

Note

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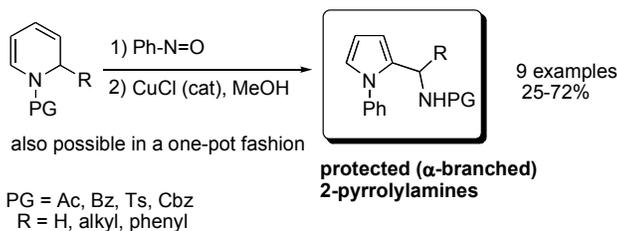


Synthesis of Protected (1-Phenyl-1*H*-pyrrol-2-yl)- alkane-1-amines from Phenylnitroso Diels-Alder Adducts with 1,2-Dihydropyridines

*Francesco Berti, Valeria Di Bussolo, and Mauro Pineschi**

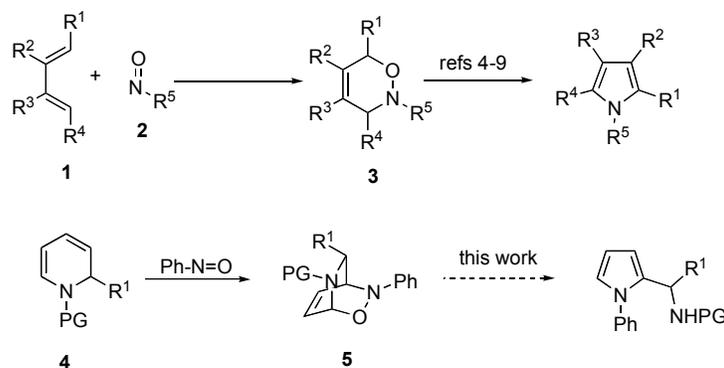
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The reductive cleavage of nitrosobenzene-derived cycloadducts with appropriately protected 1,2-dihydropyridines allows a novel and simple obtainment of substituted N-[1-(1-phenyl-1*H*-pyrrol-2-yl)alkyl]amides. This synthesis can also be carried out in a very simple, mild and practical one-pot procedure without isolation of the corresponding nitrosobenzene cycloadduct by means of catalytic amounts of CuCl.

The preparation of pyrrole derivatives is of special importance as this nucleus is an integral part of biologically important compounds.¹ The synthesis of pyrroles can be accomplished in several ways,² but few of them are applicable to substituted N-aryl pyrroles.³ Interestingly, dihydro-1,2-oxazines **3**, easily obtained by nitroso-Diels-Alder cycloaddition of dienes **1** to nitroso dienophiles **2**, can be converted into 1-phenyl pyrroles by photolysis,⁴ base-mediated rearrangement,⁵ under high temperature and pressure with palladium,⁶ or ruthenium catalysts,⁷ (Scheme 1). The use of Lewis acids such as BF₃-Et₂O has been reported to give low yields of pyrrole products, due the tendency of these compounds to undergo polymerization under these reaction conditions.⁸ More recently, the reductive cleavage (NaBH₄, Mo(CO)₆ in CH₃CN-H₂O at 90 °C) of the N-O bond of dihydro-1,2-oxazines followed by an oxidation reaction with manganese dioxide or Dess-Martin-periodinane of the resulting γ -amino alcohol, afforded substituted pyrroles.⁹

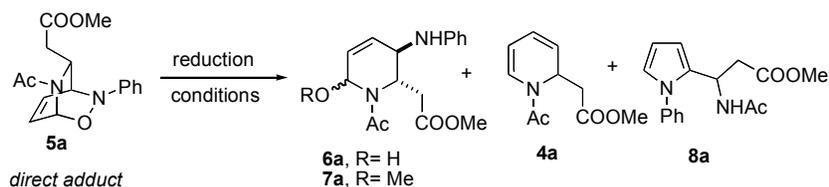


SCHEME 1. Obtainment of pyrroles from nitroso Diels-Alder cycloadducts.

It should be noted that all these reaction protocols that can be used to give pyrroles have invariably been applied to *monocyclic* nitroso Diels-Alder cycloadducts (i.e. 1,2-oxazines of type **3**). To the best of our knowledge, the use of *bicyclic* nitroso Diels-Alder cycloadducts, such as **5**, as precursors for pyrroles has not been reported (Scheme 1). In principle, these compounds

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3 cannot afford a pyrrole derivative, unless a double ring fragmentation of the *bicyclic* nitroso
4 cycloadduct occurs.
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8 We recently reported a novel preparation of N-acetyl-1,2-dihydropyridyl acetic acid methyl
9 ester **4a** (see Scheme of Table 1) and its Diels-Alder reactions with nitroso dienophiles.¹⁰ The
10 reductive cleavage of the N-O bond showed some interesting features with *inverse* adducts
11 derived from acylnitroso dienophiles.¹⁰ Remarkably, the reductive cleavage of the N-O bond of
12 phenylnitroso *direct* cycloadduct **5a** showed a completely different and, in some cases
13 unexpected behavior, which we now report in detail in Table 1. When direct adduct **5a** was
14 treated with [Mo(CO)₆] in a CH₃CN/H₂O mixture at 65 °C, only a retro Diels-Alder process was
15 found (entry 1, Table 1).¹⁰ Also the addition of NaBH₄, commonly used in the reductive cleavage
16 of N-O bonds of oxazines,^{9,11} promoted the formation of the starting dihydropyridine **4a** (entry
17 2). The use of an alane reagent such as AlH₃, freshly prepared from LiAlH₄ and sublimed
18 AlCl₃,¹² afforded a complex mixture of unidentified products (entry 3). Also SmI₂ gave a
19 complex mixture in which the signals of starting material **5a** were present (entry 4).¹³ To our
20 surprise, the use of titanocene(III) chloride (Cp₂TiCl), generated in situ from Cp₂TiCl₂ and zinc
21 metal in the presence of alcoholic solvents afforded substantial amounts of pyrrole derivative **8a**
22 without isolation of N-O cleaved product **6a** (entries 5 and 6).
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Table 1. Screening of reaction conditions for the reductive N-O cleavage of phenyl nitroso cycloadduct **5a**.^a

Entry	Reaction conditions	Products (%) ^b (6a-7a / 4a / 8a)
1	Mo(CO) ₆ , CH ₃ CN/H ₂ O, 60 °C, 5h	<2 / >96 / <2
2	Mo(CO) ₆ , NaBH ₄ , MeOH/H ₂ O, 65 °C, 15h	<2 / >96 / <2
3	AlH ₃ , Et ₂ O, 0 °C to rt, 5h	complex mixture
4	SmI ₂ , 0 °C to rt, 5h	complex mixture
5	Cp ₂ TiCl, THF/MeOH, -30 °C to rt, 20h	<2 / 35 / 65
6	Cp ₂ TiCl, THF/EtOH, -30 °C to rt, 20h	<2 / 42 / 58
7	TiCl ₃ , MeOH/H ₂ O, rt, 45 min	60 (7a), 40 (6a)
8	Zn, HCl, MeOH, rt, 15h	complex mixture
9	CuCl (1.0 eq), MeOH, rt, 3h	<15 / <2 / >80
10	CuCl (0.2 eq), MeOH, rt, 18h	<15 / <2 / >80 ^c
11 ^d	CuI (0.2 eq), MeOH, rt, 24h	<10 / <35 / >55

^a Unless stated otherwise, all reactions gave >95% conversion of **5a** in the reported reaction conditions. For details, see Supporting Information. ^b Determined by ¹H NMR of the crude mixture. ^c 72% Isolated yield of **8a** after chromatographic purification. A complex mixture of methoxylated products other than **7a** was isolated as by-product. ^d Conversion 70%.

