Integrated Transition Metal Catalysed Reactions: Synthesis of Polysubstituted 4-(Phenoxymethyl)-3-pyrrolines and Their Isomers by One-Pot Coupling of Propargylamines, Vinyl Sulfones (or Nitroalkenes) and Phenols

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Dedicated to Professor Jacques Goré on the occasion of his retirement

Keywords: Allylation / Catalysis / Multicomponent reactions / Nitrogen heterocycles / Palladium / Phenols

Polysubstituted 4-(phenoxymethyl)-3-pyrrolines and their isomeric 4-(phenoxymethylene)pyrrolidines have been prepared by sequential one-pot coupling of three components: a propargylamine, a vinyl sulfone (or nitroalkene) and a phenolic derivative. The methodology is based on the sequential integration of a Cu-catalysed cycloaddition and a Pd-catalysed allylic substitution reaction.

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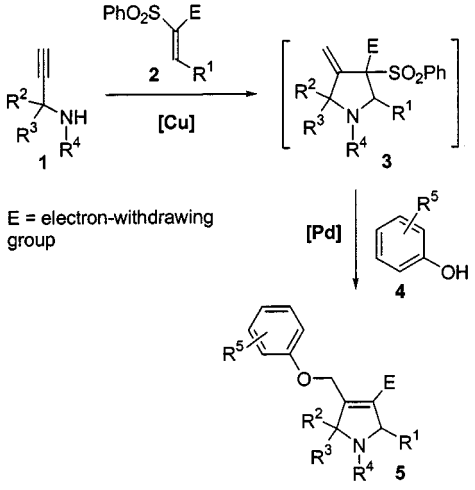
Introduction

Chemical processes that can produce elaborate heterocyclic structures in a one-pot operation through the joining of three or more different, simple building blocks are of great importance today, owing to their enormous potential for combinatorial applications and their economical and environmental significance.[1] *Multicomponent domino reactions*, in which several reactants (added at the same time) combine in a unique and ordered manner under the same reaction conditions, are highly desirable for such purposes.[2] However, the design of novel reactions that would satisfy such requirements is fraught with difficulties and most recent achievements still exploit, as in Ugi's pioneering work, the reactivity of archetype functional groups such as aldehydes and isocyanides.[3] Active efforts are also taking place on a conceptually different, and perhaps more flexible approach, consisting of the incorporation of each component into the final molecule through a *sequence of independent, consecutive transformations combined into a one-pot multi-reaction process.* The times of addition of reactants, reagents, or catalysts may be altered so as to improve efficiency and/or minimize competitive reactions. Adjustments of the reaction parameters may also be made during the course of the overall integrated chemical process.[4]

Transition metal catalysed processes have long been recognized as powerful tools for the development of domino or sequential one-pot reactions.[5] Applications to the development of multicomponent reactions for heterocycle synthesis have been the subject of recent investigations by our group[6] and others.[7] In this context, we now wish to report the results of recent studies addressing the synthesis of five-membered nitrogen heterocycles through a one-pot sequence of two metal-catalysed reactions: a Cu-catalysed cycloaddition combined with a Pd-catalysed allylic substitution.[8] In a previous paper[9] we reported that 4-methylenepyrrolidines could be obtained under mild conditions by means of cycloadditions between propargylamines **1** and electron-deficient olefins in the presence of catalytic amounts of a copper salt. We anticipated that vinyl sulfones **2** would participate in such a reaction, thus affording the



Scheme 1. One-pot conjugate addition/carbocyclisation/allylic substitution sequence

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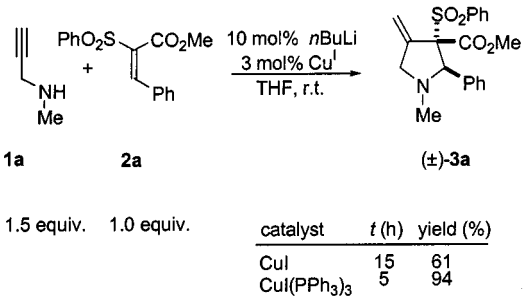
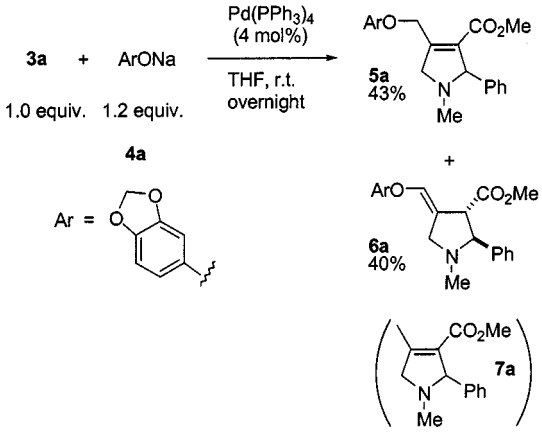
corresponding heterocyclic allylic sulfones. Since nucleophilic displacement of allylic sulfones is known to occur under palladium catalysis conditions, we set out to develop a one-pot procedure combining our Cu-catalysed cycloaddition with a subsequent Pd-catalysed allylic substitution, so as to increase the molecular diversity of the products. To this end, we thought that phenoxides would be interesting nucleophile candidates as they seemed compatible with all reactants and would afford access to a variety of densely substituted 4-(phenoxymethyl)-3-pyrrolines **5**, a great number of phenols being commercially available (Scheme 1). To the best of our knowledge, sulfinate displacement of allylic sulfones by oxygen nucleophiles under palladium catalysis conditions has not previously been reported. Most examples found in the literature involve carbon[10,11] and, on some rare occasions, nitrogen[12] nucleophiles.

