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Asymmetric nitroaldol reaction catalyzed by a chromium(III)–salen system

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Abstract—Chiral chromium(III)–salen-type complexes derived from 1,2-diaminocyclohexane and 1,2-diphenylethylenediamine were found to catalyze the enantioselective Henry reaction. Various arylaldehydes, *trans*-cinnamaldehyde, and cyclohexanecarbaldehyde reacted with nitromethane in the presence of $(i\text{-Pr})_2$NEt and salen–CrCl (2 mol %) to give the corresponding adducts in 40–76% ee and in moderate to good yields.

1. Introduction

The asymmetric Henry (nitroaldol) reaction is a powerful synthetic tool for the formation of a new C–C bond and at least one stereogenic center.[1] Chiral nitroalcohols can be further transformed into synthetically useful derivatives such a carboxylic acids[2] and amino alcohols.[3] The nitro group is also a versatile source of other functionalities via displacement by the sulfur, azide as well as carbon nucleophiles.[4]

Mechanistically, the nitroaldol reaction involves the addition of a nitronate ion, which can be generated in situ by the deprotonation of nitroalkane with an external base.[5c] The addition is facilitated either by a Lewis acid catalyst activating a carbonyl partner or by a suitable bifunctional catalyst that works as a Lewis acid–Brønsted base activating and bringing both reactants together.[12]

In recent years, effective catalysts have been developed, which provide some nitroalcohols with impressive stereoselectivity.[5] Among them, those based on lanthanum(III), copper(II), cobalt(II), and zinc complexes were successfully employed. However, in many cases the relatively complex ligand structure and its substrate specificity limited broader applications in the direct nitroaldol reaction.

Easy to obtain chiral salen-type ligands strongly coordinate many metals.[7] Although Schiff base metal complexes are very effective in many useful catalytic transformations[8] (*privileged ligands*),[6] only the cobalt(II)–salen complexes have been extensively tested in the nitroaldol reaction.[9,10] In spite of the catalyst effectiveness, the reaction required a long reaction time and suffered some problems in the purification of the product. All of these facts encouraged us to evaluate the other metal–salen systems in the Henry reaction.

2. Results and discussion

The required chiral salen ligands **1** were prepared by the condensation of salicylic-type aldehydes with enantiomerically pure diamines.[7,11] Their metal complexes were easily obtained from the ligands and commercially available $AlMe_3$, Et_2Zn, $Ti(OPr\text{-}i)_4$, and the corresponding transition metal salts (Scheme 1).

Following the literature precedent,[9] we examined the reaction of nitromethane **3** with the aromatic aldehydes **2** in dichloromethane[13] in the presence of stoichiometric amounts of diisopropylethylamine (DIPEA) and 2 mol % of the respective metal–salen complex (Scheme 2). The results are summarized in Table 1.

Thus, the reaction of 2-chlorobenzaldehyde with nitromethane in the presence of DIPEA without a catalyst gave the racemic nitroalcohol in 81% yield (Table 1, entry 1).

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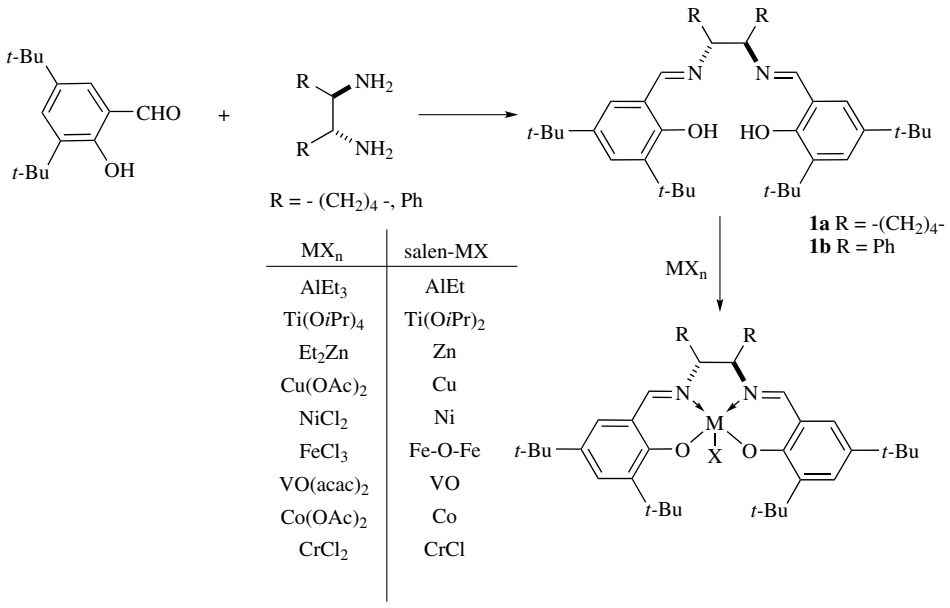
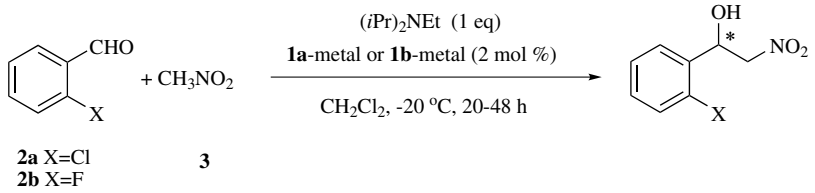


