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Enantioselective conjugate addition of diethylzinc to chalcones catalysed by *N*-trityl aziridine-2-(*S*)-(diphenyl)methanol and Ni(acac)$_2$

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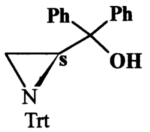
Abstract—The chiral Ni(II) complex prepared from Ni(acac)$_2$ and *N*-trityl aziridine-2-(*S*)-(diphenyl)methanol catalyses the enantioselective conjugate addition of diethylzinc to chalcones in good yield with ees of upto 93%. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

There has been great interest in the catalytic enantioselective Michael addition of organometallic reagents to prochiral enones to yield chiral ketones.[1] Chiral β-amino-alcohols and binaphthol derived phosphorus amidites in the presence of transition metals have been proven to be effective catalysts for the above purpose. Among various transition metals, the application of organozinc reagents in the above reaction is of special value due to their high tolerance of many functional groups.[2] We wish to report herein a new type of chiral auxiliary, *N*-trityl aziridine-2-(*S*)-(diphenyl)methanol (**1**), for the enantioselective conjugate addition of diethylzinc to chalcones.



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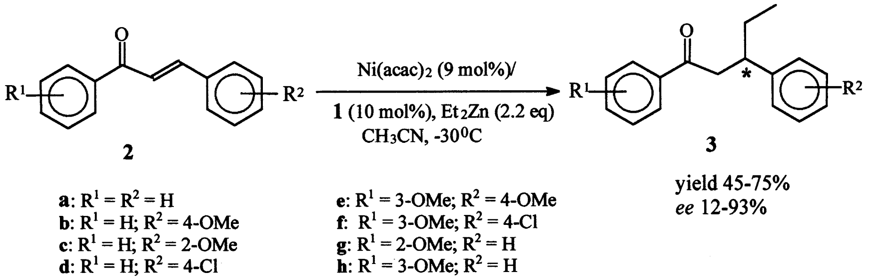
2. Results and discussion

Chiral β-amino alcohols have been found to be efficient ligands for the enantioselective alkyl transfer from diorganozinc reagents to prochiral enones in the presence of Ni(II) salts. Recently, Feringa et al.[1e] used a mixture of Ni(acac)$_2$ and (−)-*cis*-*exo*-*N*,*N*-dimethyl-3-aminoisoborneol (DAIB) as a chiral catalyst for the conjugate addition of diethylzinc to chalcone giving ees of 51–81%. Similarly, Soai et al. used the chiral complex derived from Ni(acac)$_2$ and *N*,*N*-dibutylnorephedrine in the enantioselective Michael addition to enones leading to poor ee in the product (12–45%).[1h] Very recently we observed[3] that the chiral catalyst **1** is highly efficient for the enantioselective addition of diethylzinc to aldehydes with an ee up to 98%. This prompted us to use **1** in the enantioselective conjugate addition of diethylzinc to chalcones (Scheme 1).

Compound **1** was prepared in high yield from L-serine following the literature procedure.[4] Initially, a combination of 9 mol% of Ni(acac)$_2$ and 2 mol% of **1** in acetonitrile were



Scheme 1. Enantioselective conjugate addition of diethylzinc to chalcones.

Keywords: asymmetric synthesis; chalcones; zinc compounds; aziridine.

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Table 1. Enantioselective conjugate addition of diethylzinc to chalcone **2a** using Ni(acac)$_2$–**1** as catalyst: variation of catalyst concentration, solvent and temperature

Entry	Substrate	Ni(acac)$_2$–**1** (mol%)[a]	Solvent	Yield (%)[b] of **3a**	% ee[c] (config.)	Rep % ee (config.)[1e]
1	**2a**	9:2	CH_3CN	68	24 (*R*)	–
2	**2a**	9:5	CH_3CN	69	30 (*R*)	–
3	**2a**	9:10	CH_3CN	75	78 (*R*)	65 (*R*)
4	**2a**	9:20	CH_3CN	70	77 (*R*)	–
5	**2a**	9:10	Hexane	–		–
6	**2a**	9:10	Toluene	67	28 (*R*)	–
7	**2a**	9:10	THF	65	67 (*R*)	–
8	**2a**	9:10	THF–hexane (1:1)	63	65 (*R*)	–
9	**2a**	9:10	CH_3CN	55	27 (*R*)	–

All conjugate addition reactions were carried out with 2.2 equiv. of diethylzinc in the presence of chiral catalyst prepared in situ by mixing Ni(acac)$_2$ with **1** at −30°C except in entry 9 which was carried out at 25°C.

