Note

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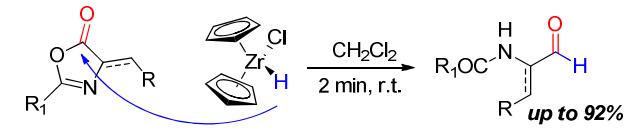
TOC graphics



Abstract

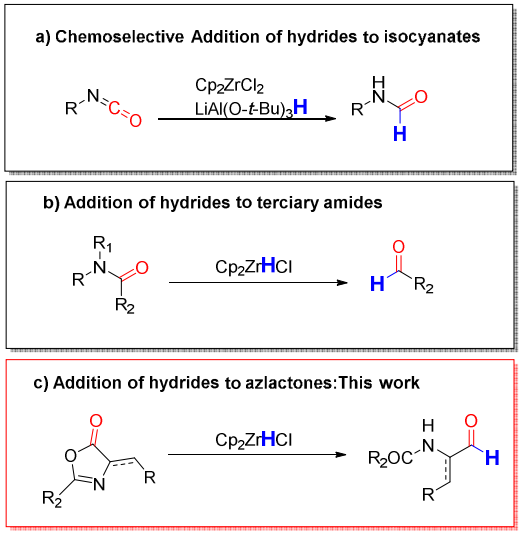
Highly chemoselective addition of Schwartz's reagent to widely available azlactones is described. This method allows the preparation of challenged functionalized α-amino aldehydes, in good to high isolated yields at room temperature, after only two minutes reaction. The presence of sensitive functionalities or electronic factors do not compromise the potential of the method. The use of an excess of the reducing reagent gave a very functionalized allylic alcohol derivative in 86% yield.

Synthesis of non-natural amino acids and their precursors is essential. Peptides built from non-natural amino acids are less prone to degradation and excretion.[1] α-Amino aldehydes are versatile non-natural amino acid precursors which can be transformed into useful 1,2-amino alcohols and other building blocks.[2]

Daoust *et al* showed a new method to synthesize α-nitrogenated γ,δ-unsaturated aldehydes in three-step sequence. The strategy involves two copper coupling reactions and a Claisen rearrangement. The products were obtained with excellent yields and selectivities. However the preparation of α-amino α,β-unsaturated aldehydes is not demonstrated.[3] Synthesis involving those functionalized aldehydes is more scarcer in the literature due the synthetic challenge.

In the present study we demonstrate a practical and selective synthesis of α-amino α,β-unsaturated aldehydes and α-amino aldehydes through the reduction of azlactones[4] using Schwartz´s reagent[5] (Figure 1). Reactions using this zirconocene complex allow the reduction of carbonyl bonds, which represent important tool to prepare various builting blocks. Reduction of nitriles[6], esters, ketones[7], thioketones[8], aldehydes[9], imines, nitro groups, phosphine oxides and sulfides[10], as well as secondary amides[11] are some important transformations in which this reducing agent has been adopted.

Figure 1. Selective reactions using Schwartz´s reagent



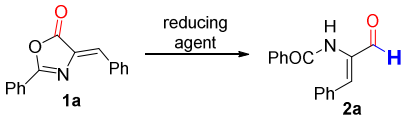
A route to *N*-formamides was developed by Langer *et al* through the highly chemoselective nucleophilic addition of the *in situ* generated Schwartz's reagent to reduce isocyanates. Products with uniformly high yields, full retention of the steric information and high chemoselectivity were obtained.[12]

An investigation of the hydrozirconation of tertiary amides with the Schwartz reagent also was reported by Georg *et al*. The authors have demonstrated that hydrozirconation is one of the most general method for the formation of aldehydes from amides with the highest functional group tolerance reported.[13]

Therefore, Schwartz's reagent was chose to reduce selectively azlactones to aldehydes. Moreover, this selective reduction of azlactones to aldehydes has not been described in the literature.

We began our investigation using $NaBH_4$ to investigate the selectivity of azlactone core reduction. However, this reagent afforded a mixture of products. To our delight, the use of Cp_2ZrHCl (1.2 equiv.) in CH_2Cl_2, at room temperature, 2 minutes reaction, the selectivity was dramatically improved (Table 1- entry 2). Nevertheless, the conversion was far away from optimal, even in the presence of different solvents, temperatures, concentration or longer reaction times (Table 1- entries 4, 5 and 6). Further improvement could be observed by carried out the reaction using 2 equiv. of Cp_2ZrHCl in CH_2Cl_2 (Table 1- entry 8). Concentration at 0.2 mol L^{-1} gave the highest level of conversion (Table 1- entry 13).

