ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

$PhI(OCOCF_3)_2$-Mediated C–C Bond Formation Concomitant with a 1,2-Aryl Shift in a Metal-Free Synthesis of 3-Arylquinolin-2-ones

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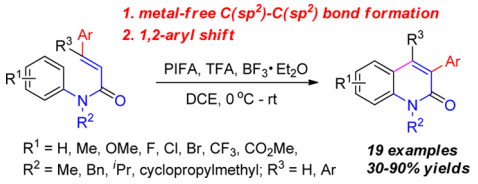
Received March 19, 2013

ABSTRACT



The reaction of the readily available *N*-methyl-*N*-phenylcinnamamides with phenyliodine bis(trifluoroacetate) (PIFA) in the presence of Lewis acids provides a general and efficient assembly of a variety of 3-arylquinolin-2-one compounds. This novel approach features not only metal-free oxidative C(sp^2)–C(sp^2) bond formation but also an exclusive 1,2-aryl migration.

The development of a transition-metal-free approach for direct oxidative C–C bond formation is undoubtedly a topic of great interest in organic synthesis since such transformations represent an attractive alternative to the traditional transition metal-catalyzed oxidative C–C coupling reactions.[1] In recent decades, hypervalent iodine reagents[2] have emerged as a class of efficient and environmentally benign nonmetal oxidants that can realize the constructions of C–C bonds[3] without the involvement of transition metals.[4] Furthermore, the hypervalent iodine reagents may also trigger a particular 1,2-aryl shift in some I(III)-mediated rearrangement reactions[5] of aryl-substituted alkenes. To the best of our knowledge, the utilization of hypervalent iodine reagent to realize a concurrent

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(2) For selected reviews, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (b) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402. (c) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185. (d) Ding, Q.; Ye, Y.; Fan, R. *Synthesis* **2013**, *45*, 1.

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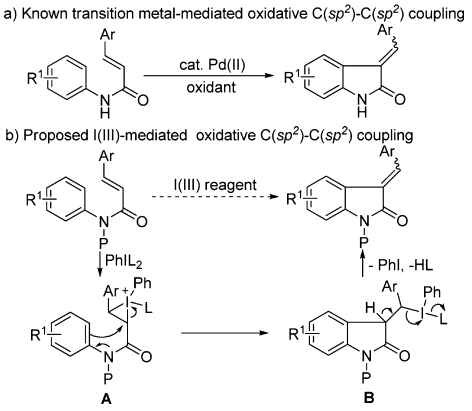
10.1021/ol400743r

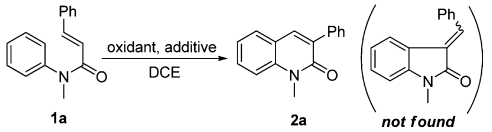
Scheme 1. Proposed I(III)-Mediated C(sp^2)−C(sp^2) Oxidative Coupling of *N*-Phenylcinnamamides Based on the Previously Reported Transition-Metal-Mediated Coupling Reaction



oxidative C(sp^2)−C(sp^2) bond formation and 1,2-aryl shift has never been reported. In this communication, we disclose that *N,N*-disubstituted arylcinnamamide compounds can be converted to the biologically important 3-arylquinolin-2-ones through an unprecedented I(III)-mediated oxidative C(sp^2)−C(sp^2) bond formation, along with a simultaneous aryl migration (see the graphical abstract). As far as we know, this methodology represents a rare application of hypervalent iodine reagents in which both C(sp^2)−C(sp^2) bond formation and aryl migration are realized at the same time.

β-Unsubstituted *N*-arylacrylamide derivatives have been well studied as a useful substrate for the construction of heterocyclic framework through oxidative C−C bond formation.[6] Notably, starting from the readily available *N*-phenylcinnamamide substrates, Nagasawa and co-workers[6e] realized the synthesis of 3- alkylideneoxindoles through palladium-catalyzed aromatic C−H functionalization/intramolecular alkenylation (Scheme 1, a). Inspired by the fact that the oxidative role played by hypervalent iodine reagents in some C(sp^2)−C(sp^2) coupling reactions considerably resemble that of the transition-metal/oxidant system,[7] we envisaged that the same oxidative C−C bond formation might also be achieved from the reaction between a suitable iodine(III) reagent and an *N*-acryloylaniline substrate. We postulate that the electrophilic addition of the iodine(III) reagent to the double bond in the substrate affords the intermediate A,[8] which undergoes annulation (and forms intermediate **B**) and the subsequent elimination to give the expected alkylideneoxindoles (Scheme 1, b).

