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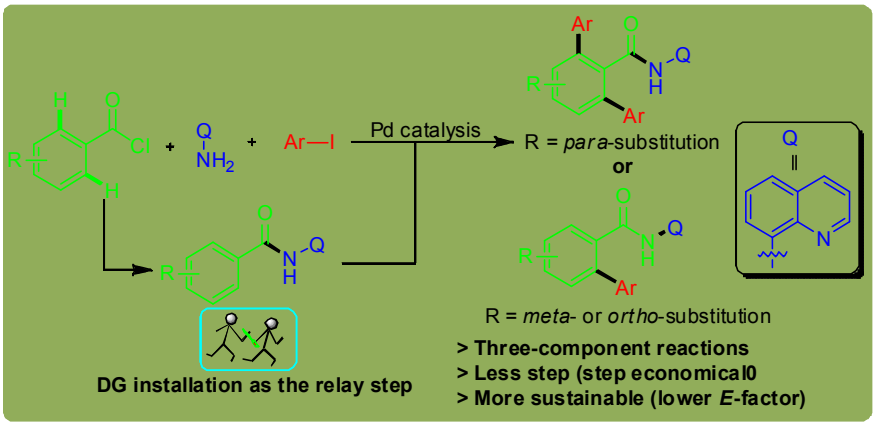

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Step economical synthesis of *o*-aryl benzamides via C-H activation relayed by the *in situ* installation of directing group: a multicomponent method

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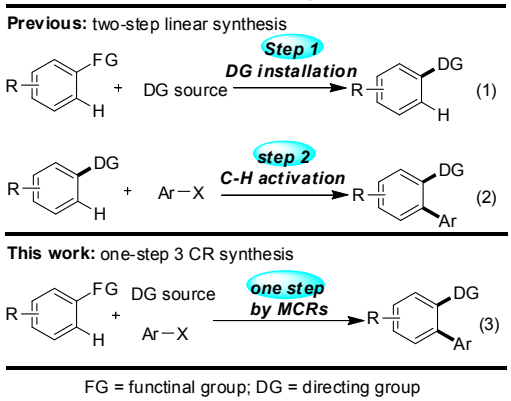
Multicomponent reaction has been successfully applied as a platform for designing the step economical C-H activation-based organic synthesis wherein the in situ installation of directing group (DG) and the subsequent C-H activation-based amide arylation have been achieved in one-stp. This multicomponent strategy allows the efficient synthesis of 2,6-biarylatd or 6-arylated benzamides with significantly improved sustainability and discloses the potential of designing "ideal" synthesis by combining the concepts of C-H activation and multicomponent reaction.

The direct activation of the inert C-H bonds is one of the most momentous synthetic strategies emerged in modern organic chemistry. During the last decade, the overwhelming expansion of the C-H activation to numerous synthetic areas such as natural products, small organic molecule libraries, organic materials and other useful organic products has demonstrated the leading position of C-H activation as a powerful tool in the science of organic synthesis.[1] Along with the rapid expansion of the C-H activation-based synthesis, some limits have also been noticed. One of the major current challenges is that most C-H activation processes rely on the assistance of a directing group (DG).[2] The presence of DG is not desirable in most cases from the viewpoint of synthetic efficiency because of the additional work required by installing and removing the DG required for these C-H bond activation. In this regard, it has become more and more desirable to devise more ideal C-H activation-based synthetic tactic that fulfils the principles of atom economy and step economy.[3]

In order to minimize the negative impact brought by the DG, tremendous efforts have been made. In recent years, several concepts such as traceless, removable and/or modifiable DG have been proved to be successful in reducing the additional chemical process in DG-assisted synthesis.[4] While elegant examples on organocatalytic or oxidative C-H activation are also available,[5] the overall availability on generally applicable strategies allowing step economical C-H activation is still rather scarce. Therefore, developing complementary technology to enhance the efficiency of DG-based C-H activation transformation is of high present emergency.

