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Palladium-Catalyzed Tandem Intramolecular Oxy/Amino-Palladation/Isocyanide Insertion: Synthesis of α-Benzofuranyl/Indolylacetamides

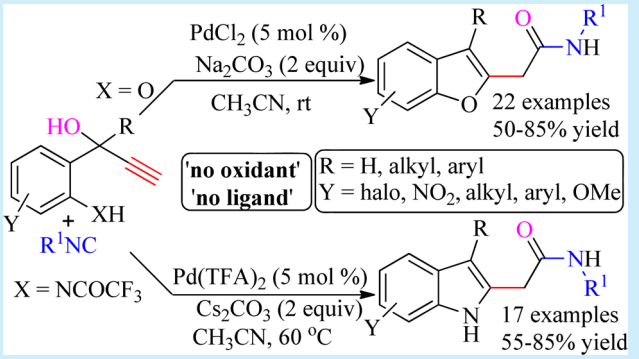
Nuligonda Thirupathi,[†] Madala Hari Babu,[†] Vikas Dwivedi,[†] Ruchir Kant,[§] and Maddi Sridhar Reddy*[,†,‡]

[†]Medicinal & Process Chemistry Division and [§]Molecular & Structural Biology Division, CSIR-Central Drug Research Institute, BS-10/1, Sector 10, Jankipuram extension, Sitapur Road, P.O. Box 173, Lucknow 226031, India

[‡]Academy of Scientific and Innovative Research, New Delhi 110001, India

Supporting Information

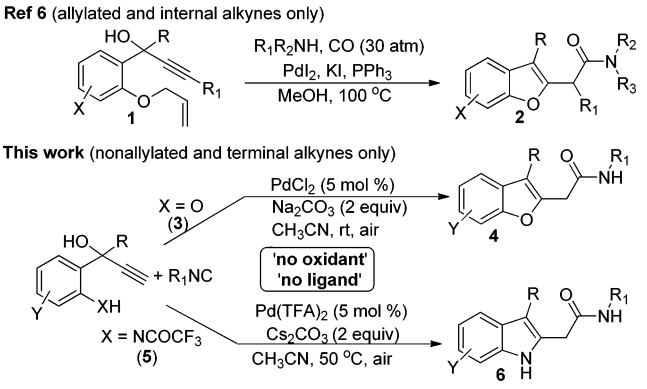
ABSTRACT: A novel palladium-catalyzed approach to 2-benzofuranyl/indolylacetamides from 1-(*o*-hydroxy/amino-phenyl)propargylic alcohols and isocyanides is described. The reaction proceeds through a cascade that includes oxy/aminopalladation, isocyanide insertion, and 1,4-hydroxyl migration. No oxidant or ligand is needed to promote the cascade, and the reactions are carried out under mild conditions to afford the products through high functional tolerance.



Isocyanide insertion has taken a new turn, for its reemergence, in recent chemistry with the assistance of palladium catalysis. Recent works by the groups of Wu,[1] Jiang,[2] Orru,[3] and others[3] for the synthesis of a variety of cyclic and acyclic motifs ensure a promising future for the profound usage of isocyanide as one carbon unit for a facile and simultaneous Pd-catalyzed stitching of two new and valuable C−C or C−heteroatom bonds. In continuation of our interest in the electrophilic cyclization of functionalized alkynes,[4] we herein report the synthesis of α-benzofuranyl/indolylacetamides via tandem intramolecular oxy/aminopalladation and isocyanide insertion. Benzofuran and indole derivatives have been considered among the highly privileged scaffolds for various medicinal chemistry aspects.[5] Synthesis of these moieties with diverse substitution patterns has always been one of the top priorities of chemists.

Earlier, Gabriele et al. reported a novel conversion of **1** to the α-benzofuranylacetamides **2** through CO insertion (Scheme 1).[6] The reaction required high pressure (30 atm) and temperature (100 °C), rendering it a specific benchtop reaction. Moreover, allylation was necessary for the initial palladium coordination, and the reaction was applicable for internal alkynes only (to produce branched substitution), whereas terminal alkynes adopted a different mode of cyclization.[7] Herein, we report a facile conversion of various nonallylated hydroxyphenyl propargyl alcohols **3** with a terminal alkyne to the corresponding α-benzofurnaylacetamides **4** at room temperature using $PdCl_2$ as the catalyst where no assistance of any ligand or additive was required (Scheme 1). Additionally, various aminophenyl propargyl alcohols **5** were converted to the α-indolylacetamides **6** under slightly modified conditions.

