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Effect of achiral and mixed chiral ligands on the asymmetric synthesis of γ-nitrophosphonates via Michael addition

Vishal Rai and Irishi N. N. Namboothiri*

Department of Chemistry, Indian Institute of Technology Bombay, Mumbai 400 076, India

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Abstract—Changes in the diastereo- and/or enantioselectivity were observed when the Li–cinchonine catalyzed conjugate addition of phosphonates to nitroalkenes was carried out in the presence of achiral/chiral additives. Although the conjugate addition in the absence of such additives proceeded in better yields and selectivities as reported previously, the dramatic change in selectivity in the presence of additives provides an opportunity to synthesize different stereoisomers of the product, γ-nitrophosphonate, using primarily the same chiral source.

1. Introduction

The stereoselective synthesis of a molecule in both the enantiomeric forms is a challenging task if only one of the enantiomers of the chiral source is easily available.[1] Convenient and economical means of overcoming this difficulty involve controlling the reactivity of the existing chiral source, for example, a ligand–metal complex, via structural modification[2] or via changing the local chiral atmosphere by employing additional chiral/achiral ligands that can bind to the metal centre.[3] If ligands L1 and L2 are employed as a mixture, three catalyst combinations, that is, two homochiral ML1L1, ML2L2 and one heterochiral ML1L2, that interconvert rapidly are generated and if the heterochiral combination is more active than the homochiral ones, a new catalyst profile emerges.[4] This approach is particularly attractive because the active catalyst species is generated in situ by mixing ligands, thus obviating the need to pre-synthesize and screen numerous ligands for asymmetric catalysis. Application of such dynamic combinatorial libraries of ligand-metal complexes in asymmetric catalysis is currently attracting considerable interest.[3]

The role of achiral ligands in enhancing the reactivity and selectivity in asymmetric reactions has been investigated by several groups in recent years.[3,5–13] Thus, catalysis by metal-ligand complexes containing both achiral and chiral ligands has been reported in the asymmetric alkylation of aldehydes,[5] hydrogenation of imines[6] and olefins,[7] hydroformylation[8] and the addition of organozinc reagents to α-keto esters.[9] However, reports on the reversal of enantioselectivity by achiral ligands are limited to metal–ligand catalyzed boronic acid addition to activated olefins,[10] olefin hydrogenation,[11] dialkylzinc addition to aldehydes[12] and Diels–Alder reactions.[13]

Non-linear effects due to mixtures of chiral ligands complexed with a metal have been observed in Sharpless asymmetric dihydroxylation,[14] the addition of dialkylzinc to aldehydes,[15] hydrogenation[2,4,16,17] and alkylation and arylation of aldehydes.[18] To the best of our knowledge, inversion of enantioselectivity induced by an auxiliary chiral ligand remains unreported. Furthermore, besides one recent example,[10] there are no reports on the effect of achiral and mixed chiral ligands on ligand-metal catalyzed Michael addition to activated alkenes.

2. Results and discussion

Recently, we reported the lithiated cinchonine catalyzed diastereo- and enantioselective synthesis of γ-nitrophosphonates by the Michael addition of phosphonates to nitroalkenes (Scheme 1).[19] Herein, we report on the dramatic catalytic role of achiral ligands and the mixture of chiral ligands which enabled us to synthesize various stereoisomers of γ-nitrophosphonates in a selective fashion. Whilst

* Corresponding author. Tel.: +91 22 2576 7196; fax: +91 22 2576 7152; e-mail: irishi@iitb.ac.in

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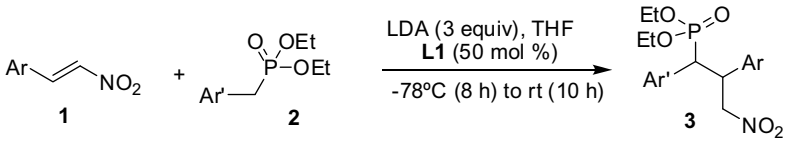


Scheme 1. Michael addition of phosphonates **2** to nitroalkenes **1**.

the same chiral source in the presence of different achiral ligands has been employed in the first approach, the second approach utilized heterochiral species generated from a mixture of pseudoenantiomers.[20]

