Microwave-Assisted Cascade Cycloaddition for C–N Bond Formation: An Approach to the Construction of 1,4,5,6-Tetrahydropyrimidine and 2-Imidazoline Derivatives

Shujuan An, Bing Yin, Ping Liu, Xiangnan Li, Chen Li, Jianli Li,* Zhen Shi

Key Laboratory of Synthetic and Natural Functional Molecule Chemistry of the Ministry of Education and College of Chemistry & Materials Science, Northwest University, Xi'an Shaanxi 710069, P. R. of China
Fax +86(29)88308396; E-mail: lijianli@nwu.edu.cn

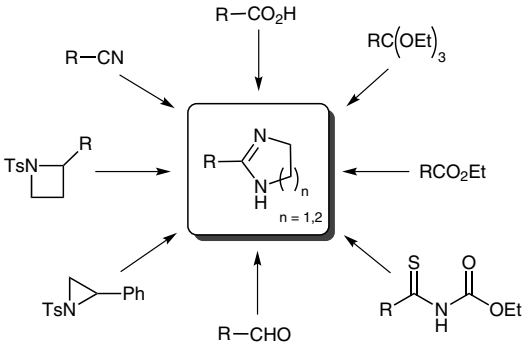
Received: 15.04.2013; Accepted after revision: 18.06.2013

Abstract: An efficient strategy for the synthesis of various 1,4,5,6-tetrahydropyrimidine and 2-imidazoline derivatives has been reported. The reactions proceeded from nitriles with ethylenediamine or 1,3-diaminopropane via cascade cycloaddition in the presence of CuL_2 (L = 2-hydroxy-2-phenylacetate) to afford the corresponding 1,4,5,6-tetrahydropyrimidine or 2-imidazoline derivatives under reflux conditions or microwave irradiation in excellent yields.

Key words: catalysis, cycloaddition, nitrogen heterocycles, nitriles, synthesis

Nitrogen-containing heterocycles are ubiquitous subunits in a variety of biologically active molecules and they are also widely used in materials science, bioorganic chemistry, and organometallic chemistry.[1] In particularly, 2-substituted 1,4,5,6-tetrahydropyrimidine and 2-imidazoline derivatives have frequently been used as powerful building blocks in molecules with biological and pharmacological activity.[2] They have potential anthelmintic, antidepressant, antibacterial, and fungicide activity, and they are also used for the treatment of various diseases including hypercholesterolemia, cancer, and AIDS related opportunistic pathogens.[3,4] The wide demand for diverse 1,4,5,6-tetrahydropyrimidine and 2-imidazoline derivatives in various fields has promote the development different synthetic methods. Many methods for the synthesis of 1,4,5,6-tetrahydropyrimidine and 2-imidazoline derivatives are now available (Scheme 1).[5,6] For example, Prasad and co-workers described [4 + 2] cycloaddition of 2-aryl-*N*-tosylazetidines with nitriles in the presence of boron trifluoride–diethyl ether complex for the synthesis of tetrahydropyrimidines,[7a] and also contributed a protocol for the synthesis of 2-imidazolines derivatives with boron trifluoride–diethyl ether complex or triethyloxonium tetrafluoroborate as a catalyst for the [3+2] cycloaddition of aziridines with nitriles.[7b]

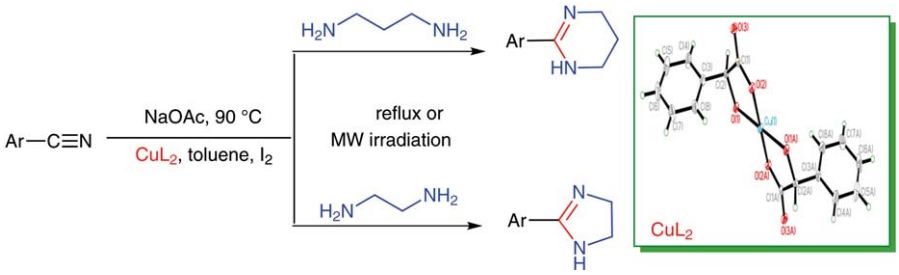
Mohammadpoor-Baltork et al. reported that nano-silica gel solid acid catalyzed cyclocondensation reaction of arenecarbonitriles with 1,3-diaminopropane afforded the corresponding tetrahydropyrimidines.[7c] However, these procedures generally suffer from poor functional group tolerance or low product yields, or they require the use of more expensive catalysts. Versatile and efficient methods for the direct construction of tetrahydropyrimidine and imidazoline rings remain highly desirable. Recently, cascade reactions that are mediated by various catalysts have made great progress in the synthesis of useful heterocyclic compounds via C–X (X = N, O, S) bond formation.[8–10] Our group performed copper-catalyzed reactions for the synthesis of 2-thiazolines and 2-oxazolines.[11] On the basis of a previous study, we envision that cascade cycloaddition of a nitrile with a diamine would be a direct approach for the construction of tetrahydropyrimidine and imidazoline rings in accordance with the principles of green chemistry. Copper-catalyzed reactions have received considerable attentions because of their efficiency and low cost.[12] However, to the best of our knowledge, the catalytic activity of copper has not been fully explored in this reaction. In consequence, we explored the capability of bis(2-hydroxy-κ*O*-2-phenylacetato)copper(II) (CuL_2) as an inexpensive, reusable, and efficient catalyst for the construction of 1,4,5,6-tetrahydropyrimidine or 2-imidazoline derivatives from nitriles with ethylenediamine or 1,3-diaminopropane under reflux conditions or microwave irradiation (Scheme 2).



