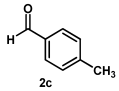
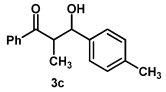
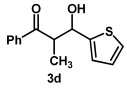
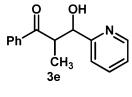
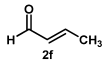
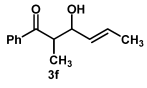
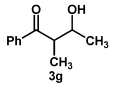
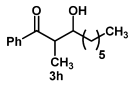
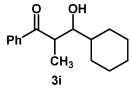
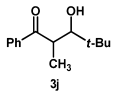
Having established optimized reaction conditions, we probed the generality of ligand **I** and $Nd(OTf)_3$ in the Mukaiyama aldol reaction of (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane with a variety of aromatic and aliphatic aldehydes in EtOH/H_2O (Table 6). Notably, a broad substrate scope was observed. Aromatic aldehydes with electron-withdrawing (Table 6, entry 2) or -donating (Table 6, entry 3) substituents were investigated, and the effect of these substituents on the enantioselectivity of products was found to be negligible. However, diastereoselectivity was lower (12:1) with electron-withdrawing substituents relative to electron-donating substituents or unsubstituted aromatic aldehydes (Table 6, entries 1–3). Heteroaromatic aldehydes also effectively engaged in the Mukaiyama aldol reaction (Table 6, entries 4 and 5), affording excellent er (94:6 and 89:11) and high diastereoselectivities (>99:1). The reactions of the α,β-unsaturated and aliphatic aldehydes also gave excellent stereoselectivities (Table 6, entries 6–9); however, bulky aldehydes (Table 6, entries 9 and 10) afforded little or no product (percent yields of 10 and 0) likely because of steric hindrance preventing the aldehyde from binding with Nd^{3+} resulting in unreacted starting material. At higher temperatures (>−20 °C), we see a drop in selectivity; this loss in selectivity may be due to changes in the relative rates of *syn* and *anti* product formation or due to uncomplexed metal catalyzing the formation of racemic product. Finally, when the (*S*,*S*)-enantiomer of ligand **I** was used in place of the (*R*,*R*)-enantiomer, the er of the product (Table 6, entry 1) switched from 96:4 with the (*R*,*R*) isomer to 7:93 with the (*S*,*S*) isomer. These examples illustrate that different aldehydes affect yields, but the enantioselectivity of catalysis is minimally affected by aldehyde selection when the silyl enol ether is derived from an aromatic ketone.

The variation of the substitution pattern on the phenyl ring of silyl enol ethers was also investigated (Table 7). Electron-

dx.doi.org/10.1021/jo300800b | J. Org. Chem. 2012, 77, 5624–5632

Table 6. Mukaiyama Aldol Reaction of (*Z*)-Trimethyl(1-phenylprop-1-enyloxy)silane with Different Aldehydes[a]



entry	aldehyde	product	yield (%)[c]	*syn*:*anti*[d]	er (*syn*)[d]
1	**2a**	**3a**	93	36:1	96:4[e]
2			90	12:1	95:5
3			85	36:1	96:4
4			82	>99:1	94:6
5			55	>99:1	89:11
6			63	8:1	95:5
7			56	1:3	97:3[f]
8			19	8:1	97:3
9			10	1:15	97:3[f]
10			nr[g]	nd[h]	nd[h]

[a]Reaction conditions: To a mixture of ligand **I** (42 mol %) and $Nd(OTf)_3$ (20 mol %), which was stirred at 50 °C for 2 h and then cooled to −25 °C, were added (*Z*)-trimethyl(1-phenylprop-1-enyloxy)silane (48.8 μmol, 1.5 equiv) and aldehyde (32.5 μmol, 1.0 equiv). [b]Ligand *syn*:*anti* > 99:1. [c]Isolated yield. [d]Determined by chiral HPLC analysis. [e]er of *syn* product was 7:93 if (*S*,*S*) chiral ligand **I** was used. [f]*anti*. [g]No reaction. [h]Not determined.

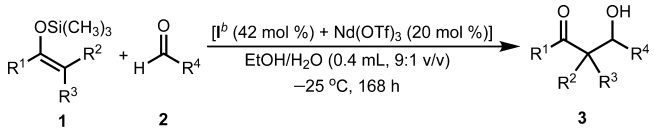
withdrawing (Table 7, entries 2 and 6) and electron-donating (Table 7, entries 3 and 7) substituents on the silyl enol ether have limited effects on yield and enantioselectivity, but as with the aldehydes in Table 6, the electron-withdrawing chloro-substituent lowered diastereoselectivity slightly. In general, good yields (89−93%) were observed when the substrate was benzaldehyde, and low yields (10−56%) were observed when the substrate was heptanal. However, the enantioselectivities remained excellent (er 96:4−98:2) whether the substrate was an aromatic or an aliphatic aldehyde. With trimethyl(1-phenylvinyloxy)silane (Table 7, entry 4), the yield was low (73%) because trimethyl(1-phenylvinyloxy)silane is prone to hydrolysis,[24−26] and the poor enantioselectivity of this example suggests that substitution on the double bond is helpful in the control of product enantioselectivity. We were unable detect product in the reaction between the aliphatic aldehyde **2h** and the aliphatic silyl enol ether **1e** (Table 7, entry 8).

