# An Efficient and Simple Entry to *N*-Substituted *β*-Enamino Acid Derivatives from 2-Alkyl-2-oxazolines and 2-Alkyl-2-thiazolines†

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Reaction of azaenolates of 2-alkyl-oxa(thia)zolines **6** with imidoyl chlorides **7** as electrophiles to furnish masked *N*-substituted *β*-enamino acid derivatives **1**−**2** in 70−90% yield is described. Alternative routes are discussed. Compounds **1**−**2** generally appear in one tautomeric form, imino or enamino, depending on the nature of the imidoyl chloride. The configuration of the enamino moiety (*Z*) and the conformation (*s-cis*) of compounds **1**−**2** obtained were established by an NMR study and unequivocally set by nuclear Overhauser effect difference experiments. An X-ray structure of compound **1e** is also reported, showing a strong intramolecular NH···N hydrogen bond. *Ab initio* calculations (HF/3-21G and HF/3-21+G) have been carried out on several representative examples (**1e**, **1p**, and **1l**) in an attempt to support and provide the correct geometry of these derivatives. Structural considerations among the possible isomers of compounds **1** are discussed. From these studies it was concluded that the theoretical calculations agree with the experimental results. In addition, a very simple *one-pot* procedure for the preparation of masked *N*-substituted α-alkylated *β*-enamino acid derivatives **2** from **6**, **7**, and different alkyl halides ($R^3Y$) is described.

## Introduction

Among 1,3-difunctionalized compounds, the *β*-amino acid unit is one of the most interesting target structures due to its pharmacology[1] and its utility in several aspects of synthetic organic chemistry,[2] such as chiral auxiliaries, chiral building blocks, and intermediates in the synthesis of *β*-lactams, and because this functionality is found in several biologically active natural products.[3] Therefore, a great deal of attention has been given, in recent years, to the development of new methodologies for the preparation of such compounds.[4] Although several attractive routes to *β*-amino acids have been recently described,[5] the chemoselective reduction of the enaminic function in *β*-enamino acid derivatives still remains as one of the least studied strategies.[6] This is probably due to the difficulty in achieving this selective reduction in an effective manner and also, in part, because of the high reactivity of the ester functionality toward a great number of reducing agents.[6,7] A simple way to overcome this problem would be through the use of protecting groups to block this functionality. Heterocyclic systems, such as $\Delta^2$-thiazolines, $\Delta^2$-imidazolines, and, especially, $\Delta^2$-oxazolines, have been extensively used as masked carboxylic acids.[8] The great stability of these heterocycles toward a large variety of reagents, along with the possibility of introducing chirality into their structure,

† This paper is dedicated to Professor Herbert Lehmkuhl on the occasion of his 70th Birthday.

‡ X-ray Analysis.

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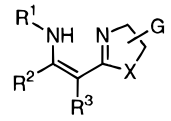
makes these versatile substrates the protecting groups of choice for this purpose.

On the other hand, acyclic $\beta$-enamino acid derivatives are well-known as useful starting materials in a variety of synthetic processes. They have, therefore, recently been used as building blocks in the synthesis of alkaloids, mainly through aza-annulation processes,[9] and other biologically active compounds, such as toxins,[10] 1,4-dihydropyridines,[11] nalidixic acid derivatives,[12] $\beta$-amino acids,[6e,13] and $\gamma$-amino alcohols.[14] In addition, they have proven to be of great utility in asymmetric synthesis[15] and also as prodrugs of primary amines.[16] Although simple $\beta$-enamino esters are usually synthesized by condensation of $\beta$-keto esters with ammonia or amines,[17] other methods have alternatively been developed in order to ensure the generality and efficiency of such processes. Nucleophilic addition of alkyl ester enolates to nitriles,[18] Michael addition of amines to alkynoates,[19] and reaction of imines with activated carbonic acid derivatives[20] are some of the strategies which, with more or less success, have been used. In this context, we have recently reported two new different approaches to $\beta$-enamino acid derivatives. A simple route to masked $\beta$-dehydroamino acids (**1**−**2**, $R^1$ = H, $R^2$ = alkyl or aryl, $R^3$ = or ≠ H) starting from 2-alkyl-2-oxazolines or 2-alkyl-2-thiazolines and nitriles was initially described (Chart 1).[21,22] More recently, a mild two-step procedure to synthesize $\beta$-enamino esters by reaction of ketimines with 1,1′-carbonyl diimidazole and subsequent addition of the corresponding alcohols was developed.[23]

In line with our efforts toward the synthesis of masked $\beta$-dehydroamino acids[21] (**1**−**2**) and keeping in mind the lack of general methods for their preparation, along with our own interest in the study of their reactivity as precursors of $\beta$-amino acids, we report a new and general entry to masked *N*-substituted $\beta$-enamino acid derivatives (**1**−**2**) ($R^1$ ≠ H) by reacting α-metalated 2-oxa- and 2-thiazolines with imidoyl halides. In addition, alternative routes are also discussed.

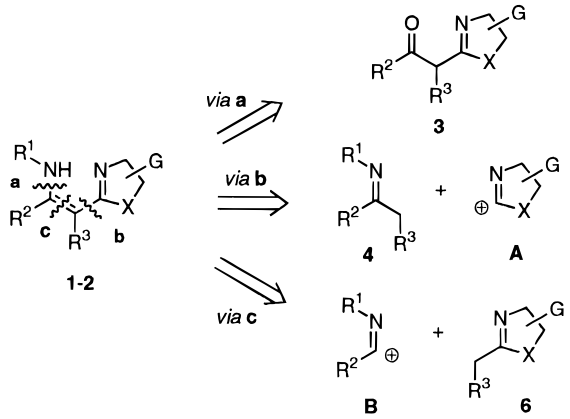
**Chart 1**



**1** ($R^1$=H, $R^2$=alkyl or aryl, $R^3$= H)
**2** ($R^1$=H, $R^2$=alkyl or aryl, $R^3$≠ H)

(X=O, S)

**Scheme 1**




## Results and Discussion

In order to obtain compounds **1**−**2** we have considered three possible alternative strategies, as shown in Scheme 1. Apparently, the most simple access to **1**−**2** would be, similar to the synthesis of $\beta$-enamino esters, the condensation of $\beta$-keto-2-oxazolines (**3**) with amines (*via* a, Scheme 1). However, although the synthesis of $\beta$-keto-2-oxazolines has been described,[24] several authors[22] have indicated that such a process leads to a complex mixture of products and never to the desired enamines **1**−**2**. Therefore, the other two alternatives (*via* b and c) were tested. The second approach (*via* b) implies the reaction of azaenolates derived from ketimines with type **A** synthons, which may be regarded as masked formyl groups. We have studied this reaction using methylketimines, derived from aliphatic and aromatic amines, and 2-(methylthio)-2-thiazoline (**5**)[25] in different reaction conditions, and we have found that, in only a few cases (*i.e.*, $R^1$ = *n*-butyl, $R^2$ = Ar) and always with very low yields (<20%), the process yielded the target $\beta$-dehydroaminoacids (**1**, X = S, Scheme 2).

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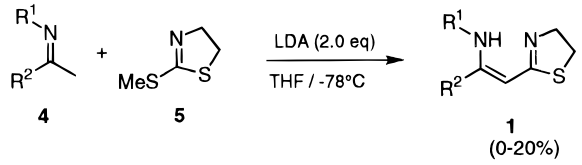
**Scheme 2**




These results prompted us to study the third alternative, which involves, in a similar way, the reaction of azaenolates, now derived from 2-alkyl-2-oxazolines and 2-alkyl-2-thiazolines (**6**), with imidoyl carbocation **B** (*via* c, Scheme 1). As the acylimidoyl species **B** we have used *N*-alkyl- and *N*-arylimidoyl chlorides (**7**).

Imidoyl halides,[26] especially perfluoroalkyl derivatives,[27] are promising building blocks in organic synthesis because of their high reactivity and their participation in numerous synthetic processes, including the synthesis of nitrogen heterocycles[28] and other interesting fluorinated derivatives.[29] In addition, they have shown their utility in several fields of medicinal and agricultural chemistry.[26] *N*-Alkyl- and *N*-arylimidoyl chlorides (**7**) have been obtained by standard methods, starting either from amides by treatment with $Cl_2SO$ or $PCl_5$[30] or directly from carboxylic acids, following the procedure recently described by Uneyama.[26] On some occasions, particularly for the thermally unstable *N*-1-phenylethyl derivatives,[31] these compounds (**7**) have been used directly, without later purification of the crude reaction mixture. No significant change in the chemical yield of the process was observed in these cases.

Thus, the treatment of 2-methyl-2-oxa(thia)zolines (**6**, 1.0 equiv) with lithium diisopropylamide (LDA, 2.0 equiv) at −78 °C in tetrahydrofuran (THF) for 2 h generated a slightly yellow solution of the corresponding lithium azaenolate. Addition of a variety of *N*-alkyl- or *N*-arylimidoyl chlorides (**7**, 1.0 equiv) to this solution gave, after standard workup, the corresponding *β*-dehydroamino acids (**1**−**2**) as the only products[32] (Scheme 3). Table 1 and Table 2 (entries 2, 4, 6, and 11−13) summarize the obtained results.

From Tables 1 and 2 it can be seen that the reaction works well. High yields are, in general, obtained, and it does not require the use of an excess of reagents, with the exception of the base (LDA) for which a 2-fold excess of LDA is necessary.[33] To form the lithium intermediate

**Scheme 3**

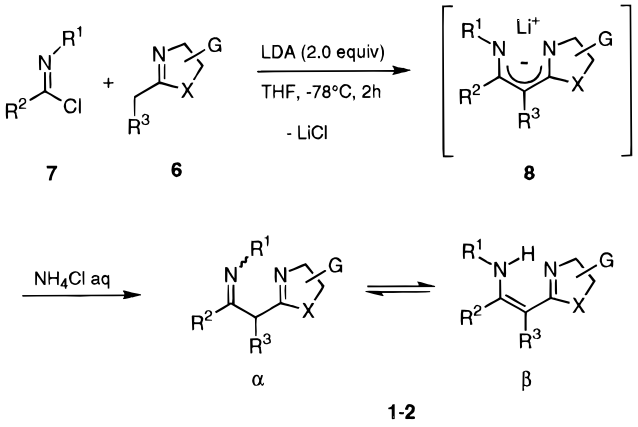
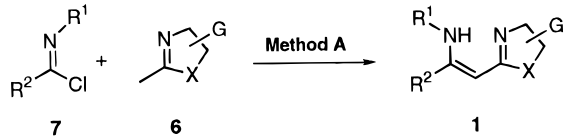



