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Application of chiral ligands: carbohydrates, nucleoside-lanthanides and other Lewis acid complexes to control regio- and stereoselectivity of the dipolar cycloaddition reactions of nitrile oxides and esters†

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Chiral Lewis acid mediated 1,3-dipolar cycloaddition reactions of 4-trifluoromethylbenzonitrile oxide to methyl crotonate as well to β-substituted acrylates and (*Z*)-pent-2-en-1-yl esters were examined. Excellent enantioselectivities with moderate to good regioselectivities were achieved for crotonates with complexes of $BiBr_3$ with (+)-(4,6-benzylidene)methyl-α-D-glucopyranoside **C**, with the L-ascorbic acid **I**–$FeCl_3$ system, and with lipase *Candida antarctica*. High enantiomeric excess was observed for isopropyl ester and benzyl ester. The outstanding ee values were achieved for acrylates with β-*t*-butyl, cyclohexyl, and 1,3-benzodioxol-5-yl groups in cycloadditions catalyzed by **C**–$Yb(OTf)_3$ and the (+)-2-hydroxy-3-pinanone **N**–$TiCl_4$ system. High enantioselectivities were found in reactions of (*Z*)-pent-2-en-1-yl esters mediated by complexes **N**–$Mg(OTf)_2$ and **N**–$TiCl_4$.

Introduction

We have reported recently the application of chiral Lewis acids as catalysts in the 1,3-dipolar cycloaddition reaction of aryl nitrile oxides and secondary α- or β-substituted acrylamides. Excellent enantioselectivities with moderate to good regioselectivities were achieved for crotonamides with complexes of carbohydrates with $Yb(OTf)_3$, $TiCl_4$, $Mg(OTf)_2$, and CsF as well as with the (−)-sparteine–$Yb(OTf)_3$ system. High enantiomeric excess and high regioselectivity were observed for cinnamides in reactions mediated by $Yb(OTf)_3$ complexes with carbohydrate, *R*-BINOL, and (−)-sparteine.[1]

1,3-Dipolar cycloaddition of nitrile oxides to alkenes is the most synthetically useful method of preparation of 2-isoxazolines[2] which can be easily reduced to several synthetically important 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 furnish regioselectively 5-substituted 4,5-dihydroisoxazoles while 1,2-disubstituted olefins usually afford mixtures of regio- and stereoisomers.

To control regio- and stereoselectivity of the reaction several approaches were used such as application of optically active reagents,[4] chiral auxiliaries,[5–7] chiral metal catalysts,[8–10] or organocatalysts.[11,12]

Imines derived from (+)- and (−)-2-hydroxy-3-pinanone were used as chiral auxiliaries in enantioselective syntheses of anabasine, a naturally occurring nicotinic acetylcholine receptor ligand,[13] and in syntheses of

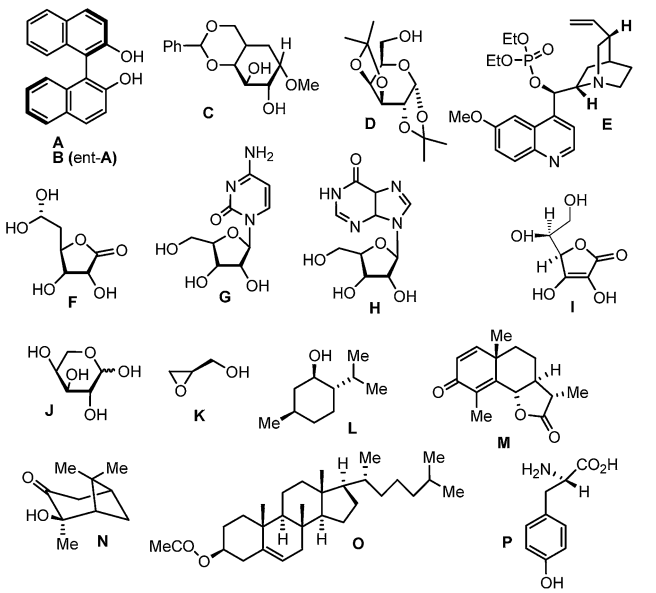

Fig. 1 Chiral ligands used in nitrile oxides 1,3-dipolar cycloaddition reactions.

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Table 1 Enantioselective 4-trifluoromethylbenzonitrile oxide cycloaddition reactions to crotonate **3a**

Entry	Chiral catalyst[a]	Yield[b] (%)	R_s[c] **5a**/**6a**	% ee **5a**	% ee **6a**
1	**A**–Yb(OTf)$_3$[d]	90	62/38	99.8	1.4
2	**B**–Yb(OTf)$_3$	67	40/60	7.6	5.6
3	**C**–Yb(OTf)$_3$	65	89/11	8.0	70
4[d]	**C**–Yb(OTf)$_3$	28	45/55	10.8	18.2
5	**G**–Yb(OTf)$_3$	80	70/30	14.0	0.1
6	**H**–Yb(OTf)$_3$	73	72/28	14.4	3.0
7	**M**–Yb(OTf)$_3$	52	82/18	5.0	4.2
8	**N**–Yb(OTf)$_3$	96	84/16	18.8	1.8
9	**J**–Yb(OTf)$_3$	27	73/27	34.4	1.4
10	**K**–Yb(OTf)$_3$	69	82/18	10.4	1.4
11	**O**–Yb(OTf)$_3$	56	63/37	3.4	0
12	**I**–Yb(OTf)$_3$	90	75/25	0.2	1.4
13	**F**–Yb(OTf)$_3$	35	76/24	6.0	1.4
14	**L**–Yb(OTf)$_3$	72	62/38	13.2	0.8
15	**D**	45	76/24	0.4	3.0
16	**D**–Yb(OTf)$_3$	88	71/29	23.6	0.1
17	**P**–Yb(OTf)$_3$	38	67/37	12.0	0.2
18	**E**–Yb(OTf)$_3$	54	69/31	10.0	50
19	**C**–Ag(OTf)	59	55/45	2.4	0.1
20	**C**–Cu(OTf)$_2$	24	82/18	2.4	0.6
21	**C**–Hf(OTf)$_4$	39	65/35	0.8	0.2
22	**C**–AuBr$_3$	18	17/83	1.0	19.2
23	**C**–PdCl$_2$	15	76/24	55.8	6.2
24	**C**–BiBr$_3$	18	17/83	73.2	99.9
25	**C**–FeCl$_3$	24	46/54	3.4	2.8
26	—	42	50/50	—	—
27	**C**–LiClO$_4$	41	65/35	19.4	0.6
28	**C**–CsF	30	61/39	35.8	0.1
29	**C**–Mg(OTf)$_2$	19	70/30	22.8	0.4
30	**C**–Co(CH$_3$COO)$_2$·4H$_2$O	30	64/36	9.2	2.0
31	**C**–(40%)Yb(ClO$_4$)$_3$/(60%)H$_2$O	31	53/47	43.6	0.8
32	**I**–Fe$_2$O$_3$	45	64/36	18.6	0.2
33	**I**–Fe$_3$O$_4$	44	50/50	8.6	0.1
34	**I**–Yb$_2$O$_3$	31	66/34	7.6	1.2
35	**I**–TiCl$_4$	37	79/21	8.0	0.2
36	**I**–CsF	47	77/23	10.0	0.2
37	**I**–FeCl$_3$	27	68/32	84.4	0.4
38	**N**–YbF$_3$	87	48/52	10.0	0.6
39	**N**–TiCl$_4$	79	55/45	47.0	0.02
40	**N**–LiClO$_4$	73	63/37	10.4	8.8
41	**N**–Fe$_2$O$_3$	67	46/54	10.2	2.4
42	Lipase "*Candida antarctica*"	56	82/18	7.0	1.2
43[d]	Lipase "*Candida antarctica*"	90	97/3	98.8	1.4
44	Lipase "*Candida rugosa*"	36	37/63	11.2	0.2

[a] *R*-BINOL-**A**, *S*-BINOL-**B**, (+)-(4,6-benzylidene)methyl-α-D-glucopyranoside-**C**, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose-**D**, quinine diethyl phosphate-**E**, L-gulonic acid γ-lactone-**F**, cytidine-**G**, inosine-**H**, L-ascorbic acid-**I**, L-(+)-arabinose-**J**, *R*-(+)-glycidol-**K**, (−)-menthol-**L**, (−)-α-santonin-**M**, (+)-2-hydroxy-3-pinanone-**N**, cholesteryl acetate-**O**, L-tyrosine-**P**. [b] Isolated yield of esters **5a** and **6a**. [c] Regioisomer **5a**/regioisomer **6a**. [d] Reaction in Et$_2$O.

(*S*)-glutamic acid receptors.[14] (+)-2-Hydroxy-3-pinanone derivatives were used to prepare imino-triphenylphosphine ligands in palladium-catalyzed asymmetric Diels–Alder reactions.[15]

Copper(II) sulfate–sodium ascorbate system (generating Cu(I)) catalyzed azide–alkyne cycloaddition reactions.[16] Mixtures of ascorbate and copper reacted as oxidizing agent, catalyzing the formation of reactive hydroxyl radicals *via* Fenton reaction.[17] Ascorbic acid based ionic liquid and a copper catalyst in an ionic liquid were used in 1,3-dipolar cycloaddition reactions under microwave irradiation.[18]

Immobilized lipase B from *Candida antarctica* was applied in enantioselective hydrolyses and amminolyses of diethyl-3-hydroxyglutarate and dimethyl-3-hydroxyglutarate.[19]

Candida rugosa lipase immobilized on calix[4]arene carboxylic acid-grafted magnetic nanoparticles was highly active both in the enantioselective hydrolysis of racemic naproxen and *p*-nitrophenylpalmitate methyl esters.[20]

A combination of an achiral pyrazolidinone ligand and chiral Lewis acids was applied to successfully relay stereochemical information from the chiral ligand to the reaction center in enantioselective Diels–Alder cycloadditions.[21] Similarly, rare earth-chiral phosphate complexes were in some cases highly effective in the presence of achiral additives in the asymmetric hetero-Diels–Alder reaction of aldehydes with the Danishefsky's diene.[22]

In quest of controlling stereochemistry and regiochemistry of nitrile oxides 1,3-dipolar cycloaddition reaction to α,β-unsaturated esters, we have examined new catalytic systems, comprising chiral ligands (Fig. 1, Table 1), as well as inorganic and organic salts of metals belonging to several groups of elements, especially lanthanides.

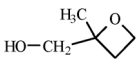
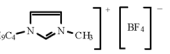
Results and discussion

We have applied first 1,3-dipolar cycloaddition reaction of 4-trifluoromethylbenzonitrile oxide to methyl crotonate **5a** as a model ester to test the efficiency of all used catalytic systems. The results yields, regioselectivity, and enantioselectivity of the obtained 2-isoxazolines are presented in the Table 1.

