JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Chiral Surfactant-Type Catalyst: Enantioselective Reduction of Long-Chain Aliphatic Ketoesters in Water

Zechao Lin,[†,§] Jiahong Li,[†,§] Qingfei Huang,[†] Qiuya Huang,[†] Qiwei Wang,[†] Lei Tang,[#] Deying Gong,[#] Jun Yang,[#] Jin Zhu,[†] and Jingen Deng*[,†,‡]

[†]Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China

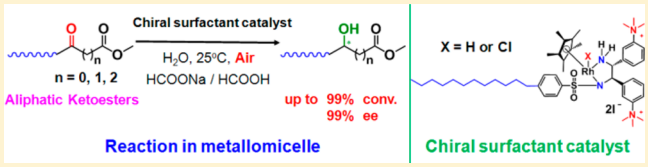
[‡]Key Laboratory of Drug-Targeting of Education Ministry, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

[§]Graduate University of Chinese Academy of Sciences, Beijing 100049, China

[#]Laboratory of Anesthesia and Critical Care Medicine, Translational Neuroscience Center, West China Hospital, Sichuan University, Chengdu 610041, China

Supporting Information

ABSTRACT: A series of amphiphilic ligands were designed and synthesized. The rhodium complexes with the ligands were applied to the asymmetric transfer hydrogenation of broad range of long-chained aliphatic ketoesters in neat water. Quantitative conversion and excellent enantioselectivity (up to 99% ee) was observed for α-, β-, γ-, δ- and ε-ketoesters as well as for α- and β-acyloxyketone using chiral surfactant-type catalyst **2**. The CH/π interaction and the strong hydrophobic interaction of long aliphatic chains between the catalyst and the substrate in the metallomicelle core played a key role in the catalytic transition state. Synergistic effects between the metal-catalyzed site and the hydrophobic microenvironment of the core in the micelle contributed to high stereoselectivity.



INTRODUCTION

Optically active aliphatic hydroxy acids and derivatives are versatile chiral building blocks for many key structural elements in pharmaceuticals and natural products (Figure 1).[1] It is well established that the most efficient and convenient route to chiral aliphatic hydroxy acid esters is the asymmetric reduction of the related ketoesters. Significant advancements have been made in the asymmetric reduction of ketoesters (Figure 2), such as the enzyme-catalyzed asymmetric reduction,[2] the asymmetric hydrogenation (AH),[3] and the asymmetric transfer hydrogenation (ATH);[4] however, these methods mainly limited to aromatic ketoesters and short chain aliphatic ketoesters. Unfortunately, little progress has been achieved for asymmetric reduction of long-chain aliphatic ketoesters, especially for β-, γ- and higher ketoesters.[3a] Therefore, it is still highly challenging to develop an efficient catalytic system for asymmetric reduction of long chain aliphatic ketoesters with high enantioselectivitiy and broad range of substrates.

Recently, asymmetric transfer hydrogenation (ATH) of ketones has attracted increasing attention due to its safety and easy operation.[5] Among the catalysts explored so far, the Noyori–Ikariya catalysts (Ru, Rh, and Ir complexes of TsDPEN (**L1**, Figure 3))[5a,b] and their modifications were highly efficient for ATH of aromatic ketones,[5c−e,6] especially ATH in water.[5c,e,7] As a consequence of increasing demand for environmentally friendly methods, water as a solvent for chemical transformations is of great interest. Water has the advantages of being safe, nontoxic, environmentally benign, and inexpensive; however, the insolubility of organic compounds in aqueous media limits its application in various chemical transformations. An efficient way to address this matter is to use surfactant additives or surfactant-like catalysts. Amphiphiles surfactants, consisting of a polar hydrophilic headgroup and a hydrophobic tail, can form micelles in water as microreactors[8] to enhance not only the solubility of lipophilic substrates, but also the reactivity and stereoselectivity due to the micelle effect.[9] Moreover, the alkyl chains of amphiphiles are ordered in a regular fashion in micelles, which should be advantageous for stereoselective reactions.[9b] Thus, the use of micellar surfactants as addictives or catalysts has attracted much attention in aqueous reactions in recent years.[9,10] Furthermore, the metallomicelle, bearing chiral surfactants as ligands, have the unique characteristic that they can mimic not only the active center but also the hydrophobic microenvironment of metal-loenzymes, which serve as important natural catalyst in living beings.[9a] However, there are only a few reports of successful asymmetric synthesis with high enantioselectivity in chiral micellar systems,[9,10b,11,12] especially in chiral metallomicelles.[9,10b,12] Herein we describe the ATH of long-chain aliphatic ketoesters in neat water in air using chiral surfactant-type metal catalyst with ligand **L6**, providing excellent enantioselectivity for broad range of substrates.

Received: February 5, 2015
Published: April 1, 2015

ACS Publications © 2015 American Chemical Society

DOI: 10.1021/acs.joc.5b00241
J. Org. Chem. 2015, 80, 4419−4429

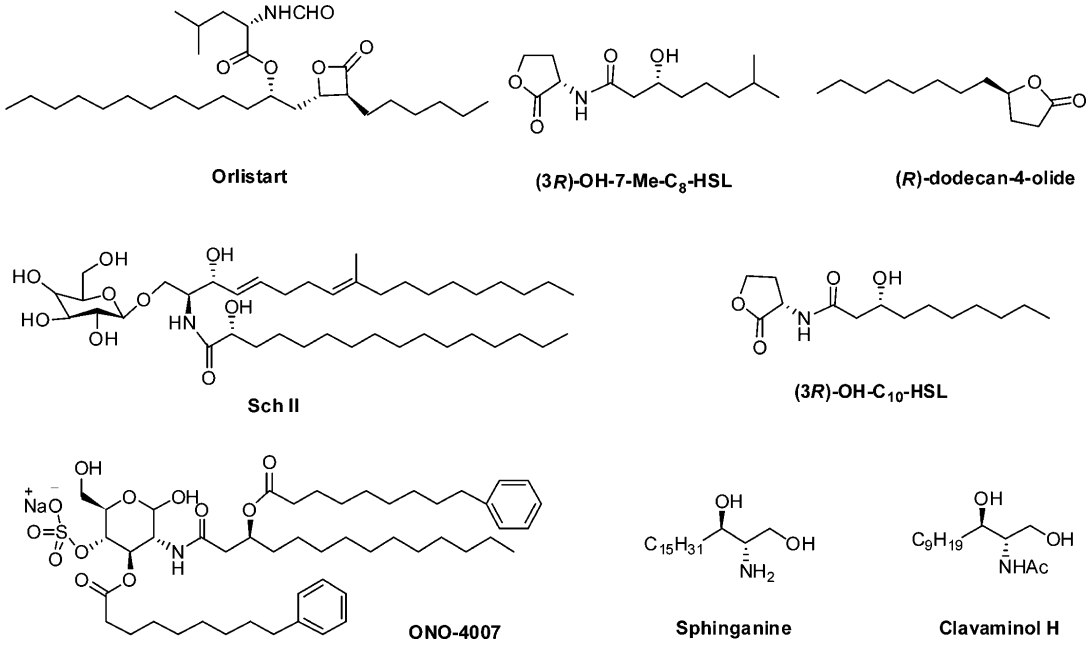


Figure 1. Representative structures of biologically active hydroxy acid derivatives.

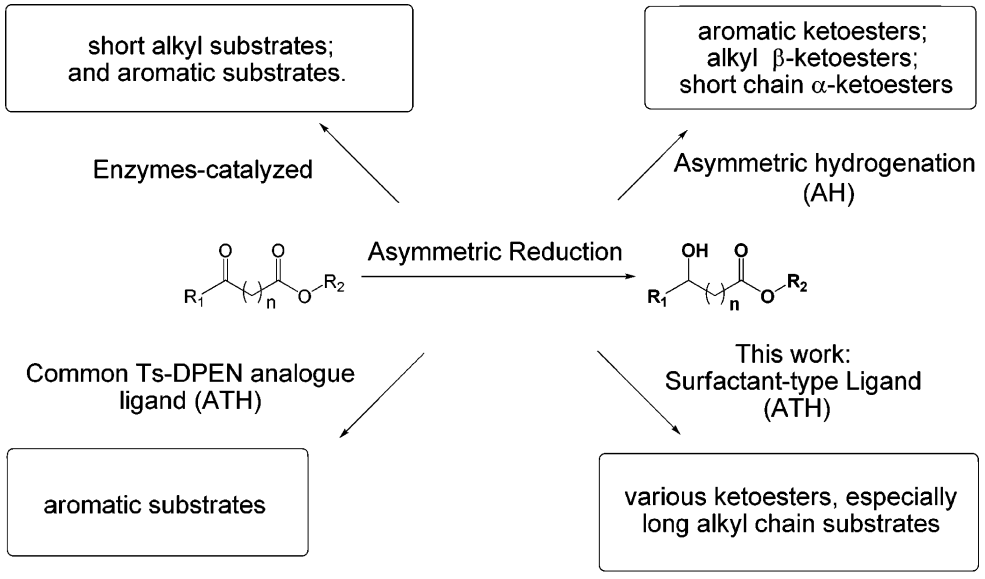


Figure 2. Asymmetric reduction of ketoesters.

RESULTS AND DICUSSION

In our previous work,[10b] we found that a rhodium complex with chiral surfactant-type ligand **L6** can form metallomicelles by self-association in water, providing excellent conversion and enantioselectivity (up to 95% ee) for ATH of aliphatic ketones in aqueous media. We believed that the positive charges polar head of the surfactants on the surface of micelle could elevate the concentration of hydrogen source formate ions via the electrostatic attraction to accelerate the reaction rate, and the hydrophobic interaction between alkyl chain of catalyst and substrate in the core of micelle contributed high enantioselectivities. It is noted that amphiphiles with short alkyl do not form micelles but can also form associates, and the hydrophobic chain of amphiphiles must have a certain length to enable successful micelle formation and the CMC (critical micelle concentration) generally drops as the chain length increases.[9b] Therefore, we designed and synthesized a series of amphiphile ligands (**L2**−**L7**) (Figure 3) with different length alky chains but the same positive charge polar head groups to investigate the hydrophobic interaction between catalyst and substrate. And chiral amphiphilic ligand **L8** (Figure 3) bearing an elongated hydrophilic headgroup was synthesized as well.