Table 1. Optimization of Iodine(III)-Mediated C−C Oxidative Coupling and 1,2-Aryl Shift[a]



entry	oxidant	additive	time (h)	yield[b] (%)
1	PIFA		24	NR
2	PIFA	$BF_3\cdot Et_2O$ (1)	12	20
3	PIFA	TFA (5)	24	43
4	PIFA	$BF_3\cdot Et_2O$ (1)/TFA (5)	12	60
5	PIFA	$BF_3\cdot Et_2O$ (1)/TFA (10)	6	68
6[c]	PIFA	$BF_3\cdot Et_2O$ (1)	0.5	55
7[d]	PIFA	$BF_3\cdot Et_2O$ (1)/TFA (10)	6	67
8[e]	PIFA	$BF_3\cdot Et_2O$ (1)/TFA (10)	6	72
9[f]	PIFA	$BF_3\cdot Et_2O$ (1)/TFA (10)	6	88
10	PIDA	$BF_3\cdot Et_2O$ (1)/TFA (10)	8	65
11	PhIO	$BF_3\cdot Et_2O$ (1)/TFA (10)	24	NR

[a] All reactions were carried out with **1a** (0.4 mmol) and oxidant (1.5 equiv) in DCE (16 mL) unless otherwise stated. [b] Isolated yields. [c] TFA was used as the solvent. [d] 2.0 equiv of oxidant was used. [e] The concentration of the reaction was 0.05 M. [f] The concentration of the reaction was 0.025 M.

Initially, the readily available *N*-methyl-*N*-phenylcinnamamide **1a** was selected as the model substrate to probe the feasibility of the proposed conversion. To our surprise and delight, the reaction of **1** equiv of **1a** with 1.5 equiv of PIFA in the presence of 1 equiv of $BF_3\cdot Et_2O$ in DCE did not give the expected five-membered oxindole product but afforded 20% yield of a six-membered *N*-methyl-3-phenylquinolin-2(1*H*)-one **2a** (the structure of which was unambiguously confirmed through X-ray crystallographic analysis), the process of which obviously involves an interesting oxidative C−C bond formation and 1,2-aryl shift. Further condition screening was carried out to formulate the most optimal conditions for this extraordinary reaction.

The results are summarized in Table 1. When $BF_3\cdot Et_2O$ was used together with TFA as additive, the yield of **2a**

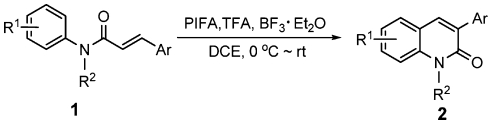
(5) For selected examples, see: (a) Singh, F. V.; Rehbein, J.; Wirth, T. *ChemistryOpen* **2012**, *1*, 245. (b) Justik, M. W.; Koser, G. F. *Tetrahedron Lett.* **2004**, *45*, 6159. (c) Kawamura, Y.; Maruyama, M.; Tokuoka, T.; Tsukayama, M. *Synthesis* **2002**, 2490. (d) Prakash, O.; Tanwar, M. P. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1168. (e) Prakash, O.; Pahuja, S.; Goyal, S.; Sawhney, S. N.; Moriarty, R. M. *Synlett* **1990**, *6*, 337. (f) Guerard, K. C.; Guerinot, A.; Bouchard-Aubin, C.; Menard, M.; Lepage, M.; Beaulieu, M. A.; Canesi, S. *J. Org. Chem.* **2012**, *77*, 2121.