Table 1. Reduction of azlactones to aldehydes: optimization

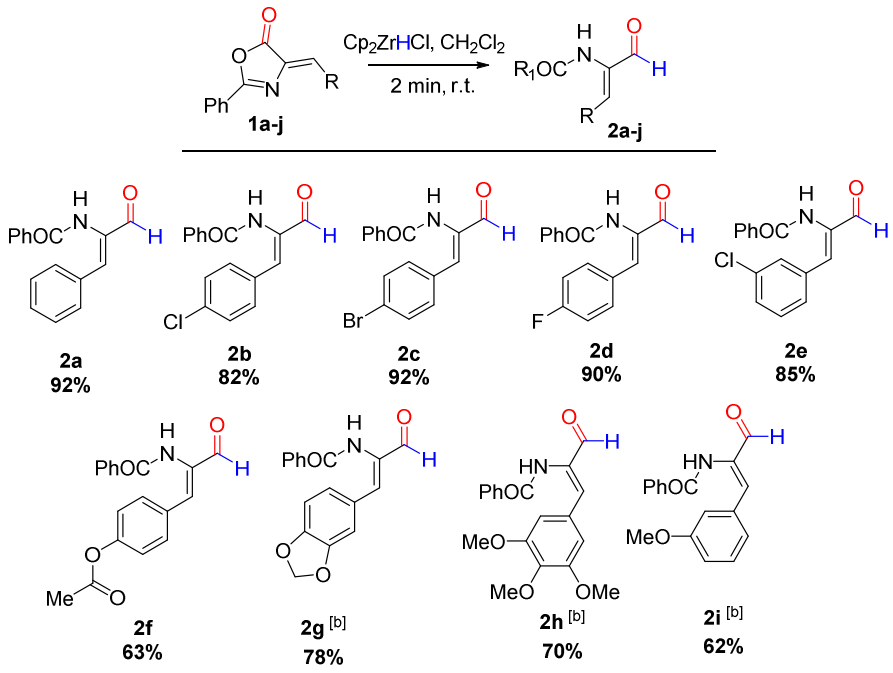


Entry	Reducing agent (equiv.)	Solvent	Conc. (mol L^{-1})	Temp. (°C)/time (min)	Conversion (%)[a]
1	$NaBH_4$ (1.0)	THF	0.1	0/30	Mix of products
2	Cp_2ZrHCl[b] (1.2)	CH_2Cl_2	0.1	r.t./2	55
3	Cp_2ZrHCl (1.2)	CH_3CN	0.1	r.t./120	4
4	Cp_2ZrHCl (1.2)	CH_3CN	0.1	60/120	5
5	Cp_2ZrHCl (1.2)	THF	0.1	60/120	16
6	Cp_2ZrHCl (1.2)	CH_2Cl_2	0.3	r.t./2	71
7	Cp_2ZrHCl (1.2)	MeOH	0.2	r.t./10	1
8	Cp_2ZrHCl (2.0)	CH_2Cl_2	0.1	r.t./2	83
9	Cp_2ZrHCl (2.0)	CH_2Cl_2	0.1	0/2	79
10	Cp_2ZrHCl (2.0)	CH_2Cl_2	0.1	r.t./60	86
11	Cp_2ZrHCl (2.0)	CH_3CN	0.1	r.t./120	7
12	Cp_2ZrHCl (2.0)	THF	0.1	60/120	18
13	Cp_2ZrHCl (2.0)	CH_2Cl_2	0.2	r.t./2	96
14	Cp_2ZrHCl (2.0)	CH_2Cl_2	0.3	r.t./2	83
15	Cp_2ZrHCl (3.0)	CH_2Cl_2	0.1	r.t./2	86

[a] Measured by ^1H NMR spectroscopy analysis of the crude reaction mixture. [b] Schwartz's reagent

To demonstrate the scope and potential of the method, a serie of different functionalized azlactones were tested (table 2 and 3). Substitution on the aromatic ring does not adversely influence the reaction outcome. Electron-withdrawing functionalities such as both halogens in *para* and *meta* position gave the corresponding products (**2b**, **2c**, **2d** and **2e**) with high yield. Acetoxy substituent also was able to be used to obtain aldehyde (**2f**) in 63% yield. Electron-donating groups such as piperonal derivatives (**2g** and **2h**) tolerated the reaction condition, affording products with 78% and 70% yield. The use of methoxy in *meta* position was possible and the corresponding product **2i** was isolated in 62% yield. It is important to mention, the stereochemistry *Z* of the double bond is maintained.[14]

