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Highly Enantioselective 3-Furylation of Ketones Using (3-Furyl)titanium Nucleophile

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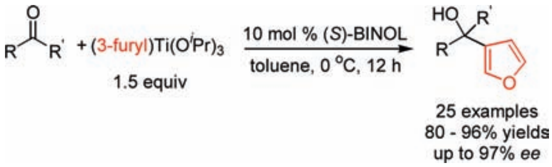
ABSTRACT



A novel asymmetric 3-furyl addition of (3-furyl)Ti(O^{i}Pr)$_3$ to ketones in the presence of 10 mol % (*S*)-BINOL is reported. The catalytic system works excellently for aromatic ketones, α- or β-halophenones, α,β-unsaturated ketones, and acetylfuran, affording products in high yields with excellent enantioselectivities of up to 97% ee.

The enantioselective addition of organozinc reagents to organic carbonyls is the most important and straightforward strategy for the synthesis of optically active alcohols.[1] Chiral zinc[2,3] and titanium[2r,4] catalysts are the two major systems that have been extensively studied in parallel in the past two decades. For zinc catalytic systems, the active metallic species are generated from reactions of organozinc reagents with chiral ligands, and the mechanisms of alkylzinc addition reactions have been well established experimentally[5] and theoretically.[6] In contrast, the titanium catalytic systems are more complicated. Studies of asymmetric alkylation reactions catalyzed by

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titanium catalysts of TADDOLs,[7] BINOLs,[8] or *N*-sulfonylated amino alcohols[9] have suggested that the catalytic reaction initially proceeds via a transmetalation of the organic nucleophile from the zinc to the titanium metal center, followed by an addition of the nucleophile to aldehydes via the titanium active species. Despite evidence supporting additions of organotitanium reagents, direct asymmetric additions to organic carbonyls have been demonstrated in only a few studies. Seebach and Weber reported the first asymmetric organotitanium additions of $RTi(O^iPr)_3$ (R = alkyl or aryl) to aldehydes catalyzed by the titanium complexes of 20 mol % TADDOLs.[10] The reactions had been carried out first at a low temperature of −78 °C, suggesting a high reactivity of organotitanium compounds. In a delicate mechanistic study of titanium-catalyzed dialkylzinc addition reactions, Walsh et al. demonstrated the direct asymmetric $MeTi(O^iPr)_3$ addition to aldehydes at 0 °C catalyzed by 20 mol % $Ti(BINOLate)(O^iPr)_2$, affording secondary alcohols in ~50% ee.[8] Cozzi and Alesi reported a titanium phenylacetylide addition reaction to ketones in the presence of 10 mol % (*R*)-BINOL conducted at temperatures ≤ -15 °C to give the chiral propargyl alcohols in moderate yields with moderate to good enantioselectivities.[11] Although aryltitanium compounds of $ArTi(O^iPr)_3$ have been used in recent years as nucleophilic reagents in a few cases of late-transition metal catalyzed asymmetric reactions[12] and coupling reactions,[13] it seems that the high reactivity of organotitanium reagents limits their direct use in titanium-catalyzed asymmetric reactions. Recently, we discovered that organoaluminum compounds were effective reagents in asymmetric additions to organic carbonyls, affording secondary and tertiary alcohols in excellent enantioselectivities.[14] The reactions of the organotitanium reagents and aldehydes in the presence of a stoichiometric amount of chiral titanium catalyst precursor gave addition products in enantioselectivities similar to those of products obtained from titanium-catalyzed organozinc or organoaluminum addition reactions,[9,14a] further supporting the argument of organotitanium compounds as the actual addition reagents. For titanium-catalyzed reactions, general features of excess $Ti(O^iPr)_4$ and high equivalent of addition reagents are in general required in order to achieve high enantioselectivities of desired products.[14,15] The roles of excess $Ti(O^iPr)_4$ are (1) the transmetalation of an organic nucelophile from the organozinc or organoaluminum compounds to form the organotitanium reagents and (2) the formation of the dititanium active species.[8,9,16] Both Seebach's[10] and Walsh's[8] works show that the use of organotitanium reagents does not require the addition of $Ti(O^iPr)_4$ and that a slight excess of organotitanium reagents is sufficient to induce the reactions. However, key factors for the direct use of the highly reactive organotitanium reagents for achieving excellent stereocontrol are either to suppress the background reaction or to use a highly efficient catalytic system. In this study, we report a direct asymmetric catalytic addition of (3-furyl)tris(2-propoxide)titanium to a wide variety of ketones, affording chiral tertiary alcohols containing 3-furyl moiety in excellent enantioselectivities.