First, we selected methyl 2-oxodecanoate (**5a**) as the standard substrate to explore ATH of α-ketoesters using our chiral amphiphilic ligands (**L2**−**L8**, Figure 3). Precatalyst was prepared by mixing the ligand (**L2**−**L8**) with metal precursor in water at 40 °C for 2 h, and then it was subjected to catalyze ATH of **5a** with HCO_2Na as hydrogen source in neat water. As shown in Table 1, the length of alkyl chain of ligands greatly influenced the reactivity and enantioselectivity of the surfactant-type catalysts. The conversion and enantioselectivity gradually enhanced with increasing the length of alkyl chains of ligands

DOI: 10.1021/acs.joc.5b00241
J. Org. Chem. 2015, 80, 4419−4429

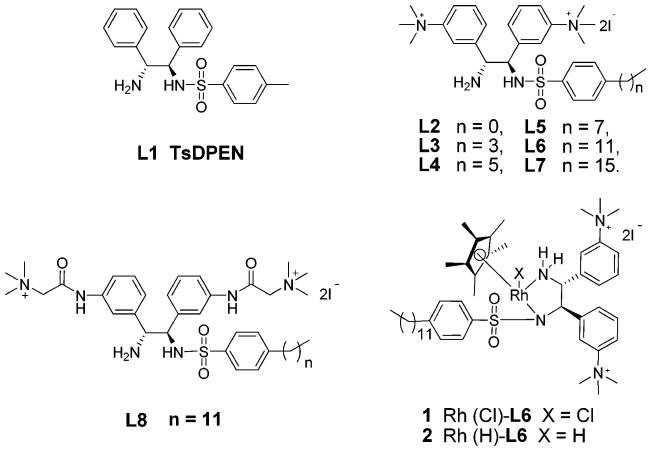
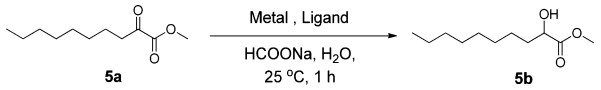


Figure 3. Chiral diamine ligands and catalysts.

Table 1. ATH of Methyl 2-Oxodecanoate with Different Metal Precursors and Ligands[a]



entry	ligand	metal precursor	conv.[b] (%)	ee[c] (%)
1	**L2**	$[RhCl_2Cp^*]_2$	13	70*R*
2	**L3**	$[RhCl_2Cp^*]_2$	14	73*R*
3	**L4**	$[RhCl_2Cp^*]_2$	16	77*R*
4	**L5**	$[RhCl_2Cp^*]_2$	22	86*R*
5	**L6**	$[RhCl_2Cp^*]_2$	40	88*R*
6	**L7**	$[RhCl_2Cp^*]_2$	41	88*R*
7	**L6**	$[RuCl_2(p\text{-cymene})]_2$	14	73*R*
8	**L6**	$[Cp^*IrCl_2]_2$	>99	66*R*
9	**L8**	$[RhCl_2Cp^*]_2$	40	82*R*
10	**L1**	$[RhCl_2Cp^*]_2$	24	77*R*

[a]Reaction conditions: 0.004 mmol of ligand, 0.002 mmol of metal precursor, 5.0 mL of H_2O, 2 mmol of HCOONa, 0.4 mmol of Methyl 2-oxodecanoate, S/C = 100, 1 h, 25 °C, stirring rate: 1500 r/min. [b]Conversion was determined by GC analysis using decane as internal standard. [c]Enantiomeric excess was determined by GC analysis.

(entry 1−5). Hydrophilic ligand **L2** (70% ee, entry 1) and short-chain amphiphilic ligand **L3** (73% ee, entry 2) and **L4** (77% ee, entry 3) provided similar enantioselectivity as that of TsDPEN **L1** (77% ee, entry 10). However, a significant increase of enantioselectivity was observed for ligand **L5** (86% ee, entry 4). It suggested that the catalyst from **L5** may form the micelle by self-association, which greatly improved the enantioselectivity. Interestingly, the enantioselectivity reached a maximum 88% ee (entry 5), when **L6** was used as a ligand. Unfortunately, further extension of the alkyl chain ligand **L7** did not increase the enantioselectivity anymore, but the conversion was a little higher than **L6** (entry 6 vs 5). Ligand **L8**, bearing the same alkyl chain as **L6** but with distanced hydrophilic head groups, showed lower ee value (82% ee, entry 9) compared to **L6** (88% ee, entry 5), despite the fact that it gave the same conversion (40%, entry 5 vs 9).

Different metal precursors such as $[RuCl_2(p\text{-cymene})]_2$, $[Cp^*IrCl_2]_2$, and $[Cp^*RhCl_2]_2$, were also tested using **L6** as a ligand, and the Rh complex **2** (Figure 3) turned out to be the best steroselective (88% ee, entry 5−8). Although Ir complex gave the best conversion (>99%, entry 8), the enantioselectivity was much lower than that of Rh catalyst **2** (66% ee vs 88% ee).

Taking into consideration that synthesis of **L6** is much easier and cheaper than **L7**, and **L6** showed as good enantioselectivity as **L7**, in this paper we would select **L6** as a ligand to investigate the ATH of aliphatic ketoesters.

The significant increase of enantioselectivity implied that the formation of metallomicelles in Rh catalysts with ligand **L5**, **L6** and **L7** may promote greatly the conversion and enantioselectivity in aqueous reaction. In fact, the formation of spherical metallomicelles with precatalysts Rh(Cl)-**L5**, Rh(Cl)-**L6**, Rh(Cl)-**L7** in water were confirmed by TEM analyses (SI Figure S1). Interestingly, along with increasing the hydrophobic chain of the ligand, the average diameter of micelles was reduced and the morphology of micelle became more spherical (SI Figure S1a,b,c).

Apart from the alky chain and the polar head of ligand, a lot of conditions have been explored in hope to gain more insight in to the micelle reaction system. The reaction was strongly dependent on temperature (SI, Table S6). The conversion was gradually increased with the elevation of temperature, quantitative conversion (>99%) was obtained at 40 °C. However, the best enantioselectivity (94% ee) was observed between 5 and 25 °C, further increasing the temperature led to decrease of the ee value. The best result was obtained with 72% conversion and 94% ee at 25 °C. It was possible that increasing the reaction temperature disfavored micelle formation.[13]

We also explored the effects of hydrogen sources on ATH of **5a** and HCOONa showed the best result (40% conversion, 88% ee, Table S1). Then, the effect of initial pH value was also investigated by altering the HCOOH/HCOONa ratio of hydrogen source. Indeed, the reaction was highly dependent on the initial pH value of reaction solution (Figure 4). The

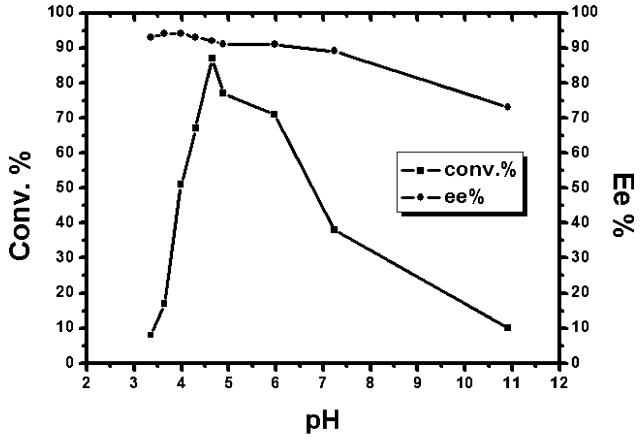


Figure 4. Effect of the initial pH on ATH of methyl 2-oxodecanoate catalyzed by Rh−**L6** complex.

highest ee value (93−94% ee) was observed with pH value of 3.35−4.30, then it dropped gradually until pH = 7.24 (89% ee). The enantioselectivity dramatically dropped to 73% ee under basic condition (pH = 10.91). The conversion rapidly improved from 8 to 87% when pH going from 3.35 to 4.65, then dramatically dropped, which is slightly different from the ATH of aromatic ketones in water using nonamphiphilic ligands.[14] In contrast, it is noteworthy that the best conversion (>99%) and enantioselectivity (86% ee) were obtained in weak base condition for β-ketoester substrates (SI, Table S7), which is similar to the ATH of aromatic β-ketoester in water using nonamphiphilic ligands.[15]

DOI: 10.1021/acs.joc.5b00241
J. Org. Chem. 2015, 80, 4419−4429

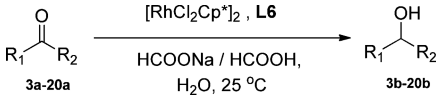
With optimized conditions in hand, we applied chiral surfactant-type catalyst **2** for ATH of various aliphatic ketoesters such as α-, β- and γ-ketoesters (Table 2). For various aliphatic α-ketoester substrates, especially long chain substrates, the quantitative conversion and excellent enantioselectivity (82−99% ee, entry 1−7) was obtained in 6 h. For instance, methyl 2-oxohexadecanoate **8a** was reduced to methyl 2-hydroxyhexadecanoate **8b** in 99% ee, which is a key intermediate for synthesis of side chain of Sch II (Figure 1). Furthermore, aliphatic α-ketoesters (**9a**) bearing an aromatic functional group was also tolerated (88% ee, entry 7).

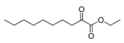
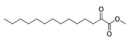
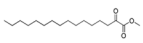
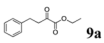
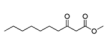
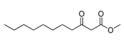
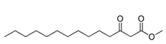
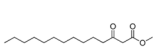
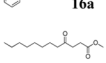
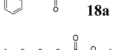
For aliphatic β-ketoester substrates, the rhodium catalyst with classic TsDPEN (**L1**, Figure 3) in Noyori−Ikariya ATH system, only 11% ee was obtained for **14a** (entry 13, Table 2). Strikingly, our surfactant-type catalyst **2** from amphiphilic ligand **L6** gave 91% ee for **14a** (entry 12, Table 2). The dramatic increase of enantioselectivity for our catalyst **2** implied the formation of metallomicelles, which greatly improved the stereochemistry. As expected, quantitative conversion and high enantioselectivity (85−96% ee) was observed for broad range of β-ketoester substrates (entry 9−15, Table 2). Terminal branched β-ketoester **11a** was hydrogenated to **11b** (87% ee, entry 9), which is a key intermediate for constructing (3*R*)-OH-7-Me-C_8-HSL[1a] (Figure 1). **12b**, a key chiral synthon for (3*R*)-OH-C_{10}-HSL[1a] (Figure 1), was obtained with 86% ee (entry 10). Both (3*R*)-OH-7-Me-C_8-HSL and (3*R*)-OH-C_{10}-HSL are important molecules for microbial signaling. Methyl 3-oxomyristate (**14a**) was hydrogenated to methyl 3-hydroxymyristate (**14b**) (91% ee, entry 12) as a key intermediate of orlistart[1c,f] and ONO-4007[1g] (Figure 1). **15a** bearing an aromatic ring in the aliphatic chain terminal provided 85% ee (entry 14). Furthermore, ethyl benzoyl formate **10a** was successfully reduced in 4 h, with 74% ee (entry 8), and aromatic β-ketoester **16a** also gave excellent enantioselectivity (96% ee, entry 14). It suggested that surfactant-type catalyst **2** worked well for both aliphatic and aromatic α- and β-ketoester substrates.

