Final version published in: *Eur. J. Org. Chem.* **2017**, 1902–1910. DOI: 10.1002/ejoc.201700165

Palladium-Catalyzed Intramolecular Cyclization of Nitroalkenes: Synthesis of Thienopyrroles

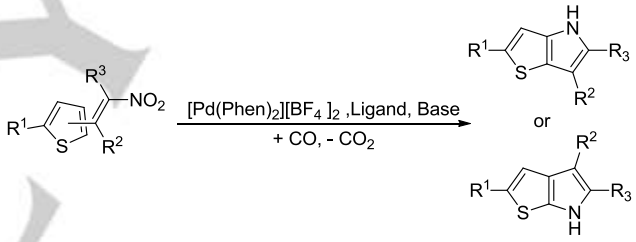
Mohamed A. EL-Atawy,[a,b] Francesco Ferretti,[a] and Fabio Ragaini*[a]

Abstract: In the presence of carbon monoxide, the palladium/phenanthroline system catalyzes the C-H amination of thiophene rings by the nitroalkene moiety directly attached to the S-heterocyclic ring. An optimization of the ligand and reaction conditions allowed synthesizing a series of thienopyrroles aryl/alkyl substituted either in position 2 or 3 of the pyrrole ring. Using low pressures of carbon monoxide (5 bars) high yields of the fused bicyclic compounds have been obtained (up to 98 % yield).

Introduction

Bicyclic pyrrolo-fused aromatic or heteroaromatic rings are important compounds because of their potential biological activity. Among the others, thienopyrroles have unique electronic properties and their pharmaceutical applications are constantly increasing even if their chemistry is underdeveloped with respect to their bioisosteric indole analogues. For instance thienopyrroles were found biologically active as glycogen phosphorylase inhibitors,[1] antiviral agents,[2] modulators of lipid storage,[3] inhibitors of cell releasing tumor necrosis factor,[4] cannabinoid receptor antagonists,[5] CRTH2 modulators,[6] ITK inhibitors[7] and histone demethylase inhibitors.[8] In addition, they also have characteristic photophysical properties that make them of interest for the preparation of organic electroluminescent devices,[9] as photosensitizers in photodynamic therapy,[10] in photovoltaic cells[11] and in the synthesis of conducting polymeric materials.[12] The limited number of thienopyrroles syntheses, and the laborious nature[13] of most of them are probably the main reasons for which the chemistry of thienopyrroles is not as studied as that of indoles. In addition, thienopyrrole are less stable then indoles. Thus, most of the classical syntheses of indole derivatives are not applicable to their preparation. Some synthetic alternatives have been reported in the literature, but they often require several steps.[14] One of the most interesting methods is the palladium catalyzed reductive cyclization of 3-alkenyl-2-nitrothiophenes.[15] In spite of the mild conditions and the good yields obtained, the major limitation of this method is the requirement for a prefunctionalized thiophene with two suitable adjacent functional groups in the 2 and 3 positions. The preparation of these starting materials often requires several synthetic steps.

Recently our group reported a procedure for the synthesis of 2- and 3-alkyl and aryl-substituted indoles from β-nitrostyrenes catalyzed by palladium and phenanthroline complexes.[16],[17] In this reaction, the starting materials are easily synthesizable from carbonyl compounds and nitroalkenes by a nitroaldol condensation (Henry reaction). Owing to our interest in the synthesis of indoles and related compounds,[18] we herein present a method for the synthesis of thienopyrroles from thienyl-substituted nitroalkenes (Scheme 1). As for other nitroarene reductions by CO,[18d] the only stoichiometric byproduct is CO_2.



Scheme 1. Synthesis of thienopyrroles from thienyl-β-nitro alkenes.

Results and Discussion

As stated above, the strength of this method is sited in the straightforward synthesis of the substrates. All the aldehyde-derived compounds can be synthesized by a Henry reaction between a thiophenecarboxaldehyde and a nitroalkane (Scheme 2A). For the olefins with a substituent in the α position, a procedure was developed by combining for the first time two reactions adapted from the literature (Scheme 2B). The first is the synthesis of primary ketoimines from a nitrile and a Grignard reagent; in this case thienylmagnesium bromide. The second is the condensation of the obtained ketoimine with nitromethane. The use of a ketoimine formally derived from ammonia as an activated form of the generally unreactive ketones in the Henry condensation was reported in the literature only for the commercially available benzophenoneimine.

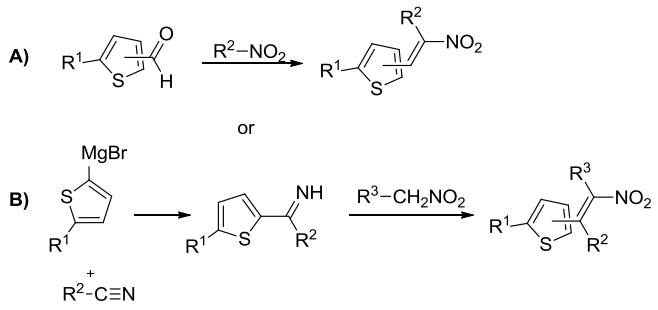
Our initial investigations were done using the cyclization of (*E*)-2-(2-nitropropenyl)thiophene (**1a**) to thieno[3,2-b]pyrrole (**2a**) as a model reaction. Based on our previous work on the cyclization of β-nitrostyrenes to indoles, we employed 1 mol% of $[Pd(Phen)_2][BF_4]$ as pre-catalyst using CH_3CN as solvent in the

[a] Dr. M. A. EL-Atawy, Dr. F. Ferretti, Prof. Dr. F. Ragaini
Dipartimento di Chimica
Università degli Studi di Milano
Via Golgi 19, 20133 Milano, Italy
E-mail: fabio.ragaini@unimi.it

[b] Dr. M. A. EL-Atawy
Chemistry Department, Faculty of Science
Alexandria University
P.O. 426 Ibrahemia, Alexandria 21321 (Egypt)

Supporting information for this article is given via a link at the end of the document.

presence of a 16 fold excess of phenanthroline and with Et_3N as additive. From the first run, it was evident that the sulfur-containing substrate is less reactive than the corresponding β-nitrostyrene (conversion: 77 %, thienopyrrole selectivity: 35%). The substrate amount was thus halved and an extensive optimization of the catalytic system was started.



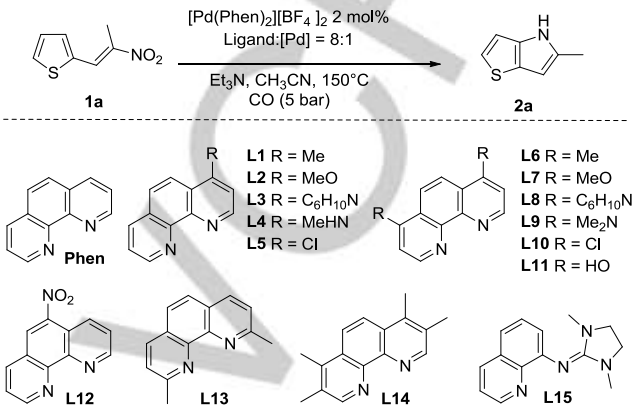
Scheme 2. Synthesis of thienyl substituted nitroalkenes.

We first investigated the use of differently substituted phenanthrolines (Table 1), because we have recently shown that the ligand structure can strongly affect the activity of the catalytic system in the related reductive carbonylation of nitroarenes.[19] Phosphorus ligands were not tested because in the presence of $-NO_2$ groups they can be oxidized leading to catalyst deactivation.[20]

Unsubstituted 1,10-phenanthroline (Phen) gave a good catalytic activity but moderate selectivity for the bicyclic product. Electron poor ligands (**L5**, **L10** and **L12**) gave low catalytic activities. According to the reaction mechanism previously proposed by us for the related cyclization reaction of β-nitrostyrenes to give indoles, the formation of a radical anion by a single-electron transfer from the metal to the nitro group should be the first step of the catalytic cycle. Thus, it is not unexpected that a lower electron density on the metal leads to a reduced reaction rate. In addition, during the catalytic reaction, the nitro group on **L12** may be reduced to -NO or $-NH_2$, leading to a ligand with different electronic properties and the C-Cl bond on **L5** and **L10** could be subjected to oxidative addition to the metal center.

