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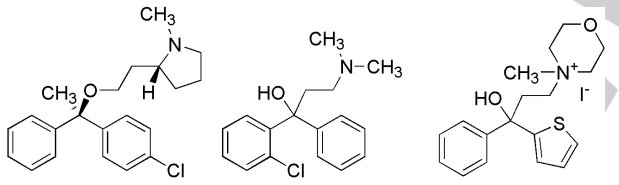
Practical Method for the Catalytic Enantioselective Arylation and Heteroarylation of Ketones with Organotitanium Reagents Generated *in situ* from Bromide and Heteroarene Precursors

Atsushi Matsuda, Tomoya Ushimaru, Yusuke Kobayashi, and Toshiro Harada*[a]

Dedication

Abstract: A practically useful, catalytic enantioselective method has been developed for the synthesis of tertiary diaryl and aryl heteroaryl carbinols starting from commercially available aromatic ketones and aryl or heteroaryl bromides. In this method, organotitanium reagents are generated *in situ* from the bromides by lithiation with BuLi followed by transmetallation of the resulting organolithiums with $ClTi(OiPr)_3$. Treatment of the ketones with the titanium reagents in the presence of (*R*)-3-(3,5-bistrifluoromehthylphenyl)-1,1'-bi-2-naphthol (BTFP-BINOL) affords the corresponding tertiary alcohols in high enantioselectivities and yields. The reaction can also start with furan and 2-thienyllithium. The method is operationally simple and can be conducted on a 10-mmol scale without any difficulties.

The catalytic enantioselective addition of organometallic reagents to aldehydes and ketones is a fundamental method for the synthesis of optically active alcohols with simultaneous carbon–carbon bond-formation. Despite great advances in chiral catalyst systems that have realized a high level of asymmetric induction,[1] reactions are generally carried out at relatively large catalyst loadings, making them less practical for scale-up applications. The reduction of catalyst loadings has remained undeveloped especially for the addition to ketones due to the lower reactivity of the carbonyl group in comparison with aldehydes.



1a **1b** **1c**

Figure 1. Bioactive compounds containing chiral tertiary diaryl carbinols.

Chiral tertiary diaryl carbinols are key building blocks for the synthesis of pharmaceuticals such as clemastine (**1a**), chlophedianol (**1b**), and tiemonium iodide (**1c**) (Figure 1).[2] For the enantioselective synthesis, much effort has been directed toward the development of the catalytic enantioselective addition of arylmetal reagents to alkyl aryl ketones.[3] In the pioneering work of catalytic enantioselective phenyl addition to ketones, Fu and co-worker employed a mixed alkoxy phenyl zinc reagent, generated by treatment of Ph_2Zn with MeOH, as a phenyl source of higher reactivity in the presence of a chiral zinc catalyst derived from DAIB **2** (15 mol%).[4] Recently, significant improvement was made by Ishihara and coworkers in the activity of chiral zinc catalysts by the development of a chiral phosphoramide (**3**)-zinc complex (10 mol%) for the reaction using ArZnEt as an aryl source.[5] Walsh and coworkers have developed a chiral titanium catalyst derived from bis(sulfonamide) diol ligand **4**, which exhibited high activity as well as high enantioselectivity at 10 mol% catalyst loading in the reaction employing a mixed reagent of Ph_2Zn and $Ti(OiPr)_4$.[6,7] Arylaluminum reagents ($ArAlR_2$; R = Ar or Et) was successfully employed by Gau and coworkers as mixed reagents with $Ti(OiPr)_4$ in the enantioselective ketone arylation catalyzed by a chiral titanium complex derived from BINOL **6a** (10 mol%).[8] Availability of arylmetal reagents from inexpensive and easily handled aryl sources is also an important issue in the practical use of the enantioselective arylation. In this regard, methods for *in-situ* preparation of arylzinc reagents from Grignard reagents and boronic acids have been developed and utilized in the chiral zinc catalyzed reactions.[5b,6,7] Quite recently, a chiral Rh complex-catalyzed enantioselective addition of arylboron reagents has been reported by Deng, Tang, and coworkers.[9] By using arylboroxines [$(ArBO)_3$] (2 equiv) as aryl sources and WingPhos **5** (3.6 mol%) as a chiral ligand, the reaction provided a range of chiral tertiary diaryl carbinols in excellent enantioselectivities (up to >99% ee) and yields.[10,11]

