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Facile ligand-free Pd-catalyzed tandem C–C/C–N coupling reaction: a novel access to highly diverse tetrazole tag isoindoline derivatives

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ABSTRACT

A novel and robust route for the synthesis of diversely substituted isoindoline skeletons through a ligand-free Pd-catalyzed cascade consisting of isocyanide insertion into Ugi-tetrazole has been developed. The tetrazole precursor is prepared in one step by the Ugi-four component reaction. The reaction proceeds smoothly under mild conditions with high efficiency. This chemistry is simple, economical, and is believed to be the key step during the synthesis of significant pharmaceuticals.

Introduction

The isoindolines and 1-substituted isoindolin-3-ones nuclei are substructures present in many natural products such as fumaridine and lennoxamine.[1–3] and the core skeleton of some biologically active compounds (Fig. 1).[4] These heterocyclic frameworks have attracted considerable attention in synthetic organic and medicinal chemistry due to their broad structural diversity and broad-spectrum biological activities, including: Endothelin-A Receptor Antagonists,[5] inhibition of prolyl dipeptidase DPP8,[6] PPARδ agonists,[7] histone deacetylase inhibitors,[8] inhibitors of selective serotonin reuptake,[9] diuretic, NMDA receptor antagonists, herbicidal,[10] anti-inflammatory, and antileukemic agents.[11] Furthermore, isoindolines inhibit the amyloid protein aggregation which demonstrate a potency in the treatment of Alzheimer's disease, the ligand affinity for the melanocortin subtype-4 receptor (MC4R) (D), act as multidrug resistance reversal agents, and fibrinogen receptor antagonists.[12,13] On the other side, tetrazole is an extremely valuable scaffolds due to their diverse biological activity.[14]

A variety of synthetic procedures have been reported for the preparation of isoindoline core structural skeletons.[15] However, most of them usually require the use of expensive starting materials/catalysts or high catalyst loadings, suffer from long reaction time, difficulty in workup, high temperature, and with fewer points of diversity.[16] Hence, the fascinating biological profiles of this group of compounds has spurred organic chemists to devise new, efficient, and straightforward methods for their viable preparation with increased molecular diversity and complexity.

Transition metal catalyzed synthesis of substituted isoindoline analogues has received noteworthy attention.[17] In this perspective, palladium catalysis is of undisputed importance in organic synthesis for the formation of carbon–carbon and carbon–heteroatom bonds. In the recent past, synthesis of biologically important heterocycles by isocyanide insertion under palladium catalysis is an efficient but relatively unexplored method.[18]

Due to the presence of a formally divalent carbon atom, isocyanides have been recognized as powerful building blocks for constructing functional molecules with increased molecular diversity for drug discovery and natural product synthesis.[19] On the other hand, isocyanides serve not simply as a carbon monoxide equivalent but also as a unique C1 source to substitute the well-known CO insertions, such as more practical handling and an extra diversity point for scaffold embellishment.[20]