Results and Discussion

Preliminary studies focusing on the separate optimisation of each reaction were conducted with *N*-methylpropargylamine (**1a**), methyl 3-phenyl-2-(phenylsulfonyl)propenoate (**2a**) and sesamol (**4a**) as model substrates. The cycloaddition reaction was successfully achieved under our previously reported standard conditions (1.5 equiv. **1a**, 1.0 equiv. **2a**, 10 mol % *n*BuLi, 3 mol % CuI, THF, room temp.) to yield 4-methylenepyrrolidine **3a** as a single diastereomer, but in only moderate yield. A significant improvement was obtained by using the more soluble complex $[CuI(PPh_3)_3]$ as catalyst. The *trans* relationship at C-2 and C-3 in **3a**, inferred from the shielding of the ester protons *syn* to the phenyl group, was consistent with our previous work on similar structures (Scheme 2).[11,13] On the other hand, investigations into the feasibility of the allylic substitution reaction showed that, under identical conditions (use of *n*BuLi to deprotonate the phenolic derivative, THF, room temp.), none of the expected products were formed, regardless of the nature of the catalyst employed {$[Pd(PPh_3)_4]$, $[PdCl_2(PPh_3)_2]$/*n*BuLi, $[Pd(OAc)_2(PPh_3)_2]$}. After further screening of the reaction parameters, we found that the use of NaH as the base in combination with $[Pd(PPh_3)_4]$ as the most effective catalyst enabled the phenolic component to be introduced cleanly and in high yield (Scheme 3). The allylic substitution proved totally regioselective, attack of the phenoxide occurring exclusively at the less hindered terminus of the allylic unit, thereby conjugating the double bond to the ester to give 4-(phenoxymethyl)-3-pyrroline **5a**, unexpectedly accompanied by its isomeric 4-(phenoxymethylene)pyrrolidine **6a**. The latter was easily isolated from the mixture by medium pressure chromatography and its stereochemistry was assigned by extensive NMR experiments (NOE, COSY, HMBC, HSQC). A brief study undertaken in an attempt to identify the factors governing the isomerisation **5** → **6** did not provide conclusive information. We assumed that the acidity of the allylic hydrogen atoms α to the phenol moiety was perhaps playing an important part in this process, sodium phenoxide possibly acting as a base. However, all attempts to drive the isomerisation reaction to completion, even by addition of an external base, failed. The isomeric distribution seemed to be dependent neither upon the amount of phenoxide nor upon the reaction parameters (temperature, reaction time). In addition, **5a** proved stable when subjected to reaction conditions identical to those applied to **3a**.



Scheme 2. Cu-catalysed reaction between *N*-methylpropargylamine (**1a**) and methyl 3-phenyl-2-phenylsulfonylpropenoate (**2a**)



Scheme 3. Pd-catalysed substitution of allylic sulfone **3a** by sesamol (**4a**)

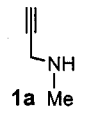
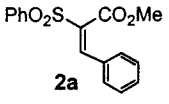
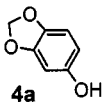
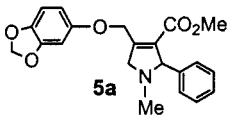
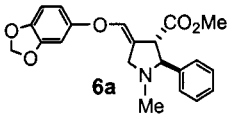
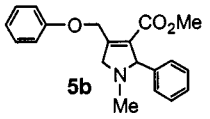
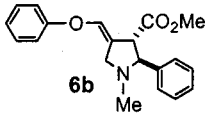
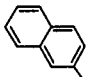
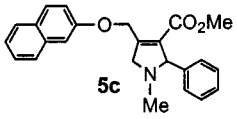
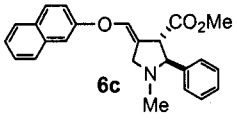
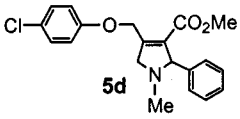
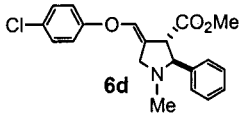
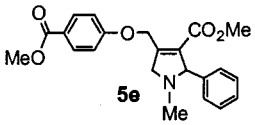
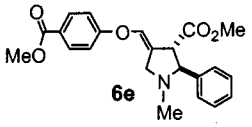
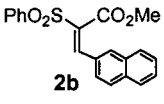
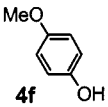
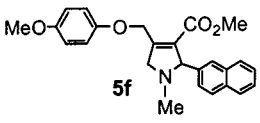
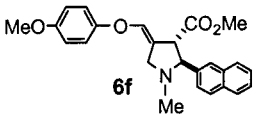
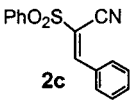
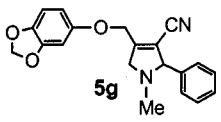
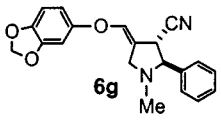
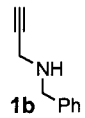
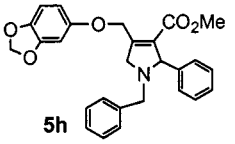
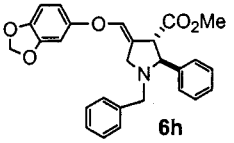
Having optimized each step under the same set of conditions, we embarked on the development of a one-pot procedure in which all the three components would be assembled in the same vessel. Attempts involving the addition of all reactants and catalysts at the start of the reaction proved unpromising. Complex mixtures of products and reactants were obtained, with the 4-methyl-3-pyrroline **7a**, resulting from Pd-mediated reductive desulfonation[11] of the intermediate allyl sulfone **3a**, often being isolated as the major product. We therefore turned our attention to the alternative strategy: a one-pot sequential addition approach in which the phenolate component would only enter the sequence once the cycloaddition had gone to completion. Gratifyingly, this strategy proved successful. The optimised procedure was finally set up as follows: propargylamine **1a** (1.1 equiv.) and vinyl sulfone **2a** (1 equiv.) underwent cycloaddition in THF at room temperature in the presence of 3 mol % of $[CuI(PPh_3)_3]$. After the reaction had reached

completion, as indicated by TLC (ca. 6 h), a THF solution of sodium phenoxide **4a** (2 equiv.) was added, followed by 4 mol % of [$Pd(PPh_3)_4$], and the reaction mixture was stirred overnight at 40 °C. This afforded a nearly 1:1 mixture of compounds **5a** and **6a** in 63% isolated yield.