**Table 1. *N*-Substituted *β*-Enamino Acid Derivatives 1 ($R^3$ = H) Obtained from Oxa(thia)zolines 6 and Imidoyl Chlorides 7**




| | | imidoyl chlorides (**7**) | | | yield |
|---|---|---|---|---|---|
| entry | **6**[a] | $R^1$ | $R^2$ | product | (%)[c] |
| 1 | **6a** | Ph | Ph | **1a** | 87 |
| 2 | **6a** | *c*-$C_6H_{11}$ | Ph | **1b** | 75 |
| 3 | **6a** | *p*-$MeOC_6H_4$ | Ph | **1c** | 72 |
| 4 | **6a** | (±)-$C_6H_5$(Me)CH | Ph | **1d** | 81 |
| 5 | **6a** | Ph | *p*-$MeOC_6H_4$ | **1e** | 95 |
| 6 | **6a** | *p*-$MeOC_6H_4$ | $CF_3$ | **1f** | 87 |
| 7 | **6a** | *p*-$MeC_6H_4$ | $CF_3$ | **1g** | 88 |
| 8 | **6a** | (±)-$C_6H_5$(Me)CH | $CF_3$ | **1h** | 75 |
| 9 | **6a** | *p*-$MeOC_6H_4$ | 3-pyridyl | **1i** | 85 |
| 10 | **6a** | *p*-$MeOC_6H_4$ | *i*-Pr | **1j** | 70 |
| 11 | **6a** | *p*-$MeC_6H_4$ | $Me_2CHCH_2$ | **1k** | 73 |
| 12 | **6a** | *p*-$MeC_6H_4$ | *t*-Bu | **1l** | 70[d] |
| 13 | **6a** | (*S*)-(−)-$C_6H_5$(Me)CH | Ph | **1m** | 75 |
| 14 | **6b** | Ph | Ph | **1n** | 78 |
| 15 | **6b** | Ph | *p*-$MeOC_6H_4$ | **1o** | 90 |
| 16 | **6b** | *p*-$MeOC_6H_4$ | $CF_3$ | **1p** | 80 |
| 17 | **6b** | *p*-$MeOC_6H_4$ | 3-pyridyl | **1q** | 83 |
| 18 | **6b** | *p*-$MeC_6H_4$ | $Me_2CHCH_2$ | **1r** | 82 |
| 19 | **6b** | *p*-$MeC_6H_4$ | *t*-Bu | **1s** | 75[c] |
| 20 | **6c** | (±)-$C_6H_5$(Me)CH | Ph | **1t** | 78 |
| 21 | **6c** | *p*-$MeOC_6H_4$ | $CF_3$ | **1u** | 78 |
| 22 | **6c** | *p*-$MeC_6H_4$ | $CF_3$ | **1v** | 83 |
| 23 | **6c** | *p*-$MeC_6H_4$ | *t*-Bu | **1w** | 72[c] |
| 24 | **6d** | Ph | *p*-$MeOC_6H_4$ | **1x** | 90 |
| 25 | **6d** | (*S*)-(−)-$C_6H_5$(Me)CH | Ph | **1y** | 78 |
| 26 | **6e** | (*S*)-(−)-$C_6H_5$(Me)CH | Ph | **1z** | 90 |

[a] **6a**, 2-Methyl-2-oxazoline; **6b**, 2,4,4-trimethyl-2-oxazoline; **6c**, 2-methyl-2-thiazoline; **6d**, *trans*-(4*S*,5*S*)-(+)-2-methyl-4-methoxymethyl-5-phenyl-2-oxazoline; **6e**, *cis*-(4*R*,5*S*)-(+)-2,4-dimethyl-5-phenyl-2-oxazoline. [b] Yield after purification. [c] Only the imino form was observed. [d] Enamino and imino tautomers were observed (see ref 36).

**8**, reaction of the product that is initially formed with the second equivalent of LDA protects it from undesired reactions and significantly improves the chemical yield of the process, as has already been postulated in related systems.[29] It is also worth noting that these compounds appear generally in one tautomeric form, imino (α) or enamino (*β*), which depends on the nature of substituents $R^1$ and $R^2$ (Scheme 3).

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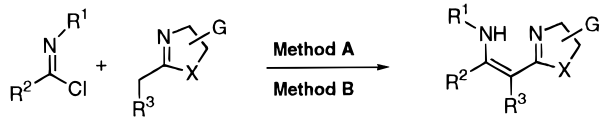
(31) The preparation of such compounds, using the thionyl chloride method, requires purification of the crude reaction by distillation. In these cases, a partial thermal decomposition affording the corresponding nitriles and alkylhalides has been observed (von Braun reaction). See: Vaughan, W.; Carlson, D. R. *J. Am. Chem. Soc.* **1962**, *84*, 769. Therefore, the Uneyama method (ref 27) was the only procedure applied for obtaining these derivatives.

(32) In most instances, small amounts of amides resulting from the hydrolysis of unreacted imidoyl chlorides (**7**) were identified in the crude mixture of the reaction. These byproducts were easily separated by flash chromatography.

(33) In contrast with other related processes (ref 21), bases, such as *n*-butyl lithium, cannot be used in this reaction due to the high reactivity of the imidoyl halides toward nucleophiles. See also refs 28 and 29.

**Table 2. *N*-Substituted α-Alkylated *β*-Enamino Acid Derivatives 2 ($R^3 \neq H$), *One-Pot* Synthesis**




7 6 2

| entry | 6[a] | $R^1$ | $R^2$ | $R^3$ | method[b] | product | yield (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **6a** | Ph | Ph | Me | B | **2a** | 90 |
| 2 | **6f** | | | | A | | 82 |
| 3 | **6a** | (±)-$C_6H_5$(Me)CH | Ph | Me | B | **2b** | 61[d] |
| 4 | **6f** | | | | A | | 90 |
| 5 | **6a** | *p*-$MeOC_6H_4$ | $CF_3$ | Me | B | **2c** | 65[d,e] |
| 6 | **6f** | | | | A | | 92 |
| 7 | **6a** | *p*-$MeOC_6H_4$ | 3-pyridyl | *n*-Bu | B | **2d** | 65[d] |
| 8 | **6b** | Ph | *p*-$MeOC_6H_4$ | Bn | B | **2e** | 60[d] |
| 9 | **6a** | Ph | *p*-$MeOC_6H_4$ | $EtO_2CCH_2$ | B | **2f** | 55[d] |
| 10 | **6b** | Ph | *p*-$MeOC_6H_4$ | $EtO_2CCH_2$ | B | **2g** | 50[d] |
| 11 | **6f** | (*S*)-(−)-$C_6H_5$(Me)CH | Ph | Me | A | **2h** | 80 |
| 12 | **6f** | Ph | *p*-$MeOC_6H_4$ | Me | A | **2i** | 88 |
| 13 | **6f** | *p*-$MeC_6H_4$ | *t*-Bu | Me | A | **2j** | 70[f] |

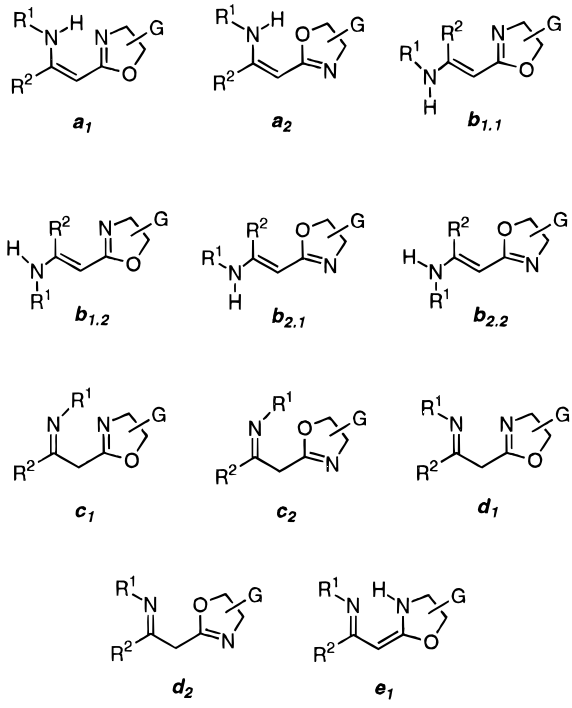
[a] **6a**, 2-Methyl-2-oxazoline; **6b**, 2,4,4,-trimethyl-2-oxazoline; **6f**, 2-ethyl-2-oxazoline. [b] method A, Obtained directly from 2-ethyl-2-oxazoline (**6f**); method B, *one-pot* reaction from 2-methyl-2-oxazolines (**6**, $R^3$ = H), imidoyl halides (**7**), and alkyl halides ($R^3$Y, MeI, *n*-BuI, BnBr, and $EtO_2CCH_2Br$ were used as electrophiles). [c] Yield after purification. [d] Variable amounts (15−25%) of compounds **1** resulting from the first step of the reaction of **6** ($R^3$ = H) and **7** were also identified and by MPLC isolated (see Table 1, entries 4−6, 9, and 17). [e] Enamino and imino tautomers (3:1) were observed (see Experimental Section). [f] Only the imino form was observed.

This methodology appears to be general for both the heterocyclic ring system and the imidoyl halide as shown in Tables 1 and 2. Of particular interest is its applicability to the synthesis of trifluoromethyl derivatives due to the importance and utility of such compounds in several fields of organic chemistry.

The structural assignment of compounds **1**−**2** was made on the basis of their spectral and analytical data. The resulting compounds **1**−**2** were, in most cases, isolated in the tautomer enaminic form *β* as seen from the NMR spectra (Scheme 3). Thus, for example, in the case of compound **1e** (Table 1, entry 5), the $^1$H NMR spectrum exhibits characteristic signals at *δ* 4.89 (s, 1H) and 10.56 (br s, 1H) corresponding to the vinyl proton in the *H*C═C grouping and N*H* grouping, respectively. This spectrum is in accordance with the tautomeric form **1e***β*, suggesting also, as consequence of the large shift downfield of the NH proton, an intramolecular hydrogen bond, probably between the amino group and the sp$^2$ nitrogen atom of the oxazoline ring.[34]

In order to determine the correct stereochemistry of the enaminic double bond moiety in compounds **1**−**2** (***a*****$_1$**, ***a*****$_2$** or ***b*****$_{1.1}$**, ***b*****$_{1.2}$**, ***b*****$_{2.1}$**, ***b*****$_{2.2}$** in Chart 2), $^1$H NMR NOE-difference experiments were applied over compound **1e**. This study showed that compound **1e** exists predominantly in the (*Z*) configuration (***a*****$_1$** or ***a*****$_2$**) in $CDCl_3$ solution. Thus, by irradiation of the vinylic hydrogen at 4.89 ppm, a positive NOE (8.28%) was obtained for the *ortho* hydrogens of the *p*-methoxyphenyl ring at 7.22 ppm. Analogous nuclear Overhauser effect (NOE) enhancements resulted from the saturation of the doublet at 7.22 ppm. An additional positive NOE (2.48%) with the *ortho* hydrogens of the phenylamino ring at 6.65 ppm was also detected, confirming the proposed structure. This experiment, however, did not allow us to distinguish between the two possible conformers (*Z*)-*s*-*cis* (***a*****$_1$**) and

**Chart 2**




(*Z*)-*s*-*trans* (***a*****$_2$**). Therefore, a single-crystal X-ray diffraction analysis was performed for compound **1e**. Certain selected bond lengths, bond angles, and dihedral angles of **1e** are listed in Table 3, and a plot of the molecular geometry is given in Figure 1. The crystal structure of compound **1e** shows that it was in agreement with the initially proposed (*Z*)-*s*-*cis* configuration (***a*****$_1$**) and confirms the results of previous experiments. (The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the director, Cambridge Crystallographic data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.) Inspection of the structural data in Table 3 reveals a strong intramolecular hydrogen bond between N2−H21 and N1 (N1−H21 2.04 Å) forming

(34) Similar hydrogen bond interactions have been observed for related systems. (a) See, *e.g.*, refs 20c, 21, 22. (b) Chowdhry, M. M.; Burrows, A. D.; Mingos, D. M.; White, A. J.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1521. (c) Dixit, A. N.; Reddy, K. V.; Deshmukh, A. R.; Rajappa, S.; Ganguly, B.; Chandrasekhar, J. *Tetrahedron* **1995**, *51*, 1437.

