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Direct Asymmetric Catalytic Thienylaluminum Addition to Ketones: A Concise Approach to the Synthesis of (*S*)-Tiemonium Iodide

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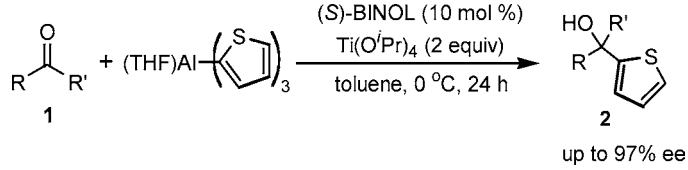
ABSTRACT



A direct asymmetric addition of a (2-thienyl)aluminum reagent to ketones catalyzed by a titanium catalyst of (*S*)-BINOL to afford chiral tertiary 2-thienyl alcohols is reported. The catalytic system works excellently for aromatic ketones and for 1-acetylcyclohexene, furnishing products in excellent enantioselectivities of up to 97% ee. However, the additions to dialkyl ketones afford products in low enantioselectivities of 8−17% ee. Importantly, a concise 3-step synthesis of (*S*)-tiemonium iodide with an 84% yield is demonstrated.

Catalytic asymmetric synthesis of chiral alcohols is of great importance for the syntheses of enantiomerically pure natural products and pharmaceuticals,[1] and the addition of carbon-based nucleophiles to organic carbonyls constitutes the most straightforward strategy.[2] However, fewer catalysts have been established for additions to ketones.[3] In addition to organozinc reagents, organoaluminum compounds were proven to be excellent reagents for asymmetric addition reactions, but in limited cases.[4] Recently, there has been increasing interest in asymmetric

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catalysis with organoaluminum nucleophiles because of their greater reactivities.[5]

Tertiary thienyl alcohols are well-known for their biological activity as well as key substructures in bioactive compounds and pharmaceuticals such as tiemonium iodide (**a**)[6] and compounds **b**[7] and **c**[8] (Figure 1). Tiemonium

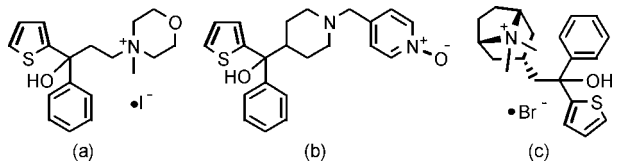


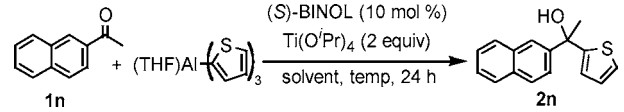
Figure 1. Bioactive compounds or drugs containing 2-thienyl alcohols.

iodide is sold as an anticholinergic/spasmolytic drug, and compound **b** is an antiallergic/antiasthmatic drug. Compound **c** shows a bioactivity against chronic obstructive pulmonary disease. Despite the importance of tertiary thienyl alcohols, their syntheses were reported in only a few papers via additions of organometallic reagents to thienylketones.[9] Recently, the optically active thienyl aryl methanols were obtained in good yields and high enantioselectivities through additions of thienylboronic acid to aldehydes in the presence of $ZnEt_2$ and 20 mol % chiral Schiff-base amino alcohol ligands.[10] To continue our efforts in developing organoaluminum reagents for asymmetric catalysis, we report herein the first catalytic asymmetric thienylaluminum additions to ketones catalyzed by in situ-prepared $Ti(O^iPr)_4$ complexes of (*S*)-BINOL and the application of the resulting tertiary alcohol to the preparation of enantiomerically pure tiemonium iodide.

In this study, the 2-thienylaluminum reagent, Al(2-thienyl)$_3$(THF),[11] was prepared and addition reactions were optimized on 2′-acetonaphthone (**1n**) in the presence of $Ti(O^iPr)_4$ and a catalytic amount of 10 mol % (*S*)-BINOL. The results are summarized in Table 1. The reaction condition of 1.7 equiv of Al(2-thienyl)$_3$(THF) and 2 equiv of $Ti(O^iPr)_4$ at 0 °C in toluene was found to furnish product **2n** in the best 99% conversion and the best enantioselectivity of 92% ee (entry 7).

Having established the optimized conditions, we then examined the catalytic reactions with functionalized ketones and the results are shown in Table 2. For aromatic ketones with either an electron-withdrawing or an electron-donating substituent at 2′-, 3′-, or 4′-positions, 2-thienyl additions afforded tertiary alcohols in excellent enantioselectivities of 90% ee or greater except for substrates of 2′-methoxyacetophenone and α-bromo-2′-acetonaphthone which afforded the products in 45% and 80% ee (entries 5 and 16). The catalytic systems of both (*S*)- and (*R*)-BINOL ligands were