The generality of the process was then explored with other amines, vinyl sulfones and phenols. The results summarised in Table 1 demonstrate that a variety of the three reactants were tolerated. Importantly, purification of the products proved very easy. Excess phenoxide and sodium benzenesulfinate, produced as a side product, were removed by aqueous base washes. Careful filtration of the crude reaction mixtures through a short pad of silica gel allowed for removal of any polar material (such as triphenylphosphane oxide) generated in the process, to afford the desired heterocycles in satisfactory purities (Table 1).[14]

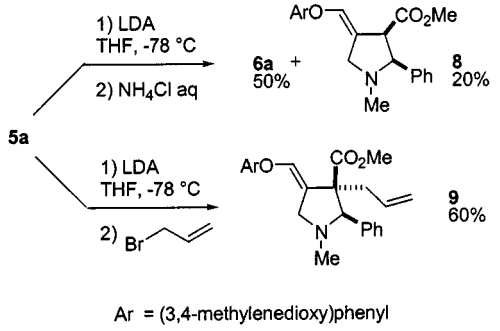
It is worth noting that the two isomers may, if necessary, be separated by conventional chromatographic techniques. Interestingly, we also observed that, in some cases, pyrrolines **5** could be produced selectively by performing the

Table 1. One-pot coupling of propargylamines, vinyl sulfones and phenols[a]

Entry	Amine **1**	Vinyl sulfone **2**	Phenol **4**	Product(s) **5**	Product(s) **6**[b]	Yield (%)[c]
1	 **1a**	 **2a**	 **4a**	 **5a**	 **6a**	63 (56:44)[d]
2	**1a**	**2a**	 **4b**	 **5b**	 **6b**	59 (54:46)
3	**1a**	**2a**	 **4c**	 **5c**	 **6c**	65 (100:0)
4	**1a**	**2a**	 **4d**	 **5d**	 **6d**	34 (>95:5)
5	**1a**	**2a**	 **4e**	 **5e**	 **6e**	60 (75:25)
6	**1a**	 **2b**	 **4f**	 **5f**	 **6f**	49 (55:45)
7	**1a**	 **2c**	**4a**	 **5g**	 **6g**	54 (>95:5)
8[e]	 **1b**	**2a**	**4a**	 **5h**	 **6h**	69 (100:0)

[a] Reaction conditions: 1.1 equiv. of the propargylamine **1** (treated with 10 mol % *n*BuLi), 1.0 equiv. of the vinyl sulfone **2**, 3 mol % [$CuI(PPh_3)_3$], THF, room temp., 6 h; then 2.0 equiv. of the phenol **4** (treated with 2.0 equiv. of NaH), 4 mol % [$Pd(PPh_3)_4$], 40 °C, 10 h. [b] One enantiomer drawn. [c] Isolated yields (**5** + **6**). [d] **5/6** ratio. [e] 1.5 equiv. of **1b** was needed.

three-component reactions in the presence of an excess of the propargylamine (1.5 equiv.). This approach, for example, enabled **5a** and **5b** to be obtained as single products in 63% and 79% isolated yields, respectively (compare with Entries 1 and 2, Table 1; see also Entry 8). However, Pd-mediated reductive desulfonation[11] of the intermediate allyl sulfones often competed with allylic substitution under these conditions, thus making isolation of the desired heterocycles less practical and hence the method less attractive for possible combinatorial applications. Furthermore, we found that, on treatment with LDA in THF at −78 °C, the pyrrolines may either be converted into their isomeric pyrrolidines, after hydrolysis with aqueous NH_4Cl, or be alkylated at the C-3 position, thus introducing an additional element of diversity into the products. For instance, isomerisation of **5a** produced a mixture of two diastereomers **6a** and **8** in 50% and 20% isolated yields, respectively. On the other hand, treatment of the dienolate intermediate with 6 equiv. of 3-bromopropene furnished pyrrolidine **9** as a single diastereomer, the stereochemistry of which was assigned by NOE experiments (Scheme 4). Further work to



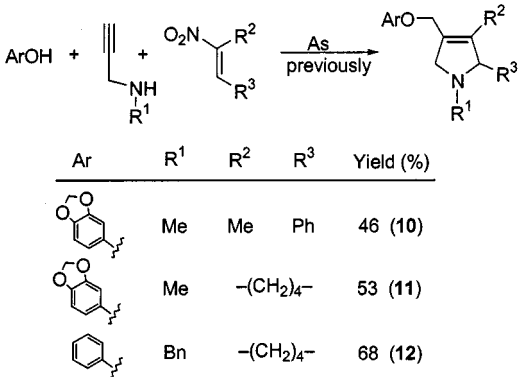
Scheme 4. Base-induced isomerisation and alkylation of pyrroline **5a**

explain and exploit these valuable observations is underway.

