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Development of Four-Component Synthesis of Tetra- and Pentasubstituted Polyfunctional Dihydropyrroles: Free Permutation and Combination of Aromatic and Aliphatic Amines

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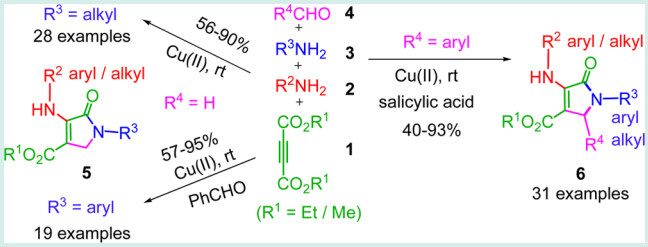
Supporting Information

ABSTRACT: We previously reported the novel efficient proton/heat-promoted four-component reactions (4CRs) of but-2-ynedioates, two same/different primary amines, and aldehydes for the synthesis of tetra- and pentasubstituted polyfunctional dihydropyrroles. If aromatic and aliphatic amines were used as reagents, four different series of products should be obtained via the permutation and combination of aromatic and aliphatic primary amines. However, only three/two rather four different series of tetra-/pentasubstisuted dihydropyrroles could be prepared via the proton/heat-promoted 4CRs. Herein, $Cu(OAc)_2 \cdot H_2O$, a Lewis acid being stable in air and water, was found to be an efficient catalyst for the 4CR synthesis of all the four different series of tetra-/pentasubstisuted dihydropyrroles. The copper-catalyzed 4CR could produce target products at room temperature in good to excellent yields. Interestingly, benzaldehyde, in addition to being used as a useful reactant for the synthesis of pentasubstituted dihydropyrroles, was found to be an excellent additive for preventing the oxidation of aromatic amines with copper(II) and ensuring the sooth conduct of the 4CRs for the synthesis of tetrasubstituted dihydropyrroles with aryl R^3. In addition, salicylic acid was found to be needed to increase the activities and yields of the copper-catalyzed 4CRs for the synthesis of petasubstituted diyhydropyrroles. On the basis of experimental results, the enamination/amidation/intramolecular cyclization mechanism was proposed and amidation is expected to be the rate-limited step in the copper-catalyzed 4CRs.



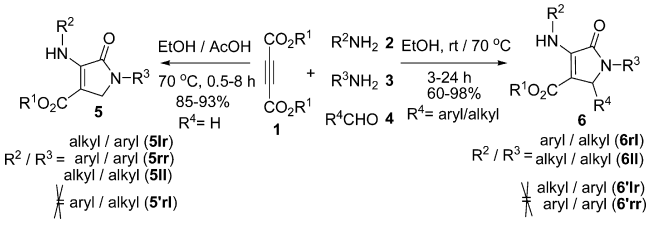
KEYWORDS: *copper catalysis, dihydropyrroles, multicomponent reactions, nitrogen heterocycles, one-pot reaction, synthetic methods*

INTRODUCTION

Dihydropyrroles are important azaheterocycles with various biological activities. For example, dihydropyrrole derivatives have been used as the inhibitors of bacterial peptide deformylase,[1] human mitotic kinesin Eg5,[2] cardiac cAMP phosphodiesterase,[3] human immunodeficiency virus (HIV) integrase,[4] and vascular endothelial growth factor receptors (VEGFR).[5] They are also useful intermediates in the synthesis of natural products[6] and chemicals.[7] Thus, the development of efficient synthetic methodologies for novel dihydropyrroles has attracted tremendous interests in synthetic chemistry.[8]

Multicomponent reactions (MCRs) have attracted increased attention in combinational, synthetic, and pharmaceutical chemistry for their distinct advantages, such as atom economy, simplified workup procedures, high overall yields, and molecular diversity products.[9] MCRs have played an important role in the process of drug development.[10] We recently synthesized a novel series of polysubstituted dihydropyrroles with enamine and α,β-aminocarboxylate moieties, tetra-, and pentasubstituted dihydropyrroles **5** and **6**, via the convenient four-component reactions (4CRs) of but-2-ynedioates **1**, primary amines **2**, primary amines **3**, and aldehydes **4** under different conditions (Scheme 1).[11] Since enamine and α,β-aminocarboxylates are also useful intermediates in synthetic[12] and medicinal[13] chemistry besides important dihydropyrrole scaffolds, it is expected that **5** and **6** would be attractive compounds. In fact, we have found that **5** and **6** exhibit significant activity against HIV-1 (human immunodeficiency virus)[11a] and caspase-3 (cysteinyl aspartate-specific protease).[14] Although the 4CRs[11b] afforded efficient and convenient protocols for the synthesis of large numbers of **5** and **6**, only three permutation-combination series of tetrasubstituted dihydropyrroles **5** (**5lr**, **5rr**, **5ll**, R^2/R^3 = alkyl/aryl, aryl/aryl,

Scheme 1. 4CRs for the Synthesis of Polyfunctional Dihydropyrroles 5 and 6[11b]



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and alkyl/alkyl, respectively) and two permutation-combination series of pentasubstituted dihydropyrroles **6** (**6rl** and **6ll**, R^2/R^3 = aryl/alkyl and alkyl/alkyl, respectively) could be obtained when using aromatic and aliphatic amines, respectively, as reactants **2** and **3** (Scheme 1). The preparation of the series of **5** with R^2/R^3 = aryl/alkyl (**5′rl**) and the two series of **6** with R^3 = aryl (alkyl/aryl and aryl/aryl, **6′lr** and **6′rr**) remains a challenge (Scheme 1). To the best of our knowledge, only a few analogs of **5** and **6** were reported previously and synthesized by the condensation reaction of amines with 2,3-dioxopyrrolidines.[15] Recently, **5** has been reported under molecular iodine catalysis[16] rather than by proton catalysis (Scheme 1). However, the iodine-catalyzed 4CR for the synthesis of **5** also meets difficulty for that of **5′rl**.

Copper-mediated reactions have gained popularity because of mild reaction conditions, low toxicity, low cost, and applicability to the formation of C−C, C−N, C−O, and C−S bonds.[17] To meet the challenges mentioned above, considerable effort has been dedicated toward the discovery of an efficient catalysis system for the synthesis of **5′rl**, **6′lr**, and **6′rr**. We found that all the four permutation-combination series of **5** or **6** could be successfully synthesized at room temperature using $Cu(OAc)_2{\cdot}H_2O$ as catalyst in the absence or presence of an additive (benzaldehyde or salicylic acid) in good to excellent yields.

