DOI: 10.1002/ejoc.200800719

Synthesis of Ethyl 5-Hydroxyisoxazolidine-4-carboxylates via Michael Addition/Intramolecular Hemiketalisation

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Keywords: Michael addition / Alkylideneacetoacetates / N,O-Heterocycles / Hemiketalisation / Computer chemistry / Reaction mechanism

The 1,4-addition of *N*,*O*-bis(trimethylsilyl)hydroxylamine to alkylideneacetoacetates gave, in high yield, new 5-hydroxyisoxazolidine-4-carboxylates. The results of the accurate computational investigation on the mechanism at the DFT level are in complete agreement with the experimental evidence and the crystallographic data.

Introduction

The conjugate addition of nitrogen-containing nucleophiles to electron-deficient olefins represents one of the most employed and versatile methods for C–N bond construction in organic chemistry.[1] The reaction may be performed under catalytic conditions, and the use of chiral Lewis acids[2] or, more recently, of organocatalysts[3] has been described in the literature.

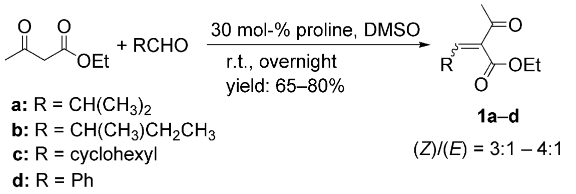
Alkylidenemalonates have been intensively employed as Michael acceptors.[4] In particular, a chiral Lewis acid catalysed Michael addition of hydroxylamine derivatives to alkylidenemalonates has been reported by our group.[5] Herein, we describe the highly stereocontrolled synthesis of ethyl 5-hydroxyisoxazolidine-4-carboxylate through a Lewis acid induced Michael addition of hydroxylamine derivatives to alkylideneacetoacetates, followed by intramolecular hemiketal formation. The use of acetoacetates in this field is rather unusual and has the advantage of introducing a reactive keto functionality that may be further elaborated.

Isoxazolidines are interesting heterocyclic compounds that may be regarded as unusual constrained β-amino acids[6] or as furanose mimetics,[7] and have also been exploited as analogues of natural products.[8]

An organocatalytic synthesis of 5-hydroxyisoxazolidine from *N*-protected hydroxylamines and α,β-unsaturated aldehydes has been previously reported by Córdova and coworkers.[9] Our contribution concerns the description of a novel and straightforward Lewis acid catalysed protocol and the study of more complex substrates. In addition, we report the results of an accurate computational investigation at the Density Functional Theory (DFT) level of the mechanism of this reaction. The computational finding satisfactorily explains the stereochemical outcome.

Results and Discussion

Alkylideneacetoacetates have been prepared by a Knøvenagel reaction between ethyl acetoacetate and various aldehydes in the presence of a catalytic amount of proline (Scheme 1).[10] Proline was chosen among other bases since it was demonstrated to afford the best results in terms of yields and (*Z*)/(*E*) product selectivity.



Scheme 1. Synthesis of alkylideneacetoacetates **1a**–**d**.

The stereochemical assignment for **1a**–**d** was made on the basis of DPFGSE-NOE (Double Pulse Field Gradient Spin Echo NOE) experiments. We found that the major isomer (*Z*) exhibited a strong NOE between the vinyl H atom and the ketone CH$_3$ group, whereas the minor isomer (*E*) showed a strong NOE between the vinyl H atom and the ester CH$_2$ group.

The conjugate addition of *N*,*O*-bis(trimethylsilyl)hydroxylamine (TMSONHTMS) to alkylideneacetoacetates was first examined in the absence of catalysts (Scheme 2). The reaction conditions were optimized in order to induce the regioselective formation of 1,4-addition products rather than oximes, which would derive from a 1,2-addition pro-

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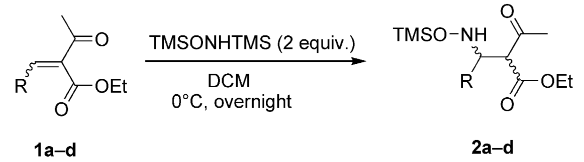
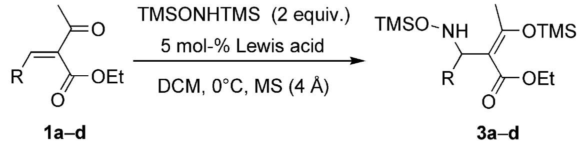
cess.[11] The reactions were completed in 16 h, and the *syn* and *anti* 1,4-adducts **2a–d** were obtained in quantitative yields in a 60:40 (*Z*)/(*E*) ratio, as indicated by the ^{1}H NMR spectrum of the crude reaction. The loss of the trimethylsilyl group on the nitrogen atom occurred during reaction workup. In order to characterize the intermediates, a very fast chromatography on silica gel allowed **2a–d** to be obtained as inseparable mixtures of *syn*/*anti* isomers. The stereochemical assignment was made by comparing the ^{1}H NMR coupling constants of **2a–d** with data available in the literature[12] (J_{syn} = 3.6 Hz, J_{anti} = 7.2 Hz).



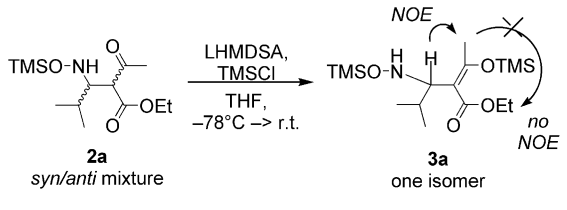
Scheme 2. Michael addition of TMSONHTMS to alkylideneacetoacetates **1a–d**.

Notably, the reaction carried out on the pure (*Z*) or (*E*) isomer of **1a–d** always gave **2a–d** in the same *syn*/*anti* ratio, as did the mixture of isomeric starting material. When this reaction was performed in the presence of a catalyst [scandium(III) triflate or copper(II) triflate], the 1,4-addition quickly occurred (0.5–1 h), and the resulting adducts were isolated as silyl enol ether derivatives **3a–d** (Scheme 3).



Scheme 3. Lewis acid catalysed Michael addition of TMSONHTMS to alkylideneacetoacetates **1a–d**.

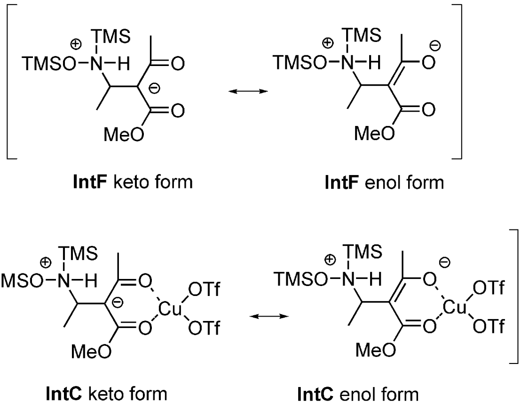
The structure of **3a–d** has been proposed on the basis of their ^{1}H and ^{13}C NMR spectra. Further evidence of the nature of **3a–d** was obtained by treating the 1,4-adduct **2a** with LHMDSA and TMSCl (Scheme 4).



Scheme 4. Conversion of adducts **2a** into silyl enol ether **3a**.

To summarize the results thus far, starting from an inseparable 60:40 mixture of *syn*/*anti* isomers of **2a**, the reaction gave **3a**, whose (*Z*) configuration was assigned by means of NOE experiments and could be extended to **3b–d** on the basis of the complete regularity of their NMR spectra.

An explanation for the different outcomes of the uncatalysed (adducts **2a–d** in Scheme 2) and catalysed (silyl enol ethers **3a–d** in Scheme 3) conjugate additions may come from DFT theoretical computations on the plausible intermediates of the 1,4-addition. The conjugate addition of TMSONHTMS to the methyl ester of isopropylideneacetoacetate gave results in complete agreement with those obtained for the corresponding ethyl esters.[13] This allowed for the simplification of the model system as reported in Scheme 5. It is reasonable to believe that, after the C–N bond formation, the resulting species has a zwitterionic nature, with a positive charge on the nitrogen atom and a negative charge delocalised on the enolate moiety.[14] The optimum structures of this intermediate, either as a free species (**IntF**) or as a complex with the Lewis acid (**IntC**), have been computed (Scheme 5).