In the cycloaddition reaction of nitrile oxide to methyl crotonate catalytic systems were used, which on one hand were tested and selected as the most efficient in the cycloaddition to the aromatic amides,[1] and on the other hand the systems affecting stereochemistry and regiochemistry, which have been proved to be effective for the other dipolarophiles.[23,24] Forty four different catalytic systems consisting of Lewis acids (LA) and chiral ligands were used (Table 1). Different ligands of the same LA as well as different LA for the same chiral ligands were applied. The best yields were obtained with catalytic systems comprising (+)-2-hydroxy-3-pinanone (ligand **N**); its influence on regioselectivity depended on the type of LA used. This catalyst affords a large increase of yield (96%) (Table 1, reaction no. 8) compared to the reaction without a catalyst (42%, reaction no. 26). Applying this ligand with different LA (Table 1, reactions no. 8, 38–41) one can see changes of all the parameters specified in this table. Good yields were also obtained for the systems involving $Yb(OTf)_3$ and carbohydrates **C** and **D** as ligands. Catalytic systems comprising this ligands and other LA described in the literature to complex different other ligands were also tested.[25] Those examined systems included combination of **C** with $AuBr_3$, AgOTf, $PdCl_2$, $Cu(OTf)_2$, $Hf(OTf)_4$, $FeCl_3$, CsF, $Mg(OTf)_2$ and additionally undescribed in the literature salts such as $LiClO_4$ and $BiBr_3$. The best enantioselectivity was obtained with *R*-BINOL–$Yb(OTf)_3$ (Table 1, reaction no. 1), carbohydrate **C**–$BiBr_3$ system for both regioisomers (Table 1, reaction no. 24), with L-ascorbic acid **I**–$FeCl_3$ system (Table 1, reaction no. 37), and with lipase *Candida antarctica* for regioisomer **5a**. It is the first report of a highly efficient application of this enzyme to catalyze enantioselective 1,3-dipolar cycloaddition reaction. Immobilized lipases were used before in enantioselective hydrolyses and amminolyses of esters (*vide supra*). Combination of the carbohydrate **C**–$Yb(OTf)_3$ afforded good enantioselectivity (ee of 70%) for one of the regioisomers (Table 1, reaction no. 3). Satisfactory effect was also obtained for quinine diethyl phosphate (ligand **E**) and ytterbium triflate as LA (Table 1, reaction no. 18).

In another approach to control the above cycloaddition reaction mixed catalytic systems involving LA-ligand-1 (1 eq.) – ligand-2 (2 eq.) were examined (Table 2). The source of chirality

Table 2 Results of 4-trifluoromethylbenzonitrile oxide cycloaddition reactions to crotonate **3a** in the presence of $Yb(OTf)_3$ and chiral and achiral ligands

Entry	Ligands-1 1 eq.	Ligands-2 2 eq.	Yield[a] (%)	R_s[b] **5a**/**6a**	% ee reg. **5a**	% ee reg. **6a**
1	(**A** + **B**)	**K**	45	28/72	30.0	0.6
2	(**A** + **B**)	**L**	43	82/18	14.8	1.6
3	**A**	$P(C_6H_5)_3$	5	50/50	—	85.0
4	**A**	DMAP	39	33/67	5.8	1.4
5	**A**	Aniline	47	62/38	7.6	6.0
6	**A**		74	64/36	41.4	33.4
7	**A**		25	55/45	63.6	13.4
8	**A**		87	45/55	14.4	4.0
9	**A**		73	57/43	11.8	0.6
10	**A**		69	62/38	8.4	1.2

[a] Isolated yield of esters **5a** and **6a**. [b] Regioisomer **5a**/regioisomer **6a**.

was either ligand-1 or ligand-2; as ligand-1 chiral or racemic BINOL (ligand **A** + **B**) was used. It was expected that increased steric demands of such a mixed catalyst would create a chiral sphere where an approach of the dipol to one side of the bound dipolarophile will be preferred. The best enantioselectivity was achieved for a combination of BINOL **A** with voluminous triphenyl phosphine (Table 2, reaction no. 3, ee = 85%) and with *N*-cyclohexyl-*N*,*N*-dimethylamine (Table 2, reaction no. 7, ee = 63.6%).

Having selected the most efficient catalytic systems in the model cycloaddition to methyl crotonate the next step was to analyze influence of dipolarophile structure on stereoselectivity of the reaction. An effect of the ester type and character of the double bond substituent was analyzed. The best enantioselectivity was observed for isopropyl ester (Table 3, reaction no. 6), benzyl ester (Table 3, reaction no. 24), where excellent ee values were noticed for both regioisomers, phenyl ester (Table 3, no. 26), and pyrrolidine-2,5-dione-1-yl ester (Table 3, reaction no. 22). These results indicate a beneficial effect of a bulky ester function. Similarly, voluminous olefinic substituents contribute to increase enantioselectivity of the reaction. The outstanding ee values were achieved for *t*-butyl and cyclohexyl groups (Table 3, reactions no., respectively, 15 and 17). Good result was also obtained for 1,3-benzodioxol-5-yl group (Table 3, reaction no. 30). *N*-Decyl substituent was much more effective than methyl group in this respect (*cf.* entries 8 and 2). Interactions of the catalytic complex with amide and alcohol type dipolarophiles were described in one of our previous papers.[26]

The same steric factors favour also regioselectivity of the process, which is most pronounced for *t*-butyl (Table 3, reaction no. 14), 2-furanyl (Table 3, reaction no. 28) and for 1,3-benzodioxol-5-yl group (Table 3, reaction no. 30).

Results of cycloadditions to (*Z*)-pent-2-en-1-yl esters are presented (Table 4). High enantioselectivity was achieved for three different catalytic systems, better on average enantioselectivity than one observed in case of *E*-esters. In all these experiments higher enantioselectivities were found for regioisomers **5** than for regioisomers **4**. Such a difference of enantioselectivities between regioisomers **4** and **5** has been also recorded before (Scheme 2).[27]

Analyzing values of electron charges on double bond carbon atoms of the dipolarophiles some regularities can be noticed between charges and yields as well as regiochemistry of the cycloaddition reaction (Table 5). The smaller is a difference between values of charges on C-2 and C-3 carbon atoms in the dipolarophile, the greater is yield of the reaction.

Table 3 Enantioselective 4-trifluoromethylbenzonitrile oxide cycloaddition reactions to esters **3b–p**

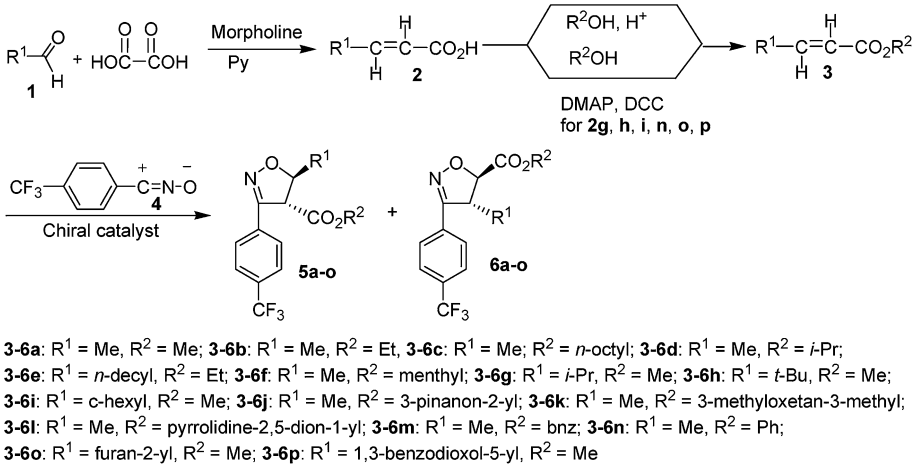
Entry	5/6	R^1	R^2	Catalyst	Yield[a] (%)	R_s[b] 5/6	% ee reg. **5**	% ee reg. **6**
1	**b**	Me	Et	—	92.6	71/29	—	—
2	**b**	Me	Et	**D**–$Yb(OTf)_3$	31.0	63/37	1.4	2.6
3	**c**	Me	*n*-Octyl	—	2.0	5050	—	—
4	**c**	Me	*n*-Octyl	**E**–$Yb(OTf)_3$	59	70/30	12.5	1.0
5	**d**	Me	i-Pr	—	80	40/60	—	—
6	**d**	Me	i-Pr	**E**–$Yb(OTf)_3$	34	70/30	96.8	0.8
7	**e**	*n*-Decyl	Et	—	19	50/50	—	—
8	**e**	*n*-Decyl	Et	**E**–$Yb(OTf)_3$	30	71/29	30.0	64.6
9	**e**	*n*-Decyl	Et	**D**–$Yb(OTf)_3$	15	65/35	34.0	34.0
10	**f**	Me	Menthyl	—	84	60/40	20.0	10.0
11	**f**	Me	Menthyl	$Yb(OTf)_3$	90	75/25	22.0	8.0
12	**g**	i-Pr	Me	—	75	77/23	—	—
13	**g**	i-Pr	Me	**C**–$Yb(OTf)_3$	27	66/34	1.8	13.0
14	**h**	*t*-Bu	Me	—	70	88/12	—	—
15	**h**	*t*-Bu	Me	**C**–$Yb(OTf)_3$	49	30/70	55.2	99.0
16	**i**	Cyclohexyl	Me	—	75	60/40	—	—
17	**i**	Cyclohexyl	Me	**N**–$TiCl_4$	37	25/75	99.0	30.6
18	**j**	Me	3-Pinanon-2-yl	(**A** + **B**)–$Yb(OTf)_3$	17	50/50	1.0	3.0
19	**k**	Me	3-Methyloxetan-3-methyl	—	33	69/31	—	—
20	**k**	Me	3-Methyloxetane-3-methyl	**E**–$Yb(OTf)_3$	50	70/30	30.0	30.0
21	**l**	Me	Pyrrolidine-2,5-dione-1-yl	—	40	70/30	—	—
22	**l**	Me	Pyrrolidine-2,5-dione-1-yl	**C**–$Yb(OTf)_3$	27	85/15	79.6	4.2
23	**m**	Me	Benzyl	—	70	60/40	—	—
24	**m**	Me	Benzyl	**N**–$TiCl_4$	40	65/35	93.2	100
25	**n**	Me	Phenyl	—	40	50/50	—	—
26	**n**	Me	Phenyl	**N**–$La(OTf)_3$	27	81/19	17.0	83.2
27	**o**	Furan-2-yl	Me	—	70	97/3	—	—
28	**o**	Furan-2-yl	Me	**D**–$Yb(OTf)_3$	39	95/5	2.0	—
29	**p**	1,3-Benzodioxol-5-yl	Me	—	65	25/75	—	—
30	**p**	1,3-Benzodioxol-5-yl	Me	**C**–$Yb(OTf)_3$	67	7/93	54.8	85.0

[a] Isolated yield of esters **5** and **6**. [b] Regioisomer **5**/regioisomer **6**.

Table 4 Enantioselective 4-trifluoromethylbenzonitrile oxide cycloaddition reactions to *Z*-pent-2-en-1-yl esters **7a** and **7b**

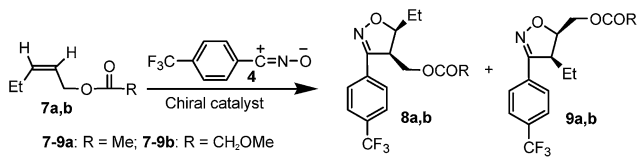
Entry	8/9	R^3	Catalyst	Yield[a] (%)	R_s[b] 8/9	% ee reg. **8a, 8b**	% ee reg. **9a, 9b**
1	**a**	Me	—	40	68/32	—	—
2	**a**	Me	**N**–$TiCl_4$	32	82/18	64.6	97.2
3	**b**	CH_2OMe	—	45	65/35	—	—
4	**b**	CH_2OMe	**N**–$TiCl_4$	37	81/19	25.8	99
5	**b**	CH_2OMe	**N**–$Mg(OTf)_2$	34	20/80	16.0	99
6	**b**	CH_2OMe	**C**–$Yb(OTf)_3$	70	28/72	32.0	44

[a] Isolated yield of esters **8** and **9**. [b] Regioisomer **8**/regioisomer **9**.



3-6a: R^1 = Me, R^2 = Me; **3-6b**: R^1 = Me, R^2 = Et, **3-6c**: R^1 = Me; R^2 = *n*-octyl; **3-6d**: R^1 = Me, R^2 = *i*-Pr;
3-6e: R^1 = *n*-decyl, R^2 = Et; **3-6f**: R^1 = Me, R^2 = menthyl; **3-6g**: R^1 = *i*-Pr, R^2 = Me; **3-6h**: R^1 = *t*-Bu, R^2 = Me;
3-6i: R^1 = c-hexyl, R^2 = Me; **3-6j**: R^1 = Me, R^2 = 3-pinanon-2-yl; **3-6k**: R^1 = Me, R^2 = 3-methyloxetan-3-methyl;
3-6l: R^1 = Me, R^2 = pyrrolidine-2,5-dion-1-yl; **3-6m**: R^1 = Me, R^2 = bnz; **3-6n**: R^1 = Me, R^2 = Ph;
3-6o: R^1 = furan-2-yl, R^2 = Me; **3-6p**: R^1 = 1,3-benzodioxol-5-yl, R^2 = Me

Scheme 1 Nitrile oxide cycloaddition reaction to esters **3a–p**.



