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The readily available *tert*-pentyl group as a most effective simple directing group for asymmetric synthesis: a case study on Salen–Mn(III)-catalyzed epoxidation

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Abstract—The *tert*-pentyl group has been found to produce a pronounced stereodirecting effect, which is manifested in a study on Salen–Mn(III) complexes bearing such groups.

1. Introduction

Steric effects often play the most important role in asymmetric catalysis. While a variety of groups can serve to act as steric/directing groups as a result of their bulk, simple groups are the most favorable due to practical considerations and cost-effectiveness. The ideal *simple* directing group should be easily synthesized, and should possess characters of effectiveness, solubility, and stability. By and large, not many simple groups can provide desirable steric effectiveness. The *tert*-butyl group is a unique directing group that has been widely used in many catalysts.[1–6] Recently, we disclosed that the *tert*-pentyl (*t*-Pen) group gave a superb directing effect in Salen–Ti catalysts for asymmetric cyanation.[7] The *t*-Pen group is simple, and readily available from commercially inexpensive phenols. However, its general potential as a directing group has never been thoroughly examined. We reasoned that the flexibility of the ethyl unit of the *t*-Pen group can offer significant rotational freedoms (Fig. 1a). The steric effect generated in such ways can efficiently cover more areas by attaching two *t*-Pen groups at the 3- and 3′- positions of Salen-based catalysts (Fig. 1b).

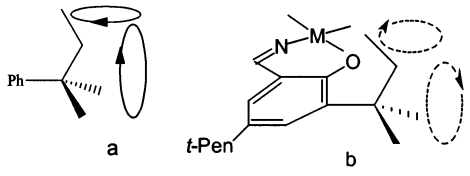

Figure 1.

Asymmetric epoxidation by Salen–Mn complexes[8,9] is a suitable reaction for testing this idea because over the past decade it has been one of most intensively studied reactions, in which many simple and more elaborate directing groups have been investigated.[10–13] Available data can therefore be used directly as a reference. Herein, we wish to report the results from asymmetric epoxidation using Salen–Mn catalysts incorporating *t*-pentyl groups.

The new catalysts were prepared from the corresponding Salen ligands, which were developed from the reaction of the readily available 3,5-di-*tert*-pentylsalicylaldehyde[7] with (1*R*,2*R*)-(+)-1,2-diaminocyclohexane or (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine. According to Jacobsen's procedure,[14,15] treatment of *cis*-β-methylstyrene with NaOCl in the presence of **1** (10 mol%) in methylene chloride at 4°C afforded (+)-(1*R*,2*S*)-*cis*-1-phenylpropylene oxide with ee of 94% (Scheme 1).[16] This high enantioselectivity is comparable to that (92% ee) induced when the *t*-Bu analogue was used as a catalyst.[15] The present result is achieved without the use of any additives.

When **2** (10 mol%) was employed together with 0.4 equiv. of 4-phenylpyridine *N*-oxide (4-PPNO), the reaction gave product with 91% ee. Again, this high ee is

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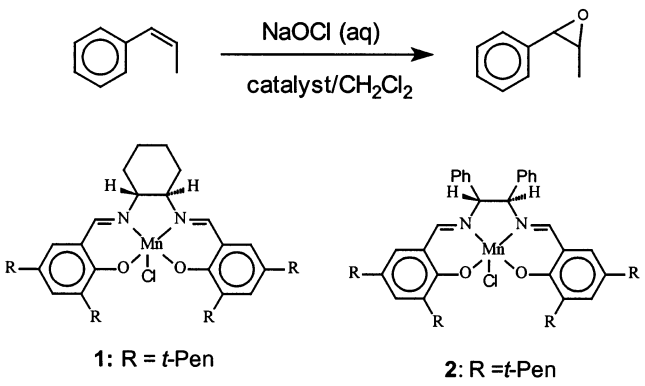


Scheme 1.

very similar to those observed using the *t*-Bu analogues. It is notable that two structurally similar *t*-Bu analogues gave 83%[9] and 88%[15] ee, respectively.