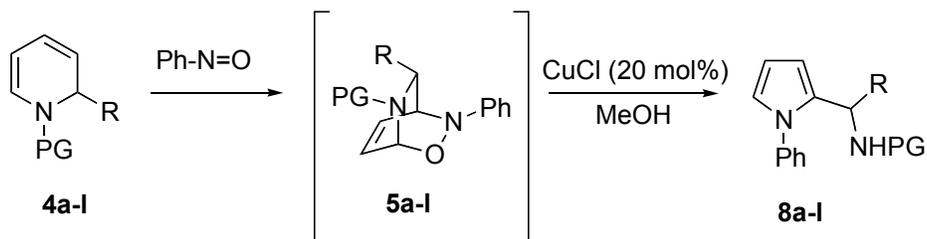
The obtainment of an N-phenyl pyrrole derivative from an N-phenyl nitroso cycloadduct of this kind has not been previously reported, and can be admitted only by a tandem reductive cleavage-fragmentation-intramolecular amination. It should be noted that although the reaction started at -30 °C, as previously reported for the N-O cleavage of N-acylated bicyclic oxazines,¹⁴ it needed several hours at room temperature to reach complete conversion of the N-phenyl substrate. It was also interesting to find that TiCl₃, which is usually the preferred source of titanium(III), being

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3 commercially available as a solution in hydrochloric acid, did not afford pyrrole derivatives or
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5 starting dihydropyridine **4a**, but only promoted the reductive cleavage of the N-O bond
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7 (compound **6a**) accompanied by 1,2,3,6-tetrahydropyridine **7a**, which derives from the ring
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9 opening with methanol, followed by reduction of the intermediate hydroxylamine (entry 7). It
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11 was also found that a Ti(III) species is not essential to obtain pyrrole derivatives. For example,
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13 simple zinc metal in hydrochloric MeOH at room temperature afforded compound **8a**, albeit with
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15 very low yield and in a complex reaction mixture (entry 8). The heterogeneous reaction
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17 conditions and the long reaction time connected with the use of Cp₂TiCl stimulated the search for
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19 other procedures. A satisfactory solution was found by the use of stoichiometric amounts of CuCl
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21 in MeOH at room temperature.¹⁵ To our delight, the reaction was complete in 3h at rt and pyrrole
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23 **8a** was isolated with a good yield after chromatographic purification (entry 9). From the same
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25 chromatography it was also possible to obtain in the second eluting fractions a mixture of
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27 inseparable tetrahydropyridines, including compounds **6a** and **7a**. Two facts are worthy of
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29 mention: i) the reaction can be carried out at room temperature and ii) also catalytic amounts of
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31 CuCl (20 mol%) gave the same results, although it was necessary to use a prolonged reaction
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33 time (entry 10). The use of catalytic amounts of CuI proved to be less effective and less selective
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35 for the formation of the pyrrole derivative (entry 11). It should be noted that while the synthesis
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37 of 2-pyrrolylalanine has been reported in view of its peculiarity in peptide chemistry,¹⁶ the
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39 synthesis of 2-pyrrolyl-β-alanine derivatives, such as **8a**, has only few precedents which
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41 furthermore have scarce preparative importance.¹⁷

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50 The scope of the synthesis of (1-phenyl-1*H*-pyrrol-2-yl)-alkane-1-amines from N-
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52 phenylnitroso cycloadducts with a variety of 1,2-dihydropyridines was examined in detail. In
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54 general, the synthesis of 1,2-dihydropyridines bearing different protecting groups (PG) on the
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56 nitrogen and substituents at the 2-position **4b-1** was accomplished by organometallic addition to
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3 N-protected pyridinium salts (see Experimental Section).¹⁸ The subsequent use of nitrosobenzene
4 afforded with complete regioselectivity the corresponding 3-oxa-2,5-diazabicyclo[2.2.2]oct-7-
5 enes (**5b-l**), which were used as precursors of pyrrole derivatives **8b-l** using catalytic amounts (20
6 mol%) of CuCl (**procedure A**, Table 2). With cycloadducts **5b** and **5c** derived from acetyl and
7 benzoyl protected dihydropyridines **4b** and **4c**, respectively, the corresponding pyrrole derivatives
8 were obtained with moderate yields after 16h at room temperature (entries 1 and 2, Table 2). On
9 the other hand, the use of sulfonyl or carbobenzyloxy protecting groups in the same reaction
10 conditions proved to be less effective (entries 3-7). In particular, N-tosyl derived adduct **5d** was
11 not reactive with CuCl at room temperature (entry 3). However, it was possible to obtain with a
12 good yield the corresponding pyrrole derivative just by warming the reaction mixture at 70 °C for
13 3 h (entry 4). On the other hand, Cbz-protected adducts **5e** and **5f** mainly produced a complex
14 mixture of ring opening products even at room temperature (entries 5 and 6). The corresponding
15 pyrrole derivative **8f** was obtained only with a low yield with the phenyl-substituted compound
16 **5f** in refluxing methanol (entry 7) or in the simplified one-pot procedure (vide infra, entry 15).
17 Moderate yields of pyrrole derivatives were obtained with nitrosobenzene cycloadducts with
18 substituted amide protected 1,2-dihydropyridine (entries 8-10).
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41 As found for compound **5a**,¹⁰ also direct adducts **5b-i** showed some decomposition via retro
42 Diels-Alder reactions to the corresponding starting dihydropyridines **4b-i** during
43 chromatographic purification on silica gel.¹² To address this problem, a one-pot two-step
44 procedure (**procedure B**) without the isolation of the intermediate nitrosobenzene-1,2-
45 dihydropyridine cycloadduct was in some cases applied (entries 11-15).
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Table 2 Synthesis of Protected (1-phenyl-1*H*-pyrrol-2-yl)-alkane-1-amines.^a

