DOI: 10.1002/adsc.201600512
Advanced Synthesis & Catalysis

Metal-Free Synthesis of 3-Arylquinolin-2-ones from *N*,2-Diarylacrylamides *via* Phenyliodine(III) Bis(2,2-dimethylpropanoate)-Mediated Direct Oxidative C–C Bond Formation

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Received: May 14, 2016; Revised: July 20, 2016; Published online on ■■ ■■, 0000

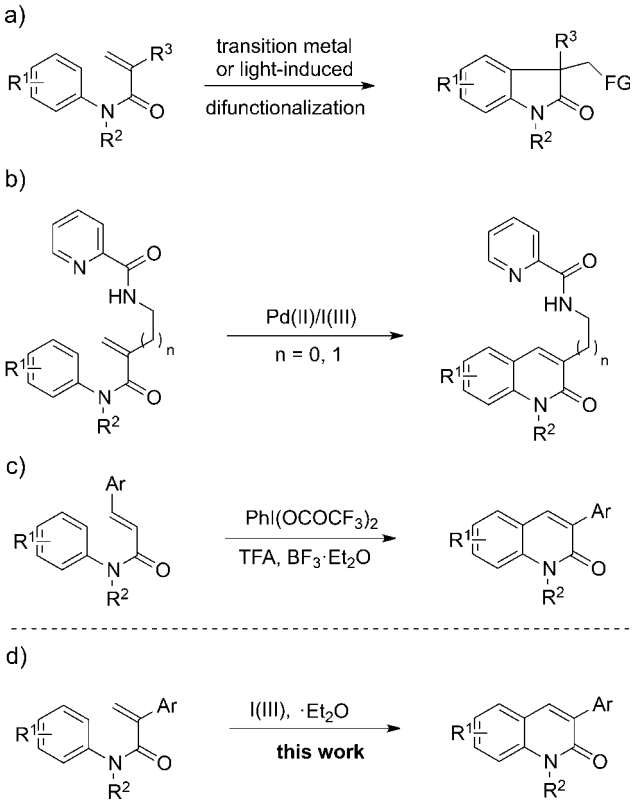
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201600512.

Abstract: Treatment of *N*,2-diarylacrylamides with the organoiodine(III) compound phenyliodine(III) bis(2,2-dimethylpropanoate) [$PhI(O_2C$-*t*-$Bu)_2$] and boron trifluoride etherate ($BF_3{\cdot}Et_2O$) resulted in a direct and selective oxidative C(sp^2)–C(sp^2) bond formation leading to a convenient assemblage, under mild conditions, of the biologically important 3-arylquinolin-2-one skeleton. Differing from the five-membered oxindole products from oxidative cyclizations mediated by transition metals, this metal-free approach realized a direct annulation of the *N*-arylacrylamide into a six-membered 3-arylquinolin-2-one skeleton.

Keywords: 3-arylquinolin-2-ones; C(sp^2)–C(sp^2) bond formation; organoiodine(III) compounds; oxidative annulation

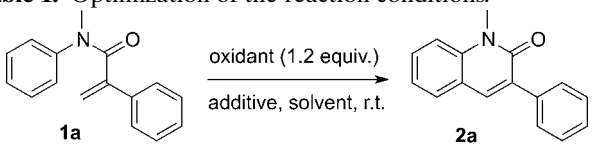
The 3-quinolin-2-one scaffold, especially that of 3-arylquinolin-2-one, is an important structural motif is not only found in many naturally occurring compounds[1] and pharmaceutically active molecules possessing anticancer,[2] anti-HIV,[3] antibiotic,[4] antiviral,[5] antihypersensitivity[5] and other biological activities,[6] but is also used as valuable building blocks for the syntheses of many natural alkaloids.[7] For this reason, many synthetic efforts have been devoted to the assemblage of this significant skeleton. Aside from the well-known Friedländer reaction, Knorr synthesis and Vilsmeier approach,[8] intra-[9a] or intermolecular[9b,c] carbocyclization of internal alkynes, amidation of *o*-carbonyl-substituted aryl halides,[10] tandem decarboxylative radical addition/cyclization of *N*-arylcinnamides with aliphatic carboxylic acids,[11] carbonylation and annulation of simple CO-containing anilines[12] withalkynes and a [5+2-1] transformation between isatins and alkynes[13] have all been applied to the syntheses of quinolin-2-one compounds. While each of the aforementioned methods has, in its own right, unique merits in constructing the corresponding quinolin-2-one compounds, developing a more efficient and/or more economical method, preferably under metal-free conditions and with readily available starting materials remains highly desirable.

