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Copper-Promoted Regioselective Synthesis of Polysubstituted Pyrroles from Aldehydes, Amines and Nitroalkenes *via* 1,2-Phenyl/Alkyl Migration

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KEYWORDS: Copper catalysis • 1,2-migration • pyrroles • nitrostyrenes • *α*-methyl substituted aldehydes

ABSTRACT: The facile Copper-catalyzed synthesis of polysubstituted pyrroles from aldehydes, amines and *β*-nitroalkenesis reported. Remarkably, the use of *α*-methyl substituted aldehydes provide efficient access to a series of tetra- and pentasubstituted pyrroles *via* an overwhelming

1,2-phenyl/alkyl migration. The present methodology is also accessible to non α-substituted aldehydes yielding the corresponding trisubstituted pyrroles. On the contrary, the use of ketones, in place of aldehydes, does not promote the organic transformation signifying the necessity of α-substituted aldehydes. The reaction proceeds under mild catalytic conditions with low catalyst loading (0.3 – 1 mol %), a broad scope, very good functional-group tolerance, high yields and can be easily scaled up to more than 3 mmol of product, thus highlighting a useful synthetic application of the present catalytic protocol. Based on formal kinetic studies, a possible radical pathway is proposed that involves the formation of an allylic nitrogen radical intermediate, which in turn reacts with the nitroalkene to yield the desired pyrrole framework *via* a radical 1,2-phenyl or alkyl migration.

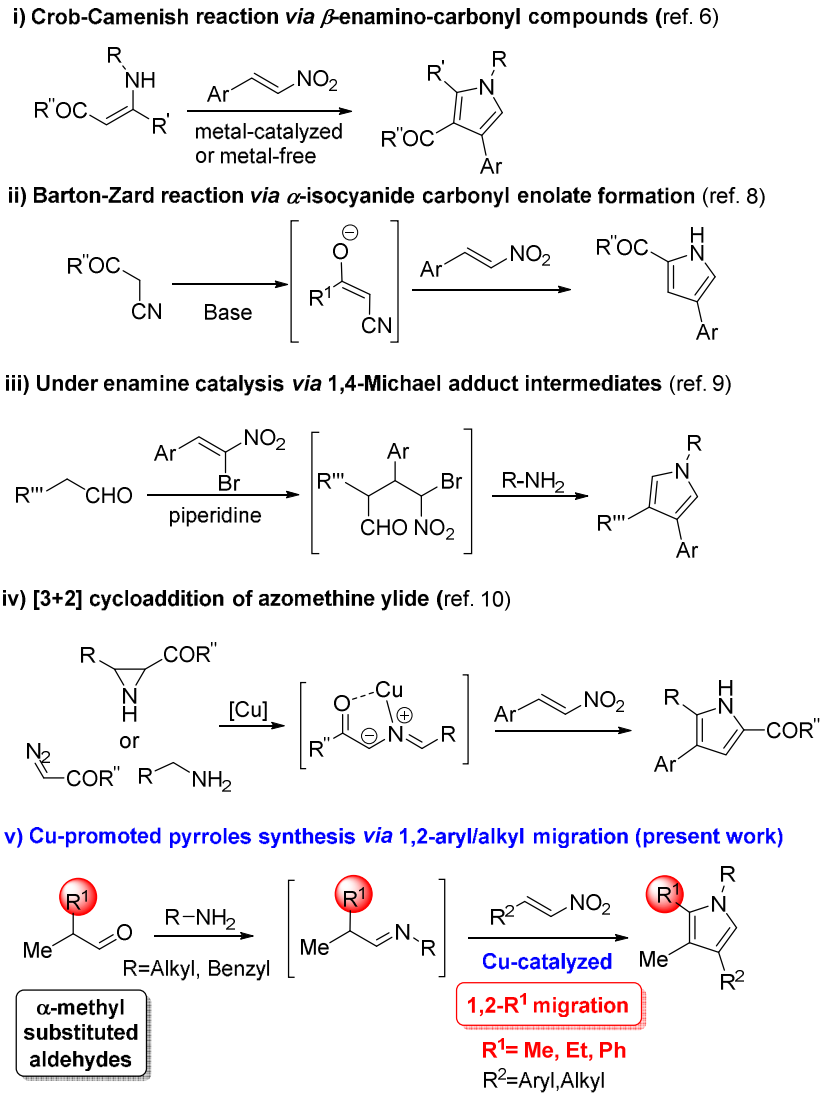
INTRODUCTION

Pyrroles represent one of the most important five-membered *N*-containing heterocyclic scaffolds and key structural cores in natural products with bioactive and therapeutic properties.[1] Several synthetic strategies including the well-known Hantzsch, Knorr, and Paal-Knorr synthesis have been developed to harvest the pyrrole framework.[2] At present, emphasis is given on the development of 3d transition metal based catalysts as well multicomponent reactions (MCRs) for high atom economy, bond-forming efficiency as well minimization of waste, time, and cost.[2,3] An interesting approach towards the synthesis of pyrroles is based on MCRs incorporating β-nitrostyrenes; the latter are versatile electrophiles and have extensively been used in heterocycle synthesis.[4,5] To date, four methodologies report the use of the nitrostyrene scaffold to produce pyrroles; the Crob-Camenisch includes β-enamino-carbonyl compounds as key intermediates

(Scheme 1, i),[6,7] the Barton-Zard incorporates the formation of α-isocyanide carbonyl enolate (Scheme 1, ii),[8] the "Lego method" uses β-bromo nitrostyrenes under enamine catalysis (Scheme 1, iii)[9] and the [3+2] cycloaddition protocol of azomethineylide intermediates with nitrostyrenes (Scheme 1, iv).[10] Consequently, the efficient and versatile synthesis of poly-substituted pyrroles, by easily accessible precursors, wide diversity and precise introduction of substituents into a certain position on the pyrrole ring, remains a great challenge.

Our groups have developed successful protocols for organic transformations promoted by a family of one dimensional (1D) Copper based coordination polymers (CPs).[11] These CPs are made from commercial available starting materials, in two steps and excellent yields and promote the chemical transformations with catalyst loadings of one order of magnitude lower when compared to metal salts, in better yields and, most importantly, absence of by-products.[11] Herein, we employ this catalytic library in the MCR of α-substituted aldehydes, amines and β-nitroalkenes (Scheme 1, v) that yields polysubstituted pyrroles in a fast and regioselective manner *via* an 1,2-phenyl/alkyl migration. Notwithstanding, few similar MCR protocols have been reported, however our current methodology has significant variations and benefits. For example, the MCR studies that involved aldehydes or cycloketones, promoted by $Sm(O\textit{i}\text{-}Pr)_3$[12a] or in absence of catalyst,[12b] required multistep and stepwise protocol with imine formation and isolation,[12a] as well as showed limited applicability.[12b] Moreover, the use of silica gel[13a] or alumina[13b] under microwave conditions or the molten ammonium salt[13c] promote the pyrrole formation, however only a limited variation of 2-methyl or 2-ethyl substituted pyrroles can be produced starting with the corresponding β-methyl or ethyl substituted nitroalkenes.

Scheme 1. Procedures for Pyrroles Synthesis Starting from Nitroalkenes.



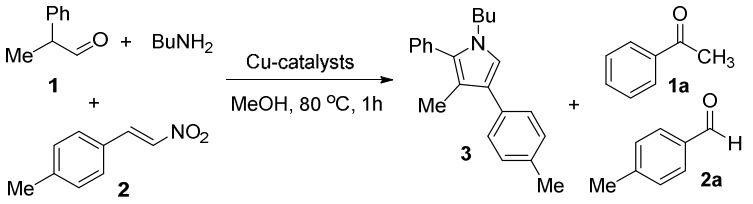
RESULTS AND DISCUSSIONS

The present catalytic protocol involves the reaction of 2-phenyl propionaldehyde (**1**), butyl amine ($BuNH_2$), and (*E*)-1-methyl-4-(2-nitrovinyl)benzene (**2**), catalyzed by various copper [Cu(II) and Cu(I)] salts (see Table 1) and the recently reported CPs formulated $[M(II)(L)_2(Z)_2]\cdot 2(ClO_4)\cdot 2MeCN$ (M=Cu, Z=MeCN, **Cu-1**), $[Cu(II)(L)_2(NO_3)_2]$ (**Cu-2**),