**Table 3. Comparison of Selected Calculated Bond Lengths, Bond Angles, and Dihedral Angles for 1e ($a_1$) [(*Z*)-*s*-*cis*] and 1e ($a_2$) [(*Z*)-*s*-*trans*] with Those Experimentally Observed for 1e ($a_1$) [(*Z*)-*s*-*cis*]**

| | | calculated[b] ($a_1$) | | calculated[b] ($a_2$) | |
|---|---|---|---|---|---|
| | observed[a] ($a_1$) | HF/3-21G | HF/3-21+G | HF/3-21G | HF/3-21+G |
| | | bond lengths (Å) | | | |
| N2−H21 | 0.86(2) | 1.013 | 1.011 | 1.004 | 1.003 |
| N2−C3 | 1.367(3) | 1.365 | 1.370 | 1.374 | 1.380 |
| C3−C4 | 1.356(3) | 1.350 | 1.353 | 1.344 | 1.248 |
| C4−C51 | 1.441(3) | 1.434 | 1.433 | 1.442 | 1.441 |
| C51−N1 | 1.275(3) | 1.270 | 1.275 | | |
| C51−O2 | | | | 1.402 | 1.407 |
| N1···H21 | 2.04(2) | 1.914 | 1.956 | | |
| O2···H21 | | | | 1.880 | 1.904 |
| N2−N1 | 2.747(3) | 2.740 | 2.763 | | |
| O2−N2 | | | | 2.679 | 2.689 |
| | | bond angles (deg) | | | |
| N2−C3−C4 | 121.3(2) | 121.7 | 121.9 | 123.5 | 123.7 |
| C3−C4−C51 | 123.7(2) | 122.9 | 123.1 | 126.6 | 126.9 |
| C4−C51−N1 | 127.1(2) | 128.3 | 128.8 | | |
| C4−C51−O2 | | | | 117.5 | 117.4 |
| C51−N1···H21 | 93.7(7) | 96.1 | 96.1 | | |
| C51−O2···H21 | | | | 102.3 | 103.0 |
| N1···H21−N2 | 140.0(1) | 136.6 | 134.8 | | |
| O2···H21−N2 | | | | 134.2 | 132.0 |
| | | dihedral angles (deg) | | | |
| H21−N2−C3−C4 | −3.1(1.5) | −5.7 | −5.1 | −7.8 | −6.6 |
| N2−C3−C4−C51 | −4.7(1) | −2.8 | −1.8 | −4.3 | −2.9 |
| C3−C4−C51−N1 | 9.2(4) | 4.7 | 3.5 | | |
| C3−C4−C51−O2 | | | | 5.6 | 4.5 |
| C4−C51−N1···H21 | −7.7(4)[c] | 0.0 | 0.0 | | |
| C4−C51−O2···H21 | | | | 1.0 | 0.4 |

[a] For experimental details see the Experimental Section (X-ray). Estimated standard deviations in parentheses. [b] See computational methods in the Experimental Section. [c] Dihedral angle between crystallographic planes.

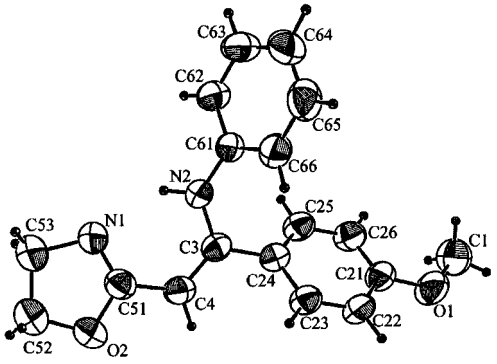



**Figure 1.** ORTEP diagram of the X-ray crystal structure of **1e** showing the intramolecular N2···H interaction. Arbitrary numbering system.

a six-membered ring. The 7.7° angle between the planes of the oxazoline ring and the enamino moiety of along with bond lengths corresponding to the N=C−C=C grouping suggest the formation of a delocalized $\pi$-system that extends to include the N1···H21 bond. The steric hindrance between the aromatic rings displays the torsion of the phenyl group plane in an angle of 111.3°, as can be seen in Figure 1.

In order to understand more about the relative stabilities of the representative configurations or conformations of selected compounds, such as **1e**, **1p**, and **1l** (Table 1), we began comparative theoretical *ab initio* molecular orbital calculations.[35] Geometry optimizations were carried out at the HF/3-21G level and additional calculations of some representative structures, *e.g.*, **1e,** have also been optimized at the HF/3-21+G level. Structures are shown in Chart 2, and their total and relative energies, in kcal mol$^{-1}$, are listed in Table 4. On the basis of the computed conformational energy differences, the conformer **1e** ($a_1$) has the strongest intramolecular interaction. Selected data for the optimized geometries are shown in Table 3. As shown in Table 3, there is a good agreement between the HF/3-21G and the HF/3-21+G geometries for the compound **1e** ($a_1$ *vs* $a_2$) and the experimental geometry for **1e** ($a_1$). Due to this and also to the large number of atoms in these types of structures, the other selected compounds were only optimized with HF/3-21G calculations. As expected, enamino forms $a_1$ and $a_2$ appear to be more stable than the imino tautomers ***c*** and ***d***. The great stability introduced by the strong hydrogen intramolecular bond between the NH moiety and the N ($sp^2$) atom in the $a_1$ structure is reflected in the lower energy of this structure compared to $b_{1.1}$, and $b_{1.2}$, 12.9 (or 11.4 at the HF/3-21+G) and 11.1 kcal mol$^{-1}$, respectively, and this also justifies the preferred *Z* stereochemistry of the enamino double bond (Table 4).

Two conformations, however, are possible for the (*Z*) enamino isomer: *s-cis* ($a_1$) and *s-trans* ($a_2$). Even though, in general, *s-trans* conformations are preferred to *s-cis* and hydrogen bonding NH···O is stronger than NH···N, the most stable conformation is still the *s-cis* ($a_1$) with an $E_{rel}$ of 3.3 and 2.8 kcal mol$^{-1}$ for **1e** and **1p**, respectively. This fact can be explained by taking into account that in the $a_1$ conformation, a major delocalization of the $\pi$-system occurs, which includes the hydrogen bond and formation of a six-membered ring.

Other tautomeric forms implying the oxazoline ring as an NH enaminic moeity, *i.e.*, $e_1$, have been also consid-

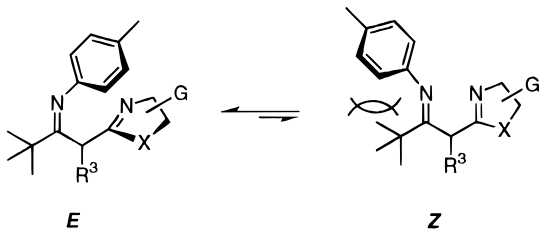
(35) Frisch, M. J.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, N.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andrés, J. L.; Replogle, E. S.; Gomperts, R.; Martín, R. L.; Fox, D. J.; Binkley, J. S.; DeFrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; González, C.; Pople, J. A. *GAUSSIAN 94*, RevisionC.3; Gaussian Inc.: Pittsburgh, PA, 1995.

**Table 4. Calculated Total (Hartree) and Relative Energies (kcal mol$^{-1}$) of Optimized Structures[a] of Compounds 1e, 1p, and 1l**

| | HF/3-21G//3-21G[a] | | | | |
|---|---|---|---|---|---|
| structure | $E_{tot}$ | $E_{rel}$ | structure | $E_{tot}$ | $E_{rel}$ |
| | **1e** | | | **1p** | |
| ***a*$_1$ [(*Z*)-*s*-*cis*] | −945.41534 | 0.0 | ***a*$_1$ [(*Z*)-*s*-*cis*] | −1128.59989 | 0.0 |
| | (−945.53485) | (0.0)[b] | | | |
| | [−950.70086] | [0.0][c] | | | |
| ***a*$_2$ [(*Z*)-*s*-*trans*] | −945.41011 | 3.3 | ***a*$_2$ [(*Z*)-*s*-*trans*] | −1128.59543 | 2.8 |
| | (−945.52988) | (3.1)[b] | | | |
| | [−950.69437] | [4.1][c] | | | |
| ***b*$_{1.1}$[(*E*)-*s*-*cis*] | −945.39486 | 12.9 | ***c*$_1$ (*E*) | −1128.57944 | 12.8 |
| | (−945.51664) | (11.4)[b] | | | |
| | [−950.68465] | [10.2][c] | | | |
| ***b*$_{1.2}$ [(*E*′)-*s*-*cis*] | −945.39770 | 11.1 | | | |
| | [−950.68749] | [8.4][c] | | | |
| ***b*$_{2.1}$ [(*E*)-*s*-*trans*] | −945.39437 | 13.2 | | | |
| ***b*$_{2.2}$ [(*E*′)-*s*-*trans*] | −945.39715 | 11.4 | | | |
| | [−950.68842] | [7.8][c] | | | |
| | | | | **1l** | |
| ***c*$_1$ (*E*) | −945.39187 | 14.7 | ***a*$_1$ [(*Z*)-*s*-*cis*] | −797.98415 | −3.9 |
| | | | | [−802.43324] | [0.9][c] |
| ***c*$_2$ (*E*′) | −945.38987 | 16.0 | ***c*$_1$ (*E*) | −797.97795 | 0.0 |
| | | | | [−802.44044] | [0.0][c] |
| ***d*$_1$ (*Z*) | −945.39317 | 13.9 | ***c*$_2$ (*E*′) | −797.97764 | 0.2 |
| ***d*$_2$ (*Z*′) | −945.39051 | 15.6 | ***d*$_1$ (*Z*) | −797.96529 | 7.9 |
| $e_1$ | −945.40731 | 5.0 | ***d*$_2$ (*Z*′) | −797.96381 | 8.9 |

[a] Full geometries are available in the Supporting Information. [b] Basis set used: HF/3-21+G. [c] Single-point energies at HF/6-31G*//3-21G level.

**Scheme 4**




***E*** ***Z***

ered. This structure would show very similar $^1$H and $^{13}$C NMR spectra to that of ***a*$_1$**. However, **1e** (***e*$_1$**) is 5.0 kcal mol$^{-1}$ higher in energy than **1e** (***a*$_1$**), which confirms, once again, the experimental results.

In contrast with the above results, spectral data for compounds **1**−**2**, in which R$^1$ is a bulky group such as *tert*-butyl and R$^2$ an aromatic ring [for instance for compound **1w** (R$^1$ = *t*-Bu, R$^2$ = *p*-MeC$_6$H$_4$, Table 1, entry 23)], indicated that these derivatives appear generally in the imino form α[36] (Scheme 3, see also Table 1, entries 12 and 19, and Table 2, entry 13). Thus, the most characteristic features of the $^1$H NMR spectrum of **1w** were three sets of signals centered at δ 3.13 (t, 2H, *J* = 8.4 Hz), 3.37 (t, 2H, $^4J$ = 1.8 Hz), and 4.03 (dt, 2H, *J* = 8.4, and $^4J$ = 1.8 Hz). The multiplicity of the signals and the coupling constants were consistent with the proposed **1w**α structure.

In these compounds, however, two main different isomers, *cis*-*trans* (*Z*−*E*), are possible (Scheme 4, see also ***c*$_1$**, ***c*$_2$**, ***d*$_1$**, and ***d*$_2$** in Chart 2). Because only one of them was observed by NMR in the crude reaction mixture, *ab initio* calculations for **1l** (Table 1, entry 12) were performed in order to establish the correct geometry of these derivatives. The structural results obtained (Table 4) indicated that the imino forms ***c*$_1$** (*E*) and ***c*$_2$** (*E*′) are 7.9 and 8.9 kcal mol$^{-1}$ more stable than ***d*$_1$** (*Z*) and ***d*$_2$** (*Z*′),

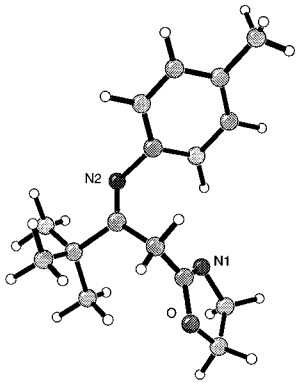


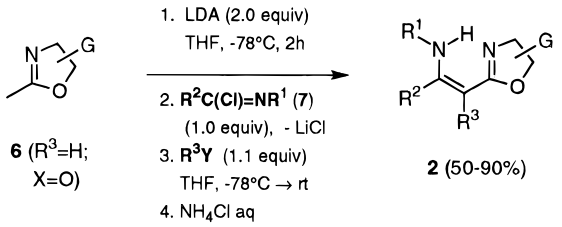

**Figure 2.** Calculated (3-21G) structure of **1l** corresponding to ***c*$_1$** configuration.

respectively. Additionally, a small difference of 0.2 kcal mol$^{-1}$ between the two isomers corresponding to the conformers ***c*$_1$** *vs* ***c*$_2$** was found. Calculations also showed a significant twisting of the plane that contains the iminic double bond with respect to the oxazoline ring (Figure 2). The most stable structure for **1l** corresponded to the ***a*$_1$** configuration, 3.9 kcal mol$^{-1}$ in respect to ***c*$_1$** , in contrast with the experimental results (see above). So, energies were now evaluated with the HF/6-31G*//3-21G level of theory for **1l** and other representative examples (Table 4). The obtained results for **1l** (***a*$_1$**) showed a strong intramolecular hydrogen bond in a planar structure, but now 0.9 kcal mol$^{-1}$ less stable than **1l** (***c*$_1$**). These facts were consistent with the experimental results,[36] and they can be easily explained if we take into account the steric hindrance among the bulky *tert*-butyl group, the aromatic ring system, and the oxazoline ring, as shown in Scheme 4.