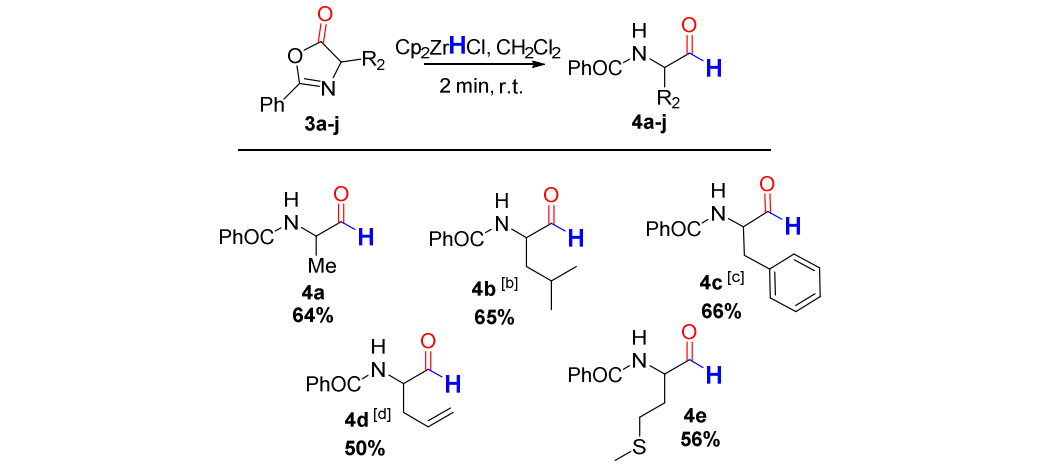
Table 2. Scope of α–amino α,β-unsaturated aldehydes [a]



[a] Reactions were carried out using 0.2 mol L^{-1} solution of **1a-j** in CH_2Cl_2 and 2 equivalents of Cp_2ZrHCl. [b] Reaction time was 8 minutes.

This protocol was also effective when applied to saturated azlactones. Aldehydes derived from simple protected amino acids could be obtained in good yields (Table 3). For example, a very interesting α-amino aldehyde derivative from allylglycine could synthesized in 50% yield. Again, all the corresponding products were obtained with total control of the chemoselectivity.

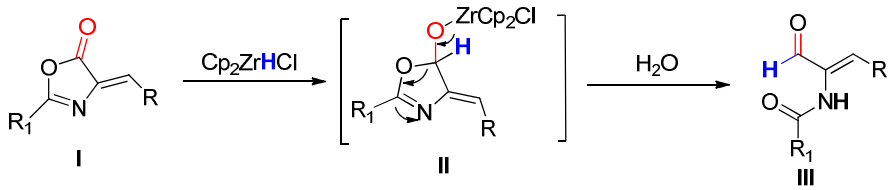
Table 3. Scope of protected α–amino aldehydes[a]



[a] Reactions were carried out using 0.2 mol L^{-1} solution of **3a-j** in CH_2Cl_2 and 2 equivalents of Cp_2ZrHCl. [b] Concentration of 0.1 mol L^{-1}. [c] Concentration of 0.1 mol L^{-1} and 6 minutes of reaction. [d] 3 equivalents of Cp_2ZrHCl used.

A plausible mechanism was also proposed. The presence of a seemingly stable intermediate is evident in this reaction, since the optimized reduction condition did not provide the alcohol. Aldehydes are known compounds for reduction by Schwartz's reagent and any aldehyde formed before the work up was prospective to be reduced to alcohol.[13] This observation led to our working hypothesis, which the azlactone ring could be incorporated by the zirconium reagent to form an sp^3-hybridized, 18-electron complexe (Scheme 1--intermediate II). Presence of water would then react with II and release the product III.[13]

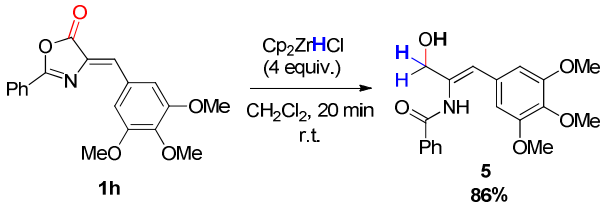
Scheme 1. Mechanism proposal for azlactone reduction using Schwartz's reagent.



The following reactions were carried out to demonstrate the versatile of this method. First, the addition of 4 equivalents of Schwartz's reagent to

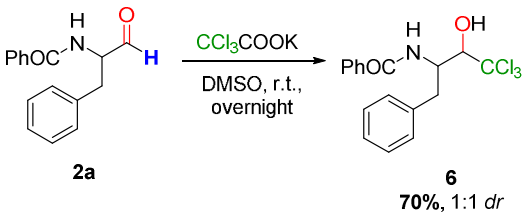
azlactone **1i**, gave a very interesting allylic alcohol **5** in 86% yield (Scheme 2). It is important to mention the corresponding highly chemoselective additions in the carbonyl groups to both azlactone and in the forming aldehyde intermediate.

