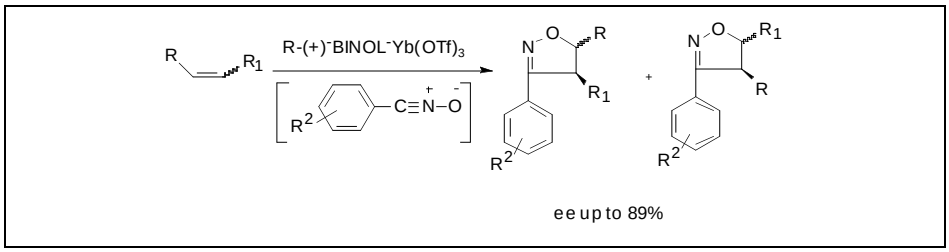
Enantioselective 1,3-Dipolar Cycloaddition Reactions Using Chiral Lanthanide Catalysts

W. Marek Gołębiewski* and Mirosław Gucma

Institute of Industrial Organic Chemistry, 03-236 Warsaw, Poland
golebiewski@ipo.waw.pl
Received May 21, 2008



Regio- and stereoselective 1,3-dipolar cycloaddition of nitrile oxides to internal 2-pentenols, α,β-unsaturated esters and amides catalyzed by *R*-(+) BINOL-lanthanide complexes affords corresponding 3-aryl-2-isoxazolines with enantioselectivities up to 89% ee.

J. Heterocyclic Chem., **45**, 1687 (2008).

INTRODUCTION

We have just reported application of chiral lanthanide - (-)-sparteine complexes as catalysts in 1,3-dipolar cycloaddition of nitrile oxides to unsaturated alcohols, where enantioselectivities up to 68% were obtained. [1] This work is an extention of the previous research to a different catalytic system and other dipolarophiles resulting in a higher enantioselectivity of the reaction.

1,3-Dipolar cycloaddition of nitrile oxides to alkenes is the most convenient method of preparation of useful building blocks - 2-isoxazolines [2]. They can be easily reduced to several synthetically important chain compounds such as β-hydroxy ketones, β-hydroxy esters, α,β-unsaturated carbonyl compounds or iminoketones [3]. Reactions of monosubstituted and 1,1-disubstituted alkenes are very regioselective favoring strongly 5-substituted 2-isoxazolines. On the other hand 1,2-disubstituted olefins usually afford mixtures of regio- and stereoisomers. Therefore synthetic application of 1,3-dipolar cycloaddition remained for a long time rather limited.

Two methods have been used to solve these problems. One approach was an application of optically active reagents, much more often of dipolarophiles than dipoles [4].

One variant of this method was the use of chiral auxiliaries temporarily linked usually by an ester or amide bond to the dipolarophiles. Literature examples of ester type groups were camphor [5] and menthol derivatives [6]. As chiral amide derivatives were applied *inter alia* Rebeck benzoxazole derivative [7], oxazoline derivatives [8], oxazolidin-2-ones [9], imidazolidin-2-ones [10], derivatives of proline benzyl ester [11], and as the most effective Oppolzer's camphorsultam [12] and its borane derivative, which allowed to achieve high regio- and stereoselectivity [13].

The second more promising approach relied on chiral metal reagents and catalysts. Shortage of reports on metal assisted 1,3-dipolar cycloadditions of nitrile oxides is due to interference of catalyst with generation of these dipoles and formation of unreactive complexes [14]. The other difficulty is ascribed to relatively low-lying HOMO energies of nitrile oxides as compared to nitrones [15]. Ukaji and Inomata performed first asymmetric metal-catalyzed 1,3-dipolar cycloaddition reaction of nitrile oxides to γ-substituted allylic alcohols with diethylzinc as a catalyst, and (*R,R*)-diisopropyl tartrate as the chiral auxiliary [16]. Later they used *N*-sulfonylated (*S,S*)-2,3-diaminosuccinate derivative as a chiral information [17]. Sibi modified a dipolarophile - crotonamide by attaching an achiral template of pyrazolidinone type and used a bulky chiral Lewis acid obtained from magnesium iodide and bisoxazoline derivative achieving excellent regio- and enantioselectivity [18a]. This approach was extended to the reaction with α,β-disubstituted acryimides [18b]. Faita and Quadrelli applied a polymer supported chiral oxazolidin-2-one- magnesium catalyst [19].

Lanthanide catalysts are also an attractive solution [20]. Large lanthanide complexes, particularly triflate derivatives, are mild Lewis acids [21]. In contrast to many other Lewis acids lanthanide triflates are not deactivated by basic nitrogen-containing compounds and their stability in the presence of water enables repeated use even in an organic-aqueous environment [22]. Lanthanides were successfully applied in the asymmetric 1,3-dipolar cycloaddition of nitrones and alkenes by two groups. Jørgensen *et al.* applied chiral complex of ytterbium triflate with 2,6-bis[4-(*S*)-isopropyl-2-oxazolidin-2-yl]pyridine (PyBOX) in cycloaddition to

N-alkenoyloxazolidinones with enantioselectivities of up to 73% [23]. Kobayashi *et al.* used a heterochiral catalyst comprising ytterbium triflate, (*S*)-binaphthol (*S*-BINOL) and chiral amine *N*-methyl-bis[(*R*)-1-phenylethyl]amine ((*R*)-MNEA) achieving enantioselectivities of up to 96% [24]. Yamamoto *et al*. have just published asymmetric 1,3-dipolar cycloaddition of benzonitrile oxides to acrylamides bearing chiral auxiliary of oxazolidinone and imidazolidinone type and a chiral complex comprising magnesium salt or ytterbium triflate as well as PyBOX ligand in equimolar amounts [25]. The best enantioselectivity was achieved at low temperature of -78 °C with magnesium bromide/ PyBOX system. Unexpectedly in some cases higher enantioselectivities were observed at room temperatures than at 0 °C.