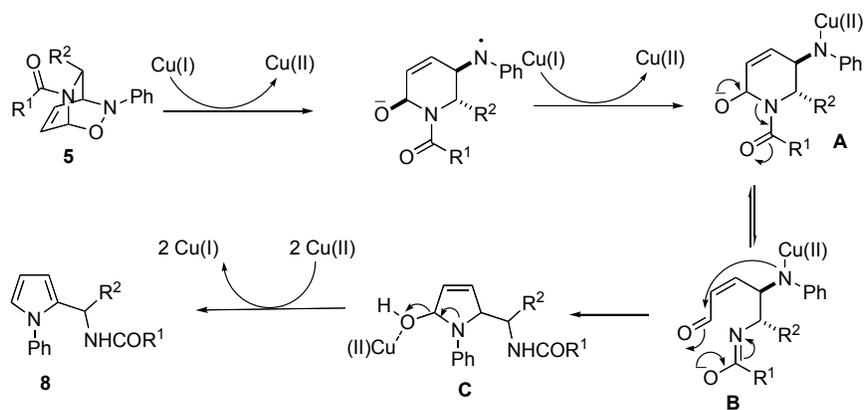
Entry	Reaction conditions	R	PG	Yield (%) ^b (Product)
1	A	CH ₃	Ac	50 (8b)
2	A	CH ₃	PhCO	60 (8c)
3	A	H	Ts	<10% conversion
4	A ^c	H	Ts	71 (8d)
5	A	H	Cbz	complex mixture
6	A	Ph	Cbz	<10% conversion
7	A ^c	Ph	Cbz	28 (8f)
8	A	PhCC	PhCO	65 (8g)
9	A	C ₆ H ₁₃	Ac	46 (8h)
10	A	Ph	Ac	60 (8i)
11	B	CH ₂ COOCH ₃	Ac	52 (8a)
12	B	Ph	PhCO	59 (8l)
13	B	C ₆ H ₁₃	Ac	37 (8h)
14	B	Ph	Ac	45 (8i)
15	B	Ph	Cbz	25 (8f)

^a Reaction conditions **A**: anhydrous CuCl (0.03 mmol), MeOH (1.15 mL), bicycle **5** (0.15 mmol), 16h at rt. Reaction conditions **B**: Compound **4** (0.20 mmol), nitrosobenzene (0.40 mmol), CH₂Cl₂ (0.4 mL), 1h rt. Then, MeOH (1.54 mL) and anhydrous CuCl (0.04 mmol), 18-24 h at rt. ^b Isolated yield after chromatographic purification. ^c Reaction carried out at 70 °C for 3h.

For example, dihydropyridine **4a** was allowed to react with nitrosobenzene (2.0 equiv) in CH₂Cl₂ at rt for 1 h. After evaporation of the solvent, methanol was added followed by anhydrous CuCl (20 mol%), continuing the stirring for 24 hours. With this simplified procedure the overall yields

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3 can be increased, as it is no more necessary to isolate the corresponding nitrosobenzene-
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5 dihydropyridine cycloadduct (entries 11-15). In fact, compounds of type **5** can be isolated from
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7 silica gel pretreated with NEt_3 with low to moderate yields (35-71%), and they are invariably
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9 obtained in mixture with the corresponding starting dihydropyridines. Without a reasonable
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11 explanation, the reaction conditions **B** allow in one case the obtainment of the corresponding
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13 pyrrole in milder reaction conditions (cfr entry 7 and entry 15). On the other hand, with a
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15 particular substitution pattern (i.e. dihydropyridine **4g**, containing a triple bond), the one-pot
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17 procedure cannot be applied.
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23 As regards the reaction mechanism, it is plausible that the reducing agent in a protic solvent
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25 reduces the N-O bond and generates the corresponding 1,2,3,6-tetrahydropyridine **A** (Scheme 2).
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27 To explain the ring fragmentation of the six-membered piperidine nucleus, it is proposed that
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29 cyclic N-acetylated hemiaminal **A**, which reasonably exists in equilibrium with the
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31 corresponding open-chain amidaldehyde **B**, undergoes an intramolecular ring closure to give the
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33 five-membered hemiaminal **C**. The subsequent dehydration of the hydroxypyrroline **C** followed
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35 by oxidation with Cu(II) furnishes the pyrrole nucleus while regenerating the copper(I) catalyst. It
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37 is important to emphasize that the transformation into pyrrole derivatives occurs effectively only
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39 when the protecting group of the endocyclic piperidine nitrogen is sufficiently electron-
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41 withdrawing (PG = Ac, PhCO, Ts) to shift the equilibrium from species **A** to open-chain species
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43 **B**. In fact, the use of Cbz as protecting group proved to be less effective for the formation of the
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45 corresponding pyrrole derivatives, and complex mixtures of methoxy tetrahydropyridines were
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47 observed as the main products.
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SCHEME 2. Schematization of the plausible mechanism for the formation of protected α -branched 2-pyrrolylamines catalyzed by CuCl.

In summary, we have developed a novel elaboration of nitrosobenzene cycloadducts with 1,2-dihydropyridines to give N-phenyl pyrroles bearing unconventional substituents at the C-2 position. The procedure described complements the other known methods to obtain substituted pyrroles from cyclic oxazines. In particular, it is now possible to obtain 2-pyrrolyl- β -alanine derivatives and protected α -branched 2-pyrrolylamines by means of a reliable, simple procedure.

EXPERIMENTAL SECTION

General Remarks and Materials: All reactions were carried out under an argon atmosphere in flame-dried, modified (Kjeldahl shape) Schlenk flasks fitted with a glass stopper or rubber septa under a positive pressure of argon. All reagents were purchased from commercially available sources. Anhydrous CH_2Cl_2 on molecular sieves and MeOH (HPLC grade) were used as the reaction solvents without any further purification. THF was distilled on sodium/benzophenone ketyl. Solvents for extraction and chromatography were distilled before use. Analytical TLC were performed on silica gel sheets with detection by exposure to ultraviolet light (254 nm) and/or by immersion in an acidic staining solution of *p*-anisaldehyde in EtOH. Silica gel 60 was used for flash chromatography. ^1H NMR spectra were recorded at 250 MHz. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuteriochloroform: δ 7.26, deuterioacetonitrile: δ 1.94). Signal patterns are indicated as follows: br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (*J*) are given in hertz (Hz). ^{13}C NMR spectra were recorded at 62.5 MHz, with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuteriochloroform: δ 77.0, deuterioacetonitrile: δ 1.32). Melting points were determined on a Kofler apparatus and are uncorrected. HRESIMS were acquired in positive ion mode on a Q-TOF premier spectrometer equipped with a nanoelectrospray ion source.

Compounds **4a**,¹⁰ **4d**,¹⁹ **4e**,²⁰ **4f**,²⁰ **4g**,²¹ **4i**,²² **4l**,²² **5a**,¹⁰ **5i**,²³ **5e**,²⁴ were prepared in accordance with the indicated literature procedures.