By analyzing the whole synthetic process of the DG assisted C-H activation, we have noticed that these syntheses usually start from the installation of the DG to the substrates before the subsequent C-H bond transformation (Eq 1-2, Scheme 1). While the application of both removable and modifiable DG focus on improving the step efficiency at the stage after the C-H bond transformation, not any efforts in reducing the synthetic process by skipping the step before the conversion of C-H bond have been made. This fact inspired us to explore the possibility of merging the two synthetic steps to one step by making use of the strategy of multicomponent reactions (MCRs) as a platform to improve the step economy (Eq 3, Scheme 1).[6]

Since the pioneer work of Daugulis and co-workers on the 8-amino quinoline (AQ) directing group assisted C-H arylation,[7] the research on C-H activation based synthesis using AQ as the directing group has received striking advances.[8] To date, the exceptional chelating power of AQ moiety has been inarguably demonstrated by its general applicability in tremendous synthesis based on the metal-catalyzed C-H bond activation



Scheme 1 Conventional linear synthesis *vs* multicomponent one-step synthesis via C-H activation

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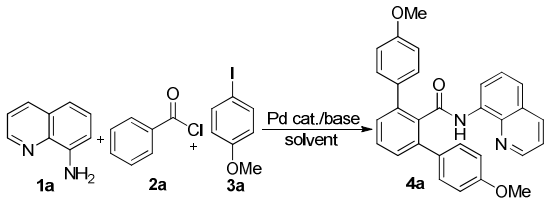
such as arylation,[9] alkenylation,[10] carbonylation,[11] thiolation,[12] alkylation,[13] oxygenation[14] and amination,[15] among others.[16] Considering the strategic merits of the AQ in the chemistry of C-H activation, we have selected this moiety as auxiliary to design the step economical C-H arylation of benzamides without prior work on installing DG. Herein, we report the first example on the AQ assisted C-H arylation of aryl amides starting directly from acyl chlorides, 8-amino quinoline and aryl halides. Besides the step economics embedded in the fashion of three-component, one-step operation, the present method is also advantageous by employing only palladium catalyst without the presence of any other metal cocatalyst.

The tentative explore on the method starts from the model reaction of 8-amino quinoline **1a**, benzoyl chloride **2a** and p-methoxyl iodobenzene **3a**. In the presence of $Pd(OAc)_2$ and K_2CO_3, the formation of C-H arylated product **4a** was successfully observed in xylene (entries 1-3, Table 1). A brief examination on the catalytic effect of different palladium species suggested that Pd (II) salts were generally able to catalyze the reaction, while Pd (0) catalyst such as Pd/C was not applicable (entries 4-6, Table 1). In the subsequent experiments using different bases, K_2CO_3 turned out to be the most favourable base among the different types of inorganic and organic bases (entries 7-11, Table 1). On the other hand, the entries employing different solvents demonstrated that non-polar solvent such as xylene, toluene were suitable for the reaction, while polar solvents such as DMF, DMSO could not effectively mediate the synthesis of **4a** via this three-component process (entries 12-15, Table 1). Finally, the variation on temperature proved that 120°C was most proper since heightening the reaction temperature could not increase the yield of product, and lowering the temperature led to the sharp decrease of the yield (entries 16-17, Table 1). The 2,6-diarylated structure of **4a** was confirmed by X-ray diffraction analysis (Fig. 1).[17]

Following the endeavour in screening reaction conditions, the application scope of the three-component reaction in the rapid synthesis of *o*-arylated benzamides was then comprehensively investigated. The synthesis of a broad array of 2,6-diarylated benzamides **4** were outlined in Table 2. Generally, a variety of different functional groups such as alkyl, alkoxyl, halogen and nitro etc all exhibited good tolerance to the synthesis of corresponding benzamides, and corresponding products (**4a**-**4s**) were given with moderate to excellent yields. According to acquired results, the iodobenzenes containing electron withdrawing group (EWG) provided evidently lower yield of related products than entries of unsubstituted or electron donating group (EDG) substituted iodobenzenes (**4a**-**4c** vs **4d**-**4f**, Table 2) owing to the side reaction of homo- Suzuki coupling of the EWG activated iodobenzenes in the presence of Pd-catalyst. On the other hand, the EWG in the *para*-position of benzoyl chloride also displayed negative effect to the formation of target products (**4r**-**4s**, Table 2) probably because of the weaker nucleophilicity of the *ortho*-carbon