Control of regio- and enantioselectivity of nitrile oxides 1,3-dipolar cycloaddition reaction is more difficult to for steric and quantum-chemical reasons [26, 15], than is the case for nitrones. Steric interaction between nitrile oxide and dipolarophile is relatively small, since N atom is unsubstituted and C atom of the dipole bears only a single substituent, while in nitrones N atom is substituted and C atom can be attached to two substituents. This situation makes planning of new chiral auxiliaries and catalysts more challenging.

RESULTS AND DISCUSSION

In continuation of our efforts to improve regioselectivity and enantioselectivity of the cycloaddition reaction we present the results of the reaction of a series of nitrile oxides with a set of dipolarophiles in the presence of lanthanide- BINOL system as a catalyst. BINOL is a versatile chiral reagent for which application in synthesis has been recently reviewed [27]. First we studied a reaction of aryl nitrile oxides with 2-penten-1-ols using racemic BINOL and different lanthanide triflates, solvents, and bases to generate nitrile oxides from the corresponding hydroximinoyl chlorides. A preferred way to obtain the dipole was passing a hydroximinoyl chloride solution through a column of Amberlyst 21 [18]. From the several tested catalyst systems one formed from BINOL and anhydrous ytterbium triflate was most promising as far as regioselectivity and yield of the reaction was concerned in comparison to praseodymium, scandium, and ytterbium triflate hydrate, similarly as in experiments with sparteine. In contrast, however, to our previous work [1] the best results were obtained with small amounts of molar 10-20% of the catalyst, as compared to equimolar amounts required by sparteine-lanthanide system to achieve satisfactory yield and selectivity. An increase in the catalyst proportion resulted in a better yield and regioselectivity of the reaction (Table, 1 entry 1 and 4). In case of sparteine-mediated reaction a reversal of regioselectivity was observed, when catalyst amount was increased twice [1].

The effect of diethyl ether and dichloromethane on regiochemistry was most pronounced as compared to the other solvents, such as acetonitrile, toluene or DMF, and the regioisomer-4 was favored in both of the components, solvents. An exception was the reaction run in dichloromethane, where regioisomer-5 was favored.

Scheme 1

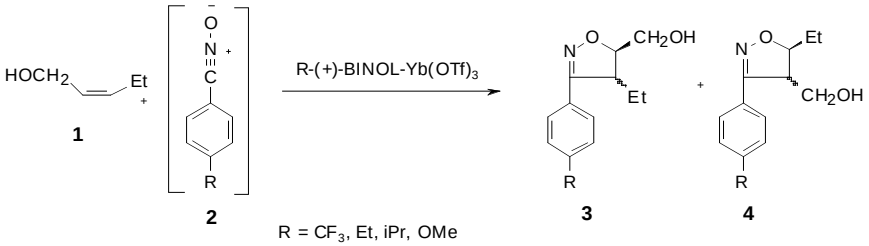


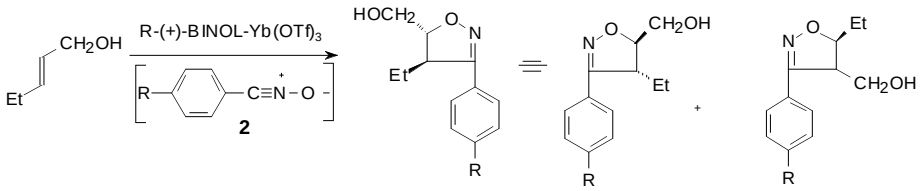
Table 1

Reactions with BINOL-(R)-Yb(OTf)$_3$ catalyst and different dipoles and 2-penten-1-ols.

Entry	**1**	R	Solvent	Cat.	Yield %	**3:4** ratio	**3** ee %	**4** ee %
1[a]	*Z*	CF_3	Et_2O	10%	41	1:1.9	60	18
2	*Z*	CF_3	Et_2O	10%	43	1:1.4	30	18
3	*Z*	CF_3	CH_2Cl_2	10%	47	1:2	28	16
4[a]	*Z*	CF_3	Et_2O	20%	64	1:3	45	68
5	*E*	CF_3	Et_2O	10%	68	1.4:1	70	60
6	*Z*	*i*-Pr	Et_2O	10%	61	1:2.9	48	71
7	*E*	*i*-Pr	CH_2Cl_2	-	27	1.7:1	-	-
8[a]	*Z*	OMe	Et_2O	10%	49	0:100	-	73

[a] Dipolarophile was added after dipole.

Scheme 2



Reactions carried out with sparteine-triflate catalyst in ether were more regioselective than those in dichloromethane, though yields were lower [1].