1-(2-Methylpyridin-1(2H)-yl)ethanone (4b). Following a modification of a previously described procedure,²⁵ a 100 mL Schlenk tube was charged, under argon protection, with pyridine (0.80 mL, 10 mmol), anhydrous THF (15 mL) and MeMgI (1.5 M in Et₂O, 13.3 mL, 20 mmol). The

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3 reaction mixture was cooled to -78 °C and freshly distilled AcCl (0.71 mL, 10 mmol) was
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5 dropwise added over 5 minutes. The reaction was allowed to reach 0 °C and vigorously stirred
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7 for 4 hours. The reaction mixture was poured into ice-water and extracted with Et₂O (3x20 mL).
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9 The combined organic layers were dried over MgSO₄ and filtered. Subsequent flash
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11 chromatography (hexanes/AcOEt= 7/3) afforded **4b** (600 mg, 44%) as an oil. ¹H NMR (250
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13 MHz, CDCl₃), major rotamer δ 6.39 (d, 1H, *J*= 7.5 Hz), 5.86 (dd, 1H, *J*= 5.2 and 9.5 Hz), 5.71-
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15 5.60 (m, 1H), 5.41-5.21 (m, 1H), 5.20-5.11 (m, 1H), 2.15 (s, 3H), 1.09 (d, 3H, *J*=6.4 Hz); ¹³C
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17 NMR (62.5 MHz, CDCl₃), major rotamer δ 169.0, 126.0, 124.4, 121.6, 120.0, 106.8, 46.5, 18.4.
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19 HRMS (ESI) *m/z*: [M+Na⁺] Calcd for C₈H₁₁NONa 160.0733; Found 160.0725.

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22 *(2-Methylpyridin-1(2H)-yl)(phenyl)methanone (4c)*. Following a modification of a previously
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24 described procedure,²⁵ a 100 mL Schlenk tube was charged, under argon protection, with
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26 pyridine (0.80 mL, 10 mmol), anhydrous THF (15 mL) and MeMgI (1.5 M in Et₂O, 13.3 mL, 20
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28 mmol). The reaction mixture was cooled to -78 °C and freshly distilled BzCl (1.2 mL, 10 mmol)
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30 was dropwise added over 5 minutes. The reaction was allowed to react at -78 °C for 3 hours and
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32 carefully quenched with NH₄Cl satd solution (5 mL). The resulting mixture was extracted with
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34 Et₂O (3x15 mL). The evaporation of the dried (MgSO₄) organic layers afforded a crude product
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36 which was purified by flash chromatography (hexanes/AcOEt= 9/1) to give a 81/19 mixture of
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38 1,2- and 1,4-dihydropyridines. Compound **4c** was isolated by preparative TLC (hexanes/CH₂Cl₂=
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40 2/8) as an oil (996 mg, 50%). ¹H NMR (250 MHz, CDCl₃), major rotamer δ 7.64-7.36 (m, 5H),
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42 6.26 (d, 1H, *J*= 5.5 Hz), 5.94 (dd, 1H, *J*= 5.5 and 9.5 Hz), 5.78-5.64 (m, 1H), 5.31-5.11 (m, 2H),
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44 1.24 (d, 3H, *J*= 6.3 Hz); ¹³C NMR (62.5 MHz, CDCl₃), major rotamer δ 169.5, 134.8, 133.3,
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46 130.5, 128.3, 126.2, 125.6, 120.5, 106.3, 47.6, 12.1. HRMS (ESI) *m/z*: [M+Na⁺] Calcd for
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48 C₁₃H₁₃NONa 222.0889; Found 222.0885.
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1-(2-Hexylpyridin-1(2H)-yl)ethanone (4h): Following a modification of a previously described procedure,²⁶ a 25 mL Schlenk tube was charged, under argon protection, with pyridine (0.40 mL, 5 mmol) and anhydrous THF (5 mL). The reaction mixture was cooled at -65 °C and hexyllithium was added (2.3 M in hexanes, 2.13 mL, 5 mmol), followed by freshly distilled AcCl (0.71 mL, 10 mmol). After 2 hours the reaction mixture was quenched with water (7.5 mL) and NaHCO₃ satd solution (1.5 mL), and extracted with CH₂Cl₂ (3x10 mL). The combined organic phase was washed with brine, dried over MgSO₄, filtered and concentrated to give an orange oil that contained a mixture of 1,2- and 1,4-dihydropyridine (55/45). Purification by flash chromatography (hexanes/AcOEt= 7/3) afforded the title compound (446 mg, 43%) as a colorless oil. ¹H NMR (250 MHz, CDCl₃), major rotamer δ 6.43 (d, 1H, *J*= 7.6 Hz), 5.91 (dd, 1H, *J*= 5.3 and 9.6 Hz), 5.68 (ddd, 1H, *J*= 1.1, 5.7 and 9.5 Hz), 5.37-5.26 (m, 1H), 5.17-5.05 (m, 1H), 2.16 (s, 3H), 1.82-1.17 (m, 10H), 0.95-0.80 (m, 3H); ¹³C NMR (62.5 MHz, CDCl₃), major rotamer δ 169.2, 125.0, 123.0, 120.6, 107.5, 50.1, 34.4, 33.4, 29.3, 24.4, 22.5, 21.5, 21.2, 14.0. HRMS (ESI) *m/z*: [M+Na⁺] Calcd for C₁₃H₂₁NONa 230.1521 found 230.1525

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General procedure for the synthesis of 3-phenyl-2-oxa-3,6-diazabicyclo[2.2.2]oct-7-enes (5):

Two equivalents of nitrosobenzene were added at room temperature to a 0.5 M solution of 1,2-dihydropyridine in CH₂Cl₂. The reaction mixture was stirred at rt and monitored by TLC analysis. Removal of the solvent in vacuum below 30°C gave a residue that was then purified as specified.

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1-((1S,4R*,6R*)-6-Methyl-2-phenyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-en-5-yl)ethanone (5b)*:

Nitrosobenzene (215 mg, 2.0 mmol) was added to a solution of **4b** (137 mg, 1.0 mmol) in 2 mL of CH₂Cl₂ at room temperature. The reaction was allowed to stir for 90 min and concentrated at rt to afford a dark brown semisolid. Silica gel column purification (hexanes/AcOEt= 7/3 + 5% of Et₃N) afforded **5b** (131 mg, 54%) as a sticky oil containing 14% of **4b**. ¹H NMR (250 MHz,

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3 CDCl₃), major rotamer δ 7.29-7.17 (m, 2H), 7.06-6.93 (m, 3H), 6.69-6.57 (m, 1H), 6.18-6.07 (m,
4 1H), 5.76 (dd, 1H, J = 1.0 and 5.5 Hz), 4.48-4.31 (m, 2H), 2.17 (s, 3H), 1.15-1.26 (m, 3H); ¹³C
5 NMR (62.5 MHz, CDCl₃), major rotamer δ 169.7, 150.0, 129.0, 128.7, 127.3, 123.0, 117.4, 77.3,
6 62.3, 51.8, 21.8, 16.5. HRMS (ESI) m/z : [M+Na⁺] Calcd for C₁₄H₁₆N₂O₂Na 267.1104; Found
7 267.1109.

