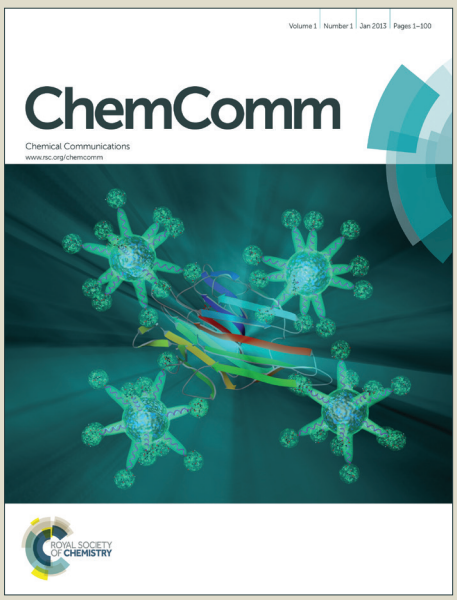
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

View Article Online
DOI: 10.1039/C4CC08717H

Journal Name

RSCPublishing

COMMUNICATION

Cite this: DOI: 10.1039/xoxxoooooox

Transition Metal Free Intramolecular Selective Oxidative C(sp^3)-N Coupling: Synthesis of *N*-Aryl-isoindolinones from 2-Alkylbenzamides

Ajay Verma[a], Saket Patel[a], Meenakshi[a], Amit Kumar[a], Abhimanyu Yadav[a], Shailesh Kumar[a], Sadhan Jana[a], Shubham Sharma[a], Ch. Durga Prasad[a], and Sangit Kumar[a]*

Received ooth January 2012,
Accepted ooth January 2012

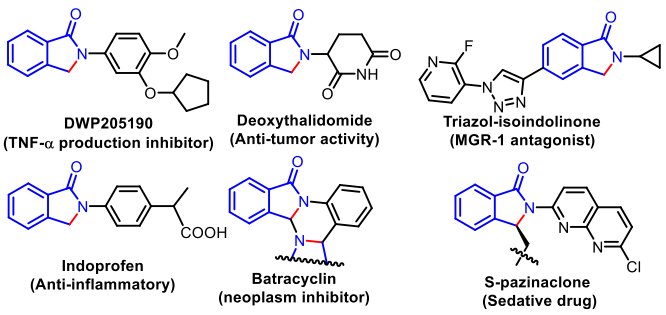
DOI: 10.1039/xoxxoooooox

www.rsc.org/

A synthetic method has been developed for the construction of biologically important isoindolinones including indoprofen and DWP205190 drugs from 2-alkylbenzamide substrates by transition metal-free intramolecular selective oxidative coupling of C(sp^3)-H and N-H bonds utilizing iodine, potassium carbonate and di-*tert*-butyl peroxide in acetonitrile at 110-140 °C.

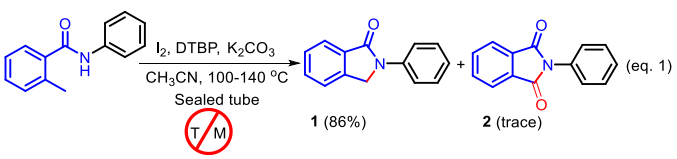
Transition metal-free coupling reactions have attracted considerable interest in recent time for the functionalization of C-H bond.[1] These reactions avoid costly transition metal and even more expensive ligands. Also removal of toxic transition metal catalysts from the drug relevant molecules is expensive and challenging.[2] Iodine-mediated coupling reactions are realized to be an alternative for TM-free approaches as iodine is readily available, economical and non-toxic. As a result, several TM-free iodine mediated methods for C(sp^2)-H functionalization have been reported in the literature,[3-4] however, selective C(sp^3)-H functionalization remains challenging and attractive. Particularly, selective coupling of C(sp^3)-H and N-H bonds would be economical and advantageous as this avoids pre-functionalization of starting materials.

