Versatile relay and cooperative Pd(0)-NHC/Cu-NHC(I) catalysis for the synthesis of tri- and tetra-substituted alkenes

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Abstract: Two new and efficient dual catalytic procedures for the synthesis of tri- and tetra-substituted alkenes using aryl bromides and chlorides are reported. The formation of these vinyl arenes occurs independently in a one-pot relay and a one-pot cooperative procedure using well-defined Pd-NHC and Cu-NHC complexes. Mechanistic studies were performed to elucidate the key role of the solvent in each procedure as well as the formation of the key intermediate, [Cu(alkenylboron)(NHC)], allowing the transmetallation with the Pd-NHC co-catalyst in the cooperative catalysis.

Introduction

Over the last few decades, independently, the developments of palladium and copper based catalysts have emerged for the construction of carbon-carbon bonds.[1] A plethora of "traditional" methods (Suzuki-Miyaura, Ullmann, Negishi, Kumada-Tamao-Corriu) have been developed for the synthesis of fine chemicals and pharmaceutical building blocks.[2] Nevertheless, most of these procedures still operate within the traditional catalysis paradigm which relies on the initial formation and isolation of the coupling partners for the desired reaction. Currently, attractive synthetic strategies based on a dual catalysis approach are gaining considerable attention.[3] In the literature, several transformations using a one-pot dual Cu(I)/Pd(0) catalytic system can be found, allowing the formation of carbon-carbon bonds such as Sonogashira reaction,[4] cyanation coupling,[5] decarboxylative coupling,[6] C-H activation,[7] benzyne coupling,[8] alkyne functionalization,[9] α-allylic alkylation[10] and formation of tetra-substituted alkenes.[11]

Nevertheless, regio- and stereo-controlled synthesis of tri- and tetra-substituted alkenes still remains an important challenge in organic synthesis.[12] Several copper-catalyzed methodologies have been developed to generate tri-[13] and tetra-substituted[14] vinylboronates, although with limited success (Scheme 1, top). Nozaki described the first synthesis of tetra-substituted borylalkenes by combining an electrophile (*e.g.*, alkyl halides) with a borylalkenylcuprate.[15] However, this strategy suffered from several drawbacks, *i.e.* the use of a highly sensitive boryllithium intermediate and stoichiometric amounts of the lithium borylcyanocuprate. Additionally, the diisopropyldiaminoboron moiety, put in place by this method, does not undergo transmetallation to palladium, and therefore needs to be further derivatized.[15b] In 2012, the Tortosa group

developed the first copper-catalyzed carboboration of alkynes **1** by treating alkyl halides with the *in situ* formed vinylboroncuprate intermediate **2** in a single-step procedure.[16] Yoshida extended the scope of this transformation using benzylchloride, $Cu(OAc)_2$ and PCy_3.[17] However, these procedures were mostly limited to terminal alkynes and symmetrical di-substituted alkynes. In addition, control of the regioselectivity remained challenging, especially in the case of unsymmetrical internal alkynes. Recently, Semba and Nakao have developed the arylboration of alkenes using a Cu/Pd dual catalysis system and applied it to one alkyne example, using diphenylacetylene and 4-bromoanisole.[18] Although limited to a sole example, this procedure supports the feasibility of a dual catalytic approach. Very recently, Brown extended the carboboration of internal alkynes with various aryl iodides.[19] Nonetheless, this strategy remains limited to aryl iodides at very high catalyst loading (10 mol% of $[Cu(Cl)(PCy_3)]$). Our group has also contributed to the construction of these highly valuable building blocks by reporting a convenient "in air" methodology to selectively afford tetra-substituted vinylboronates **3** in high yields.[20] The methodology consists of using unsymmetrical alkynes, bis-(pinacolato)diboron (B_2pin_2) and $[Cu(Cl)(IMes)]$ (IMes = *N,N'*-bis-[2,4,6-(trimethyl)phenyl] imidazole-2-ylidene) at a low catalyst loading (2 mol%).
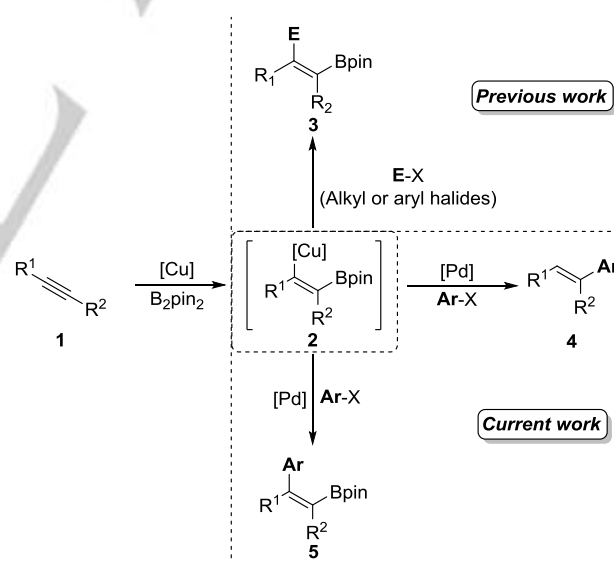
Scheme 1. Formation of tri- and tetra-substituted alkenes.