Scheme 1. Synthesis of α-Benzofuranyl/Indolylacetamides via Electrophilic Cyclization



Initially, we used the conditions, for the conversion of **3a** to **4a** (Table 1) via palladium-catalyzed tandem cyclization and isocyanide insertion, developed by Zhu et al.[3h] for the synthesis of indole-3-carboxamide via isocyanide insertion. Pleasingly, the expected product **4a** was obtained in 55% yield through a cascade of reactions (entry 1). Inspired by this result, some reaction parameters such as catalyst, solvent, and base effects were investigated for the purpose of improving the yield. Other

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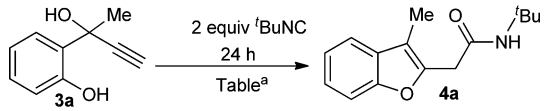
Table 1. Optimization of Reaction Conditions[a]



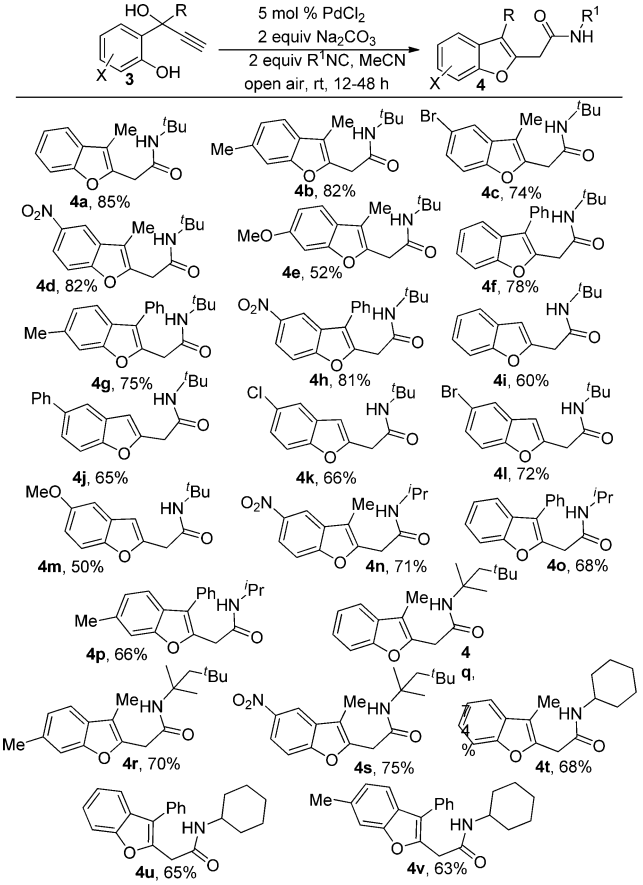
entry	catalyst	base	solvent	yield[b] (%)
1	$PdCl_2$	Na_2CO_3	DMSO	55
2	$Pd(OAc)_2$	Na_2CO_3	DMSO	30
3	$Pd(TFA)_2$	Na_2CO_3	DMSO	22
4	$PdCl_2$	Na_2CO_3	DCE	48
5	$PdCl_2$	Na_2CO_3	toluene	35
6	**$PdCl_2$**	**Na_2CO_3**	**CH_3CN**	**85**
7	$PdCl_2$	Na_2CO_3	1,4-dioxane	70
8	$PdCl_2$	K_2CO_3	CH_3CN	40
9	$PdCl_2$	CS_2CO_3	CH_3CN	20
10	$PdCl_2$	morpholine	CH_3CN	65
11	$PdCl_2$	TEA	CH_3CN	45
12	$PdCl_2$		CH_3CN	

[a]Reaction conditions: ^{t}BuNC (2.0 mmol), **3a** (1.0 mmol), base (2.0 mmol) Pd(II)-cat. (0.05 mmol), solvent (4 mL), rt, open air. [b]Isolated yield.

catalysts like $Pd(OAc)_2$ and $Pd(TFA)_2$ under the same conditions were found to be less productive (entries 2 and 3). When various solvents were screened against $PdCl_2$ catalyst (entries 4−7), CH_3CN was found to produce the best yield (85%) of the product. Change of bases (entries 8−11) only led to decrease the yield. No product was obtained in the absence of the base (entry 12). Notably, all the reactions were carried out in open-air conditions. Interestingly, the reaction proceeded equally well in anhydrous/inert conditions, suggesting that there is no role of O_2 in the regeneration of the catalyst (vide infra, see mechanism).