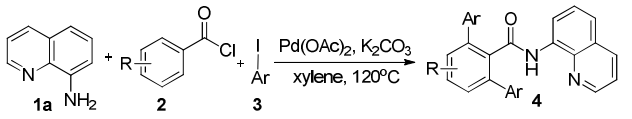
Table 1 Optimization of reaction conditions[a]



entry	catalyst	base	solvent	yield(%)[b]
1	$Pd(OAc)_2$	K_2CO_3	xylene	85
2[c]	$Pd(OAc)_2$	K_2CO_3	xylene	84
3[d]	$Pd(OAc)_2$	K_2CO_3	xylene	83
4	$PdCl_2$	K_2CO_3	xylene	75
5	$Pd(PPh_3)_4$	K_2CO_3	xylene	63
6	Pd/C	K_2CO_3	xylene	trace
7	$Pd(OAc)_2$	NaOH	xylene	trace
8	$Pd(OAc)_2$	Na_2CO_3	xylene	trace
9	$Pd(OAc)_2$	Cs_2CO_3	xylene	45
10	$Pd(OAc)_2$	$NaHCO_3$	xylene	trace
11	$Pd(OAc)_2$	^tBuONa	xylene	trace
12	$Pd(OAc)_2$	K_2CO_3	toluene	70
13	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	32
14	$Pd(OAc)_2$	K_2CO_3	DMF	trace
15	$Pd(OAc)_2$	K_2CO_3	DMSO	trace
16[e]	$Pd(OAc)_2$	K_2CO_3	xylene	67
17[f]	$Pd(OAc)_2$	K_2CO_3	xylene	83

[a]General conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), **3a** (0.9 mmol), catalyst (3 mol %), base (0.6 mmol), solvent (2 mL), stirred at 120 °C or reflux (for solvents with lower bp) for 12 h. [b]Isolated yield based on **2a**. [c]$Pd(OAc)_2$ (10 mol %). [d]$Pd(OAc)_2$ (5 mol %). [e]The temperature was 110 °C. [f]The temperature was 130 °C.

Table 2 C-H activation-based multicomponent synthesis of 2,6-disubstituted benzamides[a]



entry	R	Ar	pruduct	yield (%)[b]
1	H	4-OMe	**4a**	85
2	H	H	**4b**	95
3	H	4-Me	**4c**	87
4	H	4-Cl	**4d**	70
5	H	4-Br	**4e**	68
6	H	4-COMe	**4f**	56
7	H	3-Me	**4g**	80
8	H	3,5-dimethyl	**4h**	82
9	4-Me	H	**4i**	90
10	4-Me	4-Me	**4j**	87
11	4-Me	4-OMe	**4k**	82
12	4-Me	4-COMe	**4l**	50
13	4-Me	4-NO_2	**4m**	73
14	4-OMe	4-Me	**4n**	85
15	4-OMe	4-OMe	**4o**	76
16	4-OMe	4-Cl	**4p**	68
17	4-OMe	4-COMe	**4q**	48
18	4-Cl	H	**4r**	66
19	4-Cl	4-COMe	**4s**	49

[a]General conditions: **1a** (0.3 mmol), **2** (0.3 mmol), **3** (0.9 mmol), $Pd(OAc)_2$ (3 mol%), K_2CO_3 (0.6 mmol) in xylene (2 mL), stirred at 120 °C for 12 h. [b]Isolated yield based on **2**.

