

Copper-Free Heck–Cassar–Sonogashira and Suzuki–Miyaura Reactions of Aryl Chlorides: A Sustainable Approach

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Cite This: *ACS Sustainable Chem. Eng.* 2023, 11, 15994–16004



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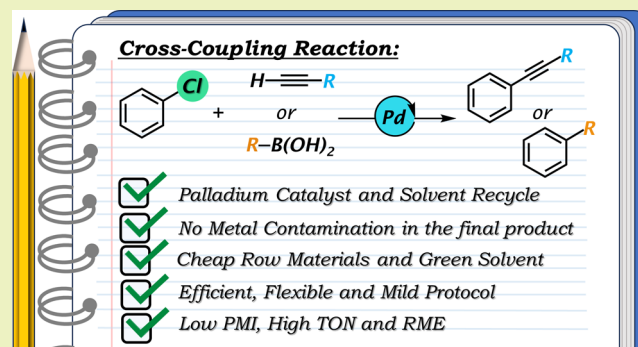
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Supporting Information

ABSTRACT: Sustainable and efficient aryl halides with copper-free Heck–Cassar–Sonogashira (HCS) and Suzuki–Miyaura (SM) cross-coupling reactions were described. Independently from the aryl chloride substituents, the green protocol based on *N*-hydroxyethylpyrrolidone (HEP)/water as solvents and sodium 2'-dicyclohexylphosphino-2,6-dimethoxy-1,1'-biphenyl-3-sulfonate (sSPhos) as ligand afforded the target products with a high turnover number (TON), high reaction mass efficiency (RME), and low process mass intensity (PMI). The best results have been obtained with TMG and Cs₂CO₃ as the base for the HCS and Cs₂CO₃ and K₂CO₃ for the SM coupling. The PMI and RME achieved are among the best in the field and allowed us to simplify purification processes that are critical for industrial applications.

KEYWORDS: copper-free Heck–Cassar–Sonogashira, Suzuki–Miyaura, palladium, green solvents, aryl chlorides



INTRODUCTION

Palladium-catalyzed cross-coupling reactions currently represent one of the most useful methodologies for carbon–carbon bond formation^{1–4} and have a prominent role in the pharmaceutical segment.^{5–8} The success of these reactions is mainly related to the very high selectivity and flexibility in terms of substrates, solvents, catalysts, reaction conditions, and the complexity of the structural modifications. However, nowadays, the reaction design must be guided by the 12 principles of green chemistry,⁹ which highlight the necessity of safe, simple, and environmentally friendly methodologies. Moving to palladium-catalyzed cross-couplings, these principles must be translated into fast, selective, flexible reactions under mild conditions using sustainable and cheap chemicals.¹⁰ Among the several green metrics, process mass intensity (PMI) is one of the most useful and can be used to guide the development of active pharmaceutical ingredient (API) synthesis.¹¹ In this context, solvents account for the majority of the waste and the identification of sustainable alternatives has been investigated by several industrial and academic research groups.^{12–14}

Since palladium is a rare and expensive metal, in order to increase the sustainability of cross-coupling reactions, there are two strategies: (i) replace it with a more abundant metal or (ii) increase the TON as well as the recovery of the catalyst. The second strategy allows us to take advantage of the high reactivity and efficiency of palladium catalysts.

In this context, with our society moving away from the fossil automotive industry, which absorbs most of the available

palladium, it is possible to forecast in the next decade a decrease in palladium demand, production, and costs.

Therefore, the design of low metal loading processes and efficient recycling procedures will be critical to promote, more than before, the use of palladium cross-coupling reactions for the synthesis of a complex architecture. In addition, in the pharmaceutical sector, regulatory agencies focused their attention on drug product elemental impurity contamination, decreasing the allowed limits.¹⁵

The Heck–Cassar–Sonogashira (HCS) palladium-catalyzed cross-coupling reaction allows the installation of a triple bond on aryl halides (Scheme 1). The Heck–Cassar (HC) protocol^{16,17} required only Pd(0) as a catalyst, while Pd(0)/Cu(I) is necessary for the Sonogashira reaction.¹⁸ This article is focused on the copper-free HCS or, in other words, the HC protocol.

A few years later, Suzuki and Miyaura described the coupling of aryl halides and boronic acids to generate a biaryl motif (Scheme 1).¹⁹ Both reactions are powerful methods for the synthesis of APIs and agrochemical products.^{20,21}

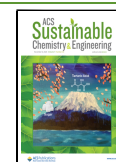
Aryl halides are very useful starting materials and the reactivity generally follows the oxidative addition reactivity (I > Br > Cl), while the cost is inversely proportional.²²

Received: August 4, 2023

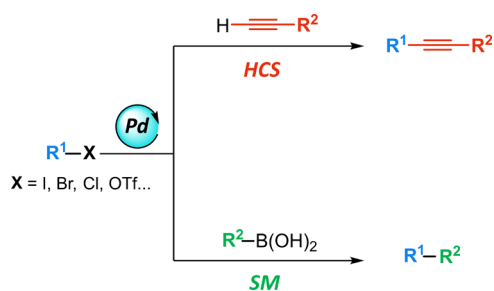
Revised: October 11, 2023

Accepted: October 12, 2023

Published: October 26, 2023



Scheme 1. General Scheme of Copper-Free HCS and SM Cross-Coupling Reactions



Buchwald introduced pioneering palladium ligands for SM cross-coupling in 1999,²³ which were subsequently used in the copper-free HC protocol.²⁴ The application of the Sonogashira procedure Pd/Cu to aryl chlorides was consistently investigated.²⁵ Recently, Ackermann and Gallou reviewed the most recent sustainable methods for the HC protocol.²⁶ However, after the Buchwald water/ CH_3CN reaction back in 2005,²⁷ only a few papers described efficient reactions with aryl chlorides in water or water mixtures, always with an excess of reagents, 0.5–1% of Pd loading and PMI around 50.^{28,29} On the contrary, several examples of sustainable protocols have been reported for SM cross-coupling. In particular by Colacot³⁰ and the micellar approach with concomitant development of new ligands by Handa/Gallou/Lipshutz.^{31–33} The lowest palladium loading was reported by Schoub and co-workers. They achieved high yield with electron-withdrawing groups and good yield with electron-donating ones using 0.005 mol % of palladium and an excess of boronic acid (1.1 equiv) at 100 °C in water.³⁴ All of the SM reactions described allowed us to obtain a pure product after chromatography.