On the contrary, no significant energy differences were observed among these isomers (***c*$_1$**, ***c*$_2$**, ***d*$_1$**, and ***d*$_2$**) for compound **1e**, where the steric interactions are diminished in comparison with **1l** (Table 4).

(36) In some cases, *i.e.*,, for compound **1l**, a mixture of enamino (β) and imino (α) tautomers (β/α ≈ 5/95) was observed by $^1$H NMR in the crude mixture of the reaction.

**Scheme 5**




In summary, these findings allow us to assume, due to the good correlation observed between the calculated and experimental results for **1e** (***a*****1**), the configuration ***c*****1** (*E*) (Scheme 4 and Figure 2) as the most probable structure for compounds **1**−**2** with bulky substituents in $R^2$.

On the other hand, *N*-substituted α-alkylated *β*-enamino acid derivatives **2** ($R^3 \neq H$) can alternatively be obtained in a simple *one-pot* sequential metalation−alkylation, starting from 2-methyl-2-oxazolines **6** ($R^3 = H$, X = O).

It is in this context that we have reported our preliminary results on the *C*-alkylation of *N*-unsubstituted *β*-amino-α,*β*-unsaturated oxazolines **1** ($R^1 = R^3 = H$) by a two-step sequence starting from 2-methyl-2-oxazolines and nitriles.[21] In a similar way, several procedures for the synthesis of α-alkylated *β*-enamino esters and of *β*-dicarbonyl derivatives, resulting from *C*-alkylation of 4-amino-1-aza-1,3-dienes, have been described.[37]

As shown in Scheme 5, alkylation products **2** are formed by treatment of azaenolate **6**−Li, generated with lithium diisopropylamide (2.0 equiv) in THF at −78 °C, with imidoyl chlorides **7** (1.0 equiv) followed by trapping of the intermediate azaenolate with the appropriate alkyl halide $R^3Y$.

In this way, the *N*-substituted α-alkylated *β*-enamino acid derivatives **2** have been obtained in 50−90% overall yield after purification by chromatography (Method B, Table 2). Similar considerations can be made in relation to this generality, structural assignment, and importance of the process, as above. Compounds **2** were fully elucidated on the basis of their $^1H$ and $^{13}C$ NMR spectroscopies and mass spectrometry results (see Experimental Section). Finally, one of the major advantages of this *one-pot* reaction is the simplicity and versatility of the process, along with the accessibility of the starting materials.

In conclusion, a very simple and efficient method for the synthesis of masked *N*-substituted *β*-enamino acid derivatives (**1**−**2**) has been, for the first time, described.[38] The structural assignment for the obtained compounds was made on the basis of their spectral properties, as well as X-ray crystallographic analysis, and has been supported by *ab initio* calculations at the HF/3-21G and HF/3-21+G level of theory. This study allowed us to predict the most probably geometry in compounds **1**−**2** with bulky substituents in $R^2$, for which the above mentioned analytical methods were not completely effective. In addition, we have studied the reactivity of compounds **1** ($R^3 = H$) in *C*-alkylation reactions, which supposes an alternative route for the synthesis of these derivatives. The scope and versatility of these processes are demonstrated by their use on a wide variety of substrates, including imidoyl chlorides, oxa- and thiazolines, and alkyl halides. Further studies related to the reactivity of **1**−**2** in reduction reactions are in progress.

## Experimental Section

**General Methods**. All reactions were run under $N_2$ atmosphere. Solvents were dried and distilled upon standard procedures before use, and THF was distilled, under $N_2$, immediately prior to use from sodium−potassium alloy and benzophenone ketyl. Commercial oxazolines and thiazolines were purchased from Aldrich Co., distilled and stored over 4 Å molecular sieves. (4*R*,5*S*)-*cis*-2,4-Dimethyl-5-phenyloxazoline[39] and imidoyl chlorides[26] were prepared according to the methods described in the literature. All other reagents were of the best commercial grade available and were used without further purification. Diisopropylamine was distilled from sodium hydride and stored over 4 Å molecular sieves. Thin layer chromatography (TLC) was performed with UV active silica gel 60 $F_{254}$ or neutral aluminum oxide 60 $F_{254}$, and the plates were visualized with UV light. Flash column chromatography and medium pressure liquid chromatography (MPLC) were carried out on silica gel 60 (0.040−0.063 and 0.015−0.040 mm respectively) and basic aluminum oxide (70−290 mesh). Melting points are uncorrected. Nuclear magnetic resonance spectra for $^1H$ and $^{13}C$ were determined on a 200, 250, and 300 MHz spectrometer, in $CDCl_3$, using tetramethylsilane as an internal standard. Chemical shift values and coupling constants, *J*, are reported in *δ* ppm and in Hz, respectively. Carbon multiplicities were established by DEPT. Infrared spectra ($cm^{-1}$) were obtained on a FT IR spectrometer. Mass spectral data, low-resolution mass spectroscopy (electron impact) (LRMS/EI) and high-resolution mass spectroscopy (HRMS), were obtained at 70 eV by electron impact. Elemental analyses were performed in the Microanalyses Service CID-CSIC of Barcelona.

**Computational Methods**. *Ab initio* calculations were performed with the GAUSSIAN 94[35] series programs. Geometry optimizations were carried out at the HF/3-21G level, and some representative structures were also fully optimized at the HF/3-21+G level of theory. In some cases, energies were evaluated with HF/6-31G*//3-21G level of theory. All the calculations in this study were performed on a Silicon Graphics Indigo-Iris, Indigo, or Cray XMP-Unicos supercomputer.

**General Procedure for the Synthesis of *N*-Substituted *β*-Enamino-2-oxa(thia)zolines 1. Method A.** To a stirred solution of diisopropylamine (2.6 mL, 20 mmol) in THF (15mL) at 0 °C was added butyllithium (2.5 M in hexanes, 8.0 mL, 20 mmol) dropwise. After being stirred for 15 min, the solution was cooled to −78 °C and 2-methyl-2-oxa(thia)zoline **6** ($R^3 = H$) (10 mmol) in THF (15mL) was added. The reaction mixture was stirred for 2 h; then a solution of the desired imidoyl chloride **7** (10 mmol) in THF (15 mL) was slowly added. When TLC analysis showed the disappearance of the starting material, the reaction was quenched by addition of saturated ammonium chloride solution. The aqueous layer was extracted with methylene chloride (3 × 25 mL). The combined organic layers were washed with brine and dried ($Na_2SO_4$), and after filtration, the solvents were removed under reduced pressure to furnish the crude product **1**. Purification was carried out as indicated in each case.

**2-[(*Z*)-(2-Anilino-2-phenyl)ethenyl]-2-oxazoline (1a).** Recrystallization (*n*-hexane−$CHCl_3$ (5:1)) gave a white solid (87%): mp 86−88 °C; $^1H$ NMR (250 MHz) 3.92 (t, *J* = 8.7, 2H), 4.13 (t, *J* = 8.7, 2H), 4.93 (s, 1H), 6.57 (d, *J* = 7.3, 2H), 6.78 (t, *J* = 7.3, 1H), 6.98 (t, *J* = 7.6, 2H), 7.18−7.31 (m, 5H), 10.60 (br s, 1H); $^{13}C$ NMR (62.8 MHz) 54.36 (t), 65.69 (t), 88.60 (d), 121.63 (d), 122.04 (d), 128.05 (d), 128.33 (d), 128.49 (d), 128.90 (d), 136.52 (s), 141.21 (s), 153.94 (s), 166.16 (s); IR (KBr)

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(38) To the best of our knowledge, only one example with a similar structure, obtained by a [2 + 2] cycloaddition reaction of an oxazolinyl alkylamide with dimethyl fumarate, has been reported. See: Ghose, S.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans 1*, **1991**,775.

(39) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.

3264, 1628, 1605; HRMS calcd for $C_{17}H_{16}N_2O$ 264.1361, found 264.1263; LRMS (EI) *m/z* 264 ($M^+$, 37), 263 ($M^+ - H$, 100). Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.11; N, 10.60. Found: C, 77.30; H, 6.15; N, 10.57.

**2-[(*Z*)-(2-Cyclohexylamino-2-phenyl)ethenyl]-2-oxazoline (1b).** The crude product was purified by flash chromatography (*n*-hexane-EtOAc (15:1)) on basic aluminum oxide ($R_f$ = 0.4). Recrystallization (*n*-hexane-$CHCl_3$ (5:1)) gave **1b** (75%) as a white solid: mp 89−91 °C; $^1$H NMR (300 MHz) 0.85−1.80 (m, 10H), 3.10 (m, 1H), 4.00 (t, *J* = 8.4, 2H), 4.15 (t, *J* = 8.4, 2H), 4.54 (s, 1H), 7.37 (s, 5H), 8.70 (br d, 1H); $^{13}$C NMR (75 MHz) 25.43 (t), 26.30 (t), 35.41 (t), 53.25 (d), 55.26 (t), 66.14 (t), 83.53 (d), 128.67 (d), 128.97 (d), 129.39 (d), 138.35 (s), 160.12 (s), 167.48 (s); IR (KBr) 3442, 3164, 1618, 1603; HRMS calcd for $C_{17}H_{22}N_2O$ 270.1654, found 270.1656; LRMS (EI) *m/z* 270 ($M^+$, 54), 269 ($M^+ - H$, 100). Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.51; H, 8.21; N, 10.37. Found: C, 75.70; H, 8.10; N, 10.40.

**2-{(*Z*)-[2-(*N*-*p*-Anisylamino)-2-phenyl]ethenyl}-2-oxazoline (1c).** Recrystallization (*n*-hexane−$CHCl_3$ (4:1)) gave a white solid (72%): mp 118−120 °C; $^1$H NMR (250 MHz) 3.69 (s, 3H), 4.00 (t, *J* = 7.5, 2H), 4.21 (t, *J* = 7.5, 2H), 4.94 (s, 1H), 6.63 (s, 4H), 7.24−7.35 (m, 5H), 10.66 (br s, 1H); $^{13}$C NMR (62.8 MHz) 54.37 (t), 55.21 (q), 65.66 (t), 87.84 (d), 113.71 (d), 121.66 (d), 121.93 (d), 128.51 (d), 129.39 (d), 133.96 (s), 141.46 (s), 153.70 (s), 160.15 (s), 166.25 (s); HRMS calcd for $C_{18}H_{18}N_2O_2$ 294.1368, found 294.1359; LRMS (EI) *m/z* 294 ($M^+$, 38), 293 ($M^+ - H$, 100). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.44; H, 6.17; N, 9.52. Found: C, 73.50; H, 6.21; N, 9.60.

**2-{(*Z*)-[2-(*N*-1-Phenylethylamino)-2-phenyl]ethenyl}-2-oxazoline (1d).** MPLC (*n*-hexane−EtOAc (3:1)) on silica gel ($R_f$ = 0.5) gave **1d** (81%) as a yellow oil: $^1$H NMR (250 MHz) 1.38 (d, *J* = 6.8, 3H), 3.93 (t, *J* = 7.5, 2H), 4.08 (t, *J* = 7.5, 2H), 4.35 (m, 1H), 4.53 (s, 1H), 7.02−7.21 (m, 10H), 9.10 (br d, 1H); $^{13}$C NMR (62.8 MHz) 24.68 (q), 53.91 (t), 54.44 (d), 65.41 (t), 83.95 (d), 125.72 (d), 126.51 (d), 127.89 (d), 127.99 (d), 128.28 (d), 128.57 (d), 138.11 (s), 145.48 (s), 159.32 (s), 166.49 (s); IR (neat) 3250, 1623, 1591; LRMS (EI) *m/z* 292 ($M^+$, 47), 291 (49), 277 (42), 207 (100), 105 (73). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.85; N, 9.59. Found: C, 78.25; H, 6.72; N, 9.65.