In general, we observed that the activity and the selectivity towards **2a** of the catalyst increases with an increase in the electron donor properties of the substituents in position 4 and 7 of the phenanthroline. Steric hindrance next to nitrogen atom leads to low activity and selectivity (entries 14 and 16). 4,7-Dimethoxyphenanthroline, **L7**, was identified as the best ligand (entry 8). The reaction was complete after only 3h affording the bicyclic product **1a** in 83 % GC yield. Substitution of the phenanthroline skeleton with even more strongly electron releasing amino groups leads to a drop of the catalyst performance (entries 4-5 and 9-10). Unlike the case of the carbonylation of nitroarenes to carbamates, no advantage was noticed in the use of non-symmetric ligand with respect to their symmetrical counterparts. For the latter reaction, the positive effect of non-symmetric phenanthrolines is connected to the formation of anilines as intermediates,[21] supporting the view that amines are not intermediates in the class of cyclization reactions here investigated.[22]

Table 1. Influence of the ligand on the palladium catalyzed reductive cyclization of (*E*)-2-(2-nitropropenyl)thiophene (**1a**) to 5-methyl-4*H*-thieno[3,2-b]pyrrole (**2a**).[a]



Entry	Ligand	Conversion %[b]	Selectivity %[b]
1	**Phen**	95	57
2	**L1**	100	66
3	**L2**	100	69
4	**L3**	98	65
5	**L4**	68	55
6	**L5**	75	60
7	**L6**	96	62
8	**L7**	100	83
9	**L8**	50	47
10	**L9**	40	40
11	**L10**	34	50
12	**L11**	4	49
13	**L12**	27	35
14	**L13**	19	43
15	**L14**	93	62
16	**L15**	95	42

[a] Reaction conditions: **1a** (0.5 mmol), $[Pd(Phen)_2][BF_4]_2$ (0.01 mmol), CH_3CN (15 mL), Et_3N (400 µl, 2.9 mmol), 150 °C, P_{CO} = 5 bar, 3h. Molar ratio **1a**/ligand/Pd = 50:8:1. [b] Determined by GC analysis using naphthalene as an internal standard.

In order to further increase the selectivity of the system we optimized the reaction parameters on the cyclization of the model substrate using **L7** as ligand.

As shown in Table 2, even if the addition of a base is not necessary, it enhances the selectivity and the activity of the catalytic system. Inorganic (entries 7-8) and strong organic bases (entries 5-6), reduce significantly the selectivity towards the cyclized product. 4-Dimethylaminopyridine (DMAP) led to the highest selectivity, but its cost, toxicity[23] and the difficulty in separating it from the product makes its use less convenient. As in our previous work on the cyclization of β-nitrostyrenes,[16] Et_3N was the base of choice. However, in contrast to our previous experience, the effect was moderate and did not affect the activity of the system but only the selectivity (compare entries 1, 4, 9 and 10). An increase in the CO pressure has little effect on the activity of the system, but negatively affects the selectivity (entries 9, 11, 12; for full experimental data see SI).

Table 2. Optimization of the reaction condition for the palladium catalyzed reductive cyclization of (*E*)-2-(2-nitropropenyl)thiophene (**1a**) to 5-methyl-4*H*-thieno[3,2-b]pyrrole (**2a**).[a]

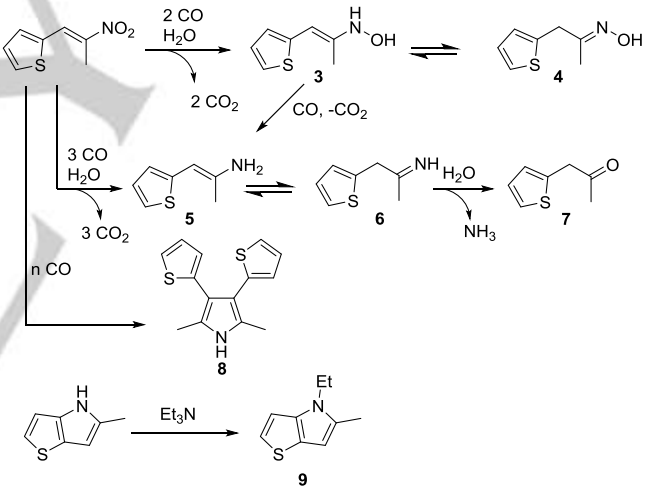
Entry	Solvent	Base	P_{CO} (bar)	Conv. %[b]	Sel. %[b]
1	CH_3CN	-	5	94	73
2	CH_3CN	Pyridine	5	97	76
3	CH_3CN	DMAP	5	93	86
4	CH_3CN	Et_3N	5	>99	77
5	CH_3CN	DABCO	5	82	63
6	CH_3CN	KO^tBu	5	100	<1
7	CH_3CN	K_2CO_3	5	100	12
8	CH_3CN	Na_2HPO_4	5	68	51
9[c]	**CH_3CN**	**Et_3N**	**5**	**100**	**82**[d]
10[e]	CH_3CN	Et_3N	5	100	76
11[c]	CH_3CN	Et_3N	20	98	77
12[c]	CH_3CN	Et_3N	10	>99	78
13[c]	CH_3CN	Et_3N	1	50	21
14[c]	DMF	Et_3N	1	73	7
15[c]	DMF	Et_3N	5	>99	70
16[c]	DME	Et_3N	5	32	47
17[c]	THF	Et_3N	5	25	55
18[c]	Toluene	Et_3N	5	1	-
19[c]	MeOH	Et_3N	5	81	13
20[c, f]	CH_3CN	Et_3N	5	100	79
21[c, g]	CH_3CN	Et_3N	5	>99	76
22[c, h]	CH_3CN	Et_3N	5	32	50

[a] Reaction conditions: **1a** (0.5 mmol), $[Pd(Phen)_2][BF_4]_2$ (0.01 mmol), CH_3CN (15 mL), base (1.4 mmol), 150 °C, 5 bar, 3h. Molar ratio **1a**/**L7**/Pd = 50:8:1. [b] Determined by GC analysis using naphthalene as an internal standard. [c] Et_3N (400 µl, 2.9 mmol). [d] Isolated yield. [e] Et_3N (500 µl, 3.6 mmol). [f] 160 °C. [g] 140 °C. [h] 100 °C.

The maximum activity and selectivity was reached at 5 bar of carbon monoxide. At 1 bar a drop of the catalytic system performance was noticed (entry 13). To rule out the possibility that the result was misled by the solvent evaporation at 1 bar of CO pressure, a reaction using DMF as the solvent was performed in order to avoid the boiling of the solvent (entry 14), but no improvement was noticed. In general, polar solvents such as acetonitrile or DMF gave the best results while the use of nonpolar solvent, such as toluene, led to a non-active system. This is again in accord with proposed activation of the nitro compound by an electron transfer. Indeed, non-polar solvents destabilize charged intermediates and slow down the reaction. The effect of solvent polarity on the activation of nitroarenes by $Ru(CO)_3$(DPPE) (DPPE = 1,2-bis(diphenylphosphino)ethane) had been earlier evidenced.[24] The use of a polar protic solvent, MeOH (entry 19), afforded a good conversion but a very poor selectivity to the thienopyrrole. Ethers (THF, DME, entries 16-17), though polar and aprotic, slow down the catalytic reaction with respect to the more polar acetonitrile and afford moderate selectivities.

The effect of the temperature was then investigated performing a series of reactions at temperatures ranging from 100 to 160 ˚C (Table 2 and Table S2). At low temperature, the performances of the catalytic system are poor (conv. 32 % and sel. 50 % at 100 °C). The activity strongly increases with an increase in the temperature, and complete conversion is reached at 140 °C (entry 21). The maximum selectivity is obtained at 150 °C above which the yield starts to decrease (entry 22). Under the best conditions, an 82 % isolated yield of **1a** could be obtained (entry 9).

Some of the byproducts of the reaction were identified by GC-MS. The little amount and the instability of some of them prevented their isolation and thus their quantification. Pathways for their formation are reported in Scheme 3. Analogue side reactions were identified also during our previous work on the cyclization of β-nitrostyrenes to indoles.[16] The formation of **3**-**7** involves the presence of water and is almost completely suppressed working with anhydrous reagents and solvents, however trace amounts were detected even under these conditions. Compound **8** and **9** are the major side products under the optimized conditions. Together with them, trace amounts of other higher molecular weight unidentified compounds were detected. When the selectivity is very low (see table 1-2), extensive polymerization either of the starting material or of the product cannot be excluded.



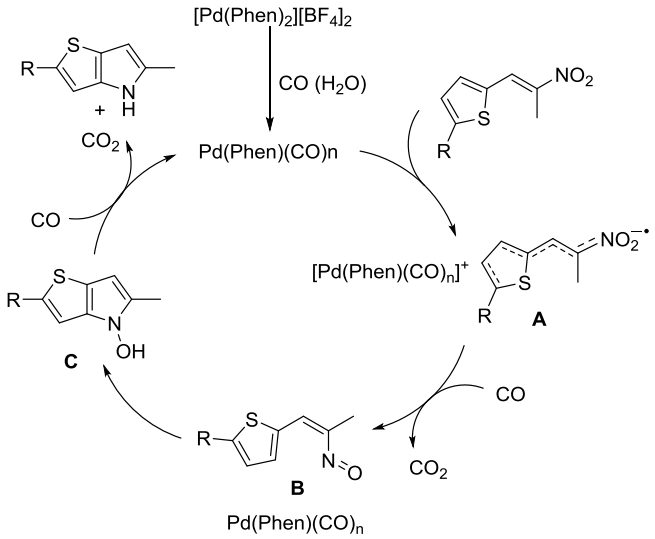
Scheme 3. Pathways for side products formation for substrate **1a**.