The target of this study is to identify a flexible, reproducible, and sustainable procedure for HCS and SM cross-coupling reactions, allowing high yields independently from the aryl substitution. The procedure must be characterized by low metal loading, in situ formation of the active Pd(0) catalyst, high reaction mass efficiency (RME), competitive PMI values considering solvent and palladium recovery, and prevention of

product metal contamination. Minimizing excess reagents and side product formation is crucial to reducing the need for extensive purification processes.

RESULTS AND DISCUSSION

Taking advantage of our experience in the Heck–Cassar–Sonogashira reaction using aryl iodides, bromides, and triflates based on the use of green protocols,^{35–37} we explored the application of commercially available Buchwald’s palladium ligand, sodium 2’-dicyclohexylphosphino-2,6-dimethoxy-1,1’-biphenyl-3-sulfonate (sSPhos), in the N-hydroxyethylpyrrolidone (HEP)/water mixture for the HCS and SM cross-coupling using aryl chlorides. HEP is a safe and potentially biogenic solvent,^{38,39} which in a mixture with water proved to be a valid alternative to the use of toxic DMF⁴⁰ or NMP.⁴¹ HEP can potentially undergo hydrolysis at high temperatures and under strongly basic conditions, leading to the formation of 4-((2-hydroxyethyl)amino)butanoic acid. This amino acid derivative contains a secondary amine that could lead to nitrosamine formation upon exposure to nitrites. However, its theoretical log *D* value remains negative at any pH,⁴² meaning even if formed in traces, it cannot be extracted into an organic solvent and will not contaminate the final product. In addition, with the HEP/water ratio of >8/2, the solvent extraction of the final product with an immiscible solvent is generally very efficient, keeping the metal in the HEP/water mixture.

As previously stated, this is an important characteristic of the protocol taking into consideration the low level of metal allowed by the elemental impurity guidelines Q3D by The International Council for Harmonization (ICH) for Active Pharmaceutical Ingredients (APIs) quality.¹⁵

The HCS cross-coupling between phenyl halide **1a** and phenylacetylene **2a** was performed under copper-free Heck–Cassar conditions. The reaction was carried out with 2 mol % of Pd⁽⁰⁾ catalyst, generated in situ starting from Pd(CH_3CN)₂Cl₂ and sSPhos, in HEP/water 70/30 and *N,N,N',N'*-tetramethyl guanidine (TMG) as a base. These standard conditions were used to evaluate the effect of the leaving group and, for PhCl **1a**^{Cl}, to define concentration, temperature, and stoichiometry (Table 1).

Table 1. Screening for the HCS in HEP/Water/TMG System Conditions^a

entry	conc (M)	X	2a (equiv)	T (°C)	t (h)	AAR ^b (h)	conv (%)	3a/4a
1	0.5	I	2.0	60	1	rapid	>99	>99/1
2	0.5	Br	2.0	60	2	rapid	>99	79/21
3	0.5	Cl	2.0	60	3	rapid	20	23/77
4	0.5	Cl	2.0	70	3	rapid	25	32/68
5	0.5	Cl	2.0	80	3	rapid	45	35/65
6	1.0	Cl	1.5	60	3	4	40	42/58
7	1.0	Cl	1.5	70	3	4	80	77/23
8	1.0	Cl	1.05	70	8	8	>99	99/1
9	1.0	Cl	1.5	80	3	3	>99	90/10
10	1.0	Cl	1.05	80	4	4	>99	>99/1
11	1.0	Cl	1.05	90	3	3	>99	>99/1

^aAll HCS couplings were carried out under a nitrogen atmosphere with 2 mol % of Pd precatalyst and 6 mol % of sSPhos ligand, 1.1 equiv of TMG, in HEP/water 7/3. Conversion and product ratios were determined by HPLC considering the appropriate relative response factor (RRF). ^bAAR = alkyne addition rate.

The enyne side product, (*E*)-4-[phenylbut-1-en-3-ynyl]-benzene, **4a**^{36,37,43} became instead the main product moving from PhI **1a**^I to PhBr **1a**^{Br} and PhCl **1a**^{Cl} at 60 °C (compare entries 1–3). These results are determined by the competition between the oxidative addition OA of ArX (Figure 1, cycle I)

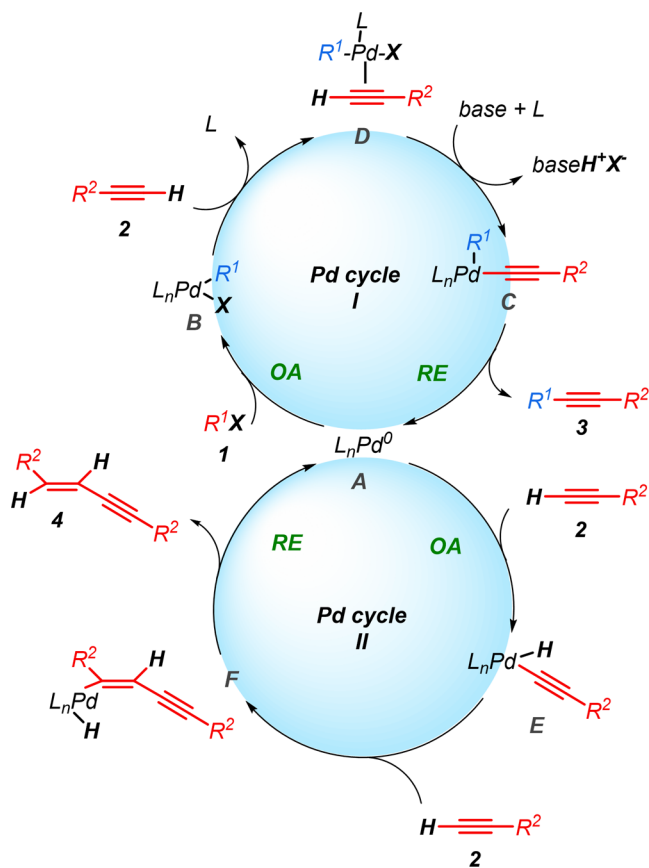


Figure 1. Mechanism of the Heck–Cassar copper-free protocol. Pd cycle I affords the main product **3**, while Pd cycle II affords enyne **4**.

and PhC≡CH **2a** (Figure 1, cycle II).³⁶ Temperature and stoichiometry increases did not change substantially the outcome of the reaction (entries 4 and 5). Based on our previous studies on the HCS coupling,³⁶ we introduced the slow addition of **2a** to limit the formation of **4a** with PhCl **1a**^{Cl}. However, at 60 °C, the OA of PhCl **1a** was too slow (entry 6), already at 70 °C with a longer addition rate, the selectivity toward **3a** was completed (entry 7 vs 8). Accordingly, complete conversion and selective formation of the bis-substituted acetylene **3a** were achieved by balancing reaction temperature and alkyne addition rate (entries 7–11). The temperatures of 80 and 90 °C guaranteed an efficient OA of PhCl **1a**^{Cl} on the Pd⁽⁰⁾ complex A and a complete conversion into **3a** with 4 and 3 h addition rates of **2a**, respectively (entries 10 and 11).

