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Copper–Catalyzed Multicomponent Reactions for Efficient Synthesis of Diverse Spirotetrahydrocarbazoles

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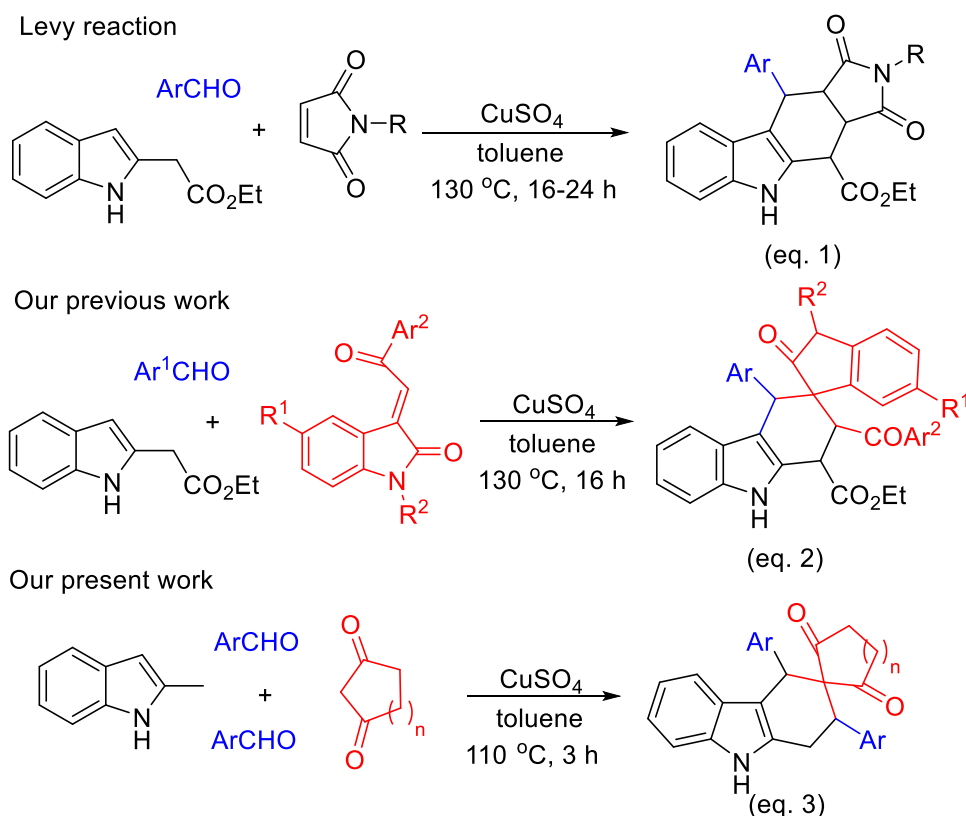*Corresponding author: Chao-Guo Yan: cgyan@yzu.edu.cn

Abstract

In the presence of copper sulphate, the three or four-component reactions of 2-methylindole, aromatic aldehydes and various cyclic dienophiles in refluxing toluene afforded diverse spirotetrahydrocarbazoles. This reaction is a important development of Levy reaction by using 2-methylindole to replacing ethyl indole-2-acetate and successfully provided facile access to important polysubstituted spiro[carbazole-3,3'-indolines], spiro[carbazole-2,3'-indolines], spiro[carbazole-3,5'-pyrimidines] and spiro[carbazole-3,1'-cycloalkanes] in satisfactory yields and with high diastereoselectivity.

Keywords

Tetrahydrocarbazole; indole; spirooxindole; indolo-2,3-quinodimethane; Diels-Alder reaction. Levy reaction.

Introduction

Tetrahydrocarbazole is one of the most privileged heterocyclic core structures. It widely existed in various naturally occurring alkaloids and pharmacologically active compounds exhibiting important bioactivities such as anti-tumor activity, anti-protein kinase C activity [1-3]. Additionally, the corresponding carbazole derivatives also showed important applications in various functional materials [4-7]. Owing to their remarkable significance, developing convenient synthetic protocols for functionalized tetrahydrocarbazoles has attracted continual attention in the synthetic and pharmaceutical chemistry [8-15]. Among many well-designed strategies for synthesis of tetrahydrocarbazoles, direct assembly the tetrahydrocyclohexenyl ring with readily available functionalized indoles as the precursors has proven to be one of the most efficient synthetic protocols [16-21]. Therefore, many [4+2] reactions of 3-vinylindolines or 2-vinylindolines with diverse dienophiles have been successfully developed for the synthesis of many tetrahydrocarbazole and carbazole derivatives [22-50]. On the other hand, Diels-alder reaction of the *in situ* generated indole-2,3-quinodimethanes with various dienophiles is also the powerful method for rapid construction of functionalized tetrahydrocarbazoles [51-69]. In this respect, Levy reported a copper catalyzed three-component reaction of aromatic aldehydes, ethyl indole-2-acetate and N-alkylmaleimides to efficient construction of polycyclic tetrahydrocarbazoles, in which indolo-2,3-quinodimethane intermediate was initially generated and sequentially underwent [4+2] cycloaddition reaction (eq. 1 in Scheme 1) [70-75]. This metal catalyzed one-pot reaction not only combined the advantages of traditional Diels-Alder reaction and the recent developed multicomponent reactions, but also meet the goal of green and sustainable chemistry. Recently, we have reported efficient construction of series of the heterocyclic spiro compounds including

Levy reaction

ArCHO

$$+$$

$$\xrightarrow[\substack{\text{toluene}\\ 130\ ^{\circ}\text{C, 16-24 h}}]{\text{CuSO}_4}$$

(eq. 1)

Our previous work

Ar^1CHO

$$+$$

$$\xrightarrow[\substack{\text{toluene}\\ 130\ ^{\circ}\text{C, 16 h}}]{\text{CuSO}_4}$$

(eq. 2)

Our present work

ArCHO

$$+$$

ArCHO

$$\xrightarrow[\substack{\text{toluene}\\ 110\ ^{\circ}\text{C, 3 h}}]{\text{CuSO}_4}$$

(eq. 3)

**Scheme 1** Construction of diverse tetrahydrocarbazoles via Levy-type reaction.

tetrahydrospiro[carbazole-3,3'-indolines] by using Levy three-component reaction of indole-2-acetate, aromatic aldehydes and various cyclic dienophiles such as 3-phenacylideneoxindoles (eq. 2 in Scheme 1) [76-78]. It was noticed that only ethyl indole-2-acetates was successfully employed as the precursors to generate active indolo-2,3-quinodimethane intermediate in Levy reaction, which greatly limited its practical synthetic values. We envisioned that other substituted indoles without electron-withdrawing activating groups could be employed in Levy reaction, which will greatly developed the potential synthetic applications of Levy-type reaction. Herein we wish to report a Levy-type reaction by using readily available 2-methylindole to replace ethyl indole-2-acetate for the efficient synthesis of diverse spiro tetrahydrocarbazoles. In the presence of CuSO₄, the multicomponent reactions of aromatic aldehydes, 2-methylindole and various cyclic dieneophiles such as 3-phenacylideneoxindoles, isatylidene malononitriles and the *in situ* generated 5-arylidene-1,3-dimethylbarbituric

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acids or 2-arylidene-1,3-ketones efficiently afforded diverse cyclic spirotetrahydrocarbazoles in good yields and with high diastereoselectivity (eq. 3 in Scheme 1).

