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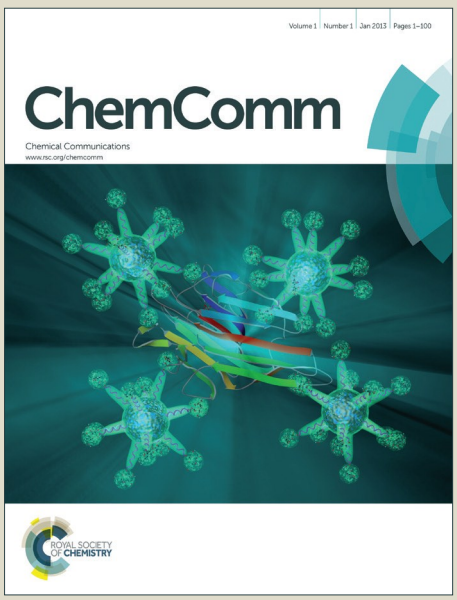

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ARTICLE

Pd-Catalyzed Sequential β-C(sp^3)–H Arylation and Intramolecular Amination of δ-C(sp^2)–H Bonds to Synthesis of Quinolinones via a N,O-Bidentate Directing Group

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The pharmacological importance of 2-quinolinone derivatives is well known. Herein, we developed an effective protocol for the synthesis of 2-quinlinolinone derivatives by palladium-catalyzed sequential β-C(sp^3)–H arylation and selective intramolecular C(sp^2)–H/N–H amination starting with aryl iodides and carboxylic acids. Synthesis used a novel directing group, glycine dimethylamide. We synthesized various quinlinolinone derivatives, including 5-substituted quinlinolinones, which are difficult to obtain using the traditional pathway. The directing group could be easily removed and could be readily transformed into other useful functional groups.

Introduction

The 2-quinolinone unit is a heterocycle present in numerous natural alkaloids, biologically active compounds, and commercial drugs.[1] Over the past decades, various synthetic methods for 2-quinolinone have been developed. These include Friedel–Crafts cyclization,[2] transition-metal-catalyzed cascade reaction,[3] and radical reactions.[4] However, further studies showed that these methods usually suffered from harsh reaction conditions, limited substrates scope or the use of prefunctionalized substrates.

In the last decades, transition-metal-catalyzed direct C–H activation has resulted in great achievements in cross-coupling reactions, which provide an alternative approach for constructing versatile synthons without requiring prefunctionalization.[5] Thus, a convergent procedure to synthesize various functional substituted 2-quinolinone derivatives through C–H functionalization would be very attractive in synthetic chemistry. Retrosynthesis of 2-quinolinone revealed that it could be performed with simple carboxylic acids and aryl iodides via palladium-catalyzed β-C(sp^3)–H arylation and subsequent intramolecular δ-C(sp^2)–H amination (Scheme **1A**). However, we anticipated several potential problems that should be addressed to ensure the applicability of the procedure for 2-quinolinone synthesis. (1) Despite the development of numerous possible directing groups for carboxylic acid, such as 8-aminoquinoline,[6] *o*-methyl hydroxyamine,[7] 2-methylthioaniline,[8] fluorinated aniline,[9] amino ester,[10] amino acid,[11] isoleucine-NH$_2$,[12] and carboxylic acids themselves,[13] there are few protocols for six-membered *N*-heterocycles using directing-group-assisted

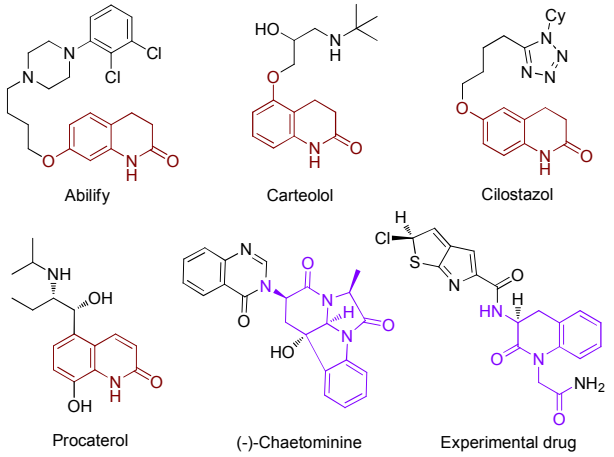

Figure 1 Drugs that contain the quinlinolinone unit.

intramolecular amination.[14] The groups of Shi[15] and Wu[16] demonstrated that a versatile intramolecular amination using an N,N-bidentate directing group and phenylalanine derivatives tends to generate four-membered *N*-heterocycles via five-membered palladacycles. Thus, a new directing group that can easily form seven-membered palladacycles, which are rare, need to be explored. (2) Although β-C(sp^3)–H arylation of