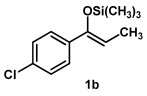
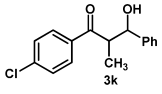
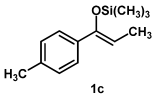
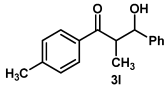
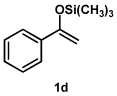
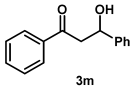
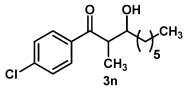
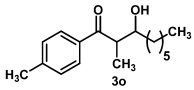
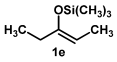
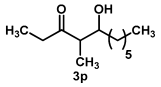
We also examined our precatalyst with a silyl enol ether derived from an aliphatic ketone. We suspected that Nd^{3+} would give similar results to Eu^{3+}. Surprisingly, we found Nd^{3+} gave a lower yield and stereoselectivity than Eu^{3+} (Table 8, entries 1 and 2). These two results suggest that Nd^{3+} is not as good as Eu^{3+} when the substrate is a silyl enol ether derived from an aliphatic ketone, and these observations could be due to the difference in Lewis acidity between the two metal ions. Next, we increased the ratio of $EtOH/H_2O$ (Table 8, entries 3 and 4) and found that the increased $EtOH/H_2O$ ratio has negligible influence on the enantioselectivity. Additionally, dimethoxyethane (DME) was tested as the organic cosolvent in this reaction because DME enabled high stereoselectivities with other catalytic systems.[15,26] However, while the use of DME with our precatalyst led to high diastereoselectivity, this solvent produced a poor yield and low er (Table 8, entry 5).

Because of the low selectivity of Nd^{3+}-based precatalysts for silyl enol ethers derived from aliphatic ketones, we used the Eu^{3+}-based version of our precatalyst to explore the scope of these substrates. Two aromatic aldehydes bearing 4-Cl and 4-CH_3 were tested (Table 9, entries 2 and 3), and the reactions

dx.doi.org/10.1021/jo300800b | *J. Org. Chem.* 2012, 77, 5624−5632

Table 7. Mukaiyama Aldol Reaction of Silyl Enol Ethers Derived from Aromatic Ketones with Benzaldehyde or Heptanal[a]



entry	enolate	aldehyde	product	yield (%)[c]	*syn*:*anti*[d]	er (*syn*)[d]
1	**1a**	**2a**	**3a**	93	36:1	96:4
2	 1b	**2a**	 3k	90	15:1	96:4
3	 1c	**2a**	 3l	89	30:1	96:4
4	 1d	**2a**	 3m	73	—	66:34
5	**1a**	**2h**	**3h**	19	8:1	97:3
6	**1b**	**2h**	 3n	19	5:1	97:3
7	**1c**	**2h**	 3o	18	22:1	98:2
8	 1e	**2h**	 3p	nr[e]	nd[f]	nd[f]

[a]Reaction conditions: To a mixture of ligand **I** (42 mol %) and $Nd(OTf)_3$ (20 mol %), which was stirred at 50 °C for 2 h and then cooled to −25 °C, were added silyl enol ether (48.8 μmol, 1.5 equiv) and aldehyde (32.5 μmol, 1.0 equiv). [b]Ligand *syn*:*anti* > 99:1. [c]Isolated yield. [d]Determined by chiral HPLC analysis. [e]No reaction. [f]Not determined.

with these substituents afforded Mukaiyama-aldol products with good enantioselectivities (er 93:7 and 92:8). However, the yields were lower with substituted benzaldehyde (Table 9, entries 1−3). These observations indicate that electronic properties of substituents on the phenyl rings of the aldehydes have negligible influence on the enantioselectivity of this reaction. But the steric hindrance introduced by substituents on the phenyl rings can affect the efficiency of this reaction. Furthermore, thiophene-2-carboxaldehyde offered the product in good er, suggesting that heteroatoms are compatible with our system (Table 9, entry 4), and cyclohexenyloxytrimethylsilane gave a low er (76:24) (Table 9, entry 5).

■ CONCLUSIONS

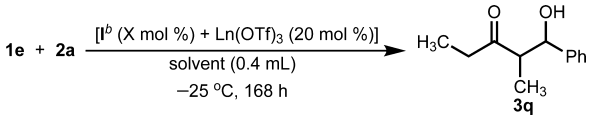
We performed a detailed study of C_2-symmetric ligands for lanthanides as precatalysts for the Mukaiyama aldol reaction in aqueous solution. The synthesis of chiral ligand **I** was improved relative to our initial report by using CH_2Cl_2 instead of CH_3CN, resulting in an increase in the *syn*:*anti* ratio from 4:1 to 16:1. We found that the loading of ligand **I** can be decreased when Nd^{3+} is used instead of Eu^{3+}. Finally, a broad substrate scope is compatible with the precatalysts described in this paper that includes relatively challenging substrates like aliphatic aldehydes and silyl enol ethers derived from aliphatic ketones. This work highlights a new class of lanthanide-based chiral precatalysts for aqueous carbon−carbon bond-forming reactions that offers a broad substrate scope, high enantioselectivity, and low cost.

