Cross-Coupling

International Edition: DOI: 10.1002/anie.201504552
German Edition: DOI: 10.1002/ange.201504552

# Palladium-Catalyzed Direct C–H Arylation of Isoxazoles at the 5-Position**

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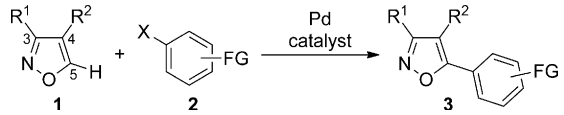
***Abstract:*** *A palladium-catalyzed direct arylation of isoxazoles with aryl iodides has been achieved. The C–H bond at the 5-position is activated selectively to give coupling products in moderate to good yields. This direct arylation was applied to the synthesis of a spiro-type chiral ligand, which proved to be most effective to the palladium-catalyzed tandem cyclization of a dialkenyl alcohol.*

Over the past decade, direct transformation of ubiquitous C–H bonds promoted by a transition-metal catalyst has emerged as a straightforward and atom-economical functionalization method.[1] Among such transformations, C–C bond-forming arylation through C–H bond activation (direct arylation) has been a primary research target, and is recognized to be an environmentally benign cross-coupling reaction.[2] This powerful approach offers a new streamlined strategy for the production of chemicals and is applied to the total synthesis of natural products.[3]

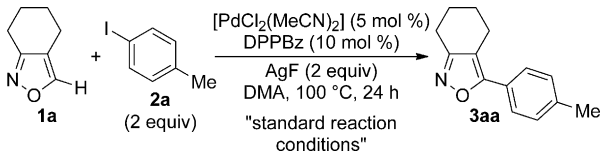
Isoxazoles are a major class of five-membered heterocycles embedded in a variety of pharmaceutical and agrochemical products.[4] This ring system, which has an N–O single bond, is used as a valuable synthetic intermediate in organic chemistry[5] and as a building block in materials science.[6] Chiral ligands having an isoxazole donor site have also been prepared.[7] Continuing efforts are therefore being made to develop more efficient synthetic methods for isoxazoles.[8] Nevertheless, in contrast to the many successful examples of direct arylation reported for other heterocyclic compounds,[9] C–C bond-forming reactions of this type involving isoxazoles are still scarce and are limited to their C4-position.[10] Hence, direct C–H arylation of isoxazoles at the 5-position would provide an alternative and versatile protocol for their preparation.[11] Herein we report an unprecedented palladium-catalyzed direct C5 arylation of the isoxazole ring (Scheme 1).[12,13]




***Scheme 1.*** Direct C–H arylation at the 5-position of isoxazoles. FG = functional group.

To explore direct C5 arylation, the reaction of tetrahydrobenzo[*c*]isoxazole (**1a**)[14] with 4-iodotoluene (**2a**) was conducted as a model reaction. After surveying a series of reaction parameters,[15] we identified the reaction conditions for formation of the desired coupling product. Specifically, treatment of **1a** with 2 equivalents of **2a** in the presence of 5 mol% of $[PdCl_2(MeCN)_2]$, 10 mol% of 1,2-bis(diphenylphosphino) benzene (DPPBz), and 2 equivalents of AgF in *N*,*N*-dimethylacetamide (DMA) at 100 °C for 24 hours gave **3aa** in 86% yield (Table 1, entry 1). No reaction was observed

***Table 1:*** Selected optimization results.[a]




| Entry | Variation from the "standard reaction conditions" | Yield [%][b] |
|---|---|---|
| 1 | none | 86 (84)[c] |
| 2 | no $[PdCl_2(MeCN)_2]$ | n.r. |
| 3 | no DPPBz | n.r. |
| 4 | no AgF | n.r. |
| 5 | $Pd(OAc)_2$ instead of $[PdCl_2(MeCN)_2]$ | 69 |
| 6 | $[Pd(dba)_2]$ instead of $[PdCl_2(MeCN)_2]$ | 67 |
| 7 | $PPh_3$ (20 mol%) instead of DPPBz | 35 |
| 8 | DPPE instead of DPPBz | 46 |
| 9 | EtCN instead of DMA | 59 |
| 10 | 1,4-dioxane instead of DMA | 25 |
| 11 | toluene instead of DMA | 12 |
| 12 | AgOAc instead of AgF | 50 |
| 13 | $Ag_2CO_3$ instead of AgF | 37 |
| 14 | KOAc instead of AgF | 13 |
| 15 | CsF instead of AgF | trace |
| 16 | $Bu_3N$ instead of AgF | n.r. |
| 17 | at 80 °C | 65 |
| 18 | at 120 °C | 56 |
| 19 | 2.5 mol% of $[PdCl_2(MeCN)_2]$/5 mol% of DPPBz | 74[d] |
| 20 | 1 mol% of $[PdCl_2(MeCN)_2]$/2 mol% of DPPBz | 61[d] |