To our surprise, excellent entantioselectivity was also achieved for ATH of γ-ketoesters using surfactant-type catalyst **2**. For example, long-chained aliphatic γ-ketoester methyl 4-oxododecano-ate **17a** was quantitatively converted into dodecan-4-olide **17b** (84% ee, entry 16), which is a small natural product involved in many biological processes (Figure 1).[1b] Moreover, aromatic γ-ketoester **18a** also gave 89% ee despite moderate conversion (entry 17). Furthermore, aliphatic α-acyloxyketone (**19a** and **20a**) was quantitatively reduced to corresponding α-acyloxyalcohol (**19b** and **20b**) with 85 and 73% ee, respectively (entry 18−19).

Chiral short-chain aliphatic hydroxyl acids and derivatives are key intermediates of many pharmaceuticals and natural products.[16] For example, methyl 3-hydroxyheptanoate is a key chiral synthon of Spinosyn A,[16c] which is a commercially important insecticidal macrocyclic lactone. However, classic Noyori−Ikariya catalysts often provided poor enantioselectivity for ATH of short-chain aliphatic ketoesters. Unfortunately, our chiral surfactant-type catalyst **2** (Figure 3) also did not work well for short-chain substrates except for α-ketoesters. For example, only 31% ee was obtained for ATH of methyl β-ketocaproate (**32a**, Figure 6). In contrast, as demonstrated above (Table 2), highly enantioselectivity for long-chain aliphatic ketoesters was successfully achieved using chiral surfactant-type catalyst **2**. Thus, an alternative strategy was proposed to generate chiral short-chain aliphatic hydroxyacid derivatives from long-chain ketoesters. For this purpose, first, the short-chain ketoacid derivatives were converted into long-chain ketoesters by adding a long aliphatic tail into the ester group. Second, the keto group was enantioselectively hydrogenated by using chiral surfactant-type catalyst **2**. Finally, the expected chiral short-chain aliphatic hydroxyacids were

Table 2. ATH of Ketoesters with the Surfactant-Type Catalyst[a]



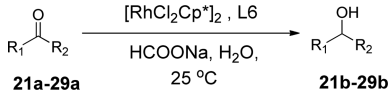
entry	substrate	Time (h)	conv.[d] (%)	e.e.[e] (%)
1[a]	 **3a**	6	>99	82*R*
2[a]	 **4a**	6	>99	87*R*
3[a]	 **5a**	6	>99	90*R*
4[a]	 **6a**	6	>99	92*R*
5[a]	 **7a**	6	>99	96*R*
6[a]	 **8a**	6	>99	99*R*
7[a]	 **9a**	6	>99	88*R*
8[a]	 **10a**	4	>99	74*S*[f]
9[b]	 **11a**	8	>99	87*R*
10[b]	 **12a**	8	>99	86*R*
11[b]	 **13a**	8	>99	86*R*
12[b]	 **14a**	8	>99	91*R*
13[b]	 **14a**	6	>99[c]	11*R*[c]
14[b]	 **15a**	8	>99	85*R*[e]
15[b]	 **16a**	8	>99	96*R*[f]
16[b]	 **17a**	48	99[g]	84*R*[g]
17[b]	**18a**	48	50[h]	89*R*[h]
18[b]	 **19a**	8	>99	85-
19[b]	**20a**	8	>99	73-

[a]Reaction conditions: 0.004 mmol of ligand **L6**, 0.002 mmol of $[Cp^*RhCl_2]_2$, 5.0 mL of H_2O, HCOONa/HCOOH (10/1, 1.2 mmol), 0.4 mmol of ketoesters, 25 °C, S/C = 100, stirring rate: 1500 r/min. [b]Reaction conditions: 0.004 mmol of ligand **L6**, 0.002 mmol of $[Cp^*RhCl_2]_2$, 5.0 mL of H_2O, HCOONa (1.2 mmol), 0.4 mmol of ketoesters, 25 °C, S/C = 100, stirring rate: 1500 r/min. [c]0.004 mmol of ligand TsDPEN. [d]Conversion was determined by GC analysis using decane as internal standard. [e]Enantiomeric excess was determined by GC analysis. [f]Enantiomeric excess was determined by HPLC analysis. [g]Conv. of dodecan-4-olide (**17b**), S/C = 50. [h]Conv. of γ-lactone (**18b**), S/C = 50.

DOI: 10.1021/acs.joc.5b00241
J. Org. Chem. 2015, 80, 4419−4429

obtained by hydrolysis of the ester group. As shown in Table 3, a series of aliphatic ketoesters (**21a**–**29a**) bearing a long alkyl

Table 3. ATH of Ketoesters with the Surfactant-Type Catalyst[a]



entry	substrate	conv.[c](%)	ee[d](%)
1	**21a**	>99	80 +
2	**22a**	>99	82 +
3	**22a**	>99[b]	14[b]
4	**23a**	>99	88 +
5	**24a**	>99	91 +
6	**25a**	>99	74 +
7	**25a**	28[b]	45[b]
8	**26a**	>99	86 +
9	**27a**	>99	91+
10	**28a**	>99	86 +
11	**29a**	37[b]	54[b]+
12	**29a**	84[e]	76[e]

[a]Reaction conditions: 0.004 mmol of ligand **L6**, 0.002 mmol of $[Cp^*RhCl_2]_2$, 5.0 mL of H_2O, HCOONa (1.2 mmol), 0.4 mmol of ketoesters, 25 °C, 6 h, S/C = 100, stirring rate: 1500 r/min. [b]0.004 mmol of ligand TsDPEN, [c]Conversion was determined by GC analysis using decane as internal standard. [d]Enantiomeric excess was determined by GC analysis. [e]48 h.

tail in the ester group were synthesized and applied for ATH catalyzed by chiral surfactant-type catalyst **2**. As we expected, quantitative conversion and excellent enantioselectivity (74–91% ee, entry 1–10, Table 3) was observed. In contrast, classic Noyori–Ikariya catalyst (Rh-TsDPEN) only gave 14% ee for **22a** compared to 82% ee obtained by surfactant-type catalyst **2** (entry 3 vs entry 2, Table 3). It is noteworthy that aliphatic δ- and ε-ketoesters (**23a**, **24a**) were also highly enantioselectively hydrogenated to the related hydroxyacid esters (**23b**, **24b**) with 88 and 91% ee (entry 4–5, Table 3), respectively. Interestingly, a tendency of gradual increase of enantioselectivity was observed when the distance between the ester function and keto group was growing (80–91% ee, entry 1–5). It may suggest that the interaction between the ester group and the metal-catalytic center had a negative effect on stereochemical induction in the catalytic transition state. Furthermore, a significant increase of ee value was also observed when the aliphatic tail of the ester group was prolonged (74–91% ee, entry 6–9), that was consistent with the tendency observed in ATH of α- and β-ketoesters (Table 2). Hexyl 5-oxohexanoate (**27a**) was reduced to **27b** with 91% ee (entry 9), which can be hydrolyzed to chiral 5-hydroxy-1-hexanol as an intermediate of angiotensin II receptor antagonists.[16a] Terminal branched substrate **28a** gave 86% ee (entry 10). Moreover, β-acyloxyketone **29a** was also hydrogenated with 76% ee (entry 11), comparable to Levulinic acid derivative **22a** (82% ee, entry 2); however, only moderate ee value was obtained when using Rh-TsDPEN (54%ee, entry 12).

Proposed Mechanisms. The absolute configurations of ATH of aromatic ketoesters such as α-ketoesters **10a**(***S***), β-ketoesters **16a** (***R***) and γ-ketoesters **18a** (***R***) in our chiral metallomicelle system using surfactant-type ligand **L6** imply that the reaction mechanism of metallomicellar catalyst Rh-**L6** resembles the concerted process suggested by Noyori and co-workers.[17] The transition state was stabilized by CH–π interaction between the Cp* (1,2,3,4,5-pentamethylcyclopentadiene) methyl group of catalyst and the aromatic ring of substrate (SI Figure S7).[18]

In our previous work,[10b] we proposed the mechanism that the strong hydrophobic interaction between the chain of the catalyst and the alkyl chain of the substrate play a key role in obtaining high enantioselectivity. As shown in Table 2, ATH of three types of long chain aliphatic ketoesters (α-, β-, γ-) using catalyst **2** provided *R*-configuration with high ee value, we propose that in the transition state, the large alkyl group of the substrate is far away from the Cp* group of the catalyst due to steric hindrance between them, and the ester group is orientated to the Cp* group via CH–π interaction (Figure 5).[18a]

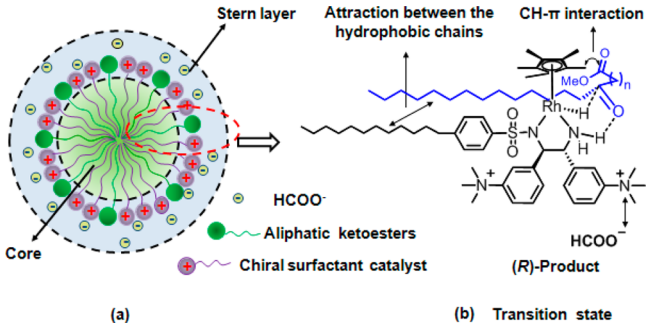


Figure 5. The proposed mechanism of ATH of aliphatic ketoesters.

For ATH of aliphatic α-ketoester substrates using catalyst **2**, high enantioselectivity (82% ee) was observed even for short-chain substrate **3a** (Figure 6); it is much higher than that of pentan-2-one **30a** (57% ee, Figure 6).[10b] This observation suggests that the CH–π interaction between the Cp* group of the catalyst and the ester function of the substrate plays a key

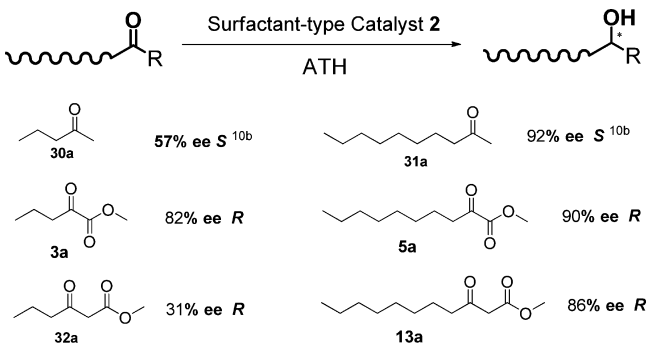


Figure 6. ATH of aliphatic ketones and ketoesters using surfactant catalyst **2**.

DOI: 10.1021/acs.joc.5b00241
J. Org. Chem. 2015, 80, 4419–4429

role in stabilizing the transition state, therefore leading to high enantioselectivity for short-chain aliphatic α-ketoester substrates. On the other hand, it is also observed that a gradual increase of ee value resulted from the prolongation of the aliphatic chain of the substrates (82−99% ee, Table 2, entry 1−6). This indicates the strong hydrophobic interaction between the long alkyl chain of the substrate and the long aliphatic tail of the catalyst in the micelle core greatly stabilizes the transition state. Thus, the two noncovalent forces in the transition state contribute to higher stereoselectivity in reduction of long-chain aliphatic α-ketoester substrates than the short-chain ones.

