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Practical Enantioselective Arylation and Heteroarylation of Aldehydes with In Situ Prepared Organotitanium Reagents Catalyzed by 3-Aryl-H_8-BINOL-Derived Titanium Complexes

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Abstract: A highly efficient and practical method for the catalytic enantioselective arylation and heteroarylation of aldehydes with organotitanium reagents, prepared in situ by the reaction of aryl- and heteroaryllithium reagents with $ClTi(OiPr)_3$, is described. Titanium complexes derived from DPP-H_8-BINOL (**3d**; DPP = 3,5-diphenylphenyl) and DTBP-H_8-BINOL (**3e**; DTBP = 3,5-di-*tert*-butylphenyl) exhibit excellent catalytic activity in terms of enantioselectivity and turnover efficiency for the transformation, providing diaryl-, aryl heteroaryl-, and diheteroarylmethanol derivatives in high enantioselectivity at low catalyst loading (0.2–2 mol%). The reaction begins with a variety of aryl and heteroaryl bromides through their conversion into organolithium intermediates by Br/Li exchange with *n*BuLi, thus providing straightforward access to a range of enantioenriched alcohols from commercially available starting materials. Various 2-thienylmethanols can be synthesized enantioselectively by using commercially available 2-thienyllithium in THF. The reaction can be carried out on a 10 mmol scale at 0.5 mol% catalyst loading, demonstrating its preparative utility.

Keywords: alcohols · aldehydes · asymmetric catalysis · lithium · titanium

Introduction

Enantioenriched diaryl-, aryl heteroaryl-, and diheteroarylmethanol derivatives are important structural motifs and precursors in the synthesis of pharmaceutically important molecules including antihistaminic, anaesthetic, diuretic, antidepressive, antiarrhythmic, and anticholinergic compounds.[1] Accordingly, there are substantial demands for their practical enantioselective synthesis and the catalytic enantioselective synthesis of diarylmethanol derivatives has been the focus of many recent studies.[2]

The enantioselective reduction of inexpensive prochiral diaryl ketones is an attractive practical approach. Indeed, highly efficient methods have been developed with chemical[3] and enzymatic catalysis.[4] However, the limitation of this approach lies in the fact that two aryl groups of the substrates must be either electronically or sterically dissymmetric to achieve good selectivity.

An alternative approach involves the catalytic enantioselective addition of aryl-metal reagents to the prochiral carbonyl group of aromatic aldehydes, through which a carbon–carbon bond and a stereogenic center are produced simultaneously.[2,5] Several efficient catalytic methods have been developed that involve phenyllithium,[6] diphenylzinc,[7] arylboronic acids,[8,9] arylaluminium reagents,[10] arylzinc bromides,[11] aryl Grignard reagents,[12,13] and aryltitanium reagents[14] as aryl sources, expanding significantly the scope of diarylmethanols that are available in enantiomerically enriched form. However, the preparation of the aryl–metal reagents entails additional reaction steps. Some reagents are commercially available but are often quite expensive. Therefore, the availability of the aryl sources is an important issue for the practical applications of this approach.

Aryllithium reagents **1** are attractive aryl sources for the enantioselective addition to aldehydes (Scheme 1) and can be generated cleanly from common aryl bromides by Br/Li exchange reactions. In addition, heteroaryllithium reagents **1′**, such as 2-thienyl- and 2-furyllithium, are readily prepared by lithiation of the parent heteroaromatics.[15] Recently, Walsh and co-workers demonstrated the utility and practicality of the approach by developing a chiral amino alcohol catalyzed enantioselective, one-pot arylation method in which aryl butylzinc reagents **2** (M = ZnBu) were generated from aryl bromides by successive treatment with *n*BuLi, $ZnCl_2$, and additional *n*BuLi.[16] The reaction was carried out in the presence of a chelating diamine to inhibit a background racemic reaction promoted by concurrently formed LiCl. It was also shown that the method could be applied with some modification to the heteroarylation of aldehydes starting from heteroaryl bromides, such as 3-bromothiophene and -furan.[16b] A recent report[17] from this laboratory revealed that the mixed titanium reagent formed from an in situ generated aryllithium reagent, $Ti(OiPr)_4$, and $MgBr_2$ un-

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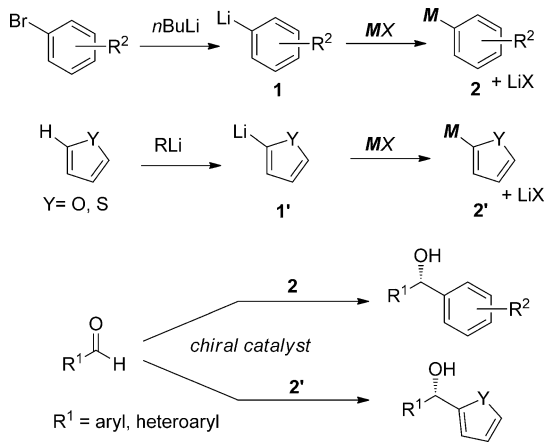


Scheme 1. Catalytic enantioselective synthesis of diaryl-, aryl heteroaryl-, and diheteroarylmethanol derivatives starting from aryl bromides and heteroaromatic compounds.

dergoes enantioselective arylation of aldehydes in the presence of a titanium catalyst derived from 3,5-diphenylphenyl (DPP)-H_8-BINOL (**3d**; Figure 1).[18,19]

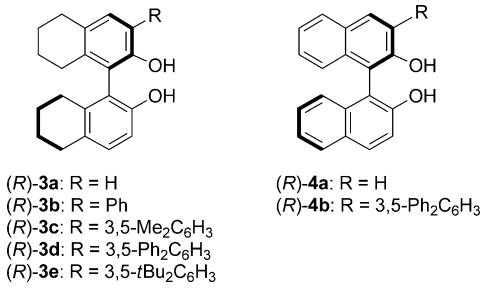


Figure 1. 3-Substituted BINOL derivatives **3a–e** and **4a** and **b**.

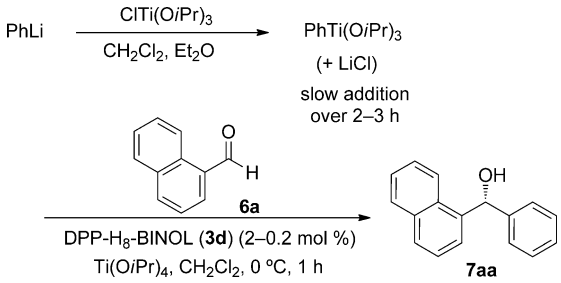
In addition to the availability of aryl sources, key issues concerning the practicality of the aldehyde arylation involve the reduction of catalyst loadings. Previously reported enantioselective arylation reactions were carried out, in most cases at 5 mol% catalyst loadings or higher, making them less practical for scale-up applications. To date, few methods are available that function satisfactorily at lower catalyst loadings.[9b,d,e,g,h] Yamamoto, Miyaura, and co-workers reported highly efficient arylation reactions with arylboronic acids catalyzed by a chiral phosporamidite-Ru^{II} complex at 2 mol%.[9d,h] The titanium catalyst derived from **3d** exhibited high enantioselectivity even at 2 mol% loadings in the arylation of aldehydes with the mixed titanium reagent of a Grignard reagent and $Ti(OiPr)_4$.[12,17,19b]

With this background in mind, we aimed to develop a practical, cost-effective, and scalable protocol for the enantioselective arylation of aldehydes. We focused our attention on the transmetalation of aryllithium reagents to titanium to generate **2** {M = $Ti(OiPr)_3$}. In the early studies of the catalytic enantioselective arylation, Seebach and co-workers employed $PhTi(OiPr)_3$, prepared from PhLi and $ClTi(OiPr)_3$, in combination with TADDOL-based chiral titanium catalysts (10 mol%).[6] To achieve high enantioselectivity, the rigorous removal of concurrently formed LiCl by centrifugation was required, otherwise the enantioselectivity was severely degraded by a racemic background reaction promoted by the salt. Some aryltitanium reagents $ArTi(OiPr)_3$ can be isolated by recrystallization from the hexane extracts of the reaction of ArMgX with $ClTi(OiPr)_3$.[20] Very recently, Gau and co-workers reported that such salt-free aryltitanium reagents underwent enantioselective addition to aldehydes in the presence of a titanium catalyst of H_8-BINOL (**3a**; 5–10 mol%).[14] We envisaged that the superior catalytic activity of the titanium complex of DPP-H_8-BINOL (**3d**) would allow highly enantioselective addition of the aryltitanium reagents without the removal LiCl even at the lower catalyst loadings, thus providing a practical protocol for the enantioselective synthesis of diarylmethanol derivatives from aryl bromides and aromatic aldehydes.

Herein, we report a practical and efficient method for the enantioselective arylation and heteroarylation of aldehydes with organotitanium reagents catalyzed by 3-substituted H_8-BINOL-based chiral titanium complexes. The titanium reagents are generated in situ from readily available aryl and heteroaryl bromides via organolithium intermediates. A variety of diaryl-, aryl heteroaryl-, and diheteroarylmethanol derivatives were synthesized in high enantioselectivity at low catalyst loadings (2–0.2 mol%). The practicality of the method is demonstrated in the successful application to gram-scale asymmetric syntheses.

