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Optically active nitrile oxides: synthesis and 1,3-dipolar cycloaddition reactions

Marcin Zagozda and Jan Plenkiewicz*

Faculty of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland

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Abstract—Baker's yeast-promoted reduction of the C=C bond in 2-aryl-1-nitropropenes gave the corresponding optically active (*R*)-2-aryl-1-nitropropanes of high enantiomeric purity (ee >90%). They were next converted with the aid of the Mukaiyama and Hoshino method into the optically active nitrile oxides, which were made to react in situ with ethyl propiolate, methylvinyl ketone and (*R*)-1-phenyl-2-(phenylsulfonyl)ethyl acrylate to yield the appropriate, enantiomerically enriched, isoxazoles or 4,5-dihydroisoxazoles as diastereomeric mixtures, respectively.

1. Introduction

Δ^2-Isoxazolines (4,5-dihydroisoxazoles) are known as versatile intermediates in the synthesis[1] of various natural products since the reductive cleavage of the isoxazoline ring can lead to many synthetically important compounds, such as β-hydroxy ketones, α,β-unsaturated ketones or γ-amino alcohols.[2] The general and most frequently used method for the synthesis of Δ^2-isoxazolines depends on the 1,3-dipolar cycloaddition of nitrile oxides to the activated double bond in alkenes; aliphatic nitrile oxides are in most cases generated in situ from primary nitro compounds in a Mukaiyama reaction,[3] while their aromatic counterparts are usually prepared by dehydrohalogenation of hydroxamoyl chlorides.[4] In most cases, 1,3-dipolar cycloadditions (1,3-DC) of nitrile oxides to alkenes proceed with high regioselectivity, with the relative configuration on the 4- and 5-carbon atoms of the isoxazoline ring dependent on the alkene geometry.

Most of the literature data on the asymmetric 1,3-DC leading to isoxazolines refer to reactions between achiral nitrile oxides and optically active alkenes.[5] Since the preparation of chiral nitrile oxides, usually from primary nitro compounds[6a,e] or chloroaldoximes,[6b–e] is rather difficult, there are only few reports on their use.[6]

Herein we report the results of the baker's yeast-promoted (*Saccharomyces cerevisae*) reduction of several 1-nitro-2-arylpropenes to the corresponding optically active 1-nitro-2-arylpropanes, subsequently converted into the optically active nitrile oxides. Cycloaddition of the nitrile oxides to ethyl propiolate and methyl vinyl ketone yielded the appropriate isoxazoles and isoxazolines.

2. Results and discussion

Optically active nitrile oxides **8** were prepared from the appropriate optically active nitroalkanes **7** with the aid of the Mukaiyama and Hoshino method and used in situ as reagents in the 1,3-DC reactions.[3] The enantiomerically enriched **7** was obtained by a dehydrogenase-catalyzed reduction of the C=C bond in the corresponding nitroalkenes **5** synthesized from α-methylstyrene derivatives **3**. The retrosynthesis shown in Scheme 1 also includes the 1,3-cycloaddition of the nitrile oxide to methyl vinyl ketone yielding 2-isoxazoline **10**.

In order to prepare the phenyl-substituted derivatives **3b–d** of α-methylstyrene, the appropriate acetophenones **1b–d** were made to react with methylmagnesium bromide[7,8] to give the corresponding dimethylphenylcarbinols **2b–d**, which were subjected to dehydration without purification[8] with a catalytic amount of *p*-toluenesulfonic acid. The yields of **3b–d** were 34–68% (Scheme 2).

* Corresponding author. Tel.: +48 22 234 75 70; fax: +48 22 628 27 41; e-mail: plenki@ch.pw.edu.pl

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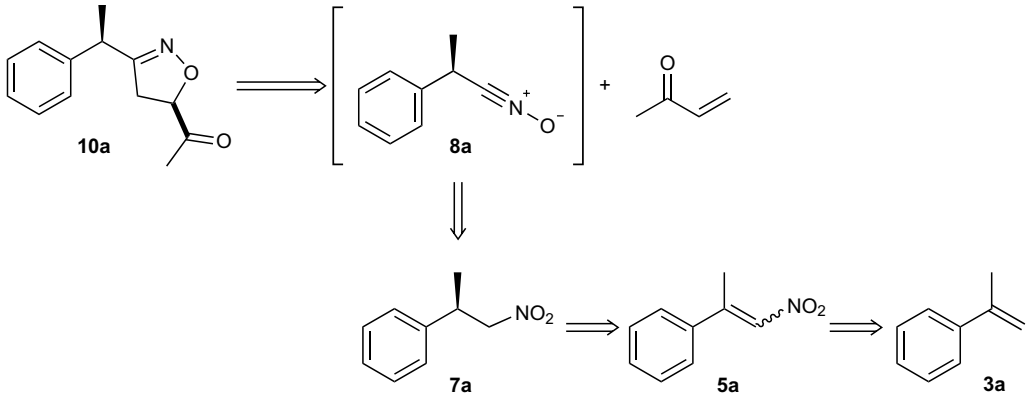
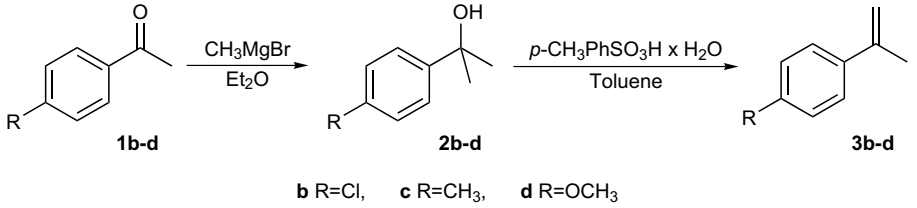


Scheme 1.



Scheme 2.

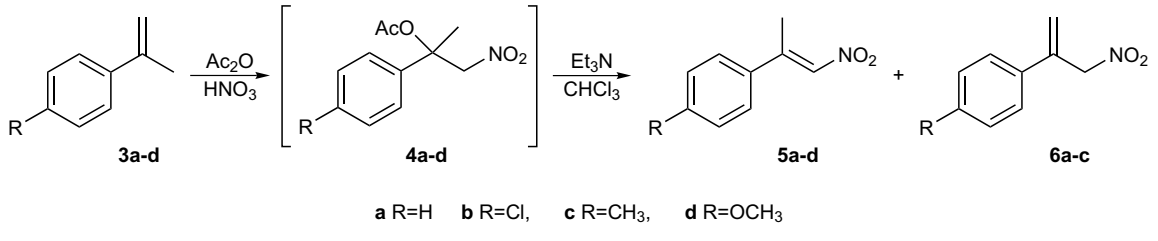
The conversion of α-methylstyrenes **3a–d** into 2-aryl-1-nitropropenes **5a–d** was accomplished by the two-step procedure described earlier.[9] At first, β-nitro acetates **4a–d** were formed by the addition of acetyl nitrate (from acetic anhydride and concentrated nitric acid) to the C=C bond of **3a–d**. In the second step, elimination of the acetic acid with triethylamine yielded the desired **5a–d** (Scheme 3). However, it is noteworthy that the reaction with triethylamine is not unidirectional and leads to two isomeric products in low-to-moderate yields. Although the desired **5a–d** predominated in the reaction products, substantial amounts of 2-aryl-3-nitropropenes **6a–c** were also formed. As determined by ^{1}H NMR spectra, the **5**:**6** ratio was roughly 2:1. Polymerization side-reactions are presumably responsible for low yields of the nitroalkene formation. Crude products **5** and **6** were purified by distillation and used in the bioreduction reactions as mixtures of isomers (Table 1).

