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Manganese(III) Acetate and Copper(II) Acetate Promoted Oxidation of β-Enaminoamides and β-Enaminoesters.

Janine Cossy*, Abderrahim Bouzide‡

Laboratoire de Chimie Organique associé au CNRS,
ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

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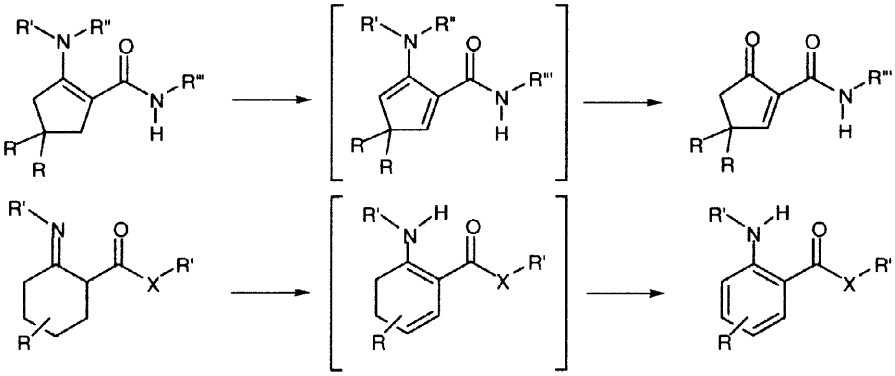
Abstract: Cyclic enamines were oxidized by manganese acetate [$Mn(OAc)_3$] and copper acetate [$Cu(OAc)_2$] to produce α,β-unsaturated imine, azadiene and aniline derivatives depending on the ring size.

The oxidation of β-ketoesters[1] and β-ketoamides[2] by metal salts such as manganese acetate [$Mn(OAc)_3$] generates free radicals. In the presence of olefins, these radicals undergo intermolecular addition or undergo intramolecular cyclization.[3] In the absence of olefins, the oxidation of β-ketoamides and β-ketoesters by $Mn(OAc)_3$, leads to the formation of dimers and oligomers.[4]

In connection with a program directed to the development of conjugate addition, we required a method for the conversion of cyclic β-ketoamides and cyclic β-ketoesters into their corresponding enones. The use of known methods for that purpose failed or gave enones in poor yields.[5] Due to the ionisation potential of enamines[6] and to their oxidation catalyzed by cupric chloride,[7] we were encouraged to oxidize β-enaminoamides and β-enaminoesters with manganese and copper salts. Here, we report that oxidation of 5-membered ring β-enaminoamides with $Mn(OAc)_3$ and $Cu(OAc)_2$ led to the expected enones *via* an imine intermediate. The oxidation of 6-membered ring β-enaminoamides and 6-membered ring β-enaminoesters led to aromatic compounds (Scheme 1).

Scheme 1: Oxidation of β-enaminoamides and β-enaminoesters



X = O, NR
R = Alkyl or H
R' = Alkyl; R" = Alkyl or H; R'" = Alkyl

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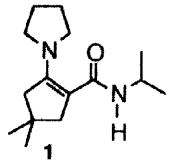
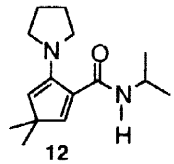
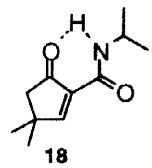
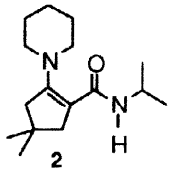
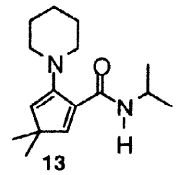
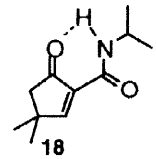
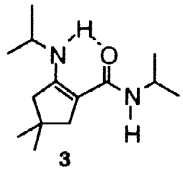
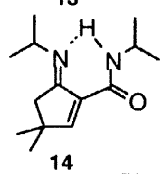
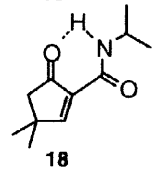
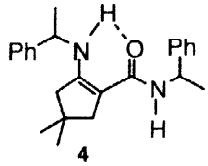
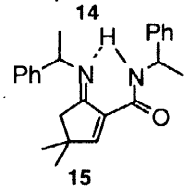
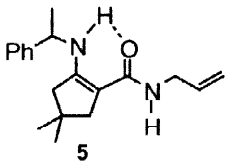
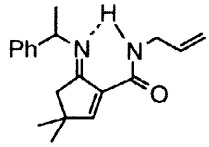
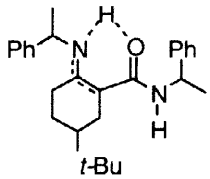
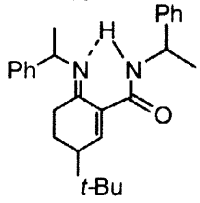
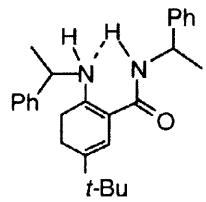
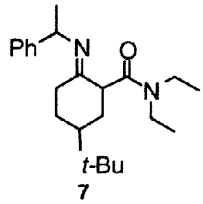
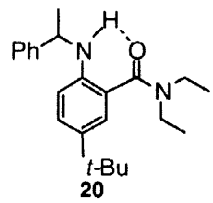
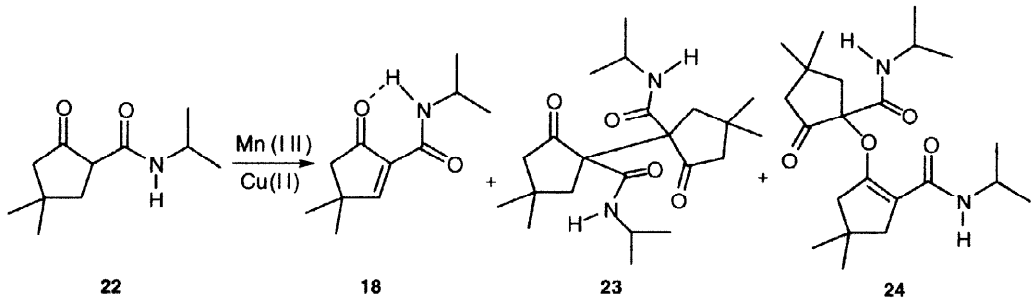
PII: S0040-4020(99)00286-0

Table 1: Oxidation of β-enamino or iminoamides

Enamines or Imines	Intermediates	Enones
 1	 12	 18
 2	 13	 18
 3	 14	 18
 4	 15	
 5	 16	
 6	 17	 19
 7		 20

