Au(I)-Catalyzed Annulation of Propargyl Amine with Aldehydes: One-Pot Cascade Synthesis of 2,5-Dimethylpyrazines

Ji Su 1,2, Huixin Liu 1 and Ruimao Hua 1,*

1 Department of Chemistry, Tsinghua University, Beijing 100084, China; E-Mails: andrew-su@163.com (J.S.); liuhuixin9015@163.com (H.L.)
2 National Engineering Laboratory for Rice and Byproduct Deep Processing, Central South University of Forestry and Technology, Changsha 410004, China

* Author to whom correspondence should be addressed; E-Mail: ruimao@mail.tsinghua.edu.cn; Tel.: +86-10-6279-2596; Fax: +86-10-6277-1149.

Academic Editor: Andreas Taubert

Received: 25 December 2014 / Accepted: 2 February 2015 / Published: 5 February 2015

Abstract: 3-Substituted 2,5-dimethylpyrazines were synthesized in high yields via a one-pot cascade annulation of easily available propargyl amine with aldehydes catalyzed by Au(PPh₂Cy)Cl.

Keywords: aldehydes; annulation; golden complex; propargyl amine; pyrazines

1. Introduction

Transition-metal-catalyzed cyclization of alkynes with nitrogen-containing compounds has provided the efficient synthetic methods for N-heterocyclic compounds [1–4]. With the interest of developing the efficient procedures approach to N-heterocyclic compounds, we have recently studied the cyclization of alkynes or 1,3-butadiynes with various nitrogen-containing compounds affording 1,2,5-trisubstituted pyrroles [5], isoquinolines [6,7], 2,4,6-triarylpyridines [8], benzo[f]quinazolines [9], indoles [10], ring-fused phenanthroimidazoles [11], and 1,2,4-oxadiazoles [12]. On the other hand, cyclic compounds containing the structural unit of 2,5-dimethylpyrazine (DMP) show interesting physiological and biological activities found to be the pheromone of ants [13,14], and fungicide active agents [15] (Scheme 1). In addition, the structural unit of DMP has become increasingly important
applications as versatile ligands in the field of supramolecular chemistry due to their coordinative ability of two symmetric nitrogen atoms [16–20].

Scheme 1. Examples of natural products having structural unit of 2,5-dimethylpyrazine (DMP).

It has been well documented that propargylic compounds, such as propargyl amines [21,22], and propargyl alcohols [23–25] have been widely applied as one of the important building blocks in the synthesis of a variety of heterocyclic compounds containing the relevant heteroatoms. As a continuation of our interest in the applications of propargylic compounds on the synthesis of heterocyclic compounds [23–25], we are interested in exploring the possible application of prop-2-yn-1-amine (a simplest molecule of propargyl amine) in the synthesis of DMP. Therefore, we designed a synthetic protocol for the formation of DMP as shown in Scheme 2. It involves the dimerization of propargyl amines via the hydroamination to give \( \alpha \)-amino enamine A and its rearranged isomer A’, which serves as a nucleophile to undergo the aldol addition with aldehyde to form \( \alpha \)-amino imine intermediate B [26]. The subsequent intramolecular hydroamination and dehydration/isomerization form cyclic structure of pyrazine. After we developed the catalytic system and finished the experiments [27], a similar procedure for the formation of pyrazine ring was recently reported [28].

Scheme 2. Proposed mechanism for the formation of pyrazine’s ring.