[a] The mol% was calculated based on chalcone used in the reaction.

[b] Isolated yield after column chromatography.

[c] Determined by HPLC analysis using a chiral column (Chirex (*R*)-phenylglycine, 4.0×250 mm). Flow rate 1 mL min^{-1}; eluant 0.1% 2-propanol in hexane.

Table 2. Enantioselective conjugate addition of diethylzinc to chalcones using Ni(acac)$_2$–**1** as catalyst

Entry	Substrate	Time (h)	Product	Yield (%)[a]	% ee[b] (config.)	Rep. % ee (config.)
1	**2b**	4	**3b**	55	70 (*R*)	57 (*R*)[1e]
2	**2c**	5	**3c**	69	78 (*R*)	–
3	**2d**	3.5	**3d**	50	78 (*R*)	61 (*R*)[1e]
4	**2e**	4.5	**3e**	72	83 (*R*)	–
5	**2f**	4.5	**3f**	70	71 (*R*)	–
6	**2g**	4.5	**3g**	45	12 (*R*)	–
7	**2h**	4.5	**3h**	67	93 (*R*)	–

All conjugate addition reactions were carried out with 2.2 equiv. of diethylzinc in the presence of chiral catalyst prepared in situ by mixing Ni(acac)$_2$ (9 mol%) and **1** (10 mol%) in acetonitrile at −30°C.

[a] Isolated yield after column chromatography.

[b] Determined by HPLC analysis using a chiral column (Chirex (*R*)-phenylglycine, 4.0×250 mm). Flow rate 1 mL min^{-1}; eluant 0.1% 2-propanol in hexane.

used to get an active species for the addition of diethylzinc to chalcone **2a** at −30°C. Smooth addition took place and the addition product **3a** was obtained in good yield (68%) with an enantiomeric excess of 24% (Table 1, entry 1). With further increase in the concentration of the ligand at a constant Ni(acac)$_2$ concentration (9 mol%), gradual increase in ee of **3a** was observed (Table 1, entries 2 and 3). However, no further increase in ee of **3a** was observed by increasing the amount of the catalyst **1** from 10 to 20 mol% (Table 1, entry 4).

In order to gain insight into other factors which influence the reaction, the effect of temperature and solvent on the conjugate addition was investigated. Thus when the above reaction was carried out in hexane in place of acetonitrile no reaction was observed and starting material was recovered quantitatively (Table 1, entry 5). However, use of toluene yielded **3a** in 67% yield and 28% ee (Table 1, entry 6). Similarly, **3a** was isolated in good yield (65%) and good enatioselectivity (ee 67%) using THF (Table 1, entry 7).

When the reaction was carried out with a 1:1 mixture of hexane and THF, **3a** was isolated in 63% yield in 65% ee. (Table 1, entry 8). Drastic reduction in the enantioselectivity was observed when the reaction was carried out in acetonitrile at ambient temperature (25°C) (Table 1, entry 9). Keeping this in view, all the subsequent reactions were carried out in acetonitrile with Ni(acac)$_2$ (9 mol%) and **1** (10 mol%) at −30°C.

To see the generality of the reaction, a variety of chalcones were prepared and used as substrates. Thus, chalcones **2b–h** underwent smooth conjugate addition with diethylzinc to **3b–h** in good chemical yield and ee ranging from 12 to 93% (Table 2).

In conclusion, the complex formed by the reaction of *N*-trityl aziridine-2-(*S*)-(diphenyl)methanol (**1**) and Ni(acac)$_2$ was found to be an efficient catalyst for the enantioselective conjugate addition of diethylzinc to chalcones. Further work on the utility of **1** in other enantioselective reactions is currently in progress.

3. Experimental

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. FT-IR spectra were run on a Nicolet spectrophotometer (model 410). ^{1}H NMR spectra were recorded with a Bruker AC 200 (200 MHz) or Varian EM 360 (60 MHz) spectrometer. Mass spectra were measured on a Shimadzu GC/MS (QP 5050) mass spectrometer. Microanalysis was performed with Carlo Erba elemental analyser (model 1110). Enantiomeric excess (ee) was determined by HPLC analysis using a chiral column (Chirex (*R*)-phenylglycine, 4.0×250 mm) with a UV detector set at 254 nm. All reactions were carried out under an argon atmosphere. THF was distilled freshly from sodium-benzophenone ketyl prior to use. Acetonitrile was dried over P_2O_5 and hexane was dried over sodium. Diethylzinc was purchased from Aldrich Chemical Co.