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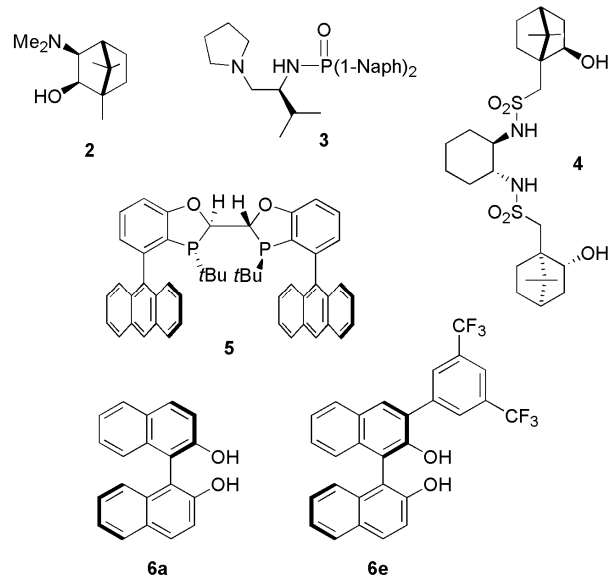
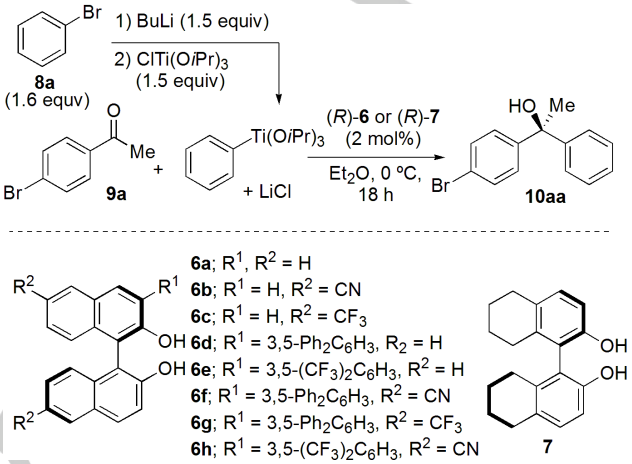


Figure 2. Chiral ligands for enantioselective arylation of ketones.

Despite these progresses, it is still a challenge to develop a practical method for the enantioselective ketone arylation in terms of lower catalyst loadings and the availability of aryl sources. We report here in a practical method for the catalytic enantioselective arylation and heteroarylation of ketones using titanium reagents, prepared *in situ* from inexpensive bromide or heteroarene precursors. Enantioselective preparation of a variety of tertiary diaryl carbinols and aryl heteroaryl carbinols could be achieved with a chiral titanium catalyst derived from a new ligand (*R*)-BTFP-BINOL **6e** at 2 mol% loading.

A relatively simple method for the enantioselective ketone arylation has been reported by Gau and coworkers recently.[12] The reaction employs aryltitanium reagent ArTi(O*i*Pr)$_3$ as an aryl source in the presence of a chiral titanium catalyst derived from BINOL **6a** (10 mol%) and Ti(O*i*Pr)$_4$, affording arylation products in high enantioselectivity. Although the aryltitanium reagents can be prepared by the reaction of aryl Grignard reagents ArMgBr with ClTi(O*i*Pr)$_4$, the resulting reagents need to be isolated by recrystallization with the rigorous exclusion of oxygen and moisture. Recently, we have developed a practical method for the enantioselective arylation of aldehydes with *in-situ* prepared ArTi(O*i*Pr)$_3$ catalyzed by 3-aryl-H$_8$-BINOL-derived chiral titanium complexes.[13] By virtue of the remarkable enhancement of the catalytic activity, the reactions could be performed at low catalyst loadings (2–0.25 mol%) using the titanium reagents, prepared from aryl bromides (ArBr) by lithiation with BuLi and subsequent transmetalation with ClTi(O*i*Pr)$_4$, without the removal of LiCl salt.

