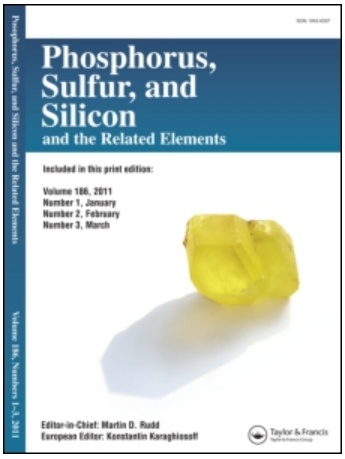

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Inversion of the Configuration of Cyanohydrins by a Mitsunobu Esterification Reaction

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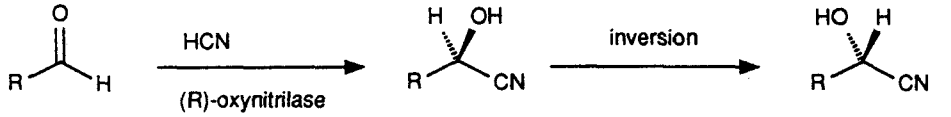
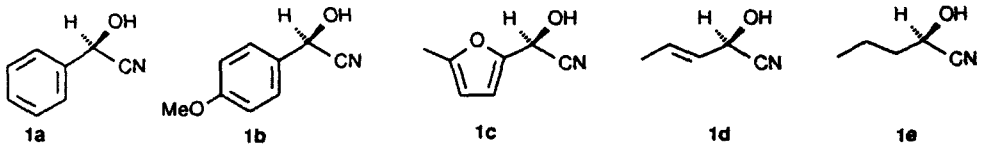
Abstract: Optically active *(R)*-cyanohydrins have been transformed into cyanohydrin esters of opposite configuration under Mitsunobu conditions and subsequently solvolyzed to *(S)*-cyanohydrins in high chemical and optical yield. The method works well for allylic and benzylic cyanohydrins. Cyanohydrins containing strongly electron donating substituents gave extensive racemization. Saturated aliphatic cyanohydrins afforded esters in which the original configuration is retained. These results are discussed in terms of the mechanism of the Mitsunobu reaction.

Chiral cyanohydrins are versatile starting materials for the synthesis of several classes of optically active compounds such as α-hydroxyacids[1] and their esters[2], α-hydroxyketones[3], α-hydroxyaldehydes[4], ß-hydroxyamines[5], and ß-hydroxy-α-aminoacids[6]. Whereas optically active cyanohydrins possessing the *(R)*-configuration are well accessible using the enzyme mandelonitrile lyase (R-oxynitrilase[2,7], E.C. 4.1.2.10), synthesis of the *(S)*-enantiomers is hampered by the limited availability of the required biocatalyst and its narrow substrate specificity[8].
It is therefore of considerable interest to find a method for the chemical conversion of *(R)*-cyanohydrins into their *(S)*-enantiomers. Effenberger et al. recently reported on their attempts to accomplish this by means of α-sulfonyloxynitriles[9]. As it turned out, these compounds are rather unstable and only in the case of cyanohydrins derived from saturated aliphatic aldehydes satisfactory results were obtained. With the chemically more interesting allylic and benzylic substrates, extensive racemization occurred. We now report on our results regarding the inversion of the chiral centre of *(R)*-cyanohydrins under Mitsunobu[10] conditions (diethyl azodicarboxylate, triphenylphosphine, carboxylate nucleophile).



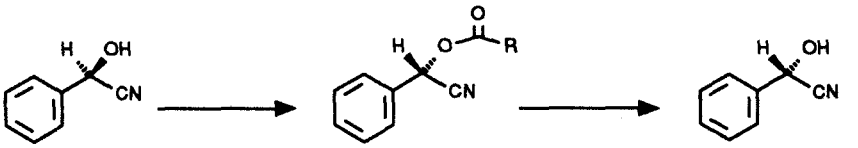
Results and Discussion

Of the five cyanohydrins tested (**1a**-**1e**), only the enantiomers of *(R)*-α-hydroxybenzeneacetonitrile (**1a**) and *(R)*-α-hydroxy-4-methoxybenzeneacetonitrile (**1b**) can be obtained with the aid of the, scarcely available, S-oxynitrilase extracted from Sorghum. The enantiomers of *(S)*-2-hydroxy-2-(5-methylfuryl)acetonitrile (**1c**)[11], *(R)*-2-hydroxypentenenitrile (**1d**) and *(R)*-2-hydroxypentanenitrile (**1e**) have not been reported to be accessible via biocatalysis.



