EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Direct C-H Arylation of Heteroarenes with Aryl Chlorides using Abnormal NHC Coordinated Palladium Catalyst

Authors: Swadhin Kumar Mandal, Jasimuddin Ahmed, Samaresh Sau, Sreejyothi P, Pradip Hota, Pavan Vardhanapu, and Gonela Vijaykumar

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201601218

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601218

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201601218

WILEY-VCH

FULL PAPER

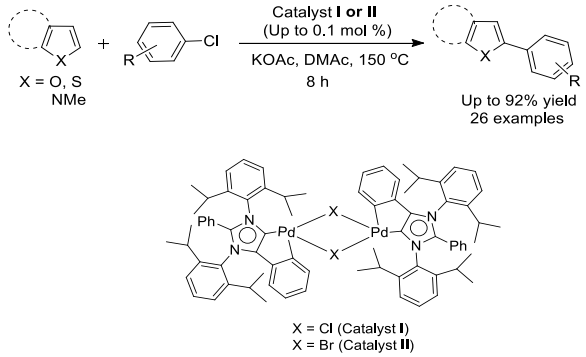
Direct C-H Arylation of Heteroarenes with Aryl Chlorides using Abnormal NHC Coordinated Palladium Catalyst

Jasimuddin Ahmed‡, Samaresh Chandra Sau‡, Sreejyothi P, Pradip Kumar Hota, Pavan K. Vardhanapu, Gonela Vijaykumar and Swadhin K. Mandal*

Abstract: Herein we report a versatile catalytic system for direct C-H arylation of heteroarenes using activated aryl chloride substrates. The catalyst successfully works for a variety of heteroarenes and aryl chloride coupling partners under very low catalyst loading condition. We have successfully performed direct C-H arylation of 1-methylpyrrole, 1-methylindole, furan, thiophene, furfural and N-benzyl-1, 2, 3-triazole with aryl chloride partners in good yield without using any additive. Furthermore, we used this catalytic process to develop one-pot synthetic protocol for a muscle relaxant drug, dantrolene in gram scale. Additionally, the present catalytic system is successful in performing consecutive arylation in one-pot.

Introduction

Arylation of heteroarenes has received considerable attention in the last decade as a very important process owing to its application in medicinal chemistry and material science.[1] Arylated heteroarenes have been widely used as important building blocks in designing organic field-effect transistors (OFETs),[2] organic light emitting diodes (OLEDs)[3] and organic solar cells (OSC).[4] Traditional ways to prepare arylated heteroarenes utilize palladium-catalyzed Suzuki, Stille or Negishi cross-coupling reactions, which require appropriate functionalization of one or both coupling partners incurring additional cost to the process. In order to avoid these inconveniences, in 1990, Ohta and co-workers developed a palladium catalyzed direct C-H arylation method of heteroarenes.[5] Gryko,[6] Doucet,[7] Fagnou,[8] Itami[9] and other research groups[10] later came up with further improvement to this particular reaction process. The literature reports on this direct C-H arylation are based mainly on palladium[10] rhodium[11] and iridium[12] metal catalysts. Most of the reports used costly halide coupling partners like aryl iodide or aryl bromide and till date very few reports are available on aryl chloride as coupling partner.[13] It is to be noted that from industrial perspective, aryl chlorides are much cheaper than their bromide or iodide analogs. In 2004, Sadighi and co-workers showed an effective way for palladium catalyzed arylation of pyrrolylzinc chloride, generated in situ from pyrrolyl sodium and zinc chloride with up to 93% yield affording arylated pyrrole as product using aryl chloride as well as aryl bromide coupling partner.[14] Daugulis and co-workers established a catalytic protocol for arylation of heteroarenes with aryl chloride coupling partners using 5 mol % of $Pd(OAc)_2$, 10 mol % of $BuAd_2P$ at 125 °C, resulting up to 84% yield of coupled product.[15] These catalysts reported for activation of aryl chloride partners utilized supporting phosphine ligands and an additive other than the base. Importantly, most of these catalysts described above were found to be specifically active to a particular class of heteroarene's arylation like C-2 arylation or C-3 arylation or decarboxylative arylation thus lacking general versatility towards a variety of heteroarene's arylation by a single catalytic system. As a result, there is a continuous urge to develop an effective direct C-H arylation method, which can be successfully applied for a variety of heteroarenes using aryl chloride coupling partners under low catalyst loading condition.



Scheme 1. The present work describing use of a variety of heteroarenes for coupling reaction.

Moreover, most of the previous reports are exclusively on the arylation at C-2 or C-5 positions as these positions of a five membered heteroarenes are generally more reactive. Till now, there are very few reports on the palladium catalyzed direct arylation of heteroarenes at C-3 or C-4 position.[16] Herein, we additionally aimed to perform the arylation at C-3 or C-4 position when C-2 and C-5 positions are blocked. In this study, we explore the potential of a bis{1,3-bis(2,6-

[a] Department of Chemical Sciences, Indian Institute of Science Education and Research, Kolkata, Mohanpur-741246, India.
Phone: 91-9903676563, Fax: (+)91-33-48092033,
E-mail: swadhin.mandal@iiserkol.ac.in,

‡ These authors contributed equally to this work.

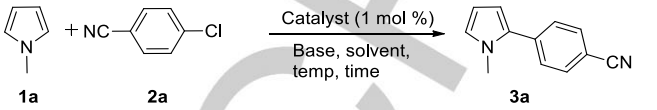
Supporting information for this article is given via a link at the end of the document.

diisopropylphenyl)-2,4-diphenylimidazolium}halobridged Pd(II) dimer (X = Cl, Catalyst **I**; X = Br, Catalyst **II**) as a catalyst in the arylation of heteroarenes. Till now there is no report of well-designed abnormal N-heterocyclic carbene based Pd catalyst in this area of direct arylation of heteroarenes. In 2004, Lebel and co-workers reported that abnormal N-heterocyclic carbenes are catalytically more efficient building block than their normal NHC counterpart.[17] Later on, Guy Bertrand and co-workers reported the isolation of the first abnormal N-heterocyclic carbene.[18] Our group recently established the application of this isolated abnormal carbene in designing catalysts for a number of homogeneous organic transformations.[19],[20] Herein, we report direct C-H arylation of a variety of heteroarenes using activated aryl chlorides as coupling partners under low catalyst loading (1 mol %) condition (Scheme 1). Also we used the present catalyst for carrying out multicatalytic process adopting consecutive arylation process. The present protocol has considerable functional group tolerance, which has been successfully applied in one pot synthesis of a muscle relaxant drug molecule, dantrolene in gram scale.