Scheme 2. Reduction of azlactone 1i to allylic alcohol 5.



We then prepared a trichloromethyl carbinol derivative, which is generally used to render α-substituted carboxylic acid derivatives.[15] The reaction of **2a** with potassium trichloroacetate salt in DMSO, provided a product **6** in 70% yield as a mixture of diastereomers (Scheme 3).

Scheme 3. Synthesis of trichloromethyl carbinol derivative 6.



In summary, a route to α-amino aldehydes through the highly chemoselective nucleophilic addition of Schwartz's reagent to widely available azlactones has been developed. Under the optimized reaction condition the corresponding protected α-amino aldehydes were isolated in good to high yields. Besides, the *Z* stereochemistry of the double bond were maintained. For the first time, the use of Schwartz reagent to selectively reduce azlactones to aldehydes was demonstrated. We also demonstrated the preparation of a allylic alcohol by using excess of Schwartz reagent. Finally, a new C-C bond formation was also possible by addition of trichloromethyl group into to one of those

aldehydes. The corresponding trichloromethyl carbinol derivative was synthetized in 70% yield.

Experimental Section

1. General information

Unless otherwise noted, all reagents were obtained commercially and used without further purification. Unless otherwise noted, all reaction mixtures were carried out in flame-dried flask under a positive pressure of dry nitrogen. Analytical thin layer chromatography (TLC) was performed on precoated glass-backed TLC plates (silica gel 60 F254) and visualized by UV lamp (254 nm). Yields refer to chromatographically purified or by recrystallization and spectroscopically pure compounds, unless stated otherwise. ^{1}H and ^{13}C spectra were recorded on a 500 MHz spectrometer. Chemical shifts are reported in ppm. ^{1}H NMR spectra were referenced to $CDCl_3$ (7.26 ppm) and ^{13}C NMR spectra were referenced to $CDCl_3$ (77.0 ppm). All ^{13}C spectra were measured with complete proton decoupling. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad; and J, coupling constant in Hz. High-resolution mass spectra were acquired in the positive ion mode using a mass spectrometer equipped with an electrospray ionization source HRMS (ESI-QTOF).

2. General procedure and characterization data for the α,β-unsaturated α-amino aldehydes

To a solution of Erlenmeyer azlactone (0.12 mmol) in dichloromethane (0.6 mL, 0.2 mol L^{-1}) was added the Schwartz reagent (61.7mg, 0.24 mmol, 2 equiv.) at room temperature for 2 min. After reaction completion, the solvent was evaporated under

reduced pressure. The product was obtained after purification through chromatography column (elution: ethyl acetate/ hexanes, 3:1).

(*Z*)-*N*-(3-oxo-1-phenylprop-1-en-2-yl)benzamide. The product **2a** was obtained as a yellow oil (27.7 mg, 92 %). **IR (KBr, cm^{-1})**: 3272, 3059,2923, 2853, 1691, 1653, 1635, 1509, 1478, 1276, 751, 690. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.53 (s, 1H), 8.10 (s, 1H), 7.94-7.92 (m, 2H), 7.61 (tt, 1H, *J* = 7.4 Hz, *J* =1.3 Hz), 7.55-7.51 (m, 4H), 7.41-7.39 (m, 3H), 7.12 (s, 1H). **13C{1H}NMR (125 MHz)** δ: 189.9, 164.7, 139.2, 139.1, 134.1, 133.5, 132.5, 132.4, 130.4, 129.0, 128.5, 127.7. **HRMS (ESI-QTOF) m/z**: [M + Na]+ Calcd for $C_{16}H_{13}NO_2Na$ 274.0844, found 274.0839.

(*Z*)-*N*-(1-(4-chlorophenyl)-3-oxoprop-1-en-2-yl)benzamide. The product **2b** was obtained as a white solid (28.0 mg, 82 %). **IR (KBr, cm^{-1})**: 3380, 2950, 2918, 2851, 1692, 1667, 1587, 1514, 1477, 1274, 1092, 754. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.50 (s, 1H), 8.18 (s, 1H), 7.93 (d, 2H, *J* = 7.4 Hz), 7.64-7.61 (m, 1H), 7.55-7.52 (m, 2H), 7.46-7.44 (m, 2H), 7.38-7.35 (m, 2H), 7.04 (s, 1H). **13C{1H}NMR (125 MHz)** δ: 189.8, 164.5, 137.4, 136.2, 133.3, 132.7, 132.6, 132.4, 131.5, 129.0, 128.8, 127.6. **HRMS (ESI-QTOF) m/z:** [M - H]- Calcd for $C_{16}H_{11}ClNO_2$ 284.0478, found 284.0470.