Herein, cinchonine–Li was used as the precatalyst under typical reaction conditions (Scheme 1). In our mixed ligand approach using achiral additives, **A1**–**A8** (Fig. 1) were used in conjunction with cinchonine **L1** (Table 1). First of all, in the absence of any additives, high yield, diastereo- and enantioselectivities were obtained as reported earlier (Table 1, entry 1).[19] Similar stereoselectivities, but low yields were obtained when TMEDA **A1** and HMPA **A2** were used as achiral additives (Table 1, entries 2 and 3). Other additives, such as ethylenediamine **A3**, ethylene glycol **A4** and 12-crown-4 **A5** provided improved yields without affecting the stereoselectivity (Table 1, entries 4–6). Surprisingly, the addition of NMM **A6** to the precatalyst, that is, **L1**–Li complex, provided low yields (25%), and caused a reversal of enantioselectivity (10:90 er, (*S*,*S*)-major isomer) whilst maintaining good diastereoselectivity (92:08 dr, Table 1, entry 7). Encouraged by such a reversal of enantioselectivity, we employed other achiral additives such as DMAP **A7** and diethyl ether **A8** (Table 1, entries 8–10). Although the yields improved with DMAP **A7** and diethyl ether **A8** as additives, both the diastereo- and enantioselectivities dropped considerably (Table 1, entries 8–9). At this point, we decided to employ diethyl ether **A8** as a solvent in the place of THF and were pleased to note the enhancement of selectivity (Table 1, entry 10). More importantly,

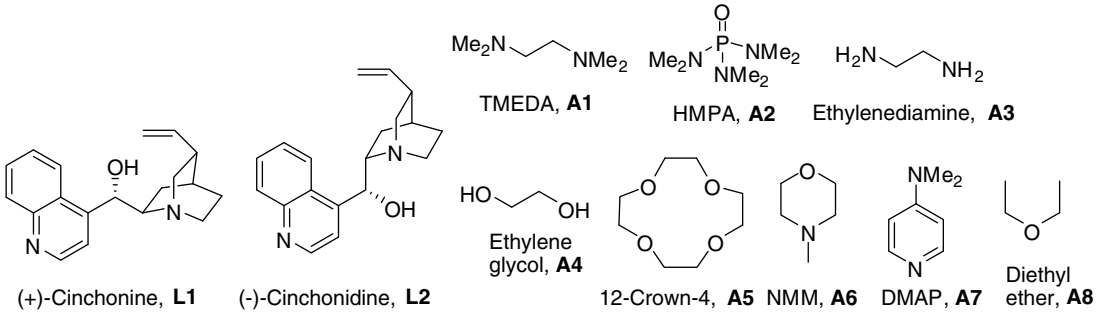
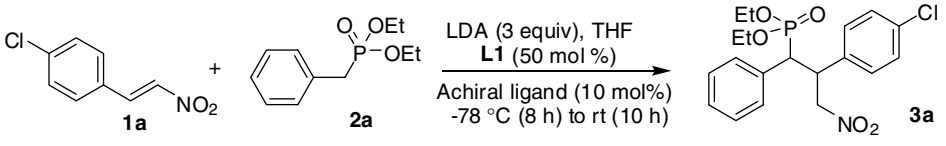


Figure 1. Catalysts and additives.

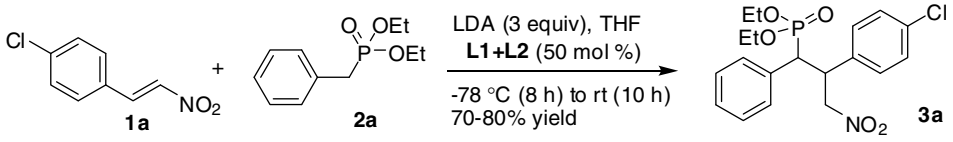
Table 1. Achiral ligand effect in the cinchonine–Li complex catalyzed Michael addition of benzyl phosphonate **2a** to *p*-chloronitrostyrene **1a**



