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C-H Functionalization

Pd-Catalyzed Csp^2–H Functionalization of Heteroarenes via Isocyanide Insertion: Concise Synthesis of Di-(Hetero)Aryl Ketones and Di-(Hetero)Aryl Alkylamines

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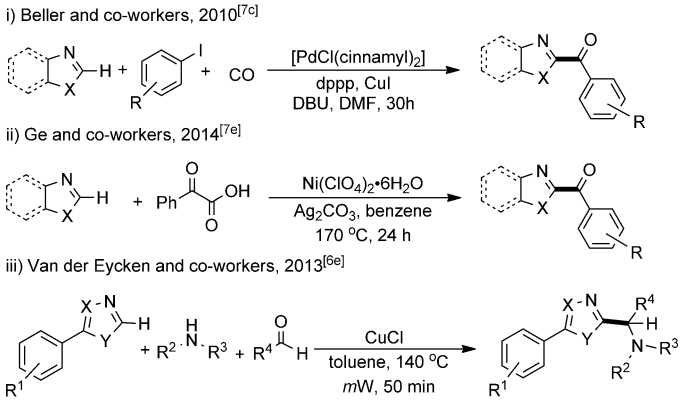
Abstract: We report herein an efficient Pd-catalyzed direct C–H bond functionalization of heteroarenes via an isocyanide insertion strategy for the synthesis of di-(hetero)aryl ketones and di-(hetero)aryl alkylamines. The methodology involves a three component reaction between an azole, a haloarene and an isocyanide resulting in the formation of an imine, which in turn is either hydrolyzed or reduced to get the desired product.

Direct C–H bond functionalization of (hetero)arenes promoted by transition metals is a valuable tool for the facile synthesis of diversified organic molecules, as it circumvents the need for pre-functionalization.[1] The heteroaryl azole skeleton[2] is a key structural unit in various biologically active compounds and finds profound applications in medicinal chemistry as well as in material sciences.[3] Over the years, substantial progress has been made in the direct arylation, alkenylation and alkynylation of azoles using aryl halides and pseudohalides as coupling partners.[4] Recently, some efficient methods have emerged regarding the direct alkylation[5,6] and acylation[7] of such heteroarenes. In contrast, the installation of a secondary alkylamine group on an azole has been confined to a few reports only (Scheme 1, iii).[6e] Among the various strategies for the acylation of azoles, transition-metal-catalyzed carbonylation has received much attention (Scheme 1, i).[7c] However, long reaction times, high pressure, and toxicity of CO limit the application of such reactions. Very recently, Ge and co-workers have reported an attractive methodology for the acylation of heteroarenes employing a decarboxylative coupling with α-oxo-carboxylic acids. Nonetheless the method requires relatively harsh reaction conditions and long reaction times (Scheme 1, ii).[7e] Thus, it would be highly desirable if such acylations could be achieved by employing readily available precursors in a milder way.

Isocyanides, which are an economic and safe alternative for CO, are irreplaceable building blocks in organic synthesis[8] and have found profound applications as versatile C1 synthons in transition-metal catalysis.[9] Since the pioneering work of Passerini[10a] and Ugi[10b] the past decade has witnessed a rapid increase in various C–C-bond-forming reactions involving isocyanides.[8–10] However, their use in C–H activation processes is much less explored especially under intermolecular conditions. Herein, we report an efficient methodology for the synthesis of a di(hetero)aryl framework through the insertion of an isocyanide into an aryl halide bond, followed by attack of a heterocycle in a domino fashion via C–H activation (Scheme 2).



Scheme 1. Methods towards acylation and secondary C–H alkylation of azoles.

Systematic studies revealed that di(hetero)aryl imine **3aa** can be synthesized (98% GC-MS yield, 90% isolated) from bromobenzene **1a** (0.2 mmol), *tert*-butyl isocyanide **2a** (0.24 mmol) and 2-phenyl-1,3,4-oxadiazole **3a** (0.24 mmol) in the presence of $Pd(OAc)_2$ (5.0 mol%), Xantphos (5.0 mol%) and Cs_2CO_3 (0.4 mmol) at 110 °C for 6 h with MeCN as solvent (for details, see Supporting Information Table S1). Subsequently, mild silica gel promoted hydrolysis of **3aa** in dichloromethane at room temperature afforded di(hetero)aryl ketone **4aa** in high yield.