It can easily be envisaged that *N*-arylacrylamide derivatives would represent the most logical choice as substrates for the construction of the 3-quinolin-2-one skeleton if a direct oxidative C(sp^2)–C(sp^2) bond formation could be realized. However, to the best of our knowledge, only a five-membered oxindole framework was formed, in all reports, *via* 5-*endo* cyclization when *N*-arylacrylamide was subjected to transition metal-mediated or light-induced C–H functionalization reactions (Scheme 1a).[14] Studies on converting *N*-arylacrylamides to the six-membered quinolinone skeleton through direct oxidative C(sp^2)–C(sp^2) bond formation have been scarce. Recently, Liu and coworkers[15] demonstrated that, by using a combination of palladium and a cyclic hypervalent iodine oxidant, *N*-arylacrylamides could be annulated directly to give the six-membered quinolone compounds (Scheme 1b). The involvement of the transition metal as well as the presence of the picolinamide moiety in the substrate was found to be essential for the formation of the C–C bond to take place. In 2013, we reported[16] the conversion of *N*-methyl-*N*-phenylcinnamides to 3-arylquinolin-2-ones through a phenyliodine bis(trifluoroacetate) (PIFA)-mediated C–C bond formation concomitant with an exclusive 1,2-aryl shift (Scheme 1c). However, the migrating aryl group was indispensable for the cyclization to occur. In this update, we report a direct oxidative C(sp^2)–C(sp^2)



Scheme 1. Existing strategies for the annulation of *N*-arylacrylamide derivatives.

Table 1. Optimization of the reaction conditions.[a]



Entry	Oxidant	Additive (equiv.)	Time [h]	Yield [%][b]
1	PIDA	none	24	–[c]
2	PIDA	$BF_3{\cdot}Et_2O$ (1.0)	1.5	75
3	PIDA	$BF_3{\cdot}Et_2O$ (1.2)	1.5	71
4	PIDA	$BF_3{\cdot}Et_2O$ (0.5)	2.0	79
5	PIDA	$BF_3{\cdot}Et_2O$ (0.3)	4.5	76
6	PIDA	TFA (1.0)	3	43
7	PIFA	$BF_3{\cdot}Et_2O$ (1.0)	1	60
8	**$PhI(O_2C\text{-}t\text{-}Bu)_2$**	**$BF_3{\cdot}Et_2O$ (0.5)**	**2**	**88**
9	$PhI(O_2C\text{-}t\text{-}Bu)_2$	$BF_3{\cdot}Et_2O$ (0.5)	2.5	52
10	$PhI(O_2C\text{-}t\text{-}Bu)_2$	none	1.0	15
11	$PhI(O_2C\text{-}t\text{-}Bu)_2$	$BF_3{\cdot}Et_2O$ (0.5)	1.5	47
12	$PhI(O_2C\text{-}t\text{-}Bu)_2$	$BF_3{\cdot}Et_2O$ (0.5)	1.5	58

[a] All reactions were carried out with **1a** (1.0 mmol) and oxidant (1.2 mmol) in DCM (10 mL) at room temperature unless otherwise stated.
[b] Isolated yield.
[c] Not detected.
[d] The reactions were run in TFE (10 mL).
[e] The reactions were run in TFA (10 mL).
[f] The reactions were run in HFIP (10 mL).
[g] The reactions were run in MeCN (10 mL).