Entry	Additive, **A1**–**A8**	% Yield[a]	dr[b]	er[b,c]
1	None	81	96:04	100:0 (*R*,*R*)[d]
2	TMEDA **A1**	15	92:08	100:0 (*R*,*R*)
3	HMPA **A2**	17	97:03	100:0 (*R*,*R*)
4	Ethylenediamine **A3**	56	97:03	100:0 (*R*,*R*)
5	Ethylene glycol **A4**	55	97:03	100:0 (*R*,*R*)
6	12-Crown-4 **A5**	44	97:03	99:01 (*R*,*R*)
7	NMM **A6**	25	92:08	10:90 (*S*,*S*)
8	DMAP **A7**	51	85:15	21:79 (*S*,*S*)
9	Diethyl ether **A8**	60	82:18	20:80 (*S*,*S*)
10	Diethyl ether **A8**[e]	55	94:06	0:100 (*S*,*S*)

[a] Isolated yield.
[b] Determined by HPLC (Chiralcel OD-H column, 5% IPA in *n*-hexane).
[c] For the major diastereomer.
[d] The absolute configuration of **3a** was determined by X-ray crystallography, see Ref. 19.
[e] Used as solvent without any THF.

Table 2. Mixed chiral ligand effect in the alkaloid–Li complex catalyzed Michael addition of benzyl phosphonate **2a** to *p*-chloronitrostyrene **1a**



Entry	**L1**:**L2**	dr[a]	er (*R*,*R*):(*S*,*S*)[a]
1	100:0	96:04	100:0
2	95:05	94:06	07:93
3	90:10	98:02	02:98
4	80:20	>99:<1	<1:>99
5	75:25	100:0	0:100
6	70:30	100:0	0:100[b]
7	60:40	99:01	<1:>99
8	50:50	86:14	05:95
9	40:60	97:03	<1:>99
10	30:70	96:04	04:96
11	20:80	96:04	02:98
12	10:90	97:03	06:94
13	05:95	98:02	08:92
14	0:100	98:02	100:0[c]

[a] Ratio was determined by HPLC (Chiralcel OD-H column, 5% IPA in *n*-hexane) whilst the absolute configuration of **3a** was determined by X-ray crystallography, see Ref. 19.

[b] When this reaction was carried out in ether, the selectivities were, respectively, 97:3 dr and 95:5 er (no reversal, but more (*S*,*S*)-isomer was formed with respect to entry 1).

[c] When this reaction was carried out in ether, the selectivities were, respectively, 100:0 dr and 0:100 er (reversal).

entries 1 and 10 (Table 1) reveal that the two enatiomers (*R*,*R*) and (*S*,*S*) could be synthesized with absolute enantioselectivity by performing the reaction in two different solvents, THF and ether, respectively.[14]

Subsequently, we proceeded to screen a mixture of chiral ligands, namely cinchonine **L1** and cinchonidine **L2**. Interestingly, in the presence of 50 mol % of either of these pseudoenantiomeric catalysts **L1** or **L2**, the same (*R*,*R*)-enantiomer of the product **3a** was formed (Table 2, entries 1 and 14). This unusual result suggested that the stereochemistry at C-8 and C-9 in **L1** and **L2** has no influence on the selectivity. In other words, the stereoinducing region of the chiral ligand is away from the site of reaction in this case.[21] A possible involvement of dimeric or oligomeric assemblies of the catalyst, which are in dynamic equilibrium with the monomer, being the active catalyst species, appears quite likely in this case (vide infra).[20]

We further investigated the influence of the **L1**/**L2** ratio on the selectivity (Table 2 and Fig. 2). A notable reversal in the selectivities was observed when mixtures of **L1** and **L2** in different ratios were employed. For instance, entries 2–13 (Table 2) show the formation of the opposite (*S*,*S*)-enantiomer of **3a** as the major or exclusive isomer over a wide range of **L1**:**L2** ratios. The presence of even small amounts of the pseudoenantiomeric catalyst was sufficient to reverse the selectivity (Table 2, entries 2 and 13), that is, **L2** controlled the selectivity in the entire range of **L1**/**L2** ratio (95:5 to 5:95).[22] Since both the pseudoenantiomeric ligands **L1** and **L2** independently provide the same (*R*,*R*) enantiomer, and the mixture of **L1** and **L2**, over a wide range of ratios (95:5 to 5:95), provides the opposite isomer, the difference in kinetic behaviour of **L1** and **L2** or different

