Aziridine-Modified Amino Alcohols as Efficient Modular Catalysts for Highly Enantioselective Alkenylzinc Additions to Aldehydes

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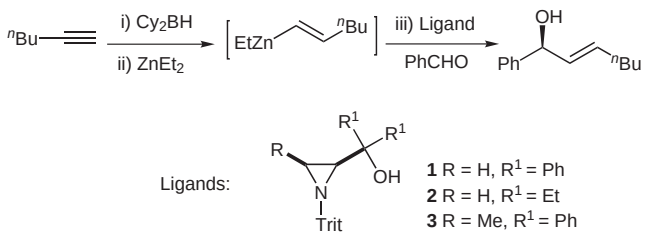
Abstract: *N*-Tritylaziridino alcohols have been easily synthesized in a straightforward synthetic route from an inexpensive and easily available chiral pool. They were used in the enantioselective alkenylzinc additions to aldehydes furnishing the products in excellent yields and stereoselectivities up to 97%.

Key words: asymmetric synthesis, allylic alcohols, vinyl addition, alkenylzinc, aziridino alcohols

The catalytic enantioselective construction of carbon–carbon bonds is still one of the most challenging goals in organic chemistry.[1] In this field, the enantioselective addition of organometallic reagents to aldehydes appears as an extremely attractive topic.[2]

Chiral, nonracemic allylic alcohols are important intermediates for the synthesis of biologically and pharmaceutically active compounds due to the vast possibilities for further stereoselective manipulations.[3] The addition of alkenylzinc derivatives to aldehydes is probably one of the most efficient approach for this purpose. These organometallic reagents can be easily prepared in situ using transmetalation protocols.[4] In this context, Oppolzer and Radinov introduced an elegant method where a vinylzinc reagent was prepared in situ by regioselective hydroboration of terminal alkynes with dicyclohexylborane followed by boron–zinc exchange.[5]

Since, ligands which effectively catalyze the vinyl transfer reactions to aldehydes have not been extensively studied.[6] The search for efficient chiral ligands to generate high enantioselectivities in such reactions still remains a challenge in this area (Scheme 1).



Scheme 1 Enantioselective synthesis of allylic alcohols

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In connection with our current interests in the asymmetric addition of organozinc reagents to aldehydes[7] and encouraged by the recent successful developments in the enantioselective arylzinc additon to aldehydes under MW irradiation using aziridine-containing amino alcohols as modular ligands,[8] we demonstrated herein the utility of these easy accessible ligand systems for the enantioselective addition of vinylzinc reagents to aldehydes.

Ligands **1**–**3** can be prepared in high yields starting from the appropriate amino acids, L-serine and L-threonine, respectively.[9] Due to the availability of the D-configured amino acids, the corresponding enantiomers of ligand **1**–**3** be can approached without any obstacles.

With the target ligands in hand, we focused our attention towards the optimization of the conditions of the C–C coupling reaction. At first, effects of catalyst loading and temperature were first investigated in detail for ligand **1** with 1-hexyne as the alkenylzinc precursor and benzaldehyde using toluene as solvent (Scheme 1, Table 1, entries 1–7).[10]

Table 1 Results for the Addition of Vinylzinc Species to Benzaldehyde under Various Conditions

Entry	Ligand (mol%)	Temp (°C)	Time (h)	Yield (%)[a]	ee (%)[b,c]
1	**1** (15)	–20	18	88	93 (*S*)
2	**1** (10)	–20	18	87	92 (*S*)
3	**1** (5)	–20	18	83	85 (*S*)
4	**1** (2.5)	–20	18	72	79 (*S*)
5	**1** (10)	–40	24	68	92 (*S*)
6	**1** (10)	–78	36	36	94 (*S*)
7[d]	**1** (10)	–20	18	84	90 (*S*)
8	**2** (10)	–20	18	82	91 (*S*)
9	**3** (10)	–20	18	79	46 (*S*)
10[e]	**1** (10)	–20	18	93	95 (*S*)

[a] Yield of isolated products.
[b] The ee values for allylic alcohols were measured by HPLC (Chiralcel OD-H).
[c] Configuration determined by comparison with literature data.[3d,6g]
[d] A 1:1 mixture of toluene and hexane was used as solvent.
[e] Me_2Zn was used instead of Et_2Zn in transmetalation.