Table 1. The yields of nitroalkenes **5** and **6**

Entry	Substrate	R	Yield (%) of **5** and **6**	Ratio of **5** to **6**[a]
1	**3a**	–H	52	67:33
2	**3b**	–Cl	36	64:36
3	**3c**	–CH_3	24	76:24
4	**3d**	–OCH_3	3	Pure **5d**

[a] Ratio of diastereomers was determined by ^{1}H NMR.

The baker's yeast reduction of 2-phenyl-1-nitro-**5a** and 2-phenyl-3-nitropropene **6a** was investigated earlier by Ohta et al.[10] who reported that both isomers gave the same reduction product, namely (*R*)-1-nitro-2-phenylpropane **7a**; a high enantiomeric excess was noted with either substrate. Following the Ohta's procedure with **5a–6a** and **5b–6b** mixtures and with growing cells of baker's yeast (*S. cerevisiae*) in a 2% glucose solution, we isolated the corresponding 1-nitro-2-arylpropanes **7a** and **7b**, but in very low yields. However, since no substrates could be detected after a 24 h incubation indicating their consumption must have been complete. There are two possible reasons for the failure. Firstly, we worked with a different brand of yeast which possibly used the substrates as a source of carbon for the growing cells; and secondly, some problems with product isolation might have arisen in spite of our



Scheme 3.

strict observance of the Ohta's procedure. This prompted us to investigate the reduction with lyophylized yeast in an organic solvent. A few solvents were investigated as the reaction medium. In moisture-containing *tert*-butyl methyl ether, the reduction of **5a** and **6a** was slower than in water while the substrate conversion into **7a** did not exceed 25% after 24 h. Satisfactory results were obtained in a less polar solvent. Thus, in either hexane or petroleum ether, the bioreduction of nitroalkenes **5** and **6** afforded the corresponding (*R*)-nitroalkanes **7a–d** in 41–82% yields, which were substantially higher than those reported by Ohta.[10] The enantiomeric excesses of the prepared (*R*)-2-aryl-1-nitropropanes **7a–d** were high (91–99% ee) while the (*R*) absolute configurations were established by comparing the signs of specific rotations with those reported in the literature.[10] The results of the experiments are presented in Table 2 (Scheme 4).

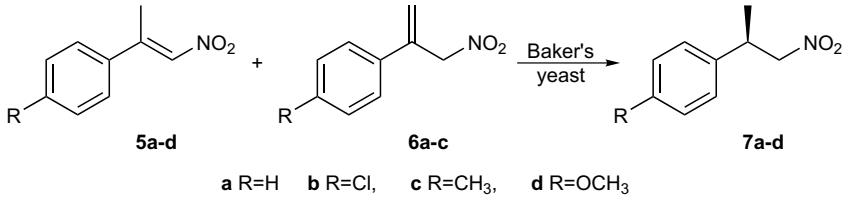
Our investigations on the use of optically active nitroalkanes **7a** and **7b** in the preparation of optically active nitrile oxides started with the reaction of nitroalkane dehydration with phenyl isocyanate according to the Mukaiyama procedure. Ethyl propiolate was used as the dipolarophile. Unfortunately under these conditions, the reaction gave a hardly definable mixture of products. When di-*tert*-butyl-dicarbonate (Boc_2O) and 4-dimethylaminopyridine (DMAP) were used instead of phenyl isocyanate, the expected ethyl 3-[(1*R*)-1-phenylethyl]isoxazole-5-carboxylate **9a** and ethyl 3-[(1*R*)-1-(4-chlorophenyl)-ethyl]-isoxazole-5-carboxylate **9b** were obtained in 72% and 64% yields, respectively (Scheme 5). The reactions proceeded beside the stereogenic centre and with full preservation of enantiomerc purity. The obtained isoxazole derivatives **9a** and **9b** showed the same enantiomeric excesses as the starting nitroalkanes. That means that in both reaction steps the enantiomeric purity of the substrates remained unaffected.

There were no such problems with the use of phenyl isocyanate as the dehydrating agent in the 1,3-DC reactions with methyl vinyl ketone. However, the reactions with this dipolarophile were not stereoselective and the in situ generated optically active nitrile oxides yielded diastereomeric mixtures of 4,5-dihydroisoxazoles **10a–d** in 35–55% yields, relative to the nitroalkane substrate (Scheme 6). Detailed results, including the diastereomeric ratios as determined by ^1H NMR spectra, are presented in Table 3. As it may

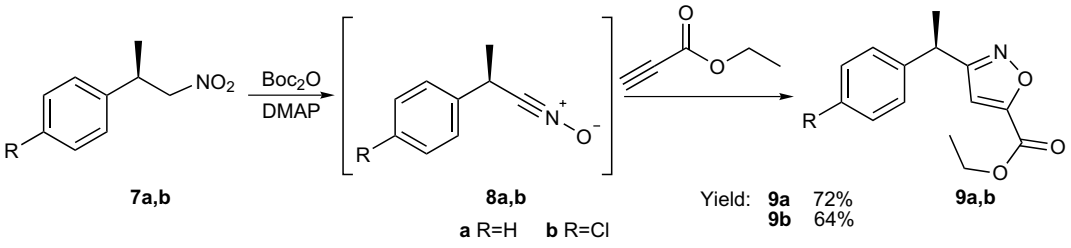
Table 2. Reduction of nitroalkenes **5** and **6** to optically active nitroalkanes (*R*)-**7a–d**