Results and Discussion

Palladium (II) dimers (catalysts **I** and **II**) bearing an aNHC backbone were synthesized by following the synthetic route reported previously.[20] 1-Methylpyrrole was used as a benchmark substrate for our optimization study. We studied the coupling reaction between 1-methylpyrrole (**1a**) and 4-chlorobenzonitrile (**2a**) to optimize the best condition for C-2 arylation reaction (Table 1). This reaction was first optimized with respect to different solvents, in presence of 1 mol % catalyst loading and 2 equiv. of KOAc for 12 h. The product formation was monitored by ^{1}H NMR spectroscopy. In case of N, N-dimethylacetamide (DMAc) as solvent, the isolated yield was 87% of the product **3a** (Table 1, entry 1). When NMP was the solvent, it led to 72% conversion (Table 1, entry 4). In DMF, DMSO or THF reaction proceeds with very low conversion of 10%, 20% and 25% respectively (Table 1, entries 2, 5 and 6). In case of 1,4-dioxane as solvent, no reaction was observed (Table 1, entry 3) at 100 °C. To study the effect of base on this reaction, different bases were tested. In presence of K_2CO_3, K_3PO_4, NaOMe, KO^{t}Bu and Cs_2CO_3 the reaction did not proceed (Table 1, entries 7-10 and 13). Both NaO^{t}Bu and Na_2CO_3 led nearly 40% conversion (Table 1, entries 11 and 12). The use of LiO^{t}Bu as a base led to 70% conversion (Table 1, entry 14). When the reaction was performed at 100 °C and 130 °C, it resulted in 10% and 82% conversion, respectively (Table 1, entries 16-17). During optimization study, 90% conversion was observed after 6 h (Table 1, entry 20). We did not find any further improvement in the yield when this reaction was allowed for 8 h or 10 h (Table 1, entries 18 and 19). Under the standardized reaction condition, catalyst **I** was found to be less efficient, affording only 70% conversion of product (Table 1, entry 15) whereas catalyst **II** led to 87% yield (Table 1, entry 1). Next we performed the low catalyst loading experiments. It was noticed that even at 0.1 mol % catalyst loading, the catalyst results in quite good conversion (nearly 80%, Table 1, entries 21 and 22).

Table 1. Influence of different reaction conditions on the direct arylation of 1-methylpyrrole (**1a**) with 4-chlorobenzonitrile (**2a**).[a]



1a **2a** **3a**

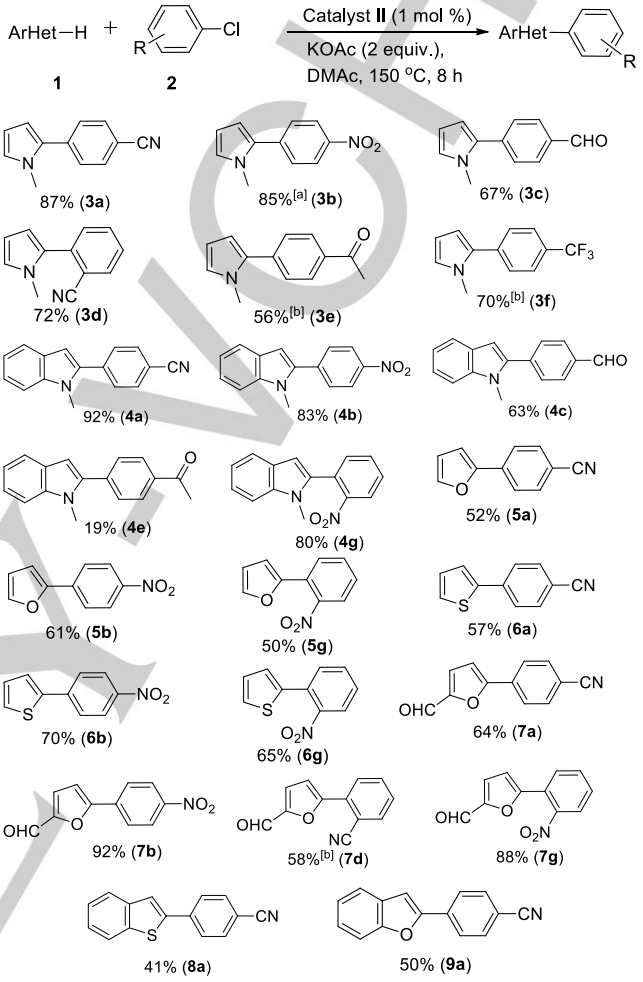
Entry	Solvent	Base	Catalyst	T (h)	Temp (°C)	Conversion (%)
1	**DMAc**	**KOAc**	**II**	**12**	**150**	**87%[b]**
2	DMF	KOAc	**II**	12	150	10
3	1,4-Dioxane	KOAc	**II**	12	100	N.R
4	NMP	KOAc	**II**	12	150	72
5	DMSO	KOAc	**II**	12	150	20
6	THF	KOAc	**II**	12	70	25
7	DMAc	K_2CO_3	**II**	12	150	N.R
8	DMAc	K_3PO_4	**II**	12	150	N.R
9	DMAc	NaOMe	**II**	12	150	N.R
10	DMAc	KO^{t}Bu	**II**	12	150	N.R
11	DMAc	NaO^{t}Bu	**II**	12	150	40
12	DMAc	Na_2CO_3	**II**	12	150	40
13	DMAc	Cs_2CO_3	**II**	12	150	N.R
14	DMAc	LiO^{t}Bu	**II**	12	150	70
15	DMAc	KOAc	**I**	12	150	70
16	DMAc	KOAc	**II**	12	100	10
17	DMAc	KOAc	**II**	12	130	82
18	DMAc	KOAc	**II**	10	150	92
19	DMAc	KOAc	**II**	8	150	92
20	DMAc	KOAc	**II**	6	150	90
21[c]	DMAc	KOAc	**II**	12	150	85
22[d]	DMAc	KOAc	**II**	12	150	72
23	DMAC	KOAc	-	8	150	N.R
24[e]	DMAC	KOAc	**II**	8	150	N.R

[a] Reaction conditions: N-methylpyrrole (2.75 mmol), 4-chlorobenzonitrile (0.69 mmol), KOAc (1.37 mmol), catalyst **II** (0.0069 mmol) and solvent DMAc (3 mL). [b] Isolated yield. [c] 0.5 mol% catalyst loading. [d] 0.1 mol% catalyst loading. [e] 1-*tert*-Butyl-4-chlorobenzene (0.69 mmol) coupling partner. N.R. stands for "No Reaction". "T" Stands for time.