When an ethanolic solution of enamine **1** was treated with two equivalents of manganese acetate [$Mn(OAc)_3$] for 30 min. at rt, α,β-unsaturated β-ketoamide **18** was isolated after flash chromatography on silica gel in 42% yield (Table 1). The addition of base such as potassium carbonate (K_2CO_3) (1 equiv.) to the reaction mixture increases the yield to 57%. When the reaction was performed in the presence of $Cu(OAc)_2$[8] in refluxing ethanol, enone **18** was obtained in 55% yield and the yield was increased to 65% when the reaction was carried out in the presence of two equivalents of $Mn(OAc)_3$ and one equivalent of $Cu(OAc)_2$. Due to the importance of these synthons in racemic as well as asymmetric conjugate addition, the reaction was extended to other enamines. Treatment of **2** under the same conditions (i.e. Mn(III)/Cu(II): 2 equiv./1 equiv.) led to enone **18** in 59% yield. Intermediates **12** and **13**, resulting respectively from the oxidation of **1** and **2**, were detected by ^1H NMR spectra in the crude reaction mixture, but could not be isolated despite several attempts to purify the crude on basic alumina. In the case of enamine **3**, treatment with Mn(III)/Cu(II) afforded imine **14** in good yield (73%) after purification by flash chromatography on alumina. Hydrolysis with a 50% aqueous acetic acid solution afforded the corresponding enone **18** in 83% yield. Similarly, the oxidation of chiral enamines **4** and **5** led respectively to imines **15** (86% yield) and **16** (67% yield) after purification by flash chromatography on silica gel. It is worth noting that the direct oxidation of β-ketoamide **22** with Mn(III)/Cu(II) led to the dimeric products **23** (21%) and **24** (37%), and oligomeric materials as well as a trace of **18** (11%) (Scheme 2).

Scheme 2: Oxidation of β-ketoamide **22**



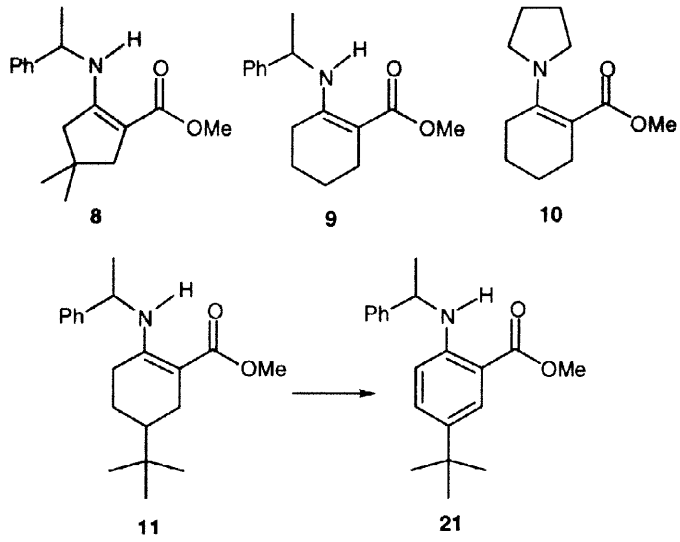
22 **18** **23** **24**

The extension of this oxidative reaction to 6-membered ring β-enaminoamides **6** and **7** was achieved. Treatment of imine/enamine **6** with Mn(III)/Cu(II) (2 equiv./1 equiv.) led, after purification on alumina, to unsaturated imine **17** (72%) accompanied by traces of dienamine **19** (< 5%) (Table 1). When the reaction mixture was purified on silica gel, the dienamine **19** was the only isolated product (77%). It appears that under slightly acidic conditions, imine **17** tautomerizes into dienamine **19**. Finally, the oxidation of β-iminocarboxamide **7**, containing a *N,N*-disubstituted amide with Mn(III)/Cu(II) (2 equiv./ 1 equiv.) afforded only the highly fluorescent aromatic compound **20** in 35% yield while 51% of the unreacted starting material was recovered. To convey the reaction to completion 4 equivalents of $Mn(OAc)_3$ and 1 equivalent of $Cu(OAc)_2$ were necessary to produce **20** in 67% yield.

Contrary to the oxidation of β-enaminoamides, no enone was detected when β-enaminoesters **8**, **9** or **10** were treated with Mn(III)/Cu(II) salts. Only starting materials along with oligomeric products were formed. However, when 6-membered cyclic β-enaminoester **11** was treated with 4 equivalents of

$Mn(OAc)_3$ and 1 equivalent of $Cu(OAc)_2$, the highly fluorescent aromatic compound **21** was isolated in 76% yield (Scheme 3).

Scheme 3: Oxidation of β-enaminoesters



The ^1H NMR spectra analysis of the oxidized compounds **14**, **15**, **16**, **17** and **19** showed that the amide proton (NH) is highly deshielded compared to the amide proton of the starting material **3**, **4**, **5** and **6**. This is probably due to its involvement in strong hydrogen bonding with the imine group (Table 2).

Table 2: Chemical shift of the amide proton (NH)

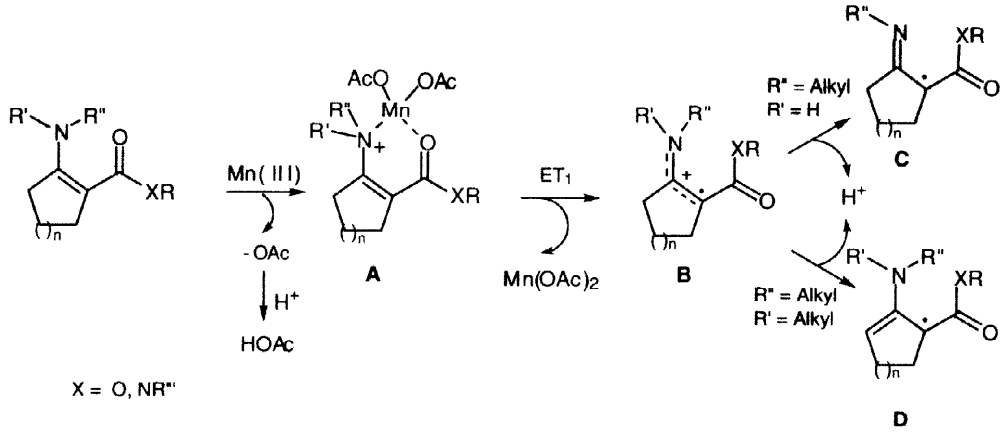
Compounds	δ (ppm) of NH
3	7.8
14	10.0
4	8.2
15	10.5
5	8.3
16	10.0
6	5.4, 10.1 (enamine form)
17	11.35 (imine form)
19	10.4, 13.2 (dienamine form)

The formation of unsaturated imines and aromatic compounds was interpreted in terms of electron transfer between metallic salts and enamines. The first step is the chelation of $Mn(OAc)_3$ with β-enaminoamides and β-enaminoesters to produce complexes of type **A** (Scheme 4).

