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Application of isocyanides as an amide surrogate for the synthesis of diverse isoindolin-1-one derivatives *via* Palladium-catalyzed tandem Carboxamidation/Hydroamidation reaction

Ramdas S Pathare,[a] Shivani Sharma,[a] Sathish Elagandhula,[b] Vaishali Saini,[b] Devesh M Sawant,[b*] Monika Yadav,[c] Ashoke Sharon,[c] Shahnawaz Khan,[d*] Ram T Pardasani[a*]

Abstract Rapid synthesis of the isoindolinone skeleton has been accomplished using Palladium-catalyzed one-pot tandem process consisting isocyanide insertion-hydration (carboxamidation) followed by 5-*exo*-dig cyclo-isomerization (hydroamidation) reaction in good to excellent yield. This is an example of sequential C-C/C-O/C- N bond formation. Preliminary mechanistic studies suggest that carboxamidation is Palladium-dependent process, while hydroamidation is mediated solely by base and is driven by electrophilicity of alkynes.

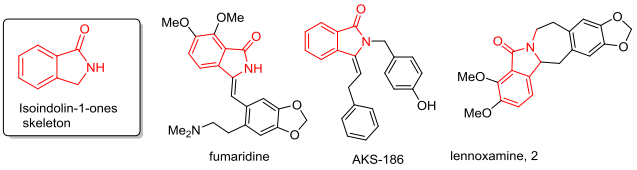
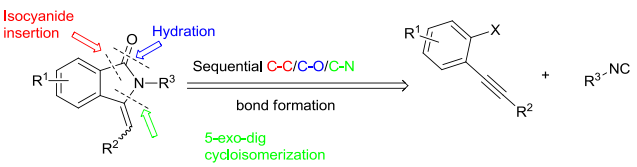


Figure 1: Selected examples of biological relevant Isoindolin-1-ones.

Introduction

Isocyanide is a modern artist of current synthetic architectures. Its stability and compatibility with a spectrum of reagents offers an incredible opportunity to design tandem processes for the rapid and efficient generation of complex molecules.[1] Isocyanide, structurally and functionally analogous to carbon monoxide, inherits unique reactivity by virtue of its ambivalent nature at carbon and transforms itself into an amide functional group.[2] This ability had been elegantly exploited in Ugi and Passerini multicomponent reactions.[3] Isocyanides also introduce an additional diversity in the molecular framework. Recently, isocyanides have been used to generate benzamides using Pd-catalyzed carboxamidation from readily available aryl halides.[4] This has prompted us to opening of new opportunities to utilize isocyanides as “amide surrogates”. Similarly, alkynes represent an attractive and diverse building blocks for the construction of complex molecular structures.[5] In this context, metal-catalyzed isocyanide insertion[6,7] and intramolecular cyclization of alkynes[8,9] offer incredible opportunities for the construction of an array of heterocycles *via* tandem C-C or C-X bond formation.

Isoindolin-1-one is a structural motif that exists in an array of naturally occurring and pharmacologically interesting substances such as stachybotrin C,[10] fumaridine[11] and lennoxamine,[12] pagoclone,[13] zopiclone,[14] AKS-186,[15] pictonamine,[16] and pazinaclone[17] (Figure 1). Besides it also has a noteworthy biological profile like HIV-1 inhibiting,[18,19] anti-hypertensive,[20] antileukemic,[21] antimicrobial,[22] anti-inflammatory,[23] antihyperglycemic activity,[24] and TACE inhibiting activities.[25] Consequently, substantial synthetic methodologies have been developed for the preparation of isoindolinone derivatives[26,27] such as tandem



Scheme 1: Pd-catalyzed tandem isocyanide insertion strategy toward isoindolin-1-ones from 1-halo-2-alkynylbenzenes

elimination–cyclization– Suzuki coupling sequence reported by Couture and coworkers,[27] Heck–Suzuki–Miyaura domino reactions of ynamides and arylboronic acids,[28] reaction of phosphorous ylides with phthalimide derivatives,[29] a Pd-catalyzed oxidative cyclization–alkoxycarbonylation sequence published by Kondo et al,[30] one-pot Sonogashira coupling-carbonylation–hydroamination reactions of dihalides,[31] an Ullman coupling-heteroannulation of 2-bromobenzamides and terminal alkynes,[32] intramolecular

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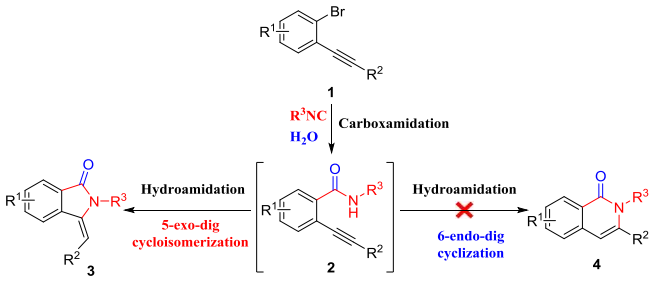


Scheme 2: The design of tandem carboxamidation-hydroamidation.

Heck reactions of enamides,[33] a Pd-catalyzed aminocarbonylation approach for the synthesis of fluorinated isoindolinones[34] and intramolecular cyclization of acyl radicals on to an azide group.[35] Majorities of the existing methods go through certain limitations with respect to the yield, substrate scope, extra-dry conditions, or dependency over complex precursors, which are generated through multi-step syntheses. Thus, they are not suitable for the preparation of compound libraries and hence there is a considerable scope for the advancements. Thus in continuation to our studies on the development of novel synthetic pathways for the preparation of bioactive heterocycles,[36] herein, we report a novel and efficient regio- and stereo-selective synthetic route to isoindolinones through a sequential one-pot Pd-catalyzed isocyanide insertion (C-C bond formation), hydration of imine intermediate (C-O bond formation) and 5-exo-dig cyclo-isomerization (C-N bond formation, Scheme 1 and 2).

Results and Discussion

We envisaged isocyanide as an amide surrogate that can be elegantly exploited to generate 2-alkynylbenzamide **2** *in situ* from *ortho*-haloarylalkynes **1**, and subsequently cyclized to either isoindole **3** or isoquinolone **4** in a one-pot tandem sequence of carboxamidation and hydroamidation (Scheme 2). We embarked our studies by investigating the sequential isocyanide insertion and hydroamidation of **1aa** using 5 mol % of $Pd(OAc)_2$/dppf as a catalyst system and 2.0 equivalents of Cs_2CO_3 as a base at 100 °C in DMF/H_2O (refer table 1 for details). To our delight, the desired product **3aa** was isolated in 30% yield (entry 1). The isoindole **3aa** was fully characterized by ^1H, ^{13}C NMR and mass spectroscopic data. Further, X-ray crystallographic analysis of compound **3cb** unequivocally confirmed the formation of regioisomer **3** and not **4** (refer Fig 2 and Scheme 3). Initial screening of catalyst and ligand suggested that $Pd(OAc)_2$ along with XantPhos afforded the maximum yield (entries 1-10). The reaction failed to initiate in the absence of catalyst, ligand or base (entries 11-13). Thus all three components were critical for the success of tandem reaction. Among various bases screened, Cs_2CO_3 proved to be the most effective (entries 5, 14-17). Solvent studies revealed that the combination of DMF/H_2O in the ratio 9:1

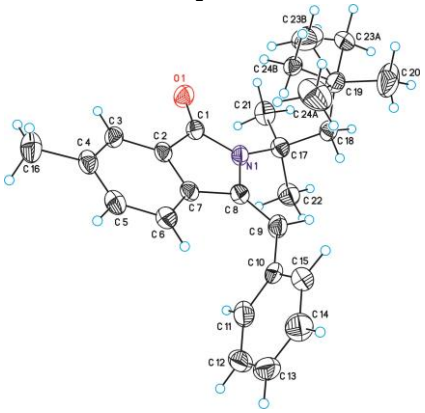


Figure 2: ORTEP diagram (50% probability) for the X-ray crystal structure of the compound **3cb** with an atom numbering scheme showing C8-C9 exo-double bond with E-configuration (CCDC 1472755). [37]

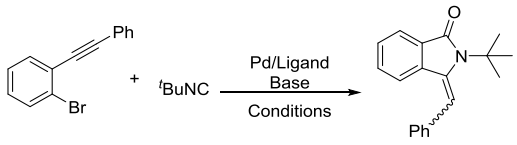
produced maximum yield of **3aa** (entries 5, 18-20). The reaction failed to initiate in extra dry DMF (entry 18). The catalytic efficiency of $Pd(OAc)_2$ remain unperturbed despite of reducing it to 3 mol% (entry 21), however its further reduction to 1 mol% furnished poor yield (entry 22). At lower temperature, the reaction produced poor conversions and most of the starting material was recovered, while raising the temperature had detrimental effects on the reaction producing multiple spots. In general, 3.0 mol% of $Pd(OAc)_2$, 3.0 mol% of XantPhos, 2.0 equiv Cs_2CO_3 as the base at 100 °C in DMF/H_2O (9:1) was considered as the best optimal condition and produced the excellent result with 89% isolated yield of **3aa** (entry 21).