Entry	Product	R	Reaction medium	Time (h)	Conv.[a] (%)	Yield[b] (%)	ee[c] (%)
1	**7a**	–H	Water	24	59	25	>98
2	**7a**	–H	Petroleum ether	48	83	70	>98
3	**7a**	–H	*t*-Butyl methyl ether	20	2	—	—
4	**7a**	–H	Hexane	24	90	82	>98
5	**7b**	–Cl	Water	24	90	12	—
6	**7b**	–Cl	Petroleum ether	48	64	41	91
7	**7b**	–Cl	Hexane	24	55	47	91
8	**7c**	$–CH_3$	Hexane	48	59	47	97
9	**7d**	$–OCH_3$	Hexane	24	80	45	>99

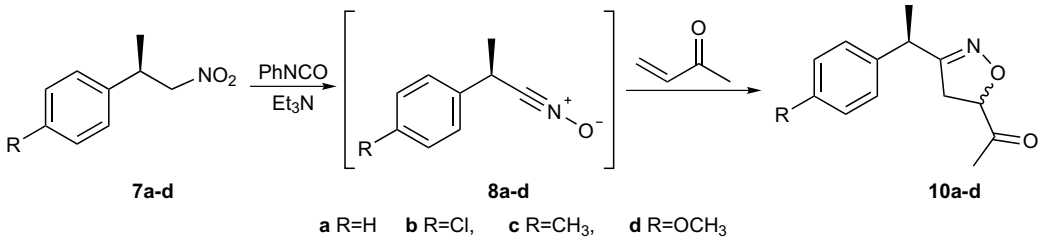
[a] Conversion of nitroalkenes was determined by GC analysis.
[b] Isolated yield of (*R*)-**7a–d** after purification by column chromatography.
[c] Enantiomeric excesses were determined by HPLC using Chiralcel OD-H column in comparison with racemic compounds.



Scheme 4.



Scheme 5.



Scheme 6.

Table 3. 1,3-DC of chiral nitrile oxides **8a–d** with methyl vinyl ketone

Entry	Product	R	Time (h)	Yield[a] (%)	Ratio of diastereomers[b]
1	**10a**	–H	24	47	50:50
2	**10b**	–Cl	24	55	50:50
3	**10c**	$–CH_3$	24	35	45:55
4	**10d**	$–OCH_3$	24	42	43:57

[a] Isolated yield of **10a–d** after column chromatography.
[b] Ratio of diastereomers was determined by ^{1}H NMR.

be seen, low stereoselectivity was the case only in the reactions of 4-methylphenyl- and 4-methoxyphenyl derivatives **7c** and **7d**; and the ratios of the 4,5-dihydroisoxazoles **10c** and **10d** obtained were not equal (45:55 and 43:57, respectively). The results presented in Table 3 indicate that the configuration of the chiral centre in the optically active nitrile oxides **8a–d** did not affect the stereochemistry of the cycloaddition reaction.

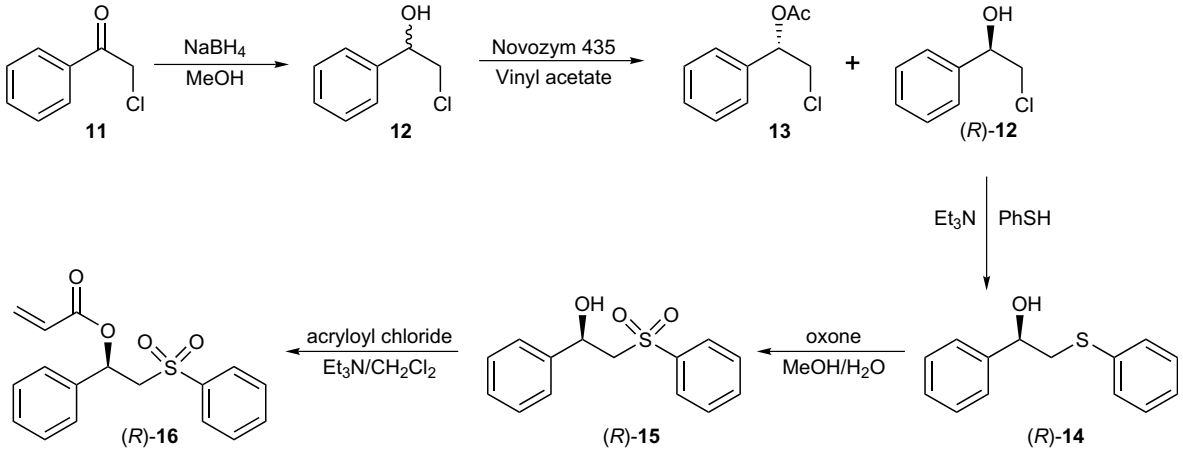
When in the reaction of **7a**, and methyl vinyl ketone di-*tert*-butyl-dicarbonate was used to replace phenyl isocyanate as the dehydrating agent, the yield of **10a** was increased (64%) although there was no change in the diastereomeric ratio (1:1).

In an attempt to improve the stereoselectivity of the cycloaddition reaction, we decided to use an optically active bulky alkene instead of methyl vinyl ketone in 1,3-DC with optically active nitrile oxide. Alkene (*R*)-**16** was obtained in several steps from α-chloroacetophenone. At first, ketone **11** was reduced by sodium borohydride to the racemic alcohol **12**. A kinetic resolution of the racemate yielded the optically active alcohol (*R*)-**12** and its acetate (*S*)-**13**. The reaction of (*R*)-**12** with thiophenol gave β-hydroxysulfide (*R*)-**14** which was oxidized by Oxone® to the optically active β-hydroxysulfone (*R*)-**15**. In the last step the optically active (*R*)-1-phenyl-2-(phenylsulfonyl)ethyl acrylate (*R*)-**16** was prepared from acryloyl chloride and sulfone (*R*)-**15** (Scheme 7).

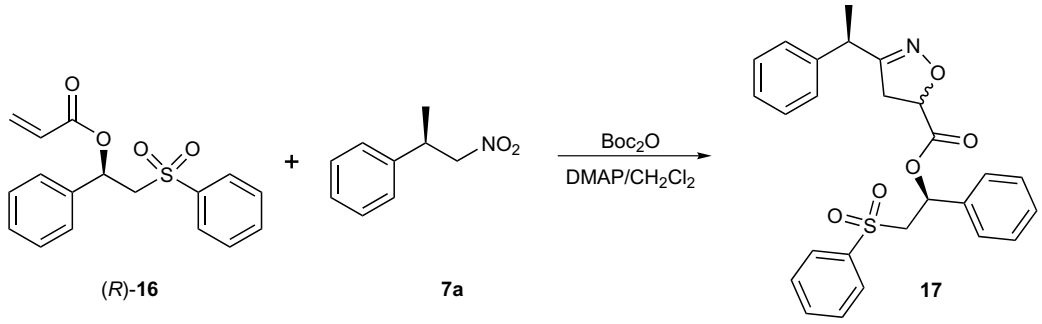
Using the optically active alkene (*R*)-**16** as the dipolarophile in the 1,3-DC with (*R*)-2-phenylpropionitrile oxide we obtained, in 53% yield, a diastereomeric mixture of the corresponding 4,5-dihydroisoxazoles **17** in the 65:35 ratio (de = 30%) (Scheme 8). That showed some improvement in the reaction stereoselectivity when compared with the earlier results with methyl vinyl ketone. Nevertheless, attempts to obtain complete stereoselectivity of the cycloaddition proved unsuccessful.

