Chiral tertiary 2-furyl alcohols: diversified key intermediates to bioactive compounds. Their enantioselective synthesis *via* (2-furyl)aluminium addition to ketones catalyzed by a titanium catalyst of (*S*)-BINOL†

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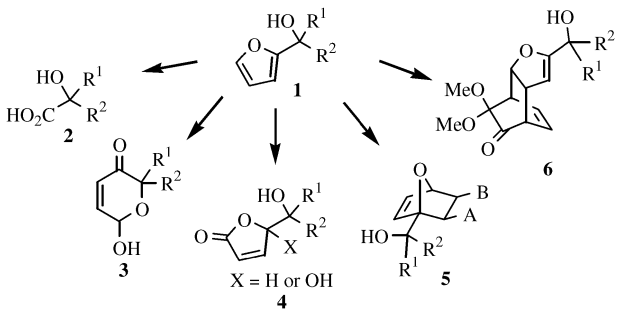
Novel asymmetric 2-furyl additions of (2-furyl)$AlEt_2$(THF) to aromatic ketones and one α,β-unsaturated ketone catalyzed by a titanium catalyst of 10–20 mol% (*S*)-BINOL are reported to furnish tertiary furyl alcohols in good to excellent enantioselectivities of 87–93% ee.

Substituted furans are key sub-structures in many natural products and medicines,[1] and synthetically they are important intermediates leading to a wide variety of bioactive compounds.[2] Due to the diversified flexibilities of the furan skeleton, furyl alcohols **1** can be converted into many useful synthetic intermediates or chiral auxiliaries (Scheme 1) such as α-hydroxy acids **2**,[3] 6-hydroxy-6*H*-pyran-3-ones (**3**),[4] 5-hydroxymethyl-5*H*-furan-2-ones (**4**),[5] (7-oxa-bicyclo[2,2,1]hept-1-yl)-alcohols (**5**),[6] masked *o*-benzoquinones (**6**),[7] and others.[8] Compounds **2** are unnatural lactic acids which are important subunits in many peptide drugs and natural products, and **3** and **4** are skeletons of carbohydrates and others. Both chiral compounds **5** and **6** are precursors of highly substituted ring systems, and **5** can also be used for the synthesis of chiral polycyclic systems. Despite the importance of chiral furyl alcohols, asymmetric syntheses of **1** remains a challenge to chemists and their syntheses are scattered across some papers *via* chiral auxiliary induced metallic furyl additions to organic carbonyls or *via* additions of organometallic reagents to furylaldehydes.[2a,9] In asymmetric catalysis, studies reported to date have demonstrated, in general, one example each of an addition of the organometallic nucleophile to a furyl aldehyde or a furyl ketone.[10] Since organic carbonyls are one of the most important functionalities in modern synthetic chemistry, asymmetric catalytic additions of furyl groups to organic carbonyls are a more appealing synthetic approach. In the past few years, extensive efforts have been devoted to studies of addition reactions to carbonyls,[10,11] especially works of nucleophilic additions to ketones.[11c,12] Recently, we discovered that triarylaluminium compounds are excellent aryl sources in asymmetric additions to aldehydes or ketones catalyzed by titanium complexes of H_8-BINOL or BINOL[13] and in coupling reactions with aryl bromides or chlorides catalyzed by the economic $Pd(OAc)_2/PCy_3$ system,[14] and it is expected that the furylaluminium addition to organic carbonyls will prove to be a highly potential route for the synthesis of chiral furyl alcohols **1**.



Scheme 1

To continue our efforts in developing organoaluminium reagents for asymmetric catalysis, we report herein the first catalytic asymmetric furylaluminium additions to ketones employing a titanium catalyst of (*S*)-BINOL ligand (eqn (1)). This is a practical catalytic system since the BINOL ligands, which are commercially available, have been established so as to be applicable to the most diversified asymmetric catalytic reactions.[15] The furylaluminium reagent designated as (2-furyl)$AlEt_2$(THF) (**7**) can be prepared easily from a reaction of $AlEt_2X$ (X = Cl or Br) and furyllithium, which is obtained in turn from a reaction of furan and *n*-butyllithium. The ^{1}H NMR spectrum of **7** reveals only one set of signals belonging to the coordinated THF. However, three sets of ethyl resonances and two sets of furyl signals were observed, indicating that **7** in $CDCl_3$ solution contained a mixture of three major species. By comparing the spectrum of $AlEt_3$(THF) with that of **7** and examining integrals of ethyl and furyl ^{1}H resonances, the three species were assigned as (2-furyl)$_x$$AlEt_{3-x}$(THF) ($x$ = 0, 1, or 2) with relative percentages of 25 : 60 : 15% (see the electronic supplementary information for the spectrum and ^{1}H NMR assignments†). Although the reagent **7** also contained trace amounts of unidentified impurities, it was used directly in catalytic reactions without a need of further treatment. In this study, catalytic reaction conditions were optimized on an acetophenone (eqn (1)) and results are summarized in Table 1. The

