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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

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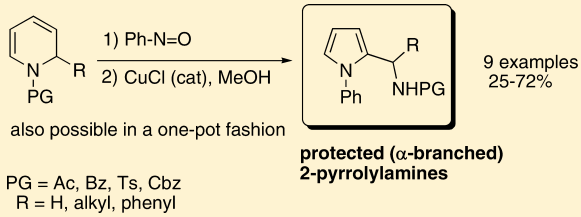
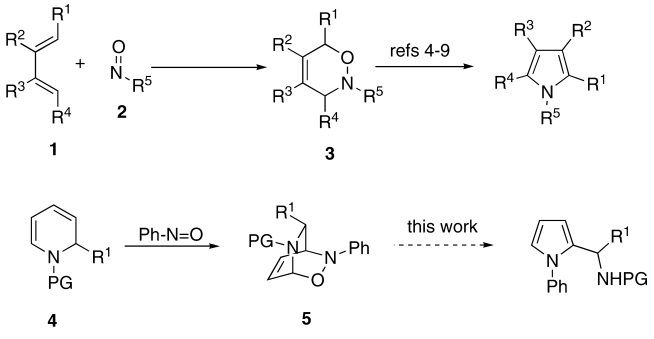
Supporting Information

ABSTRACT: 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)alkylamides. 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 BF_3–Et_2O has been reported to give low yields of pyrrole products, because of the tendency of these compounds to undergo polymerization under these reaction conditions.[8] More recently, the reductive cleavage ($NaBH_4$, $Mo(CO)_6$ in CH_3CN–H_2O 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 cannot afford a pyrrole derivative, unless a double ring fragmentation of the *bicyclic* nitroso cycloadduct occurs.

We recently reported a novel preparation of *N*-acetyl-1,2-dihydropyridyl acetic acid methyl ester **4a** (see Scheme of Table 1) and its Diels–Alder reactions with nitroso dienophiles.[10] The reductive cleavage of the N–O bond showed some interesting features with *inverse* adducts derived from acylnitroso dienophiles.[10] Remarkably, the reductive cleavage of the N–O bond of phenylnitroso *direct* cycloadduct **5a** showed a completely different and in some cases unexpected behavior, which we now report in detail in Table 1. When direct adduct **5a** was treated with $[Mo(CO)_6]$ in a CH_3CN/H_2O mixture at 65 °C, only a retro-Diels–Alder process was found (entry 1, Table 1).[10] Also the addition of $NaBH_4$, commonly used in the reductive cleavage of N–O bonds of oxazines,[9,11] promoted the formation of the starting dihydropyridine **4a** (entry 2). The use of an alane reagent such as AlH_3, freshly prepared from $LiAlH_4$ and sublimed $AlCl_3$,[12] afforded a complex mixture of unidentified products (entry 3). Also SmI_2 gave a complex mixture in which the signals of starting material **5a** were present (entry 4).[13] To our surprise, the use of titanocene(III) chloride (Cp_2TiCl), generated in situ from Cp_2TiCl_2 and zinc metal in the presence of alcoholic solvents afforded substantial amounts of pyrrole derivative **8a** without isolation of N–O cleaved product **6a** (entries 5 and 6).

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

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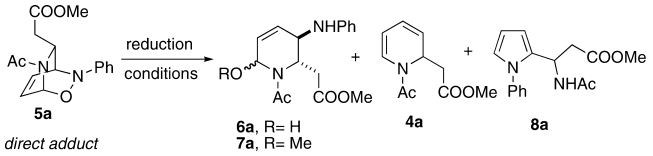
Table 1. Screening of Reaction Conditions for the Reductive N−O Cleavage of Phenyl Nitroso Cycloadduct 5a[a]