3. Conclusion

The baker's yeast-promoted reduction of the mixtures of 2-aryl-1-nitro-1-propenes and 2-aryl-3-nitro-1-propenes gave only the optically active (*R*)-2-aryl-1-nitropropanes. The yields of the reduction carried out either in hexane or petroleum ether were higher than those noted in water. The enantiomeric excesses of the optically active nitroalkanes were high both in an organic solvent and in water as the reaction medium.



Scheme 7.



Scheme 8.

Conversion of the nitroalkanes into optically active nitrile oxides proceeded with full preservation of the enantiomeric excess but their further cycloaddition to methyl vinyl ketone yielded the appropriate 4,5-dihydroisoxazoles of low diastereoselectivity. It seems possible that the methyl and phenyl substituents at the α-position to the 1,3 dipole of chiral nitrile oxides are not bulky enough to constrain stereoselectivity. For this reason the optically active alkene (*R*)-**16** possesing bulky substituents was prepared and subjected to the 1,3-DC with (*R*)-2-phenylpropionitrile oxide. Improved diastereoselectivity of this 1,3-dipolar cycloaddition reaction was then observed.

4. Experimental

4.1. General

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with Varian Mercury 400 MHz spectrometer in $CDCl_3$ solution, and chemical shifts (δ) are reported in ppm. Optical rotations were measured in $CHCl_3$ using a PolAAr 32 polarimeter. Enantiomeric excesses (ee%) were determined by HPLC analysis on a Thermo-Separation Products P-100 instrument with Chiralcel OD-H or Whelk01 (*S*,*S*) column in *n*-hexane/*iso*-propanol as the eluent in comparison with racemates. The course of the biotransformations were monitored by GC with Hewlett-Packard Model 5890 II MSD 5972A chromatograph with Helium as the carrier gas. Preparative chromatographic separations were carried on Merck Silica Gel 60 (230–400 mesh).

4.2. General procedure for the synthesis of 2-arylpropenes 3b–d

α-Methylstyrene is commercially available. The phenyl ring substituted derivatives of α-methylstyrene were obtained by dehydration of the corresponding aryldimethylcarbinols prepared from acetophenone derivatives and methylmagnesium bromide by a slightly modified literature method[7,8] as follows.

To a solution of methylmagnesium bromide in dry ether (from methyl bromide 50.0 g, 0.53 mol and magnesium 12.88 g, 0.53 mol in 100 mL of dry ether), a solution of the appropriate acetophenone derivative 0.30 mol in 100 mL of dry ether was added dropwise during 1 h at rt. The mixture was stirred for 5 h and then poured into ice-water. The content of the flask was acidified with 1 M HCl and then aqueous layer was three times extracted with ether. The combined organic layers were dried over magnesium sulfate. Removal of the solvent under reduced pressure gave an oily crude carbinol, which was used without purification in dehydration reaction.

A solution of the appropriate carbinol and catalytic amount of *p*-toluenesulfonic acid in toluene was heated at reflux and the liberated water was separated. The reaction was usually complete after 2 h, and the mixture was washed with water, dried and evaporated to dryness. The resulting crude alkene was purified by distillation under reduced pressure. The yields and properties of the propenes are given below.

4.2.1. 2-(4-Chlorophenyl)propene 3b. Yield: 68%; bp 95–97 °C/19 mm Hg (lit.[11] bp 93–95 °C/20 mm Hg).

4.2.2. 2-(4-Methylphenyl)propene 3c. Yield: 62%; bp 84–86 °C/20 mm Hg (lit.[12] bp 82–83 °C/20 mm Hg).

4.2.3. 2-(4-Methoxyphenyl)propene 3d. Yield: 34%; bp 110–113 °C/21 mm Hg (lit.[13] bp 107–110 °C/17 mm Hg).

4.3. Synthesis of 1-nitro-2-arylpropenes 5a–d and 3-nitro-2 arylpropenes 6a–c

The 2-arylnitropropenes were prepared from 2-arylpropenes and acetyl nitrate as described in the literature for 1-nitro-2-phenylpropene.[10]

4.3.1. (*E*)-1-Nitro-2-phenylpropene 5a and 3-nitro-2-phenylpropene 6a. Yield 52%, the ratio of **5a** to **6a** 2:1, bp = 107–112 °C/2.0 mm Hg. Anal. Calcd C: 66.12; H, 5.72; N, 8.49. Found: C, 66.25; H, 5.56; N, 8.58. Compound **5a** ^{1}H NMR: 2.65 (d, $J = 1.6$ Hz, 3H), 7.31 (q, $J = 1.6$ Hz, 1H), 7.43–7.47 (m, 5H); ^{13}C NMR: 18.6, 126.8, 128.8, 129.0, 137.9, 138.3, 150.0. Compound **6a** ^{1}H NMR: 5.67 (d, $J = 0.8$ Hz, 2H), 5.54 (s, 1H), 5.83 (s, 1H), 7.32–7.42 (m, 5H); ^{13}C NMR: 79.5, 121.7, 125.7, 128.7, 130.3, 136.3, 136.8.

4.3.2. (*E*)-1-Nitro-2-(4-chlorophenyl)propene 5b and 3-nitro-2-(4-chlorophenyl)propene 6b. Yield 36%, the ratio of **5b** to **6b**: 1.8:1, bp = 124–130 °C/2.0 mm Hg. Anal. Calcd C, 54.84; H, 4.18; N, 6.95. Found: C, 54.70; H, 4.08; N,

7.09. Compound **5b** ^{1}H NMR: 2.62 (d, $J = 1.6$ Hz, 3H), 7.28 (q, $J = 1.6$ Hz, 1H), 7.38–7.44 (m, 4H); ^{13}C NMR: 18.4, 128.1, 129.3, 136.4, 136.6, 147.7, 148.5. Compound **6b** ^{1}H NMR: 5.34 (d, $J = 0.8$ Hz, 2H), 5.56 (m, 1H), 5.81 (s, 1H), 7.34–7.38 (m, 4H); ^{13}C NMR: 79.4, 122.4, 127.1, 129.0, 134.7, 135.2, 136.9.

