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Catalytic Enantioselective Alkylation and Arylation of Aldehydes by Using Grignard Reagents

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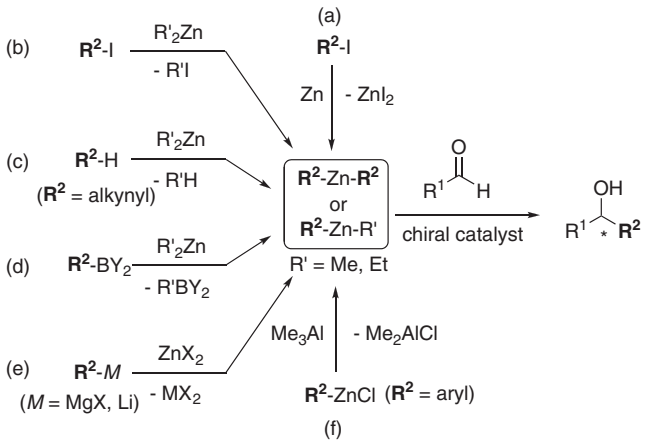
We have developed an efficient and practical method for the catalytic enantioselective alkylation and arylation of aldehydes by using Grignard reagents in combination with titanium tetraisopropoxide. Grignard reagents and titanium tetraisopropoxide are mixed in a molar ratio of ca. 1:2. In the presence of catalyst (2–4 mol %), which is formed in situ from a BINOL ligand **4a** and **4b** and titanium tetraisopropoxide, the resulting mixed titanium reagents undergo addition to aldehydes with high enantioselectivities (typically >90% ee) and high yields. The method is applicable to various combination of aldehydes (R^1CHO; R^1 = aryl, heteroaryl, 1-alkenyl, and alkyl) and Grignard reagents (R^2MgX; R^2 = primary alkyl and aryl). Thus, a variety of enantiomerically enriched secondary alcohols ($R^1CH^*(OH)R^2$) can be prepared. It has also been demonstrated that functionalized aryl Grignard reagents can be employed to generate highly functionalized diarylmethanols. The preparative utility of the method has been shown by the fact that the reaction is operationally simple, can be carried out on a 10-mmol scale without any difficulty, and the ligands can be readily recovered.

The catalytic enantioselective addition of organometallic reagents to aldehydes and ketones leading to enantiomerically enriched secondary and tertiary alcohols is a reaction of fundamental importance in modern synthetic organic chemistry. The development of efficient catalytic systems has received widespread attention for a long time.[1] In the early days, attempts were made to employ Grignard reagents and organolithium reagents in the presence of more than stoichiometric amounts of chiral diamines or other chiral modifiers.[2,3] However, the development of the catalytic reaction had been hampered by the high reactivity of these organometallic reagents. In 1984, Oguni and Omi discovered that diethylzinc undergoes enantioselective addition to aldehydes in the presence of chiral amino alcohols.[4] In 1986, Noyori and coworkers developed highly efficient DAIB catalyst, by which the catalytic enantioselective alkylation of aldehydes was realized for the first time with high enantioselectivity at low catalyst-loading (2 mol %).[1b,5] In the absence of catalysts, dialkylzincs hardly react with aldehydes. These pioneering works clearly showed that it is essential to use less reactive diorganozinc reagents with the aid of ligand acceleration to realize efficient catalytic enantioselective addition. Since then, remarkable advances have been made in catalytic enantioselective addition by using diorganozinc reagents, expanding the scope of both nucleophiles (alkylation,[1,6–9] arylation,[10–13] alkynylation,[14–16] and alkenylation[17–19]) and electrophiles (aldehydes and ketones[20–24]).

The use of diorganozinc reagents in catalytic enantioselective addition has an inherent drawback critical to practical applications. In their standard method for preparation, the insertion of zinc metal to alkyl iodides leads to alkylzinc iodides, which after distillation or sublimation, provide dialkylzinc reagents (Scheme 1a).[25] Due to the thermal instability of higher homologs, the method is applicable only to lower diorganozinc reagents. Indeed, only limited numbers of them are commercially available.



Scheme 1.

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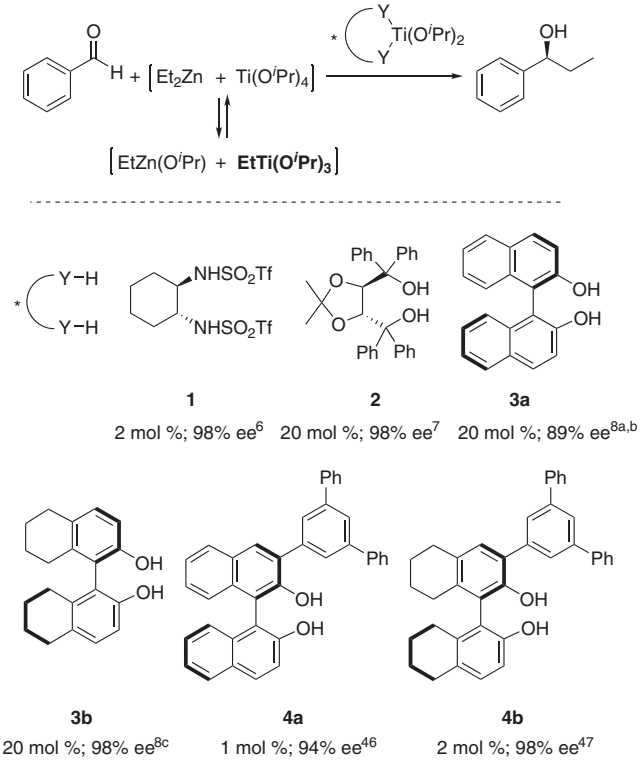
To circumvent this intrinsic problem, several methods have been developed for preparing diorganozinc reagents in situ (Schemes 1b–1f) and employed in subsequent enantioselective additions. Functionalized dialkylzinc reagents were prepared by iodine–zinc exchange with neat Et_2Zn (excess) and used after the removal of ethyl iodide and surplus Et_2Zn (Scheme 1b).[26] Recently, the catalytic enantioselective arylation of aldehydes with functionalized diarylzinc reagents prepared in situ from a Li(acac)-catalyzed iodine–zinc exchange reaction with Et_2Zn has been reported.[27,28] Zincation of terminal alkynes with Me_2Zn or Et_2Zn gives alkynylzinc reagents, which have been used in the enantioselective alkynylation of aldehydes and ketones (Scheme 1c).[14–16] Alkyl- and alkenylboranes, prepared by hydroboration, were converted into the corresponding zinc reagent by boron–zinc exchange reaction and employed in enantioselective alkylation[29] and alkenylation[18c,19] (Scheme 1d).[30] Similarly, functionalized arylzinc reagents prepared in situ from arylboronic acids or their derivatives have been used in catalytic enantioselective arylation.[13,31] The in situ preparation of diorganozinc reagents from Grignard and organolithium reagents by transmetalation with zinc salts (ZnX_2; X = Cl, Br, and OMe) has been also reported (Scheme 1e).[32] In this method, concomitantly produced magnesium and lithium salts should be removed as thoroughly as possible by their precipitation with complexing agents and filtration or centrifugation. Otherwise, enantioselectivity is degraded significantly by a competing racemic reaction promoted by the salts. Recently it has been shown that arylzinc chlorides can be converted to ArZnMe by treatment with Me_3Al (Scheme 1f).[33] The resulting mixed organozinc reagents selectively undergo aryl transfer and are utilized in the enantioselective arylation of aldehydes.

Although major efforts have been made in the use of diorganozinc reagents, organotitanium reagents have also been employed as an alternative in catalytic enantioselective addition. Seebach and co-workers showed that alkyl- and aryltitanium reagents [R–Ti(O^iPr)$_3$] underwent enantioselective addition to aldehydes through catalysis by TADDOLate–Ti(O^iPr)$_2$.[34,35] A variety of organotitanium reagents were prepared from Grignard and organolithium reagents by transmetalation with Cl–Ti(O^iPr)$_3$ and used successfully after the strict removal of magnesium and lithium salts.

Although being less apparent, organotitanium reagents have been described as active organometallic species in catalytic enantioselective additions using diorganozinc reagents in combination with titanium tetraisopropoxide (Scheme 2).[34b,36] In 1989, Yoshioka, Ohno, and Kobayashi reported a highly efficient titanium catalyst based on bis(sulfonamide) **1**.[6] In the presence of titanium tetraisopropoxide, the catalyst exhibits excellent enantioselectivity at very low loadings (<2 mol %). Subsequently, the mixed reagents of dialkylzincs and titanium tetraisopropoxide have been applied successfully to a TADDOL (**2**)-based catalyst by Seebach et al.[7] and a BINOL (**3a**)-based catalyst by Nakai et al. and by Chan et al.[8] Followed by these reports, many efficient chiral titanium catalysts have been developed by using the mixed reagents of diorganozinc reagents and titanium tetraisopropoxide.[15c,15d,16d,16e,37] The enhanced reactivity of the mixed reagents has been utilized especially in the enantioselective addition to ketones.[21a–21g,23c,24]



Scheme 2.

In the presence of Ti(O^iPr)$_4$, organoaluminum[38] and organoboron reagents[39] have also been used in catalytic enantioselective additions. Gau and Wu reported the formation of a bimetallic complex [Ar–Ti(O^iPr)$_3$·Ar$_2$Al(O^iPr)] from Ar$_3$Al·THF and titanium tetraisopropoxide in the enantioselective arylation of aldehydes catalyzed by a titanium complex derived from H_8-BINOL (**3b**).[38d] A recent report from our laboratory revealed that trialkylboranes can be used in enantioselective alkylation of aldehydes in the presence of DPP–BINOL (**4a**) or DPP–H_8-BINOL (**4b**) (2 mol %) and excess titanium tetraisopropoxide (3 equiv).[39] It is most probable that the alkyl group attached to a boron atom is first transferred to a titanium atom and then reacts with aldehydes.