Results and Discussion

Catalytic enantioselective arylation of aldehydes: The phenylation of 1-naphthaldehyde (**6a**) was first carried out with separately prepared salt-free $PhTi(OiPr)_3$[20] (Scheme 2).



Scheme 2. Enantioselective phenylation of 1-naphthaldehyde (**6a**) with $PhTi(OiPr)_3$ catalyzed by a titanium complex derived from **3d**.

Slow addition of a solution of $PhTi(OiPr)_3$ (1.2 equiv) in CH_2Cl_2 and Et_2O over 2 h to a solution of the aldehyde, DPP-H_8-BINOL (**3d**; 2 mol%), and $Ti(OiPr)_4$ (0.2 equiv) in CH_2Cl_2 at 0°C and an additional 1 h stirring afforded diarylmethanol **7aa** in 95% yield and in 98% *ee* (Table 1, entry 1). We then examined the reaction of **6a** with $PhTi(OiPr)_3$, prepared in situ by treatment of PhLi with $ClTi(OiPr)_3$, under similar conditions (Table 1, entry 2). The re-

Table 1. Enantioselective phenylation of 1-naphthaldehyde (**6a**) with $PhTi(OiPr)_3$ catalyzed by a titanium complex derived from **3d**.[a]

Entry	**3d** [mol%]	$Ti(OiPr)_4$ [equiv]	Yield [%]	*ee* [%]
1[b]	2	0.2	95	98
2	2	0.2	97	97
3[c]	2	0.2	98	77
4[d]	2	0.2	85	88
5[e]	2	0.2	77	90
6[f]	2	0.2	93	94
7	2	0	75	97
8[g]	1	0.2	89	97
9[g]	0.5	0.2	72	96
10[g]	0.2	0.2	77	88
11[g,h]	0.2	0.2	84	93
12	0	0	88	–

[a] Unless otherwise noted, reactions were carried out by adding in situ prepared $PhTi(OiPr)_3$ (1.2 equiv) in CH_2Cl_2 (8 mL) and Et_2O (0.5 mL) dropwise over 2 h by using a syringe pump to a solution of **6a** (1 mmol), **3b**, and $Ti(OiPr)_4$ in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was stirred for a further 1 h before workup. [b] LiCl-free $PhTi(OiPr)_3$ was used. [c] $PhTi(OiPr)_3$ was added in one portion. [d] A solution of **6a** in CH_2Cl_2 (4 mL) was added. [e] The reaction was carried out without using Et_2O as a co-solvent. [f] THF (2.6 mL) was employed as a co-solvent. [g] $PhTi(OiPr)_3$ was added steadily by immersing the syringe needle into the reaction mixture. [h] The reactions were carried out by adding in situ prepared $PhTi(OiPr)_3$ (1.5 equiv) in CH_2Cl_2 (15 mL) and Et_2O (0.5 mL) to a solution of **6a** (1 mmol), **3d**, and $Ti(OiPr)_4$ in CH_2Cl_2 (8 mL) over 3 h at 0 °C.

action afforded **7aa** in 97% yield and in 97% *ee*, demonstrating that the enantioselectivity was not affected by LiCl contamination.

As anticipated from previous studies,[21] the phenyltitanium reagent underwent facile addition to the aldehyde in the absence of the catalyst, giving rise to the racemic product (Table 1, entry 12). Judging from the high enantioselectivities detailed in Table 1, entries 1 and 2, potential racemic background reaction was almost completely overridden by the enantioselective catalytic reaction when the titanium reagent was slowly introduced into the reaction mixture over 2 h. Even when the titanium reagent was added at once, **7aa** was obtained in 77% *ee*, indicating the high activity of the titanium catalyst (Table 1, entry 3). Slow addition of the aldehyde also improved the enantioselectivity (Table 1, entry 4) although not as much as the slow addition of the phenyltitanium reagent. Without Et_2O as a co-solvent, the reaction resulted in slightly lower selectivity (Table 1, entry 5). The use of THF as a co-solvent also provided high enantioselectivity (Table 1, entry 6). It should be noted that additional $Ti(OiPr)_4$ was not necessary for the formation of the titanium catalyst. When the phenyltitanium reagent was added to the solution of **6a** and ligand **3d** (2 mol%), **7aa** was obtained with essentially the same efficiency (Table 1, entry 7). In the absence of $Ti(OiPr)_4$, (DPP-H_8-BINOLate)$Ti(OiPr)_2$, a plausible titanium catalyst, might be formed by the reaction of **3d** with $PhTi(OiPr)_3$.

The amount of chiral ligand **3d** could be reduced to 0.5 mol% without erosion of enantioselectivity (Table 1, entries 8 and 9). At 0.2 mol% catalyst loading, the reaction resulted in a decreased selectivity of 88% *ee* (Table 1, entry 10). Gratifyingly, however, a high enantioselectivity (93% *ee*) could be obtained even at such low catalyst loading by carrying out the reaction by slow addition of $PhTi(OiPr)_3$ (1.5 equiv) over 3 h under dilute conditions (Table 1, entry 11).

The performance of a series of H_8-BINOL derivatives **3a–e** and BINOL derivatives **4a** and **b** was evaluated in the phenylation of **6a** (Table 2). Parent BINOL **4a** and H_8-BINOL **3a** exhibited only moderate enantioselectivity at 2 mol% catalyst loading (Table 2, entries 1 and 3). Introduction of the 3,5-diphenylphenyl group at the 3-position resulted in enhanced selectivity of the reaction with DPP-BINOL (**4b**; 80% *ee*) and DPP-H_8-BINOL (**3d**; 97% *ee*; Table 2, entries 2 and 8). BINOL derivatives **4a** and **b** are inferior ligands compared with H_8-BINOL derivatives **3a** and **d**.

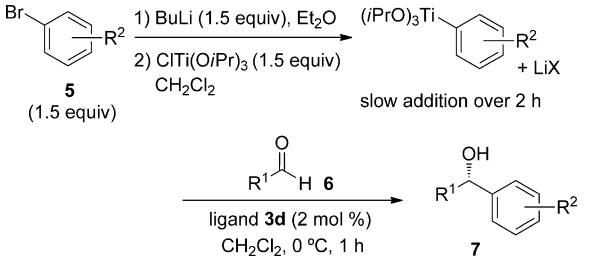
Table 2. Enantioselectivity of chiral ligands **3a–e** and **4a** and **b** in the phenylation of **6a**.[a]

Entry	Ligand	[mol%]	Yield [%]	*ee* [%]
1	**4a**	2	68	60
2	**4b**	2	72	80
3	**3a**	2	69	77
4[b]	**3b**	2	77	97
5[b]	**3b**	0.5	76	61
6[b]	**3c**	2	81	94
7[b]	**3c**	0.5	73	90
8	**3d**	2	97	97
9[b]	**3d**	0.5	72	96
10[b]	**3e**	2	82	99
11[b]	**3e**	0.5	82	95

[a] Unless otherwise noted, reactions were carried out by adding in situ prepared $PhTi(OiPr)_3$ (1.2 equiv) in CH_2Cl_2 (8 mL) and Et_2O (0.5 mL) dropwise over 2 h by using a syringe pump to a solution of **6a** (1 mmol), ligand, and $Ti(OiPr)_4$ (0.2 equiv) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was stirred for a further 1 h before workup. [b] $PhTi(OiPr)_3$ was added steadily by immersing the syringe needle into the reaction mixture.

To clarify the effect of substituents at the 3-position, reactions were also carried out with 3-aryl-H_8-BINOLs **3b**, **c** and **e**. At 2 mol% catalyst loading, all these ligands showed high selectivity (94–99% *ee*) similar to **3d** (Table 2, entries 4, 6 and 10). However, at 0.5 mol% loading, the enantioselectivity was increased in the order of phenyl derivative **3b** (61% *ee*), 3,5-dimethylphenyl derivative **3c** (90% *ee*), 3,5-di-*tert*-butylphenyl (DTBP) derivative **3e** (95% *ee*), and DPP derivative **3d** (96% *ee*), indicating that the selectivity is increased by increasing the size of the 3-aryl substituents (Table 2, entries 5, 7, 9 and 11). It is most probable that the inherent enantioselectivity is equally high for 3-aryl-H_8-BINOLs **3b–e**, judging from the result at 0.5 mol% loading. Sterically demanding substituents at the 3-position might accelerate the turnover of the titanium catalyst to minimize the participation of noncatalyzed background reaction and exhibit high selectivity at lower catalyst loadings.