We tested the blank reaction without using the catalyst while keeping other conditions similar. The reaction without catalyst did not produce any arylated product indicating the importance of the catalyst during this reaction (Table 1, entry 23). This protocol was not successful for arylation of 1-methylpyrrole (**1a**) when tested with different unactivated arylchloride coupling partners 1-*tert*-

butyl-4-chlorobenzene (Table 1, entry 24), chlorobenzene, 4-chloroanisole and 4-chloro-N, N-dimethylaniline (see SI, Table S1). After looking at these results, we can conclude that for the C-H arylation of 1-methylpyrrole (**1a**) with 4-chlorobenzonitrile (**2a**) in DMAc solvent in presence of 2 equiv. of KOAc using 1 mol % catalyst **II** can give coupling product (**3a**) with the most effective yield within 8 h at 150 °C (Table 1, entry 1).

To elaborate the scope of this arylation process, at first 1-methylpyrrole (**1a**) was successfully coupled with six different aryl chlorides in presence of 1 mol % catalyst **II** and 2 equiv. of KOAc as base in DMAc at 150 °C. Selective C-2 arylated products (**3a-f**) were obtained with 56 - 87% isolated yield (Scheme 2). To check the effect of sterically hindered as well as heterocyclic arylchloride coupling partner on the catalytic reaction, we performed the arylation of 1-methylpyrrole (**1a**) with sterically hindered (1-chloronaphthalene and 2,6-dimethylchlorobenzene) and heterocyclic arylchloride coupling partners (2-chloropyridine and 2-chlorothiophene), which did not yield the desired product (see SI, Table S1). Using aryl iodide coupling partners, Gryko and co-workers have earlier performed the same reaction at 100 °C with 5 mol % $PdCl_2(PPh_3)_2$ catalyst in presence of AgOAc as additive, affording 50-80% yield of arylated product.[6] This recent catalytic protocol was effectively applied on arylation of different heteroarenes, like 1-methylindole, furan, thiophene and 2-furfuraldehyde with moderate to good yield of arylated products (Scheme 2).1-Methylindole was coupled with different activated aryl chloride coupling partners to afford 19% to 92% yield of C-2 arylated products (**4a-c**, **4e** and **4g**) (Scheme 2). Doucet and co-workers have earlier performed similar coupling reaction at 150 °C with 0.5 mol % of $Pd(OAc)_2$ as catalyst in presence of 0.5 mol % of sylphos and 1 equivalent of Bu_4NBr using 4-chlorobezonitrile as coupling partner which afforded **4a** in 42% yield along with minor C-3 arylated product.[16] Arylation of both furan and thiophene is very important for synthesis of materials with interesting electronic properties[2],[3] and biomedical applications.[21] With our standard catalytic condition, direct C-H arylation at C-2 position of furan and thiophene using aryl chlorides, which resulted in good yield of the corresponding products **5a**, **5b**, **5g** ,**6a**, **6b** and **6g** respectively (Scheme 2) with 50-70% isolated yields. The lower yield may be attributed to low boiling point of furan (30-34 °C) and thiophene (84 °C). Denmark and co-workers have earlier performed the same reaction with 5 mol % $Pd_2(dba)_2.CHCl_3$ catalyst in presence of NaH as additive, which afforded 67% yield of arylated product **6a** using silanolates and aryl iodide coupling partners.[22] This protocol was extented on the arylation of 2-furfuraldehyde, on which very few reports are there due to the presence of a chemically reactive formyl group. McClure and co-workers have earlier performed arylation reaction of furfural with 5 mol % $PdCl_2$ catalyst in presence of Bu_4NBr (1equiv.) and Cy_3P (10 mol %) as additive, affording 88% yield of arylated product **7b** using aryl iodide coupling partners.[23] In the present study, we used only 1 mol % catalyst **II** at 150 °C to obtain 92% yield of product **7b** by coupling between furfural and aryl chloride coupling partner, 1-chloro-4-nitrobenzene. However, 4-chlorobenzonitrile (**2a**) afforded lower yield (64%) of coupled product **7a**. When 2-chlorobenzonitrile and 1-chloro-2-nitrobenzene were subjected to this coupling reaction, it yielded 58% and 88% of corresponding products **7d** and **7g**, respectively (Scheme 2).

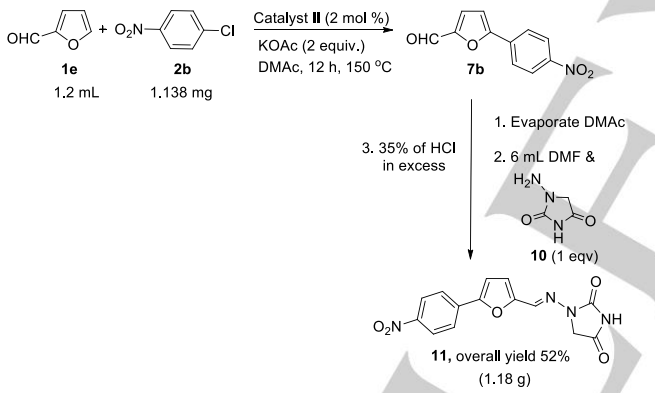


Scheme 2. Direct arylation of heteroarenes with aryl chlorides. Reaction conditions: 1-methylpyrrole/1-methylindole (2.75 mmol), furan/2-furfuraldehyde/benzofuran/benzothiophene (1.37 mmol), thiophene (3.44 mmol), aryl chlorides (**2**, 0.69 mmol), KOAc (1.37 mmol), catalyst **II** (0.0069 mmol) and solvent DMAc (3 mL), 8 h, 150 °C. Isolated yields. [a] At 130 °C. [b] NMR spectroscopic conversion.