Results and Discussion

Initially, (*E*)-1-benzyl-3-(2-oxo-2-phenylethylidene)indolin-2-one, benzaldehyde, and 2-methylindole was served as model substrates for optimization of reaction conditions. Inspired by our previous work,[15] we first screened different catalysts (entries 1−5) with toluene as the solvent and found that CuSO₄ was the best choice, providing **1a** in 58% isolated yield. Notably, the yield of the byproduct **1a'** was also obtained in less than 5% yield, which indicated the high diastereoselectivity of this reaction. Several other solvents such as EtOH and MeCN were explored, the product **1a** was formed in lower yields (entries 6-7). Importantly, the reaction also proceeded smoothly when the temperature was reduced to 90 °C and with better yield at 110 °C (entries 8-9). Moreover, different reaction times and the catalyst loadings were also examined (entries 10 and 11-12), but no better results were observed. Therefore, a mixture of 2-methylindole (0.5 mmol), benzaldehyde (1.2 equiv.), and 3-methyleneoxindole (1.0 equiv.) with CuSO₄ (0.1 mmol) as the catalyst in toluene (10.0 mL) reacting at 110 °C for 3 h were selected as the optimal reaction conditions.

Table 1 Optimization of reaction conditions[a]
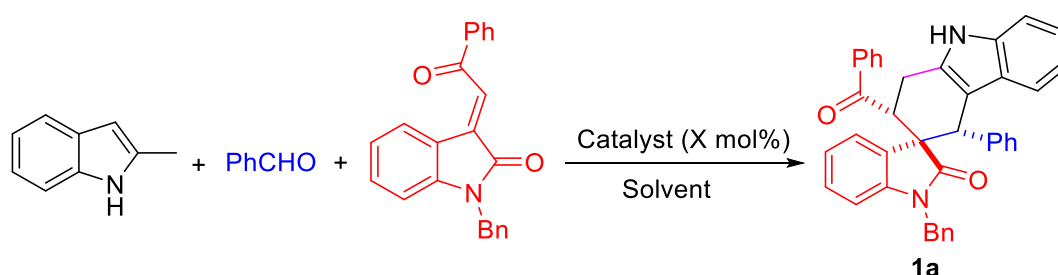
Entry	catalyst	Solvent	Time (h)	Temp (°C)	Yield (%)[b]

1	FeCl$_3$	Toluene	3	130	<10
2	CuI	Toluene	3	130	<10
3	Cu(OTf)$_2$	Toluene	3	130	30
4	Cu(OAc)$_2$	Toluene	3	130	25
5	CuSO$_4$	Toluene	3	130	58
6	CuSO$_4$	EtOH	3	130	30
7	CuSO$_4$	MeCN	3	130	40
8	**CuSO$_4$**	**Toluene**	**3**	**110**	**61**
9	CuSO$_4$	Toluene	3	90	50
10	CuSO$_4$	Toluene	6	110	61
11[c]	CuSO$_4$	Toluene	3	110	58
12[d]	CuSO$_4$	Toluene	3	110	61

[a.] Reaction conditions: 2-methylindole (0.5 mmol), aldehyde (0.6 mmol), 3-phenacyloxindole (0.5 mmol), catalyst (0.1 mmol), solvent (10.0 mL). [b.] Isolated yields. [c.] CuSO$_4$ (0.05 mmol). [d.] CuSO$_4$ (0.2 mmol).

Having established the optimal reaction conditions, we first sought to determine the generality of the aromatic aldehydes. As illustrated in Table 2, the reaction usually resulted in mixture of major isomers **1a-1j** and the minor isomers **1a'-1j'** with the molecular ratios of 6:1 to 20:1. Aromatic aldehydes with both electron-donating and electron-withdrawing groups were compatible. This reaction tolerated many kinds of functional groups, including Me (**1b**), OMe (**1c** and **1j**), Cl (**1d**, **1e** and **1f**), and NO$_2$ (**1g**, **1h** and **1i**) groups. Besides different aromatic aldehydes, we further tested the generality of various 3-phenacylideneoxindoles. Unsurprisingly, a wide range of 3-methyleneoxindoles containing different substituents at various positions (**1e-1j**) reacted smoothly to give the corresponding products with good to excellent diastereoselectivity. Other protecting N-butyl group (**1e**) also could promote such a transformation with good yield and high diastereoselectivity. All major isomers **1a-1j** and some minor isomers **1a'**, **1b'**, **1f'**, **1g'**, **1j'** were successfully isolated and fully characterized with various spectroscopy. Notably, the relative configuration of major