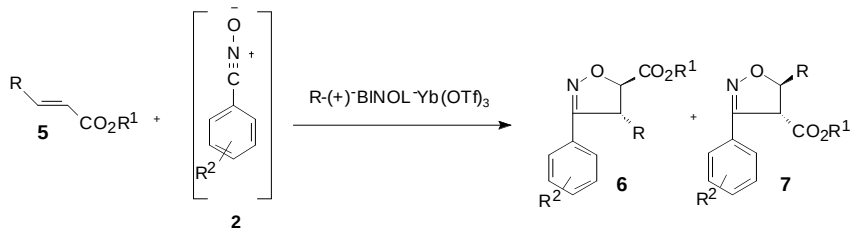
Reaction of aryl nitryl oxides with *Z*- and *E*-2-penten-1-ol in the presence of chiral *R*-(+) BINOL-ytterbium triflate complex was next examined (Scheme 1, Table 1). The degree of chiral induction depended on addition order of the components, on dipole substitution pattern, and on dipolarophile configuration. It was higher when dipolarophile was added after the dipole (entries 1, 4, 8), similarly as in experiments mediated by sparteine complex. Electron-donating substituents in the dipole facilitated chirality transfer from both the catalytic systems. Regioisomer-4 was favored for *Z*-pentenol and in reaction of 4-methoxybenzonitrile was the only detected form showing the best enantioselectivity with ee of 73% (reaction 8). In case of *E*-2-penten-1-ol (entries 5 and 7) regioisomer-5 was favored and *E*-2-pentenol showed higher ee than *Z*-counterpart.

The idea of metal catalyst application is based on the preferential coordination of one partner of the reaction, which results in lowering its Frontier Molecular Orbitals (FMOs). As a consequence a relevant HOMO-LUMO energy gap decreases, overlap of FMOs is enhanced and the catalyzed reaction is accelerated. If both reaction partners were coordinated resultant lowering of all FMOs would not be so unequivocal for acceleration of the cycloaddition, though Kanemasa reported calculations on interaction of magnesium alkoxide with allyl alcohol and formonitrile oxide, where FMOs of the dipole were lowered, and those of the dipolarophile were raised [14]. Reactions of the alkenes with electron-donating substituents and moderately electron-withdrawing substituents (ester group) are controlled by $LUMO_{dipol}$ – $HOMO_{alkene}$ interaction since $LUMO_{alkene}$ – $HOMO_{dipol}$ energy gap is higher [28]. This corresponds to a preferred coordination of the nitrile oxide to ytterbium, as witnessed by our observation, that regioselectivities were higher, when dipole was added before dipolarophile to the catalyst. Results of the reaction for *E*-2-pentenol (Table 1, entry 5) could be rationalized by a proposed Scheme 2, where *E*-pentenol is hydrogen-bonded to the BiNOL OH group. Direction of the asymmetric induction follows from the geometry of a transient, presumably, octahedral complex of ytterbium triflate, where the *si*-face of pentenols is shielded by hydrogen-bonded solvent molecule (diethyl ether) – axially twisted BINOL moiety. As a consequence an attack of nitrile oxide occurs from the pentenols *re*-face. The absolute configuration of 4-ethyl-5-hydroxymethyl-3-(4-trifluoromethyl)phenyl-2-isoxazoline (Table 1, entry 5) was proposed to be 4*R*,5*R* by comparison of specific optical rotation with that of an analogous compound [16a].

We examined next application of the chiral lanthanide catalyst in the enantioselective cycloaddition reaction of aryl nitrile oxides to electron-deficient dipolarophiles, unsaturated esters (Scheme 3, Table 2). It was gratifying to find unexpectedly high ee of 89% for regioisomer 4 (Table 2, entry 5) in a reaction with 10% load of the catalyst.

The examined esters included 2-pentenecarboxylates, crotonates, and methyl acrylate. Regioselectivity of the reaction depended on steric demands of the ester function

Scheme 3



R = Et, Me, H; R^1 = Et, Me, tBu; R^2 = CF_3, Cl_n, iPr, OMe

Table 2

Reactions with BINOL-(R)-Yb(OTf)$_3$ catalyst and different dipoles and esters

Entry	R	R^1	R^2	Cat.	Yield %	**6:7** ratio	**6** ee %	**7** ee %
1	Et	Me	4-CF_3	-	70	1:2.1	-	-
2	Me	Me	2,3,6-Cl_3	-	64	1:3	-	-
3	Et	Me	4-CF_3	Yb(OTf)$_3$ [a]	63	1:1.9	-	-
4	Et	Me	4-CF_3	10%	49	1:2.5	6	85
5	Me	Me	4-CF_3	10%	68	1.6:1	25	89
6	H	Et	4-CF_3	10%	92	100:0	34	-
7	Et	t-Bu	4-CF_3	10%	51	1:100	-	65
8	Me	Me	2,4-Cl_2	10%	68	1:2	20	77
9	Me	Me	4-i-Pr	10%	28	1:32	-	45
10	Me	Me	4-OMe	10%	91	1:14	56	56

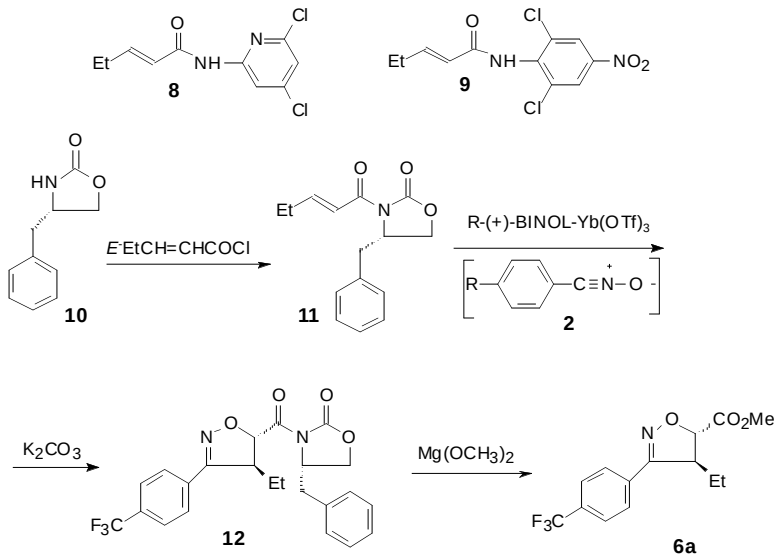
[a] Without BINOL.