Scheme 1 General methods for the synthesis of 1,4,5,6-tetrahydropyrimidines and 2-imidazolines

To begin our study, 3-cyanopyridine (**1b**) and 1,3-diaminopropane (**2**) were chosen as model substrates to optimize the reaction conditions. As can be seen from Table 1, screening various transition-metal catalysts (entries 1–13) revealed that bis(2-hydroxy-κ*O*-2-phenylacetato)copper(II) (CuL_2) displayed greater catalytic reactivity in the reactions (entry 5); only 10% yield of the desired product was obtained in the absence of CuL_2 (entry 14). Moreover,

SYNTHESIS 2013, 45, 2525–2532
Advanced online publication: 24.07.2013
DOI: 10.1055/s-0033-1339406; Art ID: SS-2013-H0287-OP



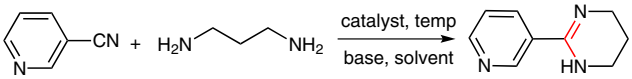
Scheme 2 Synthesis of 1,4,5,6-tetrahydropyrimidines and 2-imidazolines

several additives were tested including iodine, sulfur, and DBU (entries 15–17); iodine performed better than other additives (entry 16). Additionally, various bases were investigated (entries 18–20); sodium acetate is beneficial for high reaction efficiency and low reagent cost (entry 20). Next, different temperatures were examined (entries 21–23), and 90 °C was found to be the optimal temperature (entry 22). Finally, solvent effects were also examined, and toluene proved to be the best solvent (entries 24–26). We also performed the reaction under microwave irradiation and the desired product **3b** was obtained in 26% yield in the absence of CuL_2, and the yield increased to 95% in the presence of CuL_2 under the same conditions (entries 27 and 28).

Using the optimized reaction conditions, we next explored the substrate scope. The results of the reaction of various nitriles with 1,3-diaminopropane (**2**) are summarized in Table 2. These transformations displayed high functional group tolerance. The nitriles possessing pyridyl, pyrimidyl, thienyl, and pyrazinyl groups underwent the desired reaction to give the corresponding 1,4,5,6-tetrahydropyrimidine products **3a**–**g** in good yields (entries 1–7). In addition, nitriles with nitro, chloro, amino, and bromo groups on the phenyl ring gave the corresponding 1,4,5,6-tetrahydropyrimidines **3i**–**l** in excellent yields in the reactions (entries 9–12). An extensive investigation of the reaction showed that dinitriles, such as phthalonitrile and terephthalonitrile, were converted into the respective monotetrahydropyrimidines **3m** and **3n** with excellent chemoselectivity (entries 13–15). However, 2-aminophenyl-substituted **3h** and 4-tolyl-substituted **3p** were obtained in trace amounts (entries 8 and 16). It is noteworthy that: (1) To the best of our knowledge, **3m**, **3e**, and **3f** are novel (entries 5, 6, and 12). (2) For electronic effects of the transformation, we found that electron-deficient aromatic nitriles showed better reactivity and gave higher yields than electron-rich aromatic nitriles. (3) Mixtures of dinitriles (4 mmol) with double 1,3-diaminopropane (10 mmol) gave only monotetrahydropyrimidines. The transformation of dinitriles into monotetrahydropyrimidines is of practical significance because the remaining nitrile group can be converted into other important functional groups.

For further examination of CuL_2 in C–N bond formation, ethylenediamine (**4**) was examined as the condensation partner, and the results are given in Table 3. Satisfactorily, the reactions afforded the corresponding 2-imidazolines **5**

Table 1 Optimization of the Reaction Conditions[a]

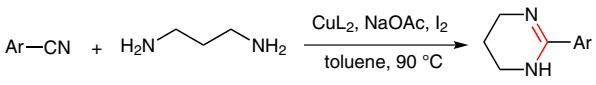


1b 2 3b

Entry	Catalyst[b]	Additive	Base	Solvent	Temp (°C)	Yield[c] (%)
1	$Co(L^1)_2$	–	–	toluene	80	62
2	CoL_2	–	–	toluene	80	61
3	$Fe(L^1)_3$	–	–	toluene	80	15
4	$Mn(L^1)_2$	–	–	toluene	80	43
5	CuL_2	–	–	toluene	80	80
6	$Cu(L^1)_2$	–	–	toluene	80	73
7	$Cu(L^2)_2$	–	–	toluene	80	61
8	$Cu(L^3)_2$	–	–	toluene	80	71
9	$Cu(L^4)_2$	–	–	toluene	80	74
10	$Cu(L^5)_2$	–	–	toluene	80	70
11	$Cu(IAA)_2$	–	–	toluene	80	69
12	CuC_2O_4	–	–	toluene	80	20
13	$Cu(OAc)_2$	–	–	toluene	80	64
14	–	–	–	toluene	80	10
15	CuL_2	DBU	–	toluene	80	80
16	CuL_2	I_2	–	toluene	80	83
17	CuL_2	S	–	toluene	80	81
18	CuL_2	I_2	K_2CO_3	toluene	80	85
19	CuL_2	I_2	$NaHSO_3$	toluene	80	84
20	CuL_2	I_2	NaOAc	toluene	80	86
21	CuL_2	I_2	NaOAc	toluene	70	82
22	CuL_2	I_2	NaOAc	toluene	90	90
23	CuL_2	I_2	NaOAc	toluene	100	90
24	CuL_2	I_2	NaOAc	MeCN	90	85
25	CuL_2	I_2	NaOAc	EtOH	90	84
26	CuL_2	I_2	NaOAc	NMP	90	73
27[d]	CuL_2	I_2	NaOAc	toluene	90	95
28[d]	–	I_2	NaOAc	toluene	90	26

[a] Reaction conditions: **1b** (4 mmol), **2** (5 mmol), base (1.1 mmol), additive (0.4 mmol), catalyst (0.4 mmol), solvent (1 mL), 90 °C, 4 h.
[b] L = 2-hydroxy-2-phenylacetate; L^1 = cinnamate; L^2 = benzoate; L^3 = 3-nitrobenzoate; L^4 = 4-nitrobenzoate; L^5 = 4-hydroxybenzoate; IAA = indole-3-acetate.
[c] The yield was determined by GC analysis with *n*-dodecane as the internal standard.
[d] The reactions performed at 90 °C under microwave irradiation with 800 W applied power for 20 min.