**2-[(*Z*)-(2-Anilino-2-*p*-methoxyphenyl)ethenyl]-2-oxazoline (1e).** Recrystallization of the crude product (*n*-hexane−$CHCl_3$ (3:1)) gave **1e** (95%) as clear yellow crystals: mp 128−130 °C; $^1$H NMR (250 MHz) 3.71 (s, 3H), 3.92 (t, *J* = 7.5, 2H), 4.13 (t, *J* = 7.5, 2H), 4.89 (s, 1H), 6.65 (d, *J* = 8.0, 2H), 6.74 (d, *J* = 8.0, 2H), 6.81 (t, *J* = 8.0, 1H), 6.97 (t, *J* = 8.0, 1H), 7.22 (d, *J* = 8.0, 3H), 10.56 (br s, 1H); $^{13}$C NMR (62.8 MHz) 54.37 (t), 55.21 (q), 65.66 (t), 87.84 (d), 113.72 (d), 121.65 (d), 128.51 (d), 128.76 (d), 129.39 (d), 133.96 (s), 141.46 (s), 153.69 (s), 160.15 (s), 166.25 (s); IR (KBr) 3073, 1623, 1602; HRMS calcd for $C_{18}H_{18}N_2O_2$ 294.1368, found 294.1360; LRMS (EI) *m/z* 294 ($M^+$, 39), 293 ($M^+ - H$, 100). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.44; H, 6.17; N, 9.52. Found: C, 73.40; H, 6.20; N, 9.55.

**2-{(*Z*)-2-(*N*-*p*-Anisylamino)-3,3,3-trifluoropropenyl}-2-oxazoline (1f).** Flash chromatography (*n*-hexane-EtOAc (20:1)) on silica gel ($R_f$ = 0.5) furnished **1f** (87%) as a yellow oil: $^1$H NMR (250 MHz) 3.72 (s, 3H), 3.89 (t, *J* = 7.5, 2H), 4.15 (t, *J* = 7.5, 2H), 5.21 (s, 1H), 6.75 (d, *J* = 9.0, 2H), 7.02 (d, *J* = 9.0, 2H), 10.15 (br s, 1H); $^{13}$C NMR (62.8 MHz) 54.19, 55.34, 66.04, 84.30 (q, $J_{C-C-C-F}$ = 6.3), 113.82, 120.70 (q, $J_{C-F}$=275.5), 127.94, 131.71, 143.44 (q, $J_{C-C-F}$ = 31.3), 157.97, 165.43; IR (neat) 3411, 1645, 1511; LRMS (EI) *m/z* 286 ($M^+$, 86), 217 ($M^+ - CF_3$, 100). Anal. Calcd for $C_{13}H_{13}F_3N_2O_2$: C, 54.53; H, 4.58; N, 9.79. Found: C, 54.62; H, 4.40; N, 9.82.

**2-{(*Z*)-2-(*N*-*p*-Tolylamino)-3,3,3-trifluoropropenyl}-2-oxazoline (1g).** Flash chromatography (*n*-hexane-EtOAc (15:1)) on silica gel ($R_f$ = 0.4) gave **1g** (88%) as a clear yellow solid: mp 46−48 °C; $^1$H NMR (250 MHz) 2.34 (s, 3H), 4.02 (t, *J* = 7.5, 2H), 4.24 (d, *J* = 7.5, 2H), 5.32 (s, 1H), 7.05−7.15 (m, 4H), 10.25 (br s, 1H); $^{13}$C NMR (62.8 MHz) 20.92, 54.20, 66.06, 85.06 (q, $J_{C-C-C-F}$ = 5.8), 120.94 (q, $J_{C-F}$ = 250.7), 125.72, 129.35, 135.71, 136.48, 142.99 (q, $J_{C-C-F}$ = 30.9), 165.36; LRMS (EI) *m/z* 270 ($M^+$, 54), 201 ($M^+ - CF_3$, 100). Anal. Calcd for $C_{13}H_{13}F_3N_2O$: C, 57.76; H, 4.85; N, 10.37. Found: C, 57.68; H, 4.84; N, 10.30.

**2-{(*Z*)-2-(*N*-1-Phenylethylamino)-3,3,3-trifluoropropenyl}-2-oxazoline (1h).** Flash chromatography (*n*-hexane−EtOAc (9:1)) on silica gel ($R_f$ = 0.5) gave **1h** (75%) as a clear yellow oil: $^1$H NMR (250 MHz) 1.58 (d, *J* = 6.8, 3H), 4.04 (t, *J* = 7.5, 2H), 4.22 (t, *J* = 7.5, 2H), 4.78 (m, 1H), 5.19 (s, 1H), 7.30−7.40 (m, 5H), 9.21 (br d, 1H); $^{13}$C NMR (62.8 MHz) 25.33, 53.92, 54.38, 65.84, 82.80 (q, $J_{C-C-C-F}$ = 6.8), 120.85 (q, $J_{C-F}$ = 274.6), 125.37, 126.93, 128.51, 143.30 (q, $J_{C-C-F}$ = 31.1), 144.86, 165.55; IR(neat) 3442, 1646, 1608; HRMS calcd for $C_{14}H_{15}F_3N_2O$ 284.1136 found 234.1138; LRMS (EI) *m/z* 284 ($M^+$, 27), 269 ($M^+ - CH_3$, 27), 199 (27), 105 (100). Anal. Calcd for $C_{14}H_{15}F_3N_2O$: C, 59.13; H, 5.32; N, 9.86. Found: C, 59.21; H, 5.39; N, 9.80.

**2-{(*Z*)-[2-(*N*-*p*-Anisylamino)-2-(3-pyridyl)]ethenyl}-2-oxazoline (1i).** MPLC (*n*-hexane−EtOAc (3:1)) on silica gel ($R_f$ = 0.4) gave **1i** (85%) as a yellow solid: mp 114−116 °C; $^1$H NMR (200 MHz) 3.63 (s, 3H), 3.98 (t, *J* = 8.3, 2H), 4.16 (t, *J* = 8.3, 2H), 4.88 (s, 1H), 6.59 (s, 4H), 7.09 (m, 1H), 7.50 (m, 1H), 8.44 (m, 1H), 8.54 (d, *J* = 2.2, 1H), 10.49 (br s, 1H); $^{13}$C NMR (75 MHz) 55.14 (t), 56.17 (q), 66.64 (t), 88.61 (d), 114.87 (d), 123.76 (d), 125.37 (d), 133.21 (s), 134.49 (s), 136.44 (d), 149.91 (d), 150.56 (d), 152.38 (s), 156.59 (s), 166.93 (s); IR (KBr) 3437, 1617, 1595; LRMS (EI) *m/z* 295($M^+$, 86), 294 ($M^+ - H$, 100). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.12; H, 5.81; N, 14.23. Found: C, 69.15; H, 5.86; N, 14.20.

**2-{(*Z*)-[2-(*N*-*p*-Anisylamino)-3-methyl]-but-1-enyl}-2-oxazoline (1j).** MPLC (*n*-hexane−EtOAc (3:1)) on silica gel ($R_f$ = 0.3) gave **1j** (70%) as a clear yellow oil: $^1$H NMR (300 MHz) 1.06 (d, *J* = 6.6, 6H), 2.79 (m, 1H), 3.80 (s, 3H), 3.95 (t, *J* = 7.5, 2H), 4.18 (t, *J* = 7.5, 2H), 4.67 (s, 1H), 6.84 (d, *J* = 9.0, 2H), 7.03 (d, *J* = 9.0, 2H), 10.40 (br s, 1H); $^{13}$C NMR (75 MHz) 22.08 (q), 28.07 (d), 54.24 (t), 55.39 (q), 65.28 (t), 77.51 (d), 114.07 (d), 127.58 (d), 132.76 (s), 157.19 (s), 165.30 (s), 167.35 (s); IR (neat) 3390, 1627, 1596, 1507; HRMS calcd for $C_{15}H_{20}N_2O_2$ 260.1525, found 260.1517; LRMS (EI) *m/z* 260 ($M^+$, 69), 217 ($M^+$ − *i*-Pr, 100). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.17; H, 7.75; N, 10.77. Found: C, 69.23; H, 7.81; N, 10.72.

**2-{(*Z*)-[2-(*N*-*p*-Tolylamino)-4-methyl]pent-1-enyl}-2-oxazoline (1k).** MPLC (*n*-hexane−EtOAc (1:1)) on silica gel ($R_f$ = 0.2) gave **1k** (73%) as a clear yellow oil: $^1$H NMR (250 MHz) 0.73 (d, *J* = 6.5, 6H), 1.58 (m, 1H), 2.13 (d, *J* = 6.5, 2H), 2.25 (s, 3H), 3.86 (t, *J* = 8.6, 2H), 4.08 (t, *J* = 8.6, 2H), 4.55 (s, 1H), 6.90 (d, *J* = 8.7, 2H), 7.03 (d, *J* = 8.7, 2H), 10.40 (br s, 1H); $^{13}$C NMR (62.8 MHz) 20.86 (q), 22.29 (q), 26.86 (d), 41.48 (t), 54.27 (t), 65.34 (t), 82.73 (d), 124.81 (d), 129.46 (d), 133.99 (s), 137.74 (s), 156.81 (s), 166.71 (s); IR (neat) 3395, 1629, 1598; HRMS calcd for $C_{16}H_{22}N_2O$ 258.1732, found 258.1727; LRMS (EI) *m/z* 258 ($M^+$, 89), 201 ($M^+$ − *t*-Bu, 86), 107 (100). Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.37; H, 8.59; N, 10.85. Found: C, 74.30; H, 8.52; N, 10.88.

**2-[(*Z*)-(3,3-Dimethyl-2-*N*-*p*-tolylimino)butyl]-2-oxazoline (1l).** MPLC (*n*-hexane−EtOAc (3:2)) on silica gel ($R_f$ = 0.4) gave **1l** (70%) as a clear yellow oil: $^1$H NMR (250 MHz) 1.18 (s, 9H), 2.22 (s, 3H), 3.18 (t, $^4J$ = 1.4, 2H), 3.64 (t, *J* = 9.0, 2H), 4.05 (t, *J* = 9.0, 2H), 6.55 (d, *J* = 8.5, 2H), 6.99 (d, *J* = 8.5, 2H); $^{13}$C NMR (62.8 MHz) 20.63 (q), 27.88 (q), 28.18 (t), 40.64 (s), 54.17 (t), 67.09 (t), 118.64 (d), 129.05 (d), 131.95 (s), 148.25 (s), 163.88 (s), 172.46 (s); HRMS calcd for $C_{16}H_{22}N_2O$ 258.1732, found 258.1732; LRMS (EI) *m/z* 258 ($M^+$, 19), 201 ($M^+$ − *t*-Bu, 100). Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.37; H, 8.59; N, 10.85. Found: C, 74.47; H, 8.67; N, 10.79.

**(*S*)-2-{(*Z*)-[2-(*N*-1-Phenylethylamino)-2-phenyl]ethenyl}-2-oxazoline (1m).** MPLC (*n*-hexane−EtOAc (3:1)) on silica gel ($R_f$ = 0.5) gave **1m** (75%) as a yellow oil: $[\alpha]^{25}_D$ +479.0° (*c* 0.80, $CH_2Cl_2$); $^1$H NMR (250 MHz) 1.38 (d, *J* = 6.8, 3H), 3.93 (t, *J* = 7.5, 2H), 4.08 (t, *J* = 7.5, 2H), 4.35 (m, 1H), 4.53 (s, 1H), 7.02−7.21 (m, 10H), 9.10 (br d, 1H); $^{13}$C NMR (62.8 MHz) 24.68 (q), 53.91 (t), 54.44 (d), 65.41 (t), 83.95 (d), 125.72 (d), 126.51 (d), 127.89 (d), 127.99 (d), 128.28 (d), 128.57 (d), 138.11 (s), 145.48 (s), 159.32 (s), 166.49 (s); HRMS calcd for $C_{19}H_{20}N_2O$ 292.1576, found 292.1584; LRMS (EI) *m/z* 292 ($M^+$, 59), 291 (47), 277 (42), 207 (100), 105 (73). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.85; N, 9.59. Found: C, 78.21; H, 6.98; N, 9.42.