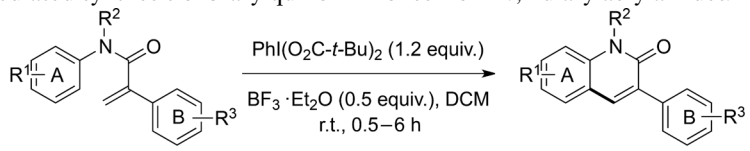
bond formation approach to afford a six-membered 3-arylquinolin-2-one from an *N*,2-diarylacrylamide compound by applying a hypervalent iodine(III) reagent as the oxidant in the presence of $BF_3{\cdot}Et_2O$ as additive (Scheme 1d). This method likely represents the first direct annulation of *N*-arylacrylamides to construct the 3-arylquinolin-2-one skeleton in a metal-free environment.

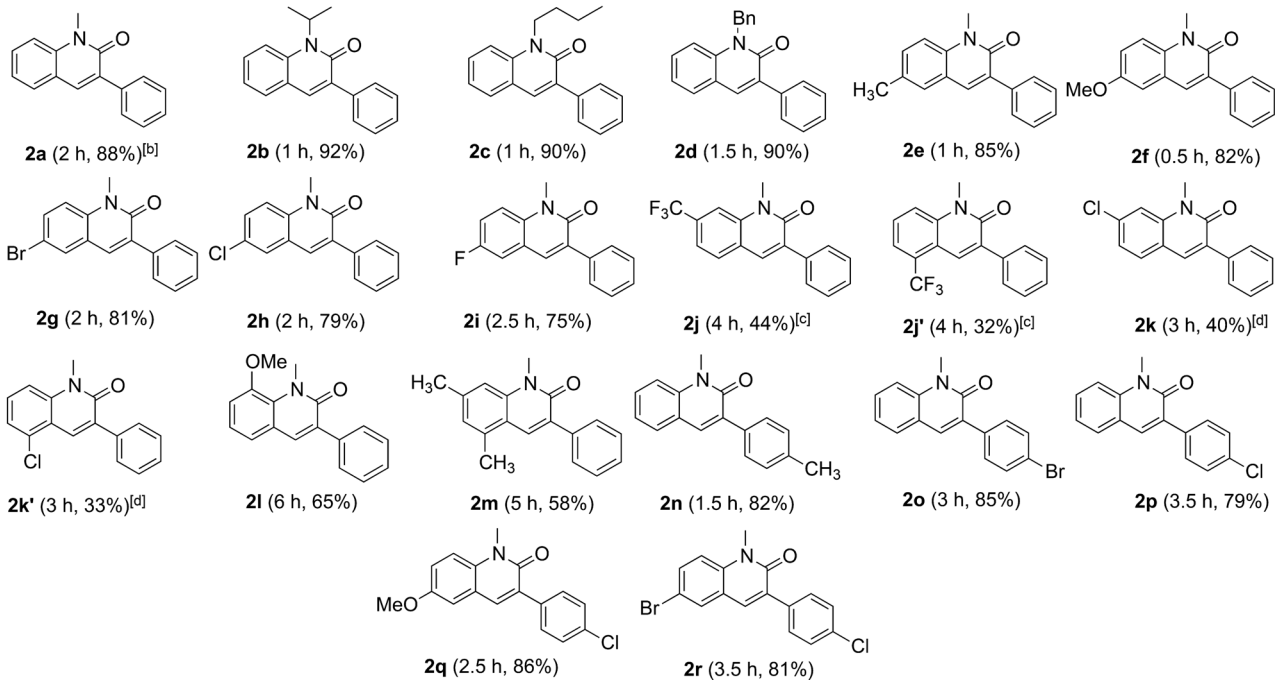
The readily available *N*,2-diarylacrylamide **1a** was initially used as a benchmark substrate to probe the feasibility of the expected direct oxidative annulation facilitated by hypervalent iodine as oxidant. Exposure of **1a** to phenyliodine diacetate (PIDA) in dichloromethane (DCM) for 24 h showed no cyclized product (Table 1, entry 1). However, when 1.0 equivalent of $BF_3{\cdot}Et_2O$ was introduced to the reaction, the desired product **2a** was isolated in 75% yield (Table 1, entry 2). Inscreasing the dosage of $BF_3{\cdot}Et_2O$ to 1.2 equivalents brought about a slightly descreased yield of **2a** (Table 1, entry 3); while a reduced dosage of 0.5 equivalent improved the yield to 79% (Table 1, entry 4). Further decrease of the dosage of $BF_3{\cdot}Et_2O$ to 0.3 equivalent afforded a similar yield, but at the cost of a much lengthened reaction time (Table 1, entry 5). Switching the additive to trifluoroacetic acid (TFA) significantly decreased the desired product yield to only 43% (Table 1, entry 6).