Given their popularity in organic synthesis, Grignard reagents[40] would be one of the most ideal organometallic reagents for the catalytic enantioselective additions. Preparation of large numbers of derivatives has been well established. Some of them are commercially available. Moreover, recent work by Knochel and co-workers shows that Grignard reagents can tolerate many functionalities.[41] In this regard the use of Grignard reagents via transmetallation to diorganozinc and organotitanium reagents (eqs 1 and 2) has significantly expanded the scope of the catalytic enantioselective addition. However, concurrent formation of magnesium salts complicates the reaction procedure and impedes the reduction of catalyst loading, making this approach less attractive for practical applications.

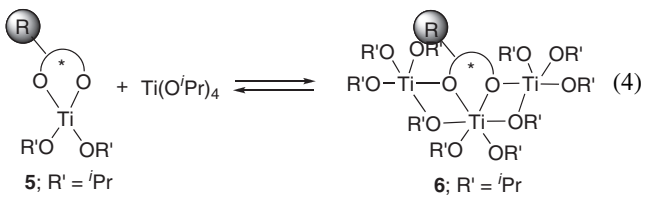
$$2RMgX + ZnX'_2 \rightarrow R_2Zn + 2MgXX' \quad (1)$$

$$RMgX + Cl\text{–}Ti(O^iPr)_3 \rightarrow R\text{–}Ti(O^iPr)_3 + MgXCl \quad (2)$$

$$RMgX + Ti(O^iPr)_4 \rightarrow R\text{–}Ti(O^iPr)_4\cdot MgX \quad (3)$$

Although not examined previously, Grignard reagents could be employed in catalytic enantioselective addition by converting them to organotitanate reagents in situ by treatment with titanium tetraisopropoxide (eq 3). Organotitanate reagents, R–Ti(OR)$_4$·M (M = MgX and Li), have been known for a long time[42] while their precise structures have not been well proven. The reagents exhibit characteristic reactivity against carbonyl compounds distinct from Grignard and organotitanium reagents,[43] and have been utilized in organic synthesis.[44] The previous studies suggest strongly that the ate-complex formation is an irreversible process. The reactivity of Grignard reagents is anticipated to be reduced in the form of organotitanates. In addition, unlike transmetalation (eqs 1 and 2), ate-complex formation (eq 3) is not accompanied by undesirable magnesium salt-formation.

We recently reported that titanium complexes derived from DPP–BINOL (**4a**)[45] and DPP–H$_8$-BINOL (**4b**)[46] exhibit a remarkably enhanced catalytic activity in the enantioselective alkylation of aldehydes with a mixed reagent of diethylzinc and titanium tetraisopropoxide (Scheme 2). Low catalyst-loadings, 1 mol % of **4a** and 2 mol % of **4b**, are sufficient to achieve high enantioselectivity superior to 20 mol % of parent BINOL (**3a**)[8a,8b] and H$_8$-BINOL (**3b**).[8c] Owing to a high molar ratio of titanium tetraisopropoxide against BINOL ligands **4** at the lower catalyst loadings, BINOLate–Ti(O^iPr)$_2$ complex **5** (R = H) might undergo aggregation with titanium tetraisopropoxide to form a non-active 1:2 complex **6**, which serves as a catalyst sink to reduce overall catalyst activity (eq 4). The enhanced activity of the titanium catalyst derived from **4a** and **4b** was rationalized by the inhibition of the aggregation to form **6** (R = 3,5-diphenylphenyl) by the aryl group at the 3-position. Superior activity observed in the presence of excess titanium tetraisopropoxide prompted us to examine catalysts derived from **4a** and **4b** in the reaction employing Grignard reagents.

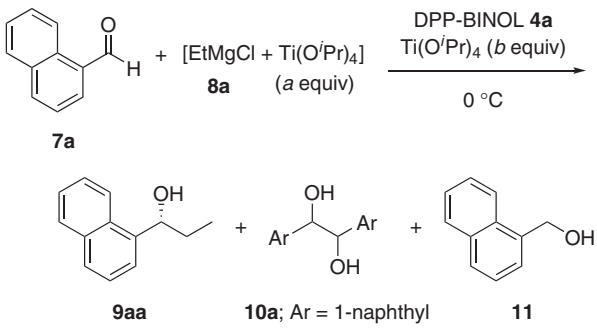


5; R' = ^{i}Pr **6**; R' = ^{i}Pr (4)

We herein report the full details of our development of a catalytic enantioselective alkylation and arylation of aldehydes with mixed titanium reagents derived from Grignard reagents and titanium tetraisopropoxide. Titanium(IV) complexes of BINOL derivatives **4a** and **4b** are demonstrated to catalyze the reaction with high enantioselectivity at low loadings (2–4 mol %). Application to the enantioselective preparation of functionalized diarylmethanols by the employment of functionalized Grignard reagents is also described.[47]

Results and Discussion

Examination of Reaction Parameters. We initiated our investigation with ethylation of 1-naphthaldehyde (**7a**) by using a THF (2 M) solution of EtMgCl (**8a**) (eq 5). When Grignard reagent **8a** (1.1 equiv) was added to a solution of **7a**, (*R*)-DPP–BINOL (**4a**) (5 mol %), and titanium tetraisopropoxide (1.4 equiv) in toluene at 0 °C, ethylation product **9aa** was obtained in 52% yield and in 37% ee. The absolute configuration of the major enantiomer was *R* as in the enantioselective ethylation with Et_2Zn.[46] In order to suppress a direct Grignard addition, the reaction procedure was modified in such a way that the Grignard reagent was previously mixed with titanium tetraisopropoxide. Thus, the addition of aldehyde **7a** to a solution of the Grignard reagent (1.1 equiv), titanium tetraisopropoxide (1.4 equiv), and ligand **4a** (5 mol %) in toluene at 0 °C afforded **9aa** in 50% ee but in low yield (6%). When 2.8 equiv of titanium tetraisopropoxide was employed under these conditions, the selectivity and yield were improved to 71% ee and 17%, respectively.



(5)

Further improvement in enantioselectivity was obtained by the addition of a mixture of the Grignard reagent and titanium tetraisopropoxide (Table 1). Slow addition of a mixture of **8a** (1.1 equiv) and titanium tetraisopropoxide (1.4 equiv) for 2 h to a solution of **7a**, **4a** (5 mol %), and titanium tetraisopropoxide (2.1 equiv) in toluene afforded **9aa** in 90% ee (Entry 1). The yield of **9aa** increased by using CH_2Cl_2 as a solvent (Entry 2) and with the increased amount of **8a** (2.2 equiv) and titanium tetraisopropoxide (4.4 equiv) (Entry 3). Solvent for the Grignard reagent was influential. Excellent selectivity (95% ee) as well as satisfactory yield (62%) was attained by the use of **8a** in Et_2O (2 M) (Entry 4). Under these conditions, the reaction could be carried out at a low catalyst loading (2 mol %) without lowering the selectivity (Entry 5). On the other hand, enantioselectivity was moderate (85% ee) when a parent BINOL (**3a**) (5 mol %) was used (Entry 6).

A titanium reagent generated by treatment of titanium tetraisopropoxide with excess (2–3 equiv) EtMgBr has been

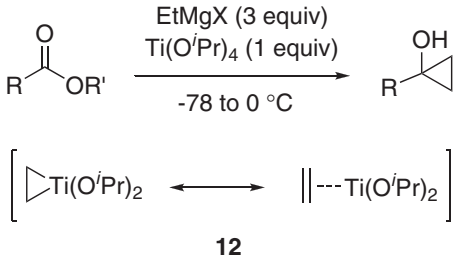
Table 1. Catalytic Asymmetric Ethylation of 1-Naphthaldehyde (**7a**) by Using EtMgCl (**8a**)[a)]

Entry	EtMgCl		Ti(O^iPr)$_4$		Yield/%[b)]	ee/%
	equiv	Solvent	*a*	*b*		
1[c)]	1.1	THF	1.4	2.1	23	90
2	1.1	THF	1.4	2.1	31	93
3	2.2	THF	4.4	1.4	52	86
4	2.2	Et_2O	4.4	1.4	62	95
5[d)]	2.2	Et_2O	4.4	1.4	56	94
6[e)]	2.2	Et_2O	4.4	1.4	52	85

a) Unless otherwise noted, reactions were carried out by adding a mixture of **8a** and Ti(O^iPr)$_4$ (*a* equiv) in CH_2Cl_2 to a solution of **7a**, **4a** (5 mol %), and Ti(O^iPr)$_4$ (*b* equiv) at 0 °C in CH_2Cl_2 for 2 h and quenched immediately in Entries 1 and 2 or after 1-h stirring in Entries 3–6. b) Isolated yield. c) The reaction was carried out in toluene. d) 2 mol % of **4a** was used. e) 5 mol % of **3a** was used.

utilized in the reductive cyclopropanation of esters (the Kulinkovich reaction) (Scheme 3).[48,49] Olefin–titanium complex **12** has been assumed to be a cyclopropanation agent.[50] Complex **12** is thermally unstable and used at low temperatures. Decomposition of **12** produces low-valent (II and/or III) titanium species. A pinacol coupling reaction induced by a putative titanium species has been reported in which a titanium(III) alkoxide might be formed by treatment of titanium tetraisopropoxide with EtMgBr (1 equiv).[51]

In the present ethylation reaction with a mixed reagent of EtMgCl and titanium tetraisopropoxide, pinacol **10a** and 1-naphthylmethanol (**11**) were formed as major by-products. For example, in Entry 5, **10a** and **11** were formed in 22% and 4% yield, respectively. At −78 °C in CH_2Cl_2 and Et_2O, a 1:2 mixture of EtMgCl and titanium tetraisopropoxide was colorless solution. However, during slow addition in a syringe at room temperature, it gradually turned black with evolution of a small amount of gas, possibly ethane and ethylene. In spite of the partial decomposition of the mixed titanium reagents, the ethylation product was obtained in satisfactory yield under the conditions of Entries 4 and 5. The reductive side reactions were significantly retarded in butylation of aldehydes employing BuMgCl (**8b**). Thus, under the conditions optimized for ethylation (Entry 5), the reaction of **7a** (Ar = 1-naphthyl) with a mixture of BuMgCl and titanium tetraisopropoxide gave the butylation product **9ab** (96% ee) in 90% yield with minor formation of **10b** (4%) and **11** (1%) (eq 6), indicating that the mixed titanium reagents are stable enough to be used in the slow addition procedure.