Once the condition for tandem C-C/C-O/C-N cross-coupling reaction sequences was optimized, we next investigated the scope and limitation of this reaction by employing various *ortho*-haloarylalkynes **1** and isocyanides (Scheme 3). The nature of R^2 substituent attached to triple bond had a major impact on the success of the reaction. Electron withdrawing substituents on arenes at R^2 increased the efficiency of the reactions to produce **3** in good to excellent yield (in **3af**, **3ag**, **3bc** and **3be**). The reactions involving electron donating substituents on arenes at R^2 were sluggish and produced title compounds in diminished yield (**3ac**, **3ad** and **3ah**). In contrast, alkyl- and alkenyl-substituents at R^2 failed to produce the cyclized product **3** and instead furnished amide intermediate **2** as the only product. Thus, electron withdrawing nature of R^2 favors hydroamidation by decreasing the electron density on the proximal end of the triple bond. Interestingly, good yields were obtained when R^2 was naphthalene (in **3bd**) and heteroaryl group (in **3ea**, **3ga** and **3gb**). Interestingly, in all cases *E*-isomers were established as a major product and was confirmed by ^1H NMR and X-ray crystallographic analysis.(refer supporting information for further details).[38]

In order to gain the mechanistic insights, we first performed the reaction in presence of TEMPO and Galvinoxyl (Scheme 4A). It was observed that the radical scavengers had negligible effects on tandem reaction. Hence a non-radical path is playing a role in the formation of **3aa.** To study the effect of reactants on

the.tandem reaction, we designed control experiments to dichotomize the tandem reaction into two discrete sets of

Table 1. Reaction Optimization for Isoindolin-1-one formation.[a]



1aa **3aa**

Entry	Catalyst (mol %)	Ligand (mol %)	Base (mol %)	Solvent	Yield[b] (%)
1.	$Pd(OAc)_2$ (5)	dppf (5)	Cs_2CO_3 (2)	DMF/H_2O	30
2.	$Pd(OAc)_2$ (5)	PPh_3 (5)	Cs_2CO_3 (2)	DMF/H_2O	40
3.	$Pd(OAc)_2$ (5)	Pcy_3 (5)	Cs_2CO_3 (2)	DMF/H_2O	45
4.	$Pd(OAc)_2$ (5)	X-Phos (5)	Cs_2CO_3 (2)	DMF/H_2O	55
5.	$Pd(OAc)_2$ (5)	XantPhos (5)	Cs_2CO_3 (2)	DMF/H_2O[c]	90
6.	$Pd(dppf)_2Cl_2$ (5)	XantPhos (5)	Cs_2CO_3 (2)	DMF/H_2O	trace
7.	$PdCl_2$ (5)	XantPhos (5)	Cs_2CO_3 (2)	DMF/H_2O	10
8.	$Pd(PPh3)_2Cl_2$ (5)	XantPhos (5)	Cs_2CO_3 (2)	DMF/H_2O	25
9.	$Pd_2(dba)_3$ (5)	XantPhos (5)	Cs_2CO_3 (2)	DMF/H_2O	35
10.	$Pd(CH_3CN)_2Cl_2$ (5)	XantPhos (5)	Cs_2CO_3 (2)	DMF/H_2O	45
11.	-	XantPhos (5)	Cs_2CO_3 (2)	DMF/H_2O	n.r.
12.	$Pd(OAc)_2$ (5)	-	Cs_2CO_3 (2)	DMF/H_2O	n.r.
13.	$Pd(OAc)_2$ (5)	XantPhos (5)	-	DMF/H_2O	n.r.
14.	$Pd(OAc)_2$ (5)	XantPhos (5)	K_2CO_3 (2)	DMF/H_2O	30
15.	$Pd(OAc)_2$ (5)	XantPhos (5)	Dabco (2)	DMF/H_2O	32
16.	$Pd(OAc)_2$ (5)	XantPhos (5)	CsF (2)	DMF/H_2O	45
17.	$Pd(OAc)_2$ (5)	XantPhos (5)	K^{t}OBu (2)	DMF/H_2O	8
18.	$Pd(OAc)_2$ (5)	XantPhos (5)	Cs_2CO_3 (2)	DMF	trace
19.	$Pd(OAc)_2$ (5)	XantPhos (5)	Cs_2CO_3 (2)	DMSO/H_2O	35
20.	$Pd(OAc)_2$ (5)	XantPhos (5)	Cs_2CO_3 (2)	Dioxane	trace
21.	**$Pd(OAc)_2$ (3)**	**XantPhos (3)**	**Cs_2CO_3 (2)**	**DMF/H_2O[c]**	**89[d,e]**
22.	$Pd(OAc)_2$ (1)	XantPhos (1)	Cs_2CO_3 (2)	DMF/H_2O	30

[a] Reaction condition: all reaction were performed in sealed tube on 0.3 mmol scale using **1a** (1.0 equiv), **^{t}BuNC** (1.5 equiv), $Pd(OAc)_2$ (3 mol %), and ligand (3 mol %) and base (2.0 equiv) in 0.1 mL of H_2O in 1.0 mL of solvent at 100 ^oC for 4h.

[b] Isolated yield.
n.r. – no reaction.

[c] Among various compositions tried 9:1 ratio of DMF/ H_2O produced best results.

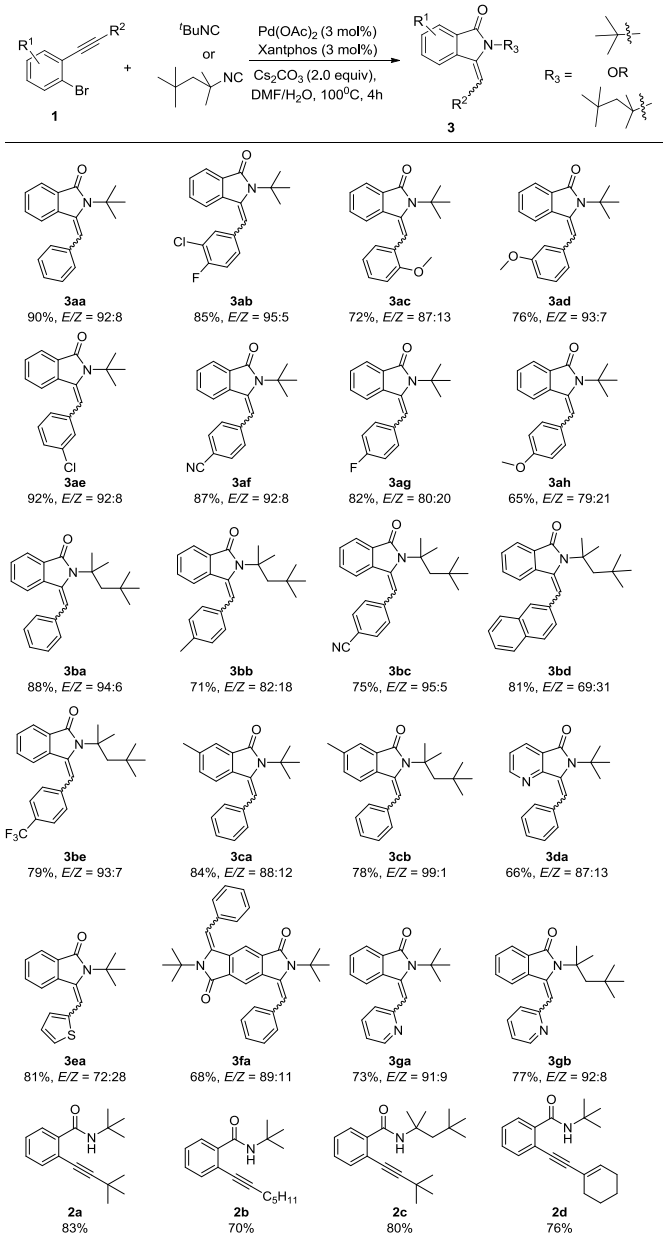
[d] Reaction failed to initiate at 50 ^oC, 70 ^oC, and furnished poor yields at higher temperatures.