In contrast, ATH of short-chain aliphatic β-ketoesters catalyzed by catalyst **2** only provided poor enantioselectivity (e.g., 31% ee for **32a**, Figure 6). It implied that the CH−π interaction between the Cp* group of the catalyst and the ester function of the β-substrate is too weak to stabilize the transition state, thus leading to poor enantioselectivity for short-chain aliphatic substrates. However, the strong hydrophobic interaction between the long alkyl chain of the substrate and the aliphatic tail of the catalyst in the metallomicelle core may greatly improve the stability of the catalytic transition state (Figure 5), thus resulting in high enantioselectivities in reduction of long-chain aliphatic β-ketoesters (86−91% ee, Table 2, entry 9−12). It is also consistent with the observation that poor enantioselectivity (11% ee, Table 2, entry 13) was obtained for long-chain aliphatic β-ketoester substrates using Rh-TsDPEN catalyst due to lack of strong hydrophobic attraction in the transition state. In the case of aliphatic γ-ketoesters, we propose that the aliphatic γ-ketoesters may have the same mechanism as β-ketoesters.

We also investigated the mechanism of aliphatic ketoesters bearing acetyl ketone group (**21**−**29a**). We propose that the absolute configurations was controlled with a similar mechanism as that of aliphatic ketones (SI Figure S8),[10b] but the ester group of the substrate may have some interaction with the catalyst playing a negative role on the transition state, which could be explained by the phenomena that decreasing the space of two carbonyl groups of substrates leads to lower enantioselectivity (Table 3 entries 1−5). On the other hand, the reason for high enantioselectivity of product is explained by the fact that strong hydrophobic interaction between the chain of the catalyst and the alkyl chain of the substrate may stabilize the transition state.

CONCLUSION

A series of amphiphilic ligands were designed and synthesized. Metallomicelle could be formed from only surfactant-type catalyst and can increase the enantioselectivity and conversion greatly. The rhodium catalysts from the ligands were applied to asymmetric transfer hydrogenation of broad range of long-chain aliphatic ketoesters in neat water. The rhodium complexes formed from the surfactant-type ligand **L6** have been successfully applied in ATH of broad range of aliphatic ketoesters in neat water, especially those might form key intermediates of bioactive compounds and natural products.[1,16] Quantitative conversion and excellent enantioselectivity (up to 99% ee) were observed for α-, β-, γ-, δ- and ε-ketoesters as well as for α- and β-acyloxyketone using chiral surfactant-type catalyst **2**. The reactivity and enantioselectivity depend on the temperature, the pH, the volume of water, and the alkyl chain length of the aliphatic ketoesters as well as the surfactant-type ligand. The positive charges polar head of the surfactants on the micelle surface elevated the concentration of hydrogen source formate ions by electrostatic attraction to accelerate the reaction rate. The formation of metallomicelles with the precatalysts in water was confirmed by TEM analysis. The reaction mechanism of the chiral surfactant-type catalyst resembles the concerted process suggested by Noyori and coworkers. On the basis of the stereochemistry of the product, a hypothetical transition state was proposed, in which the stereochemistry is controlled by two types of molecular force: the steric hindrance between the large alkyl group of the substrate and the Cp* group of the catalyst, as well as CH−π interaction between the ester group of the substrate and Cp* group of the catalyst. Strong hydrophobic attraction between the large alkyl chain of the ketoesters and the long aliphatic chain of the catalyst in the metallomicelle core contribute to high enantioselectivity in the reduction of aliphatic ketoesters. This work will reveal a new aspect of asymmetric synthesis in chiral metalmicelles. More efficient surfactant-type catalysts for other types of reactions in water are underway.

EXPERIMENTAL SECTION

General Methods. All commercially available reagents were used as received without further purification. All organic solvents used in the reactions were distilled from appropriate drying agents prior to use. All reactions were performed in air. ^{1}H NMR and ^{13}C NMR were acquired at 300 MHz (or 400 MHz) and 75 MHz (or 100 MHz), respectively. Enantiomeric excesses were determined by GC analysis Chirasil-Dex CB (CP7502, 25 m × 0.25 mm).

Procedure for TEM Analyses. (1) Precatalysts $[Cp^*RhCl_2]_2$ (0.002 mmol) and ligand (0.004 mmol) were dissolved in 1 mL of H_2O. The mixture was stirred at 40 °C for 2 h. the solution was cooled to 20 °C. (2) A drop of the colloidal aqueous suspensions was deposited on a carbon-coated copper grid. Then the excess solution was immediately removed with the help of filter paper. The grid was dried in air and then observed by TEM.

Procedure A for the Synthesis of the Ketoesters.[19] The Grignard reagent (2 M in THF, 18.4 mL, 36.8 mmol) was added over 1 h using a syringe automate to a solution of dimethyl oxalate (4.1 g, 35 mmol) in THF (50 mL) at −78 °C. After 1 h at −78 °C, the mixture was warmed to 10 °C and quenched with 3 N HCl solution (20 mL) and H_2O (20 mL). The two phase was separated and the aqueous phase extracted with Et_2O (3×). The combined organic phases were washed with a saturated NaCl solution and dried over $MgSO_4$. The volatile compounds were removed in vacuo and the crude product was purified by flash chromatography (hexane−Et_2O) to afford the pure α-ketoester. And the data of ketoesters are seen in Supporting Information.

Procedure B for the Synthesis of the Ketoesters.[20] A THF solution of LDA (2.5 equiv) was prepared by the addition of *n*-BuLi (15%, hexane) to a solution of *i*-Pr_2NH (2.5 equiv) in THF. To this solution was added methyl acetoacetate (1.0 equiv) at 0 °C. The deep yellow clear solution was stirred at 0 °C for 1 h. To this solution was added the alkyl halide (1.2 equiv) at −78 °C. The temperature was allowed to rise to ambient temperature over 14 h and the solution was stirred at rt for 2 h. To the solution was added HCl (10%, 200 mL) and the mixture was extracted with Et_2O (4 × 250 mL). The organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (hexane−Et_2O) to give the β-ketoesters. And the data of ketoesters are seen in Supporting Information.

Procedure C for the Synthesis of the Ketoesters. The Grignard reagent (2 M in THF, 18.4 mL, 36.8 mmol) was added over 1 h using a syringe automate to a solution of Chloride derivatives (4.1 g, 35 mmol) in THF (50 mL) at −78 °C. After 1 h at −78 °C, the mixture was warmed to 10 °C and quenched with 3 N HCl solution (20 mL) and H_2O (20 mL). The two phase was separated and the aqueous phase extracted with Et_2O (3×). The combined organic phases were washed with a saturated NaCl solution and dried over

DOI: 10.1021/acs.joc.5b00241
J. Org. Chem. 2015, 80, 4419−4429

$MgSO_4$. The volatile compounds were removed in vacuo and the crude product was purified by flash chromatography (hexane−Et_2O) to afford the pure keto esters.

Procedure D for the Synthesis of the Ketoesters.[21] To a stirred solution of benzene (60 mL) and Succinic anhydride (4.40 g, 44 mmol) was added powdered anhydrous $AlCl_3$ (96.5 mmol) at 0 °C and the resulting mixture was refluxed for 1 h. The reaction mixture was then cooled to 0 °C, quenched slowly with water at the same temperature, neutralized and extracted with saturated Na_2CO_3 solution. After acidification with HCl to pH 1 the aqueous solution was concentrated, and was extracted with EtOAc (100 mL × 3). The extract was dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield the desired 4-aryl-4-oxo- butyric acid as a crude product.

The crude 4-aryl-4-oxo- butyric acid was dissolved in EtOH (40−100 mL) and several drops of conc.H_2SO_4 (0.5−1.0 mL) were added. The reaction mixture was refluxed for 7 h and conentrated in vacuo to yield a residue. The residue was diluted with EtOAc (30−50 mL), and neutralized with 1 N NaOH to pH 7 at 0 °C. The organic solution was separated and the aqueous solution was extracted with EtOAc (50 mL × 3). The combined organic solution was dried overanhydrous $MgSO_4$, concentrated in vacuo. The residue was chromatographied on silica gel column with EtOAc/petroleum ether as a eluent to offer the corresponding ketoester.

Procedure E for the Synthesis of the Ketoesters.[22] Oxalyl chloride (1.62 g,12.8 mmol) was added for a period of 10 min to a solution of carboxylic acid derivatives (1.00 g, 4.27 mmol), and DMF (0.2 mL) of anhydrous dichloromethane (10 mL) at 0 °C under magnetic stirring in an argon atmosphere. After a period of 2 h, at room temperature, the solution was evaporated under a vacuum, and the yellowish liquid residue was extracted with dichloromethane (20 mL), and added over a period of 20 min to a mixture of alcohol derivatives (1.10 g,10.3 mmol) and triethylamine (1.29 g, 12.8 mmol), at rt. After 30 min of magnetic stirring, the mixture was concentrated under a vacuum, extracted with Et_2O (100 mL) and treated with aqueous HCl (2 × 70 mL). The organic phase was washed with a saturated solution of sodium chloride (50 mL). The organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. The residue was purified by chromatography (hexane−Et_2O) to give the products.

Procedure F for the Synthesis of the Ketoesters.[23] $BF_3{\cdot}Et_2O$ (15 mol %) was added to a stirred mixture of β-ketoester (2.0 mmol) and alcohol (3.0 mmol) in toluene (10 mL). The resulting reaction mixture was refluxed for an appropriate time. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled, the contents of the flask were poured into water to remove the catalyst, and the mixture was extracted with Et_2O. The organic phase was dried with anhydrous Na_2SO_4, and the solvent was removed. The resulting crude product was purified by column chromatography (hexane−Et_2O) to give the products.

Procedure G for the Synthesis of the Ketoesters.[24] A solution of α-bromoketone (10.0 mmol), formic acid derivative (15.0 mmol), tetrabutyl iodinated amine (1.0 mmol) and K_2CO_3 (15.0 mmol) in CH_2Cl_2 (40 mL) and H_2O (20 mL) was stirred for 12−24 h at room temperature. After the starting material was consumed (TLC), the mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a crude product, which was then purified by a flash chromatography (hexane−Et_2O) to afford α-acyloxy ketone.

Compound Methyl 2-oxopentanoate ***3a***.[25] According to the general procedure A yielding Methyl 2-oxopentanoate as colorless oil (81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 2.83 (t, J = 7.2 Hz, 2H), 1.70−1.65 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H) ppm.

Compound Methyl 2-oxoheptanoate ***4a***.[26] According to the general procedure A yielding Methyl 2-oxoheptanoate as colorless oil (79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 2.84 (t, J = 7.6 Hz, 2H), 1.66−1.62 (m, 2H), 1.34−1.30 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H) ppm.

Compound Methyl 2-oxodecanoate ***5a***. According to the general procedure A yielding Methyl 2-oxodecanoate as colorless oil (72% yield). ^{1}H NMR (300 MHz, DMSO) δ 3.76 (s, 3H), 2.79 (t, J = 7.1 Hz, 2H), 1.50−1.46 (m, 2H), 1.24 (brs, 10H), 0.85 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO) 13.9, 22.2, 22.4, 28.4, 28.6, 28.8, 31.3, 38.6, 52.5, 161.1, 193.8. ESI-HRMS [M + Na]$^+$ calcd for $C_{11}H_{20}O_3Na$ 223.1310, found 223.1306.