Electron transfer (ET_1) can occur between Mn(III) and an enamine, to produce a radical cation of type **B** and $Mn(OAc)_2$. Intermediate of type **B** then undergoes deprotonation to generate the free imine-

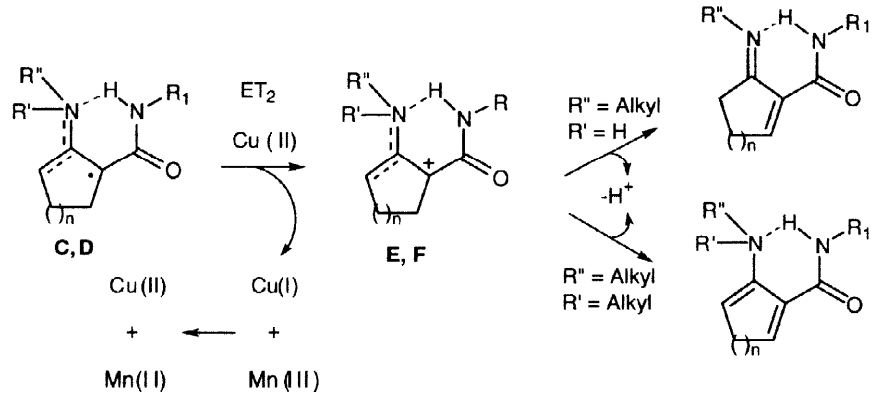
radical **C** or the enamine-radical **D**. We have to point out that acetic acid formed during the process will be neutralized by K_2CO_3. In the case of *N*,*N*-disubstituted amides bearing an unsaturated alkyl group, intermediates **C** and **D** underwent a cyclization reaction.[9, 10] Meanwhile, in the case of unsaturated *N*-substituted amides such as **5**, an intramolecular hydrogen bonding takes place and precludes the addition of the tertiary radical onto the alkene, by restricting the conformation.

Scheme 4: Electron transfer ET_1



In the presence of $Cu(OAc)_2$ or $Mn(OAc)_3$, the oxidation of radical **C** or **D** to the corresponding carbocation **E** or **F**, occurs faster (ET_2) than the hydrogen atom transfer from ethanol.[11] Finally, a deprotonation takes place to give the observed α,β-unsaturated imine or enamine (Scheme 5). During this process, unstable monovalent Cu(OAc) is produced. This species instantly reduces $Mn(OAc)_3$ to $Mn(OAc)_2$ thus regenerating $Cu(OAc)_2$. Therefore, a catalytic amount of $Cu(OAc)_2$, in the presence of an excess of $Mn(OAc)_3$ is sufficient to run the reaction to completion.

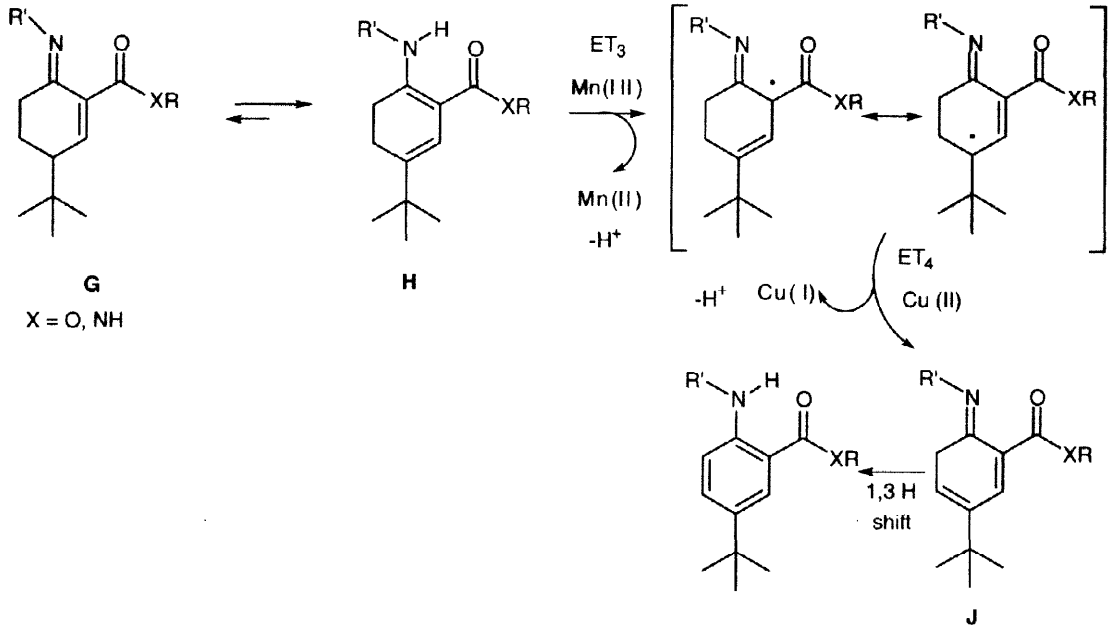
Scheme 5: Electron transfer ET_2



As mentionned earlier, both β-iminoamide **7** and β-enaminoester **11**, were transformed to aromatic compounds even when a stoichiometric amount of the oxidizing agent was used. This result indicates that intermediate α,β-unsaturated imine **G**, which is in equilibrium with enamine **H**, is oxidized faster than the

starting material to afford dienamine **J**, through a two electron-transfer process (ET_3 and ET_4). Intermediate **J** aromatizes easily to produce **20** and **21** (Scheme 6).

Scheme 6: Oxidation of 6-membered ring β-enaminoesters and β-enaminoamides



Our study has revealed that Mn(III)/Cu(II) oxidation of 5-membered ring β-enaminoamides leads easily and efficiently to α,β-unsaturated imine intermediates which are hydrolyzed to their corresponding enones. We have also shown that disubstituted anilines can be obtained efficiently by oxidation of substituted 6-membered ring β-enaminoamides or β-enaminoesters.

Experimental Part

General: All experiments were run under an argon atmosphere. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-300 FT (respectively 300 MHz and 75 MHz) instrument, in $CDCl_3$ (unless otherwise indicated). IR spectra (film) were recorded with a 298 Perkin-Elmer spectrophotometer. Mass spectra were run on a GC-MS device and were obtained on a 5971 Hewlett Packard instrument at 70 eV. Microanalyses and HRMS were performed at the service de Microanalyses de l'Université Pierre et Marie Curie. Flash chromatographies were carried on Merck silica gel 60 (230-400 mesh) with petroleum ether (PE) and ethyl acetate (AcOEt). Chromatographies on alumina were performed on alumina 507 C neutral (100-125 mesh).