This versatile catalytic protocol was carried out with comparatively low catalst loading (1 mol %) with out any additives other than base at 150 °C. From the yields, it may be noted that ortho substitution in the aryl chloride coupling partner has to some extent negative impact on yield (**3d**, **4g**, **5g**, **6g**, **7g** and **7d**) which may be attributed to the steric reason. Another important thing to notice here that formyl group is well tolerated in this reaction condition (Scheme 2). Here we obtained only mono-substituted product at C-2 position of heteroarene partners (1-methylpyrrole, 1-methylindole, furan, 2-furfuraldehyde and thiophene), no bi-substitution or C-3 arylation was observed. Our protocol has been successfully

extended to arylation of benzothiophene and benzofuran with 4-chlorobenzonitrile (**2a**), affording 41% and 50% yield of **8a** and **9a**, respectively.

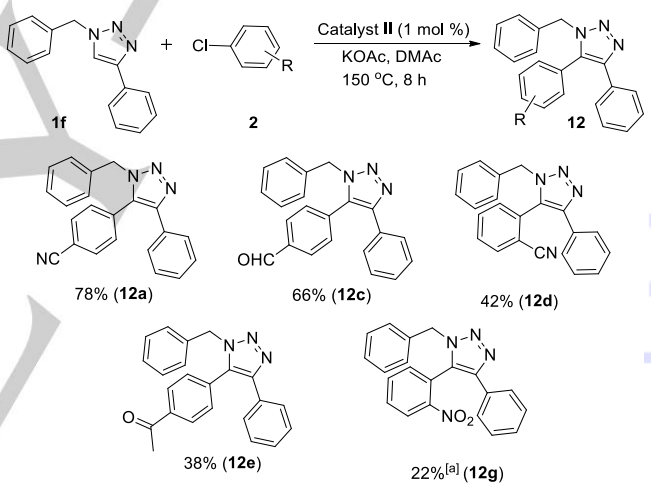
As seen in scheme 2, the arylation of 2-furfuraldehyde can be performed with different aryl chlorides (**2**) using this catalytic condition delivering good yield of the coupled products (**7a**, **7b**, **7d** and **7g**). Thus, to further demonstrate the synthetic potential of our catalytic condition, we undertook one pot synthesis of a commercially available muscle relaxant drug, dantrolene (**11**) in the same reaction pot (Scheme 3). Snyder et al.[24] earlier reported the Meerwein arylation reaction[25] as a key step in the synthesis of dantrolene and related compounds by the coupling of arenediazonium salts, prepared from anilines, with furfuralin the presence of Cu(II) catalyst, followed by condensation of 5-aryl-2-furaldehydes with 1-aminohydantoin hydrochloride (**10**).This method was suffering from reaction step economy due to the preparation of arenediazonium salt. Suzuki and co-workers also employed a general synthetic procedure of dantrolene analogs by palladium-catalyzed cross-coupling reactions of aryl derivatives and a stannylated or boronated furfural.[26] This method also suffers from the fact that Suzuki coupling condition mandates the use of appropriately functionalized coupling partners, which is not cost-effective.



Scheme 3. One pot synthesis of the muscle relaxant drug dantrolene in gram scale

In this regard, we successfully applied our coupling protocol in the one-pot synthesis of dantrolene.[27] We performed the arylation of furfural (**1e**) with 1-chloro-4-nitrobenzene (**2b**) using this catalytic condition, followed by condensation of the resulting coupled product **7b** with1-aminohydantoin hydrochloride (**10**) within the same reaction pot. It resulted dantrolene in 52% overall yield. This synthetic protocol was successfully extended for gram scale synthesis of dantrolene (Scheme 3).

Furthermore, arylation of 1, 2, 3-triazoles is considered as a very important reaction due to its relevance in medicinal chemistry. The conventional way to synthesize different kind of arylated 1, 2, 3-triazoles are copper[28], [19] or ruthenium[29] catalyzed 1, 3-dipolar [3+2] cycloadditions of azides and alkynes.[30] These catalytic [3+2] cycloadditions are highly regio-selective with terminal alkynes, but in the case of internal alkynes regio-selectivity is less, leading to mixture of arylated triazoles. To overcome this problem, direct C-H arylation can be considered as a very good approach. Most of the known direct arylations of 1, 2, 3-triazoles have been accomplished under rhodium or palladium catalysis, applying aryl iodides, bromides, or triflates as electrophiles.[31] We probed the scope of our catalyst in the direct arylation of N-benzyle-1, 2, 3-triazoles (**1f**) with various electron deficient aryl chlorides 2 (Scheme 4) under the optimized catalytic condition. N-benzyl-1, 2, 3-triazole was efficiently converted into corresponding product **12a** with 78% yield (Scheme 4) after coupling with 4-chlorobenzonitrile (**2a**). Other aryl chlorides as coupling partners, in this direct Arylation of N-benzyl-1, 2, 3-triazole delivered moderate to good yields (Scheme 4) of the corresponding products **12c**, **12d** and **12e**.

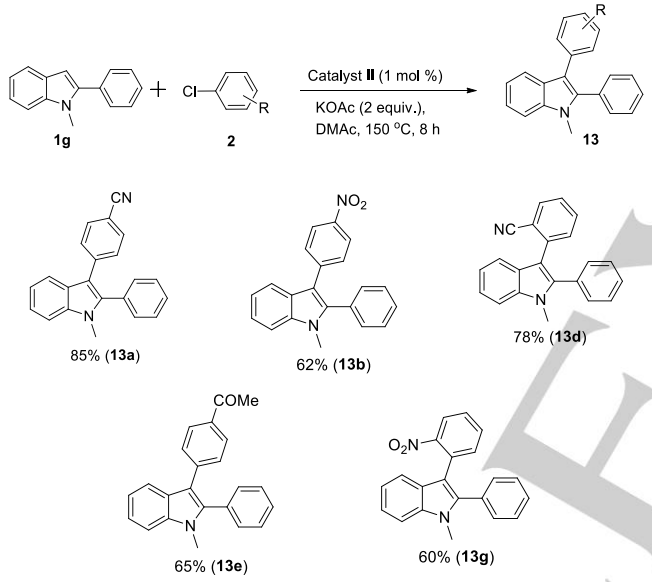


Scheme 4. Direct arylation of N-benzyl-1, 2, 3-triazole with aryl chlorides. Reaction conditions: N-Benzyl-1, 2, 3-triazole (1.035 mmol), aryl chlorides (0.69 mmol), KOAc (1.37 mmol), catalyst **II** (0.0069 mmol) and solvent DMAc (3 mL), 8 h, 150 °C. [a] NMR spectroscopic conversion.