Table 1. Optimizations of Asymmetric 2-Thienyl Additions to 2′-Acetonaphthone Catalyzed by in Situ-Formed (*S*)-BINOL/$Ti(O^iPr)_4$ Systems[a]



entry	Al reagent (equiv)	$Ti(O^iPr)_4$ (equiv)	solvent	temp (°C)	convn (%)[b]	ee (%)[c]
1	2	3	THF	rt	99	65
2	2	3	THF	0−rt	99	73
3	1.5	3	THF	0−rt	99	77
4	1.5	3	THF	0	68	85
5	1.5	2	THF	0	67	88
6	1.5	2	toluene	0	94	92
7	1.7	2	toluene	0	99	92
8	1.9	2	toluene	0	99	85

[a] 2′-Acetonaphthone, 0.50 mmol; equivalents of Al reagent and $Ti(O^iPr)_4$ are relative to 2′-acetonaphthone. [b] Conversions were based on ^{1}H NMR spectra. [c] Enantioselectivities were determined by HPLC.

used for 2-thienyl additions to 3-bromo-1-phenylpropan-1-one (**1q**), affording both enantiomeric products of (*S*)-**2q** and (*R*)-**2q** in 94% and 93% ee (entries 17 and 18), respectively. The above results reveal minimal effects of types of substituent and substituted positions on the aromatic group in terms of stereoselectivities. For the conjugated enone of 1-acetylcyclohexene, the reaction gave tertiary alcohol **2r** exclusively in high yield with a high enantioselectivity of 91% ee (entry19).

However, the 2-thienyl addition to α-tetralone under the optimized conditions gave **2s** in a moderate 61% ee with an excellent 92% yield (entry 20). The aliphatic ketones were also examined, and the reactions afforded the products in high yields but with low enantioselectivities of 8−17% ee (entries 21−23). The addition to 2′-methoxyacetophenone afforded the product **2e** in high yield due to the chelate effect of the substrate, which facilitates the coordination of 2′-methoxyacetophenone to the active metal center. However, small differentiations of both directions accessing the metal center lowered the enantioselectivity.

To demonstrate the synthesis of chiral tiemonium iodide, we initially carried out the 2-thienyl addition to the aromatic ketone **1w** containing the morpholine moiety. **1w** was prepared in 63% yield from reactions of morpholine hydrochloride, paraformaldehyde, and acetophenone in refluxing ethanol.[12] However, the reaction did not take place at all even with the use of 5 equiv of Al(2-thienyl)$_3$(THF) (entry 24). Fortunately, chiral tiemonium iodide could be prepared from 3-bromo-1-phenylpropan-1-one (**1q**) (Scheme 1). 2-Thienyl additions to **1q** catalyzed by a titanium catalyst of (*S*)- or (*R*)-BINOL furnished **2q** in excellent yields and enantioselectivities. Treatment of **2q** with morpholine produced **3q** in high yields and similar enantioselectivities to those of

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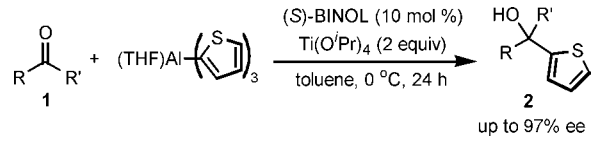
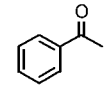
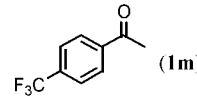
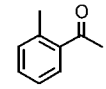
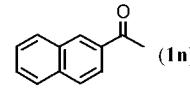
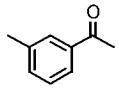
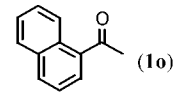
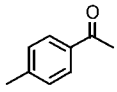
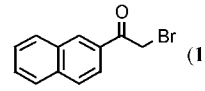
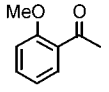
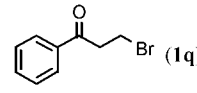
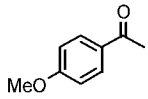
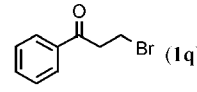
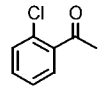
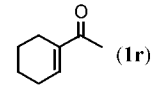
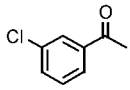
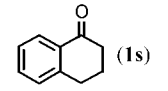
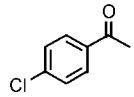
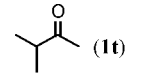
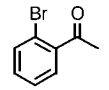
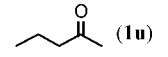
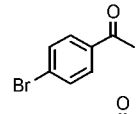
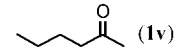
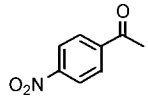
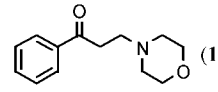
Table 2. Asymmetric 2-Thienyl Additions to Ketones Catalyzed by in Situ-Formed (*S*)-BINOL/Ti(O^iPr)$_4$ Systems[a]



