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Palladium-Catalyzed Domino Synthesis of 2,3-Difunctionalized Indoles *via* Migratory Insertion of Isocyanides in Batch and Continuous Flow

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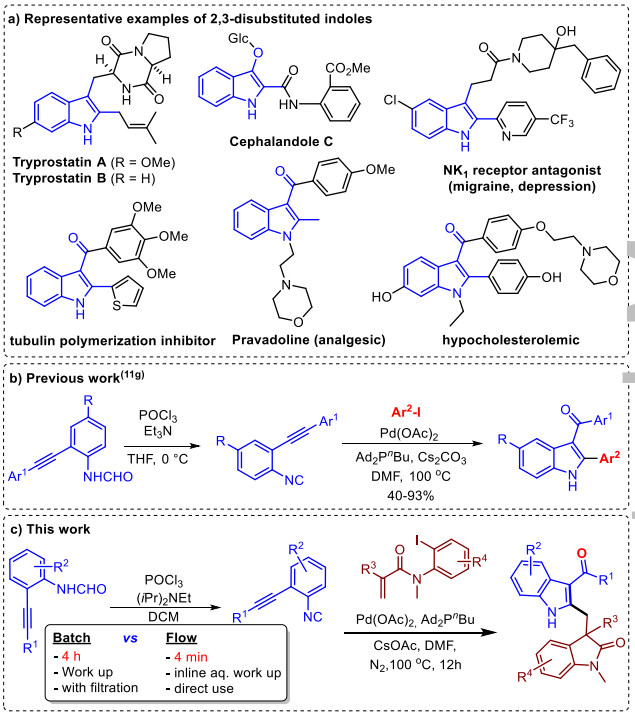
Abstract. We report, herein, a palladium-catalyzed cascade comprising carbopalladation, migratory insertion of isocyanide and triple bond activation followed by a nucleophilic attack (OR^-) to construct difunctionalized acyl indoles. The process involves multiple bond formations *via* key palladium-chemistry steps, to construct these bis-heterocycles containing two privileged scaffolds (indole and oxindole) in a single operational step, along with attempts to generate enantioselectivity at a quaternary carbon center. The methodology also demonstrates a continuous-flow process to synthesize aryl isocyanides within minutes and using them in a telescopic manner.

Keywords: Palladium-catalyzed cascade reaction; domino cyclizations; isocyanide insertion; triple bond activation; acyl indoles.

Isocyanides have been at the center stage of various multicomponent reactions such as the Passerini and Ugi reaction as irreplaceable building blocks.[1] Because of their unique reactivity they play an important role in the synthesis of various heterocycles, besides being important C-1 precursor analogues to CO.[2] In addition, their ability to coordinate transition-metal centers, especially palladium, has resulted in a variety of innovative chemical reactions.[3] Palladium-catalyzed iminoacylation generated by isocyanide insertion is an efficient pathway for the construction of C-C, C-O and C-N bonds as well as involving cascade C-H activation processes. Likewise, the Heck-Mizoroki reaction[4] has been particularly well studied for forming carbo- and heterocyclic scaffolds such as indoles, benzofurans, and oxindoles, via σ–alkyl palladium intermediates in a domino process with a variety of nucleophiles[5] as well as *via* intramolecular cascades.[6] In this work, we envisioned creating an amalgamation of these transient palladium species



Scheme 1. Background on 2,3-difunctionalized indoles.

toward the rapid generation of molecular diversity and complexity in a minimum number of steps.

2,3-Difunctionalized indoles have generated a lot of interest among synthetic chemists due to their biological value (Scheme 1a).[7] Among these, some representative examples (both of natural as well as of synthetic origin) find relevance in medicinal chemistry and hence are useful targets. For example, tryprostatins A and B, natural products isolated from *Aspergillus fumigatus* BM939, can selectively arrest the cell cycle at the mitotic phase in tsFT210 cells.[8] Similarly, Pravadoline is an analgesic drug with