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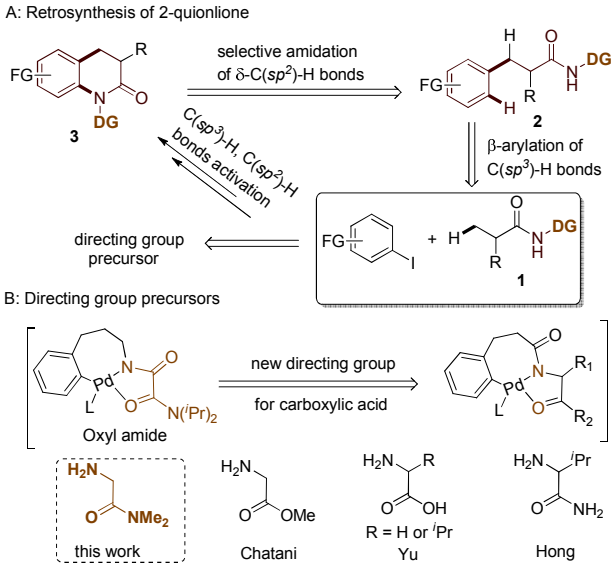
carboxylic acid derivatives with aryl iodides using directing groups has been reported,[6-12, 17] *ortho*-substituted aryl iodides have seldom been used as coupling partners.[11] *Ortho*-substituted aryl iodides are the main substrates for the synthesis of important drugs such as carteolol and procaterol.



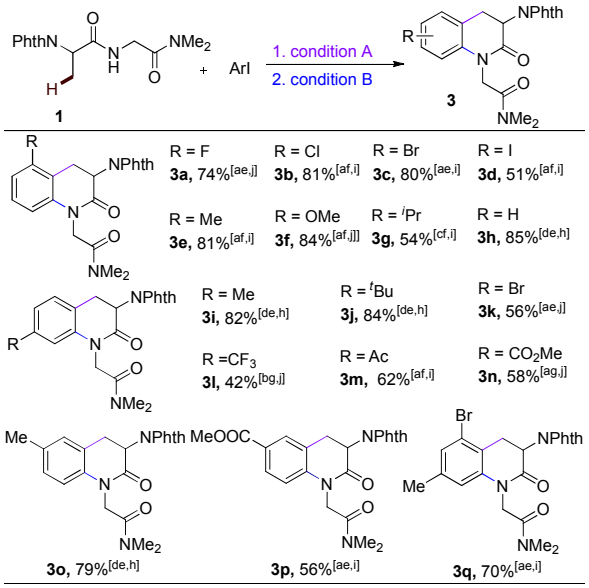
Scheme 1 Use of GDMA as an auxiliary for carboxylic acid.

Thus, there is a need for protocols that use various *ortho*-substituted aryl iodides as coupling partners, which give the key intermediate for the synthesis of various 2-quinolinones. (3) The directing group should be easily removable or should allow further transformation to other desired functional groups. Herein, we report a convenient, effective, and readily applicable protocol for the synthesis of 2-quinolinone derivatives from carboxylic acids and aryl iodides via palladium-catalyzed sequential C–H arylation and intramolecular amination using a novel N,O-bidentate directing group. The newly developed protocol provides a convergent path for the synthesis of key intermediates of bioactive compounds. More importantly, various 5-substituted 2-tetrahydroquinolinones, which are difficult to synthesize through traditional paths, were obtained in good yield (Scheme 1).

Results and discussion

Our group demonstrated that the N,O-bidentate directing group has high activity in forming C–H bonds at the ε position,[18] which leads to a rare seven-membered palladacycle. On the basis of these observations, we propose that glycine dimethylamide (GDMA) might be a suitable directing group for promoting remote C–H functionalization via the palladacycle (Scheme **1B**). At the start of our study, we explored 2-quinolinone synthesis at 120 °C through a general method using various directing groups, namely, protected phenylpropionic acid, $PhI(OAc)_2$, and $Pd(OAc)_2$ in dichloridethane. The groups of Yu, Chatani, and Hong respectively found that the directing groups including α-amino acid, α-amino ester, and α-amino amide exhibit high activity in palladium-catalyzed β-arylation of carboxyl acid derivatives. However, none of them obtained the intramolecular amination products, recovering the starting material only (see SI, Table S1). As expected, phenylpropionic acid protected by GDMA

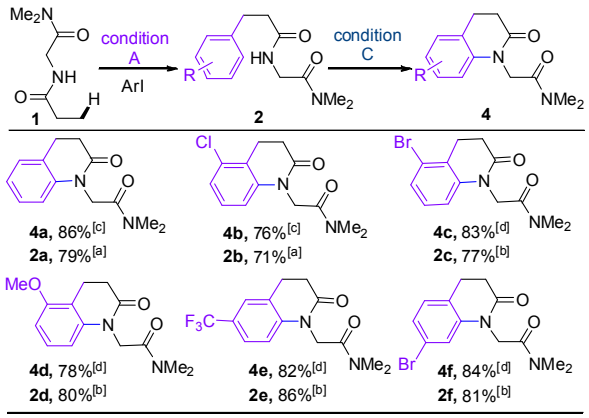
Table 1 Synthesis of quinolinones from alanine with aryl idodies by palladium catalyzed cascade C-H functionalization