(*Z*)-*N*-(1-(4-bromophenyl)-3-oxoprop-1-en-2-yl)benzamide. The product **2c** was obtained as a white solid (36.4 mg, 92 %). **IR (KBr, cm^{-1})**: 3271, 3062, 2915, 2851, 1692, 1666, 1636, 1580, 1580, 1510, 1476, 1269, 1169, 754. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.49 (s, 1H), 8.20 (s, 1H), 7.92-7.63 (m, 2H), 7.62 (tt, 1H, *J* =7.4 Hz, *J* = 1.2 Hz), 7.54-7.520 (m, 4H), 7.37-7.35 (m, 2H), 7.01 (s, 1H). **13C{1H}NMR (125 MHz)** δ: 189.8, 164.6, 137.4, 133.3, 133.1, 132.6, 132.5, 131.7, 131.6, 129.0, 127.6, 124.7. **HRMS (ESI-QTOF) m/z**: [M - H]- Calcd for $C_{16}H_{11}BrNO_2$ 327.9973, found 327.9965.

(*Z*)-*N*-(1-(4-fluorophenyl)-3-oxoprop-1-en-2-yl)benzamide. The product **2d** was obtained as a yellow oil (29.1 mg, 90 %). **IR (KBr, cm^{-1})**: 3271, 3072, 2921, 2852, 1688, 1647, 1603, 1505, 1477, 1279, 1234, 1158, 7550.**^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.50 (s, 1H), 8.15 (s, 1H), 7.94-7.92 (m, 2H), 7.62 (tt, 1H, *J* = 7.5 Hz, *J* = 1.5 Hz), 7.55-7.51 (m, 4H), 7.10-7.07 (m, 3H). **13C{1H}NMR (125 MHz)** δ: 189.8, 164.5, 163.3 (d, 1F, *J* = 270.3 Hz), 138.0, 133.4, 132.6 (d, 1F, *J* = 9.0 Hz), 132.0, 130.4 (d, 1F, *J* = 3.4 Hz), 128.9, 127.6, 115.7 (d, 1F, *J* = 21.8 Hz). **HRMS (ESI-QTOF) m/z**: [M - H]- Calcd for $C_{16}H_{11}FNO_2$ 268.0774, found 268.0779.

(*Z*)-*N*-(1-(3-chlorophenyl)-3-oxoprop-1-en-2-yl)benzamide. The product **2e** was obtained as a yellow oil (29.1 mg, 85%). **IR (KBr, cm^{-1})**: 3280, 3065, 3007, 2988, 2916, 1849, 1674, 1654, 1638, 1601, 1508, 1478, 1276, 749. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.51 (s, 1H), 8.18 (s, 1H), 7.92-7.90 (m, 2H), 7.61 (tt, 1H, *J* = 7.5 Hz, *J* = 1.3 Hz), 7.54-7.50 (m, 3H), 7.40 (dt, 1H, *J* = 7.40 Hz, *J* = 1.4 Hz), 7.36-7.30 (m, 2H), 7.01 (s, 1H). **13C{1H}NMR (125 MHz)** δ: 189.7, 164.6, 136.8, 136.7, 136.0, 134.4, 133.3, 133.0, 132.6, 130.1, 129.6, 128.9, 128.0, 127.6. **HRMS (ESI-QTOF) m/z**: [M - H]- Calcd for $C_{16}H_{11}ClNO_2$ 284.0478, found 248.0477.

(*Z*)-4-(2-benzamido-3-oxoprop-1-en-1-yl)phenyl acetate. The product **2f** was obtained as a yellow oil (23.4 mg, 63 %) **IR (KBr, cm^{-1})**: 3290, 3064, 2958, 2925, 2846, 1768, 1691, 1653, 1600, 1503, 1479, 1277, 1198, 1172, 1011. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.51 (s, 1H), 8.11 (s, 1H), 7.94-7.92 (m, 2H), 7.61 (tt, 1H, *J* = 7.5 Hz, *J* = 1.3 Hz), 7.57-7.52 (m, 4H), 7.16-7.13 (m, 2H), 7.08 (s, 1H), 2.32 (s, 3H). **13C{1H}NMR (125 MHz)** δ: 189.8, 169.0, 164.8, 151.9, 138.0, 133.4, 132.6, 132.3, 131.7, 129.0, 128.9, 127.6, 121.7, 21.2. **HRMS (ESI-QTOF) m/z**: [M - H]- Calcd for $C_{18}H_{14}NO_4$ 308.0923, found 308.0928.