In order to expand the scope of this methodology further, we have also examined the use of nitroalkenes as conjugate acceptors, since the corresponding allylic nitro heterocycles would also be expected to be good substrates for use in Pd-catalysed allylic substitutions.[15] This would enable direct introduction of alkyl or even aryl substituents at the C-3 position.[9] Promising results have been achieved, and are illustrated with the synthesis of pyrrolines **10**−**12**, obtained from commercially available nitroalkenes (Scheme 5). These reactions provided single isomers, in contrast with what was generally observed in the synthesis of 3-(methoxycarbonyl)- or 3-cyanopyrrolidines.

Conclusions

We have developed a new one-pot, three-component coupling strategy based on two consecutive metal-catalysed reactions, providing a straightforward route to elaborate five-membered nitrogen heterocycles through the coupling of three flexible and readily available classes of starting materials: propargylamines, vinyl sulfones (or nitroalkenes) and phenols. The procedure is simple and seems well suited for combinatorial applications. We also believe the methodology should find broader applications, as many other nucleophiles are likely to participate in the allylic substitution reactions.



Ar	R^1	R^2	R^3	Yield (%)
	Me	Me	Ph	46 (**10**)
	Me	−$(CH_2)_4$−		53 (**11**)
	Bn	−$(CH_2)_4$−		68 (**12**)

Scheme 5. Nitroalkenes as conjugate acceptors

Experimental Section

General Remarks: Unless otherwise noted, all reactions were carried out under nitrogen by standard syringe, cannula and septa techniques. Commercially available reagents were used as purchased. Vinyl sulfones **2** were prepared by Knoevenagel condensations (Et_2NH, HCl; cat. KF; refluxing toluene).[16] Tetrahydrofuran was dried by distillation from sodium/benzophenone ketyl. Thin-layer chromatography was carried out on Merck silica 60/F-254 aluminium-backed plates. Flash chromatography was performed using Merck silica gel 60 (40−63 μm). NMR spectra were recorded in $CDCl_3$. Chemical shifts (δ) are quoted in ppm; *J* values are given in Hz.

(±)-[3-Methyl (2*SR*,3*SR*)-1-Methyl-4-methylene-2-phenyl-3-(phenylsulfonyl)pyrrolidine-3-carboxylate] (3a): *n*BuLi (2.0 M in hexanes, 50 μL, 0.1 mmol) was added dropwise to a solution of *N*-methylpropargylamine (**1a**, 125 μL, 1.5 mmol) in THF (3 mL) under nitrogen, and the solution was stirred for 5 min at room temperature. Methyl 3-phenyl-2-(phenylsulfonyl)propenoate (**2a**, 302 mg, 1.0 mmol) and $CuI(PPh_3)_3$ (30 mg, 0.03 mmol) were then added successively. The reaction mixture was stirred for 5 h and then concentrated in vacuo. The residue was purified by column chromatography (silica gel; ethyl acetate/petroleum ether/Et_3N) to afford **3a** (349 mg, 94%) as a colourless solid. IR (KBr): $\tilde{\nu}$ = 3060 cm^{-1}, 2960, 2760, 1740, 1665, 1580, 1500, 1450, 1220, 920. ^1H NMR ($CDCl_3$, 300 MHz): δ = 8.05 (dd, *J* = 1.1, 8.5 Hz, 2 H), 7.66 (m, 1 H), 7.53 (m, 2 H), 7.35−7.20 (m, 5 H), 5.51 (s, 1 H), 5.19 (s, 1 H), 4.54 (s, 1 H), 3.70 (d, *J* = 12.1 Hz, 1 H), 3.19 (s, 3 H), 3.16 (br. d, *J* = 12.1 Hz, 1 H), 2.20 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.8, 141.5, 136.6, 136.5, 134.2, 132.4, 128.8, 128.3, 128.1, 116.0, 85.8, 74.4, 60.9, 53.3, 39.6. $C_{20}H_{21}NO_4S$ (371.5): calcd. C 64.67, H 5.70; found C 64.86, H 5.63.

Representative Experimental Procedure: One-Pot Preparation of Methyl 1-Methyl-4-{[3,4-(methylenedioxy)phenoxy]methyl}-2-phenylpyrroline-3-carboxylate (5a) and (±)-[Methyl (2*RS*,3*RS*)-1-Methyl-4-{[3,4-(methylenedioxy)phenoxy]methylene}-2-phenylpyrrolidine-3-carboxylate] (6a). *n*BuLi (2.0 M in hexanes, 50