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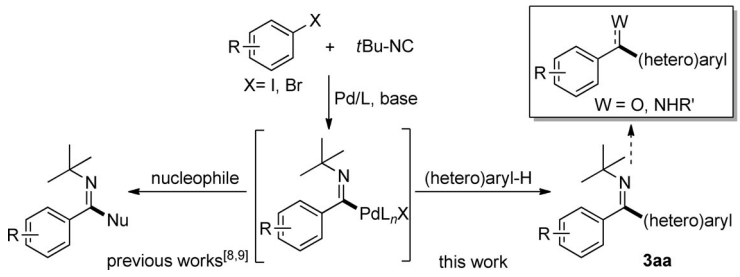


Scheme 2. A typical isocyanide insertion versus C–H activation.

Having established the optimal reaction conditions, we subsequently investigated the influence of different isocyanides on the efficiency of the insertion reaction (Table 1). While *tert*-butyl-, *n*-butyl- and 1,1,3,3-tetramethylbutyl isocyanide provided almost similar yields (entries 1–3), a significantly lower yield was obtained with cyclohexyl isocyanide (entry 4). Only traces (< 10%) were observed with benzyl isocyanide (entry 5) while the reaction failed completely with *p*-methoxyphenyl isocyanide (entry 6).

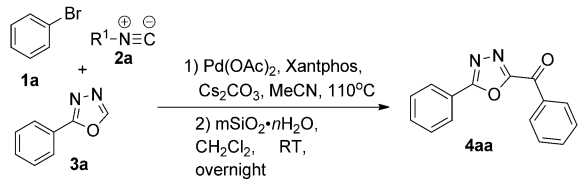
Then, we evaluated the scope of this methodology for different aryl halides with 2-phenyl-1,3,4-oxadiazole and *tert*-butyl isocyanide (Table 2). The reaction proceeded well with various substituted aryl bromides, phenyl iodide and phenyl triflate (**4aa**–**4ak**). However, it failed completely with phenyl chloride. The satisfying formation of *o*-subsituted heteroaryl ketone **4af** in contrast to the work of Ge and co-workers[7e] is particularly notable. Heteroaryl bromides (**4ah**–**4ag**) and bulky 1-naphthyl or 4-biphenyl bromide (**4aj**–**4ak**) were also found to be good coupling partners to give products in good to high yields.

Subsequently, the scope of different oxadizole derivatives and related azoles with similar structures was investigated (Table 3). Good to high yields were obtained in the presence of electron-donating or electron-withdrawing groups (**5aa**–**5ae**) on the phenyl ring of the oxadiazole, except in case of nitro derivative (**5af**). Also, replacement of the phenyl ring of the oxadiazole with a benzyl group (**5ag**) or a 3-pyridyl ring (**5ah**) led to the desired products in high yields.

Similarly, good yields were obtained with 2-phenyl oxazole (**5ai**) and benzoxazole (**5ak**) while relatively lower yields were observed with sulfur analogues **5aj** and **5al**. However, the reaction was not found compatible with nitrogen analogues such as *N*-methyl indole, benzimidazole and caffeine.