To have a further understanding of the competitive pathway leading to enyne **4**, density functional theory (DFT) calculations were performed using Gaussian 16 with the B3LYP hybrid functional.

In Figure 2, the differences in energy between the oxidative addition process of different aryl halides using SPhos as the ligand and the first step of the enyne formation are compared. The reaction coordinate was studied starting from the monoligated Pd-SPhos complex A, since it is considered the active palladium species, while SPhos was chosen as ligand

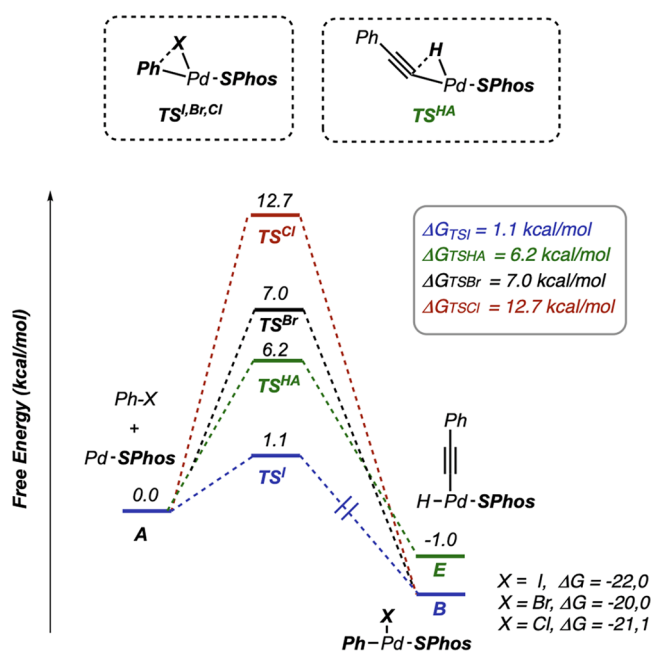


Figure 2. DFT calculations in DMF of the OA of aryl halides and the first step of the phenylacetylene insertion to give the enyne byproduct **4**.

instead of the sulfonated sSPhos to simplify the calculations.⁴⁴ Since the experimental results demonstrated that the enyne byproduct is formed when the oxidative addition is slow, we expected the alkyne insertion to have an energy similar to that of the transition state of the oxidative addition of the phenyl bromide. Indeed, the Gibbs free energy barrier for the oxidative addition of the PhI **1a**^I is only 1.1 kcal/mol, while the phenylacetylene addition to the Pd-SPhos complex has a TS^{SHA} of 6.2 kcal/mol.

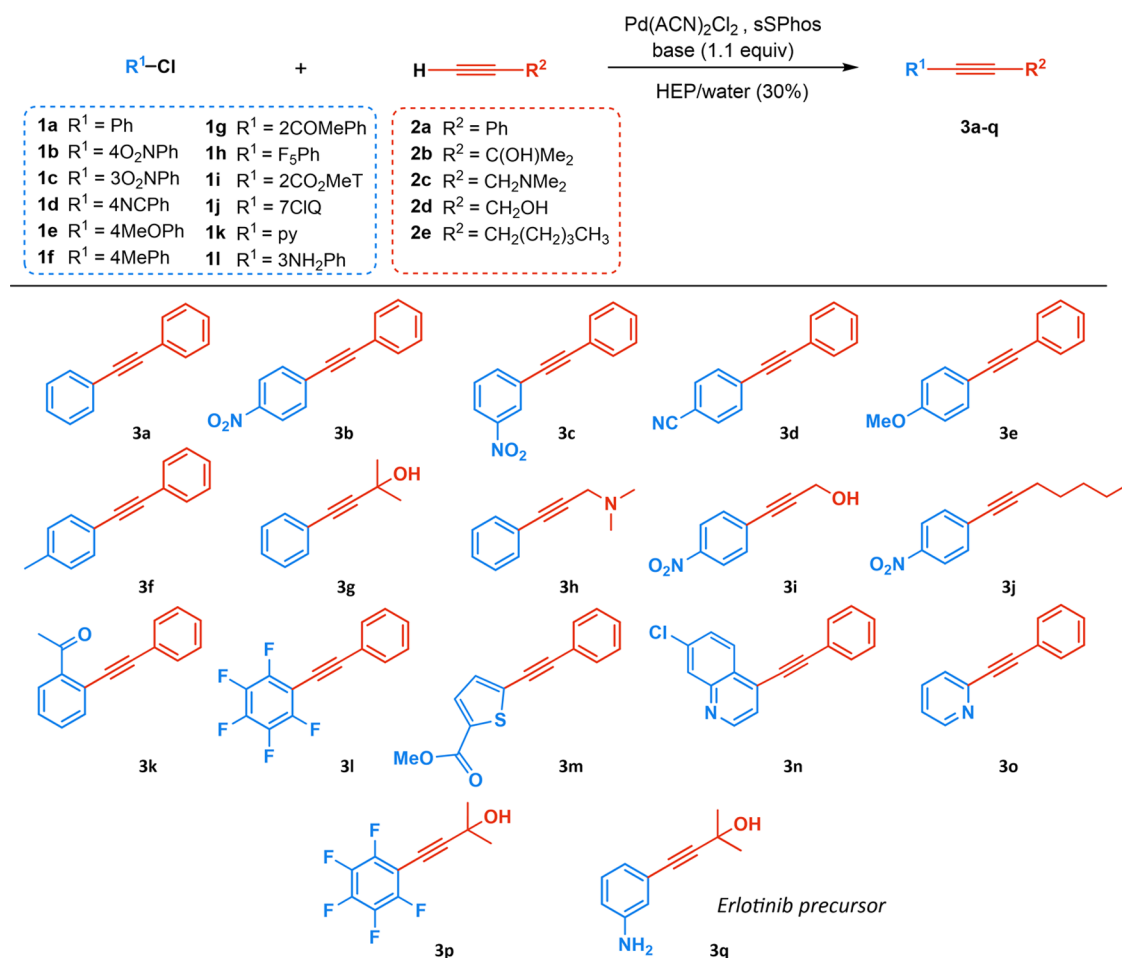
These calculations are in line with the fact that the byproduct is not present when the HCS reaction is performed with aryl iodides. On the contrary, the energy barriers for the oxidative addition of PhBr **1a**^{Br} and PhCl **1a**^{Cl} are 7.0 and 12.7 kcal, respectively. DFT data confirm the experimental results described in Table 1. In fact, the formation of enyne **4** competed with the HCS coupling product **3** moving to bromide and chloride as leaving groups.