RESULTS AND DISCUSSION

Synthesis of Tetrasubstituted Dihydropyrroles with R^2/R^3 = Aryl/Alkyl, 5′rl. The structures of the reagents used in this paper are shown in Figure 1. Our research began with the 4CR synthesis of methyl 1-benzyl-2,5-dihydro-5-oxo-4-(phenylamino)-1*H*-pyrrole-3-carboxylate **5′rl**{*1,1,1,1*} (Table 1). Both dimethyl but-2-ynedioate **1**{*1*} and aniline **2**{**r**(*1*)} were used as limiting reactants in the 4CR because **1**{*1*} and **2**{**r**(*1*)} could react fast (10 min) and quantitatively.[18] The amounts of phenylmethanamine **3**{**l**(*1*)} and formaldehyde **4**{*1*} are 1.5 and 1.2 equiv to **1**{*1*} and **2**{**r**(*1*)}, respectively. After screening a wide range of catalysts, $Cu(OAc)_2{\cdot}H_2O$ was found to be the best one (entry 1 in Table S1 in Supporting Information). Then, the screening of solvents (entries 2−5), as well as the amounts of $Cu(OAc)_2{\cdot}H_2O$, **3**{**l**(*1*)} and **4**{*1*} were investigated (entries 6−11), which led to the yield of **5′rl**{*1,1,1,1*} up to 90% (entry 7). The increase of reaction time did not lead to the changes in the yield of **5′rl**{*1,1,1,1*} (entry 12). The 4CR gave lower yield of **5′rl**{*1,1,1,1*} at 40 °C (entry 13) than that at room temperature (entry 7). Therefore, the optimal conditions for the 4CR synthesis of **5′rl**{*1,1,1,1*} are those in entry 7, **1**{*1*}/**2**{**r**(*1*)}/**3**{**l**(*1*)}/**4**{*1*}/$Cu(OAc)_2{\cdot}H_2O$ = 1:1:1.4:1.2:0.2 in MeOH at room temperature for 8 h. Under the optimal conditions, the addition orders of reactants and catalyst were screened (Supporting Information Scheme S1). The suitable addition order is order 1 (Supporting Information Scheme S1) as described in the footnote of Table 1.

Scope of the Copper-Catalyzed 4CR for the Synthesis of Tetrasubstituted Dihydropyrroles 5 with Alkyl R^3. Under the optimal reaction conditions mentioned above, various tetrasubstituted dihydropyrroles **5** with R^2/R^3 = aryl/alkyl (**5′rl**) were successfully synthesized via the 4CRs of but-2-ynedioates **1**{*1*−*2*}, aromatic primary amines **2**{**r**(*1*−*12*)}, aliphatic primary amines **3**{**l**(*1*−*6*)} and formaldehyde **4**{*1*} in 56−92% yields (Table 2). The position of substituent at R^2 phenyl ring shows no significant effect on the yields of products **5′rl** (entries 7−9). Using aromatic amines with strongly

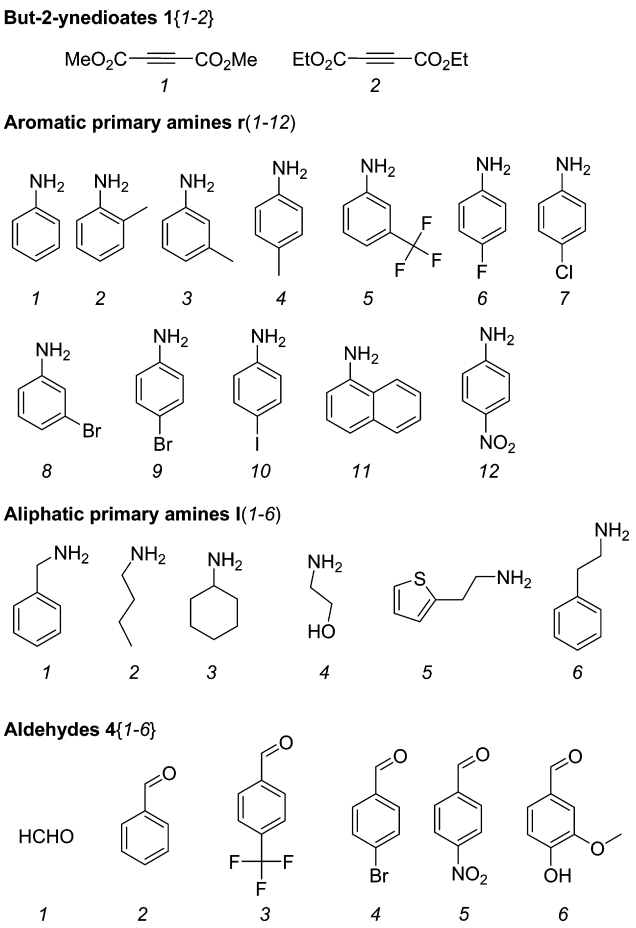

Figure 1. Diversity reagents.

electron-withdrawing group, such as $-NO_2$, as reactants **2** also afforded the desired products in moderate yield (entry 25). Different kinds of aliphatic amines could be used as the efficient reactants **3** of the 4CRs (entries 1−6). Replacement of methyl in **1**{*1*} with ethyl presented little influence on the 4CRs (Comparing entries 17 and 26). Dihydropyrrole **5′rl**{*1,1,1,1*} is the only one dihydropyrrole **5** with R^2/R^3 = aryl/alkyl synthesized via the iodine-catalyzed 4CR in much lower yield[16] than via the copper-catalyzed 4CR (entry 1).

In addition, **5** with alkyl R^2 and R^3, **5ll** {*1*−*2,1,1,1*} (entries 27 and 28 in Table 2), were also synthesized via the copper-catalyzed 4CR in good yields at lower temperature (rt) with less amount of reactants **2** (1.4 equiv) and **3** (1.2 equiv) than those (70 °C, 3 equiv of **2** and 2 equiv of **3**, entry 28) reported in our previous work.[11b] The activity and yields of the copper-catalyzed 4CRs for the synthesis of **5** with aryl R^2 are higher than those for the synthesis of **5** with alkyl R^2 (comparing entry 1 and 27).

When an aromatic amine, such as aniline, was used as reactant **3**, the 4CR mixture would become dark black and turbid soon (in 10 min) with complex products. In addition, the replacement of **4**{*1*} with other aldehydes led to no or poor yields of target pentasubstituted dihydropyrroles **6**.

Synthesis of Tetrasubstituted Dihydropyrrole 5 with Aryl R^2 and R^3, 5rr. Very interestingly, benzaldehyde was found to be an effective additive for the 4CR synthesis of methyl 2,5-dihydro-5-oxo-1-phenyl-4-(phenylamino)-1*H*-pyrrole-3-carboxylate **5rr**{*1,1,1,1*} when we tried other reactions. Therefore, we screened the reaction conditions of the 4CR for

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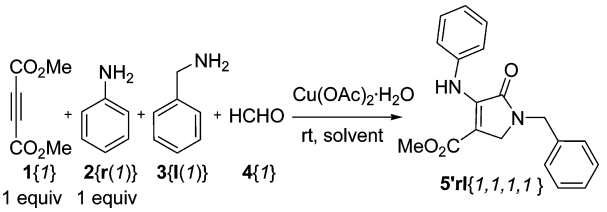
Table 1. Condition Optimizations for the 4CR Synthesis of 5′rl{1,1,1,1}[a]



entry	solvent	3{l(1)} (equiv)	4{1}	cata.	t (h)	yield (%)[b]
1	MeOH	1.5	1.2	0.2	8	85
2	EtOH	1.5	1.2	0.2	8	78
3	DMSO	1.5	1.2	0.2	8	trace
4	DMF	1.5	1.2	0.2	8	trace
5	DCM	1.5	1.2	0.2	8	trace
6	MeOH	2	1.2	0.2	8	72
7	MeOH	1.4	1.2	0.2	8	90
8	MeOH	1.4	1.2	0.1	8	76
9	MeOH	1.4	1.2	0.3	8	82
10	MeOH	1.4	1.1	0.2	8	86
11	MeOH	1.4	1.3	0.2	8	85
12	MeOH	1.4	1.2	0.2	12	90
13[c]	MeOH	1.4	1.2	0.2	8	74

