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STEREOSELECTIVE CONJUGATE ADDITION OF METALLATED 2-METHYLPYRIDINE TO FUNCTIONALIZED α,β -UNSATURATED CARBONYL COMPOUNDS

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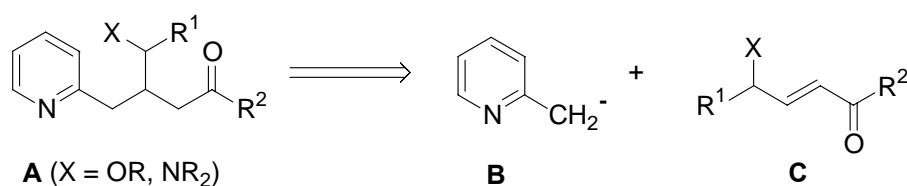
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Abstract – The reaction of *bis*-(2-pyridylmethyl)cyanocuprate (**3**) with a variety of α,β -unsaturated carbonyl compounds is reported. It has been found that while the reaction with enone goes through a 1,2-addition path, the outcome of the reaction with α,β -unsaturated esters depends on the structure of the electrophile, giving the conjugate addition product with γ -hetero-substituted α,β -unsaturated esters. On the other hand, the reaction of **3** with oxygenated butenolides is stereoselective, affording the 1,4-addition product.

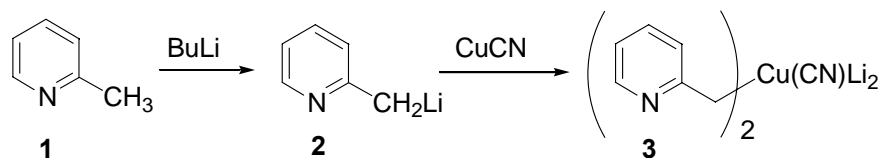
INTRODUCTION

The pyridine ring is an ubiquitous structural features in natural products and biologically-active compounds.¹ In connection with an ongoing project on the synthesis and structure of polyannular heterocycles² and peptide-heterocycle hybrids,³ we have required derivatives of 2-alkylpyridine functionalized at the side chain (such as **A**, Scheme 1). An expeditious access to this kind of compounds might be the conjugate addition of deprotonated 2-methylpyridine (**B**) to α,β -unsaturated carbonyl compounds (**C**).



Scheme 1

Although the deprotonation of 2-methylpyridine (**1**) with *n*-butyllithium to give 2-pyridylmethyl lithium (**2**),⁴ and its transformation to the cognate higher-order cyanocuprate (**3**) are known (Scheme 2);⁵ the conjugate addition of metallated 2-methylpyridine has not been studied.⁶



Scheme 2

In this paper we present our results on the reaction of a variety of α,β -unsaturated compounds with the cyanocuprate (**3**), whose outcome depends on the structure of the electrophilic counterpart.