Our studies had started employing catalyst loadings of 15 mol% to achieve excellent levels of enantioselectivity (entry 1). Decreased ligand loading to 10 mol% gave similar results but reducing the catalyst loading to 5 mol% resulted in a decrease in the enantioselectivity and yield (entries 2 vs. 3). Further decrease of the catalyst loading to 2.5 mol% caused a slight decrease in yield and in enantioselectivity (entry 4). Lowering the reaction temperature to –40 °C or –78 °C had a little effect on the selectivity; instead, the reactivity was significantly decreased (entries 5 and 6).

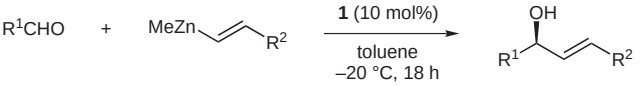
The influence of the solvent was also examined. The use of toluene is crucial for a high enantioselectivity, since a lower ee was obtained by employing a mixture of toluene–hexane (entry 7). This fact is probably due to a poor solubility of the reactive zinc species resulting from the boron–zinc exchange reaction.[6c]

We decided to extend this study to other chiral aziridine ligands. For this reason, the electronic and steric properties of the R and R^1 groups have been briefly investigated. Decreasing the size of the chiral ligand by switching from **1** (R^1 = Ph) to **2** (R^1 = Et) gave comparable yield and ee (entries 2 vs. 8). However, variations in the R group have shown that it plays a great impact on the enantioselectivity of the reaction. The best result was achieved with the catalyst **1** with R = H (entries 2 vs. 9). Therefore, one can assume that steric factors play a dominant role in the stereochemical outcome in this series of ligands. We next examined alternative methods to generate the vinylzinc reagent. An improvement of the enantioselectivity was observed, when dimethylzinc was used in the transmetalation step instead of diethylzinc (entry 10).

To study the generality of catalyst **1** we examined the scope of the reactions catalyzed by this ligand by first varying the structure of the vinylzinc reagent (Table 2). We found that the substituents on the propargylic position had a very little effect on the enantioselectivity of the reaction. For example, *n*-hexylacetylene gave the corresponding allylic alcohol in 94% ee and the bulky *tert*-butylacetylene gave the desired product in 97% ee (entries 1 vs. 2). Using cyclohexylacetylene, a very high enantiomeric excess of the corresponding product was achieved (entry 3). In fact, all substrates tested gave in general >90% ee.

Finally, we investigated the applicability of our ligand to the addition of (*E*)-(3,3-dimethylbut-1-enyl) zinc to several aromatic aldehydes with diverse electronic and steric properties (Table 2, entries 4–9). Reaction with *p*-tolualdehyde underwent smooth vinyl addition in very high enantiomeric excess in good yield (entry 4). When *p*-methoxybenzaldehyde was employed, a decreased enantiomeric excess of the corresponding product was achieved (entry 5). On the other hand, when electron-withdrawing groups were present in the aldehyde, the enantioselectivity decreased compared to using benzaldehyde (entries 2 vs. 6–8). The presence of substituents at the *ortho* position of the aromatic aldehyde shows some difference in the stereodifferentiation event. For example, *p*-bromobenzaldehyde undergoes smooth vinyl addition, to achieve the corresponding product in 95% ee, while the *o*-bromo derivative resulted in much lower enantioselectivity (entries 7 vs. 9). This fact can be explained by the influence of steric effects.

Table 2 Vinylzinc Addition to Various Aldehydes Catalyzed by Ligand **1**[11]



Entry	Terminal alkynes (R^1)	Aldehyde (R^2)	Yield (%)[a]	ee (%)[b,c]
1	*n*-Hex	Ph	94	94 (*S*)
2	*t*-Bu	Ph	96	97 (*S*)
3	*c*-Hex	Ph	92	97 (*S*)
4	*t*-Bu	*p*-MeC_6H_4	83	95 (*S*)
5	*t*-Bu	*p*-$OMeC_6H_4$	86	88 (*S*)
6	*t*-Bu	*p*-ClC_6H_4	89	91 (*S*)
7	*t*-Bu	*p*-BrC_6H_4	88	95 (*S*)
8	*t*-Bu	*p*-$MeCO_2C_6H_4$	97	90 (*S*)
9	*t*-Bu	*o*-BrC_6H_4	89	81 (*S*)