Adding electron-withdrawing groups, such as NO₂, to aryl chlorides lowers the activation energy barrier for the oxidative addition of OA. In the case of 4-NO₂-phenyl chloride **1b**, this reduces the energy barrier difference between aryl chloride and alkyne oxidative additions from 12.7 to 7.5 kcal, making the reactions more accessible, see the Supporting Information.

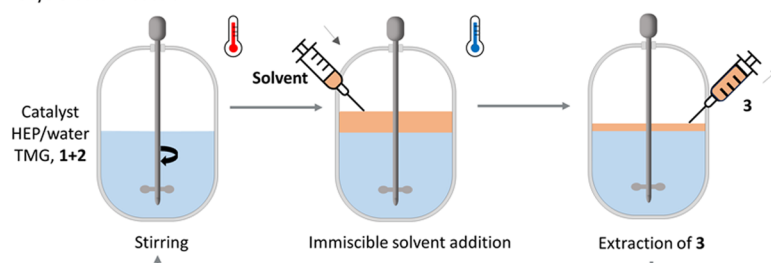
The copper-free HCS reaction scope is described in Scheme 2. The couplings have been performed using a recycling or thermomorphic procedure (Figure 3 and Table 2) and a low Pd loading protocol in Table 3.

The goal of the study was to create a green and sustainable protocol, performing efficient and fast reactions under mild conditions using a low percentage of palladium catalyst. We started from the optimized conditions (Table 1 entries 10 and 11) trying to recycle the catalyst starting from 2 mol %. After the complete conversion of aryl chloride **1a** in diphenylacetylene **3a**, the simple extraction with an immiscible solvent allowed the easy recovery of the final product, leaving the catalyst in the HEP/water phase. The catalyst solution was then used in the following reaction cycle by simply adding the two reagents and

Scheme 2. Copper-Free HCS Cross-Coupling Scope



(a) Recycle batch reaction



(b) Thermomorphic conditions

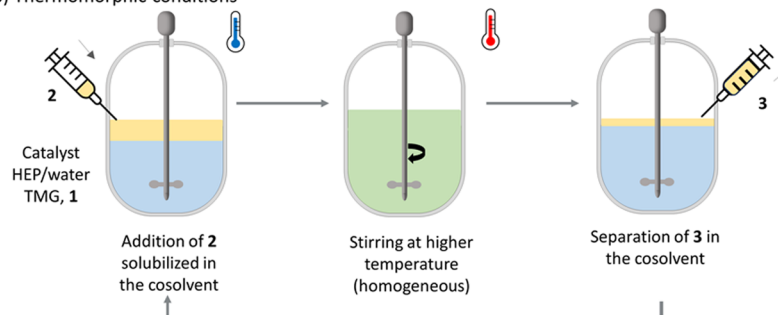


Figure 3. Batch reaction with catalyst recycling (a) and thermomorphic protocol (b).

the TMG base. The results reported in Table 2 show that the catalyst generated in the HEP/water/TMG system could be

easily recycled up to five times, always maintaining a conversion of over 95% (entry 1).

Table 2. HCS Reaction Scope and Catalyst Recycling^a

$$\text{R}^1\text{-Cl} + \text{H-C}\equiv\text{C-R}^2 \xrightarrow[\text{HEP/water (30\%)}]{\text{Pd(ACN)}_2\text{Cl}_2 \text{ (2 mol\%)} \\ \text{sSPhos (6 mol\%)} \\ \text{TMG (1.1 equiv)}} \text{R}^1\text{-C}\equiv\text{C-R}^2$$

1.0 M

entry	R ¹ -Cl	alkyne	alkyne (equiv)	T (°C)	cycle time (h)	AAR (h)	cycles	TON	product	yield ^b (%)
1 ^c	1a	2a	1.05	90	3	3	5	230	3a	90
2 ^c	1b	2a	1.05	80	3	3	5	235	3b	94
3 ^c	1c	2a	1.05	80	3	3	5	235	3c	94
4	1d	2a	1.05	80	3	3	5	233	3d	93
5	1e	2a	1.05	90	4	4	3	138	3e	92
6	1f	2a	1.05	90	4	4	3	138	3f	92
7	1a	2b	1.5	90	4	4	3	135	3g	90
8	1a	2c	1.5	90	4	4	3	132	3h	88
9	1b	2d	1.5	90	4	4	3	134	3i	89
10	1b	2e	1.5	90	4	4	3	129	3j	86
11 ^d	1a	2a	1.05	90	3	3	5	232	3a	92
12 ^e	1a	2a	1.05	90	3	3	3	135	3a	90
13 ^f	1a	2a	1.05	90	3	3	3	135	3a	92

^aAll HCS couplings were carried out under a nitrogen atmosphere and the cycle time corresponded to the alkyne addition time. At the given time, the reactions were cooled at rt, extracted with the appropriate organic solvent, and the HEP/water phase containing the catalyst was recycled. ^bThe combined extraction solvents were distilled, and the crude was subsequently purified by flash chromatography when necessary. ^cReaction time extended to 4 h in the last two cycles. ^dThe reaction was performed using Cs₂CO₃ instead of TMG. ^eReaction performed thermomorphically through the slow addition of acetylene in toluene over the course of the reaction. ^fReaction performed thermomorphically through the slow addition of acetylene in IBA over the course of the reaction.