Based on our previous result, we first examined the phenylation of *p*-bromoacetophenone (**9a**) with PhTi(O*i*Pr)$_3$, generated from bromobenzene (**8a**), in the presence of (*R*)-BINOL **6a** (Scheme 1). Thus, **8a** (1.6 equiv) was treated successively with BuLi and ClTi(O*i*Pr)$_3$ (1.5 equiv each) in Et$_2$O and the resulting titanium reagent was allowed to react with **9a** in the presence of (*R*)-**6a** (2 mol%) at 0 ℃ for 6 h (Table 1, entry 2). The reaction afforded phenyl product (*S*)-**10aa** in 50% yield and in 82% ee with 39% recovery of **9a**. Under otherwise identical conditions, the reaction in the absence of the chiral ligand gave racemic product *rac*-**10aa** in 10% yield with 80% recovery of **9a** (entry 1). The result implies that a concurrent direct reaction of the phenyltitanium reagent degraded the enantioselectivity in the catalytic reaction.



Scheme 1. Enantioselective Addition of Phenyltitanium Reagent to Ketone **9a** Catalyzed by Chiral Titanium Complexes.

Table 1. Optimization of the Reaction Conditions for Catalytic Enantioselective Addition of Phenyltitanium Reagent to Ketone **9a**.[a]

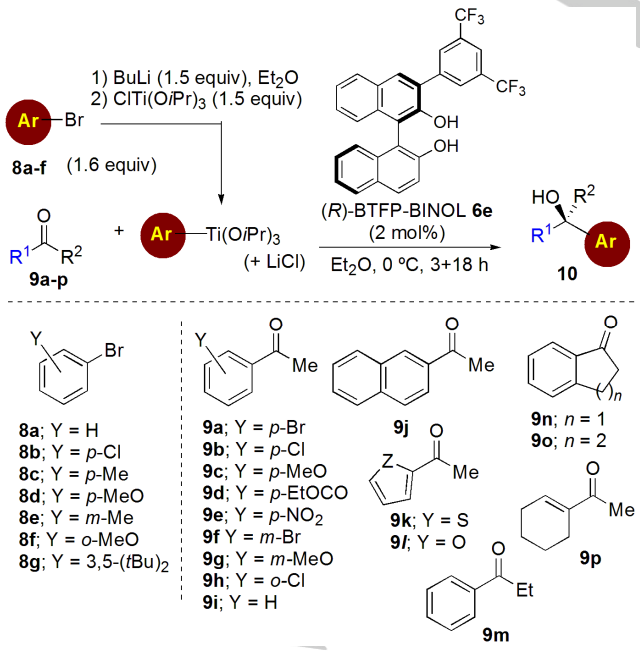
entry	ligand	R^1	R^2	yield (%)	ee (%)
1	none			10	–
2	**6a**	H	H	50	82
3	**7**			36	6
4	**6b**	H	CN	81	82
5	**6c**	H	CF$_3$	70	84
6	**6d**	3,5-Ph$_2$C$_6$H$_3$	H	69	80
7	**6e**	3,5-(CF$_3$)$_2$C$_6$H$_3$	H	87	84
8[b]	**6e**			50	82
9[c]	**6e**			65	90
10[d]	**6e**			93	90
11	**6f**	3,5-Ph$_2$C$_6$H$_3$	CN	84	84
12[d]	**6f**			98	79
13	**6g**	3,5-Ph$_2$C$_6$H$_3$	CF$_3$	85	84
14	**6h**	3,5-(CF$_3$)$_2$C$_6$H$_3$	CN	94	76

[a] Unless otherwise noted, the reaction of **9a** (0.5 mmol) were carried out with **8a** (1.6 equiv), BuLi (1.5 equiv), ClTi(O*i*Pr)$_3$ (1.5 equiv), and (*R*)-**6a-h** or (*R*)-**7** (2 mol%) in Et$_2$O at 0 ℃ for 6 h. [b] Ketone **9a** was added slowly over 3 h via a syringe pump and then the reaction mixture was quenched immediately. [c] The phenyltitanium reagent was added slowly over 3 h via a syringe pump and then the reaction mixture was quenched immediately. [d] The phenyltitanium reagent was added slowly over 3 h via a syringe pump and the reaction mixture was quenched after additional 18 h-stirring.