The high activity of the titanium catalysts derived from DPP-H_8-BINOL **3d** and DTBP-H_8-BINOL **3e** prompted us to examine the enantioselective catalytic arylation of aldehydes starting from aryl bromides **5** (Scheme 3). Thus, suc-

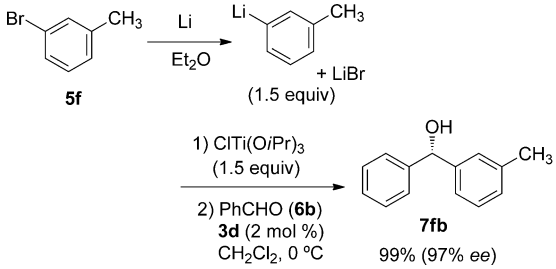


Scheme 3. Enantioselective arylation of aldehydes **6** starting from aryl bromides **5** catalyzed by a titanium complex derived from H_8-BINOL derivative **3d**.

cessive treatment of bromobenzene (**5a**; 1.5 equiv) with *n*BuLi (1.5 equiv) in Et_2O and $ClTi(OiPr)_3$ (1.5 equiv) in CH_2Cl_2, followed by slow addition of the resulting phenyltitanium reagent over 2 h to a CH_2Cl_2 solution of 1-napthaldehyde (**6a**) and **3d** (2 mol %), afforded diarylmethanol **7aa** in high yield (96 %) and high selectivity (98 % *ee*), comparable to those obtained in the reaction employing commercially available PhLi (Table 3, entry 1).

Under similar conditions, the (*p*-chlorophenyl)titanium reagent was prepared from *p*-bromochlorobenzene (**5c**). The titanium reagent underwent enantioselective addition to benzaldehyde (**6b**) to give the corresponding adduct **7cb** (98 % *ee*) in quantitative yield (Table 3, entry 4). The reaction of *p*- and *m*-substituted phenyl bromides **5b–f** and 2-naphthyl bromide (**5i**) afforded the corresponding benzaldehyde adduct **7** uniformly in high yields (75–100 %) and in high selectivities (90–98 % *ee*; Table 3, entries 3, 4, 10–12, and 15). On the other hand, reactions employing aryltitanium reagents derived from *o*-substituted bromides **5g** and **h** resulted in low enantioselectivities (Table 3, entries 13 and 14). The scope of the reaction was also examined with representative aldehydes in the reaction of phenyl titanium reagent (Table 3, entries 1 and 2) and (*p*-chlorophenyl)titanium reagent (Table 3, entries 4–9). The results showed that the present reaction is applicable to *ortho*-substituted aromatic aldehyde **6d**, heteroaromatic aldehyde **6e**, and α,β-unsaturated aldehyde **6f**. Enantioselectivity was low to moderate for aliphatic aldehydes **6g** and **h**.

The reaction could also be carried out successfully by using an aryllithium reagent prepared from aryl bromides and metallic lithium. *m*-Tolyllithium was prepared by the reaction of bromide **5f** and lithium in Et_2O [Eq. (1)].[22] Without rigorous removal of co-produced LiBr,[23] this reagent was employed in the catalytic addition to **6b** to give diarylmethanol **7fb** (97 % *ee*) in quantitative yield.



(1)

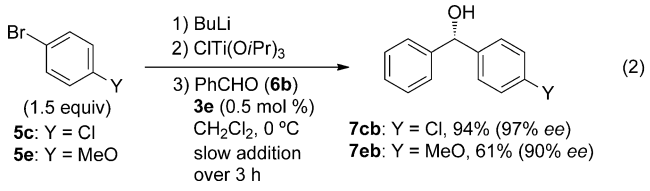
It is also worth noting that the arylation reaction could be carried out even at 0.5 mol % catalyst loading while keeping high enantioselectivity [Eq. (2)]. The reaction of **5c** and **6b** using DTBP-H_8-BINOL (**3e**; 0.5 mol %) provided diarylmethanol **7cb** in 97 % *ee* and in 94 % yield. Under similar conditions, diarylmethanol **7eb** was obtained in 90 % *ee* starting from **5e** and **6b**.

We have recently reported enantioselective arylation of aldehydes catalyzed by the DPP-H_8-BINOL-based titanium complex with mixed reagents of aryl Grignard reagents and $Ti(OiPr)_4$[12b,c] and with mixed reagents of aryllithiums, $Ti(OiPr)_4$, and $MgBr_2$.[17] Although being carried out under similar conditions, the present reaction employing aryltitanium reagents exhibited generally higher enantioselectivities (Table 3). A notable exception is a lower selectivity observed for aliphatic aldehydes **6g** and **h** (Table 3, entries 8 and 9); with these substrates the mixed reagent of *p*-ClC_6H_4MgBr and $Ti(OiPr)_4$ underwent highly enantioselective addition to **6g**.[12b,c] The results imply that the mixed titanium reagents participated in the catalytic reaction not in

Table 3. Catalytic enantioselective arylation of aldehydes by using bromides as aryl source.[a]

Entry	Bromide **5**	Aldehyde **6**	Product	Yield [%]	*ee* [%][b]	
1	PhBr (**5a**)	1-NaphCHO (**6a**)	**7aa**	96	98	(95)
2	PhBr (**5a**)	*p*-ClC_6H_4CHO (**6c**)	**7ac**	92	95	(94)
3	*p*-MeC_6H_4Br (**5b**)	PhCHO (**6b**)	**7bb**	98	93	(91) {92}
4	*p*-ClC_6H_4Br (**5c**)	PhCHO (**6b**)	*ent*-**7ac**	99	98	(91)
5[c]	*p*-ClC_6H_4Br (**5c**)	*o*-ClC_6H_4CHO (**6d**)	**7cd**	88	96	(90)
6	*p*-ClC_6H_4Br (**5c**)	2-ThiCHO (**6e**)	**7ce**	96	94	{82}
7	*p*-ClC_6H_4Br (**5c**)	CH_2=C(Me)CHO (**6f**)	**7cf**	88	98	{96}
8	*p*-ClC_6H_4Br (**5c**)	BuCHO (**6g**)	**7cg**	82	72	{96}
9[c]	*p*-ClC_6H_4Br (**5c**)	*c*-$C_6H_{11}CHO$ (**6h**)	**7ch**	97	39	–
10	*p*-FC_6H_4Br (**5d**)	PhCHO (**6b**)	**7db**	85	92	(97) {93}
11	*p*-$MeOC_6H_4Br$ (**5e**)	PhCHO (**6b**)	**7eb**	75	94	{89}
12[c]	*m*-MeC_6H_4Br (**5f**)	PhCHO (**6b**)	**7fb**	95	92	{92}
13[d]	*o*-MeC_6H_4Br (**5g**)	PhCHO (**6b**)	**7gb**	92	12	–
14	*o*-$MeOC_6H_4Br$ (**5h**)	PhCHO (**6b**)	**7hb**	93	27	{9}
15	2-NaphBr (**5i**)	PhCHO (**6b**)	**7ib**	90	90	{86}

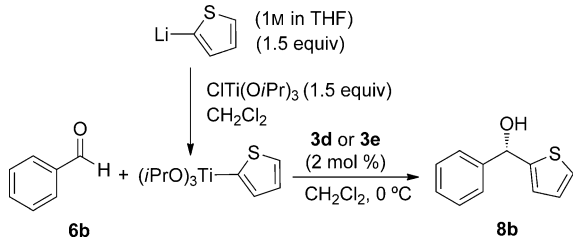
[a] Unless otherwise noted, reactions were carried out by adding aryltitanium reagents $ArTi(OiPr)_3$ prepared from aryl bromides **6** (1.5 equiv), *n*BuLi (1.5 equiv), and $ClTi(OiPr)_3$ (1.5 equiv) in CH_2Cl_2 (3 mL) and Et_2O (3 mL) dropwise over 2 h to a solution of aldehydes **6** (1 mmol) and **3d** (2 mol %) in CH_2Cl_2 (4 mL) at 0 °C. The reaction mixture was stirred for a further 1 h before workup. [b] The *ee* values reported for reactions with $ArMgBr\text{-}Ti(OiPr)_4$[12c] and with $ArLi\text{-}MgBr_2\text{-}Ti(OiPr)_4$[17] are shown in round and curly brackets, respectively. [c] The aryltitanium reagent was added steadily by immersing the syringe needle into the reaction mixture. [d] *o*-MeC_6H_4Li (1.5 equiv) was prepared from **5g** and Li in Et_2O and used after titration.



the form of $ArTi(OiPr)_3$ but in the form of titanates, $ArTi(OiPr)_4{\cdot}MgX$.

Catalytic enantioselective heteroarylation of aldehydes by organolithium reagents: Despite the importance of heteroaryl groups in medicinal chemistry, the enantioselective addition of heteroaryl groups to aldehydes has been relatively less developed.[16b,24,25] Indeed, to the best of our knowledge, the only examples of highly enantioselective heteroaryl addition to heteroaryl aldehydes giving rise to enantioenriched diheteroarylmethanols were reported by Walsh and coworkers.[16b] The method involved the transmetalation of heteroaryllithiums, such as 2- and 3-thiophenyl and 3-furyl, with EtZnCl to generate (heteroaryl)ZnEt species. To expand the scope of the present enantioselective arylation, we examined the reactions employing heteroaryltitanium reagents prepared in situ.

