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Catalytic Highly Enantioselective Alkylation of Aldehydes with Deactivated Grignard Reagents and Synthesis of Bioactive Intermediate Secondary Arylpropanols

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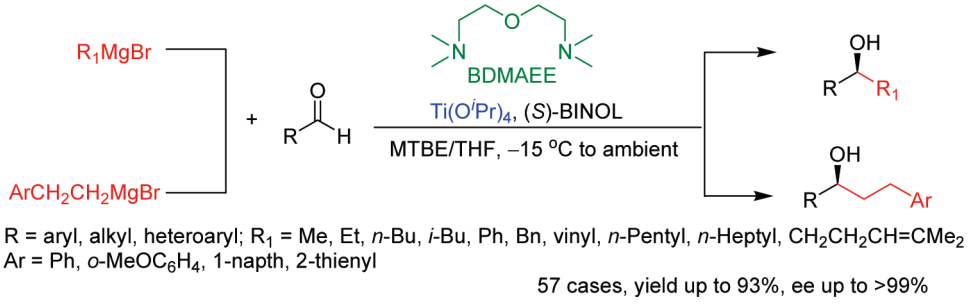

Because of the high reactivity of Grignard reagents, a direct, highly enantioselective Grignard reaction with aldehydes has rarely been disclosed. In this report, Grignard reagents were introduced with bis[2-(*N*,*N*′-dimethylamino)ethyl] ether (BDMAEE) to effectively deactivate their reactivity; thus, a highly enantioselective alkylation of aldehydes with Grignard reagents resulted from catalysis by (*S*)-BINOL-Ti(O^iPr)$_2$. It is thought that BDMAEE chelates the in situ generated salts $MgBr_2$ from a Schlenk equilibrium of RMgBr and Mg(O^iPr)Br from transmetalation of RMgBr with Ti(O^iPr)$_4$. The Mg salts can actively promote the undesired background reaction to give the racemate. The chelation definitely inhibits the catalytic activity of the Mg salts, suppresses the unwanted background reaction, and enables the highly enantioselective addition catalyzed by (*S*)-BINOL-Ti(O^iPr)$_2$. Consequently, the Mg salt byproducts were not removed, less Ti(O^iPr)$_4$ than RMgBr was used, and extremely low temperature was avoided in this catalytic asymmetric reaction in comparison with the research disclosed before. Various alkyl Grignard reagents were investigated in the asymmetric addition, and ^{i}BuMgBr resulted in the highest enantioselectivity, >99%. Furthermore, important intermediate secondary arylpropanols for chiral drug synthesis were effectively synthesized with high enantioselectivity, up to 97%, in one step.

1. Introduction

Enantioenriched secondary alcohols are very important intermediates for asymmetric synthesis of medications and their synthesis has attracted significant attraction. The current procedures to synthesize these alcohols include asymmetric addition of expensive diorganozinc reagents to aldehydes[1] and enantioselective reduction of prochiral ketones.[2] The Grignard reaction with aldehydes is an ideal method to prepare the optically active secondary alcohols, because the easily

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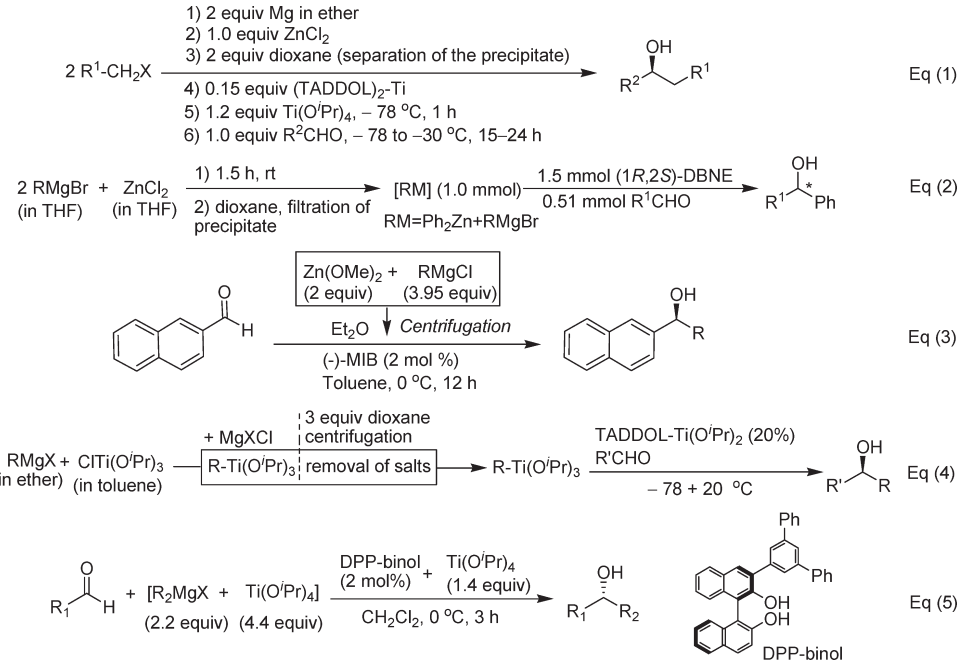
SCHEME 1. Procedures of Asymmetric Alkylation of Aldehydes with Grignard Reagents



prepared Grignard reagents are among the least expensive and most commonly used organometallic reagents in both laboratory and industry.[3] In comparison with those two forementioned asymmetric procedures, however, catalytic asymmetric Grignard additions to aldehydes have rarely been reported because of the high reactivity of Grignard reagents with these substrates. Therefore, the previous observations on asymmetric Grignard reactions were mainly focused on the use of superstoichiometric enantioenriched auxiliaries[4] or even chiral solvents.[5]

The recent procedures using Griganrd reagents as starting materials in addition to aldehydes were focused on transmetalation to form less reactive intermediates (i.e., ZnR_2, R-Ti(O^iPr)$_3$). For example, Seebach and co-worker prepared salt-free diorganozinc reagents from Grignard reagents via precipitation and filtration and used enantioenriched TADDOL as an effective chiral ligand in combination with Ti(O^iPr)$_4$ to realize a high enantioselectivity up to 99% (eq 1, Scheme 1).[6] Later, Soai and co-workers employed PhMgBr to prepare diphenylzinc in situ. The salt byproduct was removed by filtration after introduction of 1,4-dioxane into the mixture. They achieved enantioselectivities up to 82% using (1*R*,2*S*)-(+)-*N*,*N*-dibutylnorephedrine (DBNE) as a chiral ligand (eq 2).[7] More recently, Charette and Côté employed $Zn(MeO)_2$ and alkyl Grignard reagents to generate dialkyl zinc reagents and achieved enantioselecitivity as high as 98% (eq 3).[8] Like Seebach, they also needed salt-free orgonametallic intermediates, which were obtained by centrifugation and filtration. Another fascinating intermediate organometallic reagent is R-Ti(O^iPr)$_3$, which has also been successfully used in the asymmetric addition to aldehydes.[9] Seebach and Weber prepared salt-free R-Ti(O^iPr)$_3$ by direct transmetalation of Grignard reagents and Ti(O^iPr)$_3$Cl at −78 °C with centrifugation and filtration. R-Ti(O^iPr)$_3$ was then used to highly enantioselectively add to aldehydes in the catalysis of in situ generated TADDOL-Ti(O^iPr)$_2$ (eq 4).[10] A significant improvement was reported by Harada and coauthors. They used the chiral ligand DPP-binol (2%) and R-Ti(O^iPr)$_3$ in their protocol. R-Ti(O^iPr)$_3$ was prepared in situ from the Grignard reagent RMgCl and 2-fold Ti(O^iPr)$_4$ at −78 °C, and then the mixture containing R-Ti(O^iPr)$_3$ and Mg salts was very slowly introduced into another mixture at 0 °C. The second mixture contained the aldehyde and the in situ pregenerated catalyst from DPP-binol and a large excess of Ti(O^iPr)$_4$. As high as 97% enantioselectivity was realized regardless of whether or not Mg salts were removed (eq 5).[11]

On the basis of the Schlenk equilibrium (Scheme 2), the Grignard reagent RMgX (X = Cl, Br) is believed to produce

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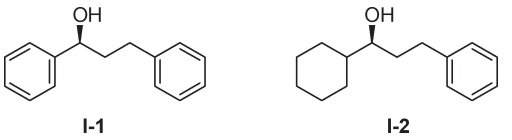
SCHEME 2. Schlenk Equilibrium

R_2Mg and the strong Lewis acid MgX_2. Both RMgX and R_2Mg can readily add to aldehydes.[12] The solvated MgX_2 can activate the aldehyde and promote formation of the racemate. Therefore, the presence of the Lewis acid Mg salts in the catalytic asymmetric reaction system is a central reason why the asymmetric Grignard reaction of aldehydes usually results in poor enantioselectivity, in spite of the presence of a chiral catalyst.

