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Metal–ligand cooperation and synergistic palladium catalysis for the dual ligand system [2,2′-bipyridin]-6(1*H*)–one/PCy_3: milder conditions for the undirected C–H arylation of arenes†

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The use of $Pd(OAc)_2$ and a mixture of the cooperating ligand [2,2′-bipyridin]-6(1*H*)–one (bipy-6-OH) and PCy_3 in an optimal mol ratio of Pd/bipy-6-OH/PCy_3 = 1 : 0.5 : 1 leads to a more active system for the non-chelate-assisted direct arylation of simple arenes. The system operates at a temperature 30 °C lower than that for the Pd/bipy-6-OH system, and it is active for aryl chlorides as arylating partners. Mechanistic experiments support the operation of a bimetallic pathway *via* two connected catalytic cycles: a Pd/PCy_3 system responsible for the oxidative addition and reductive elimination steps and a Pd/bipy-6-OH system that enables C–H activation. Both cycles are connected by a transmetalation step. The phosphine ligand is not directly involved in the C–H activation, but compared to the monoligand system, the occurrence of the bimetallic route changes the nature of the key intermediate species in the C–H activation, favoring this turnover limiting step and the overall reaction rate.

Introduction

The direct use of arenes as coupling partners in metal-catalyzed C–C bond-forming reactions is a sustainable alternative to the conventional cross-coupling processes.[1] These reactions eliminate the need to use either the main group organometallic reactant or the organic halide (sulfonate)—or even both reagents, saving the previous reaction steps required for their preparation. The direct arylation of arenes is a straightforward example, where the organometallic reactant is substituted by an arene that is converted in a biaryl derivative with an aryl halide as a reaction partner.[2] However, strong reaction conditions are generally required because a C–H activation step is needed, and it involves the coordination of the arene to the metal and the cleavage of the sluggish C–H bond. This difficulty is more pronounced for non-chelate-assisted (undirected) functionalization of simple arenes,[3] where the interaction of the arene with the metal is not facilitated by the presence of a coordinating functional group, the directing group, that anchors the substrate and allows an easier approach of the C–H bond to the metal center. The introduction of directing groups has many advantages in terms of increased reactivity and selectivity.[4] However, the prefunctionalization of the substrate arene with these groups erodes the step economy and the sustainability of the whole reaction. Recent advances in the use of transient directing groups that can be installed and detached *in situ* can alleviate this drawback.[5] In any case, more active catalytic systems that functionalize simple arenes are needed to bring the undirected C–H functionalization closer to the mild conditions of the conventional cross couplings.[6]

The functionalization of simple arenes often relies on the use of metal–ligand cooperation to enable the C–H activation step.[7,8] Ligands containing a basic group that can participate in the concerted metalation deprotonation mechanism have proved useful: *N*-monoprotected amino acids (MPPA)[9] and pyridone derivatives, both mono-[10] and bidentate,[11] are the most important, and a few examples are presented in Scheme 1. Even with the use of some of these ligands, the palladium-catalyzed direct arylation of simple arenes requires long reaction times and temperatures above 120 °C,[12] except for some specific activated substrates, such as highly fluorinated arenes[13] or pyridine oxide,[14] which have been carried out at about 110 °C.

The use of a palladium precursor and two different ligands, a so-called dual ligand system, has been used in C–H functionalization reactions, leading to more efficient catalytic systems in some cases.[15] In addition to the cooperating ligand, *i.e.*, a MPAA or a pyridone derivative that enables C–H