μL, 0.1 mmol) was added dropwise under nitrogen to a solution of *N*-methylpropargylamine (**1a**, 92 μL, 1.1 mmol) in THF (1 mL), and the solution was stirred for 5 min at room temperature. Methyl 3-phenyl-2-(phenylsulfonyl)propenoate (**2a**, 302 mg, 1.0 mmol) and [CuI(PPh_3)$_3$] (30 mg, 0.03 mmol) were then added successively. After 6 h, a solution containing 2 mmol of the sodium salt of sesamol [prepared by treatment of sesamol (**4a**, 276 mg, 2 mmol) in THF (1 mL) with NaH (60% dispersion in oil, 80 mg, 2 mmol)] was added, followed by [Pd(PPh_3)$_4$] (46 mg, 0.04 mmol). The reaction mixture was stirred at 40 °C overnight, diluted with Et_2O, and washed with 0.5 N NaOH. The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The residue was subjected to column chromatography (silica gel; ethyl acetate/petroleum ether) to afford **5a** (129 mg, 35%) as a colourless solid, and **6a** (103 mg, 28%) as a pale yellow solid. **5a**: M.p. 74−76 °C. IR (KBr): $\tilde{\nu}$ = 3080 cm^{-1}, 2900, 2780, 1700, 1655, 1630, 1480, 750, 700. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40−7.20 (m, 5 H), 6.72 (d, *J* = 8.5 Hz, 1 H), 6.54 (d, *J* = 2.6 Hz, 1 H), 6.39 (dd, *J* = 2.6, 8.5 Hz, 1 H), 5.92 (s, 2 H), 5.13 (s, 2 H), 4.59 (m, 1 H), 4.18 (dd, *J* = 5.2 and 16.5 Hz, 1 H), 3.69 (dd, *J* = 5.2 and 16.5 Hz, 1 H), 3.54 (s, 3 H), 2.32 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.1, 153.9, 152.2, 148.5, 142.1, 141.5, 130.3, 128.3, 128.2, 127.6, 108.1, 105.7, 101.2, 98.5, 76.3, 65.4, 62.6, 51.4, 39.4. $C_{21}H_{21}NO_5$ (367.4): calcd. C 68.65, H 5.76; found C 68.86, H 5.85. **6a**: M.p. 80−82 °C. IR (KBr): $\tilde{\nu}$ = 3050 cm^{-1}, 3020, 2940, 2880, 2760, 1735, 1690, 1480, 810, 750, 700. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45−7.25 (m, 5 H), 6.73 (d, *J* = 8.5 Hz, 1 H), 6.57 (d, *J* = 2.6 Hz, 1 H), 6.45 (dd, *J* = 2.6, 8.5 Hz, 1 H), 6.39 (m, 1 H), 5.94 (s, 2 H), 4.10 (d, *J* = 13.6 Hz, 1 H), 3.72 (d, *J* = 9.6 Hz, 1 H), 3.67 (s, 3 H), 3.60 (dt, *J* = 2.2, 9.6 Hz, 1 H), 3.16 (dt, *J* = 2.6 and 13.6 Hz, 1 H), 2.21 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.0, 152.7, 148.3, 143.3, 140.2, 136.2, 128.6, 128.0, 127.9, 119.7, 108.4, 108.1, 101.5, 99.6, 73.6, 57.1, 54.7, 52.1, 40.1. $C_{21}H_{21}NO_5$ (367.4): Calcd. C 68.65, H 5.76; found C 68.72, H 5.96.

Methyl 1-Methyl-4-(phenoxymethyl)-2-phenylpyrroline-3-carboxylate (5b): Oil. IR (NaCl): $\tilde{\nu}$ = 3030 cm^{-1}, 2790, 1715, 1650, 1600, 1580, 760, 740, 700, 690. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50−7.25 (m, 7 H), 7.10−6.90 (m, 3 H), 5.22 (s, 2 H), 4.62 (m, 1 H), 4.19 (dd, *J* = 5.0 and 16.4 Hz, 1 H), 3.72 (dd, *J* = 5.0 and 16.4 Hz, 1 H), 3.56 (s, 3 H), 2.33 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.5, 158.7, 152.6, 141.8, 130.0, 129.8, 128.8, 128.6, 121.6, 114.9, 76.7, 64.9, 62.9, 51.7, 39.8. $C_{20}H_{21}NO_3$ (323.4): calcd. C 74.28, H 6.55; found C 74.39, H 6.67.

Methyl 1-Methyl-4-(naphthoxymethyl)-2-phenylpyrroline-3-carboxylate (5c): Solid, m.p. 82−84 °C. IR (KBr): $\tilde{\nu}$ = 3024 cm^{-1}, 2840, 1707, 1630, 1600, 1512, 1468, 1452, 833, 747, 698. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90−7.20 (m, 12 H), 5.39 (m, 2 H), 4.68 (m, 1 H), 4.28 (dd, *J* = 5.1 and 16.5 Hz, 1 H), 3.81 (dd, *J* = 5.1 and 16.5 Hz, 1 H), 3.63 (s, 3 H), 2.37 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.7, 156.7, 152.6, 141.9, 135.0, 129.7, 130.9, 130.1, 128.7, 128.2, 128.0, 127.4, 127.0, 124.4, 119.1, 107.5, 76.7, 65.1, 63.0, 51.9, 39.8. HRMS: calcd. for $C_{24}H_{23}NO_3$ 374.1756; found 374.1752.

Methyl 1-Methyl-4-[(4-chlorophenoxy)methyl]-2-phenylpyrroline-3-carboxylate (5d): Solid, m.p. 52−54 °C. IR (KBr): $\tilde{\nu}$ = 3030 cm^{-1}, 2840, 2780, 1720, 1600, 1580, 1500, 1450, 830, 760, 700. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38−7.20 (m, 7 H), 6.19 (d, *J* = 6.6 Hz, 2 H), 5.19 (m, 2 H), 4.61 (m, 1 H), 4.16 (dd, *J* = 5.2 and 16.5 Hz, 1 H), 3.68 (dd, *J* = 5.2 and 16.5 Hz, 1 H), 3.55 (s, 3 H), 2.32 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.5, 157.3, 152.0, 141.6, 131.0, 129.9, 128.9, 128.6, 128.0, 126.5, 116.2, 76.6, 65.1, 62.8, 51.8, 39.7. $C_{20}H_{20}ClNO_3$ (357.8): calcd. C 67.13, H 5.63; found C 67.66, H 5.79.

Methyl 1-Methyl-4-{[4-(methoxycarbonyl)phenoxy]methyl}-2-phenylpyrroline-3-carboxylate (5e): Solid, m.p. 106−108 °C. IR (KBr): $\tilde{\nu}$ = 2940 cm^{-1}, 1700, 1600, 1510, 1430, 1250, 840, 730, 700. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.8 Hz, 2 H), 7.40−7.25 (m, 5 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 5.26 (d, *J* = 3.3 Hz, 2 H), 4.61 (m, 1 H), 4.16 (dd, *J* = 5.0 and 16.4 Hz, 1 H), 3.89 (s, 3 H), 3.70 (dd, *J* = 5.0 and 16.4 Hz, 1 H), 3.55 (s, 3 H), 2.32 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 167.2, 164.4, 162.4, 151.5, 141.5, 132.1, 131.1, 128.9, 128.6, 128.5, 123.6, 114.6, 76.6, 65.1, 62.7, 52.3, 51.8, 39.7. $C_{22}H_{23}NO_5$ (381.4): calcd. C 69.28, H 6.08; found C 68.85, H 6.03.