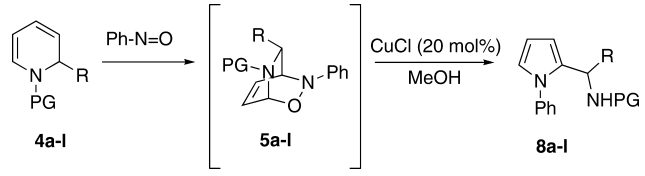
entry	reaction conditions	products (%)[b] (**6a**−**7a**/**4a**/**8a**)
1	$Mo(CO)_6$, CH_3CN/H_2O, 60 °C, 5 h	<2/>96/<2
2	$Mo(CO)_6$, $NaBH_4$, $MeOH/H_2O$, 65 °C, 15 h	<2/>96/<2
3	AlH_3, Et_2O, 0 °C to rt, 5 h	complex mixture
4	SmI_2, 0 °C to rt, 5 h	complex mixture
5	Cp_2TiCl, THF/MeOH, −30 °C to rt, 20 h	<2/35/65
6	Cp_2TiCl, THF/EtOH, −30 °C to rt, 20 h	<2/42/58
7	$TiCl_3$, $MeOH/H_2O$, rt, 45 min	60 (**7a**), 40 (**6a**)
8	Zn, HCl, MeOH, rt, 15 h	complex mixture
9	CuCl (1.0 equiv), MeOH, rt, 3 h	<15/<2/>80
10	CuCl (0.2 equiv), MeOH, rt, 18 h	<15/<2/>80[c]
11[d]	CuI (0.2 equiv), MeOH, rt, 24 h	<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 byproduct. [d]Conversion 70%.

find that $TiCl_3$, which is usually the preferred source of titanium(III), being commercially available as a solution in hydrochloric acid, did not afford pyrrole derivatives or starting dihydropyridine **4a**, but only promoted the reductive cleavage of the N−O bond (compound **6a**) accompanied by 1,2,3,6-tetrahydropyridine **7a** (entry 7). It was also found that a Ti(III) species is not essential to obtain pyrrole derivatives. For example, simple zinc metal in hydrochloric MeOH at room temperature afforded compound **8a**, albeit with very low yield and in a complex reaction mixture (entry 8). The heterogeneous reaction conditions and the long reaction time connected with the use of Cp_2TiCl stimulated the search for other procedures. A satisfactory solution was found by the use of stoichiometric amounts of CuCl in MeOH at room temperature.[15] To our delight, the reaction was complete in 3h at rt and pyrrole **8a** was isolated with a good yield after chromatographic purification (entry 9). From the same chromatography it was also possible to obtain in the second eluting fractions a mixture of inseparable tetrahydropyridines, including compounds **6a** and **7a**. Two facts are worthy of mention: (i) the reaction can be carried out at room temperature and (ii) also catalytic amounts of CuCl (20 mol %) gave the same results, although it was necessary to use a prolonged reaction time (entry 10). The use of catalytic amounts of CuI proved to be less effective and less selective for the formation of the pyrrole derivative (entry 11). It should be noted that while the synthesis of 2-pyrrolylalanine has been reported in view of its peculiarity in peptide chemistry,[16] the synthesis of 2-pyrrolyl-*β*-alanine derivatives, such as **8a**, has only few precedents, which furthermore have scarce preparative importance.[17]

The scope of the synthesis of (1-phenyl-1*H*-pyrrol-2-yl)-alkane-1-amines from *N*-phenylnitroso cycloadducts with a variety of 1,2-dihydropyridines was examined in detail. In general, the synthesis of 1,2-dihydropyridines bearing different protecting groups (PG) on the nitrogen and substituents at the 2-position **4b**−**l** was accomplished by organometallic addition to N-protected pyridinium salts (see Experimental Section).[18] The subsequent use of nitrosobenzene afforded with complete regioselectivity the corresponding 3-oxa-2,5-diazabicyclo[2.2.2]-oct-7-enes (**5b**−**l**), which were used as precursors of pyrrole derivatives **8b**−**l** using catalytic amounts (20 mol %) of CuCl (procedure A, Table 2). With cycloadducts **5b** and **5c** derived from acetyl and benzoyl protected dihydropyridines **4b** and **4c**, respectively, the corresponding pyrrole derivatives were obtained with moderate yields after 16 h at room temperature (entries 1 and 2, Table 2). On the other hand, the use of sulfonyl or carbobenzyloxy protecting groups in the same reaction

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_6H_{13}	Ac	46 (**8h**)
10	A	Ph	Ac	60 (**8i**)
11	B	CH_2COOCH_3	Ac	52 (**8a**)
12	B	Ph	PhCO	59 (**8l**)
13	B	C_6H_{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), 16 h at rt. Reaction conditions B: Compound **4** (0.20 mmol), nitrosobenzene (0.40 mmol), CH_2Cl_2 (0.4 mL), 1 h at 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 3 h.