Fig 1. Biologically active isoindolinones



The isoindolinone core having C(sp^3)-N bond is present in many natural and synthetic drug molecules possessing various biological activities namely inhibitor for the production of tumor necrosis factor (TNF-α), MGR-1 antagonist, anti-tumor, and anti-inflammatory activities (Fig. 1).[5]

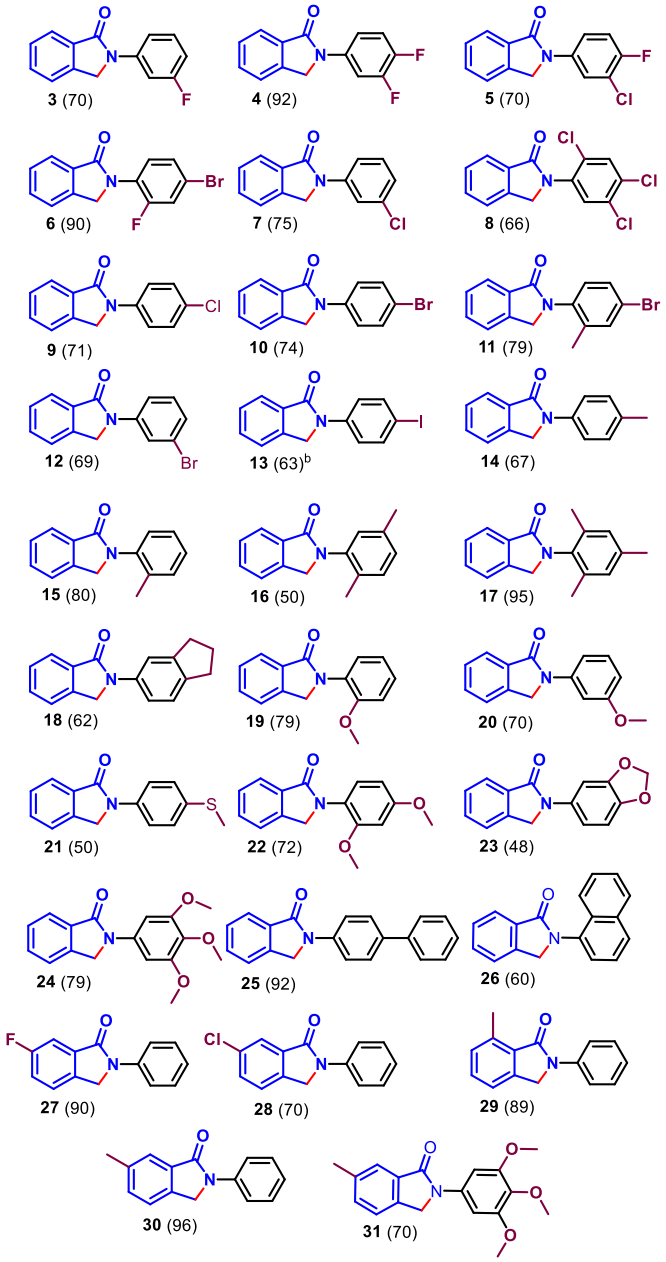
Several methods have been developed for the synthesis of *N*-substituted isoindolinones in view of their potential applications.[6-10] Selective mono-reduction of *N*-substituted phthalimides has been applied for the preparation of isoindolinones utilizing polymethylhydrosiloxane and fluoride ion as a catalyst[6a] or Sn and HCl reducing agent.[6b] TM-Catalyzed methodologies have also been developed exploiting various halogenated substrates such as 2-iodobenzylbromide, 2-iodobenzylamine, 2-bromobenzaldehyde, CO gas, 1-halo-2-alkynylbenzene, and *N*-alkyl-2-haloamides.[7-10] Recently Cao and Gu et al have reported catalysis on Pt-nanowires with 2-carboxybenzaldehyde and primary amine substrate under the pressure of H_2 gas.[8b] Several encouraging methodologies have been developed. However, most of the methods utilized halogenated substrates, expensive transition metal catalysts, highly toxic CO or flammable H_2 gas. Therefore, a method which avoids halogenated substrates, transition metals, expensive ligands, and utilizes readily available reagents and substrates would be highly desirable for the synthesis of isoindolinones. Here in continuation of our work on TM-free C-H bond functionalization,[11] synthesis of isoindolinones by the coupling of C(sp^3)-H and N-H bonds from 2-alkylbenzamides has been presented utilizing mild base K_2CO_3, I_2 and di-*tert*-butyl peroxide (DTBP) in acetonitrile.