Methyl 1-Methyl-4-[(4-methoxyphenoxy)methyl]-2-naphthylpyrroline-3-carboxylate (5f): Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90−7.86 (m, 4 H), 7.60 (d, *J* = 8.5 Hz, 1 H), 7.50 (m, 2 H), 6.98 (m, 2 H), 6.87 (m, 2 H), 5.25 (s, 2 H), 4.79 (s, 1 H), 4.28 (dd, *J* = 4.7 and 12.1 Hz, 1 H), 3.82 (s, 3 H), 3.75 (d, *J* = 12.1 Hz, 1 H), 3.53 (s, 3 H), 2.37 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.1, 154.2, 152.7, 137.5, 133.2, 128.4, 127.9, 127.7, 127.3, 126.1, 125.9, 125.3, 115.5, 114.8, 75.5, 65.2, 62.7, 55.7, 52.0, 39.3. $C_{25}H_{25}NO_4$ (403.5): calcd. C 74.42, H 6.25; found C 74.60, H 6.30.

1-Methyl-4-{[3,4-(methylenedioxy)phenoxy]methyl}-2-phenylpyrroline-3-carbonitrile (5g): Solid, m.p. 75−77 °C. IR (KBr): $\tilde{\nu}$ = 2890 cm^{-1}, 2780, 2220, 1485, 1180, 780, 700. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.50−7.30 (m, 5 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 6.54 (br. s, 1 H), 6.36 (d, *J* = 8.0 Hz, 1 H), 5.93 (s, 2 H), 4.79 (s, 2 H), 4.48 (s, 1 H), 4.16 (dd, *J* = 4.4 and 15.8 Hz, 1 H), 3.61 (dd, *J* = 4.4 and 15.8 Hz, 1 H), 2.38 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.6, 153.6, 148.9, 142.9, 138.9, 129.2, 129.0, 128.4, 113.9, 108.4, 106.1, 101.8, 98.8, 76.7, 65.3, 62.4, 39.8. $C_{20}H_{18}N_2O_3$ (334.4): calcd. C 71.84, H 5.43; found C 71.49, H 5.49.

Methyl 1-Benzyl-4-{[3,4-(methylenedioxy)phenoxy]methyl}-2-phenylpyrroline-3-carboxylate (5h): Solid, m.p. 99−101 °C. IR (KBr): $\tilde{\nu}$ = 3028 cm^{-1}, 2886, 2790, 1714, 1487, 1183, 758, 700. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40−7.15 (m, 10 H), 6.70 (d, *J* = 8.4 Hz, 1 H), 6.51 (d, *J* = 2.2 Hz, 1 H), 6.35 (dd, *J* = 2.2, 8.4 Hz, 1 H), 5.92 (s, 2 H), 5.10 (s, 2 H), 4.91 (m, 1 H), 4.05 (dd, *J* = 5.5 and 16.4 Hz, 1 H), 3.82 (d, *J* = 13.6 Hz, 1 H), 3.68 (dd, *J* = 5.1 and 16.4 Hz, 1 H), 2.54 (s, 3 H), 3.50 (d, *J* = 13.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 164.1, 153.9, 151.6, 148.4, 142.0, 141.6, 139.0, 130.4, 128.7, 128.6, 128.3, 128.0, 127.5, 127.0, 108.0, 105.8, 101.3, 98.3, 74.3, 65.5, 60.0, 56.5, 51.3. $C_{27}H_{25}NO_5$ (443.5): calcd. C 73.12, H 5.68; found C 73.01, H 6.01.

(±)-[Methyl (2*RS*,3*RS*)-1-Methyl-4-(phenoxymethylene)-2-phenylpyrrolidine-3-carboxylate] (6b): Oil. IR (NaCl): $\tilde{\nu}$ = 3040 cm^{-1}, 2840, 2770, 1740, 1600, 1500, 750, 700, 690. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.50−6.90 (m, 10 H), 6.53 (q, *J* = 2.2 Hz, 1 H), 4.14 (d, *J* = 13.6 Hz, 1 H), 3.74 (d, *J* = 9.6 Hz, 1 H), 3.68 (s, 3 H), 3.63 (dt, *J* = 2.2, 9.6 Hz, 1 H), 3.19 (dt, *J* = 2.9 and 13.6 Hz, 1 H), 2.22 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.4, 157.8, 140.5, 135.7, 130.0, 129.0, 128.3, 128.2, 123.2, 120.6, 116.7, 74.0, 57.5, 55.0, 52.5, 40.5. $C_{20}H_{21}NO_3$ (323.4): Calcd. C 74.28, H 6.55; found C 74.44, H 6.77.