With the optimized conditions in hand, we evaluated the generality of the method with respect to propargyl alcohols as well as isocyanides. A variety of hydroxyphenyl propargyl alcohols **3** were synthesized following the literature precedents.[7,9] As is evident from Scheme 2, a variety of substituents like alkyl, aryl, halogen, methoxy, and nitro groups were tolerated in the reaction to afford the products in moderate to high yields. Initially, various 3°-alcohols, the substrates prepared from *o*-hydroxyacetophenones and *o*-hydroxybenzophenones, were subjected to the reaction to obtain the corresponding products with a substitution at C3. Thus, 3,6-dimethylbenzofuranylacetamide **4b** was obtained in high yield (82%), similar to product **4a**. The presence of a bromo group as in the case of substrate **3c** did not affect the outcome, producing **4c** in 74% yield. Electron-poor substrate **3d** was found to react equally well (to yield **4d** in 82%), whereas its electron-rich counterpart **3e** produced the corresponding product **4e** in a moderate yield of 52%. Similarly, 3-phenyl-substituted benzofuran adducts **4f−h** were obtained from 3°-alcohols **3f−h** in comparative yields (75−81%). Then, various electron rich, neutral and poor 2°-alcohols, prepared from salicylaldehydes, were subjected to the cascade reaction. Delightedly, they all produced the corresponding products (**4i−m**) although in relatively slightly lower yields (50−72% compared to 52−82%). Next, we aimed to evaluate the reactivity of a variety of commercially available isocyanides. Thus, isopropyl, tetramethylbutyl, and cyclohexyl isocyanides were subjected to the transformation. All of them smoothly produced the corresponding products in 63−75% yields, although the relative productivity was less compared

Scheme 2. Synthesis of α-Benzofuranylacetamides 4 via Oxypalladation and Isocyanide Insertion[a]



[a]Reaction conditions: R^1NC (2.0 mmol), **3** (1.0 mmol), base (2.0 mmol), $PdCl_2$ (0.05 mmol), MeCN (0.2 M), open air, rt.

with *tert*-butyl isocyanide. Unfortunately, phenyl isocyanide was found to be unreactive under the given conditions. This diminished reactivity and inertness of less hindered and aryl isocyanides, respectively, is in accordance with the recent observations by Ji et al.[3f] Setting a limitation, the reaction did not work for the internal alkyne, which produced a non-isocyanide-inserted product.[8]

Our curiosity next turned toward the extension of this reaction to 2-aminophenyl propargyl alcohols **5**,[10] which might give valuable indole counterparts **6**. Under the standardized conditions described above, the corresponding product (**6**) was obtained only in traces. After some optimization studies,[11] we found that 5 mol % of $Pd(TFA)_2$ in the presence of 2 equiv of Cs_2CO_3 in acetonitrile with a slightly elevated temperature (60 °C) allowed the transformation with reasonable to high yields (Scheme 3). Thus, 3-phenyl-2-indolylacetamide (**6a**) and its 5-methyl adduct (**6b**) were obtained in 72% and 70% yields, respectively. Then a variety of the substrates were synthesized from various commercially or readily available 2-aminoacetophenones and 2-aminobenzophenones[10] to evaluate the generality of the method.

Halogen groups on the core reaction part (**5c**) as well as on the pendant phenyl ring (**5d−j**) were well tolerated in the reaction to produce the corresponding products **6c−j** in yields ranging from 65% to 85%.