2. Results and Discussion

We initiated our investigation on the reaction of prop-2-yn-1-amine with benzaldehyde (1a) in presence of Au(I) complexes, since Au(I) complexes have been found to be the efficient catalysts for the intermolecular [29,30] and intramolecular hydroamination of alkynes [31–33], as well as cycloisomerization of alkynes [34,35] to give \( N \)-heterocyclic compounds. As concluded in Table 1, when a mixture of benzaldehyde (1.0 mmol, 1a) and propargyl amine (3.0 equiv) and Au(PPh3)Cl
(0.05 mmol) in toluene was heated with stirring at 60 °C for 48 h, the analyses of the reaction mixture by GC-MS revealed that a new dehydrative cyclization of one molecule of 1a with two molecules of propargyl amine occurred to produce 3-benzyl-2,5-dimethylpyrazine (2a) in 13% GC yield (entry 1). The formation of 2a greatly depended on the solvents used. For example, when THF was used to lead to no formation of 2a at all (entry 2). However, the yield of 2a could be substantially increased to 45%, when CH3CN was employed (entry 3). Increasing the reaction temperature to 80 °C in CH3CN resulted in the reaction much more efficiently to afford 2a in 77% yield (entry 4), and the almost quantitative yields of 2a could be obtained by simply replacing PPh3 ligand to PPh2Me (entry 5) or PPh2Cy (entry 6) in CH3CN at 60 °C. In the presence of Au(PPh2Cy)Cl, repeating the reaction in toluene (entry 7) and THF (entry 8) resulted in low yield or no formation of 2a. In addition, Au(PPhMe2)Cl and Au(PCy3)Cl also showed good catalytic activities to give 2a in 72% (entry 9) and 88% GC (entry 10) yields, respectively. It should be noted that reduction of reaction time to 24 h led to the slight decrease of the yields of 2a in the cases of Au(PPh2Me)Cl (entry 11, 89%) and Au(PPh2Cy)Cl (entry 12, 92%) used.

**Table 1.** Optimizing the reaction conditions for the formation of 3-benzyl-2,5-dimethylpyrazine (2a) 

| Entry | Catalyst | Solvent | Temp. (°C)/Time (h) | Yield (%) |
|-------|----------|---------|---------------------|-----------|
| 1     | Au(PPh3)Cl | toluene | 60/48               | 13        |
| 2     | Au(PPh3)Cl | THF     | 60/48               | 0         |
| 3     | Au(PPh3)Cl | CH3CN   | 60/48               | 45        |
| 4     | Au(PPh3)Cl | CH3CN   | 80/48               | 77        |
| 5     | Au(PPh2Me)Cl | CH3CN   | 60/48               | >99       |
| 6     | Au(PPh2Cy)Cl | CH3CN   | 60/48               | >99 (92)  |
| 7     | Au(PPh2Cy)Cl | toluene | 60/48               | 20        |
| 8     | Au(PPh2Cy)Cl | THF     | 60/48               | 0         |
| 9     | Au(PPhMe2)Cl | CH3CN   | 60/48               | 72        |
| 10    | Au(PCy3)Cl | CH3CN   | 60/48               | 88        |
| 11    | Au(PPh2Me)Cl | CH3CN   | 60/24               | 89        |
| 12    | Au(PPh2Cy)Cl | CH3CN   | 60/24               | 92        |

*a* Reactions were carried out using 1.0 mmol of benzaldehyde (1a), 3.0 mmol of pro-2-yn-1-amine, and 0.05 mmol of catalyst in 2.0 mL of solvent in a sealed tube under nitrogen atmosphere; 

With the optimized reaction condition indicated in entry 6 of Table 1, the generality for the formation of 3-substituted 2,5-dimethylpyrazines was studied. As shown in Table 2, benzaldehydes bearing chloro group at para-, meta- or ortho-position, or having bromo, fluoro, methyl or methoxy group at para-position reacted with propargyl amine smoothly to afford the corresponding pyrazines 2b–f and 2h–i in high yields. No significant steric effect was observed when para-chlorobenzaldehyde (for 2b), meta-chlorobenzaldehyde (for 2c) and ortho-chlorobenzaldehyde (for 2d) were used, and the
desired products 2b–d were obtained in similar yields. By comparison of the reactions in the cases of para-chlorobenzaldehyde (for 2b), para-fluorobenzaldehyde (for 2e), para-methylbenzaldehyde (for 2h) and para-methoxybenzaldehyde (for 2i) used, the electron effect of substitute groups could not affect the formation of the corresponding pyrazines in high yields either. Only in the case of 2,4-dichlorobenzaldehyde employed, the corresponding product was formed in a declined yield (2g, 73%). In addition, it was very important to note that under the reaction conditions, C–X bond (X = F, Cl, Br) remained intact, and the obtained 3-aryl methyl-2,5-dimethylpyrazines can be easily transferred into their new derivatives by C–X bond activation and its coupling reaction. In addition, we also examined the present cyclization employing aliphatic aldehydes, and the reactions occurred smoothly to afford the corresponding desired pyrazines (2k–m) with high yields.

