COMMUNICATION

A cooperative Pd–Cu system for direct C–H bond arylation†

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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 using 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 transmetallation 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 biaryl (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 for a directing group have therefore been developed, amongst them Pd systems show significant promise, 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–Crafts type metallation/rearomatisation 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. Mori *et al.* developed a Pd/Cu system for the direct arylation of thiazole,[8] while recently, Huang and co-workers reported a Pd–Cu system enabling the arylation of heterocycles using aryl bromides.[9] 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.

Herein, we report the development of a novel bimetallic catalytic system (Fig. 1) permitting the intermolecular direct arylation of arenes and heteroarenes with aryl and alkenyl bromides and chlorides without the need for 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 transmetallation with copper[11] after C–Cl or C–Br bond cleavage, leading to the release
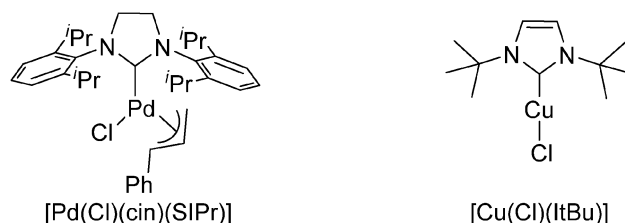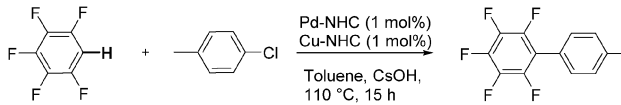
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Fig. 1 Palladium–NHC and copper–NHC enabling C–H arylation.

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] Reaction 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 or Cl), toluene (3.0 mL), 110 °C, 15 h. [b] Conversion to the coupling product based on aryl halide determined by GC. [c] No conversion using 5 mol% Pd. [d] Isolated yield.

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 case (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 transmetallation 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] and 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).

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 the 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 the 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


[Pd]/[Cu] (1/1 mol%) **7a** Cl 90%, Br 91%, OTs 27%	[Pd]/[Cu] (1/1 mol%) **7b** Cl 85%, Br 86%	[Pd]/[Cu] (1/1 mol%) **7c** Cl 90%, Br 91%
[Pd]/[Cu] (2/1 mol%) **7d** Cl 75%	[Pd]/[Cu] (1/1 mol%) **7e** Cl 89%	[Pd]/[Cu] (2/1 mol%) **7f** Br 75%
[Pd]/[Cu] (1/1 mol%) **7g** Br 85%	[Pd]/[Cu] (2/1 mol%) **7h** Br 80%	[Pd]/[Cu][c] (2/2 mol%) **7i** Cl 41%[c]
[Pd]/[Cu] (1/2 mol%) **7j** Br 98%	[Pd]/[Cu] (1/2 mol%) **7k** Br 98% (Z/E 88/10)	[Pd]/[Cu] (1/1 mol%) **7l** Br 94%
[Pd]/[Cu] (1/1 mol%) **7m** Cl 90% (75/15)[d]	[Pd]/[Cu] (1/1 mol%) **7n** Cl 76% (68/8)[d]	[Pd]/[Cu] (1/1 mol%) **7o** Cl 92% (70/22)[d]
[Pd]/[Cu] (1/2 mol%) **7p** Cl 98%	[Pd]/[Cu] (1/3 mol%) **7q** Br 50%	[Pd]/[Cu] (1/3 mol%) **7r** Br 72%

[Pd]/[Cu] (1/1 mol%) **7s** Br 70%	[Pd]/[Cu] (1/10 mol%) **7t** Br 70%

[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(diphenylmethyl)-4-methylphenyl)-imidazo-2-ylidene. [d] Mono/di-substituted.

Scheme 1 Scope of the reaction.[a,b]

biaryls by Suzuki–Miyaura cross-coupling.[15] Arylation of α- and β-bromostyrenes was achieved with full conversion and high isolated yields (**7j–k**). Coupling with an sp³ 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
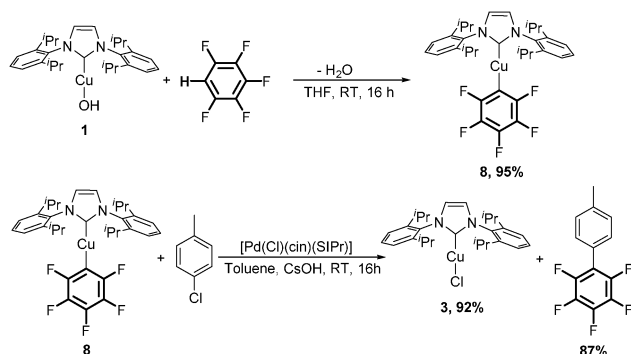
Scheme 2 Stoichiometric reactions.[17]
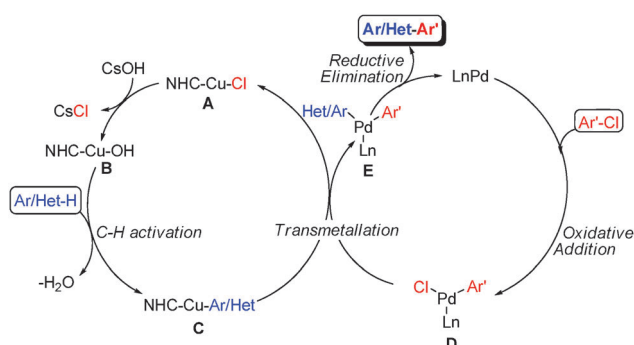
Scheme 3 Proposed mechanism.

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 by the reaction between [Cu(OH)(IPr)] **1** and pentafluorobenzene *via* C–H activation.[17] This possible intermediate species **8** was reacted with [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]

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 transmetallation 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.

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 transmetallates 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 the broadening of the range of coupling partners in this very powerful reaction sequence.

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