Condition A: [a] **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), AgOAc (2 equiv), HFIP (1 mL), 80 °C, air, 12 h. [b] 100 °C. [c] 120 °C. [d] *t*-AmylOH (1 mL). [e] **ArI** (1.2 equiv). [f] ArI (1.5 equiv). [g] **ArI** (1.05 equiv).

Condition B: [h] $PhI(OAc)_2$ (2.5 equiv), PivOH (0.3 equiv), HFIP (4 mL), 70 °C, Ar, 18 h. [i] 100 °C. [j] 120 °C.

Table 2 Synthesis of quinolinones from propionic acid with aryl idodies by palladium catalyzed cascade C-H functionalization



Condition A: [a] **1** (0.2 mmol), **ArI** (1.5 equiv), $Pd(OAc)_2$ (5 mol%), AgOAc (2 equiv), HFIP (1 mL), 80 °C, air, 36 h. [b] 100 °C.

Condition C: [c] **2** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (2 equiv), HFIP (5 mL), 70 °C, Ar, 18 h. [d] 100 °C.

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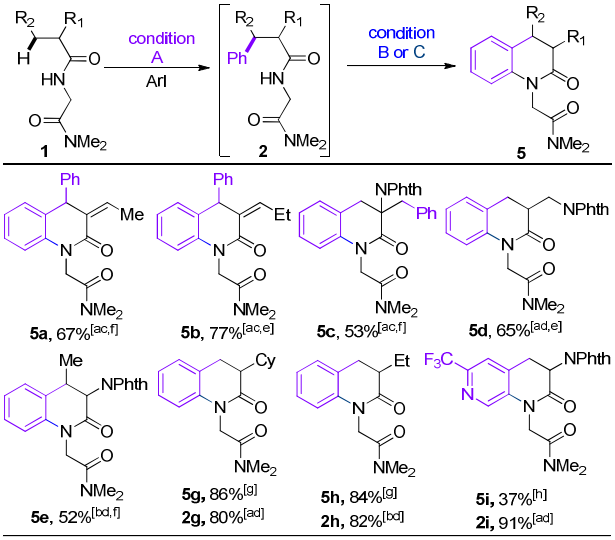
could give the six-membered N-heterocycle in good yield. Further scanning quickly revealed that the best reaction conditions, which gave **4a** in 91% isolated yield (see SI, Table S2, entry 6), consisted of substrate **2a** (1 equiv), $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (2.5 equiv) in HFIP (0.04 M), temperature of 70 °C, and reaction time of 18 h. When the TEMPO was used as additive, **4a** was obtained at 90% yield. Further controlled experiments revealed that palladium acetate was indispensable in this intramolecular amination.

Table 3 Synthesis quinolinones from general carboxylic acid with aryl idodies by palladium catalyzed cascade C-H functionalization

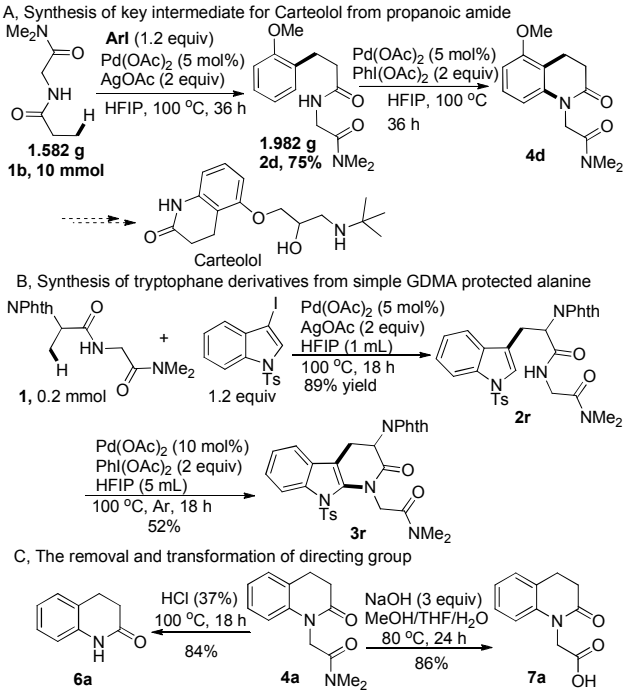


Condition A: [a] **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (2 equiv), HFIP (1 mL), 80 °C, air, 24 h. [b] 100 °C. [c] **ArI** (3 equiv). [d] **ArI** (1.5 equiv).