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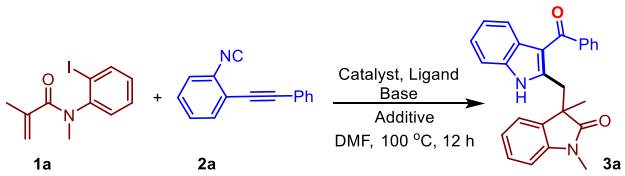
multiple bioactive derivatives.[9] Henceforth, there have been continuous efforts to synthesize these privileged scaffolds and derivatives in a more efficient manner with an intriguing diversity.[10] In recent years, cyclizations of *o*-alkynylisocyanobenzene have been well studied towards the synthesis of 5- or 6-membered *N*-containing heterocycles (Scheme 1b).[11] However, their synthetic utility has been compromised owing to their foul odor and unstable nature and hence are used without purification. Flow chemistry is an interesting alternative to develop odorless isocyanides, with easy scale-up options and telescoped synthesis towards the final product.[12]

In continuation of our work on trapping of intermediate palladium species (alkyl and vinyl) to trigger various domino reactions,[13] we, herein, report a palladium-catalyzed cascade comprising carbopalladation, migratory insertion of isocyanide and triple bond activation, followed by a nucleophilic attack (OR^-) to construct difunctionalized acyl indoles in a single operational step under enabling conditions (Scheme 1c).

Table 1. Optimization of the reaction conditions.[a]



entry	catalyst	ligand	base	additive	yield[b] (%)
1[c]	$Pd(OAc)_2$	Ad_2P^nBu	Cs_2CO_3	-	4
2	$Pd(OAc)_2$	Ad_2P^nBu	Cs_2CO_3	-	50
3	$Pd(OAc)_2$	Ad_2P^nBu	Cs_2CO_3	PivOH	trace
4	$Pd(OAc)_2$	Ad_2P^nBu	Cs_2CO_3	H_2O	4
5	$Pd(OAc)_2$	Ad_2P^nBu	Cs_2CO_3	AcOH	52
6	$Pd(OAc)_2$	Ad_2P^nBu	Na_2CO_3	AcOH	35
7	$Pd(OAc)_2$	Ad_2P^nBu	Et_3N	AcOH	51
8	$Pd(OAc)_2$	Ad_2P^nBu	NaOAc	AcOH	30
9	$Pd(OAc)_2$	MePhos	Cs_2CO_3	AcOH	50
10	$Pd(OAc)_2$	SPhos	Cs_2CO_3	AcOH	15
11	$Pd(OAc)_2$	XPhos	Cs_2CO_3	AcOH	9
12	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	AcOH	40
13	$Pd(OAc)_2$	BINAP	Cs_2CO_3	AcOH	13
14	$Pd(OAc)_2$	Xantphos	Cs_2CO_3	AcOH	10
15	$Pd(PPh_3)_4$	Ad_2P^nBu	Cs_2CO_3	AcOH	43
16	$Pd_2(dba)_3$	Ad_2P^nBu	Cs_2CO_3	AcOH	20
17	$Pd(OAc)_2$	Ad_2P^nBu	CsOAc	-	66
18	$Pd(OAc)_2$	Ad_2P^nBu	NaOAc	-	trace
19[d]	$Pd(OAc)_2$	Ad_2P^nBu	CsOAc	-	71
20[e]	**$Pd(OAc)_2$**	**Ad_2P^nBu**	**CsOAc**	-	**77**
21[e, f]	$Pd(OAc)_2$	Ad_2P^nBu	CsOAc	-	25

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), 5 mol% of catalyst, 10 mol% of ligand, 3.0 equiv of base, 2.0 equiv of additive in DMF (1 mL) with stirring under nitrogen for 12 h. Oil bath temperature 100 °C; isocyanide **2a** in DMF (2 mL) was added dropwise to the solution by using a syringe pump within 1 h.
[b] Isolated yield.
[c] No slow addition of the isocyanide.
[d] 4 equiv of base.
[e] 5 equiv of base.
[f] open air conditions. Ad = 1-adamantyl.