Herein, we describe, in parallel, a one-pot relay and a one-pot cooperative Pd(0)/Cu(I) procedure for the formation of tri-substituted **4** and tetra-substituted alkenes **5**, respectively. Alkenes **4** are accessed *via* a tandem borylation/Suzuki relay coupling and alkenes **5** are directly formed *via* a cooperative carboboration reaction (Scheme 1).

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Results and Discussion

Catalytic studies. In the case of the relay catalysis, the reaction should proceed *via* borylcupration of alkyne **1** to generate intermediate **2** *in situ*, followed by protonation to give the hydroboration product. The latter then undergoes the Pd-catalyzed Suzuki-Miyaura cross-coupling in order to yield the desired alkene **4** in a one-pot procedure. In 2010, our group developed a very efficient Pd(NHC)/phosphite complex for the Suzuki-Miyaura cross-coupling of challenging substrates at room temperature in ethanol.[21] For this reason, the studies of the relay coupling was initiated by examining the reactivity of 1-phenyl-1-butyne **1a** with 4-bromotoluene **6a** in the presence of B_2pin_2, well-defined [Cu(Cl)(IMes)] and [PdCl$_2$(IPr){P(O*i*Pr)$_3$}] catalysts in different alcohol solvents (see supporting information). Initial experiments focused on the evaluation of the base and solvent effects. During the optimization, a promising 45% conversion (Table 1, entry 1) was obtained using MeOH and KO*t*Bu. The use of a greener solvent, such as ethanol or *iso*-propanol, improved the conversion to 74% (Table 1, entries 2 and 3). Replacing the IPr ligand (IPr = *N,N'*-bis-[2,6-(di-isopropyl)phenyl]imidazo-2-ylidene) on the Pd metal center by its saturated analog SIPr (SIPr = *N,N'*-bis-[2,6-(di-isopropyl)phenyl]imidazolidin-2-ylidene) yielded a slight increase in the conversion (Table 1). Different bases were also tested. Both KO*t*Am (potassium *tert*-amylate) and KO*t*Bu (potassium *tert*-butoxide) showed high activity (see supporting information). However, KO*t*Am was slightly better and was thus chosen in the final protocol (Table 1, entry 7 *vs* entry 8). Finally, the optimized conditions allowed us to reach 93% conversion (with 91% isolated yield) using [Cu(Cl)(IMes)] (1 mol%), [PdCl$_2$(SIPr){P(O*i*Pr)$_3$}] (0.5 mol%), KO*t*Am as base in EtOH, at 80 °C for 20 h (Table 1, Entry 10).[22]