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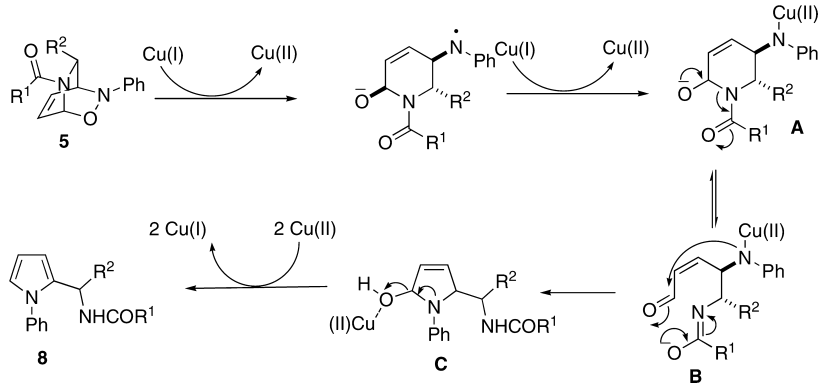
Scheme 2. Schematization of the Plausible Mechanism for the Formation of Protected α-Branched 2-Pyrrolylamines Catalyzed by CuCl



conditions proved to be less effective (entries 3−7). In particular, *N*-tosyl derived adduct **5d** was not reactive with CuCl at room temperature (entry 3). However, it was possible to obtain with a good yield the corresponding pyrrole derivative just by warming the reaction mixture at 70 °C for 3 h (entry 4). On the other hand, Cbz-protected adducts **5e** and **5f** mainly produced a complex mixture of ring-opening products even at room temperature (entries 5 and 6). The corresponding pyrrole derivative **8f** was obtained only with a low yield with the phenyl-substituted compound **5f** in refluxing methanol (entry 7) or in the simplified one-pot procedure (vide infra, entry 15). Moderate yields of pyrrole derivatives were obtained with nitrosobenzene cycloadducts with substituted amide protected 1,2-dihydropyridine (entries 8−10).

As found for compound **5a**,[10] also direct adducts **5b−i** showed some decomposition via retro-Diels−Alder reactions to the corresponding starting dihydropyridines **4b−i** during chromatographic purification on silica gel.[12] To address this problem, a one-pot two-step procedure (procedure B) without the isolation of the intermediate nitrosobenzene-1,2-dihydropyridine cycloadduct was in some cases applied (entries 11−15).

For example, dihydropyridine **4a** was allowed to react with nitrosobenzene (2.0 equiv) in CH_2Cl_2 at rt for 1 h. After evaporation of the solvent, methanol was added followed by anhydrous CuCl (20 mol %), continuing the stirring for 24 h. With this simplified procedure the overall yields can be increased, as it is no more necessary to isolate the corresponding nitrosobenzene-dihydropyridine cycloadduct (entries 11−15). In fact, compounds of type **5** can be isolated from silica gel pretreated with NEt_3 with low to moderate yields (35−71%), and they are invariably obtained in mixture with the corresponding starting dihydropyridines. Without a reasonable explanation, the reaction conditions B allow in one case the obtainment of the corresponding pyrrole in milder reaction conditions (cf. entry 7 and entry 15). On the other hand, with a particular substitution pattern (i.e., dihydropyridine **4g**, containing a triple bond), the one-pot procedure cannot be applied.