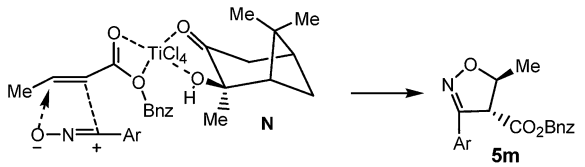
7-9a: R = Me; **7-9b**: R = CH_2OMe

Scheme 2 Nitrile oxide cycloaddition reaction to esters **7a** and **7b**.

The value of charges on C-2 is also essential, since for the relatively small absolute values with the comparable difference of C-2/C-3 charges, the reaction yield is higher than in cases with a larger absolute value of the charge on C-2 (compare values for the dipolarophiles pairs **3e** and **3f**, **3d–k** and **3a–i**). The difference between the sums of C-2 and C-3 electron charges and sums of H-2 and H-3 electron charges is also important; the smaller is the difference, the better is

Table 5 Electron charges at the alkenyl carbon atoms of the dipolarophiles **3a–p** and regioselectivity of the cycloadducts **5**/**6** (Scheme 1)

						Regioselectivity	
Dipolarophile **3**	C2	C3	H2	H3	Yield (%)	Reg.-**5**	Reg.-**6**
a	−0.210	−0.068	0.154	0.145	42	50	50
b	−0.210	−0.070	0.154	0.144	93	71	29
d	−0.207	−0.071	0.155	0.143	80	40	60
e	−0.213	−0.064	0.154	0.146	19	50	50
f	−0.207	−0.073	0.153	0.144	84	60	40
g	−0.205	−0.065	0.155	0.146	75	77	23
h	−0.206	−0.060	0.155	0.146	70	88	12
i	−0.205	−0.065	0.155	0.146	75	60	40
k	−0.212	−0.065	0.156	0.148	30	69	31
m	−0.207	−0.070	0.155	0.144	70	60	40
n	−0.214	−0.064	0.157	0.146	40	50	50
o	−0.179	−0.017	0.159	0.169	70	97	3
p	−0.195	−0.030	0.157	0.148	65	25	75



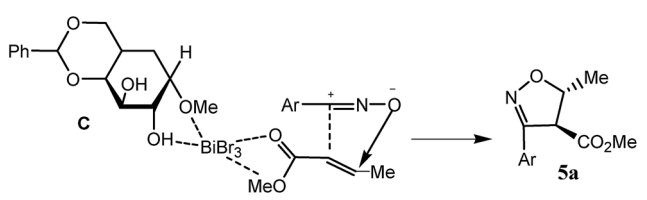
Scheme 3 Proposed mechanism of chiral induction with $TiCl_4$–**N** system.

regiochemistry (compare *e.g.* data for the dipolarophiles pair **3n** and **3o**).

The observed enantioselectivity of the reaction leading to 4-carboalkoxy derivatives could be tentatively explained by binding of the esters to the chiral catalytic complex, such as presented at Scheme 3, of titanium tetrachloride with (+)-3-hydroxy-2-pinanone (**N**), followed by a preferential attack of nitrile oxide from the lower si-face of the alkene opposite to the geminal dimethyl bridge affording isoxazolines of 4*R*,5*S* configuration. This direction of enantioselectivity was found also for complexes of ligand **N** with ytterbium triflate and lithium perchlorate, as well as for complexes of $Yb(OTf)_3$ with carbohydrate **C**, *R*-BINOL, tyrosine, cytidine, and L-menthol. The absolute configuration of the cycloadducts was established based on comparison of literature data for the similar compounds.[28]

The opposite chirality indicated by opposite elution order of enantiomers of the same compound from the chiral column and opposite sign of optical rotation was observed for the catalytic systems of (+)-(4,6-benzylidene)methyl-α-D-glucopyranoside (carbohydrate **C**) with $BiBr_3$, $PdCl_2$, $LiClO_4$, CsF, $Mg(OTf)_2$, CsF, $Yb(OTf)_3$, complexes of L-ascorbic acid (**I**) with CsF, $FeCl_3$, and reaction mediated by lipase *Candida antarctica*. In this case the observed enantioselectivity could be explained *e.g.* by a preferred attack of the nitrile oxide from upper re-face of the dipolarophile opposite to the ligand alpha-1,2-substituents affording isoxazolines of 4*S*,5*R* configuration (Scheme 4).

The obtained esters have been screened for the biological activity. Inhibition of the linear growth of fungi being pests of important cultivated plants is displayed in Table 6. Good fungicidal activity was found for esters **3l** and **5l** containing several carbonyl groups. Moderate biological potency was noticed for **5b**, **5d** and **5o**, **6k** products with four- and five-membered rings containing oxygen atom. Cycloadducts exhibit higher fungicidal activity than starting dipolarophiles (compare pairs **3l**, **5l**; **3e**, **5e**; **3k**, **6k**).



Scheme 4 Proposed mechanism of chiral induction with $BiBr_3$–**C** system.

Table 6 Fungicidal inhibitory activities[a] of compounds **3–9** at 200 mg L^{-1}

Compound	*B. c.*[b]	*F. c.*	*P. c.*	*R. s.*
3c	0	16.0	0	6.0
3e	0	22.0	0	0
3f	18.8	24.0	16.3	54.0
3j	43.8	20.0	10.0	18.0
3k	18.0	16.0	5.0	17.0
3l	32.0	29.0	100	68.0
5b	25.0	45.8	0	31.0
5c	3.8	16.7	0	0
5e	11.5	20.8	8.7	10.3
5g	20.0	19.4	1.8	48.0
5h	0	19.4	0.7	38.0
3l + **5l**	75.0	80.6	100	100
5m	8.0	0	0	34.0
5o	52.0	20.0	0	34.0
6b	26.9	37.5	0	36.2
6d	36.0	25.8	0	60.0
6g	0	3.2	6.5	38.0
6i	4.0	0	6.5	24.0
6k	38.4	47.8	6.5	37.9
6l	0	22.6	1.8	28.0
6p	44.0	0	0	0
9a	40.0	16.0	28.2	48.0
Chlorothalonil[c]	80.0	38.0	61.0	88.0

[a] Percentage of linear growth inhibition. [b] *B. c.* – *Botrytis cinerea*, *F. c.* – *Fusarium culmorum*, *P. c.* – *Phytophtora cactorum*, *R. s.* – *Rhizoctonia solani*. [c] Reference compound.

Conclusion

We have applied new chiral Lewis acids to study 1,3-dipolar cycloaddition reaction of aryl nitrile oxides and crotonates as well as substituted acrylates mediated by chiral complexes of carbohydrates **C**, **D**, **F**, **I**, **J**, **A**, nucleosides **G** and **H** as well as natural products derivatives with inorganic and organic salts of metals belonging to several groups of elements, especially lanthanides, achieving high enantioselectivity and regioselectivity for some systems. Depending on the type of catalytic system 4*R*,5*S* or 4*S*,5*R*-trisubstituted isoxazolines can be obtained. We are continuing research to diminish amount of chiral Lewis acid from equimolar to catalytic quantities.

Experimental

Reagent grade chemicals were used without further purification unless otherwise noted. Hydroximinoyl acid chlorides were prepared from the corresponding aryl aldehyde oximes and NCS in DMF.[29,30] The corresponding nitrile oxides were generated *in situ* by dehydrohalogenation of hydroximinoyl acid chlorides with triethylamine or on Amberlyst A-21 column.[27]

Spectra were obtained as follows: IR spectra on JASCO FTIR-420 spectrometer, ^1H, ^{13}C NMR on a Varian 200 UNITY plus-200 and a Varian 500 UNITY plus-500, COSY (correlation spectroscopy), HSQC (heteronuclear single quantum coherence), HMBC (heteronuclear multiple bond correlation) and NOESY (nuclear Overhauser effect spectroscopy) analyses on a Varian 500 UNITY

plus-500 and a Varian VNMRS 600 spectrometers in deuterated chloroform using TMS as internal standard, ESI and HR ESI mass spectra on Micromass LCT spectrometer. Flash-chromatography was carried out using silica gel S 230-400 mesh (Merck). Elemental analyses were performed at Microanalysis Laboratory of Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw. The electron charges were calculated using the computer program Hyperchem 7.5. Enantioselectivity of reactions was determined by HPLC analysis (AD-H chiral column).

Syntheses of dipolarophiles 3a, 3b, 3c, 3d, 3f, 3g, 3h, 3i, 3j, 3k, 3l, 3m, 3n, 3o and 3p

Acids **2g**, **2h**, **2i**, **2n**, **2o**, **2p** were prepared in the Knoevenagel condensation with malonic acid from the corresponding aldehyde.[31]

(2*E*)-4-Methylpent-2-enoic acid (2g).[32] A brownish oil (85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.99 (s, 1H, –OH), 7.07 (dd, J = 15.5; 7.5 Hz, 1H, HC=C–C=O), 5.78 (dd, J = 15.5; 1.5 Hz, 1H, –C=CH–C=O), 2.49 (m, J = 7.0; 1.5 Hz, 1H, H–C$(CH_3)_2$), 1.08 (d, J = 7.0 Hz, 6H, 2× H_3C–CH).

(2*E*)-4,4-Dimethylpent-2-enoic acid (2h).[33] A brownish oil (60%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.08 (d, J = 15.8 Hz, 1H, –HC=C–C=O), 5.75 (d, J = 15.8 Hz, 1H, –C=CH–C=O), 1.08 (s, 9H, 3× H_3C–C).

(2*E*)-3-Cyclohexylprop-2-enoic acid (2i).[34] A brownish oil (85%). IR (KBr, cm^{-1}): 2921, 1690, 1645, 1460, 1418, 1313, 1280, 1233, 1225, 1175, 1140, 995, 950, 880, 850, 780, 727, 696, 595, 535. ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.26 (s, 1H, –OH), 7.04 (dd, J = 16.0; 6.8 Hz, 1H, –HC=C–C=O), 5.77 (dd, J = 16.0; 1.4 Hz, 1H, –C=CH–C=O), 2.11 (m, 1H, HCCH_2), 1.73 (m, 5H), 1.24 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ (ppm) = 172.99 (H_3CO–C=O), 157.34 (CH), 118.51 (CH), 40.69 (1C, C-1′), 31.69 (2C, C-2′, C-6′), 26.06 (2C, C-3′, C-5′), 25.83 (C-4′).

(2*E*)-3-(Furan-2-yl)prop-2-enoic acid (2o).[35] A brownish oil (50%). IR (KBr, cm^{-1}): 3420, 3200, 3150, 3080, 2995, 2927, 2840, 2815, 2700, 2595, 2530, 2480, 2280, 1700, 1670, 1627, 1560, 1480, 1415, 1390, 1312, 1271, 1230, 1193, 1070, 1022, 976, 950, 940, 925, 880, 860, 840, 756, 665. ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.83 (s, 1H, –OH), 7.53 (d, J = 15.6 Hz, 1H, –HC=C–C=O), 7.52 (d, J = 4.3 Hz, 1H, H-2′), 6.67 (d, J = 8.5 Hz, 1H, H-5′), 6.49 (td, J = 8.5: 4.3 Hz, 1H, H-4′), 6.32 (d, J = 15.6 Hz, 1H, –C=CH–C=O).