When 1-chloro-2-nitrobenzene was used as the coupling partner, it resulted in very low conversion (**12g**, Scheme 4). In 2008, Ackermann and co-workers had reported this direct arylation of 1, 2, 3-triazoles with aryl chloride coupling partners using $Pd(OAc)_2$ (4 mol %), and PCy_3 (8 mol %) at 120 °C, which resulted in 71% yield of product **12a** and the present study reports 78% yield of **12a** using 1 mol % catalyst **II**.[32]

Also we tested this coupling reaction when the arylation process was forced to take place at C-3 after blocking the C-2 position chemically. Here we report the C-H arylation of 1-methyl-2-phenylindole (**1g**) at C-3 position using our optimized catalytic condition (Table 1, entry 1). 1-Methyl-2-phenylindole (**1g**) was successfully coupled with activated

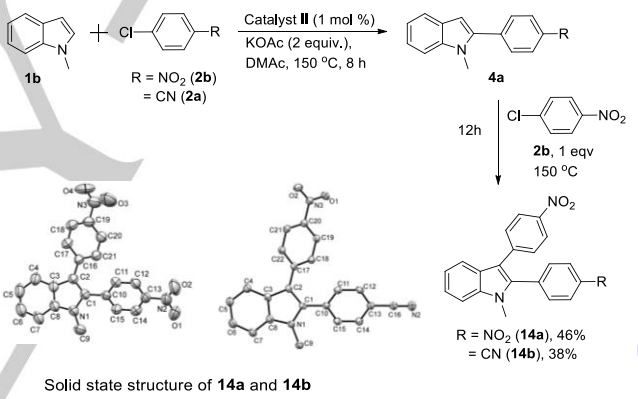
aryl chloride partners (**2**) in the presence of palladium catalyst (**II**) to yield corresponding products (Scheme 5). In this catalytic condition, 4-chlorobenzonitrile (**2a**) as chloride coupling partner led to the highest yield (85%) of the coupled product **13a** (Scheme 5). When other three aryl chloride partners were coupled at C-3 position of 1-methyl-2-phenylindole (**1g**), they afforded corresponding products **13b**, **13d** and **13g** respectively with satisfactory yields (62-78%, Scheme 5). C-3 arylation of **1g** using 4-chloroacetophenone (**2e**) was performed with 2 mol % catalyst loading to obtain 65% yield of product **13e** (Scheme 5). In 2012, Doucet and co-workers reported the C-3 arylation of 1-ethyl-2-phenylindole using different aryl chlorides in presence of 0.5 mol % of $Pd(OAc)_2$ and 0.5 mol % ferrocenyldiphosphane (sylphos) ligand at 150 °C with 31-88% yield of corresponding products.[16] The result indicates that our catalytic condition is equally efficient in arylation at C-3 as well as C-2 position.



Scheme 5. Direct arylation of C-2 blocked indole with aryl chlorides. Reaction conditions: 1-Methyl-2-phenylindole (0.69 mmol), aryl chlorides (0.69 mmol), KOAc (1.37 mmol), catalyst **II** (0.0069 mmol) and solvent DMAc (3 mL), 8 h, 150 °C.

As the present catalyst can perform arylation at C-2 position as well as at C-3 position (when C-2 position is blocked) with almost equal efficiency, it may be interesting to see whether it can perform the consecutive arylation process or not. One of the major problems in such consecutive catalytic reactions is the catalyst's stability in multiple catalytic cycles for long time. For this we first checked the in situ longevity of our catalyst. We performed consecutively five successive catalytic runs by using 1 mol % of catalyst **II**. In this experiments, after every 8 h interval, we added fresh batch of substrates (1-methylpyrrole, 4-chlorobenzonitrile) and base without adding any additional catalyst into the reaction vessel. After each 8 h interval, we checked the substrate consumption by recording ^{1}H NMR spectrum of the reaction mixture after initial workup. The ^{1}H NMR spectrum indicates that this catalyst can perform heteroarenes arylation efficiently upto fifth catalytic cycle (for details, see supporting information).

This catalyst longevity experiment encouraged us to perform consecutive arylation at C-2 followed by C-3 position in the same reaction pot by adding 2 equivalent of aryl chloride coupling partners (same or different) consecutively after 8 h interval.Consecutive arylation has been attempted first with this catalytic system using 1-methylindole (**1b**) and coupling partner 1-chloro-4-nitrobenzene (**2b**) for the coupling in both C-2 and C-3 positions, leads to formation of **14a** with 46% yield (Scheme 6). This protocol to synthesize bis-arylated product in one reaction pot was further utilized for the consecutive arylation at C-2 and C-3 positions with two different coupling partners, 4-chlorobenzonitrile (**2a**) as the first coupling partners for arylation at C-2 position. The resulting product was then subjected within the same reaction pot for second arylation at C-3 position with 1-chloro-4-nitrobenzene (**2b**) to yield the final bis-arylated product (**14b**) in 38% overall yield (Scheme 6).



Scheme 6. Consecutive bi-arylation of 1-methylindole with different coupling partner. Reaction conditions: 1-Methylindole (0.69 mmol), **2b**/**2a** (0.69 mmol), KOAc (1.37 mmol), catalyst **II** (0.0069 mmol) and solvent DMAc (3 mL), 1-chloro-4-nitrobenzene (0.69 mmol) at 150 °C. Compound **14a** and **14b** were isolated.