By analogy with the mechanism that we previously proposed for the reductive cyclization of β-nitrostyrenes to indoles,[16] we propose that the initial step of the reaction is the formation of a radical anion by single-electron transfer from the palladium complex to the nitroalkene (Scheme 4, **A**). Deoxygenation of intermediate **A** by CO yields the corresponding nitrosoalkene that cyclizes to the *N*-hydroxythienopyrrole **C**. Finally, Pd-catalyzed reduction of **C** by CO affords the thienopyrrole (Scheme 4).

After the identification of the optimal conditions, we examined the scope of the reaction (Table 3). At first, the cyclization of 2-(2-nitrovinyl)thiophenes, **1a-f,** with different substituents on the carbon carrying the nitro group was studied.

Final version published in: *Eur. J. Org. Chem.* **2017**, 1902–1910. DOI: 10.1002/ejoc.201700165

Excellent yields were obtained with aliphatic and benzylic substituents (Table 3, entries 1-2), but yield were only good when the substituent was a phenyl (entry 3). Similarly to what found for the cyclization of β-nitrostyrenes,[16] the reaction afforded mainly side products when no substituent was present



Scheme 4. Proposed reaction mechanism.

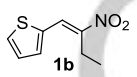
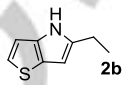
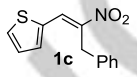
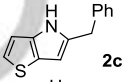
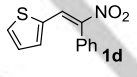
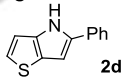
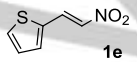
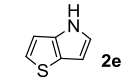
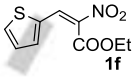
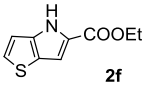
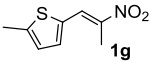
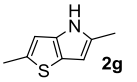
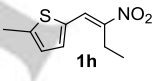
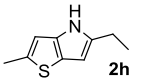
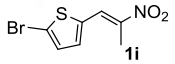
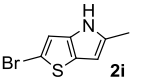
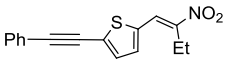
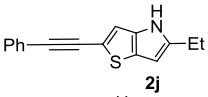
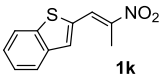
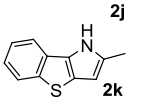
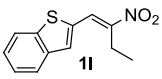
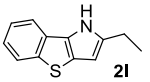
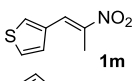
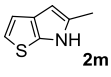
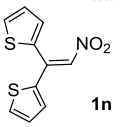
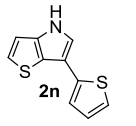
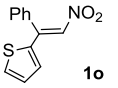
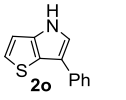
both on the carbon bearing the nitro group and on that bearing the heterocycle (entry 4). When an ester group was present, some thienopyrrole was formed (observed by GC-MS) but the product mixture was too complex, preventing its isolation. The presence of a donor group such as methyl in position 5 of the thiophene ring did not affect the reactivity allowing obtaining excellent yields (entries 6-7). Unfortunately, the presence in the same position of a bromide reduces the selectivity and the activity of the system (entry 8). Only a 28 % yield was obtained even increasing the catalyst loading to 5%. 5-Bromothiophene is an highly reactive compound and it can give side products either by radical reactions (it should be recalled that the reduction of the nitro group involves the formation of radical species)[16] or by the oxidative addition of the Br-C bond to the Pd center. We were pleased to see that the nitroalkene carrying an alkyne on the thiophene ring (entry 9) cyclized with fair yield. Highly conjugated thienopyrroles like **2j** could be interesting building blocks for the synthesis of conductive materials.

Substrates in which the thiophene ring is already fused to a benzene ring (**1k**, **1l**) are also converted to the corresponding tricyclic rings, albeit in a reduced yield, showing that the methodology can be used on more complex heteroaromatic systems.

Remarkably, also the cyclization of 3-(2-nitrovinyl)thiophene **1m**) took place in a very good yield (entry 12). In this case, the cyclization may in principle occur with activation of the C-H bond in the 2 or 4 position. Noteworthy, the reaction was selective for the 2 position.

Driven by the importance of synthesizing a bicyclic product that could be relevant as a monomer for the synthesis of conducting polymers, we explored the possibility of cyclizing substrates **1n** and **1o** (entries 13, 14).

Table 3. Palladium catalyzed cyclization of substituted 2- and 3-(2-nitrovinyl)thiophenes to thienopyrroles: reaction scope and limitation[a]

Entry	Substrate	Thienopyrrole	Yield[b]
1	 **1b**	 **2b**	90
2	 **1c**	 **2c**	98
3	 **1d**	 **2d**	62
4	 **1e**	 **2e**	n.d.[c]
5	 **1f**	 **2f**	-[d]
6	 **1g**	 **2g**	89
7	 **1h**	 **2h**	93
8[e]	 **1i**	 **2i**	28
9	 **1j**	 **2j**	42
10	 **1k**	 **2k**	32
11	 **1l**	 **2l**	37
12	 **1m**	 **2m**	78
13[e]	 **1n**	 **2n**	77
14	 **1o**	 **2o**	58[f]

[a] Reaction conditions: **1** (0.5 mmol), $[Pd(Phen)_2][BF_4]_2$ (0.01 mmol), CH_3CN (15 mL), Et_3N (400 µl, 2.9 mmol), 150 °C, P_{CO} = 5 bar, 3h. Molar ratio **1a**/**L7**/Pd = 50:8:1. [b] Isolated yield. [c] Not detected by GC-MS. [d] The product was detected by GC-MS but it was not possible to isolate it in a pure form. [e] $[Pd(Phen)_2][BF_4]_2$ (0.025 mmol). [f] 3-(thiophenyl)-1*H*-indole was formed in 40% yield (total yield in cyclized products 98 %).

Pleasingly the two compounds gave the cyclized products in very good yields. When the geminal substituents on the olefin are different (*i.e.* Ph and thienyl, entry 14) the reaction occurs preferentially on the tiophene side, although with only a low selectivity (thienopyrrole / indole ratio = 6:4). The lack of regioselectivity can be explained by the effect of competing steric and electronic factors. In fact, from the electronic point of view, once the electrophilic nitroso intermediate is formed the cyclization towards the electron rich thiophene ring should be easier. On the other hand, the orientation of the nitro group favors the formation of indole by cyclization on the phenyl ring. Moreover, even considering that an easy rotation around the O_2N-C=C double bond may occur after the initial electron transfer (see Scheme 4), still the distance between the nitrogen atom and carbon atom involved in the pyrrolic ring formation is larger in the case of the thiophene ring because of the different angles associated to 5 and 6 membered rings. This would also favor formation of indole with respect to thienopyrrole, making the reaction less selective.

Finally, a half-gram scale (3 mmol) reaction was conducted on **1a** to verify the possibility of scaling up the procedure. The reaction was conducted using 8 bar of CO for 5 h at 150 °C, affording the product in 74 % isolated yield.

Conclusions

In summary, a new synthetic method for the preparation of thienopyrroles has been developed. The procedure is simple and employs substrates that are in most cases synthesizable in one step from cheap commercial reagents. Compared to the catalytic system previously reported by us to catalyze the cyclization of β-nitrostyrenes, an improved system was developed, based on the substitution of phenanthroline with 4,7-dimethoxy-1,10-phenanthroline, **L7**, which shows a higher activity and is more selective towards the cyclized product. Noteworthy, the reaction can also be scaled up, so that the obtained compounds can be employed as starting materials for further reactions. Studies aimed at extending the applicability of the method to other pyrrole-containing heterocycles and further improving the reaction are currently ongoing in our laboratories.

Experimental Section

All reactions were conducted under a dinitrogen atmosphere. All the solvents used in catalytic reactions, were dried by distillation over CaH_2 or Na and stored under a dinitrogen atmosphere. All glassware and magnetic stirring bars were kept in an oven at 125 °C for at least two hours and let to cool under vacuum before use. 1,10-Phenanthroline (Phen), purchased as the hydrate, was dried over Na_2SO_4 after dissolution in CH_2Cl_2, followed by filtration under a dinitrogen atmosphere and evaporation of the solvent in vacuo. Then, it was stored under dinitrogen. Phenanthroline can be weighed in the air, but must be stored in an inert atmosphere to avoid water uptake. The same procedure was applied to all the ligands employed. $[Pd(Phen)_2][BF_4]_2$, was synthesized following the procedure reported in the literature.[25] If not otherwise stated, all the other reagents were purchased from Aldrich or Alfa-Aesar and used without further purification. ^1H, ^{13}C and 2D (COSY, NOESY) NMR spectra were recorded on a Bruker Avance DRX 300 or on a Bruker Avance DRX 400, operating at 300 and 400 MHz respectively. Mass spectra were obtained by GC mass spectrometry (Shimadzu GC - 17A / QP5050, equipped with SUPELCO SLB™ -5ms capillary column). Quantitative analyses of catalytic reactions were performed using fast gas-chromatography (Shimadzu GC – 2010, equipped with a SUPELCO EQUITY TM -5ms capillary column).