Scheme 5. Keto and enol resonance structures for intermediates **IntC** and **IntF**.

A schematic representation of the two possible resonance structures (keto and enol) for these two intermediate species is given in Scheme 5. A comparison between the C–C and the C–O enolate bond lengths in these molecules shows that, in the case of **IntF**, the keto form is dominant, whereas for **IntC** the enol form predominates (Figure 1). The accurate analysis performed on **IntC** and **IntF** is reported in the Supporting Information.

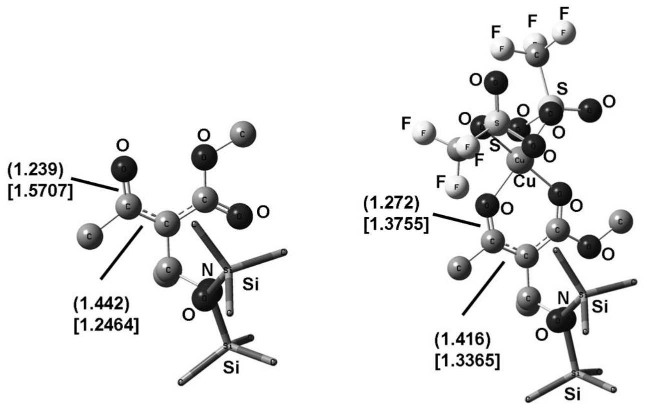
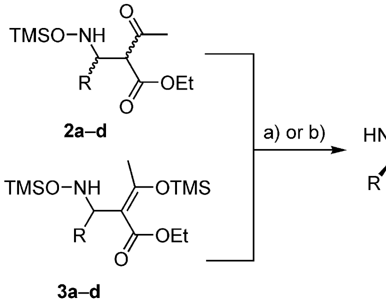


Figure 1. Optimum structures of the two intermediates **IntF** and **IntC**. Bond lengths [Å] and Wiberg bond orders are reported in round parentheses and square brackets, respectively (see the Supporting Information for details).

This finding suggests that **IntF** is likely to end up with a proton transfer to the α-carbon atom to give products **2a–d**. On the other hand, it is reasonable to believe that **IntC**, because of its structural features, may transfer a TMS group from the nitrogen atom to the enol oxygen atom to afford products **3a–d**.

Adducts **2a–d** and silyl enol ethers **3a–d** spontaneously converted to ethyl 5-hydroxyisoxazolidine-4-carboxylates **4a–d** at room temperature. In both cases, the intramolecular hemiketalisation required, on average, 24 h to be completed. Remarkably, both classes of **2a–d** and **3a–d** gave, with quantitative conversion, mixtures ranging from an 80:20 to a 75:25 ratio of the two C-5 stereoisomers of (3,4)-*trans*-hydroxyisoxazolidines **4a–d** (Scheme 6). The intramolecular hemiketalisation can be accelerated by the addition of silica gel to the crude mixture or by the use of another acidity source that facilitates ready desilylation of the reagent (e.g., treatment with aqueous acid solution or acidic resins).[15] The ethyl 5-hydroxyisoxazolidine-4-carboxylates **4a–d** were fully characterised by NMR spectroscopy (DEPT, HETCOR, COSY, and NOE).



a) 24 h, r.t.; b) SiO_2, DCM, 2 h

Scheme 6. Intramolecular hemiketalisation to **4a–d**.

We carried out a theoretical investigation on the reaction reported in Scheme 6 with the model system depicted in Figure 2. In the following discussion, the atom numbers given in parentheses refer to the numbering shown in Figure 2. The chosen model system (**2e**) emulates the ring-closure process to afford **4a–d** starting from the desilylated keto species **2a–d**, which represents the active form for the reaction. The enol forms **3a–d** were not explicitly considered since the species should immediately transform to **2a–d** after hydrolysis and expulsion of the TMS groups.

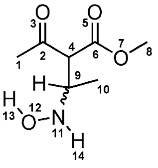


Figure 2. Schematic representation of the model system emulating the ring closure.

For both the *anti* (S^*,R^*) and *syn* (S^*,S^*) isomers of the model system, only three stable conformers exist. These are characterized by a different H-bond pattern. In **M1a** and

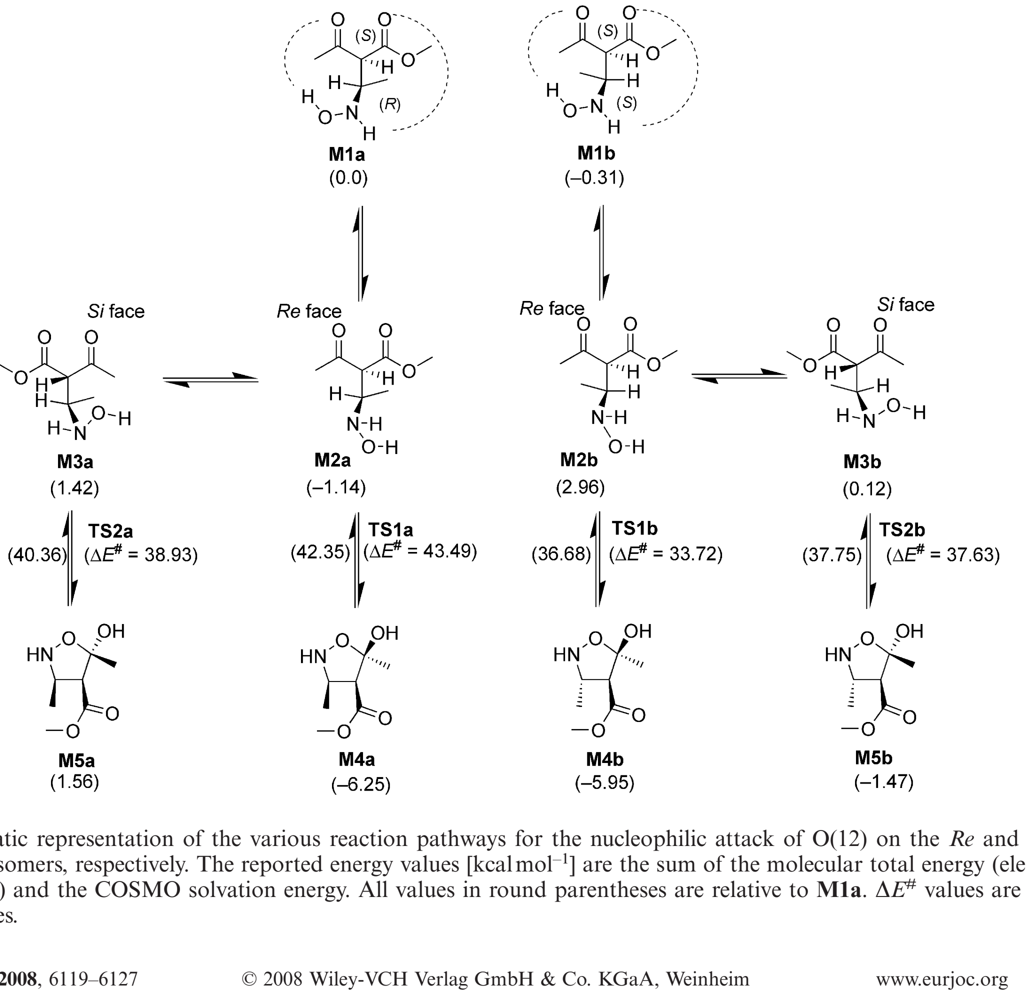


Figure 3. Schematic representation of the various reaction pathways for the nucleophilic attack of O(12) on the *Re* and *Si* face of the (*S*,*R*) and (*S*,*S*) isomers, respectively. The reported energy values [$kcal\,mol^{-1}$] are the sum of the molecular total energy (electronic energy + nuclear energy) and the COSMO solvation energy. All values in round parentheses are relative to **M1a**. $\Delta E^{\#}$ values are the computed activation energies.