When the protocol for the enantioselective arylation was applied to (2-thienyl)$Ti(OiPr)_3$, prepared in situ from commercially available 2-thienyllithium (1 M in THF), the corresponding benzaldehyde adduct **8b** was obtained in high yield but with moderate selectivity (62% *ee*; Scheme 4,



Scheme 4. Enantioselective 2-thienylation of benzaldehyde (**6b**) with (2-thienyl)-$Ti(OiPr)_3$ catalyzed by a titanium complex derived from **3d** or **e**.

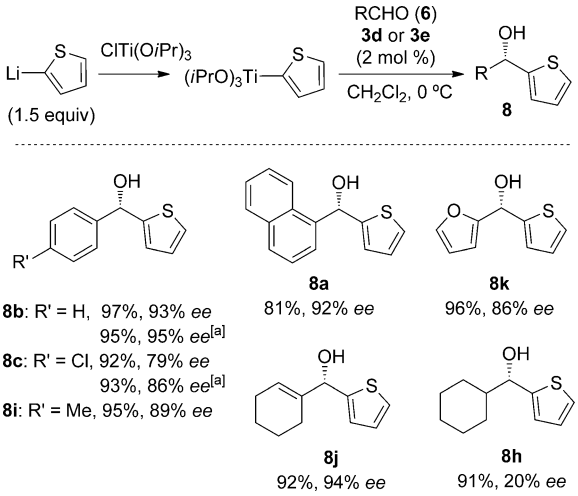
Table 4, entry 1). It was found that the manner of slow addition is influential to the enantioselectivity. In mode A (Table 4, entry 1), the 2-thienyltitanium reagent was added dropwise over 2 h by using a syringe pump. On the other hand, when the titanium reagent was added steadily for 2 h by immersing a syringe needle in the reaction mixture (mode B), the selectivity of **8b** was improved to 76% *ee* (Table 4, entry 2). Further improvement was achieved either by extending the addition times (Table 4, entry 3) or by employing dilute conditions (Table 4, entry 4). Finally, the combination of the two modifications brought about the optimal enantioselectivities of 93 and 95% *ee* with 2 mol% of ligand **3d** and **e**, respectively (Table 4, entries 5 and 6).

Table 4. Catalytic enantioselective 2-thienylation of benzaldehyde (**6b**).[a]

Entry	Slow addition Mode[b]	Time [h][c]	Concentration [M] Titanium reagent	**6b**	Yield [%]	*ee* [%]
1	A	2	0.16	0.25	90	62
2	B	2	0.16	0.25	89	76
3	B	3	0.16	0.25	92	87
4	B	2	0.08	0.13	79	90
5	B	3	0.08	0.13	97	93
6[d]	B	3	0.08	0.13	95	95

[a] Unless otherwise noted, reactions were carried out on a 1 mmol-scale by using **3d** (2 mol%). After the slow addition of the 2-thienyltitanium reagent, the reaction mixture was stirred for a further 1 h before workup. [b] Mode A: dropwise addition, mode B: steady addition by immersing a syringe needle into the reaction mixture. [c] Time for slow addition. [d] **3e** (2 mol%) was used.

Under these optimized conditions employing **3d** or **e** (2 mol%), a variety of aldehydes, including aryl, heteroaryl, and α,β-unsaturated derivatives, underwent 2-thienylation to give the corresponding adducts **8** in high enantioselectivities (86–95% *ee*) and in high yields (Scheme 5). The reaction of

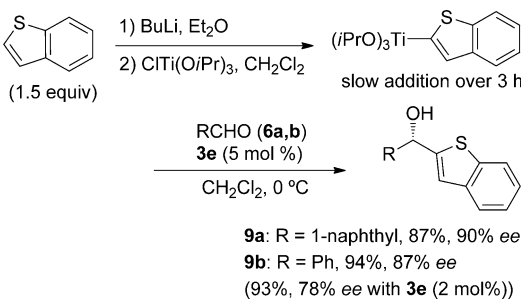


Scheme 5. Enantioselective 2-thienylation of aldehydes **6** with (2-thienyl)$Ti(OiPr)_3$ catalyzed by a titanium complex derived from **3d** or **e**. Unless otherwise noted, DPP-H_8-BINOL (**3d**) was used. [a] DTBP-H_8-BINOL (**3e**) was used.

cyclohexanecarboxaldehyde (**6h**) resulted in poor selectivity, as observed in the arylation (Table 3, entry 8). Ligand **3e** exhibited slightly higher selectivities than **3d**, as illustrated in the formation of **8b** and **c**.

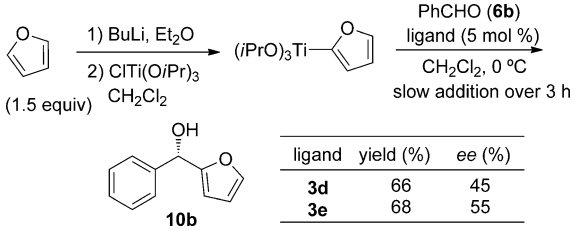
The enantioselective addition of the 2-benzothienyl group was also achievable (Scheme 6). Thus, lithiation of benzothiophene with *n*BuLi and transmetalation with $ClTi(OiPr)_3$ followed by the slow addition of the resulting (2-benzothienyl)titanium reagent to aldehydes **6a** and **b** in the presence of **3e** (5 mol%) afforded the corresponding adducts **9a** and **b** in high enantioselectivities. For 2-benzothienylation, enantioselectivities were less satisfactory at 2 mol% catalyst loading.

The modified protocol developed in the 2-thienylation were not effective in the 2-furylation of aldehydes



Scheme 6. Enantioselective addition of a 2-benzothienyl group to aldehydes **6a** and **b** catalyzed by a titanium complex derived from **3e**.

(Scheme 7). Thus, in the presence of **3d** (5 mol%), (2-furyl)Ti(O*i*Pr)$_3$, prepared in situ from furan via 2-furyllithium, gave benzaldehyde adduct **10b** in 45% *ee* and in 66% yield. The enantioselectivity was slightly improved by the use of **3e**, although still unsatisfactory.

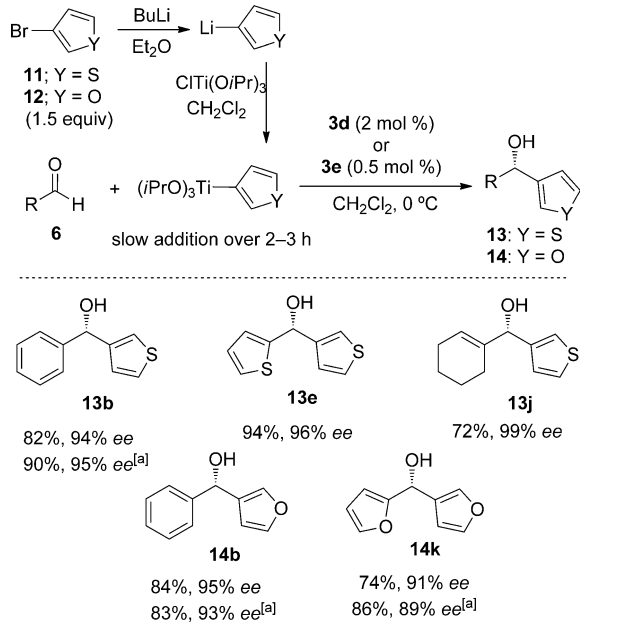


ligand	yield (%)	*ee* (%)
3d	66	45
3e	68	55

Scheme 7. Enantioselective 2-furylation of benzaldehyde (**6b**) catalyzed by a titanium complex derived from **3d** or **e**.

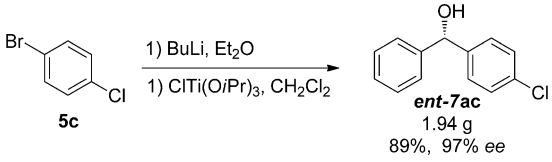
In comparison with 2-thienylation and 2-furylation, the enantioselective addition of 3-thienyl and 3-furyl groups to aldehydes proceeded in a more efficient manner (Scheme 8). The 3-thienyltitanium reagent was prepared in situ from bromide **11** via a 3-thienyllithium intermediate. Reactions were carried out with aldehydes **6** in the presence of ligand **3d** (2 mol%) by adding the titanium reagent (1.5 equiv) over 2 h. Under these conditions, not only aromatic aldehyde **6b** but also heteroaromatic aldehyde **6e** and α,β-unsaturated aldehyde **6j** underwent highly enantioselective 3-thienylation to give the corresponding adducts **13b**, **e**, and **j** (94–99% *ee*) in high yields. Under similar conditions, 3-furylation of aldehydes starting from 3-bromofuran (**12**) also proceeded efficiently to furnish adducts **14b** and **k** in high selectivities (91–95% *ee*). Remarkably, further reduction in the amount of catalyst did not result in an erosion of enantioselectivity. Thus, even with 0.5 mol% **3e**, 3-thienyl adduct **13b** and 3-furyl adducts **14b** and **k** were obtained in high selectivities (89–95% *ee*) comparable to those obtained in reactions with 2 mol% **3e**.