Scheme 1. Optimized reaction conditions on 2-methyl-*N*-phenylbenzamide

Optimization of reaction conditions was carried out on 2-methyl-*N*-phenylbenzamide substrate by screening various bases, oxidants, radical initiators, transition metal catalysts, and solvents (details presented in the SI, page S3-S6) and briefly summarized here (Scheme 1). Iodine and potassium carbonate seem to be crucial for this transformation since absence of either one failed to yield any C-N coupled isoindolinone **1**. Two equiv. of I_2 was noticed to be optimum which yielded 27% of isoindolinone **1**, as further increase or decrease of I_2 loading lowered the yield of isoindolinone **1**

considerably. Addition of DTBP (8 equiv) gave quantitative yield (86%) of C-N coupled product **1**. Only trace amount of over oxidized *N*-phenyl phthalimide **2** was observed in the reaction despite excessive use of DTBP under optimized conditions. Next, several other solvents such as DMSO, DMF, CH_3OH, 1,2-dichloroethane were screened, however, acetonitrile found to be superior.



Scheme 2. Isoindolinones obtained from 2-methylbenzamides. [b]Respective phthalimide was also obtained in 10% yield.

After screening various conditions, we have chosen two equiv of I_2, and K_2CO_3, and eight equiv of DTBP in acetonitrile at 140 °C to examine further scope of the reaction. The results are summarized in scheme 2. Fluoro, di-fluoro, fluoro-chloro, fluoro-bromo containing isoindolinones (**3-6**) were obtained in 70-92% yields. Similarly isoindolinones (**7-13**) with chloro, trichloro, bromo, even iodo substituents were obtained under the optimized reaction conditions in moderate to good yields.

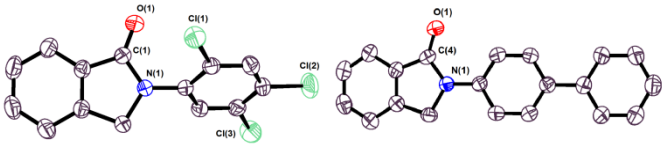


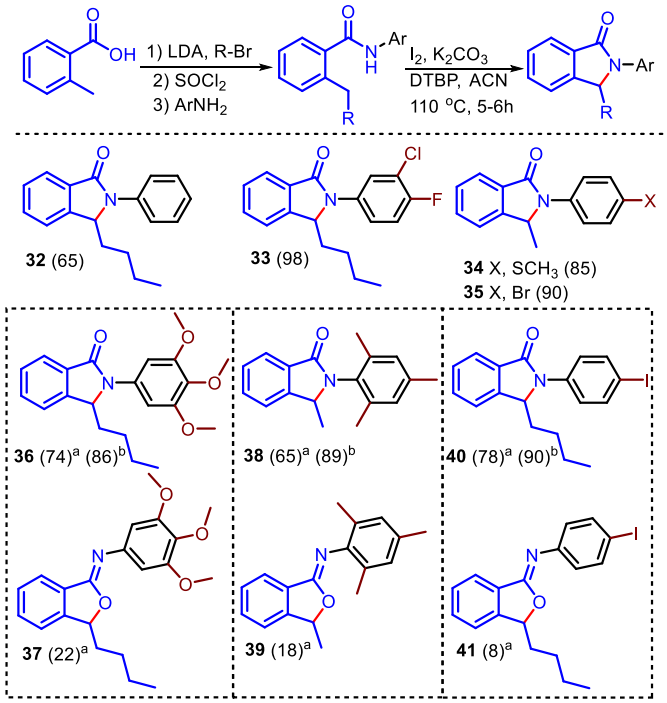
Fig. 2. ORTEP diagram of **8** (chiral space group) and **25** (planar molecule)[12]

Structures of isoindolinones **8**, **11** and **25** (*vide infra*) also established by single crystal X-ray crystallography (Fig. 2).[12]

Next, substrates with methyl substitution at various positions in the aniline ring were subjected to the TM-free iodine mediated C-N coupling reaction. Isoindolinones (**14-17**) with mono-, di- and tri-methyl substituted aniline ring were obtained in 50-95% yields. Similarly 2,3-dihydro-1*H*-indene substituted isoindolinone **18** was obtained in moderate yield (62%).