[e] Among various combinations tried, 2 equivalents of Cs_2CO_3 and 1.5 equivalents of ^{t}BuNC produced optimum yield.

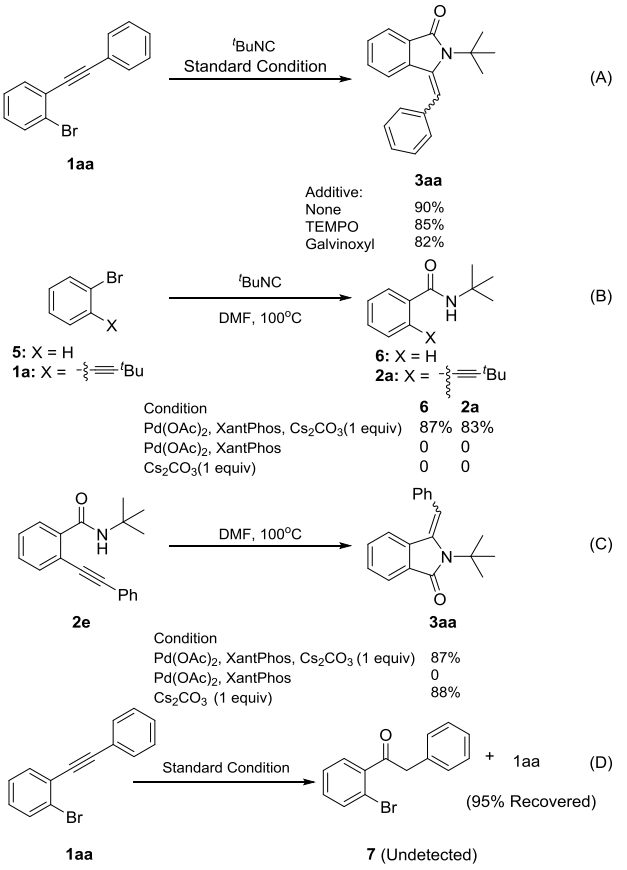
carboxamidation and hydroamidation (Scheme 4B-C). For the first step of carboxamidation, both catalyst/ligand and base (1.0 equiv) were crucial for the formation of both **6** and **2a** (Scheme 4B)[39] In contrast, the second step, hydroamidation of **2e**, was a palladium-independent process and was solely mediated by base [1.0 equiv. of Cs_2CO_3] to furnish **3aa** (Scheme 4C). To further understand the nature of reaction intermediates, we treated substrate **1aa** under the reported condition in the absence of isocyanide. The failure to formation of **7** clearly excludes hydration of **1aa** to **7** and subsequent isocyanide insertion and cyclization as a possible mechanism[39b] (Scheme 4D). The intermolecular competition experiments revealed arenes bearing electron deficient group **1bc** were preferentially converted to their corresponding product **3bc** as a sole product with no formation of **3bb** (Scheme 5A). In addition, competition between substrates bearing aryl group on the distal end of triple bond against substrates bearing alkyl and alkenyl group showed preference to the aryl substituent to furnish **3aa** exclusively (Scheme 5B-C). The failure of substrates bearing alkenyl and alkyl substituents (R^2) to participate in competition with their aryl counterparts substantiates the fact that the electrophilicity of alkyne is the driving force for the tandem reaction.

Based on experimental investigations and previous mechanistic insights,[4,40,41] a plausible mechanistic discourse is proposed in figure 3. The catalytically active species **8** on oxidative addition forms a complex **9**. Subsequently, coordination and migratory insertion of isocyanide furnishes intermediate **11**. Addition of water to C=N bond of **11** in the presence of base and β-hydride elimination gives **2** that further undergoes base-mediated hydroamidation to generate the title compounds **3**.

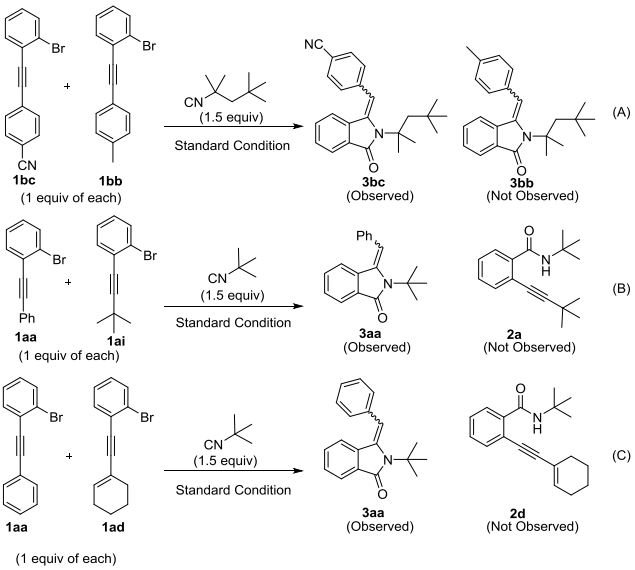
It is interesting to note that *ortho*-haloarylalkynes **1** were synthesized from Pd-catalyzed Sonogashira reaction. Conditions employed for the synthesis of **1** and subsequent reactions thereof are very similar. Thus, we developed a Pd-catalyzed one-pot self-relay protocol for the synthesis of **3aa** from 2-bromoiodobenzenes (Scheme 6).[42]



Scheme 3: Pd-catalyzed reaction of 1-bromo-2-(phenylethynyl)benzene derivatives with isonitriles.



Scheme 4: Control experiments.



Scheme 5: Intermolecular Competition Experiment.

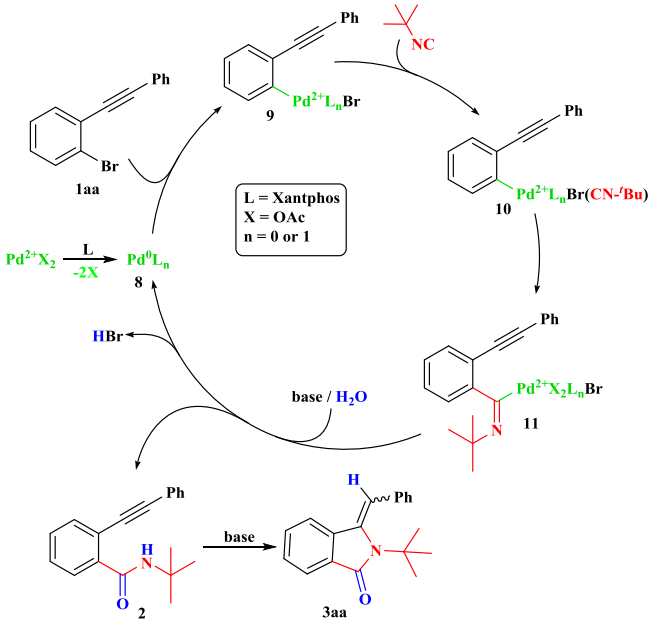
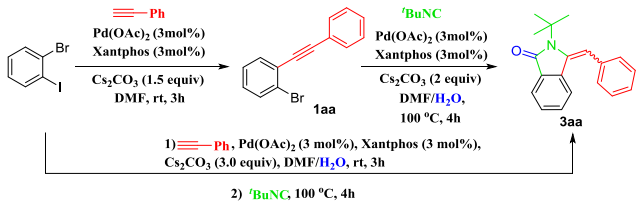


Figure 3: Plausible mechanism.