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15 *((1S*,4R*,6R*)-6-Methyl-2-phenyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-en-5-*

16 *yl)(phenyl)methanone (5c)*: A solution of **4c** (200 mg, 1.0 mmol) and nitrosobenzene (215 mg,
17 2.0 mmol) in CH₂Cl₂ (2 mL) was stirred 2 h at room temperature. Flash chromatography
18 (hexanes/AcOEt=8/2 + 5% of Et₃N) afforded a yellow semisolid (138 mg, 45%) containing ca.
19 10% of **4c**. ¹H NMR (250 MHz, CDCl₃) δ 7.57-7.37 (m, 5H), 7.06-6.91 (m, 2H), 6.74-6.61 (m,
20 3H), 6.73-6.61 (m, 1H), 6.23-6.13 (m, 1H), 5.75 (d, 1H, J = 5.0 Hz), 4.74-4.60 (m, 1H), 4.49 (bt,
21 1H, J = 2.7 Hz), 1.39-1.27 (m, 3H); ¹³C NMR (62.5 MHz, CDCl₃) δ 170.5, 150.0, 135.3, 130.4,
22 128.9, 128.6, 128.5, 128.3, 127.7, 127.5, 122.9, 117.3, 78.4, 62.1, 51.3, 16.4. HRMS (ESI) m/z :
23 [M+Na⁺] Calcd for C₁₉H₁₈N₂O₂Na 329.1260; Found 329.1255.

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36 *(1S*,4R*)-2-Phenyl-5-tosyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-ene (5d)*: A solution of **4d** (141
37 mg, 0.6 mmol) and nitrosobenzene (129 mg, 1.2 mmol,) in 1.2 mL of CH₂Cl₂ was stirred at room
38 temperature for 1.5 h. Removal of solvent gave a crude solid that was triturated with hexane and
39 methanol to afford a yellow solid (107 mg, 52%). M.p.= 115-116 °C. ¹H NMR (250 MHz,
40 CDCl₃) δ 7.84 (d, 2H, J = 8.3 Hz), 7.30 (d, 2H, J =8.6 Hz), 7.22-7.14 (m, 2H), 6.99-6.90 (m,
41 1H),6.89-6.82 (m, 2H), 6.71 (ddd, 1H, J = 2.0, 5.5 and 7.7 Hz), 6.13-6.02 (m, 2H), 4.47-4.40 (m,
42 1H), 3.62 (dd, 1H, J = 2.9 and 9.8 Hz), 3.31 (dd, 1H, J = 2.3 and 9.8 Hz), 2.41 (s, 3H); ¹³C NMR
43 (62.5 MHz, CDCl₃) δ 149.9, 143.7, 135.0, 130.9, 129.6, 128.5, 127.9, 126.2, 123.0, 117.3, 77.4,
44 56.2, 45.3, 21.6. HRMS (ESI) m/z : [M+Na⁺] Calcd for C₁₈H₁₈N₂O₃SNa 365.0930; Found
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(1*S**,4*R**,6*R**)-Benzyl 2,6-diphenyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate (**5e**).

A solution of **4e** (291 mg, 1.0 mmol) and nitrosobenzene (214 mg, 2.0 mmol,) in 2.0 mL of CH₂Cl₂ was stirred at room temperature for 1 h. Subsequent flash chromatography (hexanes/AcOEt= 9/1 + 5% Et₃N) afforded the title compound as a brownish oil (179 mg, 45%) containing ca 12% of starting **4e**. ¹H NMR (250 MHz, CD₃CN) δ 7.61-7.17 (m, 11H), 7.12 (d, 2H, *J*= 7.8 Hz), 7.03 (t, 1H, *J*=7.3 Hz), 6.90 (bs, 1H), 6.79 (bs, 1H), 6.41 (bs, 1H), 5.90-5.73 (m, 1H), 6.19-5.38 (m, 3H), 4.82 (t, 1H, 2.7 Hz); ¹³C NMR (62.5 MHz, CD₃CN) δ 156.5, 151.5, 151.3, 131.4, 130.4, 129.7, 129.6, 129.2, 128.9, 128.7, 128.5, 127.9, 127.8, 127.4, 123.7, 76.8, 67.8, 62.9, 59.6. HRMS (ESI) *m/z*: [M+Na⁺] Calcd for C₂₅H₂₂N₂O₃Na 421.1523; Found 421.1520.

Phenyl((1*S**,4*R**,6*R**)-2-Phenyl-6-(phenylethynyl)-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-en-5-yl)methanone (**5g**): A solution of **4g** (114 mg, 0.4 mmol) and nitrosobenzene (86 mg, 0.8 mmol,) in 0.8 mL of CH₂Cl₂ was stirred at room temperature for 1 hour. Removal of solvent provided a sticky oil which was purified by flash chromatography (hexanes/AcOEt=9/1+ 5% Et₃N). The title compound was recovered (82 mg, 52%) as a semisolid. The sample was not analytically pure as it contained ca 12% of starting **4g**. ¹H NMR (250 MHz, CDCl₃) (major rotamer) δ 7.59-6.64 (m, 15H), 6.84 (bs, 1H), 6.38 (t, 1H, *J*= 7.0 Hz), 5.90 (bs, 1H), 5.52 (bs, 1H), 4.85 (bs, 1H); ¹³C NMR (62.5 MHz, CDCl₃) δ 169.9, 149.4, 134.4, 131.8, 130.7, 129.8, 129.2, 128.7, 128.5, 128.3, 128.1, 127.7, 123.4, 122.2, 117.5, 84.8, 83.0, 78.0, 60.9, 47.0. HRMS (ESI) *m/z*: [M+Na⁺] Calcd for C₂₆H₂₀N₂ONa 415.1417; Found 415.1412.

1-((1*S**,4*R**,6*R**)-6-Hexyl-2-phenyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-en-5-yl)ethanone (**4h**):

A solution of **4h** (207 mg, 1.0 mmol) and nitrosobenzene (215 mg, 2.0 mmol) in CH₂Cl₂ (2 mL) was stirred 1 h at room temperature. Flash chromatography (hexanes/AcOEt= 8/2) afforded the title compound (176 mg, 56%) as a brown oil. ¹H NMR (250 MHz, CDCl₃), major rotamer δ

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3 7.28-7.16 (m, 2H), 7.03-6.92 (m, 3H), 6.67-6.52 (m, 1H), 6.22-6.06 (m, 1H), 5.76 (d, 1H, $J=5.7$
4 Hz), 4.60-4.46 (m, 1H), 4.37-4.24 (m, 1H), 2.16 (s, 3H), 1.47-1.17 (m, 10H), 0.97-0.79 (m, 3H).
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8 ^{13}C NMR (62.5 MHz, CDCl_3), major rotamer δ 170.0, 150.2, 129.2, 128.5, 127.0, 123.0, 117.5,
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10 77.4, 60.2, 56.3, 31.5, 30.4, 29.1, 25.8, 22.4, 13.9. HRMS (ESI) m/z : $[\text{M}+\text{Na}^+]$ Calcd for
11 $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_2\text{Na}$ 337.1886; Found 337.1991.