Table 2. Synthesis of 2,5-dimethylpyrazine derivatives a.

|     |     |     |     |     |
|-----|-----|-----|-----|-----|
| 2b  | 93% | 2c  | 94% | 2d  | 90% |
| 2e  | 92% | 2f  | 88% | 2g  | 73% |
| 2h  | 91% | 2i  | 89% | 2j  | 85% |
| 2k  | 84% | 2l  | 81% | 2m  | 80% |
| 2n  | 82% | 2o  | 19% |

a Reactions were carried out using 2.0 mmol of aldehyde, 6.0 mmol of prop-2-yn-1-amine, and 0.1 mmol of catalyst in 4.0 mL of MeCN at 60 °C for 48 h.

Moreover, the annulation of propargyl amine with heterocyclic aldehydes such as 2-furaldehyde and 2-thiophenaldehyde were also studied, and in the case of 2-furaldehyde used, the corresponding 2,5-dimethylpyrazine (2n) was obtained in high yield. However, when 2-thiophenaldehyde was subjected to the similar reaction conditions, the desired product (2o) formed in 19% isolated yield, accompanied with the formation of N-(prop-2-yn-1-yl)-1-thiophen-2-ylmethanimine in 70% yield resulting from the traditional nucleophilic addition of propargyl amine to aldehyde and subsequent dehydration reaction.

However, unfortunately, the reactions of 1a or 1k with 3-substituted propargyl amines such as 3-phenyl-2-propyn-1-amine and 2-heptyn-1-amine resulted in neither affording the corresponding pyrazine derivatives, nor forming other N-heterocyclic compounds.
3. Experimental Section

3.1. General Methods

All organic starting materials and solvents are analytically pure and used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECA-300 spectrometer (JEOL, Tokyo, Japan) using CDCl3 as a solvent at 298 K. 1H NMR (300 MHz) chemical shifts (δ) were referenced to internal standard TMS (for 1H, δ = 0.00 ppm). 13C NMR (75 MHz) chemical shifts were referenced to internal solvent CDCl3 (for 13C, δ = 77.16 ppm). Mass spectra (MS) were obtained on a Shimadzu GCMS-QP2010S (Shimadzu, Tokyo, Japan), and high-resolution mass spectra (ESI) were obtained with a micrOTOF-Q 10142 spectrometer (Agilent, San Diego, CA, USA).

3.2. A Typical Experiment Procedure for the Reaction of Benzaldehyde (1a) with Prop-2-yn-1-amine Affording 3-Benzyl-2,5-dimethylpyrazine (2a) (Table 1, Entry 6)

A mixture of benzaldehyde (1a) (106.0 mg, 1.0 mmol), prop-2-yn-1-amine (165.0 mg, 3.0 mmol), Au(PPh2Cy)Cl (25.0 mg, 0.05 mmol) and CH3CN (2.0 mL) was heated at 60 °C (oil bath temperature) with stirring for 48 h in a screw-capped thick-walled Pyrex tube under a nitrogen atmosphere. After the reaction mixture was cooled to room temperature, CH2Cl2 (3.0 mL) and n-octadecane (51.0 mg, 0.2 mmol as internal standard for GC analysis) was then added with stirring. After GC and GC-MS analyses of the reaction mixture, volatiles were removed under reduced pressure, and the residue was subjected to silica gel column chromatography (silica gel was alkalized by a solution of petroleum ether with 2% (v/v) triethylamine), eluted with a mixture of solvents of triethylamine/ethyl acetate/petroleum ether (1:20:80 in volume). 2a was obtained in 182.0 mg (0.92 mmol, 92%) as a yellow oil. The GC analysis of reaction mixture disclosed the formation of 2a in >99% GC yield.

Characterization data of products (the charts of 1H- and 13C-NMR are reported in Supplementary Materials):

3-Benzyl-2,5-dimethylpyrazine (2a) [36]: yellow oil; 1H NMR (300 MHz, CDCl3) δ 8.20 (s, 1H), 7.28–7.15 (m, 5H), 4.15 (s, 2H), 2.51 (s, 3H), 2.43 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 152.9, 150.1, 149.3, 141.4, 137.9, 128.6, 128.4, 126.4, 41.6, 21.4, 21.0; GCMS m/z (% rel. intensity) 198 (M+, 66), 197 (100), 183 (40), 128 (8), 91 (14); HRMS (ESI): Calcd. for C13H15N2 [M + H]+: 199.1230; found: 199.1232.