General procedure for synthesis of esters 3c, 3f, 3j, 3k, 3l[36]

N,*N*′-Dicyclohexylcarbodiimide (DCC) (14 mmol) in anhydrous CH_2Cl_2 was added with stirring at room temperature to a solution of carboxylic acid (10 mmol), alcohol (10 mmol) and 4-dimethyloaminopyridine (6.5 mmol) in a mixture of anhydrous dichloromethane–acetonitrile (5 mL, 1 : 1) under anhydrous argon. Stirring was continued for 24 h. The reaction mixture was filtered and the filter paper was washed with dichloromethane. The solution was washed with water, dilute HCl, water, aqueous solution of sodium bicarbonate, and finally several times with water. The solution was dried (Na_2SO_4) and the product obtained after evaporation of the solvent was purified by flash chromatography on silica gel using mixtures of hexane–ethyl acetate as a mobile phase. The expected esters **3** were obtained as yellowish waxes (40–80%).

Octyl (2*E*)-but-2-enoate (3c).[37] A brownish oil (55%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.97 (dq, J = 15.5; 8.4 Hz, 1H, H_3C–HC=C–), 5.84 (dq, J = 15.5; 1.8 Hz, 1H, –C=CH–C=O), 4.11 (t, J = 6.6 Hz, 2H, –O–CH_2–, H-5), 1.88 (dd, J = 6.8; 1.8 Hz, 3H, H_3C–CH=CH–, H-4), 1.63 (m, 2H), 1.28 (m, 10H), 0.88 (t, J = 6.6 Hz, 3H, H_3C–CH_2). EI-MS m/z (% intensity) 199 (M^+ + H, 5), 183 (M^+ − CH_3, 2), 155 (M^+ − C_3H_7, 2), 141 (M^+ − C_4H_9, 3), 127 (M^+ − C_5H_{11}, 3), 87 (H_3C–CH=CH–C=O–O + 1H, 80), 69 (H_3C–CH=CH–C=O, 100), 41 (H_3C–CH=CH, 70).

Propan-2-yl(2*E*)-but-2-enoate (3d).[38] A brownish oil (73%). IR (film, cm^{-1}): 2981, 2960, 2880, 1719, 1660, 1470, 1440, 1375, 1308, 1298, 1278, 1191, 1150, 1110, 1003, 965, 901, 840, 750, 690. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.94 (dq, J = 15.0; 7.0 Hz, 1H, H_3C–HC=C–C=O), 5.82 (dq, J = 15.0; 2.0 Hz, 1H, –C=CH–C=O), 5.05 (sept, J = 6.3 Hz, 1H, H_3C–CH–CH_3), 1.87 (dd, J = 6.8; 1.5 Hz, 3H, H_3C–HC=C), 1.25 (d, J = 6.8 Hz, 6H, $(H_3C)_2$CH).

Ethyl tridec-(2*E*)-2-enoate (3e).[39] NaH 60% (1.5 mmol) of THF was added dropwise with stirring at 0 °C over 10 min to the solution of diisopropyl (ethoxycarbonylmethyl)phosphonate (1 mmol) in anhydrous Et_2O and the solution was stirred at 0 °C and then at rt for 60 min. The solution was cooled to −15 °C and an aldehyde **1** (1 mmol) solution in anhydrous THF was added dropwise with stirring over 20–30 min and then the solution was stirred at rt for 24 h under anhydrous argon. The solution was washed with water, dilute NH_4Cl aqueous solution, several times with water and was dried ($MgSO_4$). The product obtained after evaporation of the solvent was purified by flash chromatography on silica gel using mixtures of hexane–ethyl acetate as a mobile phase. The expected ester **3e** was obtained as a yellowish wax (65%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.97 (dt, J = 15.6; 7.0 Hz, 1H, –H_2C–HC=C), 5.81 (dt, J = 15.6; 1.4 Hz, 1H, –C=CH–C=O), 4.18 (t, J = 7.2 Hz, 2H, O=C–O–CH_2, H-14), 2.19 (m, 2H, –H_2C–HC=C), 1.43 (m, 16H, –H_2C–CH_2), 0.88 (t, J = 6.6 Hz, 3H, H_3C–CH_2). EI-MS m/z (% intensity) 241 (M^+ + H, 10), 226 (M^+ − CH_3, 4), 213 ((M^+ − C_2H_5) + 1H, 5), 156 (M^+ − C_6H_{13}, 5), 142 (M^+ − C_7H_{15}, 5), 128 (M^+ − C_8H_{17}, 5), 114 (M^+ − C_9H_{19}, 10), 101 ((M^+ − $C_{10}H_{21}$ + 1H, 50), 86 (H_3C–CH=CH–C=O–O, 30), 69 (H_3C–CH=CH–C=O, 45), 41 (H_3C–CH=CH, 100).

Menthyl (2*E*)-but-2-enoate (3f).[40] A brownish oil (45%). IR (neat, cm^{-1}): 2955, 2880, 1718, 1659, 1447, 1370, 1307, 1290, 1187, 1101, 1040, 1016, 1000, 960, 920, 840, 760, 734, 690. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (dq, J = 15.5; 6.8 Hz, 1H, H_3C–HC=C–), 5.83 (dq, J = 15.5; 1.8 Hz, 1H, –C=CH–C=O), 4.72 (td, J = 11.0; 4.5 Hz, 1H, H-1′), 2.01 (m, 1H, H-6eq′), 1.88 (m, 1H, H-8′), 1.87 (dd, J = 6.8; 2.0 Hz, 3H, H_3C–CH=CH), 1.68 (m, 2H, H-4eq′, H-3eq′), 1.50 (m, 1H, H-5′), 1.40 (m, 1H, H-2′), 1.1 (m, 1H, H-3ax′), 0.95 (m, 1H, H-6ax′), 0.90 (d, J = 6.5 Hz, 3H, H_3C–CH), 0.89 (d, J = 7.0 Hz, 3H, H_3C–CH), 0.85 (m, 1H, H-4ax′), 0.76 (d, J = 7.5 Hz, 3H, H_3C–C=C). ^{13}C NMR (from HSQC, 150 MHz, $CDCl_3$): δ 143.0 (C-3), 122.5 (C-2), 73 (C-1′), 42 (C-2′), 41 (C-6′), 34 (C-4′), 31.5 (C-5′), 26.2 (C-8′), 23.5 (C-3′).

Methyl (2*E*)-3-cyclohexylprop-2-enoate (3i).[41] A brownish oil (70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (dd, J = 16.0; 6.5 Hz, 1H, –HC=C–C=O), 5.77 (dd, J = 16.0; 1.5 Hz, 1H, C=CH–C=O),

3.83 (s, 3H, H_3C–O–C=O), 2.25 (m, 1H, $HCCH_2$), 1.87 (m, 4H), 1.79 (m, 1H, H-4a′), 1.41 (m, 2H), 1.32 (m, 1H), 1.28 (m, 2H). ^{13}C NMR (125.9 MHz, $CDCl_3$): δ (ppm) = 167.43 (H_3C–O–C=O), 154.48 (CH), 118.42 (CH), 51.26 (H_3C–O), 40.35 (1C, C-1′), 31.62 (2C, C-2′, C-6′), 25.85 (2C, C-3′, C-5′), 25.62 (C-4′).

2,6,6-Trimethyl-3-oxobicyclo [3.1.1] hept-2-yl (2*E*) but-2-enoate (3j). A brownish oil (65%). IR (KBr, cm^{-1}): 2925, 2880, 1720, 1650, 1470, 1442, 1405, 1370, 1308, 1295, 1266, 1186, 1150, 1100, 1080, 1053, 998, 970, 855, 833, 753, 690 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 6.86 (dq, J = 15.5; 8.6 Hz, 1H, H_3C–CH=C), 5.75 (dq, J = 15.5; 1.8 Hz, 1H, C=CH–C=O), 2.97 (t, J = 6.3 Hz, 1H, C–HC–C), 2.77 (dd, J = 18.9; 2.4 Hz, 1H, H-7a), 2.65 (dt, J = 18.9; 3.2 Hz, 1H, H-7b), 2.40 (m, 1H, H-10a), 2.12 (m, 1H, H-8), 1.83 (dd, J = 6.8; 1.6 Hz, 3H, H_3C–CH=C), 1.61 (s, 3H, CH_3), 1.57 (m, 1H, H-10b), 1.35 (s, 3H, –CH_3), 0.86 (s, 3H, –CH_3). ^{13}C NMR (from HMBC, 150.8 MHz, $CDCl_3$)]: δ 206.72 (C–C=O–C), 165.10 (O=C–CH=C), 144.92 (H_3C–CH=C), 123.13 (O=CCH=C), 86.15 ([O–C–C=O(CH_3)]), 49.06 (C–CH–C), 43.30 (C-7), 38.29 (C-8), 27.77 (C-10), 27.39 (H_3C), 22.53 (H_3C), 21.29 (H_3C), 17.87 (H_3C). HR ESI-MS calcd for: $C_{14}H_{20}O_3Na$ = 259.1310. Found = 259.1310.

(3-Methyloxetan-3-yl)methyl (2*E*)-but-2-enoate (3k).[42] A brownish oil (40%). ^1H NMR (200 MHz, $CDCl_3$): δ 7.03 (dq, J = 15.5; 6.7 Hz, 1H, H_3C–HC=C), 5.89 (dq, J = 15.5; 1.8 Hz, 1H, –C=CH–C=O), 4.55 (d, J = 6.0 Hz, 2H, –O–CH_2–C-*anti*), 4.40 (d, J = 6.0 Hz, 2H, –O–CH_2–C-*syn*), 4.21 (s, 2H, –O–CH_2–, H-5), 1.90 (dd, J = 6.8; 1.6 Hz, 3H, H_3C–CH=CH–), 1.35 (s, 3H, H_3C–C, H-9). ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.68 (–O–C=O), 145.53 (C-3, H_3C–HC=C), 122.44 (C-2, C=CH–C=O), 79.78 (C-7), 79.79 (C-8), 68.48 (OCH_2), 39.34 (C-6), 21.39 (C-9), 18.20 (C-4).

2,5-Dioxopyrrolidin-1-yl (2*E*)-but-2-enoate (3l).[43] A white semisolid (55%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 (dm, J = 15.8 Hz, 1H, H_3C–HC=C), 6.05 (dq, J = 15.8; 1.5 Hz, 1H, –C=CH–C=O), 2.84 (s, 4H, H-4′, H-5′), 2.00 (dd, J = 6.5; 2.0 Hz, 3H, H_3C–CH=CH).

Benzyl (2*E*)-but-2-enoate (3m).[44] A brownish oil (35%). ^1H NMR (200 MHz, $CDCl_3$): δ 7.35–6.85 (m, 6H, H-2′, H-3′, H-4′, H-5′, H-6′ and H_3C–CH=C), 5.95 (dm, J = 15.0 Hz, 1H, O=CHC=C), 5.13 (d, J = 5.6 Hz, 2H, Ar-CH_2OC=O), 1.79 (dd, J = 6.8; 1.8 Hz, 3H, H_3C–CH=C).

Phenyl (2*E*)-but-2-enoate (3n).[45] A gray oil (35%). ^1H NMR (200 MHz, $CDCl_3$): δ 7.26–7.05 (m, 6H, H-2′, H-3′, H-4′, H-5′, H-6′ and H_3C–CH=C), 5.95 (m, 1H, O=CHC=C), 1.85 (m, 3H, H_3C–CH=C).

Methyl (2*E*)-3-(furan-2-yl)prop-2-enoate (3o).[46] A brownish oil (35%). IR (oil, cm^{-1}): 3420, 3550, 3120, 3160, 3000, 2951, 2920, 2840, 1714, 1642, 1559, 1480, 1435, 1390, 1308, 1280, 1260, 1215, 1166, 1075, 1040, 1018, 973, 930, 884, 870, 840, 750, 682. ^1H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 1.5 Hz, 1H, H-5′), 7.43 (d, J = 15.5 Hz, 1H, –HC=C–C=O), 6.60 (d, J = 3.5 Hz, 1H, H-3′), 6.45 (dd, J = 3.5; 1.5 Hz, 1H, H-4′), 6.31 (d, J = 15.5 Hz, 1H, –C=CH–C=O), 3.77 (s, 3H, H_3C–O–C=O). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 167.6 (H_3C–O–C=O), 151.0, 144.9, 131.4, 115.6, 115.0, 112.4, 51.8.