**4,4-Dimethyl-2-[(*Z*)-(2-anilino-2-phenyl)ethenyl]-2-oxazoline (1n).** Flash chromatography (*n*-hexane−EtOAc (4:

1)) on silica gel ($R_f$ = 0.7) furnished **1n** (78%) as a yellow solid: mp 89−91 °C; $^1$H NMR (200 MHz) 1.34 (s, 6H), 3.89 (s, 2H), 4.92 (s, 1H), 6.67−7.34 (m, 10H), 10.83 (br s, 1H); $^{13}$C NMR (50 MHz) 28.80 (q), 54.60 (s), 77.43 (t), 88.71 (d), 121.56 (d), 122.56 (d), 128.31 (d), 128.83 (d), 129.82 (d), 129.94 (d), 136.66 (s), 142.55 (s), 153.66 (s), 163.54 (s); IR (KBr) 3410, 1660, 1624, 1593; LRMS (EI) *m*/*z* 292 ($M^+$, 95), 291 ($M^+ - H$, 96), 277 ($M^+ - CH_3$, 100). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.08; H, 6.84; N, 9.58. Found: C, 78.03; H, 6.90; N, 9.50.

**4,4-Dimethyl-2-[(*Z*)-(2-anilino-2-*p*-methoxyphenyl)ethenyl]-2-oxazoline (1o).** MPLC (*n*-hexane) on silica gel ($R_f$ = 0.3) gave **1o** (90%) as a colorless oil: $^1$H NMR (250 MHz) 1.32 (s, 6H), 3.77 (s, 3H), 3.88 (s, 2H), 4.89 (s, 1H), 6.65 (d, *J* = 8.5, 2H), 6.81 (m, 3H), 7.08 (t, *J* = 7.4, 2H), 7.30 (d, *J* = 8.5, 2H), 10.61 (br s, 1H); $^{13}$C NMR (62.8 MHz) 28.83 (q), 55.13 (q), 66.95 (s), 77.3 (t), 87.88 (d), 113.63 (d), 121.52 (d), 121.73 (d), 128.43 (d), 128.80 (s), 129.31 (d), 141.52 (s), 153.34 (s), 160.00 (s), 163.57 (s); LRMS (EI) *m*/*z* 322 ($M^+$, 94), 321 ($M^+ - H$, 100), 307 ($M^+ - CH_3$, 94). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.20; H, 6.72; N, 8.61.

**4,4-Dimethyl-2-{(*Z*)-2-(*N*-*p*-anisylamino)-3,3,3-trifluoropropenyl}-2-oxazoline (1p).** Flash chromatography (*n*-hexane−EtOAc (9:1)) on aluminum oxide ($R_f$ = 0.5) gave **1p** (80%) as a yellow solid. Recrystallization ($CHCl_3$) gave colorless crystals: mp 50−52 °C; $^1$H NMR (250 MHz) 1.32 (s, 6H), 3.81 (s, 3H), 3.92 (s, 2H), 5.26 (s, 1H), 6.86 (d, *J* = 8.4, 2H), 7.17 (d, *J* = 8.4, 2H), 10.23 (br s, 1H); $^{13}$C NMR (62.8 MHz) 28.61, 55.27, 67.21, 77.64, 84.55 (q, $J_{C-C-C-F}$ = 5.3), 113.83, 120.66 (q, $J_{C-F}$ = 275.4), 127.95, 131.92, 143.95 (q, $J_{C-C-F}$ = 30.3), 157.96, 162.79; LRMS (EI) *m*/*z* 314 ($M^+$, 100), 245 ($M^+ - CF_3$, 77). Anal. Calcd for $C_{15}H_{17}F_3N_2O$: C, 57.30; H, 5.45; N, 8.92. Found: C, 57.42; H, 5.35; N, 8.90.

**4,4-Dimethyl-2-{(*Z*)-[2-(*N*-*p*-anisylamino)-2-(3-pyridyl)]-ethenyl}-2-oxazoline (1q).** MPLC (*n*-hexane−EtOAc (3:2)) on silica gel ($R_f$ = 0.3) gave **1q** (83%) as a yellow solid: mp 70−72 °C; $^1$H NMR (300 MHz) 1.34 (s, 6H), 3.71 (s, 3H), 3.91 (s, 2H), 4.87 (s, 1H), 6.66 (s, 4H), 7.16 (m, 1H), 7.56 (m, 1H), 8.50 (m, 1H), 8.61 (m, 1H), 10.58 (br s, 1H); $^{13}$C NMR (75 MHz) 29.68 (q), 56.21 (q), 67.91 (s), 78.31 (t), 88.73 (d), 114.83 (d), 123.72 (d), 125.37 (d), 133.42 (s), 134.64 (s), 136.43 (d), 149.91 (d), 150.46 (d), 152.09 (s), 156.53 (s), 164.28 (s); LRMS (EI) *m*/*z* 323 ($M^+$, 89), 322 ($M^+ - H$, 100). Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.55; H, 6.55; N, 13.00. Found: C, 70.57; H, 6.52; N, 13.02.

**4,4-Dimethyl-2-{(*Z*)-[2-(*N*-*p*-tolylamino)-4-methyl]pent-1-enyl}-2-oxazoline (1r).** MPLC (*n*-hexane−EtOAc (20:1)) in silica gel ($R_f$ = 0.3) gave **1r** (82%) as a clear yellow oil: $^1$H NMR (250 MHz) 0.75 (d, *J* = 6.5, 6H), 1.21 (s, 6H), 1.60 (m, 1H), 2.12 (d, *J* = 6.5, 2H), 2.25 (s, 3H), 3.75 (s, 2H), 4.47 (s, 1H), 6.90 (d, *J* = 8.3, 2H), 7.03 (d, *J* = 8.3, 2H), 10.40 (br s, 1H); $^{13}$C NMR (62.8 MHz) 20.77 (q), 22.33 (q), 26.70 (t), 28.76 (q), 41.45 (d), 66.75 (s), 76.99 (t), 82.76 (d), 124.58 (d), 129.39 (d), 133.65 (s), 138.00 (s), 156.24 (s), 163.91 (s); HRMS calcd for $C_{18}H_{26}N_2O$ 286.2045, found 286.2056; LRMS (EI) *m*/*z* 286 ($M^+$, 84), 271 ($M^+$ − Me, 87), 229 ($M^+$ − *i*-Pr, 100). Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.47; H, 9.16; N, 9.79. Found: C, 75.55; H, 9.02; N, 9.66.

**4,4-Dimethyl-2-[(*Z*)-(3,3-dimethyl-2-*N*-*p*-tolylimino)butyl]-2-oxazoline (1s).** MPLC (*n*-hexane−EtOAc (3:1)) on silica gel ($R_f$ = 0.3) gave **1s** (75%) as a clear yellow oil: $^1$H NMR (300 MHz) 1.17 (s, 6H), 1.25 (s, 9H), 2.28 (s, 3H), 3.23 (s, 2H), 3.81 (s, 2H), 6.63 (d, *J* = 8.4, 2H), 7.03 (d, *J* = 8.4, 2H); $^{13}$C NMR (75 MHz) 21.61 (q), 28.82 (q), 28.91 (q), 29.53 (t), 41.67 (s), 67.78 (s), 79.88 (t), 119.74 (d), 130.08 (d), 132.99 (s), 149.21 (s), 162.25 (s), 173.31 (s); HRMS calcd for $C_{18}H_{26}N_2O$ 286.2045, found 286.2049; LRMS (EI) *m*/*z* 286 ($M^+$, 24), 229 ($M^+$ − *t*-Bu, 100). Anal. Calcd for $C_{18}H_{26}N_2O$: C, 75.47; H, 9.16; N, 9.79. Found: C, 75.51; H, 9.11; N, 9.70.

**2-{(*Z*)-[2-(*N*-1-phenylethylamino)-2-phenyl]ethenyl}-2-thiazoline (1t).** MPLC (*n*-hexane−EtOAc (4:1)) on silica gel ($R_f$ = 0.4) gave **1t** (78%) as a yellow oil: $^1$H NMR (300 MHz) 1.46 (d, *J* = 6.5, 3H), 3.26 (t, *J* = 7.5, 2H), 4.37−4.48 (m, 3H), 4.83 (s, 1H), 7.09−7.31 (m, 10H), 9.77 (br d, 1H); $^{13}$C NMR (75 MHz) 25.71 (q), 33.57 (t), 54.78 (d), 65.25 (t), 91.94 (d), 126.56 (d), 127.43 (d), 128.81 (d), 128.87 (d), 129.19 (d), 129.45 (d), 137.55 (s), 146.26 (s), 158.09 (s), 167.37 (s); IR (neat) 3231, 1669, 1609, 1592, 1570; LRMS (EI) *m*/*z* 308 ($M^+$, 63), 207 ($M^+ - C_3H_5NS$, 55), 105 ($C_8H_9$, 100). Anal. Calcd for $C_{19}H_{20}N_2S$: C, 73.99; H, 6.54; N, 9.09; S, 10.38. Found: C, 73.97; H, 6.57; N, 9.08; S, 10.40.

**2-{(*Z*)-2-(*N*-*p*-Anisylamino)-3,3,3-trifluoropropenyl}-2-thiazoline (1u).** Flash chromatography (*n*-hexane-EtOAc (9:1)) on aluminum oxide ($R_f$ = 0.5) gave **1u** (78%) as a yellow oil: $^1$H NMR (250 MHz) 3.27 (t, *J* = 8.0, 2H), 3.79 (s, 3H), 4.33 (t, *J* = 8.0, 2H), 5.48 (s, 1H), 6.83 (d, *J* = 8.9, 2H), 7.13 (d, *J* = 8.9, 2H), 10.56 (br s, 1H); $^{13}$C NMR (62.8 MHz) 32.81, 55.37, 64.05, 90.41 (q, $J_{C-C-C-F}$=6.4), 113.83, 120.67 (q, $J_{C-F}$=275.5), 127.80, 131.68, 141.27 (q, $J_{C-C-F}$=30.3), 157.93, 166.33; IR (neat) 1634; LRMS (EI) *m*/*z* 302 ($M^+$, 17), 232 ($M^+ - CF_3$, 100). Anal. Calcd for $C_{13}H_{13}N_2F_3OS$: C, 51.64; H, 4.34; N, 9.27; S, 10.58. Found: C, 51.76; H, 4.42; N, 9.10; S, 10.32.

**2-{(*Z*)-2-(*N*-*p*-Tolylamino)-3,3,3-trifluoropropenyl}-2-thiazoline (1v).** Flash chromatography (*n*-hexane-EtOAc (9:1)) on silica gel ($R_f$ = 0.7) gave **1v** (83%) as a yellow oil: $^1$H NMR (250 MHz) 2.31 (s, 3H), 3.22 (t, *J* = 8.4, 2H), 4.29 (t, *J* = 8.4, 2H), 5.51 (s, 1H), 7.01−7.12 (m, 4H), 10.50 (br s, 1H); $^{13}$C NMR (62.8 MHz) 20.87, 32.73, 63.96, 91.10 (q, $J_{C-C-C-F}$ = 6.4), 120.76 (q, $J_{C-F}$ = 275.7), 125.61, 129.37, 135.69, 136.51, 140.82 (q, $J_{C-C-F}$ = 31.3), 166.32; IR (neat) 1630; LRMS (EI) *m*/*z* 286 ($M^+$, 83), 217 ($M^+ - CF_3$, 100). Anal. Calcd for $C_{13}H_{13}F_3N_2S$: C, 54.53; H, 4.58; N, 9.79; S, 11.18. Found: C, 54.62; H, 4.51; N, 9.85; S, 11.23.