(*Z*)-*N*-(1-(benzo[d][1,3]dioxol-5-yl)-3-oxoprop-1-en-2-yl)benzamide. The product **2g** was obtained as a yellow solid (27.6 mg, 78%) using the general methodology for 8 min. **IR (KBr, cm^{-1})**: 3297, 2954, 2920, 2852, 1687, 1657, 1601, 1510, 1484, 1258, 1038. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.45 (s, 1H), 8.07 (s, 1H), 7.95-7.93 (m, 2H), 7.61 (tt, 1H, *J* = 7.5 Hz, *J* = 1.2 Hz), 7.54-7.51 (m, 2H), 7.11 (dd, 1H, *J* = 8.2 Hz, *J* = 1.6 Hz), 7.05 (d, 1H, *J* = 1.6 Hz), 7.04 (s, 1H), 6.84 (d, 1H, *J* = 8.2 Hz), 6.01 (s, 2H). **13C{1H}NMR (125 MHz)** δ: 189.8, 165.0, 149.7, 147.9, 140.0, 133.5, 132.4, 131.0, 128.9, 128.3, 127.6, 127.0, 109.6, 108.4, 101.6. **HRMS (ESI-QTOF) m/z**: [M + Na]+ Calcd for $C_{17}H_{13}NO_4Na$ 318.0742, found 318.0740.

(*Z*)-*N*-(3-oxo-1-(3,4,5-trimethoxyphenyl)prop-1-en-2-yl)benzamide. The product **2h** was obtained as a yellow oil (31.9 mg, 78%) using the general methodology for 8 min. **IR (KBr, cm^{-1}):** 3297, 3004, 2940, 2835, 1654, 1577, 1503, 1331, 1245, 1124, 1003, 710. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.49 (s, 1H), 8.07 (s, 1H), 7.95-7.93 (m, 2H), 7.60 (tt, 1H, *J* = 7.8 Hz, *J* = 1.2 Hz), 7.53-7.50 (m, 2H), 7.06 (s, 1H), 6.83 (s, 2H), 3.90 (s, 3H), 3.73 (s, 6H). **13C{1H}NMR (125 MHz)** δ: 189.8, 165.0, 152.9, 140.1, 140.0,

133.4, 132.6, 129.1, 129.0, 127.5, 108.0, 60.9, 56.0. **HRMS (ESI-QTOF) m/z**: [M - H]- Calcd for $C_{19}H_{18}NO_5$ 340.1185, found 340.1187.

(*Z*)-*N*-(3-oxo-1-(3-trimethoxyphenyl)prop-1-en-2-yl)benzamide. The product **2i** was obtained as a yellow oil (20.9 mg, 62%) using the general procedure for 8 min. **IR (KBr, cm^{-1})**: 3366, 3006, 2958, 2919, 2850, 1722, 1652, 1600, 1486, 1277, 1260, 1157, 1041, 764, 745. **^{1}H NMR (500 MHz, $CDCl_3$)** d: 9.52 (s, 1H), 8.08 (s, 1H), 7.94-7.92 (m, 2H), 7.61 (tt, 1H, *J* = 7.4 Hz, *J* = 1.3 Hz), 7.54-7.50 (m, 2H), 7.30 (t, 1H, *J* = 8.0 Hz), 7.16-7.14 (m, 1H), 7.10 (s, 1H), 7.09-7.08 (m, 1H), 6.94 (ddd, 1H, *J* = 8.0 Hz, *J* =2.6 Hz, *J* = 1.0 Hz), 3.73 (s, 3H). **13C{1H}NMR (125 MHz)** δ: 189.9, 164.9, 159.9, 139.1, 135.2, 133.5, 132.6, 132.5, 129.5, 128.9, 127.6, 123.0, 116.6, 115.1, 55.1. **HRMS (ESI-QTOF) m/z**: [M - H]- Calcd for $C_{17}H_{14}NO_3$ 280.0974, found 280.0977.

3. General procedure and characterization data for the α,β-saturated α-amino aldehydes

To a solution of azlactone (0.2 mmol) in dichloromethane (1 mL, 0.2 mol L^{-1}) was added the Schwartz Reagent (102.8 mg, 0.4 mmol, 2 equiv.) for 2 min. After reaction completion, the solvent was evaporated under reduced pressure. The product was obtained after purification through chromatography column (ethyl acetate/ hexanes, 3:1).