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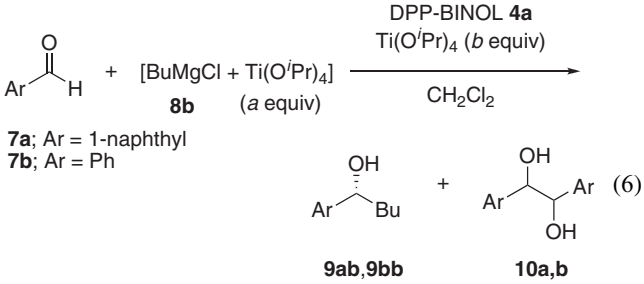
Scheme 3.



We then examined reaction parameters, such as ligands, time for slow addition, temperature, and the amount of Grignard reagent and titanium tetraisopropoxide, in the enantioselective butylation of benzaldehyde (**7b**) (eq 6, Ar = Ph). Slow addition of a mixture of Grignard reagent **8b** (2.2 equiv) and titanium tetraisopropoxide (4.4 equiv) in CH_2Cl_2 for 2 h to a solution of **7b**, **4a** (2 mol %), and titanium tetraisopropoxide (1.4 equiv) in CH_2Cl_2 at 0 °C followed by additional 1 h stirring afforded butylation product **9bb** in 86% yield and in 93% ee (Table 2, Entry 1). Under these conditions, DPP–H_8-BINOL **4b** also exhibited high enantioselectivity comparable to **1a** (Entry 2) whereas only modest selectivity was obtained with a parent BINOL (**3a**) (Entry 3). Slow addition of the mixed

Table 2. Catalytic Enantioselective Butylation of Benzaldehyde (**7b**) by Using BuMgCl (**8b**)[a)]

Entry	Ligand	BuMgCl /equiv	$Ti(O^iPr)_4$		Time /h[b)]	Temp /°C	**9bb**		**10b**
			a	*b*			Yield/%[c)]	ee/%	Yield/%[c)]
1	**4a**	2.2	4.4	1.4	2	0	86	93	4
2	**4b**	2.2	4.4	1.4	2	0	86	92	13
3	**3a**	2.2	4.4	1.4	2	0	78	79	7
4	**4a**	2.2	4.4	1.4	0.1	0	71	86	14
5	**4a**	2.2	4.4	1.4	3	0	75	95	8
6	**4b**	2.2	4.4	1.4	3	0	85	95	8
7	**4a**	2.2	4.4	1.4	2	−20	75	94	13
8	**4b**	2.2	4.4	1.4	2	−20	60	91	3
9	**4b**	2.2	4.4	1.4	2	20	81	84	8
10	**4a**	2.2	4.4	0.7	2	0	85	93	7
11	**4b**	2.2	4.4	0.7	2	0	82	94	7
12	**4a**	2.2	4.4	0.2	2	0	83	91	5
13	**4b**	2.2	4.4	0.2	2	0	87	84	10
14	**4a**	2	3	1	2	0	71	89	12
15	**4a**	1.5	3	1	2	0	57	94	1
16	**4a**	1.2	2	2	2	0	65	93	7
17[d)]	**4a**	2.2	4.4	1.4	2	0	91	95	5
18[d)]	**4a**	2.2	4.4	1.4	3	0	78	97	3
19[d)]	**4b**	2.2	4.4	1.4	2	0	86	96	8
20[d)]	**4b**	2.2	4.4	1.4	3	0	83	97	11

a) Unless otherwise noted, reactions were carried out by adding a mixture of **8b** (2 M in Et_2O) and $Ti(O^iPr)_4$ (*a* equiv) in CH_2Cl_2 to a solution of **7b**, **4a** (2 mol %), and $Ti(O^iPr)_4$ (*b* equiv) in CH_2Cl_2. The reaction mixture was stirred further for 1 h before workup. b) Time for slow addition. c) Isolated yield. d) 4 mol % of ligands were used.

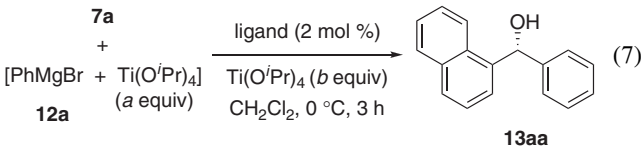
titanium reagent was necessary to achieve high selectivity (Entry 4). A longer addition time (3 h) led to a slight increase in selectivity (95% ee) both for ligand **4a** and **4b** (Entries 5 and 6). Reactions at 0 °C were optimal. At −20 °C, the full conversion of the aldehyde was not achieved (Entries 7 and 8). The enantioselectivity decreased at 20 °C (Entry 9). The amount of titanium tetraisopropoxide (*b*) used with ligands **4a** and **4b** could be reduced to 0.2 and 0.7 equiv, respectively, without significant lowering of the product yield and selectivity (Entries 10–13). On the other hand, the reduction in the amount of titanium tetraisopropoxide (*a*) used with the Grignard reagent caused decrease both in the selectivity and in the yield (Entry 14). High enantioselectivity was retained in the reaction using a reduced amount of the Grignard reagent, despite a decrease in the yield (Entries 15 and 16). Enantioselectivity was influenced by the amount of the chiral ligands. Although 2 mol % of **4a** and **4b** was sufficient to obtain high enantioselectivity (92–93% ee; Entries 1 and 2), still higher selectivity (96–97% ee) could be achieved at a 4 mol %-catalyst loading (Entries 17–20).

Reaction conditions established for the catalytic enantioselective alkylation were then applied to arylation by using PhMgBr (**12a**) (eq 7). Slow addition of a mixture of PhMgBr (**12a**) (3 M in Et_2O, 2.2 equiv) and titanium tetraisopropoxide (4.4 equiv) in CH_2Cl_2 for 2 h to a solution of aldehyde **7a**, ligand **4a** (2 mol %), and titanium tetraisopropoxide (1.4 equiv) in CH_2Cl_2 at 0 °C followed by 1 h of additional stirring afforded phenylation product **13aa** in 86% ee and in high yield (Table 3, Entry 1). The mixed titanium reagent derived from **12a** was stable and not accompanied by reductive side reactions. Again, the use of PhMgCl in THF (3 M) resulted in lower enantioselectivity (Entry 2). In butylation, DPP–H_8-BINOL (**4b**) exhibited enantioselectivity comparable to **4a** (Table 2). In contrast, the use of **4b** in the phenylation significantly improved the selectivity, affording **13aa** in 94% ee and in quantitative yield (Entry 3). Both BINOL (**3a**) and H_8-BINOL (**3b**) exhibited only moderate enantioselectivities (Entries 4 and 5). Further optimization of the reaction parameters revealed that the phenyl transfer could be carried out with a small excess of the Grignard reagent (1.2 equiv) in combination with a total 3 equiv ($a = 2$, $b = 1$) of titanium tetraisopropoxide keeping high yield (97%) and selectivity (95% ee) (Entry 7). Under these conditions, addition time could be shortened to 0.5 h (Entry 8). Enantioselectivity was decreased by further decrease in the amount of titanium tetraisopropoxide (Entries 10 and 11).

Table 3. Catalytic Enantioselective Phenylation of 1-Naphthaldehyde (**7a**) by Using PhMgBr (**12a**)[a)]

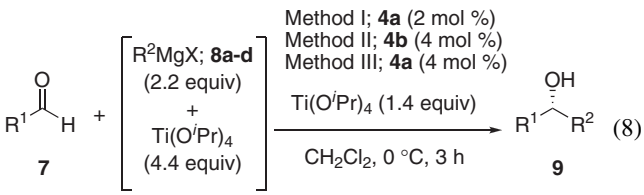
Entry	Ligand	PhMgBr /equiv	$Ti(O^iPr)_4$		Yield/%[b)]	ee/%
			a	*b*		
1	**4a**	2.2	4.4	1.4	94	86
2[c)]	**4a**	2.2	4.4	1.4	96	73
3	**4b**	2.2	4.4	1.4	98	94
4	**3a**	2.2	4.4	1.4	99	73
5	**3b**	2.2	4.4	1.4	99	81
6	**4b**	1.2	2	2	98	92
7	**4b**	1.2	2	1	97	95
8[d)]	**4b**	1.2	2	1	94	95
9[e)]	**4b**	1.2	2	1	97	78
10	**4b**	1.2	2	0.2	99	91
11	**4b**	1.2	1.5	0.2	90	87

a) Unless otherwise noted, reactions were carried out by slowly adding a mixture of **12a** (3 M in Et_2O) and $Ti(O^iPr)_4$ (*a* equiv) in CH_2Cl_2 for 2 h to a solution of **7a**, ligand (2 mol %), and $Ti(O^iPr)_4$ (*b* equiv) in CH_2Cl_2. The reaction mixture was stirred further for 1 h before workup. b) Isolated yield. c) PhMgCl (3 M in THF) was used. d) The mixed titanium reagent was added for 0.5 h. e) The mixed titanium reagent was added at once.