As regards the reaction mechanism, it is plausible that the reducing agent in a protic solvent reduces the N−O bond and generates the corresponding 1,2,3,6-tetrahydropyridine **A** (Scheme 2). To explain the ring fragmentation of the six-membered piperidine nucleus, it is proposed that cyclic *N*-acetylated hemiaminal **A**, which reasonably exists in equilibrium with the corresponding open-chain amidoaldehyde **B**, undergoes an intramolecular ring closure to give the five-membered hemiaminal **C**. The subsequent dehydration of the hydroxypyrroline **C** followed by oxidation with Cu(II) furnishes the pyrrole nucleus while regenerating the copper(I) catalyst. It is important to emphasize that the transformation into pyrrole derivatives occurs effectively only when the protecting group of the endocyclic piperidine nitrogen is sufficiently electron-withdrawing (PG = Ac, PhCO, Ts) to shift the equilibrium from species **A** to open-chain species **B**. In fact, the use of Cbz as protecting group proved to be less effective for the formation of the corresponding pyrrole derivatives, and complex mixtures of methoxy tetrahydropyridines were observed as the main products.

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. ^{1}H NMR spectra were recorded at 250 MHz. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: δ 7.26, deuteroacetonitrile: 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 (deuterochloroform: δ 77.0, deuteroacetonitrile: 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] and **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

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charged, under argon protection, with pyridine (0.80 mL, 10 mmol), anhydrous THF (15 mL) and MeMgI (1.5 M in Et_2O, 13.3 mL, 20 mmol). The reaction mixture was cooled to −78 °C, and freshly distilled AcCl (0.71 mL, 10 mmol) was dropwise added over 5 min. The reaction was allowed to reach 0 °C and vigorously stirred for 4 h. The reaction mixture was poured into ice−water and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and filtered. Subsequent flash chromatography (hexanes/AcOEt = 7/3) afforded **4b** (600 mg, 44%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$), major rotamer δ 6.39 (d, 1H, J = 7.5 Hz), 5.86 (dd, 1H, J = 5.2 and 9.5 Hz), 5.71−5.60 (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); ^{13}C NMR (62.5 MHz, $CDCl_3$), major rotamer δ 169.0, 126.0, 124.4, 121.6, 120.0, 106.8, 46.5, 18.4; HRMS (ESI) m/z [M + Na^+] Calcd for $C_8H_{11}NONa$ 160.0733, found 160.0725.

*(2-Methylpyridin-1(2H)-yl)(phenyl)methanone (**4c**).* 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 Et_2O, 13.3 mL, 20 mmol). The reaction mixture was cooled to −78 °C, and freshly distilled BzCl (1.2 mL, 10 mmol) was dropwise added over 5 min. The reaction was allowed to react at −78 °C for 3 h and carefully quenched with NH_4Cl satd solution (5 mL). The resulting mixture was extracted with Et_2O (3 × 15 mL). The evaporation of the dried ($MgSO_4$) organic layers afforded a crude product which was purified by flash chromatography (hexanes/AcOEt = 9/1) to give a 81/19 mixture of 1,2- and 1,4-dihydropyridines. Compound **4c** was isolated by preparative TLC (hexanes/CH_2Cl_2 = 2/8) as an oil (996 mg, 50%): ^{1}H NMR (250 MHz, $CDCl_3$), major rotamer δ 7.64−7.36 (m, 5H), 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), 1.24 (d, 3H, J = 6.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$), major rotamer δ 169.5, 134.8, 133.3, 130.5, 128.3, 126.2, 125.6, 120.5, 106.3, 47.6, 12.1; HRMS (ESI) m/z [M + Na^+] Calcd for $C_{13}H_{13}NONa$ 222.0889, found 222.0885.

*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 h the reaction mixture was quenched with water (7.5 mL) and $NaHCO_3$ satd solution (1.5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, 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: ^{1}H NMR (250 MHz, $CDCl_3$), 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); ^{13}C NMR (62.5 MHz, $CDCl_3$), 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 $C_{13}H_{21}NONa$ 230.1521 found 230.1525.

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 CH_2Cl_2. The reaction mixture was stirred at rt and monitored by TLC analysis. Removal of the solvent in a vacuum below 30 °C gave a residue that was then purified as specified.