■ EXPERIMENTAL SECTION

Materials. Commercial chemicals were of reagent-grade purity or better and were used without further purification. The er (97.5:2.5) of (*S*)-2-bromopropanoic acid was determined by high-performance liquid chromatography (HPLC) analysis (Chiralpak AS-H, isocratic 9:1 hexanes/2-propanol, flow rate 1.0 mL/min, λ = 210 nm) t_R = 5.69 min (minor, *R*), 6.63 min (major, *S*). Water was purified using a water purification system. (*Z*)-Trimethyl(1-phenylprop-1-enyloxy)silane (**1a**) (*Z*/*E* = 12:1),[24] (*Z*)-(1-(4-chlorophenyl)prop-1-enyloxy)-trimethylsilane (**1b**) (*Z*/*E* > 20:1),[24] (*Z*)-trimethyl-(1-*p*-tolylprop-1-

dx.doi.org/10.1021/jo300800b | J. Org. Chem. 2012, 77, 5624−5632

Table 8. Solvent Effects in the Mukaiyama Aldol Reaction of (*Z*)-Trimethyl(pent-2-en-3-yloxy)silane[a]



entry	X	ion	solvent	yield (%)[c]	*syn*:*anti*[d]	er (*syn*)[d]
1	42	Nd^{3+}	90:10 EtOH/H_2O	17	5:1	84:16
2[e]	48	Eu^{3+}	90:10 EtOH/H_2O	61	11:1	92:8
3	48	Eu^{3+}	95:5 EtOH/H_2O	46	12:1	92:8
4	48	Eu^{3+}	99:1 EtOH/H_2O	14	14:1	90:10
5	48	Eu^{3+}	90:10 DME/H_2O	8	45:1	85:15

[a]Reaction conditions: To a mixture of ligand **I** (X mol %) and $Ln(OTf)_3$ (20 mol %), which was stirred at 50 °C for 2 h and then cooled to −25 °C, were added (*Z*)-trimethyl(pent-2-en-3-yloxy)silane (48.8 μmol, 1.5 equiv) and benzaldehyde (32.5 μmol, 1.0 equiv). [b]Ligand *syn*:*anti* > 99:1. [c]Isolated yield. [d]Determined by chiral HPLC analysis. [e]From ref 14.

enyloxy)silane (**1c**) (*Z*/*E* > 34:1),[24] and (*Z*)-trimethyl(pent-2-en-3-yloxy)silane (**1e**) (*Z*/*E* = 4.5:1)[34] were synthesized using previously published procedures.

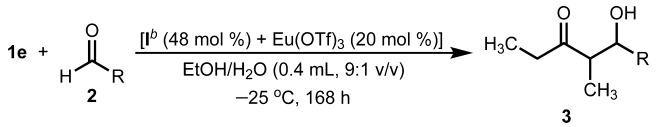
Characterization. Flash chromatography was performed using silica gel 60, 230−400 mesh.[35] Analytical thin-layer chromatography (TLC) was carried out on TLC plates precoated with silica gel 60 F_{254} (250 μm layer thickness). TLC visualization was accomplished using a UV lamp or charring with phosphomolybdic acid stain (5 g phosphomolybdic acid in 50 mL of absolute ethanol). ^{1}H NMR spectra were obtained using a 400 MHz spectrometer. ^{13}C NMR and distortionless enhancement by polarization transfer (DEPT) spectra were obtained using a 101 MHz spectrometer. DEPT spectra were used to assign ^{13}C NMR peaks. Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm) relative to residual $CHCl_3$ in $CDCl_3$ (7.27 ppm); multiplicity ("s" = singlet, "d" = doublet, "t" = triplet, "m" = multiplet, and "brs" = broad singlet); coupling constant, *J*, (Hz); and integration. Italicized elements are those that are responsible for the shifts. Data for ^{13}C NMR spectroscopy are reported as ppm relative to $CDCl_3$ (77.23 ppm). High-resolution electrospray ionization mass spectra (HRESIMS) were obtained on an electrospray time-of-flight high-resolution mass spectrometer. HPLC analyses were carried out on a liquid chromatography−mass spectrometry (LC−MS) instrument equipped with a Chiralpak AS-H, Chiralpak AD-H, Chiralcel OD-H, Chiralcel OJ-H, or Chiralpak IC column (250 × 4.6 mm) using a binary isocratic method (pump A: 2-propanol; pump B: hexanes or *n*-heptane).

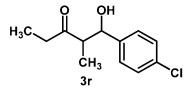
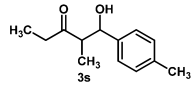
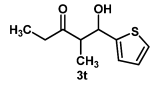
(2*R*,3*R*)-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (3a). Yield 8.0 mg, 93%: TLC R_f = 0.20 (10:1 hexanes/ethyl acetate); HPLC (Chiralpak AS-H, isocratic 9:1 hexanes/2-propanol, flow rate 1.0 mL/min, λ = 254 nm) 96:4 er; 36:1 *syn*:*anti*; t_R = 8.02 min (major, *syn*), 12.34 min (minor, *syn*), 13.99 min (major, *anti*), 18.56 min (minor, *anti*). The configuration of the product was determined as 2*R*,3*R* using a Chiralcel OJ-H column by comparison with the retention order of authentic compounds on a Chiralcel OJ column.[12]