[a] All reactions were performed on a 0.13 mmol scale at 0.25 M under a $N_2$ atmosphere in the dark. In some cases, the formation of a dimer of **1a** was observed. [b] Determined by $^1H$ NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c] Yield of the isolated product. [d] 48 h. n.r. = no reaction.

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[**] This work was supported by the Advanced Catalytic Transformation program for Carbon utilization (ACT-C), Core Research for Evolutionary Science and Technology (CREST), a Grant-in-Aid for Scientific Research from MEXT, and the JSPS Japanese-German Graduate Externship. We would like to thank the technical staff at the ISIR Comprehensive Analysis Centre at Osaka University for their assistance.

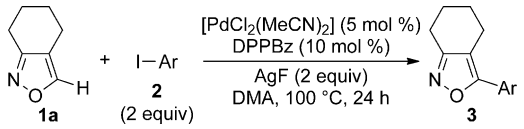
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201504552.

in the absence of any one of these components (entries 2–4). Use of either $Pd(OAc)_2$ or $[Pd(dba)_2]$ (dba = dibenzylideneacetone) instead of $[PdCl_2(MeCN)_2]$ led to a slightly diminished yield (entries 5 and 6). Rigid chelation seemed to be important in this direct arylation. For example, with the monodentate $PPh_3$, and the somewhat flexible 1,2-bis(diphenylphosphino)ethane (dppe), **3aa** was obtained in 35 and 46% yields, respectively (entries 7 and 8). The chemical yield of the coupling product was significantly lowered in less polar solvents (entries 9–11). Additive salts were found to have a large impact on the reaction efficiency (entries 12–15). Organic bases such as $Bu_3N$ did not show any positive effects (entry 16). Even at 80°C, the 5-position of **1a** was functionalized by the 4-tolyl group to give a moderate yield of **3aa**, while no improvement was achieved at higher temperatures (entries 17 and 18). This direct C5 arylation of the isoxazole proceeded even with a reduced catalyst loading of 2.5 or 1 mol% to afford **3aa** in good yields (entries 19 and 20).

The scope with respect to the aryl iodides in this palladium catalysis was then examined using **1a** as the coupling partner (Table 2). Substituting the iodide **2a** for the corresponding