Synthesis and characterization of substituted nitroalkenylthiophenes

Nitroalkenylthiophenes substituted in the β-position were prepared by the Henry condensation of the corresponding aldehyde and nitroalkane using different procedures:

Method A. In a Schlenk flask, the aldehyde (10 mmol) and ammonium acetate (5 mmol) were dissolved in nitroethane (5 mL). The mixture was stirred at reflux for 5 hours and the conversion of the aldehyde checked by TLC on silica gel. The solvent was evaporated and the residue was taken up with methylene chloride and washed with water. The organic layer was dried and evaporated in vacuo. Finally, purification over a short silica column with EtOAc/hexane as eluent afforded the nitroalkene.[26]

Method B. A solution of nitroethane (1.6 mL, 22.4 mmol) or (nitropropane), *n*-butylamine (0.9 mL, 9.1 mmol) and the aldehyde (7.9 mmol) in glacial acetic acid (4 mL) was heated at 80 °C for 2h. The crude product that separated on cooling was collected by filtration, recrystallized from methanol and finally purified using a short column of silica.[27]

Method C. A mixture of ethyl nitroacetate (2,0 g, 15 mmol), aldehyde (10 mmol), a catalytic amount of phenylalanine (0.03 g) and 1 mL of glacial acetic acid in 10 mL of anhydrous benzene was refluxed for 2 h under Dean-Stark conditions. After cooling, the reaction mixture was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. The solvent was then removed with a rotary evaporator and the residue washed with ethanol.[28]

Method D. Aldehyde (10 mmol), nitroalkane (60 mmol) and piperidine (1 mmol) were added sequentially to a round-bottomed flask containing toluene. Ferric chloride (1 mmol) was added, and the mixture was slowly heated to reflux. The progress of the reaction was monitored by TLC on silica gel. After completion of the reaction, the mixture was cooled to room temperature, the excess solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the nitroalkene product as a yellow solid.[29]

Method E. Methanol (5 mL), phenylnitromethane (11 mmol), methylamine hydrochloride (1 mmol), sodium hydrogen carbonate (0.2 mmol), and aldehyde (10 mmol), were stirred at 18–20 °C for 72 h. The resulting precipitate was collected by filtration and washed with methanol.[30]

Method F. A mixture of sodium acetate, methylamine hydrochloride, nitroethane and aldehyde in absolute ethanol was stirred for 5 h. The mixture was diluted with water and extracted with dichloromethane. The combined organic layers were washed with water and evaporated in vacuo. Finally the crude product was filtered over a short column of silica using hexane/EtOAc 7:3 as the eluent.[31]

(*E*)-2-(2-nitroprop-1-en-1-yl)thiophene (1a).[27] Method B. Yellow solid; 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K), δ = 8.31 (s, 1H, $H_{alkenyl}$), 7.67 (d, *J* = 5.1 Hz, 1H, H_{thioph}), 7.45 (d, *J* = 3.6 Hz, 1H, H_{thioph}), 7.23 - 7.18 (m, 1H, H_{thioph}), 2.57 ppm (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 144.6 (*C*), 135.4 (*C*), 134.8 (*CH*), 131.8 (*CH*), 128.4 (*CH*), 127. (*CH*), 14.2 ppm (CH_3); elemental analysis calcd (%) for $C_7H_7NO_2S$: C 49.69, H 4.17, N 8.28; found: C 49.43, H 4.13, N 8.22.

(*E*)-2-(2-nitrobutenyl)thiophene (1b). Method B. Yellow oil; 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.25 (s, 1H, $H_{alkenyl}$), 7.64 (d, *J* = 5.1 Hz, 1H, H_{thioph}), 7.43 (d, *J* = 3.6 Hz, 1H, H_{thioph}), 7.19 (dd, *J* = 5.1, 3.6 Hz, 1H, H_{thioph}), 3.04 (q, *J* = 7.4 Hz, 2H, CH_2), 1.28 ppm (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 150.3 (*C*), 135.3 (*CH*), 135.1 (*C*), 132.1 (*CH*), 128.6 (*CH*), 127.0 (*CH*), 21.8 (CH_2), 12.0 ppm (CH_3); elemental analysis calcd (%) for $C_8H_9NO_2S$: C 52.44, H 4.95, N 7.64; found C 52.73, H 5.10, N 7.44.

(*E*)-2-(2-nitro-3-phenylpropenyl)thiophene (1c). Method B. Yellow oil; 47% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.51 (s, 1H, $H_{alkenyl}$), 7.62 (d, *J* = 5.1 Hz, 1H, H_{thioph}), 7.49 (d, *J* = 3.5 Hz, 1H, H_{thioph}), 7.38 – 7.22 (m, 5H, H_{phenyl}), 7.19 (dd, *J* = 5.1, 3.5 Hz, 1H, H_{thioph}), 4.44 ppm (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 147.1 (*C*), 135.8 (*CH*), 135.7 (*C*), 134.9 (*C*), 132.4 (*CH*), 129.2 (*CH*), 129.0 (*CH*), 128.7 (*CH*), 128.3 (*CH*), 127.4 (*CH*), 33.8 ppm (CH_2); elemental analysis calcd (%) for $C_{13}H_{11}NO_2S$: C 63.65, H 4.52, N 5.71; found C 64.02, H 4.72, N 5.60.

(*E*)-2-(2-nitro-2-phenylvinyl)thiophene (1d).[32] Method E. Yellow solid; 85 % yield. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.51 (s, 1H, $H_{alkenyl}$), 7.66 - 7.53 (m, 3H, H_{phenyl}), 7.43 - 7.40 (m, 2H, H_{phenyl}), 7.39 (d, *J* = 5.0 Hz, 1H, H_{thioph}), 7.34 (d, *J* = 3.6 Hz, 1H, H_{thioph}), 7.05 ppm (dd, *J* = 5.0, 3.5 Hz, 1H, H_{thioph}); ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 146.8 (*C*), 136.2 (*CH*), 135.3 (*C*), 133.3 (*CH*), 131.1 (*CH*), 130.7 (*CH*), 129.9 (*C*), 129.7 (*CH*), 129.3 (*CH*), 127.7 ppm (*CH*); elemental analysis calcd (%) for $C_{12}H_9NO_2S$: C 62.32, H 3.92, N 6.06; found: C 62.31, H 3.86, N 6.08.

(*E*)-2-(2-nitrovinyl)thiophene (1e).[29] Method D. Yellow solid; 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.18 (d, *J* = 13.4 Hz, 1H, $H_{alkenyl}$), 7.58 (d, *J* = 5.0 Hz, 1H, H_{thioph}), 7.50 (d, *J* = 13.4 Hz, 1H, $H_{alkenyl}$), 7.48 (d, *J* = 3.1 Hz, 1H, H_{thioph}), 7.21 - 7.13 ppm (m, 1H, H $_{Thioph}$); ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 135.5 (*C*), 134.7 (*CH*), 133.9 (*CH*), 132.2 (*CH*), 131.7 (*CH*), 129.0 ppm (*CH*); elemental analysis calcd (%) for $C_6H_5NO_2S$: C 46.44, H 3.25, N 9.03; found: C 46.25, H 3.02, N 8.84.

(*E*)-ethyl 2-nitro-3-(thiophenyl)acrylate (1f).[28] Method C. Yellow solid, 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K), δ = 7.73 (s, 1H, $H_{alkenyl}$), 7.71 (d, *J* = 5.0 Hz, 1H, H_{thioph}), 7.49 (d, *J* = 3.8 Hz, 1H, H_{thioph}), 7.18 (dd, *J* = 5.0, 3.9 Hz, 1H, H_{thioph}), 4.39 (q, *J* = 7.2 Hz, 2H, CH_2), 1.40 ppm (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 159.5 (*C*), 135.7 (*CH*), 134.3 (*CH*), 131.8 (*C*), 128.5 (*CH*), 126.7 (*CH*), 62.9 (CH_2), 14.1 ppm (CH_3); EI-MS (M = 227); elemental analysis calcd (%) for $C_9H_9NO_4S$: C 47.57, H 3.99, N 6.16; found: C 47.17, H 4.06, N 6.30.