isomer **1f** (CCDC 2109575) was determined by X-ray crystallographic analysis, in which the *m*-chlorophenyl, benzoyl and the phenyl group in oxindole exist on *cis*-configuration. It has been known that the benzoyl group and the phenyl group in oxindole stand in the cis-position in the starting 3-phenacylideneoxindoles. Therefore, a concerted Diels-Alder reaction should be involved in this three-component reaction.
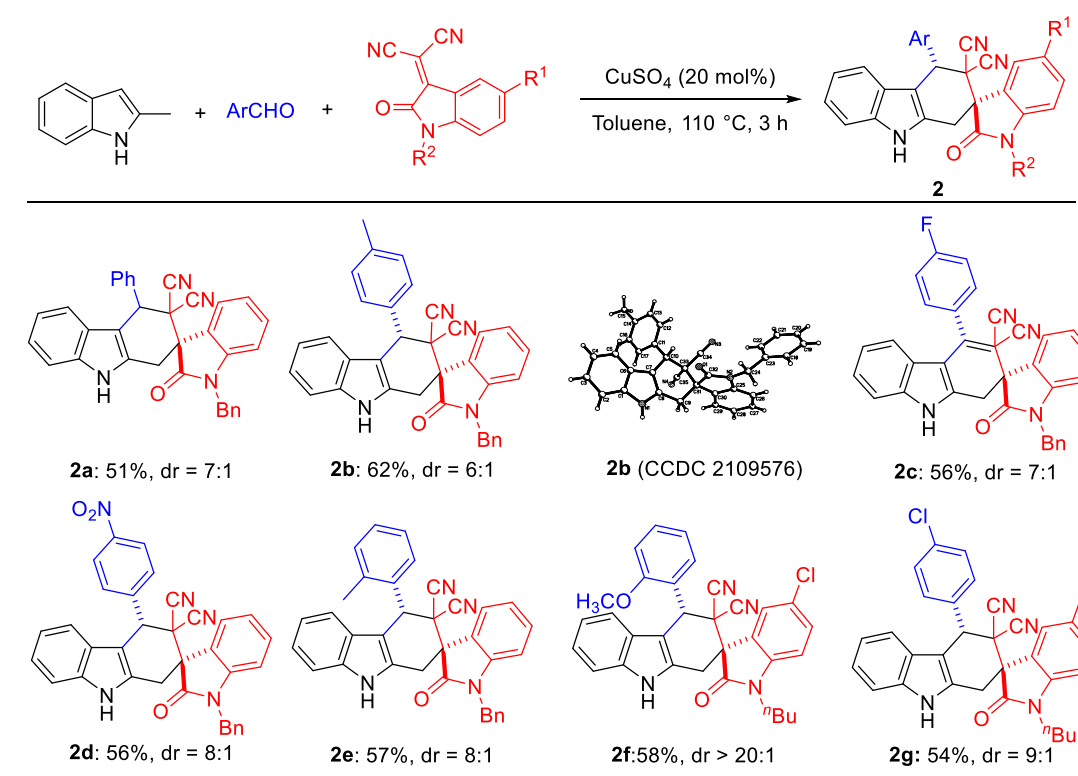
Table 2 Synthesis of spiro[carbazole-3,3'-inolines][a]
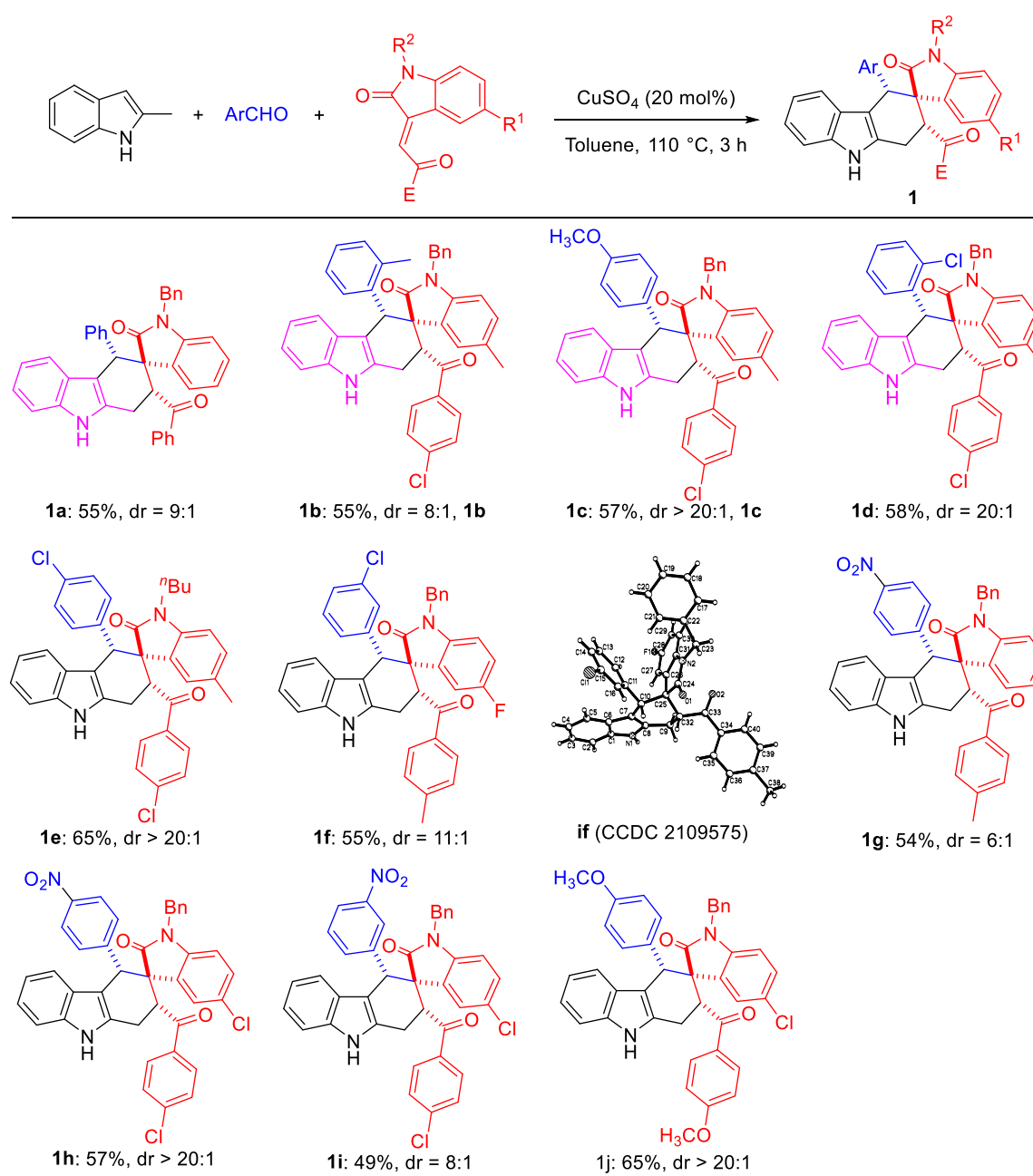
1a: 55%, dr = 9:1   **1b**: 55%, dr = 8:1, **1b**   **1c**: 57%, dr > 20:1, **1c**   **1d**: 58%, dr = 20:1

1e: 65%, dr > 20:1   **1f**: 55%, dr = 11:1   **if** (CCDC 2109575)   **1g**: 54%, dr = 6:1

1h: 57%, dr > 20:1   **1i**: 49%, dr = 8:1   1j: 65%, dr > 20:1

On the basis of this success, we further considered whether other dienophiles could be applied in such catalytic system. Under the same reaction conditions, the three-component reaction of 2-methylindole, benzaldehyde and 2-(1-benzyl-2-oxoindolin-3-ylidene)malononitrile reacted smoothly to give the expected spiro[carbazole-2,3'indolines] in 58% yield with a diastereometric ratio (dr) value of 7:1. As shown in Table 3, a wide range of aromatic aldehydes with different substituents on the aromatic ring reacted smoothly to give the desired products **2a−2e** in good yields and with good to excellent diastereoselectivity. On the other hand, we also tested various isatylidene malononitriles, the substrates with different substituted of indole ring or with different protecting groups on the indole N-1 position groups (**2f**, **2g**) all substrates reacted smoothly to give the corresponding products in moderate to good yields and with high stereoselectivity. It should be pointed out that the minor products **2a'-2e'** and **2g'** were also isolated and fully characterized with

