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1,3-Dipolar Cycloaddition of *N*-Substituted Dipolarophiles and Nitrones: Highly Efficient Solvent-Free Reaction

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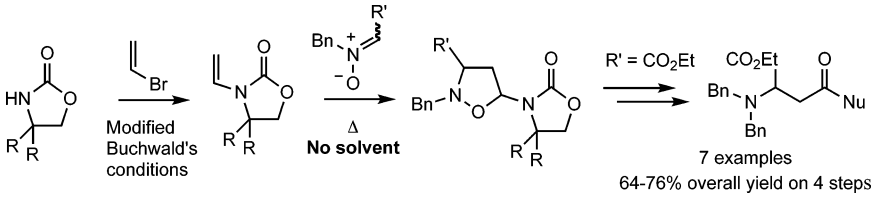
Received November 22, 2007



New isoxazolidines were synthesized in good to excellent yields by 1,3-dipolar cycloaddition of *N*-vinylamide dipolarophiles and nitrones. Strikingly, solvent-free conditions gave high conversion and yields, shortened reaction time, and minimized degradation products. *N*-Vinyloxazolidin-2-one and its analogues used in these cycloaddition reactions were conveniently prepared in excellent yields by a modified version of Buchwald's one-step copper-catalyzed vinylation using vinyl bromide. From the adducts, a two-step access to various unsymmetric aspartate derivatives was also described.

Introduction

1,3-Dipolar cycloaddition reactions of nitrones with alkenes offer one of the most powerful routes to isoxazolidines.[1,2] Reductive cleavage of the nitrogen-oxygen bond of such adducts gives 3-amino alcohols.[2] Therefore, nitrone cycloaddition can afford a versatile way for construction of nitrogen-containing carbon skeletons. Numerous applications of isoxazolidine adducts have been reported in total synthesis, often based on their ease to be transformed into polyfunctional amines including γ-amino alcohols, β-amino ketones and esters.[3] Inverse-electron-demand 1,3-dipolar cycloaddition has mostly been studied with vinyl ethers,[4] vinyl esters,[5] and *N*-acyloxazolones.[6] Our work focused on the cycloaddition between a nitrone bearing a protecting group (PG) on nitrogen and a *N*-vinylcarbamate as dipolarophile. An interesting application for these adducts (Scheme 1) could concern a novel enantioselective access to unsymmetric aspartate derivatives.

We have recently published a study on the 1,3-dipolar cycloaddition of *N*-substituted dipolarophiles and nitrones.[7] This first investigation began with the reaction under several Lewis acid catalyzed and thermal conditions (in solution). The best results were obtained under noncatalyzed thermal conditions (refluxing toluene). In this paper, we wish to report an optimized procedure to achieve the cycloaddition between a nitrone and a *N*-vinyl(amide/carbamate/imide) involving solvent-free conditions in very short reaction time (up to less than 1 min) with little or no formation of degradation products.

Enamides, which serve as versatile intermediates for synthesizing nitrogen-containing compounds, have been prepared to date by various methods including acylation of imines,[8] condensation of amides and aldehydes,[9] metal-catalyzed[10] or

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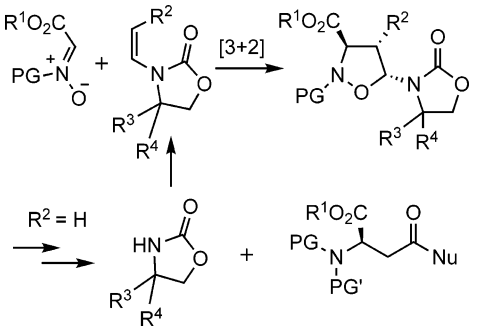
10.1021/jo702490w CCC: $40.75
Published on Web 03/11/2008

SCHEME 1



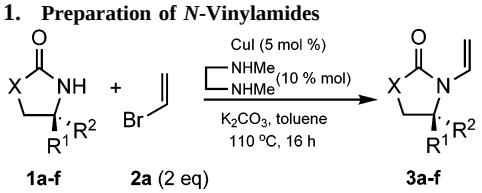
strong base-induced[11] isomerization of *N*-allylamides, elimination of alcohols from *N*-(alkoxyalkyl)amides,[12] addition of amides to acetylenes,[13] metal-catalyzed coupling of alkenes and amides,[14] and trans vinylation using alkyl vinyl ethers[15] or vinyl carboxylates,[16] vinyl bromides/iodides and amides.[17] As an extension of the Buchwald's method,[17a] we report a one-step procedure for synthesizing vinylamides from unsubstituted vinyl bromide/iodide and amides.

Results and Discussion

Preparation of Aza-Substituted Dipolarophiles. Alkenylamides are conveniently prepared by the Buchwald's one-step procedure based on the copper-catalyzed direct vinylation of amide nitrogen using vinyl bromides.[17] To the best of our knowledge, such vinylation has never been employed to unsubstituted vinyl bromide and from a more general point of view, there has been no one-step practical method for synthesizing vinylamides from unsubstituted vinyl bromide/iodide and amides.

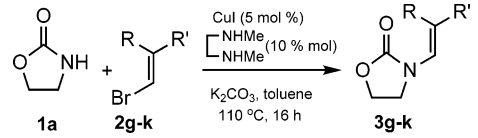
Considering the high volatility of vinyl bromide (bp 6 °C) in regard to high temperature required for coupling reaction, we carried out the reaction in a sealed tube. Using a slight excess of vinyl bromide (2 equiv) which was charged at 0 °C, this procedure afforded *N*-vinylamides in excellent yields (92−100%) (Table 1, entries 1−5). The coupling is not affected by the nature of substituent at C-4 of oxazolidinone (Table 1, entries 2−4). Vinylation could also be carried out with phthalimide (Table 1, entry 6) despite the low yield (20%).

TABLE 1. Preparation of *N*-Vinylamides



entry	amide	X	R^1	R^2	*N*-vinylamide	yield (%)
1	**1a**	O	H	H	**3a**	92
2	**1b**	O	Me	Me	**3b**	100
3	**1c**	O	H	Ph	**3c**	95
4	**1d**	O	Et	H	**3d**	95
5	**1e**	NMe	H	H	**3e**	92
6	**1f**	phthalimide			**3f**	20

TABLE 2. Preparation of *N*-Alkenyloxazolidin-2-ones



entry	alkenyl bromide	R	R′	alkenylamide	yield (%)
1	**2b**	Me	H	**3g**	95
2	**2c**	Me	Me	**3h**	95
3	**2d**	Ph	H	**3i**	98
4	**2e**	H	4-MeO−C_6H_4	**3j**	98
5	**2f**	4-NO_2-C_6H_4	H	**3k**	95

Alkenylamides were also prepared by this method (Table 2). Two volatile homologues of vinyl bromide, (*Z*)-propenyl bromide (**2b**), and 2-methylpropenyl bromide (**2c**) were utilized in excess (1.5 equiv) in order to consume all oxazolidin2-one after the reaction. Applying this procedure to β-styryl bromides (**2d**−**f**) gave also excellent yields. In these cases, the benzene ring can bear an electron donating group (Table 2, entry 4) or an electron withdrawing group (entry 5). The configuration of the double bond was retained. In all cases, a simple filtration through Celite of the crude reaction mixture followed by solvent elimination is sufficient to furnish pure products which could be used in the next step.

Cycloaddition Conditions Optimization. The reaction between *N*-benzyl-α-carbonyloxyalkylnitrone (e.g., **4a**) and β-unsubstituted vinyl amides provided good yields in refluxing toluene. However, when another nitrone was employed (namely *N*-benzyl-α-arylnitrone **4b**−**d**), varying yields of isoxazolidine adducts were observed, possibly because of the long reaction time which resulted in partial degradation. In order to extend the scope of the cycloaddition to various nitrones, we needed to find more efficient conditions that could accelerate the reaction rate and minimize the degradation. In the literature, many authors reported the cycloaddition of *N*-benzyl-α-carbonyloxyalkylnitrone with alkenes or vinyl ethers/esters.[4] Under these conditions, dipolarophiles were utilized as solvent or in large excess with or without catalyst. However, vinyl amides can hardly be used as solvent or in large excess because of their

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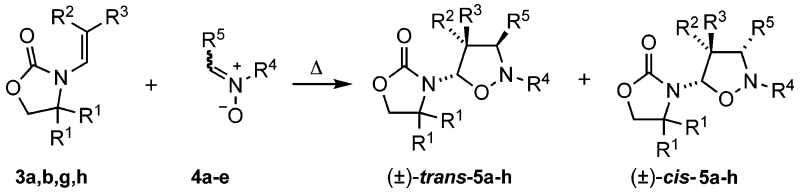
TABLE 3. 1,3-Dipolar Cycloaddition of 3/4: Comparison between Solution- and Solvent-Free Conditions



									cycloaddition in refluxing solution[a]			solvent-free cycloaddition[b]			trans/cis
entry	enamide	R^1	R^2	R^3	nitrone	R^4	R^5	adduct	solvent	time	yield[c] (%)	time	T (°C)	yield[c] (%)	ratio[d]
1	**3a**	H	H	H	**4a**	Bn	CO_2Et	**5a**	toluene	24 h	91	10 min	110	99	4:1
2	**3a**	H	H	H	**4b**	Bn	Ph	**5b**	*p*-xylene	13 d	53	3 d	110	96	1:2.3
3	**3a**	H	H	H	**4c**	Bn	4-F-Ph	**5c**	*p*-xylene	6 d	20	10 h	140	80	1.15:1
4	**3a**	H	H	H	**4d**	Bn	4-CF_3Ph	**5d**	*p*-xylene	3 d	0	2 h	160	82	1:4
5	**3a**	H	H	H	**4e**	Ph	Ph	**5e**	toluene	6 d	80	30 min	110	89	1:8
6	**3b**	Me	H	H	**4a**	Bn	CO_2Et	**5f**	toluene	24 h	89	10 min	110	95	10:1
7	**3b**	Me	H	H	**4d**	Bn	4-CF_3Ph	**5g**	*p*-xylene	6 d	20	2 h	160	75	3.3:1
8	**3g**	H	Me	H	**4a**	Bn	CO_2Et	**5h**	toluene	3 d	50	10 h	110	70	8:1[e]
9	**3h**	H	Me	Me	**4a**	Bn	CO_2Et		toluene	3 d	0[f]	3 d	110	0[f]	

[a] 1 mmol of enamide and 1 mmol of nitrone were heated in 5 mL of solvent. [b] 1 mmol of enamide and 1 mmol of nitrone were heated at indicated temperature. [c] Isolated yields of separated diastereoisomers or mixture of two diastereoisomers. [d] Based on ^{1}H NMR of crude mixture. [e] The two isomers with a trans C_4-C_5 relationship were not observed. [f] No reaction, enamide was recovered.

commercial unavailability and the difficult removal. In order to extend the scope of the thermal cycloaddition, solvent-free reactions appeared to be an interesting way. Under these conditions at 110 °C, the cycloaddition between stoichiometric amount of nitrone **4a** and *N*-vinyloxazolidin-2-one **3a** proved to be complete after 30 min without any formation of side-products and any effect on the stereoselectivity. At this temperature, melted nitrone **4a** and enamide **3a** form a homogeneous mixture that ensures close contact. Both reaction conditions (refluxing toluene/xylene vs solvent-free) were summarized in Table 3. The reactions leading to good yields of expected cycloadducts in refluxing toluene were performed with a dramatic decrease in reaction time (∼200 times) under solvent-free conditions (Table 3, entries 1, 5, and 6). The sluggish reaction of *N*-benzyl-α-arylnitrone **4b-d** in toluene was also accelerated with less degradation in solvent-free system and thus simplifying the purification process (Table 3, entries 2−4, and 7).

When **3g** bearing a *Z*-*β*-methyl group was used as dipolarophile, the cycloaddition with nitrone **4a** took place much more slowly than its unsubstituted homologues and did not go to completion in refluxing toluene. Under solvent-free conditions, the reaction was achieved after 10 h at 110 °C with partial degradation of nitrone **4a** (Table 3, entry 8) and with an interesting stereoselectivity. In case of *β*,*β*-dimethyl dipolarophile **3h**, no trace of adduct was observed after 3 days of heating (Table 3, entry 9) under both conditions.