Synthesis of β-enaminoamides and β-enaminoester

To a solution of β-ketoamide[12] or β-ketoester (10 mmol, 1 equiv.) in toluene (50 mL) was added the amine [for secondary amines (30 mmol, 3 equiv.), for primary amines (13 mmol, 1.3 equiv.)] and activated molecular sieves 3 Å (3 g). After 2 days at rt, the reaction mixture was filtered through Celite.

The solvent and the excess amine were evaporated *in vacuo*. β-Enaminoamides and β-enaminoesters were obtained in quantitative yield.

N-*Isopropyl-4,4-dimethyl-2-pyrrolidinocyclopent-1-enecarboxamide* **1**
IR: 3400; 1620; 1550; 1200 cm^{-1}.
^1H NMR (C_6D_6): δ 1.11 (s, 6H); 1.14 (d, J = 6.5 Hz, 6H); 1.80 (m, 4H); 2.37 (s, 2H); 2.42 (s, 2H); 3.35 (m, 4H); 4.10 (m, 1H); 4.90 (d, J = 7.1 Hz, 1H).
^{13}C NMR (C_6D_6): δ 23.2 (2q); 25.6 (2t); 29.9 (2t); 34.6 (s); 40.7 (d); 48.2 (t); 50.2 (t); 51.2 (2t); 94.8 (s); 137.8 (s); 153.3 (s).
MS: $C_{15}H_{26}N_2O$ *m/z* 251 (M+1, 10); 197 (5); 180 (100); 164 (7); 152 (10); 138 (7); 110 (20); 96 (20); 70 (10).
HRMS calc for $C_{15}H_{26}N_2O$ 250.2045. Found: 250. 2050.

N-*Isopropyl-4,4-dimethyl-2-piperidinocyclopent-1-enecarboxamide* **2**
IR: 3400, 1615, 1535 cm^{-1}.
^1H NMR (C_6D_6): δ 1.15 (s, 6H); 1.18 (d, J = 6.5 Hz, 6H); 1.50-1.80 (m, 6H); 2.51 (s, 2H); 3.40 (m, 4H), 4.20 (m, 1H), 5.00 (d, J = 7.1 Hz, 1H).
HRMS calc for $C_{16}H_{28}N_2O$ 264. 2201. Found: 264. 2214.

N-*Isopropyl-4,4-dimethyl-2-(isopropylamino)cyclopent-1-enecarboxamide* **3**
IR: 3700; 3100; 1735; 1640; 1525; 1450; 1360; 1230 cm^{-1}.
^1H NMR: δ 1.15 (m, 18H); 2.20 (s, 2H); 2.38 (m, 2H); 3.43 (m, 1H); 4.10 (m, 1H); 4.60 (d, J = 7.1 Hz, 1H); 7.80 (d, J = 8.7 Hz, 1H).
^{13}C NMR: δ 23.3 (2q); 24.5 (2q); 29.8 (2q); 35.6 (s); 40.2 (d); 44.2 (t); 45.8 (d); 46.3 (t); 92.2 (s); 159.0 (s); 168.5 (s).
MS: $C_{14}H_{26}N_2O$ *m/z* 238 (M^+, 16); 195 (35); 180 (100); 137 (42).
HRMS calc for $C_{14}H_{26}N_2O$ 238.2045. Found 238. 2043.

4,4-Dimethyl-N-*(1-Phenylethyl)-2-[(1-phenylethyl)amino]cyclopent-1-enecarboxamide* **4**
Rf: 0.52 (PE/AcOEt: 70/30).
IR: 3300; 1620; 1580; 1500; 1440; 1425; 1260; 1210 cm^{-1}.
^1H NMR: δ 0.90 (s, 3H); 1.08 (s, 3H); 1.46 (d, J = 7.0 Hz, 3H); 1.51 (d, J = 7.0 Hz, 3H); 2.00 (d, J = 16.3 Hz, 1H); 2.20 (d, J = 5.0 Hz, 2H); 2.31 (d, J = 16.3 Hz, 1H); 4.43 (m, 1H); 5.02 (d, J = 7.7 Hz, 1H (NH)); 5.20 (m, 1H); 7.17 - 7.37 (m, 10H); 8.25 (d, J = 8.0 Hz, 1H (NH)).
^{13}C NMR: δ 22.7 (q); 25.1 (q); 29.6 (q); 35.8 (s); 44.3 (t); 46.6 (t); 47.7 (t); 54.1 (d); 93.5 (s); 125.0 (4d); 126.1 (2d); 126.8 (d); 127.0 (d); 128.5 (d); 128.6 (d); 144.4 (s); 145.8 (s); 159.8 (s); 168.2 (s).
MS: $C_{24}H_{30}N_2O$ *m/z* 362 (M^+, 30); 347 (10); 257 (10); 240 (70); 226 (30); 215 (30); 200 (15); 156 (20); 138 (70); 105 (100); 79 (20).
Anal. Calc. for $C_{24}H_{30}N_2O$ C, 79.52; H, 8.34; N, 7.73. Found: C, 79.66; H, 8.42; N, 7.65.

N-*Allyl-2-[(1-phenylethyl)amino]cyclopent-1-enecarboxamide* **5**

IR: 3300; 1625; 1580; 1510; 1430; 1275; 920 cm^{-1}.

^1H NMR: δ 0.91 (s, 3H); 1.08 (s, 3H); 1.47 (d, J = 7.0 Hz, 3H); 2.00 (d, J = 16.4 Hz, 1H); 2.20 (d, J = 2.7 Hz, 2H); 2.32 (d, J = 16.4 Hz, 1H); 3.90 - 4.00 (m, 2H); 4.45 (m, 1H); 4.90 (s1, 1H); 5.10 - 5.25 (m, 2H); 5.83 - 5.96 (m, 1H); 7.20 - 7.35 (m, 5H); 8.30 (d, J = 8.0 Hz, 1H).

^{13}C NMR: δ 24.9 (q); 29.4 (q); 29.6 (q); 35.8 (t); 41.1 (t); 40.0 (t); 46.4 (s); 53.9 (d); 93.3 (d); 115.5 (t); 125.4 (2d); 126.6 (d); 128.4 (2d); 135.4 (d); 145.7 (s); 159.8 (s); 168.8 (s).