Methoxy-substituted substrate **5k** also smoothly transformed to the indolylacetamide **6k** in 80% yield. The 3-methyl-2-

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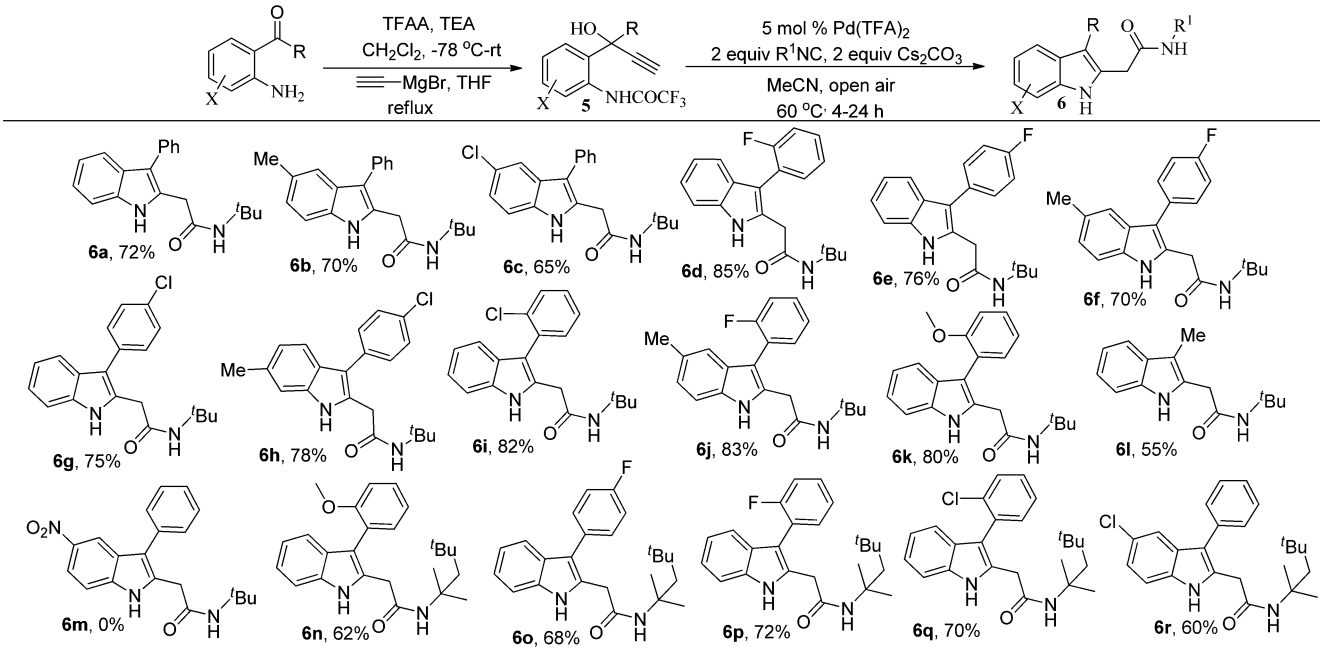
Scheme 3. Synthesis of α-Indolylacetamides 6 via Aminopalladation and Isocyanide Insertion[a]



[a]Reaction conditions: R^1NC(2.0 mmol), **5** (1.0 mmol), base (2.0 mmol), $Pd(TFA)_2$ (0.05 mmol), MeCN (0.3 M), open air, 60 °C.

indolylacetamide **6l** was obtained in moderate yield of 55%, which can be attributed to the instability of the substrate **5l** that could not be purified but was used as the crude product after the Grignard reaction. Surprisingly, electron-poor substrate **5m** was found to be unreactive in the transformation, which is in sharp contrast to its benzofuran counterpart (**4d**, **4h**, **4n**, and **4s**) synthesis. Next, tetramethylbutyl isocyanide was used as the reaction partner with various halo-substituted and methoxy-substituted substrates to obtain the corresponding products **6n**−**r** in 62−72% yields. Unfortunately, less hindered isopropyl isocyanide and phenyl isocyanide were found to be unreactive in the reaction. In addition, the internal alkyne found to be inert in the reaction even after the prolonged reaction time and at the elevated temperatures.[8]

The structures of all the products were characterized by ^1H NMR, ^{13}C NMR and HRMS. For unambiguous structure confirmation, we have taken single-crystal X-ray structures of **4b** and **6j**[12] (one from each group of products) which are depicted in Figure 1.