Despite the recent successful use of Grignard reagents in enantioselective additions to aldehydes, there are still considerable limitations. Less reactive and salt-free organometallic reagents from Grignard reagents must be prepared in advance. The procedures to remove the salt byproduct are normally laborious. The organometallic intermediates thus prepared were then employed to add to aldehydes. In many cases, extreme temperature was unavoidable. In some cases, a great excess of $Ti(O^iPr)_4$ with respect to Grignard reagents was used. These situations make it more important, challenging, and interesting to develop a catalytic, highly enantioselective alkylation of aldehydes using Grignard reagents with use of a smaller amount of $Ti(O^iPr)_4$ and no exclusion of the salts from the reaction system under mild conditions.

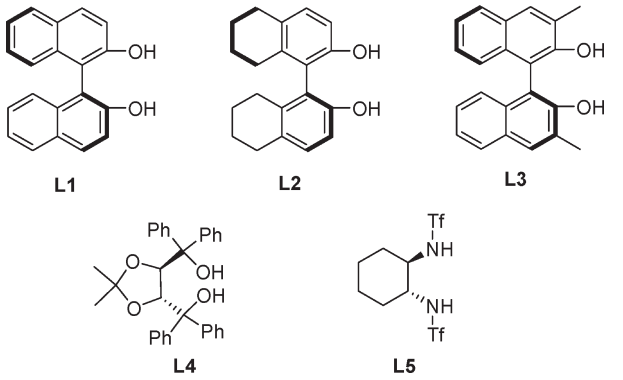
In 2007, we used these guidelines to start this work: no removal of any salt byproduct from the reaction mixture, use of less $Ti(O^iPr)_4$ than Grignard reagent, and no use of extremely low temperature. The preliminary communication of this work has recently been published.[13a] Herein we disclose the full results of this study.

Enantioenriched secondary arylpropanols are important intermediates to bioactive molecules, such as the optically active secondary alcohols **I-1** and **I-2** (Figure 1), which were used to prepare artificial immunosuppressors,[14] the high-affinity ligands of FKBP (FK 506 binding protein).[15] The ligands potentially inhibit the *cis-trans*-peptidylprolyl isomerase (rotamase) catalyzed by FK 506 (the immnosuppressor). Previously, the chiral alcohols were afforded by three steps, including a racemic Grignard reaction. As an example, we will discuss **I-1**. First, the reaction of benzaldehyde with $PhCH_2CH_2MgBr$ gave the racemic secondary alcohol **I-1**. Second, the alcohol was then oxidized to the corresponding prochiral ketone. Third, the ketone was enantioselectively reduced back to the chiral alcohol by stoichiometric (+)-*B*-chlorodiisopinocamphenyl−borane.[14,15] Finally, the enantiopure **I-1** was realized by recrystallization. Other methods to obtain **I-1** include phenylation of phenylpropionaldehyde



I-1 I-2

FIGURE 1. Intermediates for bioactive compounds.



L1 L2 L3 L4 L5

FIGURE 2. Ligands used in the study.

with expensive diphenylzinc by Bolm and co-workers[16] and the asymmetric conjugate reduction of chalcone by Xiao and co-workers.[17] In addition, reports of chiral arylpropanol synthesis include asymmetric alkylation,[18] vinylation,[19] allylation of phenylpropionaldehyde,[20] and asymmetric reduction by biocatalytic[21] and chemical protocols.[22]

On the basis of our preliminary work, we examined the enantioselective synthesis of various secondary arylpropanols via Grignard additions to aldehydes with ee's up to 97% in one step.

2. Results and Discussion

2.1. Selection of Chiral Ligands. We started this work with study of *n*BuMgBr asymmetric addition to benzaldehyde catalyzed by a series of documented enantioenriched C_2-symmetrical ligands (Figure 2). We did not have a plan to prepare salt-free *n*Bu-$Ti(O^iPr)_3$ to add to benzaldehyde. We only wanted to observe what would happen if the in situ generated *n*Bu-$Ti(O^iPr)_3$ was allowed to directly react with aldehydes on the conditions of no salt removal, less $Ti(O^iPr)_4$

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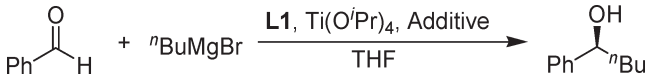
TABLE 1. Catalyzed Asymmetric Addition of *n*BuMgBr to PhCHO[a]

entry	ligand (amt (mol %))	amt of $Ti(O^iPr)_4$[b] (equiv)	amt of ^{n}BuMgBr[b] (equiv)	ee (%)[c]
1	**L1** (10)	2.8	3.85	69
2	**L2** (10)	2.8	3.85	60
3	**L3** (10)	2.8	3.85	5
4	**L4** (10)	2.8	3.85	33
5	**L5** (10)	2.8	3.85	6
6	**L1** (40)	2.8	3.58	50
7	**L1** (40)	2.8	3.58	75
8	**L1** (40)	2.8	3.58	80
9	**L1** (40)	2.8	3.58[d]	55

[a] ^{n}BuMgBr was introduced into $Ti(O^iPr)_4$ on the condition of ice-salt bath, and then the reaction temperature was naturally warmed to be ambient. [b]The amount used relative to benzaldehyde. [c]Determined by chiral HPLC. The configuration was assigned by comparison of the optical rotation of the alcohol with the reported data.[23] [d]The Grignard reagent is *n*BuMgCl.

TABLE 2. Selection of the Optimal Deactivating Additive[a]



entry	ligand (amt (mol %))	amt of $Ti(O^iPr)_4$[b] (equiv)	amt of ^{n}BuMgBr[b] (equiv)	additive[c]	ee (%)[d]
1	**L1** (10)	0.7	1.9	NMM	54
2	**L1** (10)	0.7	1.9	TMEDA	50
3	**L1** (10)	0.7	1.9	DMAP	45
4	**L1** (10)	0.7	1.9	hexamine	48
5	**L1** (10)	0.7	1.9	BDMAEE	70
6	**L1** (10)	0.7	1.9	BDMAEE	68
7	**L1** (40)	0.7	2.5	BDMAEE	98

[a] ^{n}BuMgBr was introduced into $Ti(O^iPr)_4$ at the temperature of an ice−salt bath; the reaction mixture was then naturally warmed to ambient temperature. [b]The amount used relative to benzaldehyde. [c]Conditions and abbreviations: additive/^{n}BuMgBr = 1:1; NMM, *N*-methylmorpholine; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethelenediamine; DMAP, 4-(dimethylamino)pyridine; hexamine, hexamethylenetetramine (also called urotropine). [d]Determined by chiral HPLC.

than the Grignard reagent, and mild reaction conditions. The results are included in Table 1.

It could be concluded that (*S*)-BINOL (**L1**) formed the best catalyst among the five chiral ligands examined (Table 1). (*S*)-H_8-BINOL (**L2**) exhibited lower enantioselectivity than (*S*)-BINOL (entry 2). The least enantioselective ligands were (*S*)-3,3′-Me_2BINOL (**L3**) and tosylated (1*R*,2*R*)-cyclohexanediamine (**L5**), both generating nearly racemic secondary alcohols (entries 3 and 5). Unfortunately, it was very difficult to reproduce the enantioselectivity of this transformation (entries 6−8). Replacing *n*BuMgBr with *n*BuMgCl did not give any improvement in enantioselectivity (entry 9). We ascribed this phenomenon to the intermediate salts $MgBr_2$ and $MgBr(O^iPr)$, which promote the racemic background reaction.