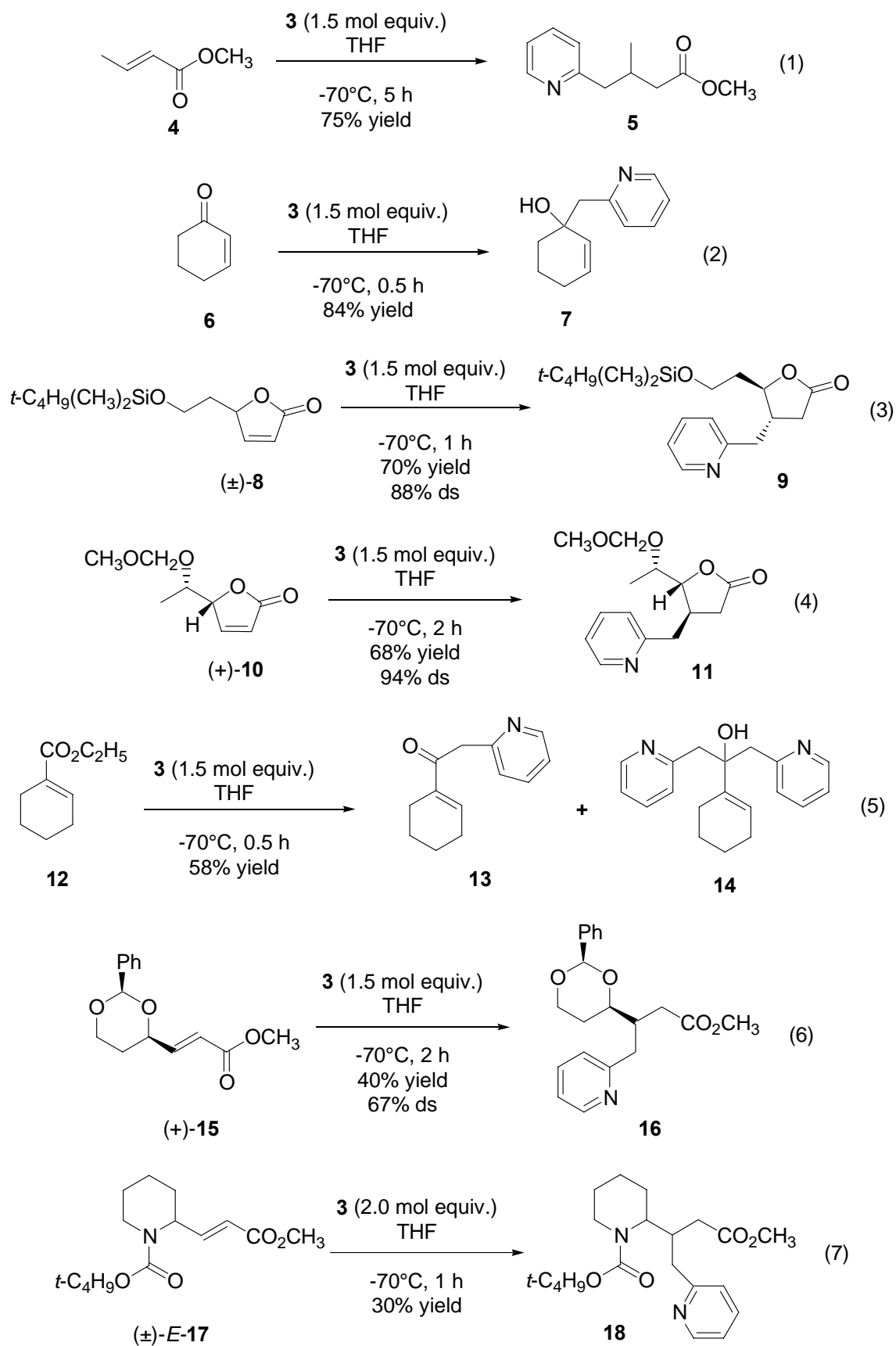
RESULTS AND DISCUSSION

With the aim to find suitable conditions, some experiments were carried out with methyl crotonate (**4**),⁷ finding that the use of 1.5 molar equivalents of **3**, tetrahydrofuran as solvent, and low temperature (-70°C) gave the most satisfactory result in terms of yield, selectivity, velocity, and reproducibility affording the conjugate addition product (**5**) in 75% yield (Scheme 3, eq. 1).

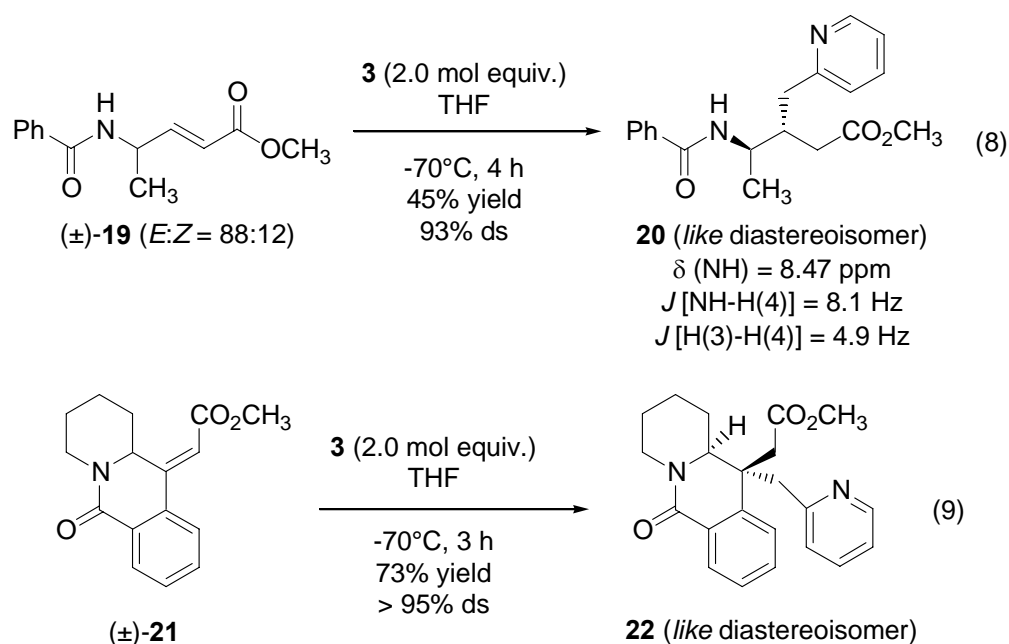
In order to establish the scope of the method, the same experimental procedure was applied to a variety of α,β -unsaturated carbonyl compounds with enone, oxygenated α,β -unsaturated lactone, alkyl substituted α,β -unsaturated ester, γ -alkoxy- α,β -unsaturated ester, and γ -acylamino- α,β -unsaturated ester functionalities. The results are indicated in Scheme 3 (equations 2-9).

The reaction of 2-cyclohexenone (**6**) with the reagent (**3**) resulted in 1,2-addition, giving the tertiary allylic alcohol (**7**) in good yield (84%) (eq. 2). The oxygenated α,β -unsaturated γ -lactones [(\pm)-**8**]⁸ and [(+)-**10**]⁹ afforded the conjugate addition products [(\pm)-**9**] and [(+)-**11**], respectively, in high yields and diastereoselectivities (equations 3 and 4). Analogously to related examples,^{9,10} the stereochemistry of the major product is *trans*.

The reaction of the cyanocuprate (**3**) with ethyl 1-cyclohexenecarboxylate (**12**) went through a 1,2-addition instead of the 1,4-addition giving nearly equimolar amounts of the ketone (**13**) and the tertiary alcohol (**14**) in moderate overall yield (eq. 5). The different reactivity of **4** and **12** with the copper reagent (**3**) seems to indicate a striking dependence on steric factors, although an electronic influence can not be ruled out. On the other hand, the cuprate (**3**) reacted with α,β -unsaturated esters with a heteroatom (N, O) at the γ -position through a 1,4-addition mode exclusively.¹¹ Thus, dioxanyl-substituted acrylate [(+)-**15**]⁸ afforded the conjugate addition product (**16**) as a *ca.* 2:1 inseparable mixture of diastereoisomers (Scheme 3, eq. 6).



Scheme 3



Scheme 3 (continued)

The reaction of the cyanocuprate (**3**) with *N*-substituted γ -amino- α,β -unsaturated esters resulted in diverse yields and stereoselectivities to furnish densely functionalized γ -amino acid derivatives (equations 7-9). The piperidine derivative (**17**)¹² reacted with the cuprate (**3**) to give a 1:1 inseparable mixture of diastereoisomers (**18**) (eq. 7).

On the other hand, the benzamide-substituted unsaturated ester (**19**)¹³ reacted with **3** in a highly stereoselective manner (ratio 14:1 in the crude material, ¹H-NMR spectral evidence), leading to an isomerically pure compound after crystallization (eq. 8). Although the relative configuration of this compound could not be unambiguously established, it has been tentatively assigned *like*-configuration,¹⁴ on basis to the following facts:

1) The NH proton is quite unshielded ($\delta = 8.47$ ppm in diluted CDCl₃ solution), which points out that this proton is engaged in hydrogen bond. This fact has been confirmed by the existence of a band at $\nu = 3315 \text{ cm}^{-1}$ in the IR spectrum. All these data indicate that, at least partly, an intramolecular hydrogen bond exists between the NH and (most likely) the ester carbonyl group, generating a structure that mimics a peptidic γ -turn.¹⁵

2) Using the existence of this intramolecular hydrogen bond as a restriction, we have carried out molecular dynamics simulations on the two possible diastereoisomers.¹⁶ The resulting most stable structures for the *like* and *unlike* isomers are depicted in Figure 1 along with the computed dihedral angles between H-3, H-4, and NH. Since the experimental proton-proton vicinal coupling of the major reaction product of **3** with **19** is $J_{3,4} = 4.9 \text{ Hz}$ and $J_{\text{NH},4} = 8.1 \text{ Hz}$, these data are more compatible with the structure (**20**) than with the structure (**20a**).