Conclusions

From the above results, it can be observed that our catalytic condition is able to conduct the arylation of diverse range of heteroarene compounds such as 1-methylpyrrole, 1-methylindole, furan, thiophene, furfural, benzothiohene, benzofuran and N-benzyl-1, 2, 3-triazole resulting only mono-substituted product. Thus the catalyst is quite versatile in terms of its activity towards a number of different types of heteroarenes. Moreover, the catalyst can work under low catalyst loading condition (up to 0.5 mol %). All these reactions have been performed without any additive other than base and using activated aryl chloride coupling partners which are cheaper compared to commonly used aryl iodide and aryl bromide coupling partners. Furthermore, it was

observed that the present catalytic condition can sustain the formyl group, which is generally considered as a challenge. Considering this as advantage of our catalyst, we have further explored successfully the gram scale one pot synthesis of a clinically active molecule, dantrolene in a cost effective route applying this catalytic protocol. It was established that the catalyst can perform C-3 arylation when the C-2 position of the heteroarene is blocked with almost equal efficiency as that of C-2 arylation. We found the catalyst can stay alive for consecutive catalytic cycles and it does not loose any efficiency up to three consecutive catalytic cycles. This prompted us to try the catalyst for multi-arylation study in the same reaction pot.

Experimental Section

Experimental Materials and Instrumentation

Catalyst synthesis was performed under dry and oxygen free atmosphere (Argon) using standard Schlenk line techniques, oven-dried glass wares (130 °C) and evacuated while hot prior to use. All solvents were distilled from Na/benzophenone prior to use. All chemicals were purchased and used as received. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on 400 and 500 MHz spectrometers in $CDCl_3$/DMSO-d_6 with residual undeuterated solvent ($CDCl_3$, 7.26/77.0; DMSO-d_6, 2.50/39.5) as an internal standard. Chemical shifts (δ) are given in ppm, and *J* values are given in Hz. All chemical shifts were reported in ppm using tetramethylsilane as a reference. Chemical shifts (δ) downfield from the reference standard were assigned positive values. The melting points were measured in a sealed glass tube on a melting point apparatus and were uncorrected. Open-column chromatography and thin-layer chromatography (TLC) were performed on silica gel (Merck silica gel 100−200 mesh). Evaporation of solvents was performed at reduced pressure using a rotary evaporator. Catalysts **I** and **II** were synthesized using the experimental procedure reported in literature.[20]

General procedure for catalytic C-H arylation at C-2 position of heteroarenes

10 mg (1 mol %) catalyst **II**, 1-methylpyrrole (2.75 mmol) / 1-methylindole, benzothiophene, benzofuran (1.37 mmol) / furan (3.44 mmol) / thiophene (3.44 mmol) / furfural (1.37 mmol), KOAc (1.37 mmol), aryl chloride (0.69 mmol) and 3 mL of DMAc as solvent were taken in a 5 mL pressure tube. Then the catalytic reactions were performed at 150 °C in a capped tube using metal clip for appropriate time as mentioned in Table 1. After completion, the reaction mixture was diluted with dichloromethane and then transferred into a separating funnel. The combined organic layer was completely evaporated under reduced pressure and the remaining residue was then purified through a short column chromatography (silica gel 100-200 mesh) using appropriate ratio of hexane and ethyl acetate to provide pure products.

Gram scale synthetic procedure of dantrolene (11) in one pot

210 mg (2 mol %) catalyst **II**, 1.2 mL of furfural (14.4 mmol), 1.27 g of KOAc (14.4 mmol), 1.138 g of 1-chloro-4-nitrobenzene (7.22 mmol) and 6 mL of DMAc as solvent were taken in a 25 mL pressure tube. Then the catalytic reactions were performed at 150 °C in a capped tube using metal clip for 8 h. After that DMAc and excess furfural were evaporated under high vacuum at 100 °C. Subsequently, to the reaction pot, 6 mL of DMF, 1.09 g of 1-aminohydantoin hydrochloride (6.5 mmol) and 7 mL of 35% HCl were added at 0 °C temperature. This resulting reaction mixture was then allowed to stir for 8 h at room temperature. After condensation reaction, the reaction mixture was filtered and residue was washed with 30 mL of water. The residue was dissolved in ethyl acetate and filtered, when a reddish-yellow colored filtrate was obtained, which was dried under reduced pressure. The product was re-dissolved in DCM and small amount of hexane was added to precipitate pure dantrolene (1.18 g, Overall yield: 52%).

General procedure for catalytic C-H arylation N-benzyl-1, 2, 3-triazole

10 mg (1 mol %) catalyst **II**, N-benzyl-1, 2, 3-triazole (0.69 mmol), KOAc (1.37 mmol), aryl chloride (0.69 mmol) and 3 mL of DMAc as solvent were taken in a 5 mL pressure tube. Then the catalytic reactions were performed at 150 °C in a capped tube using metal clip for 8 h. After completion, the reaction mixture was diluted with dichloromethane and transferred into a separating funnel. The combined organic layer was completely evaporated under reduced pressure and the remaining residue was then purified through a short column chromatography (neutral aluminum oxide) using the appropriate ratio of hexane and ethyl acetate to provide pure products.

Procedure for catalyst longevity experiment

10 mg (1 mol%) catalyst **II**, 1-methylpyrrole (2.75 mmol), KOAc (1.37 mmol), 4-chlorobenzonitrile (0.69 mmol) and 3 mL of DMAc as solvent were taken in a 5 mL pressure tube. Then the catalytic reactions were performed at 150 °C in a capped tube using metal clip for 8 h. The reaction mixture was monitored by ^{1}H NMR spectroscopy by taking aliquots of the reaction mixture at certain interval and the reaction was stopped when the substrate consumption was complete. The fresh substrates, 1-methylpyrrole (2.75 mmol), KOAc (1.37 mmol), and 4-chlorobenzonitrile (0.69 mmol) were added and the similar process was repeated for a total of five consecutive catalytic runs without addition of any further catalyst to the reaction mixture.

Catalytic reaction for consecutive bi-arylation of 1-methylindole

10 mg (1 mol %) catalyst **II**, 1-methylindole (0.69 mmol), KOAc (1.37 mmol) 1-chloro-4-nitrobenzene /4-chlorobenzonitrile (Scheme 6) (0.69 mmol) and 3 mL of DMAc as solvent were taken in a 5 mL pressure tube. Then the catalytic reactions were performed at 150 °C in a capped tube using metal clip for 8 h. After completion of this reaction, the reaction mixture was cooled and 1-chloro-4-nitrobenzene (0.69 mmol) was added to the same pot, and the resulting reaction mixture was allowed to continue for another 10 h at 150 °C. After completion, the reaction mixture was diluted with dichloromethane and transferred into a separating funnel. The combined organic layer was completely evaporated under reduced pressure and the remaining residue was then purified through a short column chromatography (silica gel 100-200 mesh) using appropriate ratio of hexane and ethyl acetate to provide pure products.