(7)

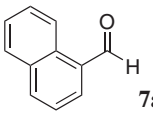
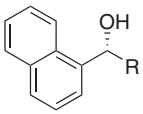
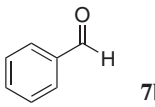
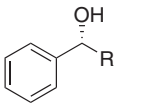
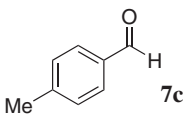
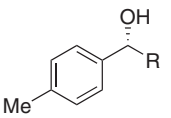
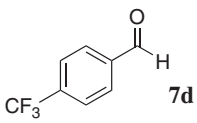
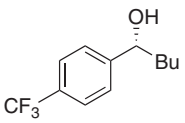
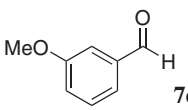
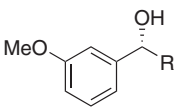
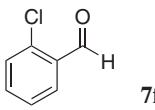
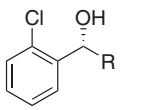
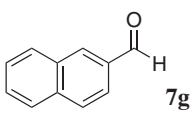
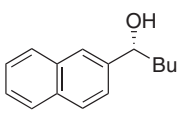
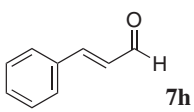
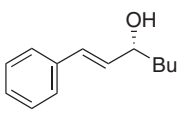
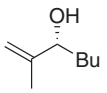
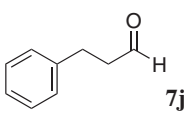
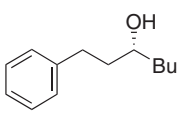
Scope and Limitations. The catalytic enantioselective alkylation was carried out for a variety of aldehydes and alkyl Grignard reagents to clarify the scope and limitations (eq 8, Table 4). Even with 2 mol % of **4a** (method I), the reaction of aromatic aldehydes with a mixed reagent of BuMgCl (2.2 equiv) and titanium tetraisopropoxide (4.4 equiv) afforded the corresponding butylation products **9** in high yields (60–92%) and in high enantioselectivities (91–96% ee) (Entries 3, 8, 15, 17, 20, 23, and 24). Superior selectivities (96–98% ee) could be realized by employing 4 mol % of **4b** (method II) (Entries 4, 10, 16, 18, and 21) and **4a** (method III) (Entry 11). The reaction is applicable to a range of benzaldehyde derivatives **7b–7f**, either with an electron-donating or -withdrawing substituent at the para, meta, and ortho position, as well as to 1- and 2-naphthaldehyde **7a** and **7g**.



(8)

The reactions of aromatic aldehydes **7a–7f** with a mixed reagent of EtMgCl (**8a**) and titanium tetraisopropoxide were also enantioselective while the yields of the ethylation products **9** were moderate owing to the instability of the reagent (Entries 1, 2, 6, 7, 14, 19, and 22). Not only chloromagnesium reagent **8a** but also bromomagnesium reagent **8a′** could be employed with comparable efficiency and selectivity (Entry 2 vs. Entry 1). Enantioselectivities of ethylation by method I were slightly lower than butylation. However, excellent selectivity was obtained by applying method II (Entry 7). A mixed reagent of PrMgCl (**8d**) and titanium tetraisopropoxide was stable enough to be used in propylation, affording the corresponding product **9bd** in high yield and in high selectivity (Entries 12 and 13). A mixed titanium reagent derived from MeMgCl (**8c**) was also stable, undergoing smooth addition to aldehyde **7a**, but exhibited only low enantioselectivity (Entry 5). Mixed titanium reagents derived from ^{i}PrMgCl, and ^{t}BuMgCl were very unstable at room temperature. Their reaction with **7b** resulted in the recovery of the aldehyde without the formation of the corresponding alkylation products.

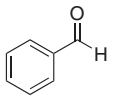
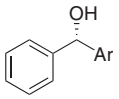
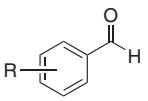
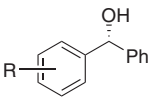
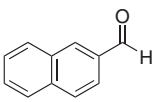
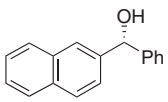
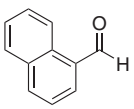
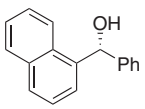
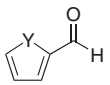
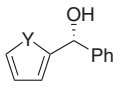
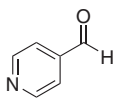
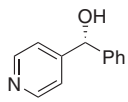
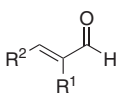
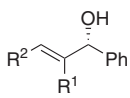
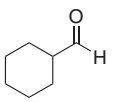
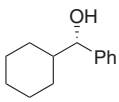
Table 4. Catalytic Enantioselective Alkylation of Aldehydes by Using Alkyl Grignard Reagents[a)]

Entry	Aldehyde	Grignard reagent	Method	Product		Yield /%[b)]	ee /%	By-product	Yield /%[b)]
1	 **7a**	EtMgCl (**8a**)	I		**9aa**; R = Et	56	94	**10a**	22
2		EtMgBr (**8a′**)	I		**9aa**; R = Et	63	93	**10a**	22
3		BuMgCl (**8b**)	I		**9ab**; R = Bu	90	96	**10a**	5
4		BuMgCl (**8b**)	II		**9ab**; R = Bu	83	98	**10a**	5
5		MeMgCl (**8c**)	I		**9ac**; R = Me	89	28	**10a**	0
6	 **7b**	EtMgCl (**8a**)	I		**9ba**; R = Et	57	90	**10b**	31
7		EtMgCl (**8a**)	II		**9ba**; R = Et	38	97	**10b**	54
8		BuMgCl (**8b**)	I		**9bb**; R = Bu	86	93	**10b**	4
9[c)]		BuMgCl (**8b**)	I		**9bb**; R = Bu	94	92	**10b**	7
10		BuMgCl (**8b**)	II		**9bb**; R = Bu	78	97	**10b**	3
11		BuMgCl (**8b**)	III		**9bb**; R = Bu	83	97	**10b**	4
12		PrMgCl (**8d**)	I		**9bd**; R = Pr	82	94	**10b**	10
13		PrMgCl (**8d**)	II		**9bd**; R = Pr	78	95	**10b**	9
14	 **7c**	EtMgCl (**8a**)	I		**9ca**; R = Et	41	88	**10c**	44
15		BuMgCl (**8b**)	I		**9cb**; R = Bu	82	95	**10c**	9
16		BuMgCl (**8b**)	II		**9cb**; R = Bu	70	96	**10c**	8
17	 **7d**	BuMgCl (**8b**)	I		**9db**	62	95	**10d**	6
18		BuMgCl (**8b**)	II			89	96	**10d**	6
19	 **7e**	EtMgCl (**8a**)	I		**9ea**; R = Et	40	95	**10e**	26
20		BuMgCl (**8b**)	I		**9eb**; R = Bu	86	95	**10e**	6
21		BuMgCl (**8b**)	II		**9eb**; R = Bu	89	98	**10e**	9
22	 **7f**	EtMgCl (**8a**)	I		**9fa**; R = Et	46	80	**10f**	32
23		BuMgCl (**8b**)	I		**9fb**; R = Bu	79	94	**10f**	9
24	 **7g**	BuMgCl (**8b**)	I		**9gb**	92	91		—[d)]
25	 **7h**	BuMgCl (**8b**)	I		**9hb**	60	91		—[d)]
26		BuMgCl (**8b**)	II		**9hb**	76	96		—[d)]
27		BuMgCl (**8b**)	III		**9hb**	76	96		—[d)]
28	 **7i**	BuMgCl (**8b**)	I		**9ib**	49	84		—[d)]
29		BuMgCl (**8b**)	II		**9ib**	39	95		—[d)]
30		BuMgCl (**8b**)	III		**9ib**	39	93		—[d)]
31	 **7j**	BuMgCl (**8b**)	I		**9jb**	36	92	**10j**	23

a) Unless otherwise noted, reactions were carried out by slowly adding a mixture of Grignard reagent **8a**–**8d** (2.2 equiv) and $Ti(O^iPr)_4$ (4.4 equiv) in CH_2Cl_2 for 2 h to a solution of aldehyde **7** (1 mmol), ligand (2–4 mol %), and $Ti(O^iPr)_4$ (1.4 equiv) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred further for 1 h before workup. b) Isolated yield. c) The reaction was carried out on a 10 mmol-scale. d) Not determined.