Application to gram-scale synthesis: To demonstrate the preparative utility of the present enantioselective arylation, gram-scale syntheses of diarylmethanol and aryl heteroarylmethanol derivatives were examined. Even with 24 mg (0.5 mol%) of chiral ligand **3e**, the reaction of aldehyde **6b**

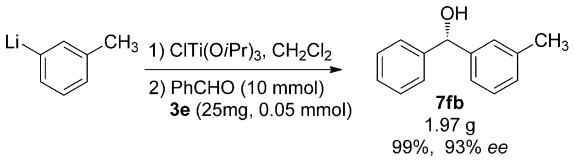


Scheme 8. Enantioselective 3-thienylation and 3-furylation of aldehydes **6** catalyzed by a titanium complex derived from **3d** or **e**. Unless otherwise noted, DPP-H$_8$-BINOL (**3d**, 2 mol%) was used with slow addition over 2 h. [a] DTBP-H$_8$-BINOL (**3e**, 0.5 mol%) was used with slow addition over 3 h.

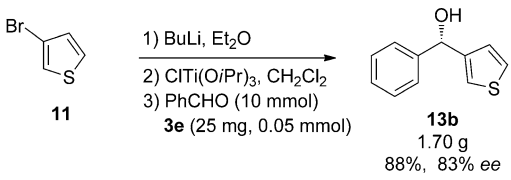
(10 mmol) and bromide **5c** (15 mmol) provided 2.05 g (94% yield) of diarylmethanol **7cb** in 97% *ee* [Eq. (3)]. Likewise, a 10 mmol-scale reaction of **6b** employing *m*-tolyllithium afforded 1.97 g (99% yield) of diarylmethanol **7fd** in 93% *ee* [Eq. (4)]. The enantiopurity of **7fb** was enhanced to 97% *ee* by recrystallization from hexane. As shown in [Eq. (5)], heteroarylation could also be carried out on a 10 mmol scale without difficulty.



(3)



(4)



(5)

Conclusion

We have developed a highly efficient and practical method for the catalytic enantioselective arylation and heteroarylation of aldehydes with organotitanium reagents, prepared in situ by the reaction of aryl- and heteroaryllithiums with $ClTi(OiPr)_4$. Titanium complexes derived from DPP-H_8-BINOL (**3d**) and DTBP-H_8-BINOL (**3e**) were shown to be excellent catalysts in terms of enantioselectivity and turnover efficiency for this transformation, providing diaryl-, aryl heteroaryl-, and diheteroarylmethanol derivatives in high enantioselectivity at low catalyst loading (0.2–2 mol%). Because the organolithium intermediates can be generated by Br/Li exchange of aryl bromides **5** and heteroaryl bromides **11** and **12** with *n*BuLi, the present reaction permits access to a wide range of enantioenriched secondary alcohols starting from commercially available bromides and aldehydes in a most straightforward manner. In addition, commercially available 2-thienyllithium in THF has been employed, for the first time, in enantioselective addition to aldehydes. The preparative utility of the present reaction has been demonstrated by conducting the reaction on a 10 mmol scale without any difficulty at 0.5 mol% catalyst loading.

Experimental Section

General: CH_2Cl_2 was dried and distilled over CaH_2. Et_2O and THF were distilled from sodium benzophenone ketyl. Aldehydes, $Ti(OiPr)_4$, and $TiCl_4$ were used after distillation. A stock solution of $ClTi(OiPr)_3$ in CH_2Cl_2 (0.5 M) was prepared by mixing $Ti(OiPr)_4$ and $TiCl_4$ in a molar ratio of 3:1 in CH_2Cl_2 at 0 °C. Ligands **3d**[12c] and **4b**[26] were prepared according to a reported procedure. The reagents *m*- and *o*-tolyllithium were prepared by reaction of *m*- and *o*-bromotoluene with lithium in Et_2O, respectively, according to a reported procedure[22] and used after filtration and titration. *n*BuLi in hexane and PhLi in cyclohexane and Et_2O were obtained from Kanto Chemicals Co. Ltd. and used after titration.[27] 2-Thienyllithium (1 M in THF) was purchased from Aldrich and used without titration.

(*R*)-3-(3,5-Di-*tert*-butylphenyl)-2,2′-dihydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (3e): A mixture of (*R*)-3-bromo-2,2′-dimethoxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl[12c] (0.503 g, 1.25 mmol), (3,5-di-*tert*-butyl)phenylboronic acid (0.323 g, 1.38 mmol),[28] $[Pd(PPh_3)_4]$ (36 mg, 0.031 mmol), and $Ba(OH)_2{\cdot}8H_2O$ (0.435 g, 1.38 mmol) in water (4 mL) and 1,4-dioxane (12.5 mL) was heated to reflux for 19 h under an argon atmosphere. The reaction mixture was passed through a plug of Celite and the filtrate was 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 (3% ethyl acetate in hexane) to give (*R*)-3-(3,5-di-*tert*-butylphenyl)-2,2′-dimethoxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (0.594 g, 93%) as an amorphous solid. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.38$ (s, 18H), 1.62–1.87 (m, 8H), 2.11–2.21 (m, 2H), 2.35 (m, 1H), 2.48 (m, 1H), 2.78–2.91 (m, 4H), 3.22 (s, 3H), 3.76 (s, 3H), 6.82 (d, $J = 8.4$ Hz, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.14 (s, 1H), 7.38 (s, 1H), 7.44 ppm (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 23.1$ (2C), 23.2 (2C), 27.0, 27.4, 29.4, 29.6, 31.6, 34.9, 55.3, 60.3, 107.9, 120.3, 123.5, 126.0, 128.7, 129.6, 130.8, 131.0, 132.3, 133.0, 135.9, 136.7. 138.3, 150.1, 153.0, 154.8 ppm; HRMS (FAB): *m*/*z* calcd for $C_{36}H_{46}O_2$: 510.3498; found: 510.3495.

Boron tribromide (0.55 mL, 5.8 mmol) was added to a solution of the above dimethyl ether (594 mg, 1.16 mmol) in CH_2Cl_2 (7.5 mL) at −10 °C under an argon atmosphere and 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 (5% ethyl acetate in hexane) to give **3e** (411 mg, 73%) as an amorphous solid. $[\alpha]_D^{23} = +63.3$ ($c = 1.03$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.37$ (s, 18H), 1.64–1.82 (m, 8H), 2.17–2.29 (m, 2H), 2.31–2.45 (m, 2H), 2.73–2.85 (m, 4H), 4.69 (br, 1H), 5.00 (br, 1H), 6.85 (d, $J = 8.3$ Hz, 1H), 7.07 (d, $J = 8.3$ Hz, 1H), 7.16 (s, 1H), 7.38–7.44 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.9$, 23.0 (3C), 23.1, 27.1, 27.2, 29.3, 31.5, 34.9, 112.8, 119.6, 120.1, 121.4, 123.5, 127.1, 129.9, 130.1, 130.7, 131.7, 136.5, 136.7, 136.8, 148.3, 150.9, 151.0 ppm; HRMS (FAB): *m*/*z* calcd for $C_{34}H_{42}O_2$: 482.3185; found: 482.3177.

Typical procedure for the catalytic enantioselective arylation of aldehydes with aryl bromides at 2 mol% catalyst loading—(*S*)-phenyl-*p*-tolylmethanol (7bb; Table 3, entry 3):[11b] *n*BuLi (1.4 M in hexane, 1.07 mL, 1.5 mmol) was added over 10 min to a solution of *p*-bromotoluene (**5b**; 257 mg, 1.5 mmol) in Et_2O (3 mL) at −30 °C under argon. After stirring at RT for 30 min, the resulting solution of *p*-tolyllithium was cooled to −78 °C. To this was added $ClTi(OiPr)_3$ (0.5 M in CH_2Cl_2, 3.0 mL, 1.5 mmol) and the mixture was allowed to warm to RT for 15 min. The resulting suspension was added dropwise over 2 h, by using a syringe pump, to a solution of ligand **3d** (10.5 mg, 0.020 mmol) and benzaldehyde (**6b**; 106 mg, 1.0 mmol) in CH_2Cl_2 (4 mL) at 0 °C. After stirring further at 0 °C for 1 h, the reaction mixture was quenched by the addition of aqueous HCl (1 N) and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous $NaHCO_3$ (5%) and with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel; 1% ethyl acetate in toluene) gave **7bb** (193 mg, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.22$ (br s, 1H), 2.35 (s, 3H), 5.80 (s, 1H), 7.16 (m, 2H), 7.27–7.29 (m, 3H), 7.33–7.40 ppm (m, 4H); HPLC (Chiralcel OD-H, 5% *i*PrOH in *n*-hexane, 0.5 mL min^{-1}): $t_R = 30.5$ (major *S* enantiomer), 34.0 min (minor *R* enantiomer); *ee*: 93%. The retention times were concordant with published values.[11b]