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0040-4039/

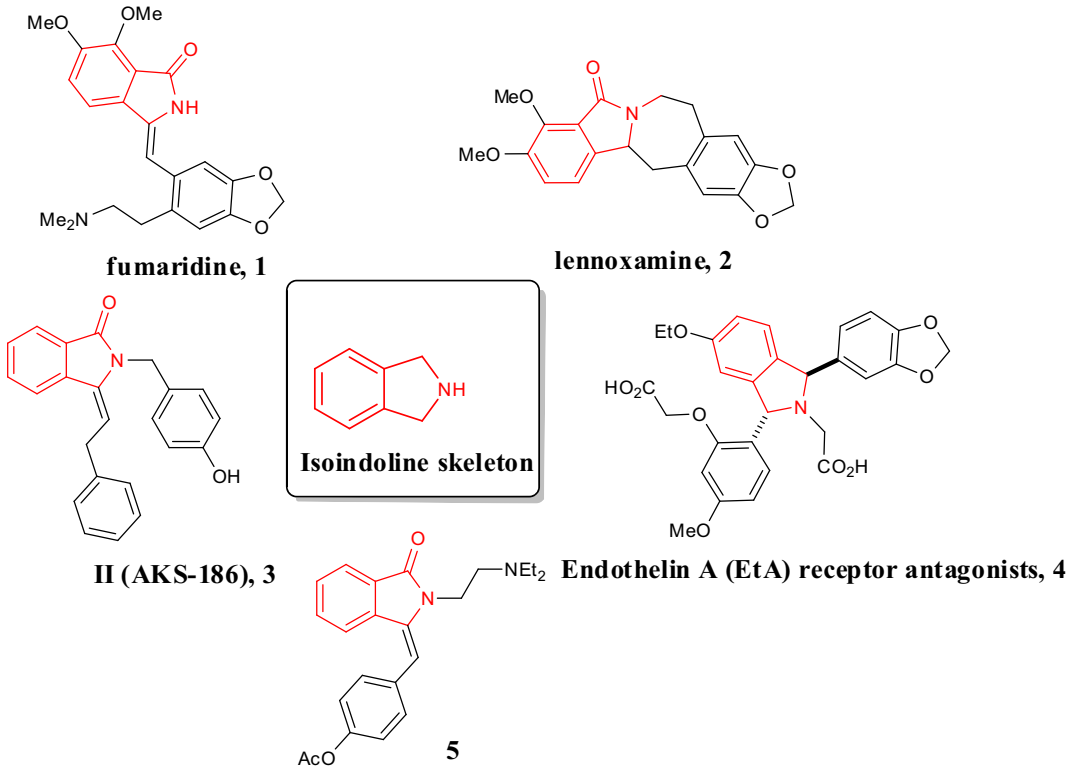


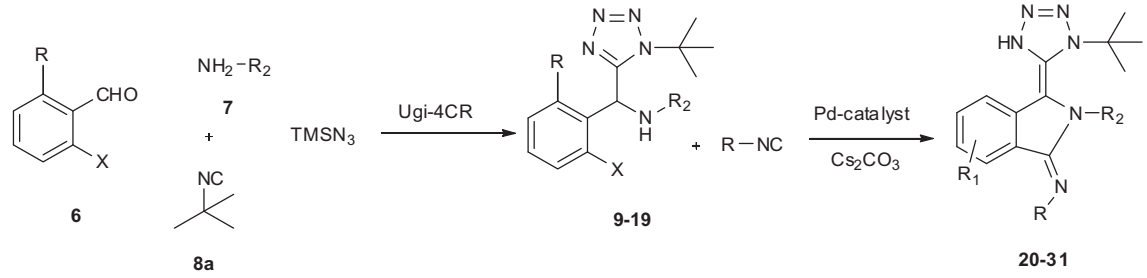
Figure 1. Biologically active natural products containing isoindoline scaffold.

In the past few years, we have been involved in the multicomponent Ugi reactions for generation of natural product-like compounds,[21] the chemistry involving palladium-catalyzed isocyanide insertion,[22] and new strategies for the diversity oriented synthesis of biologically important heterocycles.[23] Based on these observations, herein, we report the ligand-free Pd-catalyzed coupling cascade with the insertion of isocyanide into amine precursors, which was obtained by modified $TMSN_3$-Ugi MCR for the construction of isoindoline derivatives.[24] To the best of our knowledge, it is the first Letter to the synthesis of diverse isoindoline and isoindolinone derivatives.