Methoxy substituted isoindolinones are biologically important as these show inhibition of TNF-α production in the cancer cells (*vide supra*, Fig. 1).[13] Earlier synthetic route for the synthesis of **23** involve multi-steps; protection of 2-methylbenzoic acid to ethyl 2-methylbenzoate ester, followed by bromination to give ethyl 2-(bromomethyl)benzoate and finally coupling with amine under reflux conditions provided **23**.[13a] Here we have synthesized several methoxy substituted isoindolinones (**19-20** and **22-24**) and thio-methyl substituted isoindolinone **21** from respective 2-methyl-*N*-arylbenzamides under TM-free reaction conditions. Further substrate study showed that isoindolinones **25** and **26** containing *N*-biphenyl and *N*-naphthyl substituents can also be synthesized.

Substitution in benzamide ring was explored next. Isoindolinones **27-31** having fluoro, chloro and methyl substituent in the benzamide ring were readily obtained in 70-96% yields from respective substituted 2-methyl-*N*-Aryl-benzamide substrates in 2-4 h.

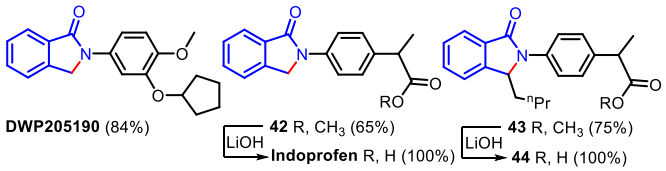


Scheme 3. Synthesis of 3-alkylisoindolinones. Indolinones **32-36, 38,** and **40** were obtained from respective benzamides using 2 equiv of I_2, and K_2CO_3, 6 equiv of DTBP in acetoniltrile in 4-5 h at 110 °C. [a] Respective C-O coupled products **37**, **39** and **41** were also observed. [b] Yields obtained by heating the reaction mixture at 140 °C.

View Article Online
DOI: 10.1039/C4CC08717H
COMMUNICATION

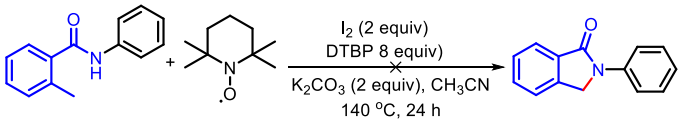
Next, 2-alkyl substituted benzamide substrates were studied in the TM-free oxidative C-N coupling reaction. 2-Alkyl substituted-benzamides were prepared from respective 2-alkyl benzoic acids which were readily accessed by *ortho*-lithiation of 2-toluic acid, followed by quenching with alkyl bromides (Scheme 3). To our delight, benzamides with 2-ethyl and pentyl chain underwent oxidative C-N coupling reaction successfully and indeed, 3-substituted isoindolinones (**32**-**36**, **38** and **40**) were obtained in good (65-98%) yields in shorter period (4-6 h) at 110 °C. The formation of *N*-aryl-3-methylisobenzofuran-1(3*H*)-imines, C-O coupled products **37**, **39** and **41** in 8-22% yields was also noticed along with the expected indolinones **36**, **38** and **40**, respectively, at 110 °C. Worthy to note, isoindolinones were obtained in better yields when reaction was heated at 140 °C.

Synthesis of DWP205190 and indoprofen (Fig-1) drugs was targeted under optimized reaction conditions (Scheme 4).



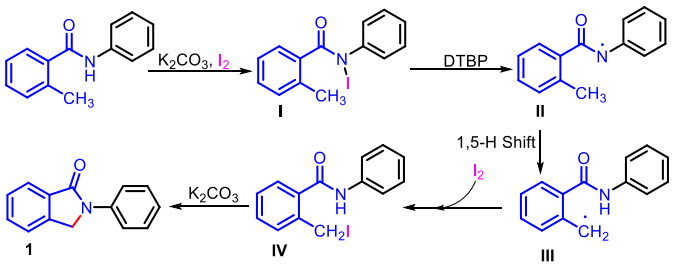
Scheme 4. Synthesis of isoindolinone based drugs (See SI page S34-S40)

Synthesis of DWP205190 has been reported by the coupling of respective amine with phthalaldehyde, followed by the selective reduction, and then cyclization using diethyl azodicarboxylate and PPh_3.[13b] Here synthesis of indoprofen and DWP205190 was achieved from less expensive 2-methylbenzoic acid in two steps, respectively, without employing brominating or reducing reagents. Additionally, 3-butyl substituted indoprofen analogue **44** has also been constructed in two steps from respective amide in 75% overall yield.