From unsubstituted *N*-vinyloxazolidin-2-one **3a**, *N*-benzyl-isoxazolidines **5a**−**d** were obtained with various trans or *cis* stereoselectivities, dependent on the nature of the nitrone substituent: *trans*-ester isoxazolidine **5a** is mainly obtained from **4a**, whereas aryl isoxazolidines **5b**−**d** are obtained in most cases with a *cis* selectivity (Table 3, entries 1−4). In contrast, a *trans* selectivity is observed for both adducts **5f,g** deriving from the 4,4-disubstituted *N*-vinyloxazolidin-2-one **3b** (Table 3, entries 6 and 7). Moreover, it should be noticed that the *N*-phenyl adduct **5e** was efficiently obtained with a good *cis* selectivity (Table 3, entry 5).

The relative configuration of all adducts could be unambiguously elucidated from NOESY experiments as exemplified in Figure 1 for compound *cis*-**5a**, *trans*-**5a**, *cis*-**5e**, and *trans*-**5h**. Three NOESY correlation peaks (between H-3 and H-4*β*, between H-4*β* and H-5, between H-5 and H-3) confirm the *cis*-relationship between the two substituents at C-3 and C-5 in *cis*-**5a** and *cis*-**5e**. Besides the presence of two NOESY correlation peaks (between H-5 and H-4*β*, between H-4α and H-3 in *trans*-**5a**; between H-3 and CH_3 at C-4, between H-4 and H-5 in *trans*-**5h**), the absence of NOESY correlation peak between H-3 and H-5 helped to deduce the trans relationship between oxazolidinone and carbonyloxyethyl moieties in *trans*-**5a** and *trans*-**5h**. The *Z* geometry of dipolarophile **3g** was retained in the major adduct **5h** (total absence of NOESY correlation peak between H-5 and CH_3 at C-4) in full agreement with the concerted nature of the thermal cycloaddition.

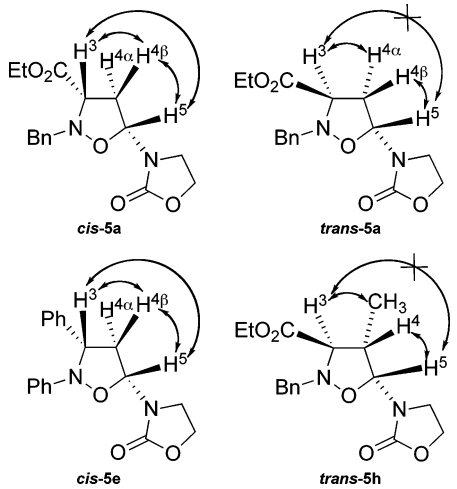
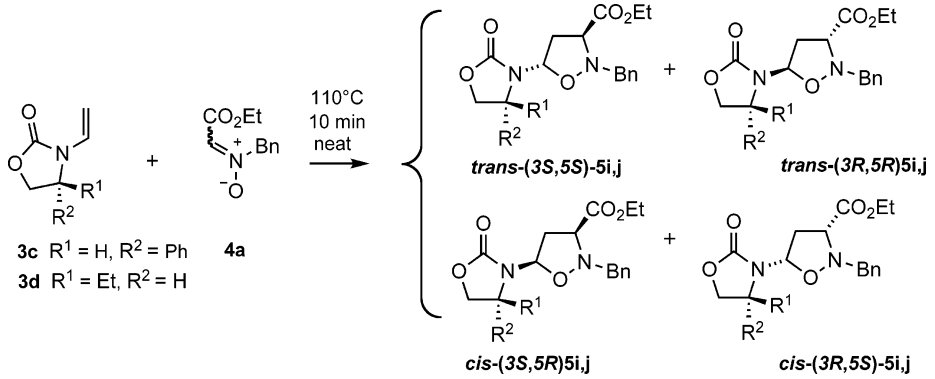


FIGURE 1. 2D NOESY correlation for adducts **5**.

All cycloadditions between **4a** and 2-styryloxazolidin-2-ones (**3i**−**l**, Scheme 2) failed to occur, regardless of double bond configuration of the enamides (*Z* in **3i** and **3j**; *E* in **3k** and **3l**) or the electronic nature of the benzene ring *p*-substituent (electron withdrawing group, e.g., **3j**, or electron-donating group, e.g., **3k**) (Scheme 2). Obviously, this cycloaddition depends

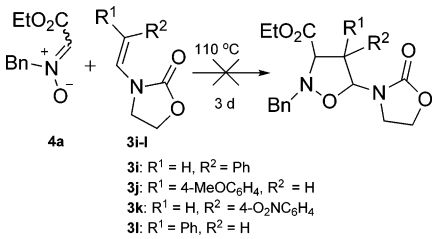
TABLE 4. Solvent-Free Cycloaddition of 4a with Chiral *N*-Vinyloxazolidin-2-ones 3c,d[a]



R^1	R^2	product	% yield[b]	diastereomeric ratio[c] *trans*-**1**/*trans*-**II**/*cis*-**1**/*cis*-**II**[d]	trans/cis ratio[c]
H	Ph	**5i**	93	49 (3*S*,5*S*):20 (3*R*,5*R*):20 (3*S*,5*R*):11 (3*R*,5*S*)[e]	69:31
Et	H	**5j**	93	42 (3*R*,5*R*):28 (3*S*,5*S*):17 (3*S*,5*R*)[e]:13 (3*R*,5*S*)	70:30

[a] **3c**,**d** (1.05 equiv). [b] Global yield of purified product after SiO_2 chromatography. [c] The ratio was determined from ^1H NMR analysis of the crude product. [d] Absolute configurations of all diastereomers were obtained after correlation with (*S*)-aspartic acid (vide infra). [e] This cis isomer was separated from the three others by SiO_2 chromatography.

SCHEME 2. Unsuccessful Cycloaddition of 3i−l and 4a



strongly on the steric hindrance at the double bond β-position in the dipolarophile.

Asymmetric Extension Using Chiral Dipolarophiles. The dipolar cycloaddition was next studied starting from chiral *N*-vinyloxazolidin-2-ones **3c**,**d** and nitrone **4a** (Table 4). Under the thermal solvent-free conditions, the reaction was achieved within 10 min at 110 °C, leading to cycloadducts in high yields after purification. However, in both cases, the adducts **5i** and **5j** were obtained as a mixture of diastereomers resulting from low *trans/cis* ($\approx$ 7:3) and facial ($\leq$4:1) selectivities. As for adducts **5a**−**e**, the *cis/trans* ratio was established on the base of the ^1H NMR signal peaks of H-5 proton, which display a higher chemical shift for both *cis* isomers than for *trans* ones. The moderate *trans* selectivity so observed appears as lower than those obtained with achiral dipolarophiles **3a** and **3b**. Before attempting to improve the facial control, we first tried to define new conditions that would ensure an efficient *trans/cis* control.

Asymmetric Extension with Chiral (*E*)-Geometry-Fixed α-Alkoxycarbonylnitrones. If we assume a concerted mechanism, the thermal 1,3-dipolar cycloaddition between a nitrone and an alkene is a $[_\pi4_s + _\pi2_s]$-type process similar to the Diels−Alder reaction.[18] The lower cis/trans stereoselectivity in nitrone cycloaddition compared to the Diels−Alder reaction can be explained by the $Z \leftrightarrows E$ isomerization of nitrone moiety during the cycloaddition. Nitrones bearing an electron-withdrawing group such as **4a** are known to exist in *Z* form in solid phase

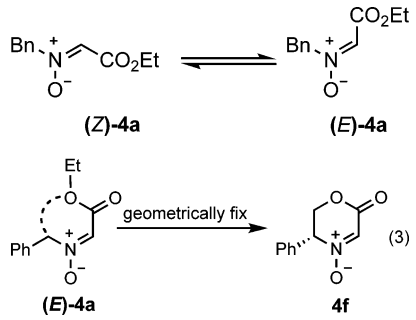


FIGURE 2. Isomerism of **4a** and use of cyclic **4f**.

and as *E*/*Z* equilibrating mixtures in solvent at room temperature (Figure 2).[19]

Consequently, cycloaddition of nitrone **4a** often leads to mixtures of *cis/trans* diastereomers.[1e] Lewis acids can be used to chelate the *Z* geometry of the double bond and to accelerate the cycloaddition reaction rate.[20] However, in our case, neither satisfactory yield nor good selectivity has ever been obtained with Lewis acid conditions ($Eu(fod)_3$, $Cu(OTf)_2$, $ZnBr_2$) due to degradation of the starting materials.

A convenient way to circumvent this problem consists in using nitrones with fixed geometry. We considered that the lactonic nitrone **4f** (Figure 2) could be the ideal dipole for this purpose since it could both ensure a good *cis/trans* selectivity due to its stable 6-membered ring configuration and could also act as a good chiral inducer due to the proximity of its stereogenic center. This chiral nitrone was designed, prepared in enantiopure form and successfully used in dipolar cycloaddition toward alkenes and alkenyl ethers by Tamura et al.[21]

Using solvent-free conditions for the cycloaddition between nitrone **4f** and dipolarophiles **3a**, **3b**, **3m**, and **3f**, we obtained the adducts in very short reaction time (the fastest reaction was completed after less than 1 min) and very good diastereoselectivities (Table 5).

The bicyclic core of cycloadducts **6**−**9** increases the rigidity of the system and their common (2*R*,3a*R*,7*R*) configuration, for

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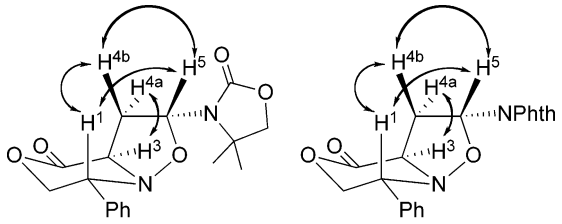


7 **9**

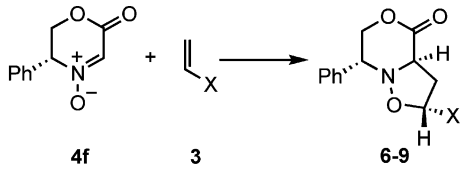
FIGURE 3. 2D NOESY correlation for adducts **7** and **9**.

the unique or the major diastereomer, could therefore be readily assigned on the basis of spectral data, including 2D COSY and NOESY NMR spectra, as exemplified in Figure 3 for compound **7** and **9**. Four NOESY correlation peaks (between H-1 and H-4b, H-4b and H-5, H-5 and H-1, and between H-3 and H-4a) confirm this structure.

Conversion of Adducts 5a and 5f into *N*-Aspartyloxazolidin-2-ones 10a,b. New 5-azaisoxazolidines such as **5** could be transformed into useful derivatives via N−O bond cleavage. The reductive ring opening of 5-carbaisoxazolidines into 1,3-aminoalcohols is well documented, using reducing agents such as Zn/H^{+},[22] H_2/Pd,[23] SmI_2[24].... However, such methods have not been successfully applied to 5-oxaisoxazolidines or 5-azaisoxazolidines up to date. In our case, starting from adducts **5**, these procedures led to the recovery of starting materials or to the formation of complex mixtures.