(was excellent in case of *t*-butyl ester) and character of the dipole substituents. Reactions with nitrile oxides bearing electron-withdrawing substituents were less regioselective than reactions with dipoles bearing electron-donating substituents (Table 2, entries 9-10). In all cases, apart from acrylate and methyl crotonate (entries 5 and 6), regioisomer-4 was favored.

Degree of the chiral induction was related to structure of the reagents and as opposed to the reactions of pentenols dipoles bearing electron-withdrawing substituents showed higher ee than dipoles with electron-donating groups (entries 9-10). High level of enantioselectivity of the reaction is more difficult to explain than in the reactions of pentenols. In the transition state nitrile oxide is probably coordinated to the axially chiral lanthanide catalyst and the dipole attacks the *re*-face of the dipolarophile, similarly as in case of pentenols affording presumably (4*R*,5*S*)-5-ethyl(methyl)-4-carboxylates.

The effect of the catalyst was most pronounced in case of amides, which were the next examined dipolarophiles. Cycloaddition of arylbenzonitrile to electron-deficient amides such as aromatic amines derivatives **8** and **9** as well as (*S*)-4-benzyl-3-((*E*)-pent-2-enoyl)-oxazolidin-2-one (**11**) (Scheme 4) was next examined. Reaction carried out in the presence of triethyl amine was not efficient (yield below 10%). Much more success was achieved in the process performed in the presence of the chiral catalytic lanthanide - (*R*)-BINOL complex with compound **11**. Dipolarophile with a chiral auxiliary group was prepared starting from the commercial L-phenyl-alanine following a described protocol [29,30]. The aminoacid was esterified with methanolic HCl, then crude iminoester was acylated with ethyl chloroformate and the ester group was reduced with calcium borohydride formed *in situ* from sodium borohydride and calcium chloride. The obtained alcohol was cyclised in the presence of

Scheme 4



Amides as dipolarophiles in cycloaddition reaction.

potassium carbonate to oxazolidinone-2 analog **10**, which was then acylated with (*E*)-2-pentenecarboxylic acid chloride after conversion to the corresponding lithium imide to afford *N*-pentenoyl derivative **11** [31]. The suggested transition state of the cycloaddition reaction with nitrile oxide involves coordination of the bidentate ligand, oxazolidinone-2, which is more favored, than coordination of the dipole, as established for reactions with participation of nitrones [32]. This coordination is accompanied by substitution of one triflate group, which occurs readily due to kinetic lability of lanthanide-X bonds and easy exchange of ligands [20]. Because *re*-face approach of the dipole is hindered by a proximate chiral α-benzyl group preferential attack of nitrile oxide follows from the more exposed upper *si*-face of the dipolarophile olefinic bond resulting in formation of 5-isoxazolidine amide **12** with 4*R*,5*R*, *S*-benzyl configuration of the major diastereoisomer. The chiral auxiliary was removed with methanolic magnesium methoxide affording chiral isoxazolidine ester with ee 77% [33].

EXPERIMENTAL

Reagent grade chemicals were used without further purification unless otherwise noted. Spectra were obtained as follows: IR spectra on JASCO FTIR-420 spectrometer, ^{1}H NMR spectra on Varian 500 UNITY plus-500 and Varian 200 UNITY plus 200 spectrometers in deuterated chloroform using TMS as internal standard, EI mass spectra on AMD M-40 spectrometer. Elemental analyses were performed at Microanalysis Laboratory of Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw. Flash-chromatography was carried out using silica gel S 230-400 mesh (Merck).

Hydroximinoyl acid chlorides were prepared from the corresponding aryl aldehyde oximes and NCS in DMF [15]. The corresponding nitrile oxides were generated *in situ* by dehydrohalogenation with triethylamine or on Amberlyst A-21 column [7].

[4/5-Ethyl-3-aryl)-4,5-dihydroisoxazol-5/4-yl]methanols **(3/4a,b,c** Table 1, entry 1, 6, 8**)** and methyl 3-(4-trifluoromethylphenyl)-4-methyl-4,5-dihydroisoxazole-5-carboxylate (**6b**) and its regioisomer (**7b**) (Table 2, entry 2) have been described before [1].

General procedure for the cycloaddition reactions. A mixture of (*R*)-BINOL (0.10 mmol), $Yb(OTf)_3$ (0.10 mmol) in dry dichloromethane was stirred at r.t. for 30 min. Dipolarophile (1 mmol) was added drop-wise followed by a solution of dipole in the same solvent generated by passing a hydroximinoyl chloride solution through a column of Amberlyst 21 over 20-30 min. The solution was stirred at r. t. for *ca*. 19 h, and water was added to quench the reaction followed by a usual work-up. The crude product was purified by flash column chromatography on silica gel and the enantiomeric excess of separated regioisomers was determined by HPLC analysis (Astec Cyclobond I 2000 RN).