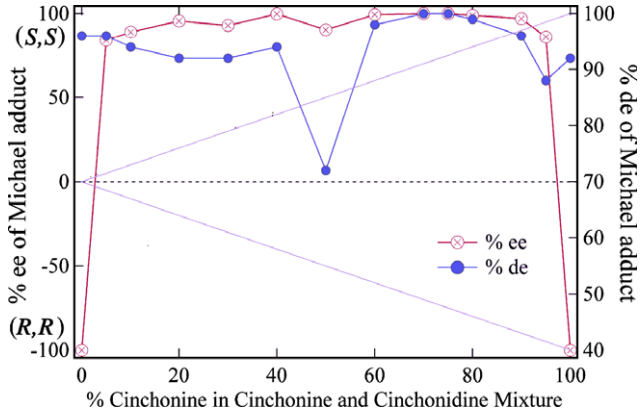


Figure 2. Non-linear effect as a result of mixture of chiral ligands.

compositions of **L1** and **L2** having any bearing on the selectivity can be ruled out. Therefore, the main reason for this non-linear effect appears to be the greater activity of the heterochiral catalyst assembly over the homochiral assembly which forms the inactive reservoir. Of course, this phenomenon arises from the structure of the catalyst complex and its kinetic behaviour.[17]

The diastereo- and enantioselectivities are relatively low at a **L1**:**L2** ratio of 50:50 which gradually increase whilst going towards either end, though the overall effect is marginal (Fig. 2).

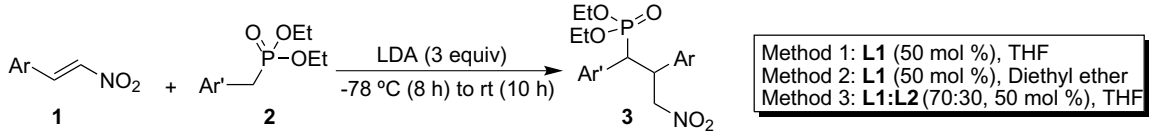
Having developed achiral and mixed chiral ligand methods for the synthesis of γ-nitrophosphonate **3a** in both the enantiomeric forms using our model substrates **1a** and **2a** (Tables 1 and 2), we proceeded to investigate whether

our methods would be suitable for the selective synthesis of stereoisomers of other γ-nitrophosphonates **3b–e**, by screening representative substrates, nitroalkenes **1a–c** and phosphonates **2a–c** (Table 3). First of all, the results of Tables 1 and 2 are summarized in entries 1–3, Table 3. Whilst the original experiment (**L1**/50 mol %, THF, method 1)[19] provides the (*R*,*R*)-isomer of **3a** in excellent yield and selectivity (entry 1, Table 3), the (*S*,*S*)-isomer could be obtained under two different conditions (methods 2 and 3). When ether is used as achiral ligand + solvent with **L1** (50 mol %) as the chiral catalyst (method 2), the yield drops, whilst the selectivities remain high (Table 3, entry 2). On the other hand, the mixed chiral ligand method (**L1**:**L2** = 70:30/50 mol %, THF, method 3) provided the (*S*,*S*)-isomer in high yield and absolute selectivity (entry 3, Table 3). The results obtained for **3b** (entries 4–6) and **3c** (entries 7–9) are as follows. The best yields and dr's were obtained by method 1 (Table 3, entries 4 and 7). Interestingly, a reversal of dr was observed (from (*R*,*R*) + (*S*,*S*) to (*R*,*S*) + (*S*,*R*)) in the case of **3b** and **3c** by both the methods (methods 2 and 3, Table 3, entries 5–6 and 8–9). However, analysis of the minor diastereomer (entries 5–6 and 8–9 in parentheses) showed no appreciable change in enantioselectivity under the conditions of methods 2 and 3, as compared to method 1 in the case of **3b**, but a dramatic reversal in the case of **3c**.

Subsequently, γ-nitrophosphonates **3d** and **3e** were prepared under the conditions of methods 2 and 3 (entries 10–15, Table 3). As in the case of **3a** and **3c**, a reversal of enantioselectivity was observed for **3d** by method 2. In stark contrast, there was no change in selectivity when method 3 was employed. Although there was no reversal in the case of **3e**, an enhancement in selectivity for the minor enantiomer under the conditions of methods 2 and 3 was observed (Table 3, entries 13–15).