3.1. General procedure for the synthesis of chalcones 2[5]

A solution of aromatic ketone (10 mmol) in ethanol (10 mL) was added gradually to an aqueous solution of 10% KOH (30 mL) at 0°C. After stirring for 15 min, aromatic aldehyde (10 mmol) was added and stirred at 0°C for 15 min. The mixture was then allowed to attain room temperature (25°C) and stirred for 4 h, after which it was refrigerated overnight. The product was then filtered on a Buchner funnel and washed with ice water until the washings were neutral to litmus and finally with rectified spirit. The crude product was purified by column chromatography (SiO_2) with pet ether–EtOAc (19:1) as eluant to afford the desired chalcone **2**. The following chalcones were prepared using the above procedure and their ^{1}H NMR spectra were identical to those in the literature.

3.1.1. 1,3-Diphenyl-2-propene-1-one (2a).[6a] Yield: 83%; yellow crystals; mp: 57°C (lit.[6a] mp: 57–58°C).

3.1.2. 3-(4-Methoxyphenyl)-1-phenyl-2-propene-1-one (2b).[6b] Yield: 57%; yellow crystals; mp: 77°C (lit.[6b] mp: 79°C).

3.1.3. 3-(2-Methoxyphenyl)-1-phenyl-2-propene-1-one (2c).[6c] Yield: 55%; yellow crystals; mp: 56°C (lit.[6c] mp: 60°C).

3.1.4. 3-(4-Chlorophenyl)-1-phenyl-2-propene-1-one (2d).[6d] Yield: 68%; white crystals; mp: 106°C (lit.[6d] mp: 104–106°C).

3.1.5. 3-(4-Methoxyphenyl)-1-(3-methoxyphenyl)-2-propene-1-one (2e).[6e] Yield: 72%; white crystals; mp: 49°C; ν_{max} (KBr): 1683, 1615, 1518, 1446 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 3.86 (s, 3H), 3.88 (m, 3H), 6.92 (d, 2H, J=8.7 Hz), 7.11–7.83 (m, 8H).

3.1.6. 3-(4-Chlorophenyl)-1-(3-methoxyphenyl)-2-propene-1-one (2f).[6e] Yield: 74%; yellow crystals; mp: 83°C; ν_{max} (KBr): 1677, 1615, 1518, 1446 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 3.89 (s, 3H), 7.13–7.8 (m, 10H).

3.1.7. 1-(2-Methoxyphenyl)-3-phenyl-2-propene-1-one (2g).[6f] Yield: 60%; yellow oil; ν_{max} (neat): 1683, 1615, 1518, 1446 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 3.89 (s, 3H), 7.26–7.63 (m, 11H).

3.1.8. 1-(3-Methoxyphenyl)-3-phenyl-2-propene-1-one (2h).[6f] Yield: 62%; yellow crystals; mp: 42°C (lit.[6f] mp: 41–42°C).

3.2. General procedure for the conjugate addition of diethylzinc to chalcones

A solution of Ni(acac)$_2$ (23.0 mg, 0.09 mmol) and **1** (46.7 mg, 0.1 mmol) in acetonitrile (20 mL) was refluxed for 1 h at 80°C under argon. The colourless solution was then cooled to −30°C and a solution of chalcone **2** (1 mmol) in acetonitrile (2 mL) and $ZnEt_2$ (2.2 mmol, 2.0 mL of a 1.1 M solution in toluene) were added. After stirring for 3 h at −30°C (monitored by TLC), the reaction mixture was quenched with saturated aqueous NH_4Cl solution (0.5 mL) and extracted with diethyl ether. The organic layer was dried (Na_2SO_4) and solvent was evaporated to give the crude reaction product which was purified by preparative thin layer chromatography (using pet ether–EtOAc=19:1 as eluant) to afford **3**. The following compounds were prepared using the above procedure.

3.2.1. 1,3-Diphenyl-1-pentanone (3a).[1c] (179 mg, 75%), thick oil, $[\alpha]_D=-6.42$ (c 2.5, EtOH), lit.[11] [for (S)-(+)**3a**, $[\alpha]_D=+10.5$ (c 2.5, EtOH)]; R_f (5% EtOAc–pet ether) 0.78.

3.2.2. 1-Phenyl-3-(4-methoxyphenyl)-1-pentanone (3b).[1c] (147 mg, 55%), thick oil, $[\alpha]_D=-6.42$ (c 2.5, EtOH); R_f (5% EtOAc–pet ether) 0.76.