2.2. Selection of the Deactivator of the Grignard Reagent. We found that the research groups of Bolm and Walsh had met with similar problems in their works about arylation of aldehydes with arylzinc reagents.[24,25] Neither group removed the salt byproducts, however. In their study of the asymmetric addition of diphenylzinc to aldehydes,[24] Bolm and co-workers found that diphenylzinc and $ZnBr_2$ could actively promote a racemic background reaction and lead to low enantioselectivity. When they added dimethyl(polyethylene glycol) (DiMPEG, M_w 2000) to the reaction mixture, the additive effectively suppressed the catalytic activity of Ph_2Zn and $ZnBr_2$ and the enantioselectivity was then remarkably increased. Later, Walsh and co-workers demonstrated a cost-effective protocol starting from inexpensive aryl bromides and butyllithium to prepare arylzinc reagents for asymmetric addition to aldehydes.[25] They similarly used *N*,*N*,*N*′,*N*′-tetraethylethylenediamine (TEEDA) as another potent inhibitor of the Lewis acidic LiCl, which was formed on the transmetalation of aryllithium to ZnCl and rapidly promoted the undesired background reaction. As a consequence, addition of TEEDA successfully improved the enantioselectivity regardless of the presence of LiCl in the reaction system.

These reports gave us some indication that we could select a chelating reagent to coordinate to Lewis acidic Mg salts. This chelation could decrease the activity of Mg salts and inhibit background reactions promoted by these Mg salts accordingly. Therefore, this chelation could deactivate the reactivity of Grignard reagents in part. A series of commercially available ligands were screened (additive/^{n}BuMgBr = 1:1), and the results are included in Table 2. It was found that only BDMAEE with three coordinating atoms improved the enantioselectivity (entries 1−5). Additionally, with BDMAEE, the enantioselecitivity could be reproduced easily (entries 5−6). While 40% (*S*)-BINOL was used, the enantioselectivity was markedly enhanced to 98% (entry 7). This result indicated that the reactivity of the Grignard reagent was effectively inhibited with the addition of BDMAEE.

2.3. Generality of Grignard Reagents. Further optimization experiments revealed that the THF/TBME (^{t}BuOMe) solvent system and 0.84 equiv of $Ti(O^iPr)_4$ with respect to the aldehyde were optimal in terms of the enantioselectivity.[13a] With these optimized reaction conditions, we then observed the generality of varieties of commonly used Grignard reagents in this protocol, and the results are included in Table 3. The results revealed that ^{i}BuMgBr achieved the highest enantioselectivity. A high enantioselectivity of 94% with benzaldehyde was the result of using 10% **L1** (entry 13). The enantioselectivity could be clearly raised to the highest value, 98%, with 15% **L1** (entries 14 and 15). As a result, the optimized reaction conditions were finally selected: 15% **L1**, 1:1 ratio of BDMAEE to Grignard reagents (2.0 equiv to aldehyde), 0.89 equiv of $Ti(O^iPr)_4$, TBME/THF solvent system, and a mild reaction temperature (ice−salt bath and then room temperature). It was found that much less $Ti(O^iPr)_4$ could be used than was the case in previously reported works.

2.4. ^{i}BuMgBr. Under these optimal reaction conditions, we checked the generality of the reaction of various aldehydes with ^{i}BuMgBr. The results are shown in Table 4. All cases realized ≥90% enantioselectivities, and aromatic aldehydes

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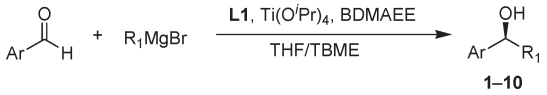
TABLE 3. Investigation on Generality of Grignard Reagents

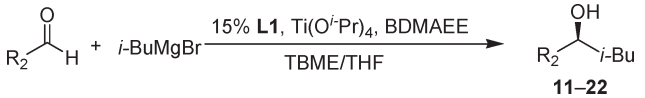


1–10

entry	R_1	Ar	amt of **L1** (mol %)	yield (%)	ee (%)[a]
1	Me	Ph	10	33	35
2[b]	Me	Ph	40	45	51
3[b]	Me	1-Naphth	40	78	72
4	Et	Ph	10	39	70
5[b]	Et	Ph	40	46	81
6[c]	Et	1-Naphth	30	54	93
7[d]	^{n}Bu	Ph	20	68	92
8	Ph	2-Naphth	10	44	34
9[b]	Ph	2-Naphth	40	58	54
10[b]	Ph	1-Naphth	40	75	58
11	Bn	Ph	10	46	48
12[b,e]	vinyl	1-Naphth	40	26	33
13	^{i}Bu	Ph	10	65	94
14[f]	^{i}Bu	Ph	15	76	98
15[d]	^{i}Bu	Ph	20	76	97

[a]Measured by chiral HPLC. The configuration was assigned by comparison of the alcohol's optical rotation with reported data.[26] [b]Conditions: 2.5 equiv of BDMAEE, 2.5 equiv of Grignard reagent, and 1.14 equiv of $Ti(O^iPr)_4$. [c]Conditions: 2.3 equiv of BDMAEE, 2.3 equiv of Grignard reagent, and 1.04 equiv of $Ti(O^iPr)_4$. [d]Conditions: 2.1 equiv of BDMAEE, 2.1 equiv of Grignard reagent, and 0.94 equiv of $Ti(O^iPr)_4$. [e]**L3** was used. [f]Conditions: 2.0 equiv of BDMAEE, 2.0 equiv of Grignard reagent, and 0.89 equiv of $Ti(O^iPr)_4$.

TABLE 4. Catalytic Asymmetric Addition of ^{i}BuMgBr to Aldehydes[a]



11–22

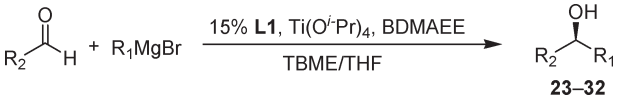
entry	R_2	yield (%)	ee (%)[b]
1	2-MeO-C_6H_4	86	97
2	3-MeO-C_6H_4	63	97
3	4-MeO-C_6H_4	75	97
4	1-Naphth	93	98
5	2-Naphth	86	97
6	4-tolyl	81	97
7	3−Cl-C_6H_4	91	>99
8	4−Cl-C_6H_4	82	98
9	4−F-C_6H_4	69	>99
10	thiophene-2	35	94
11	PhCH=CH	70	90
12	cyclohexyl	27	98[c]

[a]Conditions: 2.0 equiv of BDMAEE, 2.0 equiv of Grignard reagent, and 0.89 equiv of $Ti(O^iPr)_4$. [b]Measured by chiral HPLC. [c]Conditions: 30% **L1**, 2.3 equiv of BDMAEE, 2.3 equiv of Grignard reagent and 1.04 equiv of $Ti(O^iPr)_4$.

resulted in ≥97% enantioselectivity (entries 1−9). Two cases reached more than 99% enantioselecivity in this transformation (entries 7 and 9). The heteroaromatic aldehyde (entry 10) and α,β-unsaturated aldehyde (entry 11) also afforded 94% and 90% enantioselectivity, respectively. The alkyl aldehyde cyclohexanecarboxaldehyde gave high enantioselctivity (98%) but also a low yield (entry 12). The low yield might be ascribed to the low reactivity of the alkyl aldehyde and the strongly basic mixture, which reduced the aldehyde into the checked primary alcohol.

2.5. Other Alkyl Grignard Reagents with High Enantioselectivity. The other alkyl Grignard reagents were investigated with this procedure, and the results are included in Table 5. With *n*-butyl, *n*-pentyl, and *n*-heptyl Grignard reagents, 87%−92% enantioselectivity was observed, even with an alkyl aldehyde (Table 5, entries 1−8). It was found that the enantioselectivity slowly dropped with the gradual elongation of the alkyl chain of the Grignard reagent (entry 1 vs 4 and entry 2 vs 6 vs 7). Furthermore, a functional Grignard reagent with a remote carbon−carbon double bond (C=C) was also observed, and it achieved ≥90% enantioselectivity (entries 9−11).