Scheme 1.



Scheme 2.

Table 1. Enantioselective nitroaldol reactions catalyzed by metal–salen complexes[a]

Entry	Aldehyde	Metal–salen	Yield[b] (%)	ee[c] (%)
1	**2a**	None	81	—
2	**2a**	(*R*,*R*)-**1a**–Co	82	29 (*S*)
3	**2a**	(*R*,*R*)-**1a**–CrCl	54	44 (*S*)
4	**2b**	(*R*,*R*)-**1a**–CrCl	76	45 (*S*)
5	**2b**	(*S*,*S*)-**1a**–CrCl	64	49 (*R*)
6	**2b**	(*R*,*R*)-**1b**–CrCl	80	62 (*S*)

[a] Reactions were performed on a 1.0 mmol scale, 1 equiv of DIPEA, 2 mol % of catalyst, 1.0 mL of CH_3NO_2 and 4.0 mL of CH_2Cl_2 for 48 h (entries 1–3) or 20 h (entries 4–6).

[b] Yield of isolated product.

[c] Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column.

Moreover, various metal–**1a** complexes tested in this reaction, namely **1a**–AlMe, **1a**–Cu, **1a**–Ni, (Fe–**1a**)$_2$O, **1a**–VO, and **1a**–MnCl, proved to be almost inactive as chiral inducers, giving nearly racemic products. Both zinc **1a**–Zn and titanium **1a**–Ti(OPr-*i*)$_2$ complexes provided the product with a poor but legible enantiomeric excess of 9%. The application of cobalt(II)–salen complex, which has already been tested by Yamada et al.[9] led in our hands to a good yield of product, but the stereoselectivity was 29% ee, much less than reported. However, the enantiomeric excess increased upon application of chromium–salen complex **1a**–CrCl, providing the product in 44% ee. It is noteworthy that for both Co(II) and Cr(III) complexes with the same (*R*,*R*)-**1a** ligand, we observed the same sense of stereochemical induction leading to the *S*-product. We also noted the corresponding yield decrease (cf. entries 2 and 3). Indeed, when a stronger Lewis acid (**1a**–CrCl) was applied, the respective nitroalkene as a side product formed was due to the consecutive elimination reaction. Interestingly, application of 2-fluorobenzaldehyde as substrate **2b** gave a higher yield of the corresponding nitroalcohol product, essentially without the elimination product. Anyhow, the reaction catalyzed by **1a**–CrCl was clearly enantiospecific, since *ent*-**1a** led to the opposite enantiomer of the product (cf. Table 1, entry 5).

After screening of the metal–salen complexes, we examined the influence of temperature and nature of the counterion on enantioselectivity in the reaction of **2b** with nitromethane (Table 2).

When the reaction temperature decreased from −20 °C to −78 °C it gave a higher yield of nitroalcohol. When 5 mol % of CrCl(salen) complex (entry 3) was used, we noted an increase of ee, but the yield of the product decreased.