Compound Ethyl 2-oxodecanoate ***6a***.[27] According to the general procedure A to yield Ethyl 2-oxodecanoate as colorless oil (73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (q, J = 7.2 Hz,2H), 2.83 (t, J = 7.2 Hz, 2H), 1.65−1.61 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H), 1.33−1.26 (m, 10H), 0.88 (t, J = 7.2 Hz, 3H) ppm.

Compound Methyl 2-oxotetradecanoate ***7a***.[28] According to the general procedure A yielding Methyl 2-oxotetradecanoate as white solid(71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 2.84 (t, J = 7.2 Hz, 2H), 1.61 (brs, 2H), 1.30 (brs, 18H), 0.88 (t, J = 6.8 Hz, 3H) ppm.

Compound Methyl 2-oxohexadecanoate ***8a***. According to the general procedure A yielding Methyl 2-oxotetradecanoate as white solid (67% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 2.82 (t, J = 7.3 Hz, 2H), 1.64−1.57 (m, 2H), 1.24 (brs, 22H), 0.87 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 13.9, 22.2, 22.4, 28.4, 28.6, 28.8, 31.3, 38.6, 52.5, 161.1, 193.8. ESI-HRMS [M + Na]$^+$ calcd for $C_{17}H_{32}O_3Na$ 307.2249, found 307.2258.

Compound Methyl 3-oxoisononoate ***11a***. According to the general procedure B yielding Methyl 3-oxoisononoate as colorless oil (69% yield). ^{1}H NMR (300 MHz, DMSO) δ 3.60 (s, 3H), 3.55 (s, 2H), 2.47 (t, J = 7.3 Hz, 2H), 1.50−1.41 (m, 3H), 1.21−0.83 (m, 2H), 0.82 (d, J = 6.6 Hz, 6H) ppm; ^{13}C NMR (75 MHz, DMSO) 20.8, 22.4, 27.4, 37.8, 39.2, 42.4, 48.6, 51.8, 167.9, 203.6. ESI-HRMS [M + Na]$^+$ calcd for $C_{10}H_{18}O_3Na$ 209.1154, found 209.1153.

Compound Methyl 3-oxodecanoate ***12a***.[29] According to the general procedure B yielding Methyl 3-oxodecanoate as colorless oil (67% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.45 (s, 2H), 2.50 (t, J = 7.4 Hz, 2H), 1.58−1.53 (m, 2H), 1.24 (brs, 8H), 0.84 (t, J = 6.8 Hz, 3H), 4.95 (s, 1 H, enol-CH═C), 11.99 (s, 1 H, enol-OH) ppm.

Compound Methyl 3-oxoundecanoate ***13a***.[30] According to the general procedure B yielding Methyl 3-oxoundecanoate as colorless oil (65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.45(s, 2H), 2.53 (t, J = 7.6 Hz, 2H), 1.61−1.57 (m, 2H), 1.27 (brs, 10H), 0.88 (t, J = 6.8 Hz, 3H) ppm.

Compound Methyl 3-oxomyristate ***14a***.[31] According to the general procedure B yielding Methyl 3-oxomyristate as white solid (71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.46 (s, 2H), 2.54 (t, J = 7.6 Hz, 2H), 1.63−1.58 (m, 2H), 1.27 (brs, 16H), 0.89 (t, J = 6.8 Hz, 3H) ppm.

Compound Methyl 5-phenyl-3-oxopentanoate ***15a***.[32] According to the general procedure B yielding Methyl 5-Phenyl-3-oxopentanoate as yellow oil (68% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.26 (m, 2H), 7.22−7.17 (m, 3H), 3.71 (s, 3H), 3.44(s, 2H), 2.96−2.84 (m, 4H), ppm.

Compound Methyl 4-oxododecanoate ***17a***.[33] According to the general procedure C yielding Methyl 4-oxododecanoate as colorless oil (60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 2.73 (t, J = 6.8 Hz, 2H), 2.59 (t, J = 6.4 Hz, 2H), 2.45 (t, J = 7.6 Hz, 2H), 1.58 (t, J = 6.8 Hz, 2H), 1.27 (brs, 10H), 0.88 (t, J = 6.8 Hz, 3H) ppm.

Compound Ethyl 3-benzoylpropanoate ***18a***.[34] According to the general procedure D yielding Ehyl 3-benzoylpropanoate as yellow oil (89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.2 Hz, 2H), 4.15 (q, J = 6.8 Hz, 2H), 3.30 (t, J = 6.8 Hz, 2H), 2.75 (t, J = 6.8 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H) ppm.

Compound 1-Acetoxy-2-decanone ***19a***.[35] According to the general procedure G yielding 1-acetoxy −2-decanone as white solid (67% yield). ^{1}H NMR (300 MHz, DMSO) δ 4.72 (s, 2H), 2.39 (t, J = 7.3 Hz, 2H), 2.07 (s, 3H), 1.48−1.44 (m, 2H), 1.23 (brs, 10H), 0.85 (t, J = 6.8 Hz, 3H) ppm.

Compound 1-Acetoxy-4-phenyl-2-butanone ***20a***.[36] According to the general procedure G yielding 1-acetoxy-4-phenyl-2-butanone as white solid (71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.27

DOI: 10.1021/acs.joc.5b00241
J. Org. Chem. 2015, 80, 4419−4429

(m, 2H), 7.22−7.17 (m, 3H), 4.61 (s, 2H), 2.94 (t, J = 7.6 Hz, 2H), 2.74 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H) ppm.

Compound Nonyl 3-oxobutanoate ***21a***. According to the general procedure F yielding Nonyl 3-oxobutanoate as colorless oil (71% yield). ^{1}H NMR (300 MHz, DMSO) δ 4.03 (t, J = 6.6 Hz, 2H), 3.58 (s, 2H), 2.16 (s, 3H), 1.55 (t, J = 6.6 Hz, 2H), 1.24 (brs, 12H), 0.85 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO) 13.98, 22.14, 25.31, 28.06, 28.66, 28.94, 30.08, 31.31, 38.69, 49.62, 64.47, 167.34, 201.59. ESI-HRMS $[M + Na]^+$ calcd for $C_{13}H_{24}O_3Na$ 251.1623, found 251.1627.

Compound Octyl 4-oxopentanoate ***22a***.[37] According to the general procedure E yielding Octyl 4-oxopentanoate as colorless oil (64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (t, J = 6.8 Hz, 2H), 2.75 (t, J = 6.4 Hz, 2H), 2.58 (t, J = 6.4 Hz, 2H), 2.20(s, 3H), 1.62 (t, J = 6.8 Hz, 2H), 1.27 (m, 10H), 0.88 (t, J = 6.8 Hz, 3H) ppm

Compound Heptyl 5-oxohexanoate ***23a***. According to the general procedure E yielding Heptyl 5-oxohexanoate as colorless oil (61% yield). ^{1}H NMR (300 MHz, DMSO) δ 3.98 (t, J = 6.6 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 2.26 (t, J = 7.4 Hz, 2H), 2.06 (s, 3H), 1.73−1.63 (m, 2H), 1.54 (brs, 2H), 1.25 (brs, 8H), 0.85 (brs, 3H) ppm; ^{13}C NMR (75 MHz, DMSO) 13.9, 18.7, 22.1, 25.4, 28.2, 28.4, 29.7, 31.2, 32.7, 41.7, 63.8, 172.7, 207.8. ESI-HRMS $[M + Na]^+$ calcd for $C_{13}H_{24}O_3Na$ 251.1623, found 251.1623.

Compound Hexyl 6-oxoheptanoate ***24a***. According to the general procedure E yielding Hexyl 6-oxoheptanoate as colorless oil (63% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (t, J = 6.8 Hz, 2H), 2.42 (t, J = 6.8 Hz, 2H), 2.30−2.26 (m, 2H), 2.10 (s, 3H), 1.60−1.56 (m, 6H), 1.33−1.27 (m, 6H), 0.86 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO) 13.8, 22.0, 22.6, 24.0, 25.0, 28.1, 29.6, 30.9, 33.4, 42.3, 63.7, 172.8, 208.2. ESI-HRMS $[M + Na]^+$ calcd for $C_{13}H_{24}O_3Na$ 251.1623, found 251.1627.

Compound Butyl 5-oxohexanoate ***26a***. According to the general procedure E yielding Butyl 5-oxohexanoate as colorless oil (69% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (t, J = 6.7 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 2.29 (t, J = 7.2 Hz, 2H), 2.10 (s, 3H), 1.87−1.82 (m, 2H), 1.59−1.54 (m, 2H), 1.37−1.30 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 13.6, 18.8, 19.0, 29.8, 30.6, 33.2, 42.4, 64.2, 173.1, 207.9. ESI-HRMS $[M + H]^+$ calcd for $C_{10}H_{19}O_3$ 187.1334, found 187.1330.

Compound Hexyl 5-oxohexanoate ***27a***. According to the general procedure E yielding Hexyl 5-oxohexanoate as colorless oil (61% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (t, J = 6.7 Hz, 2H), 2.48 (t, J = 7.2 Hz, 2H), 2.30 (t, J = 7.2 Hz, 2H), 2.11 (s, 3H), 1.90−1.83 (m, 2H), 1.61−1.54 (m, 2H), 1.32 (brs, 6H), 0.86 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 13.9, 18.8, 22.4, 25.5, 28.5, 29.8, 31.3, 33.2, 42.4, 64.5, 173.2, 207.9. ESI-HRMS $[M + Na]^+$ calcd for $C_{12}H_{22}O_3$ Na 237.1467, found 237.1466.

Compound Isoamyl 5-oxohexanoate ***28a***. According to the general procedure E yielding Isoamyl 5-oxohexanoate as colorless oil (67% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (t, J = 6.8 Hz, 2H), 2.49 (t, J = 7.2 Hz, 2H), 2.31 (t, J = 7.2 Hz, 2H), 2.12 (s, 3H), 1.89−1.84 (m, 2H), 1.70−1.644 (m, 1H), 1.49 (q, J = 6.9 Hz, 2H), 0.90 (d, J = 6.6 Hz, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 18.7, 22.3, 22.3, 24.9, 29.7, 33.1, 37.1, 42.3, 62.9, 173.1, 207.8. ESI-HRMS $[M + H]^+$ calcd for $C_{11}H_{21}O_3$ 201.1491, found 201.1491.