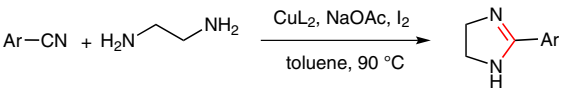
Table 2 Copper-Catalyzed Synthesis of 1,4,5,6-Tetrahydropyrimidines under Reflux Conditions and Microwave Irradiation[a,b]



Entry	Product	Ar	Time		Yield (%)	
			Reflux	MW	Reflux	MW
1	**3a**	2-pyridyl	6 h	25 min	82	85
2	**3b**	3-pyridyl	4 h	20 min	90	95
3	**3c**	4-pyridyl	4 h	20 min	95	97
4	**3d**	Ph	6 h	25 min	85	90
5	**3e**	pyrimidin-2-yl	6 h	25 min	82	88
6	**3f**	pyrazin-2-yl	6 h	25 min	78	89
7	**3g**	2-thienyl	6 h	25 min	85	92
8	**3h**	2-$H_2NC_6H_4$	10 h		trace	
9	**3i**	3-$H_2NC_6H_4$	6 h	25 min	65	75
10	**3j**	4-ClC_6H_4	6 h	25 min	80	85
11	**3k**	4-$O_2NC_6H_4$	6 h	25 min	95	97
12	**3l**	4-BrC_6H_4	6 h	25 min	80	85
13	**3m**	2-NCC_6H_4	4 h	20 min	94	97
14	**3n**	3-NCC_6H_4	4 h	20 min	95	97
15	**3o**	4-NCC_6H_4	4 h	20 min	95	98
16	**3p**	4-MeC_6H_4	10 h		trace	

[a] Reaction conditions: nitrile **1** (4 mmol), diamine **2** (5 mmol), NaOAc (1.1 mmol), I_2 (0.4 mmol), CuL_2 (0.4 mmol), toluene (1 mL), 90 °C.
[b] All MW reactions were carried out at 90 °C, with 800 W applied power.
[c] The yield was determined by GC analysis with *n*-dodecane as the internal standard.

Table 3 Copper-Catalyzed Synthesis of 2-Imidazolines under Reflux Conditions and Microwave Irradiation[a,b,c]



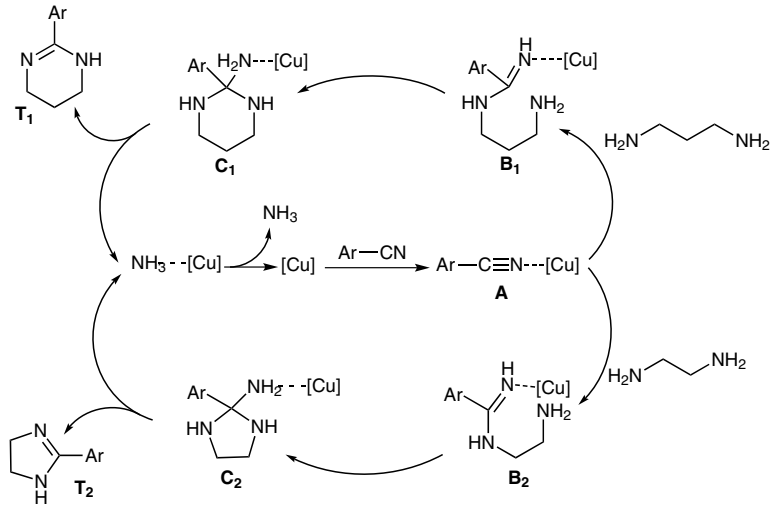
Entry	Product	Ar	Time		Yield (%)	
			Reflux	MW	Reflux	MW
1	**5a**	3-pyridyl	4 h	20 min	86	92
2	**5b**	4-pyridyl	4 h	20 min	90	93
3	**5c**	Ph	4 h	20 min	90	93
4	**5d**	2-thienyl	4 h	20 min	80	86
5	**5e**	pyrimidin-2-yl	10 h	–	trace	–
6	**5f**	pyrazin-2-yl	10 h	–	trace	–
7	**5g**	4-ClC_6H_4	4 h	20 min	80	87
8	**5h**	2-NCC_6H_4	10 h		trace	
9	**5i**	3-NCC_6H_4	2 h	15 min	90	97
10	**5j**	4-NCC_6H_4	2 h	15 min	90	98

[a] Reaction conditions: nitrile **1** (4 mmol), diamine **4** (5 mmol), NaOAc (1.1 mmol), I_2 (0.4 mmol), CuL_2 (0.4 mmol), toluene (1 mL), 90 °C.
[b] All MW reactions were carried out at 90 °C, with 800 W applied power.
[c] The yield was determined by GC analysis with *n*-dodecane as the internal standard.

with great efficiency. For heteroaryl-substituted 2-imidazolines, aromatic nitriles with pyridyl or thienyl worked well, and the desired 2-imidazolines **5a**–**d** were obtained in 80–90% yields (entries 1–4). Surprisingly, 2-imidazolines possessing pyrimidyl or pyrazinyl groups were obtained in only trace amounts (entries 5 and 6). The reactions of 4-chlorobenzonitrile with ethylenediamine (**4**) produced the expected 2-imidazoline **5g** in moderate to good yield (entry 7). Finally, we investigated transformations of dinitriles to 2-imidazolines. The results demonstrated that 2-imidazolines **5i** and **5j** were obtained in good yields (entries 8 and 9), while phthalonitrile gave trace amounts of product for the possible reason was that the reaction was sensitive to steric hindrance by the substituent on the aromatic ring (entry 10). Meanwhile, alkanenitriles were also examined; 2-alkyl-1,4,5,6-tetrahydropyrimidines and 2-alkylimidazolines are more difficult to synthesize than their aryl analogues. Therefore, the present method was only found to be effective for the conversion of arenecarbonitriles to the corresponding 1,4,5,6-tetrahydropyrimidines and 2-imidazolines.

Microwave-assisted organic synthesis (MAOS) is a powerful technique that is being used more frequently to accelerate thermal organic reactions. The notable features of the microwave approach are enhanced reaction rates, formation of purer products in higher yields and easier manipulation.[13] Therefore, we examined the effect of microwave irradiation on the synthesis from the reaction of nitriles with 1,3-diaminopropane (**2**) or ethylenediamine (**4**), respective, in the presence of CuL_2. Gratifyingly, the corresponding 1,4,5,6-tetrahydropyrimidines and 2-imidazolines were obtained in 75–98% yields within 10–25 minutes. The results are summarized in Table 2 and Table 3.

A possible mechanism for the synthesis of 1,4,5,6-tetrahydropyrimidines and 2-imidazolines is depicted in Scheme 3. First, the nitrile is activated by CuL_2 to give intermediate **A**. Nucleophilic addition of **A** with amine **2** or **4** provides $\mathbf{B_1}$ or $\mathbf{B_2}$. Intramolecular cycloaddition of $\mathbf{B_1}$ or $\mathbf{B_2}$ provides $\mathbf{C_1}$ or $\mathbf{C_2}$, intermediate $\mathbf{C_1}$ or $\mathbf{C_2}$ release [Cu] and NH_3 to afford target products $\mathbf{T_1}$ or $\mathbf{T_2}$.