After these preliminary investigations, a more thorough examination was completed to determine the efficiency of the catalysts at different loadings. We first used catalyst **1** to determine the optimal amount of catalysts and found the best loading was 10 mol%. The reactions were run for 2 h using different mol% of catalyst **1** (Table 1). The enantioselectivity is independent of the amount of catalyst used (Fig. 2, 14 h), and is always high, even in the presence of only 1 mol% of catalyst. Increased catalyst loading mainly serves to accelerate the reaction rate, a trend paralleling that of the *t*-Bu analogue.[17] The yield of the *cis*-epoxide rises greatly from <2 to 52% when the loading of **1** is increased from 1 to 10 mol%. Examination of the relationship between ee and reaction time revealed that the ee is fairly consistent during the course of the reaction (Fig. 3, 5 min to 24 h).

The effect of additives[17] was then investigated. The use of two donor molecules led to conclude that this effect depends on the backbone of the catalysts. The addition of donor molecules such as pyridine *N*-oxide (PNO) and 4-phenylpyridine *N*-oxide (4-PPNO) does not have any dramatic effect on enantioselectivity when **1** is used (Table 2). In marked contrast, the improvement by catalyst **2** is significant.

Using **2**, the ee is dramatically improved from 86% without additive to 91% when 0.4 equiv. of 4-PPNO is used (Table 3, runs 1 and 4). This additive also

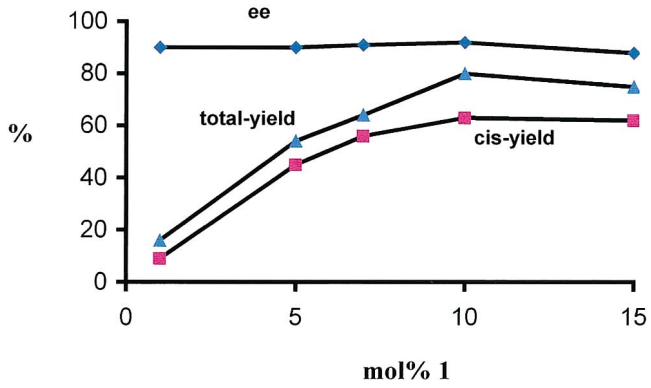


Figure 2. Enantiomeric excess (ee) and yields of product with varying amounts of **1**. The results were obtained from reactions that were run for 14 h at 4°C.

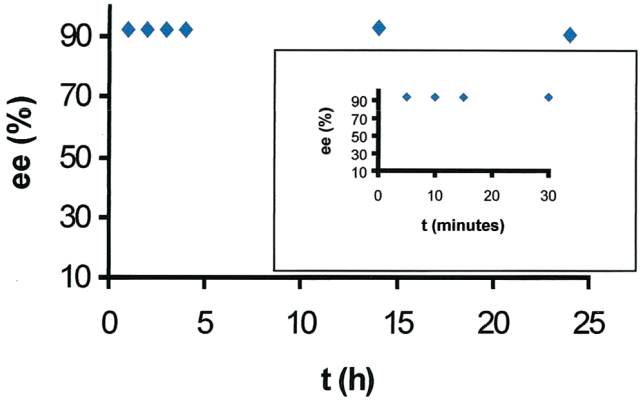


Figure 3. Enantioselectivity (ee) versus reaction time using catalyst **1** (5% mol).

improves the yield from 16 to 89% within 4 h. Moreover, it increases the *cis*/*trans* ratio from 5.30 to 14.8. Increasing the level of the additive from 0.4 to 1.0 equiv. led to further acceleration of the rate with yield enhancement from 72 to 89% in 2 h (Table 4, runs 1–3). It should be added that the reaction was complete within 2 h in the presence of 1.0 equiv. 4-PPNO as opposed to incomplete with the use of only 0.4 equiv. 4-PPNO. Based on these observations, the effectiveness of the catalyst was further evaluated with 5 and 3 mol% catalyst (Table 4, runs 4–9). The results clearly show its inherent effectiveness: 91% ee and 87% yield from 5 mol% catalyst with 1 equiv. 4-PPNO, and 91% ee and 84% yield from just 3 mol% catalyst with 2 equiv. 4-PPNO.