(1-oxopropan-2-yl)benzamide. The product **4a** was obtained as a white oil (13.6 mg, 64%). **IR (KBr, cm^{-1})**: 3433, 2988, 2916, 2850, 1653, 1636, 1617, 1276, 1260, 763, 747. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.69 (s, 1H), 7.86-7.84 (m, 2H), 7.58-7.54 (m, 1H), 7.50-7.47 (m, 2H), 6.85 (s, 1H), 4.78 (q, 1H, *J* = 7.4 Hz), 1.54 (d, 3H, *J* = 7.5 Hz). **13C{1H}NMR (125 MHz)** δ: 198.9, 167.1, 133.7, 132.0, 128.8, 128.7, 128.5, 128.1, 127.1. **HRMS (ESI-QTOF) m/z**: [M + H]+ Calcd for $C_{10}H_{12}NO_2$ 178.0868, found 178.0869.[16]

***N*-(4-methyl-1-oxopentan-2-yl)benzamide.** The product **4b** was obtained as a yellow oil (17.1 mg, 65 %) using the general procedure with concentration of 0.1 mol L^{-1} of

azlactone in dichloromethane. **IR (KBr, cm^{-1})**: 3331, 3065, 2955, 2928, 2868, 1725, 1640, 1602, 1580, 1275,762, 751, 712. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.71 (s, 1H), 7.85-7.83 (m, 2H), 7.55 (tt, 1H, *J* = 7.6 Hz, *J* = 1.3 Hz), 7.49-7.46 (m, 2H), 6,68 (s, 1H), 4.85-4.80 (m, 1H), 1.89-1.84 (m, 2H), 1.64-1.56 (m, 1H), 1,04 (d, 3H, *J* = 6.2 Hz), 1.02 (d, 3H, *J* = 6.3 Hz). **13C{1H}NMR (125 MHz)** δ: 199.6, 167.5, 152.9, 133.8, 131.9, 128.7, 127.1, 57.8, 38.2, 25.0, 23.1, 22.2. **HRMS (ESI-QTOF) m/z:** [M - H]- Calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1178.

(1-oxo-3-phenylpropan-2-yl)benzamide. The product **4c** was obtained as a white solid (20.0 mg, 66%) using the general procedure with concentration of 0.1 mol L^{-1} of azlactone in dichloromethane for 6 min. **IR (KBr, cm^{-1})**: 3332, 3058, 3024, 2914, 2830, 1735, 1627, 1538, 1601, 1278, 1253, 752, 694. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.76 (s, 1H), 7.77-7.75 (m, 2H), 7.55 (tt, 1H, *J* = 7.4 Hz, *J* = 1.1 Hz), 7.47-7.44 (m, 2H), 7.35-7.30 (m, 3H), 7.23-7.21 (m, 2H), 6.73 (s, 1H), 4.96 (q, 1H, *J* = 6.8 Hz), 3.37 (dd, 1H, *J* = 14.1 Hz, *J* = 6.8 Hz), 3.30 (dd, 1H, *J* = 14.1 Hz, *J* = 6.8 Hz). **13C{1H}NMR (125 MHz)** δ: 198.8, 167.3, 135.5, 133.6, 132.0, 129.4, 128.9, 128.7, 127.3, 127.0, 60.2, 35.2. **HRMS (ESI-QTOF) m/z:** [M - H]- Calcd for $C_{16}H_{14}NO_2$ 252.1025, found 252.1024.[17]

***N*-(1-oxopent-4-en-2-yl)benzamide-(1-oxopent-4-en-2-yl)benzamide.** The product **4d** was obtained as a white solid (31.9 mg, 78%) using the general procedure in the presence of 3 equiv. of Cp_2ZrHCl. **IR (KBr, cm^{-1})**: 3300, 3068, 2005, 2917, 2849, 1734, 1638, 1533, 1489, 1273, 1260, 765, 748. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.73 (s, 1H), 7.83-7.82 (m, 2H), 7.58-7.55 (m, 1H), 7.50-7.47 (m, 2H), 6.78 (s, 1H), 5.84-5.76 (m, 1H), 5.26-5.22 (m, 2H), 4.83 (q, 1H, *J* = 6.2 Hz), 2.83-2.78 (m, 1H), 2.75-2.70 (m, 1H) **13C{1H}NMR (125 MHz)** δ: 198.9,167.3, 133.7, 132.0, 131.8, 128.7, 127.1, 119.1, 58.3, 33.5. **HRMS (ESI-QTOF) m/z**: [M + H]+ Calcd for $C_{12}H_{14}NO_2$ 204.1025, found 204.1027.

***N*-(4-(methylthio)-1-oxobutan-2-yl)benzamide.** The product **4e** was obtained as a white oil (15.4 mg, 54%). **IR (KBr, cm^{-1})**: 3297, 3005, 2959, 2922, 2851, 1730, 1646, 1646, 1601, 1532, 1275, 1259, 766, 749. **^{1}H NMR (500 MHz, $CDCl_3$)** δ: 9.77 (s, 1H), 7.90-7.86 (m, 2H), 7.59-7.56 (m, 1H), 7.51-7.47 (m, 2H), 7.06 (s, 1H), 4.84 (q, 1H, *J* = 6.2 Hz), 2.72-2.58 (m, 2H), 2.49-2.41 (m, 1H), 2.23-2.18 (m, 1H), 2.14 (s, 3H).