Scheme 5. Reaction with TEMPO

Several control experiments were carried out to understand the mechanistic pathways. Addition of a radical quencher TEMPO halted the progress of reaction, suggesting involvement of the radicals in the formation of **1** (Scheme 5).



Scheme 6. Proposed reaction mechanism

Iodine could react with N-H bond in the substrate leading to N-I intermediate **I** (Scheme 6). This intermediate **I** would further react with DTBP forming a nitrogen-centered amide radical **II** which undergoes 1,5-H shift generating benzyl radical **III**.[4a] 1,5-H Shift seems to be the key step in this transformation. Reaction of benzyl radical with I_2 would lead to 2-(iodomethyl)-*N*-phenylbenzamide **IV**, which finally undergoes nucleophilic substitution with the benzamide moiety in the presence of K_2CO_3 to furnish C-N coupled isoindolinone **1**.

In summary, we have presented a new synthetic method for the preparation of isoindolinones from 2-alkyl-*N*-arylbenzamide substrates utilizing iodine, DTBP and potassium carbonate. This simple and TM-free oxidative coupling of C(sp^3)-H and N-H bonds in 2-alkyl-*N*-phenylbenzamides could be complementary to the earlier methods in which pre-functionalized substrates such as 2-iodobenzylbromides, 2-iodobenzylamines, 2-iodobenzaldehydes together with transition metal catalysts were used. Currently intermolecular C-N coupling mode of this reaction and mechanistic understanding are underway in our laboratory.

Acknowledgment

SK thanks to DST New Delhi, DRDO New Delhi, DAE-BRNS Mumbai, and IISER Bhopal for generous funding. AV, AK, AY, DP thanks UGC-CSIR and SJ, SK thanks to IISER Bhopal for fellowship, respectively. SK acknowledges Ms. Anusha Upadhyay for single-crystal data collection.

Dedication

This work is dedicated to Professor Lars Engman (Department of Organic Chemistry, Uppsala University, Sweden) on the occasion of his 63rd birthday.

Notes and references

[a] Department of Chemistry, Indian Institute of Science Education and Research (IISER) Bhopal, Indore By-pass Road, Bhauri, Bhopal, Madhya Pradesh, India-462 066, E-mail: sangitkumar@iiserb.ac.in

† Electronic Supplementary Information (ESI) available: See DOI:10.1039/c000000x/ and Cif file CCDC No. 1021394 (**8**), 1019580 (**11**), 1020238 (**25**).

(1) Recent Review of TM-free C-H functionalization (a-b): (a) C.-L. Sun and Z.-J. Shi, *Chem. Rev.*, 2014, DOI: dx.doi.org/10.1021/cr400274j. (b) V. P. Mehta, and B. Punji, *RSC Adv.*, 2013, **3**, 11957. (c) B. J. Li, D. G. Yu, C. L. Sun, Z. J. Shi, *Chem. Eur. J.*, 2011, **17**, 1728. (d) C. L. Sun, Y. F. Gu, W. P. Huang and Z. J. Shi, *Chem .Commun.*, 2011, **47**, 9813. (e) C. L. Sun, Y. F. Gu, B. Wang and Z. J. Shi, *Chem. Eur. J.*, 2011, **17**, 10844. (f) X. Li, H.-Y. Wang and Z.-J. Shi, *New J. Chem.*, 2013, **37**, 1704. (g) Benzylic C-H functionalization: S. S. Badsara, Y.-C. Liu, P.-A. Hsieh, J.-W. Zeng, S.-Y. Lu, Y.-W. Liu and C.-F. Lee, *Chem. Commun.*, 2014, **50**, 11374. (h) J.-W. Zeng, Y.-C. Liu, P.-A. Hsieh, Y.-T. Huang, C.-L. Yi, S. S. Badsara and C.-F. Lee, *Green Chem.*, 2014, **16**, 2644. (i) Y.-C. Liu and C.-F. Lee, *Green Chem.*, 2014, **16**, 357. (j) J.-W. Zeng, Y.-C. Liu, P.-A. Hsieh, Y.-T. Huang, C.-L. Yi, S. S. Badsara and C.-F. Lee, *Green Chem.*, 2014, **16**, 2644.

(2) From **1a** ref: The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products; London, 2002.