$[Cu(II)(L)_2(MeCN)_2]\cdot 2BF_4$ (**Cu-3**), $[Cu(II)(L)_2(OTf)_2]$ (**Cu-4**), L is 1-{2-[(1Hbenzo[d][1,2,3]triazol-1-yl)methyl]benzyl}1Hbenzo-[d][1,2,3]triazole.[11] The reaction is carried out into a sealed tube with equimolar amounts of **1**, $BuNH_2$ and **2** in 1 mL of MeOH at 80 ^oC for 1h. The alcoholic media promotes this transformation and MeOH gives the optimum results (screening tests in Tables S1). Under these conditions, Cu salts consume **2** in full, but show low or medium activity towards the synthesis of pyrrole **3** (Table 1, entries 1-10), as observed by ^1H NMR of the crude mixtures (Table 1). In all cases, two by-products were observed; acetophenone (**1a**) that is formed *via* an oxidative transformation from **1** (Figure S1),[14] and *p*-tolualdehyde (**2a**) that is produced *via* a nitromethane elimination from the Michael addition of the butylamine to nitroalkene **2** (Figure S2).[15,16] In these Cu-catalyzed reactions, the relative yields of pyrrole **3** and by-products (**1a** and **2a**) were determined by the ^1H NMR spectrum after filtration of the crude mixture on a short pad of silica in order to remove the catalyst (Figure S3). Only $Cu(OAc)_2$, CuI and $[Cu(CH_3CN)_4]BF_4$ promote the formation of **3** in moderate yields 49%, 59% and 55%, respectively (Table 1, entries 2, 9 and 10); however, 20 mol% loading is required. Other Lewis acids, such as $Sm(i\text{OPr})_3$, $AuCl_3$, $AgNO_3$, $Zn(ClO_4)_2$ and $Zn(NO_3)_2$ showed poor catalytic performance under the present conditions (Table S2). Also, the reaction of **1**, butyl amine and **2** in the presence of molten ammonium salt did not yield the corresponding pyrrole **3**.[13c] The use of **Cu-1** - **Cu-4**, in only 1 mol% loadings, give **3** in significantly increased yields (Table 1, entries 13 – 16) when compared to metal salts (Table 1, entries 1 – 10). **Cu-4** showcases superior behavior, with 89% yield (Table 1, entry 16). The use of 20 mol% of $Cu(OTf)_2$ and 20 mol% ligand L yields **3** in 45% yield (Table 1, entry 12), slightly higher when compared with $Cu(OTf)_2$ (38% yield, Table 1, entry 4). In the later two cases, a significant amount of the two by-products **1a** and **2a** was identified by the crude ^1H

NMR after filtration over a small pad of silica. In addition, control experiments in which 20 mol% of **Cu-4** and 1 mol% of CuI were performed. In the first case, the corresponding pyrrole **3** was formed in a faster manner (ca. 20min) with 80% relative yield, although a significant amount (13%) of unidentified products was observed *by* ^{1}H NMR of the crude reaction mixture (Table 1, entry 17). In contrary, in the latter case, **3** was formed in only 31%, accompanying with 26% and 13% relative yields of the by-products **1a** and **2a**, respectively (result not shown). These results support the efficiency of the **Cu-4** as catalyst with one order of magnitude less loading compared to the corresponding salt (1 mol%), as well as highlights the need of a well-defined and characterized catalyst for this process. Notably, in the absence of catalyst, **3** is formed in only 25% yield along with significant amounts of the by-products **1a** and **2a** (Table 1, entry 11). Further, the use of aniline and 4-methoxyaniline result in a mixture of unidentified products; whereas no reaction was observed in the presence of benzaldehyde or *p*-tolualdehyde (Figures S4 and S5).

Table 1. Catalyst Evaluations of Pyrrole 3 from 2-Phenyl Propionaldehyde 1, $BuNH_2$ and Nitrostyrene 2



Entry	Catalyst[a]	Conversion (%)[b]	Relative yields (%)[c]		
			3	**1a**	**2a**
1	$Cu(NO_3)_2$ $3H_2O$	78	19	16	9
2	$Cu(OAc)_2$ H_2O	100	49	18	11
3	$Cu(ClO_4)_2$ $6H_2O$	80	20	15	8

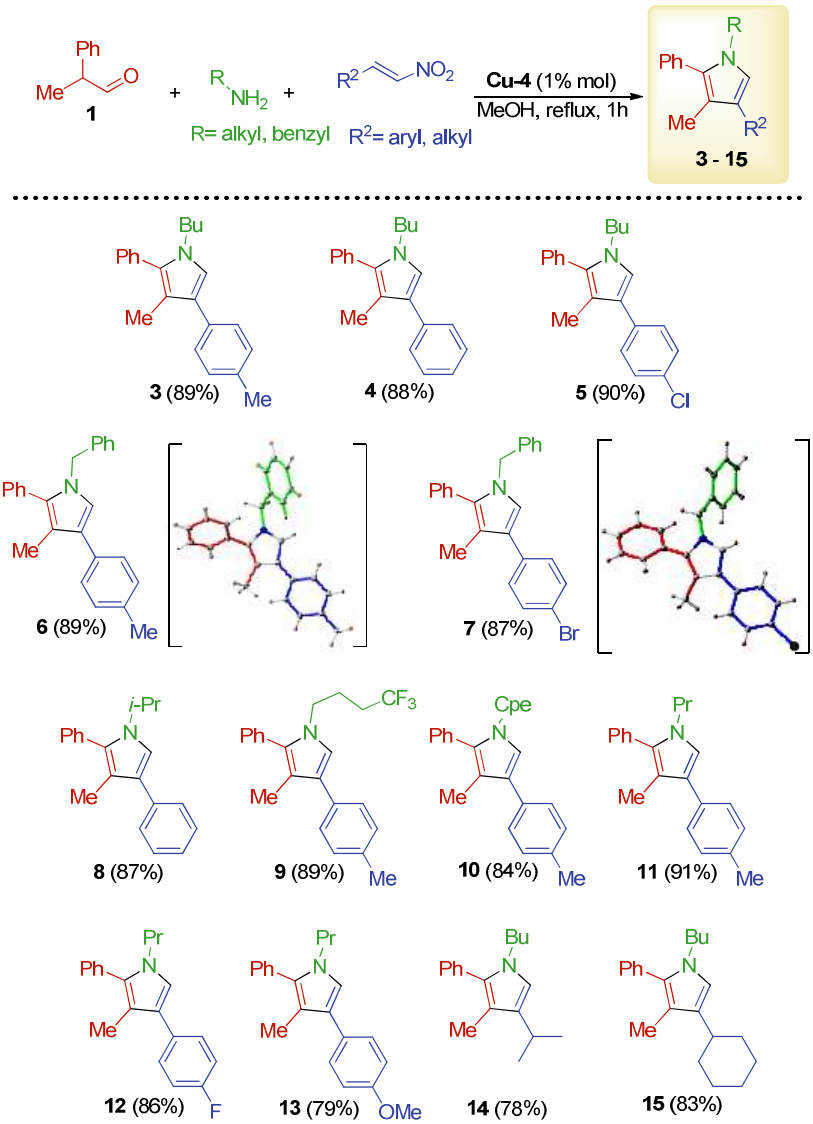
4	$Cu(OTf)_2$	100	38	23	12
5	$Cu(BF_4)_2$	100	21	29	8
6	$CuSO_4$ $5H_2O$	77	34	10	5
7	$CuBr_2$	65	32	6	4
8	CuBr	71	38	12	4
9	CuI	100	59	17	12
10	$[Cu(CH_3CN)_4]BF_4$	100	55	14	9
11[d]	—	100	25	30	12
12[e]	$Cu(OTf)_2$ + L	100	45	20	9
13	**Cu-1**	100	76	12	4
14	**Cu-2**	85	50	15	4
15	**Cu-3**	100	70	14	6
16	**Cu-4**	100	89	4	2
17[f]	**Cu-4**	100	80	5	2

[a]Conditions: **1** (0.2 mmol), $BuNH_2$ (0.2 mmol), **2** (0.2 mmol), MeOH (1 mL), at refluxfor 1h. The Cu salts were used in 20% mol, however **Cu-1** – **Cu-4** were used in 1mol%, based on **2** amount. [b]Based on the consumption of **2** determined from the crude ^{1}H NMR mixture of the reaction. [c]Relative yields determined by ^{1}H NMR of the crude mixture. In the case of Cu-salts catalyzed reactions, significant amounts of unidentified products were observed by ^{1}H NMR (see also Figure S3). [d]A significant amount of the corresponding imine **2b** formed from the reaction between **1** and $BuNH_2$ remain intact and observed by ^{1}H NMR spectrum of the crude mixture. [e]20 mol% ligand L (benzotriazole) was added into the reaction mixture. [f]The **Cu-4** was used in 20% mol and significant amount of unidentified products (13%) was observed by ^{1}H NMR within 20 min (not shown).

Herein the formation of **3** proceeds *via* a 1,2-phenyl migration,[17] a process that is not previously observed;[12,13] thus the scope and limitations of this reaction were explored with respect to the aldehyde moiety. In this context, 2-phenyl propionaldehyde (**1**) was initially used with a variety of amines (alkyl or benzyl) and nitroalkenes (aryl or alkyl) and the results are shown in Figure 1. Interestingly, the corresponding 1,2,3,4-tetrasubstituted pyrroles (**3** - **15**) were isolated in high yields. The pyrroles were characterized by HRMS and NMR spectroscopy, although their structures were determined by 1D NOE-NMR experiments, indicating that the

phenyl group is located at the C-2 position of the pyrrole ring. The pyrrole derivatives **6** and **7** were characterized by single X-ray diffraction (Figures S6 and S7). It is worth noting that the use of aliphatic nitroalkenes (isopropyl and cyclohexyl derivatives) leads to the corresponding pyrroles **14** and **15** in good isolated yields, 78% and 83% respectively (Figure 1), results that support the general applicability of the present methodology.