(*syn*)-3-(4-Chlorophenyl)-3-hydroxy-2-methyl-1-phenylpropan-1-one (3b). Yield 8.1 mg, 90%: TLC R_f = 0.20 (10:1 hexanes/ethyl acetate); HPLC (Chiralpak AD-H, isocratic 9:1 hexanes/2-propanol, flow rate 1.0 mL/min, λ = 254 nm) 95:5 er; 12:1 *syn*:*anti*; t_R = 9.71 min (major, *syn*), 11.25 min (minor, *syn*), 14.07 min (major, *anti*), 18.09 min (minor, *anti*). The configuration of the product was determined as *syn* by comparison with the retention order of authentic compounds on a Chiralpak AD-H column.[26]

(*syn*)-3-Hydroxy-2-methyl-1-phenyl-3-(*p*-tolyl)propan-1-one (3c). Yield 7.0 mg, 85%: TLC R_f = 0.20 (10:1 hexanes/ethyl acetate); HPLC (Chiralpak AD-H, isocratic 9:1 hexanes/2-propanol, flow rate

Table 9. Mukaiyama Aldol Reaction of Silyl Enol Ethers Derivated from Aliphatic Ketones with Aromatic Aldehydes[a]



entry	enolate	aldehyde	product	yield (%)[d]	*syn*:*anti*[e]	er (*syn*)[e]
1[c]	**1e**	**2a**	**3q**	61	11:1	92:8
2	**1e**	**2b**	 3r	39	9:1	93:7
3	**1e**	**2c**	 3s	33	24:1	92:8
4	**1e**	**2d**	 3t	30	>20:1[f]	91:9
5	 1f	**2a**	 3u	52	9:1	76:24

[a]Reaction conditions: To a mixture of ligand **I** (48 mol %) and $Eu(OTf)_3$ (20 mol %), which was stirred at 50 °C for 2 h and then cooled to −25 °C, were added silyl enol ether (48.8 μmol, 1.5 equiv) and aldehyde (32.5 μmol, 1.0 equiv). [b]Ligand *syn*:*anti* > 99:1. [c]From ref 14. [d]Isolated yield. [e]Determined by chiral HPLC analysis. [f]Determined by ^{1}H NMR spectroscopy.

dx.doi.org/10.1021/jo300800b | *J. Org. Chem.* 2012, 77, 5624−5632

1.0 mL/min, λ = 254 nm) 96:4 er; 36:1 *syn*:*anti*; t_R = 9.25 min (major, *syn*), 10.64 min (minor, *syn*), 14.93 min (*anti*). The configuration of the product was determined as *syn* by comparison with the retention order of authentic compounds on a Chiralpak AD-H column.[26]

(*syn*)-3-Hydroxy-2-methyl-1-phenyl-3-(thiophen-2-yl)-propan-1-one (3d). Yield 6.6 mg, 82%: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.96−7.93 (m, 2H), 7.62−7.58 (m, 1H), 7.51−7.46 (m, 2H), 7.25−7.22 (m, 1H), 7.00−6.96 (m, 2H), 5.49 (t, J = 3.2 Hz, 1H), 3.84−3.76 (m, 1H), 3.59 (d, J = 3.2 Hz, 1H), 1.32 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 205.2, 146.0, 135.7, 133.9 (CH), 129.0 (CH), 128.7 (CH), 126.9 (CH), 124.5 (CH), 123.7 (CH), 70.7 (CH), 47.9 (CH), 12.3 (CH_3); TLC R_f = 0.20 (8:1 hexanes/ethyl acetate); HRESIMS (m/z) $[M + Na]^+$ calcd for $C_{14}H_{14}O_2SNa$, 269.0612; found, 269.0615; HPLC (Chiralpak AD-H, isocratic 98.5:1.5 *n*-heptane/2-propanol, flow rate 0.8 mL/min, λ = 254 nm) 94:6 er; >99:1 *syn*:*anti*; t_R = 56.87 min (major, *syn*), 71.46 min (minor, *syn*). The configuration of the product was determined as *syn* by comparison with the ^{1}H NMR spectra of authentic compounds.[22]

(*syn*)-3-Hydroxy-2-methyl-1-phenyl-3-(pyridin-2-yl)propan-1-one (3e). Yield 4.3 mg, 55%: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.56 (d, J = 4.6 Hz, 1H), 7.99−7.95 (m, 2H), 7.71−7.66 (m, 1H), 7.60−7.55 (m, 1H), 7.52−7.44 (m, 3H), 7.20−7.16 (m, 1H), 5.24 (t, J = 4.0 Hz, 1H), 4.18 (d, J = 3.2 Hz, 1H), 4.11−4.04 (m, 1H), 1.16 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 205.2, 160.8, 148.9 (CH), 136.8 (CH), 136.0, 133.6 (CH), 128.9 (CH), 128.8 (CH), 122.6 (CH), 121.5 (CH), 73.9 (CH), 46.4 (CH), 11.9 (CH_3); TLC R_f = 0.20 (2:1 hexanes/ethyl acetate); HRESIMS (m/z) $[M + H]^+$ calcd for $C_{15}H_{16}NO_2$, 242.1181; found, 242.1184; HPLC (Chiralpak AS-H, isocratic 90:10 *n*-heptane/2-propanol, flow rate 0.3 mL/min, λ = 254 nm) 89:11 er; >99:1 *syn*:*anti*; t_R = 30.73 min (major, *syn*), 44.91 min (minor, *syn*). The configuration of the product was determined as *syn* by comparison with the ^{1}H NMR spectra and the retention order of authentic compounds.[27]