M1b (see Figure 3) H(13) and H(14) form H bonds with O(3) and O(5), respectively. A slight rotation around the N(11)–C(9) bond (see column D1 in Table 1) leads to **M2a** and **M2b**, where both H(13) and H(14) point toward the same oxygen atom, O(5). The lost interaction with O(3) allows a rotation around the C(2)–C(4) bond and, consequently, a different orientation of the C(2)–O(3) carbonyl group (see column D2 in Table 1). The energy values of these four isomers range from –1.14 to 2.96 kcal mol^{-1} (see Figure 3). In both **M2a** and **M2b**, the relative orientation of the various atoms becomes suitable for the intramolecular nucleophilic attack of O(12) on C(2) on the *Re* face of the carbonyl group. However, a further analysis of the conformational space showed the existence of two additional conformers (**M3a** and **M3b**), where a rotation around the C(9)–C(4) bond (see column D3 in Table 1) allows for the attack of the nucleophilic oxygen atom O(12) on the *Si* face of the carbonyl group.

Table 1. Computed values for the various dihedral angles describing the different conformations of reactants.

Entry	Conformer	Dihedral angle		
		D1[a]	D2[b]	D3[c]
1	**M1a**	80.0	–92.8	–69.0
2	**M2a**	39.8	10.8	–72.1
3	**M3a**	–83.2	152.4	76.5
4	**M1b**	76.1	–88.6	–70.0
5	**M2b**	41.4	2.3	–68.4
6	**M3b**	–74.3	118.7	56.9

[a] Defined as C(12)–N(11)–C(9)–C(4). [b] Defined as O(3)–C(2)–C(4)–C(6). [c] Defined as N(11)–C(9)–C(4)–C(2).

The intramolecular nucleophilic attack of O(12) on the *Re* carbonyl face of C(2) and the simultaneous proton transfer of H(13) from O(12) to O(3) leads from **M2a** and **M2b** to the cyclic adducts **M4a** and **M4b**, respectively. Two unique reaction pathways (one for **M2a** and one for **M2b**) were determined. In both cases (the corresponding transition states are **TS1a** and **TS1b**) the nucleophilic attack and the proton transfer appear to be concerted (see Figure 4). The nucleophilic attack on the *Si* face of the carbonyl group has also been explored. We found two reaction pathways leading to **M5a** and **M5b** from **M3a** (transition state **TS2a**) and **M3b** (transition state **TS2b**), respectively (see Figure 5). Thus, **M4b** and **M5b** represent the two possible *trans* products originating from the (*S**,*S**) isomer, whereas **M4a** and **M5a** are the *cis* products originating from the (*S**,*R**) isomer.

The computed activation barriers and the relative energy values of the various transition states indicated that the formation of **M4b** and **M5b** was favoured over **M4a** and **M5a**; it was evident from the relative energy values reported in Figure 3 that in the former case the corresponding transition states (**TS1b** and **TS2b**) were significantly lower in energy than those of the latter (**TS1a** and **TS2a**). This can be ascribed to a more effective H-bond network characterized by a better co-linearity of the atoms involved in proton transfer. Also, since the energy difference between **TS1b** and **TS2b** is only 1.0 kcal mol^{-1}, the reaction should afford both cyclic *trans* products differing in the configuration at C-5, in agreement with the experimental observation. However, since the *anti* and *syn* isomers are simultaneously present in the reaction mixture, some amounts of the cyclic *cis* products should also be experimentally observed. Alternatively, because of the high energy of **TS1a** and **TS2a**, a certain amount of the unreacted *anti* species should be detected in the final product mixture.

Since only the two (3,4)-*trans* isomer products were obtained experimentally, this suggests that a *syn*/*anti* isomerization took place during the cyclization, giving only the kinetically favoured (3,4)-*trans* derivatives. NOE experiments on **4a** confirmed the relative stereochemistry of the ring substituents. A further validation of the structure of

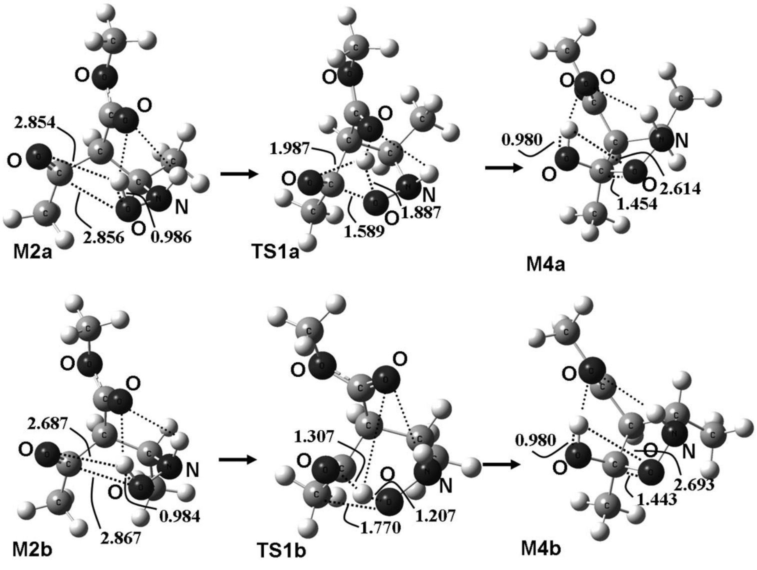


Figure 4. Schematic representation of reactants (**M2a** and **M2b**), transition states (**TS1a** and **TS1b**), and products (**M4a** and **M4b**) for the nucleophilic attack on the *Re* face of the carbonyl group.

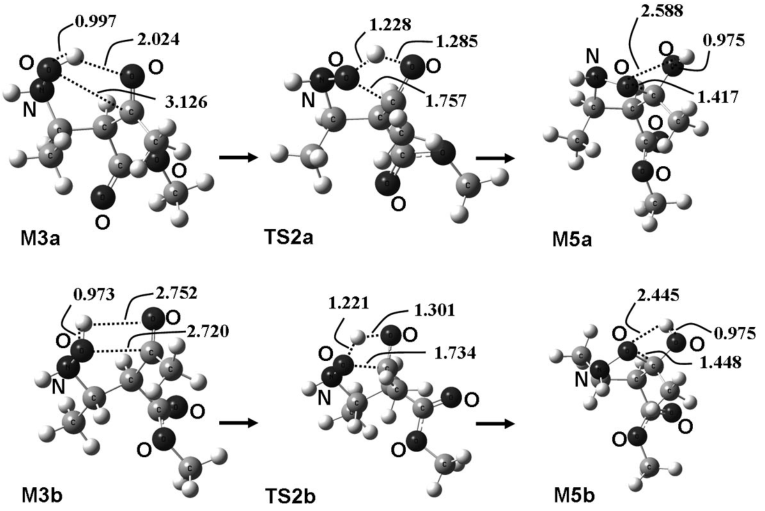
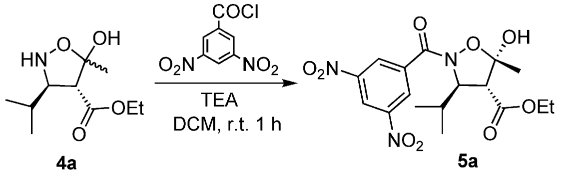


Figure 5. Schematic representation of reactants (**M3a** and **M3b**), transition states (**TS2a** and **TS2b**), and products (**M5a** and **M5b**) for the nucleophilic attack on the *Si* face of the carbonyl group.

ethyl 5-hydroxy-5-methyl-3-isopropylisoxazolidine-4-carboxylate (**4a**) was obtained by X-ray diffraction analysis of the derivative **5a**, easily obtained by the treatment of **4a** with 3,5-dinitrobenzoyl chloride and triethylamine, as shown in Scheme 7.



Scheme 7. Derivatisation of **4a** leading to **5a**.

Note that the relative configurations at C3 and C4 in the ORTEP drawing are in agreement with those of the dominant products forecasted by the computational results (Figure 6). Starting from a 78:22 diastereomeric mixture of **4a**, only one (3,4)-*trans* isomer ($J_{3\text{-H},4\text{-H}}$ = 7.2 Hz) of **5a** was obtained, suggesting that an isomerisation occurred at the hemiketal position during the reaction. Under the same conditions, **4b–c** afforded exclusively (3,4)-*trans*-**5b–c**. The transformation of **4d** to **5d** gave unsatisfactory results and a partial degradation of the starting material. Complete regularity in the ^{1}H NMR chemical shifts allowed us to extend the stereochemical attribution of **5a** to **5b–c**.