Weakly coordinating anions (ClO_4^-, OAc^-, and OTf^-) increase the Lewis acidity of the metal center, thus we expected stronger binding of aldehyde to the respective

Table 2. Temperature and counterion effect in the nitroaldol reaction of **2b** and nitromethane catalyzed by 2 mol % of **1a**–CrX[a]

Entry	CrX	Temperature (°C)	Yield[b] (%)	ee[c] (%)
1	CrCl	−20	76	45
2	CrCl	−78	98	46
3	CrCl[d]	−78	78	59
4	$Cr(ClO_4)$	−78	74	55
5	Cr(OAc)	−78	68	57
6	Cr(OTf)	−78	52	53

[a] Reactions were performed on a 1.0 mmol scale, 1 equiv of DIPEA, 2 mol % of catalyst, 1.0 mL of CH_3NO_2 and 4.0 mL of CH_2Cl_2 for 20 h.
[b] Yield of isolated product.
[c] Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column.
[d] 5 mol % of **1a**-CrCl was used.

complex. Indeed, applying other CrX(salen) complexes we observed nitroalcohols (entries 4–6) formed with higher enantioselectivities but the yields decreased when compared to the CrCl(salen) system.

Another examined factor for this transformation was the nature, strength and quantity of the base. As was noted for the Henry reaction, the enantioselectivity was very sensitive to both the nature[9] and variation in base stoichiometry.[14] Under these circumstances, various bases were screened for the reaction of **2b** and nitromethane (Table 3).

Since the use of Hunig's base was reported earlier for the Co(salen) system,[9] in our preliminary studies we also applied DIPEA. Bearing in mind that this base is able to promote a non-stereoselective Henry reaction (Table 1, entry 1), we halved its loading to 0.5 equiv. Although the yield was lowered under these conditions, we noticed some improvement of the ee. Similarly, application of quinine (QN) for generation of the respective nitronate anion paired with the chiral QN–H^+ cation led to certain improvement of enantioselectivity. DBU and DMAP (entry 5 and 7) seemed to inactivate our chiral catalytic system. Surprisingly, K_3PO_4 was able to generate reactive nitronate in spite of its rather limited solubility in dichloromethane–nitromethane system.

Table 3. Influence of bases (1 equiv) on the reaction of **2b** with nitromethane catalyzed by 2 mol % of **1a**–CrCl at −78 °C[a]

Entry	Base	Yield[b] (%)	ee[c] (%)
1	$(i\text{-Pr})_2NEt$	98	46
2	$(i\text{-Pr})_2NEt$[d]	81	52
3	NEt_3	49	40
4	DABCO	83	30
5	DBU	29	0
6	Quinine	97	52
7	DMAP	58	0
8	K_3PO_4	58	44

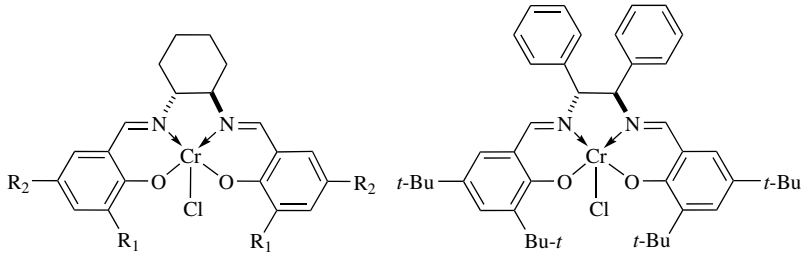
[a] Reactions were performed on a 1.0 mmol scale, 1 equiv of DIPEA, 2 mol % of catalyst, 1.0 mL of CH_3NO_2 and 4.0 mL of CH_2Cl_2 for 20 h.
[b] Yield of isolated product.
[c] Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column.
[d] 0.5 equiv of DIPEA was used.

Changing the substituents in salicylaldimine moiety or nature of the diamine part, we examined the influence of ligand structure on the performance of the resulted CrCl(**1a**–**1c**) complexes.

Chiral catalyst based on 1,2-diphenylethylenediamine (Scheme 3, **1b**) gave even higher ee when compared to that induced by **1a**–CrCl (see also Table 1, entry 6 vs 4). Lowering the temperature from −20 °C to −78 °C resulted in a lower yield and selectivity (Table 4, entry 3 vs 1), perhaps due to the partial solubility of **1b**-CrCl under these conditions. On the other hand, variations of the size of the substituent in the 5-positions of the salicylic aldimine (Me vs *t*-Bu) led to nearly the same yield and enantioselectivity. This implies that a bulky substituent in close proximity to the Lewis metal center is a crucial factor for the stereochemical outcome, while changes on the peripheries are of much less importance.

Finally, in order to evaluate the scope of the reaction, we applied the commercially available **1a**–CrCl salen complex to the reaction of various aldehydes with nitromethane (Table 5).