N-Quaternarization mediated ring opening of isoxazolidine has been also described as an effective method to cleave the N−O bond.[25] The procedures using alkylating agents (BnBr, MeI, Me_2SO_4...) in solution with or without subsequent basic treatment (DABCO, Et_3N, NaH...) were applied to 5-carba- or

TABLE 5. Solvent-Free Cycloaddition of 4f with 3[a]

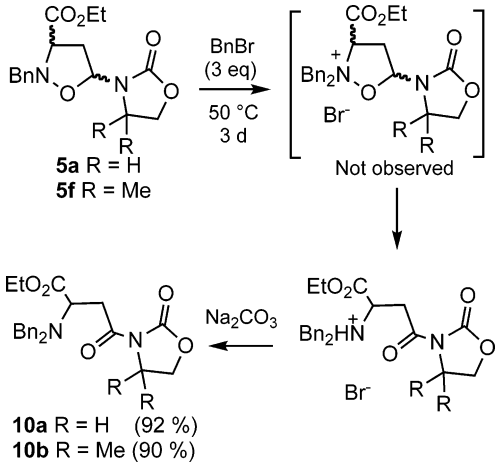


4f **3** **6-9**

entry	Enamide	time (min)	isomeric ratio[d]	product (% yield)
1	**3a**	10	86:14:0:0	**6** (97)[b]
2	**3b**	10	95:5:0:0	**7** (94)[c]
3	**3m**	10	88:12:0:0	**8** (93)[b]
4	**3f**	< 1	100:0:0:0	**9** (87)

[a] Enamides (1 equiv). [b] Purified product was obtained as a mixture of two isomers. [c] Purified product was obtained as a single isomer. [d] The ratio was determined from ^{1}H NMR analysis of crude mixture.

SCHEME 3. Ring Opening of Isoxazolidine via *N*-Quaternarization Using Benzyl Bromide



5-azaisoxazolidines to afford β-amino ketones or β-amino acid esters respectively in high yields. To the best of our knowledge, such methods have never been reported to furnish β-amino acid amides from 5-aza-isoxazolidines. Therefore, we tested **5a** and **5f** as model substrates to generate new β-amino acid imides **10a** and **10b** (Scheme 3). By applying these literature procedures, we observed low conversions and the formation of elimination side products, especially when a base (Et_3N) was used.[25c] The presence of these products (fumarate derivatives, trialkylamine) rendered the purification difficult. The required optimization of this reaction was conducted with benzyl bromide chosen by its ability to act as *N*-protecting reagent. Interestingly, we found that using 3 equiv of BnBr without solvent at 50 °C for 3 days led to the clean and total conversion of **5a** and **5f**

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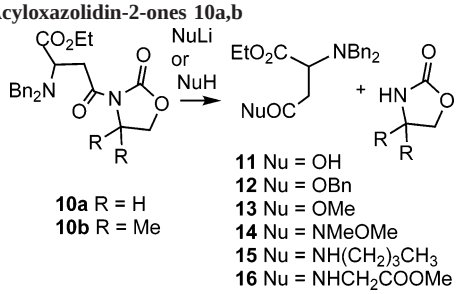
TABLE 6. Access to Unsymmetric Aspartate Derivatives 11−16 from *N*-Acyloxazolidin-2-ones 10a,b



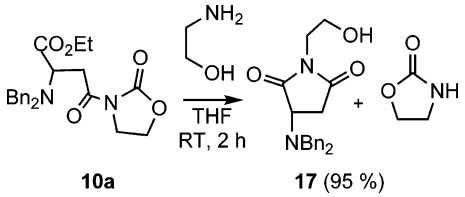
R	conditions	Nu	yield (%)
H	LiOH , THF/H_2O (1:1), rt, 30 min	OH	80
Me	LiOH , THF/H_2O (1:1), rt, 30 min	OH	85
H	BnOLi, THF, rt, 30 min	OBn	76
H	NaOMe, MeOH, rt, 30 min, then Amberlyst 15	OMe	90
H	$MeONH_2MeCl$, $AlMe_3$, CH_2Cl_2, 0 °C, 30 min	NMeOMe	83
H	*n*-$BuNH_2$ (10 equiv),10 min	NH-*n*-Bu	90
H	$NH_2GlyOMe{\cdot}HCl$, $AlMe_3$, CH_2Cl_2, 0 °C, 2 h	NHGlyOMe	79

into **10a** and **10b**, respectively (Scheme 3). The formation of the *N*,*N*-dibenzylisoxazolidinium intermediate was not observed, suggesting a spontaneous and fast ring-pening step. After basic treatment of the crude ammonium salt, imides **10a** and **10b** were obtained in excellent yields.

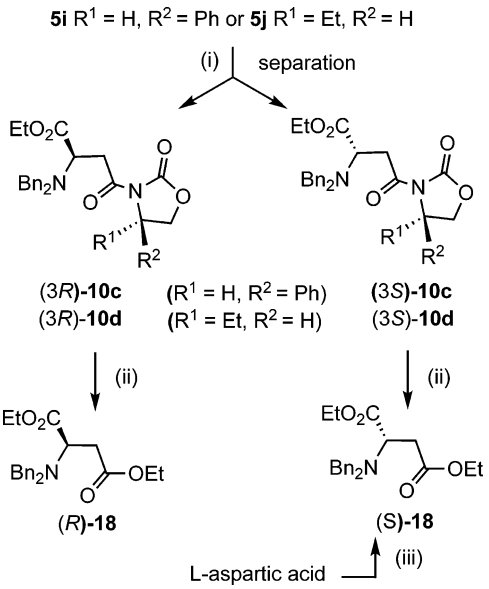
Access to Unsymmetric Aspartate Derivatives from *N*-Aspartyloxazolidin-2-ones 10a,b. Having in hand these new imides **10a**,**b** (in racemic form), we investigated the access to (±) unsymmetric aspartate derivatives by chemoselective attack of an heteronucleophile on the amide carbonyl. Many nondestructive removals of oxazolidin-2-one moieties have been reported, based on the transformation of *N*-acyloxazolidin-2-one into acid,[26] ester,[27] Weinreb amide,[28] amide,[29] and aldehyde.[30]

Adapting these conditions to the highly functionalized derivatives **10a** and **10b**, we obtained a wide range of products in high yields, including acid **11**, benzyl and methyl ester **12** and **13**, Weinreb's amide **14**, *N*-butylamide **15**, and glycine dipeptide **16** (Table 6). In all cases, the oxazolidin-2-one moiety proved to be a good leaving group, and all the tested nucleophiles attacked exclusively at the amide carbonyl. This chemoselective access to aspartate derivatives exemplified the specific synthetic utility of 5-azaisoxazolidines **5** with regard to their 5-oxa analogues.

SCHEME 4. Formation of Imide 17



SCHEME 5. Asymmetric Access to Aspartate Esters[a]



[a] Reactions and conditions: (i) BnBr, neat, 50 °C, 3 d; (ii) EtONa, EtOH, rt; (iii) (a) EtOH, AcCl, (b) BnBr, K_2CO_3(aq), Δ.

When ethanolamine was used as nucleophile in THF, succinimide **17** was obtained in high yield as a result of a double attack of the nucleophilic amine function to the amide and the ethyl ester carbonyl groups (Scheme 4).

Asymmetric Access to Unsymmetric Aspartate Derivatives. The *N*-quaternarization-mediated ring-opening reaction of isoxazolidines **5i**,**j** deriving from chiral *N*-vinyloxazolidin-2-ones **3c**,**d** was investigated on the mixture of the three unseparable diastereomers (diastereomeric ratios: (3*S*,5*S*)/(3*R*,5*R*)/(3*S*,5*R*) = 58:21:21 for **5i** and (3*R*,5*R*)/(3*S*,5*S*)/(3*R*,5*S*) = 48:43:9 for **5j**). Previously optimized conditions (BnBr in excess without solvent at 50 °C for 3 days) led to the clean and total conversion into **10c** and **10d**/ respectively, each as a pair of diastereomers in 75:25 and 56:44 ratios, respectively (Scheme 5). To our delight, we found that both diastereomers of **10c** and of **10d** were easily separable by conventional SiO_2 chromatography and isolated in pure form, leading respectively to (3*S*)-**10c** and (3*R*)-**10c** in 69% and 21% yields and to (3*R*)-**10d** and (3*S*)-**10d** in 53% and 42% yields. The absolute configuration of the major diastereomers (3*S*)-**10c** and (3*R*)-**10d** was established after ethanolysis and comparison between the specific rotations of the diethyl aspartates **18** so obtained (−112.4 and +113.7, respectively) and of the diethyl ester of *N*,*N*-dibenzyl-L-aspartic acid (−110.3). In order to fulfill the stereochemical assignment for **5i** and **5j**, the same transformation was applied to the pure isomers (3*R*,5*S*)-**5i** and (3*S*,5*R*)-**5j**,

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leading to the expected imides (3*R*)-**10c** and (*3S*)-**10d**, respectively, in pure form.

This easy conversion into both enantiomers of diethyl aspartate **18** strongly suggests that the efficient access to both diastereomers of **10c** and **10d** in pure forms described here could offer a practical entry to unsymmetrical aspartates **11**−**16** of both L and D series, via simple treament of the L or D imide precursor with the appropriate heteronucleophile.

Conclusion

We have found convenient conditions to achieve the 1,3-dipolar cycloaddition between nitrones and enamides: a thermal solvent-free reaction which allowed the reaction to complete in short time, avoided the degradation and gave excellent yields of adducts in comparison with reaction in solvent. This thermal solvent-free cycloaddition is strongly influenced by steric hindrance of the substituent at the β-position of the enamide double bond. When the geometry-fixed nitrone **4f** was used as dipole, a high facial selectivity was observed. Representative monocyclic adducts were thus transformed in two steps and high yields into unsymmetric aspartate derivatives. An asymmetric extension of this pathway was pointed out with chiral dipolarophiles via diastereomeric separation of the imide intermediates. This transformation is not efficient with adducts derived from the cycloaddition of alkyl vinyl ethers as dipolarophiles. We have also extended successfully the Buchwald's vinylation to obtain enamides which are important synthetic intermediates. Further applications of solvent-free cycloaddition conditions as well as of the adducts are currently under investigation.

Experimental Section

General Procedure for the Preparation of Vinylamides 3a−**f.** To a tube containing the amide precursor (10 mmol), *N*,*N*′-dimethylethylenediamine (1 mmol), K_2CO_3 (5.5 mmol), CuI (0.5 mmol), and toluene (3 mL) at 0 °C was injected liquid vinyl bromide (20 mmol, cooled to 0 °C). The tube was sealed and heated in an oil bath at 113 °C with magnetic stirring. After heating for 16 h, the tube was cooled to room temperature, carefully opened and purged with inert gas. The mixture was filtered through Celite, and the solid residue was rinsed with dichloromethane. The filtrate was evaporated to yield corresponding vinylamide. The product was used in cycloaddition without further purification.

3-Vinyl-2-oxazolidinone (**3a):** 1.04 g (92%); colorless oil. The characterization data match those reported in the literature.[12c]

4,4-Dimethyl-3-vinyl-oxazolidin-2-one (**3b):** 1.41 g (100%); colorless oil; IR (KBr): ν = 2975, 1758, 1640, 1402, 1384, 1321 cm^{-1}; colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (dd, J = 16.7, 10.1 Hz, 1H), 4.94 (dd, J = 16.7, 1.0 Hz, 1H), 4.55 (dd, J = 10.1, 1.0 Hz, 1H), 4.03 (s, 2H), 1.49 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 127.4, 96.4, 75.0, 58.4, 24.5; HRMS (GC/CI$^+$ CH_4) calcd for $C_7H_{12}NO_2$ [M + H$^+$] 142.0868, found 142.0861.

(*R*)-4-Phenyl-3-vinyloxazolidin-2-one (**3c):** 1.80 g (95%); colorless oil. The characterization data match those reported in the literature.[12c]

(*S*)-4-Ethyl-3-vinyloxazolidin-2-one (**3d):** 1.34 g (95%); colorless oil. The characterization data match those reported in the literature.[12c]

1-Methyl-3-vinylimidazolidin-2-one (**3e):** 1.16 g (92%); colorless liquid; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.00 (dd, J = 15.8, 9.0 Hz, 1H), 4.16 (d, J = 9.0 Hz, 1H), 4.05 (t, J = 15.8 Hz, 1H), 3.54−3.38 (m, 4H), 2.85 (s, 3H).