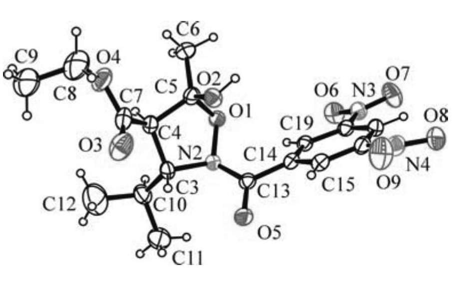


Figure 6. ORTEP drawing of **5a**.

DFT computations were carried out on the model system depicted in Figure S5 (see the Supporting Information) to investigate the structure and the stereochemistry of the *N*-(3,5-dinitrobenzoyl) derivative **5a** obtained from the isoxazolidine **4a**. All eight potential isomers were considered.[16] We found a strong preference for the isomers having a *trans* configuration of the amide bond. In particular, the (3*S**,4*S**,5*R**) isomer was the most stable structure. Its absolute configuration is in agreement with the results of the X-ray diffraction analysis of derivative **5a**, thus confirming the reliability of the computational approach adopted in this work (Figure 6).

Conclusions

In this paper we described a new protocol for the preparation of functionalized 3,4-disubstituted 5-hydroxyisoxazolidines through the 1,4-addition of TMSONHTMS to alkylideneacetoacetates. We carried out a computational DFT investigation of the reaction mechanism leading to 5-hydroxyisoxazolidine-4-carboxylates. Our computations satisfactorily explain the experimentally observed stereochemical outcome of the reaction and are in agreement with the crystallographic analysis.

Experimental Section

General: All chemicals were purchased from commercial suppliers and used without further purification. Anhydrous solvents were purchased in Sure-seal bottles over molecular sieves and used without further drying. Flash chromatography was performed with silica gel (230–400 mesh). NMR spectra were recorded with 200, 300, or 600 MHz spectrometers. Chemical shifts were reported as δ values (ppm) relative to the solvent peak of $CDCl_3$ set at δ = 7.27 (^{1}H) or δ = 77.0 (^{13}C). The preparation of acetoacetate **1** and the complete characterization of **1a** and **1c** have already been reported.[17] **1b** was prepared from the corresponding racemic aldehyde. Due to their easy conversion to **4a**–**d**, **2a**–**d** and **3a**–**d** were not submitted to elemental analysis.

(*Z*)-1b: Yield 66%, colourless clear oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.75 (t, *J* = 6.9 Hz, 3 H, *CH$_3$*CH$_2$CH), 0.97 (d, *J* = 6.6 Hz, 3 H, CH*CH$_3$*), 1.22 (t, *J* = 7.2 Hz, 3 H, *CH$_3$*CH$_2$O), 1.34 (m, 2 H, CH$_3$*CH$_2$*CH), 2.21 (s, 3 H, CO*CH$_3$*), 2.35 (m, 1 H, CH$_3$CH$_2$*CH*), 4.20 (q, *J* = 7.2 Hz, 2 H, CH$_3$*CH$_2$*O), 6.50 (d, *J* = 10.8 Hz, 1 H, CH=) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = 11.5 (CH$_3$), 13.9 (CH$_3$), 19.3 (CH), 26.5 (CH$_2$), 29.1 (CH$_3$), 36.3 (CH$_3$), 60.9 (CH$_2$), 136.0 (C), 152.8 (CH), 166.4 (C), 195.0 (C) ppm.

(*E*)-1b: ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.74 (t, *J* = 6.9 Hz, 3 H, *CH$_3$*CH$_2$CH), 0.93 (d, *J* = 6.9 Hz, 3 H, CH*CH$_3$*), 1.20 (t, *J* = 7.2 Hz, 3 H, *CH$_3$*CH$_2$O), 1.34 (m, 2 H, CH$_3$*CH$_2$*CH), 2.25 (s, 3 H, CO*CH$_3$*), 2.35 (m, 1 H, CH$_3$CH$_2$*CH*), 4.16 (q, *J* = 7.2 Hz, 2 H, CH$_3$*CH$_2$*O), 6.56 (d, *J* = 10.8 Hz, 1 H, CH=) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = 11.6 (CH$_3$), 13.9 (CH$_3$), 19.2 (CH), 26.3 (CH$_2$), 29.0 (CH$_3$), 35.4 (CH$_3$), 61.0 (CH$_2$), 134.5 (C), 153.0 (CH), 164.1 (C), 201.2 (C) ppm. $C_{11}H_{18}O_3$ (198.26): calcd. C 66.64, H 9.15; found C 66.72, H 9.14.

(*Z*)-1d: Yield 72%, yellow oil. ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 1.28 (t, *J* = 7.2 Hz, 3 H, *CH$_3$*CH$_2$O), 2.43 (s, 3 H, CO*CH$_3$*), 4.34 (q, *J* = 7.2 Hz, 2 H, CH$_3$*CH$_2$*O), 7.28–7.48 (m, 5 H, Ph), 7.58 (s, 1 H, CH=) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = 13.8 (CH$_3$), 26.5 (CH$_3$), 61.7 (CH$_2$), 128.8 (CH), 129.5 (CH), 130.7 (CH), 132.9 (C), 134.6 (C), 141.2 (CH), 167.7 (C), 194.6 (C) ppm.

(*E*)-1d: ^{1}H NMR (CDCl$_3$, 200 MHz): δ = 1.34 (t, *J* = 7.2 Hz, 3 H, *CH$_3$*CH$_2$O), 2.36 (s, 3 H, CO*CH$_3$*), 4.30 (q, *J* = 7.2 Hz, 2 H, CH$_3$*CH$_2$*O), 7.34–7.39 (m, 5 H, Ph), 7.68 (s, 1 H, CH=) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = 14.1 (CH$_3$), 31.1 (CH$_3$), 61.5 (CH$_2$), 128.8 (CH), 129.6 (CH), 130.3 (CH), 132.8 (C), 134.0 (C), 140.4, (CH), 164.3 (C), 203.3 (C) ppm. $C_{13}H_{14}O_3$ (218.25): calcd. C 71.54, H 6.47; found C 71.59, H 6.48.

General Procedure for the 1,4 Addition of *N*,*O*-Bis(trimethylsilyl)hydroxylamine to Alkylideneacetoacetate 1: To a stirred solution of **1a**–**d** (0.5 mmol) in dry CH$_2$Cl$_2$ (2.5 mL) at 0 °C under nitrogen, *N*,*O*-bis(trimethylsilyl)hydroxylamine (2 equiv., 1 mmol) was added in one portion. The reaction was monitored by TLC and quenched after 16 h with H$_2$O. The residue was then diluted with CH$_2$Cl$_2$ (10 mL) and washed with H$_2$O (2 × 10 mL). The organic layer was dried with Na$_2$SO$_4$, and the solvent was removed under reduced pressure. Compounds **2a**–**d** were purified by flash chromatography with silica gel (cyclohexane/EtOAc, 9:1).

***syn*-2a:** Yield 77%, pale yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.08 [s, 9 H, OSi(*CH$_3$*)$_3$], 0.95 (d, *J* = 6.9 Hz, 3 H, CH*CH$_3$*), 1.03 (d, *J* = 6.9 Hz, 3 H, CH*CH$_3$*), 1.28 (t, *J* = 7.2 Hz, 3 H, OCH$_2$*CH$_3$*), 1.68 (m, 1 H, CH$_3$*CH*CH$_3$), 2.25 (s, 3 H, OC*CH$_3$*), 3.26 (m, 1 H, NC*H*), 3.45 (d, *J* = 3.6 Hz, 1 H, CHCO), 4.17 (m, 2 H, O*CH$_2$*CH$_3$), 6.22 (d, *J* = 11.4 Hz, 1 H, N*H*) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = –1.1 (3 CH$_3$), 14.0 (CH$_3$), 20.5 (2 CH$_3$), 29.4 (CH), 30.1 (CH$_3$), 59.7 (CH), 60.9 (CH$_2$), 67.5 (CH), 170.1 (C), 202.9 (C) ppm.