(±)-{Methyl (2*RS*,3*RS*)-1-Methyl-4-[(4-chlorophenoxy)methylene]-2-phenylpyrrolidine-3-carboxylate} (6d): Oil. IR (NaCl): $\tilde{\nu}$ = 3020 cm^{-1}, 2780, 1745, 1700, 1580, 1490, 1450, 825, 760, 710. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45−7.25 (m, 7 H), 6.93 (d, *J* = 6.6 Hz, 2 H), 6.46 (d, *J* = 2.2 Hz, 1 H), 4.10 (d, *J* = 13.6 Hz, 1 H), 3.72 (d, *J* = 9.6 Hz, 1 H), 3.68 (s, 3 H), 3.62 (dt, *J* = 2.2, 9.6 Hz, 1 H),

3.16 (dt, J = 2.8 and 13.6 Hz, 1 H), 2.21 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.3, 156.3, 140.3, 135.4, 130.0, 129.0, 128.4, 128.3, 128.1, 121.4, 117.9, 73.9, 57.5, 55.0, 52.6, 40.4. HRMS: calcd. for $C_{20}H_{20}ClNO_3$ 358.1209; found 358.1205.

(±)-[Methyl (2*RS*,3*RS*)-1-Methyl-4-{[4-(methoxycarbonyl)phenoxy]methylene}-2-phenylpyrrolidine-3-carboxylate] (6e): Oil. IR (NaCl): $\tilde{\nu}$ = 2930 cm^{-1}, 1710, 1590, 1500, 1430, 1240, 840, 730, 700. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.01 (d, J = 8.8 Hz, 2 H), 7.50−7.25 (m, 5 H), 7.01 (d, J = 8.8 Hz, 2 H), 6.57 (d, J = 2.2 Hz, 1 H), 4.13 (d, J = 14.0 Hz, 1 H), 3.90 (s, 3 H), 3.73 (d, J = 9.6 Hz, 1 H), 3.70 (s, 3 H), 3.65 (dt, J = 2.2, 9.6 Hz, 1 H), 3.17 (dt, J = 2.9 and 14.0 Hz, 1 H), 2.20 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.4, 167.0, 161.1, 140.2, 134.5, 132.1, 129.0, 128.4, 128.3, 124.9, 122.7, 116.0, 73.9, 57.4, 55.0, 52.6, 52.4, 40.4. HRMS: calcd. for $C_{22}H_{23}NO_5$ 381.1576; found 381.1574.

(±)-{Methyl (2*RS*,3*RS*)-1-Methyl-4-[(4-methoxyphenoxy)methylene]-2-naphthylpyrrolidine-3-carboxylate} (6f): Oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.00−7.85 (m, 4 H), 7.60 (d, J = 8.5 Hz, 1 H), 7.50 (m, 2 H), 6.98 (m, 2 H), 6.87 (m, 2 H), 6.49 (s, 1 H), 4.20 (d, J = 13.7 Hz, 1 H), 4.92 (d, J = 9.6 Hz, 1 H), 3.81 (s, 3 H), 3.74 (d, J = 9.6 Hz, 1 H), 3.68 (s, 3 H), 3.23 (dt, J = 2.6 and 13.7 Hz, 1 H), 2.27 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.1, 155.4, 151.5, 137.6, 136.4, 133.4, 133.3, 128.4, 127.9, 127.7, 127.3, 126.1, 125.9, 125.3, 119.1, 117.5, 113.7, 73.8, 57.2, 55.7, 54.6, 52.1, 40.1. $C_{25}H_{25}NO_4$ (403.4): calcd. C 74.42, H 6.25; found C 74.09, H 6.33.

(±)-(2*RS*,3*RS*)-1-Methyl-4-{[3,4-(methylenedioxy)phenoxy]methylene}-2-phenylpyrrolidine-3-carbonitrile (6g): Oil. IR (NaCl): $\tilde{\nu}$ = 2900 cm^{-1}, 2780, 1700, 1480, 1260, 1180, 1040, 730, 700. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.55−7.40 (m, 5 H), 6.74 (d, J = 8.1 Hz, 1 H), 6.65−6.55 (m, 2 H), 6.45 (dd, J = 2.2, 8.1 Hz, 1 H), 5.96 (s, 2 H), 4.09 (d, J = 14.0 Hz, 1 H), 3.56 (d, J = 9.9 Hz, 1 H), 3.50 (d, J = 9.9 Hz, 1 H), 3.24 (d, J = 14.0 Hz, 1 H), 2.23 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 152.7, 148.8, 144.0, 138.1, 137.9, 129.4, 129.2, 127.9, 119.1, 116.3, 108.9, 108.5, 102.0, 100.1, 75.0, 56.6, 41.0, 40.2. HRMS: calcd. for $C_{20}H_{18}N_2O_3$ 335.1396; found 335.1397.

1,3-Dimethyl-4-{[3,4-(methylenedioxy)phenoxy]methyl}-2-phenylpyrroline (10): Oil. IR (NaCl): $\tilde{\nu}$ = 3028 cm^{-1}, 2941, 2767, 1637, 1604, 1486, 1453, 1183, 891, 849, 749, 701. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00−7.20 (m, 5 H), 6.70 (d, J = 8.4 Hz, 1 H), 6.51 (d, J = 2.2 Hz, 1 H), 6.35 (dd, J = 2.2, 8.4 Hz, 1 H), 5.91 (s, 2 H), 4.56 (s, 2 H), 4.13 (m, 1 H), 3.96 (br. d, J = 12.1 Hz, 1 H), 3.45 (br. d, J = 12.1 Hz, 1 H), 2.33 (s, 3 H), 1.43 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 154.6, 148.6, 142.2, 141.9, 137.7, 129.9, 128.9, 128.7, 127.9, 108.3, 106.5, 101.5, 98.9, 80.9, 64.8, 62.9, 40.4, 12.3. HRMS: calcd. for $C_{20}H_{21}NO_3$ 324.1599; found 324.1592.