Methyl 3-(4-trifluoromethylphenyl)-4-ethyl-4,5-dihydroisoxazole-5-carboxylate (**6a**) and **methyl 3-(4-trifluoromethylphenyl)-5-ethyl-4,5-dihydroisoxazole-4-carboxylate** (**7a**). These compounds were obtained as colorless oils. Regioisomer-5: IR (neat) 3410, 2960, 1760, 1618, 1410, 1329, 1240, 1211, 1167, 1124, 1071, 1027, 893, 850, 626 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz δ 7.81 (d, J = 8.6 Hz, 2 H, H-5', H-3'), 7.66 (d, J = 8.6 Hz, 2 H, H-2', H-6'), 4.94 (d, J = 4.1 Hz, 1 H, H-5), 3.94 (quintuplet, J = 4.1 Hz, 1 H, H-4), 3.82 (s, 3 H, CH_3O), 1.77 (m, J = 7.3 Hz, 2 H), 1.00 (t, J = 7.3 Hz, 3 H). *Anal*. Calcd. for $C_{14}H_{14}F_3NO_3$: C, 55.82, H, 4.68. Found: C, 55.73, H, 4.69. Regioisomer-4: IR (neat) 3430, 2969, 1744, 1620, 1440, 1412, 1325, 1169, 1128, 1071, 1020, 930, 845, 600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.82 (d, J = 8.6 Hz, 2 H, H-3', H-5'), 7.68 (d, J = 8.6 Hz, 2 H, H-2', H-6'), 4.96 (q, J = 6.3 Hz, 1 H, H-5), 4.15 (d, J = 6.3 Hz, 1 H, H-4), 3.73 (s, 3 H, CH_3O), 1.79 (m, 2 H), 1.04 (t, J = 7.3 Hz, 3 H). *Anal*. Calcd. for $C_{14}H_{14}F_3NO_3$: C, 55.82; H, 4.68. Found: C, 55.74; H, 4.40.

Methyl 3-(2,3,6-trichlorophenyl)-4-methyl-4,5-dihydroisoxazole-5-carboxylate (**6c**) **and methyl 3-(2,3,6-trichlorophenyl)-5-methyl-4,5-dihydroisoxazole-4-carboxylate** (**7c**). Isomer–5: IR (neat) 2955, 1746, 1570, 1437, 1393, 1300, 1210, 1179, 1100, 1021, 890, 817 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.48 (d, J = 8.7 Hz, 1 H, H-4'), 7.33 (d, J = 8.7 Hz, 1 H, H-5'), 4.84 (d, J = 6.6 Hz, 1 H, H–5), 4.15 (d, J = 6.6 Hz, 1 H, H-4), 3.86 (s, 3 H, CH_3O), 1.33 (d, J = 6.6 Hz, 3 H). *Anal*. Calcd. for $C_{13}H_{12}Cl_3NO_3$: C, 46.39; H, 3.59. Found: C, 46.10; H, 3.44. Isomer–4: IR (neat) 2940, 1743, 1560, 1440, 1400, 1210, 1190, 110, 1022, 920, 820, 780, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.49 (d, J = 8.7 Hz, 1 H, H-4'), 7.34 (d, J = 8.7 Hz, 1 H, H-5'), 5.36 (quintuplet J = 6.7 Hz, 1 H, H-5), 4,15 (d, J = 6.7 Hz, 1 H, H-4), 3.64 (s, 3 H, CH_3O), 1.55 (d, J = 6.7 Hz, 3 H). *Anal*. Calcd. for $C_{13}H_{12}Cl_3NO_3$: C, 46.39; H, 3.59. Found: C, 46.22; H, 3.51.

Ethyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole 5-carboxylate (7d) [35]. This compound was obtained as an oil; IR (neat) 3040, 2998, 2840, 1741, 1331, 1224, 1164, 841 cm^{-1}; ^{1}H nmr ($CDCl_3$, 200 MHz): δ 7.79 (d, J = 8.5 Hz, 2H, H-3', H-5'), 7.67 (d, J = 8.5 Hz, 2H, H-2', H-6'), 5.22 (dd, J = 11.0; 8.5 Hz, 1H, H-5), 4.28 (q, J = 7.0 Hz, 2H, CH_2), 3.67 (d, J = 8.5 Hz, 1H, H-4a), 3.65 (d, J = 11.0 Hz, 1H, H-4b), 1.33 (t, J = 7.0 Hz, 3H, CH_3).

***tert*-Butyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-ethyl-4-carboxylate (7e)**. This compound was obtained as an oil; IR (neat) 3204, 2904, 1740, 1675, 1600, 1520, 1470, 1326, 1225, 1180, 1131, 1067, 1016, 860, 760, 700, 600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.97 (d, J = 8.4 Hz, 1 H, H-3', H-5'), 7.79 (d, J = 8.4 Hz, 1 H, H-2', H-6'), 5.13 (m, 1 H, H-5), 4.41 (d, J = 6.4 Hz, 1 H, H-4), 2.17 (s, 9 H, tBu), 1.83 (m, 2 H), 1,12 (m, 3 H). *Anal*. Calcd. for $C_{17}H_{20}F_3NO_3$: C, 59.47; H, 5.87. Found: C, 59.27; H, 6.12.