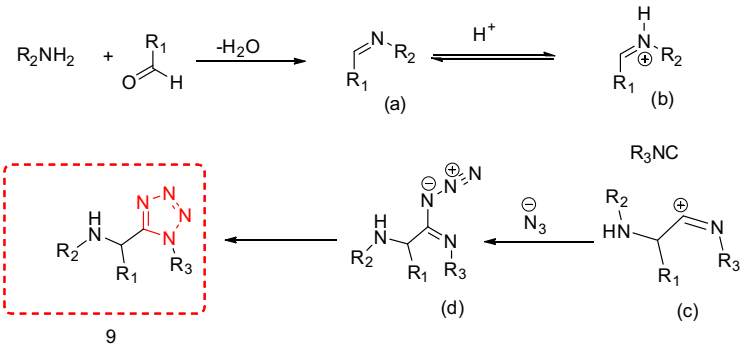
Results and discussion

As shown in Scheme 1a, we portray a rapid construction of a series of 1,5-disubstituted-1*H* tetrazoles (**9**–**19**) with good to excellent overall yields (79–95%) utilizing a catalyst free optimized modified Ugi 4-CR process employing commercially available aldehydes **6**, amines **7**, isocyanides **8,** and $TMSN_3$ in MeOH. The mechanistic pathway for the synthesis of isoindoline precursors has been shown in Scheme 1b.[25] The first step initiates with the formation of imine (**a**) by the reaction of amine and aldehydes. The imine (**a**) converts into iminium (**b**), which give nucleophilic addition with isocyanide to form intermediate (**c**). After azide insertion intermediate (**c**) gives isoindoline precursors. The corresponding isoindoline precursors, which were used as a starting substrate for the ligand-free palladium-catalyzed cascade reaction involve insertion and intramolecular cyclization of an isocyanide. Further as depicted in Scheme 2, there can be formed two probable products **A** and **B** of the same molecular weights under Pd-catalyzed conditions. ^{1}H NMR, ^{13}C NMR, and 2-D NMR data of compound **20** confirmed that the products have the general structure **B**, which; was unusual from normal probable product **A**.[26]

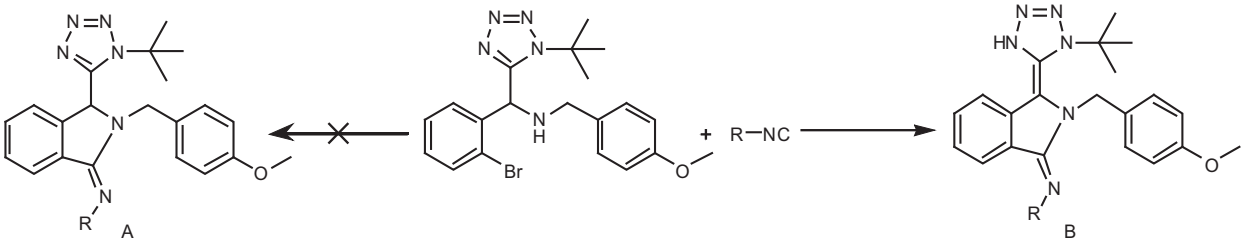
In an initial attempt, amine precursor **9** was used as a model compound for the reaction with *tert*-butyl isocyanide (**8a**) to screen the reaction conditions with a variety of bases, catalyst, and solvents (Table 1). After extensive screening of the reaction parameters, the optimal reactions that were found to involve $Pd(OAc)_2$ (5 mol %), Cs_2CO_3 (1.5 equiv) in DMF (2 mL) at 90 °C were identified (Table 1). The desired product *(E)-N-(3-(1-tert-butyl-1H-tetrazol-5-yl)-2-(4-methoxybenzyl)isoindolin-1-ylidene)-2 methylpropan-2-amine* (**20**) was obtained in 70% yield. No reaction



Scheme 1a. General strategy for the synthesis of tetrazole–isoindoline.

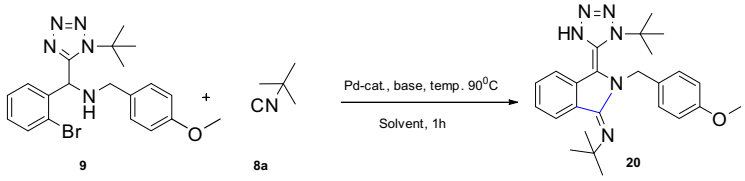


Scheme 1b. General mechanism of Ugi 4-CR tetrazole synthesis.



Scheme 2. Two possible structures in Pd-catalyzed coupling conditions.

Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Base	Solvent	Temp	Yield[b]
1	—	Cs_2CO_3	DMF	90	0[c]
2	$PdCl_2$	Cs_2CO_3	DMF	90	60
3	$Pd(OAc)_2$	Cs_2CO_3	DMF	90	70
4	$Pd(OAc)_2$	—	DMF	90	0[d]
5	$Pd(OAc)_2$	K_2CO_3	DMF	90	45
6	$Pd(OAc)_2$	Na_2CO_3	DMF	90	38
7	$Pd(OAc)_2$	$NaHCO_3$	DMF	90	26
8	$Pd(OAc)_2$	K_3PO_4	DMF	90	30
9	$Pd(OAc)_2$	KO^tBu	DMF	90	0
10	$Pd(OAc)_2$	Cs_2CO_3	DMSO	90	50
11	$Pd(OAc)_2$	Cs_2CO_3	Toluene	90	55
12	$Pd(OAc)_2$	Cs_2CO_3	Dioxane	90	30