X-Ray Crystallographic Details for Compounds 14a and 14b

Suitable single crystal of **14a** and **14b** were selected and an intensity data were collected on a SuperNova, Dual, Cu at zero, Eos diffractometer. Using Olex2,[33] the structure was solved with the Superflip[34] structure solution program using Charge Flipping and refined with the ShelXL[35] refinement package using Least Squares minimization. CCDC 1440714 (**14a**) and CCDC 1440715 (**14b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

We thank CSIR, India (Grant No. (01(2779)/14/EMR-II) for financial support. J.A, S.P and P.K.H thank to IISER-Kolkata for research fellowship. S.C.S, P.K.V and V.K.G are thankful to UGC, New Delhi, for research fellowships.

Keywords: Abnormal Carbene • Palladium (II) • C-H Activation • Aryl Chlorides • Dantrolene

Reference

[1] a) A. R. Murphy, M. Fréchet, *J. Chem. Rev*. **2007**, *107*, 1066-1096; b) J. E. Anthony, *Chem. Rev.* **2006**, *106*, 5028-5048; c) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev*. **2002**, *102*, 1359-1470.

[2] a) S. Allard, M. Forster, B. Souharce, H. Thiem, U. Scherf, *Angew. Chem. Int. Ed*. **2008**, *47*, 4070−4098; *Angew. Chem.* **2008**, *120*, 4138–4167; b) J. A. Letizia, J. Rivnay, A. Facchetti, M.A. Ratner, T. Marks, *J. Adv. Funct. Mater*. **2010**, *20*, 50−58.

[3] a) G. Gigli, M. Anni, M. Theander, R. Cingolani, G. Barbarella, L. Favaretto, O. Inganas, *Synth. Met*. **2001**, *119*, 581−582; b) J. P. J. Markham, E. B. Namdas, T. D. Anthopoulos, I. D. W. Samuel, G. J. Richards, P. L. Burn, *Appl. Phys. Lett.* **2004**, *85*, 1463−1465.

[4] a) N. Koumura, Z. S. Wang, S. Mori, M. Miyashita, E. Suzuki, K. Hara, *J. Am. Chem. Soc*. **2006**, *128,* 14256−14257; b) A. Mishra, M. K. R. Fischer, P. Bäuerle, *Angew. Chem. Int. Ed*. **2009**, *48*, 2474−2499; *Angew. Chem.* **2009**, *121*, 2510–2536.

[5] A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani, Y. Aoyagi, *Heterocycles* **1990**, *31*, 1951−1958.

[6] a) O. Vakuliuk, D. Gryko, B. Koszarna, D. T. Gryko, *J. Org. Chem*. **2009**, *74*, 9517-9520; b) O. Vakuliuk, D. T. Gryko, *Eur. J. Org. Chem*. **2011**, 2854-2859.

[7] a) A. Battace, M. Lemhadri, T. Zair, H. Doucet, M. Santelli, *Adv. Synth. Catal*. **2007**, *349*, 2507−2516; b) F. Derridj, A. L. Gottumukkala, S. Djebbar, H. Doucet, *Eur. J. Inorg. Chem*. **2008**, 2550−2559; c) J. Roger, F. Požgan, H. Doucet, *Green Chem*. **2009**, *11*, 425−432; d) J. Roger, F. Požgan, H. Doucet, *Adv. Synth. Catal*. **2010**, *352*, 696−710; e) J. Roger, H. Doucet, *Eur. J. Org. Chem*. **2010**, 4412−4425; f) F. Derridj, J. Roger, S. Djebbar, H. Doucet, *Org. Lett*. **2010**, *12*, 4320−4323; g) L. Chen, J. Roger, C. Bruneau, P. H. Dixneuf, H. Doucet, *Chem. Commun.***2011**, *47*, 1872−1874; h) C. B. Bheeter, J. K. Bera, H. Doucet, *J. Org. Chem*. **2011**, *76*, 6407−6413; i) L. Chen, J. Roger, C. Bruneau, P. H. Dixneuf, H. Doucet, *Adv. Synth. Catal*. **2011**, *353*, 2749−2760; j) S. Bensaid, H. Doucet, *ChemSusChem* **2012**, *5*, 1559−1567; k) S. Chikhi, S. Djebbar, J-F. Soulè, H. Doucet, *Chem. Asian J.* **2016**, *11*,2443–2452; l) A. Hfaiedh, K. Yuan, H. B. Ammar, B. B. Hassine, J-F. Soulè, H. Doucet, *ChemSusChem* **2015**, *8*,1794–1804.

[8] a) B. Liégault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, *J. Org. Chem.* **2009**, *74*, 1826−1834; b) B. Liégault, I. Petrov, S. I. Gorelsky, K. Fagnou, *J. Org. Chem*. **2010**, *75*, 1047−1060; c) O. René, K. Fagnou, *Org. Lett*. **2010**, *12*, 2116−2119; d) D. J. Schipper, K. Fagnou, *Chem. Mater*. **2011**, *23*, 1594−1600; e) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Org. Chem*. **2012**, *77*, 658−668; f) M. Lafrance, D. Shore, K. Fagnou, *Org. Lett.*, **2006**, *8*, 5097-5100.

[9] a) S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, *J. Am. Chem. Soc*. **2009**, *131*, 14622−14623; b) K. Ueda, S. Yanagisawa, J. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2010**, *49*, 8946− 8949; *Angew. Chem.* **2010**, *122*, 9130-9133; c) H. Kamiya, S. Yanagisawa, S. Hiroto, K. Itami, H. Shinokubo, *Org. Lett*. **2011**, *13*, 6394−6397.

[10] a) D. Roy, S. Mom, M. Beaupérin, H. Doucet, J. C. Hierso, *Angew. Chem. Int. Ed*. **2010**, *49*, 6650−6654; *Angew. Chem.* **2010**, *122*, 6800-6804; b) H. K. Potukuchi, T. Bach, *J. Org. Chem*. **2013**, *78*, 12263−12267; c) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172-1175.