**Table 1.** Optimization of the relay reaction conditions.[a]

Entry	[Pd] (0.5 mol%)	solvent	base	Conversion (%)[b]
1	[PdCl$_2$(IPr)(P(O*i*Pr)$_3$)]	MeOH	KO*t*Bu	45
2	[PdCl$_2$(IPr){P(O*i*Pr)$_3$}]	EtOH	KO*t*Bu	74
3	[PdCl$_2$(IPr){P(O*i*Pr)$_3$}]	*i*PrOH	KO*t*Bu	74
4	[PdCl$_2$(IPr){P(O*i*Pr)$_3$}]	EtOH	KO*t*Am	74
5	[PdCl$_2$(IPr){P(O*i*Pr)$_3$}]	*i*PrOH	KO*t*Am	72
6	[PdCl$_2$(SIPr){P(O*i*Pr)$_3$}]	EtOH	KO*t*Am	77
7	[PdCl$_2$(SIPr){P(O*i*Pr)$_3$}]	*i*PrOH	KO*t*Am	75
8	[PdCl$_2$(SIPr){P(O*i*Pr)$_3$}]	*i*PrOH	KO*t*Bu	68
9	[PdCl$_2$(SIPr){P(O*i*Pr)$_3$}]	EtOH	KO*t*Bu	72
10[c]	[PdCl$_2$(SIPr){P(O*i*Pr)$_3$}]	EtOH	KO*t*Am	93 **(91)**[d,e]

[a] Reaction conditions: 1-phenyl-1-butyne (0.5 mmol), 4-bromotoluene (0.5 mmol), B_2pin_2 (0.55 mmol), base (0.65 mmol), [Cu(Cl)(IMes)] (1 mol%), [Pd] (0.5 mol%), solvent (1 mL), 80 °C, 20 h. [b] Conversion to the coupling product determined by GC based on the alkyne. [c] 4-bromotoluene (0.55 mmol), base (0.75 mmol). [d] Isolated yield, average of two reactions. [e] β:α = 98:2.
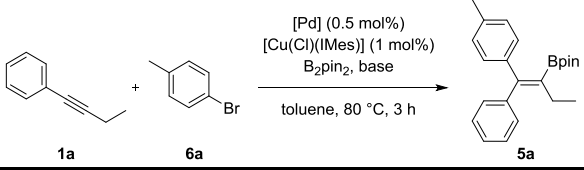
Under the optimized reaction conditions, the scope of this new one-pot relay coupling was investigated (Scheme 2). Several aryl bromides **6** and unsymmetrical alkynes **1** were tested. All products were obtained with excellent regio-selectivity. The Suzuki-Miyaura coupling occurs at the carbon situated β to the aryl group, and affords the expected *E* alkenes (except for **4k**). The method is efficient and selective for the coupling of various aryl bromides, bearing electron-withdrawing and electron-donating groups in either *ortho*, *meta* or *para* position. The system displays a good functional group tolerance, as exemplified by the results obtained with substrates bearing methoxide, acyl, methyl and fluoride groups. Heterocycles are also compatible with this method, as shown with the pyridine derivative **4f** isolated in high yield (82%). This is of particular interest considering that biologically active species often contain a heterocyclic fragment. The ability of the system to promote the reaction with highly sterically hindered bromides is remarkable, as shown with 2,4,6-trimethylbromobenzene **6g** which readily affords **4g** in 80% isolated yield. Finally, alkynes other than 1-phenyl-1-butyne can be used, as shown with the naphthyl, butyl and thiophene derivatives (**1k-m**). Although good yields were obtained in these three cases, the regioselectivity decrease significantly for **4k** and **4l**. KO*t*Am could also be replaced with KO*t*Bu, a less hazardous base, under the same conditions; however, a slight decrease in yield was observed when used to synthesise compounds **4a**, **4b**, **4c**, **4d**, **4f**, and **4h** (see supporting information).
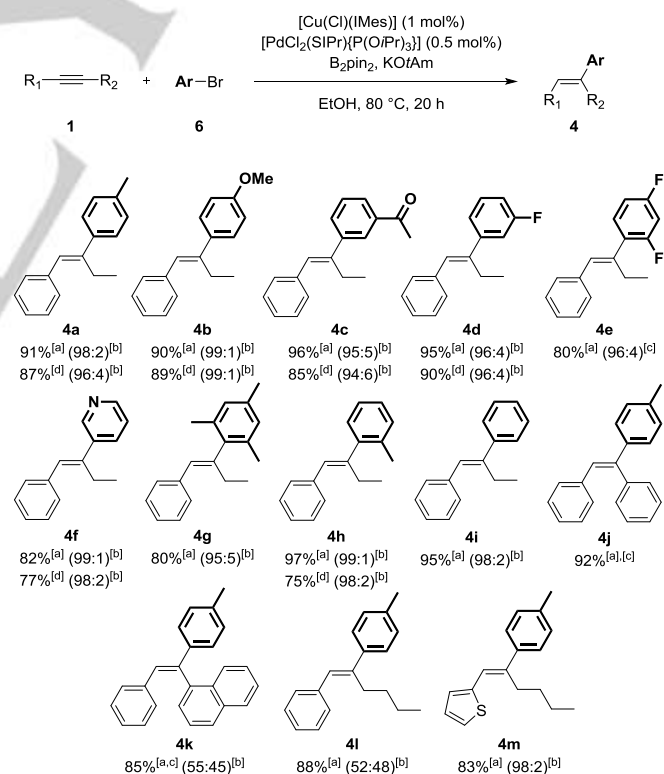
Scheme 2. Scope of the relay catalysis. Reaction conditions: alkyne (0.5 mmol), arylbromide (0.55 mmol), B_2pin_2 (0.55 mmol), KO*t*Am (0.75 mmol), [Cu(Cl)(IMes)] (1 mol%), [PdCl$_2$(SIPr){P(O*i*Pr)$_3$}] (0.5 mol%), EtOH (1 mL), 80 °C, 20 h. [a] Isolated yield, average of two reactions. [b] (β:α) regioisomers ratio determined by GC. [c] 1 mol% Pd used. [d] KO*t*Bu (0.75 mmol), isolated yield.