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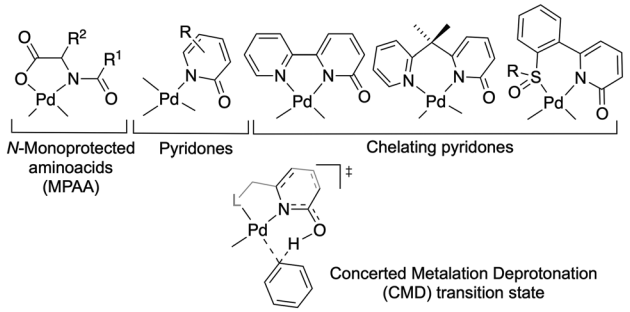
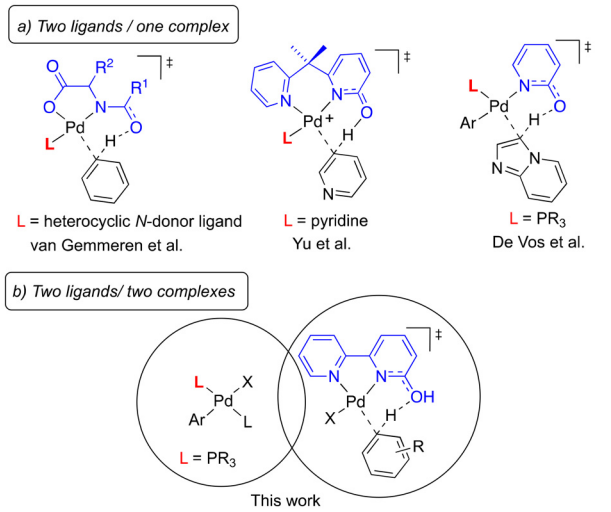


Scheme 1 Some examples of cooperating ligands in C–H activation.

activation, a second monodentate ligand is added to the mixture. In all the reported cases, the C–H activation step has been proposed to occur in an intermediate complex with *both* ligands coordinated to the metal (Scheme 2). Thus, van Gemmeren *et al.* used a combination of an *N*-monoprotected amino acid and an N-donor heterocyclic ligand, usually a pyridine (Scheme 2a), for more efficient C–H functionalization reactions of simple arenes,[16] such as olefination,[17] cyanation,[18] and alkynylation processes.[19] Yu *et al.* used a similar approach in directed C(sp^3)–H functionalization reactions,[20] and a mixture of a chelating pyridone and a monodentate pyridine was employed for the olefination of pyridine (Scheme 2a).[21] The olefination of arenes using a mixture of a MPAA and a thioether as ligands,[22] and the chalcogenation of arenes or the arylation of fluoroolefins with a MPAAs/monodentate pyridine, have also been reported.[23] De Vos's group developed the arylation of heterocycles using a mixture of a pyridone and a phosphine (Scheme 2a). As in all the above-mentioned examples, the authors proposed that both ligands are coordinated to the metal in the key steps of the reaction,



Scheme 2 Dual-ligand approach in C–H functionalization: (a) two ligands/one complex in the C–H activation step; (b) two ligands/two complexes working synergistically (this work).

and they provided experimental MS evidence of the occurrence of palladium species with both ligands attached to the metal.[24]

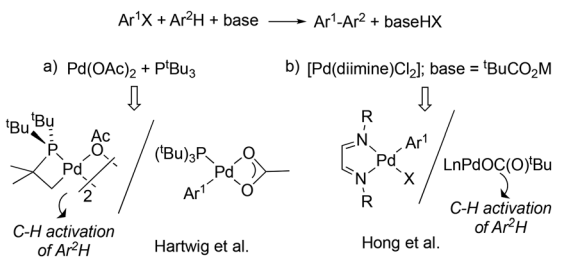
We report here a palladium catalytic system that uses a combination of a bipyridone and a phosphine ligand and shows higher activity than the cooperating monoligand system (bipyridone). At variance with the examples reported in the literature, the system requires a specific metal-to-ligand ratio that points to a synergistic bimetallic palladium route with two connected catalytic cycles. Each ligand is involved in one catalytic cycle, and they are not simultaneously coordinated to the metal (Scheme 2b).