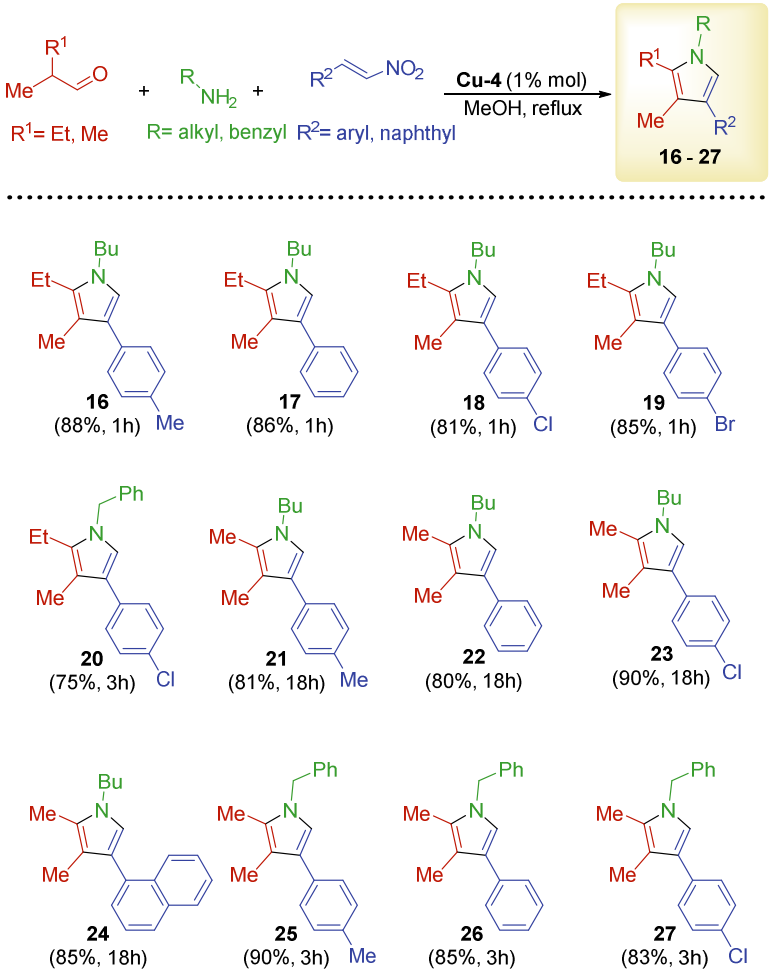
Figure 1. Cu-Catalyzed Synthesis of 1,2,3,4-Tetrasubstituted Pyrroles from 2-Phenyl Propionaldehyde (1), Amines and Nitroalkenes.



To expand the scope of this methodology, α-alkyl substituted aliphatic aldehydes, such as 2-methyl butyraldehyde (R^1 = Et) and 2-methyl propionaldehyde (R^1 = Me), were employed with a variety of amines and nitroalkenes. As shown in Figure 2, the corresponding pyrroles (**16** - **27**) were formed as major products in good to high isolated yields (75% - 90%), regardless of the nature of amine and nitroalkene. The values in parentheses show the isolated yields of the corresponding pyrroles, as well as the appropriate time for reaction completion based on TLC

analysis. In all cases, an analogous 1,2-methyl and 1,2-ethyl migration was observed to further support the potential of this protocol for the selective synthesis of polysubstituted pyrroles.

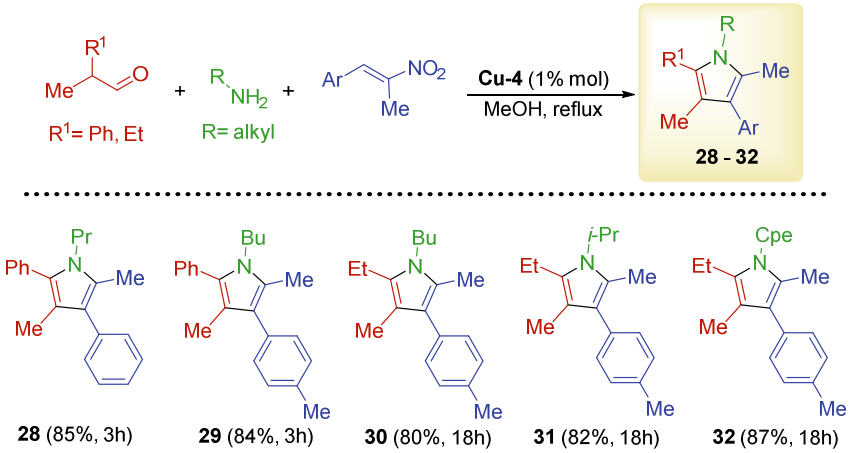
Figure 2. Cu-Catalyzed Synthesis of Various 1,2,3,4-Tetrasubstituted Pyrroles from *α*-Methyl Substituted Aliphatic Aldehydes, Amines and Nitroalkenes



It is interesting that under the present methodology even the use of *β*-methyl substituted nitrostyrenes, such as (*E*)-(2-nitroprop-1-en-1-yl)benzene and (*E*)-1-methyl-4-(2-nitroprop-1-en-1-yl)benzene, yields the corresponding pentasubstituted pyrroles (**28** - **32**) in high isolated yields in the range of 80% - 87% (Figure 3). On the contrary, *α*-methyl substituted nitrostyrene, (1-

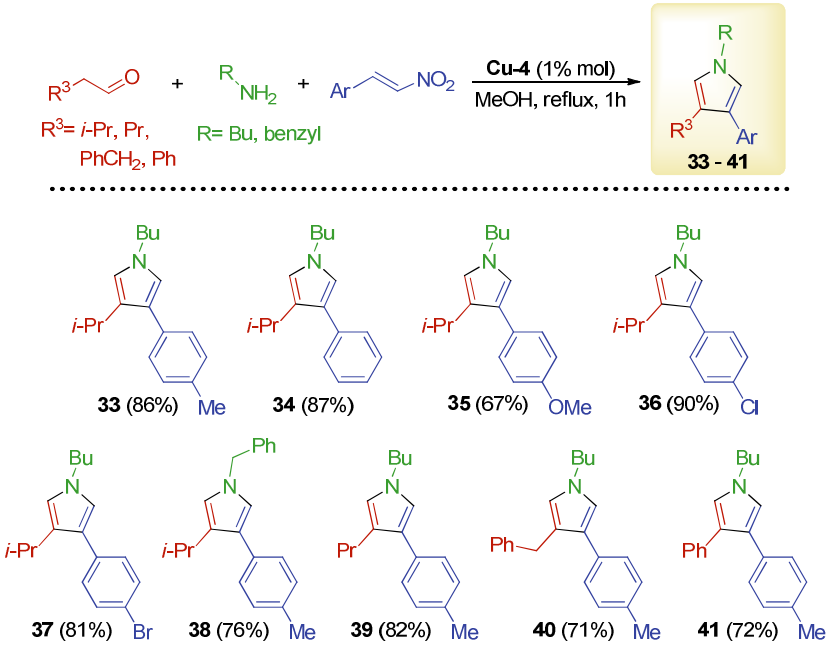
nitroprop-1-en-2-yl)benzene, degrades to the by-product acetophenone **1a**, as shown in Figure S8.

Figure 3. Cu-Catalyzed Synthesis of Pentasubstituted Pyrroles Starting with *β*-Methyl Substituted Nitrostyrenes



The general applicability of the present Cu-catalytic system (**Cu-4**) was verified by performing reaction between non *α*-alkyl substituted aldehydes, such as 3-methylbutanal (R^3 = *i*-Pr), pentanal (R^3 = Pr), 3-phenyl propionaldehyde (R^3 = $PhCH_2$) or phenylacetaldehyde (R^3 = Ph), with $BuNH_2$ or benzyl amine and a series of *β*-nitrostyrenes. As shown in Figure 4, in all cases the corresponding 1,3,4-trisubstituted pyrroles **33 - 41** were formed in good to high isolated yield 67% – 90%. Based on these promising results, the **Cu-4** catalyst was further used for possible larger-scale production of pyrrole. Thus, a reaction with 3 mmol of nitrostyrene **2**, 3 mmol of aldehyde **1**, 3 mmol of $BuNH_2$ and **Cu-4** (0.3 mol %) in 10 mL MeOH, was performed. After reaction completion (~3 h based on TLC analysis), the corresponding pyrrole **3** was isolated in 71% yield. This result corresponds to a high turnover number (TON) of 237 as measured from the ratio of product **3** (mmol) / **Cu-4** (mmol), and turnover frequency (TOF) value of 79 h^{-1}.