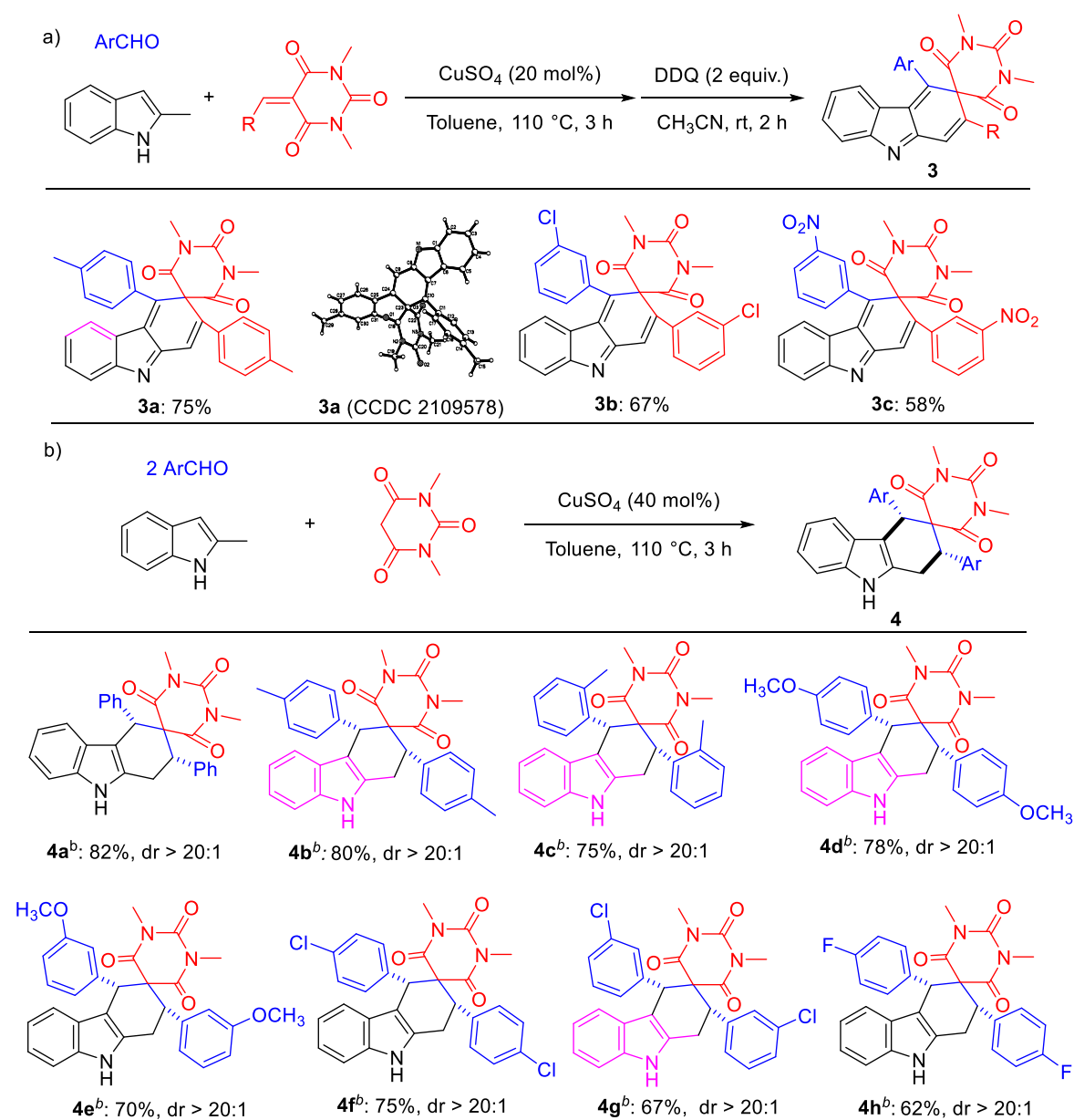**Table 3** Synthesis of spiro[carbazole-2,3'-indolines][a]

| 2a: 51%, dr = 7:1 | 2b: 62%, dr = 6:1 | 2b (CCDC 2109576) | 2c: 56%, dr = 7:1 |
| 2d: 56%, dr = 8:1 | 2e: 57%, dr = 8:1 | 2f:58%, dr > 20:1 | 2g: 54%, dr = 9:1 |

various spectroscopy. Moreover, the relative configuration of major isomer **2b** (CCDC 2109576) and minor isomer **2g'** (CCDC 2109577) were determined by X-ray crystallographic analysis. In the major isomer **2b**, the phenyl group at C4-position exists on the *cis*-position of the aryl group in oxindole scaffold, while these two groups exist on *trans*-configuration in the minor isomer **2g'**.

5-Arylidene-1,3-dimethylbarbituric acids, as the good dienophiles, could also react smoothly in such catalytic system (Table 4a). Firstly, the three-component reaction of 2-methylindole, 5-arylidene-1,3-dimethylbarbituric acid and 4-methylbenzaldehyde under the standard reaction conditions and further oxidation with DDQ generated the final aromatized product **3a** in 75% yield. Under the same reaction conditions, The similar aromatized product **3b** and **3c** were also produced in good yields with different kinds of aromatic aldehydes and 5-arylidene-1,3-dimethylbarbituric acids. Because 5-arylidene-1,3-dimethylbarbituric acids could be easily generated through Knoevenagel condensation of aromatic aldehydes and 1,3- dimethylbarbituric acid under the catalysis of Lewis acid. We envisioned whether the desired dienophiles, 5-arylidene-1,3-dimethylbarbituric acids, could be *in situ* generated by aromatic aldehydes and 1,3-dimethylbarbituric acid under the standard conditions. Therefore, the four-component reaction was carried out by using two molecular aromatic aldehydes, 1,3-dimethylbarbituric acid and 2-methylindole utilizing $CuSO_4$ as the catalyst in toluene at 110 ^oC, the desired product **4a** was obtained in 82% with excellent diastereoselectivity (dr > 20:1). In this reaction, both dienes (*o*-QDMs) and dienophiles were *in situ* formed from the starting material. As shown in Table **4b**, a wide range of aromatic aldehydes that bore different substituents at the *ortho-* (**4c**), *meta-* (**4e**, **4g**) and *para-* position (**4b**, **4d**, **4f** and **4h**) of the benzene ring reacted smoothly to give the corresponding products **4a-4h** in moderate to good yields with excellent diastereoselectivity (dr > 20:1). The

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single crystal structures of the compound **3a** (CCDC 2109578) and **4e** (CCDC 2109579) were successfully determined by X-ray diffraction. It is pleased to find that the obtained spiro[carbazole-3,5'-pyrimidines] **4a-4h** have same *cis*-configuration to that of the above prepared spiro[carbazole-3,3'-indolines] **1a-1j** and spiro[carbazole-2,3'-indolines] **2a-2h**, in which the two phenyl groups exist on the cis-position. This result clearly indicated that this reaction has similar outcome of stereochemistry.
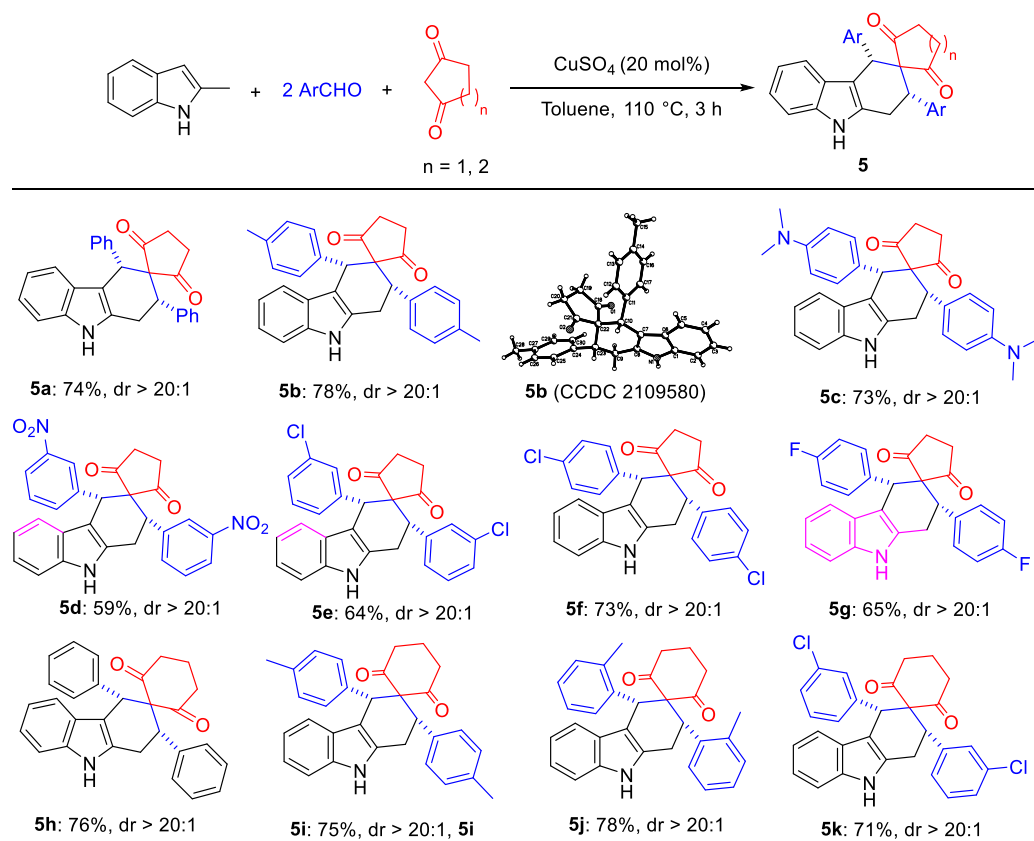
Table 4 Synthesis of tetrahydrospiro[carbazole-3,5'-pyrimidines][a]

