

**A Cooperative Pd/Cu System for Direct C-H Bond Arylation**

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Complete List of Authors:	lesieur, mathieu; University of St Andrews, EaStCHEM School of Chemistry lazreg, faima; University of St Andrews, EaStCHEM School of Chemistry Cazin, Catherine; University of St Andrews, School of Chemistry

COMMUNICATION

A Cooperative Pd/Cu System for Direct C-H Bond Arylation

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Mathieu Lesieur, Faïma Lazreg and Catherine S. J. Cazin*

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A novel and efficient method for C-H arylation using well-defined Pd- and Cu-NHC systems has been developed. This process promotes the challenging construction of C-C bonds from arenes or heteroarenes with aryl bromides and chlorides. Mechanistic studies show that [Cu(OH)(NHC)] plays a key role in the C-H activation and is involved in the transmetalation with the Pd-NHC co-catalyst.

Cross-coupling reactions have emerged as a general method for the construction of pharmaceutical scaffolds and natural compounds.^[1] During the last 30 years, numerous methods for the formation of carbon-carbon bonds using transition metal catalysts^[2] have been reported: Negishi, Mizoroki-Heck, Stille, Suzuki-Miyaura, Sonogashira and Grignard reagents are the most famous, requiring functionalisation of both coupling partners.^[2,3] Recently, studies have focused on the unreactive C-H bond and the development of atom-economical and more environmentally friendly catalytic transformations. In particular, systems enabling the formation of biaryls (or aryl-heteroaryl) fragments through non-oxidative direct arylation^[4] have received significant attention.^[5] In this area, two challenges exist, in addition to the activation of the C-H bond: homocoupling of the aryl halide must be avoided and the arylation must occur selectively at a single site. Considering the superior reactivity of aryl halides *versus* that of arenes and the presence of multiple C-H bonds in arenes, selective direct arylation remains a challenge. These issues can be addressed by the presence of directing groups on the arene substrate.^[6] This strategy leads to increased regioselectivity and reactivity, however, the scope of accessible products is limited as often only the C-H bond *ortho* to the directing group can be activated. In addition, the need for a directing group often means that additional synthetic steps are required for its incorporation and subsequent removal.^[7] Synthetic strategies avoiding the need of a directing group have therefore been developed, amongst them Pd systems show significant promise, including with challenging substrates such as tosylate derivatives.^[4,5] In such cases, the C-H activation is often believed to occur through a concerted arene metalation/deprotonation pathway or *via* a Friedel-Craft type metallation/rearomatization sequence leading to a Pd-aryl intermediate; before or after oxidative addition of the aryl halide.^[5c] The resulting intermediate is similar to those found in conventional

cross-coupling chemistry. Recently, Huang and co-workers reported a Pd/Cu system enabling the arylation of heterocycles using aryl bromides.^[8] The operative mechanism proposed relies on the presence of a *N*-donor atom on the substrate, which can coordinate the Cu centre and rearrange into a Cu-heteroaryl intermediate after deprotonation by a base. The heteroaryl fragment is then transferred to the palladium centre, and the aryl-heteroaryl product is reductively eliminated. Despite the elegance of this protocol, the substrate scope is limited to benzo-thiazole, -oxazole and -imidazole derivatives.^[9]