Catalytic enantioselective alkylation of α,β-unsaturated aldehydes **7h** and **7i** also proceeded in an efficient manner to give allylic alcohols **9hb** and **9ib** with high enantioselectivity (Entries 25–30).[52] Enantioselectivity in the range of 93–95% could be achieved by using 4 mol % of **4a** and **4b** (method II or III). Aliphatic aldehyde **7j** was less reactive in comparison

Table 5. Catalytic Enantioselective Arylation of Aldehydes by Using Aryl Grignard Reagents[a)]

Entry	Aldehyde		Grignard reagent	Product		Yield /%[b)]	ee /%
1		**7b**	*p*-MeC_6H_4MgBr (**12b**)		**13bb**; Ar = *p*-MeC_6H_4	99	91
2			*p*-ClC_6H_4MgBr (**12c**)		**13bc**; Ar = *p*-ClC_6H_4	95	91
3			*p*-FC_6H_4MgBr (**12d**)		**13bd**; Ar = *p*-FC_6H_4	94	97
4			*o*-$MeOC_6H_4MgBr$ (**12e**)		**13be**; Ar = *o*-$MeOC_6H_4$	66	9
5			2,4,6-$Me_3C_6H_2MgBr$ (**12f**)		**13bf**; Ar = 2,4,6-$Me_3C_6H_2$	89	96
6			2-ThienylMgBr (**12g**)		**13bg**; Ar = 2-thienyl	98	65
7		**7c**; R = *p*-Me	PhMgBr (**12a**)		*ent*-**13bb**; R = *p*-Me	93	90
8		**7k**; R = *p*-Cl	PhMgBr (**12a**)		*ent*-**13bc**; R = *p*-Cl	96	94
9		**7l**; R = *p*-F	PhMgBr (**12a**)		*ent*-**13bd**; R = *p*-F	97	95
10		**7m**; R = *p*-Ph	PhMgBr (**12a**)		**13ma**; R = *p*-Ph	99	91
11		**7n**; R = *p*-CN	PhMgBr (**12a**)		**13na**; R = *p*-CN	96	92
12		**7e**; R = *m*-MeO	PhMgBr (**12a**)		**13ea**; R = *m*-MeO	90	95
13		**7f**; R = *o*-Cl	PhMgBr (**12a**)		**13fa**; R = *o*-Cl	94	90
14		**7g**	PhMgBr (**12a**)		**13ga**	96	91
15		**7a**	PhMgBr (**12a**)		**13aa**	97	95
16			PhLi		**13aa**	95	50
17[c)]			PhLi		**13aa**	85	95
18		**7o**; Y = O	PhMgBr (**12a**)		**13oa**; Y = O	83	89
19		**7p**; Y = S	PhMgBr (**12a**)		*ent*-**13bg**; Y = S	85	90
20		**7q**	PhMgBr (**12a**)		**13qa**	82	82
21		**7i**; R^1 = Me, R^2 = H	PhMgBr (**12a**)		**13ia**; R^1 = Me, R^2 = H	87	97
22		**7r**; R^1 = H, R^2 = Me	PhMgBr (**12a**)		**13ra**; R^1 = H, R^2 = Me	78	86
22		**7s**	PhMgBr (**12a**)		*ent*-**9bb**	88	88
23		**7t**	PhMgBr (**12a**)		**13ta**	86	80

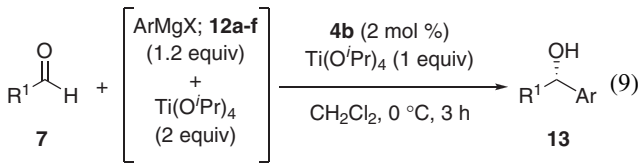
a) Unless otherwise noted, reactions were carried out by slowly adding a mixture of Grignard reagents **12** (1.2 equiv) (1.6–3 M in Et_2O) and $Ti(O^iPr)_4$ (2 equiv) in CH_2Cl_2 for 2 h to a solution of aldehyde **7** (1 mmol), **4b** (2 mol %), and $Ti(O^iPr)_4$ (1 equiv) in CH_2Cl_2. The reaction mixture was stirred further for 1 h before workup. b) Isolated yield. c) PhLi (1.2 equiv) was used after treatment with $MgBr_2$ (1.2 equiv) in Et_2O.

with aromatic and α,β-unsaturated aldehydes, affording the butylation product **9jb** in low yield but with high selectivity (Entry 31).

The catalytic alkylation reactions were carried out on a 1 mmol-scale by using a syringe pump for slow addition. To demonstrate the preparative utility, the enantioselective butylation of **7b** was carried out on a 10 mmol-scale (Entry 9). Slow addition of a mixed reagent of BuMgCl and titanium tetraisopropoxide with a dropping funnel and Kugelrohr distillation of the crude product gave **9bb** (1.62 g, 94% yield) in 92% ee. Ligand **4a** was recovered quantitatively by flash chromatography of the residue.

To investigate the scope and limitations of enantioselective arylation, reactions were carried out for a variety of aldehydes with mixed reagents derived from aryl Grignard reagents **12a**–**12g** (1.2 equiv) and titanium tetraisopropoxide (2 equiv) by using ligand **4b** (2 mol %) (eq 9). These results are summarized in Table 5. High enantioselectivities (91–97% ee) and high yields (89–99%) were obtained in the reaction of benzaldehyde with substituted phenyl Grignard reagents **12b**–**12f** except for

o-methoxy derivative **12e** (Entries 1–5). Addition of a sterically hindered 2,4,6-trimethylphenyl group proceeded efficiently to give diarylmethanol **13bf** in 96% ee (Entry 5). Enantioselectivity was moderate for the reaction with 2-thienyl Grignard reagent **12g** (Entry 6).

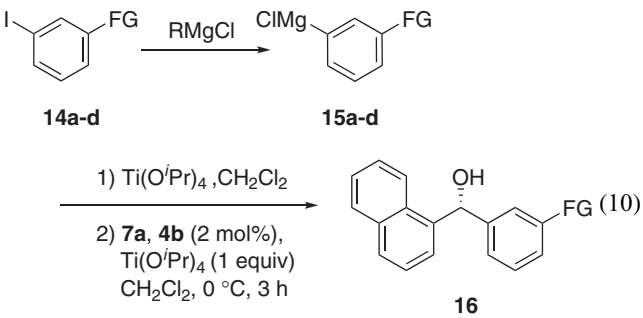


As demonstrated in Entries 7–15, a variety of aromatic aldehydes underwent phenylation with a mixed reagent derived from PhMgBr in a highly efficient manner (90–97% ee, >90% yield). Each enantiomer of diarylmethanols (**13bb**–**13bd** or *ent*-**13bb**–**13bd**) could be prepared with the same ligand (*R*)-**4b** by a proper combination of aldehydes and Grignard reagents (Entries 1–3 vs. Entries 7–9). Slightly lower, but still acceptable, selectivities (82–85% ee) were obtained for heteroaromatic aldehydes **7o**–**7q** (Entries 18–20). Not only diarylmethanols, but also secondary allylic alcohols **13ia** and **13ra** and benzylic alcohols *ent*-**9bb** and **13ta** could be prepared enantioselectively (78–88% ee) in high yields by the reaction of α,β-unsaturated aldehydes **7i** and **7r** (Entries 21 and 22) and aliphatic aldehydes **7s** and **7t** (Entries 23 and 24), respectively.

Although the use of PhLi, instead of PhMgBr, resulted in a significant reduction in enantioselectivity (Entry 16), the organolithium reagent could be employed after conversion into PhMgBr by treatment with $MgBr_2$ (Entry 17). It should be noted that the reaction was carried out without removing concomitantly produced LiBr, simply by mixing PhLi (1.2 equiv) with $MgBr_2$ (1.2 equiv) and titanium tetraisopropoxide (2 equiv), to give **13aa** in excellent enantioselectivity.

Catalytic Enantioselective Arylation Using Functionalized Grignard Reagents. Recently, considerable attention has been focused on catalytic methods that allow enantioselective transfer of functionalized aryl groups to aromatic aldehydes[13,27,33,38d–38i,53] because the resulting highly functionalized diarylmethanols are very much in demand as precursors to many biologically active compounds.[54] Arylboronic acids and their derivatives are most often employed as precursors to functionalized organozinc reagents in previous methods. Although many functionalized boronic acids are commercially available, their preparation requires several reaction steps, generally involving borylation of organolithium or Grignard precursors.[55,56] Therefore, these methods have a problem with overall atom economy for practical application. Recently, Knochel and co-workers have demonstrated that thermally unstable functionalized Grignard reagents can be prepared at low temperatures by halogen–magnesium exchange of the corresponding haloarenes.[41] To develop a practical method for the enantioselective synthesis of highly functionalized diarylmethanols, we examined the use of functionalized Grignard reagents in the present catalytic enantioselective arylation reaction.

According to the reported protocol,[41b] a THF solution of *m*-cyanophenylmagnesium chloride (**15a**) was prepared by treatment of *m*-iodobenzonitrile (**14a**) with ^{i}PrMgCl (2 M in THF) at −40 °C (eq 10). The resulting Grignard reagent was mixed with titanium tetraisopropoxide and used in the reaction with 1-naphthaldehyde. The reaction gave diarylmethanol **16aa** in high yield but with low enantioselectivity (Table 6, Entry 2). Since the use of a Grignard reagent in THF resulted in reduced enantioselectivity in comparison with that in Et_2O (Entries 1–3 in Table 1 and Entry 2 in Table 3), the preparation of **15a** in Et_2O was then examined. At −20 °C in Et_2O, ^{i}PrMgCl (2 M in Et_2O) underwent iodine–magnesium exchange reaction of **14a** rapidly within 1 h, judging from the exclusive formation of benzonitrile after hydrolysis. However, treatment of the same reaction mixture with I_2 gave **14a** contaminated by benzonitrile, which was produced by in situ protonation of **15a** most probably by concurrently produced 2-iodopropane. To suppress undesirable protonation, *c*-C_5H_9MgCl (2 M in Et_2O) was used for the iodine–magnesium exchange because iodocyclopentane is less reactive toward Grignard reagents than 2-iodopropane.[57] In accord with our anticipation, treatment of **14a** with *c*-C_5H_9MgCl at −20 °C for 0.5 h followed by treatment with titanium tetraisopropoxide and subsequent use in the enantioselective arylation of **7a** gave **16aa** in 95% ee and in 91% yield (Entry 1).

