Solvent-Controlled Cascade Reaction of Ugi/Pd-Catalyzed Intramolecular Divergent C-H Functionalization for Regioselective Synthesis of Cyclopropanated N-Heterocycles

Tianyi Shang, Yan Pan, Zhong Chen, Junjie Yang, Xinling Guo, Leilei Guo and Yan Liu*

School of biological and pharmaceutical engineering, Xinyang Agriculture and Forestry University, Xinyang 464000, China

*Corresponding author e-mail: liuyan@xyafu.edu.cn

Abstract. A novel cascade reaction of Ugi/Pd-catalyzed intramolecular divergent C-H functionalization, which is controlled by solvent effect to achieve the regioselective synthesis of spiro- and fused-cyclopropanated indolines from the Ugi adduct of N-acylated 2-bromoarylamides.

1. Introduction

Divergent catalysis, which can provide diversified target products from one precursor through ingenious design and previous control of different catalytic route, is of great significance in modern organic synthesis.[1-3] In particular, Palladium-catalyzed C-H functionalization represents one of the most straightforward, efficient, and atom-economical tools to realize regioselective catalysis.[4-7] Very recently, Lee and co-workers disclosed a tandem palladium-catalyzed Heck/regioselective C(sp³)-H activation reaction for the divergent synthesis of spiro- and fused-cyclopropanated indolines from N-acylated 2-bromoarylamides. The regioselectivity of the C-H bond activation is controlled by the solvent effect (Scheme 1a).[8]

As our continuous interests in multiple component reaction (MCR)[9-12] for diversity-oriented synthesis of highly functionalized structures in a facile and rapid manner, we envisaged that the proper union of MCR with Pd-catalyzed intramolecular divergent C-H functionalization in one pot reaction will extremely expand its application as a novel strategy for regioselective access to spiro- and fused-cyclopropanated indolines. Among named MCRs, the Ugi four-component reaction (Ugi-4CR) is, with no doubt, one of the most powerful synthetic methods due to its advantages of saving synthetic operations as well as maximizing the construction of structural complexities.[13-16] More importantly, Ugi reaction can supply the core structure of bifunctional amide for the follow-up cyclizations.

Encouraged by the initial proof of feasibility,[8] we endeavoured to assemble an allyl moiety and a N-acetylated 2-bromoarylamide precursor in one Ugi adduct followed by Pd-catalyzed intramolecular divergent C-H functionalization. Meanwhile, among the cyclopropanated N-heterocycles, spiro cyclopropane-1, 3'-indolines and tetrahydrocyclopro[a,b]indoles are ubiquitous scaffolds present in various biologically and pharmaceutically active molecules. Therefore, in its own right, it is of great importance and challenge to exploit the principle of divergent catalysis to develop a switchable access to these spiro- and fused-cyclopropanated indolines.
Herein, we describe a novel cascade reaction of Ugi/Pd-catalyzed intramolecular divergent C-H functionalization, which is controlled by solvent effect to achieve the regioselective synthesis of spiro- and fused-cyclopropanated indolines from the Ugi adduct of N-acylated 2-bromoarylamides (Scheme 1b).