MS: $C_{19}H_{26}N_2O$ *m/z* 298 (M^+, 30); 283 (20); 242 (70); 226 (40); 214 (20); 193 (20); 179 (20); 161 (15); 138 (100); 105 (90); 91 (10); 79 (20).

5-tert-*Butyl*-N-*(1-phenylethyl)-2-[(1-phenylethyl)amino]cyclohex-1-enecarboxamide* **6**

Compound **6** is constituted by a mixture of enamine/imine in a ratio 66/33 (determined by ^1H NMR).

For both forms:

IR: 3300 (large); 1715; 1635; 1525; 1450; 1360; 1220 cm^{-1}.

MS: $C_{27}H_{36}N_2O$ *m/z* 404 (M^+, 7); 299 (10); 283 (5); 257 (5); 242 (20); 208 (5); 170 (10); 147 (15); 132 (20); 105 (100); 77 (10).

HRMS calc for $C_{27}H_{36}N_2O$ 298. 2045. Found 298. 2061.

Enamine form:

^1H NMR: δ 0.85 (s, 9H); 1.00-1.40 (m, 2H); 1.47 (d, J = 6.8 Hz, 3H); 1.53 (d, J = 6.8 Hz, 3H); 1.60-2.50 (m, 5H); 4.60 (m, 1H); 5.30 (m, 1H); 5.45 (s, 1H); 7.10-7.40 (m, 10H); 10.10 (s, 1H).

^{13}C NMR: δ 22.5 (q); 23.2 (t); 25.5 (q); 25.7 (t); 27.2 (3q); 27.8 (t); 32.2 (s); 43.8 (d); 47.8 (d); 52.1 (d); 90.6 (s); 125.5 (d); 125.6 (2d); 126.5 (d); 126.8 (d); 126.9 (2d); 128.5 (3d); 144.5 (s); 146.5 (s); 156.6 (s); 170.8 (s)

Imine form:

^1H NMR: δ 0.84 (s, 9H); 1.43 (d, J = 6.8 Hz, 3H); 1.50 (d, J = 6.8 Hz, 3H); 1.60 - 2.60 (m, 8H); 4.10 (q, J = 6.9 Hz, 1H); 5.30 (m, 1H); 5.45 (s, 1H); 7.10-7.40 (m, 10H).

^{13}C NMR: δ 22.7 (q); 23.2 (t); 25.4 (q); 25.7 (t); 27.2 (3q); 27.8 (t); 32.2 (s); 43.8 (d); 44.3 (d); 47.9 (d); 52.3 (d); 125.5 (2d); 126.5 (2d); 126.9 (2d); 128.6 (4d); 144.5 (3s); 146.5; 156.6 (s); 170.8 (s).

5-tert-*Butyl*-N,N-*diethyl-2[(1-phenylethyl)imino]cyclohexanecarboxamide* **7**

Exists only in the imine form

^1H NMR: δ 0.80 (s, 9H); 1.02 (m, 6H); 1.22 (d, J = 6.8 Hz, 3H); 1.30-1.70 (m, 3H); 1.80-2.30 (m, 3H); 2.95-3.05 (m, 2H); 3.10-3.25 (m, 2H); 3.30-3.45 (m, 2H); 3.95 (q, J = 6.7 Hz, 1H); 7.05-7.25 (m, 5H).

^{13}C NMR: δ 12.8 (q); 14.5 (q); 27.6 (q); 27.5 (3q); 27.6 (t); 31.3 (t); 32.5 (s); 40.2 (t); 41.4 (t); 41.8 (t); 46.0 (d); 51.2 (d); 53.7 (d); 125.4 (2d); 126.6 (d); 128.3 (2d); 147.2 (s); 168.7 (s); 178.3 (s).

Methyl 4,4-dimethyl-2-[(1-phenylethyl)amino]cyclopent-1-enecarboxylate **8**

R_f: 0.65 (PE/AcOEt: 90/10).

IR: 3300; 1650; 1450; 1280; 1240; 1210; 1180; 1110 cm^{-1}.

^{1}H NMR: δ 0.92 (s, 3H); 1.70 (s, 3H); 1.50 (d, J = 6.9 Hz, 3H); 2.03 (d, J = 17.0 Hz, 1H); 2.30 (s, 2H); 2.35 (d, J = 6.0 Hz, 1H); 3.70 (s, 3H); 4.50 (m, 1H); 7.20-7.37 (m, 5H); 7.80 (s, 1H).
^{13}C NMR: δ 25.30 (q); 29.6 (q); 29.9 (q); 36.2 (s); 44.2(t); 47.1 (t); 50.6 (q); 54.6 (d); 92.6 (s); 125.9 (2d); 127.40 (d); 129.1 (2d); 145.6 (s); 163.8 (s); 169.5 (s).
MS: $C_{17}H_{23}NO_2$ *m/z* 273 (M^+, 40); 258 (24); 240 (7); 226 (40); 214 (10); 169 (20); 154 (23); 138 (17); 105 (100); 91 (10).
HRMS calc for $C_{17}H_{23}NO_2$ 273. 1787. Found: 273. 1794.

Methyl 2-[(1-phenylethyl)amino]cyclohex-1-enecarboxylate ***9***
IR (NaCl, film): 3260; 2920; 1640; 1595 cm^{-1}.
^{1}H NMR: δ 9.63 (s, 1H); 7.45-7.20 (m, 5H); 4.40 (d, J = 6.2 Hz, 2H); 4.15 (q, J = 6.7 Hz, 2H); 2.35-2.20 (m, 4H); 1.68 - 1.49 (m, 4H); 1.28 (t, J = 7.2 Hz, 3H).
^{13}C NMR: δ 170.7 (s); 159.2 (s); 139.5 (s); 128.5 (2d); 126.9 (d); 126.6 (2d); 90.5 (s); 58,5 (t); 45.9 (t); 26.1 (t); 23.7 (t); 22.6 (t); 22.2 (t); 14.5 (q).
MS: *m/z* 259 (M^+, 61); 230 (21); 212 (48); 186 (43); 91 (100).
HRMS calc for $C_{16}H_{21}NO_2$ 259. 1572; found: 259. 1558.

Methyl 2-pyrrolidinocyclohex-1-enecarboxylate ***10***
This compound is unstable
^{13}C NMR: δ 167.8 (s); 155.2 (s); 93.6 (s); 58.6 (t); 50.9 (2t); 30.6 (t); 27.2 (t); 25.4 (2t); 22.8 (t); 22.7 (t); 14.6 (q).
MS: $C_{12}H_{19}NO_2$ *m/z* 223 (M^+, 36); 194 (27); 178 (16); 150 (100); 123 (31).