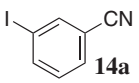
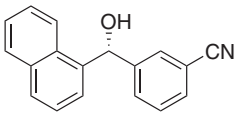
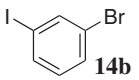
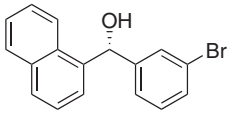
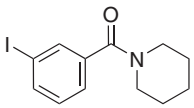
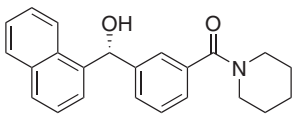
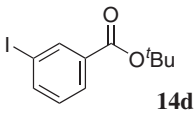
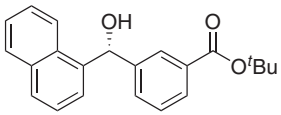


Aryl Grignard reagents **15b**–**15d** bearing bromine, piperidine-1-carbonyl, and *t*-butoxycarbonyl groups at the meta position were prepared in Et_2O by treatment of functionalized iodoarenes **14b**–**14d** with *c*-C_5H_9MgCl. The enantioselective arylation of **7a** using **15b**–**15d** gave corresponding diarylmethanols **16** in high enantioselectivity (Entries 3–5).

There are some limitations to iodine–magnesium exchange in Et_2O. Since the reaction proceeded more slowly in Et_2O than in THF, reaction conditions, such as temperature, time, and the amount of iodoarenes and *c*-C_5H_9MgCl, had to be carefully optimized beforehand for each functional group. The preparation of *m*-(ethoxycarbonyl)phenylmagnesium chloride (**15e**) in Et_2O was unsuccessful because of the preferential attack of *c*-C_5H_9MgCl to the carbonyl group. The exchange reaction was hampered by low solubility of *p*-iodobenzonitrile (**14f**) in Et_2O. To overcome such limitations, we turned out our attention again to functionalized Grignard reagents prepared in THF.

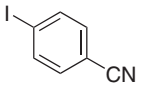
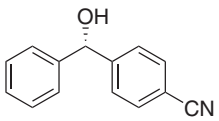
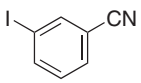
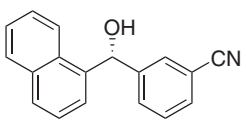
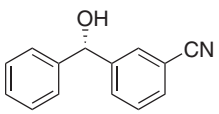
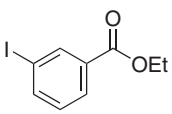
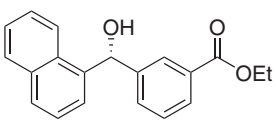
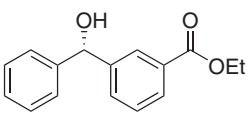
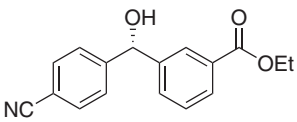
Grignard reagent **15f** was prepared from **14f** (1.5 equiv) in THF and mixed with titanium tetraisopropoxide (2.5 equiv) in CH_2Cl_2 at −78 °C (eq 11). Direct use of the resulting mixed titanium reagent in the enantioselective arylation of benzaldehyde (**7b**) afforded diarylmethanol *ent*-**13na** in 55% ee (Table 7, Entry 1). However, when it was used after the removal of THF in vacuo followed by dissolution in CH_2Cl_2, enantioselectivity was improved to 82% ee (Entry 2). Further improvement was obtained by the use of the mixed titanium

Table 6. Catalytic Enantioselective Arylation of Aldehydes by Using Functionalized Grignard Reagents Prepared in Et_2O[a)]

Entry	Iodoarene	equiv[b)]	Temp/°C[c)]	Time/h[c)]	Product		Yield/%[d)]	ee/%
1	 **14a**	1.5	−20	0.5		**16aa**	91	95
2[e)]		1.5	−20	0.5		**16aa**	82	61
3	 **14b**	2.0	0	2		**16ab**	85	92
4	 **14c**	1.5	0	1		**16ac**	73	92
5[f)]	 **14d**	2.0	−20	2		**16ad**	43	96

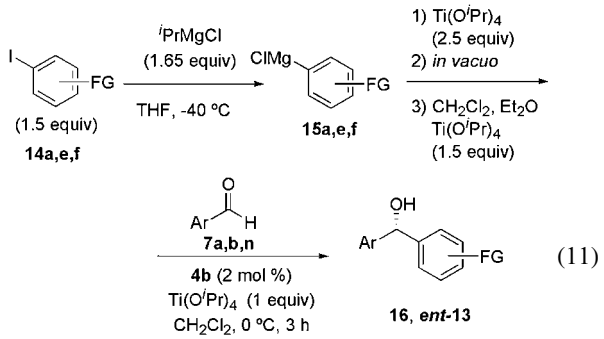
a) Unless otherwise noted, functionalized Grignard reagents **15** were prepared by treatment of iodoarenes **14** with *c*-C_5H_9MgCl (2 M in Et_2O) (1.1 equiv with respect to **14**) in Et_2O. A mixture **15** and $Ti(O^iPr)_4$ (1.7 equiv with respect to **14**) in CH_2Cl_2 was slowly added for 2 h to a solution of **7a** (1 mmol), **4b** (2 mol %), and $Ti(O^iPr)_4$ (1 equiv) in CH_2Cl_2 at 0 °C. The reaction mixture was stirred further for 1 h before workup. b) Equivalent of **14**. c) Conditions for the preparation of **15**. d) Isolated yield. e) The Grignard reagent was prepared in THF by using ^{i}PrMgCl (2 M in THF). f) Benzonitrile (4 equiv) was added in the preparation of the Grignard reagent.

Table 7. Catalytic Enantioselective Arylation of Aldehydes by Using Functionalized Grignard Reagents Prepared in THF[a)]

Entry	Iodoarene	Aldehyde	Product		Yield/%[b)]	ee/%
1[c)]	 **14f**	**7b**		*ent*-**13na**	65	55
2[d)]		**7b**		*ent*-**13na**	80	82
3[e)]		**7b**		*ent*-**13na**	86	88
4		**7b**		*ent*-**13na**	86	92
5	 **14a**	**7a**		**16aa**	90	93
6		**7b**		**16ba**	96	87
7	 **14e**	**7a**		**16ae**	97	95
8		**7b**		**16be**	94	89
9		**7n**		**16ne**	95	86

a) Unless otherwise noted, reactions were carried out under conditions shown in eq 11. b) Isolated yield. c) The mixed titanium reagent was used without removing THF in vacuo. d) The mixed titanium reagent was used after the removal of THF in vacuo and dissolution in CH_2Cl_2. e) The mixed titanium reagent was used after the removal of THF in vacuo and dissolution in CH_2Cl_2 and Et_2O.

reagent dissolved in CH_2Cl_2 and Et_2O (Entry 3). Finally, replacement of $Ti(O^iPr)_4$, partially lost in evacuation of THF, afforded optimal selectivity of 92% ee as well as high product yield (Entry 4).



(11)

Under these conditions, enantioselective transfer of the *m*-cyanophenyl group also proceeded in an efficient manner (Entries 5 and 6), exhibiting high enantioselectivity comparable to that obtained by the previous method (Table 6, Entry 1). It should be noted that Grignard reagent **15e** bearing a labile ethoxycarbonyl group could be used. The corresponding functionalized diarylmethanols **16** were obtained in high enantioselectivities (86–95% ee) (Entries 7–9).

Background Reaction and Plausible Active Titanium Species. Diorganozinc reagents generally exhibit only low reactivity toward aldehydes in the absence of catalysts.[5] In contrast, mixed titanium reagents employed in the present catalytic enantioselective addition were found to undergo addition to aldehydes without catalysis. Thus, when the reaction of **7a** with a mixed reagent of PhMgCl and titanium tetraisopropoxide was carried out in the absence of ligand **4b** under otherwise identical conditions as in Entry 7 of Table 3, racemic product *rac*-**9aa** was obtained in 76% yield and **7a** was recovered in 22%. Given the high enantioselectivity (95% ee) observed in the presence of only 2 mol % of **4b**, the rate of noncatalytic background reaction is surprisingly fast. Even so, the catalytic reaction proceeds overwhelmingly faster as a result of extremely strong ligand acceleration.

Significant decrease in enantioselectivity (78% ee) was observed when the reaction was carried out without applying the slow addition procedure (Entry 9 in Table 3). Under these conditions, the background reaction competed well with the catalytic reaction, degrading the selectivity. Although the catalytic cycle of the present enantioselective addition has not yet been clarified, the result implies that a catalyst-turnover step might be rate determining. By the addition of the mixed titanium reagents slowly, at least for 0.5 h (Entry 8 in Table 3), active catalyst is kept at sufficient concentration to exhibit high enantioselectivity.

To obtain high enantioselectivity, it was necessary to employ a ca. 1:2 mixture of Grignard reagents and titanium tetraisopropoxide. The enantioselectivity decreased with a decrease in the amount of titanium tetraisopropoxide mixed with Grignard reagents (Entry 14 in Table 2 and Entry 11 in Table 3). If we assume that a titanate $[R–Ti(O^iPr)_4\cdot MgX]$ is an active organotitanium species, the extra amount of titanium tetraisopropoxide would be necessary to facilitate the rate-determining catalyst turnover step. However, the possibility is not consistent with the observation that the enantioselectivity was not sensitive to the amount of titanium tetraisopropoxide used with chiral ligands **4a** and **4b** (Entries 10–12 in Table 2 and Entry 10 in Table 3). It is more probable that a titanate aggregate $[R–Ti_2(O^iPr)_8\cdot MgX]$ is the active species of the present catalytic enantioselective reaction.