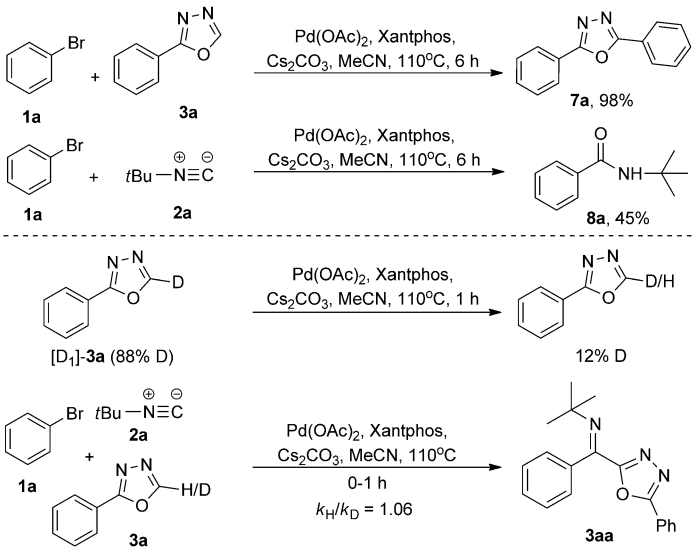
Further, to utilize the third diversity point resulting from the isocyanide and to enhance the practical utility of our methodology, we targeted the synthesis of azoles bearing an alkylamine side chain at their C2 position, as this entity is present in many natural products and drugs.[11a] Therefore we envisioned the reduction of the generated *N*-alkyl imine intermediate **3aa**. Compared with the reduction of C=O and C=C bonds, the reduction of C=N bonds remains a big challenge due to its weak reactivity.[11b] After several attempts, we were able to achieve complete conversion of imine **3aa** using two equivalents of zinc dust in alkaline solution[11c] at 60 °C for 2 h under ultrasonication, providing **6aa** in 62% yield. The results summarized in Table 4 show that imines derived from *tert*-butyl-, cyclohexyl- and 1,1,3,3-tetramethylbutyl isocyanide gave the corresponding secondary amines in moderate to good yields (**6aa**–**6al**). However, only trace amounts of desired compound were observed in case of imines resulting from linear isocyanides such as *n*-butyl or *n*-pentyl. Also, the reaction was found highly susceptible to the nature of substitution. Whereas low to moderate yields were obtained with substituted oxadiazoles (**6ad**–**6ag**), the presence of an electron-donating or electron-withdrawing group on the aryl bromide gave the corresponding products in good

Table 1. Effect of different isocyanides on the insertion reaction.[a]



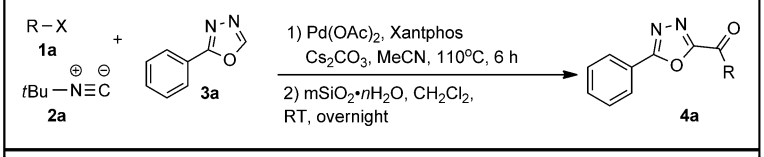
Entry	R^1	Yield [%][a,b]
1	*t*Bu	88 (98)
2[c]	*n*Bu	85 (88)
3	TMB	91 (99)
4[d]	Cy-hexyl	69 (75)
5[e]	benzyl	traces
6[e]	PMP	n.d

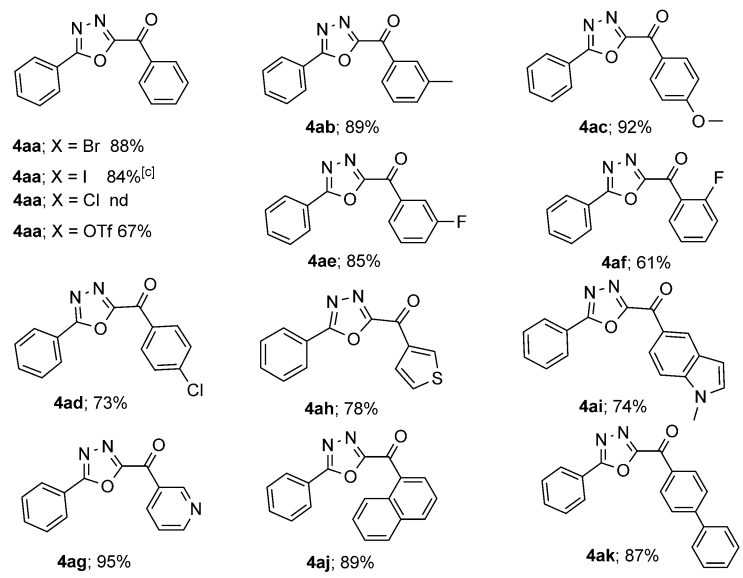
[a] Isolated yield of hydrolysed product under optimized conditions. [b] Yield of imine determined by GC-MS (in parenthesis). [c] Yield of imine after 4 h. [d] Yield of imine after 3 h. [e] After 24 h. TMB = 1,1,3,3-tetramethylbutyl; PMP = *p*-methoxyphenyl.