To obtain higher enantioselectivity and conversion, reactions were carried out with several BINOL derivatives **6a-h** and **7** that may form chiral titanium catalysts of enhanced activity. The reaction employing (*R*)-H$_8$-BINOL **7** resulted in low conversion

and low enantioselectivity (entry 3). The decreased activity of a titanium catalyst derived from (*R*)-**7** could be due to the less electron-withdrawing ability of H_8-BINOL ligand in comparison with BINOL ligand. Indeed, when BINOL derivative (*R*)-**6b**, bearing electron-withdrawing cyano groups at the 6,6'-position, was used, the yield of (*S*)-**10aa** was increased to 81% but without improvement in the enantioselectivity (82% ee) (entry 4). A titanium catalyst derived from 6,6'-bistrifluoromethyl derivative (*R*)-**6c** exhibited the enhanced activity as well (entry 5). The improved activity was also observed for catalysts derived from 3-aryl BINOLs (*R*)-**6d** and (*R*)-**6e** (entries 6 and 7). In particular, with bis(trifluoromethyl)phenyl (or BTFP-) derivative (*R*)-**6e**, the reaction was almost completed in 6 h to give (*S*)-**10aa** of 84% ee in 87% yield. The introduction of cyano or trifluoromethyl group at the 6,6'-poisition of (*R*)-**6d** also improved the activity of catalysts derived from the resulting ligands (*R*)-**6f**,**g** (entries 11 and 13). Further improvement in the activity was observed for (*R*)-**6h** bearing the BTFP group at the 3 position and cyano groups at the 6 and 6' position although the enantioselectivity was moderate (entry 14).

With the modified BINOL ligands, reaction conditions in which the ketone or the titanium reagent is slowly introduced to the reaction mixture were examined to realize higher enantioselectivity by minimizing the participation of background racemic reaction. For the catalyst system derived from (*R*)-BTFP-BINOL **6e**, the addition of ketone **9a** for 3 h was not effective (entry 8). On the other hand, when the titanium reagent was added for 3 h and the reaction was quenched immediately after the addition, (*S*)-**10aa** was obtained in 65% yield with the increased selectivity of 90% ee (entry 9). The yield was increased to 93%, while maintaining the high selectivity, by the additional reaction for 18 h (entry 10). The slow-addition protocol, however, did not give improvement in the selectivity for the reaction with ligand (*R*)-**6f** (entry 12).



Scheme 2. Catalytic enantioselective preparation of tertiary alcohols **10** starting from aryl bromides **8** and ketones **9**.

Table 2. Catalytic enantioselective preparation of tertiary alcohols **10** starting from aryl bromides **8** and ketones **9**.[a]

entry	tertiary alcohol **10**	yield (%)	ee (%)
1	**10aa**; Y = *p*-Br	93	90
2	**10ab**; Y = *p*-Cl	93	91
3	**10ac**; Y = *p*-MeO	83	87
4	**10ad**; Y = *p*-EtOCO	67	88
5	**10ae**; Y = *p*-NO_2	65	87
6	**10af**; Y = *m*-Br	80	76
7	**10ag**; Y = *m*-MeO	64	75
8	**10ah**; Y = *o*-Cl	41	78
9[b,c]	**10ah**	53	90
10	**10aj**	93	87
11	**10ak**; Z = S	48	86
12	**10al**; Z = O	70	78
11	**10bm**	48	56
12	**10an**; *n* = 1	92	87
13	**10ao**; *n* = 2	75	80
14[c]	**10ap**	70	94
15	***ent*-10ab**; Y = *p*-Cl	89	84
16[d]	**10ci**; Y = *p*-Me	93	90
17	***ent*-10ac**; Y = *p*-MeO	51	93
18	**10ei**; Y = *m*-Me	91	89
19	**10fi**; Y = *o*-MeO	70	3
20	**10gi**; Y = 3,5-(*t*Bu)$_2$	85	96
21	**10eb**	85	90