Methyl 3-(2,4-dichlorophenyl)-4-methyl-4,5-dihydroisoxazole-5-carboxylate (**6f** and **methyl 3-(2,4-dichlorophenyl)-5-methyl-4,5-dihydroisoxazole-4-carboxylate (7f)**. These compounds were obtained as oils. Isomer–5: IR (neat) 3050, 2930, 1740, 1619, 1597, 1517, 1469, 1440, 1385, 1350, 1320, 1270, 1220, 1184, 925, 860, 824, 749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.40 (m, 3 H, H-6', H-5', H-3'), 4.80 (d, J = 7.1 Hz, 1 H, H-5), 4.02 (quintuplet, J = 7.1 Hz, H-4), 3.85 (s, 3 H, CH_3O), 1.23 (d, J = 7.1 Hz, 3 H). *Anal*. Calcd. for $C_{13}H_{13}Cl_2NO_3$: C, 51.68; H, 4.34. Found: C, 51.96; H, 4.47. Isomer–4: IR (neat) 2950, 1743, 1620, 1587, 1480, 1440, 1380, 1203, 1103, 1014, 900, 822, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.54 (d, J = 8.4 Hz, 1 H, H-6'), 7.44 (d, J = 2.2 Hz, 1 H, H-3'), 7.30 (dd, J = 8.4; 2.2 Hz, 1 H, H-5'), 5.08 (quintuplet, J = 6.8 Hz, 1 H, H-5), 4.46 (d, J = 6.8 Hz, H-4), 3.65 (s, 3 H, CH_3O), 1.55 (d, J = 6.8

Hz, 3 H). *Anal*. Calcd. for $C_{13}H_{13}Cl_2NO_3$: C, 51.68; H, 4.34. Found: C, 51.87; H, 4.22.

Methyl 3-(4-isopropylphenyl)-4,5-dihydroisoxazole-4-methyl-5-carboxylate (6g) and methyl 3-(4-isopropylphenyl)-4,5-dihydroisoxazole-5-methyl-4-carboxylate (7g). These compounds were obtained as oils. Isomer–5: IR (KBr) 2970, 1730, 1617, 1600, 1517, 1466, 1380, 1270, 1214, 1148, 815, 747 cm $^{-1}$; Isomer–4: IR (KBr) 2961, 1741, 1611, 1514, 1435, 1420, 1340, 1310, 1252, 1125, 1100, 1023, 923, 838, 575 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.63 (d, J = 8.5 Hz, 2 H, H–2', H–6'), 7.25 (d, J = 8.5 Hz, 2 H, H–5', H–3'), 5.07 (quintuplet, J = 6.2 Hz, 1 H, H–5), 4.07 (d, J = 6.2 Hz, 1 H, H–4), 3.72 (s, 3 H, CH_3OCO), 2.94 (septuplet, J = 7.0 Hz, 1 H, $CH(CH_3)_2$), 1.44 (d, J = 6.2 Hz, 3 H), 1.25 (d, J =7.0 Hz, 6 H). *Anal*. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94, H, 7.33. Found: C, 69.19; H, 7.56.

Methyl 3-(4-methoxyphenyl)-4-methyl-4,5-dihydroisoxazole-5-carboxylate (**6h**) and **methyl 3-(4-methoxyphenyl)-5-methyl-4,5-dihydroisoxazole-4-carboxylate** (**7h**). These compounds were obtained as oils. Isomer–5: IR (neat) 2955, 1740, 1606, 1516, 1457, 1350, 1300, 1258, 1210, 1180, 1070, 1019, 880, 837, 700 cm $^{-1}$; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.63 (d, J = 9.1 Hz, 1 H, H- 5', H-3'), 6.92 (d, J = 9.1 Hz, 2 H, H-6', H-2'), 4.77 (d, J = 3.8 Hz, 1 H, H-5), 4.04 (m, 1 H, H-4), 3.93 (s, 3 H, CH_3OCO), 3.80 (s, 3 H, CH_3OPh), 1.42 (d, J = 6.5 Hz, 3 H). Isomer–4: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.64 (d, J = 6.8 Hz, 2 H, H-2', H-6'), 6.91 (d, J = 6.8 Hz, 2 H, H-5', H-3'), 5.06 (quintuplet, J = 6.2 Hz, 1 H, H-5), 4.06 (d, J = 6.2 Hz, 1 H, H-4), 3.83 (s, 3 H, CH_3OCO), 3.71 (s, 3 H, CH_3OPh), 1.45 (d, J = 6.2 Hz, 3 H). *Anal*. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64, H, 6.07. Found: C, 62.89, H, 6.16.

(*E*)-Pent-2-enoic acid (4,6-dichloropyrimidin-2-yl)-amide (8). This compound was obtained as an oil. IR (neat) 3395, 3220, 3100, 2960, 1694, 1644, 1542, 1500, 1410, 1300, 1250, 1210, 1164, 1103, 823, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1 H, NH), 7.23 (dt, J = 15.4; 6.1 Hz, 1 H, CH_2**CH**=C), 7.05 (s, 1 H, H-5'), 6.61 (dt, J = 15.4, 1.7 Hz, 1 H, OC**H**=C), 2.30 (qd, J = 7.4; 1.8 Hz, 1 H), 2.33 (qd, J = 6.8; 1.8 Hz, 1 H), 1.14 (d, J = 6.8 Hz, 1 H), 1.10 (d, J = 7.4 Hz, 2 H).). *Anal*. Calcd. for $C_9H_9Cl_2N_3O$: C, 68.94, H, 7.33. Found: C, 69.19; H, 7.56.