13C{1H}NMR (125 MHz) δ: 198.5, 167.4, 133.4, 132.1, 128.7, 127.1, 58.7, 29.7, 28.4, 15.5. **HRMS (ESI-QTOF) m/z**: [M + H]+ Calcd for $C_{12}H_{16}NO_2S$ 238.0902, found 238.0903.

4. Procedure and characterization data for allylic alcohol

To a solution of Erlenmeyer azlactone (0.12 mmol) in dichloromethane (1.2 mL, 0.1 mol L^{-1}) was added the Schwartz reagent (123.3 mg, 0.48 mmol, 4.0 equiv.). The mixture reaction was stirred until completion of reaction (monitored by TLC) the solvent was evaporated under reduced pressure. The product was obtained after purification through chromatography column (elution: ethyl acetate/ hexanes, 2:1).

(*Z*)-*N*-(3-hydroxy-1-(3,4,5-trimethoxyphenyl)prop-1-en-2-yl)benzamide. The product **5** was obtained as a yellow solid (35.0 mg, 86 %). **IR (KBr, cm^{-1})**: 3410, 3001, 2923, 2849, 1648, 1582, 1508, 1239, 1126, 1001, 712. **^{1}H NMR (500 MHz, $CDCl_3$)** d: 8.37 (s, 1H), 7.76-7.75 (m, 2H), 7.59-7.56 (m, 1H), 7.49-7.46 (m, 2H), 6.57 (s, 2H), 6.03 (s, 1H), 4.76 (t, 1H, *J* = 7.3 Hz), 4.51 (d, 2H, *J* = 7.3 Hz), 3.90 (s, 3H), 3.81 (s, 6H). **13C{1H}NMR (125 MHz)** δ: 165.3, 153.9, 137.5, 136.5, 133.4, 132.5, 130.2, 129.0, 127.0, 116.0, 105.4, 105.3, 64.2, 56.2, 56.1. **HRMS (ESI-QTOF) m/z**: [M - H]- Calcd for $C_{19}H_{20}NO_5$ 342.1341, found 342.1338.

5. Procedure and characterization data for the allylic trichloromethyl alcohol

In a round-bottom flask **4c** (15.1 mg, 0.06 mmol) was added DMSO (0.3 mL), potassium trichloroacetate (36.2 mg, 0.18 mmol, 3 equiv.) and then stirred until completion of reaction (monitored by TLC). After completion, the mixture was diluted in dichloromethane (10 mL) and extracted with H_2O (5 x 10 mL). The organic phases

were combined and dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure.

(*Z*)-*N*-(3-hydroxy-1-(3,4,5-trimethoxyphenyl)prop-1-en-2-yl)benzamide. The product **6** was obtained as a mixture of diastereomers as a yellow oil (14.8. mg, 70 %). **IR (KBr, cm^{-1})**: 3439, 3196, 2962, 2920, 2851, 1662, 1459, 1402, 1382, 700. **^{1}H NMR (500 MHz, $CDCl_3$)** d: 7.73-7.71 (m, 2H), 7.60-7.58 (m, 2H), 7.53-7.50 (m, 2H), 7.46-7.40 (m, 5H), 7.35-7.31 (m, 6H), 7.27-7.24 (m, 3H), 6.74 (d, 1H, *J* = 8.2 Hz), 6.40 (d, 1H', *J* = 7.5 Hz), 4.97 (s, 1H), 4.93-4.88 (m, 1H), 4.71-4.66 (m, 2H), 4.58 (s, 1H), 4.20 (s, 1H), 3.45 (dd, 1H *J* = 14.3 Hz, *J* = 3.8 Hz), 3.35 (dd, 1H, *J* = 13.6 Hz, *J* = 6.9 Hz), 3.23 (dd, 1H, *J* = 14.3 Hz, *J* = 10.9 Hz), 3.03 (dd, 1H, *J* = 13.7 Hz, *J* = 8.5 Hz). **13C{1H}NMR (125 MHz):** d: 168.4, 168.0, 138.0, 137.1, 134.1, 133.8, 132.0, 131.9, 129.4, 129.2, 128.8, 128.7, 128.6, 127.1, 127.0, 126.9, 102.1, 101.3, 83.9, 81.2, 55.2, 52.5, 39.2, 34.8.**HRMS (ESI-QTOF) m/z**: [M + H]+ Calcd for $C_{17}H_{17}Cl_3NO_2$ 372.0325, found 372.0324.

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Supporting Information

Copies of 1H and 13C NMR spectra for the final products.

Dedication

This work is dedicated to Professor Ronaldo Aloise Pilli in recognition of his outstanding contributions to Brazilian chemistry.

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