(*E*)-2-methyl-5-(2-nitropropenyl)thiophene (1g).[33] Method A. Yellow solid; 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.22 (s, 1H, $H_{alkenyl}$), 7.26 (d, *J* = 3.3 Hz, 1H, H_{thioph}), 6.86 (d, *J* = 3.6 Hz, 1H, H_{thioph}), 2.58 (s, 3H, CH_3), 2.52 ppm (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 148.2 (*C*), 143.4 (*C*), 136.1 (*CH*), 133.7 (*C*), 128.2 (*CH*), 127.2 (*CH*), 16.2 (CH_3), 14.6 ppm (CH_3); elemental analysis calcd (%) for $C_8H_9NO_2S$: C 52.44, H 4.95, N 7.64; found: C 52.54, H 4.90, N 7.56.

(*E*)-2-methyl-5-(2-nitrobutenyl)thiophene (1h). Method A. Yellow solid; 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.15 (s, 1H, $H_{alkenyl}$), 7.24 (d, *J* = 3.6 Hz, 1H, $H_{thioph.}$), 6.84 (d, *J* = 3.6 Hz, 1H, H_{thioph}), 2.97 (q, *J* = 7.4 Hz, 2H, CH_2), 2.56 (s, 3H, CH_3), 1.24 ppm (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 149.0 (*C*), 148.4 (*C*), 136.3 (*CH*), 133.1 (*C*), 127.7 (*CH*), 127.2 (*CH*), 21.7 (CH_2), 16.1 (CH_3), 12.0 ppm (CH_3); elemental analysis calcd (%) for $C_9H_{11}NO_2S$: C 54.80, H 5.62, N 7.10; found: C 54.72, H 5.63, N 7.09.

(*E*)-2-bromo-5-(2-nitropropenyl)thiophene (1i).[27] Method A. Yellow solid; 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.18 (s, 1H, $H_{alkenyl}$), 7.20 (d, *J* = 4.0 Hz, 1H, H_{thioph}), 7.17 (d, *J* = 4.0 Hz, 1H, H_{thioph}), 2.51 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 144.7 (*C*), 136.8 (*C*), 135.0 (*CH*), 131.2 (*CH*), 126.7 (*CH*), 119.8 (*C*), 14.4 ppm (CH_3); elemental analysis calcd (%) for $C_7H_6BrNO_2$: C 33.89, H 2.44, N 5.65; found: C 34.00, H 2.32, N 5.56.

(*E*)-2-(2-nitrobutenyl)-5-(phenylethynyl)thiophene (1j). Method A. Yellow solid; 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.19 (s, 1H, $H_{alkenyl}$), 7.65 - 7.51 (m, 2H, H_{phenyl}), 7.41 (s, 3H, H_{phenyl}), 7.33 (d, *J* = 3.9 Hz, 1H, H_{thioph}), 7.31 (d, *J* = 3.9 Hz, 1H, H_{thioph}), 3.04 (q, *J* = 7.4 Hz, 2H, CH_2), 1.31 ppm (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 150.4 (*C*), 135.5 (*C*), 135.1 (*CH*), 132.4 (*CH*), 131.6 (*CH*), 129.9 (*C*), 129.2(*CH*), 128.5 (*CH*), 126.3 (*CH*), 122.1 (*C*), 97.3 (*C*), 81.9 (*C*), 21.6 (CH_2), 11.7 ppm (CH_3); elemental analysis calcd (%) for $C_{16}H_{13}NO_2S$: C 67.82, H 4.62, N 4.94; found: C 67.43, H 4.70; N, 4.86.

(*E*)-2-(2-nitropropenyl)benzo[b]thiophene (1k).[34] Method A. Yellow solid; 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.37 (s, 1H, $H_{alkenyl}$), 7.88 (d, *J* = 7.5 Hz, 2H, H_{phenyl}), 7.68 (s, 1H, H_{thioph}), 7.46 (dd, *J* = 7.5, 3.9 Hz, 2H, H_{phenyl}), 2.66 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 146.2 (*C*), 142.0 (*C*), 138.6 (*C*), 134.9 (*CH*), 132.1 (*C*), 127.8 (*CH*), 126.7 (*CH*), 125.3 (*CH*), 124.8 (*CH*), 122.4 (*CH*), 14.3 ppm (CH_3); elemental analysis calcd (%) for $C_{11}H_9NO_2S$: C 60.26, H 4.14, N 6.39; found: C 60.52, H 4.18, N 6.15.

(*E*)-2-(2-nitrobutenyl)benzo[b]thiophene (1l). Method A. Yellow solid; 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.31 (s, 1H, $H_{alkenyl}$), 7.88 (d, *J* = 6.9 Hz, 2H, H_{phenyl}), 7.66 (s, 1H, H_{thioph}), 7.46 (t, *J* = 5.0 Hz, 2H, H_{phenyl}), 3.12 (q, *J* = 7.4 Hz, 2H, CH_2), 1.34 ppm (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 151.7 (*C*), 142.0 (*C*), 138.5 (*C*), 134.5 (*C*), 132.2 (*CH*), 127.2 (*CH*), 126.7 (*CH*), 125.3 (*CH*), 124.7 (*CH*), 122.5 (*CH*), 21.6 (CH_2), 12.3 ppm (CH_3); elemental analysis calcd (%) for $C_{12}H_{11}NO_2S$: C 61.78, H 4.75, N 6.00; found: C 61.77, H 4.64, N 5.69.

(*E*)-3-(2-nitropropenyl)thiophene (1m).[35] Method A. Yellow solid; 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.09 (s, 1H, $H_{alkenyl}$), 7.62 (d, *J* = 2.5 Hz, 1H, H_{thioph}), 7.46 (dd, *J* = 5.1, 2.9 Hz, 1H, H_{thioph}), 7.30 (d, *J* = 5.1 Hz, 1H, H_{thioph}), 2.51 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 146.4 (*C*), 133.8 (*C*), 129.9 (*CH*), 128.2 (*CH*), 127.6 (*CH*), 127.0 (*CH*), 14.2 ppm (CH_3); elemental analysis calcd (%) for $C_7H_7NO_2S$: C 49.69, H 4.17, N 8.28; found: C 49.94, H 4.14, N 8.20.

General procedure for the synthesis of α-substituted nitroalkenylthiophenes.

Mg turnings (370 mg, 15.2 mmol) were placed in a Schlenk flask and heated under vacuum. After filling the flask with dinitrogen, THF (10 mL) and a small crystal of iodine were added. Then 2-bromothiophene (2.0 g, 12.2 mmol) in THF (10 mL) was added dropwise to the mixture while stirring at such a rate as to avoid the boiling of the solvent. After the addition, the reaction mixture was stirred for a further 3h. The organomagnesium reagent was filtered on a frit to remove excess Mg and then added dropwise at RT to a solution of the nitrile (10.7 mmol) in THF (5 mL). The solution was then heated at 60 °C for 4 h. Completion of

the reaction was check by TLC. The reaction was quenched with MeOH (5 mL) and the solvent was evaporated in vacuo. The residue was taken up with anhydrous, degassed CH_2Cl_2 (30 mL) and filtered over a small pad of silica gel under dinitrogen. The solvent was evaporated and CH_3NO_2 (10 mL) was added. The mixture was refluxed for 8h. Nitromethane was evaporated under vacuum and the residue purified by column chromatography (silica gel, hexane/AcOEt = 95:5).

2,2'-(2-nitroetheneyl)dithiophene (1n). Orange solid; 24% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.58 (d, *J* = 4.9 Hz, 1H, H_{thioph}), 7.53 (d, *J* = 5.1 Hz, 1H, H_{thioph}), 7.51 (s, 1H, $H_{alkenyl}$), 7.29 - 7.20 (m, 2H, H_{thioph}), 7.16 - 7.06 ppm (m, 2H, H_{thioph}); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.4 (*C*), 137.2 (*C*), 134.6 (*C*), 132.5 (*C*H), 132.4 (*C*H), 131.5 (*C*H), 130.8 (*C*H), 129.7 (*C*H), 128.6 (*C*H), 127.3 ppm (*C*H); elemental analysis calcd (%) for $C_{10}H_7NO_2S_2$: C 50.62, H 2.97, N 5.90; found: C 50.60, H 3.15, N 6.10.

(*E*)-2-(2-nitro-1-phenylvinyl)thiophene (1o). Orange solid; 10% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62 (s, 1H, $H_{alkenyl}$), 7.51 (dd, *J* = 5.0, 1.1 Hz, 1H, $H_{thioph.}$), 7.49 - 7.44 (m, 3H, H_{phenyl}), 7.32 - 7.28 (m, 2H, H_{phenyl}), 7.06 (dd, *J* = 5.0, 3.8 Hz, 1H, $H_{thioph.}$), 7.03 (dd, *J* = 3.8, 1.1 Hz, 1H, $H_{thioph.}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.7 (*C*), 140.3 (*C*), 134.9 (*C*), 132.6 (*C*H), 132.1 (*C*H), 130.7 (*C*H), 129.3 (*C*H), 128.6 (*C*H), 128.4 (*C*H), 128.3 ppm (*C*H); elemental analysis calcd (%) for $C_{12}H_9NO_2S$: C 62.32, H 3.92, N 6.06; found: C 62.35, H 3.99, N 6.17. It was not possible to isolate the corresponding *Z* isomer from the reaction mixture.