1a 1b 1c 1d 1e

First, the inversion of **1a** (e.e. 99%) under standard Mitsunobu conditions was studied, employing acetic acid as the protonated nucleophile. The acetate was obtained as an oil in only moderate yield (65%). The optical rotation revealed an inversion of the configuration {$[\alpha]_D^{20}$ -5.8° (c=1, $CHCl_3$); lit. $[\alpha]_D^{20}$ -5.8° (c=1, $CHCl_3$) for the *(S)*-enantiomer}. HPLC analysis (Chiralcel OD) showed an e.e. of 92%. Since the ester function is not compatible with several desirable subsequent tranformations such as $LiAlH_4$[5] or DIBAL[4] reductions and Grignard reactions[3], it should be replaced by a proper protecting group. Basic hydrolysis of the ester function is not a viable option in this case because of the base lability of the product. Therefore solvolysis under acidic conditions was investigated, using the acetate of **1a** as a model substrate. Best results were obtained with methanesulfonic acid and with *p*-toluenesulfonic acid in concentrations up to one equivalent in methanol. Applying aqueous acidic conditions such as concentrated hydrochloric acid or 20% sulfuric acid resulted in partial hydrolysis of the nitrile. Dilute hydrochloric or sulfuric acid caused no reaction at all. Also direct $NaBH_4$ reduction of the ester was not satisfactory because of extensive racemization. Since the Mitsunobu reaction afforded a product of good e.e. but still gave some loss of optical purity, a series of carboxylic acids was investigated in order to find an ester that could be crystallized to optically pure product. The results are presented in the Table. As it turned out, benzoate and substituted benzoates gave excellent results (entries 1-3).



entry	nucleophile RCOO⁻	yield (%)	e.e.(%)	$[\alpha]_D^{20}$	hydrolysis of ester	crystalline ester	*R/S*
1	C_6H_5	90	92	-24.3	-	-	*S*
2	4-$CH_3OC_6H_4$	85	92	-37.0	-	-	*S*
3	4-$NO_2C_6H_4$	76	99	-38.6	-	+	*S*
4	CH_3	65	92	-5.8	++	-	*S*
5	CH_3OCH_2	95	92	+7.3	++	-	*S*
6	$C_6H_5CH_2$	95	92	+10.8	+	-	*S*
7	$(C_6H_5)_2CH$	90	92	+5.1	+	-	*S*
8	4-$CH_3OC_6H_4CH_2$	70	91	+2.9	+	-	*S*
9	4-$NO_2C_6H_4CH_2$	75	99	+11.5	+	+	*S*

The corresponding esters of opposite configuration were obtained in high chemical and optical yield. The 4-nitrobenzoate was obtained in > 99% optical purity after a single crystallization. Unfortunately, all attempts to solvolyse these esters without racemization remained without success. In order to meet with all criteria (good S_N2 behaviour, crystallizability, solvolyzable without racemization), several substituted acetates were studied (entries 5-9). As can be seen in the table, some loss of optical purity occurs in all cases. Typically, e.e.-values of 91-92% were found. Crystallization of the crude ester therefore remains necessary. Of the acetates studied, only the 4-nitrophenylacetate proved to be crystalline. One crystallization afforded the pure *S*-ester in 75% yield. The acetate and methoxyacetate were most readily solvolyzed. Acid catalyzed solvolysis of the 4-nitrophenylacetate, although appreciably slower, could be performed with minimal (< 2%) racemization. The TBS ether of the *(S)*-mandelonitrile obtained was shown by HPLC to have an e.e. of 96,5%.