4.3.3. (*E*)-1-Nitro-2-(4-methylphenyl)propene 5c and 3-nitro-2-(4-methylphenyl)propene 6c. Yield 24%, the ratio of **5c** to **6c**: 3.1:1, bp = 126–132 °C/3.0 mm Hg. Anal. Calcd C, 67.91; H, 6.33; N, 7.78. Found: C, 67.78; H, 6.26; N, 7.90. Compound **5c** ^{1}H NMR: 2.40 (s, 3H), 2.64 (d, $J = 1.2$ Hz, 3H), 7.22–7.27 (m, 2H), 7.31–7.39 (m, 3H); ^{13}C NMR: 18.4, 21.3 126.7, 129.7, 135.2, 135.7, 140.9, 150.0. Compound **6c** ^{1}H NMR: 2.36 (s, 3H), 5.35 (d, $J = 0.8$ Hz, 2H), 5.48 (s, 1H), 5.80 (s, 1H), 7.15–7.20 (m, 2H), 7.32–7.36 (m, 2H); ^{13}C NMR: 21.1, 79.6, 120.8, 125.6, 129.5, 133.8, 137.7, 138.7.

4.3.4. (*E*)-1-Nitro-2-(4-methoxyphenyl)propene 5d. Yield 3.2%, purification by column chromatography (hexane–ethyl acetate 20:1). Anal. Calcd C, 62.02; H, 5.80; N, 7.19. Found: C, 62.17; H, 5.74; N, 7.25. Compound **5d** ^{1}H NMR: 2.64 (d, $J = 1.6$ Hz, 3H), 3.85 (s, 3H), 6.92–6.98 (m, 2H), 7.34 (q, $J = 1.6$ Hz, 1H), 7.41–7.46 (m, 2H); ^{13}C NMR: 18.3, 55.4, 114.4, 128.3, 130.0, 135.0, 149.8, 161.2.

4.4. General procedure for reduction of nitropropenes 5 and 6 by baker's yeast

To a solution of 6.2 mmol of the appropriate nitropropene mixture (**5** and **6**) in 370 mL of hexane (or petroleum ether) 38 g of Mauripan baker's yeast and 25 mL of tap water were added. The slurry was shaken at 30 °C and the conversion monitored by GC. After an appropriate time the mixture was filtered and the biomass was washed twice with ethyl acetate. The combined filtrates were dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The crude mixture was purified by column chromatography (hexane–ethyl acetate 20:1) yielding the appropriate (*R*)-2-aryl-1-nitropropane.

4.4.1. (*R*)-2-Nitro-1-phenylpropane 7a.[10] Yield 82%; reaction time in hexane 24 h (in petroleum ether 48 h); ee = 98%. $[\alpha]_D^{30} = +42.0$ (*c* 1.91 $CHCl_3$). Anal. Calcd C, 65.32; H, 6.58; N, 8.37. Found: C, 65.44; H, 6.71; N, 8.48. ^{1}H NMR: 1.37 (d, $J = 6.8$ Hz, 3H), 3.59–3.68 (m, 1H), 4.49 (dd, $J = 12.0$; 8.4 Hz, 1H), 4.56 (dd, $J = 12.0$; 7.2 Hz, 1H), 7.22–7.37 (m, 5H); ^{13}C NMR: 18.7, 38.6, 81.8, 126.9, 127.5, 128.9, 140.8.

4.4.2. (*R*)-2-Nitro-1-(4-chlorophenyl)propane 7b. Yield 47%; reaction time in hexane 24 h (in petroleum ether 48 h); ee = 91%. $[\alpha]_D^{31} = +37.0$ (*c* 2.11 $CHCl_3$). Anal. Calcd C, 54.07; H, 5.00; N, 6.95. Found: C, 54.15; H, 5.05; N, 7.02. ^{1}H NMR: 1.37 (d, $J = 7.2$ Hz, 3H), 3.57–3.67 (m, 1H), 4.47 (dd, $J = 12.4$; 8.0 Hz, 1H), 4.52 (dd, $J = 12.4$; 7.6 Hz, 1H), 7.14–7.19 (m, 2H), 7.29–7.34 (m, 2H); ^{13}C NMR: 18.7, 38.0, 81.5, 128.3, 129.1, 133.3, 139.3.

4.4.3. (*R*)-2-Nitro-1-(4-methylphenyl)propane 7c. Yield 47%; reaction time in hexane 48 h; ee = 97%. $[\alpha]_D^{27} = +39.2$ (*c* 2.01 $CHCl_3$). Anal. Calcd C, 66.92; H, 7.29; N, 7.60. Found: C, 67.02; H, 7.31; N, 7.82. ^{1}H NMR: 1.36 (d, $J = 7.2$ Hz, 3H), 2.33 (s, 3H), 3.55–3.64 (m, 1H), 4.46 (dd, $J = 12.0$; 8.4 Hz, 1H), 4.53 (dd, $J = 12.0$; 7.2 Hz, 1H), 7.10–7.17 (m, 5H); ^{13}C NMR: 18.7, 21.0, 38.3, 81.9, 126.7, 129.6, 137.2, 137.8.

4.4.4. (*R*)-2-Nitro-1-(4-methoxyphenyl)propane 7d. Yield 45%; reaction time in hexane 24 h; ee = 99%. $[\alpha]_D^{28} = +43.7$ (*c* 1.02 $CHCl_3$). Anal. Calcd C, 61.49; H, 6.63; N, 7.01. Found: C, 61.53; H, 6.71; N, 7.17. ^{1}H NMR: 1.35 (d, $J = 6.8$ Hz, 3H), 3.54–3.64 (m, 1H), 3.79 (s, 3H), 4.45 (dd, $J = 12.0$; 8.4 Hz, 1H), 4.51 (dd, $J = 12.0$; 7.2 Hz, 1H), 6.85–6.89 (m, 2H), 7.13–7.17 (m, 2H); ^{13}C NMR: 18.9, 38.1, 55.4, 114.2, 82.0, 127.9, 132.7, 158.7.

4.5. General procedure for the isoxazoles 9a,b synthesis

To a stirred solution of di-*tert*-butyl-dicarbonate (1.44 mmol), ethyl propiolate (1.98 mmol) and dimethylaminopyridine (0.09 mmol) in acetonitrile (3.5 mL) at room temperature, the acetonitrile solution of (*R*)-2-aryl-1-nitropropane (0.60 mmol) in 2.5 mL of acetonitrile was slowly (over 2 h) added. The mixture was stirred for 48 h and then concentrated under reduced pressure. The crude product was purified by column chromatography (hexane–ethyl acetate 15:1) affording optically active isoxazole.