3-(4-Chlorobenzyl)-2,5-dimethylpyrazine (2b): yellow oil; 1H NMR (300 MHz, CDCl3) δ 8.22 (s, 1H), 7.22 (d, 2H, J = 8.6 Hz), 7.11 (d, 2H, J = 8.3 Hz), 4.11 (s, 2H), 2.51 (s, 3H), 2.43 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 153.3, 150.3, 149.1, 141.5, 136.4, 132.2, 129.9, 128.5, 40.8, 21.3, 21.0; GCMS m/z (% rel. intensity) 233 (44), 232 (M+, 79), 231 (100), 217 (34), 197 (23), 196 (24), 182 (17); HRMS (ESI): Calcd. for C13H14ClN2 [M + H]+: 233.0840; found: 233.0847.

3-(3-Chlorobenzyl)-2,5-dimethylpyrazine (2c): yellow oil; 1H NMR (300 MHz, CDCl3) δ 8.23 (s, 1H), 7.25–7.12 (m, 3H), 7.07 (m, 1H), 4.13 (s, 2H), 2.52 (s, 3H), 2.45 (s, 3H); 13C NMR (75 MHz, CDCl3) δ 152.1, 150.4, 149.2, 141.7, 140.0, 134.3, 129.7, 128.6, 126.8, 126.6, 41.1, 21.4, 21.1; GCMS m/z (% rel. intensity) 233 (41), 232 (M+, 76), 231 (100), 217 (47), 197 (24), 196 (27), 182 (19), 116 (22); HRMS (ESI): Calcd. for C13H14ClN2 [M + H]+: 233.0840; found: 233.0847.
3-(2-Chlorobenzyl)-2,5-dimethylpyrazine (2d): yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.24 (s, 1H), 7.38 (d, 1H, $J = 7.9$ Hz), 7.20–7.08 (m, 2H), 6.88 (d, 1H, $J = 7.2$ Hz), 4.27 (s, 2H), 2.50 (s, 3H), 2.43 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 152.0, 150.4, 149.6, 141.6, 136.0, 134.1, 129.9, 129.4, 127.8, 126.8, 38.6, 21.3, 21.1; GCMS m/z (% rel. intensity) 197 (100), 116 (8), 89 (7); HRMS (ESI): Calcd. for C$_{13}$H$_{14}$ClN$_2$ [M + H]$^+$: 233.0840; found: 233.0838.

3-(4-Fluorobenzyl)-2,5-dimethylpyrazine (2e): yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.22 (s, 1H), 7.20–2.09 (m, 2H), 6.97–6.90 (m, 2H), 4.12 (s, 2H), 2.52 (s, 3H), 2.44 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 161.5 (d, $J_{C-F} = 242.4$ Hz), 152.7, 150.3, 149.1, 141.5, 133.6 (d, $J_{C-F} = 2.9$ Hz), 130.0 (d, $J_{C-F} = 7.9$ Hz), 115.2 (d, $J_{C-F} = 20.8$ Hz), 40.7, 21.3, 21.0; GCMS m/z (% rel. intensity) 216 (M$^+$, 71), 215 (100), 201 (38), 109 (22); HRMS (ESI): Calcd. for C$_{13}$H$_{14}$FN$_2$ [M + H]$^+$: 217.1136; found: 217.1126.

3-(2-Bromobenzyl)-2,5-dimethylpyrazine (2f): yellow solid; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.24 (s, 1H), 7.56 (d, 1H, $J = 6.5$ Hz), 7.20–7.01 (m, 2H), 6.84 (d, 1H, $J = 7.6$ Hz), 4.26 (s, 2H), 2.49 (s, 3H), 2.43 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.9, 150.3, 149.6, 141.6, 137.7, 132.7, 129.9, 128.0, 127.4, 124.7, 41.3, 21.3, 21.0; GCMS m/z (% rel. intensity) 197 (M–Br$^-$, 100), 154 (5), 128 (10), 89 (9), 63 (5); HRMS (ESI): Calcd. for C$_{13}$H$_{14}$BrN$_2$ [M + H]$^+$: 277.0335; found: 277.0327.