TABLE 5. Catalytic Asymmetric Addition of Alkyl RMgBr to Aldehydes[a]



23–32

entry	R_2	R_1	yield (%)	ee (%)[b]
1	Ph	^{n}Bu	68	92[c]
2	1-Naphth	^{n}Bu	60	91[d]
3	phenylethyl	^{n}Bu	23	88[e]
4	Ph	*n*-pentyl	53	90
5	2-Naphth	*n*-pentyl	77	90[d]
6	1-Naphth	*n*-pentyl	79	90
7	1-Naphth	*n*-heptyl	52	87[d]
8	2-Naphth	*n*-heptyl	46	88[d]
9	4-MeO-C_6H_4	Me_2C=$CHCH_2CH_2$	50	92[d]
10	1-Naphth	Me_2C=$CHCH_2CH_2$	62	91
11	2-Naphth	Me_2C=$CHCH_2CH_2$	36	90

[a]Conditions: 2.0 equiv of BDMAEE, 2.0 equiv of Grignard reagent, and 0.89 equiv of $Ti(O^iPr)_4$. [b]Measured by chiral HPLC. [c]Conditions: 20% of **L1**, 2.1 equiv of BDMAEE, 2.1 equiv of Grignard reagent, and 0.94 equiv of $Ti(O^iPr)_4$. [d]Conditions: 20% of **L1**, 2.3 equiv of BDMAEE, 2.3 equiv of Grignard reagent, and 1.04 equiv of $Ti(O^iPr)_4$. [e]Conditions: 30% of **L1**, 2.1 equiv of BDMAEE, 2.1 equiv of Grignard reagent, and 0.94 equiv of $Ti(O^iPr)_4$.

2.6. Optimization of Conditions of $PhCH_2CH_2MgBr$ Reaction with Aldehydes. As outlined in the Introduction, the enantioenriched secondary arylpropanols are important intermediates for the synthesis of medications. Their published preparative procedure includes three synthetic steps and a further recrystallization of the final synthetic alcohols (eq 6, Scheme 3). Our protocol of catalytic asymmetric alkylation of aldehydes with Grignard reagents gave us the opportunity to prepare these important alcohols in one straightforward step (eq 7). Direct use of the previously optimized reaction conditions did not gave satisfactory enantioselectivity. Therefore, we optimized the reaction again and obtained the optimal reaction conditions. The amount of each reagent used with respect to the aldehyde was 20 mol % (*S*)-BINOL, 1.35 equiv of $Ti(O^iPr)_4$, 2.4 equiv of $PhCH_2CH_2MgBr$, and 2.4 equiv of BDMAEE. The optimized solvent system was still THF/TBME. The aldehyde was introduced at −15 °C, and then the reaction was allowed to continue at room temperature. The optimized experimental results are shown in the Tables S1 and S2 in the Supporting Information.

2.7. $Ar(CH_2)_2MgBr$. Under the optimized reaction conditions, the catalytic asymmetric reaction of $PhCH_2CH_2MgBr$ and an array of aromatic and aliphatic aldehydes were first investigated (Table 6, entries 1−14). Benzaldehyde achieved as high as 96% enantioselectivity (entry 1). Two naphthaldehydes resulted in yields higher than for other aryl aldehydes (entries 1−10), and 1-naphthaldehyde and 2-naphthaldehyde achieved 93% and 90% enantioselectivity, respectively (entries 2). The *meta*-substituted substrates generated higher enantiomeric excess than para- and ortho-substituted

SCHEME 3. Different Synthetic Methods of I-1 or I-2

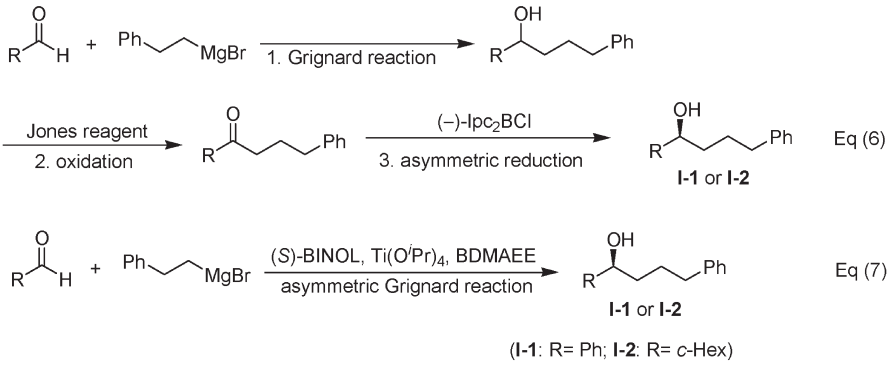
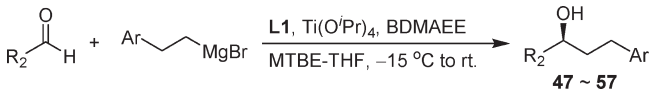


TABLE 6. Catalytic Asymmetric Arylethylation of Aldehydes[a]



entry	Ar	R_2	yield (%)	ee (%)[b]
1	Ph	Ph	62	96 (>99)
2	Ph	1-napth	86	93
3	Ph	2-napth	88	90
4	Ph	*p*-$MeOC_6H_4$	63	88
5	Ph	*m*-$MeOC_6H_4$	65	89
6	Ph	*o*-$MeOC_6H_4$	68	77
7	Ph	*p*-MeC_6H_4	63	90
8	Ph	*o*-ClC_6H_4	60	82
9	Ph	*m*-$F_3CC_6H_4$	80	92
10	Ph	*p*-$F_3CC_6H_4$	75	88
11	Ph	2-thienyl	52	88
12	Ph	PhCH=CH	70	79
13	Ph	*c*-hex	43	96 (>99)
14	Ph	*n*-Pr	46	90
15	*o*-$MeOC_6H_4$	1-napth	77	85
16	*o*-$MeOC_6H_4$	*c*-hex	43	84
17	*o*-$MeOC_6H_4$	Ph	53	82
18	1-napth	1-napth	80	83
19	1-napth	*c*-hex	40	91
20	1-napth	Ph	56	81
21	2-thienyl	1-napth	78	97
22	2-thienyl	*c*-hex	42	93
23	2-thienyl	Ph	51	93
24	2-thienyl	2-napth	81	93
25	2-thienyl	2-thienyl	53	90

[a]Conditions: BINOL (20 mol %), $Ti(O^iPr)_4$ (1.35 equiv), BDMAEE (2.4 equiv), and Grignard reagents (2.4 equiv) in TBME-THF, room temperature. [b]Determined by chiral HPLC. Data in parentheses are the ee values after a simple recrystallization with hexane. The configuration was assigned by comparison of the sign of the optical rotation with the reported data.[28]

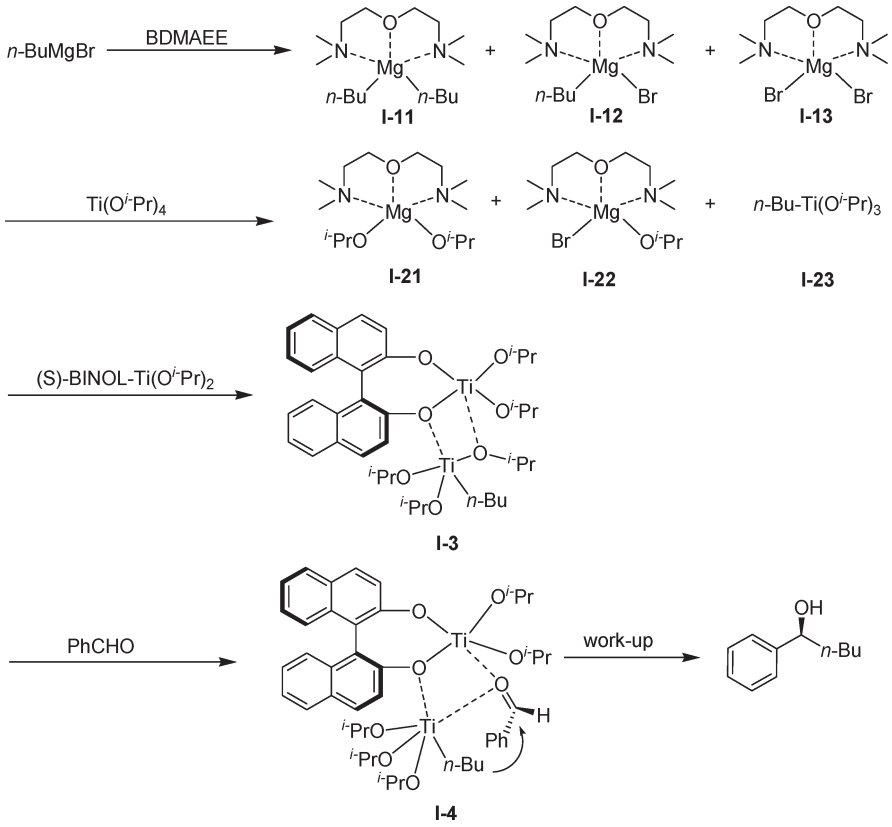
benzaldehydes (entries 4−6 and 9−10). The heteroatom-containing arylaldehyde also resulted in a high enantioselectivity (entry 11), while the α,β-unsaturated aldehyde achieved a good enantioselectivity (entry 12). In comparison with the aryl aldehydes, however, the two alkyl aldehydes cyclohexanecarbaldehyde and butyraldehyde both resulted in high enantioselectivity (entries 13 and 14): cyclohexanecarbaldehyde afforded a high enantioselectivity of 96%. It is noteworthy that the interesting chiral drug intermediates **I-1** and **I-2** (Figure 1) could be readily enriched into >99% ee by a simple recrystallization from hexane (entries 1 and 13).