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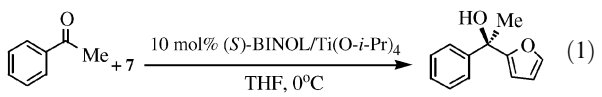
† Electronic supplementary information (ESI) available: The synthesis and ^{1}H NMR data of (2-furyl)$AlEt_2$(THF) and HPLC analytic conditions and spectroscopic data of tertiary furyl alcohols. See DOI: 10.1039/b802441c

Table 1 Optimizations of (2-furyl)$AlEt_2$(THF) (**7**) additions to acetophenone catalyzed by the *in situ*-formed titanium catalysts of (*S*)-BINOL[a]

Entry	2-(Furyl)$AlEt_2$(THF) (equiv.)	Ti(O-*i*-Pr)$_4$ (equiv.)	Yield[b] (%)	ee[c] (%)
1	2.0	2.1	59	92
2	2.0	2.3	61	92
3	2.2	2.3	75	92
4	2.3	2.3	90	88
5	2.2	2.5	94	89
6	2.3	2.5	94	89
7[d]	2.2	2.3	96	93

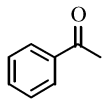
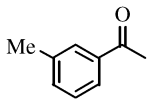
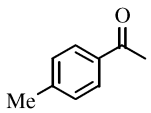
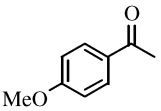
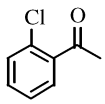
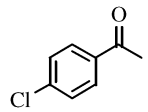
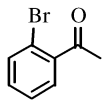
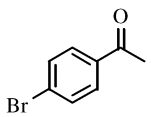
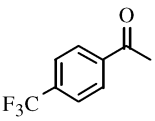
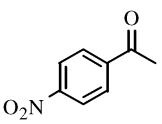
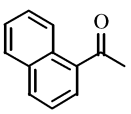
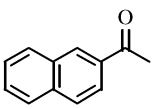
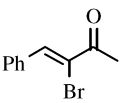
[a] BINOL: 0.050 mmol, $PhCOCH_3$: 0.50 mmol, temp: 0 °C, time: 12 h, THF, 6.0 mL. [b] Yields were based ^{1}H NMR. [c] ee values were determined by HPLC using Chiralcel OD column. [d] $PhCOCH_3$ was added to the catalytic solution of (*S*)-BINOL/Ti(O-*i*-Pr)$_4$ followed by the addition of **7**.

reactions were first examined using 10 mol% (*S*)-BINOL and Ti(O-*i*-Pr)$_4$ as catalytic systems followed by an addition of **7** and then the acetophenone [Procedure A].‡ Under a reaction condition of 2.1 equiv. Ti(O-*i*-Pr)$_4$ and 2.0 equiv. furyl reagent **7**, the reaction afforded the furyl alcohol in an excellent 92% ee but the yield was only a moderate 59% (entry 1). In order to improve product yields, quantities of both furylaluminium and Ti(O-*i*-Pr)$_4$ were tuned (entries 2–6). It was found that yields of the product increased by increasing the quantity of Ti(O-*i*-Pr)$_4$. Though the product in excellent 94% yields was obtained in catalytic systems of 2.5 equiv. Ti(O-*i*-Pr)$_4$ (entries 5 and 6), enantioselectivities dropped slightly to 89% ee. We later discovered that the product in the highest 96% yield and the best 93% ee (entry 7) was achieved when the substrate was added prior to the furylaluminium **7** [Procedure B]‡ in a reaction condition of 2.2 equiv. **7** and 2.3 equiv. Ti(O-*i*-Pr)$_4$.