In contrast to other heterometal combinations, synergistic Pd–Pd catalysis is rare, and only a few examples have been reported,[25] even fewer in the realm of C–H activation. Studying the direct arylation of pyridine oxide with the mixture of Pd(OAc)$_2$ and P^{t}Bu$_3$ as catalyst system, Hartwig *et al.* reported a bimetallic mechanism where the metalation of P^{t}Bu$_3$ led to a palladacycle responsible for the C–H activation step, whereas the oxidative addition of the aryl halide takes place in a palladium–phosphino complex (Scheme 3a).[26] Hong *et al.* observed a similar process using a diimine palladium complex, where the chelating nitrogen-donor ligand is not involved in the C–H activation step; this occurs in the absence of ligand *via* a CMD mechanism assisted by the carboxylate used as a base (Scheme 3b).[27] A bimetallic pathway has also been observed by Stahl *et al.* in the oxidative coupling of two arenes to give biaryl derivatives.[28] The direct arylation reactions in Scheme 3 still required high temperatures and long reaction times. The combination of a cooperating chelating bypiridone and a phosphine shown here affords, by optimization of each ligand role, a more active catalyst system that allows a shift to milder reaction conditions.

Results and discussion

Reaction optimization and arylation examples

The direct arylation of toluene with aryl iodides can be carried out using a Pd-catalyst with [2,2′-bipyridin]-6(1*H*)–one (bipy-6-OH) as the only ligand at 130 °C, as has been shown previously.[11a,29] The effect of the addition of a phosphine ligand was tested using the coupling between toluene and



Scheme 3 Catalysts for the direct arylation of arenes that operate by a bimetallic mechanism.

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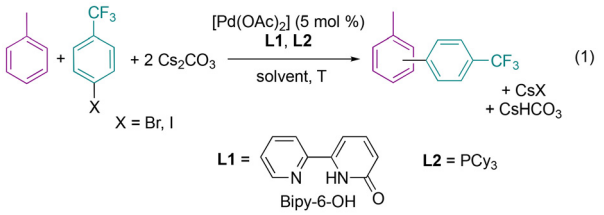
p-$CF_3C_6H_4X$ (an aryl that allows the easy monitoring of the reaction by ^{19}F NMR) as a model reaction (eqn (1)). With toluene as a reactant and solvent at 130 °C and using bipy-6-OH as the only ligand, the biaryl derivative is formed in 20% yield after 6 h (Table 1, entry 1; 91% after 24 h, see the ESI†). The use of a combination of the bipyridone ligand and tricyclohexylphosphine has a beneficial effect on the reaction, and the mixture of $Pd(OAc)_2$ (5 mol%)/bipy-6-OH (2.5 mol%)/PCy_3 (5 mol%) accelerated the reaction, which was complete in 6 h (90% yield *vs.* 22% in the absence of PCy_3, Table 1, entries 1 and 2). This effect is also observed for the corresponding and less expensive bromoaryl, and a respectable 59% of the coupling product was obtained after 6 h, *vs.* 16% in absence of PCy_3 (entries 3 and 4, Table 1).

Other phosphines such as PPh_3 and P^tBu_3 were also tested under these conditions, as well as other Pd precursors, but PCy_3 and $Pd(OAc)_2$ gave the best results (see Table S1, ESI†). The use of a cosolvent such as DMA or pinacolone accelerates this type of reaction, and this has been shown and studied before.[29]

Thus, the use of a toluene/DMA mixture allowed the lowering of temperature to 100 °C and the reaction to complete in 3 h (entry 6, Table 1). Excellent yields were obtained at 90 °C after 24 h, (96% yield), but the conversion is too low at 80 °C (entries 7 and 8, Table 1). A lower excess of toluene (mol ratio toluene/ArX = 10 : 1) led to a strong decrease in the yield (29% after 24 h). The rate of the reaction and yield are not affected by the way the precatalyst mixture is prepared. The reactions in Table 1 were carried out by mixing $Pd(OAc)_2$ and both ligands in the reaction flask. Under the same conditions, the previous independent mixtures (in separate flasks of $Pd(OAc)_2/PCy_3$ on the one hand and $Pd(OAc)_2$/bipy-6-OH on the other hand), before addition to the solution of the reactants, gave the same results shown in entry 6, Table 1.