4.5.1. Ethyl 3-[(1*R*)-1-phenylethyl]isoxazole-5-carboxylate 9a. Yield 72%; ee = 98%. $[\alpha]_D^{28} = -36.6$ (*c* 0.63 $CHCl_3$). Anal. Calcd C, 68.56; H, 6.16; N, 5.71. Found: C, 68.42; H, 6.28; N, 5.96. ^{1}H NMR: 1.37 (t, $J = 7.2$ Hz, 3H), 1.70 (d, $J = 7.6$ Hz, 3H), 4.29 (q, $J = 7.2$ Hz, 1H), 4.38 (q, $J = 7.2$ Hz, 2H), 6.67 (s, 1H), 7.20–7.36 (m, 5H); ^{13}C NMR: 14.1, 20.0, 37.6, 62.1, 108.6, 127.1, 127.3, 128.8, 142.3, 156.8, 160.2, 168.0.

4.5.2. Ethyl 3-[(1*R*)-1-(4-chlorophenyl)ethyl]isoxazole-5-carboxylate 9b. Yield 64%; ee = 91%. $[\alpha]_D^{28} = -27.7$ (*c* 1.08 $CHCl_3$). Anal. Calcd C, 60.11; H, 5.04; N, 5.01; Cl, 12.67. Found: C, 60.35; H, 5.10; N, 5.16; Cl, 12.82. ^{1}H NMR: 1.37 (t, $J = 7.2$ Hz, 3H), 1.67 (d, $J = 7.2$ Hz, 3H), 4.26 (q, $J = 7.2$ Hz, 1H), 4.38 (q, $J = 7.2$ Hz, 2H), 6.65 (s, 1H), 7.17–7.31 (m, 4H); ^{13}C NMR: 14.1, 20.0, 37.0, 62.2, 108.4, 128.7, 128.9, 132.9, 140.8, 156.7, 160.4, 167.6.

4.6. General procedure of synthesis of 4,5-dihydroisoxazoles 10a–d

To a stirred solution of the appropriate (*R*)-2-aryl-1-nitropropane (1.5 mmol) and methyl vinyl ketone (1,5 mmol) in dry benzene (7.5 mL), triethylamine (65 μL) and benzene (1.0 mL) solution of phenyl isocyanate (3.8 mmol) were added dropwise at 40 °C. The mixture was stirred for 24 h and then the precipitate was filtered off. The filtrate was concentrated under reduced pressure and crude product was purified by column chromatography (hexane–ethyl acetate 5:1) affording the diastereomeric mixture of 4,5-dihydroisoxazoles.

4.6.1. 5-Acetyl-3-(1-phenylethyl)-4,5-dihydroisoxazole 10a. Yield 47%; Anal. Calcd C, 71.89; H, 6.77; N, 6.52. Found: C, 71.87; H, 6.96; N, 6.45. ^{1}H NMR: 1.54 (d, $J = 7.2$ Hz, 2.85H), 1.55 (d, $J = 7.2$ Hz, 3H), 2.25 (s, 2.85H), 2.26 (s, 3H), 2.87–3.04 (m, 3.90H), 3.76–3.86 (m, 1.95H), 4.74–3.82 (m, 1.95H), 7.19–7.36 (m, 9.75H); ^{13}C NMR: δ 18.5, 18.6, 26.1, 26.2, 37.9, 38.2, 38.9, 39.1, 83.5, 83.5, 127.1, 127.2, 127.3, 128.9, 140.9, 140.9, 161.6, 161.7, 207.1, 207.3.

4.6.2. 5-Acetyl-3-[1-(4-chlorophenyl)ethyl]-4,5-dihydroisoxazole 10b. Yield 55%; Anal. Calcd C, 62.11; H, 5.54; N, 5.66. Found: C, 62.03; H, 5.61; N, 5.56. ^{1}H NMR: 1.51 (d, $J = 6.8$ Hz, 2.70H), 1.52 (d, $J = 6.8$ Hz, 3H), 2.25 (s, 2.70H), 2.26 (s, 3H), 2.85–3.04 (m, 3.80H), 3.74–3.83 (m, 1.90H), 4.75–3.82 (m, 1.90H), 7.12–7.17 (m, 3.80H), 7.27–7.32 (m, 3.80H); ^{13}C NMR: 18.5, 18.6, 26.2, 26.3, 37.6, 37.8, 38.4, 38.6, 83.5, 128.5, 128.6, 128.9, 129.0, 161.2, 161.3, 207.1, 207.3.

4.6.3. 5-Acetyl-3-[1-(4-methylphenyl)ethyl]-4,5-dihydroisoxazole 10c. Yield 35%; Anal. Calcd C, 72.56; H, 7.46; N, 5.93. Found: C, 72.70; H, 7.41; N, 6.06. ^{1}H NMR: 1.52 (d, $J = 7.2$ Hz, 3H), 1.53 (d, $J = 7.2$ Hz, 2.40H), 2.25 (s, 3H), 2.26 (s, 2.40H), 2.32 (s, 5.40H), 2.85–3.05 (m, 3.60H), 3.74–3.81 (m, 1.80H), 4.73–3.80 (m, 1.80H), 7.08–7.15 (m, 7.20H); ^{13}C NMR: 18.5, 18.7, 20.9, 26.1, 26.2, 38.0, 38.2, 38.5, 38.7, 83.5, 83.5, 126.9, 127.0, 128.3, 128.8, 128.9, 129.5, 136.9, 136.9, 161.8, 161.9, 207.6, 207.7.

4.6.4. 5-Acetyl-3-[1-(4-methoxyphenyl)ethyl]-4,5-dihydroisoxazole 10d. Yield 42%; Anal. Calcd C, 68.05; H, 6.73; N, 5.78. Found: C, 68.00; H, 6.93; N, 5.66. ^{1}H NMR: 1.51 (d, $J = 7.2$ Hz, 2.25H), 1.52 (d, $J = 6.8$ Hz, 3H), 2.25 (s, 2.25H), 2.25 (s, 3H), 2.86–3.05 (m, 3.50H), 3.72–3.81 (m, 1.75H), 3.78 (s, 5.25H), 4.73–3.80 (m, 1.75H), 6.86–6.89 (m, 3.50H), 7.10–7.15 (m, 3.50H); ^{13}C NMR: 18.6, 18.8, 26.1, 26.2, 38.0, 38.1, 38.2, 38.3, 55.2, 83.5, 114.2, 128.1, 128.2, 132.8, 132.9, 158.7, 161.9, 162.0, 207.6, 207.7.