Applying the more potent oxidant PIFA led to a lowered yield of 60% (Table 1, entry 7). Much screening of appropriate oxidants led us to discover that phenyliodine(III) bis(2,2-dimethylpropanoate) [$PhI(O_2C\text{-}t\text{-}Bu)_2$] facilitated a much improved, satisfactory yield of 88% (Table 1, entry 8). This result indicated that a hypervalent iodine reagent bearing a bulky ligand was beneficial for the yield of the reaction. Further attempts to improve the outcome of the reaction such as by switching to other solvents including 2,2,2-trifluoroethanol (TFE), trifluoroacetic acid (TFA), hexafluoroisopropyl alcohol (HFIP) and acetonitrile (MeCN) proved to be futile (Table 1, entries 9–12).

Under the optimized conditions (Table 1, entry 8), the generality and scope of this newly established method was investigated. The results are shown in Table 2. It was found that the alkyl substituent on the nitrogen atom was crucial, as the reaction for the unsubstituted substrate ($R^2 = H$) resulted in a complex mixture (not shown). Substrates bearing an alkyl R^2 group of various sizes including isopropyl (**1b**), *n*-butyl (**1c**) and benzyl (**1d**) were all converted to the corresponding products in similarly high yields (Table 2, **2b–d**).

Table 2. PhI(O_2C-*t*-Bu)$_2$-mediated synthesis of 3-arylquinolin-2-ones from *N*,2-diarylacrylamides.[a]





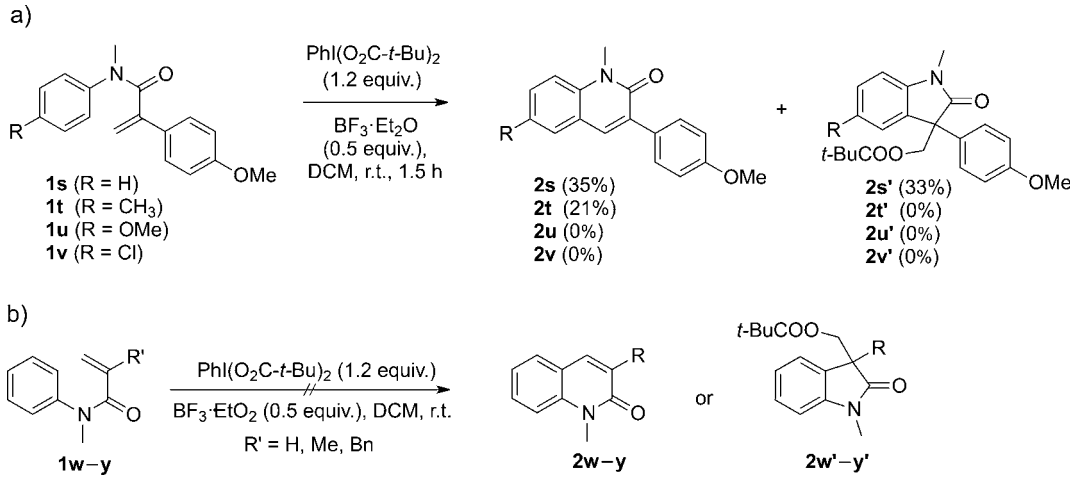
[a] *Reaction conditions*: **1** (1.0 mmol), PhI(O_2C-*t*-Bu)$_2$ (1.2 mmol) in DCM (10 mL) at room temperature.
[b] Isolated yield unless otherwise stated.
[c] The ratio of two separable products, **2j** (7-CF_3) and **2j′** (5-CF_3), was 1.4:1.
[d] The ratio of two separable products, **2k** (7-Cl) and **2k′** (5-Cl), was 1.2:1.