2-Vinylisoindoline-1,3-dione (**3f):** 0.35 g (20%) from phthalimide and 0.34 g (20%) from potassium phthalimide (without K_2CO_3 added). The characterization data match those reported in the literature.[31]

General Procedure for Preparation of Alkenylamides. A mixture of amide (10 mmol), alkenyl bromide (15 mmol for (Z)-1-bromopropene and 2-methyl-1-bromopropene; 10 mmol for styryl bromides), *N*,*N*′-dimethylethylenediamine (1 mmol), K_2CO_3 (11 mmol), CuI (0.5 mmol), and toluene (3 mL) was placed in a tightly closed sealed tube fitted with a magnetic stirbar. The mixture was stirred for 16 h at 113 °C and then cooled to room temperature. The tube was carefully opened, and its contents were filtered through celite, the solid residue was rinsed with CH_2Cl_2, and the combined filtrates were evaporated to yield the vinylamides **3g**−**k**. These products were used in cycloaddition without further purification.

(*Z*)-3-Propenyloxazolidin-2-one (3g: 1.21 g (95%); colorless liquid; IR (KBr) ν = 2923, 1751, 1670, 1483, 1421, 1249, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24−6.22 (m, 1H), 5.01−4.93 (m, 1H), 4.40 (m, 2H), 3.99 (m, 2H), 1.77−1.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 123.5, 110.4, 62.3, 45.6, 12.0; HRMS (GC/CI$^+$ CH_4) calcd for $C_6H_{10}NO_2$ [M + H$^+$] 128.0712, found 128.0696.

3-(2-Methylprop-1-enyl)oxazolidin-2-one (3h): 1.34 g (95%); colorless oil. The characterization data match those reported in the literature.[17]

(*Z*)-3-(2-Styryl)oxazolidin-2-one (3i): 1.85 g (98%); colorless liquid; IR (KBr) ν = 3078, 3054, 3024, 2991, 2915, 1759, 1653, 1415, 1239, 1070, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H), 6.66 (d, J = 9.9 Hz, 1H), 5.99 (d, J = 9.9 Hz, 1H), 4.26 (t, J = 8.0 Hz, 2H), 3.37 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 135.3, 129.1, 127.8, 126.9, 124.0, 112.6, 62.5, 44.8; HRMS (GC/CI$^+$ CH_4) calcd for $C_{11}H_{12}NO_2$ [M + H$^+$] 190.0868, found 190.0852.

(*E*)-3-[2-(4-Methoxyphenyl)vinyl]oxazolidin-2-one (3j): 2.14 g (98%); colorless crystals; mp 154−156 °C (dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 14.7 Hz, 1H), 6.85 (d, J = 8.6 Hz, 2H), 5.74 (d, J = 14.7 Hz, 1H), 4.50 (∼t, J = 8.1 Hz, 2H), 3.84 (t, J = 8.1 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 155.6, 128.6, 126.8, 122.5, 114.3, 110.9, 62.4, 55.4, 42.7; HRMS (DCI$^+$ CH_4) calcd for $C_{12}H_{14}NO_3$ [M + H$^+$]; HRMS 220.0974, found 220.0990.

(*Z*)-3-[2-(4-Nitrophenyl)vinyl]oxazolidin-2-one (3k): 222 mg (95%); yellow crystals; mp 163 °C (dichloromethane); IR (KBr) ν = 2987, 2915, 1744, 1509, 1341 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (m, 2H), 7.38 (m, 2H), 6.83 (d, J = 9.9 Hz, 1H), 5.99 (d, J = 9.9 Hz, 1H), 4.35 (t, J = 8.0 Hz, 2H), 3.39 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 146.5, 142.7, 130.0, 126.8, 123.2, 110.0, 62.8, 45.1; HRMS (DCI$^+$ CH_4) calcd for $C_{11}H_{11}N_2O_4$ [M + H$^+$]; HRMS 235.0719, found 235.078.

General Procedure for Preparation of *N*-Benzylnitrones. A mixture of *N*-benzylhydroxylamine hydrochloride (1.595 g, 10 mmol), $NaHCO_3$ (1.26 g, 15 mmol), 3 Å molecular sieves (2.00 g), and the corresponding aldehyde (10 mmol) in CH_3OH (10 mL) was stirred at room temperature for 3 h. The reaction mixture was filtered through Celite. The filtrate was concentrated under reduced pressure to afford the crude nitrone. The compound was further purified by recrystallization (dichloromethane, petroleum ether).

(*Z*)-*N*-(4-Fluorobenzylidene)(phenyl)methanamine Oxide (4c). From 4-fluorobenzaldehyde, nitrone **4c** was obtained as colorless crystals (2.12 g, 80%): mp 110−111 °C (dichloromethane); IR (KBr) ν = 3071, 3037, 1598, 1576, 1503, 1458, 1230, 1157, 1146 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.23 (m, 2H), 7.44−7.39 (m, 5H), 7.37 (s, 1H), 7.10−7.05 (m, 2H), 5.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, J^1_{C-F} = 253 Hz), 133.10; 133.05, 130.8, 129.3, 129.1, 129.0, 126.8 (d, J^3_{C-F} = 4 Hz), 115.6 (d, J^2_{C-F} = 21 Hz), 71.1; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −107,6 (tt, J = 8.0, 5.7 Hz, 1F); HRMS (FD) calcd for $C_{14}H_{12}NOF$ [M + H$^+$]; HRMS 229.0903, found 229.0900.

Nitrone **4f** was prepared according to reported procedures.[21]

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General Procedure for Cycloaddition in Solution (Procedure A). A solution of the enamide (1 mmol) and the nitrone (1 mmol) in toluene/xylene (5 mL) was heated and stirred under reflux. After completion of the reaction (monitored by TLC, see Table 3), the solvent was then removed under vacuum. The crude product was purified by chromatography over silica gel column or by recrystallization.

General Procedure for Solvent-Free Cycloaddition (Procedure B). A mixture of enamide (1 mmol) and nitrone (1 mmol) was heated with stirring at the temperature shown in Table 3. If necessary, the reaction mixture was homogenized with CH_2Cl_2 which was then evaporated under vacuum prior to heating. The crude product was purified by chromatography over silica gel column or by recrystallization.

***cis*-Ethyl 2-Benzyl-5-(2-oxooxazolidin-3-yl)isoxazolidine-3-carboxylate (*cis*-5a).** From **3a** and **4a**. Purification by flash chromatography (diethyl ether) afforded the title compound as a pale yellow oil: R_f = 0.4 (diethyl ether), 61 mg (19%) after procedure A and 58 mg (18%) after procedure B; pale yellow liquid; IR (neat) ν = 1738, 1194, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.28 (m, 5H), 5.92 (dd, J = 8.2, 4.1 Hz, 1H), 4.12 (m, 3H), 4.29 (m, 2H), 4.00 (dd, J = 13.5 Hz, 1H), 3.84 (q, J = 9.1 Hz, 1H), 3.75 (dt, J = 9.1, 5.9 Hz, 1H), δ 3.55 (dd, J = 9.1, 7.6 Hz, 1H), 2.87 (ddd, J = 13.6, 9.1, 8.2 Hz, 1H), 2.57 (ddd, J = 13.6, 7.6, 4.1 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz ($CDCl_3$) δ 169.8, 157.6, 135.8, 129.1, 128.2, 127.6, 81.5, 66.6, 62.3, 61.6, 61.5, 40.8, 36.3, 13.9; HRMS (DCI$^+$ CH_4) calcd for $C_{16}H_{21}N_2O_5$ [M + H$^+$]; HRMS 321.1450, found 321.1446.

***trans*-Ethyl 2-Benzyl-5-(2-oxooxazolidin-3-yl)isoxazolidine-3-carboxylate (*trans*-5a).** From **3a** and **4a.** Purification by flash chromatography (diethyl ether) afforded the title compound as a pale yellow oil: R_f = 0.2 (diethyl ether), 230 mg (72%) after procedure A and 260 mg (81%) after procedure B; pale yellow liquid; IR (neat) ν = 1737, 1182, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 5.84 (dd, J = 7.9, 4.4 Hz, 1H), 4.30 (t, J = 7.3 Hz, 2H), 4.19 (d, J= 14.4 Hz, 1H), 4.17 (d, J= 14.4 Hz, 1H), 4.11 (m, 2H), 3.74 (m, 1H), 3.54 (t, J = 7.9 Hz, 2H), 2.83 (ddd, J = 13.3, 7.9, 6.9 Hz, 1H), 2.55 (ddd, J = 13.3, 7.9, 4.4 Hz, 1H), 1.28 (t, J= 7.1 Hz, 3H); ^{13}C NMR (100 MHz ($CDCl_3$) δ 169.1, 157.0, 135.6, 129.1, 128.1, 127.5, 81.9, 65.1, 61.9, 61.3, 60.1, 40.2, 35.1, 14.0; HRMS (DCI$^+$ CH_4) calcd for $C_{16}H_{21}N_2O_5$ [M + H$^+$]; HRMS 321.1450, found 321.1455.

***cis*-3-(2-Benzyl-3-phenylisoxazolidin-5-yl)oxazolidin-2-one (*cis*-5b).** From **3a** and **4b**. Purification by flash chromatography (cyclohexane/ethyl acetate 9:1 to 1:1) afforded the title compound as a colorless solid: R_f = 0.57 (diethyl ether), 119 mg (37%) after procedure A and 217 mg (67%) after procedure B; mp 152−153 °C; IR (neat) ν = 1741, 1417, 1242, 1072, 1017 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 2H). 7.38 (m, J = 7 Hz, 2H), 7.32 (m, 1H), 7.29 (m, 4H), 7.26 (m, 1H), 5.92 (dd, 1H, J = 8.4, 5.0 Hz, 1H), 4.32 (ddd, J = 9.1, 8.4, 5.3 Hz, 1H), 4.28 (q, J= 8.4 Hz, 1H), 3.97 (d, J = 13.6 Hz, 1H), 3.65 (d, J = 13.6 Hz, 1H), 3.88 (q, J = 8.4 Hz, 1H), 3.84 (dd, J = 9.9, 7.8 Hz, 1H), 3.74 (td, J= 8.4, 5.7 Hz, 1H), 2.99 (ddd, J = 13.6, 8.2, 7.8 Hz, 1H), 2.32 (ddd, J = 13.7, 9.9, 5.0 Hz, 1H); ^{13}C NMR (100 MHz ($CDCl_3$) δ 157.8, 138.0, 137.4, 129.0, 128.7, 128.3, 128.2, 127.4, 127.3, 81.3, 70.7, 62.2, 59.7, 43.0, 40.6; HRMS (DCI$^+$ CH_4) calcd for $C_{19}H_{21}N_2O_3$ [M + H$^+$]; HRMS 325.1552, found 325.1567.

***trans*-3-(2-Benzyl-3-phenylisoxazolidin-5-yl)oxazolidin-2-one (*trans*-5b).** From **3a** and **4b**. Purification by flash chromatography (cyclohexane/ethyl acetate 9:1 to 1:1) afforded the title compound as a colorless solid: R_f = 0.3 (diethyl ether); 52 mg (16%) after procedure A and 94 mg (29%) after procedure B; mp 155 °C; IR (neat) ν = 1741, 1416, 1244, 1076, 1014 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.21 (m, 10H), 5.91 (m, 1H), 4.33−4.29 (m, 2H), 4.01−3.81 (m, 2H), 3.70 (d, J = 14.4 Hz, 1H), 3.56−3.65 (m, 2H), 2.68−2.49 (m, 2H); ^{13}C NMR (100 MHz ($CDCl_3$) δ 157.2, 137.9, 136.6, 129.0, 128.9, 128.3, 128.2, 127.9, 127.3, 81.5, 68.6, 62.1, 58.8, 41.5, 40.0; HRMS (DCI$^+$ CH_4) calcd for $C_{19}H_{21}N_2O_3$ [M + H$^+$]; HRMS 325.1552, found 325.1551.