(3) I_2-Mediated/ catalyzed coupling reactions: (a) R. D. Richardson and T. Wirth, *Angew. Chem., Int. Ed.*, 2006, **45**, 4402. (b) K. Hess, A. Ushmorov, J. Fiedler, R. E. Brenner and T. Wirth, *Bone*, 2009, **45**, 367. (c) T. Dohi and Y. Kita, *Chem. Commun.*, 2009, 2073. (d) J. Zhang, D. Zhu, C. Yu, C. Wan and Z. Wang, *Org. Lett.*, 2010, **12,** 2841. (e) S. M. Altermann, S. Schäfer and T. Wirth, *Tetrahedron*, 2010, **66**, 5902. (f) Y. Yan and Z. Wang, *Chem. Commun.*, 2011, **47**, 9513. (g) Y. X. Li, K. G. Ji, H. X. Wang, S. Ali and Y. M. Liang, *J. Org. Chem.*, 2011, **76**, 744. (h) K. Xu, Y. Hu, S. Zhang, Z. Zha and Z. Wang, *Chem. Eur. J.*, 2012, **18**, 9793. (i) Y. J. Li, H. M. Huang, H. Q. Dong, J. H. Jia, L. Han, Q. Ye and J. R. Gao, *J. Org. Chem.*, 2013, **78**, 9424. (j) W. Yu, G. Huang, Y. Zhang, H. Liu, L. Dong, X. Yu, Y.

Li and J. Chang, *J. Org. Chem*., 2013, **78**, 10337. (k) Z. J. Cai, S. Y. Wang and S. J. Ji, *Org. Lett.*, 2013, **15**, 5226. (l) A. Gogoi, A. Modi, S. Guin, S. K. Rout, D. Das and B. K. Patel, *Chem. Commun.*, 2014, **50**, 10445 (m) F. Xiao, H. Chen, H. Xie, S. Chen, L. Yang and G. J. Deng, *Org. Lett.*, 2014, **16**, 50. (n) Y. Zi, Z. J. Cai, S. Y. Wang and S. J. Ji, *Org. Lett.*, 2014, **16**, 3094. (o) G. Majji, S. K. Rout, S. Guin, A. Gogoi and B. K. Patel, *RSC Adv.*, 2014, **4**, 5357. (p) F. V. Singh and T. Wirth, *Chem. Asian. J*., 2014, **9**, 950.

(4) (a) Phosphonamides synthesis by C-N coupling: Y. R. Kim, S. Cho, and P. H. Lee, *Org. Lett*., 2014,**16**, 3098 . (b) TM assisted oxidative C-H and N-H coupling: L. Zhou, S. Tang, X. Qi, C. Lin, K. Liu, C. Liu, Y. Lan and A. Lei, *Org. Lett*., 2014, **16**, 3404. (c) Iodide catalyzed C-H functionalization: S. Tang, Y. Wu, W. Liao, R. Bai, C. Liu, and A. Lei, *Chem. Commun.*, 2014, **50**, 4496. (d) J. Yuan, X. Ma, H. Yi, C. Liu, and A. Lei, *Chem. Commun.*, 2014, **50**,.14386. (e) J. Zhao, P. Li, C. Xia, and F. Li, *Chem. Commun*., 2014, **50**, 4751. (f) Fe-catalyzed coupling of C-H and N-H bonds: J. Wang, C. Liu, J. Yuan, and A. Lei, *Chem. Commun.*, 2014, **50**, 4736. (g) Oxidative C-N Coupling: M. Gao, J. Tian, and A. Lei, *Chem. Asian J*., 2014, **9**, 2068. (h) Recent article on oxidative C-N coupling: J. Yuan, C. Liu, and A. Lei, *Chem. Comm.*, 2014, DOI: 10.1039/C4CC08116A.

(5) (a) M. H. Norman, D. J. Minick, and G. C. Rigdon, *J. Med. Chem.*, 1996, **39**, 149. (b) J. S. Park, S. C. Moon, K. U. Baik, J. Y. Cho, E. S. Yoo, Y. S. Byun, and M. H. Park, *Arch Pharm Res*., 2002, **125**, 137. (c) M. Uno, H. S. Ban, H. Nakamura, *Bioorg. Med. Chem. Lett*., 2009, **19**, 3166. (d) U. Ghosh, R. Bhattacharyya, and A. Keche, *Tetrahedron*, 2010, **66**, 2148.