4.7. 2-Chloro-1-phenylethanol 12

Compound **11** was obtained by reduction of α-chloroacetophenone by the method described in the literature.[14]

4.8. Kinetic resolution of racemic 2-chloro-1-phenylethanol 12

To a di-*iso*-propyl ether solution (300 mL) of 2-chloro-1-phenylethanol **12** (2.00 g, 12.8 mmol) and vinyl acetate (11.8 mL, 0.128 mol), *Novozym 435*® (from *Candida antartica, lipase B*) (1.60 g) was added. The mixture was shaken at 30 °C and the conversion was monitored by GC. After 11 days the enzyme was filtrated off, and washed with di-*iso*-propyl ether. The solvent was evaporated under reduced pressure, and crude mixture was separated by column chromatography (hexane–ethyl acetate 7:1) yielding (*R*)-2-chloro-1-phenylethanol (*R*)-**12** and (*S*)-2-chloro-1-phenylethyl acetate (*S*)-**13**.

4.8.1. (*R*)-2-Chloro-1-phenylethanol (*R*)-12. Yield 31%; ee = 95%. $[\alpha]_D^{23} = -54.1$ (*c* 1.02 $CHCl_3$) ^{1}H NMR: 2.78 (s, 1H), 3.65 (dd, $J = 11.2$; 8.8 Hz, 1H), 3.74 (dd, $J = 11.2$; 3.6 Hz, 1H), 4.90 (dd, $J = 8.8$; 3.6 Hz, 1H), 7.32–7.41 (m, 5H).

4.8.2. (*S*)-2-Chloro-1-phenylethyl acetate (*S*)-13. Yield 50%, ee = 77%, ^{1}H NMR: 2.15 (s, 3H), 3.73 (dd, $J = 11.6$; 4.4 Hz, 1H), 3.80 (dd, $J = 11.6$; 8.0 Hz, 1H), 5.96 (dd, $J = 8.0$; 4.4 Hz, 1H), 7.34–7.40 (m, 5H).

4.9. (*R*)-1-Phenyl-2-(phenylthio)ethanol (*R*)-14

To a DMF (9.0 mL) solution of sodium hydroxide (0.170 g; 4.25 mmol), and thiophenol (0.42 mL; 4.10 mmol), a DMF (2.5 mL) solution of (*R*)-2-chloro-1-phenylethanol (*R*)-**12** (0.567 g; 3.62 mmol) was added. The mixture was stirred at room temperature for 3 h. Next, the flask contents were diluted with CH_2Cl_2 (15 mL), and acidified with 1 M HCl. The organic layer was separated, and aqueous layer extracted with CH_2Cl_2. The organic extracts were dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography (hexane–ethyl acetate 7:1) yielding (*R*)-1-phenyl-2-(phenylthio)ethanol (*R*)-**14** (0.715 g; 86% yield) as colourless oil, ee = 95%. ^{1}H NMR: 2.85 (s, 1H), 3.10 (dd, $J = 13.6$; 9.4 Hz, 1H), 3.33 (dd, $J = 13.6$; 3.6 Hz, 1H), 4.73 (dd, $J = 9.4$; 3.6 Hz, 1H), 7.24–7.44 (m, 10H).

4.10. (*R*)-1-Phenyl-2-(phenylsulfonyl)ethanol (*R*)-15

Compound (*R*)-**15** was obtained from (*R*)-1-phenyl-2-(phenylthio)ethanol (*R*)-**14** by oxidation with Oxone® according to the method described in the literature.[15] Yield 97%; mp 113–115 °C ^{1}H NMR: 3.35 (dd, $J = 14.4$; 2.0 Hz, 1H), 3.51 (dd, $J = 14.4$; 10.4 Hz, 1H), 3.67 (d, $J = 1.6$ Hz, 1H), 5.29 (m, 1H), 7.29–7.35 (m, 5H), 7.58–7.62 (m, 2H), 7.67–7.72 (m, 1H), 7.95–7.99 (m, 2H).

4.11. (*R*)-1-Phenyl-2-(phenylsulfonyl)ethyl acrylate (*R*)-16

To a CH_2Cl_2 (35.0 mL) solution of (*R*)-1-phenyl-2-(phenylsulfonyl)ethanol (*R*)-**15** (0.762 g; 2.90 mmol) and triethylamine (0.82 mL; 5.87 mmol), a CH_2Cl_2 (5.0 mL) solution of acryloyl chloride (0.24 mL; 2.95 mmol) was added. The mixture was stirred at room temperature for 1.5 h. Next 20 mL of water was added and after separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over magnesium sulfate. The solvent was then removed under reduced pressure. The crude product was purified by column chromatography (hexane–ethyl acetate 3:1) yielding (*R*)-1-phenyl-2-(phenylsulfonyl)ethyl acrylate (*R*)-**16** (0.506 g; 55% yield) ee = 94%. $[\alpha]_D^{24} = -39.5$ (*c* 1.09 $CHCl_3$). Anal. Calcd C, 64.54; H, 5.10; S, 10.14. Found: C, 64.60; H, 5.21; S, 10.19. ^{1}H NMR: 3.47 (dd, $J = 15.0$; 2.6 Hz, 1H), 3.88 (dd, $J = 15.0$; 9.8 Hz, 1H), 5.73 (dd, $J = 10.4$; 1.8 Hz, 1H), 5.81 (dd, $J = 16.8$; 10.4 Hz, 1H), 6.22 (dd, $J = 16.8$; 1.8 Hz, 1H), 6.28 (dd, $J = 9.8$; 2.6 Hz, 1H), 7.25–7.32 (m, 5H), 7.51–7.56 (m, 2H), 7.61–7.66 (m, 1H), 7.88–7.91 (m, 2H); ^{13}C NMR: 61.3, 70.3, 126.2, 127.4, 128.1, 128.9, 129.3, 131.7, 133.8, 137.6, 139.4, 164.2.

4.12. [1-Phenyl-2-(phenylsulfonyl)ethyl] 3-(1-phenylethyl)-4,5-dihydroisoxazole-5-carboxylate 17