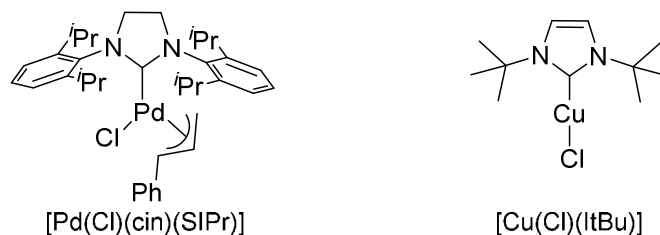


Figure 1 Palladium-NHC and copper NHC enabling C-H arylation

Herein, we report the development of a novel bimetallic catalytic system (Figure 1) permitting the intermolecular direct arylation of arenes and heteroarenes with aryl and alkenyl bromides and chlorides without the need of a directing group. The working hypothesis is based on the ability of [Cu(OH)(NHC)] to perform C-H activation,^[10] and the subsequent use of the efficiency of Pd-NHC complexes to allow transmetalation with copper^[11] after C-Cl or C-Br bond cleavage, leading to the release of the desired compound. In order to validate this hypothesis, pentafluorobenzene and chlorotoluene were selected as coupling partners for the optimisation of reaction conditions. Background reactions were first performed using only Pd-NHC or Cu-NHC, and no conversion was observed in either cases (Table 1, entries 1 and 2). Well-defined [Cu(OH)(IPr)] **1**^[10a] (IPr = *N,N'*-bis[2,6-(di-*iso*-propyl)phenyl]imidazol-2-ylidene) complex in combination with [Pd(Cl)(cin)(SIPr)] **2**^[12] (SIPr = *N,N'*-bis[2,6-(di-*iso*-propyl)phenyl]imidazolidin-2-ylidene; cin = cinnamyl = 3-phenylallyl) represents an initial *proof-of-concept* in providing the direct arylation product in low conversion (14%, Table

1, entry 3). [Cu(Cl)(IPr)] **3**^[13] was next tested as it is likely to be the intermediate species post transmetalation with Pd (see mechanistic discussion below). This chloride derivative leads to the same catalytic activity as its hydroxide congener [Cu(OH)(IPr)] **1** (Table 1, entries 3 and 4), confirming the possible presence of [Cu(Cl)(IPr)] **3** in the catalytic cycle. Several Pd-NHC and [Cu(Cl)(NHC)] complexes were tested,^[14] the combination of [Pd(Cl)(cin)(SIPr)] **2** and [Cu(Cl)(ItBu)] **4** (ItBu = *N,N'*-(di-*tert*-butyl)imidazol-2-ylidene) showed the best result using CsOH as base and toluene as solvent (Table 1, Entry 5).

Table 1 Optimisation of reaction conditions^[a]

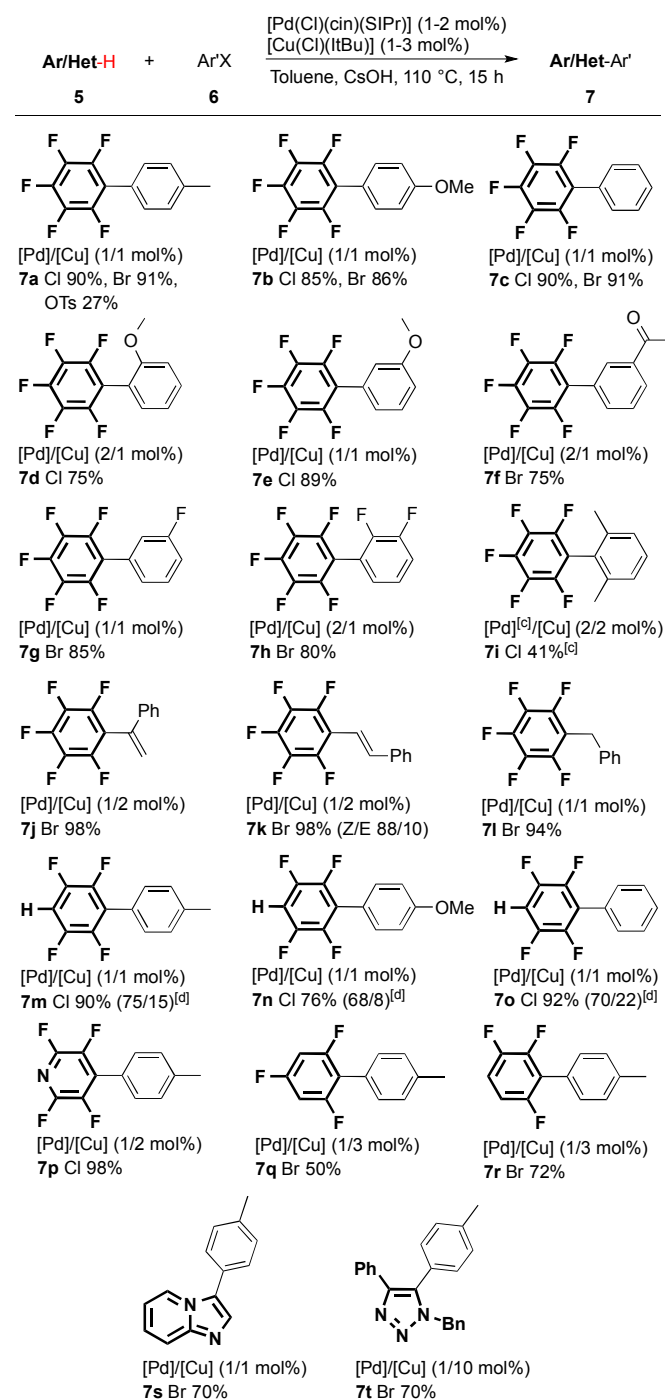
Entry	[Pd] (1 mol%)	[Cu] (1 mol%)	Conv. (%) ^[b]
1	[Pd(Cl)(cin)(SIPr)] 2 ^[c]	-	0
2	-	[Cu(OH)(IPr)] 1	0
3	[Pd(Cl)(cin)(SIPr)] 2	[Cu(OH)(IPr)] 1	14
4	[Pd(Cl)(cin)(SIPr)] 2	[Cu(Cl)(IPr)] 3	13
5	[Pd(Cl)(cin)(SIPr)] 2	[Cu(Cl)(ItBu)] 4	93(90) ^[d]