Next, we took up the challenge to extend the dual catalysis procedure to the formation of tetra-substituted alkenylboryl compounds of type **5**. The working hypothesis was that, in the absence of a proton source (solvent), the alkenyl moiety coordinated to Cu (intermediate **2** in Scheme 1) should undergo transmetallation to Pd instead of protonation. In order to verify this hypothesis, 1-phenyl-1-butyne **1a** was again combined with 4-bromotoluene **6a** in the presence of B₂pin₂ and the catalysts, but in the absence of a protic solvent. A range of palladium catalysts was compared (Table 2, entries 1-5). The [Pd(μ-Cl)Cl(IPr)]₂ dimer showed an excellent 97% conversion with only 0.25 mol% loading.[22] Different bases were also screened, confirming that the counter-anion has an important impact on the conversion (Table 2, entry 1 *vs* entry 6). The NHC ligand was also varied, but no improvement to the conversion was observed (Table 2, entry 1 *vs* entries 8 and 9). At this stage of the optimization, an isolated yield of 95% was obtained for **5a** after 3 hours, using 0.25 mol% of [Pd(μ-Cl)Cl(IPr)]₂ and 1 mol% of [Cu(Cl)(IMes)] in toluene at 80 °C.

**Table 2.** Optimization of the cooperative reaction[a].

Entry	[Pd] (mol%)	base	Conversion[b] (%)
1	[Pd(μ-Cl)Cl(IPr)]₂ (0.25)	NaOtBu	97 (**95**)[c]
2	[Pd(Cl)(cin)IPr] (0.5)	NaOtBu	77
3	[PdCl₂(IPr)(XPhos)] (0.5)	NaOtBu	6
4	[PdCl₂(IPr){P(OiPr)₃}] (0.5)	NaOtBu	9
5	[PdCl₂(IPr)(PEPPSI)] (0.5)	NaOtBu	93
6	[Pd(μ-Cl)Cl(IPr)]₂ (0.25)	KOtBu	32
7	[Pd(μ-Cl)Cl(IPr)]₂ (0.25)	KOtAm	41
8	[Pd(μ-Cl)Cl(SIPr)]₂ (0.25)	NaOtBu	79
9	[Pd(μ-Cl)Cl(IMes)]₂ (0.25)	NaOtBu	59

[a] Reaction conditions: 1-phenyl-1-butyne (0.5 mmol), 4-bromotoluene (0.55 mmol), B₂pin₂ (0.55 mmol), base (0.75 mmol), [Cu(Cl)(IMes)] (1 mol%), [Pd] (0.25-0.5 mol%Pd), toluene (1 mL), 80 °C, 3 h. [b] Conversion to coupling product determined by GC based on alkyne **1a**; β:α ratio = 98:2 (position of the Bpin relative to the phenyl group). [c] Isolated yield in parentheses, average of two reactions.