Figure 4. Synthesis of 1,3,4-Trisubstituted Pyrroles under Cu-Catalyzed Conditions



Regarding the reaction mechanism, we observed the following:

a) The reaction, under N_2 saturated solution, proceeds with similar conversion and relative product yield of **3** (87%). However, under O_2 saturated solution, a significant decrease in the yield of the pyrrole **3** (35%) and increase in the yield of the corresponding degradation product acetophenone **1a**, in ca. 30% relative yield, were observed (Table S1, entries 2 and 3). Also, the use of 50 mol% of TEMPO decreases the reaction conversion to 90% and the relative yield of **3** to 37% (Table S1, entry 4). These results support the predominance of a radical pathway, although a plausible Lewis acid mediated reaction pathway cannot be excluded (Scheme 3).[18]

b) The use of 3-propiophenone (**1'**) in place of 2-phenyl propionaldehyde **1**, did not yield the expected pyrrole **3** (Scheme 2). In addition, the use of 3-pentanone, propiophenone or acetophenone, in place of **1**, did not promote the transformation (Scheme 2). These observations may exclude the use of ketones as starting carbonyl compounds and support the necessity of *α*-

substituted aldehydes towards the convenient synthesis of polysubstituted pyrroles. Probably, a transient slowly formation of the corresponding enamine can be an explanation of the observed incompatibility of using ketones as starting materials.

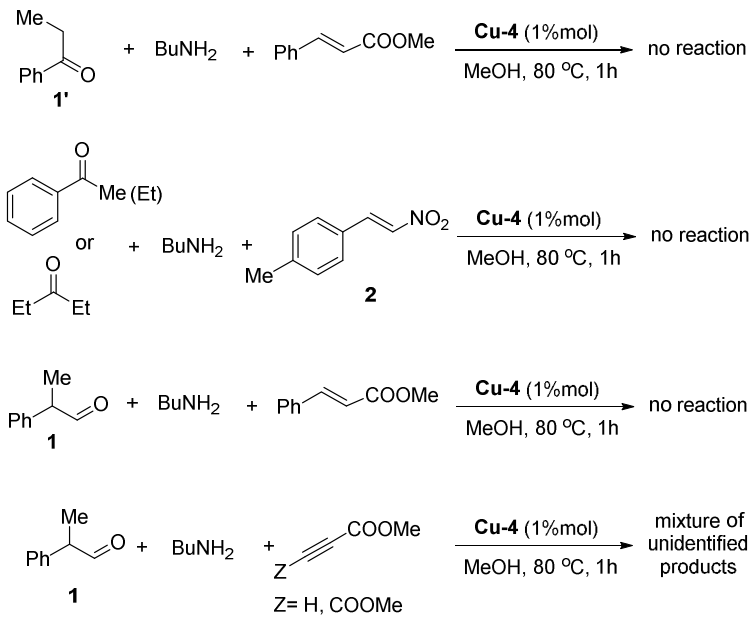
c) The use of other conjugated compounds, such as *trans*-methyl cinnamate, in place of *β*-nitrostyrene **2**, showed no reactivity under the present conditions (Scheme 2). However, the use of methyl propiolate or dimethyl acetylene dicarboxylate (DMAD),[19] instead of *β*-nitrostyrene **2**, yield a mixture of unidentified products (Scheme 2). These results indicate the necessity of the conjugated nitroalkenes for the pyrrole synthesis.

d) The *in-situ* mixture of equivalent amounts of ligand L (20% mol) and $Cu(OTf)_2$ (20% mol) in the given reaction slightly increases the relative yield of pyrrole **3** to 45% (from 38% in absence of L), whereas the formation of other by-products is observed. In addition, This result indicates that the use of the well-characterized catalyst, i.e. **Cu-4** in such low loading 1%, in which the Cu center has a pre-determined octahedral (N_4O_2) geometry, provides, in high yields, the catalytically active specie (we envisage this to be the $Cu^{II}L(TfO)_2$, see text below and Figure S9 and precludes the, *in-situ*, formation of other non-catalytically active Cu_xL_y species (not shown).

e) Finally, the nature of the protic solvent has a significant role to the reaction process. MeOH promotes the catalytic reaction in a faster and selective manner when compared to EtOH or ^{t}BuOH (Table S1). Interestingly, a significant increase of pyrrole **3** relative yield (51%) was observed when the reaction was carried out in CF_3CH_2OH as solvent, compared to EtOH, in which a 22% of **3** was measured. These results support the reaction promotion by the alcoholic media, as well as dependence on the pyrrole **3** relative yield and the different *p*Ka values of the

alcoholic solvents was observed.[20] In addition, experiment in CF_3CH_2OH and in the absence of catalyst (**Cu-4**) gave a lower relative yield of **3** (35%) with significant amounts of the by-products **1a** (21%) and **2a** (14%) and the remain imine **2b** (25%) (Table S1). This result confirms the catalytic enhancement of the present synthetic methodology. However, the use of CF_3CH_2OH as solvent is not recommended for environmental and costing reasons.

Scheme 2. Substrate Evaluation for the Cu(II)-Catalyzed Synthesis of Pyrroles

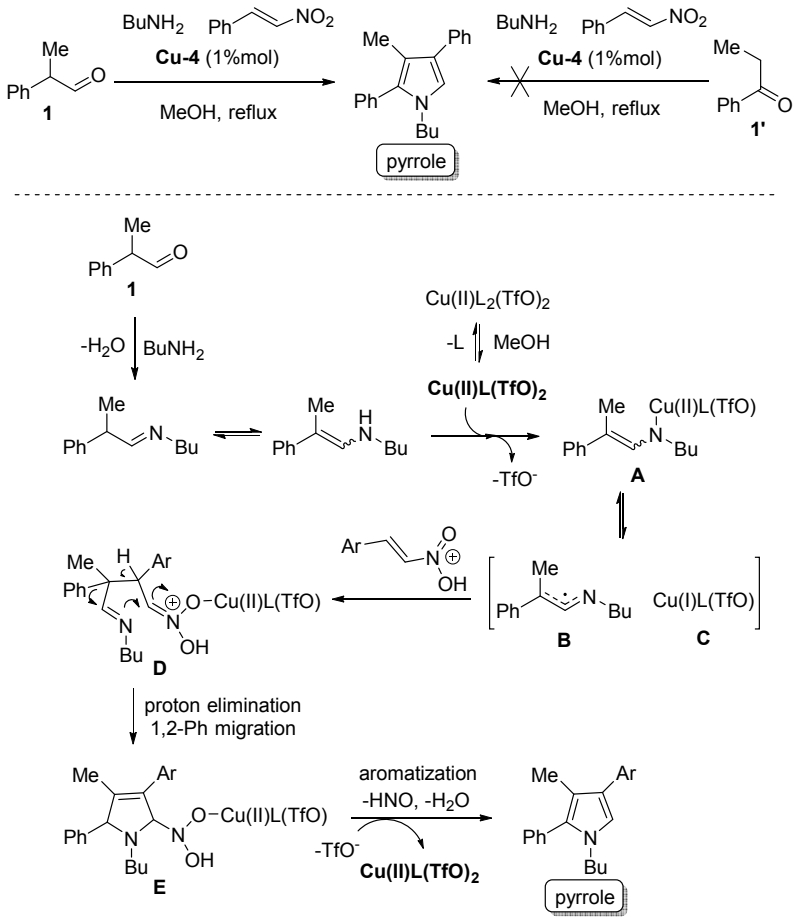


Regarding the active catalytic species, taking into account: i) the ESI-MS spectra of **Cu-4** (see Figure S10 for its structure) in methanolic solution shows the presence of various speciation, ii) the partial dissociation of the ligand (L) from the coordination sphere of the Cu center; observed in the crude ^{1}H-NMR spectra when higher loadings of **Cu-4** were involved, iii) the crystallographic characterization of the "de-activated" catalyst, formulated as $Cu(I)LCl_2$ in previous studies,[11a] iv) the significant decrease in the yield of the pyrrole formation (Table 1 entry 13) when **Cu-3** is used in which the coordination geometry of the Cu(II) center and the anion are different when compared with **Cu-4**, v) the reversible $Cu(II)L_2(OTf)_2 \leftrightarrow Cu(I)L_2(OTf)$

behavior as observed in cyclic voltammetry studies,[11b] and vi) other reports in which organic transformations are promoted from the suggested tetrasubstituted CuN_2X_2 species,[21] we envisage that [Cu(II)L(TfO)$_2$] (Figure S9) might be the catalytically active specie.[11,22] Efforts to isolate as well crystallographically and spectroscopically characterize other derivatives of the catalyst **Cu-4** are in progress.

Based on these observations, we propose that the first step involves the formation of the imine from the aldehyde and amine. Then, the imine probably tautomerizes to the corresponding enamine, which in turn reacts with the active species of the catalyst (Scheme 3). Ligand exchange with enamine yields the amino–Cu(II) intermediate **A**, which is in equilibrium with the nitrogen radical **B** and the Cu(I) complex **C**.[21,23] In the presence of the *β*-nitrostyrene (excellent radical acceptor), the nitrogen radical **B** couples with the double bond, generating the intermediate **D**, which in turn is transformed into the desired cyclo-intermediate **E** through a proton elimination/1,2-phenyl migration cyclization process. The reactions under the O_2 saturated solution and in the presence of TEMPO probably prevent the formation of this radical intermediate leading to the degradation product acetophenone **1a** in significant amount, as described above. Finally, after the HNO and H_2O elimination and the Cu-catalyst regeneration, intermediate **E** converts to the desired pyrrole (Scheme 3). A similar *N*-radical intermediate mechanism was proposed in the Cu(II) promoted coupling reactions between vinyl arenes and anilines, as well as intramolecular alkene oxidative amination for the synthesis of indoles.[23] Further mechanistic studies to support the present proposed catalytic mechanism are in progress using different mono nuclear Cu(II) and Cu(I) complexes as well as deuterium labeled organic starting materials.