Table 1. Epoxidation of *cis*-β-methylstyrene using different mol% catalyst **1**

Run	mol%	*t* (h)	ee (%)[a]	Yield$_{cis}$ (%)[b]	Yield$_{total}$ (%)[c]
1	1	2	94	<2	2
2	5	2	94	12	15
3	7	2	94	16	20
4	10	2	94	52	63

[a] Determined by GC using chiral G-TA (Gamma-cyclodextrin, Trifluoroacetyl) column.
[b] Determined by GC (G-TA column) against an internal standard.
[c] The sum of yields of *cis*- and *trans*-isomers.

Table 2. Epoxidation of *cis*-β-methylstyrene using 10 mol% catalyst **1** with or without additives

Run	Additive	*t* (h)	ee (%)[a]	$Yield_{cis}$ (%)[a]	$Yield_{total}$ (%)[a]
1	None	2	94	52	63
2	PNO	2	93	55	64
3	4-PPNO	2	92	53	63
4	None	4	94	66	77

[a] Determinations and definitions are the same as those in Table 1 footnotes.

Table 3. Epoxidation using 10 mol% of catalyst **2** with or without additives

Run	*t* (h)	Additive (equiv.)	ee (%)[a]	$Yield_{cis}$[a] (%)	$Yield_{total}$[a] (%)	*cis*/*trans*
1	4	None	86	16	19	5.30
2	4	PNO (0.4)	91	39	42	13.0
3	14	PNO (0.4)	90	72	76	18.0
4	4	PPNO (0.4)	91	89	95	14.8
5	14	PPNO (0.4)	91	87	92	17.4

[a] Determinations and definitions are the same as those in Table 1 footnotes.

Table 4. Effect of amount of additive 4-PPNO on ee

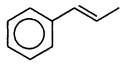
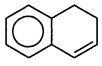
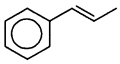
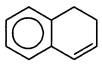
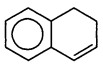
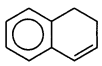
Run	% mol **2**	*t* (h)	4-PPNO (equiv.)	ee (%)[a]	$Yield_{cis}$[a] (%)	$Yield_{total}$[a] (%)	*cis*/*trans*
1	10	2	0.2	91	42	45	14.0
2	10	2	0.4	91	72	76	18.0
3	10	2	1.0	91	89	95	14.8
4	5	4	1.0	91	87	91	21.8
5	5	2	1.0	91	57	60	19.0
6	5	2	2.0	90	75	80	15.0
7	3	4	1.0	90	73	77	18.3
8	3	4	2.0	91	84	88	21.0
9	3	4	3.0	90	85	90	17.0

[a] Determinations and definitions are the same as those in Table 1 footnotes.

With these results, we have extended the applications of these catalysts to other substrates. In order to make comparison possible, we used Jacobsen's catalyst (*t*-Bu analogue of **1**) for the epoxidation of 1,2-dihydronaphthalene to obtain 70% ee without any additive and 75% ee using PNO as additive, respectively, as reference. For the same reaction, the catalyst **1** gave 78% ee without additives and 85% ee with PNO (Table 5, runs 3 and 4), respectively. We then used Jacobsen's catalyst for the epoxidation of *trans*-β-methyl styrene without additives to obtain the corresponding epoxide with 22% ee. The catalysts **1** gave 33% ee under the same conditions (Table 5, run 1). The results from similar reactions using **2** are listed in Table 6.