Preliminary analysis of the phosphonate **2a**–Li complex and the phosphonate **2a**–Li–alkaloid complex using ^{31}P NMR suggests the involvement of higher order catalyst species. For instance, benzyl phosphonate **2a** appears as a sharp peak at δ 25.89 in the ^{31}P NMR spectrum. Upon treatment with LDA, three peaks resonating at δ 28.04, 32.46 and 45.83 are observed in an integration ratio of 9.4:53.9:36.5. Whilst the peak at δ 28.04 is sharp, the other two are broad, indicating that the peaks at δ 32.46 and 45.83 represent the two tautomeric forms of lithiated benzyl phosphonate. The sharp peak at δ 28.04 in all probability is a relatively stable and symmetrical complex. This lithiated phosphonate on treatment with cinchonidine **L2** presumably leads to the formation of the **2a**–Li–**L2** complex. Examination of the spectrum reveals that one of the tautomers of lithiated **2a** remains as such (δ 32.43), whilst the other formed a complex with **L2**. More importantly, two new peaks appeared at δ 27.71 and 28.30, and the peak for free **2a** reappeared at δ 25.77. These two new peaks in a ~1:3 ratio can be attributed to **2a**–Li–**L2** complexes. Although the structure and geometry of the complexes

Table 3. Michael addition of phosphonates **2a–c** to various nitroalkenes **1a–c**[23]



1a: Ar = *p*-ClPh **2a**: Ar' = Ph **3a**: Ar = *p*-ClPh, Ar' = Ph **3d**: Ar = Ph, Ar' = Ph
1b: Ar = *p*-OMePh **2b**: Ar' = *p*-ClPh **3b**: Ar = *p*-OMePh, Ar' = Ph **3e**: Ar = *p*-ClPh, Ar' = Naph
1c: Ar = Ph **2c**: Ar' = Naph **3c**: Ar = *p*-ClPh, Ar' = *p*-ClPh

Entry	3	M[a]	% Yield[b]	dr[c] (d_1:d_2)[d]	er[c,e]	Major diastereomer	Ligand effect
1		M1	81	96:04	100:0	(*R*,*R*):(*S*,*S*)[f]	
2	**3a**	M2	55	94:06	0:100	(*R*,*R*):(*S*,*S*)	er reversal
3		M3	78	100:0	0:100	(*R*,*R*):(*S*,*S*)	er reversal
4		M1	99	88:12	91:09	(*R*,*R*):(*S*,*S*)	
5	**3b**	M2	51	11:89	62:38 [88:12][e]	(*R*,*S*):(*S*,*R*) or (*S*,*R*):(*R*,*S*) [(*R*,*R*):(*S*,*S*)][d,e]	dr reversal [er no major change]
6		M3	81	41:59	100:0 [98:02][e]	(*R*,*S*):(*S*,*R*) or (*S*,*R*):(*R*,*S*) [(*R*,*R*):(*S*,*S*)][d,e]	dr reversal [er no major change]
7		M1	69	100:0	100:0	(*R*,*R*):(*S*,*S*)	
8	**3c**	M2	42	22:78	83:17 [25:75][e]	(*R*,*S*):(*S*,*R*) or (*S*,*R*):(*R*,*S*) [(*R*,*R*):(*S*,*S*)][d,e]	dr reversal [er reversal]
9		M3	44	37:63	96:04 [25:75][e]	(*R*,*S*):(*S*,*R*) or (*S*,*R*):(*R*,*S*) [(*R*,*R*):(*S*,*S*)][d,e]	dr reversal [er reversal]
10		M1	95	68:32	99:01	(*R*,*R*):(*S*,*S*)	
11	**3d**	M2	52	94:06	34:66	(*R*,*R*):(*S*,*S*)	er reversal
12		M3	64	62:38	100:0	(*R*,*R*):(*S*,*S*)	No major change
13		M1	74	0:100	100:0	(*R*,*S*):(*S*,*R*) or (*S*,*R*):(*R*,*S*)	
14	**3e**	M2	42	39:61	86:14	(*R*,*S*):(*S*,*R*) or (*S*,*R*):(*R*,*S*)	dr and er enhancement for minor
15		M3	46	18:82	74:26	(*R*,*S*):(*S*,*R*) or (*S*,*R*):(*R*,*S*)	dr and er enhancement for minor