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 CH_2Cl_2 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 Et_3N) afforded **5b** (131 mg, 54%) as a sticky oil containing 14% of **4b**: ^{1}H NMR (250 MHz, $CDCl_3$), 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, 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); ^{13}C NMR (62.5 MHz, $CDCl_3$), major rotamer δ 169.7, 150.0, 129.0, 128.7, 127.3, 123.0, 117.4, 77.3, 62.3, 51.8, 21.8, 16.5; HRMS (ESI) m/z [M + Na^+] Calcd for $C_{14}H_{16}N_2O_2Na$ 267.1104, found 267.1109.

((1S,4R*,6R*)-6-Methyl-2-phenyl-3-oxa-2,5-diazabicyclo[2.2.2]-oct-7-en-5-yl)(phenyl)methanone (**5c**).* A solution of **4c** (200 mg, 1.0 mmol) and nitrosobenzene (215 mg, 2.0 mmol) in CH_2Cl_2 (2 mL) was stirred 2 h at room temperature. Flash chromatography (hexanes/AcOEt =8/2 + 5% of Et_3N) afforded a yellow semisolid (138 mg, 45%) containing ca. 10% of **4c**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.57−7.37 (m, 5H), 7.06−6.91 (m, 2H), 6.74−6.61 (m, 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, 1H, J = 2.7 Hz), 1.39−1.27 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.5, 150.0, 135.3, 130.4, 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 [M + Na^+] Calcd for $C_{19}H_{18}N_2O_2Na$ 329.1260, found 329.1255.

(1S,4R*)-2-Phenyl-5-tosyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-ene (**5d**).* A solution of **4d** (141 mg, 0.6 mmol) and nitrosobenzene (129 mg, 1.2 mmol,) in 1.2 mL of CH_2Cl_2 was stirred at room temperature for 1.5 h. Removal of solvent gave a crude solid that was triturated with hexane and methanol to afford a yellow solid (107 mg, 52%): mp = 115−116 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 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, 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, 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); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 149.9, 143.7, 135.0, 130.9, 129.6, 128.5, 127.9, 126.2, 123.0, 117.3, 77.4, 56.2, 45.3, 21.6; HRMS (ESI) m/z [M + Na^+] Calcd for $C_{18}H_{18}N_2O_3SNa$ 365.0930, found 365.0928.

(1S,4R*,6R*)-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 CH_2Cl_2 was stirred at room temperature for 1 h. Subsequent flash chromatography (hexanes/AcOEt = 9/1 + 5% Et_3N) afforded the title compound as a brownish oil (179 mg, 45%) containing ca. 12% of starting **4e**: ^{1}H NMR (250 MHz, CD_3CN) 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); ^{13}C NMR (62.5 MHz, CD_3CN) 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 $C_{25}H_{22}N_2O_3Na$ 421.1523, found 421.1520.

Phenyl((1S,4R*,6R*)-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 CH_2Cl_2 was stirred at room temperature for 1 h. Removal of solvent provided a sticky oil, which was purified by flash chromatography (hexanes/AcOEt = 9/1+ 5% Et_3N). 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**: ^{1}H NMR (250 MHz, $CDCl_3$) (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); ^{13}C NMR (62.5 MHz, $CDCl_3$) 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 $C_{26}H_{20}N_2ONa$ 415.1417, found 415.1412.

1-((1S,4R*,6R*)-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 CH_2Cl_2 (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: ^{1}H NMR (250 MHz, $CDCl_3$), major rotamer δ 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 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); ^{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, 77.4, 60.2, 56.3, 31.5, 30.4, 29.1, 25.8, 22.4, 13.9; HRMS (ESI) m/z [M + Na^+] Calcd for $C_{19}H_{26}N_2O_2Na$ 337.1886, found 337.1991.

((1S,4R*,6R*)-2,6-Diphenyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-en-5-yl)(phenyl)methanone (**5l**).* A solution of **4l** (261 mg, 1.0 mmol) and nitrosobenzene (214 mg, 2.0 mmol) in 2.0 mL of CH_2Cl_2 was stirred at room temperature 30 min. Removal of solvent provided a

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sticky oil purified by flash chromatography (hexanes/AcOEt = 8/2 + 5% Et_3N). The title compound was recovered after trituration (methanol) (224.7 mg, 61%) as a semisolid containing ca. 13% of **4l**: ^{1}H 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, 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, 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, 57.7; HRMS (ESI) m/z [M + Na$^+$] Calcd for $C_{24}H_{20}N_2O_2Na$ 391.1417 found 391.1412.