3a: 75%   **3a** (CCDC 2109578)   **3b**: 67%   **3c**: 58%

4a[b]: 82%, dr > 20:1   **4b**[b]: 80%, dr > 20:1   **4c**[b]: 75%, dr > 20:1   **4d**[b]: 78%, dr > 20:1

4e[b]: 70%, dr > 20:1   **4f**[b]: 75%, dr > 20:1   **4g**[b]: 67%, dr > 20:1   **4h**[b]: 62%, dr > 20:1

[a.] Reaction conditions: 2-methylindole (0.5 mmol), aromatic aldehyde (0.6 mmol), 5-arylidene-1,3-dimethylbarbituric acid (0.5 mmol), CuSO$_4$ (0.1 mmol), toluene (15.0 mL), 110 °C, 3 h, and then DDQ (1.0 mmol), CH$_3$CN (10. 0 mL), rt, 2 h. [b]Reaction conditions: 2-methylindole (0.5 mmol), aromatic aldehyde (1.2 mmol), 1,3-dimethylbarbituric acid (0.5 mmol), CuSO$_4$ (0.1 mmol), toluene (6.0 mL), 110 °C, 3 h. [c]Isolated yields. [d] The dr values were determined by ^{1}H NMR.

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Based on the success of the four-component reaction through *in situ* generation of dienes and dienophiles, we further considered whether more common cyclic 1,3-diones could be applied in such catalytic system. To our delight, when cyclopentane-1,3-dione was used to replace 1,3-dimethylbarbituiric acid under the same conditions, the desired product **5a** was obtained in 74% yield with excellent diastereoselectivity (dr > 20:1). Furthermore, we examined the scope of aromatic aldehydes (Table 5), different substituents on the aromatic ring showed marginal effect. The spiro compounds **5a-5g** were produced in moderate to excellent yields with excellent diastereoselectivity (dr > 20:1). Cyclohexane-1,3-dione also reacted smoothly to produce corresponding products **5h-5k** in high yields with excellent diastereoselectivity. The single crystal structure of the compound **5b** (CCDC 2109580) clearly indicated that the two aryl groups exist on the *cis*-position.

Table 5 Synthesis of tetrahydrospiro[carbazole-3,1'-cycloalkane]-diones[a]

5a: 74%, dr > 20:1   **5b**: 78%, dr > 20:1   **5b** (CCDC 2109580)   **5c**: 73%, dr > 20:1

5d: 59%, dr > 20:1   **5e**: 64%, dr > 20:1   **5f**: 73%, dr > 20:1   **5g**: 65%, dr > 20:1

5h: 76%, dr > 20:1   **5i**: 75%, dr > 20:1, **5i**   **5j**: 78%, dr > 20:1   **5k**: 71%, dr > 20:1

a. Reaction conditions: 2-methylindole (0.5 mmol), aromatic aldehyde (1.0 mmol), cyclic 1,3-dione (0.5 mmol), CuSO$_4$ (0.1 mmol), toluene (6.0 mL), 110 °C, 3 h. [b]Isolated yields. [c] The dr values were determined by ^{1}H NMR.

When we did not add the dienophiles to this system, 4-methylbenzaldehyde could react with two molecules of 2-methylindole under the same reaction conditions to generate the well-known 3,3'-(p-tolylmethylene)bis(2-methylindole) **6a** in 75% yield. Subsequently, we sought to determine the generality of aromatic aldehydes. As illustrated in Table 6, a diversity of functional groups, which include Me (**6a**), OMe (**6b**, **6c**), NMe$_2$ (**6d**), NO$_2$ (**6e**), and Cl (**6f**, **6g**), could be well tolerated in this reaction. Importantly, the reaction is not sensitive to the electronic property of the arenes, as the substrates that bore either electron-donating (**6b-6d**), electron-neutral (**6a**), or electron-withdrawing (**6e-6g**) groups on the aryl ring were all transformed smoothly into the corresponding desired products **6a-6g** with good to excellent yields.

Table 6 Synthesis of 3,3'-(arylmethylene)bis(2-methyl-1H-indole)[a]

75%, **6a**

72%, **6b**

71%, **6c**

70%, **6d**

65%, **6e**

70%, **6f**

76%, 6g
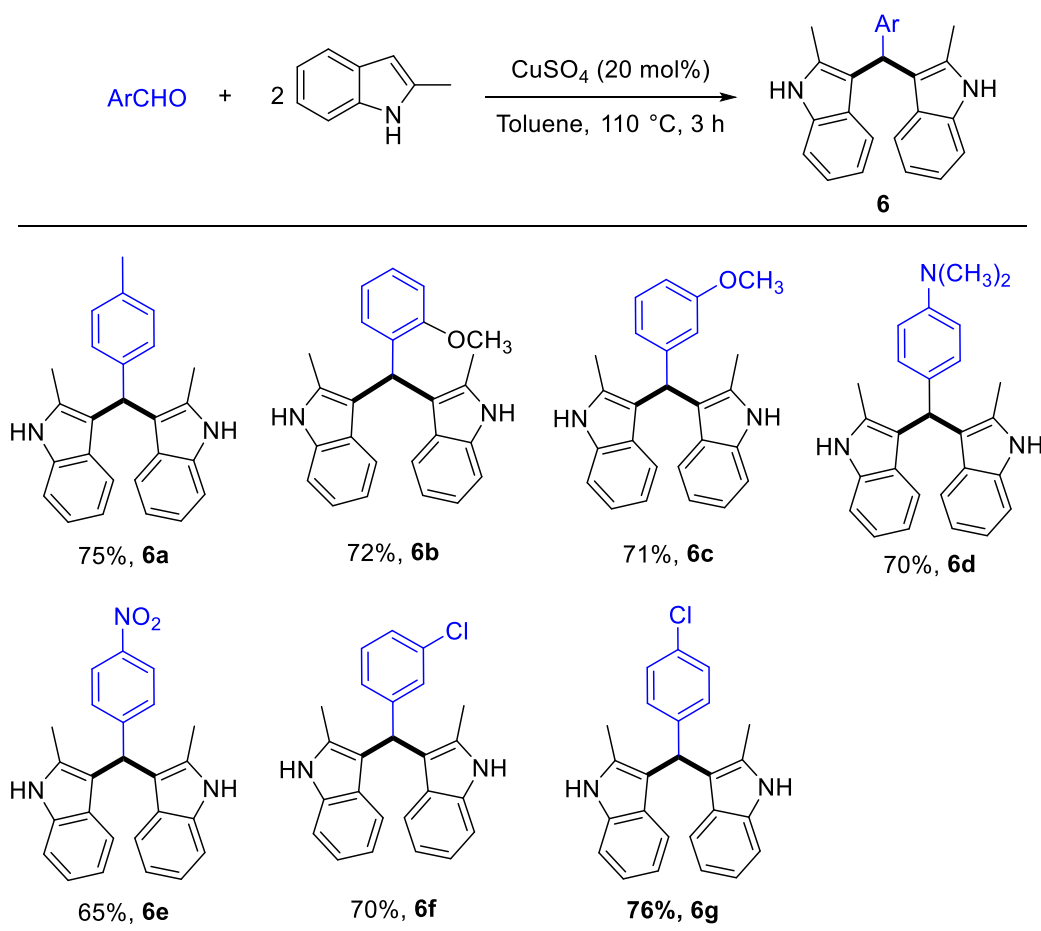
[a] Reaction conditions: 2-methylindole (1.0 mmol), aromatic aldehyde (0.5 mmol), CuSO$_4$ (0.1 mmol), toluene