Typical Catalytic Reaction

The catalyst, the ligand and the nitroalkene were weighed in the air in a glass liner and then placed inside a Schlenk tube with a wide mouth under a dinitrogen atmosphere. The solvent and triethylamine (Et_3N) were added by volume and the liner was closed with a screw cap having a glass wool-filled open mouth that allows gaseous reagents to exchange. The resulting solution was stirred for 10 minutes and then the Schlenk tube was immersed in liquid nitrogen until the solvent froze and evacuated and filled with dinitrogen for three times. The liner was rapidly transferred to a 200 mL stainless steel autoclave equipped with magnetic stirring. The autoclave was then evacuated and filled with dinitrogen three times. CO was charged at room temperature at the required pressure and the autoclave was immersed in a preheated oil bath. The experimental conditions are reported in the captions to the tables in the text. At the end of the reaction, the autoclave was quickly cooled with an ice bath, and vented. Quantitative analyses of reaction mixtures in the optimization experiments (**1a** as substrate) were carried out by fast gas chromatography using naphthalene as the internal standard (1/4 by weight with respect to the initial substrate). The calibration curve was determined by using isolated **2a**. The substrate scope was investigated by isolating the products by column chromatography (gradient elution from hexane to hexane/AcOEt 9:1 with the addition of 1% Et_3N). Conversions, selectivities and yields are reported in the tables in the text.

Characterization of thienopyrroles

5-methyl-4*H*-thieno[3,2-b]pyrrole (2a).[36] Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.96 (br s, 1H; exchangeable, NH), 7.00 (d, *J* = 5.2 Hz, 1H, H_{thioph}), 6.90 (d, *J* = 5.2 Hz, 1H, H_{thioph}), 6.17 (s, 1H, $H_{pyrrole}$), 2.43 ppm (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ = 138.3 (*C*), 133.9 (*C*), 123.0 (*C*), 121.0 (*C*H), 112.0 (*C*H), 98.6 (*C*H), 14.2 ppm (CH_3); elemental analysis calcd (%) for C_7H_7NS: C 61.28, H 5.14, N 10.21; found: C 60.91, H 5.07, N 9.96.

5-ethyl-4*H*-thieno[3,2-b]pyrrole (2b). Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 7.96 (br s, exchangeable, 1H, NH), 7.02 (d, *J* = 5.2 Hz, 1H, H_{thioph}), 6.92 (dd, *J* = 5.2, 0.7 Hz, 1H, H_{thioph}), 6.22 (s, 1H, $H_{pyrrole}$), 2.78 (q, *J* = 7.6 Hz, 2H, CH_2), 1.34 ppm (t, *J* = 7.6 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 140.6 (*C*), 138.1 (*C*), 124.5 (*C*), 122.2 (*C*H), 111.3 (*C*H), 98.3 (*C*H), 22.3 (CH_2), 14.1 ppm (CH_3); elemental analysis calcd (%) for C_8H_9NS: C 63.54, H 6.00, N 9.26; found: C 63.22, H 6.05, N 8.97.

5-benzyl-4*H*-thieno[3,2-b]pyrrole (2c). Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 7.85 (br s, exchangeable, 1H, NH), 7.40 - 7.25 (m, 5H, H_{phenyl}), 7.02 (d, *J* = 5.2 Hz, 1H, $H_{thioph.}$), 6.87 (d, *J* = 5.2 Hz, 1H, $H_{thioph.}$), 6.30 (s, 1H, $H_{pyrrole}$), 4.11 ppm (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 139.3 (*C*), 138.6 (*C*), 136.8 (*C*), 129.2 (*C*H), 129.1 (*C*H), 127.2 (*C*H), 124.7 (*C*), 122.7 (*C*H), 111.3 (*C*H), 100.4 (*C*H), 35.5 ppm (CH_2); elemental analysis calcd (%) for $C_{13}H_{11}NS$: C 73.20, H 5.20, N 6.57; found: C 73.21, H 4.93, N 6.48.

5-phenyl-4*H*-thieno[3,2-b]pyrrole (2d).[37] Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.45 (br s, exchangeable, 1H, NH), 7.62 – 7.51 (m, 2H, H_{phenyl}), 7.43 (t, *J* = 7.7 Hz, 2H, H_{phenyl}), 7.34 – 7.27 (m, 1H, H_{phenyl}), 7.12 (d, *J* = 5.2 Hz, 1H, $H_{thioph.}$), 7.00 (d, *J* = 5.0 Hz, 1H, H_{thioph}), 6.79 ppm (d, *J* = 1.4 Hz, 1H, $H_{pyrrole}$). ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 139.8 (*C*), 137.9 (*C*), 133.4 (*C*), 129.6 (*C*H), 127.3 (*C*H), 126.1 (*C*), 124.7 (*C*H), 124.3 (*C*H), 111.4 (*C*H), 99.5 ppm (*C*H); elemental analysis calcd (%) for $C_{12}H_9NS$: C 72.33, H 4.55, N 7.03; found: C 72.27, H 4.35, N 7.22.

2,5-dimethyl-4*H*-thieno[3,2-b]pyrrole (2g). Colorless solid; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 7.78 (br s, exchangeable, 1H, NH), 6.59 (s, 1H, H_{thioph}), 6.08 (s, 1H, $H_{pyrrole}$) 2.54 (s, 3H, CH_3), 2.39 ppm (s, 3H, CH_3).^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 137.1 (C), 136.9 (C), 131.8 (*C*), 122.4 (*C*), 109.7 (*C*H), 99.7 (*C*H), 16.8 (CH_3), 14.3 ppm (CH_3); elemental analysis calcd (%) for C_8H_9NS: C 63.54, H 6.00, N 9.26; found: C 63.11, H 6.09, N 9.12.

5-ethyl-2-methyl-4*H*-thieno[3,2-b]pyrrole (2h). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) δ = 7.76 (br s, exchangeable, 1H, NH), 6.62 (s, 1H, H_{thioph}), 6.17 (s, 1H, $H_{pyrrole}$), 2.75 (q, *J* = 7.6 Hz, 2H, CH_2), 2.60 (s, 3H, CH_3), 1.35 ppm (t, *J* = 7.6 Hz, 3H, CH_3).^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 138.7 (*C*), 137.1 (*C*), 136.9 (*C*), 122.3 (*C*), 109.9 (*C*H), 98.1 (*C*H), 22.1 (CH_2), 16.9 (CH_3), 14.2 ppm (CH_3); elemental analysis calcd (%) for $C_9H_{11}NS$: C 65.41, H 6.71, N 8.48; found: C 65.97, H 7.02, N 8.23.

5-bromo-4*H*-thieno[3,2-b]pyrrole (2i). Isolated under a dinitrogen atmosphere. Colorless oil; ^{1}H NMR (400 MHz, C_6D_6, 300 K) δ = 7.82 (br s, exchangeable, 1H, NH), 6.81 (s, 1H, H_{thioph}), 5.96 (s, 1H, $H_{pyrrole}$), 2.27 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, C_6D_6, 300 K) δ = 114.6 (*C*H), 107.8 (*C*), 99.6 (*C*H), 13.3 ppm (CH_3). Three quaternary carbons were not detected or overlap with C_6D_6. Due to the low stability of the compound, it was not possible to obtain a reliable elemental analysis.

5-ethyl-2-(phenylethynyl)-4H-thieno[3,2-b]pyrrole (2j). Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 7.99 (broad s, exchangeable, 1H, NH), 7.54 (m, 2H, H_{phenyl}), 7.37 (m, 3H, H_{phenyl}), 7.11 (s, 1H, $H_{thioph.}$), 6.17 (s, 1H, $H_{pyrrole}$), 2.77 (q, *J* = 7.6 Hz, 2H, CH_2), 1.34 ppm (t, *J* = 7.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 142.5 (*C*), 136.1 (*C*), 131.3 (*C*H), 128.5 (*C*H), 128.1 (*C*H), 126.2 (*C*), 123.6 (*C*), 118.6 (*C*), 115.7 (*C*H), 98.3 (*C*H), 92.7 (*C*), 85.2 (*C*), 22.0 (CH_2), 13.6 ppm (CH_3). elemental analysis calcd (%) for $C_{16}H_{13}NS$: C 76.46, H 5.21, N 5.57; found C 76.26, H 5.49, N 5.42.