[a] Method.
[b] Isolated yield.
[c] Determined by HPLC (Chiralcel OD-H column, 5% IPA in *n*-hexane).
[d] d_1:d_2 = [(*R*,*R*) + (*S*,*S*)]:[(*R*,*S*) + (*S*,*R*)].
[e] er of minor diastereomer in parenthesis.
[f] The absolute configuration of **3a** was determined by X-ray crystallography whilst for **3b–e**, it was based on comparison of the ^1H NMR chemical shifts for the CH_2NO_2 group, see Ref. 19.

are a matter of speculation, the ratio of (Li–**2a**–**L2**): (**2a**+Li–**2a**) = 11.07:88.93 = 1:8 suggests that the catalyst complex could be oligomeric in nature. Investigations are currently underway to better understand the exact nature of the catalyst species.

3. Conclusions

In conclusion, the effect of achiral and a mixture of chiral ligands on the stereoselectivity in the conjugate addition of phosphonates to nitroalkenes has been investigated. Amongst the various achiral additives screened, in conjunction with a cinchonine–Li complex as the catalyst, diethyl ether turned out to be superior to others when used as an additive as well as a solvent, providing stereoisomers different from the ones obtained in THF, often with a reversal of enantioselectivity. When a pseudoenantiomeric mixture of catalysts (cinchonine/cinchonidine 70:30) was used, similar change in selectivity was observed indicating the kinetic advantage of heterochiral complexes in controlling the stereochemical outcome. The major advantage of these approaches over traditional approaches in asymmetric catalysis is that the catalyst can be optimized by utilizing achiral ligands and the mixture of chiral ligands offering flexibility and ready access to a diverse array of potential catalysts. Detailed investigations to determine the exact origin of the selectivity change/reversal,[24] and the application of this strategy to other reactions are currently underway in our laboratory.

Acknowledgements

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23. *General procedure for methods 1–3*: A solution of LDA (1.5 mmol) in solvent (1.5 ml) was prepared by dropwise addition of *n*-BuLi (0.95 ml, 1.5 mmol, 1.6 M solution in hexanes) to diisopropylamine (0.21 ml, 152 mg, 1.5 mmol) in solvent (1.5 ml) at 0 °C followed by stirring for 30 min at the same temperature. To this freshly prepared LDA, cooled to −78 °C, phosphonate **2** (0.5 mmol) was added dropwise. After stirring the reaction mixture for 1 h, cinchonine **L1** (74 mg, 0.25 mmol, for methods 1 and 2) or cinchonine **L1** + cinchonidine **L2** (52 + 22 mg, 70:30, 0.25 mmol, for method 3) in solvent (1 ml) was added and the reaction mixture was stirred for an additional 30 min. Subsequently, nitroalkene **1** (0.75 mmol) in solvent (1 ml) was added to the reaction mixture and the temperature was maintained at −78 °C for an additional 8 h. The reaction mixture was warmed to ambient temperature and stirring continued for 10 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (2 ml), further saturated with NaCl and extracted with ethyl acetate (3 × 5 ml). The combined organic layers were washed with brine (5 ml), dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/pet ether, 0–50%, gradient elution). The solvent was THF for methods 1 and 3, and diethylether for method 2.
24. In order to test the possible reversibility of the reaction and its influence on the stereoselectivity, we treated diastereo- and enantiomerically pure (*S*,*S*)-**3a** with LDA/cinchonine **L1** under standard conditions (see Ref. 23). Analysis of the reaction mixture by ^1H NMR showed the presence of two diastereomers of **3a**, 4-chloronitrostyrene **1a** and benzyl phosphonate **2a** in a 56:02:21:21 ratio. This means that 26%

of the product **3a** underwent reverse reaction to the starting materials whereas 2% of **3a** epimerized. Further HPLC analysis showed that the major diastereomer of **3a** (56%) consisted of (*S*,*S*)- and (*R*,*R*)-isomers in 99:1 ratio and the minor diastereomer (2%), (*R*,*S*) + (*S*,*R*) or (*S*,*R*) + (*R*,*S*), in 86:14 ratio. We conclude from these results that although the reaction is reversible, the equilibrium is in favour of the product (in the presence of excess of one of the starting materials, for example, nitroalkene, as in our original experiment, the equilibrium is further shifted towards the product). In other words, under our experimental conditions, the diastereo- or enantioselectivity reversal does not seem to take place to any significant extent via a reverse reaction and readdition.