Additionally, other three $ArCH_2CH_2MgBr$ were also observed to extend the versatility of the protocol (Table 6, entries 15−25). With regard to 2-MeO-C_6H_4-CH_2CH_2MgBr, aryl and alkyl aldehydes nearly resulted in similarly high enantioselectivity (entries 15−17). 1-Naph$MgCH_2CH_2MgBr$ afforded higher enantioselectivity with cyclohexanecarboxaldehyde than with the aromatic aldehyde (entries 18−20). In comparison to other arylethyl Grignard reagents, interestingly, the heteroatom-containing Grignard reagent (2-thienylethyl)magnesium bromide obviously afforded the highest enantioselectivity among these Grignard reagents (entries 21−25). All cases with it gave >90% enatioselectivities except for the heteroatom-containing aldehyde, which also resulted in a 90% high enantioselectivity, and 1-naphthaldehyde yielded the highest enantioselectivity, 97%, among the all investigated cases with $ArCH_2CH_2MgBr$ (entry 21).

2.8. Mechanism. We observed that the ^{n}BuMgBr-BDMAEE complex rapidly reacted with benzaldehyde in the absence of $Ti(O^iPr)_4$. It was also indeed the case that ^{n}BuMgBr-$Ti(O^iPr)_4$ rapidly reacted with benzaldehyde in the absence of BDMAEE. Interestingly, however, the ^{n}BuMgBr-BDMAEE-$Ti(O^iPr)_4$ combination did not react with benzaldehyde within 4 h in the absence of BINOL. After $MgBr_2$ was additionally added, the addition rapidly proceeded. This result revealed that the two reagents BDMAEE and $Ti(O^iPr)_4$ cooperated to decrease the reactivity of ^{n}BuMgBr. On the basis of the Schlenk equilibrium, transmetalation of the Grignard reagents and $Ti(O^iPr)_4$, and the investigations of Bolm and Walsh, the mechanism is thought to occur as shown in Scheme 4. BDMAEE coordinates to the Grignard reagent to generate the three intermediates **I-11**, **I-12**, and **I-13**. Importantly, the salt $MgBr_2$ is well chelated by BDMAEE and partly loses its catalytic activity. With the introduction of $Ti(O^iPr)_4$, the chelated **I-11** and **I-12** are converted into the two chelated salts **I-21** and **I-22**, and one additional reactive intermediate, ^{n}Bu-$Ti(O^iPr)_3$ (**I-23**). Naturally, **I-22** is a less reactive Lewis acid than **I-13**, and **I-23** is much less reactive than the Grignard reagent itself (**I-11** or **I-12**). This might be the reason the three-component species ^{n}BuMgBr-BDMAEE-$Ti(O^iPr)_4$ does not react with benzaldehyde in the absence of the chiral catalyst. Then, **I-23** can coordinate with the chiral catalyst (*S*)-BINOL-$Ti(O^iPr)_2$ and successively with benzaldehyde to

(26) (a) Homman, M. J.; Vail, R. B.; Previte, E.; Tamarez, M.; Morgan, B.; Dodds, D. R.; Zaks, A. *Tetrahedron* **2004**, *60*, 789. (b) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364. (c) Xie, J.-H.; Wang, L.-X.; Fu, Y.; Zhu, S.-F.; Fan, B.-M.; Duan, H.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2003**, *125*, 4404. (d) Huang, W. S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222.

SCHEME 4. Proposed Reaction Mechanism



form the bimetallic nuclear complexes **I-3** and **I-4**, separately.[9d,27] Owing to steric effects, the phenyl group of benzaldehyde should be positioned far away from the three bulky isopropoxy groups of ^{n}Bu-Ti(O^{i}Pr)$_3$ coordinated to the chiral catalyst (*S*)-BINOL-Ti(O^{i}Pr)$_2$. This location will favor the *Si*-face addition of the ^{n}Bu group to benzaldehyde and predominantly result in an *S* alcohol.

3. Conclusions and Outlook

In conclusion, we have successfully developed a protocol of highly catalytic enantioselective alkylation of aldehydes with Grignard reagents. In this protocol, the high reactivity of Grignard reagents is effectively deactivated by the additive BDMAEE. BDMAEE chelates $MgBr_2$ from a Schlenk equilibrium of RMgBr and Mg(O^{i}Pr)Br from transmetalation between RMgBr and Ti(O^{i}Pr)$_4$. These two salts can rapidly promote the racemic background reaction and consequently result in low enantioselectivity. The chelation of the Mg salts effectively inhibits this background reaction. Simultaneously the transmetalation of the Grignard reagent RMgBr with Ti(O^{i}Pr)$_4$ generates in situ the intermediate R-Ti(O^{i}Pr)$_3$. As a result, the chiral catalyst (*S*)-BINOL-Ti(O^{i}Pr)$_2$ catalyzes the addition of R-Ti(O^{i}Pr)$_3$ to aldehydes with high enantioselectivity. In comparison to previously reported procedures, reactive Mg salts were not removed from the reaction system, less Ti(O^{i}Pr)$_4$ than the Grignard reagent was used, and the reaction was performed under mild reaction conditions in this work. This protocol is particularly effective for alkyl Grignard reagents. A variety of alkyl Grignard reagents were investigated, and ^{i}BuMgBr results in the highest enantioselectivity, up to 99%, among the investigated Grignard reagents. In addition, this protocol enables the synthesis of a variety of biologically interesting enantioenriched secondary arylpropanols in one step. Several arylethyl Grignard reagents were successfully used to add to aldehydes to prepare these valuable secondary alcohols, and aromatic and aliphatic aldehydes both afforded high enantioselectivities. The heteroatom-containing Grignard reagent (2-thienylethyl)magnesium bromide showed the highest enantioselectivity among the four observed arylethyl Grignard reagents. This protocol gives us a promising clue to apply a variety of more useful Grignard reagents in this catalytic asymmetric reaction to synthesize an array of interesting enantioselectively pure secondary alcohols, and such works are underway in our laboratory at present.

4. Experimental Section

For details on the synthesis and characterization of compounds **1**−**32**, see the reported results.[13a]

4.1. General Procedure for Catalytic Asymmetric Addition of (Arylethyl)magnesium Bromide to Aldehydes. In flask A, (191.8 mg, 0.675 mmol) of Ti(O^{i}Pr)$_4$ was added dropwise into a solution of 28.6 mg (0.1 mmol) of (*S*)-BINOL in 1.0 mL of dry TBME under an argon atmosphere at ambient temperature, and the mixture was stirred for a further 0.5 h. In flask B, 1.14 mL (1.2 mmol, 1.05 mmol/mL in THF) of phenethylmagnesium bromide was slowly added to 192.3 mg (1.2 mmol) of BDMAEE in 2.0 mL of dry MTBE in an ice−water bath under argon within

(27) (a) Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 699. (b) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739.

(28) (a) Belzecki, C.; Panfil, I. *J. Org. Chem.* **1979**, *44*, 1212. (b) Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772.

5 min and then the mixture was stirred for 30 min. Mixture A was introduced into the mixture B in an ice−water bath. After the solution reached ambient temperature, the combined yellow mixture was stirred for 1.0 h. The solution was cooled with an ice−salt bath, and 0.5 mmol of aldehyde was added dropwise. The mixture was warmed to ambient temperature and stirred until the aldehyde was consumed (by TLC). The reaction mixture was quenched with 5% cold aqueous HCl and extracted three times with 50 mL of ether. The combined organic layers were dried with anhydrous Na_2SO_4 and evaporated in vacuo, and the residue was purified by flash column chromatography to give the product. The ee was determined by chiral HPLC. The absolute configuration of the alcohol was assigned by comparison of the optical rotation to the reported value.