(6) For selected examples, see: (a) Piou, T.; Neuville, L.; Zhu, J. *Org. Lett.* **2012**, *14*, 3760. (b) Wu, T.; Mu, X.; Liu, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 12578. (c) Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem. −Eur. J* **2007**, *13*, 961. (d) Wei, H.; Piou, T.; Dufour, J.; Neuville, L.; Zhu, J. *Org. Lett.* **2011**, *13*, 2247. (e) Ueada, S.; Okada, T.; Nagasawa, H. *Chem. Commun.* **2010**, *46*, 2462. (f) Liu, X.; Xin, X.; Xiang, D.; Zhang, R.; Kumar, S.; Zhou, F.; Dong, D. *Org. Biomol. Chem.* **2012**, *10*, 5643. (g) Jaegil, S.; Dufour, J.; Wei, H.; Piou, T.; Duan, X.; Vors, J.; Neuville, L.; Zhu, J. *Org. Lett.* **2010**, *12*, 4498. (h) Yip, K.; Yang, D. *Org. Lett.* **2011**, *13*, 2134. (i) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948. (j) Zhang, G.; Luo, Y.; Wang, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4450. (k) Lovick, H.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249. (l) Wei, W.; Zhou, M.; Fan, J.; Liu, W.; Song, R.; Liu, Y.; Hu, M.; Xie, P.; Li, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1. (m) Li, Y.; Sun, M.; Wang, H.; Tian, Q.; Yang, S. *Angew. Chem., Int. Ed.* **2012**, *52*, 1.

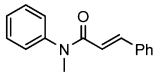
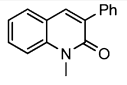
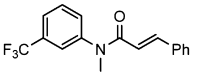
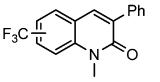
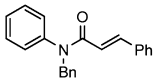
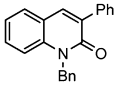
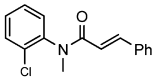
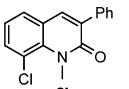
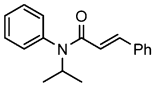
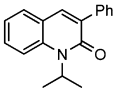
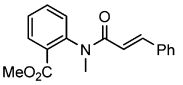
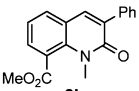
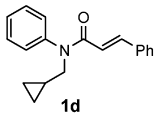
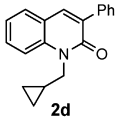
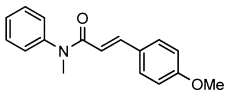
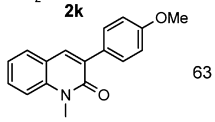
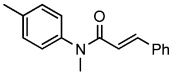
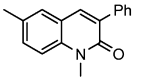
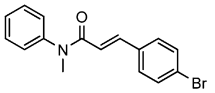
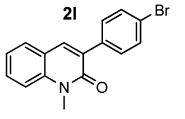
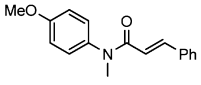
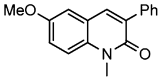
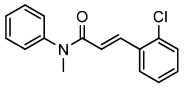
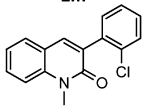
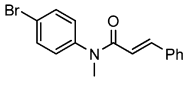
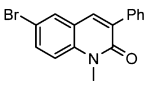
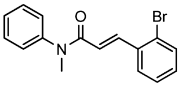
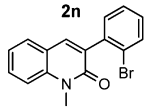
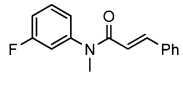
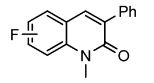
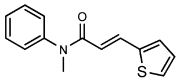
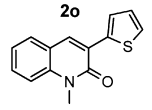
(7) A notable fact is that the *N*-arylenamines can be converted to indole products via either the $Pd(OAc)_2/Cu(OAc)_2$- or $PhI(OAc)_2$-mediated oxidative C−C coupling. For the transition-metal method developed by Glorius, see: (a) Wurtz, S.; Rakshit, S.; Neumann, J. J.; Droge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230. For the I(III)-mediated approach developed by our group, see: (b) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417.

(8) (a) Tu, D.; Ma, L.; Tong, X.; Deng, X.; Xia, C. *Org. Lett.* **2012**, *14*, 4830. (b) Fujita, M.; Yoshida, Y.; Miyata, K.; Wakisaka, A.; Sugimura, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7068.