Conclusions

In conclusion, we have reported application of isocyanide as an amide surrogate for the synthesis of isoindolinones. An efficient method based on $Pd(OAc)_2$/XantPhos has been developed to synthesize isoindolin-1-ones derivatives. The methodology demonstrated wide substrate scope and applications. The reaction was operationally simple and avoid using toxic carbon monoxide and acid chloride, which require an inert/ dry conditions. Mechanistic investigations revealed that carboxamidation indeed depends on both catalyst/ ligand and base, in contrast hydroamidation was Pd-independent process and mediated by base. Electrophilicity of the alkyne was the driving force for hydroamidation and lack of electrophilic assistance led to formation of amides 2a-2d. Interestingly, isocyanides also furnished an additional diversity in the title compound. Here, we also developed a one pot protocol for straightforward synthesis of valuable isoindolin-1-one derivatives from simple and easily available precursors.



Scheme 6: Development of one-pot self-relay protocol.

Experimental Section

A 10 mL schlenk tube equipped with a stir-bar was charged with 1-bromo-2-(phenylethynyl)benzene (0.1 g, 0.388 mmol) and DMF/H_2O (1.0 mL, 9:1) as a solvent. The reaction tube was purged with argon. Then after 5-10 min *tert*-butylisocyanide (0.048 g, 0.583 mmol), Cs_2CO_3 (0.253 g, 0.78 mmol), XantPhos (0.007 g, 0.01 mmol) and $Pd(OAc)_2$ (0.003 g, 0.01 mmol) was added to the reaction mixture followed by argon purging. The mixture was stirred at 100°C for 4 hrs. After cooling to room temperature, the reaction mixture was passed through celite bed and washed with EtOAc. The reaction mixture was diluted with EtOAc, which was washed with water and brine successively, dried over anhydrous sodium sulphate, filtered, and concentrated in vacuo. Purification by silica gel (100-200 mesh) chromatography (EtOAc: Hexane) to yield the desired product.

3-benzylidene-2-(tert-butyl)isoindolin-1-one (3aa) (known compound).[38] Brown Oil (97 mg, 90%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.74 (d, *J* = 7.5 Hz, 1H), 7.45-7.39 (m, 5H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.02 (s, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 1.86 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 167.92, 137.43, 136.35, 135.48, 131.10, 131.03, 129.54, 128.80, 128.69, 127.68, 123.11, 122.66, 114.56, 57.62, 30.61; HRMS (ESI) calcd. for $C_{19}H_{20}NO$ ($[M + H]^+$) 278.1545, found, 278.1552. Product contains *E*- and *Z*-isomer in the ratio of 92:8.

2-(tert-butyl)-3-(3-chloro-4-fluorobenzylidene)isoindolin-1-one (**3ab**). Pale yellow oil (90 mg, 85%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.75 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 6.95 Hz, 1H), 7.38 (t, *J* = 7.4 Hz, 1H), 7.29-7.20 (m, 3H), 6.86 (s, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 1.85 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 167.82, 158.58 ($J_{C\text{-}F}$ = 248.75 Hz), 138.39, 135.04, 133.46 ($J_{C\text{-}F}$ = 3.75 Hz), 131.72, 131.37, 131.04, 129.56 ($J_{C\text{-}F}$ = 7.5 Hz), 129.13, 122.92, 121.38 ($J_{C\text{-}F}$ = 18.75 Hz), 117.11, 116.94, 111.54, 57.71, 30.53; ^{19}F NMR (470.385 MHz, $CDCl_3$): -116.42; HRMS (ESI) calcd for $C_{19}H_{18}ClFNO$ ($[M + H]^+$) 330.1061, found, 330.1071. Product contains *E*- and *Z*-isomer in the ratio of 95:5

2-(tert-butyl)-3-(2-methoxybenzylidene)isoindolin-1-one (**3ac**). Yellow oil (77 mg, 72%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.73 (d, *J* = 7.5 Hz, 1H), 7.43-7.37 (m, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.21-7.18 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.00-6.98 (m, 2H), 6.89 (s, 1H), 3.85 (s, 3H), 1.87 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 167.86, 157.56, 140.36, 136.65, 135.59, 132.79, 131.54, 131.06, 131.04, 129.49, 128.54, 128.43, 124.78, 122.84, 122.61, 120.45, 111.77, 110.78, 57.57, 55.63, 30.66; HRMS (ESI) calcd for $C_{20}H_{22}NO_2$ ($[M + H]^+$) 308.1650, found, 308.1656. Product contains *E*- and *Z*-isomer in the ratio of 87:13. Despite repeated drying on high vacuum, a significant solvent peak is observed in ^{1}H and ^{13}C NMR spectra. The isolated yield has been modified from 78% to 72 %.

2-(tert-butyl)-3-(3-methoxybenzylidene)isoindolin-1-one (**3ad**). Pale yellow oil (86 mg, 76%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.73 (d, *J* = 7.5 Hz, 1H), 7.36-7.32 (m, 2H), 7.21-7.18 (m, 1H), 6.99-6.91 (m, 5H), 3.83 (s, 3H), 1.86 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 167.91, 159.90, 137.67, 137.47, 135.41, 131.16, 130.99, 129.87, 128.73, 123.29, 122.63, 121.89, 114.53, 114.33, 113.58, 57.62, 55.35, 30.60; HRMS (ESI) calcd for $C_{20}H_{22}NO_2$ ($[M + H]^+$) 308.1650, found, 308.1656. Product contains *E*- and *Z*-isomer in the ratio of 93:7.

2-(tert-butyl)-3-(3-chlorobenzylidene)isoindolin-1-one (**3ae**). Colourless oil (98 mg, 92%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.74 (d, *J* = 7.5 Hz, 1H), 7.41 (s, 1H), 7.37-7.35 (m, 3H), 7.29-7.28 (m, 1H), 7.23-7.20 (m, 1H), 6.90 (s, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 1.85 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 167.86, 138.22, 138.12, 135.17, 134.63, 131.30, 131.03, 130.07, 129.63, 129.01, 127.85, 127.78, 123.04, 122.82, 112.57, 57.69, 30.55; HRMS (ESI) calcd for $C_{19}H_{19}ClNO$ ($[M + H]^+$) 312.1155, found, 312.1146. Product contains *E*- and *Z*-isomer in the ratio of 92:8.

4-((2-(tert-butyl)-3-oxoisoindolin-1-ylidene)methyl)benzonitrile (**3af**). Colourless oil (88 mg, 82%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.76-7.72 (m, 3H), 7.54 (d, *J* = 8 Hz, 2H), 7.39 (t, *J* = 7.4Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.90 (s, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 1.85 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 167.80, 141.53, 138.77, 134.88, 132.53, 131.38, 131.06, 130.58, 129.42, 123.06, 122.77, 118.76, 111.77, 111.32, 57.84, 30.53; HRMS (ESI) calcd for $C_{20}H_{19}N_2O$ ($[M + H]^+$) 303.1497, found. 303.1488. Product contains *E*- and *Z*-isomer in the

ratio of 92:8. Despite repeated drying on high vacuum, a significant solvent peak is observed in ^{1}H and ^{13}C NMR spectra. The isolated yield has been modified from 87% to 82 %.