Table 3. Direct HCS Reaction between Aryl Chlorides 1a–l and Alkynes 2a–e^a

$$\text{R}^1\text{-Cl} + \text{H-C}\equiv\text{C-R}^2 \xrightarrow[\text{HEP/water (30\%)}]{\text{Pd(ACN)}_2\text{Cl}_2, \text{ sSPhos} \\ \text{base (1.1 equiv)}} \text{R}^1\text{-C}\equiv\text{C-R}^2$$

90°C, 16h

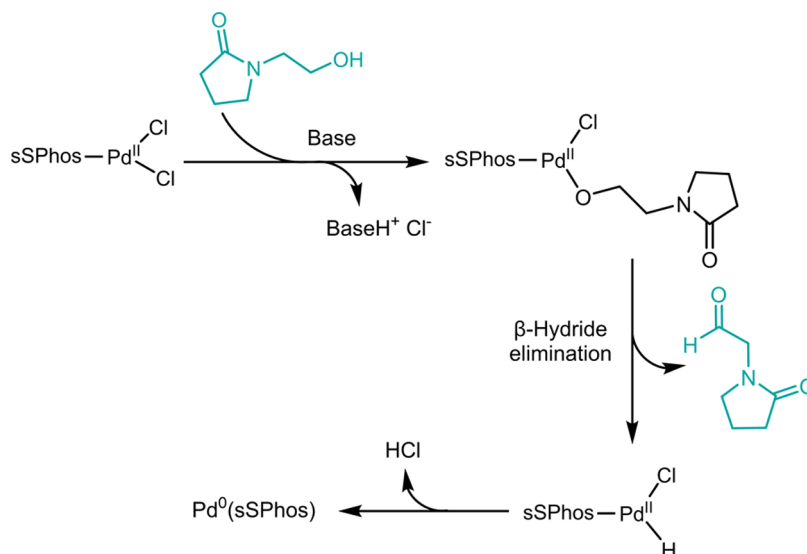
entry	conc (M)	R ¹ -Cl	alkyne	alkyne (equiv)	Pd(II) (mol %)	base	conv ^b (%)	yield (%)	TON	product
1	1.0	1a	2a	1.05	0.4	TMG	70	65	163	3a
2	1.0	1e	2a	1.05	0.6	TMG	61	56	140	3e
3	1.0	1a	2a	1.05	0.4	Cs ₂ CO ₃	>99	94	235	3a
4	1.0	1e	2a	1.05	0.6	Cs ₂ CO ₃	>99	92	150	3e
5	2.5	1a	2a	1.05	0.2	Cs ₂ CO ₃	>99	93	465	3a
6	2.5	1b	2a	1.05	0.2	Cs ₂ CO ₃	>99	94	470	3b
7	2.5	1c	2a	1.05	0.2	Cs ₂ CO ₃	>99	95	475	3c
8	2.5	1d	2a	1.05	0.2	Cs ₂ CO ₃	>99	93	465	3d
9	2.5	1e	2a	1.05	0.4	Cs ₂ CO ₃	>99	90	225	3e
10	2.5	1f	2a	1.05	0.4	Cs ₂ CO ₃	>99	91	228	3f
11	2.5	1a	2b	1.2	0.4	Cs ₂ CO ₃	>99	90	225	3g
12	2.5	1a	2c	1.2	0.4	Cs ₂ CO ₃	>99	91	228	3h
13	2.5	1b	2d	1.2	0.4	Cs ₂ CO ₃	>99	90	225	3i
14	2.5	1b	2e	1.2	0.4	Cs ₂ CO ₃	>99	90	225	3j
15	2.5	1g	2a	1.5	0.4	Cs ₂ CO ₃	>99	94	235	3k
16	2.5	1h	2a	1.5	0.4	Cs ₂ CO ₃	>99	92	230	3l
17	2.5	1i	2a	1.5	0.4	Cs ₂ CO ₃	>99	93	233	3m
18	2.5	1j	2a	1.5	0.4	Cs ₂ CO ₃	>99	90	225	3n
19	2.5	1k	2a	1.5	0.4	Cs ₂ CO ₃	>99	91	228	3o
20	2.5	1h	2b	2.0	0.4	Cs ₂ CO ₃	>99	91	228	3p
21	2.5	1l	2b	2.0	0.4	Cs ₂ CO ₃	61	52	130	3q

^aAll HCS couplings were carried out under nitrogen in a HEP/water 7/3 solution and the alkyne 2 was slowly added within the given reaction time. The reactions were cooled at rt and extracted with the appropriate organic solvent. The extraction solvent was distilled and the crude was subsequently purified with flash chromatography when necessary. ^bDetermined with HPLC considering the appropriate RRF.

The reaction was extended to substituted aryl chlorides and acetylenes to demonstrate the robustness of the protocol. For each couple of substrates, the mildest conditions to reach complete conversion were investigated, starting from the best

conditions identified in the model reaction between 1a and 2a. While the presence of electron-withdrawing groups on the aromatic ring did not affect the reactivity (entries 2–4), the transformation of differently substituted acetylenes and

Scheme 3. HEP-Promoted Pd(II) Complex Reduction



electron-donating substrates required applying modified conditions. Even when the temperature was increased to 90 °C and the acetylene addition was slowed down to 4 h, it was still possible to get three recycles and maintain conversions higher than 95% and good yields (entries 5–10).

The only alternative inorganic base that produced good results in the HCS was Cs_2CO_3 (entry 11, see the [Supporting Information](#)).⁴⁵

Another interesting characteristic of the HEP/water 7/3 mixture was the possibility of performing the reaction under thermomorphic conditions by adding a third solvent. In fact, with a cosolvent like toluene or isobutyl acetate (IBA), the mixture was immiscible at room temperature, while a homogeneous solution was observed at temperatures >80 °C. Therefore, the HCS protocol was investigated using the new thermomorphic mixtures⁴⁶ of HEP/water/toluene or HEP/water/IBA in a 7/3/5 ratio. A solution of **2a** in toluene or IBA was added over 3 h to the reaction mixture and after cooling to room temperature **3a** was easily recovered by phase separation and the catalyst was recycled (see entries 12 and 13 and [Figure 3b](#)). The reported thermomorphic procedures for the HCS coupling are carried at $T > 100$ °C with aryl iodides and bromides as unsustainable solvents.^{47,48}

The recycling procedure is ideal for products sensitive to temperature.³⁶ In fact, if the reaction was carried out using low palladium loading, the reaction time consistently increased (see [Table 3](#)). Aryl chlorides **1a** and **1e** were selected as model examples to assess the validity of the study. Unfortunately, low palladium loading resulted in low conversions using TMG, which decomposes during long reaction times ([Table 3](#), entries 1 and 2).^{49,50} However, by replacing TMG with Cs_2CO_3 , complete conversions were successfully achieved (entries 3 and 4). The process was then further optimized to decrease the required amount of Pd catalyst, enhance the TON, and decrease the PMI of the protocol. Therefore, the catalyst amount was decreased to 0.2 mol % in a 2.5 M solution, achieving conversions higher than 95% for the model reaction and for the ones with substrates containing electron-withdrawing groups (entries 5–8), while 0.4 mol % was necessary for more difficult substrates (entries 9–21).