Scheme 3 Possible copper-catalyzed mechanism for the synthesis of 1,4,5,6-tetrahydropyrimidines and 2-imidazolines

For a better understanding, DFT[14] calculations based on the Fukui function $f^{+}_{(r)}$[14] [Equation 1 (a)] were performed for the catalyst with B3LYP[15] functional. Basis set of double-ζ quality (6-31G** for C, H elements, 6-31+G* for O element and SVP[16] for Cu element) is used for the geometry optimization and larger triple-ζ basis set (6-311G** for C, H elements, 6-311+G* for O element, and TZVP[17] for Cu element) is used for the following single point energy calculation. The optimized structure is proven to be the local minimum based on the results of vibration analysis. All the calculations are performed with Gaussian 03 program.[18] where N is the number of electrons, ν is the external potential, q_X is the electronic population of atom X in a molecule.

$$f^{+}_{(r)} = \left(\frac{\partial\rho(\vec{r})}{\partial N}\right)_{v} = \left(\rho(\vec{r})_{N+1} - \rho(\vec{r})_{N}\right)_{v} \quad (1a)$$

$$f^{+}_{(X)} = q^{N+1}_{X} - q^{N}_{X} \quad (1b)$$

Equation 1

The reactivity concerning nucleophilic attack has been successfully described by the Fukui function $f^{+}_{(r)}$,[19] e.g., nitrile attack in this work. As shown in Figure 1 (a), the 3D representation of $f^{+}_{(r)}$ clearly demonstrates that the region around the copper atom possesses higher reactivity than other parts of the catalyst. The condensed Fukui function of individual atom [Figure 1 (b)], obtained from NBO analysis,[20] indicates that the copper atom should be the first choice for the nitrile attack since its value of condensed Fukui function, 0.5073, is larger than those of other atoms by at least one magnitude. This theoretical prediction supports the proposed reaction mechanism in Scheme 3.

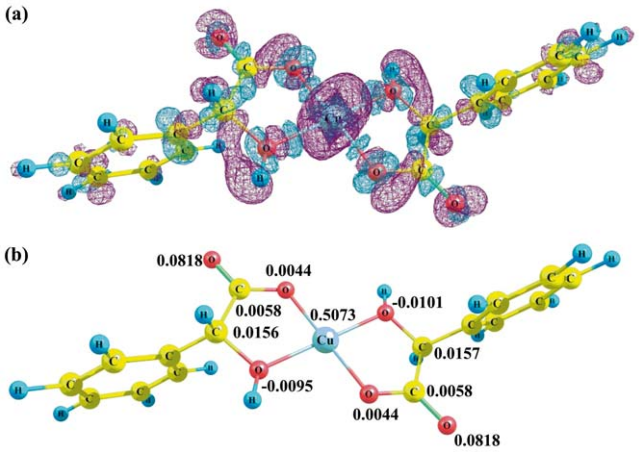


Figure 1 (a) The 3D representation of the Fukui function $f^{+}_{(r)}$ of the isovalue of 0.002 a.u. (positive in red color and negative in green color). (b) The condensed Fukui function $f^{+}_{(r)}$ of copper and other surrounding atoms.

Following the results of Fukui function, we further explored the frontier molecular orbitals involved in the interaction between the catalyst and benzonitrile, which is an example of an aromatic nitriles. As shown in Figure 2, the HOMO of benzonitrile has significant contribution from the lone pair of the nitrogen atom. Correspondingly, the LUMO of the catalyst is distributed mainly within the region around the copper atom. The small energy difference (3.49 eV) between these two orbitals should facilitate the electron transfer from the nitrogen atom to the copper atom and thus the catalyst could active aromatic nitrile as shown in Scheme 3.

In summary, we have first demonstrated that CuL_2 can be used as a reusable and inexpensive catalyst for efficient synthesis of 1,4,5,6-tetrahydropyrimidine or 2-imidazoline derivatives under either reflux conditions or microwave irradiation. The mild reaction conditions, excellent conversion, and high functional group tolerance have

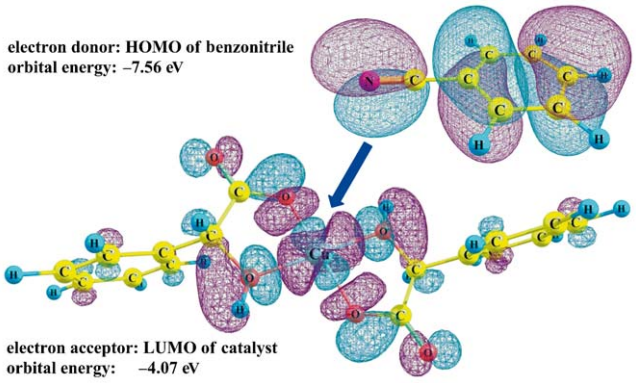


Figure 2 The 3D representation and orbital energies of the frontier molecular orbitals involved in the interaction between the catalyst and benzonitrile

made the approach distinctly superior to other protocols reported for the preparation of various 2-substituted 1,4,5,6-tetrahydropyrimidines and 2-imidazolines in a benign manner.

Column chromatography was performed with silica gel (200–300 mesh). Melting points were determined using a standard melting point instrument and are uncorrected. ^{1}H NMR spectra were recorded on 400 MHz instrument and ^{13}C NMR spectra were recorded on 101 MHz instrument; internal standard TMS. IR spectra were recorded on a FT-IR spectrophotometer. The MS data were measured on a GC-MS with electron ionization. All reactions were carried out under an atmosphere of air.