(2*R*,3*S*)-3-Hydroxy-2-methyl-1-phenylhex-4-en-1-one (3f). Yield 4.2 mg, 63%: TLC R_f = 0.20 (10:1 hexanes/ethyl acetate); HPLC analysis (Chiralcel OD−H, isocratic 99:1 *n*-heptane/2-propanol, flow rate 0.8 mL/min, λ = 254 nm) 95:5 er; 8:1 *syn*:*anti*; t_R = 21.37 min (major, *syn*), 28.32 min (minor, *syn*), 41.35 min (minor, *anti*), 44.44 min (major, *anti*). The configuration of the product was determined as 2*R*,3*S* on a Chiralcel OD-H column by comparison with the retention order of authentic compounds on a Chiralcel OD-H column.[36]

(*anti*)-3-Hydroxy-2-methyl-1-phenylbutan-1-one (3g). Yield 3.2 mg, 56%: TLC R_f = 0.20 (8:1 hexanes/ethyl acetate); HPLC (Chiralpak AS-H, isocratic 95:5 *n*-heptane/2-propanol, flow rate 0.6 mL/min, λ = 254 nm) 97:3 er; 3:1 *anti*:*syn*; t_R = 16.10 min (major, *anti*), 23.24 min (minor, *anti*), 19.82 min (major, *syn*), 37.49 min (minor, *syn*). The configuration of the product was determined as *anti* by comparison with the ^{1}H NMR spectra of authentic compounds.[37]

(*syn*)-3-Hydroxy-2-methyl-1-phenylnonan-1-one (3h). Yield 1.5 mg, 19%: TLC R_f = 0.30 (10:1 hexanes/ethyl acetate); HPLC (Chiralpak AS-H, isocratic 95:5 *n*-heptane/2-propanol, flow rate 0.3 mL/min, λ = 254 nm) 97:3 er; 8:1 *syn*:*anti*; t_R = 20.25 min (major, *syn*), 26.87 min (minor, *syn*), 21.27 min (major, *anti*), 50.15 min (minor, *anti*). The configuration of the product was determined as *syn* by comparison with the retention order of authentic compounds on a Chiralpak AS-H column.[26]

(*anti*)-3-Cyclohexyl-3-hydroxy-2-methyl-1-phenylpropan-1-one (3i). Yield 0.8 mg, 10%: TLC R_f = 0.25 (10:1 hexanes/ethyl acetate); HPLC (Chiralpak AS-H, isocratic 95:5 *n*-heptane/2-propanol, flow rate 0.6 mL/min, λ = 254 nm) 97:3 er; 15:1 *anti*:*syn*; t_R = 12.25 min (major, *anti*), 21.45 min (minor, *anti*), 11.38 min (major, *syn*), 29.02 min (minor, *syn*). The configuration of the product was determined as *anti* by comparison with the ^{1}H NMR spectra of authentic compounds.[21]

(*syn*)-1-(4-Chlorophenyl)-3-hydroxy-2-methyl-3-phenylpropan-1-one (3k). Yield 8.1 mg, 90%: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.88−7.85 (m, 2H), 7.46−7.44 (m, 2H), 7.41−7.33 (m, 4H), 7.30−7.25 (m, 1H), 5.23 (t, J = 2.4 Hz, 1H), 3.69−3.62 (m, 1H), 3.48 (d, J = 2.4 Hz, 1H), 1.21 (d, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 204.6, 141.9, 140.3, 134.2, 130.1 (CH), 129.3 (CH), 128.5 (CH), 127.7 (CH), 126.2 (CH), 73.4 (CH), 47.4 (CH), 11.6 (CH_3); TLC R_f = 0.20 (10:1 hexanes/ethyl acetate); HRESIMS (m/z) $[M + Na]^+$ calcd for $C_{16}H_{15}O_2ClNa$, 297.0658; found, 297.0660; HPLC (Chiralpak AD-H, isocratic 90:10 *n*-heptane/2-propanol, flow rate 0.8 mL/min, λ = 254 nm) 96:4 er; 15:1 *syn*:*anti*; t_R = 14.59 min (major, *syn*), 19.60 min (minor, *syn*), 18.03 min (minor, *anti*), 32.93 min (major, *anti*). The configuration of the product was determined as *syn* by comparison with the ^{1}H NMR spectra of authentic compounds.[24]

(*syn*)-3-Hydroxy-2-methyl-3-phenyl-1-(*p*-tolyl)propan-1-one (3l). Yield 7.4 mg, 89%: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.87−7.84 (m, 2H), 7.43−7.34 (m, 4H), 7.29−7.25 (m, 3H), 5.25 (t, J = 2.4 Hz, 1H), 3.77 (d, J = 1.6 Hz, 1H), 3.72−3.64 (m, 1H), 2.43 (s, 3H), 1.18 (d, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 205.8, 144.8, 142.1, 133.3, 129.7 (CH), 128.9 (CH), 128.4 (CH), 127.5 (CH), 126.3 (CH), 73.2 (CH), 47.0 (CH), 21.9 (CH_3), 11.3 (CH_3); TLC R_f = 0.20 (10:1 hexanes/ethyl acetate); HRESIMS (m/z) $[M + Na]^+$ calcd for $C_{17}H_{18}O_2Na$, 277.1204; found, 277.1196; HPLC (Chiralpak AD-H, isocratic 90:10 *n*-heptane/2-propanol, flow rate 0.8 mL/min, λ = 254 nm) 96:4 er; 30:1 *syn*:*anti*; t_R = 12.36 min (major, *syn*), 15.95 min (minor, *syn*), 23.69 min (minor, *anti*), 30.30 min (major, *anti*). The configuration of the product was determined as *syn* by comparison with the ^{1}H NMR spectra of authentic compounds.[24]