3-(2,4-Dichlorobenzyl)-2,5-dimethylpyrazine (2g): yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.24 (s, 1H), 7.40 (s, 1H), 7.12 (d, 1H, $J = 7.5$ Hz), 6.86 (d, 1H, $J = 8.2$ Hz), 4.21 (s, 2H), 2.49 (s, 3H), 2.44 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.5, 150.6, 149.5, 141.8, 134.7, 133.5, 132.9, 131.0, 129.2, 127.1, 38.0, 21.3, 21.1; GCMS m/z (% rel. intensity) 231 (M–Cl$^-$, 100), 196 (84), 150 (8), 80 (8), 51 (5); HRMS (ESI): Calcd. for C$_{13}$H$_{13}$Cl$_2$N$_2$ [M + H]$^+$: 267.0450; found: 267.0457.

3-(4-Methylbenzyl)-2,5-dimethylpyrazine (2h): yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.18 (s, 1H), 7.10–7.00 (m, 4H), 4.10 (s, 2H), 2.49 (s, 3H), 2.42 (s, 3H), 2.25 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 152.9, 149.8, 149.0, 141.0, 135.6, 134.6, 128.9, 128.3, 41.0, 21.2, 20.8, 20.7; GCMS m/z (% rel. intensity) 212 (M$^+$, 75), 211 (100), 197 (53), 128 (11), 105 (30), 77 (16); HRMS (ESI): Calcd. for C$_{14}$H$_{17}$N$_2$ [M + H]$^+$: 213.1385; found: 213.1385.

3-(4-Methoxybenzyl)-2,5-dimethylpyrazine (2i): yellow solid; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.20 (s, 1H), 7.10 (d, 2H, $J = 8.3$ Hz), 6.81 (d, 2H, $J = 8.2$ Hz), 4.10 (s, 2H), 3.75 (s, 3H), 2.52 (s, 3H), 2.44 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 158.2, 153.3, 150.2, 149.3, 141.3, 130.0, 129.2, 127.4, 124.7, 40.9, 21.5, 21.1; GCMS m/z (% rel. intensity) 228 (M$^+$, 100), 227 (44), 213 (74), 185 (17), 121 (87), 91 (14); HRMS (ESI): Calcd. for C$_{14}$H$_{17}$N$_2$O [M + H]$^+$: 267.0450; found: 267.0457.

3-(2-Naphthylmethyl)-2,5-dimethylpyrazine (2j): yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.19 (s, 1H), 7.75–7.66 (m, 3H), 7.53 (s, 1H), 7.41–7.30 (m, 3H), 4.27 (s, 2H), 2.50 (s, 3H), 2.43 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 152.7, 150.1, 149.4, 141.4, 135.4, 133.4, 132.1, 128.1, 127.5, 127.4, 127.0, 126.8, 126.0, 125.4, 41.7, 21.4, 21.0; GCMS m/z (% rel. intensity) 228 (M$^+$, 85), 247 (100), 233 (42), 141 (29), 115 (27); HRMS (ESI): Calcd. for C$_{17}$H$_{17}$N$_2$ [M + H]$^+$: 249.1386; found: 249.1392.

3-Octyl-2,5-dimethylpyrazine (2k): yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.15 (s, 1H), 2.76 (t, 2H, $J = 7.6$ Hz), 2.53 (s, 3H), 2.49 (s, 3H), 1.73–1.62 (m, 2H), 1.48–1.21 (m, 10H), 0.88 (t, 3H, $J = 6.5$ Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 152.9, 150.0, 149.5, 140.6, 35.2, 31.9, 29.7, 29.5, 29.3,
3-Cinnamyl-2,5-dimethylpyrazine (2l): orange oil; $^1$H NMR (300 MHz, CDCl₃) δ 8.20 (s, 1H), 7.35–7.20 (m, 5H), 6.50–6.31 (m, 2H), 3.71 (d, 2H, $J = 5.8$ Hz), 2.55 (s, 3H), 2.50 (s, 3H); $^{13}$C NMR (75 MHz, CDCl₃) δ 152.4, 150.4, 149.1, 141.4, 137.2, 131.9, 128.5, 127.4, 126.2, 125.9, 39.2, 21.2, 21.1; GCMS $m/z$ (% rel. intensity) 224 (M⁺, 47), 223 (28), 209 (34). 147 (45), 122 (100), 115 (27), 91 (15); HRMS (ESI): Calcd. for C₁₄H₂₅N₂ [M + H]⁺: 221.2012; found: 221.2019.