***anti*-2a:** ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.11 [s, 9 H, OSi(*CH$_3$*)$_3$], 0.93 (m, 6 H, CH*CH$_3$*), 1.26 (t, *J* = 7.2 Hz, 3 H, OCH$_2$*CH$_3$*), 1.94 (m, 1 H, CH$_3$*CH*CH$_3$), 2.29 (s, 3 H, OC*CH$_3$*), 3.37 (m, 1 H, NC*H*), 3.71 (d, *J* = 7.2 Hz, 1 H, CHCO), 4.17 (m, 2 H, O*CH$_2$*CH$_3$), 5.55 (d, *J* = 9.6 Hz, 1 H, N*H*) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = –0.6 (3 CH$_3$), 14.0 (CH$_3$), 18.5 (CH$_3$), 21.6 (CH$_3$), 28.6 (CH), 30.1 (CH$_3$), 60.3 (CH), 61.3 (CH$_2$), 69.8 (CH), 168.7 (C), 200.6 (C) ppm.

***syn*-2b:** Yield 70%, pale yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.09 [s, 9 H, OSi(*CH$_3$*)$_3$], 0.66–1.06 (m, 8 H, CHCH$_2$*CH$_3$*, CH*CH$_2$*CH$_3$, CH*CH$_3$*), 1.26 (t, *J* = 6.9 Hz, 3 H, OCH$_2$*CH$_3$*), 1.46 (m, 1 H, CH$_3$C*H*CH$_2$), 2.23 (s, 3 H, OC*CH$_3$*), 3.36 (m, 1 H, NC*H*), 3.42 (d, *J* = 9.6 Hz, 1 H, C*H*CO), 4.18 (m, 2 H, O*CH$_2$*CH$_3$), 6.0 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = –1.1 (3CH$_3$), 11.2 (CH$_3$), 14.0 (CH$_3$), 16.3 (CH$_3$), 26.4 (CH$_2$), 28.6 (CH$_3$), 35.6 (CH), 60.0 (CH$_2$), 60.9 (CH), 67.5 (CH), 170.0 (C), 202.8 (C) ppm.

***anti*-2b:** ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.06 [s, 9 H, OSi(*CH$_3$*)$_3$], 0.66–1.06 (m, 8 H, CHCH$_2$*CH$_3$*, CH*CH$_2$*CH$_3$, CH*CH$_3$*), 1.18 (m, 1 H, CH$_3$C*H*CH$_2$), 1.25 (t, *J* = 6.9 Hz, 3 H, OCH$_2$*CH$_3$*), 2.27 (s, 3 H, OC*CH$_3$*), 3.69 (d, *J* = 8.1 Hz, CHCO), 3.83 (m, 1 H, NC*H*), 4.18 (m, 2 H, O*CH$_2$*CH$_3$), 6.2 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = –0.6 (3 CH$_3$), 11.8 (CH$_3$), 13.9 (CH$_3$), 15.6 (CH$_3$), 26.7 (CH$_2$), 29.7 (CH$_3$), 36.0 (CH), 59.3 (CH$_2$), 61.2 (CH), 68.4 (CH), 168.9 (C), 200.3 (C) ppm.

***syn*-2c:** Yield 75%, pale yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.07 [s, 9 H, OSi(*CH$_3$*)$_3$], 0.90–1.22 (m, 5 H, cyclohexyl), 1.27 (t, *J* = 7.2 Hz, 3 H, OCH$_2$*CH$_3$*), 1.44–1.80 (m, 6 H, cyclohexyl), 2.25 (s, 3 H, OC*CH$_3$*), 3.36 (m, 1 H, NC*H*), 3.44 (d, *J* = 3.3 Hz, 1 H, CHCO), 4.12 (m, 2 H, O*CH$_2$*CH$_3$), 6.20 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = –1.1 (3CH$_3$), 14.0 (CH$_3$), 26.2 (2CH$_2$), 28.6 (CH), 29.2 (CH$_2$), 30.4 (CH$_2$), 30.9 (CH$_2$), 38.8 (CH$_3$), 59.2 (CH), 60.9 (CH$_2$), 69.0 (CH), 170.2 (C), 203.1 (C) ppm.

***anti*-2c**: ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.13 [s, 9 H, OSi(*CH$_3$*)$_3$], 0.90–1.22 (m, 5 H, cyclohexyl), 1.25 (t, *J* = 7.2 Hz, 3 H, OCH$_2$*CH$_3$*), 1.44–1.80 (m, 6 H, cyclohexyl), 2.28 (s, 3 H, OC*CH$_3$*), 3.36 (m, 1 H, NC*H*), 3.72 (d, *J* = 3.3 Hz, 1 H, CHCO), 4.20 (m, 2 H, O*CH$_2$*CH$_3$), 6.20 (br. s, 1 H, N*H*) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = –1.2 (3CH$_3$), 14.1 (CH$_3$), 26.0 (CH$_2$), 26.5 (CH$_2$), 29.3 (CH), 30.3 (CH$_2$), 30.6 (CH$_2$), 31.0 (CH$_2$), 39.2 (CH$_3$), 59.7 (CH), 61.2 (CH$_2$), 67.5 (CH), 169.4 (C), 204.0 (C) ppm.

***syn*-2d:** Yield 66%, pale yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.03 [s, 9 H, OSi(*CH$_3$*)$_3$], 0.94 (t, *J* = 7.2 Hz, 3 H, OCH$_2$*CH$_3$*), 2.36 (s, 3 H, OC*CH$_3$*), 3.90 (q, *J* = 7.2 Hz, 2 H, O*CH$_2$*CH$_3$), 4.15 (d, *J* = 7.8 Hz, 1 H, CHCO), 4.68 (d, *J* = 7.8 Hz, 1 H, NC*H*), 5.59 (br. s, 1 H, N*H*), 7.20–7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = –0.8 (3 CH$_3$), 13.6 (CH$_3$), 29.6 (CH$_3$), 61.3 (CH$_2$), 63.0 (CH), 65.8 (CH), 128.0 (CH), 128.4 (CH), 128.8 (CH), 137.6 (C), 167.2 (C), 201.7 (C) ppm.

***anti*-2d:** ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.01 [s, 9 H, OSi(*CH$_3$*)$_3$], 1.26 (t, *J* = 7.2 Hz, 3 H, OCH$_2$*CH$_3$*), 2.06 (s, 3 H, OC*CH$_3$*), 4.05 (d, *J* = 8.7 Hz, 1 H, CHCO), 4.20 (q, *J* = 7.2 Hz, 2 H, O*CH$_2$*CH$_3$), 4.65 (d, *J* = 8.7 Hz, 1 H, NC*H*), 5.91 (br. s, 1 H, N*H*), 7.20–7.50 (m, 5 H, Ph) ppm. ^{13}C NMR (CDCl$_3$, 300 MHz): δ = –1.2 (3CH$_3$), 13.9 (CH$_3$), 29.8 (CH$_3$), 61.5 (CH$_2$), 62.4 (CH), 65.8 (CH), 127.8 (CH), 128.2 (CH), 129.5 (CH), 137.6 (C), 168.6 (C), 201.3 (C) ppm.

General Procedure for the Catalyzed 1,4-Addition of *N*,*O*-Bis(trimethylsilyl)hydroxylamine to Alkylideneacetoacetate 1: To a stirred solution of **1a**–**d** (0.5 mmol) in dry CH$_2$Cl$_2$ (2.5 mL) under nitrogen, a catalytic amount of scandium(III) triflate or copper(II) triflate (0.025 mmol) was added. The reaction mixture was cooled to 0 °C, and *N*,*O*-bis(-trimethylsilyl)hydroxylamine (2 equiv., 1 mmol) was added in one portion. The mixture was stirred for 1 h at the same temperature and then filtered through a Celite pad. The solvent was removed under reduced pressure to afford **3a**–**d**.

3a: Yield >95%, colourless clear oil. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 0.17 [s, 9 H, OSi(*CH$_3$*)$_3$], 0.26 [s, 9 H, OSi(*CH$_3$*)$_3$], 0.81 (d, *J* = 6.9 Hz, 3 H, CH*CH$_3$*), 1.07 (d, *J* = 6.6 Hz, 3 H, CH*CH$_3$*), 1.28 (t, *J* = 6.9 Hz, 3 H, OCH$_2$*CH$_3$*), 1.54–1.64 (m, 1 H, CH$_3$*CH*CH$_3$), 1.92 (s, 3 H, OC*CH$_3$*), 3.12 (t, *J* = 10.8 Hz, 1 H, NC*H*), 4.09–4.20

(m, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.88 (d, *J* = 11.4 Hz, 1 H, NH) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = –0.9 (3 $\mathrm{CH_3}$), 0.4 (3 $\mathrm{CH_3}$), 14.3 ($\mathrm{CH_3}$), 20.5 ($\mathrm{CH_3}$), 21.3 ($\mathrm{CH_3}$), 28.9 (CH), 59.7 ($\mathrm{CH_2}$), 69.7 (CH), 112.8 (C), 157.3 (C), 168.4 (C) ppm.