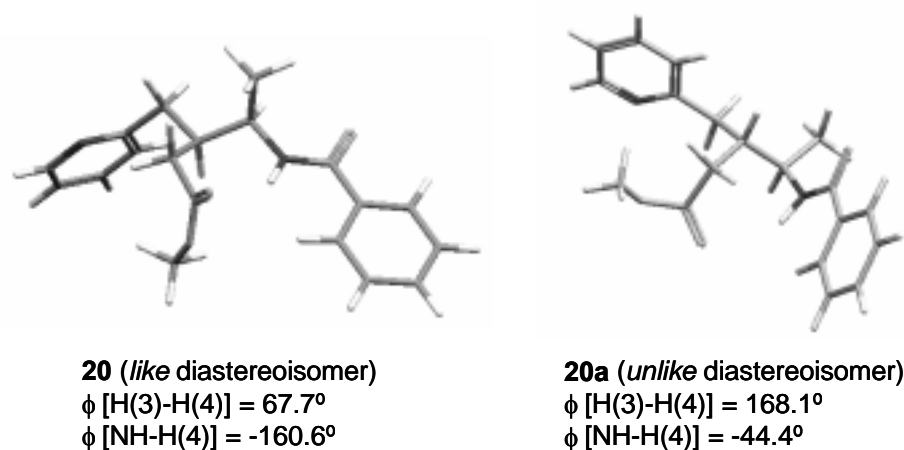


Figure 1. Results of the computational modeling of compounds (**20**) and (**20a**).

The pyrido[1,2-*b*]isoquinoline derivative [(±)-**21**]^{2a} has been previously used as template for the generation of peptide-heterocycle hybrids³ having activity as calpain inhibitors.^{3a} The reaction of the copper reagent (**3**) with the γ -amino- α,β -unsaturated ester (**21**) was totally stereoselective, giving the conjugate addition product (**22**) in 75% isolated yield. The relative stereochemistry of **22** was established by single-crystal X-Ray diffraction (Figure 2),¹⁷ that proves that the nucleophilic addition takes place from the less hindered face of the olefinic double bond.

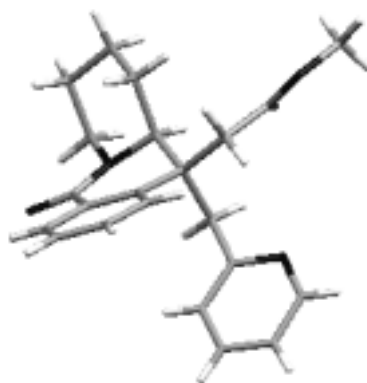


Figure 2. Molecular solid state structure of **22**.

Summarizing, we have reported the first example of conjugate addition of metallated 2-methylpyridine to α,β -unsaturated carbonyl compounds. Although the outcome of the reaction depends on the structure of the electrophile, the method works quite efficiently with amino- and alkoxy-substituted α,β -unsaturated esters and lactones, what constitutes a straightforward method to prepare densely functionalized 2-alkylpyridines (**A**, Scheme 1). Work is in progress to apply compounds (**A**) to the synthesis of polyannular heterocycles and peptide-heterocycle hybrids.

EXPERIMENTAL

All the reactions with sensitive materials were carried out using dry solvents under argon atmosphere. All the solvents and reagents were commercially available and, unless otherwise indicated, were used as received. THF was freshly distilled from sodium-benzophenoneketyl under argon atmosphere. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were measured in Varian-INOVA-300, Varian-GEMINI-200, or Bruker-AM-200; chemical shifts (δ) are reported in ppm, and the coupling constants are indicated in Hz. Unless otherwise indicated, all the NMR spectra were taken at room temperature (*ca.* 295 K). $^1\text{H-NMR}$ spectra were referenced to the chemical shift of either TMS ($\delta = 0.00$ ppm) or the residual proton in the deuterated solvent. $^{13}\text{C-NMR}$ spectra were referenced to the chemical shift of the deuterated solvent. The multiplicity of the signals in the $^{13}\text{C-NMR}$ spectra was determined by APT, DEPT, or HMQC experiments. The IR spectra were measured in a Perkin-Elmer 657 spectrophotometer; the frequencies in the IR spectra are indicated in cm^{-1} . The electron-impact ionization MS were recorded in a RMU-GMG spectrometer (Hitachi-Perkin-Elmer). Combustion analyses were realized in a Carlo Erba EA 1180-Elemental Analyzer. The optical rotations were determined in a Perkin-Elmer 241 MC polarimeter at room temperature (*ca.* 295 K). The melting points were measured on a Kofler hot-stage apparatus and are uncorrected. All the preparative chromatographies were done with silica gel (40-63 μm).

General procedure for the reaction of lithium *bis*-(2-pyridylmethyl)cyanocuprate (3**) with α,β -unsaturated carbonyl compounds.** A 1.5 M solution of n-BuLi in hexane (3.0 to 5.0 molar equiv., depending on the substrate, see Scheme 3) was dropwise added to a stirred solution of 2-methylpyridine (3.0 to 5.0 mol equiv., depending on the substrate, see Scheme 3) in anhydrous THF (5 mL per mmol of 2-methylpyridine) at -70°C , under argon. After the addition, the solution was warmed to 0°C and stirred for 30 min at this temperature. Then, the solution was cooled to -70°C and dropwise added (*via* cannula) to a stirred suspension of CuCN (1.5 to 2.5 mol equiv., depending on the substrate, see Scheme 3) in anhydrous THF (5 mL per mmol of CuCN) at 0°C . After stirring for 30 min at 0°C the mixture was cooled to -70°C and a solution of the corresponding α,β -unsaturated carbonyl compound (1.0 mol equiv.) in anhydrous THF (4 mL per mmol of electrophile) was added *via* cannula. The mixture was stirred until no starting material remained (TLC) and then an aqueous solution of $\text{NH}_3/\text{NH}_4\text{Cl}$ (pH = 8) was added. The aqueous phase was extracted with AcOEt (3 times). The combined organic extracts were washed with $\text{NH}_3/\text{NH}_4\text{Cl}$ solution (pH = 8), H_2O , and saturated aqueous solution of NaCl. Drying over MgSO_4 and solvent evaporation gave crude compounds that were purified by chromatography. The experimental details and the analytical and spectroscopic data for all the compounds are indicated below.