***cis*-3-(2-Benzyl-3-(4-fluorophenyl)isoxazolidin-5-yl)oxazolidin-2-one (*cis*-5c).** From **3a** and **4c**. Purification by flash chromatography (cyclohexane/ethyl acetate 8:2) afforded the title compound as a colorless oil which crystallizes on standing: R_f = 0.40 (diethyl ether); 34 mg (10%) after procedure A and 127 mg (37%) after procedure B; IR (KBr) ν = 2984, 2957, 1741, 1507, 1257, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.38 (m, 2H), 7.32−7.22 (m, 5H), 7.09−7.04 (m, 2H), 5.91 (dd, J = 8.1, 5.0 Hz, 1H), 4.34−4.24 (m, 2H), 3.93 (d, J = 14.4 Hz, 1H), 3.88−3.81 (m, 2H), 3.73−3.68 (m, 1H), 3.66 (d, J = 14.4 Hz, 1H), 2.97 (ddd, J = 13.6, 8.1, 7.6), 2.28 (ddd, J = 13.6, 9.9, 5.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J^1_{C-F} = 247.4 Hz), 158, 137.1, 133.6 (d, J^4_{C-F} = 2.9 Hz), 128.9 (d, J^3_{C-F} = 8.1 Hz), 128.6, 128.2, 127.2, 115.8 (d, J^2_{C-F} = 21.2 Hz), 81.2, 69.9, 62.1, 59.6, 42.8, 40.4; ^{19}F NMR (376.5 MHz, $CDCl_3$) −113.6 (tt, J = 8.0, 4.6 Hz, 1F); HRMS (DCI + methane) calcd for $C_{19}H_{20}N_2O_3F$ [M + H$^+$]; HRMS 343.1458, found 343.1455.

***trans*-3-(2-Benzyl-3-(4-fluorophenyl)isoxazolidin-5-yl)oxazolidin-2-one (*trans*-5c).** From **3a** and **4c**. Purification by flash chromatography (cyclohexane/ethyl acetate 8:2) afforded the title compound as a colorless oil which crystallizes on standing: R_f = 0.38 (diethyl ether); 36 mg (10%) after procedure A and 146 mg (43%) after procedure B; IR (KBr) ν = 3063, 2957, 1741, 1507 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.40 (m, 2H), 7.24−7.32 (m, 5H), 7.10−7.05 (m, 2H), 5.99−5.90 (br, 1H), 4.37−4.33 (m, 2H), 3.78−3.74 (m, 2H), 3.71−3.61 (m, 3H), 2.65 (m, 2H); some characteristic signals ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 161.4, 57.1, 129.2, 128.2, 127.7, 115.9 (d, J^2_{C-F} = 22.0 Hz), 82.2, 68.0, 62.1, 58.6, 40.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −113.3 (m, 1F).

***cis*-3-(2-Benzyl-3-(4-(trifluoromethyl)phenyl)isoxazolidin-5-yl)oxazolidin-2-one (*cis*-5d).** From **3a** and **4d**. Purification by flash chromatography (diethyl ether/cyclohexane 3:1) afforded the title compound as a colorless oil: R_f = 0.40 (diethyl ether); 65 mg (17%) after procedure B; IR (KBr) ν = 3059, 3022, 1746, 1502, 1250 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.32−7.22 (m, 5H), 5.94 (dd, J = 8.1, 5.1 Hz, 1H), 4.34−4.24 (m, 2H), 3.94 (d, J = 14.1 Hz, 1H), 3.88−3.81 (m, 1H), 3.72 (d, J = 14.1 Hz, 1H), 3.71−3.65 (m, 1H), 3.02 (ddd, J = 13.6, 8.1, 7.3), 2.29 (ddd, J = 13.6, 9.5, 5.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 142.4, 136.7, 130.7, 128.8, 128.3, 127.6, 127.5, 126.0 (q, J^4_{C-F} = 3.7 Hz), 123.8 (q, J^1_{C-F} = 272.2 Hz), 81.4, 69.9, 62.2, 60.0, 42.8, 40.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) −62.6 (s, 3F); HRMS (DCI + methane) calcd for $C_{20}H_{19}N_2O_3F_3$ [M + H$^+$]; HRMS 392.1348, found 392.1346.

***trans*-3-(2-Benzyl-3-(4-(trifluoromethyl)phenyl)isoxazolidin-5-yl)oxazolidin-2-one (*trans*-5d).** From **3a** and **4d**. Purification by flash chromatography (diethyl ether/cyclohexane 3:1) afforded the title compound as a colorless oil: R_f = 0.20 (diethyl ether); 255 mg (65%) after procedure B; IR (KBr) ν = 3057, 3021, 1745, 1500, 1251 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.34−7.23 (m, 5H), 5.89 (dd, J = 8.1, 4.0 Hz, 1H), 4.40−4.31 (m, 2H), 3.98 (d, J = 14.1 Hz, 1H), 4.00−3.97 (m, 1H), 3.76 (d, J = 14.1 Hz, 1H), 3.69−3.59 (m, 2H), 2.67 (ddd, J = 13.6, 7.6, 4.0 Hz, 1H), 2.58 (ddd, J = 13.6, 8.8, 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157, 142.4, 136.1, 129.0, 128.2$_4$, 128.1$_8$, 127.5, 125.8 (q, J^3_{C-F} = 3.7 Hz), 124.0 (q, J^1_{C-F} = 272.2 Hz), 81.8, 68.0, 62.1, 59.2, 41.4, 40.3; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −62.6 (s, 3F).

***cis*-3-(2,3-Diphenylisoxazolidin-5-yl)oxazolidin-2-one (*cis*-5e).** From **3a** and **4c**. The crude products were purified by recrystallization (chloroform, *n*-hexane), 248 mg (80%) after procedure A and 276 (89%) after procedure B. An analytically pure sample of cis adduct was obtained in the first crop of recrystallization: colorless crystals; mp 159−161 °C; IR (neat) ν = 1743, 1410, 1234, 1018 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J= 7.5 Hz,

2H). 7.39 (t, *J*= 7.5 Hz, 2H), 7.31 (t, *J*= 7.5 Hz, 1H), 7.24 (t, *J*= 7.5 Hz, 2H), 7.03 (d, *J*= 7.5 Hz, 2H), 7.00 (t, *J*= 7.5 Hz, 1H), 6.13 (dd, *J* = 8.3, 5.3 Hz, 1H), 4.72 (dd, *J* = 8.3, 6.3 Hz, 1H), 4.34 (ddd, *J* = 9.1, 8.3, 5.3 Hz, 1H), 4.26 (td, *J*= 9.1, 8.3 Hz, 1H), 3.68 (q, *J* = 8.3 Hz, 1H), 3.37 (td, 8.3, 5.3 Hz, 1H), 3.04 (ddd, 1H, *J* = 13.4, 8.4, 8.3 Hz, 1H), 2.40 (ddd, *J* = 13.4, 6.3, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 150.2, 140.6, 129.0, 128.9, 127.8, 126.4, 123.2, 116.3, 82.4, 70.0, 62.3, 41.2, 40.2; HRMS (DCI$^+$ CH_4) calcd for $C_{18}H_{19}N_2O_3$ [M + H$^+$]; HRMS 311.1396, found 311.1390.

***trans*-Ethyl 2-Benzyl-5-(4,4-dimethyl-2-oxooxazolidin-3-yl)-isoxazolidine-3-carboxylate (*trans*-5f).** From **3b** and **4a**. The crude mixture was purified from degradation products by chromatography over silica gel (eluent ether, R_f = 0.45). 310 mg (89%) after procedure A and 334 mg (96%) after procedure B. An analytically pure sample of trans adduct was obtained in the last fractions of chromatography: pale yellow liquid; IR (neat) ν = 1739, 1182, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.23 (m, 5H). 5.15 (dd, *J* = 8.5, 5.2 Hz, 1H), 4.18 (d, *J* = 13.2 Hz, 1H), 4.14 (d, *J* = 13.2 Hz, 1H), 4.06−4.14 (m, 2H), 4.02 (t, *J* = 8.1 Hz, 1H), 4.00 (d, *J* = 8.6 Hz, 1H), 3.95 (d, *J* = 8.3 Hz, 1H), 3.36 (ddd, J_5 = 13.0, 8.1, 5.2 Hz, 1H), 2.64 (ddd, *J* = 13.0, 8.5, 8.1 Hz, 1H), 1.29 (s, 6H), 1.23 (t, *J*= 7.1 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.2, 160.8, 136.5, 129.3, 128.0, 127.2, 80.9, 74.4, 66.3, 62.1, 61.1, 58.9, 34.6, 26.1, 25.4, 13.9; HRMS (DCI$^+$ CH_4) calcd for $C_{18}H_{25}N_2O_5$ [M + H$^+$]; HRMS 349.1763, found 349.1762.

3-(2-Benzyl-3-(4-(trifluoromethyl)phenyl)isoxazolidin-5-yl)-4,4-dimethyloxazolidin-2-one (5g). From **3b** and **4d**. Purification by flash chromatography (diethyl ether) afforded the title compound as a colorless solid (nonseparable mixture, trans/cis 3.3:1): R_f = 0.45 (diethyl ether); 84 mg (20%) after procedure A and 345 mg (82%) after procedure B; IR (KBr) ν = 3032, 2973, 1759, 1325, 1165, 1123 cm^{-1}; some characteristic NMR signals of major adduct *trans*-**5g** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.57 (m, 4H). 7.27−7.19 (m, 5H), 5.16 (dd, *J* = 8.8, 4.0 Hz, 1H), 4.45 (dd, *J* = 9.3, 7.6 Hz, 1H), 4.04 (d, *J* = 8.2 Hz, 1H), 3.97 (d, *J* = 8.2 Hz, 1H), 3.88 (s, 1H), 3.87 (s, 1H), 3.31 (ddd, *J* = 12.6, 7.6; 4.0 Hz, 1H), 2.42 (ddd, *J* = 12.6, 9.3, 8.8 Hz, 1H), 1.35 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 143.5, 137.4, 128.2, 128.1, 127.2, 125.6 (q, J^3_{C-F} = 4 Hz), 122.6 (q, J^1_{C-F} = 272 Hz), 80.3, 74.7, 69.2, 60.4, 59.1, 41.8, 26.4, 25.7; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −62.5 (s, 3F); some characteristic NMR signals of minor adduct *cis*-**5e** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62−7.57 (m, 4H). 7.27−7.19 (m, 5H), 5.55 (dd, *J* = 6.3, 7.8 Hz, 1H), 3.90 (s, 1H), 3.89 (s, 1H), 3.17 (ddd, *J* = 13.1, 10.3; 6.3 Hz, 1H), 2.87 (ddd, *J* = 13.1, 7.8, 7.1 Hz, 1H), 1.32 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 143.5, 136.9, 128.4, 128.0, 127.2, 125.6 (q, J^3_{C-F} = 4 Hz), 122.6 (q, J^1_{C-F} = 272 Hz), 82.2, 75.1, 70.5, 60.1, 59.1, 41.8, 26.5, 25.5; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ −62.6 (s, 3F); HRMS (DCI$^+$ CH_4) calcd for $C_{22}H_{24}N_2O_3F_3$ [M + H$^+$]; HRMS 421.1739, found 421.1754.

Ethyl 2-Benzyl-4-methyl-5-(2-oxooxazolidin-3-yl)isoxazolidine-3-carboxylate (*trans*-5h). From **3g** and **4a**. The crude mixture was purified from degradation products by chromatography on silica gel (CH_2Cl_2 → CH_2Cl_2/Et_2O 1:1) to afford *trans*-**5h** (R_f = 0.45, diethyl ether). 167 mg (50%) after procedure A and 234 mg (70%) after procedure B (another less polar adduct could not be separated from degradation products): pale yellow liquid; IR ν = 2931, 1748, 1253, 1193 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (m, 5H), 5.80 (d, *J* = 7.8, 1H), 4.29 (dd, *J* = 7.3, 8.6 Hz, 2H), 4.17 (d, *J* = 13.4, 1H), 4.11 (m, 2H), 4.10 (d, *J* = 13.4, 1H), 3.61 (∼q, *J* = 8.3 Hz, 1H), 3.42 (∼q, *J* = 8.3 Hz, 1H), 3.28 (d, *J* = 10.3 Hz, 1H), 3.15 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz ($CDCl_3$) δ 168.8, 157.8, 135.1, 129.6, 128.2, 127.8, 84.7, 72.0, 62.1, 61.5, 44.6, 41.9, 14.0, 11.0; HRMS (DCI$^+$ CH_4) calcd for $C_{17}H_{23}N_2O_5$ [M + H$^+$]; HRMS 335.1607, found 335.1593.