$TiCl_3$-Mediated Reduction of Compound 5a (Table 1, entry 7). A 25 mL round-bottom flask was charged in this order with sodium acetate (300 mg, 3.65 mmol), methanol (1.25 mL), water (0.875 mL), and compound **5a** (91 mg, 0.30 mmol). The reaction mixture was stirred at room temperature while 1.2 mL of a 20% $TiCl_3$ solution in water was dropwise added. After 45 min the solution was poured in 6 mL of water and extracted with AcOEt (4 × 8 mL). Combined organic fractions were washed twice with 5 mL of 5% Na_2CO_3 to remove traces of acetic acid, and once with 5 mL of brine. Evaporation of the dried ($MgSO_4$) organic phase afforded a sticky oil that was subjected to flash chromatography (hexanes/AcOEt = 5/5 +5% Et_3N, R_f = 0.09) to give methyl 2-((2*S*,3*R*)-1-acetyl-6-hydroxy-3-(phenylamino)-1,2,3,6-tetrahydropyridin-2-yl)-acetate (**6a**) as an oil (32 mg, 35%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26−7.16 (m, 2H), 6.82−6.63 (m, 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 = 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, $CDCl_3$) 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 (ESI) m/z [M + Na$^+$] Calcd for $C_{16}H_{20}N_2O_4Na$ 327.1315, found 327.1312.

The faster eluting fraction of above flash chromatography (R_f = 0.30) afforded methyl 2-((2*S**,3*R**,6*S**)-1-acetyl-6-methoxy-3-(phenylamino)-1,2,3,6-tetrahydropyridin-2-yl)acetate (**7a**) (48 mg, 50%) as yellow solid: mp = 123−125 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25−7.16 (m, 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, 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), 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 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, 51.8, 50.8, 49.9, 36.7, 21.6; HRMS (ESI) m/z [M + Na$^+$] Calcd for $C_{17}H_{22}N_2O_4Na$ 341.1472 found 341.1466.

General Procedures for the Synthesis of Protected (1-Phenyl-1*H*-pyrrol-2-yl)-alkane-1-amines. Method A. Anhydrous CuCl (3.0 mg, 0.03 mmol) was charged into a dried Schlenk tube followed by a methanol solution (0.13 M) of nitrosobenzene cycloadduct **5** (0.15 mmol). The reaction mixture was stirred at room temperature and monitored by TLC analysis up to complete consumption of the cycloadduct (ca. 16h). After evaporation of the solvent, the crude mixture was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted again with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and filtered. The crude reaction mixture was then purified by chromatography on silica gel as specified.

Method B (One-Pot Procedure). Nitrosoarene (2.0 equiv) was added to a solution of 1,2-dihydropyridine **4** in CH_2Cl_2 (0.5 M) at room temperature and the reaction mixture was vigorously stirred until the 1,2-dihydropyridine was consumed (TLC analysis, usually 1 h). The solvent was removed under a vacuum at room temperature and the residue was diluted with MeOH under a flow of argon. A catalytic amount of anhydrous CuCl (20 mol %) was added, and the reaction was allowed to proceed at room temperature until the cycloadduct **5** was consumed (16−24 h). After evaporation of the solvent, the crude mixture was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted again with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated under a vacuum. The crude reaction mixture was then purified by chromatography on silica gel.