*Methyl 5-*tert*-butyl-2-[(1-phenylethyl)amino]cyclohex-1-enecarboxylate* ***11***
Rf: 0.25 (PE/AcOEt : 70/30).
IR: 3250; 1640; 1590; 1440; 1220 cm^{-1}.
^{1}H NMR: δ 0.86 (s, 9H); 1.50 (d, J = 6.8 Hz, 3H); 1.60-1.90 (m, 3H); 2.20-2.60 (m, 4H); 3.74 (s, 3H); 4.65 (m, 1H); 7.20-7.40 (m, 5H); 9.35 (d, J = 8.0 Hz, 1H).
^{13}C NMR: δ 23.2 (t); 24.9 (t); 25.2 (t); 27.1 (3q); 27.8 (t); 32.1 (s); 44.1 (d); 50.2 (q); 51.9 (d); 90.3 (s); 125.3 (2d); 126.6 (d); 128.9 (2d); 145.7 (s); 159.20 (s); 171.27 (s).
MS: $C_{20}H_{29}NO_2$ *m/z* 315 (M^+, 30); 300 (45); 284 (15); 286 (30); 232 (15); 216 (32); 196 (15); 180 (12); 154 (30); 127 (18); 105 (100); 91 (17).
HRMS calc for $C_{20}H_{29}NO_2$ 315. 2198. Found: 315. 2209.

Oxydation of β-enaminoamides
To a stirred solution of enamine (1 mmol, 1 equiv.) and K_2CO_3 (0.138 g; 1 mmol, 1 equiv.) in ethanol (20 mL) was added $Cu(OAc)_2$ (0.182 g, 1mmol, 1 equiv.). The reaction mixture was stirred at rt for 10 min. then anhydrous $Mn(OAc)_3$ (2 to 4 mmol) was added. The reaction mixture was stirred until complete disappearance of the starting material. The solvent was evaporated *in vacuo* and the residue was

diluted with EtOAc (25 mL) and aqueous HCl (10 %) was added until neutral pH. The organic phase was washed with water (10 mL), dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel or on alumina.

N-*Isopropyl-5-isopropylimino-3,3-dimethylcyclopent-1-enecarboxamide* ***14***
Yield = 73 %.
Rf: 0.30 (PE/AcOEt: 95/05). Purification on alumina.
IR: 3200; 1700; 1650; 1620; 1550; 1450; 1380; 1360; 1260 cm^{-1}.
^1H NMR: δ 1.15 (d, J = 6.6 Hz, 6H); 1.17 (s, 6H); 1.20 (d, J = 6.7 Hz, 6H); 2.44 (s, 2H); 3.42-3.52 (d, J = 6.2 Hz, 1H); 4.08-4.18 (d, J = 6.5 Hz, 1H); 7.53 (s, 1H); 10.00 (s, 1H).
^{13}C NMR: δ 22.58 (2q); 23.5 (2q); 28.2 (2q); 40.5 (s); 40.8 (d); 43.2 (t); 53.0 (d); 134.3 (s); 162.1 (s); 165.1 (d); 171.22 (s).
MS: $C_{14}H_{24}N_2O$ *m/z* 236 (M^+, 85);221 (60); 193 (10); 178 (30); 162 (100); 149 (45); 136 (30); 120 (10); 108 (20); 93 (20); 77 (15).
Anal. calcd. for $C_{14}H_{24}N_2O$ C, 71.14; H, 10.23; N, 11.85. Found: C, 71.25; H, 10.31; N, 11.89.

3,3-Dimethyl-N-*(1-phenylethyl)-5-[(1-phenylethyl)imino]cyclopent-1-enecarboxamide* ***15***
Yield = 86 %.
Rf: 0.25 (PE/AcOEt: 70/30). Purification on silica gel.
IR: 3400; 3200; 1660; 1620; 1540; 1490; 1450; 1300 cm^{-1}.
^1H NMR: δ 1.13 (s, 3H); 1.19 (s, 3H); 1.45 (d, J = 6.5 Hz, 3H); 1.53 (d, J = 6.8 Hz, 3H); 2.40 (d, J = 17.6 Hz, 1H); 2.55 (d, J = 17.6 Hz, 1H); 4.46 (q, J = 6.6 (Hz, 1H); 5.23 (m, 1H); 7.20-7.42 (m, 10H); 7.58 (s, 1H); 10.47 (d, J = 7.2 Hz, 1H).
^{13}C NMR: δ 22.7 (q); 24.9 (q); 28.0 (q) ; 28.1 (q); 40.7 (s); 43.7 (t); 48.6 (d); 61.9 (d); 125.9 (3d); 126.8 (3d); 126.9 (2d); 128.4 (d); 128.5 (d); 134.2 (s); 143.8 (s); 145.1 (s); 161.9 (s); 166.6 (d); 173.0 (s).
MS: $C_{24}H_{28}N_2O$ *m/z*360 (M^+, 35); 345 (10); 255 (50); 238 (25); 224 (40); 196 (20); 170 (10); 136 (30); 120 (15); 105 (100); 79 (20).
Anal. calcd. for $C_{24}H_{28}N_2O$ C, 79.86; H, 7.83; N, 7.77. Found: C, 79.99; H, 7.87; N, 7.75.

N-*Allyl-3,3-dimethyl-5-[(1-phenylethyl)imino]cyclopent-1-enecarboxamide* ***16***
Yield = 67 %
Rf: 0.37 (PE/AcOEt: 75/25). Purification on silica gel.
IR: 3300, 1700; 1660; 1620; 1540; 1450; 1250; 1150 cm^{-1}.
^1H NMR: δ 1.09 (s, 3H); 1.22 (s, 3H); 1.48 (d, J = 6.5 Hz, 3H); 2.40 (d, J = 17.5 Hz, 1H); 2.57 (d, J = 17.5 Hz, 1H); 4.03 (m, 2H); 4.47 (q, J = 6.5 Hz, 1H); 5.10-5.30 (m, 2H); 5.80-6.00 (m, 1H); 7.25-7.33 (m, 5H); 7.60 (s, 1H); 10.00 (s, 1H).
^{13}C NMR: δ 24.8 (q); 27.9 (q); 28.0 (q); 40. 6(s); 41.0 (t); 43.6 (t); 61.3 (d); 115.5 (t); 126.2 (2d); 126.8 (d); 128.4 (2d); 134.1 (d); 134.2 (s); 144.9 (s); 162.6 (s); 166.5 (d); 172.7 (s).

MS: $C_{19}H_{24}N_2O$ *m/z* 296 (M^+, 40); 281 (15); 255 (10); 238 (13); 224 (70); 210 (20); 196 (50); 170 (20); 136 (20); 105 (100); 77 (30).

