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Asymmetric trialkylaluminium addition to aldehydes catalyzed by titanium complexes of *N*-sulfonylated amino alcohols with two stereogenic centers

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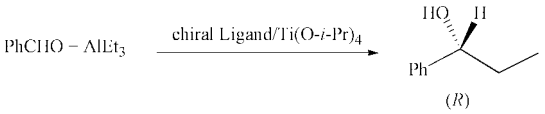
The asymmetric methylation, ethylation and allylation of aldehydes using trialkylaluminium reagents catalyzed by titanium(IV) complexes of *N*-sulfonylated amino alcohols gave excellent enantioselectivities of up to 99% ee.

Catalytic asymmetric carbon–carbon bond formation has been one of the most studied subjects in the past 10 years.[1] In these studies, the enantioselective additions of organozinc to aldehydes are one of the most reliable processes and thus gain much attention from chemists.[2–6] For alkylation reagents, trialkylaluminium reagents are more interesting since they are economically obtained in industrial scale.[7] Therefore the successful alkylation of aldehydes by trialkylaluminium should have great potential for practical applications. Unlike the diethylzinc addition to aldehydes which is extremely slow in the absence of a catalyst, trialkylaluminium reagents themselves are known to add to aldehydes at room temperature within hours. Due to competing reactions, the development of enantioselective catalysts for trialkylaluminium addition becomes much more challenging. Recently, Chan *et al.* reported the first example of asymmetric $AlEt_3$ addition to aldehydes employing titanium–BINOL systems with excellent ee's.[8] Subsequently, two papers dealing with the asymmetric methylation[9] and ethylation[10] of aldehydes by trialkylaluminium reagents were also reported.

Following our recent interest in titanium chemistry,[11] we herein report the synthesis of a family of amino alcohol derivatives **1**–**4** with one or two stereogenic centers. For *N*-sulfonylated amino alcohol derivative (*S*)-**1a** or (*S*)-**1b** as a chiral ligand, the asymmetric triethylaluminium addition to benzaldehyde was examined to afford low ee values of 29% (*R*) and 2% (*S*), respectively. The above results prompted us to synthesize a series of amino alcohols with two stereogenic centers, hoping to learn more about the structural factors that influence the enantioselectivity. Based on the route described by Reetz *et al.*,[12] amino alcohols **2** with two stereogenic centers starting from (*S*)-amino acids were synthesized. Compound **2** further reacted with arylsulfonyl chloride to give *N*-sulfonylated amino alcohol derivatives (*R*,*S*)-**3a**, (*R*,*S*)-**4a**–**c**, and (*S*,*S*)-**4a**.

Asymmetric triethylaluminium additions to benzaldehyde catalyzed by titanium(IV) complexes were conducted [eqn. (1)],



(1)

and the results are listed in Table 1.‡ While using 10 mol% of *N*-sulfonylated β-amino alcohol (*S*)-**1a** or (*S*)-**1b**, the reaction gave low ee values (entries 1 and 2). In using bidentate (*R*,*S*)-**3a** with two stereogenic centers, the ee value dramatically improved to 70% (entry 3). From entries 4–6, the tridentate ligands (*R*,*S*)-**4a** were examined with variation of the amount of $Ti(O\text{-}i\text{-}Pr)_4$ added. Without the addition of $Ti(O\text{-}i\text{-}Pr)_4$, the yield of 1-phenylpropanol is 44% with ee value of only 4% (*R*) (entry 4). With the addition of 0.05 mmol $Ti(O\text{-}i\text{-}Pr)_4$ (10 mol%), which gives a molar ratio of 1 : 1 of $Ti(O\text{-}i\text{-}Pr)_4$–(*R*,*S*)-**4a**, the ee value improves to 45% (*R*) (entry 5). Similar to previous studies of asymmetric diethylzinc addition to aldehydes, excess $Ti(O\text{-}i\text{-}Pr)_4$ is required in order to obtain the best enantioselectivity and, in this study, the best ee value of 96% was obtained for a catalytic system with a $Ti(O\text{-}i\text{-}Pr)_4$–(*R*,*S*)-**4a** ratio of 18 (entry