[a] Yield of isolated products.
[b] The ee (%) of allylic alcohols as measured by HPLC.
[c] Configuration determined by comparison with literature data.[3d,6g]

In summary, we have demonstrated an efficient catalytic enantioselective vinylation of aromatic aldehydes using rigid chiral ligands readily available from common amino acids. The reactive alkenylzinc species is generated in situ via a boron–zinc exchange and its reaction with aldehydes gives access to several chiral allylic alcohols in high yields and ee. The selectivities are comparable to those obtained with the best ligand known for this reaction.[6] Studies dealing with the mechanism of the reaction and application of this catalyst system in other asymmetric catalytic reactions are currently in progress in our laboratories.

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(9) **General Procedure for the Synthesis of Ligands 1–3**
The Grignard reagent (25 mmol) in THF (10 mL, 2.5 M solution) was added dropwise over a period of 10 min to a solution of the appropriate aziridine ester (5 mmol) in 10 mL of THF. After 1.5 h the reaction was quenched with sat. aq NH_4Cl (30 mL) followed by the evaporation of the organic solvents. The residue was extracted with Et_2O (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated to give the product. The crude product was purified by flash column chromatography on silica (hexane–EtOAc, 12:1); Et_3N was added to the eluent to prevent detritylation of the product during the purification procedure. Recrystallization was achieved from MeOH–Et_3N by a hot solution.

(10) Compound **1**: yield 70%; mp 133.5–134.5 °C; $[\alpha]_D^{22}$ –78.8 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.34 (d, 2 H, *J* = 7.3 Hz), 7.32–7.12 (m, 8 H), 7.09–7.04 (m, 15 H), 4.44 (br s, 1 H), 2.38 (dd, 1 H, *J* = 6.2, 3.1 Hz), 2.08 (d, 1 H, *J* = 3.1 Hz), 1.32 (d, 1 H, *J* = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.79, 145.25, 143.44, 129.04, 127.77, 127.59, 127.22, 126.62, 126.55, 126.50, 126.04, 125.72, 73.95, 73.89, 41.46, 23.80. ESI-HRMS: *m/z* calcd for $C_{34}H_{29}NO$ + Na^+: 490.2147; found: $C_{34}H_{29}NO$ + Na^+: 490.2141.
Compound **2**: yield 74%; pale yellow oil; $[\alpha]_D^{22}$ –82.8 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.18 (m, 15 H), 3.05 (br s, 1 H), 1.94 (d, 1 H, *J* = 3.3 Hz), 1.62–1.43 (m, 1 H), 1.41–1.29 (m, 4 H), 1.14 (d, 1 H, *J* = 6.4 Hz), 0.73 (q, 6 H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.03, 129.37, 127.40, 126.68, 73.97, 70.82, 40.18, 31.93, 28.23, 23.51, 8.13, 7.73. ESI-HRMS: *m/z* calcd for $C_{26}H_{29}NO$ + Na^+: 394.2141; found: $C_{26}H_{29}NO$ + Na^+: 394.2147
Compound **3**: yield 82%; mp 174–176 °C; $[\alpha]_D^{22}$ +22 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–6.98 (m, 25 H), 3.05 (s, 1 H), 2.20 (d, 1 H, *J* = 6.7 Hz), 1.66 (q, 1 H, *J* = 6.0 Hz), 1.19 (d, 3 H, *J* = 5.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.39, 146.04, 143.80, 143.68, 129.34, 128.60, 127.80, 127.74, 127.29, 126.79, 126.64, 126.03, 125.52, 75.17, 73.50, 45.21, 31.99, 1376. ESI-HRMS: *m/z* calcd for $C_{35}H_{31}NO$ + Na^+: 504.2303; found: $C_{35}H_{31}NO$ + Na^+: 504.2297.