3-tert-*Butyl*-N-*(1-Phenylethyl)-6-[(1-phenylethyl)imino]cyclohex-1-enecarboxamide* ***17***

Yield = 86 %

Rf: 0.42 (PE/AcOEt: 90/10). Purification on alumina.

^{1}H NMR: δ 0.95 (s, 9H); 1.10-2.20 (m, 11H); 4.80 (q, J = 6.5 Hz, 1H); 5.20 (m, 1H); 7.20-7.40 (m, 10H); 7.92 (m, 1H); 11.35 (s, 1H).

^{13}C NMR: δ 22.3 (q); 23.7 (t); 24.6 (q); 27.2 (3q); 27.4 (t); 33.0 (s); 46.9 (d); 48.9 (d); 58.5 (d); 126.1 (4d); 126.8 (2d; 128.5 (4d); 144.1 (s); 144.8 (s); 145.1 (s); 151.6 (d); 165.1 (s); 179.4 (s).

MS: $C_{27}H_{34}N_2O$ *m/z* 400 (M^+-2, 30); 295 (20); 278 (60); 264 (90); 250 (11); 236 (10); 202 (15); 176 (30); 160 (30); 120 (30).

N-*Isopropyl-3, 3-dimethyl-5-oxocyclopent-1-enecarboxamide* ***18***

From ***1***

18 was obtained from **1** with 57% yield and from **2** with 59% yield.

From ***14***

To a solution of **14** (0.120 g; 0.5 mmol) in THF (2 mL) was added a 50% aqueous AcOH solution (0.150 mL, 5 mmol). The reaction mixture was stirred overnight, then diluted with water (4 mL) and EtOAc (10 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered on silica gel to give **18** (0.083 g, 85%)

Rf: 0.45 (PE/AcOEt: 70/30).

IR: 3320; 1735; 1655; 1600; 1520; 1460; 1260; 1220 cm^{-1}.

^{1}H NMR: δ 1.22 (d, J = 6.6 Hz, 6H); 1.27 (s, 6H); 2.47 (s, 2H); 4.15 (t, J = 6.6 Hz, 1H) ; 7.85 (s, 1H); 8.27 (s, 1H).

^{13}C NMR: δ 22.5 (2q); 27.4 (2q); 38.6 (s); 40.91 (d); 51.5 (t); 134.7 (s); 160.0 (s); 179.8 (d); 207.5 (s).

MS: $C_{11}H_{17}NO_2$ *m/z* 195 (M^+, 20); 180 (50); 152 (5); 137 (100); 121 (10).

Anal. calcd for $C_{11}H_{17}NO_2$. calcd C: 67.66; H: 8.77; N: 7.17. Found C: 67.68; H: 8.81; N: 7.19.

5-tert-*Butyl*-N-*(1-phenylethyl)-2-[(1-phenylethyl)amino]cyclohexa-1,5-dienecarboxamide* **19**

Yield = 77 %

Rf: 0.42 (PE/AcOEt: 90/10). Purification on silica gel.

IR: 3200; 1700; 1630; 1580; 1530; 1480; 1450; 1420; 1370 cm^{-1}.

^{1}H NMR: δ 0.95 (s, 9H); 1.53 (d, J = 7.0 Hz, 3H); 1.63 (d, J = 6.7 Hz, 3H); 2.03-2.18 (m, 1H); 2.40-2.54 (m, 1H); 2.72-2.95 (m, 2H); 4.86 (m, 1H); 5.23 (m, 1H); 7.20-7.40 (m, 10H); 9.43 (s, 1H); 10.40 (d, J = 8.0 Hz, 1H); 13.25 (d, J = 6.5 Hz, 1H).

^{13}C NMR: δ 21.5 (t); 23.5 (q); 24.7 (q); 26.3 (3q); 35.8 (t); 43.8 (s); 47.9 (d); 54.0 (d); 100.5 (s); 125.7 (2d); 126.0 (2d); 126.8 (d); 127.8 (d); 128.5 (2d); 129.1 (2d); 143.3 (s); 144.4 (s); 168.9 (s); 175.6 (s); 185.3 (s); 212.5 (s).

MS: $C_{27}H_{34}N_2O$ *m/z* 400 (M^+-2, 30); 295 (20); 278 (60); 264 (90); 250 (11); 236 (10); 202 (15); 176 (30); 160 (30); 120 (30).

Anal. calcd. for $C_{27}H_{34}N_2O$ C, 80.55; H, 8.51; N, 6.95. Found: C, 80.63; H, 8.60; N, 7.03.

5-tert-Butyl-N,N-diethyl-2-[(1-phenylethyl)amino]benzamide **20**

(4 equiv. of $Mn(OAc)_3$ were used and the reaction mixture was stirred overnight).

Yield = 67 %

Rf: 0.55 (PE/AcOEt: 95/5). Purification on silica gel.

IR: 3380; 1710; 1620; 1510; 1450; 1360; 1250 cm^{-1}.

^{1}H NMR: δ 0.90 (s, 6H); 1.22 (s, 9H); 1.45 (d, J = 6.9 Hz, 3H); 3.30-3.65 (m, 4H); 4.45 (q, J = 6.9 Hz, 1H); 4.95-5.05 (s1, 1H); 6.40 (d, J = 9.5 Hz, 1H); 7.05 (m, 2H); 7.15-7.40 (m, 5H).

^{13}C NMR: δ 25.2 (q); 27.4 (q); 31.3 (3q); 33.6 (s); 39.2 (t); 41.4 (t); 43.2 (d); 53.2 (d); 81.6 (s); 112.4 (d); 120.7 (s); 123.6 (d); 125.7 (2d); 126.6 (d); 126.8 (d); 128.5 (2d); 138.5 (s); 145.4 (s); 174.5 (s).

MS $C_{23}H_{32}N_2O$ *m/z* 352 (M^+, 67); 337 (30); 278 (15); 264 (100); 250 (45); 233 (37); 176 (45); 160 (32); 133 (17); 105 (36).

Anal. calcd. for $C_{23}H_{32}N_2O$ C, 78.36; H, 9.15; N, 7.95. Found C, 78.45; H, 9.25; N, 7.92.

Methyl 5-tert-butyl-2-[(1-phenylethyl)amino]benzoate **21**

(4 equiv. of $Mn(OAc)_3$ were used and the reaction mixture was stirred overnight).

Yield = 67 %.

R_f: 0.70 (PE/AcOEt: 95/5). Purification on silica gel.

IR: 3320; 1680; 1650; 1570; 1500; 1430; 1350; 1280 cm^{-1}.