Bis(2-Hydroxy-κ*O*-2-phenylacetato)copper(II) (CuL_2, L = 2-hydroxy-2-phenylacetate)

2-Hydroxy-2-phenylacetic acid (10 mmol) was slowly added to a soln of NaOH [NaOH (8 mmol) in H_2O (10 mL)] whilst stirring. To the soln, an aq soln of $CuCl_2$ [$CuCl_2{\cdot}2\ H_2O$ (4 mmol) in H_2O (14 mL)] was added, and the mixture was stirred for 5 min to give a blue precipitate that was collected by filtration, washed with H_2O, and dried in vacuo to provide CuL_2 (0.87 g, 92%). Single crystals suitable for X-ray diffraction were obtained by allowing Et_2O to diffuse into a saturated soln of CuL_2 in MeCN.[21]

2-Aryl-1,4,5,6-tetrahydropyrimidines 3a–n or 2-Aryl-4,5-dihydro-1*H*-imidazoles 5a–j; General Procedure under Reflux Conditions

A mixture of nitrile (4 mmol), ethylenediamine or 1,3-diaminopropane (5 mmol), NaOAc (1.1 mmol), I_2 (0.4 mmol), and CuL_2 (0.4 mmol) was stirred at 90 °C for the appropriate time. The progress of the reaction was monitored by TLC (EtOAc–MeOH, 3:1). After completion of the reaction, the mixture was cooled to r.t., diluted with $CHCl_3$ (10 mL) and the catalyst was removed by filtration. The solvent was evaporated, all compounds was purified by chromatography (silica gel) to afford the pure product.

2-Aryl-1,4,5,6-tetrahydropyrimidines 3a–n or 2-Aryl-4,5-dihydro-1*H*-imidazoles 5a–j ; General Procedure under Microwave Irradiation

A mixture of nitrile (4 mmol), ethylenediamine or 1,3-diaminopropane (5 mmol), NaOAc (1.1 mmol), I_2 (0.4 mmol), and CuL_2 (0.4 mmol) was irradiated with microwave (800 W) for 10–25 min by pulsed irradiation. At the end of the reaction (monitored by TLC, EtOAc–MeOH, 3:1), the mixture was cooled to r.t., $CHCl_3$ was then added and the catalyst was filtered. Evaporation of the solvent gave the almost pure product. Further purification was performed as for the procedure used in the synthesis of imidazolines and tetrahydropyrimidines under reflux conditions.

2-(Pyridin-2-yl)-1,4,5,6-tetrahydropyrimidine (3a)[5g]

Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.31) to provide **3a** (3.28 mmol, 82%) as yellow oil.

IR (KBr): 3447, 3058, 2968, 1657, 1605, 1578, 1470, 1206, 741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.24 (d, *J* = 8.0 Hz, 1 H), 8.63 (d, *J* = 4.5 Hz, 1 H), 8.05 (t, *J* = 7.8 Hz, 1 H), 7.58 (m, 1 H), 3.76 (t, *J* = 5.7 Hz, 4 H), 2.14 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.97, 148.80, 142.48, 138.86, 128.10, 124.37, 39.17, 18.34.

MS (EI): *m*/*z* = 161 $[M]^+$.

2-(Pyridin-3-yl)-1,4,5,6-tetrahydropyrimidine (3b)[6b]

Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.35) to provide **3b** (3.60 mmol, 90%) as a yellow solid; mp 97–98 °C.

IR (KBr): 3289, 2935, 1623, 1521, 1473, 1417, 1195, 709 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.87 (s, 1 H), 8.64 (d, *J* = 4.8 Hz, 1 H), 8.02 (d, *J* = 7.9 Hz, 1 H), 7.34–7.31 (m, 1 H), 3.53 (t, *J* = 5.7 Hz, 4 H), 2.09–1.75 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.11, 150.59, 147.40, 134.14, 132.52, 123.18, 42.02, 20.40.

MS (EI): *m*/*z* = 161 $[M]^+$.

2-(Pyridin-4-yl)-1,4,5,6-tetrahydropyrimidine (3c)[6b]

Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.41) to provide **3c** (3.80 mmol, 95%) as a white solid; mp 97–99 °C.

IR (KBr): 3425, 2939, 1624, 1543, 1412, 1308, 1042, 835 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (dd, *J* = 4.5, 1.6 Hz, 2 H), 7.57 (dd, *J* = 4.5, 1.6 Hz, 2 H), 3.55 (t, *J* = 4.0 Hz, 4 H), 1.93–1.87 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.70, 150.01, 144.47, 120.50, 42.23, 20.42.

MS (EI): *m*/*z* = 161 $[M]^+$.

2-Phenyl-1,4,5,6-tetrahydropyrimidine (3d)[5g]

Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.42) to provide **3d** (3.40 mmol, 85%) as a white solid; mp 85–88 °C.

IR (KBr): 3242, 2940, 2840, 1620, 1574, 1531, 1488, 1195, 784, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, *J* = 7.6, 1.8 Hz, 2 H), 7.43–7.35 (m, 3 H), 3.54 (t, *J* = 6.0 Hz, 4 H), 1.91–1.85 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.51, 137.37, 129.64, 128.34, 125.99, 42.39, 20.77.

MS (EI): *m*/*z* = 160 $[M]^+$.

2-(1,4,5,6-Tetrahydropyrimidin-2-yl)pyrimidine (3e)

Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.35) to provide **3e** (3.28 mmol, 82%) as a yellow solid; mp 284–285 °C.

IR (KBr): 3448, 3273, 3086, 2964, 1678, 1594, 1570, 1209, 715 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 9.15 (d, *J* = 4.9 Hz, 2 H), 7.92 (t, *J* = 4.9 Hz, 1 H), 3.54 (t, *J* = 5.5 Hz, 4 H), 2.01–1.95 (m, 2 H).

^{13}C NMR (101 MHz, DMSO): δ = 160.89, 155.82, 154.90, 127.41, 41.41, 20.08.

MS (EI): *m*/*z* = 162 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{11}N_4$: 163.0984; found: 163.1038.

2-(Pyrazin-2-yl)-1,4,5,6-tetrahydropyrimidine (3f)
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.35) to provide **3f** (3.12 mmol, 78%) as a white solid; mp 114–116 °C.

IR (KBr): 3361, 2950, 2929, 2849, 1630, 1573, 1469, 1155, 774 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.41 (s, 1 H), 8.60 (d, *J* = 2.3 Hz, 1 H), 8.44 (d, *J* = 1.2 Hz, 1 H), 3.58 (s, 4 H), 1.87–1.91 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.53, 146.87, 145.10, 143.13, 141.85, 35.80, 20.66.

MS (EI): *m*/*z* = 162 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{11}N_4$: 163.0984; found: 163.1038.

2-(Thiophen-2-yl)-1,4,5,6-tetrahydropyrimidine (3g)[6b]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.26) to provide **3g** (3.40 mmol, 85%) as a yellow solid; mp 185–186 °C.