We initial explored the feasibility of the proposed strategy in the reaction by applying *N*-(2-Iodophenyl)-*N*-methylacrylamide (**1a**) and 2-(2-phenylethynyl)phenyl isocyanide (**2a**) as test substrates (Table 1) in the presence of $Pd(OAc)_2$ (5 mol%), Ad_2P^nBu (10 mol%), and Cs_2CO_3 (3.0 equiv) in DMF (3 mL) at 100 °C for 12 h (Table 1, entry 1). This reaction condition resulted in poor conversion providing the desired product **3a** in 4% yield (for X-ray crystal structure analysis, see Table 2 and the Supporting Information). Based on previous reports, we found that using the syringe pump to slowly drip the 2-(2-Phenylethynyl)phenyl isocyanide (**2a**) to the reaction solution significantly improved the product **3a** in 50% yield (entry 2). Considering the oxygen source (nucleophile) for the last step of this reaction, different additives were screened (entries 3-5), and preliminary results showed that the addition of acetic acid (2 equiv) slightly increased the yield to 52%. Thereafter, the screening of the bases revealed that Cs_2CO_3 performed better than other bases such as Na_2CO_3, Et_3N, and NaOAc (entries 6-8). Further, we tested the effect of phosphine ligands (MePhos, Sphos, Xphos, PPh_3, BINAP, Xantphos) (entries 9-14) and palladium catalysts ($Pd(PPh_3)_4$, $Pd_2(dba)_3$) (entries 15-16), but without any positive effects. Considering the acid-sensitive nature of the isocyanide in the reaction, we tried CsOAc (3 equiv) to replace the combination of Cs_2CO_3 and AcOH (entry 17), which effectively increased the yield of **3a** to 66%. Replacing CsOAc with NaOAc (3 equiv) alone as the base, trace amount of product was formed (entry 18). We concluded that in this reaction CsOAc is not only acting as a base but also as source of nucleophile under these reaction conditions as higher yields were obtained by increasing the amount of CsOAc (entries 19-20). We finally established the optimized conditions as **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), Ad_2P^nBu (10 mol%), and CsOAc (5 equiv) in DMF at 100 °C for 12 h (entry 20).

Encouraged by these results, we investigated the substrate scope of this reaction under the optimal conditions. Initially, substituted 2-(2-phenylethynyl)phenyl isocyanides **2** were examined and most of the functional groups were found to be well tolerated (Table 2). The effect of the R^1 substituent was first investigated. It was found that a methyl group at the *para* and *ortho* position reacted efficiently to give the desired products **3b** and **3d** in good yield (71%, 70%), while methyl substitution at the *meta* position decreased the yield to 43% (**3c**). Thereafter, few electron-donating groups in *para* position (methoxy, ethyl, pentyl and phenyl) were investigated which afforded the corresponding products **3e-3h** in a range of 85% to 60%. The weakly electron-withdrawing *Cl*-substitution was tolerated at the *para* (**3i**, 35%), *meta* (**3j**, 54%) and *ortho* position (**3k**, 47%) with moderate yields. Strong electron-withdrawing R^1 substituents (CF_3 and CO_2Me) were also investigated and gave the desired products **3l−3m** in 60% and 20% yields, respectively. This indicates

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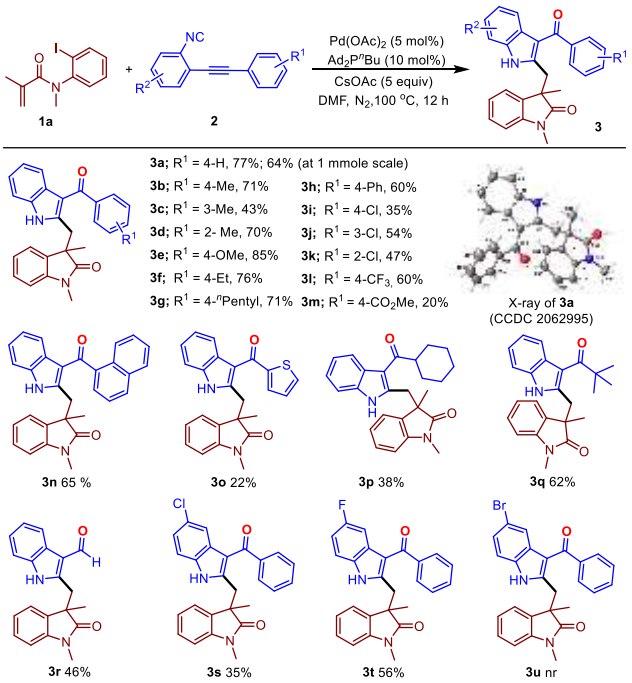
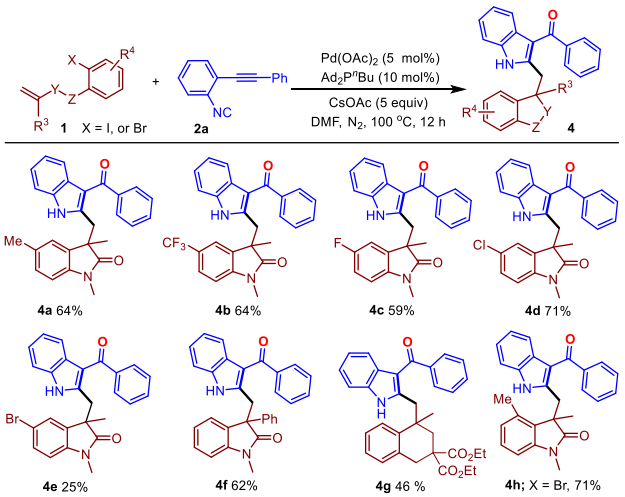
that the electronic nature of R^1 substitution of the aryl isocyanides has a strong influence on the reaction yield.