2-(tert-butyl)-3-(4-fluorobenzylidene)isoindolin-1-one (**3ag**). Colourless oil (87 mg, 82%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.74 (d, *J* = 7.5 Hz, 1H), 7.40- 7.34 (m, 3H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 8.6 Hz, 2H), 6.94 (s, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 1.85 (s, 9H); Z (minor): 7.80 (d, *J* =7.6 Hz, 1H), 7.67 (d, *J* = 7.75 Hz, 1H), 7.55 (t, *J* = 7.45 Hz, 1H), 7.43 (t, *J* = 7.45 Hz, 1H), 7.40-7.34 (m, 2H), 7.08 (t, *J* = 8.6 Hz, 2H), 6.62 (s, 1H), 1.42 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$) (Mixture of E and Z): 167.88, 163.31, 161.34, 139.34, 137.78, 135.30, 132.22 ($J_{C\text{-}F}$ = 3.75 Hz), 131.89, 131.30, 131.24 ($J_{C\text{-}F}$ = 7.5 Hz), 131.04, 128.84, 128.30 122.88 ($J_{C\text{-}F}$ = 12.5 Hz), 118.53, 115.96, 115.79, 115.63, 114.11, 113.24, 109.66, 60.01, 57.65, 30.58, 29.41; ^{19}F NMR (470.385 MHz, $CDCl_3$): -114.06; HRMS (ESI) calcd for $C_{19}H_{19}FNO$ ([M + H]$^+$) 296.1450, found 296.1442, found 296.1430. Product contains *E*- and *Z*-isomer in the ratio of 80:20.

2-(tert-butyl)-3-(4-methoxybenzylidene)isoindolin-1-one (**3ah**) (known compound).[38] Yellow oil (69 mg, 65%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.73 (d, *J* = 7.5 Hz, 1H), 7.35-7.30 (m, 3H), 7.19 (t, *J* = 8.0 Hz, 1H), 6.97-6.93 (m, 4H), 3.88 (s, 3H), 1.85 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 167.87, 159.14, 137.12 , 135.50, 131.07, 130.97, 130.76, 128.56, 128.43, 123.03, 122.63, 114.50, 114.17, 57.57, 55.37, 30.63; HRMS (ESI) calcd for $C_{20}H_{22}NO_2$ ([M + H]$^+$) 308.1650, found 308.1654**.** Product contains *E*- and *Z*-isomer in the ratio of 79:21.

3-benzylidene-2-(2,4,4-trimethylpentan-2-yl)isoindolin-1-one (**3ba**). Brown oil (114 mg, 88%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.74-7.72 (m, 1H), 7.45-7.37 (m, 5H), 7.35-7.32 (m, 1H), 7.18-7.15 (m, 1H), 7.08 (s, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 2.09 (s, 2H), 1.94 (s, 6H), 1.03 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 168.49, 138.15, 136.50, 135.53, 131.10, 131.02, 129.49, 128.85, 128.64, 127.71, 123.19, 122.70, 115.39, 61.40, 51.98, 32.14, 32.08, 31.27; HRMS (ESI) calcd for $C_{23}H_{28}NO$ ([M + H]$^+$) 334.2171, found 334.2180. Product contains *E*- and *Z*-isomer in the ratio of 94:6.

3-(4-methylbenzylidene)-2-(2,4,4-trimethylpentan-2-yl)isoindolin-1-one (**3bb**). Yellow oil (91 mg, 71%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.73 (d, *J* = 7.5, 1H), 7.35-7.31 (m, 1H), 7.28-7.23 (m, 4H), 7.19-7.16 (m, 1H), 7.04 (s, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 2.44 (s, 3H), 2.07 (s, 2H), 1.93 (s, 6H), 1.02 (s, 9H), Z (minor) : 7.78 (d, *J* = 7.4 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.55-7.52 (m, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.35-7.16 (m, 4H), 6.72 (s, 1H), 2.38 (s, 3H), 1.78 (s, 2H), 1.42 (s, 6H), 0.80 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 168.47, 137.91, 137.52, 135.59, 133.37, 131.05, 129.53, 129.35, 128.55, 123.20, 122.66, 115.62, 61.35, 51.98, 32.17, 32.09, 31.27, 21.39; HRMS (ESI) calcd for $C_{24}H_{30}NO$ ([M + H]$^+$) 348.2327, found 348.2335. Product contains *E*- and *Z*-isomer in the ratio of 82:18.

4-((3-oxo-2-(2,4,4-trimethylpentan-2-yl)isoindolin-1 ylidene)methyl)benzonitrile (**3bc**). Off white solid (95 mg, 75 %); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.76-7.72 (m, 3H), 7.53 (d, *J* = 7.9 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.23-7.20 (m, 1H), 6.96 (s, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 2.07 (s, 2H), 1.93 (s, 6H), 1.02 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 168.36, 141.66, 139.48, 134.94, 132.56, 131.38, 131.07, 130.55, 129.37, 123.11, 122.84, 118.72, 112.58, 112.53, 111.39, 61.66, 51.94, 32.05, 31.26; HRMS (ESI) calcd for $C_{24}H_{27}N_2O$ ([M + H]$^+$) 359.2123, found 359.2130. Product contains *E*- and *Z*-isomer in the ratio of 95:5.

3-(naphthalen-2-ylmethylene)-2-(2,4,4-trimethylpentan-2-yl)isoindolin-1-one (**3bd**). Reddish oil (101 mg, 81%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.98 (d, *J* = 8.1 Hz, 1H), 7.92 (t, *J* = 8.6 Hz, 2H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.75-7.44 (m, 4H), 7.27 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.98 (t, *J* = 8.0 Hz, 1H), 6.45 (d, *J* = 7.9 Hz, 1H), 2.15 (s, 2H), 2.01(s, 6H), 1.08 (s, 9H), Z (minor): 8.02 (d, *J* = 7.9 Hz, 1H), 7.94-7.88 (m, 1H), 7.82-7.76 (m, 3H), 7.75-7.44 (m, 6H), 7.03 (s, 1H), 1.28-1.24 (m, 8H), 0.70 (s, 9H*)*; ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$) (Mixture of E/Z): 171.22, 168.57, 138.84, 135.56, 133.93, 133.81, 132.09, 131.73, 131.19, 131.02, 128.64, 128.61, 128.40, 127.68, 126.64, 126.57, 126.44, 125.77, 125.46, 125.23, 123.35, 122.74, 122.69, 113.37, 108.09, 63.39, 61.50, 52.05, 50.27, 32.28, 32.20, 31.38, 31.21, 29.76, 29.63; HRMS (ESI) calcd for $C_{27}H_{30}NO$ ([M + H]$^+$) 384.2327, found, 384.2318. Product contains *E*- and *Z*-isomer in the ratio of 69:31. Despite repeated drying on high vaccum, a significant solvent peak is observed in ^{1}H and ^{13}C NMR spectra. The isolated yield has been modified from 88 % to 81 %.

3-(4-(trifluoromethyl)benzylidene)-2-(2,4,4-trimethylpentan-2-yl)isoindolin-1-one (**3be**). Pale yellow oil (97 mg, 79%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.75 (d, *J* = 7.5 Hz, 1H), 7.69 (d, J = 7.9 Hz, 2H), 7.52 (d, *J* = 7.7 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.00 (s, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 2.08 (s, 2H), 1.94 (s, 6H), 1.03 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 168.43, 140.37, 139.03, 135.12, 131.35, 131.05, 130.03, 129.92 ($J_{C\text{-}F}$ = 5.0 Hz), 129.14, 125.77 ($J_{C\text{-}F}$ = 3.75 Hz), 122.92 ($J_{C\text{-}F}$ = 12.5 Hz), 118.86, 113.24, 64.08, 61.55, 51.95, 50.67, 32.09, 31.27; ^{19}F NMR (470.385 MHz, $CDCl_3$): -62.37; HRMS (ESI) calcd for $C_{24}H_{27}F_3NO$ ([M + H]$^+$) 402.2044, found, 402.2035. Product contains *E*- and *Z*-isomer in the ratio of 93:7.

3-benzylidene-2-(tert-butyl)-6-methylisoindolin-1-one (**3ca**). Pale yellow oil (97 mg, 84%); ^{1}H NMR (δ ppm) (500 MHz,$CDCl_3$), *E* (major): 7.52 (s, 1H), 7.44-7.37 (m, 5H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.95 (s, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 2.35 (s, 3H), 1.85 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 168.06, 139.01, 137.47, 136.52, 132.95, 132.15, 131.25, 129.61, 128.74, 128.56, 122.92, 122.77, 113.76, 57.56, 30.62, 21.38; HRMS (ESI) calcd for $C_{20}H_{22}NO$ ([M + H]$^+$) 292.1701, found 292.1710. Product contains *E*- and *Z*-isomer in the ratio of 88:12.