(*E*)-Pent-2-enoic acid (2,6-dichloro-4-nitrophenyl)-amide (**9**). This compound was obtained as an oil. IR (KBr) 3233, 3100, 2990, 1672, 1649, 1506, 1390, 1346, 1190, 812, 740 cm $^{-1}$; ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 2 H, H–3', H-5'), 7.19 (s, 1 H, NH), 7.15 (dt, J = 15.3; 6.2 Hz, 1 H, CH_2*CH*=C), 6.04 (dt, J = 15.3, 1.7 Hz, 1 H, OC*CH*=C), 2.32 (qd, J = 6.7; 1.7 Hz, 1 H), 2.30 (qd, J = 7.4 Hz, 1 H), 1.14 (t, J = 6.7 Hz, 1 H), 1.10 (t, J = 7.4 Hz, 2 H). *Anal*. Calcd. for $C_{11}H_{10}Cl_2N_2O_3$: C, 47.70, H, 3.49. Found: C, 47.53; H, 3.38.

(*S*)-Benzyl-3-(*E*)-pent-2-enoyl)-oxazolidin-2-one (11) [31b]. This compound was prepared by the published procedure, (86 %), $[\alpha]_D^{22}$ = + 126.6 (c 1.2, acetone); IR (neat) 3040, 2967, 2890, 1779, 1685, 1638, 1450, 1355, 1300, 1212, 1103, 1050, 1000, 860, 800, 760, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5 H), 7.29 (m, 1 H, CH z C=*CH*CO), 4.68 (m, 1 H, H-4, N*CH*$(CH_2)_2$), 4.19 (d, J = 7.8 Hz, 1 H, H- 5a, O*CH*$_2$CH), 4.18 (d, J = 4.0 Hz, 1 H, H–5b), 3.34 (dd, J = 13.4; 3.2 Hz, 1 H, H-6a, Ar*CH*$_2$CH), 2.79 (dd, J = 13.4; 9.6 Hz, 1 H, H-6*b*, Ar*CH*$_2$CH), 2.33 (m, 2 H, CH*CH*$_2$$CH_3$), 1.13 (t, J = 7.4 Hz, 3 H); GC-MS m/z (%) 259 (M^+, 35), 230 (M^+ - Et), 91 ($C_6H_5CH_2$, 20), 83 (CH_3CH_2CH=CH-CO, 100), 55 (C_2H_5CH=CH, 50).

Cycloaddition reaction of the amides. 4-Benzyl-3-[4-ethyl-3-(4-trifluoromethyl-phenyl)-4,5-dihydroisoxazole-5-carbonyl]-oxazolidin-2-one (12) and 4-benzyl-3-[5-ethyl-3-(4-trifluoromethyl-phenyl)-4,5-dihydro-isoxazole-4-carbonyl]-oxazolidin-2-one (13). The reaction was carried out in diethyl ether for 8 days and afforded product in 55% yield as a mixture of oily regioisomers 5/4 in 3:1 ratio. Regioisomer–5: $[\alpha]_D$= + 113,5 (c 0.7, acetone); IR (neat) 2931, 1783, 1704, 1392, 1327, 1220, 1170, 1125, 1069, 1020, 900, 846, 704 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8.3 Hz, 2 H, H-6', H-2'), 7.68 (d, J = 8.3 Hz, 2 H, H-5', H-3'), 7.26 (m, 5 H), 5.98 (dd, J = 10.5; 3.3 Hz, 1 H, H-5), 4.68 (m, 1 H, N*CH*$(CH_2)_2$), 4.31 (m, 2 H, OCH_2), 4.00 (m, 1 H, H-4), 3.31 (m, 1 H, H –12*b*, Ar*CH*$_2$), 2.84 (m, 1 H, H-12*a*, Ar*CH*$_2$), 1.88 (m 2 H), 0.94 (t, J = 7,5 Hz, 3 H); EIMS m/z (%) 446 (M^+, 5), 417 (M^+ -Et), 242 ($CF_3C_6H_4CNOCHCHC_2H_5$, 100), 214 ($CF_3C_6H_4CNOCHCH$, 50). *Anal*. Calcd. for $C_{24}H_{26}N_2O_4$: C, 61.88; H, 4.74. Found: C, 61.61; H, 4.98. Regioisomer-4: $[\alpha]_D$= + 25.4 (c 0.5, acetone); IR (neat) 3040, 2960, 1779, 1683, 1616, 1598, 1510, 1471, 1440, 1382, 1321, 1278, 1250, 1220, 1178, 1150, 1125, 980, 860, 827, 751, 700, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.99 (d, J = 8.7 Hz, 2 H, H-6', H-2'), 7.65 (d, J = 8.7 Hz, 2 H, H-5', H-3'), 7.28 (m, 5 H), 5.42 (d, J = 4.2 Hz, 1 H, H-4), 4.71 (m, 2 H, H-5, H-10), 4.32 (dd, J = 6.8; 4.6 Hz, 1 H, H-6a -OCH_2), 4.19 (dd, J = 6.8; 3.6 Hz, 1 H, H-6b OCH_2), 3.30 (dd, J = 13.3; 3.0 Hz, 1 H, H-12a Ar*CH*$_2$), 2.85 (dd, J = 13.3; 9.2 Hz, 1 H, H-12b Ar*CH*$_2$), 1.86 (q, J = 7.4 Hz, 2 H), 1.05 (t, J = 7.4 Hz, 3 H). *Anal*. Calcd. for $C_{24}H_{26}N_2O_4$: C, 61.88; H, 4.74. Found: C, 61.72; H, 4.93.