entry	ketone (**1**)	product	yield (%)[b]	ee (%)[c]	entry	ketone (**1**)	product	yield (%)[b]	ee (%)[c]
1	 (**1a**)	**2a**	94	93	13	 (**1m**)	**2m**	96	93
2	 (**1b**)	**2b**	75	91	14	 (**1n**)	**2n**	94	92
3	 (**1c**)	**2c**	96	90	15	 (**1o**)	**2o**	70	93
4	 (**1d**)	**2d**	95	93	16	 (**1p**)	**2p**	95	80
5	 (**1e**)	**2e**	96	45	17	 (**1q**)	(*S*)-**2q**	90	94
6	 (**1f**)	**2f**	92	92	18[d]	 (**1q**)	(*R*)-**2q**	91	93
7	 (**1g**)	**2g**	92	97	19	 (**1r**)	**2r**	95	91
8	 (**1h**)	**2h**	95	90	20	 (**1s**)	**2s**	92	61
9	 (**1i**)	**2i**	96	95	21	 (**1t**)	**2t**	96	17
10	 (**1j**)	**2j**	93	96	22	 (**1u**)	**2u**	96	8
11	 (**1k**)	**2k**	95	93	23	 (**1v**)	**2v**	96	11
12	 (**1l**)	**2l**	95	94	24	 (**1w**)	**2w**	NR[e]	-

[a] Ketone/(2-$C_4H_3S)_3$Al(THF)/Ti(O^iPr)$_4$ = 0.50/0.85/1.0 mmol. [b] Isolated yields. [c] Enantioselectivities were determined by HPLC. [d] (*R*)-BINOL was used. [e] NR: no reaction.

2q. **3q** obtained from the catalytic system of (*S*)-BINOL reacted with methyl iodide to furnish tiemonium iodide (**4q**), which was subjected for an X-ray diffraction study. The crystal data confirmed an *S*-confiuration for **4q** (Figure 2).[13] This three-step synthesis produced (*S*)-tiemonium iodide ((*S*)-**4q**) in an overall yield of 84%.

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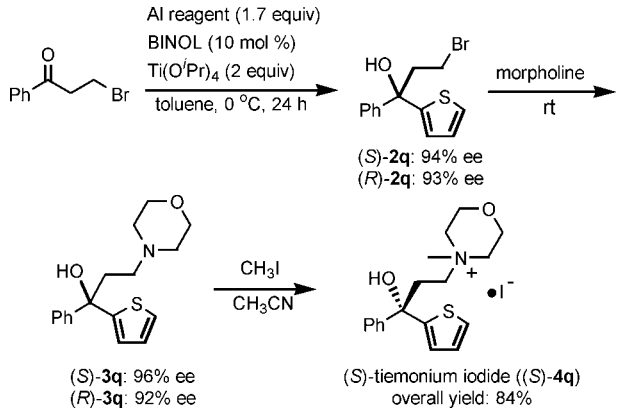
Scheme 1. Asymmetric Synthesis of (*S*)-Tiemonium Iodide



In summary, we have developed the first asymmetric catalytic 2-thienylaluminum additions to varieties of ketones. The catalytic system worked excellently for aromatic ketones having either an electron-donating or an electron-withdrawing substituent on the aromatic ring and for 1-acetylcyclohexene with excellent enantioselectivities of up to 97% ee. In contrast, the additions of 2-thienyl to aliphatic ketones produced corresponding tertiary alcohols in low enantioselectivities of 8−17% ee. Importantly, a concise synthesis of (*S*)-tiemonium iodide in 3 steps with an overall 84% yield was also demonstrated.

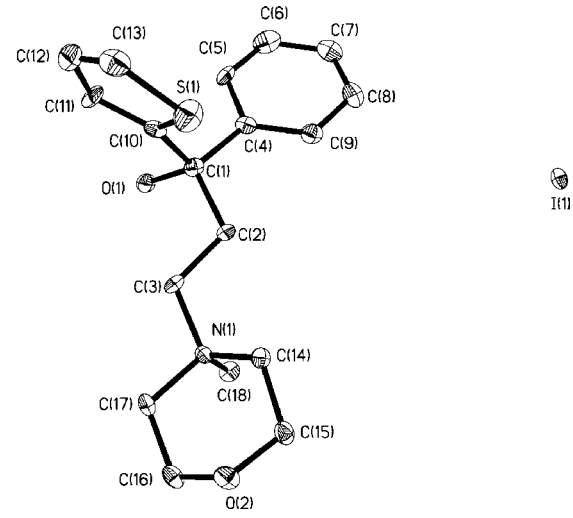


Figure 2. Molecular structure of (*S*)-tiemonium iodide. Hydrogen atoms are omitted for clarity.

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

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(13) Crystal data for (*S*)-tiemonium iodide: $C_{18}H_{24}INO_2S$, $M = 445.34$, monoclinic, space group $P2_1$, $T = 100$ (2) K, $a = 10.8791(2)$ Å, $b = 9.4754$ (2) Å, $c = 18.4279(4)$ Å, $\beta = 99.751(2)°$, $V = 1872.17(7)$ Å^3, $Z = 4$, absorption coefficient = 1.831 cm^{-1}, total reflections collected 16307, unique reflections collected 7336 ($R_{int} = 0.0265$), goodness-of-fit indicator = 0.929, $R_1 = 0.0232$, $wR_2 = 0.0469$. Absolute structure parameter = −0.016(11).