(11) **General Procedure for the Alkenylzinc Addition to Aldehydes**
Cyclohexene (608 μL, 3.0 mmol) was added under argon at 0 °C to a magnetically stirred solution of borane dimethylsulfide complex (142 μL, 1.5 mmol) in toluene (1 mL). After 2 h at 0 °C the alkyne (1.5 mmol) was added and the mixture was stirred for 30 min at r.t. The mixture was cooled to –78 °C and a solution of Et_2Zn (2 mL, 1 mmol, 1.0 M in toluene) or Me_2Zn solution (1.5 mL, 3 mmol, 2 M in toluene) was added slowly to this and after 1 h at –78 °C, a toluene solution of ligand (0.1 mL, 1 M in toluene, 0.1 mmol) was added. After warming from –78 °C to –30 °C over a period of 1 h, toluene (1 mL) and the aldehyde (1 mmol) were added and the mixture was stirred for 18 h at –20 °C. The reaction mixture was quenched with H_2O, Et_2O was added and the organic layer was subsequently extracted with brine. The organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified through column chromatography on silica gel to provide the enantiomerically pure allyl alcohol.
Conditions for Determining Enantiomeric Excess by HPLC Analysis
All measurements were performed at a 20 °C column temperature using a UV detector at 219 nm.
(*S*,*E*)-1-Phenylhept-2-en-1-ol (Table 1, entries 1–10): Chiralcel OD-H column eluted with hexane–2-PrOH (99:1) at 1.0 mL/min; t_R = 22.0 min for *R* and t_R = 32.3 min for *S*.
(*S*,*E*)-1-Phenylnon-2-en-1-ol (Table 2, entry 1): Chiralcel OD-H column eluted with hexane–2-PrOH (99:1) at 1.0 mL/min; t_R = 20.7 min for *R* and t_R = 32.3 min for *S*.
(*S*,*E*)-4,4-Dimethyl-1-phenylpent-2-en-1-ol (Table 2, entry 2): Chiralcel OD-H column eluted with hexane–2-PrOH (99:1) at 1.0 mL/min; t_R = 14.1 min for *R* and t_R = 22.3 min for *S*.
(*S*,*E*)-3-Cyclohexyl-1-phenylprop-2-en-1-ol (Table 2, entry 3): Chiralcel OD-H column eluted with hexane–2-PrOH (99:1) at 1.0 mL/min; t_R = 21.9 min for *R* and t_R = 33.2 min for *S*.
(*S*,*E*)-(4-Tolylphenyl)-4,4-dimethylpent-2-en-1-ol (Table 2, entry 4): Chiralcel OD-H column eluted with hexane–2-PrOH (98:2) at 0.5 mL/min; t_R = 18.3 min for *R* and t_R = 20.5 min for *S*.
(*S*,*E*)-1-(4-Methoxyphenyl)-4,4-dimethylpent-2-en-1-ol (Table 2, entry 5): Chiralcel OD-H column eluted with hexane–2-PrOH (99:1) at 1.0 mL/min; t_R = 25.5 min for *R* and t_R = 32.5 min for *S*.

(*S*,*E*)-(4-Chlorophenyl)-4,4-dimethylpent-2-en-1-ol (Table 2, entry 6): Chiralcel AD-H column eluted with hexane–2-PrOH (95:5) at 1.0 mL/min: t_R = 7.15 min for *R* and t_R = 8.14 min for *S*.

(*S*,*E*)-(4-Bromophenyl)-4,4-dimethylpent-2-en-1-ol (Table 2, entry 7): Chiralcel AD-H column eluted with hexane–2-PrOH (95:5) at 1.0 mL/min: t_R = 7.64 min for *R* and t_R = 9.07 min for *S*.

(*S*,*E*)-Methyl 4-(1-hydroxy-4,4-dimethylpent-2-enyl)benzoate (Table 2, entry 8): Chiralcel OD-H column eluted with hexane–2-PrOH (95:5) at 1.0 mL/min; t_R = 13.7 min for *S* and t_R = 14.8 min for *R*.

(*S*,*E*)-(2-Bromophenyl)-4,4-dimethylpent-2-en-1-ol (Table 2, entry 9): Chiralcel OD-H column eluted with hexane–2-PrOH (97:7) at 1.0 mL/min: t_R = 13.2 min for *R* and t_R = 15.7 min for *S*.