3-Cyclohexylmethyl-2,5-dimethylpyrazine (2m): yellow oil; $^1$H NMR (300 MHz, CDCl₃) δ 8.14 (s, 1H), 2.66 (d, 2H, $J = 7.2$ Hz), 2.52 (s, 3H), 2.50 (s, 3H), 1.85–1.63 (m, 6H), 1.29–0.99 (m, 5H); $^{13}$C NMR (75 MHz, CDCl₃) δ 154.1, 150.0, 149.0, 140.6, 42.5, 38.3, 33.3, 26.5, 26.3, 21.6, 21.2; GCMS $m/z$ (% rel. intensity) 204 (M⁺, 0.2), 189 (1), 161 (2), 147 (2), 122 (100), 80 (2), 55 (4); HRMS (ESI): Calcd. for C₁₃H₂₁N₂ [M + H]⁺: 205.1699; found: 205.1702.

3-(2-Furylmethyl)-2,5-dimethylpyrazine (2n): yellow oil; $^1$H NMR (300 MHz, CDCl₃) δ 8.23 (s, 1H), 7.13 (d, 1H, $J = 6.5$ Hz), 6.90 (dd, 1H, $J = 3.4$ Hz, 5.1 Hz), 6.78 (m, 1H), 4.32 (s, 2H), 2.52 (s, 6H); $^{13}$C NMR (75 MHz, CDCl₃) δ 152.1, 150.4, 149.0, 141.8, 140.4, 126.8, 125.4, 124.3, 36.2, 21.3, 21.1; GCMS $m/z$ (% rel. intensity) 204 (100), 189 (15), 171 (30), 159 (35), 97 (95), 80 (9), 53 (16); HRMS (ESI): Calcd. for C₁₁H₁₃N₂O [M + H]⁺: 205.0794; found: 205.0790.

4. Conclusions

In summary, we have developed a cascade annulation of propargyl amine with aldehydes approach to 3-substituted 2,5-dimethylpyrazines in high yields catalyzed by Au(PPh₃Cy)Cl, which involves the intermolecular hydroamination and intramolecular cyclic hydroamination, as well as the dehydration reaction. The present work has developed the application of propargyl amines in the synthesis of nitrogen-containing heterocycles with the advantages of readily accessible starting materials and high atom-efficiency.

Supplementary Materials

Supplementary materials can be found at http://www.mdpi.com/1422-0067/16/02/3599/s1.

Acknowledgments

This project was supported by the National Natural Science Foundation of China (21473097, 21273125, 21032004), and the Specialized Research Fund for the Doctoral Program of Higher Education (20110002110051).
Author Contributions