Based on the above experimental results and the previously works,[14,15] a plausible reaction pathway is illustrated in Scheme 2. At first, 2-methylindole reacts with aromatic aldehydes in the presence of the catalyst $CuSO_4$ to generate the intermediate 3-substituted indole, which undergoes dehydration to form the key intermediate indole-based *ortho*-quinodimethanes (*o*-QDMs, **A**). In the meantime, the cyclic 1,3-diones and aromatic aldehyde undergo the Knoevenagel condensation to afford the different kinds of dienophiles. Subsequently, the Diels-Alder cycloaddition reaction between the indole-based *ortho*-quinodimethanes (*o*-QDMs, **A**) and dienophiles affords the final spiro compounds **1**, **2**, **4**, **5** as major isomers through an *endo*-transition state. Due to the different polarity, 3-phenacylideneoxindole and isatylidene malononitrile resulted in regioisomeric spiro[carbazole-3,3'-indoline] **1** and spiro[carbazole-2,3'-indoline] **2** as the final products. It can be seen that the two aryl groups at 1,3-positions actually exist on the *e*-bonds in the newly formed cyclohexyl ring in the spiro compounds **4** and **5**. This also means that the major isomers **4** and **5** are the thermodynamically stable isomers. In the major isomer **1**, the aryl group and the benzoyl group at 1,3-position also stand on the *e*-bonds, which indicated that the major isomer **1** is also belonging to the thermodynamically stable isomer. This result showed that this reaction is a thermodynamically controlled reaction. On the other hand, the tetrahydrospiro[carbazole-3,5'-pyrimidine] **4** can be converted to aromatized spiro spiro[carbazole-3,5'-pyrimidine] **3** through the oxidation of DDQ. In the absence of the effective dienophile, The normal Friedel-Crafts alkylation of 2-methylindole with aromatic aldehyde gives the well-known 3,3'-(arylmethylene)bis(2-methylindoles) **6**.
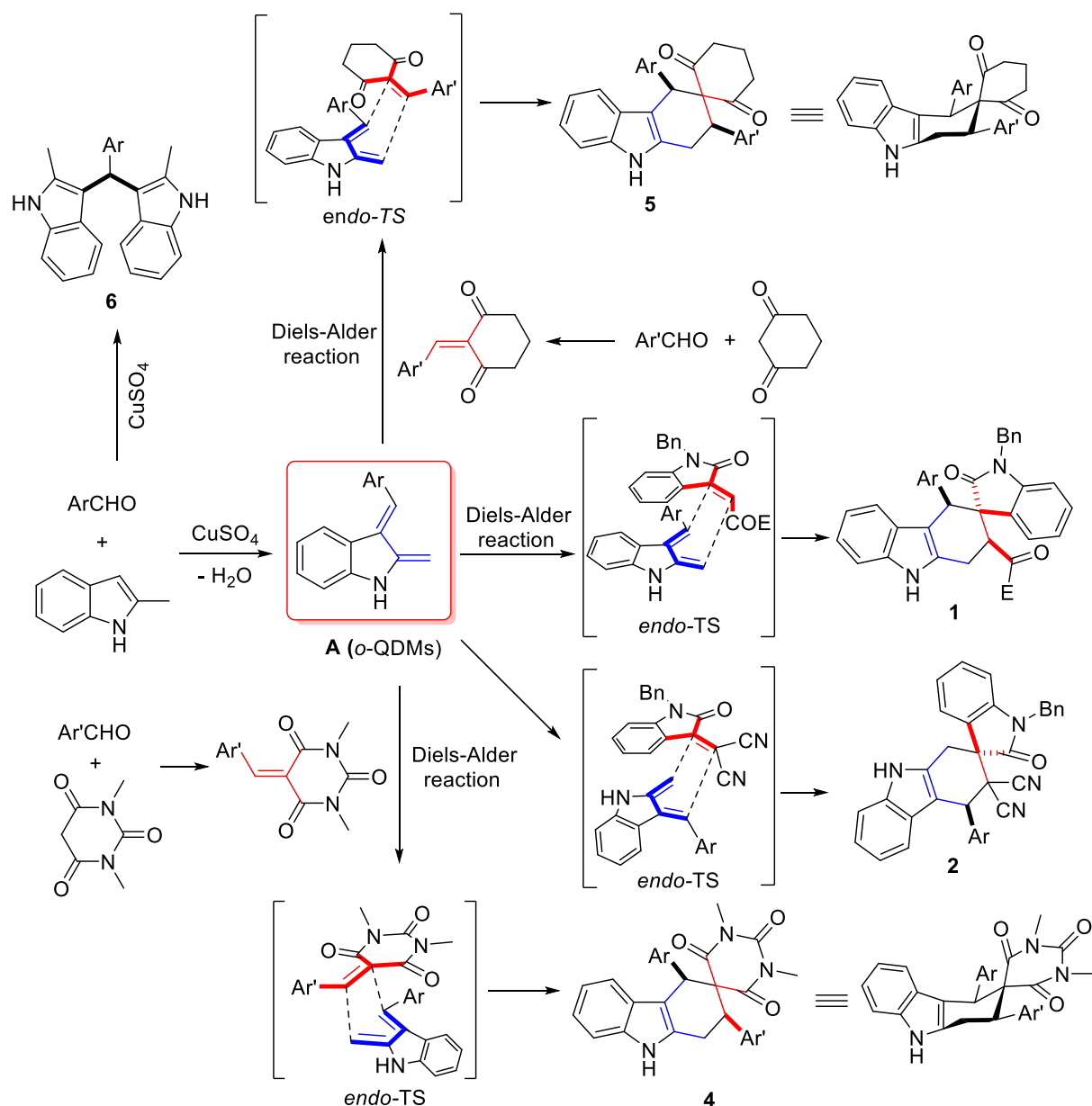
Scheme 2 Proposed reaction mechanism for the multicomponent reaction

Conclusion

In summary, we have developed the copper–catalyzed multicomponent Diels–Alder reactions of 2-methylindole, aromatic aldehydes and 1,3-diones through *in situ* generation of dienes and dienophiles under the same condition. These strategies are sustainable, general and practical, providing facile access to important polysubstituted spiro[carbazole-3,3'-indolines], spiro[carbazole-2,3'-indolines], spiro[carbazole-3,5'-

pyrimidines] and spiro[carbazole-3,1'-cycloalkanes] with good yields and high diastereoselectivity. This reaction actually developed the practical synthetic values of the well-known Levy reaction. The outcome of diastereoselectivity of the reaction was clearly elucidated by determination of the several single crystal structures and the analysis of the reaction mechanism. Moreover, this protocol exhibited good functional group tolerance, broad substrate scope, facile scalability and so provides great potential for applications in organic synthesis, pharmaceutical chemistry and materials science. The experimental results indicate the *in situ* generation of both indole-based *ortho*-quinodimethanes (*o*-QDMs) as active dienes and cyclic dienophiles are the key intermediates in these reactions.