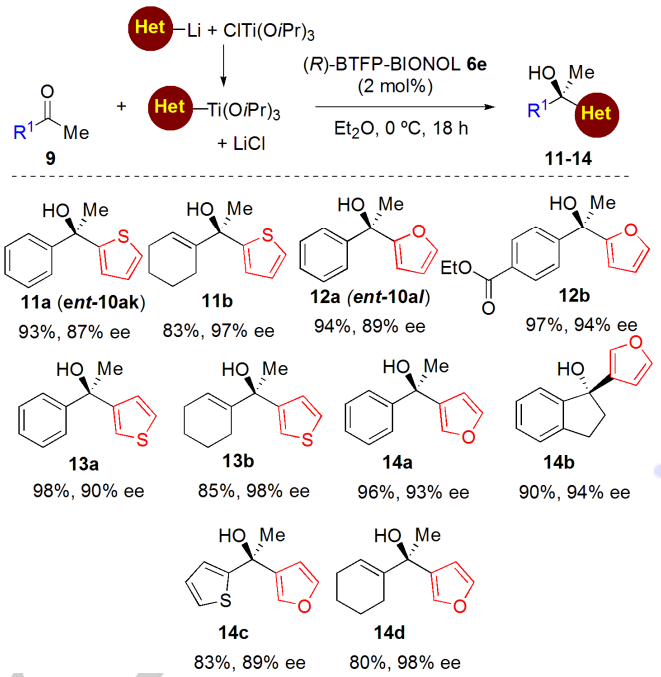
[a] Unless otherwise noted, reactions were carried out under the conditions of entry 10 in Table 1. [b] The reaction was carried out with ligand (*R*)-**6g** (2 mol%). [c] The reaction was carried out for 42 h after the slow addition of the titanium reagent. [d] The reaction was carried out with two equiv of the aryltitanium reagent.

Under the optimized conditions of entry 10 in Table 1, the scope of the present reaction for the enantioselective preparation of tertiary diaryl alcohols **10** was examined for aryl bromides **8a-g** and ketones **9a-p** (Scheme 2). For phenylation reaction starting from bromobenzene (**8a**), a variety of *para* substituted acetophenones **9a-e**, 2-naphthophenone (**9j**), and 2-acetylthiophene (**9k**) exhibited high enantioselectivity (85–91% ee; Table 2, entries 1–5, 10, and 11). Ester and nitro group are well tolerated under the reaction conditions although the rate of reaction was somewhat decreased. Enantioselectivities were

moderate (75–78% ee) for the *meta* and *ortho* substituted acetophenones **9f-h** and 2-acetylfuran (**9*l***) (entries 6–8 and 12). Improved selectivity of 90% ee could be achieved for *ortho* substituted derivative **9h** with ligand (*R*)-**6g** (entry 9). Enantioselectivity was low for ethyl ketone **9m** as shown in the reaction of *p*-chlorophenyltitanium reagent generated from the corresponding bromide **8b** (entry 11). On the other hand, aromatic cyclic ketones, especially indanone (**9n**) served as good substrates (entries 12 and 13). The present reaction was successfully applicable to unsaturated ketone **9p** to give tertiary allylic alcohol **10ap** in high enantioselectivity (entry 14).

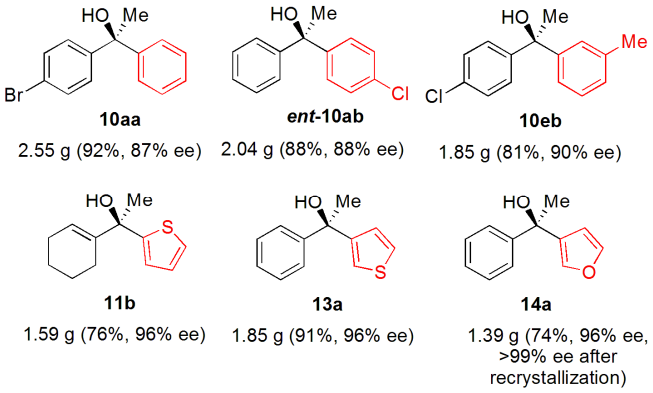
The scope of the reaction for aryl bromides was examined in the reaction of acetophenone (**9i**). Aryltitanium reagents generated from *para* and *meta* substituted bromobenzenes (**8b-e**) underwent addition to **9i** to afford the corresponding diaryl carbinols **10** with high enantioselectivity (84–93% ee; entries 15–18).[14] 3,5-Di-*tert*-butylphenyltitanium also exhibited excellent selectivity (96% ee; entry 20). On the other hand, the reaction of *o*-methoxyphenyltitanium reagent resulted in racemic product formation (entry 19). With a proper combination of bromides **8** and ketones **9**, a variety of diaryl carbinols can be prepared in an enantioenriched form by the present reaction, as demonstrated, for example, by the preparation of **10eb** of 90% ee starting from *m*-bromotoluene **8b** and *p*-chloroacetophenone **9b** (entry 21).