**2-[(*Z*)-(3,3-Dimethyl-2-*N*-*p*-tolylimino)butyl]-2-thiazoline (1w).** MPLC (*n*-hexane−EtOAc (3:1)) on silica gel ($R_f$ = 0.2) gave **1w** (72%) as a yellow oil: $^1$H NMR (250 MHz) 1.18 (s, 9H), 2.22 (s, 3H), 3.13 (t, *J* = 8.4, 2H), 3.37 (t, $^4J$ = 1.8, 2H), 4.03 (dt, *J* = 8.4, $^4J$ = 1.8, 2H), 6.55 (d, *J* = 8.0, 2H), 7.00 (d, *J* = 8.0, 2H); $^{13}$C NMR (62.8 MHz) 20.76 (q), 28.18 (q), 34.08 (t), 34.21 (t), 40.79 (s), 64.37 (t), 118.73 (d), 129.14 (d), 132.08 (s), 148.39 (s), 166.26 (s), 173.82 (s); HRMS calcd for $C_{16}H_{22}N_2S$ 274.1504, found 274.1496; LRMS (EI) *m*/*z* 274 ($M^+$, 26), 217 ($M^+$ − *t*-Bu, 100). Anal. Calcd for $C_{16}H_{22}N_2S$: C, 70.03; H, 8.09; N, 10.22; S, 11.66. Found: C, 70.12; H, 8.22; N, 10.10; S, 11.55.

**(4*S*,5*S*)-4-Methoxymethyl-5-phenyl-2-[(*Z*)-(2-anilino-2-*p*-methoxyphenyl) ethenyl]-2-oxazoline (1x).** MPLC (*n*-hexane−EtOAc (3:1)) on silica gel ($R_f$ = 0.6) gave **1x** (90%) as a yellow oil: $[\alpha]_D^{25}$ +10.9° (*c* 1.25, $CH_2Cl_2$); $^1$H NMR (250 MHz) 3.38 (s, 3H), 3.46 (dd, *J* = 9.5, 7.3, 1H), 3.63 (dd, *J* = 9.9, 4.4, 1H), 3.74 (s, 3H), 4.23 (m, 1H), 4.99 (s, 1H), 5.22 (d, *J* = 6.6, 1H), 6.63 (d, *J* = 7.3, 2H), 6.74−6.85 (m, 3H), 7.04 (t, *J* = 7.3, 2H), 7.25−7.32 (m, 7H), 10.60 (br s, 1H); $^{13}$C NMR (62.8 MHz) 54.93 (q), 59.08 (q), 74.19 (d), 74.91 (t), 81.63 (d), 87.28 (d), 113.58 (d), 121.54 (d), 121.91 (d), 125.39 (d), 127.70 (d), 128.39 (d), 128.44 (d), 128.46 (s), 129.27 (d), 141.18 (s), 154.16 (s), 160.03 (s), 165.75 (s); HRMS calcd for $C_{26}H_{26}N_2O_3$ 414.1943, found 414.1939; LRMS (EI) *m*/*z* 414 ($M^+$, 52), 369 ($M^+ - CH_2OMe$, 100). Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.33; H, 6.33; N, 6.76. Found: C, 75.25; H, 6.20; N, 6.68.

**(*S*)-(4*S*,5*S*)-4-Methoxymethyl-5-phenyl-2-{(*Z*)-[2-(*N*-1-phenylethylamino)-2-phenyl] ethenyl}-2-oxazoline (1y).** MPLC (*n*-hexane−EtOAc (9:1)) on silica gel ($R_f$ = 0.4) gave **1y** (78%) as clear yellow solid: mp 75−76 °C;$[\alpha]_D^{25}$ +215.8° (*c* 1.00, $CH_2Cl_2$); $^1$H NMR (250 MHz) 1.33 (d, *J* = 6.9, 3H), 3.34 (s, 3H), 3.49 (dd, *J* = 9.5, 7.3, 1H), 3.80 (dd, *J* = 9.2, 4.4, 1H), 4.30 (m, 1H), 4.32 (m, 1H), 4.66 (s, 1H), 5.16 (d, *J* = 5.8, 1H), 7.02−7.30 (m, 15H), 9.08 (br d, 1H); $^{13}$C NMR (62.8 MHz) 24.84 (q), 54.21 (d), 59.24 (d), 74.30 (t), 75.42 (d), 81.70 (d), 84.21 (d), 125.54 (d), 126.57 (d), 127.72 (d), 127.92 (d), 128.07 (d), 128.25 (d), 128.31 (d), 128.56 (d), 128.76 (d), 136.98 (s), 141.70 (s), 145.38 (s), 159.98 (s), 166.17 (s); IR (KBr) 3414, 1628, 1603, 1591; HRMS calcd for $C_{27}H_{28}N_2O_2$ 412.2151, found 412.2141; LRMS (EI) *m*/*z* 412 ($M^+$, 15), 367 ($M^+ - CH_2OMe$, 100). Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.60; H, 6.85; N, 6.79. Found: C, 78.55; H, 6.72; N, 6.66.

**(4*R*,5*S*)-4-Methyl-5-phenyl-(*S*)-2-{(*Z*)-[2-(*N*-1-phenylethylamino)-2-phenyl]ethenyl}-2-oxazoline (1z).** MPLC (*n*-hexane−EtOAc (9:1)) on silica gel ($R_f$ = 0.8) gave **1z** (90%) as a yellow oil:$[\alpha]^{25}_D$ +263.1° (*c* 0.32, $CHCl_3$);$^1$H NMR (250 MHz) 0.85 (d, *J* = 6.8, 3H), 1.47 (d, *J* = 6.8, 3H), 4.45 (m, 1H), 4.61 (m, 1H), 4.76 (s, 1H), 5.53 (d, *J* = 9.2, 1H), 7.08−7.36 (m, 15H), 9.25 (br d, *J* = 9.8, 1H); $^{13}$C NMR (62.8 MHz) 19.26 (q),

25.69 (q), 55.22 (d), 65.54 (d), 82.96 (d), 85.42 (d), 126.60 (d), 126.73 (d), 127.05 (d), 127.37 (d), 127.71 (d), 128.30 (d), 128.81 (d), 128.94 (d), 129.11 (d), 137.97 (s), 138.61 (s), 146.28 (s), 160.69 (s), 165.97 (s); IR (neat) 3379, 1624, 1527; HRMS calcd for $C_{26}H_{26}N_2O$ 282.2045, found 282.2037; LRMS (EI) *m*/*z* 282 ($M^+$, 19), 105 (100). Anal. Calcd for $C_{26}H_{26}N_2O$: C, 81.73; H, 6.86; N, 7.33. Found: C, 81.79; H, 6.79; N, 7.37.

**General Procedure for the synthesis of α-Alkyl *N*-substituted *β*-enamino-2-oxazolines 2. Method A.** Following the general procedure for the synthesis of **1** ($R^3$ = H) but in this case the reaction was performed by using 2-ethyl-2-oxazoline **6f** ($R^3$ = Me) as the starting material.

**Method B.** A 2-methyl-2-oxazoline **6a** or **6b** ($R^3$ = H, 5 mmol) in THF (20 mL) was deprotonated with LDA [prepared from butyllithium (2.5M in hexanes, 10 mmol) and diisopropylamine (12 mmol)] at −78 °C, and the desired imidoyl chloride **7** (5 mmol) in THF (10 mL) was slowly added. When TLC analysis showed that product **1** was formed (see Table 1), a solution of an alkyl halide ($R^3Y$, 6 mmol) in THF (10 mL) was added and the mixture was allowed to warm to room temperature. TLC analysis showed the complete or partial disappearance of **1** (see Table 2), and when the reaction was over, usual workup gave the crude product **2**. Purification of the crude product is indicated in each case.

**2-[(*Z*)-(2-Anilino-1-methyl-2-phenyl)ethenyl]-2-oxazoline (2a).** Recrystallization (n-hexane−$CHCl_3$ (4:1)) gave a white solid: (90%) mp 102−104 °C; $^1$H NMR (250 MHz) 1.69 (s, 3H), 3.99 (t, *J* = 8.3, 2H), 4.18 (t, *J* = 8.3, 2H), 6.45 (d, *J* = 5.0, 2H), 6.69 (t, *J* = 5.0, 1H), 6.89 (t, *J* = 5.0, 2H), 7.18−7.24 (m, 5H), 10.40 (br s, 1H); $^{13}$C NMR (62.8 MHz) 14.41 (q), 54.43 (t), 65.60 (t), 92.62 (s), 120.96 (d), 121.18 (d), 128.20 (d), 128.24 (d), 128.36 (d), 129.81 (d), 135.78 (s), 141.89 (s), 150.19 (s), 168.37 (s); IR (KBr) 3264, 1664, 1599, 1495; LRMS (EI) *m*/*z* 278 ($M^+$, 72), 277 ($M^+ - C_5H_9NO$, 100). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.69; H, 6.47; N, 10.07. Found: C, 77.50; H, 6.61; N, 10.02.

**2-{(*Z*)-[1-Methyl-2-(*N*-1-phenylethylamino)-2-phenyl]-ethenyl}-2-oxazoline (2b).** MPLC (*n*-hexane) on silica gel ($R_f$ = 0.3) gave **2b** (90%) as a clear yellow oil: $^1$H NMR (250 MHz) 1.35 (d, *J* = 6.5, 3H), 1.45 (s, 3H), 3.92 (m, 3H), 4.15 (t, *J* = 7.5, 2H), 6.95 (d, *J* = 8.0, 2H), 7.09−7.35 (m, 8H), 10.70 (br d, 1H); $^{13}$C NMR (62.8 MHz) 14.26 (q), 24.95 (q), 54.12 (t), 54.56 (d), 65.34 (t), 87.95 (s), 125.78 (d), 126.29 (d), 127.80 (d), 127.99 (d), 128.17 (d), 128.56 (d), 136.29 (s), 146.33 (s), 155.59 (s), 169.19 (s); IR (neat) 3393, 1617, 1581; LRMS (EI) *m*/*z* 306 ($M^+$, 68), 291 ($M^+ - CH_3$, 86), 201 ($M^+$ − Ph(Me)CH, 100). Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.39; H, 7.24; N, 9.15. Found: C, 78.41; H, 7.20; N, 9.05.

**2-{(*Z*)-2-(*N*-*p*-Anisylamino)-1-methyl-3,3,3-trifluoropropenyl}-2-oxazoline (2c).** Flash chromatography (*n*-hexane-EtOAc (9:1)) on aluminum oxide ($R_f$ = 0.5) gave **2c** (92%) as a yellow oil: $^1$H NMR (250 MHz) 2.07 (q, $J_{CH_3-F}$ = 2.5, 3H), 3.86 (s, 3H), 3.94 (t, *J* = 7.5, 2H), 4.21 (t, *J* = 7.5, 2H), 6.80 (d, *J* = 8.8, 2H), 6.90 (d, *J* = 8.8, 2H), 10.12 (br s, 1H); $^1$H NMR (250 MHz) minor tautomer (imino form) 1.46 (br d, *J* = 7.3, 3H), 3.78 (s, 3H); $^{13}$C NMR (62.8 MHz) 13.15 (q, $J_{C-C-C-C-F}$=2.7), 54.33, 55.34, 66.01, 105.62 (q, $J_{C-C-C-F}$ = 2.8), 114.34, 120.08 (q, $J_{C-F}$ = 275.5), 124.43, 136.28, 138.15 (q, $J_{C-C-F}$ = 31.0), 156.05, 166.65; IR (neat) 3137, 1630; LRMS (EI) *m*/*z* 300 ($M^+$, 86), 231 ($M^+ - CF_3$, 100), 205 (77). Anal. Calcd for $C_{14}H_{15}N_2F_3O_2$: C, 55.98; H, 5.04; N, 9.33. Found: C, 55.72; H, 5.12; N, 9.22.