Experimental

1. General procedure for the preparation of the spiro[carbazole-3,3'-inolines] 1a-1j and **1a'-1j':** A mixture of 2-methyl-1H-indole (0.5 mmol, 1.0 equiv), aldehyde (0.6 mmol, 1.2 equiv), 3-methyleneoxindole (0.5 mmol, 1.0 equiv) and CuSO$_4$ (0.1 mmol, 0.4 equiv) in dry toluene (6.0 mL) was stirred at 110°C for about three hours. After removing the solvent by evaporating at reduced pressure, the residue was subjected to column chromatography with ethyl acetate and light petroleum (V/V = 1:5-1:8) as eluent to give pure **1a-1j** and **1a'-1j'**.

2-Benzoyl-1'-benzyl-4-phenyl-1,2,4,9-tetrahydrospiro[carbazole-3,3'-indolin]-2'-one (1a): purple solid, 55%, m.p. 182-185 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.23 (s, 1H, NH), 7.89 (d, *J* = 7.2 Hz, 1H, ArH), 7.54 (t, *J* = 7.2 Hz, 1H, ArH), 7.43-7.39 (m, 3H, ArH), 7.30 (d, *J* = 8.0 Hz, 1H, ArH), 7.23-7.15 (m, 2H, ArH), 7.14-7.08 (m, 5H, ArH), 6.99 (t, *J* = 7.6 Hz, 1H, ArH), 6.83-6.73 (m, 3H, ArH), 6.63-6.62 (m, 2H, ArH), 6.36 (d, *J* = 7.6 Hz, 1H, ArH), 6.28 (t, *J* = 7.2 Hz, 2H, ArH), 5.00 (s, 1H, CH), 4.83 (dd, J_1 = 12.4

Hz, J_2 = 5.2 Hz, 1H, CH), 4.60 (d, J = 16.0 Hz, 1H, CH), 4.46 (d, J = 16.0 Hz, 1H, CH),

3.49 (t, J = 12.4 Hz, 1H, CH), 3.26 (dd, J_1 = 16.8 Hz, J_2 = 5.2 Hz, 1H, CH); ^{13}C NMR

(100 MHz, CDCl$_3$) δ: 199.3, 178.0, 143.6, 136.6, 136.5, 136.2, 135.2, 133.3, 132.3,

130.9, 130.0, 128.7, 128.6, 128.4, 128.2, 127.9, 127.7, 127.0, 126.9, 126.7, 126.5,

125.6, 121.8, 121.5, 120.2, 119.1, 110.7, 110.7, 109.0, 56.1, 50.0, 48.8, 43.6, 25.4;

IR(KBr) υ: 3367, 3210, 3155, 3017, 2980, 2831, 2864, 1877, 1623, 1611, 1507, 1456,

1355, 1241, 1178, 1143, 955, 931, 849, 789 cm^{-1}; MS (*m/z*): HRMS (ESI) Calcd. for

C$_{39}$H$_{30}$N$_2$O$_2$([M+Na]$^+$): 581.2199, found: 581.2191.

2. General procedure for the preparation of the spiro[carbazole-2,3'-indolines]
2a-2g and 2a'-2g': A mixture of 2-methyl-1*H*-indole (0.5 mmol, 1.0 equiv), aldehyde

(0.6 mmol, 1.2 equiv), 2-(1-benzyl-2-oxoindolin-3-ylidene)malononitrile (0.5 mmol, 1.0

equiv) and CuSO$_4$ (0.1 mmol, 0.4 equiv) in dry toluene (6.0 mL) was stirred at 110°C

for about three hours. After removing the solvent by evaporating at reduced pressure,

the residue was subjected to column chromatography with ethyl acetate and light

petroleum (V/V=1:5-1:8) as eluent to give pure **2a-2g** and **2a'-2g'**.

1'-Benzyl-2'-oxo-4-phenyl-4,9-dihydrospiro[carbazole-2,3'-indoline]-3,3(1*H*)-
dicarbonitrile (2a): white solid, 51%, m.p. 201-204 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ:

8.27 (s, 1H, NH), 7.52-7.46 (m, 3H, ArH), 7.43-7.38 (m, 4H, ArH), 7.35-7.28 (m, 5H,

ArH), 7.20 (t, *J*=7.6 Hz, 1H, CH), 6.95-6.90 (m, 4H, ArH), 6.54 (d, *J*=8.0 Hz, 1H, CH),

5.14 (d, *J*=15.6 Hz, 1H, CH), 4.96 (d, *J*=15.6 Hz, 1H, CH), 4.89 (s, 1H, CH), 4.10 (dd,

J_1 = 16.4 Hz, J_2 = 2.4 Hz, 1H, CH), 2.96 (d, *J* = 16.4 Hz, 1H, CH); ^{13}C NMR (100 MHz,

CDCl$_3$) δ: 173.2, 136.6, 134.7, 133.6, 130.9, 129.4, 128.8, 128.0, 127.6, 125.0, 123.6,

122.7, 120.2, 120.1, 112.7, 111.0, 110.4, 106.9, 51.8, 47.6, 46.2, 44.7, 29.1; IR(KBr)

υ: 3355, 3207, 3117, 3048, 2963, 2831, 2167, 1871, 1641, 1633, 1554, 1431, 1370,

1240, 1131, 1100, 972, 961, 881, 764 cm^{-1}; MS (*m/z*): HRMS (ESI) Calcd. for

C$_{34}$H$_{24}$N$_4$O ([M+Na]$^+$): 527.1842, found: 527.1849.

3. General procedure for the preparation of the tetrahydrospiro[carbazole-3,5'-pyrimidines] 3a-3c: A mixture of 2-methyl-1*H*-indole (0.5 mmol, 1.0 equiv), aldehyde (0.6 mmol, 1.2 equiv), 5-arylidene-1,3-dimethylbaribituric acid (0.5 mmol, 1.0 equiv) and $CuSO_4$ (0.1 mmol, 0.4 equiv) in dry toluene (6.0 mL) was stirred at 110°C for about three hours. After removing the solvent by evaporating at reduced pressure, the mixture of the above obtained product and DDQ (1.0 mmol, 0.227 g, 2.0 equiv) in dry acetonitrile (10.0 mL) was stirred at room temperature for about four hours. After removing the solvent by evaporating at reduced pressure, the residue was subjected to column chromatography with ethyl acetate and light petroleum (V/V=1:3-1:6) as eluent to give pure products **3a-3c**.