(*S*)-3-Hydroxy-1,3-diphenylpropan-1-one (3m). Yield 5.4 mg, 73%: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.04−7.96 (m, 2H), 7.63−7.58 (m, 1H), 7.58−7.44 (m, 4H), 7.42−7.37 (m, 2H), 7.34−7.29 (m, 1H), 5.39−5.34 (m, 1H), 3.60 (d, J = 3.2 Hz, 1H), 3.39 (d, J = 5.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 200.5, 143.1, 136.8, 133.9 (CH), 128.9 (CH), 128.8 (CH), 128.4 (CH), 127.9 (CH), 126.0 (CH), 70.2 (CH), 47.6 (CH_2); TLC R_f = 0.20 (10:1 hexanes/ethyl acetate); HRESIMS (m/z) $[M + Na]^+$ calcd for $C_{15}H_{14}O_2Na$, 249.0891; found, 249.0890; HPLC (Chiralcel OD−H, isocratic 90:10 hexanes/2-propanol, flow rate 1.0 mL/min, λ = 254 nm) 68:32 er; t_R = 12.47 min (*S*, major), 13.96 min (*R*, minor). The configuration of the product was determined as *S* by comparison with the retention order of authentic compounds on a Chiralcel OD−H column.[38]

(*syn*)-1-(4-Chlorophenyl)-3-hydroxy-2-methylnonan-1-one (3n). Yield 1.8 mg, 19%: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.91−7.87 (m, 2H), 7.48−7.45 (m, 2H), 4.05−3.99 (m, 1H), 3.45−3.37 (m, 1H), 2.94 (d, J = 3.2 Hz, 1H), 1.62−1.23 (m, 13H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 204.8, 140.2, 134.5, 130.1 (CH), 129.3 (CH), 71.5 (CH), 44.8 (CH), 34.6 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 26.3 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 11.3 (CH_3); TLC R_f = 0.30 (10:1 hexanes/ethyl acetate); HRESIMS (m/z) $[M + Na]^+$ calcd for $C_{16}H_{23}O_2NaCl$, 305.1284; found, 305.1291; HPLC (Chiralpak AS-H, isocratic 95:5 *n*-Heptane/2-propanol, flow rate 0.3 mL/min, λ = 254 nm) 97:3 er; 5:1 *syn*:*anti*; t_R = 20.23 min (major, *syn*), 29.75 min (minor, *syn*), 22.23 min (major, *anti*), 44.37 min (minor, *anti*). The configuration of the product was determined as *syn* by the comparation of $^3J_{HH}$ of the *syn* and *anti* isomers ($^3J_{HH}$ (*syn*) = 2.4 Hz, $^3J_{HH}$ (*anti*) = 7.0 Hz).[39]

3-Hydroxy-2-methyl-1-(*p*-tolyl)nonan-1-one (3o). Yield 1.5 mg, 18%: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.86 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.05−4.00 (m, 1H), 3.49−3.40 (m, 1H), 2.44 (s, 3H), 1.62−1.24 (m, 13H), 0.89 (t, J = 5.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 205.9, 144.6, 133.6, 129.7 (CH), 128.8 (CH), 71.5 (CH), 44.4 (CH), 34.5 (CH_2), 32.0 (CH_2), 29.5 (CH_2), 26.3 (CH_2), 22.9 (CH_2), 21.9 (CH_3), 14.3 (CH_3), 11.3 (CH_3); TLC R_f = 0.30 (10:1 hexanes/ethyl acetate); HRESIMS (m/z) $[M + Na]^+$ calcd for $C_{17}H_{26}O_2Na$, 285.1831; found, 285.1823; HPLC (Chiralpak AS-H, isocratic 95:5 *n*-Heptane/2-propanol, flow rate 0.3 mL/min, λ = 254 nm) 98:2 er; 22:1 *syn*:*anti*; t_R = 19.58 min (major, *syn*), 30.93 min (minor, *syn*), 21.87 min (major, *anti*), 59.31 min (minor, *anti*). The configuration of the product was determined as *syn* by the comparation of $^3J_{HH}$ of the *syn* and *anti* isomers ($^3J_{HH}$ (*syn*) = 2.4 Hz, $^3J_{HH}$ (*anti*) = 6.4 Hz).[39]