Both co-authors did the research work including optimization of reaction conditions and study on the substrate scope.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Varela, J.A.; Saá, C. Construction of pyridine rings by metal-mediated [2 + 2 + 2] cycloaddition. *Chem. Rev.* 2003, *103*, 3787–3801.
2. Nakamura, I.; Yamamoto, Y. Transition metal catalyzed reactions in heterocyclic synthesis. *Chem. Rev.* 2004, *104*, 2127–2198.
3. Hua, R.; Abrenica, M.V.A.; Wang, P. Cycloaddition of alkynes: Atom-economic protocols for constructing six-membered cycles. *Curr. Org. Chem.* 2011, *15*, 712–729.
4. Nizami, T.A.; Hua, R. Cycloaddition of 1,3-butadiynes: Efficient synthesis of carbo- and heterocycles. *Molecules* 2014, *19*, 13788–13802.
5. Zheng, Q.; Hua, R. CuCl-catalyzed cycloaddition of 1,3-butadiynes with primary amines: An atom-economic process for synthesis of 1,2,5-trisubsituted pyrroles. *Tetrahedron Lett.* 2010, *51*, 4512–4514.
6. Zheng, L.; Ju, J.; Bin, Y.; Hua, R. Synthesis of isoquinolines and heterocycle-fused pyridines via three-component cascade reaction of aryl ketones, hydroxylamine, and alkynes. *J. Org. Chem.* 2012, *77*, 5794–5800.
7. Ju, J.; Hua, R. Copper-catalyzed synthesis of isoquinolines by the cyclocondensation of ortho-alkynyl aromatic aldehydes or ketones with urea. *Curr. Org. Synth.* 2013, *10*, 328–332.
8. Wang, P.; Hua, R.; Li, C.-J. One-pot synthesis of 2,4,6-triarylpyridines by the oxidative cyclocondensation of benzaldehydes, aromatic alkynes and ammonium bifluoride. *Curr. Org. Synth.* 2013, *10*, 655–660.
9. Yang, L.; Hua, R. Cycloaddition of 1,4-diaryl-1,3-butadiynes with nitriles: An atom-economic one-pot approach to benzo[ff]quinazolines. *Chem. Lett.* 2013, *42*, 769–771.
10. Zheng, L.; Hua, R. Rhodium(III)-catalyzed C–H activation and indole synthesis with hydrazone as an auto-formed and auto-cleavable directing group. *Chem. Eur. J.* 2014, *20*, 2352–2356.
11. Zheng, L.; Hua, R. Modular assembly of ring-fused and π-extended phenanthroimidazoles via C–H activation and alkyne annulation. *J. Org. Chem.* 2014, *79*, 3930–3936.
12. Guo, J.; Hua, R.; Sui, Y.; Cao, J. Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles and their behavior of liquid crystallines. *Tetrahedron Lett.* 2014, *55*, 1557–1560.
13. Sato, N.; Matsuura, T. Studies on pyrazines. Part 32. Synthesis of trisubstituted and tetrasubstituted pyrazines as ant pheromones. *J. Chem. Soc. Perkin Trans. 1* 1996, *2345–2350*, doi:10.1039/P19960002345.
14. Ali, M.F.; Morgan, E.D.; Detrain, C.; Attygalle, A.B. Identification of a component of the trail pheromone of the ant *Pheidole pullidulu* (Hymenoptera: Formicidae). *Physiol. Entomol.* **1988**, *13*, 251–265.

15. Beier, C.; Benting, J.; Bernier, D.; Christian, I.; Coqueron, P.-Y.; Desbordes, P.; Dubost, C.; Genix, P.; Grosjean-Cournoyer, M.-C.; Portz, D.; *et al.* Preparation of Fungicide Hydroximoyl-Heterocycles Derivatives. PCT Int. Appl. WO 2009130193 A1, 21 April 2009.

16. Awwadi, F.F.; Landee, C.P.; Turnbull, M.M.; Twamley, B.; Wells, B.M. Low-dimensional quantum magnetic systems: Synthesis, structure and magnetic behavior of (2,5-dimethylpyrazine)copper(II) chloride and synthesis and magnetic behavior of bis(2,6-dimethylpyrazine)copper(II) chloride. *Polyhedron* **2005**, *24*, 2153–2159.

17. Yeung, W.-F.; Gao, S.; Wong, W.-T.; Lau, T.-C. Antiferromagnetic ordering in a novel five-connected 3D polymer {Cu$_2$(2,5- Me$_2$pyz)[N(CN)$_2$]$_4$}$_n$ (2,5-Me$_2$pyz = 2,5-dimethylpyrazine). *New J. Chem.* **2002**, *26*, 523–525.

18. Otieno, T.; Blanton, J.R.; Lanham, K.J.; Parkin, S. Poly-$\mu$-2,5-dimethylpyrazine-$\mu$-dithiocyanato-N,S,S-dicopper(I): A three-dimensional coordination polymer containing both molecular and anionic rod ligands. *J. Chem. Cryst.* **2003**, *33*, 335–339.

19. Wriedt, M.; Jeß, I.; Näther, C. Synthesis, crystal structures, and thermal properties of new [ZnX$_2$(2,5-dimethylpyrazine)] (X = Cl, Br, I) coordination compounds. *Eur. J. Inorg. Chem.* **2009**, 2009, 363–372.

20. Wang, Z.-H.; Wang, D.-F.; Zhang, T.; Huang, R.-B.; Zheng, L.-S. Effect of different carboxylates on two Ag(I) coordination polymers with 2,5-dimethylpyrazine ligand. *J. Mol. Struct.* **2014**, *1064*, 27–31.

21. Shi, M.; Shen, Y.-M. Transition-metal-catalyzed reactions of propargylamine with carbon dioxide and carbon disulfide. *J. Org. Chem.* **2002**, *67*, 16–21.