(6) By selective reduction of N-substituted phthalimides: (a) S. Das, D. Addis, L. R. Knopke, U. Bentrup, K. Junge, A. Brukner, and M. Beller, *Angew. Chem. Int. Ed.*, 2011, **50**, 9180. (b) A. Jóźwiak, P. M. Zagorski, M. W. Płotka, and D. Cal, *Tetrahedron Lett.*, 2014, **55**, 2420. (c) Using TMSCN reagent from 2-carboxybenzaldehyde: L.-J. Hu, Z.-J. Zhan, M. Lei, and L.-H. Hu, *ARKIVOC*, 2013, **III**, 189.

(7) Pd-Catalyzed synthesis from 2-halobenzamides: (a) C. S. Cho, and W. X. Ren, *Tetrahedron Lett.*, 2009, **50**, 2097. (b) S. Rousseaux, S. I. Gorelsky, B. K. W. Chung and K. Fagnou, *J. Am. Chem. Soc*., 2010, **132**, 10692.

(8) TM catalyzed synthesis of isoindolinones using CO gas: (a) S. Murahashi, *J. Am. Chem. Soc*., 1955, **77**, 6403. (b) K. Orito, M. Miyazawa, T. Nakamura, A. Horibata, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, T. Yamazaki, and M. Tokuda, *J. Org. Chem.*, 2006, **71**, 5951-5958. (c) H. Cao, L. M.-Namee, and H. Alper, *Org. Lett*., 2008, **10**, 5281. (d) D. M.-Haskó, A. Takács, Z. Riedl, and L. Kollár, *Tetrahedron*, 2011, **67**, 1036. (e) Rh-catalyzed C-N coupling: S. Park, B. Seo, S. Shin, J.-Y. Son, and P. H. Lee, *Chem. Commun*., 2013, **49**, 8671.

(9) Synthesis from 2-halobenzamide substrates: (a) Pt-Catalyzed: F. Marion, J. Coulomb, A. Servais, C. Courillon, L. Fensterbank, and M. Malacria, *Tetrahedron*, 2006, **62**, 3856. (b) Pt-catalyzed using H_2 gas: L. Shi, L. Hu, J. Wang, X. Cao, and H. Gu, *Org. Lett*., 2012, **14,** 1876. (c) KO^{t}Bu-mediated: B. S. Bhakuni, A. Yadav, S. Kumar, S. Patel, S. Sharma, and S. Kumar, *J. Org. Chem.*, 2014, **79**, 2944;

(10) From prefunctionalized alkynylbenzamide substrates: (a) using I_2 or ICl reagent: T. Yao and R. C. Larock, *J. Org. Chem.* 2005, **70**, 1432. (b) Using organic super base: C. Kanazawa and M. Terada, *Chem. Asian J*., 2009, **4**, 1668. (c) Pd-Catalyzed: G. Yang and W. Zhang, *Org. Lett.*, 2012, **14**, 268.

(11) Our recent work on TM free C–H functionalization: (a) B. S. Bhakuni, A. Kumar, S. J. Balkrishna, J. A. Sheikh, S. Konar, and S. Kumar, *Org. Lett.*, 2012, **14**, 2838; (b) A. Kumar, A. Yadav, A. Verma, S. Jana, M. Sattar, S. Kumar, C. D. Prasad, and S. Kumar, *Chem. Commun*., 2014, **50**, 9481.

(12) Trichloro-isoindolinone **8** is crystallized in chiral space group $P2_12_12_1$. Isoindolinone **11** is crystallized in space group $P2_1/n$. Isoindolinone **25** is a planar structure (page S56) as all four rings in the molecule lie in one plane, crystallizes in $P2_1/c$. Details of crystal data and Figures for **8**, **11** and **25** have been mentioned in SI (page S42-S65).

(13) Synthesis of **18** and **23**: (a) WIPO WO2009/042904A1, 2009. (b) Synthesis of DWP205190: J. S. Park, K. U. Baik, H. J. Son, J. H. Lee, S. J. Lee, J. Y. Cho, J. Park, E. S. Yoo, Y. S. Byun, and M. H. Park, *Arch. Pharm. Res.*, 2000, **23,** 332. (c) Synthesis of indoprofen: N. J. Lawrence, J. Liddle, S. M. Bushell, and D A. Jackson, *J. Org. Chem.*, 2002, **67**, 457.