***Table 2:*** Scope with respect to aryl iodides.[a]



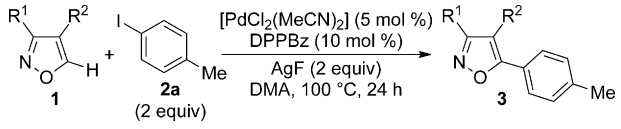

| Entry | 2 | Ar | 3 | Yield [%][b] |
|---|---|---|---|---|
| 1 | **2a** | 4-$MeC_6H_4$ | **3aa** | 84 |
| 2 | **2a′**[c] | 4-$MeC_6H_4$ | **3aa** | 26[d] |
| 3 | **2b** | 4-$FC_6H_4$ | **3ab** | 63 |
| 4 | **2c** | 4-$ClC_6H_4$ | **3ac** | 70 |
| 5 | **2d** | 4-$BrC_6H_4$ | **3ad** | 62 |
| 6 | **2e** | Ph | **3ae** | 77 |
| 7 | **2f** | 4-$MeOC_6H_4$ | **3af** | 71[e] |
| 8 | **2g** | 4-$Me_2NC_6H_4$ | **3ag** | n.r. |
| 9 | **2h** | 4-MeOC(O)$C_6H_4$ | **3ah** | 74 |
| 10 | **2i** | 4-MeC(O)$C_6H_4$ | **3ai** | 47[e] |
| 11 | **2j** | 4-$CF_3C_6H_4$ | **3aj** | 65[e] |
| 12 | **2k** | 4-$NCC_6H_4$ | **3ak** | 51[e] |
| 13 | **2l** | 4-$NO_2C_6H_4$ | **3al** | –[f] |
| 14 | **2m** | 3-$MeC_6H_4$ | **3am** | 68 |
| 15 | **2n** | 2-$MeC_6H_4$ | **3an** | 65 |
| 16 | **2o** | 2-$MeOC_6H_4$ | **3ao** | 45 |
| 17 | **2p** | 2-$BrC_6H_4$ | **3ap** | 43 |
| 18 | **2q** | 1-naphthyl | **3aq** | 79[e] |
| 19 | **2r** | 1-pyrenyl | **3ar** | 79[e] |
| 20 | **2s** | 2,6-$Me_2C_6H_3$ | **3as** | n.r. |
| 21 | **2t** | 2-pyridyl | **3at** | –[f] |
| 22 | **2u** | (*E*)-$C_6H_{13}$CH=CH | **3au** | n.r. |

[a] All reactions were performed on a 0.13 mmol scale at 0.25 M under a $N_2$ atmosphere in the dark. [b] Yield of isolated product. [c] 4-Bromotoluene was used. [d] Determined by $^1H$ NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [e] 48 h. [f] Complex mixture.

bromide **2a′** furnished only 26% yield of **3aa**, thus indicating low reactivity of the C($sp^2$)–Br bond under these reaction conditions (entry 2).[16] Fluoro, chloro, and bromo substituents at the *para* position of iodoarenes **2b–d** remained intact throughout the C–C bond-forming process (entries 3–5). Reaction with iodobenzene (**2e**) simply gave the phenylated isoxazole **3ae** in 77% yield (entry 6). 4-Iodoanisole (**2f**) was successfully employed to afford **3af** in 71% yield after 48 hours, whereas no reaction took place for the more-electron-rich substrate **2g**, which possesses a dimethylamino group (entries 7 and 8). Carbonyl functionalities were tolerated under these reaction conditions to give **3ah** bearing an ester moiety, and **3ai** bearing a ketone moiety (entries 9 and 10). For electron-deficient aryl iodides **2j**, having a trifluoromethyl group, and **2k**, having a nitrile group, the desired coupling products **3aj** and **3ak** were obtained in moderate yields (entries 11 and 12). A strongly electron-withdrawing nitro unit played an adverse role in this transformation, thus resulting in a complex mixture (entry 13). A substituent at the *meta*-position exerted little influence on direct arylation. The reaction with 3-iodotoluene (**2m**) led to the target product **3am** in 68% yield (entry 14). Although a 2-tolyl group was introduced despite the steric hindrance, other *ortho* substituents slightly retarded the cross coupling reaction (entries 15–17). 1-Iodonaphthalene (**2q**) and 1-iodopyrene (**2r**) were also able to participate, albeit sluggishly, in this C–H functionalization (entries 18 and 19). A 2,6-xylyl group was, however, too bulky to be installed at the 5-position of the isoxazole ring (entry 20). A complex mixture was formed in the reaction with 2-iodopyridine (**2t**), and is most likely due to the high reactivity of its α-C–H bond (entry 21). When the alkenyl iodide **2u** was used in place of aryl iodides, the desired product **3au** was not obtained at all (entry 22).