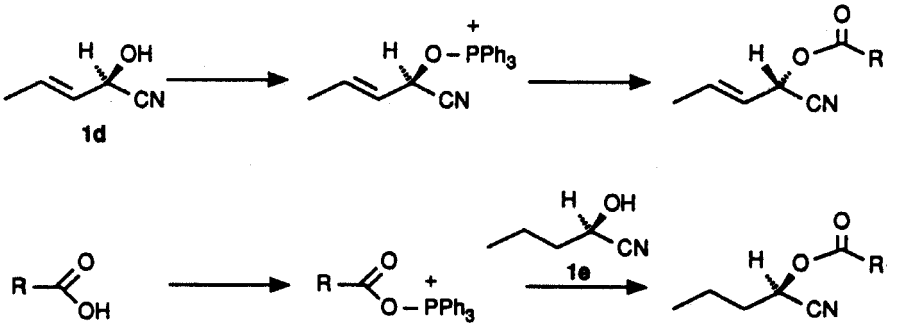
entry	cyanohydrin	nucleophile RCOO⁻	yield (%)	e.e.(%)	$[\alpha]_D^{20}$	hydrolysis of ester	crystalline ester	*R/S*
1	1b	CH_3	90	5	+1.5	++	-	*S*
2	1b	$4\text{-}NO_2C_6H_4$	80	0	0	-	+	-
3	1c	$4\text{-}NO_2C_6H_4$	70	40	+6.7	-	+	*R*
4	1d	$4\text{-}NO_2C_6H_4CH_2$	75	98	+15.5	+	+	*S*
5	1d	$4\text{-}NO_2C_6H_4$	75	98	+10.6	-	+	*S*
6	1e	$4\text{-}NO_2C_6H_4CH_2$	70	85	+51.6	+	-	*R*

The results obtained with the other substrates (**1b-1e**) are presented above. For α-hydroxy-4-methoxybenzeneacetonitrile (**1b**) the method appeared to be of little value since both acetic acid and 4-nitrobenzoic acid (entries 1,2) gave extensive racemization. With cyanohydrin **1c**, derived from 5-methylfurfural, an enantiomeric excess of only 40% was found. Apparently, the carbocation-stabilizing effect of the 4-methoxyphenyl and 5-methylfuryl substituents causes unimolecular nucleophilic substitution to become a serious side reaction in these cases.

Far better results were obtained with the allylic cyanohydrin **1d** (entries 4,5). Both acids that gave crystalline esters for **1a** did so for **1d**. The optical purity was 98% in each case (HPLC). As expected, only the 4-nitrophenylacetate could be easily solvolyzed. The TBDPS ether of the *(S)*-2-hydroxypentenenitrile obtained showed an e.e. of 96.5%.

Subjecting the saturated aliphatic cyanohydrin **1e** to the conditions of the Mitsunobu esterification yielded the 4-nitrophenylacetate as an oil. Comparison with the ester obtained from **1e** by reaction with 4-nitrophenylacetic anhydride learned that the reaction had provided the *R*-enantiomer in 85% optical purity. This remarkable result can be understood by considering the mechanism of the Mitsunobu reaction. In the events leading to inversion of the configuration, the protonated azoester-triphenylphosphine complex reacts with the alcohol to give, via a pentacoordinated intermediate, the O-triphenylphosphonium activated alcohol, which reacts with the carboxylate in a clean S_N2 reaction. If, on the other hand, the azoester complex reacts with the nucleophile, an activated acyl intermediate is formed, which will react with the

alcohol with retention of configuration. With the allylic and benzylic substrates **1a** and **1d**, reaction of the activated alcohol is by far the fastest and almost complete inversion results. In the case of the saturated aliphatic substrate **1e** the chiral centre is insufficiently activated towards nucleophilic substitution and acylation of the alcohol takes over, resulting in retention.



Conclusion

A method has been developed for inverting the configuration of *(R)*-cyanohydrins **1a** and **1d** by means of a Mitsunobu esterification, using 4-nitrophenylacetic acid as the protonated nucleophile. The inverted esters can be obtained in optically pure form by crystallization and can be subsequently solvolyzed to the free cyanohydrins under acidic conditions. Our investigations have also clearly indicated the limitations of the Mitsunobu approach. Cyanohydrins containing strongly cation-stabilizing substituents (4-methoxyphenyl, 5-methylfuryl) give rise to extensive racemization. With cyanohydrins derived from saturated aliphatic aldehydes, the S_N2 reaction is slow and esterification via an activated acyl intermediate takes over. The area between these limits may be fairly small, but contains cyanohydrins (allylic and benzylic) that are of special interest for subsequent chemical transformations.

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11. Cyanohydrin **1c** possesses a similar spatial arrangement as **1a**, **1b**, **1d**, and **1e**. Due to the priority rules its configuration must be designated as (*S*).