Methyl 3-Methyl-4-(pyridin-2-yl)-butyrate (5**).** Starting from 150 mg (1.44 mmol) of methyl crotonate (**4**), the reaction was carried out for 5 h following the general procedure using 1.5 molar equivalents of **3**, to give compound (**5**) (208 mg, 75%) as a thick oil after chromatography (7:3 hexane/AcOEt). $^1\text{H-NMR}$

(300 MHz, CDCl₃) δ 8.52 (m, 1H, Py-H-6), 7.58 (m, 1H, Py-4), 7.14 (m, 2H, Py-H5, Py-H-3), 3.63 (s, 3H, CH₃OCO), 2.74 (A of ABX system, 1H, $J_{A,B} = 13.3$, H-4a), 2.64 (B of ABX system, 1H, $J_{A,B} = 13.3$, H-4b), 2.46 (X of ABX system, 1H, H-3), 2.33 (A of ABX system, 1H, $J_{2a,2b} = 15.0$, H-2a), 2.14 (B of ABX system, 1H, $J_{2a,2b} = 15.0$, H-2b), 0.92 (d, 3H, $J = 6.6$, CH₃-CH). ¹³C-NMR (75 MHz, CDCl₃) δ 172.8 (s), 160.0 (s), 148.8 (d), 135.8 (d), 123.2 (d), 120.8 (d), 50.9 (q), 44.6 (t), 40.4 (t), 30.8 (d), 19.3 (q). IR (neat) ν 3010, 2960, 2940, 2880, 2850, 1740, 1595, 1575, 1480, 1440, 1370, 1320, 1270, 1210, 1160, 1100, 1050, 1010, 995, 760, 735. MS m/z 193 (M⁺, < 1), 162 (7), 135 (2), 134 (23), 132 (2), 120 (19), 118 (7), 117 (6), 94 (6), 93 (100), 79 (2), 78 (5), 66 (4), 65 (9), 63 (2), 52 (2), 51 (4), 41 (4), 39 (8). Anal. Calcd for C₁₁H₁₅NO₂: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.58; H, 8.05; N, 7.39.

1-(Pyridin-2-ylmethyl)cyclohex-2-enol [(±)-7]. Starting from 200 mg (2.08 mmol) of cyclohex-2-enone (**6**), the reaction was carried out for 0.5 h following the general procedure using 1.5 molar equivalents of **3**, to give the allylic alcohol (**5**) (330 mg, 84%) as a thick oil after chromatography (7:3, hexane/AcOEt). Oil. ¹H-NMR (200 MHz, CDCl₃) δ 8.49 (ddd, 1H, $J = 4.9, 1.7, 0.9$, Py-H-6), 7.61 (ddd, 1H, $J = 7.7, 7.6, 1.9$, Py-H-4), 7.14 (m, 2H, Py-H-3, Py-H-5), 5.75 (m, 2H, OH, H-3), 5.53 (m, 1H, H-2), 2.97 (AB system, 2H, $J_{A,B} = 14.3$, $\Delta\nu = 17$, Py-CH₂-C(OH)), 2.20-1.50 (m, 6H, 2 x H-4, 2 x H-5, 2 x H-6). ¹³C-NMR (50 MHz, CDCl₃) δ 158.9 (s), 147.9 (d), 136.3 (d), 132.2 (d), 128.4 (d), 124.3 (d), 121.1 (d), 69.5 (s), 47.4 (t), 35.8 (t), 24.8 (t), 18.8 (t). IR (neat) ν 3350, 3020, 2940, 2870, 2840, 1595, 1570, 1475, 1440, 1325, 1195, 1100, 1050, 1000, 990, 880, 850, 780, 750, 730, 690. MS m/z 162 (M-27, 19), 149 (12), 146 (14), 130 (10), 126 (15), 112 (13), 106 (18), 97 (29), 93 (100), 83 (23), 81 (21), 72 (60), 69 (38), 59 (87), 57 (37), 55 (64).

trans-5-[2-(tert-Butyldimethylsilyloxy)ethyl]-4-(pyridin-2-ylmethyl)-4,5-dihydro-2(3H)-furanone [(±)-9]. Starting from 174 mg (0.72 mmol) of lactone (**8**), the reaction was carried out for 1 h following the general procedure using 1.5 molar equivalents of **3**, to give a 88:12 mixture of diastereoisomers. The major diastereoisomer (**9**) (169 mg, 70%) was obtained as thick oil after chromatography (1:1, hexane/AcOEt). ¹H-NMR (300 MHz, CDCl₃) δ 8.54 (ddd, 1H, $J = 4.9, 1.9, 1.0$, Py-H-6), 7.62 (td, 1H, $J = 7.5, 1.9$, Py-H-4), 7.16 (dt, 1H, $J = 7.5, 1.0$, Py-H-3), 7.08 (ddd, 1H, $J = 7.5, 4.9, 1.0$, Py-H-5), 4.45 (m, 1H, H-5), 3.74 (dd, 2H, $J = 7.0, 5.0$, CH₂-OSi), 3.03 (A of ABX system, 1H, $J_{A,B} = 13.2$, C4-C(H_aH_b)-Py), 2.85 (B of ABX system, 1H, $J_{A,B} = 13.2$, C4-C(H_aH_b)-Py), 2.80 (X of ABX system, 1H, H-4), 2.63 (A of ABX system, 1H, $J_{3a,3b} = 17.6$, H-3a), 2.37 (B of ABX system, 1H, $J_{3a,3b} = 17.6$, H-3b), 1.79 (m, 2H, CH₂-C5), 0.87 (s, 9H, *t*Bu-Si), 0.04 (s, 3H, CH₃-Si), 0.03 (s, 3H, CH₃-Si). ¹³C-NMR (75 MHz, CDCl₃) δ 176.2 (s), 158.2 (s), 149.5 (d), 136.5 (d), 123.4 (d), 121.7 (d), 81.8 (d), 56.0 (t), 40.7 (d), 40.6 (t), 37.5 (t), 34.6 (t), 25.8 (q, 3C), 18.1 (s), -5.53 (q), -5.50 (q). IR (neat) ν 2960, 2940, 2890, 2860, 1780, 1590, 1570, 1475, 1435, 1260, 1210, 1175, 1095, 840, 780. MS m/z 336 (M⁺ + 1; 2), 320 (10), 279 (27), 278 (100), 248 (8), 186 (9), 174 (5), 160 (3), 158 (9), 155 (8), 150 (3), 146 (3), 144 (5), 130 (6), 118 (6), 101 (3), 93 (21), 75 (12), 73 (5),