The synthesis of erlotinib intermediate **3q** starting from 3-chloro-aniline **11** is not competitive with respect to the industrial process that uses the corresponding bromide as the starting material.¹⁰ The conversion was only 61% (entry 21) and the catalyst increase did not change the reaction performances. Based on our previous studies, the aniline moiety is able to enter the coordination sphere of the metal slowing down the reaction rate.³⁶

Interestingly, no conversion was observed when the reactions with Cs_2CO_3 as a base were performed in DMF. The explanation of this result is in the ability of HEP to reduce a $\text{Pd}(\text{II})$ complex to $\text{Pd}(\text{0})$ thanks to its primary alcohol moiety.^{51,52} In fact, HEP is oxidized to the corresponding aldehyde with the concomitant reduction of the precatalyst ([Scheme 3](#)) (see Section 7 of the [Supporting Information](#) for ³¹P NMR studies).

The PMI and the PMI after recovery (PMIr) were calculated in [Tables 2](#) and [3](#) at 5 and 10 mmol scales, respectively. The recycling of the catalyst and solvent for the reactions described in [Table 2](#) allowed us to achieve a PMI of 18. After recovery of the extraction solvent, HEP and palladium achieve a PMIr value close to 3. In the reactions reported in [Table 3](#) at a concentration of 2.5 M with 0.2–0.4 mol % of catalyst, the PMI reached 11, while the PMIr was around 4 for all entries (see Section 3 of the [Supporting Information](#) for detailed PMI calculation). These PMIs achieved are the lowest described in the literature.

Suzuki–Miyaura Cross-Coupling. In order to demonstrate the versatility of the HEP/water system with sulfonated phosphines, we selected the Suzuki–Miyaura cross-coupling as further proof. The main advantage of the SM reactions over other cross-coupling protocols is the use of boron compounds as coupling partners, which are readily available and provide high yields and good selectivity with a broad functional group tolerance.

In the SM protocol, the coupling between **1a** and **5a** was used as a standard reaction to explore the use of different inorganic bases at 45/60/90 °C, see [Table 4](#) (see Section 4 of the [Supporting Information](#) for complete screening). The results indicated that Cs_2CO_3 and K_2CO_3 were superior to Na_2CO_3 and K_3PO_4 . At 45 °C, complete conversions were achieved with increasing Cs_2CO_3 palladium loading and boronic acid excess

Table 4. SM Screening Inorganic Base Screening^a

Ph-Cl		Ph-B(OH) ₂		Pd(ACN) ₂ Cl ₂ , sSPhos Base (1.1 equiv)			Ph-Ph
1.0 mmol		5a		HEP/water (40%) 1.0 M			6a
entry	Pd (%)	5a (equiv)	base	T (°C)	time (h)	conv ^b (%)	
1	0.1	1.2	Cs ₂ CO ₃	45	16	100	
2	0.2	1.05	Cs ₂ CO ₃	45	16	100	
3	0.2	1.05	K ₂ CO ₃	45	16	100	
4	0.2	1.05	Na ₂ CO ₃	45	16	100	
5	0.2	1.05	K ₃ PO ₄	45	16	100	
6	0.05	1.05	Cs ₂ CO ₃	60	8	100	
7	0.05	1.05	K ₂ CO ₃	60	16	85	
8	0.05	1.05	Na ₂ CO ₃	60	16	83	
9	0.05	1.05	K ₃ PO ₄	60	16	76	
10	0.05	1.05	Cs ₂ CO ₃	90	4	100	
11	0.05	1.05	K ₂ CO ₃	90	4	100	

^aAll SM couplings were carried out under nitrogen in a HEP/water 6/4 solution. ^bDetermined with HPLC considering the appropriate RRF.

(entries 1 and 2), and similar data have been achieved with K₂CO₃ (entry 3). At 60 °C, complete conversion has been achieved only with Cs₂CO₃, using 0.05 mol % of Pd, 0.15 mol % of sSPhos, and 5% excess boronic acid (compared entries 6 vs 7–9). At 90 °C, the results of Cs₂CO₃ and K₂CO₃ are identical. The reaction described in entry 10 was replicated for pure HEP (60%) and pure H₂O (80%) after 12 h at 90 °C.

The reaction scope shown in Scheme 4 was defined using the rapid protocol at 90 °C with K₂CO₃, while that with Cs₂CO₃ was efficient also at 60 °C. The former ensures rapidity, while the

latter requires less energy in terms of temperature but a longer reaction time. Using these optimized reaction conditions, independently from the substitutions on the aryl chlorides and boronic acids, the conversions were always >99 with yields exceeding 90%.