Compound Nonanoic acid-2-oxobutyl ester ***29a***. According to the general procedure E yielding Nonanoic acid-2-oxobutyl ester as colorless oil (56% yield). ^{1}H NMR (300 MHz, DMSO) δ 4.16 (t, J = 6.2 Hz, 2H), 2.74 (t, J = 6.2 Hz, 2H), 2.21 (t, J = 7.3 Hz, 2H), 2.09 (s, 3H), 1.48−1.44 (m, 2H), 1.21 (brs, 10H), 0.83 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO) 13.93, 22.11, 24.45, 28.44, 28.58, 28.69, 29.85, 31.26, 33.42, 41.64, 58.98, 172.82, 205.93. ESI-HRMS $[M + Na]^+$ calcd for $C_{13}H_{24}O_3Na$ 251.1623, found 251.1626.

Typical Procedure for Asymmetric Reduction. $[Cp^*RhCl_2]_2$ (1.3 mg 0.002 mmol) and ligand (0.004 mmol) were dissolved in 5 mL of H_2O. After stirring at 40 °C for 2 h, the solution was cooled to 25 °C. HCOONa (1.2 mmol) and ketoesters (0.4 mmol) were added to the solution. Then the mixture was allowed to react at 25 °C for a certain period of time. The organic phase was extracted with EtOAc (5 mL × 3). The combined organic layer was subjected to GC analysis.

Compound (R)-Methyl 2-hydroxypentanoate ***3b***.[38] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (96% yield). $[\alpha]^{20}_D$ −4.5 (c 0.60, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20−4.16 (m, 1H), 3.76 (s, 3H), 2.67 (brs, 1H), 1.73−1.59 (m, 2H), 1.47−1.40 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 100 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 7.97 min, t_R = 9.20 min.

Compound (R)-Methyl 2-hydroxyheptanoate ***4b***.[39] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (97% yield). $[\alpha]^{20}_D$ −4.7 (c 0.73, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18−4.14 (m, 1H), 3.75 (s, 3H), 2.87 (brs, 1H), 1.74−1.60 (m, 2H), 1.29 (brs, 6H), 0.86 (t, J = 6.5 Hz, 3H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 125 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 9.19 min, t_R = 9.78 min.

Compound (R)-Methyl 2-hydroxydecanoate ***5b***.[40] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (94% yield). $[\alpha]^{20}_D$ −5.6 (c 1.18, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (brs, 1H), 3.76 (s, 3H), 2.87 (brs, 1H), 1.78−1.59 (m, 2H), 1.25 (brs, 12H), 0.85 (t, J = 6.8 Hz, 3H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 140 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 16.16 min, t_R = 16.89 min.

Compound (−)-Ethyl 2-hydroxydecanoate ***6b***. The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (97% yield). $[\alpha]^{20}_D$ −1.1 (c 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (q, J = 7.1 Hz, 2H), 4.18−4.13 (m, 1H), 2.75 (brs, 1H), 1.75−1.60 (m, 2H), 1.43−1.26 (m, 15H), 0.86 (t, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) 14.0, 14.2, 22.6, 24.7, 29.2, 29.3, 29.4, 31.8, 34.4, 61.5, 70.4, 175.4. ESI-HRMS $[M + Na]^+$ calcd for $C_{12}H_{24}O_3Na$ 239.1623, found 239.1625. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 130 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 34.32 min, t_R = 35.87 min.

Compound (R)-Methyl 2-hydroxytetradecanoate ***7b***.[39] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure product (95% yield). $[\alpha]^{20}_D$ −4.3 (c 1.01, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19−4.15 (m, 1H), 3.76 (s, 3H), 2.69 (brs, 1H), 1.77−1.60 (m, 2H), 1.25 (brs, 20H), 0.86 (t, J = 6.8 Hz, 3H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 155 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 57.20 min, t_R = 59.06 min.

Compound (R)-Methyl 2-hydroxyhexadecanoate ***8b***.[39] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure product (93% yield). $[\alpha]^{20}_D$ −5.7 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21−4.15 (m, 1H), 3.78 (s, 3H), 2.75 (d, J = 5.5 Hz, 1H), 1.79−1.60 (m, 2H), 1.43−1.24 (m, 24H), 0.87 (t, J = 6.8 Hz, 3H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 155 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 84.94 min, t_R = 87.27 min.

Compound (R)-Ethyl 2-hydroxy-4-phenylbutyrate ***9b***.[41] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (96% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.18(m, 5H), 4.24−4.16 (m, 3H), 2.91 (d, J = 3.9 Hz, 1H), 2.80−2.75 (m, 2H), 2.14−2.09 (m, 1H), 2.00−1.93 (m, 1H), 1.29 (t, J = 5.4 Hz, 3H) ppm. GC

DOI: 10.1021/acs.joc.5b00241
J. Org. Chem. 2015, 80, 4419−4429

conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 150 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R (***R***)= 23.33 min, t_R (***S***)= 24.59 min.

Compound (S)-Ethyl 2-hydroxy-2-phenylacetate ***10b***.[42] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.27(m, 5H), 5.17 (d, J = 7.1 Hz, 1H), 4.30−4.16 (m, 2H), 3.57 (d, J = 5.6 Hz, 1H), 1.27−1.20 (m, 3H) ppm. HPLC conditions: Chiralcel OD-H column (25 cm × 0.46 cm ID); *n*-hexane/2-propanol = 90:10; flow rate = 1.0 mL/min; 254 nm UV detector; t_R (***S***) = 7.0 min.; t_R (***R***) = 11.5 min.

Compound (R)-Methyl 3-hydroxyhexanoate ***32b***.[43] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (96% yield). $[\alpha]^{20}_D$ −11.2 (c 0.80, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07−3.94 (m, 1H), 3.70 (s, 3H), 2.91 (brs,1H), 2.43−2.37 (m, 2H), 1.31−1.54 (m,4H), 0.92 (t, J = 6.9 Hz, 3H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 100 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 16.43 min, t_R = 17.38 min.

Compound (R)-Methyl 3-hydroxyisononoate ***11b***.[44] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (95% yield). $[\alpha]^{20}_D$ −12.1 (c 0.70, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01−3.95 (m, 1H), 3.68 (s, 3H), 2.81 (brs,1H), 2.47−2.40 (m, 2H), 1.51−1.40 (m,7H), 0.85 (d, J = 6.6 Hz, 6H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 120 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 25.95 min, t_R = 26.95 min.

Compound (R)-Methyl 3-hydroxydecanoate ***12b***.[29] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (97% yield). $[\alpha]^{20}_D$ −12.9 (c 0.75, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (brs, 1H), 3.68 (s, 3H), 2.94 (brs,1H), 2.52−2.34 (m, 2H), 1.49−1.25 (m,12H), 0.85 (t, J = 6.8 Hz, 3H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 135 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 23.66 min, t_R = 24.79 min.

Compound (R)-Methyl 3-hydroxyundecanoate ***13b***.[30] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (94% yield). $[\alpha]^{20}_D$ −12.5 (c 0.80, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (brs, 1H), 3.68 (s, 3H), 2.86 (brs,1H), 2.51−2.34 (m, 2H), 1.51−1.24 (m,14H), 0.85 (brs, 3H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 140 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 30.82 min, t_R = 32.32 min.

Compound (R)-Methyl 3-hydroxymyristate ***14b***.[31] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure product (94% yield). $[\alpha]^{20}_D$ −12.9 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (brs, 1H), 3.71 (s, 3H), 2.97 (brs,1H), 2.54−2.38 (m, 2H), 1.54−1.19 (m,20H), 0.88 (t, J = 7.2 Hz, 3H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 170 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 40.84 min, t_R = 41.66 min.

Compound (R)-Methyl 5-phenyl-3-hydroxypentanoate ***15b***.[43] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (96% yield). $[\alpha]^{20}_D$ −2.3 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.26 (m, 2H), 7.22−7.16 (m, 3H), 4.04 (brs, 1H), 3.71 (s, 3H), 3.04 (brs,1H), 2.83−2.70 (m, 2H), 2.51−2.47 (m, 2H), 1.87−1.73 (m, 2H) ppm. HPLC conditions: Chiralcel AD-H column; *n*-hexane/2-propanol = 95:5; flow rate = 1.0 mL/min; 254 nm UV detector; t_R = 17.87 min.; t_R = 19.86 min.

Compound (R)-Ethyl 3-hydroxy-3-phenylpropanoate ***16b***.[45] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.25 (m, 5H), 5.13−5.09 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.38 (d, J = 3.6 Hz, 1H), 2.77−2.65 (m, 2H), 1.24 (t, J = 7.2 Hz, 3H) ppm. HPLC conditions: Chiralcel OD column (25 cm × 0.46 cm ID); *n*-hexane/2-propanol = 85:15; flow rate = 1.0 mL/min; 254 nm UV detector; t_R (***S***) = 6.6 min.; t_R (***R***) = 7.9 min.

Compound (R)-Dodecan-4-olide ***17b***.[46] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (93% yield). $[\alpha]^{20}_D$ +25.3 (c 0.90, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52−4.43 (m, 1H), 2.52 (dd, J = 6.8, 9.6 Hz, 2H), 2.34−2.27 (m, 1H), 1.87−1.83 (m, 1H), 1.70−1.58 (m, 1H), 1.39−1.30 (m, 1H), 1.25 (brs, 12H), 0.86 (t, J = 7.0 Hz, 3H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 140 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 52.60 min, t_R = 54.51 min.

Compound (R)-γ-Phenyl-γ-butyrolactone ***18b***.[47] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give a crude product which was then purified by a flash chromatography (hexane−EtOAc) to give the pure light yellow oil (43% yield). $[\alpha]^{20}_D$ +13.8 (c 0.90, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.31 (m, 5H), 5.52−5.47 (m, 1H), 2.69−2.61 (m, 3H), 2.22−2.14 (m, 1H) ppm. GC conditions: Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 150 °C, inject temperature = 240 °C, detector temperature = 260 °C, inlet pressure = 12.1 psi; t_R = 19.72 min, t_R = 21.15 min.

Compound (−)-1-Acetoxy-2-decanol ***19b***.[48] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (93% yield). $[\alpha]^{20}_D$ −12.3 (c 0.86, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15−4.10 (m, 1H), 3.97−3.90 (m, 1H), 3.84−3.81 (m, 1H), 2.08 (brs, 4H), 1.38 (brs, 2H), 1.25 (brs, 12H), 0.86 (t, J = 7.0 Hz, 3H) ppm. GC conditions: The enantioselectivities were measured by converting the products to their acetates. Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 110 °C, 1 min // 2.5 °C/min, 140 °C, 60 min; inject temperature = 240 °C; detector temperature = 260 °C; inlet pressure = 12.1 psi; t_R = 36.84 min, t_R = 37.52 min.

Compound (−)-1-Acetoxy-4-phenyl-2-butanol ***20b***.[49] The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (95% yield). $[\alpha]^{20}_D$ −12.5 (c 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ7.32−7.27 (m, 2H), 7.22−7.17 (m, 3H), 4.17−4.12 (m, 1H), 4.03−3.97 (m, 1H), 3.86 (brs, 1H), 2.84−2.71 (m, 2H), 2.09 (brs, 4H), 1.84−1.76 (m, 2H) ppm. HPLC conditions: The enantioselectivities were measured by converting the products to their acetates. Chiralcel AD-H column (25 cm × 0.46 cm ID); *n*-hexane/2-propanol = 95:5; flow rate = 1.0 mL/min; 254 nm UV detector; t_R = 6.6 min.; t_R = 9.4 min.