*Methyl 3-acetamido-3-(1-phenyl-1H-pyrrol-2-yl)propanoate (**8a**) (Table 1, entry 10).* Following general procedure A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl (3.0 mg, 0.03 mmol), methanol (1.15 mL) and bicycle **5a** (46 mg, 0.15 mmol). The reaction was vigorously stirred at room temperature for 16 h. After the usual workup, the crude reaction mixture was subjected to flash chromatography (hexanes/AcOEt = 2/3) to afford **8a** (31 mg, 72%), as a pale brown amorphous solid: ^{1}H NMR (250 MHz, CD_3CN) δ 7.53−7.34 (m, 5H); 6.81 (dd, 1H, J = 1.8, 2.9 Hz); 6.60 (m, 1H, exchange with D_2O, N*H*); 6.28 (ddd, 1H, J = 1.0, 1.8, 3.8 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 = 7.5 Hz); 1.78 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.4, 168.4, 139.4, 131.7, 129.3, 127.8, 126.2, 123.4, 108.2, 107.2, 51.7, 42.5, 38.8, 23.0; HRMS (ESI) m/z [M + Na$^+$] Calcd for $C_{16}H_{18}N_2O_3Na$ 309.1210, found 309.1213.

*N-(1-(1-Phenyl-1H-pyrrol-2-yl)ethyl)acetamide (**8b**) (Table 2, entry 1).* Following general procedure A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl (4.0 mg, 0.04 mmol), methanol (1.53 mL) and bicycle **5b** (45 mg, 0.20 mmol). After 16 h, the usual workup afforded a crude mixture that was purified by preparative TLC (hexanes/AcOEt = 1/1) to afford **11b** as a colorless solid (23 mg, 50%): mp = 114−117 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 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), 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, 129.3, 127.7, 126.0, 123.2, 108.0, 106.9, 41.6, 23.0, 20.9; HRMS (ESI) m/z [M + Na$^+$] Calcd for $C_{14}H_{16}N_2ONa$ 251.1151, found 251.1158.

*N-(1-(1-Phenyl-1H-pyrrol-2-yl)ethyl)benzamide (**8c**) (Table 2, entry 2).* Following general procedure A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl (0.03 mmol, 3.0 mg), methanol (1.15 mL) and bicycle **5c** (46 mg, 0.15 mmol). The reaction was vigorously stirred at room temperature for 16 h. The usual work up gave a crude solid that was purified by flash chromatography (hexanes/AcOEt = 4/1) to afford **8c** (26.1 mg, 60%) as a white solid: mp = 106−109 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.58−7.27 (m, 10H), 6.83 (dd, 1H, J = 1.8 and 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), 5.41−5.27 (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, 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 [M + Na$^+$] Calcd for $C_{19}H_{18}N_2ONa$ 313.1311, found 313.1314.

*4-Methyl-N-((1-phenyl-1H-pyrrol-2-yl)methyl)benzenesulfonamide (**8d**) (Table 2, entry 4).* Following method A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl (3.0 mg, 0.03 mmol), methanol and **5d** (52 mg, 0.15 mmol). The reaction mixture was stirred at 70 °C for 3 h. The usual workup afforded a crude reaction mixture that was purified by preparative TLC to give the title compound (34 mg, 71%), as a pale yellow solid: mp = 115−117 °C; ^{1}H 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), 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), 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, 125.5, 123.5, 110.7, 108.5, 39.2, 21.5; HRMS (ESI) m/z [M + Na$^+$] Calcd for $C_{18}H_{18}N_2O_2SNa$ 349.0981, found 349.0985.

*Benzyl (phenyl(1-phenyl-1H-pyrrol-2-yl)methyl)carbamate (**8f**) (Table 2, entry 7).* In accordance with general procedure A, a 10 mL flame-dried Schlenk tube was charged with anhydrous CuCl (3.0 mg, 0.03 mmol), methanol (1.15 mL) and cycloadduct **5f** (60 mg, 0.15 mmol). The reaction mixture was stirred at 70 °C for 2 h. The usual workup provided a complex reaction mixture from which the title compound was isolated by preparative TLC (hexanes/AcOEt = 7:3) (16 mg, 28%) as a brownish oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.46−7.11 (m, 15H), 6.77 (dd, 1H J = 1.9, 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 Hz), 5.08−4.91 (m, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 154.9, 141.0, 139.5, 136.4, 133.5, 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 (ESI) m/z [M + Na$^+$] Calcd for $C_{25}H_{22}N_2O_2Na$ 405.1573, found 405.1575.