[a]Reaction was run with the following steps: (a) **1**{*1*} (0.2 mmol) and **2**{**r**(*1*)} (0.2 mmol) were added into 1 mL of solvent and kept at room temperature for 10 min; (b) **3**{**l**(*1*)}, **4**{*1*} and $Cu(OAc)_2·H_2O$ were added to the above mixture in sequence, and stirred at room temperature for desired time. [b]Isolated yield. [c]Reaction was carried out at 40 °C.

the synthesis of **5rr**{*1,1,1,1*} (Table 3). The 4CR mixture of **1**{*1*}, **2**{**r**(*1*)}, **3**{**r**(*1*)}, and **4**{*1*} did not become black and the yield of **5rr**{*1,1,1,1*} increased from trace to 80% in the presence of benzaldehyde (entry 1 in Table 3). Then, the amounts of benzaldehyde, **3**{**r**(*1*)} and **4**{*1*} were screened (entries 2−10) and 91% yield of **5rr**{*1,1,1,1*} was obtained (entry 7). The increase of the reaction time did not lead to the increase of **5rr**{*1,1,1,1*} (entry 11). Replacements of solvents (entries 12−15) and additives (entries 16−21) did not improve the yield of **5rr**{*1,1,1,1*}. Therefore, the optimal conditions of the 4CR for the synthesis of **5rr**{*1,1,1,1*} were **1**{*1*}/**2**{**r**(*1*)}/**3**{**r**(*1*)}/**4**{*1*}/benzylaldehyde/$Cu(OAc)_2·H_2O$ = 1:1:1.6:1.4:2:0.4 in methanol at room temperature for 6 h (entry 7). Under the optimal conditions, **5rr**{*1,1,1,1*} could precipitate from reactant solution in a pure form. Then, the addition orders of reactants, additive and catalyst were screened (Supporting Information Scheme S2). The suitable addition order is the order 5 (Supporting Information Scheme S2) as described in the footnote of Table 3.

Scope of the Copper/Benzaldehyde-Catalyzed 4CR for the Synthesis of Tetrasubstituted Dihydropyrroles 5 with Aryl R^3. As shown in Table 4, the optimal reaction conditions for the synthesis of **5rr**{*1,1,1,1*} are suitable to a wide scope of substrates for the 4CR synthesis of **5** with aryl R^2 and R^3 (**5rr**, entries 1−17) and with alkyl R^2 and aryl R^3 (**5lr**, entry 18 and 19). The ortho substituent on the R^2 phenyl ring shows a steric effect leading to a significant yield decrease of target products (comparing entries 2−4 in Table 4). The products **5rr** were obtained in good to excellent yields using electron-rich (entries 3 and 4) or weakly electron-poor (entries 6 and 7) aromatic amines as reactants **2** and **3** for the 4CR. Strongly electron-poor aromatic amines decrease the activity and yield of the 4CR significantly (entries 5 and 13). It is worth mentioning that target products could be obtained in moderate yields using 4-nitrobenzenamine as reactant **2** (entry 13), but only trace yield using 4-nitrobenzenamine as reactant **3**. The 4CRs could produce different products just by altering the added orders of aromatic amines (entries 8−11). Good yields of **5** with alky R^2 and aryl R^3, **5lr**{*1−2,1,1,1*}, were also obtained via the copper−benzaldehyde catalyzed 4CR (entries 18 and 19). Most of **5** in Table 4 precipitated from reactant solutions in a pure form. Similar to the copper-catalyzed 4CR for the synthesis of **5′rl** and **5ll** in Table 2, the copper−benzaldehyde-catalyzed 4CRs for the synthesis of **5rr** (R^2 = aryl) show higher activity and yields than those for the synthesis of **5lr** (R^2 = alkyl) (comparing entries 1 and 18 in Table 4). When aliphatic aldehyde, such as acetaldehyde, was used as reactant **4**, poor yield of pentasubstituted dihydropyrrole **6** with phenyl rather ethyl R^4 was obtained.

Dihydropyrroles **5** with aryl R^3 could be synthesized via the proton-promoted 4CR (Scheme 1)[11b] and the iodine-catalyzed 4CR.[16] The proton-promoted 4CR[11b] could afford target products in almost the same yields as the copper-catalyzed 4CR (entries 15−18 in Table 4), but much higher temperature (at 70 °C) and a greater amount (4 equiv) of reactants **3** were needed. The iodine-catalyzed 4CR was used to synthesize **5** with aryl R^3 in less than 83% yield with the limitation of R^2 and R^3 to the same phenyl and electron-rich aryl.[16]

Compared to the proton-promoted[11b] and the iodine-catalyzed[16] 4CRs, the copper-catalyzed 4CR not only realized the synthesis of novel series of **5′rl** but also is the most efficient method for the synthesis of diverse **5ll** and **5rr** except **5lr**. The proton-promoted one is the most suitable protocol for the synthesis of **5lr** in terms of the yields and the structural diversity of the products (Supporting Information Table S2).

All compounds **5** with alkyl R^3 (**5′rl** and **5ll**) in Table 2 and with aryl R^3 (**5rr** and **5lr**) in Table 4 show the ^1H NMR spectral characteristics of C2−H_2 (s, 3.9−4.2/4.4−4.6 ppm for R^3 = alkyl/aryl), N−H (b, 6.9−7.1 ppm for R^2 = alkyl; s, 8.0−8.2 ppm for R^2 = aryl), and CH_3CH_2O (q, 4.2 ppm; t, 1.3 ppm, J = 7.2 Hz) or CH_3O (s, 3.7−3.8 ppm), which are closely consistent with the single crystal structure of **5′rl**{*1,5,1,1*} (Figure 2).

Synthesis of Pentasubstituted Dihydropyrroles with Aryl R^3. To develop an efficient methodology for the synthesis of **6** with aryl R^3 (**6′lr** and **6′rr**), the condition optimizations of the 4CR for the synthesis of methyl 4-(benzylamino)-2,5-dihydro-5-oxo-1,2-diphenyl-1*H*-pyrrole-3-carboxylate **6′lr**{*1,1,1,2*} were first investigated (Table 5). Under the same conditions as those in entry 7 in Table 3 except without additives, **6′lr**{*1,1,1,2*} was obtained in only 25% yield (entries 1). Then, the amounts of aniline **3**{**r**(*1*)} and benzaldehyde **4**{*2*} were screened (entries 2−5), which led to the increase of **6′lr**{*1,1,1,2*} from 25% (entry 1) to 50% yield (entry 3). In order to increase yield, additives were screened (entries 6−13). Salicylic acid (2-HOC_6H_4COOH) was found to be the most suitable additive (entry 10). The amount optimization of salicylic acid (entries 10, 14 and 15) led to the increase of **6′lr**{*1,1,1,2*} to 69% (entry 14). Methanol is the most suitable solvent for the 4CR (Comparing entries 14 and 16−19) and 24 h is needed for the completion of the 4CR (comparing entries 14, 20, and 21). Therefore, the optimal conditions for the 4CR synthesis of **6′lr**{*1,1,1,2*} are those in entry 14, **1**{*1*}/**2**{**l**(*1*)}/**3**{**r**(*1*)}/**4**{*2*}/2-HOC_6H_4COOH/$Cu(OAc)_2·H_2O$ = 1:1:1.6:3.5:0.3:0.4 in methanol at room temperature for 24 h.