[a] Reaction conditions: substrate **9** (1 equiv), *tert*-butylisocyanide **8a** (1.1 equiv), catalyst (5 mol %), base (1.5 equiv), solvent (2 ml), reaction temperature (90 °C), reaction time (1 h).
[b] Isolated yield.
[c] No addition of catalyst.
[d] No addition of base.

occurred, and the starting substrate **9** remained intact when palladium was excluded (Table 1, entry 1). Among the two catalysts $PdCl_2$ and $Pd(OAc)_2$ used, $Pd(OAc)_2$ was found to be the best and provided the product **20** in 70% yield when the reaction was run in DMF as a solvent at 90 °C (Table 1, entry 3). In the presence of the $Pd(OAc)_2$ catalyst (5 mol %), no desired product was observed without any base (Table 1, entry 4). On the other hand $PdCl_2$ resulted in moderate yields of **20** (Table 1, entries 2). Also, various bases K_2CO_3, K_3PO_4, Na_2CO_3, $NaHCO_3$, and KO^tBu were tested and the best result was obtained when Cs_2CO_3 (1.5 equiv) was utilized as the base, affording **20** in 70% yield (compare entries 5–9 and 3 Table 1) in DMF at 90 °C. Using $Pd(OAc)_2$ as the catalyst and Cs_2CO_3 as the base in DMSO resulted in a slightly lower yield (Table 1, entry 10), while using toluene and dioxane under the same conditions provided **20** in only poor yields (Table 1, entries 11 and 12). The reaction proceeded to completion in 1 h under heating conditions at 90 °C. Further attempts to optimize the isocyanide insertion, including increasing the catalyst loadings,

Table 2
Scope of the two step procedure[a]