Scheme 3. Proposed Mechanism for the Cu(II)-Catalyzed Reaction of *α*-Methyl Substituted Aldehydes, Amines and Nitrostyrenes Towards Pyrrole Synthesis.



CONCLUSIONS

In conclusion, the one-pot Copper(II) catalyzed regioselective protocol of polysubstituted pyrroles from commercial available *β*-nitroalkenes, *α*-alkyl substituted aldehydes and amines is been presented. The reaction proceeds under mild catalytic conditions with low catalyst loading (0.3 - 1mol %), a broad scope, very good functional-group tolerance and can be easily scaled up. The access to a wide range of tri-, tetra- or pentasubstituted pyrroles, *via* an overwhelming 1,2-

phenyl/alkyl migration, dependent on the aldehyde moiety, represents, the exceptional prospect of this synthetic protocol and to the best of our knowledge this opportunity was not feasible before. The use of ketones, in place of α-alkyl substituted aldehydes, does not promote the transformation showcasing the necessity of the use of α-substituted aldehydes in the present catalytic conditions. From the mechanistic point of view, a possible radical pathway is proposed including the formation of a nitrogen radical intermediate, which in turn reacts with the nitroalkene to yield the desired pyrrole.

EXPERIMENTAL SECTION

General: Chemicals (reagent grade) were purchased from Sigma-Aldrich, Acros Organics, and Alfa Aesar. Materials and solvents were used with no further purification. Safety note: perchlorate salts are potentially explosive; such compounds should be used in small quantities and handled with caution and utmost care at all times.

Preparation of catalysts: Ligand L and compounds **Cu-1** – **Cu-4** were synthesized according to the reported procedure.[11]

Catalytic procedure for the synthesis of pyrroles: To a sealed tube containing equimolar amounts of the aldehyde (0.2 mmol) and the tube containing equimolar amounts of the aldehyde (0.2 mmol) and the amine (0.2 mmol) in methanol (1 mL), 0.2 mmol of the nitroalkene and 1 mol% of the catalyst were added and the mixture was stirred at reflux for the appropriate time. After reaction completion (monitored by TLC), the slurry was filtered through a short pad of Celite and silica gel to withhold the catalyst using MeOH (~5 mL) as an eluent. The solvent was then evaporated under vacuum and the residue was separated by column chromatography using

silica gel and the mixture solvent hexane/EtOAc = from 50/1 to 20/1 as eluent, to give the corresponding pyrrole in pure form. It is worth noting that, electron rich polysubstituted pyrroles are unstable molecules during the chromatographic purification procedure. For this reason, neutralized silica (with the addition of a few drops of triethylamine in the eluent solvent mixture) was used for the column chromatography, as well as pretreated $CDCl_3$ with K_2CO_3 was used for accomplished the NMR spectra. Product analysis was conducted by ^1H NMR and ^{13}C NMR spectroscopy (Agilent AM 500). Mass spectra were determined on an electrospray ionization mass spectrometry (ESI-MS), by using a ThermoFisher Scientific (Bremen, Germany) model LTQ Orbitrap Discovery MS, at a flow rate of 10 μL/min using syringe pump. The infusion experiments were run using a standard ESI source operating in a positive ionization mode. Source operating conditions were a 3.7 kV spray voltage and a 300 ^oC heated capillary temperature. LCMS-2010 EV Instrument (Shimadzu) under Electrospray Ionization (ESI) conditions and on a MS EV AutospecFissins instrument (EI at 70eV) were also used for the mass determination.

Synthesis of aromatic *β*-nitrostyrenes: Aromatic *β*-nitrostyrenes were synthesized according to the literature procedure.[24] To a solution of ammonium acetate (12.5 mmol) in acetic acid (10 mL), *p*-substituted benzaldehyde (5 mmol) and nitromethane (15.5 mmol) were added in one portion. The mixture was heated at reflux for 4 hours. The reaction mixture was cooled at room temperature and then poured into ice-water to precipitate the corresponding nitrostyrene. After extraction with organic solvent (EtOAc) the organic layer was evaporated under vacuum and the residue was purified by column chromatography using silica gel, to give final the corresponding products in 55-72% yields.

Synthesis of (*E*)-1-methyl-4-(2-nitroprop-1-en-1-yl)benzene: (*E*)-1-methyl-4-(2-nitroprop-1-en-1-yl)benzene was synthesized according to the literature procedure.[24] To a solution of ammonium acetate (12.5 mmol) in acetic acid (10 mL), *p*-tolualdehyde (5 mmol) and nitroethane (15.5 mmol) were added. The mixture was heated at reflux for 4 hours. The reaction mixture was cooled at room temperature and then poured into ice-water to form the solid mixture of product that was isolated by filtration through a short path of silica. The organic solvent was then evaporated under vacuum and the residue was separated by column chromatography using silica gel to give the corresponding product in 59% yield.

Synthesis of (*E*)-(1-nitroprop-1-en-2-yl)benzene: (*E*)-(1-nitroprop-1-en-2-yl)benzene was synthesized according to the literature procedure.[25] To a sealed tube charged with molecular sieves, DCE (5 mL), *α*-methyl styrene (2 mmol), silver nitrite (3 mmol) and TEMPO (1 mmol) were added in one portion. The mixture was heated at 70 °C for 12 hours. The reaction mixture was cooled at room temperature and filtered through a short pad of Celite with ethyl acetate as eluent. The organic solvent was then evaporated under vacuum and the residue was separated by column chromatography using silica gel to give the corresponding product in 80% yield.

Synthesis of aliphatic nitroalkenes: Aliphatic nitroalkenes were synthesized according to the literature procedure.[26] To a solution of aliphatic aldehyde (5 mmol) and nitromethane (5 mmol) in methanol (4 mL), a solution of sodium hydroxide (6 mmol) in ice-water (2 mL) was added dropwise at 0 °C. External 2 mL of methanol were added into the above reaction mixture and stirred at 0 °C for 1 hour. Then water was added and the mixture was acidified with concentrated hydrochloric acid. The aqueous mixture was extracted with DCM (10 mL x3) and the combined organic layers were dried over sodium sulfate. The organic solvent was then

evaporated under vacuum and the residue was separated by column chromatography using silica gel to give the corresponding products in pure form in 35-65% yields.

1-butyl-3-methyl-2-phenyl-4-(p-tolyl)-1H-pyrrole (***3***): colorless oil (54 mg, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.46 – 7.43 (m, 2H), 7.40 – 7.35 (m, 5H), 7.20 (d, J = 8.0 Hz, 2H), 6.83 (s, 1H), 3.81 (t, J = 7.4 Hz, 2H), 2.38 (s, 3H), 2.13 (s, 3H), 1.63 – 1.57 (m, 2H), 1.25 – 1.18 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 134.7, 133.7, 132.9, 131.9, 130.6, 129.0, 128.2, 127.6, 127.0, 123.9, 118.4, 114.4, 46.9, 33.5, 21.1, 19.8, 13.6, 11.3. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}N$ 304.2060; found 304.2047.

1-butyl-3-methyl-2,4-diphenyl-1H-pyrrole (***4***): colorless oil (51 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.49 (d, J = 7.3 Hz, 2H), 7.46 – 7.43 (m, 2H), 7.39 – 7.35 (m, 5H), 7.22 (t, J = 7.3 Hz, 1H), 6.86 (s, 1H), 3.82 (t, J = 7.4 Hz, 2H), 2.14 (s, 3H), 1.63 – 1.57 (m, 2H), 1.26 – 1.18 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 136.7, 132.9, 132.1, 130.6, 128.3, 128.2, 127.7, 127.1, 125.2, 124.0, 118.6, 114.4, 46.9, 33.5, 19.8, 13.6, 11.3. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}N$ 290.1903; found 290.1891.

1-butyl-4-(4-chlorophenyl)-3-methyl-2-phenyl-1H-pyrrole (***5***): colorless oil (58 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.46 – 7.32 (m, 9H), 6.83 (s, 1H), 3.80 (t, J = 7.3 Hz, 2H), 2.10 (s, 3H), 1.61 – 1.57 (m, 2H), 1.24 – 1.17 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 135.2, 132.7, 132.3, 130.9, 130.6, 128.8, 128.4, 128.3, 127.2, 122.9, 118.6, 114.3, 46.9, 33.5, 19.8, 13.6, 11.3. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{21}H_{23}ClN$ 324.1514/326.1484; found 324.1509/326.1482.

1-benzyl-3-methyl-2-phenyl-4-(p-tolyl)-1H-pyrrole (***6***): white crystals (60 mg, 89% yield), mp. 142-144. ^{1}H NMR (500 MHz, $CDCl_3$): 7.40 – 7.38 (m, 4H), 7.34 – 7.22 (m, 6H), 7.19 (d, J = 7.9 Hz, 2H), 7.03 (d, J = 7.0 Hz, 2H), 6.82 (s, 1H), 5.02 (s, 2H), 2.38 (s, 3H), 2.18 (s, 3H). ^{13}C

NMR (125 MHz, $CDCl_3$): 138.6, 134.9, 133.5, 132.6, 132.5, 130.7, 129.0, 128.5, 128.2, 127.6, 127.23, 127.16, 126.8, 124.7, 119.2, 114.8, 50.8, 21.1, 11.4. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{25}H_{24}N$ 338.1903; found 338.1889.