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15 *((1S*,4R*,6R*)-2,6-Diphenyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-en-5-yl)(phenyl)methanone (5I):*

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17 A solution of **4I** (261 mg, 1.0 mmol) and nitrosobenzene (214 mg, 2.0 mmol) in 2.0 mL of
18 CH_2Cl_2 was stirred at room temperature 30 min. Removal of solvent provided a sticky oil
19 purified by flash chromatography (hexanes/AcOEt=8/2+ 5% Et_3N). The title compound was
20 recovered after trituration (methanol) (224.7 mg, 61%) as a semisolid containing ca 13% of **4I**.
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22 ^1H NMR (250 MHz, CDCl_3) δ 7.70-6.76 (m, 16H), 6.05 (d, 1H, $J=4.7$ Hz), 5.98 (app t, 1H,
23 $J=6.7$ Hz), 5.69 (bs, 1H), 4.73 (bs, 1H). ^{13}C NMR (62.5 MHz, CDCl_3) δ 170.3, 149.8, 137.4,
24 134.9, 130.8, 128.7, 128.4, 128.3, 123.8, 127.8, 127.7, 126.5, 123.1, 121.1, 117.3, 79.1, 63.0,
25 57.7. HRMS (ESI) m/z : $[\text{M}+\text{Na}^+]$ Calcd for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ 391.1417 found 391.1412.

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36 **TiCl₃-mediated reduction of compound 5a** (Table 1, entry 7): A 25 mL round-bottom flask
37 was charged in this order with sodium acetate (300 mg, 3.65 mmol), methanol (1.25 mL), water
38 (0.875 mL), and compound **5a** (91 mg, 0.30 mmol). The reaction mixture was stirred at room
39 temperature while 1.2 mL of a 20% TiCl_3 solution in water was dropwise added. After 45 min
40 the solution was poured in 6 mL of water and extracted with AcOEt (4x8 mL). Combined
41 organic fractions were washed twice with 5 mL of 5% Na_2CO_3 to remove trace of acetic acid,
42 and once with 5 mL of brine. Evaporation of the dried (MgSO_4) organic phase afforded a sticky
43 oil that was subjected to flash chromatography (hexanes/AcOEt= 5/5 +5% Et_3N , $R_f=0.09$) to give
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methyl 2-((2S,3R)-1-acetyl-6-hydroxy-3-(phenylamino)-1,2,3,6-tetrahydropyridin-2-yl)acetate
(6a) as an oil (32 mg, 35%). ^1H NMR (250 MHz, CDCl_3) δ 7.26-7.16 (m, 2H), 6.82-6.63 (m,