65 (2), 59 (4), 57 (2), 55 (2). Anal. Calcd for $C_{18}H_{29}NO_3Si$: C, 64.44; H, 8.71; N, 4.17. Found: C, 64.78; H, 8.70; N, 4.37.

(4R,5R)-5-[(S)-1-Methoxymethoxyethyl]-4-(2-pyridin-2-ylmethyl)-4,5-dihydro-2(3H)-furanone

[(+)-11]. Starting from 160 mg (0.93 mmol) of unsaturated lactone **[(+)-10]**, the reaction was carried out for 2 h following the general procedure using 1.5 molar equivalents of **3**, to give a 94:6 mixture of diastereoisomers. The major isomer **[(+)-11]** (168 mg, 68%) was obtained as thick oil after flash chromatography (6:4 hexane/AcOEt). $[\alpha]_D^{27} = +27^\circ$ ($c = 1$, $CHCl_3$). 1H -NMR (300 MHz, C_6D_6) δ 8.32 (ddd, 1H, $J = 4.7, 1.8, 0.8$, Py-H-6), 7.58 (ddd, 1H, $J = 7.7, 7.6, 1.8$, Py-H-4), 6.52 (ddd, 1H, $J = 7.6, 4.7, 0.5$, Py-H-5), 6.43 (ddd, 1H, $J = 7.7, 0.8, 0.5$, Py-H-3), 4.34 (AB system, 2H, $J_{A,B} = 6.8$, $\Delta\nu = 7.0$, OCH_2O), 3.86 (dd, 1H, $J_{4,5} = 3.3$, $J_{5,1'} = 3.2$, H-5), 3.66 (qd, 1H, $J_{Me,1'} = 6.6$, $J_{5,1'} = 3.2$, H-1'), 3.11 (s, 3H, CH_3O), 2.86 (X of ABX system, 1H, H-4), 2.56 (A of ABX system, 1H, $J_{3a,3b} = 17.7$, H-3a), 2.52 (A of ABX system, 1H, $J_{A,B} = 13.8$, C-4-C(HaHb)-Py), 2.34 (B of ABX system, 1H, $J_{A,B} = 13.8$, C-4-C(HaHb)-Py), 1.96 (B of ABX system, 1H, $J_{3a,3b} = 17.7$, H-3b), 0.72 (d, 3H, $J_{Me,1'} = 6.6$, CH_3-C1'). 1H -NMR (300 MHz, $CDCl_3$) δ 8.54 (ddd, 1H, $J = 4.7, 1.8, 1.0$, Py-H-6), 7.62 (td, 1H, $J = 7.7, 1.8$, Py-H-4), 7.15 (m, 2H, Py-H-5, Py-H-3), 4.60 (AB system, 2H, $J_{A,B} = 6.8$, $\Delta\nu = 19.0$, OCH_2O), 4.25 (dd, 1H, $J_{4,5} = 3.1$, $J_{5,1'} = 3.0$, H-5), 3.94 (qd, 1H, $J_{Me,1'} = 6.4$, $J_{5,1'} = 3.0$, H-1'), 3.32 (s, 3H, CH_3O), 3.08 (X of ABX system, 1H, H-4), 2.95 (AB of ABX system, 2H, $J_{A,B} = 13.5$, C-4- CH_2 -Py), 2.82 (A of ABX system, 1H, $J_{3a,3b} = 17.9$, H-3a), 2.11 (B of ABX system, 1H, $J_{3a,3b} = 17.9$, H-3b), 1.01 (d, 3H, $J_{Me,1'} = 6.4$, CH_3-C1'). ^{13}C -NMR (50 MHz, C_6D_6) δ 175.7 (s), 159.1 (s), 149.7 (d), 135.9 (d), 123.4 (d), 121.4 (d), 95.3 (t), 86.0 (d), 73.9 (d), 55.3 (q), 42.7 (t), 35.0 (t), 34.9 (d), 15.5 (q). ^{13}C -NMR (75 MHz, $CDCl_3$) δ 176.8 (s), 158.2 (s), 149.5 (d), 136.4 (d), 123.5 (d), 121.6 (d), 95.1 (t), 86.4 (d), 73.5 (d), 55.4 (q), 42.5 (t), 34.8 (t), 34.6 (d), 15.3 (q). IR (neat) ν 2980, 2940, 2900, 2830, 1780, 1590, 1570, 1475, 1440, 1380, 1210, 1180, 1150, 1100, 1040, 920, 775, 755. MS m/z 266 ($M^+ + 1$; 1), 250 (4), 220 (4), 204 (10), 203 (8), 176 (48), 148 (23), 146 (7), 130 (5), 122 (11), 118 (41), 106 (5), 94 (11), 93 (100), 89 (4), 78 (7), 65 (12). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.11; H, 7.40; N, 5.37.