*N-(3-Phenyl-1-(1-phenyl-1H-pyrrol-2-yl)prop-2-yn-1-yl)-benzamide (**8g**) (Table 2, entry 8).* Following general procedure A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl (3.0 mg, 0.03 mmol), methanol (1.15 mL) and **5g** (59 mg, 0.15 mmol). The reaction was vigorously stirred at rt for 19 h. After the usual workup, preparative TLC (hexanes/CH_2Cl_2 = 1/9) afforded the title compound (37 mg, 65%) as a pale yellow solid: mp = 112−115 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.66−7.58 (m, 2H), 7.52−7.27 (m, 13H), 6.86 (dd, 1H, J = 1.9 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), 6.30 (dd, 1H, J=3.0 and 3.5 Hz); ^{13}C NMR

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(62.5 MHz, $CDCl_3$) δ 165.5, 139.4, 133.8, 131.8, 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, 83.2, 39.0; HRMS (ESI) m/z [M + Na^+] Calcd for $C_{26}H_{20}N_2ONa$ 399.1468, found 399.1474.

*N-(1-(1-Phenyl-1H-pyrrol-2-yl)heptyl)acetamide (**8h**) (Table 2, entry 9).* In accordance with general procedure B, nitrosobenzene (43 mg, 0.4 mmol) was added to a solution of **4h** (42 mg, 0.20 mmol) in CH_2Cl_2 (0.4 mL) and stirred at rt. The residue was diluted with methanol (1.54 mL) and anhydrous CuCl (4.0 mg, 0.04 mmol) was added. After 24 h, the usual workup afforded a crude mixture that was purified by preparative TLC (hexanes/AcOEt = 7/3) to afford **8h** as a pale yellow amorphous solid (26 mg, 46%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28−7.45 (m, 5H); 6.77 (app t, 1H, J = 2.0 Hz); 6.21−6.26 (m, 2H); 5.47 (bd, 1H, J = 8.0 Hz, N*H*); 4.96 (app q, 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); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.5, 139.8, 134.4, 129.4, 127.9, 126.5, 123.0, 108.3, 106.6, 46.0, 35.9, 31.6, 29.0, 26.0, 23.0, 22.6, 14.2; HRMS (ESI) m/z [M + Na^+] Calcd for $C_{19}H_{26}N_2ONa$ 321.1937, found 321.1943.

*N-(Phenyl(1-phenyl-1H-pyrrol-2-yl)methyl)acetamide (**8i**) (Table 2, entry 10).* In accordance with general procedure A, a 10 mL dried Schlenk tube was charged with anhydrous CuCl (0.03 mmol, 3.0 mg), methanol (1.15 mL) and bicycle **5i** (43 mg, 0.15 mmol). The reaction was vigorously stirred at room temperature for 16 h. The usual workup afforded a crude mixture that was purified by flash chromatography (hexanes/AcOEt = 7/3) to give the title compound as an amorphous solid (26 mg, 60%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.45−7.11 (m, 10H), 6.83−6.78 (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, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 168.4, 140.8, 133.4, 132.3, 129.2, 128.3, 127.8, 127.3, 127.0, 126.3, 123.3, 108.9, 108.1, 50.1, 23.0; HRMS (ESI) m/z [M + Na^+] Calcd for $C_{19}H_{18}N_2ONa$ 313.1311, found 313.1320.

*N-(Phenyl(1-phenyl-1H-pyrrol-2-yl)methyl)benzamide (**8l**) (Table 2, entry 12).* In accordance with general procedure B, nitrosobenzene (43 mg, 0.4 mmol) was added to a solution of **4l** (52 mg, 0.20 mmol) in CH_2Cl_2 (0.4 mL) and stirred at rt. The residue was diluted with methanol (1.54 mL), and anhydrous CuCl (0.04 mmol, 4.0 mg) was added. After 18 h, the usual workup afforded a crude mixture that was subjected to flash chromatography to give **8l** (41 mg, 59%) as a yellow amorphous solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.68−7.60 (m, 2H), 7.53−7.18 (m, 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), 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, 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 [M + Na^+] Calcd for $C_{24}H_{20}N_2ONa$ 375.1468, found 375.1471.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text giving detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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