(3*R*,5*S*)-Ethyl 2-Benzyl-5-((*R*)-4-phenyl-2-oxooxazolidin-3-yl)-isoxazolidine-3-carboxylate ((3*R*,5*S*)-5i). From **3d** and **4a**. Purification by flash chromatography (Et_2O/cyclohexane 1:2 → 2/1) afforded the title compound as a pale yellow oil: R_f = 0.53 (diethyl ether), 120 mg (10%); $[\alpha]^{23}_D$ = +1.9 (*c* 2.75, chloroform); IR (KBr) ν = 2981, 1758, 1399, 1211, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.27 (m, 10H), 5.99 (dd, *J* = 8.3, 5.3 Hz, 1H), 5.26 (dd, *J* = 9.1, 4.8 Hz, 1H), 4.53 (dd, *J* = 9.1, 8.6 Hz, 1H), 4.25 (d, *J* = 13.6 Hz, 1H), 4.04 (dd, *J* = 8.6, 4.8 Hz, 1H), 4.00−3.93 (m, 2H), 3.91 (d, *J* = 13.6 Hz, 1H), 3.41 (t, *J* = 8.6 Hz, 1H), 2.47 (ddd, *J* = 13.6, 8.6, 8.3 Hz, 1H), 2.09 (ddd, *J* = 13.6, 8.6, 5.3 Hz, 1H), 1.12 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 158.8, 140.8, 136.2, 129.2, 128.9, 128.4, 128.2, 127.5, 126.7, 82.1, 71.0, 66.2, 61.5, 61.0, 56.2, 34.8, 13.8; HRMS (DCI + methane) calcd for $C_{22}H_{25}N_2O_5$ [M + H$^+$]; HRMS 397.1763, found 397.1773.

(3*S*,5*R*)-, (3*R*,5*R*)-, and (3*S*,5*S*)-Ethyl 2-Benzyl-5-((*R*)-4-phenyl-2-oxooxazolidin-3-yl)isoxazolidine-3-carboxylate ((3*S*,5*R*)-, (3*R*,5*R*)-, and (3*S*,5*S*)-5i). From **3d** and **4a**. Purification by flash chromatography (Et_2O/cyclohexane 1:2 → 2/1) afforded the title compound as a pale yellow oil nonseparable mixture ((3*S*,5*R*)/(3*S*,5*S*)/(3*R*,5*R*) 1.0:2.5:1.0): R_f = 0.48 (diethyl ether); 857 mg (82%); IR (KBr) ν = 2982, 1759, 1398, 1212, 1041 cm^{-1}; some characteristic NMR signals of (3*S*,5*R*) adduct ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (dd, *J* = 8.6, 4.8 Hz, 1H), 3.35−3.31 (m, 1H), 2.45 (ddd, *J* = 13.1, 8.6, 7.1 Hz, 1H), 2.02 (ddd, *J* = 13.1, 7.8, 4.8 Hz, 1H); some characteristic NMR signals of (3*S*,5*S*) adduct ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (dd, *J* = 8.1, 4.3 Hz, 1H), 3.93 (d, *J* = 13.3, 1H), 3.84 (t, *J* = 7.8, 1H), 3.29 (ddd, *J* = 12.9, 8.1, 4.3 Hz, 1H), 2.61 (ddd, *J* = 12.9, 8.1, 7.3 Hz, 1H); ^{13}C NMR (100 MHz ($CDCl_3$) δ 169.9, 156.2, 136.6, 82.9, 69.7, 65.8, 61.2, 60.2, 34.6, 14.0; some characteristic NMR signals of (3*R*,5*R*) adduct ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (dd, *J* = 7.3, 2.9 Hz, 1H), 3.44 (dd, *J* = 9.6, 7.2 Hz, 1H), 3.12 (ddd, *J* = 13.6, 7.2, 2.9 Hz, 1H), 2.84 (ddd, *J* = 13.6, 9.6, 7.3 Hz, 1H).

(3*S*,5*R*)-Ethyl 2-Benzyl-5-((*S*)-4-ethyl-2-oxooxazolidin-3-yl)-isoxazolidine-3-carboxylate ((3*S*,5*R*)-5j). From **3c** and **4a**. Purification by flash chromatography (Et_2O/cyclohexane 1:2 → 2/1) afforded the title compound as a pale yellow oil: R_f = 0.64 (diethyl ether), 113 mg (11%); $[\alpha]^{23}_D$ = −83.5 (c 1.50, chloroform); IR (KBr) ν = 1748, 1404, 1219 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 5.90 (dd, *J* = 8.3, 5.1 Hz, 1H), 4.25 (dd, *J* = 8.6, 8.3 Hz, 1H), 4.18 5d, *J* = 13.6 Hz), 4.16 (q, *J* = 7.1 Hz, 2H), 4.17−4.04 (m, 2H), 3.95 (dd, *J* = 8.3, 5.6 Hz, 1H), 3.92 (d, *J* = 13.6 Hz, 1H), 2.90 (ddd, *J* = 13.6, 8.5, 8.3 Hz, 1H), 2.67 (ddd, *J* = 13.6, 9.1, 5.1 Hz, 1H), 2.13−2.03 (m, 1H), 1.79−1.68 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz ($CDCl_3$) δ 169.5, 158.8, 136.3, 129.1, 128.3, 127.6, 82.6, 67.7, 67.2, 61.6, 61.5, 53.7, 38.1, 26.3, 14.0, 8.1; HRMS (DCI + methane) calcd for $C_{18}H_{25}N_2O_5$ [M + H$^+$]; HRMS 349.1763, found 349.1775.

(3*R*,5*S*)-, (3*R*,5*R*)-, and (3*S*,5*S*)-Ethyl 2-Benzyl-5-((*S*)-4-ethyl-2-oxooxazolidin-3-yl)isoxazolidine-3-carboxylate ((3*R*,5*S*)-, (3*R*,5*R*)-, and (3*S*,5*S*)-5j). From **3c** and **4a**. Purification by flash chromatography (Et_2O/cyclohexane 1:2 → 2/1) afforded the title compound as a pale yellow oil non-separable mixture ((3*R*,5*S*)/(3*R*,5*R*)/(3*S*,5*S*) 1.0:3.4:2.2): R_f = 0.48 (diethyl ether); 857 mg (82%); IR (KBr) ν = 1748, 1404, 1219 cm^{-1}; some characteristic NMR signals of (3*S*,5*R*) adduct ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (dd, *J* = 7.8, 4.7 Hz, 1H), 3.56 (d, *J* = 8.3 Hz, H), 0.70 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz ($CDCl_3$) δ 169.9, 82.2, 61.5, 26.2, 14.0, 7.7; some characteristic NMR signals of (3*S*,5*S*) adduct ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (dd, *J* = 7.8, 5.6 Hz, 1H), 0.81 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz ($CDCl_3$) δ 169.8, 82.4, 61.3, 25.6, 14.0, 7.7; some characteristic NMR signals of (3*R*,5*R*) adduct ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 5.40 (dd, *J* = 7.3, 5.3 Hz, 1H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz ($CDCl_3$) δ 169.7, 83.8, 61.8, 26.5, 14.0, 7.8.

(2*R*,3a*R*,7*R*)-2-(2-Oxooxazolidin-3-yl)-7-phenyltetrahydroisoxazolo[3,2-*c*][1,4]oxazin-4(2*H*)-one (6). From **3a** and **4f** after

procedure B. The crude mixture was purified from degradation products by chromatography over silica gel (eluent ether, $R_f = 0.4$) to afford 289 mg of the title compound (97%) as a mixture of two diastereomers (86:14 ratio): pale yellow oil; $\nu = 2972, 1743, 1340, 1223, 1040$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 7.43−7.32 (m, 5H), 5.94 (dd, $J = 8.3, 3.0$ Hz, 1H), 4.43−4.27 (m, 5H), 4.18 (dd, $J = 9.9, 3.8$ Hz, 1H), 3.81−3.75 (m, 1H), 3.67−3.61 (m, 1H), 3.09 (ddd, $J = 14.1, 8.3, 7.5$ Hz, 1H), 2.76 (ddd, $J = 14.1, 8.8, 3.0$ Hz, 1H); characteristic signal of the minor isomer 6.01 (dd, $J = 7.3, 3.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 157.0, 135.0, 128.5, 128.3, 127.1, 81.3, 69.0, 62.7, 61.9, 60.6, 39.8, 34.4; HRMS (DCI$^+$ CH_4) calcd for $C_{15}H_{17}N_2O_5$ [M + H$^+$]; HRMS 305.1137, found 305.1140.

(2*R*,3a*R*,7*R*)-2-(4,4-Dimethyl-2-oxooxazolidin-3-yl)-7-phenyltetrahydroisoxazolo[3,2-*c*][1,4]oxazin-4-(2*H*)-one (7). From **3b** and **4f** after procedure B. The crude mixture was purified from degradation products by chromatography over silica gel (eluent diethyl ether, $R_f = 0.3$) to afford 312 mg of the title compound (94%) as colorless crystals: mp 189−191 °C; $[\alpha]^{23}_D = -170.0$ (*c* 1.00, chloroform); IR (KBr) $\nu = 2973, 1742, 1341, 1225, 1041$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.44 (m, 2H), 7.40−7.31 (m, 3H), 5.19 (dd, $J = 8.6, 2.8$ Hz, 1H), 4.90 (t, $J = 8.3$ Hz, 1H), 4.30 (dd, $J = 11.9, 4.0$ Hz, 1H), 4.23 (dd, $J = 11.9, 10.4$ Hz, 1H), 4.08 (dd, $J = 10.4, 4.0$ Hz, 1H), 3.96 (d, $J = 8.3$ Hz, 1H), 3.92 (d, $J = 8.3$ Hz, 1H), 3.41 (ddd, $J = 13.4, 9.1, 2.5$ Hz, 1H), 2.96 (ddd, $J = 13.4, 8.6, 8.1$ Hz, 1H), 1.18 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 155.2, 136.6, 129.3, 128.0, 127.3, 81.0, 74.5, 66.3, 62.1, 61.1, 59.0, 34.6, 26.1, 25.5, 13.9; HRMS (DCI$^+$ CH_4) calcd for $C_{17}H_{21}N_2O_5$ [M + H$^+$]; HRMS 333.1450, found 333.1454.

(2*R*,3a*R*,7*R*)-2-(2-Oxopyrrolidin-1-yl)-7-phenyltetrahydroisoxazolo[3,2-*c*][1,4]oxazin-4(2*H*)-one (8). From **3m** and **4f**. After procedure B, the crude mixture was purified from degradation products by chromatography over silica gel (eluent ether, $R_f = 0.4$) to afford 281 mg of the title compound (93%) as a mixture of two diastereomers (88:12 ratio): pale yellow liquid; IR (KBr) $\nu = 2957, 1751, 1686, 1420, 1288, 1231$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 7.43−7.32 (m, 5H), 6.16 (dd, $J = 8.6, 3.3$ Hz, 1H), 4.44 (dd, $J = 8.8, 8.3$ Hz, 1H), 4.33 (dd, $J = 11.9, 3.8$ Hz, 1H), 4.25 (dd, $J = 11.9, 10.4$ Hz, 1H), 4.14 (dd, $J = 10.1, 3.8$ Hz, 1H), 3.58−3.51 (m, 1H), 3.47−3.36 (m, 1H), 2.98 (ddd, $J = 13.9, 8.6, 8.3$ Hz, 1H), 2.66 (ddd, $J = 13.9, 8.8, 3.3$ Hz, 1H), 2.40−2.26 (m, 2H), 2.05−1.94 (m, 2H); characteristic signal of the minor isomer 6.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 168.6, 134.9, 128.7, 128.5, 127.4, 79.1, 69.5, 62.4, 61.4, 42.0, 34.8, 31.0, 17.6; HRMS (DCI$^+$ CH_4) calcd for $C_{16}H_{19}N_2O_4$ [M + H$^+$]; HRMS 303.1345, found 303.1340.