1-(Cyclohex-1-enyl)-2-(pyridin-2-yl)ethanone (13) and 2-(cyclohex-1-enyl)-1,3-di(pyridin-2-yl)propan-2-ol (14). Starting from 200 mg (1.42 mmol) of α,β -unsaturated ester **(12)** the reaction was carried out for 0.5 h following the general procedure using 1.5 molar equivalents of **3**, to give **9** (160 mg, 28%) and **10** (250 mg, 30%) after chromatography (6:4 hexane/AcOEt).

1-(Cyclohex-1-enyl)-2-(pyridin-2-yl)ethanone (13). Oil. 1H -NMR (200 MHz, $CDCl_3$) δ 8.52 (ddd, 1H, $J = 4.9, 1.8, 1.0$, Py-H-6), 7.61 (ddd, 1H, $J = 7.7, 7.6, 1.9$, Py-H-4), 7.16 (m, 3H, Py-H-3, Py-H-5, olefinic H), 4.15 (s, 2H, Py- CH_2 -CO), 2.22 (m, 4H), 1.60 (m, 4H). ^{13}C -NMR (50 MHz, $CDCl_3$) δ 197.5 (s), 155.8 (s), 149.1 (d), 144.8 (s), 141.9 (d), 136.2 (d), 123.9 (d), 121.4 (d), 46.7 (t), 26.0 (t), 22.9 (t), 21.6 (t), 21.2 (t). **2-(Cyclohex-1-enyl)-1,3-di(pyridin-2-yl)propan-2-ol (14)**. Oil. 1H -NMR (200 MHz, $CDCl_3$) δ 8.41

(ddd, 2H, $J = 4.9, 1.8, 0.9$, 2 x Py-H-6), 7.54 (ddd, 2H, $J = 7.7, 7.6, 1.9$, 2 x Py-H-4), 7.14 (ddd, 2H, $J = 7.7, 1.2, 0.9$, 2 x Py-H-3), 7.07 (ddd, 2H, $J = 7.6, 4.9, 1.2$, 2 x Py-H-5), 6.47 (br s, 1H, OH), 5.56 (m, 1H, H-2'), 3.04 (AB system, 4H, $J_{A,B} = 14.0$, $\Delta\nu = 14.0$, CH₂-1, CH₂-3), 1.97 (m, 2H), 1.74 (m, 2H), 1.50-1.20 (m, 4H). ¹³C-NMR (50 MHz, CDCl₃) δ 160.0 (s, 2C), 147.8 (d, 2C), 139.7 (s), 135.7 (d, 2C), 124.7 (d, 2C), 121.9 (d), 120.9 (d, 2C), 77.5 (s), 45.9 (t, 2C), 25.2 (t), 24.7 (t), 22.7 (t), 21.9 (t).

(R,S)-Methyl 3-[(2R,4R)-2-phenyl[1,3]dioxan-4-yl]-4-(pyridin-2-yl)butyrate (16). Starting from 200 mg (0.81 mmol) of α,β -unsaturated ester [(+)-**15**] the reaction was carried out for 2 h following the general procedure using 1.5 molar equivalents of **3**, to give an inseparable mixture of isomers (2:1; ¹H-NMR spectral evidence). The isolated yield after flash chromatography (4:1 hexane/AcOEt) was 40% (112 mg). Oil. ¹H-NMR (300 MHz, CDCl₃) δ 8.53 (m, 1H, Py-H-6, **M+m**), 7.58 (m, 1H, Py-H-4, **M+m**), 7.46 (m, 2H, aromatic H, **M+m**), 7.34 (m, 3H, aromatic H, **M+m**), 7.20 (m, 1H, Py-H-3, **M+m**), 7.11 (m, 1H, Py-H-5, **M+m**), 5.48 (s, 1H, H-2', **M**), 5.45 (s, 1H, H-2', **m**), 4.27 (m, 1H, H-4', **M+m**), 3.94 (m, 2H, 2 x H-6', **M+m**), 3.56 (s, 3H, CH₃OCO, **M**), 3.53 (s, 3H, CH₃OCO, **m**), 3.10 (A of ABX system, 1H, $J_{A,B} = 13.4$, C-3-C(HaHb)-Py, **M**), 3.05 (A of ABX system, 1H, $J_{A,B} = 13.2$, C-3-C(HaHb)-Py, **m**), 2.84 (B of ABX system, 1H, $J_{A,B} = 13.4$, C-3-C(HaHb)-Py, **M**), 2.82 (A of ABX system, 1H, $J_{A,B} = 13.2$, C-3-C(HaHb)-Py, **m**), 2.73 (X of ABX system, 1H, H-3, **M+m**), 2.58 (A of ABX system, 1H, $J_{2a,2b} = 16.0$, H-2a, **M**), 2.55 (A of ABX system, 1H, $J_{2a,2b} = 16.1$, H-2a, **m**), 2.43 (B of ABX system, 1H, $J_{2a,2b} = 16.1$, H-2b, **m**), 2.35 (B of ABX system, 1H, $J_{2a,2b} = 16.0$, H-2b, **M**), 1.96 (m, 1H, H-5'a, **M+m**), 1.56 (m, 1H, H-5'b, **M+m**) (**m** = minor epimer; **M** = major epimer). ¹³C-NMR (75 MHz, CDCl₃) δ 173.4 (s, **M**), 173.2 (s, **m**), 160.0 (s, **M**), 159.7 (s, **m**), 149.14 (d, **m**), 149.08 (d, **M**), 138.5 (s, **M+m**), 136.3 (d, **M+m**), 128.6 (d, **M+m**), 128.0 (d, 2C, **M+m**), 125.9 (d, 2C, **M+m**), 123.8 (d, **m**), 123.7 (d, **M**), 121.3 (d, **m**), 121.2 (d, **M**), 101.0 (d, **M+m**), 78.2 (d, **m**), 78.1 (d, **M**), 66.84 (t, **M**), 66.82 (t, **m**), 51.36 (q, **M**), 51.31 (q, **m**), 40.5 (d, **m**), 40.0 (d, **M**), 38.7 (t, **m**), 37.7 (t, **M**), 34.2 (t, **M**), 34.0 (t, **m**), 28.5 (t, **m**), 27.3 (t, **M**) (**m** = minor epimer; **M** = major epimer). Anal. Calcd for C₂₀H₂₃NO₄: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.38; H, 6.58; N, 4.18.