2-methyl-1*H*[1]benzothieno[3,2-b]pyrrole (2k). Colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.35 (br s, exchangeable,1H, NH), 7.79 (d, *J* = 8.1 Hz, 1H, $H_{benz.}$), 7.63 (d, *J* = 7.9 Hz, 1H, H_{benz}), 7.33 (dd, *J*

= 7.9, 1.0 Hz, 1H, H_{benz}), 7.21 (dd, *J* = 8.1, 1.1 Hz, 1H, H_{benz}), 6.24 (s, 1H, $H_{pyrrole}$), 2.49 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 141.3 (*C*), 133.7 (*C*), 131.2 (*C*), 127.0 (*C*), 124.1 (*C*H), 123.9 (*C*H), 123.2 (*C*), 122.0 (*C*H), 117.4 (*C*H), 100.5 (*C*H), 14.2 ppm (CH_3); elemental analysis calcd (%) for $C_{11}H_9NS$: C 70.55, H 4.84, N 7.48; found: C 70.27, H 5.13, N 7.69.

2-ethyl-1*H*[1]benzothieno[3,2-b]pyrrole (2l). Colorless solid; ^1H NMR (300 MHz, $CDCl_3$, 300 K) δ = 8.38 (br s, exchangeable,1H, NH), 7.80 (d, *J* = 8.0 Hz, 1H, H_{benz}), 7.64 (d, *J* = 7.9 Hz, 1H, H_{benz}), 7.37-7.33 (m, 1H, H_{benz}), 7.23 - 7.19 (m, 1H, H_{benz}), 6.27 (s, 1H, $H_{pyrrole}$), 2.83 (q, *J* = 7.6 Hz, 2H, CH_2), 1.38 ppm (t, *J* = 7.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, 300 K) δ = 141.7 (*C*), 140.7 (*C*), 131.4 (*C*), 127.5 (*C*), 124.5 (*C*H), 124.3 (*C*H), 123.4 (*C*), 122.4 (*C*H), 117.9 (*C*H), 99.4 (*C*H), 22.3 (CH_2), 14.1 ppm (CH_3); elemental analysis calcd (%) for $C_{12}H_{11}NS$: C 71.60, H 5.51, N 6.96; found: C 71.32, H 5.48, N 6.59.

5-methyl-6*H*-thieno[2,3-b]pyrrole (2m).[38] Colorless solid; ^1H NMR (400 MHz, $CDCl_3$, 300 K) δ = 7.82 (br s, exchangeable, 1H, NH), 6.99 (d, *J* = 5.2 Hz ,1H, H_{thioph}), 6.84 (d, *J* = 5.2 Hz, 1H, H_{thioph}) 6.19 (s, 1H, $H_{pyrrole}$), 2.40 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 134.6 (*C*), 132.0 (*C*), 131.3 (*C*), 117.4 (*C*H), 117.1 (*C*H), 99.4 (*C*H), 14.0 ppm (CH_3); elemental analysis calcd (%) for C_7H_7NS: C 61.28, H 5.14, N 10.21; found: C 60.97, H 5.29, N 9.86.

6-(thiophenyl)-4*H*-thieno[3,2-b]pyrrole (2n). Colorless solid; ^1H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.22 (br, NH), 7.25 (s, 1H, $H_{pyrrole}$), 7.20 (d, J = 4.0 Hz, 2H, H_{thioph}), 7.17 (d, J = 5.1 Hz, 1H, H_{thioph}), 7.09 (dd, J = 5.0, 3.6 Hz, 1H, H_{thioph}), 6.97 ppm (d, J = 5.2 Hz, 1H, H_{thioph}); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ 138.8 (*C*), 137.8 (*C*), 127.7 (*C*H), 124.7 (*C*H), 122.0 (*C*H), 121.96 (*C*), 121.8 (*C*H), 119.3 (*C*H), 112.9 (*C*H), 111.5 ppm (*C*H); elemental analysis calcd (%) for $C_{10}H_7NS_2$: C 58.50, H 3.44, N, 6.82; found: C 58.44, H 3.57, N, 6.48.

6-phenyl-4*H*-thieno[3,2-b]pyrrole (2o). Colorless solid; ^1H NMR (400 MHz, $CDCl_3$, 300 K) δ = 8.34 (br s, exchangeable, 1H, NH), 7.66 (d, *J* = 7.7 Hz, 2H, H_{phenyl}), 7.42 (t, *J* = 7.7 Hz, 2H, H_{phenyl}), 7.39 – 7.35 (m, 1H, $H_{pyrrole}$), 7.28 – 7.16 (m, 2H, H_{thioph}, H_{phenyl}), 7.01 ppm (d, *J* = 5.2 Hz, 1H, H_{thioph}); ^{13}C NMR (100 MHz, $CDCl_3$, 300 K) δ = 139.2 (*C*), 134.6 (*C*), 129.0 (*C*H), 125.9 (*C*H), 125.1 (*C*H), 124.5 (*C*H), 121.8 (*C*), 119.3 (*C*H), 118.3 (*C*), 111.4 ppm (*C*H); elemental analysis calcd (%) for $C_{12}H_9NS$: C 72.33, H 4.55, N 7.03; found: C 71.97, H 4.65, N 6.89.

3-(thiophenyl)-1*H*-indole. Colorless solid; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.21 (br s, exchangeable, 1H, NH), 7.98 (d, *J* = 6.8 Hz, 1H), 7.38 (m, 2H), 7.31 – 7.18 (m, 4H), 7.11 ppm (dd, *J* = 5.1, 3.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.8 (*C*), 136.5 (*C*), 127.69, 125.6 (*C*), 122.8 (*C*H), 122.7 (*C*H), 122.7 (*C*H), 122.0 (*C*H), 120.7 (*C*H), 120.1 (*C*H), 112.0 (*C*), 111.5 ppm (*C*H); elemental analysis calcd (%) for $C_{12}H_9NS$: C 72.33, H 4.55, N 7.03; found C 72.01, H 4.67, N 6.98.

Acknowledgements

We acknowledge the Ministero dell'Università e della Ricerca (MIUR) for financial support (PRIN 20154X9ATP). The authors thank Prof. Dr. Alessandro Caselli for fruitful discussions, Mr. Pasquale Illiano and Mr. Mario Rosa for excellent analytical assistance. F.F. thanks the University of Milano for a postdoctoral fellowship.

Keywords: C–H amination • Nitrogen heterocycles • Nitroalkenes • Palladium • Sulfur heterocycles

[1] a) P. R. O. Whittamore, M. S. Addie, S. N. L. Bennett, A. M. Birch, M. Butters, L. Godfrey, P. W. Kenny, A. D. Morley, P. M. Murray, N. G. Oikonomakos, L. R. Otterbein, A. D. Pannifer, J. S. Parker, K. Readman, P. S. Siedlecki, P. Schofield, A. Stocker, M. J. Taylor, L. A. Townsend, D. P. Whalley, J. Whitehouse, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5567-5571; b) A. M. Birch, I. Simpson, A. Stocker, P. R. O. Whittamore, WO2005020987A1, **2005**

[2] a) K.-C. Ching, Y.-W. Kam, A. Merits, L. F. P. Ng, C. L. L. Chai, *J. Med. Chem.* **2015**, *58*, 9196-9213; b) D. J. Miller, D. C. Peltier, W. Peng, WO2010057141A2, **2010**; c) J. I. Martin Hernando, J. M. Ontoria, S. Malancona, B. Attenni, F. Fiore, F. Bonelli, U. Koch, S. Di Marco, S. Colarusso, S. Ponzi, N. Gennari, S. E. Vignetti, M. del Rosario Rico Ferreira, J. Habermann, M. Rowley, F. Narjes, *ChemMedChem* **2009**, *4*, 1695-1713; d) F. U. Schmitz, C. D. Roberts, R. C. Griffith, J. Botyanszki, S. M. Pham, WO2008008907A2, **2008**

[3] M. B. Boxer, M. Beller, K. Tschapalda, M. Shen, L. Liu, Y. Zhang, Z. Li, C. Sztalryd, WO2013078413A1, **2013**

[4] H. Zhang, WO2008058448A1, **2008**

[5] J. Rohde, C. Kim, T. Nakai, WO2011100324A1, **2011**

[6] T. Nakai, J. Jia, J. Rohde, R. Graul, A. Mermerian, WO2012009137A1, **2012**

[7] S. Kumar, A. Thomas, N. Khairatkar-Joshi, D. M. Shah, WO2014041518A1, **2014**

[8] P. Vianello, L. Sartori, M. Varasi, C. Mercurio, E. Zagarri, A. Cappa, A. Romussi, M. Villa, G. Meroni, L. Moretti, WO2016034946A2, **2016**

[9] H. S. Son, Y. Beak, H. Park, C. J. Lee, J. Shin, T. H. Kim, M.-S. Eum, WO2014081166A1, **2014**

[10] G. Mazzone, A. D. Quartarolo, N. Russo, *Dyes Pigm.* **2016**, *130*, 9-15.