Functionalized furans are found in a variety of natural products and pharmaceutical agents. In addition, furan derivatives are versatile intermediates in organic synthesis owing to their facile conversions to a series of functional groups.[17] However, functionalized furans at the C-3 position were less reported as a result of difficulties in the metalation processes in which 3-furyllithium converts to 2-furyllithium at low temperatures.[17a,f] In this study, the (3-furyl)titanium reagent, $[(3\text{-furyl})Ti(O^iPr)_3]_2$ (**1**), was synthesized from a reaction of 3-furyllithium with $Ti(O^iPr)_3Cl$ in THF at −78 °C. An X-ray diffraction study of complex **1** (Figure 1) confirmed that the (3-furyl)tris(2-propoxo)titanium complex has the dimeric structure with a Ti_2O_2 core bridging through the oxygen atom of two 2-propoxide ligands. Compound **1** is represented as $(3\text{-furyl})Ti(O^iPr)_3$ for simplification. Unlike 3-furyllithium, **1** is stable enough to be manipulated under a dry nitrogen atmosphere at room temperature.

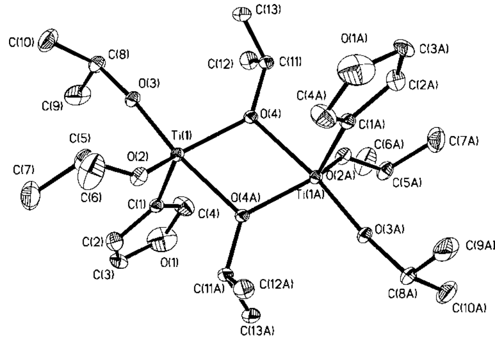
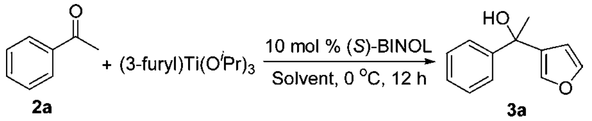


Figure 1. Molecular structure of **1**.

Asymmetric 3-furyl addition reactions were optimized on acetophenone (**2a**) with $(3\text{-furyl})Ti(O^iPr)_3$ in the presence of 10 mol % of (*S*)-BINOL. The results are summarized in Table 1. The optimal reaction conditions of 1.5 equiv of (3-furyl)-

Table 1. Optimization of Enantioselective 3-Furyl Addition to Acetophenone Catalyzed by a Titanium Catalyst of (*S*)-BINOL[a]



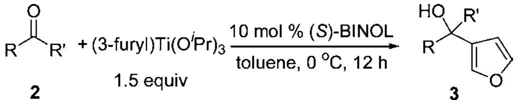
entry	solvent	$Ti(3\text{-furyl})(O^iPr)_3$ (equiv)[b]	convn (%)[c]	ee (%)[d]
1	THF	1.4	92	87
2	CH_2Cl_2	1.4	93	86
3	hexane	1.4	85	94
4	toluene	1.4	86	95
5	toluene	1.3	78	95
6	toluene	1.5	100	94
7	toluene	1.6	100	93
8[e]	toluene	1.5	100	89
9[f]	toluene	1.5	30	

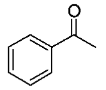
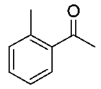
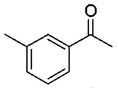
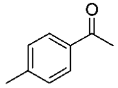
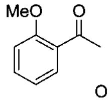
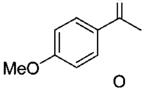
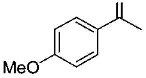
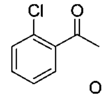
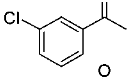
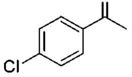
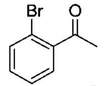
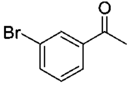
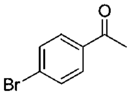
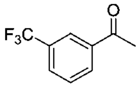
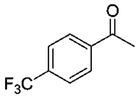
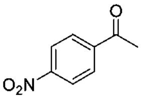
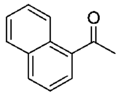
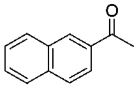
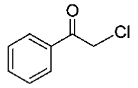
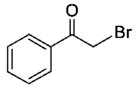
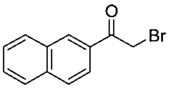
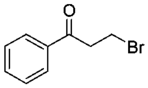
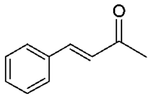
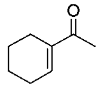
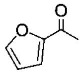
[a] 0.050 mmol of (*S*)-BINOL, 0.50 mmol of acetophenone, toluene (6 mL), 0 °C. [b] Equivalent of $(3\text{-furyl})Ti(O^iPr)_3$ is relative to acetophenone. [c] Conversions were determined by ^1H NMR. [d] Enantioselectivities were determined by HPLC. [e] At room temperature. [f] In situ prepared $(3\text{-furyl})Ti(O^iPr)_3$.

Ti(O^{i}Pr)$_3$ in toluene at 0 °C were found to furnish product **3a** in a 100% conversion with an excellent 94% ee (entry 6). In the reaction, the active catalytic species was generated in situ from a reaction of (3-furyl)Ti(O^{i}Pr)$_3$ and (*S*)-BINOL, and an excess of only 0.3 equiv of (3-furyl)Ti(O^{i}Pr)$_3$ was used relative to the ketone substrate. The reaction at room temperature was also examined to furnish **3a** in a good enantioselectivity of 89% ee (entry 8). However, the addition of in situ prepared (3-furyl)Ti(O^{i}Pr)$_3$ to **2a** afforded **3a** in a low conversion of only 30% (entry 9).