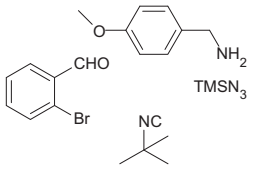
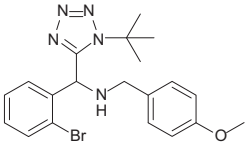
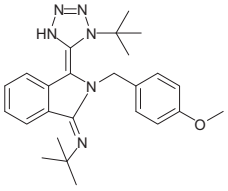
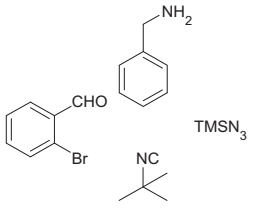
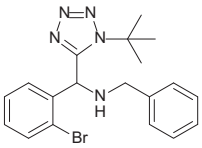
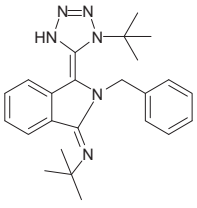
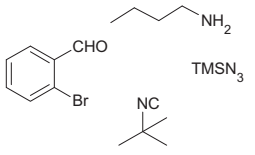
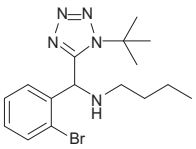
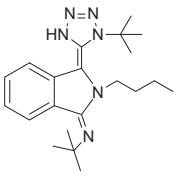
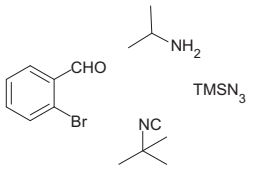
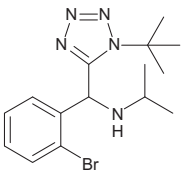
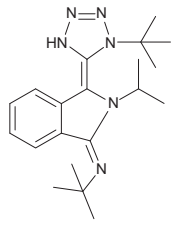
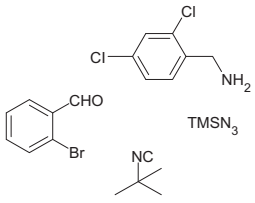
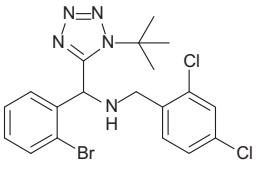
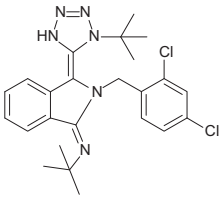
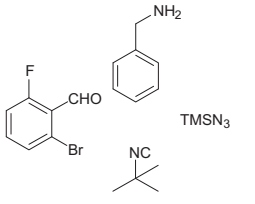
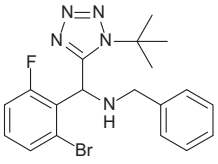
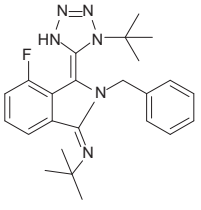
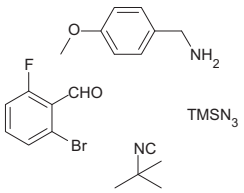
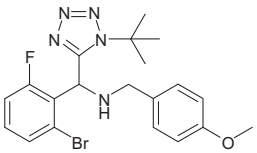
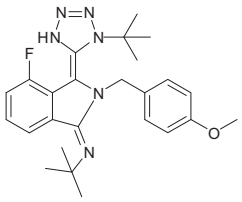
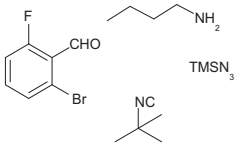
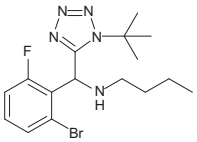
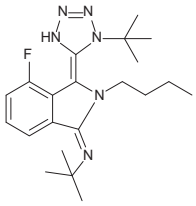
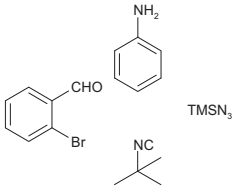
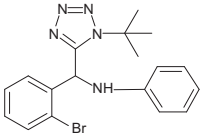
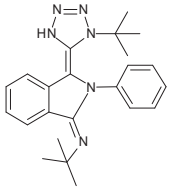
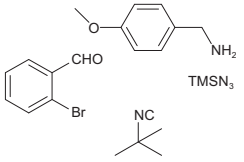
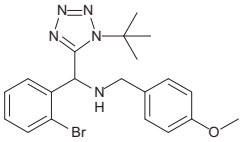
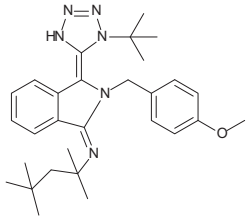
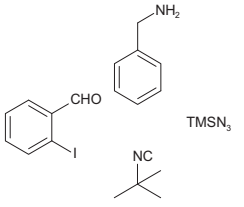
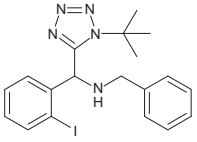
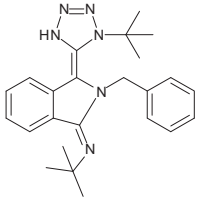
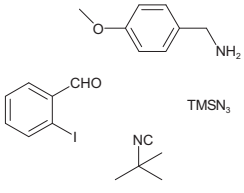
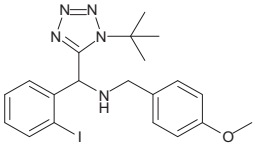
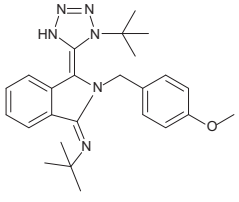
Entry	Starting material	IMCR products yield[b] (%)	Coupling products yield[b] (%)
1		 **9 95%**	 **20 70%**
2		 **10 85%**	 **21 72%**
3		 **11 88%**	 **22 70%**
4		 **12 90%**	 **23 74%**
5		 **13 80%**	 **24 67%**
6		 **14 89%**	 **25 70%**

Table 2 (*continued*)

Entry	Starting material	IMCR products yield[b] (%)	Coupling products yield[b] (%)
7		 **15 85%**	 **26 68%**
8		 **16 79%**	 **27 72%**
9		 **17 88%**	 **28 75%**
10		 **9 85%**	 **29 71%**
11		 **18 80%**	 **30 70%**
12		 **19 82%**	 **31 65%**

[a] Reaction conditions: substrate **9** (1 equiv), $Pd(OAc)_2$ catalyst (5 mol %), Cs_2CO_3 (1.5 equiv), DMF (2 mL), 90 °C, 1 h.
[b] Isolated yield after column chromatography.