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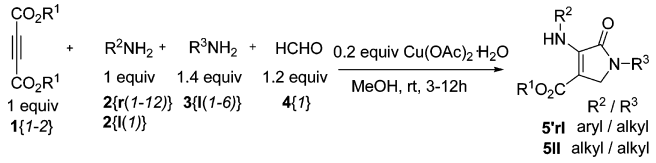
Table 2. Scope of the Copper-Catalyzed 4CRs for the Synthesis of 5 with Alkyl R^3[a]



entry	1	2	3	t /(h)	5	yield (%)[b]
1	*1*	**r**(*1*)	**l**(*1*)	8 (4)[c]	**5′rl**{*1,1,1,1*}	90 (68)[c]
2	*1*	**r**(*1*)	**l**(*2*)	6	**5′rl**{*1,1,2,1*}	72
3	*1*	**r**(*1*)	**l**(*3*)	8	**5′rl**{*1,1,3,1*}	80
4	*1*	**r**(*1*)	**l**(*4*)	9	**5′rl**{*1,1,4,1*}	80
5	*1*	**r**(*1*)	**l**(*5*)	3	**5′rl**{*1,1,5,1*}	75
6	*1*	**r**(*1*)	**l**(*6*)	9	**5′rl**{*1,1,6,1*}	60
7	*1*	**r**(*2*)	**l**(*1*)	8	**5′rl**{*1,2,1,1*}	82
8	*1*	**r**(*3*)	**l**(*1*)	10	**5′rl**{*1,3,1,1*}	80
9	*1*	**r**(*4*)	**l**(*1*)	8	**5′rl**{*1,4,1,1*}	75
10	*1*	**r**(*5*)	**l**(*1*)	10	**5′rl**{*1,5,1,1*}[d]	72
11	*1*	**r**(*6*)	**l**(*1*)	6	**5′rl**{*1,6,1,1*}	84
12	*1*	**r**(*7*)	**l**(*1*)	3	**5′rl**{*1,7,1,1*}	90
13	*1*	**r**(*8*)	**l**(*1*)	6	**5′rl**{*1,8,1,1*}	70
14	*1*	**r**(*9*)	**l**(*1*)	6	**5′rl**{*1,9,1,1*}	79
15	*1*	**r**(*10*)	**l**(*1*)	6	**5′rl**{*1,10,1,1*}	85
16	*1*	**r**(*11*)	**l**(*1*)	10	**5′rl**{*1,11,1,1*}	90
17	*1*	**r**(*4*)	**l**(*2*)	5	**5′rl**{*1,4,2,1*}	65
18	*1*	**r**(*5*)	**l**(*2*)	5	**5′rl**{*1,5,2,1*}	65
19	*1*	**r**(*9*)	**l**(*2*)	4	**5′rl**{*1,9,2,1*}	64
20	*1*	**r**(*10*)	**l**(*2*)	6	**5′rl**{*1,10,2,1*}	71
21	*1*	**r**(*3*)	**l**(*3*)	6	**5′rl**{*1,3,3,1*}	78
22	*1*	**r**(*4*)	**l**(*3*)	8	**5′rl**{*1,4,3,1*}	78
23	*1*	**r**(*5*)	**l**(*3*)	10	**5′rl**{*1,5,3,1*}	61
24	*1*	**r**(*8*)	**l**(*3*)	10	**5′rl**{*1,8,3,1*}	81
25	*2*	**r**(*12*)	**l**(*1*)	12	**5′rl**{*2,12,1,1*}	56
26	*2*	**r**(*4*)	**l**(*2*)	5	**5′rl**{*2,4,2,1*}	67
27	*1*	**l**(*1*)	**l**(*1*)	9	**5ll**{*1,1,1,1*}	83
28	*2*	**l**(*1*)	**l**(*1*)	10 (70 °C, 8)[e]	**5ll**{*2,1,1,1*}	80 (86)[e]

[a]All reactions were run with the following steps: (a) **1** (1 mmol) and **2** (1 mmol) were added into 5 mL of MeOH, kept at room temperature for 10−30 min; (b) **3** (1.4 mmol), 38% **4**{*1*} (96 μL, 1.2 mmol) and $Cu(OAc)_2·H_2O$ (40 mg, 0.2 mmol) were dropwise added into the above mixture in sequence, and stirred at room temperature for desired time. [b]Isolated yield. [c]The only dihydropyrrole **5′** synthesized via the recently reported iodine-catalyzed 4CR.[16] [d]The structure of **5′rl**{*1,5,1,1*} was confirmed by single-crystal X-ray diffraction analysis (Figure 2). [e]The data in parentheses refer to those in our previous work.[11b]

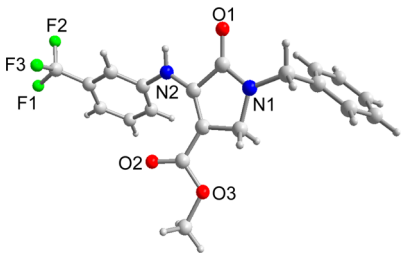


Figure 2. Single-Crystal Structure of **5′rl**{*1,5,1,1*} (CCDC 850812).[19]

Under the optimal conditions, the addition orders and time of reactants, additive and catalyst were screened (Supporting Information Scheme S3). The suitable addition order and time are those in the procedure 2 (Supporting Information Scheme S3) as described in the footnote of Table 5. It is worth noting that the mixture of **1**{*1*} and **2**{**l**(*1*)} in methanol needed to keep for 30 min at room temperature or for 10 min in a cold water bath (procedure 2 in Supporting Information Scheme S3) for decreasing the mixture temperature to room temperature because the mixing of **1**{*1*} and **2**{**l**(*1*)} in methanol would release a large amount of heat. Otherwise, only 48% yield of **6′lr**{*1,1,1,2*} would be obtained (procedure 3 in Supporting Information Scheme S3).

Scope of the Copper-Salicylic Acid Catalyzed 4CR for the Synthesis of Pentasubstituted Dihydropyrroles (6). Under the optimal reaction conditions (entry 14 in Table 5), the scope of the 4CRs for the synthesis of **6** was investigated. As shown in Table 6, both aliphatic and aromatic amines can be used as reactants **2** (R^2NH_2) and **3** (R^3NH_2). Not only pentasubstituted dihydropyrroles **6** with R^2/ R^3 = alkyl/aryl (**6′lr**, entries 1−17) and aryl/aryl (**6′rr**, entries 18−29) but also R^2/R^3 = alkyl/alkyl (**6ll**, entry 30) and aryl/alkyl (**6rl**, entry 31) were successfully synthesized under the optimal conditions. Four target products would be obtained using one aromatic and one aliphatic amines as reactants **2** and **3** (entries 17, 28, 30, and 31).