To further explore the potential of this new cooperative procedure, the reactivity of a broad scope of aryl bromides and chlorides was tested under our optimized conditions. Aryl bromides bearing electron-donating substituents in the *para* position were tolerated, leading to excellent isolated yields of **5a** (95%) and **5b** (96%). It should be noted that an excellent regioselectivity towards the *β*-borylated isomer was consistently maintained (98:2). A slight increase to 0.5 mol% or 1 mol% of the catalyst loading was required for some of the more challenging substrates. Interestingly, aryl chloride substrates bearing methyl- (**5a**), methoxy- (**5h**) and cyano- (**5j**) groups were coupled in 70% to 94% isolated yields, thus confirming the

efficiency of this dual catalysis. 2-chloropyridine and 3-bromopyridine were also readily tested leading to high isolated yields (**5i**, 86% and **5d**, 83% respectively). Other substitutions on the alkyne, *i.e.* a longer alkyl chain (**5k**) and a pyridine moiety (**7l**) were also tolerated, although with a slight decrease in the regioselectivity.
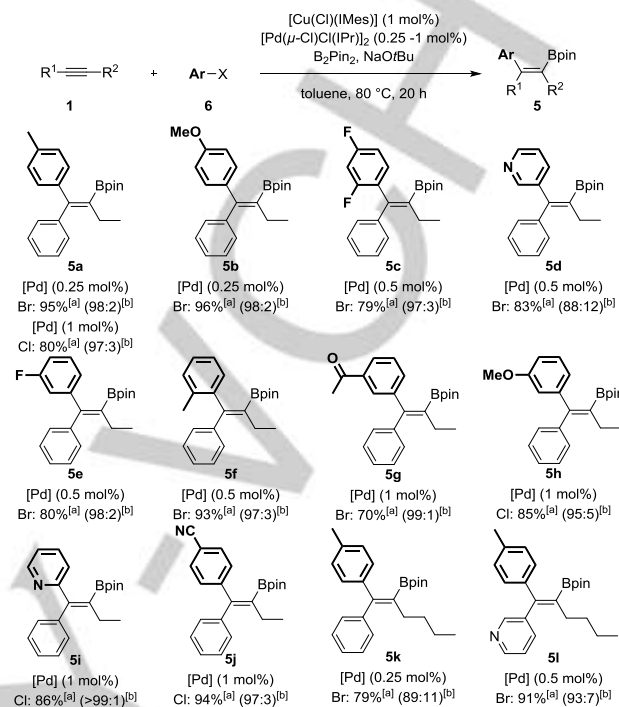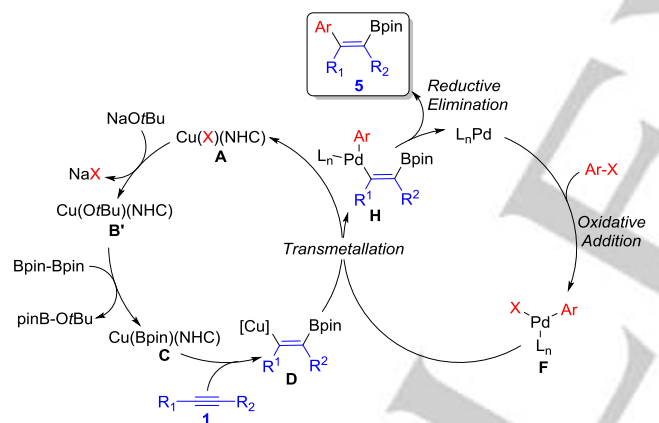

Scheme 3. Scope of the cooperative catalysis. Reaction conditions: alkyne (0.5 mmol), arylhalide (0.55 mmol), B₂pin₂ (0.55 mmol), NaOtBu (0.75 mmol), [Cu(Cl)(IMes)] (1 mol%), [Pd(μ-Cl)Cl(IPr)]₂ (0.25-1 mol%), toluene (1 mL), 80 °C, 20 h. [a] Isolated yield, average of two reactions. [b] β:α regioisomers ratio determined by GC.