Despite the importance of heteroaryl groups in medicinal chemistry, few methods have been developed for the enantioselective addition of heteroaryl groups to ketones.[15] Gau and coworkers have reported the enantioselective heteroarylation with $(2\text{-thienyl})_3Al$,[15d] $(2\text{-furyl})AlEt_2$,[15a] and 3-furylTi(O*i*Pr)$_3$[15c] catalyzed by the chiral titanium complex derived from BINOL (10–20 mol%). To expand the scope of the active chiral titanium catalyst derived from (*R*)-BTFP-BINOL **6e**, reactions were examined by employing *in-situ* prepared heteroaryltitanium reagents at 2 mol% catalyst loading. When the protocol for the enantioselective arylation was applied to (2-thienyl)Ti(OiPr)$_3$, prepared from a commercially available 2-thienyllithium (1M in THF and hexanes), the corresponding acetophenone adduct **11a** (= ***ent*-10ak**) was obtained in 93% yield and 87% ee (Scheme 3). The reaction was further applied to 2-furylation. Thus, the 2-furyltitanium reagent was prepared by lithiation of furan with BuLi and subsequent transmetalation. The reaction of the titanium reagent and **9i** in the presence of **6e** (2 mol%) afforded the corresponding tertiary alcohol **12a** (= ***ent*-10a*l***) in high enantioselectivity. The 3-thienylation and 3-furylation of **9i** were realized as well with the corresponding heteroaryltitanium reagents, generated from 3-bromothiophene and –furan, respectively, through the lithiation/transmetalation sequence. The reactions afforded the heteroarylation product **13a** and **14a** in high yields and enantioselectivities. The present heteroarylation reaction was successfully applicable to other ketones, including enone **9p** and cyclic ketone **9n**, as shown by the enantioselective synthesis of **11b**, **12b**, **13b**, and **14b-d**. Notably, the 3-thienyl- and 3-furyltitanium reagents exhibited enantioselectivity higher than the aryltitanium reagents.



Scheme 3. Catalytic enantioselective preparation of tertiary 1-heteroarylethanols **11**–**14**.

Finally, to demonstrate the preparative utility of the present enantioselective arylation, the enantioselective synthesis of chiral tertiary alcohols was examined on 10-mmol scale (Scheme 4). Even with 0.1 g (2 mol%) of ligand (*R*)-**6e**, the reaction of acetophenone (**9i**) and *p*-bromochlorobenzene (**8b**) and subsequent isolation by distillation provided 2.04 g (88% yield) of ***ent*-10ab** (88% ee), a key intermediate in the synthesis of the antihistamine drug clemastine (**1**). Ligand (*R*)-**6e** could be recovered in 88% yield by silica gel column chromatography. As demonstrated by other five examples, the gram-scale synthesis could be achieved without trouble both for arylation and for heteroarylation by keeping the enantioselectivity observed in 0.5-mmol scale reactions in Table 2.



Scheme 4. Application to Gram-Scale Synthesis

In summary, we have developed an efficient and practical method for the catalytic enantioselective arylation and heteroarylation of ketones with organotitanium reagents, which are prepared by the reaction of aryl- and heteroaryllithiums with ClTi(O*i*Pr)$_4$. The titanium complex derived from (*R*)-BTFP-BINOL (**6e**) was demonstrated to be an excellent catalyst in terms of enantioselectivity and activity, providing tertiary diaryl-, aryl heteroaryl-, and diheteroaryl carbinols in good to high enantioselectivity at 2 mol% catalyst loading. As the organolithium intermediates can be generated by the Br/Li exchange of bromides or by the lithiation of heteroarenes, the present reaction permits a straightforward access to a range of enantioenriched tertiary alcohols from commercially available low-cost starting materials. The preparative utility of the present reaction has been shown by the fact that the reaction is operationally simple and can be conducted on a 10-mmol scale without any difficulties.