The enantioselectivities obtained for most of the aromatic aldehydes (Table 5, entries 1–9, 12) were close to 60% ee. Unexpectedly, the yield of the isolated products varied from 14% to 98%. Essentially, a reaction time of up to 20 h gave no further conversion. In the case of the dramatically decreased yield, longer reaction times were applied. Since nitroalcohol itself offers a donating center, it could block a free vacancy on the metal center. We performed the reaction of benzaldehyde and nitromethane at −17 °C in a mixture containing additional amount of racemic nitroalcohol (50 mol %). In this case, the formation of



1a R_1, R_2 = *t*-Bu
1c R_1 = *t*-Bu, R_2 = Me

1b

Scheme 3.

Table 4. Influence of the ligand structure on the reaction of **2b** with nitromethane[a]

Entry	Complex	Yield[b] (%)	ee[c] (%)
1	**1a**–CrCl	98	46
2	**1b**–CrCl[d]	80	62
3	**1b**–CrCl	66	57
4	**1c**–CrCl	76	44

[a] Reactions were performed on a 1.0 mmol scale, 1 equiv of DIPEA, 2 mol % of catalyst, 1.0 mL of CH_3NO_2 and 4.0 mL of CH_2Cl_2 for 20 h.
[b] Yield of isolated product.
[c] Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column.
[d] Reaction was performed at −20 °C.

nitroalcohol in 39% yield and 42% ee was observed. Since the standard reaction at this temperature gave 72% yield and 54% ee, we supposed that the addition of an extra quantity of product led to partial inactivation of the catalyst. The product can also undergo a retro-nitroaldol reaction as it has already been noted by other groups.[15] Thus, the cooperative effect of both aforementioned factors might affect the reaction outcome.

Aromatic aldehydes with either electron-donating or electron-withdrawing groups gave the products with moderate to good ee's and yields. The best result was obtained for electron rich and *ortho*-substituted 2-methoxybenzaldehyde (Table 5, entry 3). *p*-Nitrobenzaldehyde led to the desired product with modest yield but the enantioselectivity was only 40% (entry 10). In this case we observed the formation of a side product derived from the Michael addition of a nitronate anion to β-nitrostyrene. In the reaction of *trans*-cinnamaldehyde, the product of the addition of nitronate to the carbonyl group was only isolated, (entry 11) without the corresponding product of the Michael reaction. When we applied aliphatic acyclic aldehydes namely hexanal and isobutyraldehyde no nitroalcohol products could be detected. However, cyclohexanecarbaldehyde gave the desired product with 76% ee and 24% yield.

Table 5. Enantioselective nitroaldol reactions catalyzed by metal–salen complexes[a]

Entry	Aldehyde RCHO	Time (h)	Yield[b] (%)	ee[c] (%)
1	Ph	20	38 (72)[d]	60 (54)[d]
2	2-Naphthyl	20	42	66
3	*o*-$MeOC_6H_4$	20	88	73
4	*o*-FC_6H_4	20	98	46
5	*o*-ClC_6H_4	20	64	49
6	*p*-ClC_6H_4	20	47	60
7	*o*-BrC_6H_4	20	75	64
8	*o*-MeC_6H_4	45	42	56
9	*p*-MeC_6H_4	92	14	66
10	*p*-$NO_2C_6H_4$	20	56	40
11	PhCH=CH–	71	33	45
12	2-Furyl	96	42	59
13	*c*-Hex	40	24	76

[a] Reactions were performed on a 1.0 mmol scale, 1 equiv of DIPEA, 2 mol % of catalyst, 1.0 mL of CH_3NO_2 and 4.0 mL of CH_2Cl_2 at −78 °C.
[b] Yield of isolated product.
[c] Enantiomeric excess was determined by HPLC using a Chiralpak AD-H column or Chiracel OD-H column.
[d] Reaction was performed at −17 °C.

3. Conclusion

In conclusion, the commercially available **1a**–CrCl–salen complex was found to be a fairly effective chiral catalyst for the direct asymmetric nitroaldol reaction that afforded respective nitroalcohols in ee's ranging from 40% to 76%. The other salen–CrCl complex **1b**–CrCl was found to be even more selective. These observations support recent claims that CrCl–salen represents a privileged metal complex, able to transmit chiral information in a variety of processes.[16] Further studies on the application of chiral salen-type chromium catalysts in the Henry reaction as well as transformations involving other carbonyl compounds are currently underway.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were measured on a Bruker Avance DRX (^1H, 300 MHz) spectrometer using TMS as an internal standard. Observed rotations at 589 nm were measured using an Optical Activity Ltd Model AA-5 automatic polarimeter. The enantiomeric compositions of the nitroalcohols were determined by HPLC analysis using a chiral stationary phase (Chiracel OD-H or Daicel Chiralpak AD-H). The absolute configuration of the major enantiomers was assigned according to the sign of the specific rotation as well as by comparison of the retention times with the reported data.[9,15,24]