2-((2*R*,3a*R*,7*R*)-4-Oxo-7-phenylhexahydroisoxazolo[3,2-*c*][1,4]-oxazin-2-yl)isoindoline-1,3-dione (9). From **3f** and **4f**. After procedure B, the crude mixture was purified from degradation products by recrystallization (toluene) to afford 317 mg of the title compound (87%) as colorless crystals:mp 210−212 °C (dichloromethane); $[\alpha]^{23}_D = -146.8$ (c 0.70, chloroform); IR (KBr) $\nu = 2945, 1775, 1749, 1722, 1363, 1234$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, $J = 5.6, 3.3$ Hz, 2H), 7.75 (dd, $J = 5.6, 3.3$ Hz, 2H), 7.45−7.42 (m, 2H), 7.37−7.30 (m, 3H), 6.19 (dd, $J = 8.8, 2.5$ Hz, 1H), 5.15 (t, $J = 8.8$ Hz, 1H), 4.34 (dd, $J = 7.8, 4.0$ Hz, 1H), 4.29 (dd, $J = 11.0, 7.8$ Hz, 1H), 4.15 (dd, $J = 11.0, 4.0$ Hz, 1H), 3.32 (ddd, $J = 13.6, 9.1, 2.5$ Hz, 1H), 3.14 (ddd, $J = 13.6, 9.1, 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 167.1, 135.1, 134.5, 131.5, 128.8, 128.6, 127.4, 123.6, 100.0, 69.8, 63.3, 61.6, 35.8; HRMS (DCI$^+$ CH_4) calcd for $C_{20}H_{17}N_2O_5$ [M + H$^+$]; HRMS 365.1137, found 365.1159.

General Procedure for Preparation of 10a and 10b. Compound **5a**, **5f**, **5i**, or **5j** (either a single isomer or a mixture could be used) (1 mmol) was heated at 50 °C for 3 d with benzyl bromide (3 equiv). Excess benzyl bromide was removed by distillation under vacuum (short path distillation apparatus, 50 °C, 0,01 mmHg). The solid residue was dissolved in Et_2O (100 mL) and treated with 5% Na_2CO_3 aqueous solution (20 mL). The organic phase was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The oily residue was purified by chromatography on silica gel (CH_2Cl_2).

Ethyl 2-(Dibenzylamino)-4-oxo-4-(2-oxooxazolidin-3-yl)butanoate (10a). From 320 mg of **5a**, 377 mg (92%) of **10a** was obtained as an off-white solid: $R_f = 0.3$ (dichloromethane); mp = 139−140 °C (dichloromethane); IR (KBr) $\nu = 3062, 3028, 2982, 2926, 2848, 1775, 1728, 1391, 1221$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.36 (m, 4H), 7.31−7.27 (m, 4H), 7.24−7.20 (m, 2H), 4.34−4.14 (m, 4H), 3.97 (dd, $J = 8.3, 6.7$ Hz, 1H), 3.87−3.74 (m, 2H), 3.83 (d, $J = 13.6$ Hz, 2H), 3.59 (dd, $J = 16.2, 8.3$ Hz, 1H), 3.57 (d, $J = 13.6$ Hz, 2H), 3.08 (dd, $J = 16.2, 6.7$ Hz, 1H), 1.36 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.4, 170.7, 153.1, 139.1, 129.0, 128.2, 127.0, 61.9, 60.7, 57.3, 54.7, 42.2, 35.8, 14.5; HRMS (DCI$^+$ CH_4) calcd for [M + H$^+$]; HRMS$C_{23}H_{27}N_2O_5$ 411.1920, found 411.1917.

Ethyl 2-(Dibenzylamino)-4-(4,4-dimethyl-2-oxooxazolidin-3-yl)-4-oxobutanoate (10b). From 348 mg of **5f**, 394 mg (90%) of **10b** was obtained as a colorless oil: $R_f = 0.3$ (dichloromethane); IR (KBr) $\nu = 2980, 2928, 2910, 1780, 1721, 1699, 1383, 1329, 1179, 1096$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.35 (m, 4H), 7.31−7.28 (m, 4H), 7.25−7.21 (m, 2H), 4.34−4.17 (m, 2H), 3.98 (dd, $J = 9.6, 5.3$ Hz, 1H), 3.94 (d, $J = 8.3$ Hz, 1H), 3.92 (d, $J = 8.3$ Hz, 1H), 3.82 (d, $J = 13.9$ Hz, 2H), 3.60 (d, $J = 13.9$ Hz, 2H), 3.59 (dd, $J = 17.2, 9.3$ Hz, 1H), 3.10 (dd, $J = 17.2, 5.6$ Hz, 1H), 1.50 (s, 6H), 1.36 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.7, 171.5, 153.9, 139.1, 128.8, 128.2, 127.0, 75.1, 60.5, 60.2, 57.5, 54.9, 37.1, 24.8, 24.4, 14.5; HRMS (DCI$^+$ CH_4) calcd for [M + H$^+$]; HRMS$C_{25}H_{31}N_2O_5$:439.2233, found 439.2238.

(*S*)-Ethyl 2-(Dibenzylamino)-4-((*R*)-4-phenyl-2-oxooxazolidin-3-yl)-4-oxobutanoate ((4′*R*,3*S*)-10c). From 198 mg of (3*S*,5*R*)-, (3*R*,5*R*)-, and (3*S*,5*S*)-**5i** as a mixture of three nonseparable diastereomers, 167 mg (69%) of (*R*,*S*)-**10c** was obtained as a pale yellow oil: $R_f = 0.25$ (dichloromethane); $[\alpha]^{23}_D = -113.6$ (*c* 1.20, chloroform); IR (KBr) $\nu = 3062, 3029, 2979, 2931, 2844, 1781, 1385, 1205$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.19 (m, 15H), 5.32 (dd, $J = 8.6, 4.1$ Hz, 1H), 4.61 (dd, $J = 8.8, 8.6$ Hz, 1H), 4.22 (dd, $J = 8.8, 4.1$ Hz, 1H), 4.16−4.01 (m, 2H), 3.94 (dd, $J = 9.9, 4.5$ Hz, 1H), 3.81 (d, $J = 13.9$ Hz, 2H), 3.70 (dd, $J = 17.7, 10.0$ Hz, 1H), 3.59 (d, $J = 13.9$ Hz, 2H), 3.15 (dd, $J = 17.7, 4.5$ Hz, 1H), 1.17 (t, $J = 7.1$ Hz, 3H; ^{13}C NMR (100 MHz, $CDCl_3$) 171.2, 170.4, 153.6, 139.1, 138.6, 129.1, 128.7, 128.6, 128.3, 127.1, 125.8, 70.0, 60.5, 57.6, 57.5, 55.0, 39.4, 14.3; HRMS (DCI-) calcd for [M]; HRMS$C_{29}H_{30}N_2O_5$ 486.2155, found 486.2158.

(*R*)-Ethyl 2-(Dibenzylamino)-4-((*R*)-4-phenyl-2-oxooxazolidin-3-yl)-4-oxobutanoate ((4′*R*,3*R*)-10c). From 174 mg of (3*S*,5*R*)-, (3*R*,5*R*)-, and (3*S*,5*S*)-**5i** as a mixture of 3 non-separable diastereomers, 50 mg (21%) of (*R*,*R*)-**10c** was obtained as a pale yellow oil: $R_f = 0.16$ (dichloromethane); $[\alpha]^{23}_D = +0.1$ (*c* 0.91, chloroform); IR (KBr) $\nu = 3062, 3029, 2980, 2928, 2845, 1770, 1385, 1181$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.20 (m, 15H), 5.27 (dd, $J = 8.6, 3.3$ Hz, 1H), 4.55 (dd, $J = 8.8, 8.6$ Hz, 1H), 4.20 (dd, $J = 8.8, 3.3$ Hz, 1H), 4.33−4.15 (m, 2H), 3.92 (dd, $J = 8.6, 6.3$ Hz, 1H), 3.79 (d, $J = 13.9$ Hz, 2H), 3.68 (dd, $J = 16.7, 8.6$ Hz, 1H), 3.56 (d, $J = 13.6$ Hz, 2H), 3.07 (dd, $J = 16.7, 6.3$ Hz, 1H), 1.35 (t, $J = 7.1$ Hz, 3H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 170.1, 153.5, 139.1, 139.0, 129.1, 128.9, 128.7, 128.2, 127.0, 125.9, 70.0, 60.7, 57.4$_7$, 57.4$_4$, 54.8, 35.8, 14.5.

(*R*)-Ethyl 2-(Dibenzylamino)-4-((*S*)-4-ethyl-2-oxooxazolidin-3-yl)-4-oxobutanoate ((4′*S*,3*R*)-10d). From 174 mg of (3*R*,5*S*)-, (3*R*,5*R*)-, and (3*S*,5*S*)-**5i** as a mixture of three nonseparable diastereomers, 116 mg (53%) of **(*S*,*R*)-10d** was obtained as a pale yellow oil: $R_f = 0.24$ (dichloromethane); $[\alpha]^{23}_D = +24.6$ (*c* 1.30, chloroform); IR (KBr) $\nu = 2976, 1780, 1726, 1391, 1209$ cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.35 (m, 4H), 7.31−7.27 (m, 4H), 7.23−7.19 (m, 2H), 4.34−4.16 (m, 4H), 4.04−3.93 (m, 2H), 3.83 (d, $J = 13.6$ Hz, 2H), 3.70−3.57 (m, 3H), 3.10 (dd, $J = 17.4, 5.1$ Hz, 1H), 1.81−1.70 (m, 1H), 1.68−1.56 (m, 1H), 1.38−1.32

(m, 3H), 0.86−0.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.4, 170.6, 153.5, 139.0, 128.8, 128.2, 127.0, 66.7, 60.5, 57.4, 54.9, 54.8, 35.8, 14.5, 8.1; HRMS (DCI + methane) calcd for [M + H^+]; HRMS $C_{25}H_{31}N_2O_5$ 439.2233, found 439.2254.

(*S*)-Ethyl 2-(Dibenzylamino)-4-((*S*)-4-ethyl-2-oxooxazolidin-3-yl)-4-oxobutanoate ((4′*S*,3*S*)-10d). From 174 mg of (3*R*,5*S*)-, (3*R*,5*R*)-, and (3*S*,5*S*)-**5i** as a mixture of three nonseparable diastereomers, 91 mg (42%) of (*S*,*S*)-**10d** was obtained as a pale yellow oil: R_f = 0.14 (dichloromethane); $[\alpha]^{23}_D$ = −13.2 (*c* 1.05, chloroform); IR (KBr) ν = 2975, 1781, 1726, 1392, 1207 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.35 (m, 4H), 7.33−7.27 (m, 4H), 7.25−7.21 (m, 2H), 4.35−4.18 (m, 4H), 4.04 (dd, *J* = 8.0, 2.1 Hz, 1H), 3.95 (dd, *J* = 8.8, 5.8 Hz, 1H), 3.83 (d, *J* = 13.6 Hz, 2H), 3.63 (dd, *J* = 16.7, 8.8 Hz, 1H), 3.57 (d, *J* = 13.6 Hz, 2H), 3.09 (dd, *J* = 16.7, 5.8 Hz, 1H), 1.83−1.75 (m, 1H), 1.71−1.61 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.5, 170.6, 153.5, 139.1, 128.9, 128.2, 127.1, 66.7, 60.7, 57.4, 55.1, 54.8, 36.0, 25.0, 14.5, 8.1.