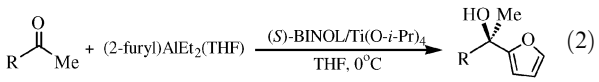
To demonstrate general applications of the furylaluminium reagent, asymmetric additions of **7** to a variety of ketones (eqn (2)) were examined by employing titanium catalysts of 10 or 20 mol% (*S*)-BINOL. Quantities of Ti(O-*i*-Pr)$_4$ and (2-furyl)AlEt_2(THF) used in asymmetric reactions varied slightly for different substrates (see the electronic supplementary information for details).† The ketones studied include aromatic ketones with an electron-withdrawing or an electron-donating substituent at the 2′-, 3′-, or 4′-position on the aromatic ring and an α,β-unsaturated ketone. Results are listed in Table 2. For acetophenone, the furyl addition gave the chiral tertiary furyl alcohol an isolated 90% yield and 93% ee (entry 1), and the product had a reversed absolute configuration relative to the furyl alcohol obtained from the phenyl addition to the furyl methyl ketone.[13b] For aromatic ketones with an electron-donating substituent, such as a methyl or a methoxy group at 3′- or 4′-position, the furyl addition reactions in 12 h afforded desired furyl alcohols in good yields with excellent enantioselectivities of 90–93% ee (entries 2–4). In cases of the methyl substituent on the aromatic ring (entries 2 and 3), a higher ligand loading of 20 mol% (*S*)-BINOL was used. The furyl additions to aromatic ketones with an electron-withdrawing

Table 2 $AlEt_2$(2-furyl)(THF) additions to ketones catalyzed by the *in situ*-formed titanium complex of (*S*)-BINOL[a]

Entry	Ketone	(*S*)-BINOL (mol%)	Time/ h	Yield[d] (%)	ee (%)
1[c]		10	12	90	93
2[b]		20	12	74	90
3[b]		20	12	78	93
4[c]		10	12	74	92
5[c]		10	24	70	92
6[c]		10	12	86	91
7[b]		20	24	40	93
8[c]		10	12	92	90
9[c]		10	12	90	91
10[b]		20	12	88	92
11[b]		20	24	28	87
12[c]		10	12	94	90
13[b]		20	12	88	88

[a] Ketone/Ti(O-*i*-Pr)$_4$/$AlEt_2$(2-furyl)(THF) = 0.500/1.00–1.20/1.00–1.15 mmol; THF, 6 mL. [b] Procedure A. [c] Procedure B. [d] Isolated yield.

substituent such as a chloro, a bromo, a CF_3, or a NO_2 at the 2′- or 4′-position gave corresponding furyl alcohols also with excellent enantioselectivities of 90–93% ee (entries 5–10). It is worth noting that the furyl addition to 2′-chloroacetophenone with a substituent at the *ortho*-position on the aromatic ring required a longer reaction time of 24 h to afford the product in 70% yield (entry 5). The furyl addition to 2′-bromoacetophenone required a higher ligand loading of 20 mol% and a reaction time of 24 h to give the product in only 40% yield (entry 7). A similar phenomenon was also observed for the addition to 1′-acetonaphthone employing 20 mol% (*S*)-BINOL in 24 h, furnishing the product at a mere 28% yield but with a good enantioselectivity of 87% ee (entry 11). In contrast, the furyl addition to 2′-acetonaphthone afforded the product an excellent 94% yield and 90% ee (entry 12). With the use of 20 mol% (*S*)-BINOL, the furyl addition to the α,β-unsaturated ketone (entry 13) gave the furyl alcohol an 88% yield and a good 88% ee.



(2)

In summary, the first extensive study of asymmetric catalytic furylaluminium additions to aromatic ketones and one α,β-unsaturated ketone are as follows. Though the furylaluminium reagent **7** was prepared as a mixture of three species of formulas (2-furyl)$_x$AlEt$_{3-x}$(THF) (x = 0, 1, or 2), the addition reactions gave only chiral furyl alcohol with no observations of ethylation products. The catalytic system works excellently for aromatic ketones, having either an electron-donating or an electron-withdrawing substituent on the aromatic group, and furyl alcohols in enantioselectivities from 87 to 93% ee were achieved. This study opens up a new and easy route for the synthesis of highly reactive and extremely flexible furyl alcohols **1** in high enantioselectivities. Further studies of organoaluminium reagents in catalysis are currently underway.

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Notes and references

‡ Procedure A: (*S*)-BINOL (10 or 20 mol%) and Ti(O-*i*-Pr)$_4$ (1.00–1.20 mmol) were mixed in 3 mL dry THF at room temperature. The mixture was stirred for 1 h and the solution was cooled to 0 °C. A solution of (2-furyl)AlEt$_2$(THF) (**7**) (1.00–1.15 mmol) in 3 mL THF was added to the above solution followed by a ketone (0.500 mmol). The mixture was stirred at 0 °C for 12 h and quenched with 4 M aqueous NaOH. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography to give the tertiary alcohol. The enantiomeric purity of the product was determined by HPLC. The quantities of Ti(O-*i*-Pr)$_4$ and (2-furyl)AlEt$_2$(THF) used for asymmetric reactions depend on the substrate and are given in the supporting information.

† Procedure B: the procedure is similar to Procedure A except that the ketone was added prior to (2-furyl)AlEt$_2$(THF).

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