Table 2. Synthesis of 4-Unsubstituted 3-Arylquinolin-2-one via PIFA-Mediated C−C Bond Formation and 1,2-Aryl Shift[a]



1 2

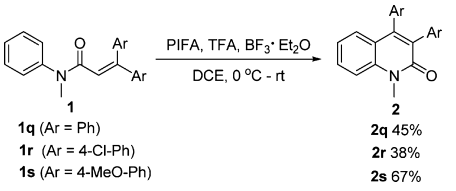
entry	substrate	product	yield(%)[b]	entry	substrate	product	yield(%)[b]
1	 1a	 2a	88	9[d]	 1i	 2i/2i'	77
2	 1b	 2b	75	10	 1j	 2j	78
3	 1c	 2c	90	11	 1k	 2k	44
4	 1d	 2d	71	12[e]	 1l	 2l	63
5	 1e	 2e	55	13	 1m	 2m	34
6	 1f	 2f	48	14[e]	 1n	 2n	41
7	 1g	 2g	87	15[e]	 1o	 2o	44
8[c]	 1h	 2h/2h'	50	16	 1p	 2p	30

[a] All reactions were carried out at rt with **1a** (0.4 mmol), PIFA (1.5 equiv), $BF_3 \cdot Et_2O$ (1 equiv), and TFA (10 equiv) in DCE (16 mL) unless other stated. [b] Isolated yield. [c] The ratio of **2h** (7-F) and **2h'** (5-F) is 1.2:1. [d] The ratio of **2i** (7-CF_3) and **2i'** (5-CF_3) is 1.3:1. [e] TFA was used as the solvent.

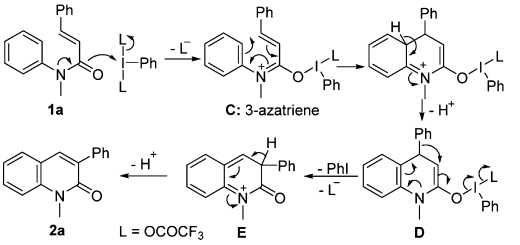
was dramatically increased to 60% (Table 1, entry 4). With the increase of the dosage of TFA, the yield was raised to 68% and the reaction time was greatly shortened (Table 1, entry 5). However, when TFA was used as the sole solvent, the reaction produced more unidentified byproducts which resulted in a decreased yield of **2a** (Table 1, entry 6). Further screening shows that the concentration of substrate **1a** in the solvent can also influence the yield of the product (Table 1, entries 8 and 9). Specifically, when the reaction was carried out at a concentration of 0.025 M, the reaction became much cleaner and the desired product **2a** could be isolated in an excellent yield of 88%. Solvent study shows that none of the other solvents such as TFE, toluene, EtOAc, CH_3CN, or THF is superior to DCE (not shown). The other hypervalent iodine reagents were also tested under the optimized conditions, and it was found that the less potent $PhI(OAc)_2$ provided **2a** in comparable lower yield (Table 1, entry 10), while another iodine(III) reagent, i.e., iodosobenzene, failed to afford the desired product under the same conditions (Table 1, entry 11).

Upon optimal reaction conditions (Table 1, entry 9), we proceeded to explore the generality of this newly developed method. Cinnamamides bearing other substituents such as benzyl (**1b**), isopropyl (**1c**), and cyclopropylmethyl (**1d**) substituents on the nitrogen atom were all converted to the desired cyclized/migrated products **2**[9] in satisfactory to excellent yields (Table 2, entries 2−4). However, for the cinnamamide that bears no substitution on the nitrogen atom, the reaction afforded a complex mixture (not shown). Our results also show that both the electron-donating and the electron-withdrawing group at the *para*-position of the anilide moiety could be well tolerated (Table 2, entries 5−7). However, the electron-rich amide **1f** led to **2f** in a lower yield due to the formation of more unidentified byproducts.

Scheme 2. Investigations of the Reactions Involved 3,3-Disubstituted Acrylic Acid Amides



Scheme 3. Plausible Mechanistic Pathway



In the case of *meta*-substituted substrates bearing either an F or a CF_3 group (Table 2, entries 8 and 9), two separable regioisomeric 3-arylquinolin-2-one products **2h**/**2h′** and **2i**/**2i′** were formed in each case, with the cyclization occurred preferentially at the less hindered position. *Ortho*-substituted substrates were also tolerable as demonstrated by the formation of **2j** and **2k** (Table 2, entries 10 and 11).