As already reported for the HCS reaction, the HEP/water mixture has a beneficial effect on lowering the catalyst loading. This is related to the efficient reduction of the precatalyst, substrate solubility, and probably the Pd⁽⁰⁾ catalyst stabilization with no effect on the transmetalation step (Figure 4).⁵³

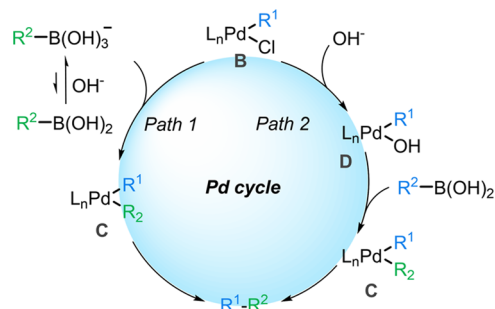
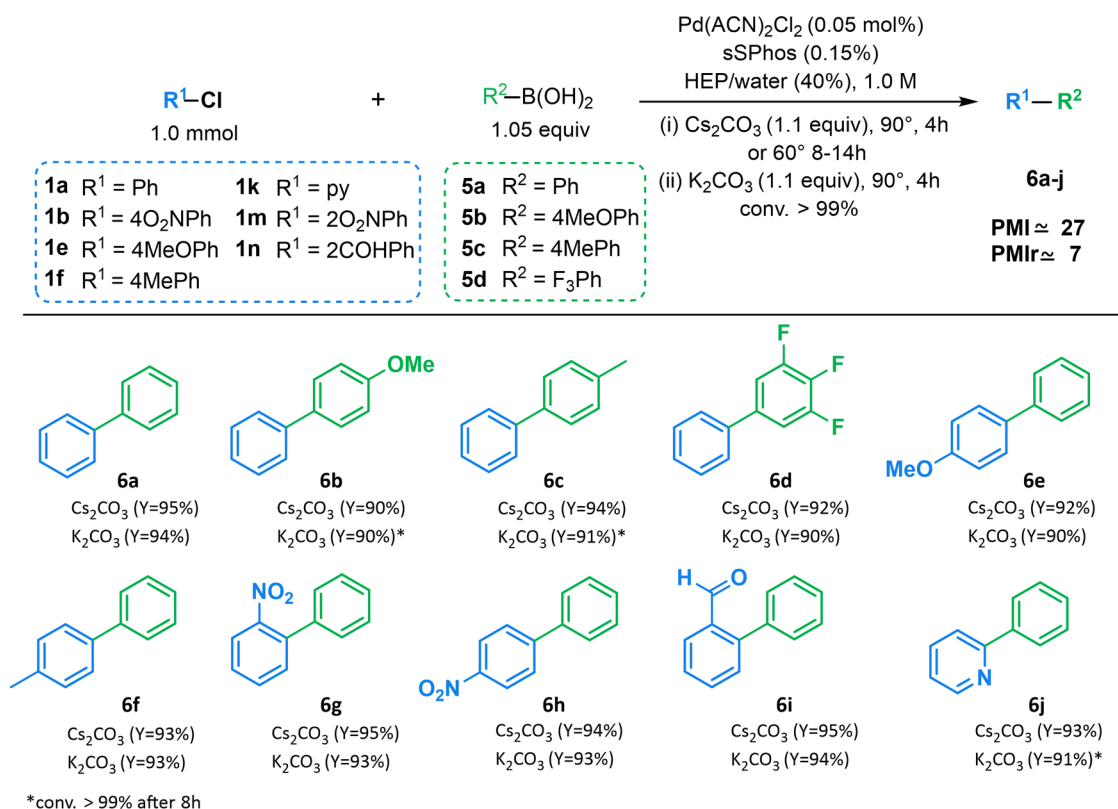


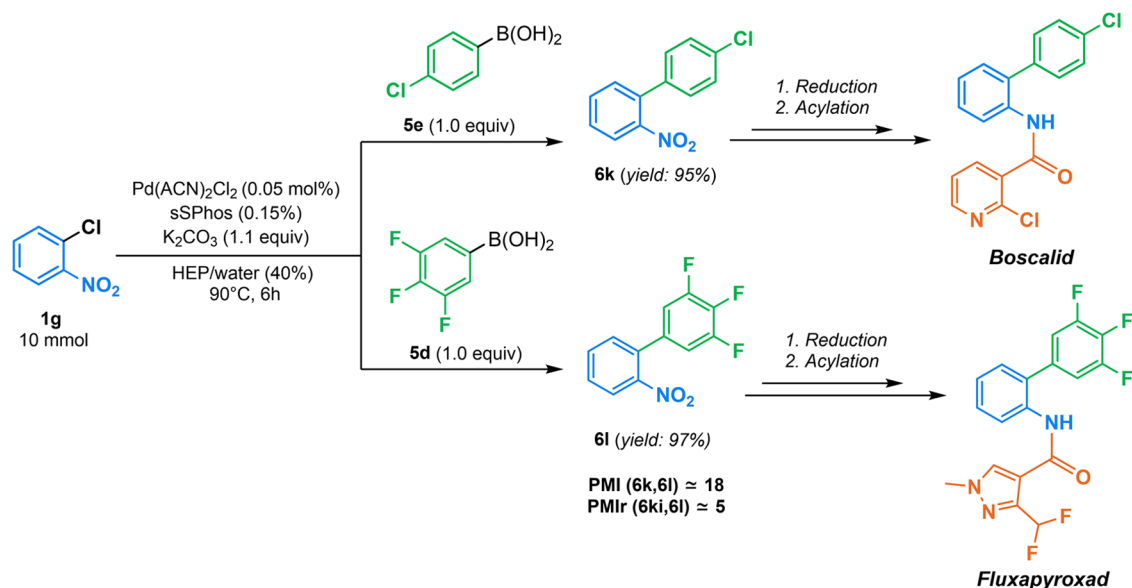
Figure 4. Transmetalation mechanism of the Suzuki–Miyaura cross-coupling reaction.

The simplicity of the workup procedure and the high purity of the product are crucial aspects of this reaction protocol. The use of readily available solvents like cyclohexane and *tert*-butyl acetate for extraction, followed by direct isolation through evaporation, streamlines the process, making it efficient and cost-effective. The high purity of the product eliminates the need for additional purification steps, saving time and resources. Such