3b: Yield >95%, colourless clear oil. ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 0.10 [s, 9 H, $\mathrm{OSi(C}H_3\mathrm{)_3}$], 0.20 [s, 9 H, $\mathrm{OSi(C}H_3\mathrm{)_3}$], 0.79 (d, *J* = 6.9 Hz, 3 H, $\mathrm{CHCH_2C}H_3$), 0.82–0.90 (m, 2 H, $\mathrm{CHC}H_2\mathrm{CH_3}$), 1.05 (d, *J* = 6.6 Hz, 3 H, $\mathrm{CHC}H_3$), 1.23–1.30 (m, 3 H, $\mathrm{OCH_2C}H_3$), 1.35–1.49 (m, 1 H, $\mathrm{CH_3C}H\mathrm{CH_2}$), 1.92 (s, 3 H, $\mathrm{OCC}H_3$), 3.22 (bt, *J* = 9.3 Hz, 1 H, $\mathrm{NC}H$), 4.07–4.27 (m, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.88 (br. s, 1 H, N$H$) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = –0.8 (3 $\mathrm{CH_3}$), 0.5 (3 $\mathrm{CH_3}$), 10.5 ($\mathrm{CH_3}$), 14.4 ($\mathrm{CH_3}$), 16.9 ($\mathrm{CH_3}$), 20.5 (CH), 26.6 ($\mathrm{CH_2}$), 34.8 ($\mathrm{CH_3}$), 59.7 ($\mathrm{CH_2}$), 68.2 (CH), 112.8 (C), 156.9 (C), 168.5 (C) ppm.

3c: Yield >95%, colourless clear oil. ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 0.14 [s, 9 H, $\mathrm{OSi(C}H_3\mathrm{)_3}$], 0.24 [s, 9 H, $\mathrm{OSi(C}H_3\mathrm{)_3}$], 0.86–1.40 (m, 6 H, cyclohexyl), 1.32 (t, *J* = 7.2 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 1.65–1.80 (m, 4 H, cyclohexyl), 1.96 (s, 3 H, $\mathrm{OCC}H_3$), 2.27 (bd, *J* = 13.2 Hz, 1 H, cyclohexyl), 3.29 (d, *J* = 10.5 Hz, 1 H, NCH), 4.12–4.23 (m, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.92 (br. s, 1 H, N$H$) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = –0.8 (3 $\mathrm{CH_3}$), 0.5 (3 $\mathrm{CH_3}$), 14.4 ($\mathrm{CH_3}$), 20.6 (CH), 25.9 ($\mathrm{CH_2}$), 26.2 ($\mathrm{CH_2}$), 26.6 ($\mathrm{CH_2}$), 30.7 ($\mathrm{CH_2}$), 31.8 ($\mathrm{CH_2}$), 38.3 ($\mathrm{CH_3}$), 59.7 ($\mathrm{CH_2}$), 68.3 (CH), 112.5 (C), 157.3 (C), 168.5 (C) ppm.

3d: Yield >95%, colourless clear oil. ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 0.21 [s, 9 H, $\mathrm{OSi(C}H_3\mathrm{)_3}$], 0.30 [s, 9 H, $\mathrm{OSi(C}H_3\mathrm{)_3}$], 1.08 (t, *J* = 7.2 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 2.05 (s, 3 H, $\mathrm{OCC}H_3$), 4.05 (q, *J* = 6.9 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 4.89 (d, *J* = 11.4 Hz, 1 H, $\mathrm{HNC}H$) 6.27 (d, *J* = 11.4 Hz, 1 H, NH), 7.29–7.35 (m, 5 H, Ph) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = –0.9 (3 $\mathrm{CH_3}$), 0.5 (3 $\mathrm{CH_3}$), 14.0 ($\mathrm{CH_3}$), 20.9 ($\mathrm{CH_3}$), 59.7 ($\mathrm{CH_2}$), 60.9 (CH), 113.13 (C), 126.8 (2 CH), 128.0 (2 CH), 128.6 (CH), 139.9 (C), 153.4 (C), 167.5 (C) ppm.

General Procedure for the Cyclisation of 2a–d or 3a–d to 5-Hydroxyisoxazolidine-4-carboxylates 4a–d: To a stirred solution of **2a**–**d** or **3a**–**d** (0.5 mmol) in $\mathrm{CH_2Cl_2}$ (5 mL), wet silica gel or Amberlist H15 (100 mg) was added, and the reaction mixture was stirred at room temperature for 2 h. The mixture was filtered through a Gouch filter, the silica gel was washed with methanol (10 mL), and the filtrate was concentrated under reduced pressure to afford **4a**–**d**.

4a (Methyl Ester): Yield >95%, colourless clear oil. Major anomer: ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 0.88 (d, *J* = 6.6 Hz, 3 H, $\mathrm{CHC}H_3$), 0.97 (d, *J* = 6.6 Hz, 3 H, $\mathrm{CHC}H_3$), 1.67 (s, 3 H, $\mathrm{HOCC}H_3$), 1.69 (m, 1 H, $\mathrm{CH_3C}H\mathrm{CH_3}$), 2.96 (d, *J* = 5.4 Hz, 1 H, $\mathrm{C}H\mathrm{CO}$), 3.56 (dd, *J* = 5.4, 7.5 Hz, 1 H, $\mathrm{HNC}H$), 3.76 (s, 3 H, $\mathrm{OC}H_3$) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 18.7 ($\mathrm{CH_3}$), 19.2 ($\mathrm{CH_3}$), 23.8 (CH), 32.5 ($\mathrm{CH_3}$), 52.4 (CH), 60.2 ($\mathrm{CH_3}$), 67.9 (CH), 106.5 (C), 171.0 (C) ppm. Minor anomer: ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 0.92 (d, *J* = 6.9 Hz 3 H, $\mathrm{CHC}H_3$), 1.00 (d, *J* = 6.6 Hz, 3 H, $\mathrm{CHC}H_3$), 1.50 (s, 3 H, $\mathrm{HOCC}H_3$), 1.70 (m, 1 H, $\mathrm{CH_3C}H\mathrm{CH_3}$), 2.95 (d, *J* = 7.6 Hz 1 H, $\mathrm{C}H\mathrm{CO}$), 3.58 (m, 1 H, $\mathrm{HNC}H$), 3.74 (s, 3 H, $\mathrm{OC}H_3$) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 19.6 ($\mathrm{CH_3}$), 20.3 ($\mathrm{CH_3}$), 22.2 (CH), 30.1 ($\mathrm{CH_3}$), 52.2 (CH), 62.0 ($\mathrm{CH_3}$), 71.3 (CH), 108.4 (C), 172.0 (C) ppm. $\mathrm{C_9H_{17}NO_4}$ (203.24): calcd. C 53.19, H 8.43, N 6.89; found C 53.14, H 8.45, N 6.92.