To a stirred acetonitrile (4.0 mL) solution of di-*tert*-butyldicarbonate (0.174 g, 0.795 mmol), (*R*)-1-phenyl-2-(phenylsulfonyl)ethyl acrylate (*R*)-**16** (0.102 g, 0.321 mmol) and dimethylaminopyridine (0.006 g, 0.047 mmol), an acetonitrile (2.0 mL) solution of (*R*)-1-nitro-2-phenylpropane (0.052 g, 0.312 mmol) was added dropwise at room temperature within 3 h. The mixture was stirred at room temperature for 48 h and then evaporated to dryness under reduced pressure. The crude product was purified by column chromatography (hexane–ethyl acetate 3:1) yielding isoxazole **17** (0.077 g, 53% yield). Anal. Calcd C, 67.37; H, 5.44; N, 3.02; S, 6.92. Found: C, 67.45; H, 5.46; N, 2.93; S, 7.03. ^{1}H NMR: 1.51 (d, $J = 7.2$ Hz, 3.0H), 1.58 (d, $J = 7.2$ Hz, 1.62H), 2.96–3.01 (m, 1.08H), 2.94 (ddd, $J = 17.2$; 11.2, 0.4 Hz, 1H), 3.15 (ddd, $J = 17.2$; 6.0, 0.4 Hz, 1H), 3.39 (dd, $J = 15.0$; 2.8 Hz, 0.54H), 3.41 (dd, $J = 15.0$; 2.8 Hz, 1H), 3.72 (dd, $J = 15.0$; 10.0 Hz, 0.54H), 3.79–3.86 (m, 2H), 3.82 (q, $J = 7.2$ Hz, 0.54H), 4.73 (dd, $J = 11.2$; 6.0 Hz, 1H), 4.73 (dd, $J = 9.8$; 7.8 Hz, 0.54H), 6.25 (dd, $J = 10.0$; 2.8 Hz, 1H), 6.27 (dd, $J = 9.8$; 2.6 Hz, 0.54H), 7.14–7.32 (m, 10H), 7.19–7.35 (m, 5.4H), 7.53–7.68 (m, 3H), 7.55–7.71 (m, 1.62H), 7.86–7.97 (m, 2H), 7.87–7.99 (m, 1.08H). ^{13}C NMR: 18.72, 18.75, 38.63, 39.06, 39.14, 40.51, 60.95, 60.96, 70.32, 70.48, 76.83, 126.16, 126.18, 127.23, 127.26, 127.31, 128.12, 128.13, 128.83, 128.87, 128.88, 128.97, 128.98, 129.08, 129.09, 129.40, 129.45, 134.00, 134.06, 136.92, 136.96, 139.01, 139.06, 140.81, 141.11, 160.94, 161.23, 168.75, 168.76.

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References

1. (a) Kozikowski, A. P.; Chen, Y. Y.; Wang, B. C.; Xu, Z. B. *Tetrahedron* **1984**, *40*, 2345–2358; (b) Martin, S. F.; Colapret, J. A.; Dappen, M. S.; Dupre, B.; Murphy, C. J. *J. Org. Chem.* **1989**, *54*, 2209–2216; (c) Smith, A. L.; Pitsinos, E. N.; Hwang, C. K.; Mizuno, Y.; Saimoto, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7612–7624; (d) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410–6424; (e) Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Jo, H.; Kim, S. *J. Org. Chem.* **2002**, *67*, 764–771.
2. Caramella, P.; Grunanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley Interscience: New York, 1984; Vol. 1, p 291.
3. Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339–5342.
4. (a) Huisgen, R.; Mack, W. *Tetrahedron Lett.* **1961**, 583–586; (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988.
5. (a) Kametani, T.; Nagahara, T.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3048–3052; (b) Kozikowski, A. P.; Ghosh, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 5788–5789; (c) Houk, K. N.; Moses, S. R.; Wu, Y. D.; Rondan, N. G.; Jager, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880–3882; (d) Wade, P. A.; Singh, S. M.; Pillay, K. M. *Tetrahedron* **1984**, *40*, 601–611; (e) Curran, D. P.; Kim, B. H. *Synthesis* **1986**, 312–315; (f) Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137–2141; (g) Olsson, T.; Stern, K.; Sundell, S. *J. Org. Chem.* **1988**, *53*, 2468–2472; (h) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1988**, *44*, 4645–4652; (i) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555–3558; (j) Curran, D. P.; Jeong, K.-S.; Heffner, T. A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1989**, *111*, 9238–9240; (k) Brandi, A.; Cannavo', P.; Pietrusiewicz, K. M.; Zablocka, M.; Wieczorek, M. *J. Org. Chem.* **1989**, *54*, 3073–3077; (l) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585–4595; (m) Olsson, T.; Stern, K.; Wastman, G.; Sundell, S. *Tetrahedron* **1990**, *46*, 2473–2482; (n) Akiyama, T.; Okada, K.; Ozaki, S. *Tetrahedron Lett.* **1992**, *33*, 5763–5766; (o) Kim, Y. H.; Kim, S. H.; Park, D. H. *Tetrahedron Lett.* **1993**, *34*, 6063–6066; (p) Boa, A. N.; Dawkins, D. A.; Hergueta, A. R.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 953–960; (q) Yang, K.-S.; Lain, J.-C.; Lin, C.-H.; Chen, K. *Tetrahedron Lett.* **2000**, *41*, 1453–1456; (r) Tamai, T.; Asano, S.; Totani, K.; Takao, K.; Tadano, K. *Synlett* **2003**, 1865–1867; (s) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366–5367.
6. (a) Kozikowski, A. P.; Kitagawa, Y.; Springer, J. P. *J. Chem. Soc., Chem. Commun.* **1983**, 1460–1462; (b) Jones, R. H.; Robinson, G. C.; Thomas, E. J. *Tetrahedron* **1984**, *40*, 177–184; (c) Larsen, K. E.; Torssell, K. B. G. *Tetrahedron* **1984**, *40*, 2985–2988; (d) Kim, B. H.; Chung, Y. J.; Keum, G.; Kim, J.; Kim, K. *Tetrahedron Lett.* **1992**, *33*, 6811–6814; (e) Kudyba, I.; JóŸwik, J.; Romañski, J.; Raczko, J.; Jurczak, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2257–2262.
7. (a) Vogel, A. I. *Preparatyka Organiczna*; WNT: Warszawa, 1984, p 307; (b) Jun-ichi, T.; Akihiro, K.; Masaaki, T.; Sakae, U. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2169–2173.
8. Thomas, A. F.; Egger, J.-C. *Helv. Chim. Acta* **1981**, *64*, 2393–2396.
9. (a) Bordwell, F. G.; Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 3588–3598; (b) Bordwell, F. G.; Garbisch, E. W., Jr. *J. Org. Chem.* **1962**, *27*, 2322–2325.
10. Ohta, H.; Kobayashi, N.; Ozaki, K. *J. Org. Chem.* **1989**, *54*, 1802–1804.
11. Noltes, J. G. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 1076–1081.
12. Michejda, C. J.; Campbell, D. H. *J. Am. Chem. Soc.* **1979**, *101*, 7687–7693.
13. Marvel, C. S.; Dunphy, J. F. *J. Org. Chem.* **1960**, *25*, 2209–2210.
14. Hiratake, J.; Inagaki, M.; Nishioka, T.; Oda, J. *J. Org. Chem.* **1988**, *53*, 6130–6133.
15. Node, M.; Nishise, K.; Shigeta, Y.; Obata, K.; Shiraki, H.; Kunishige, H. *Tetrahedron* **1997**, *53*, 12883–12894.