Typical procedure for the catalytic enantioselective arylation of aldehydes with aryllithium reagents [Eq. (1)]—(*S*)-phenyl-*m*-tolylmethanol (7fb):[11b] $ClTi(OiPr)_3$ (0.5 M in CH_2Cl_2, 3.0 mL, 1.5 mmol) was diluted with CH_2Cl_2 (7 mL) and cooled to −78 °C under an argon atmosphere and *m*-tolyllithium (0.56 M in Et_2O, 2.7 mL, 1.5 mmol) was added. The mixture was allowed to warm to RT for 15 min and the resulting suspension was added with a syringe pump over 2 h to a solution of ligand **3d** (10.5 mg, 0.020 mmol) and benzaldehyde (**6b**; 106 mg, 1.0 mmol) in CH_2Cl_2 (4 mL) at 0 °C. During the addition, the syringe needle was immersed in the solution so that the titanium reagent was introduced steadily. After stirring further at 0 °C for 1 h, the reaction mixture was quenched by the addition of aqueous HCl (1 N) and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous $NaHCO_3$ (5%) and with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel; 1% ethyl acetate in toluene) gave **7fb** (196 mg, 99% yield). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.22$ (br s, 1H), 2.35 (s, 3H), 5.81 (s, 1H), 7.10 (d, $J = 7.4$ Hz, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 7.22–7.31 (m, 3H), 7.34–7.42 ppm (m, 4H); HPLC (Chiralcel OB-H, 10% *i*PrOH in *n*-hexane, 1 mL min^{-1}): $t_R = 27.1$ (major *S* enantiomer), 12.7 min (minor *R* enantiomer); *ee*: 98%. The retention times were concordant with published values.[11b]

Typical procedure for the catalytic enantioselective arylation of aldehydes with aryl bromides at 0.5 mol% catalyst loading [Eq. (2)]—(*S*)-(4-chlorophenyl)phenylmethanol (*ent*-7ac):[29] *n*BuLi (1.54 M in hexane, 0.97 mL, 1.5 mmol) was added over 5 min to a solution of 4-bromo-1-chlorobenzene (**5c**; 287 mg, 1.5 mmol) in Et_2O (3 mL) at 0 °C under argon. After stirring at RT for 20 min, the resulting solution of 4-chlorophenyllithium was cooled to −78 °C, and $ClTi(OiPr)_3$ (0.5 M in CH_2Cl_2, 2.86 mL, 1.43 mmol) was added. After diluting with CH_2Cl_2 (12.2 mL), the mixture was allowed to warm to RT for 15 min. The resulting suspension was added by using a syringe pump over 3 h to a solution of ligand **3e** (2.5 mg, 0.005 mmol) and benzaldehyde (**6b**; 106 mg, 1.0 mmol) in

CH_2Cl_2 (8 mL) at 0 °C. During the addition, the syringe needle was immersed in the solution so that the titanium reagent was introduced steadily. After stirring further at 0 °C for 1 h, the reaction mixture was quenched by the addition of aqueous HCl (1 N) and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous $NaHCO_3$ (5%) and with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel; 1% ethyl acetate in toluene) gave *ent*-**7ac** (205 mg, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (br s, 1H), 5.83 (s, 1H), 7.26–7.35 ppm (m, 9H); HPLC (Chiralcel OB-H, 9% *i*PrOH in *n*-hexane, 1 mL min^{-1}): t_R = 25.9 (major *S* enantiomer), 17.4 min (minor *R* enantiomer); *ee*: 97%. The retention times were concordant with published values.[29]

Typical procedure for the catalytic enantioselective 2-thienylation of aldehydes (Scheme 5)—(*S*)-phenylthiophen-2-ylmethanol (8b):[9d] $ClTi(OiPr)_3$ (0.5 M in CH_2Cl_2, 3.0 mL, 1.5 mmol) was diluted with CH_2Cl_2 (14.5 mL) and cooled to −78 °C. 2-Thienyllithium (1 M in THF, 1.5 mL, 1.5 mmol) was added and the mixture was allowed to warm to RT for 15 min. The resulting suspension was added by using a syringe pump over 3 h to a solution of ligand **3d** (10.5 mg, 0.02 mmol) and benzaldehyde (**6b**) (106 mg, 1.0 mmol) CH_2Cl_2 (8 mL) at 0 °C. During the addition, the syringe needle was immersed in the solution so that the titanium reagent was introduced steadily. After stirring further at 0 °C for 1 h, the reaction mixture was quenched by the addition of aqueous HCl (1 N) and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous $NaHCO_3$ (5%) and with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel; 1% ethyl acetate in toluene) gave **8b** (185 mg, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.43 (br s, 1H), 6.06 (1H, s), 6.89 (d, J = 3.5 Hz, 1H), 6.95 (m, 1H), 7.27 (d, J = 5.8 Hz, 1H), 7.32 (m, 1H), 7.38 (m, 2H), 7.45 ppm (m, 2H); HPLC (Chiralcel OD-H, 2% *i*PrOH in *n*-hexane, 1 mL min^{-1}): t_R = 40.6 min (major *S* enantiomer), 46.0 min (minor *R* enantiomer); *ee*: 93%. The retention times were concordant with published values.[9d]

Typical procedure for the catalytic enantioselective 2-benzothienylation of aldehydes (Scheme 6)—(*S*)-benzo[*b*]thiophen-2-yl-naphthalen-1-ylmethanol (9a):[30] *n*BuLi (1.41 M in hexane, 1.06 mL, 1.5 mmol) was added to a solution of benzo[*b*]thiophene (287 mg, 2.14 mmol) in Et_2O (4.7 mL) at 0 °C under argon over 5 min. After stirring at RT for 30 min, the resulting solution of 2-benzothienyllithium was cooled at −78 °C and $ClTi(OiPr)_3$ (0.5 M in CH_2Cl_2, 3.0 mL, 1.5 mmol) was added. After diluting with CH_2Cl_2 (10.3 mL), the mixture was allowed to warm to RT for 15 min and the resulting suspension was added by using a syringe pump over 3 h to a solution of ligand **3e** (24.9 mg, 0.05 mmol) and 1-naphthaldehyde (**6a**) (156 mg, 1.0 mmol) in CH_2Cl_2 (8 mL) at 0 °C. During the addition, the syringe needle was immersed in the solution so that the titanium reagent was introduced steadily. After stirring further at 0 °C for 1 h, the reaction mixture was quenched by the addition of aqueous HCl (1 N) and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous $NaHCO_3$ (5%) and with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel; 1% ethyl acetate in toluene) gave **9a** (253 mg, 87% yield). $[\alpha]_D^{30}$ = +97.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.66 (br s, 1H), 6.80 (s, 1H), 7.08 (s, 1H), 7.27–7.32 (m, 2H), 7.44–7.50 (m, 2H), 7.53 (dd, J = 7.3, 8.1 Hz, 1H), 7.63 (m, 1H), 7.77–7.82 (m, 2H), 7.86–7.92 (m, 2H), 8.12 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 70.5, 122.8, 122.4, 123.6, 123.8, 124.2 (2C), 124.4, 125.4, 125.8, 126.4, 128.8, 129.1, 130.5, 133.9, 137.8, 139.5, 139.9, 148.1 ppm; HPLC (Chiralcel OD-H, 10% *i*PrOH in *n*-hexane, 1 mL min^{-1}): t_R = 42.5 (major *S* enantiomer), 20.7 min (minor *R* enantiomer); *ee*: 90%. The absolute structure was assumed by analogy.

Typical procedure for the catalytic enantioselective 2-furylation of benzaldehyde (6b; Scheme 7)—(*S*)-furan-2-ylphenylmethanol (10b):[7c] *n*BuLi (1.41 M in hexane, 1.06 mL, 1.5 mmol) was added to a solution of furan (0.13 mL, 1.8 mmol) in Et_2O (1 mL) at 10 °C under argon over 5 min. After stirring at RT for 1.5 h, the resulting solution of 2-furyllithium was cooled at −78 °C and $ClTi(OiPr)_3$ (0.5 M in CH_2Cl_2, 3.0 mL, 1.5 mmol) was added. After diluting with CH_2Cl_2 (14 mL), the mixture was allowed to warm to RT for 15 min and the resulting suspension was added by using a syringe pump over 3 h to a solution of ligand **3e** (24.9 mg, 0.05 mmol) and benzaldehyde (**6b**; 106 mg, 1.0 mmol) in CH_2Cl_2 (8 mL) at 0 °C. During the addition, the syringe needle was immersed in the solution so that the titanium reagent was introduced steadily. After stirring further at 0 °C for 1 h, the reaction mixture was quenched by the addition of aqueous HCl (1 N) and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous $NaHCO_3$ (5%) and with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel; 1% ethyl acetate in toluene) gave **10b** (118 mg, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (br s, 1H), 5.84 (s, 1H), 6.12 (d, J = 4.1 Hz, 1H), 6.32 (dd, J = 2.3, 4.1 Hz, 1H), 7.31–7.46 ppm (m, 6H); HPLC: (Chiralcel OD-H, 5% *i*PrOH in *n*-hexane, 1.0 mL min^{-1}): t_R = 16.2 (major *R* enantiomer), 20.1 min (minor *S* enantiomer); *ee*: 55%. The retention times were concordant with published values.[7c]