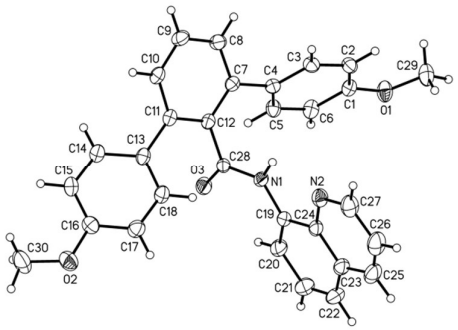
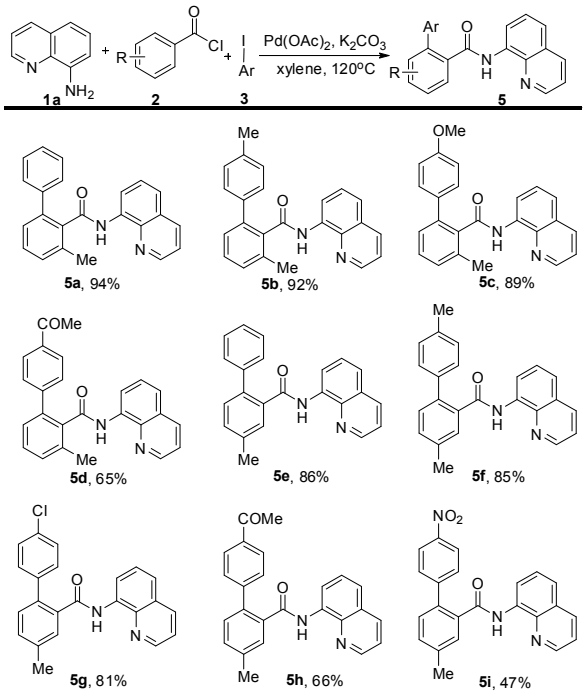


Figure 1 Crystal structural of **4a**

atom resulted from the EWG.

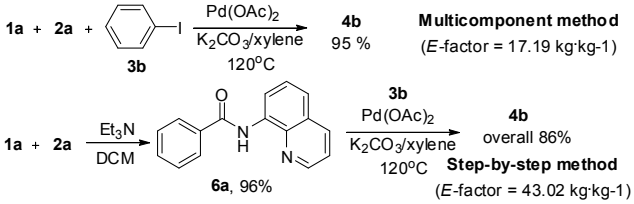
Interestingly, a different chemo-selectivity in forming 2-substituted benzamides was observed in the entries using *o*- and *m*-substituted benzoyl chlorides as substrates which could be attributed to steric hindrance of the substituent. As showing in Table 3, the mono C-H arylated benzamides were synthesized by the three-component assembly with general applicability when *o*- or *m*-substituted benzoyl chloride were subjected to the catalytic atmosphere. Similar tendency of the electronic effect on the iodobenzene component was observed as in the experiments of Table 2.

Table 3 C-H activation-based multicomponent synthesis of *o*-arylated benzamides[a,b]



[a]General conditions: **1a** (0.3 mmol), **2** (0.3 mmol), **3** (0.45 mmol), $Pd(OAc)_2$ (3 mol%), K_2CO_3 (0.6 mmol) in xylene (2 mL), stirred at 120 °C for 12 h. [b]Isolated yield based on **2**.

To compare the efficiency and sustainability of the present multicomponent strategy and conventional step-by-step method, we performed the synthesis of **4b** by directly using prior prepared *N*-quinolin-8-yl benzamide **6a** under standard conditions. It was found that the overall yield of product **4b** was slightly lower than the multicomponent method. Notably, even without considering the chemical consumption during the isolation of **6a**, the *E*-factor of the multicomponent version was remarkably lower than that of the step-by-step synthesis (see ESI for the detail on *E*-factor calculation), demonstrating the significant improvement of the multicomponent method in synthetic sustainability (Scheme 2).



Scheme 2 Comparison of the E-factor of the multicomponent and step-by-step synthesis

In conclusion, we have established a concise multicomponent method for the C-H activation-based synthesis of *o*-arylated benzamides starting from 8-aminoquinoline, benzoyl chlorides and iodobenzenes wherein the installation of the AQ-based DG acted as the relay step for subsequent C-H arylation. Comparing with the conventional step-by-step synthesis using prior prepared *N*-quinolin-8-yl benzamies, the present method provides an obviously more sustainable and rapid new approach to these useful products. More meaningfully, the success of such a synthetic protocol discloses the possibility and unique benefits of combining the concepts of multicomponent reactions and C-H activation.

Acknowledgements

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17 CCDC 1058763 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