Methyl (2*E*)-3-(1,3-benzodioxol-5-yl)prop-2-enoate (3p).[47] A greyish semisolid (87%). IR (film, cm^{-1}): 3430, 3040, 2960, 2900, 2840, 2800, 1703, 1625, 1600, 1497, 1455, 1448, 1360, 1310, 1255, 1201, 1174, 1130, 1102, 1037, 1004, 925, 860, 825, 727, 718. ^1H NMR (200 MHz, $CDCl_3$): δ 7.59 (d, J = 16.0 Hz, 1H, Ar-HC=C–C=O), 7.02 (d, J = 1.8 Hz, H-3′), 7.00 (dd, J = 7.8; 1.8 Hz, 1H, H-5′), 6.80 (d, J = 7.8 Hz, 1H, H-6′), 6.26 (d, J = 16.0 Hz, 1H, –C=CH–C=O), 6.00 (s, 2H, OCH_2O), 3.78 (s, 3H, H_3C–O–C=O).

General procedure for the cycloaddition reactions

A mixture of a chiral ligand-1 (1.0 mmol) and a Lewis acid (1.0 mmol) in anhydrous dichloromethane was stirred at rt for 60 min. Chiral ligand-2 (2.0 mmol) in anhydrous dichloromethane was stirred at rt for 60 min. A solution of 4-trifluoromethylbenzonitrile oxide was added dropwise over 20 min to the solution of esters **3**, **7** in anhydrous dichloromethane, and the solution was stirred overnight at room temperature. Water was added, organic layer was separated and the aqueous one extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and the product obtained after evaporation of the solvent was purified by flash chromatography on silica gel using mixtures of hexane–ethyl acetate as a mobile phase.

Methyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-methyl-4-carboxylate (5a). A yellow oil (yield in Table 2). $[\alpha]_D^{25}$ = −150.0 (c 0.2 in acetone) [99.8% ee, (*R*, *S*) rich]. ^1H NMR (200 MHz, $CDCl_3$): δ 7.82 (d, J = 8.6 Hz, 2H, H-5′, H-3′), 7.65 (d, J = 8.6 Hz, 2H, H-6′, H-2′), 5.15 (quintet, J = 6.3 Hz, 1H, H-5), 4.11 (dq, J = 6.3 Hz, H-4), 3.73 (s, 3H, CH_3O), 1.49 (d, J = 6.3 Hz, 3H, CH_3–CH). Anal. calcd for $C_{13}H_{12}F_3NO_3$: C 54.4: H 4.2. Found: C 54.4; H 4.0%.

Methyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-methyl-5-carboxylate (6a).[48] A yellow oil; ^1H NMR (200 MHz, $CDCl_3$): δ 7.97 (d, J = 8.1 Hz, 2H, H-5′, H-3′), 7.68 (d, J = 8.1 Hz, 2H, H-6′, H-2′), 4.84 (d, J = 4.2 Hz, 1H, H-5), 4.02 (dq, J = 7.3; 4.2 Hz, H-4), 3.81 (s, 3H, CH_3O–), 1.43 (d, J = 7.3 Hz, 3H, CH_3–CH).

Ethyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-methyl-4-carboxylate (5b). A yellow oil (yield in Table 3). IR (KBr, cm^{-1}): 2980, 2932, 1737, 1619, 1600, 1560, 1448, 1412, 1350, 1326, 1300, 1160, 1127, 1070, 1027, 933, 900, 847, 780. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.99–7.60 (m, 4H, H-3′, H-5′, H-2′, H-6′), 5.16 (m, J = 6.3; 6.6 Hz, 1H, H-5), 4.19 (qd, J = 7.2; 1.5 Hz, 2H, OCH_2CH_3), 4.09 (d, J = 6.3 Hz, 1H, H-4), 1.50 (d, J = 6.3 Hz, 3H, H_3C–CH), 1.19 (t, J = 7.2 Hz, 3H, O–CH_2–CH_3). EI-MS *m*/*z* (% intensity) 301 (M^+, 18), 282 (M^+ − F, 19), 228 (M^+ − C=$OOCH_2CH_3$, 16), 214 (M^+ − C=$OOCH_2CH_3CH_3$, 45), 187 (F_3-CC_6H_4CNO, 12), 145 ($F_3CC_6H_4$, 32), 69 (CF_3, 15), 43 (100). Anal. calcd for $C_{14}H_{14}F_3NO_3$: C 55.8: H 4.7. Found: C 55.6; H 4.8%.

Ethyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-methyl-5-carboxylate (6b). A yellow oil; IR (KBr, cm^{-1}): 2960, 2925, 1738, 1615, 1598, 1525, 1463, 1405, 1380, 1325, 1260, 1200, 1170, 1127, 1070, 1040, 900, 847. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.99–7.60 (m, 4H, H-3′, H-5′, H-2′, H-6′), 4.82 (d, J = 4.2 Hz, 1H, H-5), 4.28 (q, J = 7.1 Hz, 2H, O–CH_2CH_3), 4.02 (dq, J = 7.2; 4.2 Hz, 1H, H-4), 1.43 (d, J = 7.2 Hz, 3H, H_3C–CH), 1.32 (t, J = ^{49}7.1 Hz, 3H, OCH_2CH_3). EI-MS *m*/*z* (% intensity) 301 (M^+, 12), 282 (M^+ − F, 14), 228 (M C=$OOCH_2CH_3$, 100), 214 (M^+ − C=$OOCH_2CH_3CH_3$, 12), 187 ($F_3CC_6H_4CNO$, 30), 145 ($F_3CC_6H_4$, 32), 69 (CF_3, 8). Anal. calcd for $C_{14}H_{14}F_3NO_3$: C 55.8: H 4.7. Found: C 55.9; H 4.9%.

Octyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-methyl-4-carboxylate (5c). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.65 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 5.15 (quintet, J = 6.4 Hz, 1H, H-5), 4.11 (t, J = 6.4 Hz, 2H, OCH_2CH_2), 4.10 (d, J = 6.4 Hz, 1H, H-4), 1.50 (d, J = 6.4 Hz, 3H, H_3C–CH), 1.59–1.10 (m, 12H), 0.88 (t, J = 6.6 Hz, 3H, H_3C–CH_2). ^{13}C NMR (125.90 MHz, $CDCl_3$): δ 169.01 (–O–C=O), 152.87 (1C, C-3), 132.44 (1C, C-1′), 131.79 (q, J = 32.8 Hz, 1C, C-4′), 127.11 (2C, C-6′, C-2′), 125.65 (q, J = 3.8 Hz, 2C, C-5′, C-3′), 123.8 (q, 1C, J = 272 Hz, F_3C-Ar), 82.82 (1C, C-5), 66.33 (1C, O=C–OCH_2CH_2), 59.80 (C-4), 31.74, 29.09, 29.04, 28.37, 25.69, 22.58, 20.73, 14.04. HR-ESI-MS calcd for: $C_{20}H_{26}O_3NF_3Na$ = 408.1762. Found = 408.1778.

Octyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-methyl-5-carboxylate (6c). A yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.84–7.63 (m, 4H, H-3′, H-5′, H-2′, H-6′), 4.82 (d, J = 4.4 Hz, 1H, H-5), 4.19 (t, J = 6.7 Hz, 2H, O–CH_2CH_2), 4.00 (dd, J = 7.1; 4.4 Hz, 1H, H-4), 1.43 (d, J = 7.1 Hz, 3H, H_3C–CH), 1.59–1.10 (m, 12H, CH_2–CH_2–CH_2), 0.87 (t, J = 6.6 Hz, 3H, H_3C–CH_2). EI-MS m/z (% intensity) 385 (M^+, 5), 370 ($M^+ - CH_3$, 12), 328 ($M^+ - C_4H_9$, 3), 286 ($M^+ - C_7H_{15}$, 2), 228 (M^+ – C=OOC_8H_{17}, 100), 214 (M^+ – C=$OOC_8H_{17}CH_3$, 50), 187 ($F_3CC_6H_4CNO$, 20), 145 ($F_3CC_6H_4$, 40), 69 (CF_3, 45). Found: C, 62.1; H, 6.7. Calcd for $C_{20}H_{26}F_3NO_3$: C 62.3, H 4.5%.

Isopropyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-methyl-4-carboxylate (5d). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (d, J = 8.1 Hz, 2H, H-5′, H-3′), 7.65 (d, J = 8.1 Hz, 2H, H-6′, H-2′), 5.12 (m, 1H, H-5), 5.07 [m, 1H, O–CH–$(CH_3)_2$], 4.06 (d, J = 6.6 Hz, 1H, H-4), 1.50 (d, J = 6.6 Hz, 3H, CH_3–CH), 1.18 (d, J = 6.2 Hz, 3H), 1.15 (d, J = 5.8 Hz, 3H). EI-MS m/z 315 (M^+), 296 (M^+ – F), 214 ($M^+ - CH_3C$=$OOCH_3$ + H), 145 ($F_3CC_6H_4$), 43 (–$HC(CH_3)_2$). Found: C, 57.3; H, 5.0. Calcd for $C_{15}H_{16}F_3NO_3$: C 57.1, H 5.1%.

Isopropyl 3 (4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-methyl-5-carboxylate (6d). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (d, J = 8.0 Hz, 2H, H-5′, H-3′), 7.68 (d, J = 8.0 Hz, 2H, H-6′, H-2′), 5.09 [m, 1H, O–CH–$(CH_3)_2$], 4.78 (d, J = 4.6 Hz, 1H, H-5), 4.00 (m, 1H, H-4), 1.52–1.16 (m, 9H). HR EI-MS calcd for: $C_{15}H_{16}F_3NO_3$ = 315.1082. Found = 315.1082.

Ethyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-decyl-4-carboxylate (5e). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (d, J = 8.1 Hz, 2H, H-2′, H-6′), 7.65 (d, J = 8.1 Hz, H, H-3′, H-5′), 4.99 (dt, J = 6.6; 6.4 Hz, 1H, H-5), 4.18 (q, J = 7.3 Hz, 2H, O–CH_2CH_3), 4.13 (d, J = 6.6 Hz, 1H, H-4), 1.90–1.10 (m, 14H), 0.88 (m, 6H, 2× H_3C–CH_2). EI-MS m/z (% intensity) 427 (M^+, 5), 408 (M^+ – 1F, 7), 354 (M^+ – C=$OOCH_2CH_3$, 12), 286 ($M^+ - C_{10}H_{21}$, 100), 214 (M^+ – C=$OOCH_2CH_3C_{10}H_{21}$, 7), 187 ($F_3CC_6H_4CNO$, 10), 145 ($F_3CC_6H_4$, 8), 69 (CF_3, 10). Found: C, 64.35; H, 7.4. Calcd for $C_{23}H_{32}F_3NO_3$: C 64.6, H 7.55%.

Ethyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-decyl-5-carboxylate (6e). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, J = 8.4 Hz, 2H, H-2′, H-6′), 7.68 (d, J = 8.4 Hz, H, H-3′, H-5′), 4.91 (d, J = 3.8 Hz, 1H, H-5), 4.26 (q, J = 7.2 Hz, 2H, O–CH_2CH_2), 3.93 (dt, J = 7.4; 3.8 Hz, 1H, H-4), 1.80–1.10 (m, 14H, CH_2–CH_2–CH_2), 0.87 (m, 6H, 2× H_3C–CH_2). EI-MS m/z (% intensity) 427 (M^+, 5), 408 (M^+ – F, 5), 354 (M^+ – C=$OOCH_2CH_3$, 100), 214 (M^+ – C=$OOCH_2CH_3C_{10}H_{21}$, 10), 145 ($F_3CC_6H_4$, 10), 69 (CF_3, 12). Found: C, 64.7; H, 7.5. Calcd for $C_{23}H_{32}F_3NO_3$: C 64.6, H 7.55%.