Table 1 Arylation of toluene with *p*-$CF_3C_6H_4X$ according to eqn (1) using different reaction conditions[a]



(1)

Entry	L1[b] (mol %)	L2[b] (mol %)	X	Solvent	*T* (°C)	Crude yield, %, (Conv., %), 6 h[c]
1[d]	5	—	I	Toluene	130	20 (22)
2	2.5	5	I	Toluene	130	90 (100)
3	5	—	Br	Toluene	130	16 (16)
4	2.5	5	Br	Toluene	130	59 (65)
5	2.5	5	Br	Toluene	100	25 (28)
6	2.5	5	Br	Toluene/DMA[e]	100	90 (94)[f]
7	2.5	5	Br	Toluene/DMA[e]	90	42 (44)[g]
8	2.5	5	Br	Toluene/DMA[e]	80	15 (15)[h]

[a] Reaction conditions: *p*-$CF_3C_6H_4X$ (0.34 mmol), Cs_2CO_3 (0.68 mmol), total volume 3 mL. [b] **L1** = bipy-6-OH; **L2** = PCy_3. [c] Crude yields determined by ^{19}F NMR of the reaction mixture. The reduction of the arylbromide (ArH) and the homocoupling (Ar–Ar) are the observed byproducts. [d] Data from the literature (ref. 29). [e] 1/1 volume ratio (mol ratio toluene/ArX = 40 : 1). [f] Reaction time 3 h. [g] 96% yield after 24 h. [h] 33% yield after 24 h.

Under the optimum conditions of solvent and temperature (dry DMA as co-solvent and 100 °C, eqn (2)), other ligands and ligand ratios were tested, and the results are presented in Table 2. The absence of PCy_3 or bipy-6-OH results in no C–C cross-coupling product, and aryl bromide is mainly converted into the dehalogenated ArH derivative, so both ligands are necessary under those conditions (entries 1–3, Table 2). The C–H functionalization was not observed for analogous ligands to bipy-6-OH that cannot be involved in metal–ligand cooperation because of the lack of a cooperating pyridone moiety (*i.e.* bipy) or because, upon coordination, the pyridone oxygen is far from the metal (*i.e.* bipy-4-OH, eqn (2)) (entries 4 and 5, Table 2).

Modifications in the bipy scaffold resulted in a loss of activity (entry 6, Table 2). MPAA-type ligands and the monodentate 2-pyridone were also tried, but they gave no coupling product (entries 7 and 8, Table 2). Different phosphines were tested: PPh_3 and P^tBu_3 led to moderate or low yields; however, XPhos produced similar results to PCy_3 but in longer reaction times (entries 9–11, Table 2). Thus, bulky and electron-donating phosphines are adequate for this dual system; the inability of P^tBu_3 to accelerate the reaction might be related to its known ability to form P–C palladacycles, which are not active under the reaction conditions used here.[26] Tricyclohexylphosphonium tetrafluoroborate, less sensitive than PCy_3 and easily deprotonated under the reaction conditions, also gave excellent yields (entry 12, Table 2). Different ligand concentrations were also tested: a 5 mol% of bipy-6-OH has a small effect on the reaction rate and yield; however, increasing or decreasing the molar ratio of PCy_3 results in lower rates (entries 13–16, Table 2). In these cases, the reactions need longer times for completion, but good yields (80–90%) were obtained after 24 h.

We decided to test the reaction using preformed palladium complexes with coordinated PCy_3. Thus, the mixture $Pd(OAc)_2$ + bipy-6-OH was combined with the corresponding palladium phosphino complex. These complexes could be formed under catalytic conditions and even be involved as reaction intermediates. The Pd(0) derivative [$Pd(PCy_3)$], as well as the Pd(II) complex **1**, led to excellent yields of the arylated toluene but in longer reaction times than the analogous experiment using the free phosphine (6 h, entries 17 and 18 *vs.* 3 h for entry 1, Table 2). The dimeric palladium complex **2** was also tested. In this case, only one PCy_3 is coordinated to each palladium, and the effective amount of phosphine added is half that in the experiments above (entry 19, Table 2). Longer reaction times (24 h) are needed to get full conversion and good yield (87%). A fine tuning of the amount of phosphine present along with the preformed complex **2** to a final effective ratio Pd/bipy-6-OH/PCy_3 = 1 : 0.5 : 0.75, as shown in entry 20, Table 2, restored the rate and yield observed under the best conditions of entry 1, Table 2.