3-benzylidene-6-methyl-2-(2, 4, 4-trimethylpentan-2-yl)isoindolin-1-one (**3cb**). Yellow oil (89 mg, 70%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.52 (s, 1H), 7.44-7.37 (m, 5H), 7.01 (s, 1H), 6.96 (dd, *J* = 1.0, 8.0 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 2.35 (s, 3H), 2.07 (s, 2H), 1.93 (s, 6H), 1.02 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 168.63, 138.96, 138.23, 136.67, 133.04, 132.19, 131.26, 12956, 128.79, 127.60, 123.03, 122.82, 114.60, 61.31, 51.94, 32.19, 31.27, 21.36; HRMS (ESI) calcd for $C_{24}H_{30}NO$ ([M + H]$^+$) 348.2327, Found, 348.2325. Product contains *E*- and *Z*-isomer in the ratio of >99:<1.

7-benzylidene-6-(tert-butyl)-6, 7-dihydro-5H-pyrrolo[3,4-b]pyridin-5-one (**3da**). Yellow oil (71 mg, 66%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 8.56 (d, *J* = 5.9 Hz, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 7.0 Hz, 2H), 7.44 - 7.27 (m, 4H), 7.07 (s, 1H), 1.87 (s, 9H); ^{13}C NMR ; 165.80, 154.77, 152.57, 135.78, 134.58, 130.72, 130.45, 129.65, 128.60, 127.72, 127.61, 124.11, 123.46, 123.22, 118.01, 58.05, 30.73, 29.29; HRMS (ESI) calcd for $C_{18}H_{19}N_2O$ ([M + H]$^+$) 279.1497, found 279.1491. Product contains *E*- and *Z*-isomer in the ratio of 87:13.

2-(tert-butyl)-3-(thiophen-2-ylmethylene)isoindolin-1-one (**3ea**). Brown oil (87 mg, 81%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 7.73 (d, *J* = 7.5 Hz, 1H), 7.43-7.41 (m, 1H), 7.39-7.35 (m, 1H), 7.27 – 7.24 (m, 1H), 7.12-7.10 (m, 1H), 7.06-7.04 (m, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 6.82 (s, 1H), 1.84 (s, 9H), Z (minor): 7.79 (d, *J* = 7.6 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.7 Hz, 1H), 7.43 – 7.41 (m, 1H), 7.39 – 7.35 (m, 1H), 7.12 – 7.10 (m, 1H), 7.06 – 7.04 (m, 1H), 6.66 (s, 1H), 1.51 (s, 9H); ^{13}C NMR (Mixture of *E/Z*) ; 172.22,167.95, 141.64, 140.86, 140.04, 139.80, 137.87, 137.80, 135.16, 133.72, 131.90, 131.43, 130.82, 129.09, 128.37, 128.30, 127.64, 127.61, 127.48, 126.73, 126.67, 123.26, 122.91, 122.69, 122.61, 118.62, 105.79, 103.39, 60.35, 57.76, 30.55, 29.31. HRMS (ESI) calcd for $C_{17}H_{18}NOS$ ([M + H]$^+$) 284.1109, found 284.1101. Product contains *E*- and *Z*-isomer in the ratio of 72:28.

3,7-di((E)-benzylidene)-2,6-di-tert-butyl-2,3,6,7-tetrahydropyrrolo[3,4-f]isoindole-1,5-dione (**3fa**). Green solid (74 mg, 68%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *EE* (major): 7.50 - 7.40 (m, 6H), 7.37 - 7.35 (m, 4H), 7.19 (s, 2H), 7.03 (s, 2H), 1.80 (s, 18H), EZ (minor): 8.01 (s, 1H), 7.50 - 7.40 (m, 7H), 7.37-7.35 (m, 4H), 7.08 (s, 1H), 6.75 (s, 1H), 1.88 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 166.87, 136.65, 135.55, 135.34, 133.58, 129.31, 129.07, 128.35, 117.80, 115.78, 57.93, 30.52; HRMS (ESI) calcd for $C_{32}H_{33}N_2O_2$ ([M + H]$^+$) 477.2542, Found 477.2535. Product contains *E*- and *Z*-isomer in the ratio of 89:11. Despite repeated drying on high vaccum, a significant solvent peak is observed in ^{1}H and ^{13}C NMR spectra. The isolated yield has been modified from 72 % to 68 %.

2-(tert-butyl)-3-(pyridin-2-ylmethylene)isoindolin-1-one (**3ga**). Yellow Oil (79 mg, 73%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 8.73 (d, *J* = 4.3 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.09 (d, *J* = 7.9 Hz, 1H), 6.98 (s,

1H), 1.86 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 168.09, 155.34, 149.86, 139.62, 136.59, 135.04, 131.34, 131.04, 129.28, 125.31, 123.23, 122.75, 122.37, 113.29, 57.84, 30.59; HRMS (ESI) calcd for $C_{18}H_{19}N_2O$ ($[M + H]^+$) 279.1497, Found, 279.1487. Product contains *E*- and *Z*-isomer in the ratio of 91:9. Despite repeated drying on high vaccum, a significant solvent peak is observed in ^{1}H and ^{13}C NMR spectra. The isolated yield has been modified from 79 % to 73 %.

3-(pyridin-2-ylmethylene)-2-(2, 4, 4-trimethylpentan-2-yl)isoindolin-1-one (**3gb**). Colourless oil (99 mg, 77%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$), *E* (major): 8.74 (d, *J* = 4.5 Hz, 1H), 7.75-7.72 (m, 2H), 7.45 (d, *J* = 7.5Hz, 1H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.30-7.28 (m, 1H), 7.23 (t, *J* = 7.0 Hz, 1H) 7.05 (d, *J* = 7.9 Hz, 1H), 7.02 (s, 1H), 2.10 (s, 2H), 1.94 (s, 6H), 1.03 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 168.60, 155.46, 149.91, 140.19, 136.56, 135.13, 131.34, 131.01, 129.23, 125.37,123.23, 122.79, 122.35, 114.12, 108.84, 61.67, 52.01, 32.10, 31.28; HRMS (ESI) calcd for $C_{22}H_{27}N_2O$ ($[M + H]^+$) 335.2123, found 335.2131. Product contains *E*- and *Z*-isomer in the ratio of 92:8

N-(tert-butyl)-2-(3, 3-dimethylbut-1-yn-1-yl)benzamide (**2a**). Colourless oil (90 mg, 83%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$): 7.93 - 7.91 (m, 1H), 7.44-7.42 (m, 1H), 7.34 - 7.33 (m, 2H), 7.08 (bs, 1H), 1.50 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 165.94, 136.45, 134.07, 129.85, 129.47, 128.03, 120.01, 104.85, 77.93, 51.87, 30.95, 28.93, 28.39; HRMS (ESI) calcd for $C_{17}H_{24}NO$ ($[M + H]^+$) 258.1858, found 258.1851.

N-(tert-butyl)-2-(hept-1-yn-1-yl)benzamide (**2b**). Colourless oil (87 mg, 70%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$): 8.02-8.00 (m, 1H), 7.46 - 7.44 (m, 2H), 7.37-7.35 (m, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 1.68 - 1.62 (m, 2H), 1.48 (s, 9H), 1.45 – 1.43 (m, 2H), 1.38 – 1.36 (m, 2H), 0.92 (t, *J* = 7.25 Hz, 3H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 165.50, 136.30, 133.61, 130.05, 129.63, 128.18, 120.07, 97.30, 79.46, 51.49, 31.23, 28.86, 28.27, 22.26, 19.65, 14.0; HRMS (ESI) calcd for $C_{18}H_{26}NO$ ($[M + H]^+$) 272.2014, found 272.2006.

2-(3, 3-dimethylbut-1-yn-1-yl)-N-(2, 4, 4-trimethylpentan-2-yl)benzamide (2c). Colourless oil (80 mg, 76%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$): 7.94 - 7.92 (m, 1H), 7.45 - 7.43 (m, 1H), 7.35 - 7.33 (m, 2H), 7.08 (bs, 1H), 1.95 (s, 2H), 1.55 (s, 6H), 1.37 (s, 9H), 1.02 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 165.61, 136.44, 134.28, 131.33, 129.79, 129.42, 128.03, 120.03, 104.91, 78.09, 55.79, 50.97, 31.77, 31.49, 30.96, 29.58, 28.41; HRMS (ESI) calcd for $C_{21}H_{32}NO$ ($[M + H]^+$) 314.2484, found 314.2491.