Menthyl 5-methyl-3-[4-(trifluoromethyl)phenyl]-4,5-dihydroisoxazole-4-carboxylate (diastereoisomers A and B) (5f). A yellow wax; **A**/**B** = 60/40. **A:** ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.65 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 5.07 (m, 1H, H-5), 4.62 (m, 1H, J = 10.9 Hz, H-1″), 4.11 (d, J = 7.2 Hz, 1H, H-4), 2.00–1.80 (m, 1H, H-6eq″), 1.66–1.39 (m, 3H, H-4eq″, H-3eq″, H-7″), 1.53 (d, J = 6.4 Hz, 3H, H-6, H_3C), 1.5–1.35 (m, 1H, H-2″), 1.38–1.17 (m, 1H, H-5″), 1.10–0.70 (m, 3H, H-4ax″, H-3ax″, H-6ax″), 0.88 (d, J = 6.2 Hz, 3H, H-10″, H_3C), 0.64 (d, J = 6.8 Hz, 3H, H-8″, H_3C), 0.44 (d, J = 7.0 Hz, 3H, H-9″, H_3C). ^{13}C NMR from HMBC (150.3 MHz, $CDCl_3$): δ 168.46 (H_3CO–C=O), 153.03 (C-3), 132.52 (C-4′), 131.74 (1C, C-1), 127.05 (2C, C-6′, C-2′), 125.49 (2C, C-5′, C-3′), 83.01 (C-5), 76.37 (C-1″), 60.55 (C-4), 46.68 (C-2″), 40.43 (C-6″), 33.98 (C-4″), 31.35 (C-5″), 25.78 (C-7″), 20.41 (C-10″), 15.53 (C-9″).

B: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.65 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 5.10 (m, 1H, H-5), 4.66 (m, H-1″), 4.09 (d, J = 6.0 Hz, 1H, H-4), 2.00–1.80 (m, 1H, H-6eq″), 1.66–1.39 (m, 3H, H-4eq″, H-3eq″, H-7″), 1.50 (d, J = 6.4 Hz, 3H, H-6), 1.5–1.35 (m, 1H, H-2″), 1.38–1.17 (m, 1H, H-5″), 1.10–0.70 (m, 3H, H-4ax″, H-3ax″, H-6ax″), 0.84 (d, 3H, H-10″, H_3C), 0.78 (d, J = 7.2 Hz, 3H, H-8″, H_3C), 0.64 (d, J = 6.8 Hz, 3H, H-9″, H_3C). ^{13}C NMR (from HMBC, 150.3 MHz, $CDCl_3$): δ 168.46 (H_3C–O–C=O), 153.03 (C-3), 132.52 (C-4′), 131.74 (C-1), 127.05 (2C, C-6′, C-2′), 125.49 (2C, C-5′, C-3′), 82.71 (C-5), 76 (C-1″), 60.06 (C-4), 46.68 (C-2″), 40.43 (C-6″), 33.98 (C-4″), 31.35 (C-5″), 25.78 (C-7″), 20.41 (C-10″), 15.53 (C-9″). HR-ESI-MS m/z calcd for: $C_{22}H_{28}F_3NO_3Na$ = 434.1919. Found = 434.1903.

Menthyl 4-methyl-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-carboxylate (diastereoisomers C and D) (6f). (**C** + **D**): a yellow wax; IR (KBr, cm^{-1}): 2958, 2920, 2860, 1732, 1620, 1598, 1560, 1456, 1415, 1360, 1326, 1245, 1171, 1130, 1071, 1013, 932, 846, 780. **C:** ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.81 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.67 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 4.79 (m, 1H, H-5), 4.78 (m, 1H, H-1″), 3.96 (m, 1H, H-4), 1.66–0.40 (m, H-4a″, H-3a″, H-8″, H-6, H_3C–, H-5″, H-2″, H-4b″, H-3b″, H-6b″, H-7″, H_3C–, H-10″, H_3C–, H-9″, H_3C).

D: ^{1}H NMR (200 MHz, $CDCl_3$): 7.81 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.67 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 4.81 (m, 1H, H-5), 4.63 (m, 1H, H-1″), 3.92 (m, 1H, H-4), 1.66–0.40 (m, H-4a″, H-3a″, H-8″, H-6, H_3C–, H-5″, H-2″, H-4b″, H-3b″, H-6b″, H-7″, H_3C–, H-10″, H_3C–, H-9″, H_3C). Found: C, 64.5; H, 6.7. Calcd for $C_{22}H_{28}F_3NO_3$: C 64.2, H 6.85%.

Methyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-isopropyl-4-carboxylate (5g). A grey oil; IR (neat, cm^{-1}): 2964, 2930, 2860, 1743, 1619, 1598, 1560, 1470, 1437, 1412, 1395, 1340, 1326, 1170, 1128, 1071, 1016, 941, 860, 845, 770. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (d, J = 8.3 Hz, 2H, H-2′, H-6′), 7.65 (d, J = 8.3 Hz, 2H, H-3′, H-5′), 4.78 (dd, J = 7.0; 6.6 Hz, 1H, H-5), 4.22 (d, J = 7.0 Hz, 1H, H-4), 3.73 (s, 3H, H_3C–O–C=O), 1.99 (septet, 1H, $HC(CH_3)_2$), 1.03 (d, J = 6.9 Hz, 3H, $(H_3C)_2CH$), 1.0 (d, J = 7.0 Hz, 3H, $(H_3C)_2CH$). EI-MS m/z (% intensity) 315 (M^+, 20), 296 (M^+ – F, 14), 212 ($M^+ - HC(CH_3)_2C$=$OOCH_3$, 100), 145 ($F_3CC_6H_4$, 40), 59 (H_3COC=O, 38), 43 (H–$C(CH_3)_3$, 67). Found: C, 57.0; H, 5.3. Calcd for $C_{15}H_{16}F_3NO_3$: C 57.15, H 5.1%.

Methyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-isopropyl-5-carboxylate (6g). A yellow oil, IR (neat, cm^{-1}): 2963, 2930, 2852, 1760, 1744, 1619, 1600, 1560, 1466, 1430, 1412, 1370, 1326, 1170, 1129, 1070, 1017, 900, 883, 853, 770, 700. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.81 (d, $J = 8.3$ Hz, 2H, H-2′, H-6′), 7.67 (d, $J = 8.3$ Hz, 2H, H-3′, H-5′), 4.98 (d, $J = 3.9$ Hz, 1H, H-5), 3.94 (t, $J = 3.9$ Hz, 1H, H-4), 3.82 (s, 3H, H_3C–OC═O), 2.19 (dm, $J = 7.0$ Hz, 1H, $HC(CH_3)_2$), 1.09 (d, $J = 7.0$ Hz, 3H, $(H_3C)_2CH$), 0.79 (d, $J = 6.8$ Hz, 3H, $(H_3C)_2CH$). EI-MS m/z 315 (% intensity) (M^+, 12), 296 ($M^+ - F$, 14), 214 ($M^+ - HC(CH_3)_2C$═$OOCH_3 + H$, 100), 145 ($F_3CC_6H_4$, 30), 69 (F_3C, 7). Found: C, 56.95; H, 4.95. Calcd for $C_{15}H_{16}F_3NO_3$: C 57.15, H 5.1%.

Methyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-(*tert*-butyl)-4-carboxylate (5h). A yellow oil; IR (neat, cm^{-1}): 2960, 2860, 1743, 1619, 1600, 1560, 1475, 1437, 1412, 1369, 1326, 1169, 1128, 1072, 1017, 943, 870, 845, 770, 695, 602. ^1H NMR (200 MHz, $CDCl_3$): δ 7.81 (d, $J = 8.2$ Hz, 2H, H-2′, H-6′), 7.65 (d, $J = 8.2$ Hz, 2H, H-3′, H-5′), 4.70 (d, $J = 7.2$ Hz, 1H, H-5), 4.25 (d, $J = 7.2$ Hz, 1H, H-4), 3.73 (s, 3H, H_3C–O–C═O), 0.99 (s, 9H, $(H_3C)_3C$). EI-MS m/z (% intensity) 329 (M^+, 18), 310 ($M^+ - F$, 15), 213 ($M^+ - C(CH_3)_3C$═$OOCH_3$, 42), 212 ($M^+ - HC(CH_3)_3C$═$OOCH_3$, 42), 187 ($F_3CC_6H_4CNO$, 12), 145 ($F_3CC_6H_4$, 15), 69 (F_3C, 8), 57 ($C(CH_3)_3$, 100). Found: C, 58.65; H, 5.7. Calcd for $C_{16}H_{18}F_3NO_3$: C 58.35, H 5.5%.

Methyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-(*tert*-butyl)-5-carboxylate (6h). A yellow oil; IR (neat, cm^{-1}): 2926, 2852, 1741, 1618, 1600, 1550, 1468, 1430, 1411, 1380, 1325, 1170, 1130, 1069, 1016, 880, 847, 770, 700, 630. ^1H NMR (200 MHz, $CDCl_3$): δ 7.80–7.60 (m, 4H, H-2′, H-6′, H-3′, H-5′), 5.07 (d, $J = 2.9$ Hz, 1H, H-5), 3.76 (d, $J = 2.9$ Hz, 1H, H-4), 3.81 (s, 3H, H_3C–O–C═O), 0.93 (s, 9H, $(H_3C)_3C$). EI-MS m/z (% intensity) 329 (M^+, 10), 310 ($M^+ - F$, 12), 214 ($M^+ - C(CH_3)_3C$═$OOCH_3 + H$, 100), 145 ($F_3CC_6H_4$, 20), 69 (F_3C, 5), 57 ($C(CH_3)_3$, 72). Found: C, 58.4; H, 5.6. Calcd for $C_{16}H_{18}F_3NO_3$: C 58.35, H 5.5%.

Methyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-cyclohexyl-4-carboxylate (5i). A yellow oil; IR (neat, cm^{-1}): 2930, 2856, 1743, 1620, 1596, 1560, 1520, 1451, 1435, 1411, 1324, 1260, 1175, 1129, 1070, 1017, 1000, 938, 895, 860, 846, 770, 690. ^1H NMR (200 MHz, $CDCl_3$): δ 7.81 (d, $J = 8.2$ Hz, 2H, H-2′, H-6′), 7.65 (d, $J = 8.2$ Hz, 2H, H-3′, H-5′), 4.78 (dd, $J = 6.7$; 6.6 Hz, 1H, H-5), 4.25 (d, $J = 6.5$ Hz, 1H, H-4), 3.72 (s, 3H, H_3C–O–C═O), 1.89–1.60 (m), 1.35–1.00 (m). EI-MS m/z (% intensity) 355 (M^+, 23), 336 ($M^+ - F$, 18), 314 (100), 272 ($M^+ - C_6H_{11}$, 20), 213 ($M^+ - C_6H_{11}C$═$OOCH_3$, 35), 145 ($F_3CC_6H_4$, 25), 83 (C_6H_{11}, 60). HR EI-MS calcd for: $C_{18}H_{20}F_3NO_3$ = 355.1395. Found = 355.1391.

Methyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-cyclohexyl-5-carboxylate (6i). A yellow oil; ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, $J = 8.4$ Hz, 2H, H-2′, H-6′), 7.67 (d, $J = 8.4$ Hz, 2H, H-3′, H-5′), 5.02 (d, $J = 3.8$ Hz, 1H, H-5), 3.91 (dd, $J = 3.8$; 3.4 Hz, 1H, H-4), 3.80 (s, 3H, H_3CO–C═O), 1.73 (m), 1.45–0.90 (m). Found: C, 60.7; H, 5.8. Calcd for $C_{18}H_{20}F_3NO_3$: C 60.85, H 5.65%.