Condition B: [e] $PhI(OAc)_2$ (2.5 equiv), PivOH (0.3 equiv), HFIP (4 mL), 80 °C, Ar, 18 h. [f] 100 °C.

Condition C: [g] **2** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (2 equiv), HFIP (5 mL), 70 °C, Ar, 18 h. [h] 100 °C.

Having identified the directing group and optimized the catalytic system, we examined the importance of our directing group in the construction of bioactive units by sequential C–H functionalization (Table 1). For example, the skeleton of the product **3** is the key structure in a series of bioactive compounds.[19] More importantly, the directing group can be part of the functional group of these bioactive compounds. On the basis of these results, GDMA-protected 2-phthalimidopropionic acid was first treated with iodobenzene (1.2 equiv), AgOAc (2 equiv), and $Pd(OAc)_2$ (5 mol%) in HFIP at 80 °C for 12 h. NMR spectroscopy showed a nearly quantitative yield of the crude β-arylated product. Thus, we directly used the oxidant $PhI(OAc)_2$ (2.5 equiv), the additive PivOH (0.3 equiv), and the solvent HFIP (4 mL) in the arylation. Further reaction at 70 °C for another 18 h led to the desired cyclized product **3a** at 85% yield. We then synthesized various 2-quinolinones by using different aryl iodides using the two-step one–pot method. Gratifyingly, a broad range of electron-withdrawing (F, Cl, Br, I, CF_3 and COOMe) or electron-donating groups (Me, MeO, *i*Pr, and *t*Bu) substituted with aryl iodides could be used in the transformation. Notably, *ortho*-substituted aryl iodides afforded the corresponding products in good to excellent yield (**3a–h**). *Meta*-and *para*-substituted aryl iodides also worked well in this transformation, resulting in good to excellent yield of products (**3i–q**).



Scheme 2 The removal and transformation of directing group.

3,4-Dihydro-2(1*H*)-quinolinone derivatives were also prepared by using GDMA-protected propionic acid and various aryl iodides through palladium-catalyzed sequential C–H arylation and intramolecular amination (Table 2). Gratifyingly, the newly developed N,O-bidentate directing group displayed strong ability to promote β-C(sp^3)–H arylation. Even the *ortho*-substituted aryl iodides, which have never been used as coupling partners with propionic amide in previous reports, provided 5-substituted 3,4-dihydro-2(1*H*)-quinolinone derivatives in good yield in two steps; such derivatives are difficult to prepare through the traditional route.[20] The halide-substituted arene thus can give access to different functional groups by cross-coupling reaction (**4b**, **4c**, and **4f**).

We then explored the GDMA-directed intramolecular amination of simple carboxylic acid derivatives under standard conditions (Table 3). Generally, β-arylation of the Me group using the one-pot two–step method affords the cyclized products (**5a–d**) in good yield. Interestingly, **5a** and **5b** underwent selective diarylation at the β-C(sp^3)–H position rather than at the β-C(sp^2)–H position, indicating spatial effects on C–H activation. The β-methylene C–H bond could also be sequentially arylated and aminated, affording 5e in synthetic acceptable yield. However, products **5g–i** obtained by one-pot synthesis had low yield. Herein, we first isolated the β-arylated products **2g–i** and then treated them under standard

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conditions for intramolecular amination. The cyclized products (**5g–i**) were obtained in good yield.

To determine the synthetic utility of sequential arylation and intramolecular amination, we conducted a gram reaction to form product **4d** (52% total yield) from GDMA-protected propanoic acid in two steps (Scheme **2A**). Importantly, the product of **4d** is a key intermediate for the synthesis of drug Carteolol.[21] The product **3r** could be observed in good yield by employing the **1a** as starting material in two steps. The directing group, GDMA, could be easily removed with concentrated hydrochloric acid to afford **6a** in 84% yield.[22] The GDMA could be transformed into carboxylic acid **7a** in 86% yield under basic conditions[23] (Scheme **2C**).

Conclusions

In conclusion, we developed an effective procedure for the synthesis of 2-quinlinolinone derivatives by palladium-catalyzed sequential β-C(sp^3)–H arylation and selective intramolecular C(sp2)–H/N–H amination starting with aryl iodide and carboxylic acid. Synthesis uses a novel auxiliary directing group, GDMA. The GDMA exhibits strong ability in promoting β-C(sp^3)–H arylation and intramolecular amination, which lead to key intermediates for bioactive compounds. Our method provides a convenient route for the synthesis of 5-hydroxy-3,4-dihydro-1*H*-quinolin-2-one, which is the key intermediate for carteolol. GDMA can be easily removed and can be readily transformed into useful functional groups. Further mechanistic studies on new applications of GDMA as a directing group are underway in our laboratory.

Acknowledgements

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