Conclusion

We have developed a highly efficient and practical method for the catalytic enantioselective alkylation and arylation of aldehydes by using Grignard reagents in combination with $Ti(O^iPr)_4$. Titanium complexes derived from DPP–BINOL (**4a**) and DPP–H_8-BINOL (**4b**) are demonstrated to be excellent catalysts for this transformation, providing secondary alcohol products in high enantioselectivity at low catalyst loading (2–4 mol %). Both Grignard reagents and aldehydes can be broadly altered, permitting access to a wide range of enantiomerically enriched secondary alcohols. The scope of the reaction has been extended to include the enantioselective additions of functionalized aryl Grignard reagents. The preparative utility of the present method has been shown by the fact that the reaction is operationally simple, can be carried out on a 10-mmol scale without any difficulty, and the ligands can be readily recovered.

In spite of their popularity in catalytic enantioselective addition, the use of diorganozinc reagents has several problems critical to practical applications, such as a structural limitation in available reagents and a complicated operation for their in situ preparation. The successful use of Grignard reagents provides a solution to these problems. Also noteworthy is the high atom efficiency of the method especially in the aryl transfer, in which aryl Grignard reagents in small excess (1.2–1.5 equiv) are employed. Although titanium tetraisopropoxide is required in excess, its low cost and benign nature of the by-product (TiO_2) make the present method attractive for preparative use.[43a,43b] Finally, the present study has demonstrated that the highly reactive Grignard reagents can be tamed for the catalytic enantioselective addition simply by mixing with ca. 2 equiv of titanium tetraisopropoxide in the form of organotitanates, in which even a labile carbonyl functionality is well tolerated. The modified reactivity of the organotitanate reagents could be exploited in other catalytic enantioselective processes.

Experimental

General. Dichloromethane was dried and distilled over CaH_2. Et_2O was distilled from sodium benzophenone ketyl. Aldehydes and titanium tetraisopropoxide were used after distillation. Ligand **4a** was prepared according to a reported procedure.[45] The following Grignard reagents were purchased from Aldrich and used without titration; BuMgCl (2 M in Et_2O), PrMgCl (2 M in Et_2O), EtMgCl (2 M in Et_2O and 1.6 M in THF), EtMgBr (3 M in Et_2O), MeMgCl (3 M in THF), PhMgBr (3 M in Et_2O), PhMgCl (3 M in THF), *p*-MeC_6H_4MgBr (0.5 M in Et_2O), *p*-ClC_6H_4MgBr (1 M in Et_2O), *p*-FC_6H_4MgBr (2 M in Et_2O), *o*-$MeOC_6H_4MgBr$ (1 M in Et_2O), 2,4,6-$Me_3C_6H_2MgBr$ (1 M in Et_2O), ^{i}PrMgCl (2 M in Et_2O and 2 M in THF), and *c*-C_5H_9MgCl (2.0 M in Et_2O). PhLi (0.98 M in cyclohexane and Et_2O) was obtained from Kanto Chemicals Co., Ltd. and used without titration. 2-Thienylmagnesium bromide was prepared in Et_2O (0.8 M) from 2-bromothiophene and Mg.

(*R*)-3-Bromo-2,2′-dimethoxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl. Bromine (0.19 M in dichloromethane, 9.8 mL, 1.86 mmol) was added to a solution of (*R*)-2,2′-dimethoxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl[58] (0.600 g, 1.86 mmol) in dichloromethane (28 mL) at 0 °C. After being stirred for 5 min, the red solution was poured into a 5% solution of $NaHSO_3$, and the mixture was extracted three times with dichloromethane. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (1% ethyl acetate and 25% toluene in hexane) to give 0.496 g (66% yield) of the bromide as an amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.58–1.73 (8H, m), 1.98–2.04 (2H, m), 2.22 (1H, m), 2.35 (1H, m), 2.71–2.83 (4H, m), 3.46 (3H, s), 3.71 (3H, s), 6.76 (1H, d, $J = 8.4$ Hz), 7.08 (1H, d, $J = 8.4$ Hz), 7.29 (1H, s); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 22.7, 22.8, 23.0, 23.1, 26.8, 27.2, 29.3, 29.4, 107.8, 113.8, 124.8, 129.1, 129.7, 132.4, 132.7, 134.6, 136.6, 136.7, 151.9, 154.3; HRMS (EI) calcd for $C_{22}H_{25}{}^{79}BrO_2$: 400.1038, found: 400.1042.

(*R*)-3-(3,5-Diphenylphenyl)-2,2′-dimethoxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl. A mixture of bromide (*R*)-3-bromo-2,2′-dimethoxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (0.340 g, 0.847 mmol), (3,5-diphenyl)phenylboronic acid (0.256 g, 0.934 mmol),[59] $Pd(PPh_3)_4$ (49 mg, 0.042 mmol), and $Ba(OH)_2 \cdot 8H_2O$ (0.294 g, 0.932 mmol) in water (2.17 mL) and 1,4-dioxane (6.23 mL) was heated under reflux for 18 h under argon atmosphere. The reaction mixture was poured into water and extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (0.5% ethyl acetate and 25% toluene in hexane) to give 0.433 g (93% yield) of the 3,5-diphenylphenyl derivative as an amorphous solid: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.64–1.86 (8H, m), 2.12–2.22 (2H, m), 2.36 (1H, m), 2.47 (1H, m), 2.78–2.94 (4H, m), 3.27 (3H, s), 3.76 (3H, s), 6.81 (1H, d, $J = 8.4$ Hz), 7.10 (1H, d, $J = 8.4$ Hz), 7.24 (1H, s), 7.38 (2H, t, $J = 7.4$ Hz), 7.48 (4H, t, $J = 7.5$ Hz), 7.72 (4H, dd, $J = 1.0$ and 8.0 Hz), 7.78 (1H, t, $J = 1.7$ Hz), 7.86 (2H, d, $J = 1.7$ Hz); ^{13}C NMR (126 MHz, $CDCl_3$): 23.05, 23.10, 23.15, 23.22, 27.0, 27.4, 29.4, 29.6, 55.3, 60.4, 107.9, 124.5, 125.8, 127.0, 127.28, 127.32, 128.73, 128.76, 129.6, 130.7, 131.4, 131.6, 132.8, 136.65, 136.68, 140.2, 141.4, 141.5, 152.9, 154.5; HRMS (EI) calcd for $C_{40}H_{38}O_2$: 550.2872, found: 550.2864.

(*R*)-3-(3,5-Diphenylphenyl)-2,2′-dihydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (4b). To a solution of (*R*)-3-(3,5-diphenylphenyl)-2,2′-dimethoxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (450 mg, 0.817 mmol) in dichloromethane (5.5 mL) at −10 °C under argon atmosphere was added boron tribromide (0.77 mL, 8.17 mmol). The solution was stirred at this temperature for 2 h. The reaction mixture was poured into water, and extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (20% ethyl acetate in hexane) to give 409.1 mg (96% yield) of **4b** as an amorphous solid: $[\alpha]_D^{25}$ +69.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.68–1.83 (8H, m), 2.21–2.30 (2H, m), 2.34–2.45 (2H, m), 2.78 (2H, t, $J = 6.0$ Hz), 2.85 (2H, t, $J = 6.2$ Hz), 4.71 (1H, br), 4.95 (1H, br), 6.87 (1H, d, $J = 8.3$ Hz), 7.09 (1H, d, $J = 8.3$ Hz), 7.30 (1H, s), 7.38 (2H, t, $J = 7.4$ Hz), 7.47 (4H, t, $J = 7.5$ Hz), 7.70 (4H, d, $J = 7.2$ Hz), 7.78 (1H, t, $J = 1.6$ Hz), 7.84 (2H, d, $J = 1.6$ Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 22.9, 23.0 (3C), 27.14, 27.19, 29.2 (2C), 113.0, 119.1, 119.8, 125.0, 125.8, 127.2, 127.4 (2C), 128.7, 130.2, 130.4, 131.1, 131.8, 137.0, 137.1, 138.8, 141.2, 141.9, 148.3, 151.3; HRMS (EI) calcd for $C_{38}H_{34}O_2$: 522.2559, found: 522.2567.