Compound (+)-Hexyl 6-hydroxyheptanoate ***24b***. The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (95% yield). $[\alpha]^{20}_D$ +7.1 (c 0.91, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO) δ 4.32 (d, J = 4.7 Hz, 1H), 3.97 (t, J = 6.6 Hz, 2H), 3.56−3.49 (m, 1H), 2.24 (t, J = 7.3 Hz, 2H), 1.55−1.44 (m, 4H), 1.35−1.24 (m, 10H), 1.00 (d, J = 6.1 Hz, 3H), 0.84 (t, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (75 MHz, DMSO) 13.8, 22.0, 23.6, 24.7, 24.9, 25.1, 28.2, 30.9, 33.7, 38.7, 63.7, 65.6, 173.0. ESI-HRMS $[M + H]^+$ calcd for $C_{13}H_{27}O_3$ 231.1960, found 231.1956. GC conditions: The enantioselectivities were measured by converting the products to their acetates. Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 160 °C; inject temperature = 240 °C;

DOI: 10.1021/acs.joc.5b00241
J. Org. Chem. 2015, 80, 4419−4429

detector temperature = 260 °C; inlet pressure = 12.1 psi; t_R = 20.28 min, t_R = 21.11 min. The product was reduced by $LiAlH_4$ to get (*S*)-6-hydoxyheptanol.[50]

Compound (+)-Hexyl 5-hydroxyhexanoate ***27b***. The organic phase was extracted with Et_2O (5 mL × 3), the organic layers were dried over Na_2SO_4, filtered, and the filtrate was concentrated in vacuo to give the pure light yellow oil (96% yield). $[\alpha]^{20}_D$ +4.8 (c 0.86, $CHCl_3$). ^1H NMR (300 MHz, DMSO) δ 3.97 (t, J = 6.6 Hz, 2H), 3.59−3.49 (m, 1H), 2.24 (t, J = 7.4 Hz, 2H), 1.59−1.46 (m, 4H), 1.32−1.24 (m, 8H), 1.00 (d, J = 6.1 Hz, 3H), 0.84 (t, J = 6.7 Hz, 3H) ppm. ^{13}C NMR (75 MHz, DMSO) 13.8, 21.1, 22.0, 23.6, 25.1, 28.2, 30.9, 33.7, 38.3, 63.6, 65.5, 173.0. ESI-HRMS $[M + H]^+$ calcd for $C_{12}H_{24}O_3$ 217.1804, found 217.1801. GC conditions: The enantioselectivities were measured by converting the products to their acetates. Chirasil-Dex CB (CP7502, 25 m × 0.25 mm). column temperature = 160 °C; inject temperature = 240 °C; detector temperature = 260 °C; inlet pressure = 12.1 psi; t_R = 13.33 min, t_R = 13.87 min. The product was reduced by $LiAlH_4$ to get (*S*)-5-hydoxyhexanol.[50]

■ ASSOCIATED CONTENT

Supporting Information

Materials, instruments and additional data and discussion. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jgdeng@cioc.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank National Natural Science Foundation of China (Grant No. 20972154 and No. 21372161), National Basic Research Program of China (973 Program, No. 2010CB833300), and Sichuan University for financial support. Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, and West China School of Pharmacy, Sichuan University, contributed equally to this work.

■ REFERENCES

(1) (a) Yajima, A. *Tetrahedron Lett.* **2014**, *55*, 2773−2780. (b) Chalier, P.; Crouzet, J. *Chirality* **1998**, *10*, 786−790. (c) Mulzer, M.; Tiegs, B. J.; Wang, Y.; Coates, G. W.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2014**, *136*, 10814−10820. (d) Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2013**, *15*, 4838−4841. (e) Ait-Youcef, R.; Moreau, X.; Greck, C. *J. Org. Chem.* **2010**, *75*, 5312−5315. (f) Ma, G.; Zancanella, M.; Oyola, Y.; Richardson, R. D.; Smith, J. W.; Romo, D. *Org. Lett.* **2006**, *8*, 4497−4500. (g) Graul, A.; Martel, A.; CASTANER, J. *Drugs Future* **1997**, *22*, 841−845.

(2) For enzyme-catalyzed asymmetric reduction of ketoesters, see: (a) Nakamura, K.; Inoue, K.; Ushio, K.; Oka, S.; Ohno, A. *J. Org. Chem.* **1988**, *53*, 2589−2593. (b) Nakamura, K.; Kondo, S.; Nakajima, N.; Ohno, A. *Tetrahedron* **1995**, *51*, 687−694. (c) Ishihara, K.; Nakajima, N. *Biosci., Biotechnol., Biochem.* **2006**, *70*, 3077−3080. (d) Chen, Y.-Z.; Lin, H.; Xu, X.-Y.; Xia, S.-W.; Wang, L.-X. *Adv. Synth. Catal.* **2008**, *350*, 426−430. (e) Ema, T.; Moriya, H.; Kofukuda, T.; Ishida, T.; Maehara, K.; Utaka, M.; Sakai, T. *J. Org. Chem.* **2001**, *66*, 8682−8684. (f) Ema, T.; Yagasaki, H.; Okita, N.; Nishikawa, K.; Korenaga, T.; Sakai, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1075−1078. (g) Zeror, S.; Collin, J.; Fiaud, J.-C.; Zouioueche, L. A. *Tetrahedron: Asymmetry* **2010**, *21*, 1211−1215. (h) Ma, H.-M.; Yang, L.-L.; Ni, Y.; Zhang, J.; Li, C.-X.; Zheng, G.-W.; Yang, H.-Y.; Xua, J.-H. *Adv. Synth. Catal.* **2012**, *354*, 1765−1772. (i) Shen, N.-D.; Ni, Y.; Ma, H.-M.; Wang, L.-J.; Li, C.-X.; Zheng, G.-W.; Zhang, J.; Xu, J.-H. *Org. Lett.* **2012**, *14*, 1982−1985. (j) Ema, T.; Yagasaki, H.; Okita, N.; Takeda, M.; Sakai, T. *Tetrahedron* **2006**, *62*, 6143−6149. (k) Gutman, A. L.; Zuobi, K.; Bravdo, T. *J. Org. Chem.* **1990**, *55*, 3546−3552.

(3) For asymmetric hydrogenation of ketoesters, see: (a) Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423−4424. (b) Benincori, T.; Piccolo, O.; Rizzo, S.; Sannicolò, F. *J. Org. Chem.* **2000**, *65*, 8340−8347. (c) Boaz, N. W.; Debenham, S. D.; Mackenzie, E. B.; Larg, S. E. *Org. Lett.* **2002**, *4*, 2421−2424. (d) Boaz, N. W.; Mackenzie, E. B.; Debenham, S. D.; Large, S. E.; Ponasik, J. A. *J. Org. Chem.* **2005**, *70*, 1872−1880. (e) Qiu, L.-Q.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.-S.; Yu, W.-Y.; Li, Y.-M.; Guo, R.-W.; Zhou, Z.-Y.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955−5965. (f) Sun, X.-F.; Zhou, L.; Li, W.; Zhang, X.-M. *J. Org. Chem.* **2008**, *73*, 1143−1146. (g) Sun, Q.; Meng, X.-J.; Liu, X.; Zhang, X.-M.; Yang, Y.; Yang, Q.-H.; Xiao, F.-S. *Chem. Commun.* **2012**, *48*, 10505−10507. (h) Xie, J.-H.; Liu, X.-Y.; Yang, X.-H.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 201−203. (i) Starodubtseva, E. V.; Turova, O. V.; Vinogradov, M. G.; Gorshkova, L. S.; Ferapontov, V. A.; Struchkova, M. I. *Tetrahedron* **2008**, *64*, 11713−11717.

(4) For asymmetric transfer hydrogenation of ketoesters, see: (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522. (b) Everaere, K.; Carpentier, J.-F.; Mortreux, A.; Bulliard, M. *Tetrahedron: Asymmetry* **1998**, *9*, 2971−2974. (c) Liu, W.-G.; Cui, X.; Cun, L.-F.; Zhu, J.; Deng, J.-G. *Tetrahedron: Asymmetry* **2005**, *16*, 2525−2530. (d) Yang, J. W.; List, B. *Org. Lett.* **2006**, *8*, 5653−5655. (e) Yin, L.; Jia, X.; Li, X.-S.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2009**, *20*, 2033−2037. (f) Ariger, M. A.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 4522−4524. For DKA asymmetric transfer hydrogenation, see: (g) Cartigny, D.; Puntener, K.; Ayad, T.; Scalone, M.; Ratovelomanana-Vidal, V. *Org. Lett.* **2010**, *12*, 3788−3791. (h) Seashore-Ludlow, B.; Saint-Dizier, F.; Somfai, P. *Org. Lett.* **2012**, *14*, 6334−6337. (i) Liu, Z.-Q.; Shultz, C. S.; Sherwood, C. A.; Krska, S.; Dormer, P. G.; Desmond, R.; Lee, C.; Sherer, E. C.; Shpungin, J.; Cuff, J.; Xu, F. *Tetrahedron Lett.* **2011**, *52*, 1685−1688. (j) Steward, K. M.; Corbett, M. T.; Goodman, C. G.; Johnson, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 20197−20206. (k) Goodman, C. G.; Do, D. T.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2446−2449.

(5) For selected reviews on ATH of ketones, see: (a) Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300−1308. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102. (c) Wang, C.; Wu, X.; Xiao, J. *Chem.—Asian J.* **2008**, *3*, 1750−1770. (d) Wu, X.; Wang, C.; Xiao, J. *Platinum Met. Rev.* **2010**, *54*, 3−19. (e) Wu, X.; Xiao, J. *Chem. Commun.* **2007**, 2449−2466. (f) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045−2061.

(6) Štefane, B.; Požgan, F. *Catal. Rev.* **2014**, *56*, 82−174.

(7) (a) Talwar, D.; Wu, X.; Saidi, O.; Salguero, N. P.; Xiao, J. *Chem.—Eur. J.* **2014**, *20*, 12835−12842. (b) Kang, G.; Lin, S.; Shiwakoti, A.; Ni, B. *Catal. Commun.* **2014**, *57*, 111−114.

(8) Tung, C.-H.; Wu, L.-Z.; Zhang, L.-P.; Chen, B. *Acc. Chem. Res.* **2003**, *36*, 39−47.

(9) For reviews on reactions in micellar systems, see: (a) Zhang, J.; Meng, X.-G.; Zeng, X.-C.; Yu, X.-Q. *Coord. Chem. Rev.* **2009**, *253*, 2166−2177. (b) Dwars, T.; Paetzold, E.; Oehme, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7174−7199.