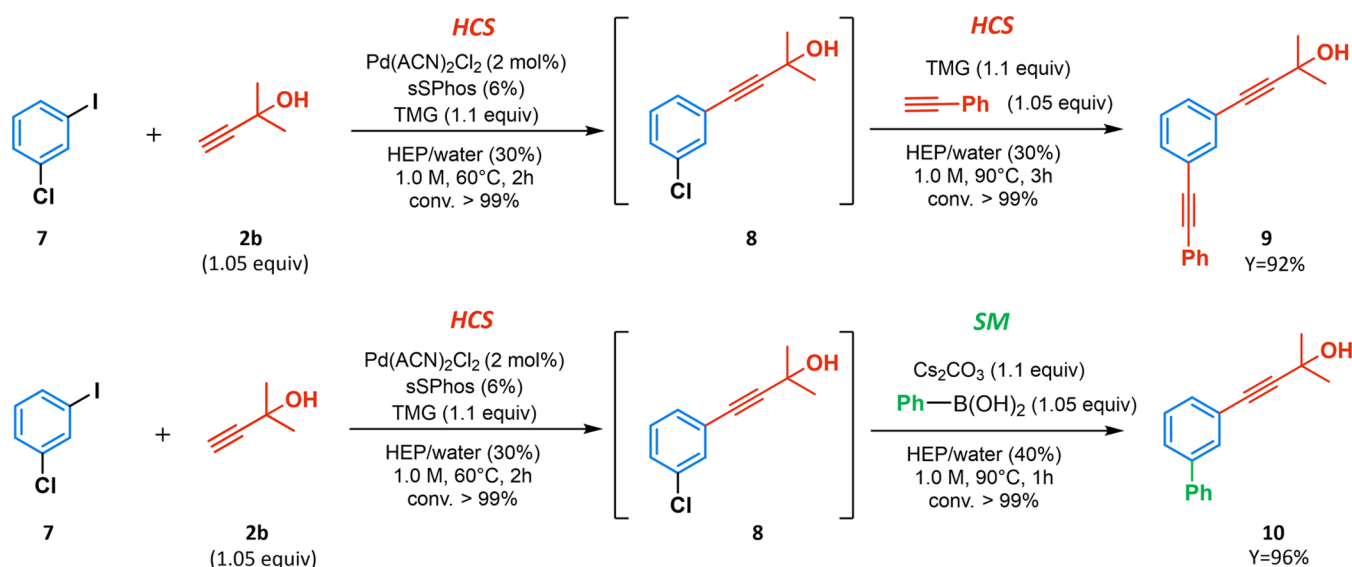
Scheme 4. SM Reaction Scope



Scheme 5. General Sequence for the Industrial Synthesis of Boscalid and Fluxapyroxad



Scheme 6. One-Pot Reactions: HCS–HCS and HCS–SM



optimized procedures are significant for the development of industrial synthesis, as they contribute to increased productivity and ensure the production of high-quality compounds.

This protocol allowed also to perform the reaction with differently substituted phenyl boronic acids, allowing a complete conversion in all cases.

To validate this methodology, the synthesis of two fungicides containing a biaryl-motive, namely, Boscalid and Fluxapyroxad, was explored (Scheme 5). The key step in the processes of their production requires an SM reaction and, due to the high volume of these products requested by the market,^{54,55} a low PMI together with the reduction in Pd loading. The reaction between **1g** and **5d/5e** in HEP/water was therefore studied and carried out following a procedure similar to the one described in Scheme 4, giving complete conversions to the desired product after 6 h.

The average PMI calculated for the reactions reported in Scheme 4 was around 27 and after recovery of solvent and the metal decreased to 7. Similarly, for the SM of Boscalid and

Fluxapyroxad, the PMI was around 18 and the PMIr was 5. These values are among the best results in the field. The reaction mass efficiency with the 5% excess of boronic acid is around 65–68%. However, the 5% excess of the boronic acid was used only because of the small scale. The synthesis of Boscalid and Fluxapyroxad intermediated was scaled up 10 times with an equimolar ratio between the reagents increasing the RME of >70%.

One-Pot HCS–HCS and HCS–SM Sequences. Thanks to the exceptional reaction efficiency and chemoselectivity of the described protocols, the one-pot sequences of HCS–HCS and HCS–SM reactions were performed (Scheme 6). To achieve our purpose, we selected 1-chloro-3-iodobenzene **7** as a model substrate and performed a one-pot HCS–HCS reaction in one case (Scheme 6a) and a one-pot HCS–SM in the other (Scheme 6b), exploiting the different reactivity of the iodide-leaving group with respect to chloride. The reaction between **7** and alkyne **2b** with 2 mol % of palladium catalyst and TMG as a base afforded the selectively product **8** with complete conversion in 2

h at 60 °C. At this point, without the need for any workup, the direct slow addition of phenylacetylene **2a** together with TMG at 90 °C allowed to achieve complete conversion to product **9**. In a similar way, adding in the second step, after the formation of product **8**, phenyl boronic acid **5a**, and Cs₂CO₃ at 90 °C, a one-pot HCS–SM cross-coupling reaction sequence afforded product **10** with 99% conversion and no need of further purification (see Section 6 of the Supporting Information for the detailed procedure).

CONCLUSIONS

The Heck–Cassar and Suzuki–Miyaura cross-coupling reactions on different aryl chlorides were carried out in the sustainable mixture HEP/water, giving excellent results in terms of yield, TON, RME, and PMI. The cross-coupling protocols can be adapted to specific substrate requirements. Reactions were performed using a solution, thermomorphic recycling, or direct low-loading reaction.

While HCS cross-coupling requires the use of Cs₂CO₃ as the base for reaction with low palladium loading, the SM can be performed also in the presence of K₂CO₃. The protocols proved to be suitable for activated and inactivated chlorides. The control of the stoichiometry in the Heck–Cassar copper-free protocol, and the SM as well as the high chemoselectivity allowed us to generate products with high yield and for the SM without any purification.

Sustainable purification processes are indeed critical for industrial applications due to their impacts on PMI in other words, waste reduction, environmental impact, energy efficiency, product quality, and competitiveness. The SM protocol allowed the acquisition of pure products with 0.05 mol % of catalyst loading with fast and selective reactions at 90 or 60 °C with longer reaction times. The applicability of this system was also demonstrated in the synthesis of agrochemical active ingredients such as Boscalid and Fluxapyroxad with excellent yields, proving the efficacy and the flexibility of the protocol with PMI and RME, respectively, around 19 and 72%.

The two reactions can be performed in sequence, taking advantage of the different reactivities of aryl halides, giving access to complex architectures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.3c04926>.

General procedures, product characterization, original data to generate tables, and DFT calculations are included (PDF)

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Author Contributions

†C.P. and T.F. contributed equally to the investigation. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. W.C. and T.F. conceptualized the study and reviewed and edited the manuscript.

Funding

Financial support was provided by the Alma Mater Studiorum – University of Bologna. C.P.’s Ph.D. was part of the MIUR-PON program “PhD 37 cycle grant FSE REACT-EU-A.A. 2021/2022”.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge Enrico Faggi S.p.A. for the supply of palladium catalysts. DFT calculations for this work were performed at CINECA, through the Italian Super Computing Resource Al-location – ISCR.

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