IR (KBr): 3193, 3012, 2934, 2832, 1606, 1549, 1514, 1325, 1167, 712 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 4.0 Hz, 2 H), 7.03 (dd, *J* = 6.4, 2.3 Hz, 1 H), 3.51 (t, *J* = 5.7 Hz, 4 H), 1.92–1.88 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.35, 140.50, 127.72, 127.19, 124.69, 41.83, 20.59.

MS (EI): *m*/*z* = 166 $[M]^+$.

3-(1,4,5,6-Tetrahydropyrimidin-2-yl)aniline (3i)[22]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.30) to provide **3i** (2.60 mmol, 65%) as a yellow oil.

IR (KBr): 3308, 3208, 3125, 2996, 1644, 1629, 1593, 1495, 1046, 791, 719 cm^{-1}.

^1H NMR (400 MHz, DMSO): δ = 7.20 (t, *J* = 8.0 Hz, 1 H), 6.85–6.80 (m, 3 H), 5.59 (s, 2 H), 3.43 (t, *J* = 4.0 Hz, 4 H), 1.94–1.92 (m, 2 H).

^{13}C NMR (101 MHz, DMSO): δ = 162.67, 151.91, 132.26, 132.13, 120.69, 116.87, 114.40, 41.31, 20.45.

MS (EI): *m*/*z* = 175 $[M]^+$.

2-(4-Chlorophenyl)-1,4,5,6-tetrahydropyrimidine (3j)[6b]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.36) to provide **3j** (3.20 mmol, 80%) as a white solid; mp 124–128 °C.

IR (KBr): 3178, 2952, 2853, 1623, 1541, 1488, 1194, 1036, 836 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 6.7 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 3.51 (t, *J* = 4.0 Hz, 4 H), 1.92–1.85 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.69, 135.76, 134.83, 128.35, 127.70, 41.76, 20.31.

MS (EI): *m*/*z* = 194 $[M]^+$.

2-(4-Nitrophenyl)-1,4,5,6-tetrahydropyrimidine (3k)[6b]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.42) to provide **3k** (3.80 mmol, 95%) as a yellow solid; mp 140–142 °C.

IR (KBr): 3424, 3179, 2936, 2854, 1625, 1598, 1521, 1487, 1343, 1107, 861, 810 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 8.7 Hz, 2 H), 7.87 (d, *J* = 8.7 Hz, 2 H), 3.57 (t, *J* = 5.7 Hz, 4 H), 1.92 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.95, 148.47, 143.10, 127.17, 123.55, 42.39, 20.44.

MS (EI): *m*/*z* = 205 $[M]^+$.

2-(4-Bromophenyl)-1,4,5,6-tetrahydropyrimidine (3l)[5g]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.29) to provide **3l** (3.20 mmol, 80%) as a white solid; mp 155–156 °C.

IR (KBr): 3424, 3284, 3124, 2997, 2647, 1608, 1536, 1175, 727 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 7.68 (d, *J* = 7.2 Hz, 2 H), 7.56 (d, *J* = 8.0 Hz, 2 H), 3.51 (t, *J* = 4.0 Hz, 4 H), 1.99 (m, 2 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 159.57, 133.12, 129.88, 127.10, 41.51, 20.16.

MS (EI): *m*/*z* = 238 $[M]^+$.

2-(1,4,5,6-Tetrahydropyrimidin-2-yl)benzonitrile (3m)
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc; R_f = 0.35) to provide **3m** (3.76 mmol, 94%) as a white solid; mp 142–144 °C.

IR (KBr): 3429, 3211, 2957, 2851, 1643, 1472, 1427, 1360, 1093, 774, 712 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 3.9, 2.6 Hz, 1 H), 7.76 (d, *J* = 3.2 Hz, 1 H), 7.64–7.58 (m, 2 H), 3.87 (t, *J* = 6.0 Hz, 2 H), 3.79 (t, *J* = 5.6 Hz, 2 H), 2.09–2.02 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.54, 151.90, 133.75, 131.74, 131.42, 130.80, 121.19, 120.76, 45.26, 37.59, 20.29.

MS (EI): *m*/*z* = 185 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{12}N_3$: 186.1026; found: 186.1092.

3-(1,4,5,6-Tetrahydropyrimidin-2-yl)benzonitrile (3n)[7c]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc; R_f = 0.33) to provide **3n** (3.80 mmol, 95%) as a white solid; mp 136–137 °C.

IR (KBr): 3424, 3117, 2996, 2777, 2233, 1648, 1617, 1449, 1103, 884, 807, 710 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.91 (d, *J* = 7.8 Hz, 1 H), 7.68 (d, *J* = 7.6 Hz, 1 H), 7.50 (m, 1 H), 3.53 (t, *J* = 5.7 Hz, 4 H), 1.91–1.85 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.09, 138.37, 132.84, 130.55, 130.08, 129.11, 118.51, 112.14, 42.17, 20.48.

MS (EI): *m*/*z* = 185 $[M]^+$.

4-(1,4,5,6-Tetrahydropyrimidin-2-yl)benzonitrile (3o)[7c]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc; R_f = 0.40) to provide **3o** (3.80 mmol, 95%) as a white solid; mp 69–71 °C.

IR (KBr): 3431, 3052, 2361, 2232, 1630, 1504, 1401, 1199, 845 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (dd, *J* = 8.2, 3.6 Hz, 2 H), 7.68 (dd, *J* = 8.3, 4.2 Hz, 2 H), 3.54 (t, *J* = 4.0 Hz, 4 H), 1.92–1.85 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.29, 141.47, 132.10, 126.89, 118.57, 112.97, 42.27, 20.45.

MS (EI): *m*/*z* = 185 $[M]^+$.

3-(4,5-Dihydro-1*H*-imidazol-2-yl)pyridine (5a)[6f]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.35) to provide **5a** (3.44 mmol, 86%) as a white solid; mp 102 °C.

IR (KBr): 3160, 2938, 2854, 1609, 1587, 1513, 1485, 1277, 984, 706 cm^{-1}.

^1H NMR (400 MHz, DMSO): δ = 9.02 (s, 1 H), 8.66 (d, *J* = 3.6 Hz, 1 H), 8.18 (d, *J* = 7.8 Hz, 1 H), 7.48 (dd, *J* = 7.3, 5.0 Hz, 1 H), 3.65 (s, 4 H).

^{13}C NMR (101 MHz, DMSO): δ = 166.88, 156.23, 153.30, 139.68, 131.34, 128.59, 54.68.