Table 2: Substrate scope for various isocyanides.[a]



[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), Ad_2P^nBu (10 mol%), CsOAc (5 equiv) in DMF (1 mL) at 100 °C under N_2 for 12 h. A solution of isocyanide **2** in DMF (2 mL) was added by using a syringe pump within 1 h.

Table 3: Substrate scope of acrylamide.[a]

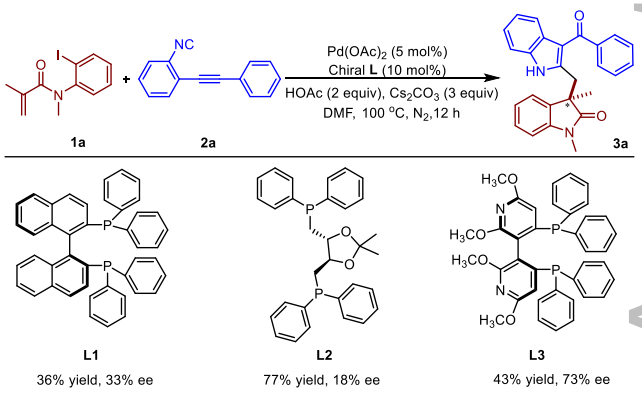


[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), Ad_2P^nBu (10 mol%), CsOAc (5 equiv) in DMF (1 mL) at 100 °C, in N_2 for 12 h. A solution of isocyanide **2a** in DMF (2 mL) was added by using a syringe pump within 1 h.

Furthermore, the replacement of the phenyl group with a naphthyl, thiophenyl and even an aliphatic substituent (*tert*-butyl, and cyclohexyl) affords the desired products **3n-3q** in low to moderate yields. The employment of a trimethylsilyl group (TMS) resulted in desilyation **3r** in 46% yield. Introduction of substituents of R^2 (4-F and 4-Cl) was well tolerated, giving the corresponding products **3s** and **3t** in 35% and 56%, respectively. However, the substrate bearing a 4-Br substituent did not afford the desired product **3u**, as some unidentified side products were formed.

We next turned our attention to examine *N*-(2-Iodophenyl)-*N*-methylacrylamide derivatives (**1**) under standard conditions (Table 3). Introducing an electron-donating methyl group or an electron-withdrawing group (CF_3) to the 2-iodoaniline core resulted in 64% yield. Notably, employing other electron-withdrawing groups, such as fluoro, chloro and bromo the indoles **4c**, **4d** and **4e** could be isolated in 59%, 71% and 25% yield, respectively, offering the possibility for further functionalization. Then, the substitution on the acrylamide core was evaluated. The desired domino reaction of 2-phenylacrylamide proceeded smoothly giving the corresponding acyl indole **4f** in 62% yield. Furthermore, the analogous reaction with carbocyclic aryl halides provided the corresponding carbohalogenated product **4g** in 46% yield. We also examined the effect of the haloaniline subunit on the reaction outcome, whereby *N*-(2-bromo-3-methylphenyl)-*N*-methylmethacrylamide afforded the target product **4h** in 71% yield.