(+)-3-Pinanon-2-yl 5-methyl-3-(4-(trifluoromethylphenyl)-4,5-dihydroisoxazole-4-carboxylate) (diastereoisomers A and B) (5j). A grey oil; **A**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, $J = 8.5$ Hz, 2H, H-6′, H-2′), 7.68 (d, $J = 8.5$ Hz, 2H, H-5′, H-3′), 5.07 (d, $J = 6.5$ Hz, 1H, H-5), 4.03 (d, $J = 6.5$ Hz, 1H, H-4), 2.96 (m, 1H, H-13), 2.81–2.32 (m, 1H, H-9a, H-9b), 2.26–2.20 (m, 2H, H-10b, H-12a), 2.09–2.06 (m, 1H, H-10b), 1.50 (s, 3H, H_3C), 1.65–1.20 (m, 9H, H-12b, H-13, H-6, H_3C–CH, H-16, H_3C), 0.83 (s, 3H, H-15, H_3C).

B: ^1H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, $J = 8.5$ Hz, 2H, H-6′, H-2′), 7.65 (d, $J = 8.5$ Hz, 2H, H-5′, H-3′), 5.16 (d, $J = 6.5$ Hz, 1H, H-5), 4.05 (d, $J = 6.5$ Hz, 1H, H-4), 2.8 (t, $J = 6.0$ Hz, 1H, H-13), 2.81–2.32 (m, 2H, H-9a, H-9b), 2.26–2.20 (m, 2H, H-12a, H-10a), 2.03–2.00 (m, 1H, H-10b), 1.54 (s, 3H, H_3C), 1.65–1.20 (m, 9H, H-12b, H-13, H-6, H_3C–CH, H-15, H_3C), 0.81 (s, 3H, H-16, H_3C).

(**A** + **B**) HR-ESI-MS calcd for: $C_{22}H_{24}O_4NF_3Na$ = 446.1555. Found = 446.1548.

(+)-3-Pinanon-2-yl 4-methyl-3-(4-(trifluoromethylphenyl)-4,5-dihydroisoxazole-5 carboxylate) (diastereoisomers C and D) (6j). A yellow oil; **C**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, $J = 8.5$ Hz, 2H, H-6′, H-2′), 7.68 (d, $J = 8.5$ Hz, 2H, H-5′, H-3′), 4.72 (d, $J = 4.5$ Hz, 1H, H-5), 3.89 (d, $J = 4.5$ Hz, 1H, H-4), 2.89 (t, $J = 6.0$ Hz, 1H, H-13), 2.81–2.75 (m, 1H, H-9a, H-9b), 2.72–2.65 (m, 2H, H-12a, H-10a), 2.15 (m, 1H, H-10b), 1.64 (s, 3H, H_3C), 1.58–1.20 (m, 9H, H-12b, H-13, H-6, H_3C–CH, H-15, H_3C), 0.88 (s, 3H, H-16, H_3C) ppm.

D: ^1H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, $J = 8.5$ Hz, 2H, H-6′, H-2′), 7.68 (d, $J = 8.5$ Hz, 2H, H-5′, H-3′), 4.72 (d, $J = 4.5$ Hz, 1H, H-5), 3.96 (d, $J = 4.5$ Hz, 1H, H-4), 2.81 (t, $J = 6.0$ Hz, 1H, H-13), 2.81–2.32 (m, 1H, H-9a, H-9b), 2.26–2.10 (m, 2H, H-10a, H-12a), 2.02 (m, 1H, H-10), 1.65 (s, 3H, H_3C), 1.59–1.20 (m, 9H), 0.87 (s, 3H, H-15, H_3C).

(**C** + **D**) HR-ESI-MS calcd for: $C_{22}H_{24}O_4NF_3Na$ = 446.1555. Found = 446.1558.

(3-Methyloxetan-3-yl)-methyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-methyl-4-carboxylate (5k). A green oil; ^1H NMR (200 MHz, $CDCl_3$): δ 7.82 (d, $J = 8.1$ Hz, 2H, H-2′, H-6′), 7.66 (d, $J = 8.1$ Hz, 2H, H-3′, H-5′), 5.20 (dq, $J = 6.5$; 6.1 Hz, 1H, H-5), 4.29 (d, $J = 2.2$ Hz, 2H, H-9), 4.27 (d, $J = 2.2$ Hz, 2H, H-10), 4.21 (s, 2H, –O–CH_2C), 4.17 (d, $J = 6.1$ Hz, 1H, H-4), 1.50 (d, $J = 6.5$ Hz, 3H, H_3C–CH), 1.15 (s, 3H, H_3C–C). ^{13}C NMR (125.9 MHz, $CDCl_3$): δ 168.86 (O–C═O), 152.59 (1C, C-3), 132.37 (1C, C-4′), 124.79 (1C, C-1′), 127.12 (2C, C-6′, C-2′), 125.76 (q, $J = 3.8$ Hz, 2C, C-5′, C-3′), 82.71 (1C, C-5), 79.13 (C-9), 79.09 (C-10), 70.25 (1C, –C–CH_2–O), 59.52 (1C, C-4), 39.06 (1C, C-8, –C–), 20.76 (1C, H_3C–C, C-11), 20.74 (1C, C-9, H_3C–CH–). HR ESI-MS calcd for: $C_{17}H_{18}O_4NF_3$-Na = 380.1086. Found = 380.1082.

(3-Methyloxetan-3-yl)-methyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-methyl-5-carboxylate (6k). A yellow oil; ^1H NMR (200 MHz, $CDCl_3$): δ 7.81 (d, $J = 8.2$ Hz, 2H, H-2′, H-6′), 7.68 (d, $J = 8.2$ Hz, 2H, H-3′, H-5′), 4.87 (d, $J = 4.1$ Hz, 1H, H-5), 4.55–4.15 (m, 4H, H-9, H-10), 4.31 (s, 2H, OCH_2C), 4.05 (dd, $J = 7.2$; 4.1 Hz, 1H, H-4), 1.44 (d, $J = 7.2$ Hz, 3H, H_3C–CH), 1.34 (s, 3H, H_3C–C). EI-MS m/z (% intensity) 358 ($M^+ + H$, 2), 338 ($M^+ - F$, 15), 228 (100), 157 ($M^+ - (CH_2OCH_2CCH_3)CH_2OC$═O, 25), 145 ($F_3CC_6H_4$, 35), 72 ($H_2COCH_2CCH_3 + H$, 85). Found: C, 57.2; H, 4.35. Calcd for $C_{17}H_{15}F_3NO_4$: C 57.15, H 4.25%.

Pyrrolidine-2,5-dione-1-yl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-methyl-4-carboxylate (5l). A yellow oil; ^1H NMR (200 MHz, $CDCl_3$): δ 7.97–7.64 (m, 4H, H-2′, H-6′, H-3′, H-5′), 5.23 (dq, $J = 7.0$; 6.5 Hz, 1H, H-5), 4.39 (d, $J = 6.5$ Hz, 1H, H-

4), 2.84 (m, 4H), 1.61 (d, J = 7.0 Hz, 3H, H_3C–CH). Found: C, 51.7; H, 3.7. Calcd for $C_{16}H_{13}F_3N_2O_5$: C 51.9, H 3.55%.

Pyrrolidine-2,5-dione-1-yl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-methyl-5-carboxylate (6l). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.67 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 4.99 (d, J = 4.1 Hz, 1H, H-5), 4.27 (dq, J = 7.0; 4.1 Hz, 1H, H-4), 2.10–1.00 (m, 4H), 1.36 (d, J = 7.0 Hz, 3H, H_3C–CH). EI-MS m/z (% intensity) 363 (M^+, 2), 344 (M^+ − F, 2), 212 (M^+ − H(CH_3)C=$OOCH_2C_6H_5$, 5), 145 ($F_3CC_6H_4$, 50), 91 ($H_2CC_6H_5$, 30), 83 (100). Found: C, 52.2; H, 3.8. Calcd for $C_{16}H_{13}F_3N_2O_5$: C 51.9, H 3.55%.

Benzyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-methyl-4-carboxylate (5m). A yellow oil; $[\alpha]_D^{25}$ = −115.0 (c 0.45 in acetone [93.2% ee, (*R*, *S*) rich]). IR (KBr, cm^{-1}): 3435, 2970, 2930, 1738, 1619, 1599, 1499, 1456, 1412, 1377, 1327, 1169, 1128, 1071, 1014, 938, 909, 853, 756, 701. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.55 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 7.27 (m, 2H, H-2″, H-6″), 7.14 (m, 3H, H-3″, H-4″, H-5″), 5.14 (m, 3H, $ArCH_2O$ and H-5), 4.12 (d, J = 6.6 Hz, 1H, H-4), 1.49 (d, J = 6.4 Hz, 3H, H_3C–CH). EI-MS m/z (% intensity) 363 (M^+, 23), 344 (M^+ − F, 18), 212 (M^+ − H(CH_3)C=$OOCH_2C_6H_5$, 12), 145 ($F_3CC_6H_4$, 15), 91 ($H_2CC_6H_5$, 100). Found: C, 62.5; H, 4.1. Calcd for $C_{19}H_{16}F_3NO_3$: C 62.8, H 3.9%.

Benzyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-methyl-5-carboxylate (6m). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.81–7.53 (m, 5H) and 7.30–7.09 (m, 4H), 5.23 (s, 2H, $ArCH_2$–O), 4.85 (d, J = 4.4 Hz, 1H, H-5), 3.96 (dq, J = 7.2; 4.4 Hz, 1H, H-4), 1.41 (d, J = 7.2 Hz, 3H, H_3C–CH). Found: C, 62.7; H, 3.8. Calcd for $C_{19}H_{16}F_3NO_3$: C 62.8, H 3.9%.

Phenyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-methyl-4-carboxylate (5n). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.94–6.91 (m, 10H, H-2′, H-3′, H-4′, H-5′, H-6′, H-2″, H-3″, H-4″, H-5″, H-6″), 5.33 (dm, J = 6.4 Hz, 1H, H-5), 4.33 (d, J = 6.4 Hz, 1H, H-4), 1.59 (d, J = 6.4 Hz, 3H, H_3C–CH). HR-EI-MS calcd for: $C_{18}H_{14}F_3NO_3$ = 349.0926. Found = 349.0944.

Phenyl 3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-methyl-5-carboxylate (6n). A yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94–6.90 (m, 9H, aryl), 5.06 (d, J = 4.3 Hz, 1H, H-5), 4.17 (dq, J = 7.2; 4.3 Hz, 1H, H-4), 1.51 (d, J = 7.2 Hz, 3H, H_3C–CH). EI-MS m/z (% intensity) 349 (M^+, 15), 330 (M^+ − F, 10), 273 (M^+ − C_6H_5 + H, 5), 256 (M^+ − C_6H_5O, 35), 228 (M^+ − C_6H_5OC=O, 100), 212 (M^+ − H(CH_3)OC=OC_6H_5, 20), 145 ($F_3CC_6H_4$, 70). Found: C, 62.25; H, 4.2. Calcd for $C_{18}H_{14}F_3NO_3$: C 61.9, H 4.05%.

Methyl 5-(2-furanyl)-3-(4-(trifluoromethylphenyl)-4,5-dihydroisoxazole-4-carboxylate) (5o). A yellow oil; IR (KBr, cm^{-1}): 3440, 3130, 3010, 2970, 2840, 1745, 1620, 1600, 1560, 1500, 1437, 1413, 1326, 1300, 1250, 1220, 1170, 1160, 1131, 1070, 1014, 997, 921, 848, 830, 754. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.89 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.68 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 7.42 (dd, J = 1.8; 0.6 Hz, 1H, H-9), 6.48 (dd, J = 3.2; 0.6 Hz, 1H, H-7), 6.38 (dd, J = 3.2; 1.8 Hz, 1H, H-8), 6.03 (d, J = 6.4 Hz, 1H, H-5), 4.80 (d, J = 6.4 Hz, 1H, H-4), 3.75 (s, 3H, H_3CO–C=O). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 168.97 (H_3CO–C=O), 152.92 (C-3), 150.04 (C-6, OC=CH), 143.97 (C-9), 132.15 (q, J = 33.0 Hz, C-4′), 131.99 (C-1′), 127.55 (2C, C-6′, C-2′), 125.94 (q, J = 4.0 Hz, 2C, C-5′, C-3′), 124.0 (q, J = 272.3 Hz, Ar-CF_3), 110.93 (C-7, C=CH–CH=CH–O), 110.18 (C-8, C=CH–CH=CH–O), 80.61 (C-5), 57.01 (C-4), 53.53 (H_3CO–C=O). HR ESI-MS calcd for: $C_{16}H_{12}F_3NO_4Na$ = 362.0616, Found = 362.0610.