Investigation on the substitution effect of the acrylic motif shows that the reactants containing substituted aryl groups all delivered the corresponding 3-arylquinolinones in lower yields than the unsubstituted counterpart **1a**, regardless the electronic nature of the substituent (Table 2, entries 12−15). It is also worth noting that 3-(2-bromophenyl)-1-methyl-1,2-dihydroquinoline (**2o**), a key intermediate to access naturally occurring cryptotackieine **1** and cryptosanguinolentine **2**,[10] can be successfully obtained in acceptable yield by this method (Table 2, entry 15). However, for an alkyl-substituted arylic amide, i.e., *N*-methyl-*N*-phenylbut-2-enamide, we failed to get the desired product under the described conditions (not shown).

To gain further insight into the scope of the method, various 3,3-disubstituted acrylic acid amides were synthesized and studied. To our delight, 3,3-diarylacrylic acid amides that bear two aryl substrates (**1q**−**s**) underwent the same C−C bond formation and 1,2-aryl shift process to give the desired product **2q**−**s**, respectively (Scheme 2). Yield values show that the substrate bearing a *p*-methoxy group gave a better yield (Scheme 2, **2s**), but on the other hand, all doubly substituted substrates give lower yields than the singly substituted **1a**.

A possible mechanistic pathway is outlined in Scheme 3.[11] First, the nucleophilic attack on the iodine center by the carbonyl oxygen of the amide moiety[12] in **1a** affords 3-azatriene **C**, which undergoes an electrocyclic ring closure[13] and the subsequent proton elimination to give intermediate **D**. Assisted by the nitrogen lone-pair conjugation, a concerted process including the 1,2-aryl shift and the breakage of the O−I bond occurs to convert **D** to the iminium salt **E**, along with the release of phenyl iodide and the trifluoroacetate. Finally, intermediate **E** gives 3-phenylquinolin-2-one **2a** with the removal of one proton.

In conclusion, we have discovered an I(III)-mediated metal-free approach for the assembly of the biologically important 3-arylquinolin-2-one skeleton. Compared with that existing transition-metal-catalyzed C−C oxidative coupling that affords the five-membered oxindole products, this novel approach has realized the construction of the six-membered quinolin-2-one skeleton through an unprecedented metal-free oxidative C(sp^2)−C(sp^2) bond formation, along with an exclusive 1,2-aryl migration. Further investigation on the reaction mechanism and the application of the method are underway in our laboratory.

Acknowledgment. Y.D. acknowledges the National Natural Science Foundation of China (No. 21072148) for financial support. We also thank Professor Richard P. Hsung (University of Wisconsin at Madison) for valuable discussions and suggestions.

Supporting Information Available. Experimental procedures, spectral data for all new compounds, and X-ray structural data of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.

(9) The debenzylation of **2b** could proceed smoothly with NBS in the presence of AIBN under reflux in chlorobenzene to give the debenzylated product **2b′** in 83% yield. For previous work describing this reaction, see: Baker, S. R.; Parsons, A. F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 331.

(10) (a) Fresneda, P. M.; Molina, P.; Delgado, S. *Tetrahedron Lett.* **1999**, *40*, 7275. (b) Fresneda, P. M.; Molina, P.; Delgado, S. *Tetrahedron* **2001**, *57*, 6197. (c) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, *40*, 888.

(11) The reaction may also adopt an alternative mechanistic pathway involving the formation of an alkyl aryl iodane intermediate (see the Supporting Information for details). For a recent publication describing such a similar 1,2-aryl shift reaction, see ref 5a.

(12) For selected examples, see: (a) Wang, J.; Yuan, Y.; Xiong, R.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2012**, *14*, 2210. (b) Kajiyama, D.; Inoue, K.; Ishikawa, Y.; Nishiyama, S. *Tetrahedron* **2010**, *66*, 9779.

(13) For selected examples, see: (a) Sklenicka, H. M.; Hsung, R. P.; McLaughlin, M. J.; Wei, L.; Gerasyuto, A. I.; Brennessel, W. B. *J. Am. Chem. Soc.* **2002**, *124*, 10442. (b) Parker, K.; Mindt, T. L. *Org. Lett.* **2001**, *3*, 3875. (c) Clayden, J.; Purewal, S.; Helliwell, M.; Mantell, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1049.