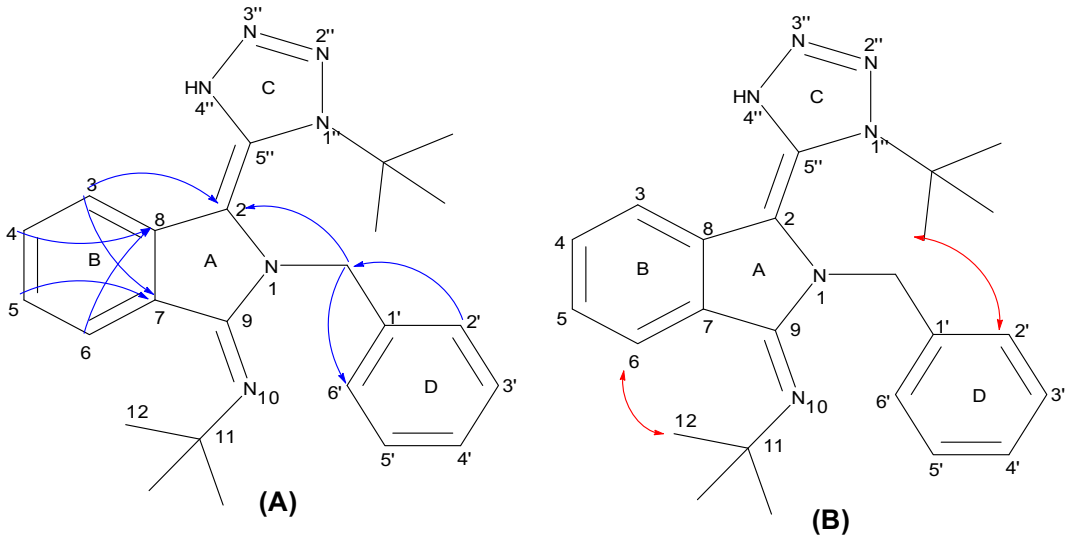


Figure 2. Important (A) HMBC and (B) NOE correlations of **21**.

different type of ligands (DPPE, Xphos, and PPh_3), and temperature of the reaction, did not improve the yield of the reaction.

With this result in hand, we next investigated the scope of the reaction to other amines precursors (**9**–**19**) and isocyanides. Reactions furnish the corresponding tetrazole–isoindolines (**20**–**31**, Scheme 2) in moderate to good yield. The amine precursors (**9**–**19**) were synthesized from the different substituted benzaldehydes, various amines and isocyanides via different Ugi-MCR in excellent yields. Interestingly, various substituted amines including different types of benzylamine, alkyl amines (*n*-butylamine and $i Pr_2NH$), and aniline were examined in the reaction, and the corresponding products were furnished in good yields. Whatever the group at the amine nitrogen in the tetrazole compounds did not affect significantly on the yields of final products. Other isocyanides such as 1,1,3,3-tetramethylbutyl isocyanide and cyclohexyl isocyanide were also tried in the meantime but only *tert*-butylisocyanide was found to effectively undergo insertion and 1,1,3,3-tetramethylbutyl isocyanide was moderately effective and yielded the desired compound (**29**) in good yield (71%). Hence, *tert*-butylisocyanide was the only isocyanide used for the reaction optimization. Additionally, the reaction can also be conducted with *N-benzyl-1-(1-tert-butyl-1H-tetrazol-5-yl)-1-(2-iodophenyl) methanamine* (**18**) and *1-(1-tert-butyl-1H-tetrazol-5-yl)-1-(2-iodophenyl)-N-(4 methoxybenzyl)methanamine* (**19**). As expected, the reaction time of Ugi-MCR synthesized amine precursor was same and the desired products (**30** and **31**) were furnished in satisfactory yields (see Table 2).

The ^1H and ^{13}C NMR signal assignments and connectivity of compound **21** were determined from a combination of ^{13}C, DEPT 135, DEPT 90, COSY, HSQC, and HMBC data and spatial correlations are established by NOESY. COSY correlations established the spin systems, which were H-3, H-4, H-5, and H-6 in ring-B and H-2′,6′, H-3′,5′, and H-4′ in ring-D. H-3 and H-5 of ring B is giving a HMBC correlation with C-7 and H-4 and H-6 are giving HMBC correlations with C-8. The characteristics carbon atom C-2 at δ 100.4 ppm showed HMBC correlations with benzylic protons and H-3 which established the connectivity between the benzyl moiety and ring B to the ring A through N-1 and C-7, C-8, respectively. The NOE correlation between 12-$(CH_3)_3$ protons and H-6 strengthened the possibility of an E configuration of the compound (Fig. 2).