4a (Ethyl Ester): Yield 95%, yellow oil. Major anomer: ^{1}H NMR ($\mathrm{C_6D_6}$, 600 MHz): δ = 0.82 (d, *J* = 6.6 Hz, 3 H, $\mathrm{CHC}H_3$), 0.93 (t, *J* = 7.2 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 0.97 (d, *J* = 6.6 Hz, 3 H, $\mathrm{CHC}H_3$), 1.51 (s, 3 H, $\mathrm{HOCC}H_3$), 1.64 (m, 1 H, $\mathrm{CH_3C}H\mathrm{CH_3}$), 2.83 (d, *J* = 5.4 Hz, 1 H, $\mathrm{C}H\mathrm{CO}$), 3.58 (dd, *J* = 5.4, 7.2 Hz, 1 H, $\mathrm{HNC}H$), 3.93 (m, 1 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 3.98 (m, 1 H, $\mathrm{OC}H_2\mathrm{CH_3}$) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 14.1 ($\mathrm{CH_3}$), 18.7 ($\mathrm{CH_3}$), 19.4 ($\mathrm{CH_3}$), 23.8 (CH), 32.6 ($\mathrm{CH_3}$), 60.1 ($\mathrm{CH_2}$), 61.3 (CH), 67.9 (CH), 106.5 (C), 170.7 (C) ppm. Minor anomer: ^{1}H NMR ($\mathrm{C_6D_6}$, 600 MHz): δ = 0.86 (d, *J* = 7.2 Hz 3 H, $\mathrm{CHC}H_3$), 0.88 (d, *J* = 6.6 Hz, 3 H, $\mathrm{CHC}H_3$), 0.91 (t, *J* = 7.2 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 1.45 (s, 3 H, $\mathrm{HOCC}H_3$), 1.50 (m, 1 H, $\mathrm{CH_3C}H\mathrm{CH_3}$), 3.03 (d, *J* = 7.8 Hz 1 H, $\mathrm{C}H\mathrm{CO}$), 3.88 (dd, *J* = 7.8, 7.2 Hz, 1 H, $\mathrm{HNC}H$), 3.92 (m, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 14.2 ($\mathrm{CH_3}$), 19.6 ($\mathrm{CH_3}$), 20.4 (CH), 22.2 ($\mathrm{CH_3}$), 30.1 ($\mathrm{CH_3}$), 61.1 ($\mathrm{CH_2}$), 62.0 (CH), 71.9 (CH), 108.4 (C), 171.5 (C) ppm. $\mathrm{C_{10}H_{19}NO_4}$ (217.26): calcd. C 55.28, H 8.81, N 6.45; found C 55.31, H 8.79, N 6.43.

4b: Yield 90%, pale yellow oil. Major anomer: ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 0.80–1.06 (m, 8 H, $\mathrm{CHCH_2C}H_3$, $\mathrm{CHC}H_2\mathrm{CH_3}$, $\mathrm{CHC}H_3$) 1.30 (t, *J* = 7.2 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 1.58 (m, 1 H, $\mathrm{CH_3C}H$ $\mathrm{CH_2CH_3}$), 1.67 (s, 3 H, $\mathrm{HOCC}H_3$), 2.96 (d, *J* = 6.0 Hz, 1 H, $\mathrm{C}H\mathrm{CO}$), 3.67 (t, *J* = 6.0 Hz, 1 H, $\mathrm{HNC}H$), 4.23 (m, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 11.2 ($\mathrm{CH_3}$), 14.1 ($\mathrm{CH_3}$), 15.2 ($\mathrm{CH_3}$), 23.8 (CH), 26.2 ($\mathrm{CH_2}$), 39.0 ($\mathrm{CH_3}$), 59.8 (CH), 61.3 ($\mathrm{CH_2}$), 66.6 (CH), 106.1 (C), 170.7 (C) ppm. Minor anomer: ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 0.80–1.06 (m, 8 H, $\mathrm{CHCH_2C}H_3$, $\mathrm{CHC}H_2\mathrm{CH_3}$, $\mathrm{CHC}H_3$) 1.29 (t, *J* = 7.2 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 1.53 (s, 3 H, $\mathrm{HOCC}H_3$), 1.58 (m, 1 H, $\mathrm{CH_3C}H\mathrm{CH_2CH_3}$), 2.95 (m, 1 H, $\mathrm{C}H\mathrm{CO}$), 3.68 (m, 1 H, $\mathrm{HNC}H$), 4.25 (m, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 11.8 ($\mathrm{CH_3}$), 13.6 ($\mathrm{CH_3}$), 18.2 ($\mathrm{CH_3}$), 23.1 (CH), 26.6 ($\mathrm{CH_2}$), 40.1 ($\mathrm{CH_3}$), 60.3 (CH), 61.9 ($\mathrm{CH_2}$), 70.1 (CH), 105.0 (C), 167.2 (C) ppm. $\mathrm{C_{11}H_{21}NO_4}$ (231.29): calcd. C 57.12, H 9.15, N 6.06; found C 57.11, H 9.19, N 6.08.

4c: Yield 95%, yellow oil. Major anomer: ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 0.92–1.40 (m, 6 H, cyclohexyl), 1.29 (t, *J* = 7.2 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 1.52–1.78 (m, 4 H, cyclohexyl), 1.67 (s, 3 H, $\mathrm{OCC}H_3$), 2.00 (m, 1 H, cyclohexyl), 3.00 (d, *J* = 5.7 Hz, 1 H, $\mathrm{C}H\mathrm{CO}$), 3.56 (dd, *J* = 5.7, 8.1 Hz, 1 H, $\mathrm{HNC}H$), 4.24 (m, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 14.1 ($\mathrm{CH_3}$), 23.9 (CH), 25.8 ($\mathrm{CH_2}$), 26.0 ($\mathrm{CH_2}$), 26.3 ($\mathrm{CH_2}$), 29.4 ($\mathrm{CH_2}$), 29.9 ($\mathrm{CH_2}$), 42.3 ($\mathrm{CH_3}$), 60.1 (CH), 61.4 ($\mathrm{CH_2}$), 67.2 (CH), 106.3 (C), 170.8 (C) ppm. Minor anomer: ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 0.92–1.40 (m, 6 H, cyclohexyl), 1.33 (t, *J* = 7.2 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 1.52–1.78 (m, 4 H, cyclohexyl), 1.64 (s, 3 H, $\mathrm{OCC}H_3$), 1.85 (m, 1 H, cyclohexyl), 2.96 (d, *J* = 7.5 Hz, 1 H, $\mathrm{C}H\mathrm{CO}$), 3.56 (t, *J* = 7.5 Hz, 1 H, $\mathrm{HNC}H$), 4.30 (m, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 14.1 ($\mathrm{CH_3}$), 22.0 (CH), 25.1 ($\mathrm{CH_2}$), 25.6 ($\mathrm{CH_2}$), 26.9 ($\mathrm{CH_2}$), 30.9 ($\mathrm{CH_2}$), 31.0 ($\mathrm{CH_2}$), 40.0 ($\mathrm{CH_3}$), 61.0 (CH), 62.1 ($\mathrm{CH_2}$), 70.2 (CH), 108.2 (C), 171.4 (C) ppm. $\mathrm{C_{13}H_{23}NO_4}$ (257.33): calcd. C 60.68, H 9.01, N 5.44; found C 60.75, H 9.00, N 5.41.

4d: Yield 80%, yellow oil; Major anomer: ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 1.31 (t, *J* = 7.2 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 1.74 (s, 3 H, $\mathrm{OCC}H_3$), 3.24 (d, *J* = 5.4 Hz, 1 H, $\mathrm{C}H\mathrm{CO}$), 4.27 (q, *J* = 7.2 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 5.09 (d, *J* = 5.4 Hz, 1 H, $\mathrm{HNC}H$), 7.28–7.57 (m, 5 H, Ph) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 14.4 ($\mathrm{CH_3}$), 24.4 ($\mathrm{CH_3}$), 61.9 ($\mathrm{CH_2}$), 65.0 (CH), 70.2 (CH), 107.0 (C), 126.3 (2 CH), 127.3 (2 CH), 128.7 (CH), 134.1 (C), 178.0 (C) ppm. Minor anomer: ^{1}H NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 1.27 (t, *J* = 7.2 Hz, 3 H, $\mathrm{OCH_2C}H_3$), 1.64 (s, 3 H, $\mathrm{OCC}H_3$), 3.41 (d, *J* = 7.2 Hz, 1 H, $\mathrm{C}H\mathrm{CO}$), 4.15 (q, *J* = 7.2 Hz, 2 H, $\mathrm{OC}H_2\mathrm{CH_3}$), 4.94 (d, *J* = 7.2 Hz, 1 H, $\mathrm{HNC}H$), 7.28–7.60 (m, 5 H, Ph) ppm. ^{13}C NMR ($\mathrm{CDCl_3}$, 300 MHz): δ = 14.1 ($\mathrm{CH_3}$), 25.1 ($\mathrm{CH_3}$), 60.9 ($\mathrm{CH_2}$), 64.2 (CH), 69.3 (CH), 105.8 (C), 126.5 (2 CH), 127.1 (2 CH), 128.9 (CH), 136.1 (C), 169.4 (C) ppm. $\mathrm{C_{13}H_{17}NO_4}$ (251.28): calcd. C 62.14, H 6.82, N 5.57; found C 62.19, H 6.80, N 5.53.