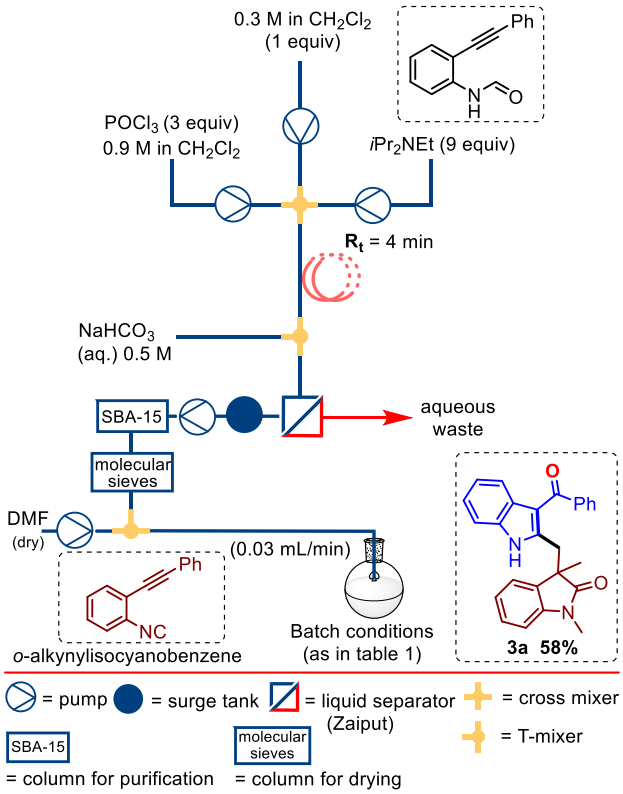
During the optimization studies, the intramolecular asymmetric carbopalladation[14] of *N*-aryl acrylamides was also attempted under conditions as described in Table 1, entry 5, which resulted in a moderate yield and enantioselectivity of **3a** (Scheme 3). Employing ligand **L1,** product **3a** was obtained in 36% yield with a low enantioselectivity. Reaction with ligand **L2** improved the yield to 77% but with low ee. However, with **L3** 43% yield with an ee of 73% was obtained. Using the optimized conditions (Table 1, entry 20), the yield and ee were not improved further (for details, see the SI).



Scheme 2: Enantioselective version of the reaction.

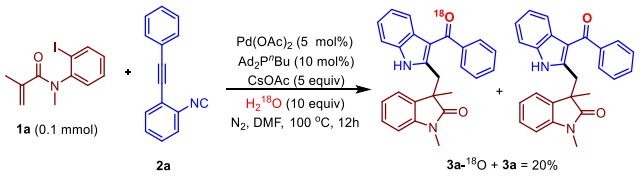
Aryl isocyanides are commonly synthesized from the corresponding anilines *via* formylation, followed by dehydration. The precursors (*N*-formylaniline and anilines) are bench stable, easy to handle, with high commercially availability in contrast to aryl isocyanides which have a pungent odor and are

unstable. Thus, encouraged by the work of Kim[12a] and Jamison,[15] we developed an odorless isocyanide chemistry in which the aryl isocyanides can be synthesized *in situ* from the formanilides (for details and optimization experiments see the SI). This telescopic procedure led to the formation of the desired compound **3a** in 58% yield in two steps (Scheme 3). To further validate our optimized flow conditions for the synthesis of difunctionalized acyl indoles **3**, we performed the preparation and in-line aqueous extraction of isocyanides to construct **3a** (82%), **3e** (88%), **3i** (35%), **3m** (29%), and **4e** (43%) under batch conditions. Pleasingly, this resulted in a slight increase in yields, compared to normal batch synthesis of isocyanides (for details see SI, Scheme S1).



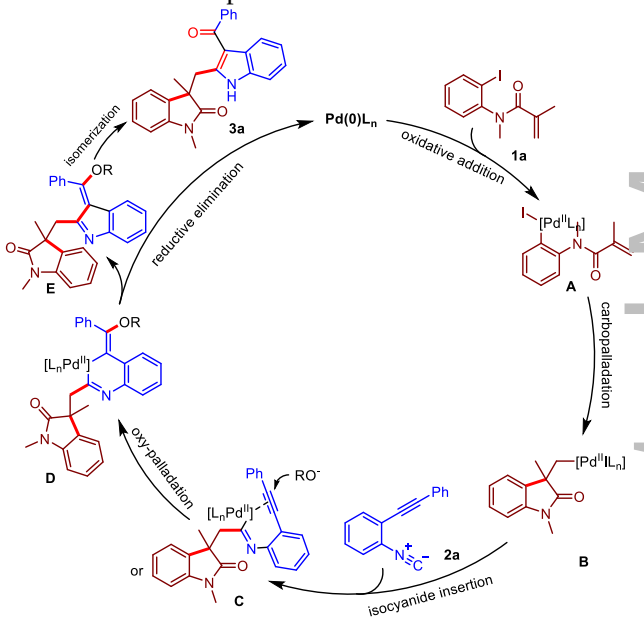
Scheme 3: Continuous-flow synthesis of isocyanide and its direct use for the synthesis of difunctionalized acyl indoles.