We were delighted to see that the method could be well applied to substrates with the aryl moieties bearing electron-donating or electron-withdrawing substituents. Our studies showed that the substituent effects of R^1 and R^3 were overall insignificant. Specifically, an electron-donating R^1 substituent (Me, MeO) imposed essentially no effect on the reaction yield while an electron-withdrawing group (F, Cl, Br, CF_3) slightly disfavored the reaction (Table 2, **2e–k′**, **2q** and **2r**). In the case of *meta*-substituted substrates bearing either a CF_3 or a Cl group (Table 2, **2j–2k′**), two separable regioisomeric 3-arylquinolin-2-one products **2j/2j′** and **2k/2k′** were formed in each case, with the cyclization occurring preferentially at the less hindered position as one would have expected. *ortho*-Substituted substrate **1l** also delivered the corresponding product **2l**, albeit in a decreased yield of only 65%, likely due to the fact there is only one *ortho* position left to cyclize at as opposed to two in the cases of *para*- and *meta*-substituted substrates (Table 2, **2l**). The substrates bearing various R^3 groups, either electron-donating (Me) or electron-withdrawing (Cl, Br) groups, all gave similar satisfactory yields like the unsubstituted counterpart (Table 2, **2n–p**).

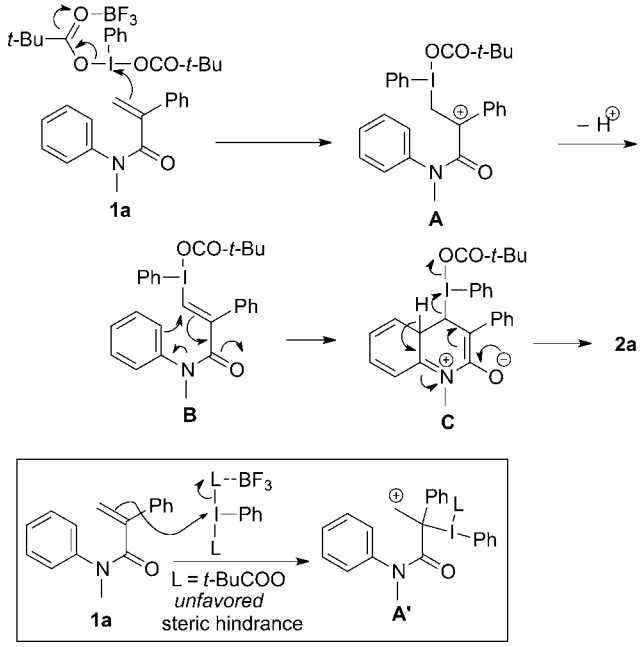
Special cases were observed for substrates with R^3 = OMe (Scheme 2a): Substrate **1s** afforded as a by-product the five-membered oxindole product **2s′** (33% yield) in addition to the six-membered product **2s** (35% yield); while substrate **1t** afforded only the six-membered product **2t** (21% yield), with no by-product **2t′**; substrates **1u** and **1v** delivered a complex mixture containing no desired product.

Additional control experiments revealed that the vinyl aryl group was indispensable for the desired cyclization to occur, as, shown in Scheme 2b, the 3-alkyl-substituted acrylamides **1w–y** could not be converted to the corresponding products under the applied, optimized conditions.

Based on all the experimental results as well as previous literature reports,[17] a plausible mechanism was formulated. A radical mechanism was ruled out since the addition of the radical scavenger (TEMPO) had no significant impact on the outcome of the yield. As is described in Scheme 3 using **1a** as an example,