General Procedure for the Conversion of 4a–c to 5a–c: To a stirred solution of **4a**–**c** (0.5 mmol) in $\mathrm{CH_2Cl_2}$ (2.5 mL) at 0 °C, $\mathrm{Et_3N}$

(1.1 equiv., 0.55 mmol) and 3,5-dinitrobenzoyl chloride (1.1 equiv., 0.55 mmol) were added. The solution was stirred for 1 h, and then the mixture was quenched with H_2O. The residue was diluted with CH_2Cl_2 (5 mL), and the biphasic mixture was washed with H_2O (2 × 5 mL). The organic layer was dried with Na_2SO_4, and the solvent was removed under reduced pressure. Compounds **5a–c** were purified by flash chromatography with silica gel (cyclohexane/ethyl acetate, 85:15).

5a: Yield 80%, white solid; m.p. 148–152 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.07 (d, J = 6.6 Hz, 6 H, CH_3CHCH_3), 1.34 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.65 (s, 3 H, $OCCH_3$), 2.05–2.16 (m, 1 H, CH_3CHCH_3) 3.16 (d, J = 6.9 Hz, 1 H, $HCCO_2$), 4.29 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.94 (t, J = 6.9 Hz, 1 H, NC*H*), 8.97 (s, 2 H, *Ph*), 9.14 (s, 1 H, *Ph*) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.0 (CH_3), 18.2 (CH_3), 18.7 (CH_3), 23.0 (CH_3), 32.4 (CH), 57.7 (CH), 62.2 (CH_2), 65.9 (CH) 106.5 (C), 120.5 (CH), 129.6 (2 CH), 137.6 (C), 148.0 (2 C), 151.0 (C), 169.9 (C) ppm. $C_{17}H_{21}NO_4$ (303.36): calcd. C 49.64, H 5.15, N 10.21; found C 49.55, H 5.13, N 10.26.

5b: Yield 70%, pale yellow solid; m.p. 120–122 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 0.95–1.05 (m, 6 H, $CH_3CHCH_2CH_3$), 1.31 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.37–1.43 (m, 2 H, $CH_3CHCH_2CH_3$), 1.51–1.60 (m, 1 H, $CH_3CHCH_2CH_3$), 1.63 (s, 3 H, $OCCH_3$), 3.15 (d, J = 6.9 Hz, 1 H, $HCCO_2$), 4.26 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 5.03 (q, J = 6.3 Hz, 1 H, NC*H*), 5.84 (br. s, O*H*), 8.93 (s, 2 H, *Ph*), 9.19 (s, 1 H, *Ph*) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 12.9 (CH_3), 14.0 (CH_3), 15.2 (CH_3), 22.7 (CH_3), 25.8 (CH_2), 39.0 (CH), 58.3 (CH), 62.1 (CH_2), 64.6 (CH) 106.5 (C), 120.4 (CH), 129.6 (2 CH), 137.4 (C), 147.9 (2 C), 158.6 (C), 169.4 (C) ppm. $C_{18}H_{23}NO_4$ (317.38): calcd. C 50.82, H 5.45, N 9.88; found C 50.85, H 5.42, N 9.90.

5c: Yield 68%, white solid; m.p. 145–148 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.02–1.31 (m, 6 H, cyclohexyl), 1.29 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.59 (s, 3 H, $OCCH_3$), 1.62–1.85 (m, 5 H, cyclohexyl), 2.14 (d, J = 6.9 Hz, 1 H, $HCCO_2$), 4.24 (q, J = 6.9 Hz, 2 H, OCH_2CH_3), 4.88 (t, J = 6.3 Hz, 1 H, NC*H*), 8.92 (s, 2 H, *Ph*), 9.09 (s, 1 H, *Ph*) ppm. ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.1 (CH_3), 23.0 (CH_3), 25.8 (CH_2), 26.1 (CH_2), 26.9 (CH_2), 28.8 (CH_2), 29.3 (CH_2), 42.2 (CH), 58.0 (CH), 62.3 (CH_2), 65.2 (CH) 106.5 (C), 120.5 (CH), 129.6 (2 CH), 137.6 (C), 148.0 (3 C), 169.9 (C) ppm. $C_{20}H_{25}NO_4$ (343.42): calcd. C 53.21, H 5.58, N 9.31; found C 53.09, H 5.59, N 9.28.

Computational Details: All calculations were carried out with the COBRAMM[18] suite of programs, which was used as an interface between the TURBOMOLE[19] and the GAUSSIAN 03 packages.[20] This approach allowed us to combine the accurate optimisation algorithms implemented in GAUSSIAN 03 and the TURBOMOLE approximated DFT[21] potential. In particular, the use of the "resolution of identity" (RI)[22] and the "multipole accelerated resolution of identity" (MARI)[23] approximations, available in TURBOMOLE for the most common DFT functionals, has proven to speed up the calculation (with a negligible loss of accuracy) by about one order of magnitude relative to non-approximated DFT approaches. In particular, we chose the GAUSSIAN 03 optimisation driver in place of that available in the TURBOMOLE package because of its faster convergence in locating minima (equilibrium structures) and saddle-points (transition states) on the potential energy surface (PES). The efficiency of this optimization algorithm is due to the employment of a redundant internal coordinates system[24] with the powerful BFGS algorithm.[25] The details of the COBRAMM interface have been extensively described in our previous paper.[13] In all computations, we have used the B3LYP DFT functional (referred to in TURBOMOLE as "b3 lyp_Gaussian"[26]) with the "m3" grid size for the density fitting and an SCF convergence criterion of 1×10^{-7}°E_h. A balanced double-ζ split valence (SP) basis set with polarisation functions (P) [referred to in TURBOMOLE as def2-SV(P) basis][27] was adopted to describe the H, C, N, and O atoms, whereas for the Cu atom, a triple-ζ split valence (SP) basis set with polarisation functions (P) (def2 TZVP basis in TURBOMOLE) was employed.[22] The proper use of the RI and MARI approximations required the introduction of an auxiliary basis set.[28] The nature of the various critical points located on the PES was ascertained by numerical frequency calculations on the optimised structures. The standard GAUSSIAN 03 convergence criteria were adopted. All geometry optimizations were carried out in the presence of solvent effects, which were evaluated with the COSMO[29] solvent continuous model approach as implemented in the TURBOMOLE package.[14] The dielectric constant for CH_2Cl_2 (ε = 8.930) and a solvent radius of r = 2.27 Å were used. In both cases an "optimised" radius[24] was assigned to the H, C, N, and O atoms, whereas a "bondii" radius[24] was used for Si and Cu, according to the TURBOMOLE manual.[14]

X-ray Crystallography: The diffraction experiments for **5a** were carried out at room temperature with a Bruker AXS Apex II CCD diffractometer with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). Intensity data were measured over full diffraction spheres with 0.3°-wide ω-scans. The SMART[30] software package was used for collecting frames of data, indexing reflections, and the determination of lattice parameters. The collected frames were then processed for integration with SAINT,[27] and an empirical absorption correction was applied with SADABS.[31] The structures were solved by direct methods (SIR 97)[32] and subsequent Fourier syntheses and refined by full-matrix least-squares calculations on F^2 (SHELXTL)[33] with anisotropic thermal parameters for the non-H atoms. The methyl and aromatic H atoms were placed in calculated positions and refined with idealized geometry, whereas the other H atoms were located in the Fourier map and refined isotropically. CCDC-694159 for **5a** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Colour representation of Figures 1, 4 and 5 of the article; computational details, including Wiberg bond order for the molecules **IntF** and **IntC**, total energy (E), Gibbs energy (G) and optimised geometries of the molecules discussed in the paper.

Acknowledgments

We thank the Ministero dell'Università e della Ricerca (MIUR) (PRIN 2006 prot. n. 2006030449_003), MAE (Italia-Messico) and University of Bologna (Strategic project ID 450) for financial support.

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Received: July 18, 2008