The presence of N–H proton in compound **20** was verified by D_2O shake experiment. During D_2O shake experiment of compound

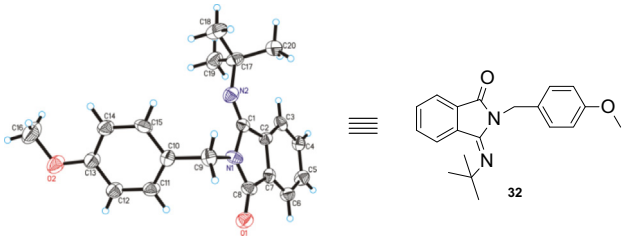
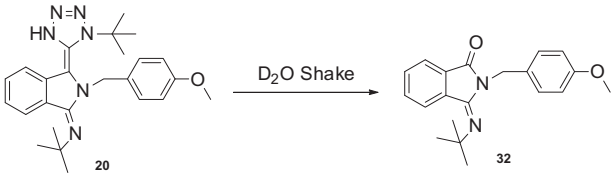


Figure 3. ORTEP diagram drawn with 30% ellipsoid probability for non-H atoms of the asymmetric unit of the crystal structure of compound **32** determined at 293 K.



Scheme 3. Transformation of compounds **20** to **32**.

20, an unexpected change in ^1H NMR spectrum was observed which indicated that compound **20** got degraded. Interestingly, the intensity of protons peak of compound **20** was diminished and a new peak pattern was observed in the ^1H NMR spectrum and each peak seemed to be double. Similar double peak pattern was observed in the ^{13}C NMR spectrum also. In the ^{13}C NMR spectrum one characteristic peak appeared at δ 167.73 ppm and peak at δ 100.45 ppm was diminished. After getting this information from NMR data, we analyzed this NMR sample and found that there were three spots on the TLC at this stage, whereas there were only one spot on the TLC before starting the D_2O shake experiment. So, it was assumed that moisture or D_2O played a significant role in the conversion of **20** into **32**. With the help of 1D and 2D NMR data (^1H, ^{13}C, DEPT135, DEPT90, COSY, HSQC, HMBC, and NOESY), the observed compound was characterized as *(E)-3-(tert-butylimino)-2-(4-methoxybenzyl)isoindolin-1-one* (**32**). It's also confirmed by single crystal X-ray analysis of representative compounds **32** (Fig. 3, CCDC No-959960). In crystal X-ray analysis, we observed

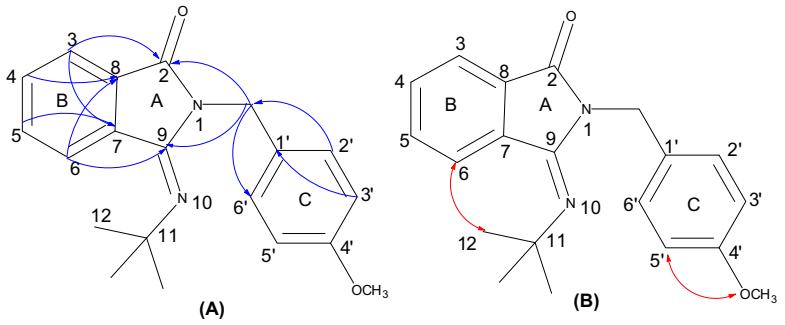
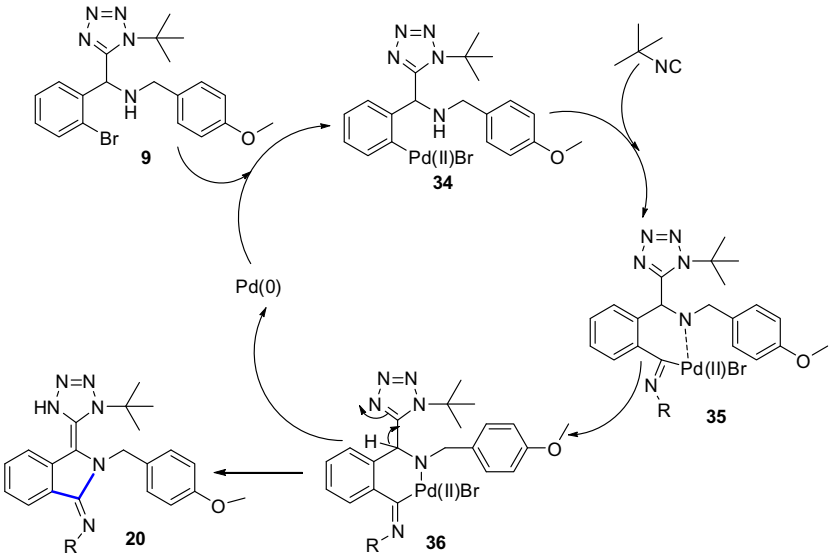