Scheme 3. Control experiments and deuterium-labelling studies.

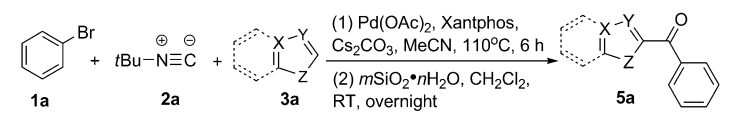
Table 2. Scope of different aryl halides with 2-phenyl-1,3,4-oxadiazole.[a,b]

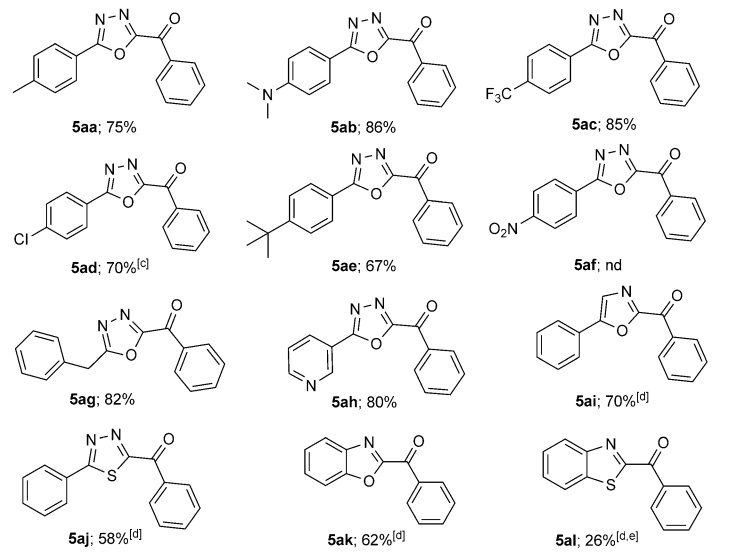




[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), *tert*-butyl isocyanide (0.24 mmol), $Pd(OAc)_2$ (5 mol%), Xantphos (5 mol%), Cs_2CO_3 (0.4 mmol) in MeCN (2.0 mL) at 110 °C for 6 h. [b] Isolated yields. [c] DMSO as solvent; X = Br unless mentioned.

Table 3. Scope of different azoles with aryl bromide.[a,b]





[a] Optimized conditions as in Table 2. [b] Isolated yields. [c] Optimum yield of imine after 4 h. [d] With LiO*t*Bu. [e] Optimum yield of imine after 24 h.

to high yields (**6ah**–**6aj**). Importantly, the use of heteroaryl halides such as thiophene (**6ak**) or bulky naphthalene (**6al**) was found to be feasible, thereby enabling a facile diversification into biologically important biheterocyclic frameworks.

To get more insight in the reaction mechanism some control experiments were carried out (Scheme 3). In the absence of isocyanide **2a** as reaction partner, direct arylated oxadiazole **7a** was observed, which was also a side product encountered in few cases. Likewise when oxadiazole **3a** was omitted from the reaction, formation of amide **8a** was observed in low yield. Moreover, the presence of TEMPO did not hamper the reaction, ruling out the possibility of a free radical mechanism. Further, rapid H/D scrambling was noticed upon exposure of 2-deutero-oxadiazole [D_1]-**3a** to the catalytic conditions after one hour. The k_H/k_D was equal to 1.06 which indicates that the C–H activation step is reversible and might not be the rate determining step for this procedure.[12] Based on these outcomes, we propose the following reaction mechanism (Scheme 4). Initially, the oxidative addition of arylbenzene onto a ligated Pd^0 species generates the aryl–Pd^{II} complex **A**. This is followed by isocyanide insertion to form **B** which could be trapped by **3a** via base-assisted bromide exchange to form **C**. Reductive elimination of the imine from **C** completes the catalytic cycle and regenerates the active palladium species. The resulted imine could be hydrolyzed with silica gel or reduced to give the desired products. The aryl–Pd^{II} complex **A** can also be trapped by **3a** leading to the formation of **7a** which is an expected side reaction for this domino transformation.[7c] Moreover, the formation of **8a** as side product can be ascribed to trapping of **B** by residual H_2O.[9j,k]