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3 3H), 6.10-5.97 (m, 3H), 4.54 (t, 1H, $J=7.2$ Hz), 4.03-3.94 (m, 1H), 3.70 (s, 3H), 2.90 (dd, 1H, $J=$
4 7.5 and 17.0 Hz), 2.69 (dd, 1H, $J=7.0$ and 17.0 Hz), 1.69 (s, 3H). ^{13}C NMR (62.5 MHz, CDCl_3)
5 δ 173.7, 171.6, 145.7, 129.7, 129.4, 125.4, 118.5, 113.3, 70.3, 51.9, 50.6, 49.8, 37.3, 21.4. HRMS
6 (ESI) m/z : $[\text{M}+\text{Na}^+]$ Calcd for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}$ 327.1315; Found 327.1312.
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10 The faster eluting fraction of above flash chromatography ($R_f=0.30$) afforded *Methyl 2-*
11 *((2S*,3R*,6S*)-1-acetyl-6-methoxy-3-(phenylamino)-1,2,3,6-tetrahydropyridin-2-yl)acetate (7a)*
12 (48 mg, 50%) as yellow solid. M.p.=123-125 °C; ^1H NMR (250 MHz, CDCl_3) δ 7.25-7.16 (m,
13 2H), 6.81-6.70 (m, 1H), 6.66-6.37 (m, 2H), 6.05 (dd, 1H, $J=3.4$ and 10.1 Hz), 6.01-5.91 (m,
14 2H), 4.60 (dd, 1H, $J=5.9$ and 9.3 Hz), 3.90-3.81 (m, 1H), 3.72 (s, 3H), 3.64 (d, 1H, $J=5.1$ Hz),
15 3.31 (s, 3H), 3.05 (dd, 1H, $J=9.5$ and 17 Hz), 2.63 (dd, 1H, $J=5.8$ and 17 Hz), 2.02 (s, 3H). ^{13}C
16 NMR (62.5 MHz, CDCl_3) δ 173.2, 171.7, 145.6, 129.8, 129.0, 125.1, 118.4, 112.8, 75.7, 56.4,
17 51.8, 50.8, 49.9, 36.7, 21.6. HRMS (ESI) m/z : $[\text{M}+\text{Na}^+]$ Calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_4\text{Na}$ 341.1472
18 found 341.1466.
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33 **General procedures for the synthesis of protected (1-phenyl-1H-pyrrol-2-yl)-alkane-1-**
34 **amines. Method A:** Anhydrous CuCl (3.0 mg, 0.03 mmol) was charged into a dried Schlenk
35 tube followed by a methanol solution (0.13 M) of nitrosobenzene cycloadduct **5** (0.15 mmol).
36 The reaction mixture was stirred at room temperature and monitored by TLC analysis up to
37 complete consumption of the cycloadduct (ca 16h). After evaporation of the solvent, the crude
38 mixture was partitioned between CH_2Cl_2 and water and the aqueous layer extracted again with
39 CH_2Cl_2 . The combined organic layers were dried over MgSO_4 and filtered. The crude reaction
40 mixture was then purified by chromatography on silica gel as specified.
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52 **Method B (one-pot procedure):** Nitrosoarene (2.0 equiv) was added to a solution of 1,2-
53 dihydropyridine **4** in CH_2Cl_2 (0.5 M) at room temperature and the reaction mixture was
54 vigorously stirred until the 1,2-dihydropyridine was consumed (TLC analysis, usually 1h). The
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3 solvent was removed under a vacuum at room temperature and the residue was diluted with
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5 MeOH under a flow of argon. A catalytic amount of anhydrous CuCl (20 mol %) was added and
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7 the reaction was allowed to proceed at room temperature until the cycloadduct **5** was consumed
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9 (16-24 hours). After evaporation of the solvent, the crude mixture was partitioned between
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11 CH₂Cl₂ and water and the aqueous layer extracted again with CH₂Cl₂. The combined organic
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13 layers were dried over MgSO₄, filtered and evaporated under a vacuum. The crude reaction
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15 mixture was then purified by chromatography on silica gel.
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19 *Methyl 3-acetamido-3-(1-phenyl-1H-pyrrol-2-yl)propanoate (8a)*. (Table 1, entry 10): Following
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21 general procedure A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl (3.0 mg,
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23 0.03 mmol), methanol (1.15 mL) and bicycle **5a** (46 mg, 0.15 mmol). The reaction was
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25 vigorously stirred at room temperature for 16 hours. After the usual work-up, the crude reaction
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27 mixture was subjected to flash chromatography (hexanes/AcOEt= 2/3) to afford **8a** (31 mg,
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29 72%), as a pale brown amorphous solid; ¹H NMR (250 MHz, CD₃CN) δ 7.53-7.34 (m, 5H); 6.81
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31 (dd, 1H, *J* = 1.8, 2.9 Hz); 6.60 (m, 1H, exchange with D₂O, *NH*); 6.28 (ddd, 1H, *J* = 1.0, 1.8, 3.8
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33 Hz); 6.20 (dd, 1H, *J* = 2.8, 3.8 Hz); 5.22 (apparent q, 1H, *J* = 7.5 Hz); 3.54 (s, 3H); 2.76 (d, 2H, *J*
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35 = 7.5 Hz); 1.78 (s, 3H); ¹³C NMR (62.5 MHz, CDCl₃) δ 171.4, 168.4, 139.4, 131.7, 129.3, 127.8,
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37 126.2, 123.4, 108.2, 107.2, 51.7, 42.5, 38.8, 23.0. HRMS (ESI) *m/z*: [M+Na⁺] Calcd for
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39 C₁₆H₁₈N₂O₃Na 309.1210; Found 309.1213.
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46 *N-(1-(1-Phenyl-1H-pyrrol-2-yl)ethyl)acetamide (8b)*. (Table 2, entry 1): Following general
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48 procedure A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl (4.0 mg, 0.04
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50 mmol), methanol (1.53 mL) and bicycle **5b** (45 mg, 0.20 mmol). After 16 hours, the usual work-
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52 up afforded a crude mixture that was purified by preparative TLC (hexanes/AcOEt= 1/1) to
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54 afford **11b** as a colorless solid (23 mg, 50%); M.p.= 114-117 °C; ¹H NMR (250 MHz, CDCl₃) δ
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3 7.49-7.24 (m, 5H), 6.80 (s, 1H), 6.31-6.20 (m, 2H), 5.41 (d, 1H, $J= 6.25$ Hz), 5.19-5.05 (m, 1H),
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5 1.73 (s, 3H), 1.45 (d, 3H, $J= 6.75$ Hz); ^{13}C NMR (62.5 MHz, CDCl_3) δ 168.1, 139.6, 134.5,
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7 129.3, 127.7, 126.0, 123.2, 108.0, 106.9, 41.6, 23.0, 20.9. HRMS (ESI) m/z : $[\text{M}+\text{Na}^+]$ Calcd for
8 $\text{C}_{14}\text{H}_{16}\text{N}_2\text{ONa}$ 251.1151; Found 251.1158.
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12 *N*-(1-(1-Phenyl-1H-pyrrol-2-yl)ethyl)benzamide (**8c**). (Table 2, entry 2): Following general
13 procedure A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl (0.03 mmol, 3.0
14 mg), methanol (1.15 mL) and bicycle **5c** (46 mg, 0.15 mmol). The reaction was vigorously stirred
15 at room temperature for 16 hours. The usual work up gave a crude solid that was purified by
16 flash chromatography (hexanes/ AcOEt = 4/1) to afford **8c** (26.1 mg, 60%) as a white solid;
17 M.p.=106-109 °C; ^1H NMR (250 MHz, CDCl_3) δ 7.58-7.27 (m, 10H), 6.83 (dd, 1H, $J= 1.8$ and
18 2.7 Hz), 6.36 (ddd, 1H, $J=0.5, 1.8$ and 3.5 Hz), 6.30-6.25 (m, 1H), 6.05 (d, 1H, $J= 7.6$ Hz), 5.41-
19 5.27 (m, 1H), 1.57 (d, 3H, $J= 6.7$ Hz); ^{13}C NMR (62.5 MHz, CDCl_3) δ 165.8, 139.6, 134.4,
20 131.2, 129.3, 128.3, 127.7, 126.7, 125.9, 123.3, 108.0, 107.1, 42.0, 20.8. HRMS (ESI) m/z :
21 $[\text{M}+\text{Na}^+]$ Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{ONa}$ 313.1311; Found 313.1314.
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36 *4-Methyl-N-((1-phenyl-1H-pyrrol-2-yl)methyl)benzenesulfonamide* (**8d**). (Table 2, entry 4).
37 Following method A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl (0.03
38 mmol, 3.0 mg), methanol and **5d** (52 mg, 0.15 mmol). The reaction mixture was stirred at 70 °C
39 for 3 hours. The usual work-up afforded a crude reaction mixture that was purified by preparative
40 TLC to give the title compound (34 mg, 71%), as a pale yellow solid; M.p.=115-117 °C; ^1H
41 NMR (250 MHz, CDCl_3) δ 7.60 (app d, 2H, $J= 8.3$ Hz), 7.42-7.33 (m, 3H), 7.30-7.15 (m, 4H),
42 6.76 (dd, 1H, $J= 2.7, 1.9$ Hz), 6.20-6.10 (m, 2H), 4.34 (t, 1H, $J= 5.5$ Hz), 4.09 (d, 2H, $J= 5.7$ Hz),
43 2.43 (s, 3H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 143.3, 139.1, 136.5, 129.6, 129.3, 127.6, 127.1,
44 125.5, 123.5, 110.7, 108.5, 39.2, 21.5. HRMS (ESI) m/z : $[\text{M}+\text{Na}^+]$ Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2\text{SNa}$
45 349.0981; found 349.0985.
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4 *Benzyl (phenyl(1-phenyl-1H-pyrrol-2-yl)methyl)carbamate (8f)*. (Table 2, entry 7): In accordance
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6 with general procedure A, a 10 mL flame-dried Schlenk tube was charged with anhydrous CuCl
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8 (3.0 mg, 0.03 mmol), methanol (1.15 mL) and cycloadduct **5f** (60 mg, 0.15 mmol). The reaction
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10 mixture was stirred at 70 °C for 2 hours. The usual work-up provided a complex reaction mixture
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12 from which the title compound was isolated by preparative TLC (hexanes/AcOEt = 7 :3) (16 mg,
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14 28%) as a brownish oil. ¹H NMR (250 MHz, CDCl₃) δ 4.46-7.11 (m, 15H), 6.77 (dd, 1H *J*=1.9,
15
16 2.6 Hz), 6.20 (t, 1H, *J*=3.2 Hz), 6.04-5.98 (m, 1H), 5.92 (d, 1H, *J*=8.0 Hz), 5.27 (d, 1H, *J*=7.5
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18 Hz), 5.08-4.91 (m, 2H); ¹³C NMR (62.5 MHz, CDCl₃) δ 154.9, 141.0, 139.5, 136.4, 133.5,
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20 129.1, 128.5, 128.4, 128.1, 127.7, 127.4, 127.0, 126.5, 123.3, 108.7, 108.1, 66.8, 52.0. HRMS
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22 (ESI) *m/z*: [M+Na⁺] Calcd for C₂₅H₂₂N₂O₂Na 405.1573; Found 405.1575.