1-benzyl-4-(4-bromophenyl)-3-methyl-2-phenyl-1H-pyrrole (***7***): white crystals (70 mg, 87% yield). ^1H NMR (500 MHz, $CDCl_3$): 7.47 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 7.5 Hz, 2H), 7.36 – 7.32 (m, 3H), 7.30 – 7.26 (m, 5H), 7.01 (d, J = 7.5 Hz, 2H), 6.82 (s, 1H), 5.00 (s, 2H), 2.14 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 138.5, 135.5, 132.9, 132.4, 131.4, 130.7, 129.3, 128.6, 128.4, 127.5, 127.4, 126.9, 123.7, 119.3, 119.2, 110.1, 50.9, 11.4. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{24}H_{21}BrN$ 402.0857/404.0837; found 401.0841/403.0823.

1-isopropyl-3-methyl-2,4-diphenyl-1H-pyrrole (***8***): colorless oil (48 mg, 87% yield). ^1H NMR (500 MHz, $CDCl_3$): 7.51 (d, J = 7.5 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.40 – 7.35 (m, 5H), 7.22 (t, J = 7.3 Hz, 1H), 6.95 (s, 1H), 4.30 (sept, J = 6.7 Hz, 1H), 2.13 (s, 3H), 1.38 (d, J = 6.7 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): 136.8, 133.0, 131.8, 130.8, 128.3 (2C), 127.6, 127.1, 125.2, 124.4, 114.2, 114.0, 47.3, 24.0, 11.2. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{20}H_{22}N$ 276.1747; found 276.1736.

3-methyl-2-phenyl-4-(p-tolyl)-1-(4,4,4-trifluorobutyl)-1H-pyrrole (***9***): colorless oil (32 mg, 89% yield). ^1H NMR (500 MHz, $CDCl_3$): 7.47 (t, J = 7.6 Hz, 2H), 7.42 -7.37 (m, 3H), 7.37 -7.34 (m, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.81 (s, 1H), 3.93 (t, J = 7.0 Hz, 2H), 2.40 (s, 3H), 2.14 (s, 3H), 1.96-1.85 (m, 2H), 1.86-1.78 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 135.1, 133.5, 132.0, 130.6, 129.4, 129.1, 128.7 (q, J = 288.2 Hz), 128.5, 128.2, 127.7, 127.4, 118.4, 115.4, 45.9, 30.9 (q, J = 29.3 Hz), 23.8 (q, J = 3.0 Hz), 21.1, 11.3. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{22}H_{23}F_3N$ 358.1742; found 358.1728.

1-cyclopentyl-3-methyl-2-phenyl-4-(p-tolyl)-1H-pyrrole (***10***): colorless oil (53 mg, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.46 (t, *J* = 7.6 Hz, 2H), 7.40 – 7.35 (m, 5H), 7.20 (d, *J* = 7.8 Hz, 2H), 6.91 (s, 1H), 4.40 (p, *J* = 7.6 Hz, 1H), 2.38 (s, 3H), 2.12 (s, 3H), 2.06 – 2.02 (m, 2H), 1.87 – 1.84 (m, 4H), 1.59 (brs, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 134.7, 133.8, 133.2, 132.4, 130.8, 129.0, 128.2, 127.6, 127.1, 124.4, 114.5, 114.0, 57.2, 34.3, 24.4, 21.1, 11.2. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{23}H_{26}N$ 316.2060; found 316.2045.

3-methyl-2-phenyl-1-propyl-4-(p-tolyl)-1H-pyrrole (***11***): colorless oil (26 mg, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.46 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.40-7.35 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.85 (s, 1H), 3.79 (t, *J* = 7.4 Hz, 2H), 2.40 (s, 3H), 2.16 (s, 3H), 1.69-1.61 (m, 2H), 0.83 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 134.7, 133.1, 132.0, 130.7, 129.3, 129.0, 128.2, 127.7, 127.0, 124.0, 118.5, 114.5, 48.9, 24.6, 21.1, 11.3, 11.2. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}N$ 290.1864; found 290.1856.

4-(4-fluorophenyl)-3-methyl-2-phenyl-1-propyl-1H-pyrrole (***12***): colorless oil (25 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.48-7.41 (m, 4H), 7.36-7.32 (m, 3H), 7.06 (t, *J* = 8.7 Hz, 2H), 6.81 (s, 1H), 3.77 (t, *J* = 7.5 Hz, 2H), 2.10 (s, 3H), 1.68-1.60 (m, 2H), 0.81 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 161.2 (d, *J* = 243.2 Hz), 133.0, 132.8 (d,*J* = 3.2 Hz), 130.7, 129.1 (d, *J* = 7.7 Hz), 128.3, 127.2, 123.2, 118.5, 115.1 (d, *J* = 21.0 Hz), 115.0, 114.4, 110.0, 48.9, 24.7, 11.2 (2). HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{20}H_{21}FN$: 294.1613; found 293.1608.

4-(4-methoxyphenyl)-3-methyl-2-phenyl-1-propyl-1H-pyrrole (***13***): colorless oil (24 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.43 (t, *J* = 7.1 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.36-7.32 (m, 3H), 6.93 (d, *J* = 8.5 Hz, 2H), 6.79 (s, 1H), 3.84 (s, 3H), 3.77 (t, *J* = 7.0 Hz, 2H), 2.11 (s, 3H), 1.68-1.59 (m, 2H), 0.81 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 161.5, 133.2,

130.7, 129.4, 129.1, 128.9, 128.3, 128.2, 127.1, 118.2, 113.9, 110.1, 55.3, 48.9, 24.7, 11.3 (2). HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}NO$ 306.2850; found 305.2843.

1-butyl-4-isopropyl-3-methyl-2-phenyl-1H-pyrrole (***14***): colorless oil (40 mg, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.40 (t, J = 7.4 Hz, 2H), 7.32 – 7.29 (m, 3H), 6.48 (s, 1H), 3.73 (t, J = 7.4 Hz, 2H), 2.86 (sept, J = 6.8 Hz, 1H), 1.99 (s, 3H), 1.60 – 1.54 (m, 2H), 1.24 (d, J = 6.8 Hz, 6H), 1.22 – 1.16 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 133.2, 130.8, 130.5, 129.6, 128.1, 126.6, 115.7, 114.5, 46.7, 33.6, 25.4, 23.6, 19.9, 13.7, 10.0. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{26}N$ 256.1823; found 256.1810.

1-butyl-4-cyclohexyl-3-methyl-2-phenyl-1H-pyrrole (***15***): colorless oil (49 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.41 (t, J = 7.5 Hz, 2H), 7.31 – 7.30 (m, 3H), 6.46 (s, 1H), 3.74 (t, J = 7.4 Hz, 2H), 2.48 – 2.44 (m, 1H), 2.02 (s, 2H), 1.99 (s, 3H), 1.82 (d, J = 12.6 Hz, 2H), 1.75 (d, J = 12.6 Hz, 1H), 1.60 – 1.54 (m, 2H), 1.45 – 1.25 (m, 5H), 1.24 – 1.16 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$): 133.3, 130.6, 130.5, 128.9, 128.0, 126.6, 116.0, 114.5, 46.7, 35.6, 34.3, 33.6, 27.1, 26.5, 19.9, 13.7, 10.0. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{21}H_{30}N$ 296.2373; found 296.2359.

1-butyl-2-ethyl-3-methyl-4-(p-tolyl)-1H-pyrrole (***16***): colorless oil (45 mg, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.31 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.63 (s, 1H), 3.80 (t, J = 7.5 Hz, 2H), 2.61 (q, J = 7.5 Hz, 2H), 2.36 (s, 3H), 2.15 (s, 3H), 1.78 – 1.72 (m, 2H), 1.44 – 1.36 (m, 2H), 1.16 (t, J = 7.5 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 134.6, 134.2, 131.7, 129.1, 127.8, 123.5, 116.7, 112.0, 46.5, 34.0, 21.2, 20.3, 17.7, 14.9, 14.0, 10.6. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{26}N$ 256.2060; found 256.2054.

1-butyl-2-ethyl-3-methyl-4-phenyl-1H-pyrrole (***17***): colorless oil (41 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.42 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.4 Hz,

1H), 6.66 (s, 1H), 3.81 (t, *J*= 7.4 Hz, 2H), 2.61 (q, *J* = 7.5 Hz, 2H), 2.16 (s, 3H), 1.78 – 1.72 (m, 2H), 1.44 – 1.36 (m, 2H), 1.17 (t, *J* = 7.5 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$): 137.0, 131.7, 128.2, 127.7, 125.0, 123.4, 116.8, 111.9, 46.3, 33.8, 20.2, 17.6, 14.8, 13.8, 10.5. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{24}N$ 242.1903; found 242.1892.