^{1}H NMR: δ 1.25 (s, 9H); 1.50 (d, J = 6.7 Hz, 3H); 3.90 (s, 3H); 4.55 (m, 1H); 6.40 (d, 8.9 Hz, 1H); 7.15 (dd, J = 9.0 and 2.5 Hz, 1H); 7.20- 7.40 (m, 5H); 7.92 (d, J = 2.5 Hz, 1H); 8.10 (d, J = 5.5 Hz, 1H).

^{13}C NMR: δ 25.2 (q); 31.2 (3q); 33.5 (s); 51.2 (q); 52.7 (d); 109.2 (s); 112.4 (d); 125.3 (2d); 126.7 (d); 127.3 (d); 128.5 (2d); 131.9 (d); 137.0 (s); 145.2 (s); 148.1 (s); 171.9 (s).

MS: $C_{20}H_{25}NO_2$ *m/e* 311 (M^+, 50); 296 (100); 178 (10); 264 (92); 234 (5); 220 (15); 192 (70); 160 (30); 105 (70).

Anal. calcd. for $C_{20}H_{25}NO_2$ C, 77.13; H, 8.09; N, 4.50. Found: C, 77.24; H, 8.15; N, 4.57.

Oxidation of β-ketoamide 22

To a solution of **22** (0.200 g, 1 mmol, 1 equiv.) in ethanol (20 mL) was added $Cu(OAc)_2$ (0.182 g, 1 mmol, 1 equiv.) followed by the addition of $Mn(OAc)_3$ (0.472 g, 2 mmol, 2 equiv.) The reaction mixture was stirred overnight at rt, then concentrated under reduced pressure and the residue was diluted with EtOAc. The suspension was filtered through Celite and the filtrate was concentrated *in vacuo* to give a brown oil

which was purify by flash chromatography using petrolum ether/EtOAc (85/15) as eluent to give **18** (0.023 g 11%), **23** (0.082 g, 21%) and **24** (0.145 g, 37%).

Compound 23:

^{1}H NMR: δ 1.10-1.30 (m, 24 H), 2.15-2.60 (m, 8H), 4.15-4.24 (m, 2H), 7.10 (d, J = 7.4 Hz, 2H).

^{13}C NMR: δ 22.34 (4q), 27.23 (4q), 34.46 (2s), 40.68 (2d), 42.28 (2t), 43.57 (2t), 81.78 (2s), 166.37 (2s), 208.70 (2s).

MS: $C_{22}H_{36}N_2O_4$ *m/z* 392 (M^+, 10), 359 (30), 335 (27), 321 (10), 288 (7), 261 (10), 250 (80), 222 (100), *196 (20), 166 (23), 138 (22).*

Compound 24

^{1}H NMR: δ 1.10-1.25 (m, 24 H), 1.80-1.90 (m, 2H), 2.40 (m, 2H), 2.68 (m, 2H), 3.08 (m, 2H), 3.50 (m, 1H), 3.70 (m, 1H), 6.20 (d, J = 7.9 Hz, 1H), 6.63 (d, J = 7.50 Hz, 1H).

^{13}C NMR: δ 22.0.4 (2q), 22.40 (2q), 28.09 (2q), 30.70 (2q), 32.75 (2s), 40.65 (d), 40.70 (d), 43.10 (t), 43.53 (t), 47.20 (t), 52.67 (t), 88.92 (s), 103.67 (s), 163.47 (s), 170.46 (s), 175.29 (s), 214.50 (s).

MS: $C_{22}H_{36}N_2O_4$ *m/z* 392 (M^+,5), 212 (90), 196 (5), 184 (7), 171 (100), 154 (5), 143 (40), 129 (15), 115 (20), 97 (10).

References and Notes

‡Present address: Pharmacor Inc, 535, Bd. Cartier, Laval, Quebec, Canada, H7N 4Z3

1 - (a) Vinogradov, M. G.; Dolinko, V. I.; Nikichin, G. I. *Bull. Nat. Acad. Sci. USSR. Ser. Chem.* **1984**, 1884.

(b) Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659.

(c) Curran, D. P.; Morgan, T. M.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607.

(d) Zoretic P. A.; Weng, X.; Caspar, M. L.; Davis, D. G. *Tetrahedron Lett.* **1991**, *32*, 4819.

2 - (a) Cossy, J.; Leblanc, C. *Tetrahedron Lett.* **1989**, *30*, 4531.

(b) Cossy, J. *Pure Appl. Chem.* **1992**, *64*, 1883.

(c) Zoretic, P. A.; Weng, X.; Biggers, C. K. *Tetrahedron Lett.* **1992**, *33*, 2637.

(d) Snider, B. B.; Zhang, Q. *Tetrahedron Lett.* **1992**, *33*, 5921.

(e) Zhang, Q.; Mohan, R. M.; Cook, L.; Kazanis, S.; Peisach, D.; Foxman, B.; Snider, B. B. *J. Org. Chem.* **1993**, *58*, 7640.

3 - (a) Snider, B. *Chem. Rev.* **1996**, *96*, 339.

(b) Iqbal, J.; Bhatia, B.; Nayyar, N. *Chem. Rev.* **1994**, *94*, 519.

(c) Melikyan, G. G. *Synthesis* **1993**, 833.

4 - Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137.
5 - Schultz, A. G.; Holobosky, M. A. *Tetrahedron Lett.* **1993**, *34*, 3021, and references cited therein.
6 - Audebert, P.; Bekolo, H.; Cossy, J.; Bouzide, A. *J. of Electroanal. Chem.* **1995**, *389*, 227.
7 - (a) Bock, H.; Kaim, W.; Kira, M.; Réné, L.; Viehe, H.-G. *Z. Naturforsch.* **1984**, *39b*, 763.
(b) Itoh, T.; Kaneda, K.; Watanabe, I.; Ikeda, S.; Teranishi, S. *Chem. Lett.* **1976**, 227.
8 - Cossy, J.; Bouzide, A. *J. Chem. Soc., Chem. Commun.* **1993**, 1218.
9 - Cossy, J.; Bouzide, A.; Leblanc, C. *Synlett*, **1993**, 202.
10 - Cossy, J.; Bouzide, A. Unpublished results.
11 - (a) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524.
(b) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 2888.
(c) Kochi, J. K. *Acc. Chem. Res.* **1974**, *7*, 351.
(d) Snider, B. B.; Merrit, J. E.; Dombroski, M. A.; Buckman, B. O. *J. Org. Chem.* **1991**, *56*, 5544.
12 - (a) Cossy, J.; Belotti, D.; Thellend, A.; Pete, J. P. *Synthesis*, **1988**, 720.
(b) Cossy, J.; Thellend, A. *Synthesis* **1989**, 753.