(*R*)-1-Phenylpentan-1-ol (9bb). Typical Procedure for Asymmetric Alkylation with a Grignard Reagent: Method I (Table 4, Entries 8 and 9); To a solution of titanium tetraisopropoxide (1.30 mL, 4.4 mmol) in dry CH_2Cl_2 (16 mL) at −78 °C under argon atmosphere was added BuMgCl (2 M in Et_2O) (1.10 mL, 2.2 mmol). After being stirred for 10 min at this temperature, the resulting mixture was slowly added over a period of 2 h by using a syringe pump to a CH_2Cl_2 (4 mL) solution of **4a** (10.3 mg, 0.020 mmol), benzaldehyde (0.106 g, 1.0 mmol), and titanium tetraisopropoxide (0.41 mL, 1.4 mmol) at 0 °C under argon atmosphere. After being stirred further for 1 h, the reaction mixture was quenched by the addition of aqueous 1 M HCl and extracted three times with Et_2O. The organic layers were washed successively with aqueous 5% $NaHCO_3$ and with brine, dried ($MgSO_4$), and concentrated in vacuo. Kugelrohr distillation (150 °C/5 mmHg) gave 0.141 g (86% yield) of **9bb**[9a] (93% ee). Flash chromatography (silica gel, 10–50% ethyl acetate in hexane) of the residue gave 6.1 mg (59% recovery) of **4a** and 4.2 mg (4% yield) of 1,2-diphenylethane-1,2-diol (**10b**)[60] (meso:dl = 1.3:1). The ee value of **9bb** was determined by HPLC analysis using a Chiralcel OD column (1.0 mL min^{-1}, 2% *i*-PrOH in hexane); retention times: 11.8 min (major *R* enantiomer) and 14.7 min (minor *S* enantiomer). The absolute structure of the product was determined based on the reported retention times.[61]

The above reaction was carried out on a 10.5 mmol-scale by following the same procedure except that a dropping funnel was used for the slow addition over 2 h. Kugelrohr distillation (120–150 °C/5 mmHg) of the crude products gave 1.62 g (94% yield) of (*R*)-**9bb** (92% ee) ($[\alpha]_D^{25}$ +35.4 (*c* 3.03, C_6H_6)). Flash chromatography (silica gel, 10–50% ethyl acetate in hexane) of the residue gave 101.2 mg (98% recovery) of **4a** and 76.2 mg (7% yield) of **10b** (meso:dl = 1.4:1).

Methods II and III (Entries 10 and 11); Reactions were carried out by a procedure similar to Method I except that 4 mol % of **4b** and **4a** were used in Methods II and III, respectively.

(*R*)-Naphthalen-1-ylphenylmethanol (13aa). Typical Procedure for Asymmetric Arylation with a Grignard Reagent (Table 5, Entry 15): To a solution of titanium tetraisopropoxide (0.59 mL, 2.0 mmol) in dry CH_2Cl_2 (8 mL) at −78 °C under argon atmosphere was added PhMgBr (3 M in Et_2O) (0.40 mL, 1.2 mmol). After being stirred for 10 min at this temperature, the resulting mixture was slowly added over a period of 2 h by using a syringe pump to a CH_2Cl_2 (4 mL) solution of **4b** (10.5 mg, 0.020 mmol), 1-naphthaldehyde (**7a**) (0.156 g, 1.0 mmol), and titanium tetraisopropoxide (0.30 mL, 1.0 mmol) at 0 °C under argon atmosphere. After being stirred further for 1 h, the reaction mixture was quenched by the addition of aqueous 1 M HCl and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous 5% $NaHCO_3$ and with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (silica gel, 2–20% ethyl acetate in hexane) of the residue gave 0.226 g (97% yield) of **13aa**[53e] (95% ee). The ee value was determined by HPLC analysis using a Chiralcel OD column (1.5 mL min^{-1}, 10% *i*-PrOH in hexane); retention times: 26.8 min (major *R* enantiomer) and 11.4 min (minor *S* enantiomer). The absolute structure of the product was determined based on reported retention times.[53e]

Asymmetric Phenylation Using Phenyllithium (Table 5, Entry 17). A two-layer mixture of $MgBr_2$ in Et_2O (2 mL) was prepared by the reaction of magnesium turnings (29 mg, 1.2 mmol) with 1,2-dibromoethane (1.2 mmol, 0.10 mL) under argon atmosphere. To this was added CH_2Cl_2 (8 mL) at room temperature. To the resulting solution of $MgBr_2$ at −78 °C was added PhLi (0.98 M

in cyclohexane and Et_2O) (1.22 mL, 1.2 mmol). The resulting suspension was stirred at room temperature for 15 min and then cooled again at −78 °C. Titanium tetraisopropoxide (0.59 mL, 2.0 mmol) was added. After being stirred for 10 min at this temperature, the resulting mixture was slowly added over a period of 2 h by using a syringe pump to a CH_2Cl_2 (4 mL) solution of **4b** (10.5 mg, 0.020 mmol), 1-naphthaldehyde (**7a**) (0.156 g, 1.0 mmol), and titanium tetraisopropoxide (0.30 mL, 1.0 mmol) at 0 °C. After being stirred further for 1 h, the reaction mixture was quenched by the addition of aqueous 1 M HCl and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous 5% $NaHCO_3$ and with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (silica gel, 2–20% ethyl acetate in hexane) of the residue gave 0.199 g (85% yield) of **13aa** (95% ee).

(*R*)-3-[Hydroxy(naphthalen-1-yl)methyl]benzonitrile (16aa). Typical Procedure for Asymmetric Arylation Using Functionalized Grignard Reagents Prepared in Et_2O (Table 6, Entry 1): To a solution of 3-iodobenzonitrile (**14a**) (0.344 g, 1.50 mmol) in dry Et_2O (3 mL) at −20 °C under argon atmosphere was added *c*-C_5H_9MgCl (2 M in Et_2O) (0.825 mL, 1.65 mmol). After being stirred for 1 h at this temperature, the resulting suspension was cooled to −78 °C and diluted with CH_2Cl_2 (10 mL). To the suspension at this temperature was added titanium tetraisopropoxide (0.74 mL, 2.5 mmol). After being stirred for 10 min at this temperature, the resulting mixture was slowly added over a period of 2 h by using a syringe pump to a CH_2Cl_2 (4 mL) solution of **4b** (10.5 mg, 0.020 mmol), **7a** (0.156 g, 1.0 mmol), and titanium tetraisopropoxide (0.30 mL, 1.0 mmol) at 0 °C under argon atmosphere. After being stirred further for 1 h, the reaction mixture was quenched by the addition of aqueous 1 M HCl and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous 5% $NaHCO_3$ and with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (silica gel, 12% ethyl acetate in hexane) of the residue gave 0.235 g (94% yield) of **16aa** (95% ee): ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.51 (1H, br), 6.52 (1H, d, $J = 3.7$ Hz), 7.42 (1H, t, $J = 8.0$ Hz), 7.43–7.57 (5H, m), 7.64 (1H, d, $J = 7.9$ Hz), 7.75 (1H, s), 7.83–7.91 (2H, m), 8.00 (1H, d, $J = 8.0$ Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 73.5, 112.5, 118.8, 123.7, 125.30, 125.31, 125.9, 126.5, 129.0, 129.17, 129.24, 130.40, 130.42, 131.1, 131.2, 134.1, 137.8, 144.6; HRMS (EI) calcd for $C_{18}H_{13}NO$: 259.0997, found: 259.1006. The ee value was determined by HPLC analysis using a Chiralcel AD-H column (1 mL min^{-1}, 9% *i*-PrOH in hexane); retention times: 36.2 min (major *R* enantiomer) and 24.3 min (minor *S* enantiomer). The absolute stereochemistry was assumed by analogy.

Ethyl 3-(*R*)-[Hydroxy(naphthalen-1-yl)methyl]benzoate (16ae). Typical Procedure for Asymmetric Arylation Using Functionalized Grignard Reagents Prepared in THF (Table 7, Entry 7): To a solution of ethyl 3-iodobenzoate (**14e**) (0.414 g, 1.50 mmol) in dry THF (3 mL) at −40 °C under argon atmosphere was added *i*-PrMgCl (2 M in THF) (0.825 mL, 1.65 mmol). After being stirred for 0.5 h at this temperature, the resulting suspension was cooled to −78 °C and diluted with CH_2Cl_2 (4 mL). To the suspension at this temperature was added titanium tetraisopropoxide (0.74 mL, 2.5 mmol) and the mixture was stirred for 10 min. The solvents were removed under vacuum (0.1 mmHg, room temperature, 1 h) and the residue was dissolved with CH_2Cl_2 (10 mL) and Et_2O (3.8 mL). Titanium tetraisopropoxide (0.44 mL, 1.5 mmol) was added and the resulting mixture was slowly added over a period of 2 h by using a syringe pump to a CH_2Cl_2 (4 mL) solution of **4b** (10.5 mg, 0.020 mmol), **7a** (0.156 g, 1.0 mmol), and titanium tetraisopropoxide (0.30 mL, 1.0 mmol) at 0 °C under argon atmosphere. After being stirred further for 1 h, the reaction mixture was quenched by the addition of aqueous 1 M HCl and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous 5% $NaHCO_3$ and with brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (silica gel, 3–5% ethyl acetate in toluene) of the residue gave 0.296 g (97% yield) of **16ae** (95% ee): ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.37 (3H, t, $J = 7.4$ Hz), 2.45 (1H, d, $J = 4.0$ Hz), 4.36 (2H, d, $J = 7.4$ Hz), 6.60 (1H, d, $J = 4.0$ Hz), 7.38 (1H, t, $J = 7.7$ Hz), 7.43–7.50 (3H, m), 7.55 (1H, d, $J = 7.9$ Hz), 7.58 (1H, d, $J = 7.0$ Hz), 7.83 (1H, d, $J = 8.2$ Hz), 7.88 (1H, m), 7.96 (1H, d, $J = 7.8$ Hz), 8.05 (1H, m), 8.19 (1H, s); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 14.3, 61.0, 73.4, 123.8, 124.9, 125.3, 125.7, 126.3, 128.1, 128.5, 128.81, 128.84 (2C), 130.6, 130.8, 131.3, 134.0, 138.4, 143.5, 166.5; HRMS (EI) calcd $C_{20}H_{18}O_3$: 306.1256, found: 306.1249 (HPLC analysis using a Chiralcel AD-H column, 1 mL min^{-1}, 10% *i*-PrOH in hexane; retention times: 35.4 min (major *R* enantiomer) and 28.8 min (minor *S* enantiomer). The absolute stereochemistry was assumed by analogy.

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Supporting Information

Characterization of products. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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