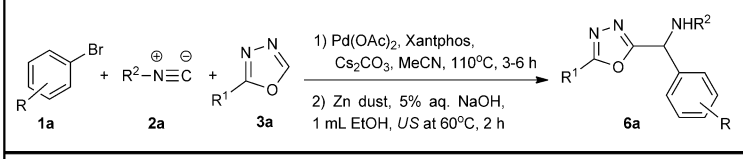
The practical applicability of the process for the synthesis of heteroaryl–ketones was successfully demonstrated by up-scaling the reaction to the gram scale, affording **4aa** in 80% yield (Scheme 5).

In conclusion, an efficient methodology involving Pd-catalyzed C_{sp^2}–H functionalization of heteroarenes via isocyanide insertion has been elaborated for the synthesis of di-(hetero)aryl imines which could then be hydrolyzed or reduced to access synthetically and biologically relevant di-(hetero)arylketones or di-(hetero)aryl amines, respectively. The broad substrate scope, the readily available starting materials, the relatively mild reaction conditions and the good yields make this method synthetically useful.

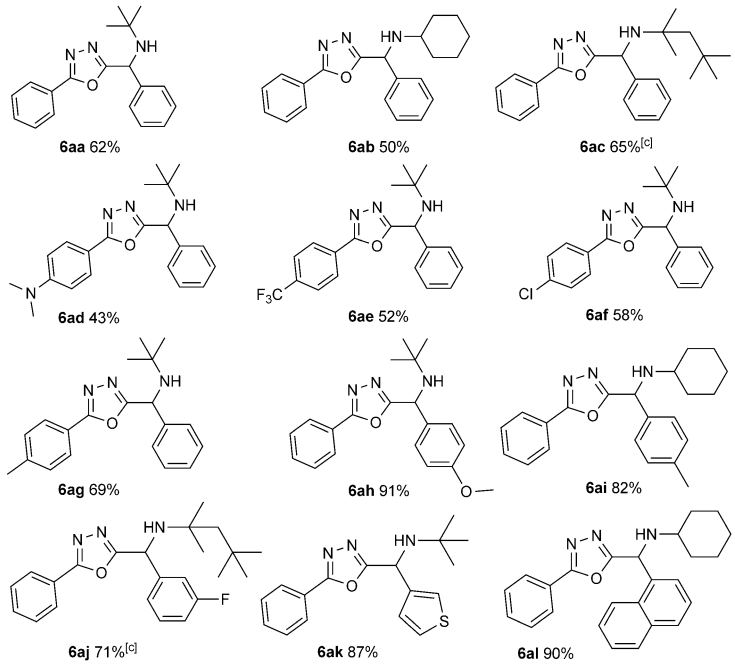
Experimental Section

To an oven dried 10 mL screw cap vial equipped with a stir-bar were added aryl halide **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), Xantphos (5 mol%), base (0.4 mmol), isocyanide **2a** (1.2 equiv), acetonitrile (2 mL) and heteroarene

Table 4. Scope for secondary amines.[a,b]