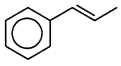
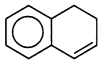
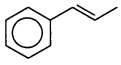
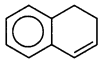
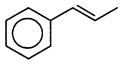
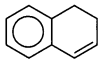
In summary, through this epoxidation study, the significant directing role played by the *t*-Pen group has been revealed. The present results, coupled with the previous

Table 5. Epoxidation of olefins using catalyst **1** with or without additives

Run	Substrate	additive	ee (%)	Run	Substrate	Additive	ee (%)
1		none	33[a]	4		PNO	85[b]
2		4-PPNO	14[a]	5		4-PPNO	79[b]
3		none	78[b]	6		imidazole	27[b]

a: Determined by GC using chiral G-TA column;
b: Determined by GC using chiral B-DA(Beta-cyclodextrin, Dialkyl) column.

Table 6. Epoxidation of olefins using catalyst **2** with or without additives

Run	Substrate	Additive	ee (%)	Run	Substrate	Additive	ee (%)
1		none	42[a]	6		none	64[b]
2		PNO	20[a]	7		PNO	77[b]
3		4-PPNO	16[a]	8		4-PPNO	75[b]

a: Determined by GC using chiral G-TA column.
b: Determined by GC using Chiral B-DA column.

ones from cyanation reactions with Salen–Ti complexes unambiguously establish the *t*-Pen group as one of the most effective simple directing groups. The inherent advantages include facile preparation and cost-effectiveness, since the ligands are readily prepared from commercially available and inexpensive phenols. The *t*-Pen group may very well be effective as a bulky group with directing effects in other asymmetric reactions.

2. Experimental

2.1. General

Melting points were obtained in open capillary tubes with a Mel-Temp II Laboratory Devices, Inc. melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on an Omnic Impact 400 FT-IR spectrometer as thin films for oil and KBr pellets for solids. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Bruker instrument with TMS as an internal standard for reference. Elemental analysis was performed at Atlantic Microlab at Norcross, Georgia. The mass spectrometry data were recorded with a Hewlett–Packard 5972 mass spectrometer. Enantiomeric excesses (ee) were determined on capillary GC using chiral column (Chiraldex, 20 m×0.25 mm ID×0.125 μm film). The oven temperature is about 100°C, and isothermal at 65 kPa. Optical rotation was obtained with a Rudolph Research Autopol III Digital Polarimeter in a thermostat cell at 20°C.

2.2. Synthesis of Schiff base ligands

2.2.1. (*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*t*-pentylsalicylidene)-1,2-diphenylethylenediamine. 2-Hydroxy-3,5-di-*t*-pentylbenzaldehyde (1.09 g, 4.16 mmol) and 1,2-diphenylethylenediamine (441 mg, 2.08 mmol) were stirred in dry ethanol (20 mL), at rt overnight. The ethanol was partially reduced under vacuum and the white solid was filtered and washed with cold ethanol. The crude product was recrystallized with hexane to afford Schiff base as a yellow solid (1.03 g, 71%). Mp. 142–144°C; $[\alpha]_D^{22} = -53$ (*c* 0.10 $CHCl_3$); IR/cm^{-1} 3463.9, 3062.8, 3031.9, 2962.5, 2875.7, 1625.9, 1598.9, 1460.0, 1382.9, 1274.9, 771.5, 696.3; ^{1}H NMR ($CDCl_3$) δ ppm: 0.59 (m, 12H), 1.18 (s, 12H), 1.35 (s, 12H), 1.52 (m, 4H), 1.90 (m, 4H), 4.71 (s, 2H), 6.89 (s, 2H), 7.17 (m, 12H), 8.36 (s, 2H), 13.53 (s, 2H); ^{13}C NMR ($CDCl_3$) δ ppm: 9.61, 10.02, 27.89, 28.87, 33.09, 37.24, 37.40, 38.90, 80.80, 118.09, 127.50, 127.93, 128.49, 128.65, 129.47, 135.03, 138.46, 140.32, 158.29, 167.76. Anal. calcd for $C_{48}H_{62}N_2O_2$: C, 82.24; H, 9.20; N, 4.00. Found: C, 82.02; H, 9.04; N, 3.97%.