A plausible mechanism for the cascade of reactions in the above transformations is described in Figure 2. We speculate that the palladium catalyst shuttles between two oxidation states (2 and 0) in each cycle, which helps effective regeneration of the catalyst without the use of any oxidant. Accordingly, activation of alkyne moiety by PdX_2 may lead to oxy/amino palladation in *anti* and 5-*exo*-*dig* fashion to give intermediate **A**. Isocyanide insertion (**B**) followed by coordination palladium with spatially closer hydroxyl group would form 6-membered oxapalladacycle **C**. Reductive elimination of Pd(0) followed by its immediate insertion in to allylic ether of **D**, a well-established phenomenon, in the newly formed strained 5-membered oxacycle may give 6-membered oxapalladacycle **E** which on protodepalladation by two molecules of HX (generated in the cycle) would lead to the formation of intermediate **F**. The concomitant 1,3-H shift and tautomerization of the iminol group would furnish **4** and protected **6** (**G**). The sensitive trifluoroacetyl group in **6** would

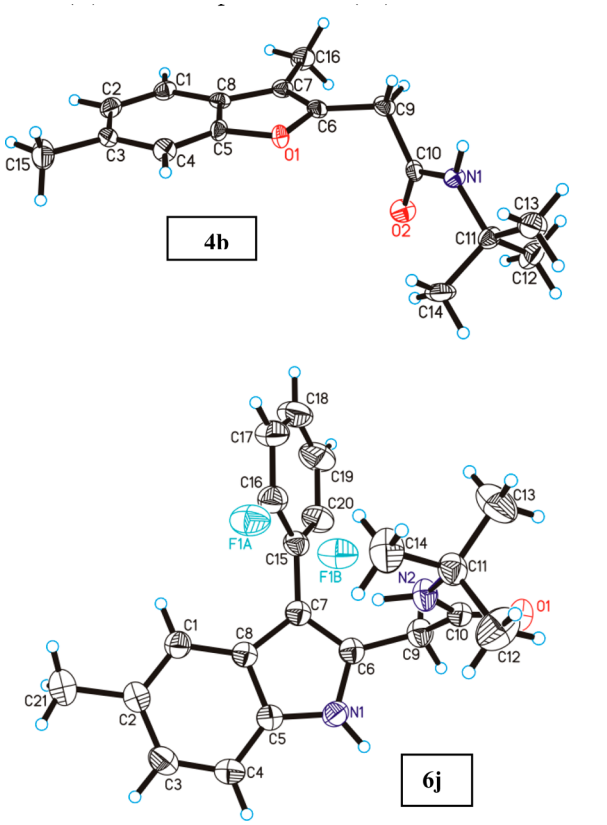


Figure 1. X-ray crystal structures of **4b** (CCDC No. 978848) and **6j** (CCDC No. 996275).[12]

subsequently undergo hydrolysis in the presence of Pd(II) with the help of moisture (air) to liberate **6**.

In conclusion, a novel and efficient palladium-catalyzed intramolecular oxy/aminopalladative isocyanide insertion approach for the synthesis of 2-benzofuranyl/indolylacetamides is

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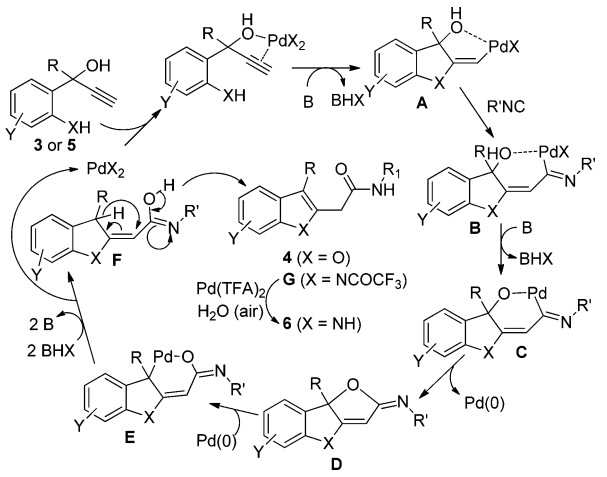

Figure 2. Proposed catalytic cycle.

demonstrated. The approach offers advantages in terms of experimental simplicity, mild reaction conditions, and broad functional group tolerance.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and copies of ^{1}H and ^{13}C spectra for compounds **4a−v**, **5**, and **6a−r**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: msreddy@cdri.res.in, sridharreddymaddi@yahoo.com.

Notes

The authors declare no competing financial interest.

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(11) For optimization studies, see the Supporting Information.

(12) The ORTEP diagram of **6j** in Figure 1 shows an average structure of two atropisomers, and hence, the F atom is shown 50% each on both ortho positions of the pendant phenyl ring.