Weakly electron-withdrawing/donating substituents on the aromatic ring of the aromatic amines show no significant influence on the 4CR (entries 3, 5, 6, and 8 in Table 6). Aromatic amines with strongly electron-withdrawn substituents, such as 4-nitrobenzenamine, could also form **6** in moderate

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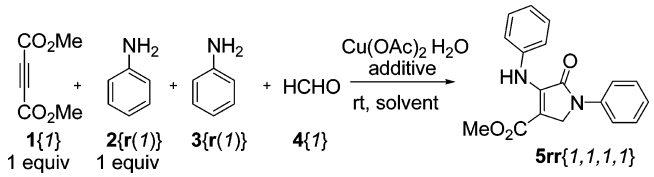
Table 3. Condition Optimizations for the 4CR Synthesis of 5rr{*1,1,1,1*}[a]



entry	solvent	3{r(*1*)} (equiv)	4{*1*}	Cu[b]	additive (equiv)	*t* (h)	yield (%)[c]
1	MeOH	1.5	1.4	0.2	PhCHO 1.5	6	80
2	MeOH	1.5	1.4	0.4	PhCHO 1.5	6	84
3	MeOH	1.5	1.4	0.6	PhCHO 1.5	6	81
4	MeOH	1.5	1.4	0.4	PhCHO 1.0	6	83
5	MeOH	1.5	1.4	0.4	PhCHO 2.0	6	85
6	MeOH	1.5	1.4	0.4	PhCHO 2.5	6	81
7	MeOH	1.6	1.4	0.4	PhCHO 2.0	6	91
8	MeOH	1.7	1.4	0.4	PhCHO 2.0	6	82
9	MeOH	1.6	1.3	0.4	PhCHO 2.0	6	81
10	MeOH	1.6	1.5	0.4	PhCHO 2.0	6	84
11	MeOH	1.6	1.4	0.4	PhCHO 2.0	12	91
12	EtOH	1.6	1.4	0.4	PhCHO 2.0	6	72
13	DMSO	1.6	1.4	0.4	PhCHO 2.0	6	30
14	DMF	1.6	1.4	0.4	PhCHO 2.0	6	35
15	DCM	1.6	1.4	0.4	PhCHO 2.0	6	60
16	MeOH	1.6	1.4	0.4	4-$NO_2C_6H_4CHO$ 2.0	6	40
17	MeOH	1.6	1.4	0.4	Vanillin 2.0	6	89
18	MeOH	1.6	1.4	0.4	Pentanal 2.0	6	32
19	MeOH	1.6	1.4	0.4	HOAc 2.0	6	20
20	MeOH	1.6	1.4	0.4	L-proline 2.0	6	69
21	MeOH	1.6	1.4	0.4	$N(Et)_3$ 2.0	6	16

[a]Reaction was run with the following steps: (a) **1**{*1*} (0.2 mmol) and **2**{**r**(*1*)} (0.2 mmol) were added into 1 mL of solvent and kept at room temperature for 10 min; (b) **3**{**r**(*1*)}, **4**{*1*}, additive and $Cu(OAc)_2{\cdot}H_2O$ were added to the above mixture in sequence, and stirred at room temperature for desired time. [b]Cu: $Cu(OAc)_2{\cdot}H_2O$. [c]Isolated yield.

yields (entries 12). Chain aliphatic amines afford higher yields than cyclic or phenyl substituted ones (comparing entries 3, 9, and 11), which may result from steric effect. Similar to the copper-catalyzed 4CR for the synthesis of **5** in Tables 2 and 4, the copper−salicylic acid catalyzed 4CRs for the synthesis of **6** with aryl R^2 (**6′rr** and **6rl** in good to excellent yields for 12 h, entries 18−29 and 31) show higher activity and yield than those with alkyl R^2 (**6′lr** and **6ll** in moderate to good yields for 24 h, entries 1−17 and 30). *O*-toluidine hinders the formation of **6**.

Aromatic aldehydes with strongly electron-withdrawing substituents, such as NO_2−, afford desired product in much higher yields (entry 26) than those with strongly electron-donating substituent HO− (entry 27). Substitution of methyl in **1**{*1*} with ethyl shows no significant influence on the 4CR (entries 1 and 17). Complex products were observed using aliphatic aldehydes as reactant **4**.

As shown in Scheme 1, the heat-promoted 4CR could afford diverse pentasubstituted dihydropyrroles **6rl** and **6ll** in good to excellent yields but met difficulty for the synthesis of **6′lr** and **6′rr**.[11b] We had tried to prepare **6′lr** and **6′rr** by adding a Bronsted acid. No or complex **6′lr** were afforded. Although **6′rr**{*2,4,4,2*} (entry 29 in Table 6) was obtained in ideal yields in the presence of acetic acid (2 equiv) in ethanol at 70 °C for 24 h,[11b] complex products were obtained when the heat and proton-promoted 4CR was carried out for the synthesis of other several pentasubstituted dihydropyrroles **6′rr**, such as **6′rr**{*1,1,1,2*} (entry 18) and **6′rr**{*1,5,5,2*} (entry 21). Therefore, only **6′rr**{*2,4,4,2*} (entry 29) were reported in our previous work.[11b] Compared with the heat-promoted 4CR for the synthesis of **6** (Scheme 1),[11b] the copper-catalyzed 4CR broadens the permutation and combination of reactants **2** and **3** yielding two novel series of **6′lr** and **6′rr** under mild conditions. In addition, the copper-catalyzed 4CR for the synthesis of **6ll** (entry 30 in Table 6) and **6rl** (entry 31) could proceed at lower temperature (70 °C to rt) for shorter time in good to excellent yields. Therefore, the copper-catalyzed 4CR could not only be an efficient method for the synthesis of tow novel series of **6′lr** and **6′rr** but also be used as an alternative methodology for the preparation of the series of **6rl** and **6ll**.

All compounds **6** in Table 6 show the ^1H NMR spectral characteristics of C2−H (s, 5.1−5.9 ppm), N−H (b, 6.9−7.3 ppm for R^2 = alkyl; s, 8.1−8.3 ppm for R^2 = aryl) and CH_3CH_2O (q, 4.0 ppm; t, 1.0 ppm, J = 7.2 Hz) or CH_3O (s, 3.5−3.6 ppm), which are closely consistent with the single-crystal structure of **6′rr**{*2,4,4,2*}.[11b]

Possible Mechanism of the Copper(II)-Catalyzed 4CR for the Synthesis of 5 and 6. According to our previous studies[11b,18] and the experiment results mentioned above, we proposed a possible mechanism for the 4CRs. As shown in Scheme 2, the copper-catalyzed 4CRs proceed three elementary steps: hydroamination/amidation/intramolecular cyclization. The hydroamination of **1** and **2** could complete in 10−30 min and give *Z*- and *E*-isomers **7** in greater than 98% yields.[18] It is expected that the condensation reactions of primary amines **3** and aldehydes **4** would take place fast under the catalysis of Cu(II) and lead to the formation of intermediates **8**. As we discussed in our previous work,[11b] both intermediates **7** and **8**