Mechanistic considerations. A plausible mechanism for the relay catalysis is shown in Scheme 4. Two independent catalytic cycles are involved. The well-defined NHC copper complex **A** reacts with the alkoxide base and bis(pinacolato)diboron to form the borylcopper species **C**. Addition of the latter to alkyne **1** affords the organoboroncuprate intermediate **D**. This species can liberate the borylated alkene **E** through protonation and concomitantly regenerate a catalytically active species of the form [Cu(OEt)(NHC)]. **E** can then enter the catalytic cycle involving palladium by transferring the alkenyl fragment to **F**, which is the result of the oxidative addition of the aryl halide to the palladium center. The resulting Pd intermediate, **G**, can then reductively eliminate the arylated alkene product **4**.
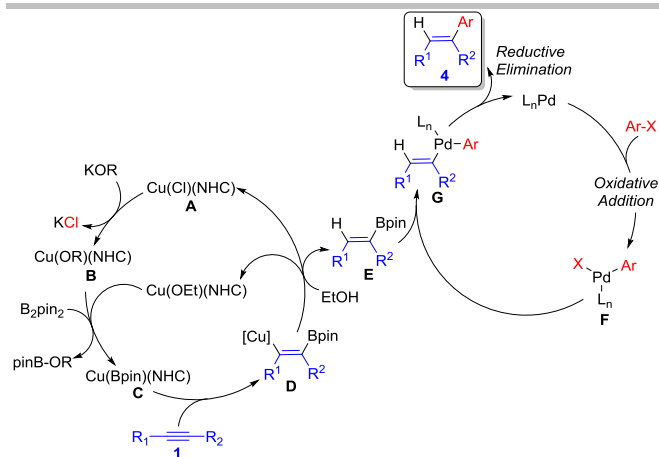
Scheme 4. Proposed mechanism for the relay catalysis.

In contrast to the aforementioned mechanism, the cooperative catalysis consists of two inherently linked catalytic cycles (Scheme 5). In the same manner as for the relay catalysis, the copper catalytic cycle generates intermediate **D**. However, in this case (*i.e.* in the absence of EtOH), protonation is inhibited and direct transmetallation to Pd occurs, leading to the intermediate species **H** and to the regeneration of [Cu(Cl)(NHC)]. This is followed by the liberation of the final product by reductive elimination with concomitant regeneration of the active Pd catalyst.

Scheme 5. Proposed mechanism for the cooperative catalysis.

To provide experimental evidence for the roles played by copper and palladium in the cooperative dual catalysis, stoichiometric reactions were carried out (Scheme 6).[23] The key copper intermediate **D'** [Cu(Alkenylboron)(IPr)] was obtained quantitatively by combining complex **C'** [Cu(Bpin)(IPr)][24] with 1-phenyl-1-butyne **1a**. This complex (**D'**) was further treated with a stoichiometric amount of [Pd(*µ*-Cl)Cl(IPr)]₂, 4-chlorotoluene and NaO*t*Bu in toluene at room temperature. This led to the formation of [Cu(Cl)(IPr)] **A'** and the tetra-substituted alkene product **5a**.
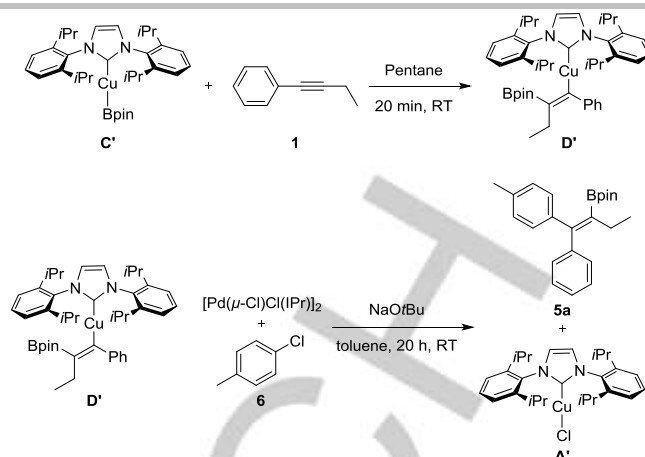
Scheme 6. Mechanistic investigation of the cooperative catalysis.