N-(*tert*-butyl)-2-(cyclohex-1-en-1-ylethynyl)benzamide (2d). Reddish oil (105 mg, 80%); ^{1}H NMR (δ ppm) (500 MHz, $CDCl_3$): 7.99-7.97 (m, 1H), 7.46 - 7.44 (m, 1H), 7.37-7.35 (m, 2H), 7.23 (bs, 1H), 6.27 - 6.25 (m, 1H), 2.25 - 2.22 (m, 2H), 2.19 – 2.16 (m, 2H), 1.71-1.67 (m, 2H), 1.66 - 1.61 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (δ ppm) (125 MHz, $CDCl_3$): 165.62, 136.63, 136.43, 133.40, 130.01, 129.64, 128.36, 120.21, 119.88, 97.51, 85.06, 51.63, 29.10, 28.86, 25.83, 22.24, 21.41; HRMS (ESI) calcd for $C_{19}H_{24}NO$ ($[M + H]^+$) 282.1858, found 282.1865

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[1] (a) A. Dömling, I. Ugi, *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3168–3210. (b) T. Vlaar, E. Ruijter, B. U. W. Maes, R. V. A. Orru, *Angew. Chemie - Int. Ed.* **2013**, *52*, 7084–7097.

[2] (a) B. Ma, Y. Wang, J. L. Peng, Q. Zhu, *J. Org. Chem*., **2011**, *76*, 6362-6366. (b) B. Haffemayer, M. Gulias, M. J. Gaunt, *J. Chem. Sci*, **2011**, *2*, 312-315. (c) Y. Wang, H. Wang, J. Peng, Q. Zhu, *Org. Lett.* **2011**, *13*, 4604–4607. (d) E. J. Yoo, M. Wasa, J. –Q. Yu, *J. Am. Chem. Soc*. **2011**, *132*, 17378-17380.

[3] (a) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89. (b) A. Dömling, W. Wang, K. Wang, *chem. Rev*. **2012**, *112*, 3083-3135 and references therein.

[4] (a) H. Jiang, B. Liu, Y. Li, A. Wang, H. Huang, *Org. Lett.* **2011**, *13*, 1028–1031. (b) U. K. Sharma, N. Sharma, J. Xu, G. Song, E. V. V. der Eycken *Chem. Eur. J.* **2016**, *22*, 5878-5882.

[5] (a) Y. Yamamoto, *Chem. Soc. Rev.* **2014**, *43*, 1575–1600. (b) A. Fusano, T. Fukuyama, S. Nishitani, T. Inouye, I. Ryu, *Org. Lett.* **2010**, *12*, 2410–2413. (c) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050–12051. (d) M. Leibeling, M. Pawliczek, D. Kratzert, D. Stalke, D. B. Werz, *Org. Lett.* **2012**, *14*, 346–349.

[6] For recent examples on palladium-catalyzed processes to synthesis of N-containing heterocycles involving isocyanide insertion, see: (a) M. Sharma, I. Khan, S. Khan, R. Mahar, S. K. Shukla, R. Kant, P. M. S. Chauhan, *Tetrahedron Lett.* **2015**, *56*, 5401–5408. (b) V. Tyagi, S. Khan, A. Giri, H. M. Gauniyal, B. Sridhar, P. M. S. Chauhan, *Org. Lett.* **2012**, *14*, 3126–3129. (c) T. Nanjo, C. Tsukano, Y. Takemoto, *Org. Lett.* **2012**, *14*, 4270–4273. (d) M. Tobisu, S. Imoto, S. Ito, N. Chatani, *J. Org. Chem.* **2010**, *75*, 4835–4840. (e) T. Miura, Y. Nishida, M. Morimoto, M. Yamauchi, M. Murakami, *Org. lett.* **2011**, *13*, 1429–1431. (f) T. Vlaar, R. C. Cioc, P. Mampuys, B. U. W. Maes, R. V. A. Orru, E. Ruijter, *Angew. Chemie - Int. Ed.* **2012**, *51*, 13058–13061. (g) Z. Hu, D. Liang, J. Zhao, J. Huang, Q. Zhu, *Chem Commun* **2012**, *48*, 7371–7373. (h) G. Qiu, C. Chen, L. Yao, J. Wu, *Adv. Synth. Catal.* **2013**, *355*, 1579–1584.

[7] For selected reviews, see: (a) S. S. Stahl, *Science (80-.).* **2005**, *309*, 1824–1826. (b) G. Liu, G. Yin, L. Wu, *Angew. Chemie - Int. Ed.* **2008**, *47*, 4733–4736. (c) W. Wu, H. Jiang, *Acc. Chem. Res.* **2012**, *45*, 1736–1748.

[8] H. Hart, In The Chemistry of Triple-Bonded Functional Groups; S. Patai, Ed.; John Wiley & Sons Ltd.: New York, 1994.

[9] For reviews, see: (a) T. E. Müller, M. Beller, *Chem. Rev.* **1998**, *98*, 675–704. (b) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chemie - Int. Ed.* **2004**, *43*, 3368–3398. (c) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3159. (d) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285–2309. (e) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127–2198. (f) N. T. Patil, Y. Yamamoto, *Chem. Rev*. **2008**, *108*, 3395–3442.

[10] Y. Nozawa, K. Yamamoto, M. Ito, N. Sakai, K. Mizoue, F. Mizobe, K. Hanada, *J. Antibio*t., **1997**, *50*, 635-640.

[11] (a) G. Blask, D. J. Gula, M. Shamma, *J. Nat. Prod.* **1982**, *45*, 105–122. (b) J. Weinstock, J. P. Hieble, J. W. Wilson, *Drugs Future*, **1985**, *10*, 645-696.

[12] A. Padwa, L. S. Beall, C. K. Eidell, K. J. Worsencroft, *J. Org. Chem.* **2001**, *66*, 2414–2421.

[13] M. De Chen, M. Z. He, X. Zhou, L. Q. Huang, Y. P. Ruan, P. Q. Huang, *Tetrahedron* **2005**, *61*, 1335–1344.

[14] (a) V. Gotor, F. Limeres, R. Garcı´a, M. Bayod, R. Brieva, *Tetrahedron: Asymmetry*, **1997**, *8*, 995-997. (b) M. Anzini, A. Cappelli, S. Vomero, G. Giorgi, T. Langer, G. Bruni, M. R. Romeo, A. S. Basile, *J. Med. Chem*., **1996**, *39,* 4275-4284.

[15] K. Achinami, N. Ashizawa, F. Kobayashi, *Jpn Patent JP 03,* **1991**, ***133***, 955; *Chem. Abstr*., **1991**, *115*, 255977.

[16] E. Valencia, V. Fajardo, A. J. Freyer, M. Shamma, *Tetrahedron Lett.* **1985**, *26*, 993–996.

[17] T. Kondo, K. Yoshida, Y. Yoshimura, S. Tanayama, *Biopharm. Drug Dispos.* **1995**, *16*, 755–773.

[18] X. Z. Zhao, K. Maddali, C. Marchand, Y. Pommier, T. R. Burke, *Bioorganic Med. Chem.* **2009**, *17*, 5318–5324.

[19] E. D. Clercq, *J. Med. Chem*., **1995**, *38*, 2491-2517.

[20] R. Volpe, L. S. Mautner, *Appl. Ther.*, **1961**, *3*, 521-528.

[21] I. R. Hardcastle, J. Liu, E. Valeur, A. Watson, S. U. Ahmed, T. J. Blackburn, K. Bennaceur, W. Clegg, C. Drummond, J. A. Endicott, B. T. Golding, R. J. Griffin, J. Gruber, K. Haggerty, R. W. Harrington, C. Hutton, S. Kemp, X. Lu, J. M. McDonnell, D. R. Newell, M. E. M. Noble, S. L. Payne, C. H. Revill, C. Riedinger, Q. Xu, J. Lunec, *J. Med. Chem.* **2011**, *54*, 1233–1243.