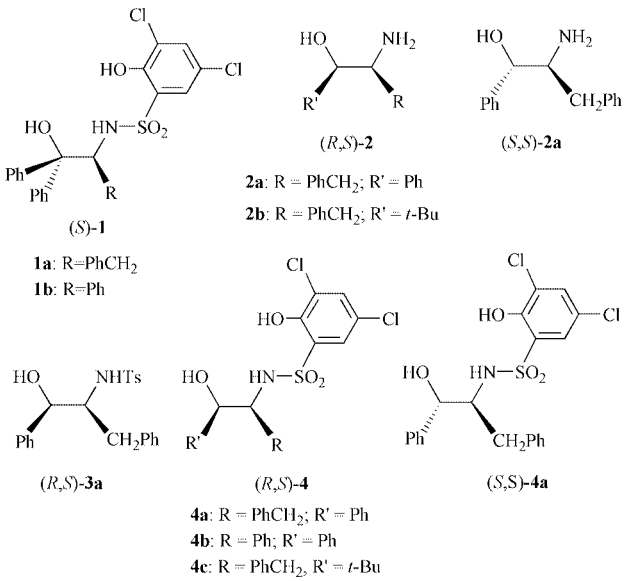


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Table 1 Enantioselective addition of trialkylaluminium to benzaldehyde catalyzed by *in Situ*-formed chiral ligand–$Ti(O\text{-}i\text{-}Pr)_4$ catalytic systems in THF[a]

Entry	Compd. (mol%)	AlR_3	$Ti/O\text{-}i\text{-}Pr)_4$/mmol	Yield (%)	% ee[b]
1	(*S*)-**1a** (10)	$AlEt_3$	0.9	90	29 (*R*)
2	(*S*)-**1b** (10)	$AlEt_3$	0.9	84	2 (*S*)
3	(*R*,*S*)-**3a** (10)	$AlEt_3$	0.9	97	70 (*R*)
4	(*R*,*S*)-**4a** (10)	$AlEt_3$	0	44	4 (*R*)
5	(*R*,*S*)-**4a** (10)	$AlEt_3$	0.05	49	45 (*R*)
6	(*R*,*S*)-**4a** (10)	$AlEt_3$	0.9	98	96 (*R*)
7	(*R*,*S*)-**4a** (5)	$AlEt_3$	0.45	97	95 (*R*)
8	(*S*,*S*)-**4a** (10)	$AlEt_3$	0.9	70	26 (*S*)
9	(*R*,*S*)-**4b** (10)	$AlEt_3$	0.9	94	75 (*R*)
10	(*R*,*S*)-**4c** (10)	$AlEt_3$	0.9	66	8 (*S*)

[a] Benzaldehyde, 0.5 mmol; trialkylaluminium, 1.25 mmol; reaction temperature, 0 °C; reaction time, 12 h. [b] The ee values were determined by HPLC with a chiral OD column.

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Table 2 Enantioselective addition of trialkylaluminium to aldehydes catalyzed by *in situ*-formed 10 mol% (*R*,*S*)-**4a**–Ti(O-*i*-Pr)$_4$ catalytic systems in THF[a]

Entry	Aldehyde	AlR_3	Ti(O-*i*-Pr)$_4$/ mmol	Yield (%)	% ee[b]
1	Benzaldehyde	$AlEt_3$	0.9	98	96 (*R*)
2	4-Chlorobenzaldehyde	$AlEt_3$	0.9	100	94 (*R*)
3	1-Naphthaldehyde	$AlEt_3$	0.9	94	92 (*R*)
4	2-Naphthaldehyde	$AlEt_3$	0.9	100	92 (*R*)
5	*E*-Cinnamaldehyde	$AlEt_3$	0.9	100	88 (*R*)
6	Cyclohexanecarboxaldehyde	$AlEt_3$	0.9	54	91 (*R*)[c]
7	Benzaldehyde	$AlMe_3$	0.9	100	98 (*R*)
8	1-Naphthaldehyde	$AlMe_3$	0.9	95	96 (*R*)
9	Cyclohexanecarboxaldehyde	$AlMe_3$	0.9	100	91 (*R*)[c]
10	(*E*)-Cinnamaldehyde	$AlMe_3$	0.9	99	> 99 (*R*)
11	Benzaldehyde	(Allyl)$AlEt_2$	0.9	100	90 (*R*)
12	2-Naphthaldehyde	(Allyl)$AlEt_2$	0.9	100	96 (*R*)

[a] Aldehyde, 0.5 mmol; trialkylaluminium, 1.25 mmol; Ti(O-*i*-Pr)$_4$, 0.9 mmol; reaction temperature, 0 °C; reaction time, 12 h. [b] The ee values were determined by HPLC with a chiral OD column. [c] Determined by HPLC with a chiralcel AS column after protecting as a benzoyl ester.