Methyl 3-[1-(tert-butoxycarbonyl)piperidin-2-yl]-4-(pyridin-2-yl)butanoate [(±)-18**]**. Starting from 105 mg (0.39 mmol) of α,β -unsaturated ester (*E*-**17**) the reaction was carried out for 1 h following the general procedure using 2.0 molar equivalents of cuprate (**3**) to give an inseparable 1:1 mixture of stereoisomers (¹H-NMR spectral evidence). The isolated yield after flash chromatography (3:2 hexane/AcOEt) was 30% (43 mg). Thick oil. ¹H-NMR (300 MHz, CDCl₃) δ 8.52 (m, 1H, Py-H-6, **A** and **B**), 7.58 (m, 1H, Py-H-4, **A** and **B**), 7.20-7.06 (m, 2H, Py-H-3, Py-H-5, **A** and **B**), 5.48 (s, 1H, O-CH-O, **M**), 4.20 (m, 1H, H-6'a, **A**), 4.15 (m, 1H, H-6'a, **B**), 3.95 (m, 1H, H-2', **A** and **B**), 3.54 (s, 3H, CH₃OCO, **A**), 3.52 (s, 3H, CH₃OCO, **B**), 3.05-2.60 (m, 4H, H-6'b, H-3, 2 x H-4, **A** and **B**), 2.37 (A of ABX system, 1H, $J_{2a,2b} = 16.0$, H-2a, **A**), 2.27 (d, 1H, $J_{2,3} = 6.0$, 2H-2, **B**), 2.25 (B of ABX system, 1H, $J_{2a,2b} = 16.0$,

H-2b, **A**), 1.75-1.20 (m, 6H, 2H-3', 2H-4', 2H-5', **A** and **B**), 1.46 (s, 9H, *t*-BuOCO, **A**), 1.42 (s, 9H, *t*-BuOCO, **B**) (**A** and **B** stand for each diastereoisomer). ^{13}C -NMR (75 MHz, CDCl_3) δ 173.5 (s, **A**), 172.9 (s, **B**), 160.6 (s, **A**), 159.9 (s, **B**), 155.1 (s, **A** and **B**), 149.29 (d, **B**), 149.26 (d, **A**), 136.2 (d, **B**), 136.1 (d, **A**), 124.1 (d, **A**), 123.9 (d, **B**), 121.3 (d, **B**), 121.1 (d, **A**), 79.3 (s, **A** and **B**), 54.2 (q, **A** and **B**), 51.4 (d, **B**), 51.3 (d, **A**), 40.1 (t, **A** and **B**), 39.4 (t, **A** and **B**), 35.5 (t, **A**), 35.3 (t, **B**), 34.3 (d, **B**), 34.2 (d, **A**), 28.5 (q, 3C, **B**), 28.4 (q, 3C, **A**), 26.3 (t, **B**), 26.2 (t, **A**), 25.4 (t, **A**), 25.3 (t, **B**), 19.0 (t, **A** and **B**) (**A** and **B** stand for each diastereoisomer). IR (neat) ν 2980, 2940, 2870, 1740, 1690, 1590, 1570, 1475, 1435, 1415, 1365, 1315, 1275, 1250, 1160, 1080, 1030, 995, 870, 765. MS m/z 363 ($\text{M}^+ + 1$; 31), 289 (23), 263 (6), 261 (11), 257 (4), 245 (4), 231 (12), 229 (12), 184 (8), 178 (95), 170 (10), 146 (7), 136 (7), 128 (100), 120 (28), 118 (22), 106 (16), 93 (83), 84 (68), 57 (75), 56 (13), 55 (12). Anal. Calcd for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_4$: C, 66.27; H, 8.34; N, 7.37. Found: C, 66.07; H, 8.37; N, 7.57.

Methyl (*R,*R**)-4-(benzoylamino)-3-[(pyridin-2-yl)methyl]pentanoate [(±)-20] (like diastereoisomer).**

Starting from 218 mg (1.61 mmol) of α,β -unsaturated ester (**19**) the reaction was carried out for 4 h following the general procedure using 2.5 molar equivalents of cuprate (**3**) to give a 93:7 mixture (^1H -NMR spectrum) of diastereoisomers in 45% yield (236 mg) after chromatography (1:1 hexane/AcOEt). Crystallization from Et_2O led to isomerically pure compound (**20**). White solid, mp 106-108°C. ^1H -NMR (300 MHz, CDCl_3 , 313 K) δ 8.52 (ddd, 1H, $J = 4.9, 1.7, 0.8$, Py-H-6), 8.47 (br d, 1H, $J = 8.1$, NH), 7.84 (m, 2H, aromatic H), 7.61 (ddd, 1H, $J = 7.7, 7.6, 1.8$, Py-H-4), 7.44 (m, 3H, aromatic H), 7.21 (ddd, 1H, $J = 7.7, 1.1, 0.8$, Py-H-3), 7.14 (ddd, 1H, $J = 7.6, 4.9, 1.1$, Py-H-5), 4.33 (dq, 1H, $J = 8.1, J_{\text{Me},4} = 6.6, J = 4.9$, H-4), 3.62 (s, 3H, CH_3OCO), 3.05 (A of ABX system, 1H, $J_{\text{A,B}} = 14.7$, C-3-C(HaHb)-Py), 3.01 (B of ABX system, 1H, $J_{\text{A,B}} = 14.7$, C-3-C(HaHb)-Py), 2.68 (X of ABX system, 1H, H-3), 2.50 (A of ABX system, 1H, $J_{2a,2b} = 16.2$, H-2a), 2.34 (B of ABX system, 1H, $J_{2a,2b} = 16.2$, H-2b), 1.28 (d, 3H, $J_{\text{Me},4} = 6.6$, CH_3 -C4). ^{13}C -NMR (75 MHz, CDCl_3 , 313 K) δ 173.3 (s), 166.9 (s), 159.8 (s), 148.8 (d), 136.8 (d), 135.1 (s), 131.0 (d), 128.2 (d, 2C), 127.1 (d, 2C), 124.3 (d), 121.5 (d), 51.5 (q), 48.6 (d), 39.8 (d), 38.6 (t), 36.2 (t), 18.9 (q). IR (KBr) ν 3315, 1737, 1631, 1542, 1435, 1203, 1158, 707. MS m/z 327 ($\text{M}^+ + 1$; 11), 311 (1), 295 (4), 206 (8), 192 (2), 179 (31), 120 (48), 105 (67), 93 (100), 77 (70), 65 (8), 51 (21). Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 70.01; H, 6.76; N, 8.50.