4.2. (*S*)-1,3-Diphenylpropan-1-ol (33):[14a,28] flash column, 8/1 petroleum ether/ethyl acetate; white solid, yield 62% (65.7 mg); enantioselectivity enriched to >99% with recrystallization from hexane; mp 45 °C; $[\alpha]_D^{20} = -17°$ (c = 3, CH_3OH, >99% ee) (lit.[29] $[\alpha]_D^{20} = -14.5$ (c = 1, CH_3OH, >90% ee)); ^{1}H NMR (400 MHz) δ 1.76 (s, 1H), 2.02−2.15 (m, 2H), 2.67−2.76 (m, 2H), 4.68−4.71 (dd, J = 5.4 Hz, J = 8.0 Hz, 1H), 7.16−7.36 (m, 10H); ^{13}C NMR (100 MHz) δ 17.8, 29.6, 56.4, 98.6, 124.8, 125.5, 126.1, 127.1, 129.7, 130.9, 131.6, 133.0, 153.2; 96% ee, OD-H column (95/5 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 16.9 min, minor enantiomer t_R = 20.1 min.

4.3. (*S*)-1-(Naphthalen-1-yl)-3-phenylpropan-1-ol (34):[30] flash column, 8/1 petroleum ether/ethyl acetate; pale yellow oil, yield 86% (112.7 mg); $[\alpha]_D^{20} = -78°$ (c = 1.5, CH_3OH); ^{1}H NMR (400 MHz) δ 2.20 (s, 1H), 2.22−2.27 (m, 2H), 2.79−2.92 (m, 2H), 5.45−5.48 (dd, J = 4.6 Hz, J = 7.8 Hz, 1H), 7.18−7.31 (m, 5H), 7.43−7.49 (m, 3H), 7.66−7.68 (d, J = 6.8 Hz, 1H), 7.76−7.78 (d, J = 8.4 Hz, 1H), 7.85−7.92 (m, 2H); 93% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 12.4 min, minor enantiomer t_R = 21.3 min.

4.4. (*S*)-1-(Naphthalen-2-yl)-3-phenylpropan-1-ol (35):[30b,31] flash column, 8/1 petroleum ether/ethyl acetate; white solid, yield 88% (115.2 mg); mp 65 °C; $[\alpha]_D^{20} = -10°$ (c = 2, CH_3CH_2OH); ^{1}H NMR (400 MHz) δ 2.00 (s, 1H, OH), 2.08−2.24 (m, 2H), 2.65−2.80 (m, 2H), 4.83−4.86 (dd, J = 5.8 Hz, J = 7.4 Hz, 1H), 7.16−7.30 (m, 5H), 7.44−7.49 (m, 3H), 7.77−7.84 (m, 4H); 90% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 15.6 min, minor enantiomer t_R = 19.6 min.

4.5. (*S*)-1-(4-Methoxyphenyl)-3-phenylpropan-1-ol (36):[31b,32] flash column, 8/1 petroleum ether/ethyl acetate; white needles, yield 63% (76.2 mg); mp 70 °C; $[\alpha]_D^{20} = -26°$ (c = 1, CH_3OH); ^{1}H NMR (400 MHz) δ 1.89 (s, 1H), 1.94−2.03 (m, 1H), 2.07−2.15 (m, 1H), 2.58−2.74 (m, 2H), 3.80 (s, 3H), 4.60−4.63 (dd, J = 4.6 Hz, J = 7.8 Hz, 1H), 6.86−6.88 (d, J = 4.6 Hz, 2H), 7.17−7.19 (m, 3H), 7.24−7.28 (m, 4H); 88% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 13.5 min, minor enantiomer t_R = 15.1 min.

4.6. (*S*)-1-(3-Methoxyphenyl)-3-phenylpropan-1-ol (37):[33] flash column, 8/1 petroleum ether/ethyl acetate; colorless oil, yield 65% (78.5 mg); $[\alpha]_D^{20} = -9°$ (c = 0.4, CH_3OH); ^{1}H NMR (400 MHz) δ 1.80−1.86 (m, 1H), 1.95−2.15 (m, 2H), 2.61−2.77 (m, 2H), 3.80 (s, 3H), 4.63−4.67 (dd, J = 7.0 Hz, J = 10.2 Hz, 1H), 6.79−6.83 (m, 1H), 6.90−6.92 (t, 1H), 7.15−7.31 (m, 7H); 89% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 14.9 min, minor enantiomer t_R = 18.8 min.

4.7. (*S*)-1-(2-Methoxyphenyl)-3-phenylpropan-1-ol (38):[34] flash column, 8/1 petroleum ether/ethyl acetate; colorless oil, yield 68% (82.2 mg); $[\alpha]_D^{20} = -7°$ (c = 0.84, CH_3OH); ^{1}H NMR (400 MHz) δ 2.07−2.16 (m, 2H), 2.64−2.72 (m, 1H), 2.79−2.87 (m, 1H), 3.84 (s, 3H), 4.86−4.89 (dd, J = 5.2 Hz, J = 8.0 Hz, 1H), 6.87−6.89 (d, J = 8.0 Hz, 1H), 6.93−6.97 (t, J = 7.4 Hz, 3H), 7.15−7.31 (m, 7H); 77% ee, OD-H column (90/10 hexane/2-propanol), 1 mL/min, major enantiomer t_R = 10.1 min, minor enantiomer t_R = 14.0 min.

4.8. (*S*)-3-Phenyl-1-*p*-tolylpropan-1-ol (39):[31b,35] flash column, 8/1 petroleum ether/ethyl acetate; white solid, yield 63% (71.0 mg); mp 42 °C; $[\alpha]_D^{20} = -16°$ (c = 2.2, CH_3OH); ^{1}H NMR (400 MHz) δ 1.91 (s, 1H, OH), 1.96−2.13 (m, 2H), 2.33 (s, 3H), 2.63−2.73 (m, 2H), 4.60−4.63 (dd, J = 5.6 Hz, J = 7.6 Hz, 1H), 7.13−7.28 (m, 9H); 90% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 10.6 min, minor enantiomer t_R = 13.4 min.

4.9. (*S*)-1-(2-Chlorophenyl)-3-phenylpropan-1-ol (40): flash column, 8/1 petroleum ether/ethyl acetate; colorless oil, yield 60% (73.7 mg); $[\alpha]_D^{20} = -7°$ (c = 0.5, CH_3OH); ^{1}H NMR (400 MHz) δ 1.94−2.12 (m, 3H), 2.62−2.77 (m, 2H), 4.62−4.66 (dd, J = 5.4 Hz, J = 7.8 Hz, 1H), 6.78−6.79 (d, J = 3.2 Hz, 1H), 6.89−6.91 (m, 1H), 7.01−7.11 (d, J = 4.8 Hz, 3H), 7.17−7.33 (m, 9H); ^{13}C NMR (100 MHz) δ 31.8, 40.3, 73.1, 123.9, 125.9, 126.0, 127.6, 128.3, 128.4, 129.7, 134.3, 141.3, 146.6; HRMS m/z calcd for $(C_{15}H_{15}ClO + NH_4)^+$ 264.1150, found 264.1155; 82% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 10.3 min, minor enantiomer t_R = 13.3 min.

4.10. (*S*)-3-Phenyl-1-(3-(trifluoromethyl)phenyl)propan-1-ol (41):[36] flash column, 8/1 petroleum ether/ethyl acetate; colorless oil, yield 80% (111.8 mg); $[\alpha]_D^{20} = -10°$ (c = 0.8, CH_3OH); ^{1}H NMR (400 MHz) δ 1.99−2.14 (m, 3H), 2.65−2.76 (m, 2H), 4.70−4.75 (dd, J = 6.6 Hz, J = 10.6 Hz, 1H), 7.16−7.31 (m, 5H), 7.41−7.60 (m, 4H); 92% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 9.2 min, minor enantiomer t_R = 12.4 min.