6). Even with the use of as little as 5 mol% of (*R*,*S*)-**4a**, 95% ee was still obtained (entry 7). For chiral ligand (*S*,*S*)-**4a** which is a diastereomer of (*R*,*S*)-**4a**, a much lower ee value of 26% was obtained (entry 8). When the substituent on the amino carbon was replaced with a phenyl group ((*R*,*S*)-**4b**), the ee value decreases to only 75% (entry 9). For (*R*,*S*)-**4c** with a *tert*-butyl substituent instead of a phenyl group on the chiral alcoholic carbon in (*R*,*S*)-**4a**, an ee value of 8% of *S*-configuration was observed (entry 10). In the initial study of triethylaluminium addition to benzaldehyde, a profound solvent effect was observed, and only a coordinating solvent such as THF prompted high enantioselectivities.

The enhanced unique reactivity of the *N*-sulfonylated amino alcohol (*R*,*S*)-**4a** is suggested to arise from the following two factors: (1) phenoxides are known to form strong bonds to group 4 transition metals, and with electron withdrawing halogen groups, the phenoxide moiety may lead to enhance Lewis acidity at the metal centre; (2) the phenolic ring provides conformational rigidity which may be an important factor in the transfer of asymmetry.

For examining the substrate generality, the best performing (*R*,*S*)-**4a**–Ti(O-*i*-Pr)$_4$ catalytic system was used (Table 2). Ee values ranging from 92–96% (*R*) (entries 1–4) were recorded for aromatic aldehydes with the best result observed for benzaldehyde as a substrate. For the (*E*)-cinnamaldehyde, the ee value is somewhat lower at 88% (entry 5). Interestingly, the catalytic system catalyzed the ethylation of the aliphatic cyclohexanecarboxaldehyde with an ee value of 91% (entry 6). Though not many aldehydes were examined, the catalytic system generally seems to work well for both aromatic and aliphatic aldehydes.

In addition, other trialkylaluminium reagents such as $AlMe_3$ and $AlEt_2$(allyl)[13] were also examined. $AlMe_3$ was added to aldehydes, to give exceptional ee values from 91 to 99% (entries 7–10). More interestingly, when allyldiethylaluminium was used as an alkylation reagent, the allyl group rather than the ethyl group selectively added to aldehydes to give the secondary homoallyl alcohol with excellent ee values of 90% for benzaldehyde (entry 11) and 96% for 2-naphthaldehyde (entry 12). For catalytic allylation reactions, this is the first example of catalytically enantioselective allylation of aldehydes employing the allyldialkylaluminium reagent, to the best of our knowledge.

In summary, a family of *N*-sulfonylated amino alcohols have been developed for asymmetric alkylation reactions. The (*R*,*S*)-**4a**–Ti(O-*i*-Pr)$_4$ system is an excellent catalyst for trialkylaluminium addition to aldehydes at a convenient temperature of 0 °C. Furthermore, the (*R*,*S*)-**4a**/Ti(O-*i*-Pr)$_4$ catalytic system shows a wide generality of trialkylaluminum reagents such as $AlEt_3$, $AlMe_3$, or even (allyl)$AlEt_2$.

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Notes and references

‡ *General procedures for the addition of trialkylaluminium reagents to aldehydes*. Under a dry dinitrogen atmosphere, the ligand and Ti(O-*i*-Pr)$_4$ were mixed in 1.5 mL of dry THF at room temperature. After 1 hour, 1.25 mmol of $AlEt_3$, $AlMe_3$ or allyldiethylaluminum was added at 0 °C. After the mixture was stirred for 30 min, the orange-colored solution was treated with aldehyde (0.5 mmol) at 0 °C, kept at this temperature for 10 h, and quenched with 1 M HCl. The aqueous phase was extracted with ethyl acetate (3 × 5 mL), dried over $MgSO_4$, filtered and concentrated. Chromatography of the residue on silica gel (elution with 5:1 hexane–ethyl acetate) gave the alcohol. The enantiomeric purity of the product was determined by HPLC.

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