MS (EI): *m*/*z* = 147 [M]$^+$.

4-(4,5-Dihydro-1*H*-imidazol-2-yl)pyridine (5b)[6f]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.40) to provide **5b** (3.60 mmol, 90%) as a yellow solid; mp 134–135 °C.

IR (KBr): 3183, 2942, 2884, 1615, 1596, 1547, 1510, 1279, 686 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (dd, *J* = 4.5, 1.6 Hz, 2 H), 7.66 (dd, *J* = 4.5, 1.6 Hz, 2 H), 3.85 (s, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 150.06, 149.41, 121.18, 120.67, 49.70.

MS (EI): *m*/*z* = 147 [M]$^+$.

2-Phenyl-4,5-dihydro-1*H*-imidazole (5c)[6f]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.38) to provide **5c** (3.60 mmol, 90%) as a white solid; mp 101 °C.

IR (KBr): 3201, 2929, 2868, 1611, 1598, 1573, 1508, 1270, 982, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.0 Hz, 2 H), 7.45–7.37 (m, 3 H), 3.78 (s, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.09, 130.83, 129.82, 128.43, 127.16, 49.79.

MS (EI): *m*/*z* = 146 [M]$^+$.

2-(Thiophen-2-yl)-4,5-dihydro-1*H*-imidazole (5d)[6f]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.35) to provide **5d** (3.20 mmol, 80%) as a white solid; mp 172–173 °C.

IR (KBr): 3147, 3083, 2930, 2856, 1598, 1530, 1495, 1474, 1269, 1101, 847, 710 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 4.4 Hz, 2 H), 7.07 (m, 1 H), 3.79 (s, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.87, 133.26, 128.94, 127.92, 127.49, 50.08.

MS (EI): *m*/*z* = 152 [M]$^+$.

2-(4-Chlorophenyl)-4,5-dihydro-1*H*-imidazole (5g)[6e]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.32) to provide **5g** (3.2 mmol, 80%) as a white solid; mp 187–188 °C.

IR (KBr): 3193, 2924, 2864, 1606, 1594, 1560, 1517, 1485, 1091, 988, 838, 729 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 7.84 (d, *J* = 8.2 Hz, 2 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 3.61 (s, 4 H).

^{13}C NMR (101 MHz, DMSO): δ = 167.79, 140.03, 134.67, 134.03, 133.45, 45.32.

MS (EI): *m*/*z* = 180 [M]$^+$.

3-(4,5-Dihydro-1*H*-imidazol-2-yl)benzonitrile (5i)[11b]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.37) to provide **5i** (3.6 mmol, 90%) as a white solid; mp 105 °C.

IR (KBr): 3378, 2923, 2866, 2232, 1621, 1595, 1577, 1450, 1291, 988, 703 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 8.20 (s, 1 H), 8.16 (d, *J* = 7.7 Hz, 1 H), 7.96 (d, *J* = 7.4 Hz, 1 H), 7.69–7.65 (m, 1 H), 3.65 (s, 4 H).

^{13}C NMR (101 MHz, DMSO): δ = 167.09, 138.99, 136.92, 136.67, 135.67, 134.85, 123.61, 116.61, 54.77.

MS (EI): *m*/*z* = 171 [M]$^+$.

4-(4,5-Dihydro-1*H*-imidazol-2-yl)benzonitrile (5j)[11b]
Following the general procedure, the product was obtained by chromatography (silica gel, EtOAc–MeOH, 3:1; R_f = 0.42) to provide **5j** (3.6 mmol, 90%) as a white solid; mp 205 °C.

IR (KBr): 3157, 2948, 2361, 2225, 1596, 1552, 1490, 1273, 1115, 849 cm^{-1}.

^{1}H NMR (400 MHz, DMSO): δ = 7.98 (d, *J* = 8.2 Hz, 2 H), 7.92 (d, *J* = 8.1 Hz, 2 H), 3.65 (s, 4 H).

^{13}C NMR (101 MHz, DMSO): δ = 167.55, 139.82, 137.50, 132.99, 123.73, 117.80, 61.21.

MS (EI): *m*/*z* = 171 [M]$^+$.

Acknowledgment

The project was supported by National Natural Science Foundation of China (NSFC 20972124; 21272184; 21103137), Shaanxi Provincial Natural Science Fund Project (No. 2012JQ2007), Shaanxi Science and Technology Coordination Innovation Engineering Project (No.2011K12-77), Special Science Research Foundation of Education Committee in Shaanxi Province (No.12JK0584), and the Chinese National Innovation Experiment Program for University Students (No. 201210697011).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Roh, J.; Vávrová, K.; Hrabálek, A. *Eur. J. Org. Chem.* **2012**, 6101. (b) Wang, C.; Li, S.; Liu, H.; Jiang, Y.; Fu, H. *J. Org. Chem.* **2010**, *75*, 7936. (c) Xu, W.; Fu, H. *J. Org. Chem.* **2011**, *76*, 3846. (d) Patil, S. S.; Mhaske, P. C.; Patil, S. V.; Bobade, V. D. *J. Heterocycl. Chem.* **2011**, *48*, 652. (e) Suzuki, N.; Itoh, S.; Poon, K.; Masutani, C.; Hanaoka, F.; Ohmori, H.; Yoshizawa, I.; Shibutani, S. *Biochemistry* **2004**, *43*, 6304.

(2) (a) Dunbar, P. G.; Durant, G. J.; Fang, Z.; Abuh, Y. F.; El-Assadi, A. A.; Ngur, D. O.; Periyasamy, S.; Hoss, W. P.; Messer, W. S. *J. Med. Chem.* **1993**, *36*, 842. (b) Messer, W. S. J.; Abuh, Y. F.; Ryan, K.; Shepherd, M. A.; Schroeder, M.; Abunada, S.; Sehgal, R.; El-Assadi, A. A. *Drug. Dev. Res.* **1997**, *40*, 171. (c) Dolinkin, A. O.; Chernov'yants, M. S. *Pharm. Chem. J.* **2010**, *44*, 99.