Next, various isoxazole substrates were subjected to the C–H arylation with **2a** (Table 3). The desired reaction product was still obtained even with an aliphatic chain and

***Table 3:*** Scope with respect to isoxazoles.[a]




| Entry | 1 | $R^1$ | $R^2$ | 3 | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | **1b** | 4-$ClC_6H_4$ | Ph | **3ba** | 60 |
| 2 | **1c** | 4-$ClC_6H_4$ | $C_5H_{11}$ | **3ca** | 51 |
| 3 | **1d** | $PhCH_2CH_2$ | $NCCH_2CH_2$ | **3da** | 70 |
| 4 | **1e** | Me | $CO_2Et$ | **3ea** | 86 |
| 5 | **1f** | –CH=CH–CH=CH– | | **3fa** | 73 |
| 6[c] | **1g** | 4-$ClC_6H_4$ | H | **3ga** | 64[d] |

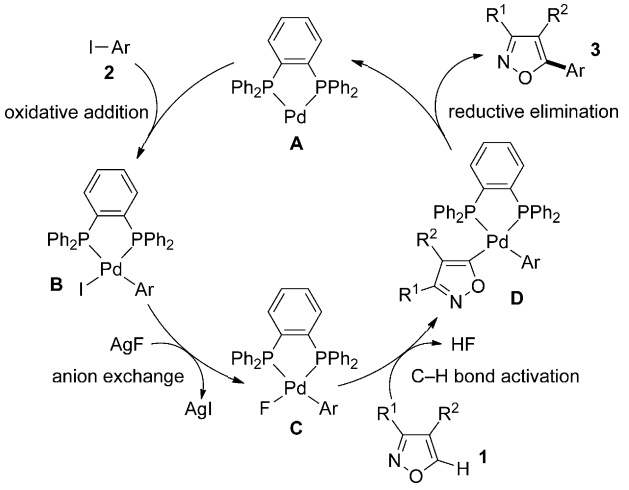
[a] All reactions were performed on a 0.13 mmol scale at 0.25 M under a $N_2$ atmosphere. [b] Yield of isolated product. [c] 1 equiv of **2a** was used. [d] Small amounts of C4-arylated and doubly arylated products were detected.

aromatic rings at the 3- and 4-positions of the isoxazoles (entries 1 and 2). In addition, nitrile and ester functionalities were compatible with this catalysis. The reaction of 3-(3-phenethylisoxazol-4-yl)propanenitrile (**1d**) and ethyl 3-methylisoxazole-4-carboxylate (**1e**) afforded products **3da** (70%) and **3ea** (86%), respectively (entries 3 and 4). A benzene-fused isoxazole substrate, anthranil (**1f**), exhibited similar reactivity to that of **1a** to furnish the product **3fa** in 73% yield

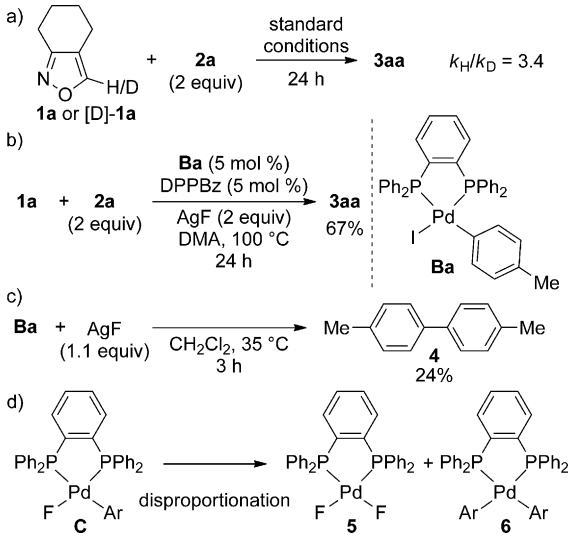
  

(entry 5).[13] This direct arylation proved to take place regioselectively at the 5-position over the 4-position. Thus, in the reaction of 3-(4-chlorophenyl)isoxazole (**1g**) with 1 equivalent of **2a**, the C5–H bond was activated to predominantly produce **3ga** in 64% yield (entry 6).[17]