Typical procedure for the catalytic enantioselective 3-thienylation and 3-furylation of aldehydes at 2 mol% catalyst loading (Scheme 8)—(*R*)-thiophen-3-ylthiophen-2-ylmethanol (13e):[16b] 3-Bromothiophene (0.14 mL, 1.5 mmol) was added over 15 min to a solution of *n*BuLi (1.41 M in hexane, 1.17 mL, 1.65 mmol) in Et_2O (1.2 mL) at −70 °C under argon. After stirring at −30 °C for 30 min, the resulting solution of 3-thienyllithium was cooled to −78 °C, then $ClTi(OiPr)_3$ (0.5 M in CH_2Cl_2, 3.0 mL, 1.5 mmol) was added. After diluting with CH_2Cl_2 (14 mL), the mixture was allowed to warm to RT for 15 min. The resulting suspension was added by using a syringe pump over 2 h to a solution of ligand **3d** (105 mg, 0.02 mmol) and thiophene-2-carbaldehyde (**6e**; 112 mg, 1.0 mmol) in CH_2Cl_2 (8 mL) at 0 °C. During the addition, the syringe needle was immersed in the solution so that the titanium reagent was introduced steadily. After being stirred further at 0 °C for 1 h, the reaction mixture was quenched by the addition of aqueous HCl (1 N) and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous $NaHCO_3$ (5%) and with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel; 1% ethyl acetate in toluene) gave **13d** (184 mg, 94% yield). $[\alpha]_D^{25}$ = −8.5 (*c* 1.01, $CHCl_3$) {Lit.[16b] $[\alpha]_D$ = +5.0 (*c* 0.015, $CHCl_3$) for *S* isomer (93% *ee*)}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.44 (br s, 1H), 6.14 (s, 1H), 6.97 (m, 2H) 7.10 (m, 1H) 7.27–7.32 ppm (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 68.8, 121.9, 124.8, 125.4, 126.2, 126.3, 126.7, 144.5, 147.5 ppm; HPLC (Chiralcel OD-H, 5% *i*PrOH in *n*-hexane, 1.0 mL min^{-1}): t_R = 21.2 (major *R* enantiomer), 23.2 min (minor *S* enantiomer); *ee*: 94%.

Typical procedure for the catalytic enantioselective 3-thienylation and 3-furylation of aldehydes at 0.5 mol% catalyst loading (Scheme 8)—(*R*)-furan-3-yl-furan-2-yl-methanol (14k):[16b] 3-Bromofuran (0.14 mL, 1.5 mmol) was added over 15 min to a solution of *n*BuLi (1.54 M in hexane, 1.07 mL, 1.65 mmol) in Et_2O (1.2 mL) at −70 °C under argon. After stirring at −40 °C for 30 min, the resulting solution of 3-furyllithium was cooled at −78 °C and $ClTi(OiPr)_3$ (0.5 M in CH_2Cl_2, 3.0 mL, 1.5 mmol) was added. After diluting with CH_2Cl_2 (14 mL), the mixture was allowed to warm to RT for 15 min. The resulting suspension was added by using a syringe pump over 3 h to a solution of ligand **3e** (2.5 mg, 0.005 mmol) and furan-2-carbaldehyde (**6e**; 96 mg, 1.0 mmol) in CH_2Cl_2 (8 mL) at 0 °C. During the addition, the syringe needle was immersed in the solution so that the titanium reagent was introduced steadily. After being stirred further at 0 °C for 1 h, the reaction mixture was quenched by the addition of aqueous HCl (1 N) and extracted three times with ethyl acetate. The organic layers were washed successively with aqueous $NaHCO_3$ (5%) and with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel; 1% ethyl acetate in toluene) gave **14k** (140 mg, 86% yield). $[\alpha]_D^{25}$ = −3.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.82 (br s, 1H), 5.74 (br s, 1H), 6.22 (br d, J = 3.3 Hz, 1H), 6.33 (dd, J = 1.9, 3.3 Hz, 1H), 4.44 (br s, 1H), 7.39 (m, 2H), 7.43 ppm (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 63.0, 107.0, 108.2, 110.2, 125.9, 140.0, 142.4, 143.2, 155.2 ppm; HPLC (Chiralcel OB-H, 3% *i*PrOH in *n*-hexane, 1.0 mL min^{-1}): t_R = 28.8 (minor *S* enantiomer), 30.8 min (major *R* enantiomer); *ee*: 89%. The absolute structure was assumed by analogy.

Typical procedure for the gram-scale synthesis of enantioenriched diarylmethanols [Eq. (3–5)]—(*S*)-(4-chlorophenyl)phenylmethanol (*ent*-7ac): *n*BuLi (1.54 M in hexane, 9.7 mL, 15 mmol) was added over 10 min to a solution of 4-bromo-1-chlorobenzene (**5c**; 2.87 g, 15.0 mmol) in Et_2O (30 mL) at 0 °C under argon. After stirring at RT for 20 min, the resulting solution of 4-chlorophenyllithium was cooled to −78 °C and $ClTi(OiPr)_3$ (0.5 M in CH_2Cl_2, 28.6 mL, 14.3 mmol) was added. After diluting with CH_2Cl_2 (122 mL), the mixture was allowed to warm to RT for 15 min. The resulting suspension was added by using a cannula (Teflon needle) over 3 h to a solution of ligand **3e** (25 mg, 0.050 mmol) and benzaldehyde (**6b**) (1.06 g, 10.0 mmol) in CH_2Cl_2 (80 mL) at 0 °C. During the addition, the needle was immersed in the solution so that the titanium reagent was introduced steadily. After stirring at 0 °C for 1 h, the reaction mixture was quenched by the addition of aqueous HCl (1 N, 150 mL) and extracted three times with CH_2Cl_2. The organic layers were washed successively with aqueous $NaHCO_3$ (5%) and with brine, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (silica gel; 1% ethyl acetate in toluene) gave *ent*-**7ac** (1.94 g, 89% yield; 97% *ee*).

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[1] a) J. L. Devalia, C. De Vos, F. Hanotte, E. Baltes, *Allergy* **2001**, *56*, 50–57; b) Y. Bolshan, C.-Y. Chen, J. R. Chilenski, F. Gosselin, D. J. Mathre, P. D. O'Shea, A. Roy, R. D. Tillyer, *Org. Lett.* **2004**, *6*, 111–114; c) E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1996**, *37*, 5675–5678; d) R. F. Rekker, H. Timmerman, A. F. Harms, W. T. Nauta, *Arzneim. Forsch.* **1971**, *21*, 688–691; e) C. Van der Stelt, W. J. Heus, W. T. Nauta, *Arzneim. Forsch.* **1969**, *19*, 2010–2012; f) A. Ebnöther, H.-P. Weber, *Helv. Chim. Acta* **1976**, *59*, 2462–2468; g) A. F. Casy, A. F. Drake, C. R. Ganellin, A. D. Mercer, C. Upton, *Chirality* **1992**, *4*, 356; h) M. N. G. James, G. J. B. Williams, *Can. J. Chem.* **1974**, *52*, 1872–1879; i) A. Shaffiée, G. Hite, *J. Med. Chem.* **1969**, *12*, 266; j) N. A. Magnus, P. B. Anzeveno, D. S. Coffey, D. A. Hay, M. E. Laurila, J. M. Schkeryantz, B. W. Shaw, M. A. Staszak, *Org. Process Res. Dev.* **2007**, *11*, 560–567.

[2] F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454–470.

[3] For reviews, see: a) R. Noyori, T. Ohkuma, *Angew. Chem.* **2001**, *113*, 40–75; *Angew. Chem. Int. Ed.* **2001**, *40*, 40–73; b) H.-U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner, M. Studer, *Adv. Synth. Catal.* **2003**, *345*, 103–151; for catalytic hydrogenation, see: c) T. Ohkuma, M. Koizumi, H. Ikehira, T. Yokozawa, R. Noyori, *Org. Lett.* **2000**, *2*, 659–662; d) J. Wu, J.-X. Ji, R. Guo, C.-H. Yeung, A. S. C. Chan, *Chem. Eur. J.* **2003**, *9*, 2963–2968; e) C.-Y. Chen, R. A. Reamer, J. R. Chilenski, C. J. McWilliams, *Org. Lett.* **2003**, *5*, 5039–5042; f) K. Kriis, T. Kanger, M. Lopp, *Tetrahedron: Asymmetry* **2004**, *15*, 2687–2691; for catalytic hydrosilylation, see: g) J. Wu, J.-X. Ji, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 3570–3575; h) N. S. Shaikh, S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 2531–2535; *Angew. Chem. Int. Ed.* **2008**, *47*, 2497–2501; i) C.-T. Lee, B. H. Lipshutz, *Org. Lett.* **2008**, *10*, 4187–4190; j) Y.-Z. Sui, X.-C. Zhang, J.-W. Wu, S. Li, J.-N. Zhou, M. Li, W. Fang, A. S. C. Chan, J. Wu, *Chem. Eur. J.* **2012**, *18*, 7486–7492.

[4] a) M. D. Truppo, D. Pollard, P. Devine, *Org. Lett.* **2007**, *9*, 335–338; b) H. Li, D. Zhu, L. Hua, E. R. Biehl, *Adv. Synth. Catal.* **2009**, *351*, 583–588.