(3) (a) Zhou, S. M.; Kern, E. R.; Gullen, E.; Cheng, Y. C.; Drach, J. C.; Matsumi, S.; Mitsuya, H.; Zemlicka, J. *J. Med. Chem.* **2004**, *47*, 6964. (b) Linger, C.; Azadi, P.; Macleod, J. K.; Dell, A.; Abdallah, M. A. *Tetrahedron Lett.* **1992**, *33*, 1737. (c) Donkor, I. O.; Clark, A. M. *Eur. J. Med. Chem.* **1999**, *34*, 639. (d) Garcia, M. B.; Grilli, S.; Lunazzi, L.; Mazzanti, A.; Orelli, L. R. *J. Org. Chem.* **2001**, *66*, 6679.

(4) (a) Li, H. Y.; Drummond, S.; DeLucca, I.; Boswell, G. A. *Tetrahedron* **1996**, *52*, 11153. (b) Sun, M.; Wu, X. Q.; Chen, J. Q.; Cai, J.; Cao, M.; Ji, M. *Eur. J. Med. Chem.* **2010**, *45*, 2299. (c) Sztanke, K.; Pasternak, K.; Sidor-Wójtowicz, A.; Truchlińska, J.; Jóźwiak, K. *Bioorg. Med. Chem.* **2006**, *14*, 3635.

(5) (a) Forsberg, J. H.; Spaziano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017. (b) Hill, A. J.; Johnston, J. V. *J. Am. Chem. Soc.* **1954**, *76*, 922. (c) Ghorai, M. K.; Das, K.; Kumar, A.; Das, A. *Tetrahedron Lett.* **2006**, *47*, 5393. (d) Levesque, G.; Gressier, J. C.; Proust, M. *Synthesis* **1981**, 963.

(e) Papadopoulos, E. P.; George, B. *J. Org. Chem.* **1977**, *42*, 2530. (f) Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Eskandari, Z. *Z. Naturforsch.* **2010**, *65*, 461. (g) Takahashi, S.; Togo, H. *Heterocycles* **2010**, *82*, 593.

(6) (a) Paliakov, E.; Elleboe, T.; Boykin, D. W. *Synthesis* **2007**, 1475. (b) Koteswara Rao, V.; Hari Babu, B.; Raveendra Babu, K.; Srinivasulu, D.; Naga Raju, C. *Synth. Commun.* **2012**, *42*, 3368. (c) Vorbrueggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471. (d) Pews, R. G. *Heterocycles* **1988**, *27*, 1867. (e) Hegedüs, A.; Vígh, I.; Hell, Z. *Heteroat. Chem.* **2004**, *15*, 428. (f) Aleksandrov, A. A.; El'chaninov, M. M. *Russ. J. Appl. Chem.* **2009**, *82*, 2161. (g) Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Eskandari, Z. *J. Heterocycl. Chem.* **2011**, *48*, 479.

(7) (a) Prasad, B. A. B.; Bisai, A.; Singh, V. K. *Org. Lett.* **2004**, *6*, 4829. (b) Prasad, B. A. B.; Pandey, G.; Singh, V. K. *Tetrahedron Lett.* **2004**, *45*, 1137. (c) Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Eskandari, Z.; Salavati, H. *J. Iran. Chem. Soc.* **2011**, *8*, S17.

(8) For recent one-pot reactions based on C–N bond formation: (a) Chen, Y.; Wang, Y.; Sun, Z.; Ma, D. *Org. Lett.* **2008**, *10*, 625. (b) Chen, Y.; Xie, G.; Ma, D. *J. Org. Chem.* **2007**, *72*, 9329. (c) Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844. (d) Martin, R.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 5521.

(9) For recent reactions based on C–O bond formation: (a) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978. (b) Viirre, R. D.; Evindar, G.; Batey, R. A. *J. Org. Chem.* **2008**, *73*, 3452.

(10) For recent reactions based on C–S bond formation: (a) Shen, G.; Lv, X.; Bao, W. *Eur. J. Org. Chem.* **2009**, 5897. (b) Murru, S.; Ghosh, H.; Sahoo, S. K.; Patel, B. K. *Org. Lett.* **2009**, *11*, 4254. (c) Zhao, Q.; Li, L.; Fang, Y.; Sun, D.; Li, C. *J. Org. Chem.* **2009**, *74*, 459. (d) You, W.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 3930.

(11) (a) Li, X.; Zhou, B.; Zhang, J.; She, M.; An, S.; Ge, H.; Li, C.; Yin, B.; Li, J.; Shi, Z. *Eur. J. Org. Chem.* **2012**, 1626. (b) Zhang, J.; Wang, X.; Yang, M.; Wan, K.; Yin, B.; Wang, Y.; Li, J.; Shi, Z. *Tetrahedron Lett.* **2011**, *52*, 1578.

(12) (a) Wang, F.; Cai, S.; Liao, Q.; Xi, C. *J. Org. Chem.* **2011**, *76*, 3174. (b) Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 3305. (c) Cortes-Salva, M.; Garvin, C.; Antilla, J. C. *J. Org. Chem.* **2011**, *76*, 1456. (d) Lu, J.; Fu, H. *J. Org. Chem.* **2011**, *76*, 4600. (e) Li, C. L.; Zhang, X. G.; Tang, R. Y.; Zhong, P.; Li, J. H. *J. Org. Chem.* **2010**, *75*, 7037.

(13) (a) Kappe, C. O.; Pieber, B.; Dallinger, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 2. (b) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250; *Angew. Chem*. **2004**, *116*, 6408 . (c) Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128.

(14) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, **1989**.

(15) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785.

(16) Schaefer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571.

(17) Schaefer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 582.

(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A. Jr; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*; Gaussian Inc: Pittsburgh, **2003**.

(19) (a) Qi, D.; Zhang, L.; Wan, L.; Zhang, Y.; Bian, Y.; Jiang, J. *Phys. Chem. Chem. Phys.* **2011**, *13*, 13277. (b) Qi, D.; Zhang, L.; Zhao, L.; Cai, X.; Jiang, J. *ChemPhysChem* **2012**, *13*, 2046.

(20) (a) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. (b) Yin, B.; Huang, Y.-H.; Wang, G.; Wang, Y. *J. Mol. Model.* **2010**, *16*, 437. (c) Yin, B.; Wang, G.; Sa, N.-Y.; Huang, Y.-H. *J. Mol. Model.* **2008**, *14*, 789.

(21) CCDC-921864 (for CuL_2) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

(22) Imoto, M.; Iwanami, T.; Akabane, M.; Tani, Y. JP 2001302643, **2001**.