Methyl 4-(2-furyl)-3-(4-(trifluoromethylphenyl)-4,5-dihydroisoxazole-5-carboxylate) (6o). A yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.3–7.6 (m, 4H, H-2′, H-6′, H-3′, H-5′), 7.5–7.3 (m, 1H, H-9), 6.54 (dm, J = 3.3 Hz, 1H, H-7), 6.42 (dd, J = 3.3; 1.9 Hz, 1H, H-8), 5.67 (d, J = 2.4 Hz, 1H, H-5), 5.51 (d, J = 2.4 Hz, 1H, H-4), 3.76 (s, 3H, H_3C–O–C=O). HR-EI-MS calcd for: $C_{16}H_{12}F_3NO_4$ = 339.0718. Found = 339.0686.

Methyl 5-(1,3-benzodioxolyl)-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-4-carboxylate (5p). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.74 (d, J = 8.1 Hz, 2H, H-2′, H-6′), 7.56 (d, J = 8.1 Hz, 2H, H-3′, H-5′), 6.79 (d, J = 9.6. Hz, 1H, H-5″), 6.78 (d, J = 9.6 Hz, 1H, H-6″), 6.71 (s, 1H, H-3″), 5.97 (m, 2H, H-7″), 5.94 (m, 1H, H-5), 4.98 (s, 1H, H-4), 3.85 (s, 3H, H_3CO–C=O). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 170.06 (H_3CO–C=O), 157.15 (C-3), 148.15 (C-2″), 147.87 (C-1″), 132.75 (C-1′), 131.93 (C-4″), 131.50 (m, C-4′), 127.78 (C-6′, C-2′), 125.60 (m, 2C, C-5′, C-3′), 121.00 (C-6″), 109.08 (C-5″), 107.50 (C-3″), 101.41 (C-7″), 86.75 (C-5), 57.57 (C-4), 53.10 (H_3CO–C=O). Found: C, 58.2; H, 3.5. Calcd for $C_{19}H_{14}F_3NO_5$: C 58.0, H 3.6%.

Methyl 4-(1,3-benzodioxolyl)-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-carboxylate (6p). A yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.84 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.65 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 6.80 (m, 3H, H-3″, H-5″, H-6″), 5.95 (m, 2H, H-7″), 5.94 (d, J = 6.9 Hz, 1H, H-5), 4.46 (d, J = 6.9 Hz, 1H, H-4), 3.77 (s, 3H, H_3CO–C=O). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 169.41 (H_3CO–C=O), 152.83 (C-3), 148.51 (C-2″), 148.31 (C-1″), 132.92 (C-1′), 132.2 (q, J = 32.4 Hz, 1C, C-4′), 127.43 (2C, C-6′, C-2′), 125.94 (q, J = 3.6 Hz, 2C, C-5′, C-3′), 123.9 (q, J = 272.3 Hz, Ar-CF_3), 119.59 (C-6″), 108.70 (C-5″), 106.09 (C-3″), 101.59 (C-7″), 87.66 (C-5), 61.30 (C-4), 53.48 (H_3CO–C=O). HR ESI-MS calcd for: $C_{19}H_{14}F_3NO_5Na$ = 416.0722, found = 416.0739.

(2*Z*)-Pent-2-en-1-yl acetate (7a).[49] A yellow oil (35%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.71–5.42 (m, 2H, H_3CCH_2HC=CH), 5.88 (dq, J = 15.4; 1.7 Hz, 1H, O=CHC=C), 4.44 (d, J = 6.6 Hz, 2H, OCH_2CH=C), 2.10 (qd, J = 7.3; 2.4 Hz, 2H, H_3CCH_2–CH=C), 2.04 (s, 3H, H_3C–C=O), 0.99 (t, J = 7.3 Hz, 3H, H_3C–CH_2).

(2*Z*)-Pent-2-en-1-yl methoxyacetate (7b). A yellow oil (35%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 5.80–5.20 (m, 2H, H_2C–CH=CH–CH_2), 4.72 (d, J = 6.6 Hz, 2H, O=C–O–CH_2–HC=C), 4.04 (s, 2H, OCH_2–C=O), 3.45 (s, 3H, H_3CO), 2.13 (m, J = 7.5 Hz, 2H, C=CH–CH_2–CH_3), 1.00 (t, J = 7.5 Hz, 3H, H_3CCH_2). Found: C, 60.9; H, 9.15. Calcd for $C_8H_{14}O_3$: C 60.7, H 8.9%.

[5-Ethyl-3-(4-(trifluoromethylphenyl)-4,5-dihydroisoxazol-4-yl)]methyl acetate (8a). A greenish oil; IR (KBr, cm^{-1}): 3436, 2964, 1746, 1635, 1619, 1450, 1400, 1385, 1337, 1324, 1238, 1167, 1127, 1075, 1050, 980, 920, 937, 846, 775. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 (d, J = 8.3 Hz, 2H, H-6′, H-2′), 7.68 (d, J = 8.3 Hz, 2H, H-5′, H-3′), 4.55 (dt, J = 8.4; 6.4 Hz, 1H, H-5), 4.23 (dd, J = 11.9; 4.6 Hz, 1H, HC–HaC–OC=O), 4.20 (dd, J = 11.9; 7.3 Hz, 1H, –HC–HbC–OC=O), 3.79 (ddd, J = 8.4; 7.3; 4.6 Hz, 1H, H-4), 2.00 (s, 3H, H_3C–C=O), 1.92 (m, 2H, HC–CH_2CH_3), 1.16 (t, J = 7.4 Hz, 3H, H_3C–CH_2). EI-MS m/z (% intensity) 339 (M^+ + H + Na, 20), 314 (M^+ − 1H, 5), 296 (M^+ − F, 5), 213 (M^+ − CH_3C=$OOCH_2C_2H_5$, 10), 187 ($F_3CC_6H_4CNO$, 85), 173 (100), 145

($F_3CC_6H_4$, 45). Found: C, 54.5; H, 4.2. Calcd for $C_{15}H_{14}F_3NO_4$: C 54.7, H 4.3%.

[4-Ethyl-3-(4-(trifluoromethylphenyl)-4,5-dihydroisoxazol-5-yl)]methyl acetate (9a). A yellow oil; IR (KBr, cm^{-1}): 2972, 2940, 2860, 1745, 1620, 1595, 1563, 1520, 1460, 1411, 1360, 1326, 1236, 1169, 1128, 1069, 1040, 1015, 920, 848, 778. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.80 (d, $J = 8.3$ Hz, 2H, H-2′, H-6′), 7.68 (d, $J = 8.3$ Hz, 2H, H-3′, H-5′), 4.83 (ddd, $J = 9.1$; 7.7; 4.2 Hz, 1H, H-5), 4.59 (dd, $J = 12.0$; 4.2 Hz, 1H, H-6a), 4.42 (dd, $J = 12.0$; 7.7 Hz, 1H, H-6b), 3.66 (dt, $J = 9.1$; 5.6 Hz, 1H, H-4), 2.15 (s, 3H, $H_3CC{=}O$), 1.68 (m, 2H, H-7, CH–CH_2–CH_3), 0.92 (t, $J = 7.5$ Hz, 3H, H-8, CH_2–CH_3). EI-MS *m*/*z* (% intensity) 316 ($M^+ + H$, 2), 296 ($M^+ - 1F$, 10), 213 ($M^+ - CH_3C{=}OOCH_2C_2H_5$, 50), 198 (100), 187 ($F_3CC_6H_4CNO$, 8), 145 ($F_3CC_6H_4$, 32). Found: C, 54.55; H, 4.15. Calcd for $C_{15}H_{14}F_3NO_4$: C 54.7, H 4.3%.

[4-Ethyl-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazol-5-yl]methyl methoxyacetate (8b). A yellow oil; ^1H NMR (200 MHz, $CDCl_3$): δ 8.10–7.66 (m, 4H, H-2′, H-6′, H-3′, H-5′), 4.23–3.20 (m, 4H, H-5, H-6a, H-6b, H-4), 4.01 (s, 2H, O=C–CH_2–O), 3.35 (s, 3H, H_3C–OC), 1.65 (m, 2H, H-7, CH–CH_2CH_3), 0.97 (t, $J = 7.2$ Hz, 3H, H-8). Found: C, 53.4; H, 4.6. Calcd for $C_{16}H_{16}F_3NO_5$: C 53.5, H 4.5%.

[5-Ethyl-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazol-4-yl]methyl methoxyacetate (9b). A greenish oil; ^1H NMR (200 MHz, $CDCl_3$): δ 7.92–7.64 (m, 4H, H-2′, H-6′, H-3′, H-5′), 5.25–3.30 (m, 4H, H-5, H-6a, H-6b, H-4), 4.02 (s, 2H, O=C–CH_2–O), 3.40 (s, 3H, H_3C–OC), 2.00–1.60 (m, 2H, H-7, CH–CH_2–CH_3), 1.16 (t, $J = 7.4$ Hz, 3H, H-8). Found: C, 53.8; H, 4.65. Calcd for $C_{16}H_{16}F_3NO_5$: C 53.5, H 4.5%.

(2*E*)-*N*-cyclohexyl-*N*′-(cyclohexylcarbamoyl)-but-2-enamide (10).[50] It was isolated as a side product in synthesis of esters **3f**, **3j**, and **3l** (with application of DCC) with yields, respectively, 15%, 25%, and 5%. A white semisolid. IR (KBr, cm^{-1}): 3420, 3258, 3050, 2924, 2855, 1706, 1661, 1613, 1544, 1450, 1393, 1375, 1348, 1302, 1275, 1260, 1233, 1173, 1108, 1082, 998, 973, 940, 898, 865, 801, 740, 695. ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 (s, 1H, –HN), 6.91 (dq, $J = 13.8$; 7.0 Hz, 1H, H_3C–HC=C), 6.13 (dq, $J = 13.8$; 1.8 Hz, 1H, C=CH–C=O), 3.98 (td, $J = 11.8$; 3.5 Hz, 1H, H-1′), 3.71 (m, 1H, H-1″), 1.96 (m, 2H), 1.81 (m, 4H), 1.73 (dt, $J = 13.5$; 4.0 Hz, 4H), 1.63 (m, 2H), 1.43–1.12 (m, 8H), 1.88 (dd, $J = 7.0$; 1.5 Hz, 3H, H_3C–CH=CH). EI-MS *m*/*z* (% intensity) 292 (M^+, 32), 211 (($M^+ - C_6H_{11}$) + 2H, 70), 166 ($M^+ - C_6H_{11}C{=}$ ONH, 20), 98 (–NC_6H_{11} + H, 65), 83 (C_6H_{11}, 52), 69 ($H_3CCH{=}$ CH–C=O, 100), 41 (–CH=$CHCH_3$, 47).

Fungicidal testing

The compounds were screened for fungicidal activity *in vitro.* The test was carried out for *Fusarium culmorum* Sacc., *Phytophthora cactorum* Schroek, *Alternaria alternata* Keissl. (Fr.), *Rhizoctonia solani* Kuhn, and *Botrytis cinerea* Pers. Ex Fr, which involved determination of mycelial growth retardation in potato glucose agar (PGA). Stock solutions of test chemicals in acetone were added to agar medium to give a concentration of 200 mg L^{-1} and dispersed into Petri dishes. Four discs containing the test fungus were placed at intervals on the surface of the solidified agar and the dishes were then inoculated for 4–8 days depending on the growth rate of the control samples, after which fungal growth was compared with that in untreated control samples. The fungicidal activity was expressed as the percentage of fungi linear growth inhibition compared to that of the control.

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