[5] a) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757–824; b) J. M. Betancort, C. Garcia, P. J. Walsh, *Synlett* **2004**, 749–760; c) M. Hatano, T. Miyamoto, K. Ishihara, *Curr. Org. Chem.* **2007**, *11*, 127–157; d) M. W. Paixão, A. L. Braga, D. S. Lüdtke, *J. Braz. Chem. Soc.* **2008**, *19*, 813–830; e) M. Hatano, K. Ishihara, *Chem. Rec.* **2008**, *8*, 143–155; f) M. Hatano, K. Ishihara, *Synthesis* **2008**, 1647–1675; g) M. R. Luderer, W. F. Bailey, M. R. Luderer, J. D. Fair, R. J. Dancer, M. B. Sommer, *Tetrahedron: Asymmetry* **2009**, *20*, 981–998.

[6] a) B. Weber, D. Seebach, *Angew. Chem.* **1992**, *104*, 96–97; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 84–86; b) B. Weber, D. Seebach, *Tetrahedron* **1994**, *50*, 7473–7484.

[7] a) P. I. Dosa, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1997**, *62*, 444–445; b) M. Fontes, X. Verdaguer, L. Solà, M. A. Pericàs, A. Riera, *J. Org. Chem.* **2004**, *69*, 2532–2543; c) J. Sedelmeier, C. Bolm, *J. Org. Chem.* **2007**, *72*, 8859–8862, and references cited therein.

[8] a) C. Bolm, J. Rudolph, *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851; b) F. Schmidt, J. Rudolph, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 703–708; c) X.-B. Wang, K. Kodama, T. Hirose, X.-F. Yang, G.-Y. Zhang, *Tetrahedron: Asymmetry* **2010**, *21*, 75–80; d) A. V. Moro, E. R. T. Tiekink, J. Zukerman-Schpector, D. S. Lüdtke, C. R. D. Correia, *Eur. J. Org. Chem.* **2010**, 3696–3703; e) M. Hatano, R. Gouzu, T. Mizuno, H. Abe, T. Yamada, K. Ishihara, *Catal. Sci. Technol.* **2011**, *1*, 1149–1158, and references cited therein.

[9] a) M. Sakai, M. Ueda, N. Miyaura, *Angew. Chem.* **1998**, *110*, 3475; *Angew. Chem. Int. Ed.* **1998**, *37*, 3279; b) H.-F. Duan, J.-H. Xie, W.-J. Shi, Q. Zhang, Q.-L. Zhou, *Org. Lett.* **2006**, *8*, 1479; c) D. Tomita, M. Kanai, M. Shibasaki, *Chem. Asian J.* **2006**, *1–2*, 161–166; d) Y. Yamamoto, K. Kurihara, N. Miyaura, *Angew. Chem.* **2009**, *121*, 4478–4480; *Angew. Chem. Int. Ed.* **2009**, *48*, 4414–4416; e) T. Nishimura, H. Kumamoto, M. Nagaosa, T. Hayashi, *Chem. Commun.* **2009**, 5713–5715; f) J. Karthikeyan, M. Jeganmohan, C.-H. Cheng, *Chem. Eur. J.* **2010**, *16*, 8989–8992; g) S. Morikawa, K. Michigami, H. Amii, *Org. Lett.* **2010**, *12*, 2520–2523; h) Y. Yamamoto, T. Shirai, M. Watanabe, K. Kurihara, N. Miyaura, *Molecules* **2011**, *16*, 5020–5034, and references cited therein.

[10] a) K.-H. Wu, H.-M. Gau, *J. Am. Chem. Soc.* **2006**, *128*, 14808–14809; b) K.-H. Wu, D.-W. Chuang, C.-A. Chen, H.-M. Gau, *Chem. Commun.* **2008**, 2343–2345; c) S. L. Zhou, D.-W. Chuang, S.-J. Chang, H.-M. Gau, *Tetrahedron: Asymmetry* **2009**, *20*, 1407–1412; d) S. Zhou, K.-H. Wu, C.-A. Chen, H.-M. Gau, *J. Org. Chem.* **2009**, *74*, 3500–3505, and references cited therein; e) D. B. Biradar, S. Zhou, H.-M. Gau, *Org. Lett.* **2009**, *11*, 3386–3389.

[11] a) J. Shannon, D. Bernier, D. Daniel, S. Woodward, *Chem. Commun.* **2007**, 3945–3947; b) D. Glynn, J. Shannon, S. Woodward, *Chem. Eur. J.* **2010**, *16*, 1053–1060.

[12] a) Y. Muramatsu, T. Harada, *Angew. Chem.* **2008**, *120*, 1104–1106; *Angew. Chem. Int. Ed.* **2008**, *47*, 1088–1090; b) Y. Muramatsu, T. Harada, *Chem. Eur. J.* **2008**, *14*, 10560–10563; c) Y. Muramatsu, S. Kanehira, M. Tanigawa, Y. Miyawaki, T. Harada, *Bull. Chem. Soc. Jpn.* **2010**, *83*, 19–32.

[13] X.-Y. Fan, Y.-X. Yang, F.-F. Zhuo, S.-L. Yu, X. Li, Q.-P. Guo, Z.-X. Du, C.-S. Da, *Chem. Eur. J.* **2010**, *16*, 1903.

[14] a) K.-H. Wu, S. Zhou, C.-A. Chen, M.-C. Yang, R.-T. Chiang, C.-R. Chen, H.-M. Gau, *Chem. Commun.* **2011**, *47*, 11668–11670; see also: b) Q. Li, H.-M. Gau, *Chirality* **2011**, *23*, 929–939.

[15] L. Brandsma, H. D. Verkruijsse, *Preparative Polar Organometallic Chemistry, Vol. 1*, Springer, Berlin, **1987**, .

[16] a) J. G. Kim, P. J. Walsh, *Angew. Chem.* **2006**, *118*, 4281; *Angew. Chem. Int. Ed.* **2006**, *45*, 4175; b) L. Salvi, J. G. Kim, P. J. Walsh, *J. Am. Chem. Soc.* **2009**, *131*, 12483–12493.

[17] Y. Nakagawa, Y. Muramatsu, T. Harada, *Eur. J. Org. Chem.* **2010**, 6535–6538.

[18] For the catalytic enantioselective arylation of aldehydes starting from functionalized aryl iodides, see: a) A. M. DeBerardinis, M. Turlington, L. Pu, *Org. Lett.* **2008**, *10*, 2709–2712; b) ref. [12e]; c) A. M. DeBerardinis, M. Turlington, J. Ko, L. Sole, L. Pu, *J. Org. Chem.* **2010**, *75*, 2836–2850.

[19] For the catalytic enantioselective arylation of aldehydes starting from functionalized aryl bromides, see: a) ref. [11b]; b) D. Itakura, T. Harada, *Synlett* **2011**, 2875–2879.

[20] H.-T. Yang, S. Zhou, F.-S. Chang, C.-R. Chen, H.-M. Gau, *Organometallics* **2009**, *28*, 5715.

[21] a) B. Weidmann, D. Seebach, *Angew. Chem.* **1983**, *95*, 12–26; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31–45; b) D. Seebach, B. Weidmann, L. Widler, *Mod. Synth. Methods* **1983**, *3*, 217–353; c) M. T. Reetz, J. Westermann, R. Steinbach, B. Wenderoth, R. Pter, R. Ostarek, S. Maus, *Chem. Ber.* **1985**, *118*, 1421–1440; d) M. T. Reetz, R. Steinbach, J. Westermann, R. Peter, B. Wenderoth, *Chem. Ber.* **1985**, *118*, 1441–1454; e) M. T. Reetz, *Organotitanium Reagents in Organic Synthesis*, Springer, Berlin, **1986**.

[22] H. Gilman, E. A. Zoelliner, W. M. Selby, *J. Am. Chem. Soc.* **1933**, *55*, 1252–1257.

[23] The reagent was used after filtration and titration.

[24] a) For reactions employing 2-thiophenylboronic acid, see: X. Liu, L. Qiu, L. Hong, W. Yan, R. Wang, *Tetrahedron: Asymmetry* **2009**, *20*, 616–620; b) for reactions employing (2-thienyl)Zn(Et) prepared in situ from 2-halothiophens and Et_2Zn, see ref. [18e].

[25] For catalytic enantioselective heteroarylation of ketones, see: a) see ref. [11b]; b) S. Zhou, C.-R. Chen, H.-M. Gau, *Org. Lett.* **2010**, *12*, 48–51.

[26] T. Harada, K. Kanda, *Org. Lett.* **2006**, *8*, 3817–3819.

[27] B. E. Love, E. G. Jones, *J. Org. Chem.* **1999**, *64*, 3755–3756.

[28] N. Nomura, R. Ishii, Y. Yamamoto, T. Kondo, *Chem. Eur. J.* **2007**, *13*, 4433–4451.

[29] M. Hatano, T. Miyamoto, K. Ishihara, *J. Org. Chem.* **2006**, *71*, 6474–6484.

[30] M. L. Tedjamulia, Y. Tominaga, R. N. Castle, M. L. Lee, *J. Heterocycl. Chem.* **1983**, *20*, 861–866.

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