(*syn*)-1-(4-Chlorophenyl)-1-hydroxy-2-methylpentan-3-one (3r). Yield 2.5 mg, 39%: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.34−7.30 (m, 2H), 7.29−2.25 (m, 2H), 5.08 (d, J = 3.2 Hz, 1H), 3.25 (brs, 1H),

dx.doi.org/10.1021/jo300800b | J. Org. Chem. 2012, 77, 5624−5632

2.84−2.77 (m, 1H), 2.61−2.51 (m, 1H), 2.45−2.34 (m, 1H), 1.07−1.02 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$, δ) 216.6, 140.5, 133.2, 128.7 (CH), 127.5 (CH), 72.6 (CH), 52.1 (CH), 35.6 (CH_2), 10.5 (CH_3), 7.7 (CH_3); TLC R_f = 0.20 (10:1 hexanes/ethyl acetate); HRESIMS (m/z) $[M + Na]^+$ calcd for $C_{12}H_{15}O_2NaCl$, 249.0658; found, 249.0651; HPLC (Chiralpak IC, isocratic 95:5 *n*-heptane/2-propanol, flow rate 1.0 mL/min, λ = 210 nm) 93:7 er; t_R = 8.32 min (minor, *syn*), 9.03 min (major, *syn*). The configuration of the product was determined as *syn* by comparison with the ^{1}H NMR spectra of authentic compounds.[40]

(*syn*)-1-Hydroxy-2-methyl-1-(*p*-tolyl)pentan-3-one (3s). Yield 1.9 mg, 33%: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.21 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 5.03 (d, J = 4.0 Hz, 1H), 2.89−2.80 (m, 1H), 2.54−2.46 (m, 1H), 2.40−2.30 (m, 1H), 2.34 (s, 3H), 1.10 (d, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 216.6, 139.0, 137.2, 129.2 (CH), 126.1 (CH), 73.4 (CH), 52.5 (CH), 35.7 (CH_2), 21.3 (CH_3), 10.9 (CH_3), 7.7 (CH_3); TLC R_f = 0.20 (10:1 hexanes/ethyl acetate); HRESIMS (m/z) $[M + Na]^+$ calcd for $C_{13}H_{18}O_2Na$, 229.1204; found, 229.1201; HPLC (Chiralpak AS-H, isocratic 90:10 *n*-heptane/2-propanol, flow rate 0.6 mL/min, λ = 210 nm) 92:8 er; 24:1 *syn*:*anti*; t_R = 11.99 min (major, *syn*), 15.14 min (minor, *syn*), 13.61 min (minor, *anti*), 18.73 min (major, *anti*). The configuration of the product was determined as *syn* by comparison with the ^{1}H NMR spectra of authentic compounds.[41]

(*syn*)-1-Hydroxy-2-methyl-1-(thiophen-2-yl)pentan-3-one (3t). Yield 1.7 mg, 30%: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.26−7.23 (m, 1H), 7.03−6.95 (m, 1H), 6.95−6.92 (m, 1H), 5.32−5.29 (m, 1H), 3.18 (d, J = 3.2 Hz, 1H), 2.98−2.91 (m, 1H), 2.61−2.51 (m, 1H), 2.45−2.34 (m, 1H), 1.21 (d, J = 6.8 Hz, 3H), 1.03 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 215.9, 145.9, 126.9 (CH), 124.6 (CH), 123.8 (CH), 70.7 (CH), 52.8 (CH), 35.6 (CH_2), 11.5 (CH_3), 7.7 (CH_3); TLC R_f = 0.20 (8:1 hexanes/ethyl acetate); HRESIMS (m/z) $[M + Na]^+$ calcd for $C_{10}H_{14}O_2NaS$, 221.0612; found, 221.0607; HPLC (Chiralpak AD-H, isocratic 90:10 *n*-heptane/2-propanol, flow rate 0.3 mL/min, λ = 210 nm) 91:9 er; >20:1 *syn*:*anti*; t_R = 24.58 min (major, *syn*), 26.60 min (minor, *syn*). The configuration of the product was determined as *syn* by comparison with the ^{1}H NMR spectra of authentic compounds.[21]

(*syn*)-2-(Hydroxy(phenyl)methyl)cyclohexanone (3u). Yield 3.0 mg, 52%: ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.37−7.24 (m, 5H), 5.40 (s, 1H), 3.04 (brs, 1H), 2.64−2.58 (m, 1H), 2.49−2.34 (m, 2H), 2.11−2.07 (m, 1H), 1.88−1.84 (m, 1H), 1.78−1.62 (m, 3H), 1.58−1.49 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, δ) 215.2, 141.6, 128.4 (CH), 127.2 (CH), 126.0 (CH), 70.8 (CH), 57.4 (CH), 42.9 (CH_2), 28.2 (CH_2), 26.2 (CH_2), 25.1 (CH_2); TLC R_f = 0.20 (10:1 hexanes/ethyl acetate); HRESIMS (m/z) $[M + Na]^+$ calcd for $C_{13}H_{16}O_2Na$, 227.1048; found, 227.1048; HPLC (Chiralpak AS-H, isocratic 95:5 *n*-heptane/2-propanol, flow rate 0.5 mL/min, λ = 210 nm) 76:24 er; 9:1 *syn*:*anti*; t_R = 30.27 min (minor, *syn*), 37.38 min (major, *syn*), 41.26 min (minor, *anti*), 45.25 min (major, *anti*). The configuration of the product was determined as *syn* by comparison with the retention order of authentic compounds on a Chiralpak AS-H column.[26]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mallen@chem.wayne.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by startup funds from Wayne State University, a Schaap Faculty Scholar Award, and a CAREER Award from the National Science Foundation (CHE-0955000).