[a] Conditions: pentafluorobenzene (0.75 mmol), 4-chlorotoluene (0.75 mmol), CsOH (0.975 mmol), [Pd(Cl)(cin)(SIPr)] (1 mol%), [Cu(X)(NHC)] (1 mol%) (X = OH, Cl), toluene (3.0 mL), 110 °C, 15 h. [b] Conversion to coupling product based on aryl halide determined by GC. [c] no conversion using 5 mol% Pd. [d] Isolated yield.

Under the optimised reaction conditions, the scope of this new direct C-H arylation using palladium-NHC and copper-NHC co-catalyst was investigated and results are presented in Scheme 1. The catalytic system performs equally well with aryl chlorides or bromides, suggesting that the oxidative addition of the aryl halide is not the rate-limiting step in this reaction (**7a-c**). *Ortho* and *meta*-substituted aryl halides, with electron donating or withdrawing groups, led to high catalytic activity (**7d-h**). Different fluoroarene derivatives were studied and results are included in Scheme 1. Tetrafluoroarenes could be mono-arylated and di-arylated in good yield (**7m-o**). Trifluoroarenes could also be arylated in good yields (**7q-r**). 2,3,5,6-Fluoropyridine affords the cross-coupling product in an excellent 98% yield (**7p**). Highly challenging and sterically congested tetra-*ortho*-substituted compounds can be synthesised in good isolated yields (**7i**) using a very bulky NHC palladium complex [Pd(Cl)(cin)(IPr*)] (IPr* = *N,N'*-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)-imidazo-2-ylidene) developed initially for the preparation of tetra-*ortho*-substituted biaryls by Suzuki-Miyaura cross-coupling.^[15] Arylation of α - and β -bromostyrenes were achieved with full conversion and high isolated yields (**7j-k**). Coupling with a sp^3 carbon is also possible as shown by the reaction of pentafluorobenzene with benzyl bromide, leading to a 94% isolated yield of the coupling product (**7l**). Imidazopyridine could also be efficiently and selectively arylated at the 5-position (**7s**). C-H arylation of challenging substrates such as 1,4-disubstituted-1,2,3-triazole (**7t**) is also achieved in good isolated yield (78%) using 1 mol% of Pd and 10 mol% of the copper co-catalyst.

In order to better understand the role played by each metal-complex in the transformation, stoichiometric reactions were carried out (Scheme 2).^[16] [Cu(C₆F₅)(IPr)] **8** was obtained quantitatively from the reaction between [Cu(OH)(IPr)] **1** and pentafluorobenzene *via* a C-H activation. This possible intermediate species **8** was reacted [Pd(Cl)(cin)(SIPr)] **2** in the presence of 4-chlorotoluene and CsOH.