Separations of products by chromatography were performed on Silica Gel 60 (230–400 mesh) purchased from Fluka. Thin layer chromatography analyses were performed using Silica Gel 60 precoated plates (Merck). Dichloromethane was initially dried with $CaCl_2$ and then heated with CaH_2 and distilled. THF used in preparation of respective chromium(III)–salen complexes was distilled with sodium and benzophenone. Nitromethane was dried with $MgSO_4$ and then distilled over $MgSO_4$. DIPEA was distilled over sodium. Ethanol was dried by heating with CaH_2 followed by distillation. Liquid aldehydes were freshly distilled and solids were recrystallized prior to use. Reaction vessels used in catalytic transformations were flame dried and allowed to cool to rt under vacuum and filled with argon. Complex **1a**–MnCl was purchased from Aldrich. Compounds **1a**–AlMe,[17,23] **1a**–Ni,[17] (Fe–**1a**)$_2$O,[17] **1a**–VO,[17] **1a**–Ti(OPr-*i*)$_2$,[18] **1a**–Zn,[18] **1a**–Cu,[19] **1a**–Co,[20] **1a** or **1b**–CrCl[21] were prepared according to the reported procedures. Complexes CrX–salen were obtained from **1a**–CrCl and suitable silver salts, according to the known procedure.[22]

4.2. General procedure of catalytic Henry reaction. Screening for the optimal metal–salen complex

Dichloromethane (2.0 mL) was added to the metal–salen catalyst (2 mol %) and the reaction vessel was sealed with a rubber septum. The resulting mixture was cooled on an ice-NaCl bath to −15 °C, then the mixture of respective

aldehyde (0.5 mmol, 1.0 equiv), nitromethane (1.0 mL, 18.6 mmol) was added via syringe, followed by the solution of DIPEA (86 μL, 1.0 equiv) in dichloromethane (2.0 mL). After 20–48 h reaction time, the mixture was allowed to warm to rt. The volatile compounds were evaporated in vacuo, the residue was dried under vacuum and purified by column chromatography (silica gel, *n*-hexane/AcOEt, 6:1, v/v) giving the desired nitroalcohol.

4.3. Catalytic Henry reaction applying titanium–salen complex

Under an argon atmosphere $Ti(OiPr)_4$ (15 μL, 0.1 mmol) was added via syringe to a solution of **1a** (27 mg, 0.05 mmol, 5 mol %) in toluene (2.0 mL) and the resulted mixture was stirred at rt for 1 h. The volatile compounds were then evaporated in vacuo, after which a stream of argon was connected and the residual waxy solid was treated with dichloromethane (4.0 mL) and cooled on an ice-NaCl bath. After 10 min, a solution of 2-chlorobenzaldehyde (112 μL, 1.0 mmol, 1.0 equiv) in dichloromethane (2.0 mL) and nitromethane (2.0 mL, 37.2 mmol) was added via syringe followed by a solution of DIPEA (172 μL, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL). The light brown mixture was stirred at −17 °C for 48 h. Product was isolated as described above.

4.4. Catalytic Henry reaction catalyzed by zinc–salen complex prepared in situ

To a stirred solution of **1a** (20 mol %) in CH_2Cl_2 (6 mL) a solution of Et_2Zn (1 M in toluene, 30 μL, 20 mol %) was added that gave rise to liberation of a gas. The resulting mixture was stirred under argon at rt for 1 h. 2-Chlorobenzaldehyde (168 μL, 1.5 mmol, 1.0 equiv) and nitromethane (3.0 mL, 55.8 mmol) were then added via syringe followed by a solution of DIPEA (258 μL, 1.5 mmol, 1.0 equiv) in CH_2Cl_2 (6.0 mL). After 48 h at −17 °C, the product was isolated as mentioned above.