2.2.2. (*R*,*R*)-(−)-*N*,*N*′-Bis(3,5-di-*t*-pentylsalicylidene)-1,2-cyclohexanediamine. The preparation of this compound is reported elsewhere.[7]

2.3. General procedure for preparation of catalysts

The chiral Salen ligand (0.143 mmol) was mixed with $Mn(OAc)_2{\cdot}4H_2O$ (38.5 mg, 0.157 mmol) in dry ethanol (3 mL) at rt overnight. The resultant solution was diluted with water (5.0 mL), and sodium chloride (1.0 g, excess) was added. The resulting mixture was stirred at rt for 24 h. After the solvent was removed under vacuum, the brown residue was dissolved in dichloromethane (5.0 mL). The organic phase was washed with water (3.0 mL) and dried with sodium sulfate. The solvent was then removed under vacuum to give a brown solid, which was purified by column chromatography on silica gel, using hexane/CH_2Cl_2 (9/1) as an eluent to afford the pure catalyst.

2.3.1. Chloro-(*R*,*R*)-(−)-[[*N*,*N*′-bis(3,5-di-*t*-pentylsalicylidene) - 1,2 - cyclohexanediamine] - *N*,*N*′,*O*,*O*′]manganese-(III), complex 1. Dark brown solid, yield: >70%, mp 299–301°C; IR/cm^{-1} 3446.6, 3138.0, 2962.5, 2873.8, 1608.5, 1535.3, 1431.1, 1384.8, 1340.5, 1305.7, 1236.3, 1166.9, 831.3, 783.1, 732.9, 563.2. Anal. calcd for $C_{40}H_{60}ClMnN_2O_2$: C, 69.50; H, 8.75; N, 4.05. Found: C, 69.50; H, 8.80; N, 4.01%.

2.3.2. Chloro-(*R*,*R*)-(−)-[[*N*,*N*′-bis(3,5-di-*t*-pentylsalicylidene) - 1,2 - diphenylethylenediamine] - *N*,*N*′,*O*,*O*′]-manganese(III), complex 2. Dark brown solid, yield, >75%, mp 310°C; IR/cm^{-1} 2926.7, 2855.4, 2367.9, 2341.1, 1557.0, 1467.5, 1384.2, 1261.6, 1088.4, 1030.0, 812.9, 516.8. Anal. calcd for $C_{48}H_{62}ClMnN_2O_2$: C, 73.03; H, 7.92; N, 3.55. Found: C, 72.75; H, 7.85; N, 3.58%.

2.4. General procedure for epoxidation reactions

Racemic mixture references were prepared as follows: a solution of *cis*-β-methylstyrene and *m*-CPBA (*meta*-chloroperbenzoic acid) in excess in dichloromethane was stirred at rt for 2 h. The reaction was quenched by an aqueous solution of sodium carbonate. The phases were then separated and the aqueous layer was extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4. The volume of solvent was properly reduced so that the concentration of racemic mixtures gave distinctive signals of two enantiomers on chiral GC.

Epoxidation reactions using catalysts **1** and **2** were carried out as follows: a solution of *cis*-β-methylstyrene (100 mg, 0.850 mmol), **2** (66 mg, 8.5×10^{-2} mmol, 10%), and 4-PPNO (58 mg, 0.34 mmol, 40%) in dichloromethane (1.0 mL) was cooled to 4°C. Buffered bleach in excess (pH 11.5, 2.5 mL), pre-cooled at 4°C, was added to the solution. The reaction mixture was vigorously stirred at 4°C for 4 h. Then the reaction temperature was allowed to reach room temperature and the phases were separated. The aqueous layer was extracted with dichloromethane (2×2.0 mL) and the combined organic phases were dried over Na_2SO_4. The crude product was purified by column chromatography, using hexane/ethyl acetate (8/2) as an eluent.

Acknowledgements

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