3.2.3. 1-Phenyl-3-(2-methoxyphenyl)-1-pentanone (3c). (185 mg, 69%), thick oil, [Found: C, 80.68; H, 7.52. $C_{18}H_{120}O_2$ requires C, 80.60; H, 7.46%]; R_f (5% EtOAc–pet ether) 0.74; $[\alpha]_D=-26.56$ (c2.5, EtOH); ν_{max} (neat): 1682, 1610, 1429 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 0.8 (t, 3H, J=7.3 Hz), 1.66–1.80 (m, 2H), 3.11–3.35 (m, 2H), 3.59–3.66 (m, 1H), 3.76 (s, 3H), 6.80–6.89 (m, 2H), 7.12–7.51 (m, 5H), 7.89–7.94 (m, 2H); m/z (EI): 268 (M$^+$, 14), 239 (17),149 (75), 121 (56), 105 (100), 91 (26), 77 (89), 65 (10), 51(18).

3.2.4. 1-Phenyl-3-(4-chlorophenyl)-1-pentanone (3d).[1c] (136 mg, 50%), thick oil, $[\alpha]_D=-5.92$ (c 2.5, EtOH); R_f (5% EtOAc–pet ether) 0.75.

3.2.5. 1-(3-Methoxyphenyl)-3-(4-methoxyphenyl)-1-pentanone (3e). (215 mg, 72%), thick oil, [Found: C, 76.42; H, 7.28. $C_{19}H_{22}O_3$ requires C, 76.51; H, 7.38%]; $[\alpha]_D=-28.8$ (c 2.5, EtOH); R_f (5% EtOAc–pet ether) 0.71; ν_{max} (neat): 1682, 1595, 1455 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 0.8 (t, 3H, J=7.3 Hz), 1.66 (m, 2H), 3.17–3.20 (m, 3H), 3.7 (s, 3H), 3.8 (s, 3H), 6.84 (d, 2H, J=8.6 Hz), 7.05–7.16 (m, 3H); 7.2–7.5 (m, 3H); m/z (EI): 298 (M$^+$, 20), 269 (13), 149 (60), 135 (100), 121 (72), 107 (42), 91 (48), 77 (75), 65 (18), 51 (7).

3.2.6. 1-(3-Methoxyphenyl)-3-(4-chlorophenyl)-1-pentanone (3f). (212 mg, 70%), $[\alpha]_D=-34.14$ (c 2.5, EtOH); thick oil, [Found: C, 71.31; H, 6.36. $C_{18}H_{19}ClO_2$ requires C, 71.40; H, 6.28%]; R_f (5% EtOAc–pet ether) 0.72; ν_{max} (neat): 1684, 1591, 1489 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 0.8 (t, 3H, J=7.3 Hz), 1.59–1.70 (m, 2H), 3.20–3.22 (m, 3H), 3.8 (s, 3H), 7.13–7.45 (m, 8H); m/z (EI): 302 (M$^+$, 37), 273 (98), 150 (98), 135 (100), 125 (45), 107 (54), 91 (40), 77 (65), 65 (17), 51 (7).

3.2.7. 1-(2-Methoxyphenyl)-3-phenyl-1-pentanone (3g). (121 mg, 45%), thick oil, [Found: C, 80.67; H, 7.38. $C_{18}H_{120}O_2$ requires C, 80.60; H, 7.46%]; $[\alpha]_D=-12.2$ (c 2.5, EtOH); R_f (5% EtOAc–pet ether) 0.74; ν_{max} (neat): 1673, 1597, 1485 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 0.8 (t, 3H, J=7.3 Hz), 1.57–1.80 (m, 2H), 3.10–3.26 (m, 3H), 3.8 (s, 3H), 6.94 (d, 2H, J=7.75 Hz), 7.18–7.51 (m, 7H); m/z (EI): 239 (M$^+$−29, 22), 150 (9), 135 (100), 105 (7), 91 (28), 77 (41), 65 (5), 51 (4).

3.2.8. 1-(3-Methoxyphenyl)-3-phenyl-1-pentanone (3h). (180 mg, 67%), thick oil, [Found: C, 80.53; H, 7.42. $C_{18}H_{120}O_2$ requires C, 80.60; H, 7.46%]; $[\alpha]_D=-57.4$ (*c* 2.5, EtOH); R_f (5% EtOAc–pet ether) 0.74; ν_{max} (neat): 1680, 1598, 1489 cm^{-1}; δ_H (200 MHz, $CDCl_3$): 0.8 (t, 3H, *J*=7.3 Hz), 1.58–1.80 (m, 2H), 3.24–3.26 (m, 3), 3.8 (s, 3H), 7.15–7.43 (m, 9H); *m/z* (EI): 239 (M^+-29, 22), 150 (9), 135 (100), 105 (8), 91 (28), 77 (35), 51 (6).

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