This led to the concomitant formation of [Cu(Cl)(IPr)] **3** and of the expected coupling product.^[14]

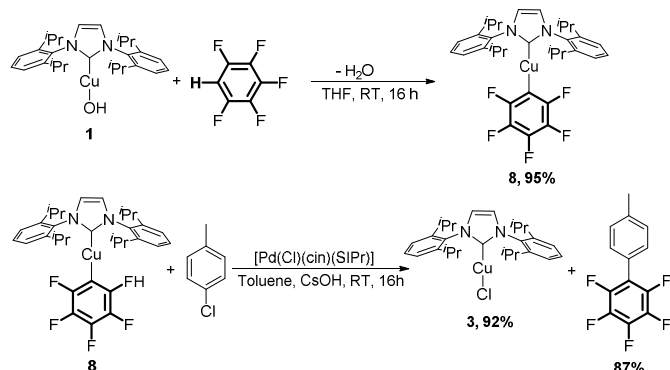


[a] Conditions: Ar/Het-H (0.75 mmol), Ar'-X (0.75 mmol), CsOH (0.975 mmol), [Pd(Cl)(cin)(SIPr)], [Cu(Cl)(ItBu)], toluene (3.0 mL), 110 °C, 15 h.

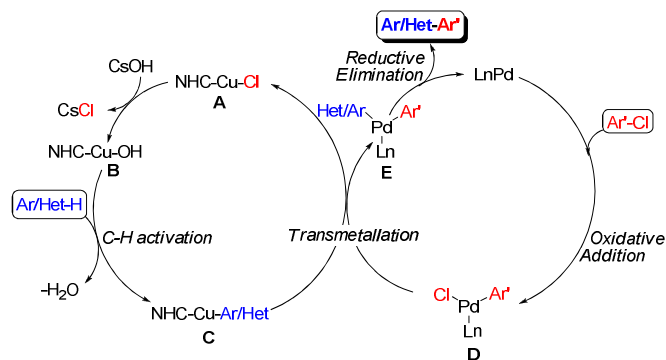
[b] Isolated yield, average of two reactions.

[c] [Pd(Cl)(cin)(IPr*)], IPr* = *N,N'*-bis(2,6-bis(diphenyl methyl)-4-methylphenyl)-imidazo-2-ylidene. [d] Mono/di-substituted.

Scheme 1 Scope of the reaction^{[a][b]}

Scheme 2 Stoichiometric reaction^[17]

From these observations a proposed catalytic cycle is depicted in Scheme 3. On the copper side of this dual catalytic cycle (left), the first step consists of the *in situ* formation of the hydroxide [Cu(OH)(NHC)] **B** from the chloride [Cu(Cl)(NHC)] **A** in a reaction involving CsOH. The following step consists of the C-H activation of the aryl or heteroaryl *via* an acid-base reaction, producing [Cu(Ar/Het)(NHC)] **C** after formation of H₂O. At this stage the transmetalation with the Ar'-Pd intermediate **D** (obtained from oxidative addition of the aryl halide to Pd (0)) occurs, leading concomitantly to the regeneration of [Cu(Cl)(NHC)] **A** and to the formation of the Ar/Het-Pd-Ar' intermediate which can release the coupling product after reductive elimination, and regenerate the Pd(0) catalyst.



Scheme 3 Proposed mechanism

In conclusion, a dual metal system involving [Cu(Cl)(NHC)] and [Pd(Cl)(cin)(NHC)] has been employed to very effectively perform the direct arylation of C-H bonds without the use of a directing group. The mechanistic studies indicate that the Cu species performs an activation involving acid/base concepts, which then transmetalates to Pd to deliver an aryl or heteroaryl fragment. This methodology is efficient for a broad range of aryl, benzyl and alkenyl bromides and chlorides reacting with aryl and heteroaryl substrates. Ongoing studies focusing on increasing the C-H reactivity of the copper-based system should permit to broaden the range of coupling partners in this very powerful reaction sequence.

Notes and references

^aEaStCHEM School of Chemistry, University of St Andrews, St Andrews, KY16 9ST, UK. E-mail: cc111@st-andrews.ac.uk.

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Electronic Supplementary Information (ESI) available: Catalyst optimisation, mechanistic studies and NMR spectra of all products. See DOI: 10.1039/c000000x/

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