(10) For selected examples of reactions in micelles, see: (a) Li, J.; Li, X.; Ma, Y.; Wu, J.; Wang, F.; Xiang, J.; Zhu, J.; Wang, Q.; Deng, J. *RSC Adv.* **2013**, *3*, 1825−1834. (b) Li, J.; Tang, Y.; Wang, Q.; Li, X.; Cun, L.; Zhang, X.; Zhu, J.; Li, L.; Deng, J. *J. Am. Chem. Soc.* **2012**, *134*, 18522−18525. (c) Ma, Y.; Liu, H.; Chen, L.; Cui, X.; Zhu, J.; Deng, J. *Org. Lett.* **2003**, *5*, 2103−2106. (d) Wang, F.; Liu, H.; Cun, L.; Zhu, J.; Deng, J.; Jiang, Y. *J. Org. Chem.* **2005**, *70*, 9424−9429. (e) Khiar, N.; Valdivia, V.; Salvador, Á.; Chelouan, A.; Alcudia, A.; Fernández, I. *Adv. Synth. Catal.* **2013**, *355*, 1303−1307. (f) Pinaka, A.; Vougioukalakis, G. C.; Dimotikali, D.; Yannakopoulou, E.; Chankvetadze, B.; Papadopoulos, K. *Chirality* **2013**, *25*, 119−125. (g) Bianchini, G.; Cavarzan, A.; Scarso, A.; Strukul, G. *Green Chem.* **2009**, *11*, 1517−1520. (h) Fallis, I. A.; Griffiths, P. C.; Cosgrove, T.; Dreiss, C. A.; Govan, N.; Heenan, R. K.; Holden, I.; Jenkins, R. L.; Mitchell, S. J.; Notman, S.; Platts, J. A.; Riches, J.; Tatchell, T. *J. Am. Chem. Soc.* **2009**, *131*, 9746−9755. (i) Schwarze, M.; Milano-Brusco, J. S.; Strempel, V.;

DOI: 10.1021/acs.joc.5b00241
J. Org. Chem. 2015, 80, 4419−4429

Hamerla, T.; Wille, S.; Fischer, C.; Baumann, W.; Arlt, W.; Schomäcker, R. *RSC Adv.* **2011**, *1*, 474−483. (j) Kunishima, M.; Kikuchi, K.; Kawai, Y.; Hioki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 2080−2083. (k) Berdugo, C.; Miravet, J. F.; Escuder, B. *Chem. Commun.* **2013**, *49*, 10608−10610. (l) Chang, T.; He, L.; Bian, L.; Han, H.; Yuan, M.; Gao, X. *RSC Adv.* **2014**, *4*, 727−731. (m) Kalsin, A. M.; Peganova, T. y. A.; Novikov, V. V.; Zhamoytina, A. I.; Gonsalvi, L.; Peruzzini, M. *Chem.—Eur. J.* **2014**, *20*, 846−854. (n) Wang, L.; Ma, H.; Song, L.; Li, L.; Wang, Y.; Wang, H. *RSC Adv.* **2014**, *4*, 1567−1569.

(11) (a) Bilé, E. G.; Cortelazzo-Polisini, E.; Denicourt-Nowicki, A.; Sassine, R.; Launay, F.; Roucoux, A. *ChemSusChem* **2012**, *5*, 91−101. (b) Dasgupta, A.; Mitra, R. N.; Roy, S.; Das, P. K. *Chem.—Asian J.* **2006**, *1*, 780−788. (c) Roy, S.; Das, D.; Dasgupta, A.; Mitra, R. N.; Das, P. K. *Langmuir* **2005**, *21*, 10398−10404.

(12) For selected examples on asymmetric synthesis in chiral micelles, see: (a) Boudou, M.; Ogawa, C.; Kobayashi, S. *Adv. Synth. Catal.* **2006**, *348*, 2585−2589. (b) Cherrier, M. V.; Engilberge, S.; Amara, P.; Chevalley, A.; Salmain, M.; Fontecilla-Camps, J. C. *Eur. J. Inorg. Chem.* **2013**, *2013*, 3596−3600.

(13) (a) Sinou, D.; Rabeyrin, C.; Nguefack, C. *Adv. Synth. Catal.* **2003**, *345*, 357−363. (b) Förster, S.; Plantenberg, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 688−714.

(14) Wu, X.; Li, X.; Zanotti-Gerosa, A.; Pettman, A.; Liu, J.; Mills, A. J.; Xiao, J. *Chem.—Eur. J.* **2008**, *14*, 2209−2222.

(15) Ariger, M. A.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 4522−4524.

(16) (a) Nicoletta, A.; N. A, Silvia, S.; Stefano, B.; Ennio, O.; Amjad, A.; L. M. Manchu WO2009/106470 A2 2009. (b) Barral, K.; Priet, S.; Sire, J.; Neyts, J.; Balzarini, J.; Canard, B.; Alvarez, K. *J. Med. Chem.* **2006**, *49*, 7799−7806. (c) Paquette, L. A.; Collado, I.; Purdie, M. *J. Am. Chem. Soc.* **1998**, *120*, 2553−2562. (d) Yu, K. L.; Bronson, J. J.; Yang, H.; Patick, A.; Alam, M.; Brankovan, V.; Datema, R.; Hitchcock, M. J. M.; Martin, J. C. *J. Med. Chem.* **1992**, *35*, 2958−2969.

(17) (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285−288. (b) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931−7944. (c) Wu, X.; Liu, J.; Tommaso, D. D.; Iggo, J. A.; Catlow, C. R. A.; Bacsa, J.; Xiao, J. *Chem.—Eur. J.* **2008**, *14*, 7699−7715.

(18) (a) Soni, R.; Collinson, J.-M.; Clarkson, G. C.; Wills, M. *Org. Lett.* **2011**, *13*, 4304−4307. (b) Šterk, D.; Stephan, M.; Mohar, B. *Org. Lett.* **2006**, *8*, 5935−5938. (c) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818−2821.

(19) Martin, N. J. A.; Cheng, X.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 13862−13863.

(20) Nguyen, V. T. H.; Bellur, E.; Appel, B.; Langer, P. *Synthesis* **2006**, *17*, 2865−2872.

(21) Yang, X.-H.; Xie, J.-H.; Liu, W.-P.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 7833−7836.

(22) Pecanha, E. P.; Figueiredo, L. J. O.; Brindeiro, R. M.; Tanuri, A.; Calazans, A. R.; Antunes, O. A. C. *Il Farmaco* **2003**, *58*, 149−157.

(23) Yang, J.-H.; Ji, C.-B.; Zhao, Y.-M.; Li, Y.-F.; Jiang, S.-Z.; Zhang, Z.-W.; Ji, Y.-Q.; Liu, W.-Y. *Synth. Commun.* **2010**, *40*, 957−963.

(24) Chen, J.-Z.; Liu, D.-L.; Butt, N.; Li, C.; Fan, D.-Y.; Liu, Y.-G.; Zhang, W.-B. *Angew. Chem., Int. Ed.* **2013**, *52*, 11632−11636.

(25) Erb, B.; Kucma, J.-P.; Mourey, S.; Struber, F. *Chem.—Eur. J.* **2003**, *9*, 2582−2588.

(26) Bulman, P.; Philip, C.; Stephen, R. *Tetrahedron Lett.* **1986**, *27*, 1947−1950.

(27) Kogler, M.; Busson, R.; Jonghe, S. D.; Rozenski, J.; Belle, K. V.; Louat, T.; Munier-Lehmann, H.; Herdewijn, P. *Chem. Biodiversity* **2012**, *9*, 536.

(28) David, B.; Schuber, F. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 16731676.

(29) Wu, C.; Miller, P. A.; Miller, M. J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2611−2615.

(30) Bauer, J.; Brandenburg, K.; Zähringer, U.; Rademann, J. *Chem.—Eur. J.* **2006**, *12*, 7116−7124.

(31) Burk, M. J.; Harper, T. G. P.; Kalberg, C. S. *J. Am. Chem. Soc.* **1995**, *117*, 4423−4424.

(32) Durham, T. B.; Miller, M. J. *J. Org. Chem.* **2003**, *68*, 27−34.

(33) Ronald, R. C.; Wheeler, C. J. *J. Org. Chem.* **1983**, *48*, 138−139.

(34) Ramachandran, P. V.; Pitre, S.; Brown, H. C. *J. Org. Chem.* **2002**, *67*, 5315−5319.

(35) Ochiai, M.; Nishitani, J.; Nishi, Y. *J. Org. Chem.* **2002**, *67*, 4407−4413.

(36) Fan, L.-J.; Adams, A. M.; Polisar, J. G.; Ganem, B. *J. Org. Chem.* **2008**, *73*, 9720−9726.

(37) Ishihara, K.; Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* **2005**, *127*, 4168−4169.

(38) Monenschein, H.; Dräger, G.; Jung, A.; Kirschning, A. *Chem.—Eur. J.* **1999**, *5*, 2270−2280.

(39) Breuning, M.; Hauser, T.; Tanzer, E.-M. *Org. Lett.* **2009**, *11*, 4032−4035.

(40) Kovacs, I.; Huszthy, P.; Berthaa, F.; Sziebert, D. *Tetrahedron: Asymmetry* **2006**, *17*, 2538−2547.

(41) Qiu, L.-Q.; Kwong, F. Y.; Wu, J.; HarLam, W.; Chan, S.-S.; Yu, W.-Y.; Li, Y.-M.; Guo, R.-W.; Zhou, Z.−Y.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955−5965.

(42) Marques, C. S.; Burke, A. J. *Tetrahedron: Asymmetry* **2013**, *24*, 628−632.

(43) Jiang, H.; Gschwend, B.; Albrecht, Ł.; Jørgensen, K. A. *Org. Lett.* **2010**, *12*, 5052−5055.

(44) Thiel, V.; Kunze, B.; Verma, P.; Wagner-Dçbler, I.; Schulz, S. *ChemBioChem* **2009**, *10*, 1861−1868.

(45) Yuan, Y.; Li, X.; Sun, J.; Ding, K. L. *J. Am. Chem. Soc.* **2002**, *124*, 14866−14867.

(46) Node, M.; Nishide, K.; Shigeta, Y.; Shiraki, H.; Obata, K. *J. Am. Chem. Soc.* **2000**, *122*, 1927−1936.

(47) Matsumura, Y.; Ogura, K.; Kouchi, Y.; Iwasaki, F.; Onomura, O. *Org. Lett.* **2006**, *8*, 3789−3792.

(48) Kirschner, A.; Bornscheuer, U. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 7004−7006.

(49) Aleu, J.; Fronza, G.; Fuganti, C.; Perozzo, V.; Serra, S. *Tetrahedron: Asymmetry* **1998**, *9*, 1589−1596.

(50) Edegger, K.; Stampfer, W.; Seisser, B.; Faber, K.; Mayer, S. F.; Oehrlein, R.; Hafner, A.; Kroutil, W. *Eur. J. Org. Chem.* **2006**, 1904−1909.

DOI: 10.1021/acs.joc.5b00241
J. Org. Chem. 2015, 80, 4419−4429