We then examined the catalytic reactions with functionalized ketones under the optimized conditions, and the results are presented in Table 2. For aromatic ketones with either an electron-withdrawing or an electron-donating substituent at the 2′-, 3′-, or 4′-position and 1′- or 2′-acetonaphthone, 3-furyl additions afforded tertiary alcohols in excellent yields with excellent enantioselectivities of 90% ee or greater (entries 1−18), except for substrates of 2′-methoxyacetophenone (**2e**) and 3′-methoxyacetophenone (**2f**), which afforded **3e** and **3f** in 38% and 83% ee (entries 5 and 6). The low

Table 2. Enantioselective 3-Furyl Addition to Ketones Catalyzed by the Titanium Catalyst of (*S*)-BINOL[a]



entry	RCOR′	product	yield (%)[b]	ee (%)[c]
1		**3a**	96	94
2		**3b**	85	90
3		**3c**	93	92
4		**3d**	95	90
5		**3e**	85	38
6		**3f**	92	83
7		**3g**	91	96
8		**3h**	80	97
9		**3i**	95	90
10		**3j**	93	94
11		**3k**	90	95
12		**3l**	95	90
13		**3m**	96	94
14		**3n**	93	91
15		**3o**	92	94
16		**3p**	91	94
17		**3q**	91	95
18		**3r**	96	94
19		**3s**	85	83
20		**3t**	89	86 (*S*)[d]
21		**3u**	93	86
22		**3v**	87	95
23		**3w**	90	74
24		**3x**	88	90
25		**3y**	90	88

[a] 0.050 mmol of (*S*)-BINOL, 0.75 mmol of (3-furyl)Ti(O^{i}Pr)$_3$, 0.50 mmol ketone, toluene (6 mL), 0 °C. [b] Isolated yields. [c] Enantioselectivities were determined by HPLC. [d] Absolute configuration was determined by an X-ray diffraction study.

enantioselectivity of **3e** is attributed to the chelate effect of **2e**, which resulted in small differentiations of both directions while coordinating to the active metal center.

The asymmetric additions to α-halophenones, such as α-chloroacetophenone, α-bromoacetophenone, and α-bromo-2′-acetonaphthone, afforded the tertiary alcohols **3s**, **3t**, and **3u** in high yields of 85−93% with good enantioselectivities of 83−86% ee (entries 19−21). It is worth noting that the asymmetric addition to the *β*-halophenone of 3-bromo-1-phenylpropan-1-one afforded **3v** in an excellent 95% ee (entry 22). To determine the absolute configuration of the 3-furylation products, the 3-furyl alcohol **3t** (Figure 2) containing a heavy bromine atom was characterized by an X-ray diffraction study, and the crystal data confirmed an *S*-configuration for **3t**. The catalytic system also applied to α,*β*-unsaturated ketones such as 1-phenyl-1-buten-3-one and 1-acetyl-1-cyclohexene and to 2-acetylfuran, furnishing **3w**, **3x**, and **3y** in good to excellent enanatioselectivities of 74%, 90%, and 88% ee (entries 23−25), respectively.

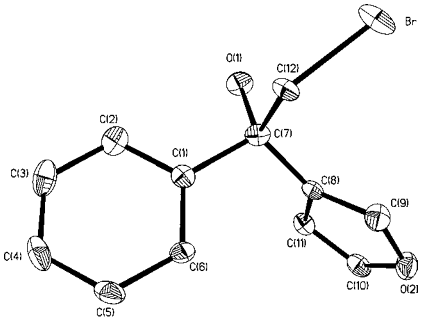


Figure 2. Molecular structure of (*S*)-**3t**.

In summary, a novel direct asymmetric 3-furyl addition of (3-furyl)Ti(O^{i}Pr)$_3$ to ketones employing 10 mol % titanium catalyst of (*S*)-BINOL is reported. A wide variety of ketones are examined to afford products in good to excellent yields with excellent enantioselectivities of 90% ee or greater for most aromatic ketones bearing either an electron-donating or an electron-withdrawing substituent on the aromatic ring. The catalytic system also applies to α- or *β*-halophenones and α,*β*-unsaturated ketones, affording products in good yields with high enantioselectivities. Importantly, the catalytic system does not require the addition of any Ti(O^{i}Pr)$_4$, and a slight excess of 0.3 equiv of (3-furyl)Ti(O^{i}Pr)$_3$ is sufficient for the reactions. This study represents the most effective titanium-catalyzed nucleophilic addition reactions to ketones with a reaction time of 12 h at a mild temperature of 0 °C even for additions to sterically hindered ketones. Further investigations of organotitaninum reagents in catalysis are currently underway.

Acknowledgment. Financial support under grant number NSC 96-2113-M-005-007-MY3 from the National Science Council of Taiwan is appreciated.

Supporting Information Available: Experimental and characterization data for all compounds and CIF file of compounds **1** and (*S*)-**3t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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