Conclusion

In conclusion, two new convenient methodologies for the synthesis of tri- and tetra-substituted alkenes were developed. In general, high regioselectivity and good to excellent yields were obtained. [Cu(Cl)(NHC)] and Pd-NHC complexes were shown to be highly effective catalysts in both dual strategies. Under the one-pot relay reaction conditions, the active Cu(NHC) species catalyzed the *β*-hydroboration of the alkyne, in the presence of ethanol. The subsequent Pd(NHC)-catalyzed Suzuki-Miyaura coupling with various aryl and heteroaryl bromides afforded the desired tri-substituted alkenes. Remarkably, the dual system [Cu(Cl)(IMes)] and [Pd(*µ*-Cl)Cl(IPr)]₂ working cooperatively, readily afforded tetra-substituted alkenylboranes in a one-pot procedure, starting from a wide range of aryl/heteroaryl halides (bromides and chlorides) and unsymmetrical alkynes. Mechanistic studies were undertaken permitting a better understanding of the role of the Cu(NHC) and Pd(NHC) catalysts in each system. We believe the two approaches facilitate the rapid construction of molecular complexity in a straightforward manner and hope to report on further examples of this approach shortly.

Experimental Section

Relay procedure: In a glovebox, a vial equipped with a stirring bar and sealed with a screw cap fitted with a septum was charged with the palladium catalyst (0.5 mol%), [Cu(Cl)(IMes)] (1 mol%), B₂pin₂ (140 mg, 0.55 mmol), KO*t*Am (95 mg, 0.75 mmol) and EtOH (1 mL). The alkyne (0.50 mmol, 1.0 equiv.) and the aryl halide (0.55 mmol) were then added. The reaction mixture was stirred (750 rpm) at 80 °C during 20 h. The solution was allowed to cool to room temperature and quenched with water (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (20 mL). The organic layer was dried over MgSO₄, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel. The reported yields are the average of two reactions.

Cooperative procedure: In a glovebox, a vial equipped with a stirring bar and sealed with a screw cap fitted with a septum was charged with the palladium catalyst (0.25-1 mol%), [Cu(Cl)(IMes)] (1 mol%), B₂pin₂ (140 mg, 0.55 mmol), NaO*t*Bu (72 mg, 0.75 mmol) and toluene (1 mL). The alkyne (0.50 mmol, 1.0 equiv.) and the aryl halide (0.55 mmol) were

then added. The reaction mixture was stirred (750 rpm) at 80 °C during 20 h. The solution was allowed to cool to room temperature, quenched with water (20 mL) and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (20 mL). The organic layer was dried over MgSO$_4$, filtered and the solvents were evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel. The reported yields are the average of two reactions.

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COMMUNICATION

A new relay and cooperative procedure using well-defined Pd(0)-NHC/Cu(I)-NHC systems have been developed. This novelty allowed in an interesting fashion the formation of tri- and tetra-substituted alkenes from unsymmetrical alkynes and aryl halides.
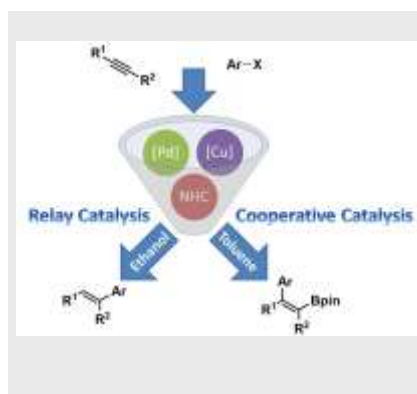
Mathieu Lesieur, Yannick D. Bidal, Faïma Lazreg, Fady Nahra, Catherine S. J. Cazin*

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Versatile relay and cooperative Pd(0)-NHC/Cu-NHC(I) catalysis for the synthesis of tri- and tetra-substituted alkenes