4.5. General procedure for asymmetric Henry reaction catalyzed by chromium(III)–salen complexes at low temperature

To a stirred solution of the respective chromium(III)–salen complex (2 mol %) in CH_2Cl_2 (2.0 mL) under an inert atmosphere at −78 °C, a mixture of the aldehyde (0.5 mmol, 1.0 equiv) and nitromethane (1.0 mL, 18.6 mmol) was added via syringe. After 5 min, a solution of DIPEA (86 μL, 0.5 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added and the red to brown mixture was stirred for the indicated time. After warming to rt, the volatile compounds were evaporated in vacuo, after which the residue was dried under vacuum and purified by column chromatography (silica gel, *n*-hexane/AcOEt, 6:1, v/v) giving the desired nitroalcohol. Products were analyzed by ^1H NMR ($CDCl_3$) and the measurement of optical rotations in CH_2Cl_2 or $CHCl_3$ was carried out. Enantiomeric excess was determined using HPLC on chiral columns (flow rate: 1.0 mL/min, $\lambda = 205$ nm). Reported values and signs of specific rotations for major enantiomers are listed below:

(S)-(+)-1-(2-Fluorophenyl)-2-nitroethan-1-ol: Diacel Chiralpak AD-H, *n*-hexane/*i*-PrOH, 9:1; $t_{major} = 10.1$ min, $t_{minor} = 11.0$ min; $[\alpha]_D = +24.6$ (*c* 1.2, CH_2Cl_2).

(S)-(+)-1-(2-Bromophenyl)-2-nitroethan-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 95:5; $t_{minor} = 12.4$ min, $t_{major} = 13.5$ min; $[\alpha]_D = +30.2$ (*c* 0.9, CH_2Cl_2).

(S)-(+)-1-(2-Chlorophenyl)-2-nitroethan-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 97.5:2.5; $t_{minor} = 21.8$ min, $t_{major} = 23.1$ min; $[\alpha]_D = +25.8$ (*c* 1.4, CH_2Cl_2).

(S)-(+)-1-(4-Chlorophenyl)-2-nitroethan-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 9:1; $t_{minor} = 13.5$ min, $t_{major} = 17.2$ min; $[\alpha]_D = +24.8$ (*c* 0.7, CH_2Cl_2).

(S)-(+)-1-Phenyl-2-nitroethan-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 9:1; $t_{minor} = 13.7$ min, $t_{major} = 16.9$ min; $[\alpha]_D = +40.7$ (*c* 0.7, CH_2Cl_2).

(S)-(+)-1-Cyclohexyl-2-nitroethan-1-ol: Diacel Chiralpak AD-H, *n*-hexane/*i*-PrOH, 9:1; $t_{minor} = 9.4$ min, $t_{major} = 10.2$ min; $[\alpha]_D = +18.7$ (*c* 0.4, $CHCl_3$).

(S)-(+)-1-(4-Methylphenyl)-2-nitroethan-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 9:1; $t_{minor} = 13.7$ min, $t_{major} = 17.3$ min; $[\alpha]_D = +10.3$ (*c* 0.3, CH_2Cl_2).

(S)-(+)-1-(2-Methylphenyl)-2-nitroethan-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 9:1; $t_{minor} = 11.0$ min, $t_{major} = 17.2$ min; $[\alpha]_D = +32.0$ (*c* 0.8, CH_2Cl_2).

(S)-(+)-1-(2-Methoxyphenyl)-2-nitroethan-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 9:1; $t_{minor} = 11.2$ min, $t_{major} = 13.2$ min; $[\alpha]_D = +42.3$ (*c* 1.1, CH_2Cl_2).

(S)-(+)-1-(4-Nitrophenyl)-2-nitroethan-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 4:1; $t_{minor} = 11.4$ min, $t_{major} = 13.8$ min; $[\alpha]_D = +11.7$ (*c* 0.9, CH_2Cl_2).

(+)-1-(2-Naphthyl)-2-nitroethan-1-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 4:1; $t_{minor} = 20.0$ min, $t_{major} = 28.4$ min; $[\alpha]_D = +24.3$ (*c* 0.8, CH_2Cl_2).

(S)-(+)-1-Nitro-4-phenyl-3-buten-2-ol: Chiracel OD-H, *n*-hexane/*i*-PrOH, 4:1; $t_{major} = 18.1$ min, $t_{minor} = 20.2$ min; $[\alpha]_D = +8.42$ (*c* 0.5, CH_2Cl_2).

(+)-1-(2-Furanyl)-2-nitroethan-1-ol: AD-H, *n*-hexane-*i*PrOH, 95:5; $t_{minor} = 26.1$ min, $t_{major} = 27.6$ min; $[\alpha]_D = +30.3$ (*c* 0.6, CH_2Cl_2).

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