4.11. (*S*)-3-Phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol (42):[37] flash column, 8/1 petroleum ether/ethyl acetate; colorless oil, yield 75% (105.0 mg); $[\alpha]_D^{20} = -18°$ (c = 0.5, CH_3OH); ^{1}H NMR (400 MHz) δ 1.98−2.12 (m, 3H), 2.67−2.74 (m, 2H), 4.71−4.74 (dd, J = 5.0 Hz, J = 7.8 Hz, 1H), 6.78−6.79 (d, J = 3.2 Hz, 1H), 7.17−7.30 (m, 5H), 7.43−7.45 (d, J = 8.0 Hz, 2H), 7.58−7.60 (d, J = 8.0 Hz, 2H) ppm; ^{13}C NMR (100 MHz) δ 31.8, 40.5, 73.1, 125.4, 126.0, 126.1, 128.4, 128.5, 141.2, 148.5; 88% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 9.9 min, minor enantiomer t_R = 11.6 min.

4.12. (*S*)-3-Phenyl-1-(thiophen-2-yl)propan-1-ol (43):[31a,38] flash column, 8/1 petroleum ether/ethyl acetate; pale yellow oil, yield 52% (56.5 mg); $[\alpha]_D^{20} = -9°$ (c = 2, CH_3CH_2OH); ^{1}H NMR (400 MHz) δ 2.02 (s, 1H, OH), 2.09−2.26 (m, 2H), 2.67−2.81 (m, 2H), 4.90−4.94 (t, J = 6.8 Hz, 1H), 6.95−6.97 (m, 2H), 7.17−7.32 (m, 6H); 88% ee, OD-H column (90/10

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hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 10.8 min, minor enantiomer t_R = 14.2 min.

4.13. (*S*,*E*)-1,5-Diphenylpent-1-en-3-ol (44):[39] flash column, 8/1 petroleum ether/ethyl acetate; colorless oil, yield 70% (83.1 mg); $[\alpha]_D^{20}$ +20° (*c* = 0.6, CH_3CH_2OH); ^{1}H NMR (400 MHz) δ 1.58−1.64 (s, 1H, OH), 1.91−2.01 (m, 2H), 2.71−2.80 (m, 2H), 4.27−4.32 (t, *J* = 6.4 Hz, *J* = 13.2 Hz, 1H), 6.21−6.27 (dd, *J* = 6.4 Hz, *J* = 15.6 Hz, 1H), 6.56−6.59 (d, 1H), 7.17−7.38 (m, 10H); 79% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, minor enantiomer t_R = 17.0 min, major enantiomer t_R = 19.8 min.

4.14. (*S*)-1-Cyclohexyl-3-phenylpropan-1-ol (45):[14,22b] flash column, 8/1 petroleum ether/ethyl acetate; colorless needles, yield 43% (46.8 mg); mp 61−63 °C; $[\alpha]_D^{20}$ = −16° (*c* = 0.6, CH_3CH_2OH) (lit.[28b,40] $[\alpha]_D^{20}$ = +28.7° (*c* = 0.91, $CHCl_3$) for *R* enantiomer); ^{1}H NMR (400 MHz) δ 0.99−1.18 (m, 3H), 1.20−1.42 (m, 4H), 1.64−1.78 (m, 7H), 2.61−2.68 (m, 1H), 2.80−2.87 (m, 1H), 3.36−3.41 (m, 1H), 7.16−7.30 (m, 5H); ^{13}C NMR (100 MHz) δ 26.1, 26.3, 26.5, 27.7, 29.1, 29.6, 32.3, 35.9, 43.8, 75.6, 125.7, 128.3, 128.4, 142.3; 96% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 5.4 min, minor enantiomer t_R = 7.9 min.

4.15. (*R*)-1-Phenylhexan-3-ol (46):[41] flash column, 8/1 petroleum ether/ethyl acetate; colorless oil, yield 46% (40.8 mg); $[\alpha]_D^{20}$ = −15° (*c* = 1.0, CH_3CH_2OH) (lit.[41a] $[\alpha]_D^{24}$ = +12.8° (*c* = 1.0, EtOH) for *S* enantiomer); ^{1}H NMR (400 MHz) δ 0.90−0.95 (t, *J* = 8.8 Hz, 3H), 1.25−1.48 (m, 5H), 1.61−1.83 (m, 2H), 2.63−2.83 (m, 2H), 3.61−3.67 (m, 1H), 7.16−7.30 (m, 3H); 90% ee, OD-H column (95/5 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 8.4 min, minor enantiomer t_R = 11.3 min.

4.16. (*S*)-3-(2-Methoxyphenyl)-1-(naphthalen-1-yl)propan-1-ol (47): flash column, 8/1 petroleum ether/ethyl acetate; colorless oil, yield 77% (112.2 mg); $[\alpha]_D^{20}$ = −67° (*c* = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz) δ 2.09−2.26 (m, 2H), 2.56 (br s, 1H, OH), 2.82−2.99 (m, 2H), 3.82 (s, 3H), 5.36−5.39 (dd, *J* = 3.2 Hz, *J* = 9.2 Hz, 1H), 6.88−6.95 (m, 2H), 7.19−7.24 (m, 2H), 7.41−7.48 (m, 3H), 7.67−7.85 (m, 4H); ^{13}C NMR (100 MHz) δ 26.9, 38.6, 55.3, 70.1, 110.3, 120.7, 122.5, 123.1, 125.3, 125.4, 125.7, 127.3, 127.7, 128.8, 129.9, 130.2, 133.8, 140.3, 157.4; HRMS *m*/*z* calcd for $(C_{20}H_{20}O_2 + NH_4)^+$ 310.1802, found 310.1803; 85% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 15.0 min, minor enantiomer t_R = 35.7 min.

4.17. (*S*)-1-Cyclohexyl-3-(2-methoxyphenyl)propan-1-ol (48): flash column, 8/1 petroleum ether/ethyl acetate; white solid, yield 43%; mp 51 °C; $[\alpha]_D^{20}$ = −20° (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz) δ 0.96−1.36 (m, 6H), 1.62−1.79 (m, 7H), 1.95 (s, 1H, OH), 2.68−2.75 (m, 2H), 3.27−3.32 (m, *J* = 4.2 Hz, *J* = 8.8 Hz, 1H), 3.82 (s, 3H), 6.84−6.91 (m, 2H), 7.14−7.25 (m, 2H); ^{13}C NMR (100 MHz) δ 24.3, 26.3, 26.5, 26.7, 27.9, 29.2, 34.5, 43.5, 55.3, 75.1, 110.3, 120.6, 127, 130.0, 130.5, 157.3; HRMS *m*/*z* calcd for $(C_{16}H_{24}O_2 + NH_4)^+$ 266.2115, found 266.2120; 84% ee, OD-H column (80/20 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 5.3 min, minor enantiomer t_R = 20.0 min.

4.18. (*S*)-3-(2-Methoxyphenyl)-1-phenylpropan-1-ol (49):[42] flash column, 8/1 petroleum ether/ethyl acetate; colorless oil, yield 53% (53.0 mg); $[\alpha]_D^{20}$ = −15 ° (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.95−2.08 (m, 2H), 2.72−2.77 (m, 2H), 3.76 (s, 3H), 4.59−4.62 (dd, *J* = 4.6 Hz, *J* = 8.6 Hz, 1H), 6.83−6.91 (m, 2H), 7.13−7.20 (m, 2H), 7.24−7.27 (m, 1H), 7.30−7.35 (m, 4H); 82% ee, OD-H column (80/20 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 8.4 min, minor enantiomer t_R = 23.1 min.

4.19. (*S*)-1,3-Bis(naphthalen-1-yl)propan-1-ol (50):[43] flash column, 6/1 petroleum ether/ethyl acetate; colorless needles, yield 80% (124.7 mg); mp 101 °C; $[\alpha]_D^{20}$ = −141° (*c* = 2, $CHCl_3$); ^{1}H NMR (400 MHz) δ 2.03 (s, 1H, OH), 2.32−2.41 (m, 2H), 3.22−3.41 (m, 2H), 5.52−5.55 (dd, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H), 7.34−7.48 (m, 7H), 7.68−7.85 (m, 6H), 7.98−8.00 (m, 1H); ^{13}C NMR (100 MHz) δ 29.5, 39.0, 70.6, 122.7, 122.9, 123.8, 125.4, 125.7, 125.9, 126.1, 126.7, 128.0, 128.7, 128.8, 130.2, 131.9, 133.8, 137.9, 140.2; 83% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 18.7 min, minor enantiomer t_R = 31.8 min.