1-butyl-4-(4-chlorophenyl)-2-ethyl-3-methyl-1H-pyrrole (***18***): colorless oil (45 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.33 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 6.64 (s, 1H), 3.80 (t, *J* = 7.5 Hz, 2H), 2.60 (q, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.77 – 1.71 (m, 2H), 1.43 – 1.35 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 135.5, 131.9, 130.6, 128.7, 128.3, 122.3, 116.9, 111.8, 46.4, 33.8, 20.1, 17.5, 14.7, 13.8, 10.5. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{23}ClN$ 276.1514/278.1484; found 276.1519/278.1495.

4-(4-bromophenyl)-1-butyl-2-ethyl-3-methyl-1H-pyrrole (***19***): colorless oil (54 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.44 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.65 (s, 1H), 3.80 (t, *J* = 7.5 Hz, 2H), 2.60 (q, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.77 – 1.71 (m, 2H), 1.43 – 1.35 (m, 2H), 1.15 (t, *J* = 7.5 Hz, 3H), 0.97 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 135.9, 132.0, 131.2, 129.1, 122.3, 118.7, 116.9, 111.8, 46.4, 33.8, 20.1, 17.5, 14.7, 13.8, 10.5. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{23}BrN$ 320.1008/322.0988 found 320.1017/322.0995.

1-benzyl-4-(4-chlorophenyl)-2-ethyl-3-methyl-1H-pyrrole (***20***): colorless oil (46 mg, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.37 – 7.27 (m, 7H), 7.08 (d, *J* = 7.5 Hz, 2H), 6.68 (s, 1H), 5.06 (s, 2H), 2.55 (q, *J* = 7.5 Hz, 2H), 2.16 (s, 3H), 1.03 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 138.4, 135.3, 132.4, 130.7, 128.8, 128.7, 128.3, 127.4, 126.5, 122.7, 117.9, 112.6, 50.4,

17.6, 14.6, 10.5. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{20}H_{21}ClN$ 310.1357/312.1328; found 310.1346/312.1307.

1-butyl-2,3-dimethyl-4-(p-tolyl)-1H-pyrrole (***21***): colorless oil (39 mg, 81% yield). ^1H NMR (500 MHz, $CDCl_3$): 7.31 (d, J = 7.5 Hz, 2H), 7.17 (d, J = 7.5 Hz, 2H), 6.65 (s, 1H), 3.80 (t, J = 7.3 Hz, 2H), 2.37 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H), 1.75 – 1.69 (m, 2H), 1.43 – 1.35 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 134.5, 134.0, 128.9, 127.7, 125.4, 123.3, 116.8, 112.5, 46.6, 33.5, 21.1, 20.0, 13.8, 10.6, 9.7. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{24}N$ 242.1903; found 242.1894.

1-butyl-2,3-dimethyl-4-phenyl-1H-pyrrole (***22***): colorless oil (36 mg, 80% yield). ^1H NMR (500 MHz, $CDCl_3$): 7.42 (d, J = 7.2 Hz, 2H), 7.35 (t, J = 7.4 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H), 6.69 (s, 1H), 3.81 (t, J = 7.4 Hz, 2H), 2.20 (s, 3H), 2.16 (s, 3H), 1.76 – 1.70 (m, 2H), 1.44 – 1.36 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 137.0, 130.5, 128.2, 127.7, 125.0, 123.4, 117.0, 112.5, 46.6, 33.4, 20.0, 13.8, 10.6, 9.7. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}N$ 228.1747; found 228.1738.

1-butyl-4-(4-chlorophenyl)-2,3-dimethyl-1H-pyrrole (***23***): colorless oil (47 mg, 90% yield). ^1H NMR (500 MHz, $CDCl_3$): 7.33 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 8.6 Hz, 2H), 6.66 (s, 1H), 3.80 (t, J = 7.4 Hz, 2H), 2.18 (s, 3H), 2.12 (s, 3H), 1.74 – 1.68 (m, 2H), 1.42 – 1.35 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 135.5, 130.7, 128.8, 128.3, 125.8, 122.2, 117.0, 112.4, 46.7, 33.4, 20.0, 13.7, 10.6, 9.7. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{16}H_{21}ClN$ 262.1357/264.1328; found 262.1352/264.1324.

1-butyl-2,3-dimethyl-4-(naphthalen-1-yl)-1H-pyrrole (***24***): colorless oil (47 mg, 85% yield). ^1H NMR (500 MHz, $CDCl_3$): 8.03 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.49 – 7.39 (m, 4H), 6.65 (s, 1H), 3.87 (t, J = 7.4 Hz, 2H), 2.26 (s, 3H), 1.89 (s, 3H),

1.80 – 1.74 (m, 2H), 1.46 – 1.39 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 135.0, 133.8, 132.9, 128.0, 127.5, 127.1, 126.3, 125.4, 125.3 (2C), 124.6, 121.5, 118.5, 114.4, 46.6, 33.5, 20.0, 13.8, 10.3, 9.9. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{20}H_{24}N$ 278.1903; found 278.1894.

1-benzyl-2,3-dimethyl-4-(p-tolyl)-1H-pyrrole (***25***): colorless oil (50 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.34 – 7.31 (m, 4H), 7.27 – 7.25 (m, 1H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 7.6 Hz, 2H), 6.71 (s, 1H), 5.03 (s, 2H), 2.36 (s, 3H), 2.15 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 138.3, 134.7, 133.9, 129.0, 128.7, 127.7, 127.3, 126.6, 125.9, 123.8, 117.7, 113.2, 50.6, 21.1, 10.7, 9.8. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{20}H_{22}N$ 276.1747; found 276.1734.

1-benzyl-2,3-dimethyl-4-phenyl-1H-pyrrole (***26***): colorless oil (44 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.43 (d, *J* = 7.1 Hz, 2H), 7.36 – 7.31 (m, 4H), 7.27 – 7.25 (m, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 7.7 Hz, 2H), 6.74 (s, 1H), 5.04 (s, 2H), 2.16 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 138.2, 136.8, 128.7, 128.2, 127.7, 127.3, 126.6, 126.1, 125.1, 123.9, 117.9, 113.2, 50.6, 10.7, 9.8. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}N$ 262.1590; found 262.1581.

1-benzyl-4-(4-chlorophenyl)-2,3-dimethyl-1H-pyrrole (***27***): colorless oil (49 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.36 – 7.27 (m, 7H), 7.07 (d, *J* = 7.5 Hz, 2H), 6.72 (s, 1H), 5.03 (s, 2H), 2.14 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 138.1, 135.3, 130.8, 128.8, 128.7, 128.4, 127.4, 126.5, 126.4, 122.7, 117.9, 113.2, 50.7, 10.7, 9.8. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{19}H_{19}ClN$ 296.1201/298.1171; found 296.1189/298.1160.

2,4-dimethyl-3,5-diphenyl-1-propyl-1H-pyrrole (***28***): colorless oil, (26 mg, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.48-7.35 (m, 10H), 3.78 (t, *J* = 7.5 Hz, 2H), 2.33 (s, 3H), 2.01 (s,

3H), 1.64-1.55 (m, 2H), 0.80 (t, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 137.0, 133.7, 130.8, 130.2, 128.6, 128.4, 128.2, 127.9, 126.8, 125.3, 125.1, 114.5, 46.0, 24.5, 11.2, 11.0, 10.8. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}N$: 290.1858; found 289.1852.

1-butyl-2,4-dimethyl-5-phenyl-3-(p-tolyl)-1H-pyrrole (***29***): colorless oil (53 mg, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.44 (t, J = 7.6 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.34 (t, J = 7.8 Hz, 1H), 7.27 – 7.25 (m, 2H), 7.22 (d, J = 7.8 Hz, 2H), 3.81 – 3.78 (m, 2H), 2.40 (s, 3H), 2.31 (s, 3H), 1.99 (s, 3H), 1.58 – 1.52 (m, 2H), 1.23 – 1.16 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 134.7, 133.8, 133.6, 130.7, 130.0, 129.9, 128.7, 128.1, 126.7, 125.0, 121.7, 114.4, 44.1, 33.3, 21.2, 19.9, 13.6, 11.0, 10.8. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{23}H_{28}N$ 318.2216; found 318.2200.

1-butyl-2-ethyl-3,5-dimethyl-4-(p-tolyl)-1H-pyrrole (***30***): colorless oil (43 mg, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$):7.20 – 7.15 (m, 5H), 3.78 – 3.75 (m, 1H), 2.62 (q, J = 7.5 Hz, 2H), 2.38 (s, 3H), 2.21 (s, 3H), 2.01 (s, 3H), 1.70 – 1.64 (m, 2H), 1.46 – 1.38 (m, 2H), 1.18 (t, J = 7.5 Hz, 3H), 0.99 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 134.4, 134.1, 130.0, 129.2, 128.6, 122.8, 120.9, 111.6, 43.6, 33.9, 21.1, 20.3, 17.8, 15.2, 13.8, 10.7, 10.0. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{19}H_{28}N$ 270.2216; found 270.2209.

2-ethyl-1-isopropyl-3,5-dimethyl-4-(p-tolyl)-1H-pyrrole (***31***): colorless oil (42 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.21-7.18 (m, 4H), 4.49 (sept, J = 7.1 Hz, 1H), 2.68 (q, J = 7.5 Hz, 2H), 2.39 (s, 3H), 2.31 (s, 3H), 1.99 (s, 3H), 1.55 (d, J = 7.1 Hz, 6H), 1.18 (t, J = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 134.4, 134.1, 130.3, 129.4, 128.5, 122.7, 122.1, 111.8, 46.9, 22.7, 21.1, 18.4, 15.4, 12.5, 10.0. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{26}N$ 256.2060; found 256.2046.