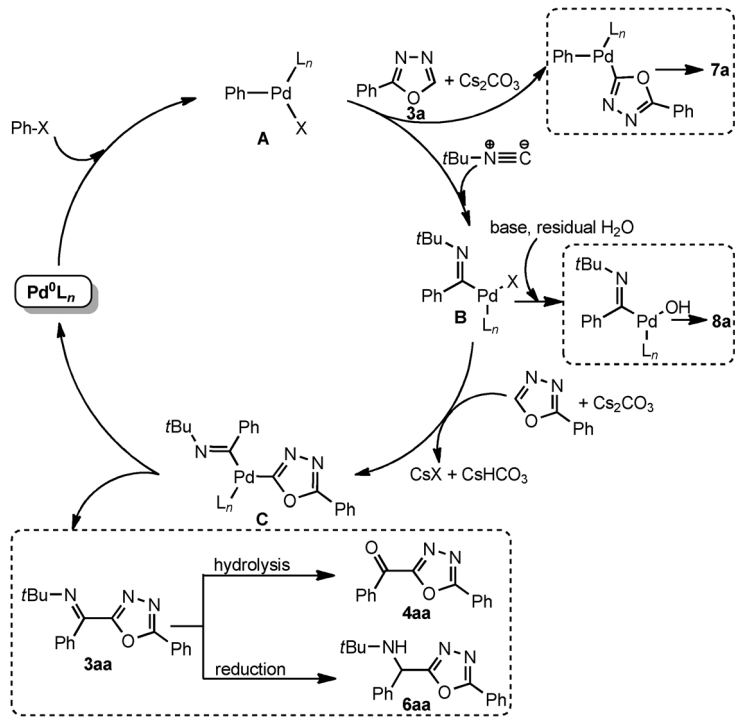


1a 2a 3a 6a



6aa 62% **6ab** 50% **6ac** 65%[c]
6ad 43% **6ae** 52% **6af** 58%
6ag 69% **6ah** 91% **6ai** 82%
6aj 71%[c] **6ak** 87% **6al** 90%

[a] Under optimized conditions as given in Table 2. [b] Isolated yields. [c] After 6 h of ultra-sonication.



Scheme 4. Proposed mechanism.

3a (1.2 equiv). The mixture was degassed, backfilled with nitrogen and then stirred under nitrogen at 110 °C for 6 h. The resulting reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (5 mL) and passed through a small bed of celite and concentrated under vacuum to provide crude imine. The crude imine was then hydrolyzed with silica gel in DCM at RT overnight or reduced under the optimized conditions. The resulting mixture was filtered, concentrated, and then the crude product was purified by column chromatography on silica gel using heptane/EtOAc as eluent. The products were further identified by ^{1}H, ^{13}C NMR and HR-MS, which were all in good agreement with the assigned structures.

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Keywords: azoles · C–H activation · heteroarenes · isocyanide insertion · palladium

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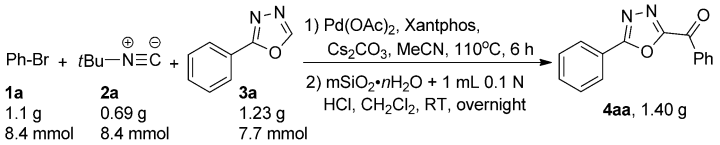

Scheme 5. Gram-scale synthesis of **4aa**.

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C-H Functionalization

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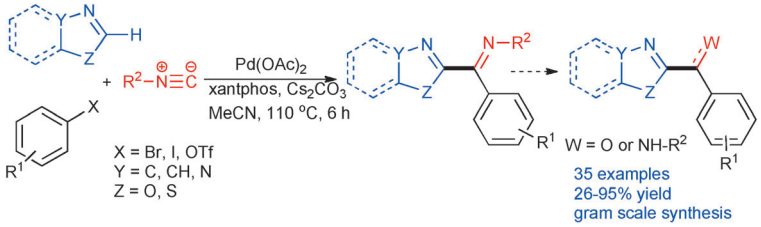
Pd-Catalyzed Csp^2–H Functionalization of Heteroarenes via Isocyanide Insertion: Concise Synthesis of Di-(Hetero)Aryl Ketones and Di-(Hetero)Aryl Alkylamines



Functionalized azoles: Pd-catalyzed direct C–H bond functionalization of heteroarenes via an isocyanide insertion strategy (see scheme) for the synthesis of di-(hetero)aryl ketones and di-(hetero)aryl alkylamines is described.