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27 *N-(3-Phenyl-1-(1-phenyl-1H-pyrrol-2-yl)prop-2-yn-1-yl)benzamide (8g)*. (Table 2, entry 8):
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29 Following general procedure A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl
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31 (3.0 mg, 0.03 mmol), methanol (1.15 mL) and **5g** (59 mg, 0.15 mmol). The reaction was
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33 vigorously stirred at rt for 19 hours. After the usual work-up, preparative TLC (hexanes/
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35 CH₂Cl₂ = 1/9) afforded the title compound (37 mg, 65%) as a pale yellow solid; M.p = 112-115
36
37 °C; ¹H NMR (250 MHz, CDCl₃) δ 7.66-7.58 (m, 2H), 7.52-7.27 (m, 13H), 6.86 (dd, 1H, *J*= 1.9
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39 and 2.8 Hz), 6.65 (dd, 1H, *J*= 1.8 and 3.5 Hz), 6.41 (d, 1H, *J*= 8.3 Hz), 6.36 (d, 1H, *J*= 8.3 Hz),
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41 6.30 (dd, 1H, *J*=3.0 and 3.5 Hz); ¹³C NMR (62.5 MHz, CDCl₃) δ 165.5, 139.4, 133.8, 131.8,
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43 131.6, 130.2, 129.4, 128.5, 128.4, 128.1, 128.0, 127.0, 126.3, 124.1, 122.6, 109.7, 108.3, 86.9,
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45 83.2, 39.0. HRMS (ESI) *m/z*: [M+Na⁺] Calcd for C₂₆H₂₀N₂ONa 399.1468; Found 399.1474.

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50 *N-(1-(1-Phenyl-1H-pyrrol-2-yl)heptyl)acetamide (8h)*. (Table 2, entry 9): In accordance with
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52 general procedure B, nitrosobenzene (43 mg, 0.4 mmol) was added to a solution of **4h** (42 mg,
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54 0.20 mmol) in CH₂Cl₂ (0.4 mL) and stirred at rt. The residue was diluted with methanol (1.54
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56 mL) and anhydrous CuCl (4.0 mg, 0.04 mmol) was added. After 24 hours, the usual work-up
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3 afforded a crude mixture that was purified by preparative TLC (hexanes/AcOEt= 7/3) to afford
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5 **8h** as a pale yellow amorphous solid (26 mg, 46%). ¹H NMR (250 MHz, CDCl₃) δ 7.28-7.45 (m,
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7 5H); 6.77 (app t, 1H, *J* = 2.0 Hz); 6.21-6.26 (m, 2H); 5.47 (bd, 1H, *J* = 8.0 Hz, *NH*); 4.96 (app q,
8
9 1H, *J* = 8.0 Hz); 1.81 (s, 3H); 1.68-1.75 (m, 2H); 1.20-1.40 (m, 8H); 0.80-0.89 (m, 3H); ¹³C
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11 NMR (62.5 MHz, CDCl₃) δ 168.5, 139.8, 134.4, 129.4, 127.9, 126.5, 123.0, 108.3, 106.6, 46.0,
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13 35.9, 31.6, 29.0, 26.0, 23.0, 22.6, 14.2. HRMS (ESI) *m/z*: [M+Na⁺] Calcd for C₁₉H₂₆N₂ONa
14
15 321.1937; Found 321.1943.
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20 *N*-(Phenyl(1-phenyl-1*H*-pyrrol-2-yl)methyl)acetamide (**8i**). (Table 2, entry 10): In accordance
21
22 with general procedure A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl (0.03
23
24 mmol, 3.0 mg), methanol (1.15 mL) and bicycle **5i** (43 mg, 0.15 mmol). The reaction was
25
26 vigorously stirred at room temperature for 16 hours. The usual work-up afforded a crude mixture
27
28 that was purified by flash chromatography (hexanes/AcOEt= 7/3) to give the title compound as
29
30 an amorphous solid (26 mg, 60%). ¹H NMR (250 MHz, CDCl₃) δ 7.45-7.11 (m, 10H), 6.83-6.78
31
32 (m, 1H), 6.25-6.16 (m, 2H), 5.99 (dd, 1H, *J* = 1.7 and 3.5 Hz), 5.91 (d, 1H, *J* = 7.7 Hz), 1.87 (s,
33
34 3H); ¹³C NMR (62.5 MHz, CDCl₃) δ 168.4, 140.8, 133.4, 132.3, 129.2, 128.3, 127.8, 127.3,
35
36 127.0, 126.3, 123.3, 108.9, 108.1, 50.1, 23.0. HRMS (ESI) *m/z*: [M+Na⁺] Calcd for
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38 C₁₉H₁₈N₂ONa 313.1311; Found 313.1320.
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44 *N*-(Phenyl(1-phenyl-1*H*-pyrrol-2-yl)methyl)benzamide (**8l**). (Table 2, entry 12): In accordance
45
46 with general procedure B, nitrosobenzene (43 mg, 0.4 mmol) was added to a solution of **4l** (52
47
48 mg, 0.20 mmol) in CH₂Cl₂ (0.4 mL) and stirred at rt. The residue was diluted with methanol
49
50 (1.54 mL) and anhydrous CuCl (0.04 mmol, 4.0 mg) was added. After 18 hours, the usual work-
51
52 up afforded a crude mixture that was subjected to flash chromatography to give **8l** (41 mg, 59%)
53
54 as a yellow amorphous solid. ¹H NMR (250 MHz, CDCl₃) δ 7.68-7.60 (m, 2H), 7.53-7.18 (m,
55
56 13H), 6.86-6.81 (m, 1H), 6.53 (d, 1H, *J* = 7.2 Hz), 6.41 (d, 1H, *J* = 7.8 Hz), 6.24 (t, 1H, *J* = 3.2 Hz),
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3 6.09-6.04 (m, 1H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 165.9, 140.8, 139.6, 134.2, 133.3, 131.5,
4
5 129.3, 128.5, 128.4, 127.8, 127.4, 127.1, 126.9, 126.3, 123.5, 108.2, 50.6. HRMS (ESI) m/z:
6
7 [M+Na⁺] Calcd for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{ONa}$ 375.1468; Found 375.1471.
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12 **Supporting Information Available:** Text giving detailed experimental procedures and
13 characterization data for all new compounds. This material is available free of charge via the
14 Internet at <http://pubs.acs.org>.
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22 Notes

23
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