1',3'-Dimethyl-2,4-di-p-tolyl-2'H-spiro[carbazole-3,5'-pyrimidine]-2',4',6'(1'H,3'H)-trione (3a): yellow solid, 75%, m.p. 190-192 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.59 (d, *J* = 7.6 Hz, 1H, ArH), 7.35-7.30 (m, 4H, ArH), 7.25-7.17 (m, 2H, ArH), 7.04 (s, 1H, ArH), 6.96-6.91 (m, 4H, ArH), 6.35 (d, *J* = 7.6 Hz, 1H, CH), 3.10 (s, 3H, CH$_3$), 3.07 (s, 3H, CH$_3$), 2.37 (s, 3H, CH$_3$), 2.34 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 165.3, 162.7, 157.9, 149.7, 149.0, 147.3, 142.6, 139.1, 138.7, 137.1, 136.0, 133.7, 130.6, 130.3, 130.0, 129.1, 128.7, 128.3, 128.0, 126.3, 126.1, 125.5, 124.7, 124.2, 123.1, 120.8, 29.6, 28.8, 21.4, 21.3; IR (KBr) υ: 3219, 3158, 3043, 2966, 2900, 1843, 1755, 1648, 1617, 1537, 1466, 1358, 1318, 1266, 1150, 987, 899, 765 cm^{-1}; MS (*m/z*): HRMS (ESI) Calcd. for $C_{31}H_{25}N_3O_3$ ([M+Na]$^+$): 510.1788, found: 510.1788.

3. General procedure for the preparation of the spiro[carbazole-3,3'-inolines] 4a-4h: A mixture of 2-methyl-1*H*-indole (0.5 mmol, 1.0 equiv), aldehyde (1.2 mmol, 1.2 equiv) and 1,3-dimethylbaribituric acid (0.5 mmol, 1.0 equiv) in dry toluene (6.0 mL) was stirred at 110°C for about three hours. After removing the solvent by evaporating at reduced pressure, the residue was subjected to column chromatography with ethyl acetate and light petroleum (V/V=1:5-1:8) as eluent to give pure **4a-4h**.

1',3'-Dimethyl-2,4-diphenyl-1,2,4,9-tetrahydro-2'*H*-spiro[carbazole-3,5'-pyrimidine]-2',4',6'(1'*H*,3'*H*)-trione (4a): purple solid, 82%, m.p. 205-208 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.02 (s, 1H, NH), 7.30-7.27 (m, 2H, ArH), 7.25-7.24 (m, 2H, ArH), 7.24-7.22 (m, 2H, ArH), 7.19-7.15 (m, 3H, ArH), 7.15-7.10 (m, 1H, ArH), 7.06 (t, *J* = 7.2 Hz, 1H, ArH), 6.94 (d, *J* = 7.2 Hz, 1H, ArH), 6.80 (t, *J* = 8.0 Hz, 1H, ArH), 6.41 (d, *J* = 8.0 Hz, 1H, ArH), 5.24 (s, 1H, CH), 4.13 (dd, J_1= 12.0 Hz, J_2= 5.6 Hz, 1H, CH), 3.90-3.82 (m, 1H, CH), 3.05 (dd, J_1= 16.4 Hz, J_2= 5.6 Hz, 1H, CH), 2.97 (s, 3H, CH$_3$), 2.81 (s, 3H, CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 171.7, 167.8, 150.0, 138.9, 137.2, 136.0, 134.6, 129.3, 128.9, 128.7, 128.2, 128.2, 128.1, 128.1, 128.1, 126.3, 121.0, 119.7, 118.9, 110.6, 107.5, 62.5, 51.1, 48.2, 28.3, 27.8, 27.7; IR (KBr) υ: 3407, 3078, 2981, 1873, 1744, 1658, 1667, 1582, 1466, 1356, 1321, 1221, 1180, 912, 833 cm^{-1}; MS (*m/z*): HRMS (ESI) Calcd. for C$_{29}$H$_{25}$N$_3$O$_3$ ([M+Na]$^+$): 486.1788, found: 486.1794.

3. General procedure for the preparation of the tetrahydrospiro[carbazole-3,1'-cycloalkane]-diones 5a-5k: A mixture of 2-methyl-1*H*-indole (0.5 mmol, 1.0 equiv), aldehyde (1.2 mmol, 2.4 equiv), 1,3-diones (0.5 mmol, 1.0 equiv) and CuSO$_4$ (0.1 mmol, 0.4 equiv) in dry toluene (6.0 mL) was stirred at 110°C for about three hours. After removing the solvent by evaporating at reduced pressure, the residue was subjected to column chromatography with ethyl acetate and light petroleum (V/V=1:5-1:8) as eluent to give pure **5a-5k**.

2,4-Diphenyl-1,2,4,9-tetrahydrospiro[carbazole-3,1'-cyclopentane]-2',5'-dione (5a): purple solid, 74%, m.p. 178-180 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 8.02 (s, 1H, NH), 7.30 (d, *J* = 8.4 Hz, 1H, ArH), 7.28-7.27 (m, 2H, ArH), 7.26-7.25 (m, 1H, ArH), 7.22 (d, *J* = 8.0 Hz, 1H, ArH), 7.19-7.17 (m, 2H, ArH), 7.14 (t, *J* = 7.6 Hz, 1H, ArH), 7.06 (t, *J* = 7.2 Hz, 1H, ArH), 6.92 (d, *J* = 8.0 Hz, 1H, ArH), 6.79 (t, *J* = 7.2 Hz, 1H, ArH), 6.39 (d, *J* = 8.0 Hz, 1H, ArH), 4.87 (s, 1H, CH), 3.97-3.90 (m, 1H, CH), 3.66 (dd, J_1 = 12.4 Hz, J_2 = 4.8 Hz, 1H, CH), 2.95 (dd, J_1 = 16.0 Hz, J_2 = 4.8 Hz, 1H, CH), 2.01-1.90

(m, 2H, CH$_2$), 1.39-1.31 (m, 1H, CH), 1.26-1.22 (m, 1H, CH); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 218.2, 216.7, 139.1, 137.8, 136.1, 134.7, 129.9, 129.5, 128.8, 128.7, 128.5, 128.2, 127.8, 127.5, 126.3, 121.0, 119.7, 118.9, 110.7, 107.8, 65.9, 48.8, 47.4, 37.3, 36.5, 26.5; IR (KBr) υ: 3200, 3173，3064, 2978, 1861, 1745, 1677, 1631, 1567, 1467, 1382, 1311, 1254, 1132, 960，841, 781 cm^{-1}; MS (*m/z*): HRMS (ESI) Calcd. for C$_{28}$H$_{23}$NO$_2$ ([M+Na]$^+$): 428.1621, found: 428.1626.

Supporting Information

Characterization data and ^{1}H NMR, ^{13}C NMR, HRMS spectra of the compounds are available. The crystallographic data of the compounds **1f** (CCDC 2109575), **2b** (CCDC 2109576), **2g'** (CCDC 2109577), **3a** (CCDC 2109578), **4e** (CCDC 2109579) and **5b** (CCDC 2109580) have been deposited at the Cambridge Crystallographic Database Center (http//www.ccdc.cam.ac.uk)

Acknowledgements

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