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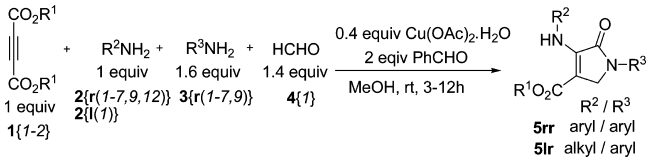
Table 4. Scope of the Copper-Benzaldehyde Catalyzed 4CRs for the Synthesis of 5 with Aryl R^3[a]



entry	1	2	3	t (h)	5	yield (%)[b]
1	*1*	r(*1*)	r(*1*)	6	5rr{*1,1,1,1*}	91 (82)[c]
2	*1*	r(*2*)	r(*2*)	8	5rr{*1,2,2,1*}	57
3	*1*	r(*3*)	r(*3*)	4	5rr{*1,3,3,1*}	95
4	*1*	r(*4*)	r(*4*)	4	5rr{*1,4,4,1*}	81 (78)[c]
5	*1*	r(*5*)	r(*5*)	8	5rr{*1,5,5,1*}	75
6	*1*	r(*7*)	r(*7*)	3	5rr{*1,7,7,1*}	86 (81)[c]
7	*1*	r(*9*)	r(*9*)	3	5rr{*1,9,9,1*}	90 (83)[c]
8	*1*	r(*4*)	r(*1*)	5	5rr{*1,4,1,1*}	80
9	*1*	r(*1*)	r(*4*)	5	5rr{*1,1,4,1*}	82
10	*1*	r(*5*)	r(*4*)	3	5rr{*1,5,4,1*}	68
11	*1*	r(*4*)	r(*5*)	7	5rr{*1,4,5,1*}	70
12	*1*	r(*9*)	r(*4*)	5	5rr{*1,9,4,1*}	84
13	*1*	r(*12*)	r(*1*)	12	5rr{*1,12,1,1*}	58
14	*2*	r(*1*)	r(*1*)	5 (1)[c] (70 °C, 4)[d]	5rr{*2,1,1,1*}	85 (81)[c] (85)[d]
15	*2*	r(*4*)	r(*4*)	4 (70 °C, 4)[d]	5rr{*2,4,4,1*}	78 (86)[d]
16	*2*	r(*9*)	r(*9*)	4 (70 °C, 4)[d]	5rr{*2,9,9,1*}	83 (89)[d]
17	*2*	r(*6*)	r(*6*)	4 (70 °C, 4)[d]	5rr{*2,6,6,1*}	89 (87)[d]
18	*1*	l(*1*)	r(*1*)	8 (1)[c] (70 °C, 0.5)[d]	5lr{*1,1,1,1*}	75 (83)[c] (89)[d]
19	*2*	l(*1*)	r(*1*)	8 (70 °C, 0.5)[d]	5lr{*2,1,1,1*}	76 (90)[d]

[a]All reactions were run with the following steps: (a) **1** (1 mmol) and **2** (1 mmol) were added into 5 mL of MeOH, kept at room temperature for 10−30 min; (b) **3** (1.6 mmol), 38% **4**{*1*} (112 μL, 1.4 mmol), benzaldehyde (212 mg, 2 mmol), and $Cu(OAc)_2·H_2O$ (80 mg, 0.4 mmol) were dropwise added into the above mixture in sequence and stirred at room temperature for desired time. [b]Isolated yield. [c]The data in parentheses refer to those in the recently reported iodine-catalyzed 4CR.[16] [d]The data in parentheses refer to those in our previous work.[11b]

have two possible reaction centers, and the reaction of **7** and **8** would take place between different reaction centers under different conditions: between the electron-rich center C_3 in **7** and the electron-deficient center imine C in **8** (aza-ene-type reaction represented by dashed arrows in Scheme 2) or between electron-deficient center C_1 in **7** and electron-rich center imine N in **8** (amidation reaction represented by solid arrows between **7** and **8** in Scheme 2).[11b] It could be deduced that **7** and **8** undergo an amidation reaction rather than aza-ene-type reaction under the catalysis of copper because aryl R^2 favors the former but alkyl R^2 favors the latter and **5** or **6** with aryl R^2 were prepared in higher yields and shorter time than those with alkyl R^2 (comparing entries 1 and 27, 1 and 18, as well as 1 and 18 in Table 2, 4 and 6, respectively.). Therefore, Cu(II) is expected to coordinate with electron-rich O in **7** (solid bond between Cu and O in Scheme 2) rather than electron-rich N in **8** (dashed bond between Cu and N in Scheme 2). The intermediates **7** coordinated with copper show high electrophilic activity and could react with various imines **8** under mild conditions, affording high active intermediates **9** and followed with the formation of **10** via intramolecular cyclization. Finally, target products **5** or **6** were obtained thorough the imine-enamine tautomerization.

It is worth mentioning that the mixture of copper(II) and aniline would become dark black and turbid in 10 min. This case is similar to the above-mentioned copper-catalyzed 4CR for the synthesis of **5rr**{*1,1,1,1*} in the absence of benzaldehyde. However, the 4CR mixture in the presence of benzaldehyde as well as the mixture of aniline, benzaldehyde and copper(II) are clear. These experimental results indicate that aniline can be oxidized to black complex compounds by copper(II) in methanol at room temperature and that benzaldehyde can efficiently prevent the oxidation by forming imine with aniline. Since the reaction of aniline and benzaldehyde is reversible, the reaction product imine can transform into aniline to afford reactant **3** needed for the 4CR, which well explain why the copper−benzaldehyde-catalyzed 4CRs in Table 4 could successfully afford target products instead of black mixture in the presence of excess aromatic amines.

■ CONCLUSION

We have developed the 4CRs of but-2-ynedioates **1**, primary amines **2**, primary amines **3**, and aldehydes **4** for the synthesis of diverse tetra- and pentasubstituted functional dihydropyrroles **5** and **6** via using air and water-stable, inexpensive and low toxic $Cu(OAc)_2·H_2O$ as catalyst. The copper-catalyzed 4CRs could produce all four permutation-combination series of **5**/**6** at room temperature in good to excellent yields when using aromatic and aliphatic amines as reactants **2** and **3**, respectively. Compared with the proton-promoted[11b] and the iodine-catalyzed[16] 4CRs for the synthesis of tetrasubstituted dihydropyrroles **5**, the present copper-catalyzed 4CR not only realized the synthesis of the novel permutation-combination series of **5′rl** (R^2/R^3 = aryl/alkyl) but also is the most efficient method for the synthesis of diverse **5ll** and **5rr** (R^2/R^3 = alkyl/alkyl and aryl/aryl, respectively) except **5lr** (R^2/R^3 = alkyl/aryl) in terms of the yields and the structure diversity of target products. The most suitable protocol for the synthesis of **5lr** is the proton-promoted one. Compared with the heat-promoted 4CR for the synthesis of pentasubstituted dihydropyrroles **6**,[11b] the copper-catalyzed 4CR broadens the permutation and