3-(Dibenzylamino)-4-ethoxy-4-oxobutanoic Acid (11). A mixture of **10a** or **10b** (0.1 mmol) and LiOH (12 mg, 0.5 mmol) in H_2O (0.5 mL) and THF (0.5 mL) was stirred at room temperature for 30 min. The reaction was quenched with HCOOH (50 μL) and extracted with dichloromethane (20 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (silica gel, dichloromethane to dichloromethane:diethyl ether 1:1) to afford acid **11** (27.2 mg (80%) from **10a**, 29.1 mg (85%) from **10b**) as a pale yellow oil: R_f = 0.5 (dichloromethane:diethyl ether 1:1); IR (KBr) ν = 3433, 2925, 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.32 (m, 8H), 7.30−7.25 (m, 2H), 4.36−4.22 (m, 2H), 3.94 (d, *J* = 13.1 Hz, 2H), 3.85 (t, *J* = 7.8 Hz, 1H), 3.62 (d, *J* = 13.1 Hz, 2H), 2.79 (d, *J* = 7.8 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 174.2, 170.2, 137.1, 129.3, 128.6, 127.7, 61.1, 57.0, 54.6, 33.5, 14.4; HRMS (FI) calcd for [M + H^+]; HRMS $C_{20}H_{24}NO_4$ 342.1705, found 342.1688.

4-Benzyl 1-Ethyl 2-(Dibenzylamino)succinate (12). To a well-stirred solution of benzyl alcohol (21.6 mg, 0.2 mmol) in THF (0.5 mL) was added *n*-BuLi (1.6 M in hexane, 94 μL, 0.15 mmol) at room temperature. The solution was stirred for 30 min, and then a solution of **10a** (41.0 mg, 0.1 mmol) in THF (1 mL) was added. After 30 min of additional stirring, the reaction was quenched with HCOOH (50 μL) and extracted with dichloromethane (20 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (silica gel, dichloromethane) to afford diester **12** (32.8 mg, 76%) as a pale yellow oil: R_f = 0.6 (diethyl ether); IR (KBr) ν = 3063, 3030, 2981, 1732, 1165, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (m, 15H), 5.13 (d, *J* = 12.4 Hz, 1H), 4.93 (d, *J* = 12.4 Hz, 1H), 4.30−4.15 (m, 2H), 3.91 (dd, *J* = 8.1, 7.1 Hz, 1H), 3.82 (d, *J* = 13.6 Hz, 2H), 3.57 (d, *J* = 13.6 Hz, 2H), 2.92 (dd, *J* = 15.7, 8.1 Hz, 1H), 2.71 (dd, *J* = 15.7, 7.1 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.4, 170.9, 138.9, 135.7, 128.9, 128. 5, 128.3, 128.2$_3$, 128.1$_9$, 127.1, 66.4, 60.7, 58.0, 54.8, 51.5, 35.2, 14.5; HRMS (FD) calcd for $C_{27}H_{29}NO_4$ 431.2097, found 431.2137.

1-Ethyl 4-Methyl 2-(Dibenzylamino)succinate (13). A solution of **10a** (41.0 mg, 0.1 mmol) and $NaOCH_3$ (16.2 mg, 0.3 mmol) in CH_3OH (1 mL) was stirred for 30 min at room temperature. The reaction was quenched with HCOOH (50 μL) and extracted with dichloromethane (20 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (silica gel, diethyl ether) to afford diester **13** (32.0 mg, 90%) as a pale yellow oil: R_f = 0.9 (diethyl ether); IR (KBr) ν = 3063, 3029, 2983, 2952, 2847, 1732, 1454, 1169, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.28 (m, 8H), 7.26−7.21 (m, 2H), 4.34−4.17 (m, 2H), 3.87 (dd, *J* = 7.8, 7.4 Hz, 1H), 3.83 (d, *J* = 13.6 Hz, 2H), 3.58 (s, 3H), 3.57 (d, *J* = 13.6 Hz, 2H), 2.85 (dd, *J* = 15.4, 7.8 Hz, 1H), 2.67 (dd, *J* = 15.4, 7.4 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.3, 171.3, 138.9, 128.8, 128.2, 127.1, 61.1, 57.8, 54.6, 51.5, 34.9, 14.4; HRMS (DCI$^+$ CH_4) calcd for [M + H^+]; HRMS $C_{21}H_{26}NO_4$ 356.1862, found 356.1862.

1-Ethyl 2-(Dibenzylamino)-4-(methoxy(methyl)amino)-4-oxobutanoate (14). To a well-stirred solution of **10a** (41.0 mg, 0.1 mmol) and Weinreb's amine hydrochloride salt CH_3ONHCH_3·HCl (29.3 mg, 0.3 mmol) under argon in dichloromethane (0.5 mL) was injected $AlMe_3$ (2 M in hexanes, 150 μL, 1 mmol) at room temperature. The mixture was stirred for 30 h, and then the solvent was evaporated under reduced pressure. The residue was flash chromatographed (diethyl ether, R_f = 0.4) to give the title compound (32.1 mg, 95%) as a pale yellow oil: IR (KBr) ν = 2927, 1728, 1664, 1454, 1177, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.37 (m, 4H), 7.32−7.28 (m, 4H), 7.25−7.20 (m, 2H), 4.35−4.17 (m, 2H), 3.94 (dd, *J* = 9.9, 5.1 Hz, 1H), 3.84 (d, *J* = 13.9 Hz, 2H), 3.61 (d, *J* = 13.9 Hz, 2H), 3.61 (s, 3H), 3.10, (s, 3H), 3.14−3.01 (m, 1H), 2.64−2.59 (m, 1H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.9, 171.8, 139.3, 128.7, 128.2, 127.0, 61.0, 60.5, 57.8, 55.1, 32.7, 14.5; HRMS (FI) calcd for $C_{22}H_{28}N_2O_4$ 384.2049, found 384.2048.

Ethyl 4-(Butylamino)-2-(dibenzylamino)-4-oxobutanoate (15). A mixture of **10a** (41.0 mg, 0.1 mmol) and *n*-butylamine (73 mg, 1 mmol) was stirred for 10 min at room temperature, and then the *n*-butylamine in excess was evaporated under reduced pressure. The residue was flash chromatographed (diethyl ether, R_f = 0.45) to give the title compound (37.6 mg, 90%) as a colorless yellow oil: IR (KBr) ν = 2924, 1721, 1663, 1452, 1177 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.24 (m, 10H), 6.38 (br b., 1H), 4.34−4.19 (m, 2H), 3.91 (d, *J* = 13.6 Hz, 2H), 3.83 (dd, *J* = 8.6, 6.1, 1H), 3.60 (d, *J* = 13.6 Hz, 2H), 3.21−3.13 (m, 1H), 3.04−2.96 (m, 1H), 2.69−2.57 (m, 2H), 1.41−1.33 (m, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); 1.33−1.24 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.0, 138.5, 129.1, 128.4, 127.4, 60.7, 58.2, 54.7, 39.0, 35.8, 32.6, 20.1, 14.5, 13.7; HRMS (DCI$^+$ CH_4) calcd for [M + H^+]; HRMS $C_{24}H_{33}N_2O_3$ 397.2491, found 397.2499.

Ethyl 2-(Dibenzylamino)-4-(2-methoxy-2-oxoethylamino)-4-oxobutanoate (16). To a well-stirred solution of **10a** (41.0 mg, 0.1 mmol) and $NH_2CH_2COOCH_3$·HCl (37.7 mg, 0.3 mmol) under argon in dichloromethane (0.5 mL) was injected $AlMe_3$ (2 M in hexanes, 150 μL, 1 mmol) at room temperature. The mixture was stirred for 2 h, and then the solvent was evaporated under reduced pressure. The residue was flash chromatographed (dichloromethane/diethyl ether 9:1, R_f = 0.3) to give the dipeptide **16** (30.1 mg, 79%) as a pale yellow oil: IR (KBr) ν = 3323, 3029, 2953, 2848, 1728, 1655, 1542, 1454, 1371, 1209, 1178, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.23 (m, 10H), 6.82 (br, 1H), 4.35−4.20 (m, 2H), 3.97 (dd, *J* = 18.2, 5.8 Hz, 1H), 3.90 (d, *J* = 13.6 Hz, 2H), 3.85 (d, *J* = 7.1 Hz, 1H), 3.74 (s, 3H), 3.73 (dd, *J* = 18.2, 5.1, 1H), 3.60 (d, *J* = 13.6 Hz, 2H), 2.69 (d, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 170.4, 170.1, 138.5, 129.2, 128.4, 127.4, 60.8, 58.1, 52.2, 44.8, 41.0, 35.6, 14.5; HRMS (DCI$^+$ CH_4) calcd for [M + H^+]; HRMS $C_{23}H_{29}N_2O_5$ 413.2076, found 413.2089.

3-(Dibenzylamino)-1-(2-hydroxyethyl)pyrrolidine-2,5-dione (17). To a well-stirred solution of **10a** (41.0 mg, 0.1 mmol) in THF (0.5 mL) was added ethanolamine (61 mg, 1 mmol) at room temperature. The mixture was stirred for 2 h, and then the solvent was evaporated under reduced pressure. The residue was flash chromatographed (diethyl ether, R_f = 0.4) to give the succinimide **18** (32.2 mg, 95%) as a pale yellow oil: IR (KBr) ν = 3454, 3028, 1699, 1398, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.38 (m, 4H), 7.35−7.30 (m, 4H), 7.28−7.24 (m, 2H), 3.97 (dd, *J* = 9.1, 5.3 Hz, 1H), 3.83 (d, *J* = 13.4 Hz, 2H), 3.77−3.73 (m, Hz, 2H), 3.71−3.68 (m, 2H), 3.65 (d, *J* = 13.4 Hz, 2H), 2.78 (dd, *J* = 18.5, 9.1 Hz, 1H), 2.65 (dd, *J* = 18.5, 5.3 Hz, 1H), 2.21 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 175.9, 138.2, 128.8, 128.5, 127.6, 60.5, 57.5,

54.7, 41.3, 32.1, 30.3; HRMS (FI) calcd for [M + H^+]; HRMS $C_{20}H_{22}N_2O_3$ 338.1630, found 338.1651.

(*S*)-Diethyl 2-(Dibenzylamino)succinate (*S*)-18. A solution of (3*S*)-**10c** (48.6 mg, 0.10 mmol) and $NaOC_2H_5$ (6.8 mg, 0.1 mmol) in EtOH (1 mL) was stirred for 30 min at room temperature. The reaction was quenched with HCOOH (50 μL) and extracted with dichloromethane (20 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography (silica gel, diethyl ether) to afford diester (*S*)-**18** (26.2 mg, 66%) as a pale yellow oil: R_f = 0.91 (diethyl ether); $[\alpha]^{23}_D$ = −112.4 (*c* 1.31, chloroform); IR (KBr) ν = 3062, 2951, 1733, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.33 (m, 4H), 7.32−7.28 (m, 4H), 7.25−7.21 (m, 2H), 4.33−4.18 (m, 2H), 4.16−4.06 (m, 1H), 4.03−3.95 (m, 1H), 3.87 (dd, *J* = 7.3, 8.1 Hz, 1H), 3.83 (d, *J* = 13.6 Hz, 2H), 3.58 (d, *J* = 13.6 Hz, 2H), 2.85 (dd, *J* = 15.7, 8.1 Hz, 1H), 2.65 (dd, *J* = 15.7, 7.3 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). An authentical sample of (*S*)-**18** was prepared from L-aspartic acid:[32] $[\alpha]^{23}_D$ = −110.3 (*c* 2.05, chloroform).

(*R*)-Diethyl 2-(Dibenzylamino)succinate (*R*)-18. (3*R*)-**10d** (43.8 mg, 0.10 mmol), submitted to the same treatment as for (*R*,*S*)-**10c**, afforded (*R*)-**18** as a pale yellow oil (28.0 mg, 76%): $[\alpha]^{23}_D$ = +113.7 (*c* 1.56, chloroform).

Acknowledgment. We thank the French Ministry of Research for T.B.N.'s PhD grant.

Supporting Information Available: NMR spectroscopic data for all new compounds **3**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702490W

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