4.20. (*S*)-1-Cyclohexyl-3-(naphthalen-1-yl)propan-1-ol (51): flash column, 6/1 petroleum ether/ethyl acetate; colorless oil, yield 40% (53.6 mg); $[\alpha]_D^{20}$ = −21° (*c* = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz) δ 0.96−1.27 (m, 5H), 1.33−1.41 (m, 1H), 1.51 (s, 1H, OH), 1.64−1.95 (m, 7H), 3.04−3.11 (m, 1H), 3.30−3.37 (m, 1H), 3.46−3.50 (dd, *J* = 5.4 Hz, *J* = 9.0 Hz, 1H), 7.34−7.53 (m, 4H), 7.70−7.72 (d, *J* = 7.6 Hz, 1H), 7.84−7.86 (d, *J* = 7.6 Hz, 1H), 8.06−8.08 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 26.1, 26.2, 26.5, 27.8, 29.2, 29.5, 35.3, 43.8, 76.0, 123.8, 125.3, 125.4, 125.5, 125.7, 125.8, 126.5, 128.7, 131.8, 133.9, 138.6; HRMS *m*/*z* calcd for $(C_{19}H_{24}O + NH_4)^+$ 286.2165, found 286.2161; 91% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 11.1 min, minor enantiomer t_R = 12.5 min.

4.21. (*S*)-3-(Naphthalen-1-yl)-1-phenylpropan-1-ol (52):[31,35b] flash column, 6/1 petroleum ether/ethyl acetate; colorless oil, yield 56% (73.3 mg); $[\alpha]_D^{20}$ = −26° (*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz) δ 1.94 (s, 1H, OH), 2.123−2.28 (m, 2H), 3.06−3.28 (m, 2H), 4.78−4.81 (dd, *J* = 5.0 Hz, *J* = 7.4 Hz, 1H), 7.24−7.50 (m, 9H), 7.69−7.71 (d, *J* = 8.0 Hz, 1H), 7.83−7.85 (m, 1H), 7.96−7.98 (t, 1H); 81% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 16.4 min, minor enantiomer t_R = 19.0 min.

4.22. (*S*)-1-(Naphthalen-1-yl)-3-(thiophen-2-yl)propan-1-ol (53): flash column, 6/1 petroleum ether/ethyl acetate; pale yellow oil, yield 78% (104.2 mg); $[\alpha]_D^{20}$ = −105° (*c* = 0.35, $CHCl_3$); ^{1}H NMR (400 MHz) δ 2.04 (s, 1H, OH), 2.19−2.33 (m, 2H), 3.04−3.08 (t, *J* = 7.8 Hz 2H), 5.46−5.50 (dd, *J* = 4.8 Hz, *J* = 7.8 Hz, 1H), 6.83−6.94 (m, 2H), 7.12−7.14 (m, 1H), 7.44−7.49 (m, 3H), 7.64−7.97 (m, 4H); ^{13}C NMR (100 MHz) δ 26.5, 39.8, 70.0, 122.8, 123.0, 123.1, 124.5, 125.4, 125.5, 126.0, 126.7, 128.0, 128.8, 130.2, 133.8, 140.0, 144.5; HRMS *m*/*z* calcd for $(C_{17}H_{16}OS + NH_4)^+$ 286.1260, found 286.1259; 97% ee, OD-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 13.7 min, minor enantiomer t_R = 26.8 min.

4.23. (S)-1-Cyclohexyl-3-(thiophen-2-yl)propan-1-ol (54): flash column, 6/1 petroleum ether/ethyl acetate; colorless needles, yield 42% (47.0 mg); mp 38 °C; $[\alpha]_D^{20}$ = −7° (*c* = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz) δ 0.96−1.36 (m, 6H), 1.53 (s, 1H, OH), 1.64−1.90 (m, 7H), 2.85−3.05 (m, 2H), 3.38−3.41 (m, 1H), 6.80−6.81 (d, *J* = 3.2 Hz, 1H), 6.90−6.92 (t, 1H), 7.10−7.11 (d, *J* = 4.8 Hz, 1H); ^{13}C NMR (100 MHz) δ 26.1, 26.2, 26.4, 27.8, 29.1, 36.0, 43.7, 75.2, 122.9, 124.1, 126.6, 145.2; HRMS *m*/ *z* calcd for $(C_{13}H_{20}OS + H)^+$ 225.1308, found 225.1311; 93% ee, OD-H column (95/5 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 7.5 min, minor enantiomer t_R = 8.0 min.

4.24. (*S*)-1-Phenyl-3-(thiophen-2-yl)propan-1-ol (55):[42] flash column, 6/1 petroleum ether/ethyl acetate; colorless oil, yield 51% (55.5 mg); $[\alpha]_D^{20}$ = −21° (*c* = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz) δ 2.02−2.18 (m, 3H), 2.87−2.93 (m, 2H), 4.67−4.70 (dd,

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J = 5.4 Hz, J = 7.8 Hz, 1H), 6.78−6.79 (d, J = 3.2 Hz, 1H), 6.89−6.91 (m, 1H), 7.01−7.11 (d, J = 4.8 Hz, 3H), 7.25−7.36 (m, 5H); ^{13}C NMR (100 MHz) δ 26.1, 40.6, 73.4, 123.0, 124.2, 125.8, 126.7, 127.6, 128.5, 144.3, 144.5; HRMS m/z calcd for $(C_{13}H_{14}OS + NH_4)^+$ 236.1104, found 236.1109; 93% ee, OD-H column (95/5 hexane/2-propanol), 1.0 mL/min, minor enantiomer t_R = 16.5 min, major enantiomer t_R = 17.8 min.

4.25. (*S*)-1-(Naphthalen-2-yl)-3-(thiophen-2-yl)propan-1-ol (56): flash column, 6/1 petroleum ether/ethyl acetate; colorless prisms, yield 81% (108.2 mg); mp 56 °C; $[\alpha]_D^{20}$ = −9° (c = 0.35, CH_3OH); ^{1}H NMR (400 MHz) δ 2.04 (s, 1H, OH), 2.11−2.30 (m, 2H), 2.90−2.97 (m, 2H), 4.86−4.89 (dd, J = 5.6 Hz, J = 7.6 Hz, 1H), 6.80−6.81 (m, 1H), 6.91−6.93 (q, J = 3.2 Hz, J = 4.8 Hz, 1H), 7.11−7.13 (q, J = 5.6 Hz, 1H), 7.44−7.50 (m, 3H), 7.77−7.84 (m, 4H); ^{13}C NMR (100 MHz) δ 26.1, 40.5, 73.5, 123.1, 123.9, 124.3, 124.46, 125.8, 126.2, 126.7, 127.9, 128.4, 133.0, 133.2, 141.6,144.5; HRMS m/z calcd for $(C_{17}H_{16}OS + Na)^+$ 291.0814, found 291.0813; 93% ee, OJ-H column (90/10 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 43.7 min, minor enantiomer t_R = 50.5 min.

4.26. (*S*)-1,3-Bis(thiophen-2-yl)propan-1-ol (57): flash column, 6/1 petroleum ether/ethyl acetate; pale yellow oil, yield 53% (59.1 mg); $[\alpha]_D^{20}$ = −5° (c = 0.4, CH_3OH); ^{1}H NMR (400 MHz) δ 2.07 (s, 1H, OH), 2.13−2.31 (m, 2H), 2.90−3.02 (m, 2H), 4.94−4.98 (t, J = 6.8 Hz, 1H), 6.81−6.81 (t, 1H), 6.91−6.98 (m, 3H), 7.11−7.13 (t, 1H), 7.24−7.26 (m, 1H); ^{13}C NMR (100 MHz) δ 25.7, 40.5, 68.8, 122.8, 123.6, 124.1, 124.4, 126.3, 126.4, 143.8, 147.9; HRMS m/z calcd for $(C_{11}H_{12}OS_2 + Na)^+$ 247.0222, found 247.0225; 90% ee, OB-H column (98/2 hexane/2-propanol), 1.0 mL/min, major enantiomer t_R = 61.7 min, minor enantiomer t_R = 67.1 min.

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Supporting Information Available: Text, figures, and tables giving characterization and spectral data of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.