1-cyclopentyl-2-ethyl-3,5-dimethyl-4-(p-tolyl)-1H-pyrrole (***32***): colorless oil (49 mg, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.22 – 7.17 (m, 4H), 4.61 (p, J = 9.3 Hz, 1H), 2.68 (q, J = 7.4 Hz, 2H), 2.39 (s, 3H), 2.29 (s, 3H), 2.10 (br, 2H), 2.05 – 2.02 (m, 2H), 1.99 (s, 3H), 1.96 – 1.92 (m, 2H), 1.73 – 1.71 (m, 2H), 1.19 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 134.5, 134.0, 130.2, 130.0, 128.6, 122.8, 122.3, 111.8, 56.3, 31.8, 25.1, 21.1, 18.4, 15.4, 12.5, 10.0. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{20}H_{28}N$ 282.2216; found 282.2206.

1-butyl-3-isopropyl-4-(p-tolyl)-1H-pyrrole (***33***): colorless oil (44 mg, 86% yield).^{1}H NMR (500 MHz, $CDCl_3$): 7.30 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 7.8 Hz, 2H), 6.62 (s, 1H), 6.48 (s, 1H), 3.83 (t, J = 7.4 Hz, 2H), 3.12 (sept, J = 6.8 Hz, 1H), 2.36 (s, 3H), 1.81 – 1.75 (m, 2H), 1.41 – 1.33 (m, 2H), 1.17 (d, J = 6.8 Hz, 6H), 0.96 (t, J = 7.4 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$): 134.7, 134.2, 129.2, 128.9, 128.0, 123.2, 118.8, 116.8, 49.4, 33.5, 25.0, 24.4, 21.1, 20.1, 13.7. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{26}N$ 256.2060, found 256.2055.

1-butyl-3-isopropyl-4-phenyl-1H-pyrrole (***34***):[12] colorless oil (42 mg, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.42 (d, J = 7.8 Hz, 2H), 7.35 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.3 Hz, 1H), 6.66 (d, J = 1.9 Hz, 1H), 6.50 (d, J = 1.9 Hz, 1H), 3.84 (t, J = 7.4 Hz, 2H), 3.15 (sept, J = 6.8Hz, 1H), 1.82 – 1.76 (m, 2H), 1.41 – 1.34 (m, 2H), 1.18 (d, J = 6.8 Hz, 6H), 0.96 (t, J = 7.4 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$): 137.2, 129.3, 128.2, 128.1, 125.2, 123.2, 118.9, 116.9, 49.4, 33.5, 25.0, 24.4, 20.1, 13.7. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{24}N$ 242.1903, found 242.1895.

1-butyl-3-isopropyl-4-(4-methoxyphenyl)-1H-pyrrole (***35***): colorless oil (36 mg, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.32 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.59 (d, J = 2.3 Hz, 1H), 6.47 (d, J = 2.3 Hz, 1H), 3.84 – 3.81 (m, 5H), 3.08 (sept, J = 6.8Hz, 1H), 1.80 – 1.74 (m, 2H), 1.40 – 1.33 (m, 2H), 1.16 (d, J = 6.8 Hz, 6H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125

MHz, $CDCl_3$): 157.6, 129.7, 129.20, 129.18, 122.9, 118.6, 116.7, 113.7, 55.2, 49.4, 33.5, 25.0, 24.3, 20.1, 13.7. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{26}NO$ 272.2009; found 272.2000.

1-butyl-3-(4-chlorophenyl)-4-isopropyl-1H-pyrrole (***36***): colorless oil (50 mg, 90% yield). ^1H NMR (500 MHz, $CDCl_3$): 7.33 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 6.63 (d, J = 1.9 Hz, 1H), 6.48 (d, J = 1.9 Hz, 1H), 3.82 (t, J = 7.4 Hz, 2H), 3.08 (sept, J = 6.8Hz, 1H), 1.80 – 1.74 (m, 2H), 1.40 – 1.32 (m, 2H), 1.16 (d, J = 6.8 Hz, 6H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 135.7, 131.0, 129.2 (2C), 128.3, 122.0, 119.0, 117.2, 49.5, 33.5, 25.0, 24.3, 20.0, 13.7. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{23}ClN$ 276.1514/278.1484; found 276.1515/278.1483.

3-(4-bromophenyl)-1-butyl-4-isopropyl-1H-pyrrole (***37***): colorless oil (52 mg, 81% yield). ^1H NMR (500 MHz, $CDCl_3$): 7.45 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 2.0 Hz, 1H), 6.49 (d, J = 2.0 Hz, 1H), 3.83 (t, J = 7.4 Hz, 2H), 3.08 (sept, J = 6.8Hz, 1H), 1.80 – 1.74 (m, 2H), 1.40 – 1.33 (m, 2H), 1.16 (d, J = 6.8 Hz, 6H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 136.1, 131.3, 129.6, 129.2 (2C), 122.0, 119.0, 117.2, 49.5, 33.4, 25.0, 24.3, 20.0, 13.7. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{17}H_{23}BrN$ 320.1008/322.0988; found 320.0997/322.0976.

1-benzyl-3-isopropyl-4-(p-tolyl)-1H-pyrrole (***38***): colorless oil (44 mg, 76% yield). ^1H NMR (500 MHz, $CDCl_3$): 7.35 (t, J = 7.4 Hz, 2H), 7.32 – 7.29 (m, 3H), 7.19 (d, J = 7.4 Hz, 2H), 7.16 (d, J = 7.7 Hz, 2H), 6.67 (d, J = 1.8 Hz, 1H), 6.54 (d, J = 1.8 Hz, 1H), 5.04 (s, 2H), 3.14 (sept, J = 6.8 Hz, 1H), 2.37 (s, 3H), 1.18 (d, J = 6.8 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): 138.1, 134.9, 134.0, 130.0, 128.9, 128.7, 128.0, 127.6, 127.2, 123.8, 119.4, 117.5, 53.4, 25.0, 24.3, 21.1. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}N$ 290.1903; found 290.1892.

1-butyl-3-propyl-4-(p-tolyl)-1H-pyrrole (***39***): colorless oil (42 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.29 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.67 (d, J = 1.8 Hz, 1H), 6.47 (s, 1H), 3.82 (t, J = 7.2 Hz, 2H), 2.58 – 2.55 (m, 2H), 2.35 (s, 3H), 1.79 – 1.73 (m, 2H), 1.61 – 1.53 (m, 2H), 1.39 – 1.32 (m, 2H), 0.96 – 0.92 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): 134.6, 134.0, 128.9, 127.7, 123.6, 121.9, 118.9, 118.6, 49.3, 33.5, 28.3, 23.7, 21.1, 20.0, 14.3, 13.7. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{18}H_{26}N$ 256.2060; found 256.2050.

3-benzyl-1-butyl-4-(p-tolyl)-1H-pyrrole (***40***): colorless oil (43 mg, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.30 – 7.26 (m, 4H), 7.23 (d, J = 7.5 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 7.13 (d, J = 7.8 Hz, 2H), 6.72 (s, 1H), 6.25 (s, 1H), 3.95 (s, 2H), 3.79 (t, J = 7.4 Hz, 2H), 2.34 (s, 3H), 1.77 – 1.71 (m, 2H), 1.38 – 1.30 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 142.2, 134.8, 133.5, 129.0, 128.8, 128.2, 127.7, 125.6, 123.9, 120.42, 120.39, 118.7, 49.4, 33.5, 32.3, 21.1, 20.0, 13.7. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}N$ 304.2060, found 304.2043.

1-butyl-3-phenyl-4-(p-tolyl)-1H-pyrrole (***41***): colorless oil (42 mg, 72% yield). ^{1}H NMR (500 MHz, $CDCl_3$): 7.29 – 7.23 (m, 4H), 7.16 (d, J = 7.8 Hz, 3H), 7.06 (d, J = 7.8 Hz, 2H), 6.75 (s, 1H), 6.74 (s, 1H), 3.90 (t, J = 7.3Hz, 2H), 2.33 (s, 3H), 1.85 – 1.80 (m, 2H), 1.45 – 1.37 (m, 2H), 0.97 (t, J = 7.3Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): 136.1, 134.9, 133.0, 128.8, 128.3, 128.2, 128.1, 125.3, 122.88, 122.85, 120.1, 120.0, 49.5, 33.4, 21.1, 20.0, 13.7. HRMS (ESI/LTQ Orbitrap) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}N$ 290.1903; found 290.1889.

ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H, ^{13}C and NOESY-1D NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

CCDC 1562315−1562316 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

I. N. L. conceived and designed the experiments; D. A. and M. G. K. performed the experiments; E. L. provided the catalysts and performed pilot catalytic experiments; E. L. and G. E. K. performed crystallographic characterization; C. G. performed HRMS characterization. I. N. L. and G.E.K. analyzed the data and wrote the paper.

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Graphical Abstract