2-Methyl-4-{[3,4-(methylenedioxy)phenoxy]methyl}-2-azabicyclo-[3.4.0]non-4-ene (11): Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.70 (d, J = 8.3 Hz, 1 H), 6.50 (d, J = 2.5 Hz, 1 H), 6.33 (dd, J = 2.5, 8.3 Hz, 1 H), 5.91 (s, 2 H), 4.50 (s, 2 H), 3.85 (dd, J = 3.2, 9.4 Hz, 1 H), 3.32 (dt, J = 4.3 and 15.8 Hz, 1 H), 3.09 (m, 2 H), 2.63 (d, J = 15.8 Hz, 1 H), 2.47 (s, 3 H), 2.15−2.10 (m, 2 H), 1.90−1.80 (m, 2 H), 1.35−1.15 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 154.4, 148.2, 141.7, 139.8, 125.3, 107.9, 106.1, 101.1, 98.4, 72.2, 63.8, 62.9, 40.5, 33.8, 25.7, 25.4, 23.8. $C_{17}H_{21}NO_3$ (287.4): calcd. C 71.06, H 7.37; found C 70.57, H 7.44.

2-Benzyl-4-(phenoxymethyl)-2-azabicyclo[3.4.0]non-4-ene (12): Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45−7.20 (m, 7 H), 7.10−6.80 (m, 3 H), 4.57 (s, 2 H), 4.04 (d, J = 12.9 Hz, 1 H), 3.77 (m, 1 H), 3.66 (d, J = 12.9 Hz, 1 H), 3.45−3.40 (m, 2 H), 2.71 (d, J = 12.9 Hz, 1 H), 2.10−1.90 (m, 2 H), 1.90−1.80 (m, 2 H), 1.40−1.20 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.9, 139.8, 129.6, 129.4, 129.0, 128.8, 128.5, 128.3, 126.9, 125.2, 120.8, 120.1, 115.7, 114.7, 70.9, 62.8, 60.9, 58.8, 34.3, 25.8, 25.6, 23.9.

(±)-[Methyl (2*RS*,3SR)-1-Methyl-4-{[3,4-(methylenedioxy)phenoxy]methylene}-2-phenylpyrrolidine-3-carboxylate] (8): A solution of pyrroline **5a** (155 mg, 0.42 mmol) in THF (4 mL) was added dropwise to LDA (0.1 M in THF/hexanes, 0.66 mmol), cooled at −78 °C. The reaction mixture was maintained at that temperature for 1 h and was then quenched with aqueous NH_4Cl (1 mL). The mixture was allowed to reach room temperature and diluted with diethyl ether. The aqueous layer was separated and extracted with diethyl ether. The organic layers were combined and concentrated in vacuo. The residue was purified by column chromatography (silica gel; ethyl acetate/petroleum ether) to afford **6a** (77 mg, 50%), and **8** (30 mg, 20%). **8**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.45−7.25 (m, 5 H), 6.70 (d, J = 8.4 Hz, 1 H), 6.57 (d, J = 2.4 Hz, 1 H), 6.44 (dd, J = 2.4, 8.4 Hz, 1 H), 6.34 (br. s, 1 H), 5.94 (s, 2 H), 4.21 (d, J = 14.1 Hz, 1 H), 3.83 (d, J = 7.7 Hz, 1 H), 3.76 (d, J = 7.7 Hz, 1 H), 3.26 (s, 3 H), 3.16 (dd, J = 2.0 and 14.1 Hz, 1 H), 2.26 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.4, 153.0, 148.7, 143.6, 138.1, 137.4, 128.6, 128.3, 128.2, 119.9, 108.7, 108.4, 101.8, 99.9, 74.1, 57.2, 53.5, 51.9, 40.9.

(±)-[Methyl (2*RS*,3*SR*)-3-Allyl-1-methyl-4-{[3,4-(methylenedioxy)-phenoxy]methylene}-2-phenylpyrrolidine-3-carboxylate] (9): A solution of pyrroline **5a** (155 mg, 0.42 mmol) in THF (4 mL) was added dropwise to LDA (0.1 M in THF/hexanes, 0.66 mmol), cooled at −78 °C. The reaction mixture was maintained at that temperature for 1 h, and allyl bromide (220 μL, 2.54 mmol) was added. The mixture was allowed to reach room temperature and quenched with aqueous NH_4Cl. The aqueous layer was separated and extracted with diethyl ether. The organic layers were combined and concentrated in vacuo. The residue was purified by column chromatography (silica gel; ethyl acetate/petroleum ether) to afford **9** (102 mg, 60%) as an oil. IR (NaCl): $\tilde{\nu}$ = 3075 cm^{-1}, 2948, 2778, 1728, 1634, 1484, 1182, 926, 750, 703. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40−7.25 (m, 5 H), 6.71 (d, J = 8.8 Hz, 1 H), 6.56 (d, J = 2.9 Hz, 1 H), 6.43 (dd, J = 2.9, 8.8 Hz, 1 H), 6.27 (br. s, 1 H), 5.94 (s, 2 H), 5.87 (m, 1 H), 5.28 (d, J = 14.7 Hz, 1 H), 5.23 (d, J = 8.8 Hz, 1 H), 4.22 (d, J = 14.0 Hz, 1 H), 3.47 (s, 1 H), 3.36 (s, 3 H), 3.11 (dd, J = 2.8 and 14.0 Hz, 1 H), 2.78 (dd, J = 5.2 and 14.7 Hz, 1 H), 2.60 (dd, J = 8.8 and 14.7 Hz, 1 H), 2.21 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.2, 152.8, 148.3, 143.1, 137.5, 137.3, 134.6, 128.2, 128.1, 128.0, 123.5, 119.4, 108.2, 108.1, 101.4, 99.4, 78.4, 60.0, 57.0, 51.7, 40.5, 39.9. HRMS: calcd. for $C_{24}H_{25}NO_5$ 408.1811; found 408.1837.

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