Removal of chiral auxiliary. Methyl 3-(4-trifluoromethyl-phenyl)-4-ethyl-4,5-dihydroisoxazole-5-carboxylate (**6a**) [33]. Methanolic 6% solution of magnesium methoxide (0.1 mL, 0.07 mmol) was added to a solution of amide **12** (0.012 g, 0.027 mmol) in methanol (1.5 mL). The mixture was stirred for 30 min. at r.t., water was added and product was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic extracts were washed with brine, dried and purified by flash-chromatography. Yield 7.4 mg (91%), $[\alpha]_D^{25}$= + 127.0 (c 0.5, acetone), ee 77%.

Acknowledgements. This work was supported in part by the Polish Ministry of Science and Higher Education Research (Grant 429E-142/S/07), what is gratefully acknowledged.

REFERENCES

[1] Gołębiewski, W. M.; Gucma, M. *J. Heterocycl. Chem*. **2008**, *45*, 241.

[2] Christl, M.; Huisgen, R. *Chem. Ber*. **1973**, *106*, 3345.

[3] Caramella, P.; Grunanger, P. In *1,3-Dipolar Cycloaddition Chemistry*, John Wiley &Sons, New York, NY, 1984, p. 177.

[4] a. Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev*. **1998**, *98*, 863; b. Pellisier, H. *Tetrahedron* **2007**, *63*, 3235.

[5] Winkler, J. D.; McCoull, W. *Tetrahedron Lett*. **1998**, *39*, 4935.

[6] Curran, D. P.; Kim, B. P.; Piyasena, H. P; Loncharich, R. J. *J. Org. Chem*. **1987**, *52*, 2137.

[7] Curran, D. P.; Yoon, M.-H. *Tetrahedron* **1997**, *53*, 1971.

[8] Kamimura, A. Kaneko, Y.; Ohta, A.; Kaheki, A.; Matsuda, H.; Kanemasa, S. *Tetrahedron Lett*. **1999**, *40*, 4349.

[9] Ager, D. J.; Prakash, J.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835.

[10] Minakata, S.; Ezoe, T.; Nakamura, K.; Ryu, I. *Tetrahedron Lett*. **1998**, *39*, 5205.

[11] Waldman, H. *Liebigs Ann. Chem*. **1990**, 1013.

[12] Curran, D. P.; Heffner, T. A. *J. Org. Chem*. **1990**, *55*, 4585.

[13] Liu, J.; Eddings, A.; Wallace, R. H. *Tetrahedron Lett*. **1997**, *38*, 6195.

[14] Kanemasa, S; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am.*

Chem. Soc. **1994**, *116*, 2324.

[15] Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem*. **1994**, *59*, 5687.

[16] a. Yoshida, Y.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett*. **1998**, 1023; b. Tsuji, M.; Ukaji, Y.; Inomata, K. *Chem. Lett*. **2002**, 1112.

[17] Serizawa, M.; Ukaji, Y.; Inomata, K. *Tetrahedron Asymm*. **2006**, *17*, 3075.

[18] a. Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc*. **2004**, *126*, 5366; b. Sibi, M. P.; Ma, Z.; Prabagaran, N.; Itoh, K.; Jasperse, C. P. *Org. Lett*. **2005**, 2349.

[19] Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron* **2001**, *57*, 8313.

[20] Kobayashi, S. In Lanthanides: Chemistry and use in organic chemistry, Springer, 1999, pp63-118.

[21] Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun*. **1998**, 19.

[22] Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A.; Shiro, M. *J. Org. Chem*. **2005**, *70*, 47.

[23] Sanchez-Blanco, A. I.; Gothelf, K. V.; Jørgensen, K. A. *Tetrahedron Lett*. **1997**, *38*, 7923.

[24] Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc*. **1998**, *120*, 5840.

[25] Yamamoto, H.; Hayashi, S.; Kubo, M.; Harada, M.; Hasegava, M.; Noguchi, M.; Sumumoto, M.; Hori, K. *Eur. J. Org. Chem*. **2007**, 2859.

[26] Curran, D. P.; Jeong, K.-S.; Heffner, T. A.; Rebek, J., Jr. *J. Am. Chem. Soc*. **1989**, *111*, 9238.

[27] Brunel, J. M. *Chem. Rev*. **2005**, *105*, 857.

[28] Fleming, I. *Frontier orbitals and organic chemical reactions*, Wiley-Interscience, New York, NY, 1976, pp. 149-161.

[29] Lewis, N.; McKillop, A.; Taylor, R. J. K.; Watson, R. *Synth. Commun*. **1995**, *25*, 561.

[30] Faita, G.; Paio, A.; Quadreli, P.; Rancati, F.; Seneci, P. *Tetrahedron Lett*. **2000**, *41*, 1265.

[31] a. Nicolas, E.; Russel, K. C.; Knollenberg, J.; Hruby, V. J. *J. Org. Chem*. **1993**, *58*, 7565; b. Rueck, K.; Kunz, H. *Synthesis* **1993**, 1018.

[32] Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun*. **2000**, 1449.

[33] Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc*. **1985**, *107*, 4346.

[34] Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem*. **1980**, *45*, 3916.

[35] Gołębiewski, W. M.; Gucma, M. *J. Heterocycl. Chem*. **2006**, *43*, 509.