[11] G. Ge, P. Dai, Z. Lu, M. Liang, H. Dong, Z. Sun, S. Xue, *Dyes Pigm.* **2016**, *128*, 8-18.

[12] a) K. Ogawa, J. A. Stafford, S. D. Rothstein, D. E. Tallman, S. C. Rasmussen, *Synth. Met.* **2005**, *152*, 137-140; b) Y.-C. Chiou, C.-K. Sha, H.-F. Chen, *Synth. Met.* **1992**, *48*, 33-38; c) R. Lazzaroni, S. Dujardin, J. P. Boutique, C. Mousty-Desbuquoit, J. Riga, J. Verbist, *Mol. Cryst. Liq. Cryst.* **1985**, *118*, 249-252; d) R. Lazzaroni, J. P. Boutique, J. Riga, J. J. Verbist, J. G. Fripiat, J. Delhalle, *J. Chem. Soc., Perkin Trans. 2* **1985**, 97-102.

[13] F. Garcia, C. Gálvez, *Synthesis* **1985**, 143-156.

[14] a) J. H. Choi, H. J. Lim, *Org. Biomol. Chem.* **2015**, *13*, 5131-5138; b) S. Vijay Kumar, B. Saraiah, G. Parameshwarappa, H. Ila, G. K. Verma, *J. Org. Chem.* **2014**, *79*, 7961-7978; c) M. Inman, A. Carbone, C. J. Moody, *J. Org. Chem.* **2012**, *77*, 1217-1232; d) G. A. Salman, M. Hussain, V. Iaroshenko, A. Villinger, P. Langer, *Adv. Synth. Catal.* **2011**, *353*, 331-336; e) Y.-Q. Fang, J. Yuen, M. Lautens, *J. Org. Chem.* **2007**, *72*, 5152-5160; f) R. Martín, C. H. Larsen, A. Cuenca, S. L. Buchwald, *Org. Lett.* **2007**, *9*, 3379-3382; g) R. Martín, M. Rodríguez Rivero, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2006**, *45*, 7079-7082; h) D. J. Lee, K. Kim, Y. J. Park, *Org. Lett.* **2002**, *4*, 873-876.

[15] S. P. Gorugantula, G. M. Carrero-Martínez, S. W. Dantale, B. C. G. Söderberg, *Tetrahedron* **2010**, *66*, 1800-1805.

[16] F. Ferretti, M. A. El-Atawy, S. Muto, M. Hagar, E. Gallo, F. Ragaini, *Eur. J. Org. Chem.* **2015**, 5712-5715.

[17] A similar system had been independently described by Dong and coworkers, but its application is limited to 3-arylsubstituted β-nitrostyrenes: T. H. H. Hsieh, V. M. Dong, *Tetrahedron* **2009**, *65*, 3062-3068.

[18] a) P. Zardi, A. Savoldelli, D. M. Carminati, A. Caselli, F. Ragaini, E. Gallo, *ACS Catal.* **2014**, *4*, 3820-3823; b) F. Ragaini, F. Ventriglia, M. Hagar, S. Fantauzzi, S. Cenini, *Eur. J. Org. Chem.* **2009**, 2185-2189; c) F. Ragaini, A. Rapetti, E. Visentin, M. Monzani, A. Caselli, S. Cenini, *J. Org. Chem.* **2006**, *71*, 3748-3753; d) F. Ragaini, S. Cenini, E. Gallo, A.

Caselli, S. Fantauzzi, *Curr. Org. Chem.* **2006**, *10*, 1479-1510. d) F. Ferretti, D. Formenti, F. Ragaini, Rend. Fis. Acc. Lincei **2017**, DOI 10.1007/s12210-017-0601-7

[19] a) F. Ferretti, E. Gallo, F. Ragaini, *J. Organomet. Chem.* **2014**, *771*, 59-67; b) F. Ferretti, F. Ragaini, R. Lariccia, E. Gallo, S. Cenini, *Organometallics* **2010**, *29*, 1465-1471.

[20] P. Wehman, H. M. A. vanDonge, A. Hagos, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Organomet. Chem.* **1997**, *535*, 183-193.

[21] F. Ragaini, M. Gasperini, S. Cenini, L. Arnera, A. Caselli, P. Macchi, N. Casati, *Chem. Eur. J.* **2009**, *15*, 8064-8077.

[22] a) A. G. Leach, K. N. Houk, I. W. Davies, *Synthesis* **2005**, 3463-3467; b) F. Ragaini, P. Sportiello, S. Cenini, *J. Organomet. Chem.* **1999**, *577*, 283-291.

[23] R. K. Henderson, A. P. Hill, A. M. Redman, H. F. Sneddon, *Green Chem.* **2015**, *17*, 945-949.

[24] S. J. Skoog, W. L. Gladfelter, *J. Am. Chem. Soc.* **1997**, *119*, 11049-11060.

[25] A. Bontempi, E. Alessio, G. Chanos, G. Mestroni, *J. Mol. Catal.* **1987**, *42*, 67-80.

[26] a) L. Munoz, A. M. Rodriguez, G. Rosell, M. P. Bosch, A. Guerrero, *Org. Biomol. Chem.* **2011**, *9*, 8171-8177; b) M. M. Goodman, G. W. Kabalka, R. C. Marks, F. F. Knapp, J. Lee, Y. Liang, *J. Med. Chem.* **1992**, *35*, 280-285.

[27] G. Vallejos, A. Fierro, M. C. Rezende, S. Sepúlveda-Boza, M. Reyes-Parada, *Biorg. Med. Chem.* **2005**, *13*, 4450-4457.

[28] L. V. Baichurina, R. I. Baichurin, N. I. Aboskalova, V. M. Berestovitskaya, *Russ. J. Gen. Chem.* **2010**, *80*, 2022-2026.

[29] S. Jalal, S. Sarkar, K. Bera, S. Maiti, U. Jana, *Eur. J. Org. Chem.* **2013**, 4823-4828.

[30] E. A. Ishmaeva, Y. A. Vereshchagina, D. V. Chachkov, O. S. Vasil'eva, E. S. Ostroglyadov, A. A. Nikonorov, I. A. Litvinov, D. B. Krivolapov, A. Z. Alimova, V. M. Berestovitskaya, *Russ. J. Gen. Chem.* **2012**, *82*, 911-920.

[31] J.-P. Strachan, D. F. O'Shea, T. Balasubramanian, J. S. Lindsey, *J. Org. Chem.* **2000**, *65*, 3160-3172.

[32] M. Ganesh, I. N. N. Namboothiri, *Tetrahedron* **2007**, *63*, 11973-11983.

[33] L. A. Shumilova, M. K. Korsakov, M. V. Dorogov, E. E. Shalygina, *Russ. Chem. Bull.* **2014**, *63*, 118-122.

[34] a) V. E. Gregor, Y. Liu, A. Anikin, C. Mikel, D. E. McGrath, G. R. Vavilala, J. C. Pickens, A. Kadushkin, L. Jiang, M. S. Thiruvazhi, S. Zozulya, R. Vairagoundar, T. Zhu, A. Chucholowski, Z. Yan, A. Khasanov, WO2009117097A1, **2009**; b) V. E. Gregor, US20150011539A1, **2015**

[35] G. Liu, X. Liu, Z. Cai, G. Jiao, G. Xu, W. Tang, *Angew. Chem. Int. Ed.* **2013**, *52*, 4235-4238.

[36] L. Rokhum, G. Bez, *Tetrahedron Lett.* **2013**, *54*, 5500-5504.

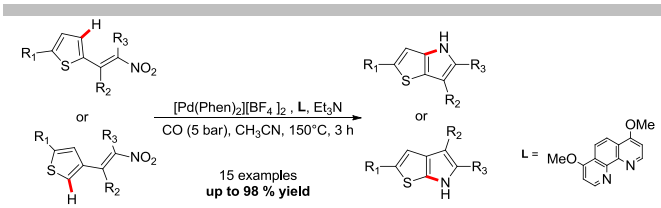
[37] K. Srinivasan, K. G. Srinivasan, K. K. Balasubramanian, S. Swaminathan, *Synthesis* **1973**, 313-315.

[38] J. H. Hutchinson, T. A. Parr, K. D. Bunker, D. Lonergan, WO2015042052A1, **2015**

Final version published in: *Eur. J. Org. Chem.* **2017**, 1902–1910. DOI: 10.1002/ejoc.201700165

Entry for the Table of Contents

FULL PAPER



Palladium/phenanthroline complexes catalyze the reductive cyclization of β-nitrothiophenes to thienopyrroles using CO as the reductant. High yields can be obtained and CO_2 is the only stoichiometric byproduct.

Fused Heterocycles

*Mohamed A. EL-Atawy, Francesco Ferretti and Fabio Ragaini**

Page No. – Page No.

Palladium-Catalyzed Intramolecular Cyclization of Nitroalkenes: Synthesis of Thienopyrroles