Methyl [(*S,*S**)-6-oxo-11-(pyridin-2-yl)methyl-1,3,4,6,11,11a-hexahydro-2H-pyrido[1,2-*b*]-isoquinolin-11-yl]acetate (**22**) (like diastereoisomer).**

Starting from 200 mg (0.74 mmol) of α,β -unsaturated ester (**21**) the reaction was carried out for 3 h following the general procedure using 2.0 molar equivalents of cuprate (**3**) to give a crude product that was purified by chromatography (7:3 hexane/AcOEt) to give **22** (196 mg, 73%). Slow evaporation of the solvent (hexane/AcOEt) afforded crystals suitable for X-Ray diffraction analysis (Figure 2). White solid, mp 151-154°C. ^1H -NMR (500 MHz, CDCl_3) δ 8.46 (ddd, 1H, $J = 4.9, 1.7, 1.0$, Py-H-6), 8.20 (dd, 1H, $J = 7.8, 1.4$, H-7), 7.28 (ddd, 1H, $J = 7.8, 7.6, 0.7$, H-8), 7.20 (td,

1H, $J = 7.6, 1.7$, Py-H-4), 7.13 (ddd, 1H, $J = 7.6, 7.5, 1.4$, H-9), 6.99 (ddd, 1H, $J = 7.6, 4.9, 1.0$, Py-H-5), 6.43 (dd, 1H, $J = 7.5, 0.7$, H-10), 6.12 (dd, 1H, $J = 7.6, 1.0$, Py-H-3), 4.85 (ddd, 1H, $J_{4\alpha,4\beta} = 12.8, 2.3, 1.9$, H-4 α), 4.16 (dd, $J = 10.5, 1.7$, H-11a), 3.77 (s, 3H, CH₃OCO), 3.575 (d, 1H, $J = 12.9$, C-11-C(H_aH_b)-Py), 3.573 (d, 1H, $J = 16.8$, C-11-C(H_aH_b)-CO₂CH₃), 3.31 (d, 1H, $J = 12.9$, C-11-C(H_aH_b)-Py), 2.84 (ddd, 1H, $J_{4\alpha,4\beta} = 12.8, J = 12.2, 2.9$, H-4 β), 2.58 (d, 1H, $J = 16.8$, C-11-C(H_aH_b)-CO₂CH₃), 1.90 (m, 1H, H-2 α), 1.65 (m, 3H, 2H-3, H-2 β), 1.25 (m, 2H, 2H-1). ¹³C-NMR (100 MHz, CDCl₃) δ 171.6 (C=O₂CH₃), 163.0 (C-6), 157.8 (Py-C-2), 148.6 (Py-C-6), 140.9 (C-10a), 135.3 (Py-C-4), 131.1 (C-9), 128.7 (C-7), 127.2 (C-8), 127.0 (C-6a), 124.9 (Py-C-3), 124.8 (C-10), 121.2 (Py-C-5), 64.4 (C-11a), 51.6 (CO₂CH₃), 46.9 (C-4), 45.0 (C-11-CH₂-Py), 42.4 (C-11), 35.3 (C-11-CH₂-CO₂CH₃), 27.4 (C-1), 25.2 (C-3), 25.0 (C-2). IR (KBr) ν 2950, 2930, 2910, 2850, 1740, 1645, 1595, 1570, 1460, 1430, 1410, 1370, 1280, 1255, 1190, 1170, 1150, 1125, 1095, 990, 790, 770, 740, 710, 695. EM m/z 365 (M⁺ + 1; 9), 333 (4), 315 (3), 291 (5), 273 (21), 272 (100), 235 (4), 212 (15), 198 (7), 158 (3), 115 (4), 94 (4), 93 (42), 92 (5), 65 (5), 55 (3). Anal. Calcd for C₂₂H₂₄N₂O₃: C, 72.49; H, 6.64; N, 7.69. Found: C, 72.73; H, 6.65; N, 7.69.

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7. Although both lithium *bis*-(2-pyridylmethyl)cuprate (Gilman reagent) and lithium *bis*-(2-pyridylmethyl)ciano cuprate (**3**) gave the conjugate addition product (**5**) in 60-75% yield, the reaction with cyanocuprate (**3**) gave more reproducible results. Et₂O and THF were used as solvent; the reaction was faster in the latter solvent. The reaction of 2-pyridylmethyllithium (**2**) and methyl crotonate (**4**), both in the presence and the absence of catalytic amounts of CuI or CuCN was studied. In all the experiments, mixtures of 1,2- and 1,4-addition products were obtained. When the reaction of **5** and *bis*-(pyridin-2-ylmethyl)cuprate (Gilman reagent) was carried out in the presence of TMSCl, the main product was 2-[(trimethylsilyl)methyl]pyridine as a relatively volatile compound [¹H-NMR (200 MHz, CDCl₃) δ 8.41 (m, 1H), 7.46 (m, 1H), 6.92 (m, 2H), 2.33 (s, 3H), 0.00 (s, 9H); ¹³C-NMR (50.3 MHz, CDCl₃) δ 161.4 (s), 149.0 (d), 135.7 (d), 122.1 (d), 119.1 (9d), 30.3 (t), -1.7 (q, 3C)]. This compound can be a useful synthetic building block (i.e.; Peterson olefination, "stable" synthetic equivalent of pyridine-2-ylmethyl anion, etc.); for related work, see: N. V. Bac and Y. Langlois, *J. Am. Chem. Soc.*, 1982, **104**, 7666. Y. Langlois, L. Konopski, N. V. Bac, A. Chiaroni, and C. Riche, *Tetrahedron Lett.*, 1990, **31**, 1865. I. P. Andrews, N. J. Lewis, A. McKillop, and A. S. Wells, *Heterocycles*, 1996, **43**, 1151.
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