■ REFERENCES

(1) Xuan, R.; Oh, H.-S.; Lee, Y.; Kang, H.-Y. *J. Org. Chem.* **2008**, *73*, 1456−1461.
(2) Park, J. W.; Oh, H.-S.; Jung, W. S.; Park, S. R.; Han, A. R.; Ban, Y.-H.; Kim, E. J.; Kang, H.-Y.; Yoon, Y. J. *Chem. Commun.* **2008**, 5782−5784.
(3) Tosin, M.; Smith, L.; Leadlay, P. F. *Angew. Chem., Int. Ed.* **2011**, *50*, 11930−11933.
(4) Pearson, A. J.; Panda, S. *Org. Lett.* **2011**, *13*, 5548−5551.
(5) Lee, Y.; Choi, J. Y.; Fu, H.; Harvey, C.; Ravindran, S.; Roush, W. R.; Boothroyd, J. C.; Khosla, C. *J. Med. Chem.* **2011**, *54*, 2792−2804.
(6) Oh, H.-S.; Kang, H.-Y. *J. Org. Chem.* **2012**, *77*, 1125−1130.
(7) Morar, M.; Pengelly, K.; Koteva, K.; Wright, G. D. *Biochemistry* **2012**, *51*, 1740−1751.
(8) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506−7525.
(9) Zhao, J.-F.; Tan, B.-H.; Loh, T.-P. *Chem. Sci.* **2011**, *2*, 349−352.
(10) Cheon, C. H.; Yamamoto, H. *Chem. Commun.* **2011**, *47*, 3043−3056.
(11) Inamoto, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2012**, *14*, 1168−1171.
(12) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333−2334.
(13) Denmark, S. E.; Heemstra, J. R., Jr. *Org. Lett.* **2003**, *5*, 2303−2306.
(14) Mei, Y.; Dissanayake, P.; Allen, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 12871−12873.
(15) Ollevier, T.; Plancq, B. *Chem. Commun.* **2012**, *48*, 2289−2291.
(16) Ratjen, L.; García-García, P.; Lay, F.; Beck, M. E.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 754−758.
(17) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590−3596.
(18) Kobayashi, S.; Nagayama, S.; Busujima, T. *Chem. Lett.* **1999**, 71−72.
(19) Nagayama, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 11531−11532.
(20) Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* **2001**, *3*, 165−167.
(21) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron* **1999**, *55*, 8739−8746.
(22) Hamada, T.; Manabe, K.; Ishikawa, S.; Nagayama, S.; Shiro, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 2989−2996.
(23) Li, H.-J.; Tian, H.-Y.; Chen, Y.-J.; Wang, D.; Li, C.-J. *Chem. Commun.* **2002**, 2994−2995.
(24) Li, H.-J.; Tian, H.-Y.; Wu, Y.-C.; Chen, Y.-J.; Liu, L.; Wang, D.; Li, C.-J. *Adv. Synth. Catal.* **2005**, *347*, 1247−1256.
(25) Mlynarski, J.; Jankowska, J. *Adv. Synth. Catal.* **2005**, *347*, 521−525.
(26) Jankowska, J.; Mlynarski, J. *J. Org. Chem.* **2006**, *71*, 1317−1321.
(27) Jankowska, J.; Paradowska, J.; Rakiel, B.; Mlynarski, J. *J. Org. Chem.* **2007**, *72*, 2228−2231.
(28) Ishikawa, S.; Hamada, T.; Manabe, K.; Kobayashi, S. *Synthesis* **2005**, 2176−2182.
(29) Dissanayake, P.; Allen, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 6342−6343.
(30) Dissanayake, P.; Mei, Y.; Allen, M. J. *ACS Catal.* **2011**, *1*, 1203−1212.
(31) Averill, D. J.; Dissanayake, P.; Allen, M. J. *Molecules* **2012**, *17*, 2073−2081.
(32) Averill, D. J.; Garcia, J.; Siriwardena-Mahanama, B. N.; Vithanarachchi, S. M.; Allen, M. J. *J. Visualized Exp.* **2011**, *53*, e2844.
(33) Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*, 2nd ed.; Elsevier: New York, 1997; pp 946 and 1233.

(34) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075−2088.
(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.
(36) Ishihara, K.; Kondo, S.; Yamamoto, H. *J. Org. Chem.* **2000**, *65*, 9125−9128.
(37) Abate, A.; Brenna, E.; Fuganti, C.; Gatti, F. G.; Giovenzana, T.; Malpezzi, L.; Serra, S. *J. Org. Chem.* **2005**, *70*, 1281−1290.
(38) Cheon, C. H.; Yamamoto, H. *Org. Lett.* **2010**, *12*, 2476−2479.
(39) Bifulco, G.; Dambruoso, P.; Gomez-Paloma, L.; Riccio, R. *Chem. Rev.* **2007**, *107*, 3744−3779.
(40) Schetter, B.; Ziemer, B.; Schnakenburg, G.; Mahrwald, R. *J. Org. Chem.* **2008**, *73*, 813−819.
(41) Rohr, K.; Herre, R.; Mahrwald, R. *Org. Lett.* **2005**, *7*, 4499−4501.