Experimental Section

General Procedure for Enantioselective Arylation (10 mmol-scale, Scheme 4). In a glove box, Ti(O*i*Pr)$_4$ (3.20 g, 11.25 mmol) and $TiCl_4$ (0.711 g, 3.75 mmol) were weighed in a flask. The flask was removed from the glove box and the resulting mixture was dissolved in anhydrous Et_2O (13.7 mL) at 0 ℃ under argon atmosphere to prepare a Et_2O solution of ClTi(O*i*Pr)$_3$. To a solution of aryl bromide **8** (16 mmol) in anhydrous Et_2O (31 mL) at 0 ℃ was added BuLi (1.64 M in hexane, 9.2 mL, 15.0 mmol) for 15 min. After being stirred at room temperature for 15 min, the reaction mixture was cooled again at 0 ℃. To this was added the solution of ClTi(O*i*Pr)$_3$ for 5 min and the reaction mixture was stirred for 10 min at 0 ℃. The stirring was stopped and LiCl was allowed to almost settle for 5 min. Thus prepared aryltitanium reagent was added to a solution of ketone **9** (10 mmol) and ligand (*R*)-**6e** (100 mg, 0.2 mmol) in anhydrous Et_2O (22 mL) at 0 ℃ for 3 h using a syringe pump. Precipitated LiCl was added as a suspension in the late stage of the addition. After being stirred further at 0 ℃ for 18–24 h, the reaction mixture was poured into aqueous 5% NH_4Cl. The resulting mixture was filtered through a pad of Celite and washed with ethyl acetate (50 mL). The filtrate was extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with aqueous 5% $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in *vacuo*. The residue was passed through a short silica gel column (10% ethyl acetate in hexane) and concentrated filtrate was purified by Kugelrohr distillation at reduced pressure in the presence of Na_2CO_3 (**10aa**; 150–160 ℃/0.2 mmHg, ***ent*-10ab**; 130–140 ℃/0.2 mmHg, **10eb**; 170 ℃/0.2 mmHg, **11b**; 110 ℃/0.2 mmHg) or by recrystallization from hexane (**13a**; mp 74–77 ℃, **14a**; mp 53–57 ℃). The filtered titanium salts and Celite were washed with 1 N aqueous HCl (50 mL) and Et_2O (50 mL). After filtration, the washing was extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with aqueous 5% $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in *vacuo*. The residue was combined with the residue of Kugelrohr distillation or recrystallization and subjected to silica gel flash chromatography (toluene) to recover ligand (*R*)-**6e** in >85% yield.

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Keywords: alcohols • ketones • asymmetric catalysis • lithium• titanium

[1] a) K. Soai, S. Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; b) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757–824; c) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2794; d) M. Hatano, T. Miyamoto, K. Ishihara, *Curr. Org. Chem.* **2006**, *11*, 127–157; e) F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454–470; f) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963−983; g) M. Yus, J. C. Gonzales-Gomez, F. Foubelo, *Chem. Rev.* **2011**, *111*, 7774−7854; h) A. Lumbroso, M. L. Cooke, B. Breit, *Angew. Chem. Int. Ed.* **2013**, *52*, 1890–1932; i) H. Pellissier, *Tetrahedron*, **2015**, *71*, 2487–2524.

[2] a) P. Duchene-Marullaz, D. Jovanovic, N. Busch, J. Vacher, *Arch. Int. Pharmacodyn. Ther.* **1963**, *141*, 465–479; b) D. Ameen, T. J. Snape, *Med. Chem. Commun.*, **2013**, *4*, 893–907.

[3] For reviews, see; a) J. M. Betancort, C. Garcia, P. J. Walsh, *Synlett* **2004,** 749–760; b) Ramon, D. J.; Yus, M. *Angew. Chem.*, *Int. Ed.* **2004**, *43*, 284–287; c) O. Riant, J. Hannedouche, *Org. Biomol. Chem.* **2007**, *5* 873–888; d) J. Rong, T. Pellegrini, S. R. Harutyunyan, *Chem. Eur. J.* **2016**, *22*, 3558–3570.

[4] I. Dosa, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 445–446.

[5] a) M. Hatano, T. Miyamoto, K. Ishihara, *Org. Lett.* **2007**, *9*, 4535–4538; b) M. Hatano, R. Gouzu, T. Mizuno, H. Abe, T. Yamada, K. Ishihara, *Catal. Sci. Technol.*, **2011**, *1*, 1149–1158.

[6] a) C. Garcia, P. J. Walsh, *Org. Lett.* **2003,** *5*, 3641–3644; b) H. Li, C. Garcia, P. J. Walsh, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5425–5427.

[7] For relevant work, see; V. J. Forrat, O. Pieto, D. J. Ramón, M. Yus, *Chem. Eur. J.* **2006**, *12*, 4431–4445.