[22] J. C. Breytenbach, S. van Dyk, I. van den Heever, S. M. Allin, C. C. Hodkinson, C. J. Northfield, M. I. Page, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1629–1631.

[23] S. Li, X. Wang, H. Guo, L. Chen, Yiyano. *Gongye* **1985**, *16*, 543-544.

[24] J. Wrobel, a Dietrich, S. a Woolson, J. Millen, M. McCaleb, M. C. Harrison, T. C. Hohman, J. Sredy, D. Sullivan, *J. Med. Chem.* **1992**, *35*, 4613–27.

[25] W. Yu, Z. Guo, P. Orth, V. Madison, L. Chen, C. Dai, R. J. Feltz, V. M. Girijavallabhan, S. H. Kim, J. A. Kozlowski, et al., *Bioorganic Med. Chem. Lett.* **2010**, *20*, 1877–1880.

[26] (a) M. A. Weidner-Wells, K. Oda, P. H. Mazzocchi, *Tetrahedron,* **1997**, *53*, 3475-3486. (b) A. G. Griesbeck, J. Hirt, W. Kramer, P. Dallakian, *Tetrahedron*, **1998**, *54*, 3169-3180. (c) M. J. Milewska, T. Bytner, T. Polonski, *Synthesis*, **1996**, *24*, 1485-1488. (d) M. Hellal, G. D. Cuny, *Tetrahedron Lett.* **2011**, *52*, 5508–5511. (e) N. G. Kundu, M. W. Khan, *Tetrahedron*, **2000**, *56*, 4777-4792.

[27] A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron* **1997**, *53*, 10313–10330.

[28] S. Couty, B. Liégault, C. Meyer, J. Cossy, *Org. Lett*. **2004**, 3, 2511-2514.

[29] H. Peters, W. Flitsch, *Tetrahedron Lett*. **1969**, *10*, 1161-1162.

[30] Y. Kondo, F. Shiga, N. Murata, T. Sakamoto, H. Yamanaka, *Tetrahedron*, **1994**, *50*, 11803–11812..

[31] H. Cao, L. McNamee, H. Alper, *Org. Lett.* **2008**, *10*, 5281–5284

[32] L. Li, M. Wang, X. Zhang, Y. Jiang, D. Ma, *Org. Lett*. **2009**, *11*, 1309-1312.

[33] A. Garcia, D. Rodriguez, L. Castedo, C. Saa, D. Dominguez, *Tetrahedron Lett*. **2001**, *42*, 1903-1905.

[34] For other aminocarbonylation protocols see: (a) M. Fujioka, T. Morimoto, T. Tsumagari, H. Tanimoto, Y. Nishiyama, K. Kakiuchi, *J. Org. Chem.* **2012**, *77*, 2911–2923. (b) R. Mancuso, I. Ziccarelli, D. Armentano, N. Marino, S. V. Giofre, B. Gabriele, *J. Org. Chem*. **2014**, *79*, 3506-3518. (c) Y. Xu, W. Hu, X. Tang, J. Zhao, W. Wu, H. Jiang, *Chem. Commun*. **2015**, *51*, 6843-6846. (d) P. Barrio, I. Ibáñez, L. Herrera, R. Román, S. Catalán, S. Fustero, *Chem. Eur. J*., **2015**, *21*, 11579-11584.

[35] J. Hu, H.-L. Qin, W. Xu, J. Li, F. Zhang, H. Zheng, *Chem. Commun.* **2014**, *50*, 15780–15783.

[36] (a) S. Sharma, R. S. Pathare, A. K. Maurya, K. Gopal, T. K. Roy, D. M. Sawant, R. T. Pardasani, *Org. Lett.* **2016**, *18*, 356–359. (b) P. Maloo, T. K. Roy, D. M. Sawant, R. T. Pardasani, M. M. Salunkhe, *RSC Adv.*, **2016**, *6*, 41897-41906. (c) A. J. Ansari, S. Sharma, R. S. Pathare, K. Gopal, D. M. Sawant, R. T. Pardasani, *ChemSelect* **2016**, *1*, 1016-1021. (d) D. Sawant, I. Singh, G. Tulsyan, K. Abbagani, R. T. Pardasani, *Synlett* **2015**, *26*, 1671–1676. (e) A. Sharma, M. Singh, N. N. Rai, D. Sawant, *Beilstein J. Org. Chem.* **2013**, *9*, 1235–1242.

[37] $C_{24}H_{29}NO$, M = 347.48, triclinic, space group: P-1, a= 10.369(2), b = 10.391(2), c = 11.416(2) Å, α = 115.44(3), β = 97.05(3), γ= 108.68(3), V = 1002.3(4) $Å^3$, T = 172(2) K, Z = 2,μ = 0.069 mm−1, F(000) = 376.0, D_c = 1.151 Mg m^{-1}, crystal size 0.35 x 0.20 x 0.07 mm, 15852 reflections measured, 3621 unique, R1 = 0.0507 for $4032F_o > 4\sigma(F_o)$, and 0.0850 for all 3621 data and 263 parameters. Unit cell determination and intensity data collection (2θ = 50.78°) was performed with 97.8 % completeness at 172 (2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F_2.

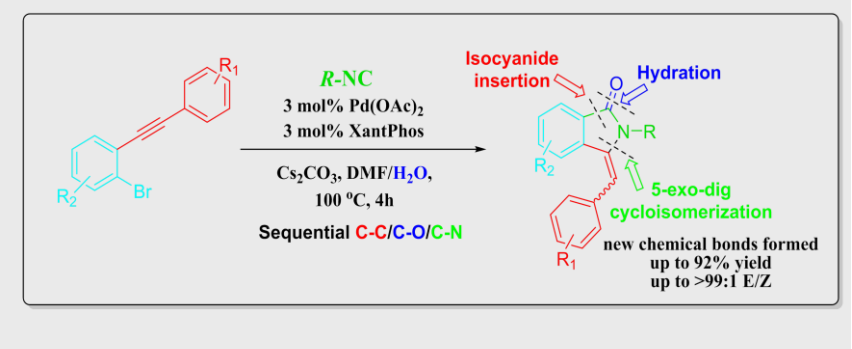
[38] C. Kanazawa, M. Terada, *Chem. - An Asian J.* **2009**, *4*, 1668–1672.

[39] (a) B. J. Khairnar, B. M. Bhanage, *Synthesis*, **2014**, *46*, 1236-1242. (b) X.-D. Fei, Z.-Y. Ge, T. Tang, Y.-M. Zhu, S.-J. Ji, *J. Org. Chem*. **2012**, *77*, 10321-10328.

[40] M. Uchiyama, H. Ozawa, K. Takuma, Y. Matsumoto, M. Yonehara, K. Hiroya, T. Sakamoto, *Org. Lett.* **2006**, *8*, 5517–5520.

[41] C. Amatore, L. E. Kaim, L. Grimaud, A. Jutand, A. Meignie, G. Romanov, *Eur. J. Org. Chem*. **2014**, *22*, 4709-4713.

[42] Although, the one pot protocol was successfully applied on **3aa** and **3ba**, the work on this protocol is still in progress to expand the substrate scop



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Application of isocyanides as an amide surrogate for the synthesis of diverse isoindolin-1-one derivatives *via* Palladium-catalyzed tandem Carboxamidation/Hydroamidation reaction

Palladium(II) catalyzed transformation of ortho-haloarylalkynes into 2-alkynylbenzamide using isocyanide as amide surrogate is described (carboxamidation). The 2-alkynylbenzamide, so generated *in-situ*, was subsequently cyclized to isoindolinone by hydroamidation of alkynes. Thus a simple precursor (ortho-haloarylalkynes) could be transformed into a bioactive heterocycle (isoindolinone). The efficacy of our protocol is the formation of four new chemical bonds with excellent regio-/stereo-control. This is the first report on the synthesis of isoindolin-1-one via Pd-catalyzed isocyanide insertion/cyclization process.