[11] a) H. M. Davies, R. T. Townsend, *J. Org. Chem*. **2001**, *66*, 6595-6603; b) S. Oi, S. I. Watanabe, S. Fukita, Y. Inoue, *Tetrahedron Lett*. **2003**, *44*, 8665-8668.

[12] B. Join, T. Yamamoto, K. Itami, *Angew. Chem. Int. Ed*. **2009**, *48*, 3644−3647; *Angew. Chem.* **2009**, *121*, 3698-3701;

[13] a) X. Chen, L. Zhou, Y. Li, T. Xie, S. Zhou, *J. Org. Chem.* **2014**, *79*, 230−239; b) E. T. Nadres, A. Lazareva, O. Daugulis, *J. Org. Chem*. **2011**, *76*, 471–483.

[14] R. D. Rieth, N. P. Mankad, E. Calimano, J. P. Sadighi, *Org. Lett*. **2004**, *6*, 3981–3983.

[15] H. A. Chiong, O. Daugulis, *Org. Lett*. **2007**, *9*, 1449-1451.

[16] D. Roy, S. Mom, S. Royer, D. Lucas, J. C. Hierso, H. Doucet, *ACS Catal*. **2012**, *2*, 1033-1041.

[17] S. P. Nolan, A. B. Charette, M. K. Janes, H. L. N. Lebel, *J. Am. Chem. Soc*. **2004**, *126*, 5046-5047.

[18] A. Perez, E. Rosenthal, A. J. B. Donnadieu, P. Parameswaran, G. Frenking, G. Bertrand, *Science* **2009**, *326*, 556-559.

[19] a) T. K. Sen, S. C. Sau, A. Mukherjee, A. Modak, S. K. Mandal, D. Koley, *Chem. Commun*. **2011**, *47*, 11972–11974; b) S. C. Sau, S. Raha Roy, S. K. Mandal, *Chem. Asian J*. **2014**, *9*, 2806 – 2813; c) S. Raha Roy, S. C. Sau, S. K. Mandal, *J. Org. Chem.* **2014**, *79*, 9150-9160; d) T. K. Sen, S. C. Sau, A. Mukherjee, P. K. Hota, S. K. Mandal. B. Maity, D. Koley,*Dalton Trans*. **2013**, *42*, 14253-14260; e) P. K. Hota, G. Vijaykumar, A. Pariyar, S. C. Sau, T. K. Sen, S. K. Mandal, *Adv. Synth. Catal.* **2015**, *357,* 3162-3170; f) S. C. Sau, S. R. Roy. T. K. Sen, D. Mullangi, S. K. Mandal, *Adv. Synth. Catal*. **2013**, *355*, 2982 – 2991. g) M. Bhunia, P. K. Hota, G. Vijaykumar, D. Adhikari, S. K. Mandal, *Organometallics* **2016**, *35,* 2930−2937.

[20] S. C. Sau, S. Santra, T. K. Sen, S. K. Mandal, D. Koley, *Chem. Commun*. **2012**, *48*, 555-557.

[21] a) J. O. Trent, G. R. Clark, A. Kumar, W. D. Wilson, D. W. Boykin, J. E. Hall, R. Tidwell, B. L. Blagburn, S. Neidle, *J. Med. Chem*. **1996**, *39*, 4554-4562; b) H. N. C. Wong, *Pure Appl. Chem*. **1996**, *68*, 335-344.

[22] J. D. Baird, S. E. Denmark, *Chem.-Eur. J*. **2006**, *12*, 4954-4963.

[23] S. M. McClure, B. Glover, E. McSorley, A. Millar, M. H. Osterhout, F. Roschangar, *Org. Lett*. **2001**, *11*, 1677-1680.

[24] a) H. R. Snyder, C. S. Davis, R. K. Bickerton, R. P. Halliday, *J. Med. Chem*. **1967**, *10*, 807-810.

[25] a) C. S. Rondestvedt, *Org. React.* **1960**, *11*, 189-260; b) C. S. Rondestvedt, *Org. React.* **1976**, *24*, 225-259.

[26] T. Hosoya, H. Aoyama, H. Ikemoto, Y. Kihara, T. Hiramatsu, M. Endoc, M. Suzukia, *Bioorg. Med. Chem*. **2003**, *11*, 663–673.

[27] F. P. Crisastomo, T. Martan, R. Carrillo, *Angew. Chem. Int. Ed.* **2014**, *53*, 2181–2185; *Angew. Chem.* **2014**, *126*, 2213-2217.

[28] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**,*40*, 2004–2021; *Angew. Chem.* **2013**, *113*, 2056-2075; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; *Angew. Chem.* **2002**, *114*, 2708-2711.

[29] L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999.

[30] R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, *2*, 565-598; *Angew. Chem.* **1963**, *75*, 604–637.

[31] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev*. **2007**, *107*, 174–238; b) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200–205; c) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev*. **2007**, *36*, 1173–1193.

[32] L. Ackermann, R. Vicente, R. Born, *Adv. Synth. Catal.* **2008**, *350*, 741–748.

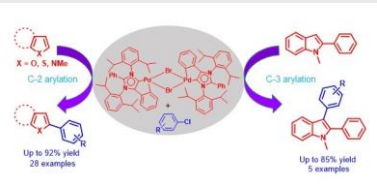
[33] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, OLEX2: a complete structure solution, refinement and analysis program. *J.Appl. Cryst.* **2009**, *42*, 339-341.
[34]SUPERFLI P, *J. Appl. Cryst.* **2007,***40*, 786-790.
[35]SHELXL, G. M. Sheldrick, *Acta Cryst.,* **2008**. *A64*, 112-122.

10.1002/ejoc.201601218

WILEY-VCH

FULL PAPER

Catalytic C-H functionalization of heteroarenes with aryl chlorides efficientin one-pot synthesis of a muscle relaxant drug.



Palladium catalyzed direct C-H arylation, applied in consecutive arylation.

Jasimuddin Ahmed[‡], Samaresh Chandra Sau[‡], Sreejyothi P, Pradip Kumar Hota, Pavan K. Vardhanapu, Gonela Vijaykumar and Swadhin K. Mandal*

Page No. – Page No.

Direct C-H Arylation of Heteroarenes with Aryl Chlorides using Abnormal NHC Coordinated Palladium Catalyst