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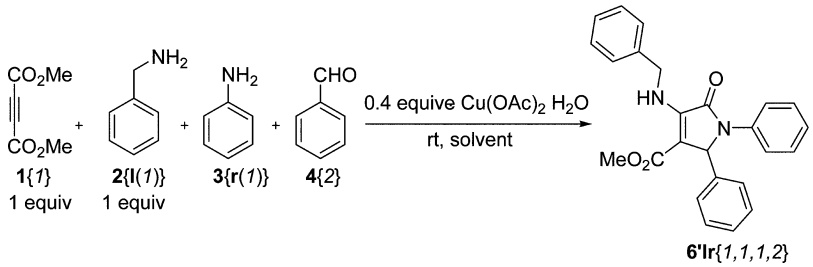
Table 5. Condition Optimizations for the 4CR Synthesis of 6′lr{*1,1,1,2*}[a]



entry	solvent	3{r(*1*)} (equiv)	4{*2*}	additive	*t* (h)	yield (%)[b]
1	MeOH	1.6	1.4		24	25
2	MeOH	1.6	2.0		24	40
3	MeOH	1.6	3.5		24	50
4	MeOH	1.6	4.0		24	45
5	MeOH	2.0	3.5		24	50
6	MeOH	2.0	3.5	HOAc (0.2)	24	48
7	MeOH	2.0	3.5	F_3CCOOH (3d)	24	56
8	MeOH	2.0	3.5	tartaric acid (0.2)	24	30
9	MeOH	2.0	3.5	5-sulfosalicylic acid (0.2)	24	60
10	MeOH	2.0	3.5	salicylic acid (0.2)	24	62
11	MeOH	2.0	3.5	$P(Ph)_3$ (0.2)	24	42
12	MeOH	2.5	3.5	$N(Et)_3$ (0.2)	24	30
13	MeOH	2.5	3.5	salicylic acid (0.2)/$P(Ph)_3$ (0.2)	24	48
14	MeOH	2.0	3.5	salicylic acid (0.3)	24	69
15	MeOH	2.0	3.5	salicylic acid (0.4)	24	67
16	EtOH	2.0	3.5	salicylic acid (0.3)	24	65
17	DMSO	2.0	3.5	salicylic acid (0.3)	24	trace
18	DMF	2.0	3.5	salicylic acid (0.3)	24	trace
19	DCM	2.0	3.5	salicylic acid (0.3)	24	30
20	MeOH	2.0	3.5	salicylic acid (0.3)	12	40
21	MeOH	2.0	3.5	salicylic acid (0.3)	36	69

[a]Reaction was run with the following steps: (a) 1{*1*} (0.2 mmol) and 2{l(*1*)} (0.2 mmol) were added into test tube A with 0.5 mL of solvent and kept at room temperature for 30 min or in cold water bath for 10 min; (b) 3{r(*1*)}, 4{*2*}, additive, and $Cu(OAc)_2{\cdot}H_2O$ were added to test tube B with 1 mL of solvent, then the mixture in tube B was added into the above mixture in tube A, and stirred at room temperature for desired time. [b]Isolated yield.

combination of aromatic and aliphatic amines **2** and **3** yielding two new permutation-combination series of **6′lr** and **6′rr** (R^2/R^3 = alkyl/aryl and aryl/aryl, respectively) under mild conditions. In addition, the copper-catalyzed 4CR could be used as an alternative methodology for the preparation of the two permutation-combination series of **6ll** and **6rl** (R^2/R^3 = alkyl/alkyl and aryl/alkyl, respectively) because it proceed at lower temperature (rt to 70 °C) in shorter or the same long time in good to excellent yields.

In addition, it was found (i) benzaldehyde, besides being used as a useful reactant for the synthesis of pentasubstituted dihydropyrroles **6**, was an excellent additive for preventing the oxidation of aromatic amines with copper(II) and ensuring the sooth conduct of the 4CRs for the synthesis of tetrasubstituted dihydropyrroles **5** with aryl R^3 (**5rr** and **5lr**); (ii) salicylic acid was needed to increase the activities and yields of the 4CRs for the synthesis of **6**. Basing on experimental results, the enamination/amidation/intramolecular cyclization mechanism was proposed and amidation is expected to be the rate-limited step in the copper-catalyzed 4CRs.

We believe that the convenient and efficient copper-catalyze 4CRs, the mechanism and the interesting additives described here will be helpful for practical application and new protocol design. Further investigations into the asymmetric synthesis of **6** and their biological activities are ongoing in our laboratory.

EXPERIMENTAL PROCEDURES

Materials and Instrumentation. All melting points were taken on a XT-4 micro melting point apparatus and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer and respectively referenced to 7.24 and 77.0 ppm for chloroform-*d* with TMS as internal standard. Mass spectra were recorded on an API 4000QTRAP or on a MAT 95XP. IR spectra were obtained as potassium bromide pellets or as liquid films on potassium bromide pellets with a Bruker Vector 22 spectrometer. Elemental analysis was performed by using an elemental analyzer Vario EL cube. TLC was performed using commercially prepared 100−400 mesh silica gel plates (GF254), and visualization was effected at 254 and 365 nm. All the other chemicals were purchased from Aldrich Chemicals.

General Procedure for the Synthesis of Tetrasubstituted Polyfunctional Dihydropyrroles 5 with Alkyl R^3 in Table 2. All reactions were run with the following steps: (a) but-2-ynedioates **1** (1 mmol) and aromatic/aliphatic primary amines **2** (1 mmol) were added into 5 mL of MeOH, kept at room temperature for 10−30 min; (b) aliphatic primary amines **3** (1.4 mmol), 38% formaldehyde 4{*1*} (96 μL, 1.2 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (40 mg, 0.2 mmol) were dropwise added into the above mixture in sequence, and stirred at room temperature

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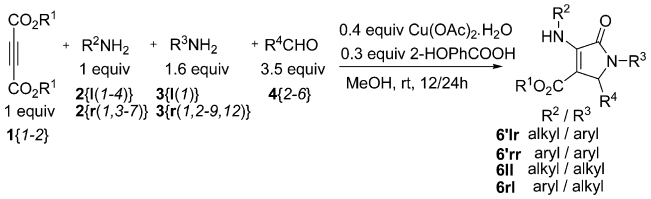
Table 6. Scope of the Copper-Salicylic Acid-Catalyzed 4CRs for the Synthesis of 6[a]