[8] a) C.-A. Chen, K.-H. Wu, H.-M. Gau, *Angew. Chem. Int. Ed.* **2007**, *46*, 5373–5376; b) S. Zhou, K.-H. Wu, C.-A. Chen, H.-M. Gau *J. Org. Chem.*, **2009**, *74*, 3500–3505.

[9] L. Huang, J. Zhu, G. Jiao, Z. Wang, X. Yu, W.-P. Deng, W. Tang *Angew. Chem. Int. Ed.* **2016**, *55*, 4527–4531.

[10] For a chiral titanium catalyzed (20 mol%) enantioselective arylation of ketones using a mixed titanium reagent of ArMgBr and Ti(O*i*Pr)$_4$, see; E Fernández-Mateos, B. Maciá, M. Yus, *Eur. J. Org. Chem.* **2014**, 6519–6526.

[11] For catalytic enantioselective alkylation of ketones, see; a) S.-J. Jeon, H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 16416–16425; b) A. V R. Madduri, A. J. Minnaard, S. R. Harutyunyan, *Chem. Commun.* **2012** *48*, 1478–1480; c) A. V. R. Madduri, S. R. Harutyunyan, A. J. Minnaard, *Angew. Chem. Int. Ed.* **2012**, 51, 3164–3167; d) J. Rong, R. Oost, A. Desmarchelier, A. J. Minnaard, S. R. Harutyunyan, *Angew. Chem. Int. Ed.* **2015**, *54*, 3038–3042; e) reference [5] and [7]; For catalytic enantioselective vinylation of ketones, see; f) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539; g) D. B. Biradar, H.-M. Gau, *Org. Lett.* **2009**, *11*, 499–502.

[12] K.-H. Wu, Y.-Y. Kuo, C.-A. Chen, Y.-L. Huang, H.-M. Gau, *Adv. Synth. Catal.* **2013**, *355*, 1001–10081.

[13] a) A. Uenishi, Y. Nakagawa, H. Osumi, and T. Harada, *Chem. Eur. J.* **2013**, *19*, 4896–4905; b) Y. Hayashi, N. Yamamura, T. Kusukawa, T. Harada, *Chem. Eur. J.* **2016**, *22*, 12095–12105; c) T. Harada, *Chem. Record* **2016**, *16*, 1256–1273.

[14] The low yield of ***ent*-10ac** in entry 17 is due to the competing *ortho*-metalation encountered in treatment of *p*-methoxy derivative **8d** with BuLi, leading to the formation of 5-bromo-2-methoxyphenyllithium as a minor component.

[15] a) K.-H. Wu, D.-W. Chuang, C.-A. Chen, H.-M. Gau, *Chem. Commun.* **2008**, 2343–2345; b) C.-A. Chen, K.-H. Wu, H.-M. Gau, *Adv. Synth. Catal.* **2008**, *350*, 1626–1634; c) S. Zhou, C.-R. Chen, H.-M. Gau, *Org. Lett.* **2010**, *12*, 48–51; d) D. B. Biradar, S. Zhou, H.-M. Gau, *Org. Lett.* **2009**, *11*, 3386–3389.

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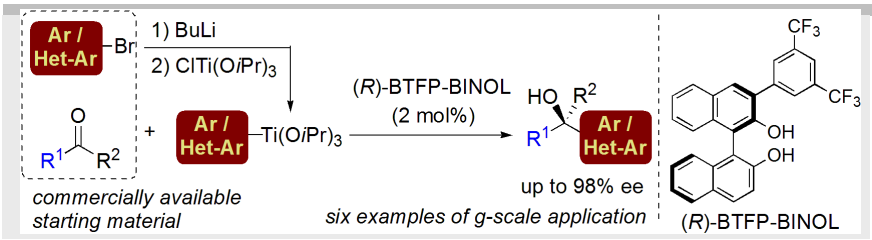

A practical method has been developed for the catalytic enantioselective arylation and heteroarylation of ketones using titanium reagents, prepared *in situ* from inexpensive bromide or heteroarene precursors. Enantioselective preparation of a variety of tertiary diaryl carbinols and aryl heteroaryl carbinols could be achieved with a chiral titanium catalyst derived from a new ligand (*R*)-BTFP-BINOL at low loading (2 mol%).

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Practical Method for the Catalytic Enantioselective Arylation and Heteroarylation of Ketones with Organotitanium Reagents Generated *in situ* from Bromide or Heteroarene Precursors