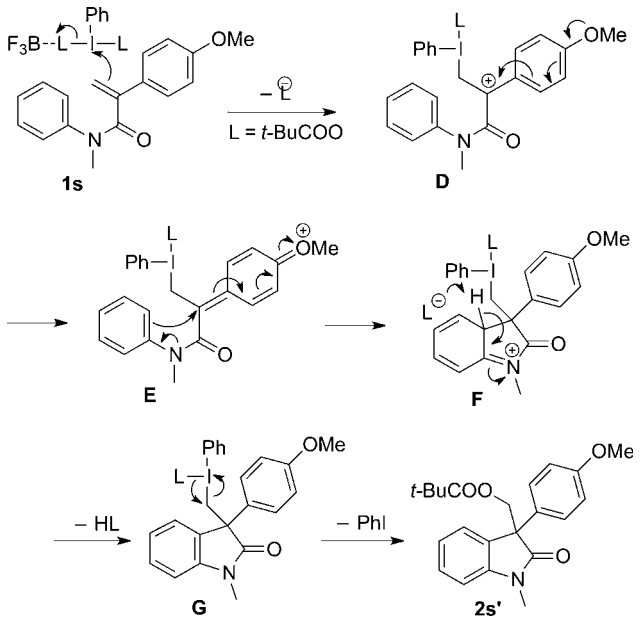
Scheme 2. Special cases of the reactions under the standard conditions.



Scheme 3. Plausible mechanistic pathway for the formation of **2a**.

the alkene moiety in *N*,2-diarylacrylamide first nucleophilically attacked the iodine center in PhI(O_2C-*t*-Bu)$_2$, after being activated by the Lewis acid BF_3·Et_2O, and gave a benzylic carbocation intermediate **A**. The crucial role played by the aryl moiety can be explained here for the formation of the benzylic carbocation for extra stability probably required for the reaction path. Next, removal of a proton in **A** formed the intermediate **B** in which cyclization occurred to give an ylide intermediate **C**. In this intramolecular nucleophilic aromatic substitution reaction step, electron-withdrawing R^1 groups would be expected to disfavor the reaction by decreasing the nucleophilicity of the benzene ring, which is consistent with our experimental results of the yield data listed in Table 2. Finally, removal of a molecule of phenyl iodide and pivalic acid in **C** with the concomitant abstraction of a proton enabled the rearomatization to give the title product **2a**.

Regarding substrate **1s**, in addition to the above reaction mechanism, the reaction also underwent an alternative pathway in a competitive manner. As depicted in Scheme 4, a conjugation occurred due to



Scheme 4. Plausible mechanistic pathway for generation **2s′**.[18]

the presence of the strong electron-donating methoxy group after the formation of the carbocation inter-

mediate **D**, and converted **D** to the oxonium intermediate **E**. Next, 5-*exo* cyclization and the abstraction of a proton from **F** gave the oxindole **G**. Finally, reductive elimination of PhI from **G** afforded the five-membered oxindole product **2s′**.

In summary, we have described a novel approach for the construction of the six-membered 3-arylquinolin-2-one framework *via* a hypervalent iodine-mediated direct oxidative C(sp^2)–C(sp^2) bond formation of *N*,2-diarylacrylamide derivatives. The methodology features readily available starting materials, mild and transition metal-free reaction conditions, and tolerance of a wide range of functional groups. The importance of the 3-arylquinolin-2-one compounds should render this method a useful organic synthetic tool.

Experimental Section

General Procedure for Preparation of 3-Arylquinolin-2-ones 2

To a solution of **1** (1.0 mmol) in DCM (6.0 mL) was slowly added PhI(O_2C-*t*-Bu)$_2$ (1.2 mmol). Then, a solution of $BF_3{\cdot}Et_2O$ (0.5 mmol) in DCM (4 mL) was added dropwise to the above mixture under stirring. The resulting mixture remained at room temperature under stirring, and the progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was poured into cold water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (50 mL) before being dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by silica gel chromatography, using a mixture of PE/EA to afford the desired product **2**.

Acknowledgements

We acknowledge the National Science Foundation of China (#21472136), Tianjin Research Program of Application Foundation and Advanced Technology (#15JCZDJC32900) and the National Basic Research Project (#2014CB932201) for financial support.

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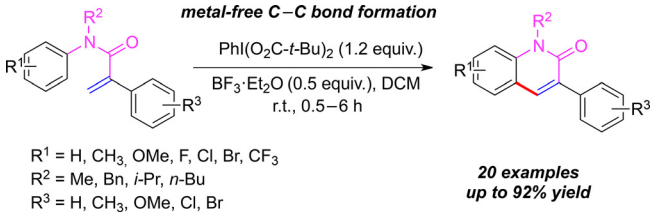

Adv. Synth. Catal. **2016**, *358*, 1–7

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