entry	1	2	3	4	t (h)	product	yield (%)[b]
1	*1*	**l**(*1*)	**r**(*1*)	*2*	24	**6′lr**{*1,1,1,2*}	69
2	*1*	**l**(*1*)	**r**(*3*)	*2*	24	**6′lr**{*1,1,3,2*}	60
3	*1*	**l**(*1*)	**r**(*4*)	*2*	24	**6′lr**{*1,1,4,2*}	70
4	*1*	**l**(*1*)	**r**(*5*)	*2*	24	**6′lr**{*1,1,5,2*}	61
5	*1*	**l**(*1*)	**r**(*6*)	*2*	24	**6′lr**{*1,1,6,2*}	75
6	*1*	**l**(*1*)	**r**(*7*)	*2*	24	**6′lr**{*1,1,7,2*}	73
7	*1*	**l**(*1*)	**r**(*8*)	*2*	24	**6′lr**{*1,1,8,2*}	65
8	*1*	**l**(*1*)	**r**(*9*)	*2*	24	**6′lr**{*1,1,9,2*}	75
9	*1*	**l**(*2*)	**r**(*4*)	*2*	24	**6′lr**{*1,2,4,2*}	85
10	*1*	**l**(*3*)	**r**(*3*)	*2*	24	**6′lr**{*1,3,3,2*}	72
11	*1*	**l**(*3*)	**r**(*4*)	*2*	24	**6′lr**{*1,3,4,2*}	73
12	*1*	**l**(*3*)	**r**(*12*)	*2*	24	**6′lr**{*1,3,12,2*}	53
13	*1*	**l**(*1*)	**r**(*1*)	*3*	24	**6′lr**{*1,1,1,3*}	60
14	*1*	**l**(*2*)	**r**(*1*)	*4*	24	**6′lr**{*1,2,1,4*}	52
15	*1*	**l**(*3*)	**r**(*1*)	*4*	24	**6′lr**{*1,3,1,4*}	46
16	*1*	**l**(*3*)	**r**(*4*)	*4*	24	**6′lr**{*1,3,4,4*}	40
17	*2*	**l**(*1*)	**r**(*1*)	*2*	24	**6′lr**{*2,1,1,2*}	75
18	*1*	**r**(*1*)	**r**(*1*)	*2*	12	**6′rr**{*1,1,1,2*}	92
19	*1*	**r**(*3*)	**r**(*3*)	*2*	12	**6′rr**{*1,3,3,2*}	87
20	*1*	**r**(*4*)	**r**(*4*)	*2*	12	**6′rr**{*1,4,4,2*}	88
21	*1*	**r**(*5*)	**r**(*5*)	*2*	12	**6′rr**{*1,5,5,2*}	83
22	*1*	**r**(*6*)	**r**(*6*)	*2*	12	**6′rr**{*1,6,6,2*}	90
23	*1*	**r**(*7*)	**r**(*7*)	*2*	12	**6′rr**{*1,7,7,2*}	84
24	*1*	**r**(*1*)	**r**(*1*)	*3*	12	**6′rr**{*1,1,1,3*}	64
25	*1*	**r**(*1*)	**r**(*1*)	*4*	12	**6′rr**{*1,1,1,4*}	83
26	*1*	**r**(*1*)	**r**(*1*)	*5*	12	**6′rr**{*1,1,1,5*}	86
27	*1*	**r**(*1*)	**r**(*1*)	*6*	12	**6′rr**{*1,1,1,6*}	49
28	*2*	**r**(*1*)	**r**(*1*)	*2*	12	**6′rr**{*2,1,1,2*}[15a]	90
29	*2*	**r**(*4*)	**r**(*4*)	*2*	12 (70 °C, 4)[c]	**6′rr**{*2,4,4,2*}	93 (92)[c]
30	*2*	**l**(*1*)	**l**(*1*)	*2*	24 (70 °C,24)[c]	**6ll**{*2,1,1,2*}	65 (86)[c]
31	*2*	**r**(*1*)	**l**(*1*)	*2*	12 (70 °C,16)[c]	**6rl**{*2,1,1,2*}	81 (87)[c]

[a]All of reactions were run with the following steps: (a) **1** (1 mmol) and **2** (1 mmol) were added into test tube A with 3 mL of MeOH and kept at room temperature for 30 min; (b) **3** (1.6 mmol), **4** (3.5 mmol), salicylic acid (41 mg, 0.3 mmol), and $Cu(OAc)_2·H_2O$ (80 mg, 0.4 mmol) were added into test tube B with 3 mL of MeOH, then the mixture in tube B was added into the above mixture in tube A, and stirred at room temperature for desired time. [b]Isolated yield. [c]The data in parentheses refer to those in our previous work.[11b]

for desired time (monitored by TLC). After the reactions were completed, the product mixtures were purified by preparative TLC with petroleum ether-ethyl acetate (6:1−1:1) as eluent to afford the desired products **5′rl** and **5ll** in 56−90% yields (Table 2).

General Procedure for the Synthesis of Tetrasubstituted Polyfunctional Dihydropyrroles 5 with Aryl R^3 in Table 4. All reactions were run with the following steps: (a) but-2-ynedioates **1** (1 mmol) and aromatic/aliphatic primary amines **2** (1 mmol) were added into 5 mL of MeOH, kept at room temperature for 10−30 min; (b) aromatic primary amines **3** (1.6 mmol), 38% formaldehyde **4**{*1*} (112 μL, 1.4 mmol), benzaldehyde (212 mg, 2 mmol), and $Cu(OAc)_2·H_2O$ (80 mg, 0.4 mmol) were dropwise added into the above mixture in sequence, and stirred at room temperature for desired time (monitored by TLC). After the reactions were completed, the product mixtures were purified by preparative TLC with petroleum ether-ethyl acetate (6:1−1:1) as eluent to afford the desired products **5rr** and **5lr** in 57−95% yields (Table 4).

General Procedure for Synthesis of the Pentasubstituted Polyfunctional Dihydropyrroles 6 in Table 6. All of reactions were run with the following steps: (a) but-2-ynedioates **1** (1 mmol) and aromatic/aliphatic primary amines **2** (1 mmol) were added into test tube A with 3 mL of MeOH and kept at room temperature for 30 min; (b) aromatic/aliphatic primary amines **3** (1.6 mmol), aromatic aldehydes **4** (3.5 mmol), salicylic acid (41 mg, 0.3 mmol), and $Cu(OAc)_2·H_2O$ (80 mg, 0.4 mmol) were added into test tube B with 3 mL of MeOH, then the mixture in tube B was added into the above mixture in tube A, and stirred at room temperature for desired time (monitored by TLC). After the reactions were completed, the product mixtures were purified by preparative TLC with petroleum ether-ethyl acetate (6:1−

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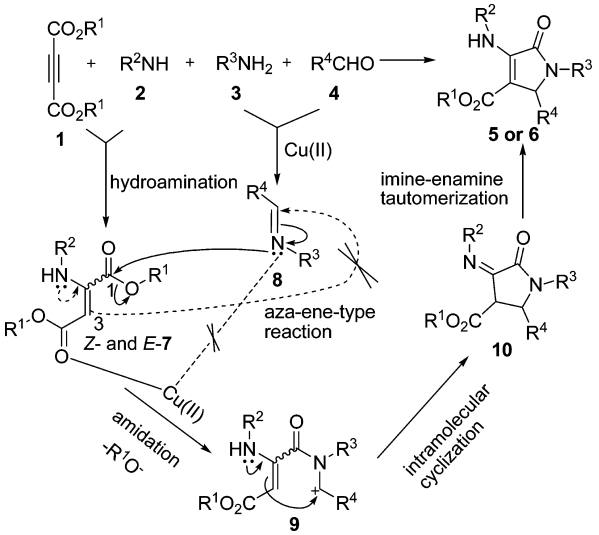
Scheme 2. Proposed Mechanism of the Copper-Catalyzed 4CR for the Synthesis of Tetra- and Pentasubstituted Polyfunctional Dihydropyrroles 5 and 6



1:1) as eluent to afford the desired products **6′lr**, **6′rr**, **6ll**, and **6rl** in 40−93% yields (Table 6).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, Tables S1−S3, Schemes S1−S3, crystallographic data for **5′rl**{*1,5,1,1*}, spectroscopic data, and ^{1}H NMR and ^{13}C NMR spectra for polyfunctional tetra- and pentasubstituted dihydropyrroles **5** and **6**. This information is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

†Longyun Lv and Sichao Zheng contributed equally to this paper. Q.Z. conceived and designed the experiments, Q.Z. and S.L. wrote the manuscript, Q.Z., L.L. and S.Z. wrote the Supporting Information. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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