**2-{(*Z*)-[1-Butyl-2-(*N*-*p*-anisylamino)-2-(3-pyridyl)]ethenyl}-2-oxazoline (2d).** MPLC (*n*-hexane−EtOAc (1:1)) on silica gel ($R_f$ = 0.6) gave **2d** (65%) as a yellow oil: $^1$H NMR (250 MHz) 0.81 (t, *J* = 7.8, 3H), 1.21 (m, 2H), 1.40 (m, 2H), 2.20 (t, *J* = 7.8, 2H), 3.78 (s, 3H), 4.16 (t, *J* = 7.5, 2H), 4.36 (t, *J* = 7.3, 2H), 6.69 (s, 4H), 7.31 (m, 1H), 7.64 (m, 1H), 8.62 (m, 2H), 11.38 (br s, 1H); $^{13}$C NMR (62.8 MHz) 13.59 (q), 22.15 (t), 27.74 (t), 33.31 (t), 54.03 (t), 55.02 (q), 65.38 (t), 97.47 (s), 113.58 (d), 122.74 (d), 124.74 (d), 131.63 (s), 133.94 (s), 137.00 (d), 148.38 (s), 148.74 (d), 150.24 (d), 155.17 (s), 167.98 (s); IR (neat) 1616; HRMS calcd for $C_{21}H_{25}N_3O_2$ 351.1947, found 351.1935; LRMS (EI) *m*/*z* 351 ($M^+$, 80), 308 ($M^+$ − Pr, 100). Anal. Calcd for $C_{21}H_{25}N_3O_2$: C, 71.76; H, 7.17; N, 11.96. Found: C, 71.67; H, 7.25; N 11.82.

**4,4-Dimethyl-2-{(*Z*)-[2-anilino-2-benzyl-2-(*N*-*p*-methoxyphenyl)]ethenyl}-2-oxazoline (2e).** MPLC (*n*-hexane-EtOAc (6:1)) on silica gel ($R_f$ = 0.3) gave **2e** (60%) as a white solid: mp 112−113 °C; $^1$H NMR (250 MHz) 1.32 (s, 6H), 3.56 (s, 2H), 3.75 (s, 3H), 3.79 (s, 2H), 6.52 (d, *J* = 8.0, 2H), 6.76 (d, *J* = 8.0, 3H), 7.00−7.20 (m, 9H), 10.08 (br s, 1H); $^{13}$C NMR (62.8 MHz) 28.78 (q), 33.58 (t), 55.11 (q), 66.91 (s), 77.10 (t), 95.40 (s), 113.67 (d), 120.79 (d), 121.05 (d), 125.16 (d), 127.56 (d), 127.76 (d), 127.92 (d), 128.40 (d), 130.70 (d), 141.95 (s), 143.02 (s), 151.36 (s), 159.47 (s), 165.53 (s); IR (KBr) 3300, 1625, 1593; HRMS calcd for $C_{27}H_{28}N_2O_2$ 412.2151, found 412.2158; LRMS (EI) *m*/*z* 412 ($M^+$, 100). Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79. Found: C, 78.55; H, 6.79; N, 6.66.

**2-[(*Z*)-(2-Anilino-1-ethylacetyl-2-*p*-methoxyphenyl)ethenyl]-2-oxazoline (2f).** MPLC (*n*-hexane−EtOAc (3:2)) on silica gel ($R_f$ = 0.3) gave **2f** (55%) as a clear yellow oil: $^1$H NMR (250 MHz) 1.23 (t, *J* = 7.1, 3H), 3.14 (s, 2H), 3.77 (s, 3H), 4.03−4.19 (m, 6H), 6.56 (d, *J* = 8.6, 2H), 6.80 (m, 3H), 7.00 (t, *J* = 7.5, 2H), 7.23 (d, *J* = 8.6, 2H), 10.30 (br s, 1H); $^{13}$C NMR (62.8 MHz) 14.17 (q), 34.52 (t), 54.39 (t), 55.06 (q), 60.28 (t), 65.71 (t), 90.20 (s), 113.76 (d), 121.44 (d), 121.65 (d), 126.92 (s), 128.32 (d), 130.65 (d), 141.30 (s), 152.75 (s), 159.63 (s), 167.35 (s), 173.34 (s); IR (neat) 3444, 1731, 1637, 1596; HRMS calcd for $C_{22}H_{24}N_2O_4$ 380.1761, found 380.1740; LRMS (EI) *m*/*z* 380 ($M^+$, 61), 307 (99), 210 (100). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.52; H, 6.44; N, 7.29.

**4,4-Dimethyl-2-[(*Z*)-(2-anilino-1-ethylacetyl-2-*p*-methoxyphenyl)ethenyl]-2-oxazoline (2g).** MPLC (*n*-hexane−EtOAc (9:1)) on silica gel ($R_f$ = 0.3) gave **2g** (50%) as a colorless oil: $^1$H NMR (250 MHz) 1.22 (t, *J* = 7.1, 3H), 1.35 (s, 6H), 3.12 (s, 2H), 3.78 (s, 3H), 3.88 (s, 2H), 4.11 (q, *J* = 7.1, 2H), 5.52 (d, *J* = 7.5, 2H), 6.83 (m, 3H), 7.00 (t, *J* = 7.5, 2H), 7.21 (d, *J* = 8.3, 2H), 10.15 (br s, 1H); $^{13}$C NMR (62.8 MHz) 14.20 (q), 28.78 (q), 34.40 (t), 55.07 (q), 60.22 (t), 67.12 (t), 77.25 (s), 90.16 (s), 113.77 (d), 121.17 (d), 121.42 (d), 127.02 (d), 128.33 (d), 130.64 (d), 141.52 (s), 152.32 (s), 159.61 (s), 164.78 (s), 173.27 (s); LRMS (EI) *m*/*z* 408 ($M^+$, 80), 407 ($M^+$ − H, 63), 363 ($M^+$ − OEt, 36), 335 ($M^+ - CO_2Et$, 82), 321 ($M^+ - CH_2CO_2Et$, 27), 210 (100). Anal. Calcd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.42; H, 6.79; N, 6.80.

**(*S*)-2-{(*Z*)-[1-Methyl-2-(*N*-1-phenylethylamino)-2-phenyl]ethenyl}-2-oxazoline (2h).** MPLC (*n*-hexane) in silica gel ($R_f$ = 0.3) gave **2h** (80%) as a clear yellow oil: $[\alpha]^{25}_D$ +381.5° (c 1.00, $CH_2Cl_2$); $^1$H NMR (250 MHz) 1.35 (d, *J* = 6.5, 3H), 1.45 (s, 3H), 3.92 (m, 3H), 4.15 (t, *J* = 7.5, 2H), 6.95 (d, *J* = 8.0, 2H), 7.09−7.35 (m, 8H), 10.70 (br d, 1H); $^{13}$C NMR (62.8 MHz) 14.26 (q), 24.95 (q), 54.12 (t), 54.56 (d), 65.34 (t), 87.95 (s), 125.78 (d), 126.29 (d), 127.80 (d), 127.99 (d), 128.17 (d), 128.56 (d), 136.29 (s), 146.33 (s), 155.59 (s), 169.19 (s); IR (neat) 3393, 1617, 1581; HRMS calcd for $C_{20}H_{22}N_2O$ 306.1732, found 306.1732; LRMS (EI) *m*/*z* 306 ($M^+$, 68), 291 ($M^+ - CH_3$, 86), 201 ($M^+$ − Ph(Me)CH, 100). Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.39; H, 7.24; N, 9.15. Found: C, 78.51; H, 7.15; N, 9.18.

**2-[(*Z*)-(2-Anilino-1-methyl-2-*p*-methoxyphenyl)ethenyl]-2-oxazoline (2i).** Recrystallization (*n*-hexane−$CHCl_3$ (3:1)) gave a white solid (88%): mp 115−116 °C; $^1$H NMR (250 MHz) 1.72 (s, 3H), 3.75 (s, 3H), 3.98 (t, *J* = 8.9, 2H), 4.17 (t, *J* = 8.9, 2H), 6.46 (d, *J* = 7.3, 2H), 6.69 (t, *J* = 7.3, 1H), 6.77 (d, *J* = 8.7, 2H), 6.93 (t, *J* = 7.3, 2H), 7.15 (t, *J* = 7.3, 2H), 10.55 (br s, 1H); $^{13}$C NMR (62.8 MHz) 14.45 (q), 54.40 (t), 55.09 (q), 65.63 (t), 92.56 (s), 113.58 (d), 120.83 (d), 127.921 (d), 128.35 (d), 129.41 (s), 131.05 (d), 142.05 (s), 149.82 (s), 159.30 (s), 168.36 (s); LRMS (EI) *m*/*z* 308 ($M^+$, 42), 307 ($M^+$ − H, 100). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 73.99; H, 6.54; N, 9.09. Found: C, 74.05; H, 6.57; N, 9.05.

**2-[(*Z*)-(1,3,3-Trimethyl-2-*N*-*p*-tolylimino)butyl]-2-oxazoline (2j).** MPLC (*n*-hexane−EtOAc (9:1)) on silica gel ($R_f$ = 0.3) gave **2j** (70%) as a yellow oil: $^1$H NMR (200 MHz) 1.18 (s, 9H), 1.35 (d, *J* = 7.6, 3H), 2.19 (s, 3H), 3.21−3.62 (m, 3H), 3.93−4.09 (m, 2H), 6.45 (d, *J* = 8.0, 2H), 6.96 (d, *J* = 8.0, 2H); $^{13}$C NMR (50 MHz) 16.89 (q), 20.65 (q), 28.49 (q), 35.63 (d), 41.60 (s), 54.15 (t), 63.04 (t), 118.27 (d), 128.76 (d), 131.44 (s), 147.69 (s), 167.86 (s), 176.25 (s); HRMS calcd for $C_{17}H_{24}N_2O$ 272.1889, found 272.1887; LRMS (EI) *m*/*z* 272 ($M^+$, 15), 215

($M^+ - t$-Bu, 97), 118 (100). Anal. Calcd for $C_{17}H_{24}N_2O$: C, 74.95; H, 8.89; N, 10.29. Found: C, 74.82; H, 8.79; N, 10.20.

**X-ray Analysis of 2-[(Z)-(2-anilino-2-p-methoxyphenyl)ethenyl]-2-oxazoline (1e).** X-ray diffractometer analyses of compound **1e** were carried out on a diffractometer equiped with a graphite monochromator. A single crystal was selected, obtained by slow evaporation of the solvent from a hexane/chloroform (6:1) solution, that was mounted on a glass fiber. The structure of **1e**, $C_{18}H_{18}N_2O_2$ ($M_w$ 294.356 amu), was determined from a triclinic crystal with dimensions of 0.19 × 0.2 × 0.2 $mm^3$ (space group *P*1) with unit cell dimensions of $a$ = 9.07 (1) Å, $b$ = 9.36 (1) Å, $c$ = 10.36 (1) Å, $\alpha$ = 93.35°(2), $\beta$ = 112.87°(2), $\gamma$ = 100.38°(2), $V$ = 790.7(3) $Å^3$. It has two molecules per cell, $D_c$ = 1.249 g·$cm^{-3}$, $\mu$ = 0.8 $cm^{-1}$, $F(000)$ = 312. The cell dimensions were determined from the setting angles of 25 reflections with 1° < $\theta$ < 25° using MoK$\alpha$ radiation ($\lambda$ = 0.71073 Å). A total of 2887 reflections were measured, $h,k,l$ values range from (0, 0,−19) to (10,12,19), 1948 of which were observed with $I > 3\sigma(I)$ using $\omega - 2\theta$ step scan technique. The structure was solved using MULTAN 82[40] and refined by full matrix least-squares methods including positional and anisotropic thermal parameters for nonhydrogen atoms. Hydrogen atoms were introduced at calculated positions and were isotropically refined. The maximum shift over the error ratio in the last cycle was less than 0.01. The standard reflections were monitored every 60 min during data collection and showed no intensity loss. No correction for absortion was made. No profile analysis was perfomed on the reflections. Some double measured reflections were averaged and refined by full matrix least-squares procedures and give $R$ = 0.038 and $R_w'$ = 0.035.

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**Supporting Information Available:** Copies of **1a**−**z** and **2a**−**j** $^1$H NMR spectra and optimized structures at the HF/3-21G level corresponding to compounds **1e**, **1p**, and **1l** (55 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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