A plausible reaction mechanism for this palladium-catalyzed direct arylation of isoxazoles is depicted in Scheme 2. As in the conventional cross-coupling reaction, the formation of **3** is initiated by the oxidative addition of the iodoarene **2** to the $Pd^0$ complex **A**, which would be generated through the reduction of the $Pd^{II}$ precatalyst by the action of fluoride.[18] Anion exchange of the resulting $Pd^{II}$ species **B** with AgF gives the fluoride complex **C**.[19] Subsequently, the key C–H bond activation of **1** delivers the intermediate **D**, where the isoxazole ring binds to Pd at its 5-position. Finally, C–C bond-forming reductive elimination from **D** provides the coupling product **3**, and the catalytic cycle is complete.[20] To gain insight into the reaction pathway, we carried out several additional experiments. Firstly, the kinetic isotope effect (KIE) was evaluated by comparison of the initial rates in parallel reactions using substrates **1a** and [D]-**1a** under the standard reaction conditions (Scheme 3a). The KIE value ($k_H/k_D$), determined to be 3.4, suggested the rate-determining step to be C–H bond activation. Subsequently, we prepared the Pd-I intermediate **Ba**[21] and employed it as the catalyst in the reaction of **1a** with **2a** (Scheme 3b). This direct cross-coupling gave product **3aa** in 67% yield, thus implying the involvement of **Ba** in the catalytic cycle. No arylated isoxazole (**3aa**) was, however, obtained in the stoichiometric reaction of **Ba** with **1a** and AgF. The corresponding fluoride complex **C** (Ar = 4-$MeC_6H_4$) could also not be synthesized. To elucidate this, careful attention was paid to the reaction mixture, in which the formation of a considerable amount of 4,4′-dimethyl-1,1′-biphenyl (**4**) was observed (Scheme 3c). We surmized that the key fluoride complex **C** would have a substantial tendency to disproportionate into difluoride complex **5** and diaryl complex **6**, the latter of which produced biaryl derivatives upon reductive elimination (Scheme 3d).



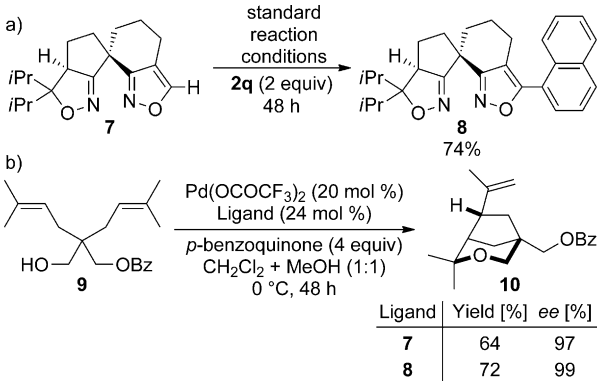

***Scheme 2.*** Plausible catalytic cycle.




***Scheme 3.*** Mechanistic study.

The kinetic investigation indeed demonstrated the undesirable possibility of such a disproportionation process. As such, an inverse relationship between the initial rate and the catalyst loading was observed in the reaction of **1a** with **2a**.[15]

The utility of the direct C5 arylation of isoxazoles was examined in the derivatization of the spiro-type chiral ligand **7**, which was developed in our laboratory (Scheme 4).[7b]




***Scheme 4.*** Application of the direct arylation of isoxazoles.

When we treated **7** with 2 equivalents of **2q** under the standard reaction conditions, the desired product **8**, bearing the 1-naphthyl group, was obtained in 74% yield (Scheme 4a). Considering the fact that Suzuki coupling marginally contributed to the formation of **8** (43% yield),[7c] this C–H functionalization would be a promising surrogate for conventional cross-coupling reactions. The arylated ligand **8** exhibited better results in asymmetric catalysis compared to the unmodified ligand **7**. The palladium-catalyzed Wacker-type tandem cyclization of the dialkenyl alcohol **9** using **7** proceeded to give bicyclic product **10** in 64% yield with 97% *ee*, while both the yield (72%) and the enantioselectivity (99% *ee*) were improved with **8** (Scheme 4b).

In summary, we developed a palladium-catalyzed direct arylation of isoxazoles with aryl iodides, and it takes place at the 5-position of isoxazoles through C–H bond cleavage. This method provides modular access to 5-arylated isoxazole derivatives with high levels of selectivity. Further studies on the application of this C–H functionalization method to organic syntheses are now in progress.

**Keywords:** arylation · C–H activation · cross-coupling · heterocycles · palladium

**How to cite:** *Angew. Chem. Int. Ed.* **2015**, *54*, 9572–9576
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Received: May 20, 2015
Published online: June 30, 2015

  