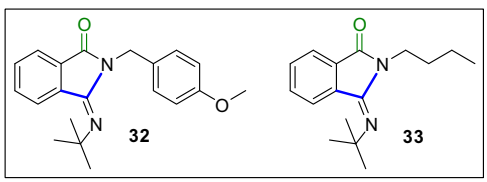
Figure 4. Important (A) HMBC and (B) NOE correlations of **32**.



Scheme 4. Proposed mechanism of the reaction.

the oxygen atom which replaced the tetrazole ring in compound **32** via hydrolysis (Scheme 3).

The ^{1}H and ^{13}C NMR signal assignments and connectivity were determined from a combination of various 1D and 2D NMR experiments and spatial correlations are established by NOESY. COSY correlations established the spin systems, which were H-3, H-4, H-5, H-6 in ring-B, and H-2′,6′ and H-3′,5′ in ring C. H-3 and H-5 of ring B is giving a HMBC correlation with C-7 and H-4 and H-6 are giving HMBC correlations with C-8. Further H-3 and H-6 are giving HMBC correlations with C-2 and C-9, respectively, and established the connectivity of ring A and B. The important HMBC correlations of benzylic protons to C-2 and C-9 clearly indicated that the substituted benzylic connected to ring A through N-1. The important NOE correlation between 12-$(CH_3)_3$ protons and H-6 showed the proximity of both protons in space and this NOE correlation showed the *E* configuration of the compound (Fig. 4).



We propose the mechanism for the synthesis of *(E)-N-(3-(1-tert-butyl-1H-tetrazol-5-yl)-2-(4-methoxybenzyl)isoindolin-1 ylidene)-2-methylpropan-2-amine* of type **20** was depicted in Scheme 4. The Palladium(0) species undergoes oxidative addition to the C–Br bond of amine precursor **9** leading to the intermediate **34** which on insertion of *tert*-butyl isocyanide leads to Pd(II) species **35**. Intermediate **35** via intramolecular cyclization provides species **20**.

Conclusions

In summary, we have demonstrated an efficient method for the synthesis of tetrazole–isoindoline via palladium-catalyzed cyclization with isocyanide insertion for the first time. The reactions are operationally simple and has several potential advantages: (1) toleration of a wide range of functional groups and the yields are moderate to good, (2) the reaction is easy to handle and the conditions are mild, (3) enriches the isoindoline family, (4) two new bonds are formed in a one-step reaction. We expect that the novel transformation can be used for further development of new isocyanide based catalytic reactions. Further studies on the scope of this novel process and the synthetic use of the nitrogen-containing heterocycles are currently underway.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.08.008.

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25. *Procedure for the synthesis of compounds* (**9**): Solution of 2-bromobenzaldehyde (1.0 equiv, 2.70 mmol), 4-methoxybenzylamine (1.0 equiv, 2.75 mmol) and *tert-butyl*isocyanide (1.0 equiv, 3.67 mmol) was stirred in anhydrous methanol (5 mL) at rt for 10 min. Thereafter, trimethylsilyl azide (1.5 equiv, 4.63 mmol) was added and the resulting mixture was further stirred for 7 h. On completion of the reaction (checked by TLC analysis), the precipitate was collected by filtration, washed with hexane, and air-dried to give target product **9** as white solid. Same protocol was used to obtain compounds **10**–**19**.
26. *General procedure for the synthesis of compounds* **20**–**31**: Ugi-MCR synthesized amine precursor (**9**–**19**, 1.0 mmol), isocyanide (1.1 mmol), $Pd(OAc)_2$ (5 mol %), Cs_2CO_3 (1.5 mmol), and DMF (2.5 mL) as a solvent were added in a 10 mL reaction glass vial containing a stirring bar under the nitrogen atmosphere, the vial was sealed tightly with a Teflon cap and the mixture was allowed to stir in an oil bath for 1 h at 90 °C. After completion of the reaction as indicated by TLC, the resulting mixture was filtered through a pad of celite, and the celite was rinsed with EtOAc. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc) affording the corresponding coupling product **20**–**31** in 65–75% yields.