To identify the oxygen source in product **3a** isotope labelling studies were performed. The ^{18}O incorporated product **3a**-^{18}O was formed in the presence of $H_2{}^{18}O$ as an additive under standard reaction conditions, delivering a mixture of **3a** and **3a**-^{18}O in 20% isolated yield. Molecule **3a**-^{18}O was detected by LC−MS (EI) analysis (see Supporting Information). The experiment suggested that H_2O is one of the oxygen sources, and other species such as acetate and carbonate could also supply an oxygen-atom (Scheme 4).



Scheme 4: Control experiment.

Based on the previous reports and control experiments, a plausible catalytic cycle of this reaction is outlined in scheme 5. The reaction begins with the oxidative addition of Pd(0) to the C-I bond of *N*-(2-Iodophenyl)-*N*-methylacrylamide **1a,** forming the arylpalladium species **A**, which undergoes intramolecular carbopalladation to generate intermediate **B**. Subsequent migratory insertion of the 2-(2-phenylethynyl)phenyl isocyanide **2a** into the intermediate **B** furnishes the imidoyl palladium species **C**. Intramolecular addition to the triple bond and further attack of an oxy-nucleophile generate intermediate **D**. Thereafter, reductive elimination of intermediate **D** resulted in the formation of intermediate **E**, followed by an isomerization step to deliver the desired product **3a**.



Scheme 5: Proposed mechanism.

In summary, we have developed an efficient methodology comprising a cascade carbopalladation, an isocyanide insertion and an alkyne functionalization to construct difunctionalized aryl indoles. Over 29 examples of structurally and functionally diverse products were successfully synthesized. Moreover, initial exploration of the asymmetric reaction provided moderate enantioselectivity. Furthermore, we have also extended the methodology to a continuous-flow platform comprising synthesis, in-line aqueous work-up and consumption of isocyanide in a single step providing odorless isocyanide chemistry.

Experimental Section

General procedure for the synthesis of isocyanides 2: To a solution of formanilide (0.200 mmol, 1equiv.) and $(iPr)_2NEt$ (1.6 mmol, 8 eqiuv.) in DCM (0.1M), was slowly added $POCl_3$ (0.3 mmol, 1.5 equiv.) at 0 °C and stirred at the same temperature for 4 h. After the total conversion of the starting material, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with DCM. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to dry. The obtained solution was filtered through alumina column chromatography with EtOAc. The obtained solution was concentrated under reduced pressure without further purification and used for the next step.

General procedure for the synthesis of product 3: A 4 mL screw cap vial equipped with a stirring bar containing **1** (0.100 mmol, 1.0 equiv.), $Pd(OAc)_2$ (5 mol%), Ad_2P^nBu (10 mol%) and CsOAc (0.5 mmol, 5.0 equiv), was evacuated and purged with nitrogen three times. *N*,*N*-Dimethylformamide (1 mL) was sequentially added to the system at rt. The reaction mixture was heated with stirring at 100 °C. Then the freshly prepared 1-isocyano-2-(phenylethynyl)benzene **2** in DMF (2 mL) was added dropwise to the solution using a syringe pump in 1 h. After the addition of isocyanide, the reaction mixture was stirred at 100 °C for another 11 h. After cooling to rt, the reaction mixture was diluted with EtOAc and washed with H_2O. The aqueous phase was extracted with EtOAc, and the combined organic phases were dried over Na_2SO_4. After filtration and evaporation under reduced pressure, the residue was purified *via* silica gel column chromatography directly by using *n*-heptane/ethyl acetate (3:1, *v/v*) as eluent to give the corresponding products. The structures were confirmed *via* ^1H NMR, ^{13}C NMR and HRMS-ESI.

X-Ray Diffraction Study of 3a

CCDC-2062995 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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