### Scheme 1. a: previous tandem palladium-catalyzed Heck/regioselective C(sp³)-H activation reaction; b: this work.

#### 2. Results and discussion

To probe the proposed solvent-controlled cascade reaction of Ugi/Pd-catalyzed intramolecular divergent C-H functionalization, we employed 2-bromoaniline 1, 3-methylbut-3-enal 2, acetic acid 3 and tert-butyl isocyanide 4 as a Ugi reaction substrats to give adduct 5 in a solution of MeOH [0.5 M] at room temperature for 12 h. 5 (0.2 mmol) without further purification was mixed with Pd catalyst (20 mol%)/ligand (50 mol%), base (1.5 equiv), and additive (1.0 equiv) in a solvent (1.0 mL,0.2 M) at 120 °C for 24 h. The yields of 6 and 7 were determined by isolation and 1H NMR. All the results were surmised in Table 1. To our delight, an obvious phenomenon of solvent-controlled C-H bond activation was obtained. As can be seen in the nonpolar solvents such as toluene and p-xylene, the type of tetrahydrocyclopropa[b]indole was predominating as the major product (entries 1 and 2). To the contrary, in the polar solvents such as DMSO and DMF, the type of spiro cyclopropane-1,3'-indoline alerted to be main transformation target (entries 3 and 4). In order to enhance the yield of product 7, several bases (Na₂CO₃ and Cs₂CO₃) and additives (PivOH, AdOH and AgNO₃) were test in the presence of DMSO (entries 5-9). Thus, the optimized conditions for the formation of spiro-cyclopropanated indoline from Ugi adduct 5 was established (entry 7). Subsequently, we turned to using Pd(OAc)₂/PPh₃ in place of Pd(PPh₃)₄ as catalyst in the presence of toluene and K₂CO₃, resulting in regioselectively furnishing the product 6/7 in a radio less than 5:24 (entry 10). Therefore, In comparison of Pd(PPh₃)₄, Pd(OAc)₂/PPh₃ might be a better catalyst aiming at the formation of fused-cyclopropanated indoline. With optimized Pd catalyst in hand, several bases (Na₂CO₃ and Cs₂CO₃) and additives (PivOH, AdOH and AgNO₃) were screened in the presence of toluene (entries 11-15) under standard conditions demonstrating that Cs₂CO₃ and PivOH should be the best base and additive. Thus, the optimized conditions for the formation of fused-cyclopropanated indoline from Ugi adduct 5 was established (entry 13).
With the two different optimal reaction parameters: Conditions A (Table 1, entry 7) and Conditions B (Table 1, entry 13) in hand for the regioselective synthesis of spiro- and fused-cyclopropanated indolines from the Ugi adduct, structures of 5, 6 and 7 were subsequently determined unambiguously by $^1$H NMR and HRMS.

### Table 1. Reaction optimization.

| Entry | Pd/ligand | Solvent | Base | Additive | Yields of 6/7 (%) |
|-------|-----------|---------|------|----------|-----------------|
| 1     | Pd(PPh$_3$)$_4$ | Toluene | K$_2$CO$_3$ | -- | ~18/18 |
| 2     | Pd(PPh$_3$)$_4$ | p-xylene | K$_2$CO$_3$ | -- | 8/13 |
| 3     | Pd(PPh$_3$)$_4$ | DMF | K$_2$CO$_3$ | -- | 22/-- |
| 4     | Pd(PPh$_3$)$_4$ | DMF | Na$_2$CO$_3$ | -- | 16/5 |
| 5     | Pd(PPh$_3$)$_4$ | DMSO | Cs$_2$CO$_3$ | -- | 16/-- |
| 6     | Pd(PPh$_3$)$_4$ | DMSO | PivOH | -- | 37/56 |
| 7     | Pd(PPh$_3$)$_4$ | DMSO | K$_2$CO$_3$ | AdOH | 24/-- |
| 8     | Pd(OAc)$_2$/PPh$_3$ | Toluene | K$_2$CO$_3$ | AgNO$_3$ | 25/28 |
| 9     | Pd(OAc)$_2$/PPh$_3$ | Toluene | Cs$_2$CO$_3$ | -- | 5/28 |
| 10    | Pd(OAc)$_2$/PPh$_3$ | Toluene | Na$_2$CO$_3$ | -- | 4/36 |
| 11    | Pd(OAc)$_2$/PPh$_3$ | Toluene | Cs$_2$CO$_3$ | AdOH | 6/36 |
| 12    | Pd(OAc)$_2$/PPh$_3$ | Toluene | Cs$_2$CO$_3$ | AgNO$_3$ | 4/28 |

*Reaction conditions: a solution of 2-bromoaniline 1, 3-methylbut-3-enal 2, acetic acid 3 and tert-butyl isocyanide 4 was allowed to be stirred in MeOH (0.5 M) at room temperature for 12 h affording the desired Ugi adduct 5. Remove the solvent and 5 (0.2 mmol) without further purification was mixed with Pd (20 mol%/ligand (50 mol%), base (1.5 equiv), and additive (1.0 equiv) in a solvent (1.0 mL, 0.2 M) at 120 °C for 24 h. The yield was determined by isolation and $^1$H NMR.

### 3. Conclusion

In summary, a novel cascade reaction of Ugi/Pd-catalyzed intramolecular divergent C-H functionalization was established, which is controlled by solvent effect to achieve the regioselective synthesis of spiro- and fused-cyclopropanated indolines from the Ugi adduct of N-acylated 2-bromoaryl amides. We anticipate that this method may have implications in the construction of diversified cyclopropanated N-heterocycles. More efforts will be paid to further increase the yields and the biological evaluation of the resulting products is underway in our lab.

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