22. Abahmane, L.; Knauer, A.; Ritter, U.; Köhler, J.M.; Groß, G.A. Heterogeneous catalyzed pyridine synthesis using montmorillonite and nanoparticle-impregnated alumina in a continuous micro flow system. *Chem. Eng. Technol.* **2009**, *32*, 1799–1805.

23. Zeng, H.; Ju, J.; Hua, R. ReCl(CO)$_3$-catalyzed cyclocondensation of phenols with 2-methyl-3-butyn-2-ol to afford 2,2-dimethyl-2H-chromenes. *Tetrahedron Lett.* **2011**, *52*, 3926–3928.

24. Su, J.; Ju, J.; Hua, R. An efficient copper-catalyzed cyclocondensation of anilines with propargyl alcohols approach to 1,2-dihydroquinolines. *Curr. Org. Synth.* **2012**, *9*, 273–277.

25. Su, J.; Hua, R. One-pot approach to 4-vinyl-1,2,3-triazoles by cycloaddition of azides with propargyl alcohols catalyzed by Cu(I)/Ru(III)/TFA. *Curr. Org. Synth.* **2012**, *9*, 898–902.

26. Bahmanyar, S.; Houk, K.N. Transition states of amine-catalyzed aldol reactions involving enamine intermediates: Theoretical studies of mechanism, reactivity, and stereoselectivity. *J. Am. Chem. Soc.* **2001**, *123*, 11273–11283.

27. Hua, R.; Su, J. Preparation Method for 2,5-Dimethylpyrazine Derivative. China Patent 201210132707, 28 April 2012.

28. Alcaide, B.; Almendros, P.; Alonso, J.M.; Fernández, I.; Gómez-Campillos, G.; Torres, M.R. A gold-catalysed imine–propargylamine cascade sequence: Synthesis of 3-substituted-2,5-dimethylpyrazines and the reaction mechanism. *Chem. Commun.* **2014**, *50*, 4567–4570.
29. Duan, H.; Sengupta, S.; Petersen, J.L.; Akhmedov, N.G.; Shi, X. Triazole-Au(I) complexes: A new class of catalysts with improved thermal stability and reactivity for intermolecular alkyne hydroamination. *J. Am. Chem. Soc.* **2009**, *131*, 12100–12102.

30. Hesp, K.D.; Stradiotto, M. Stereo- and regioselective gold-catalyzed hydroamination of internal alkynes with dialkylamines. *J. Am. Chem. Soc.* **2010**, *132*, 18026–18029.

31. Surmont, R.; Verniest, G.; Kimpe, N.D. Gold-catalyzed synthesis of 2-aryl-3-fluoropyrroles. *Org. Lett.* **2010**, *11*, 2920–2923.

32. Zhang, L.; Ye, D.J.; Zhou, Y.; Liu, G.N.; Feng, E.G.; Jiang, H.L.; Liu, H. Regioselective synthesis of 3-benzazepinones and unexpected 5-bromo-3-benzazepinones. *J. Org. Chem.* **2010**, *75*, 3671–3677.

33. Huang, J.; Huang, X.; Liu, B. Gold-catalyzed synthesis of nitrogen-containing heterocycles from ε-N-protected propargylic esters. *Org. Biomol. Chem.* **2010**, *8*, 2697–2699.

34. Davies, P.W.; Martin, N. An efficient and selective synthesis of 2,5-substituted pyrroles by gold-catalysed ring expansion of alkynyl aziridines. *J. Organomet. Chem.* **2011**, *696*, 159–164.

35. Kern, N.; Blanc, A.; Weibel, J.-M.; Pale, P. Gold(I)-catalyzed rearrangement of aryl alkynylaziridines to spiro[isochroman-4,2’-pyrrolines]. *Chem. Commun.* **2011**, *47*, 6665–6667.

36. Flament, I.; Sonnay, P.; Ohloff, G. Pyrazines. III. Condensation of dihydropyrazines with carbonyl compounds: Synthesis of substituted pyrazines and 6,7-dihydro-5H-cyclopenta[b]pyrazines. *Bull. Soc. Chim. Belg.* **1979**, *88*, 941–950.

© 2015 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution license (http://creativecommons.org/licenses/by/4.0/).