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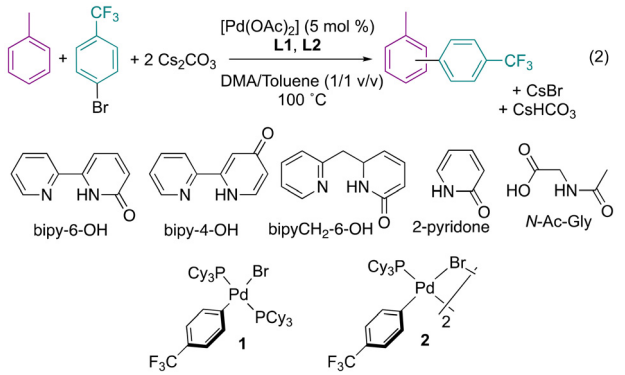
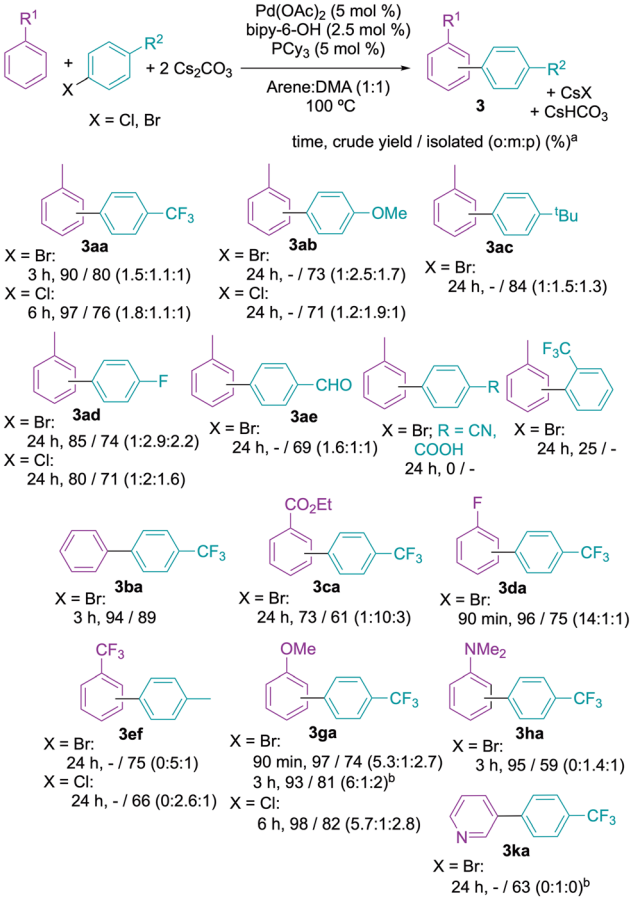
Table 2 Catalyst screening for the arylation of toluene with p-$CF_3C_6H_4Br$ according to eqn (2) [a]



Entry	$Pd(OAc)_2$ (mol %)	**L1** (mol %)	**L2** (mol %)	Crude yield, %, (Conv., %), 6 h [b]
1	**5**	**Bipy-6-OH (2.5)**	**PCy_3 (5)**	**90 (94)** [c]
2	5	Bipy-6-OH (5)	—	0 (100)
3	5	—	PCy_3 (10)	0 (100)
4	5	Bipy (2.5)	PCy_3 (5)	0 (22)
5	5	Bipy-4-OH (2.5)	PCy_3 (5)	0 (0)
6	5	$BipyCH_2$-6-OH (2.5)	PCy_3 (5)	3 (10)
7	5	*N*-Ac-Gly (2.5)	PCy_3 (5)	0 (5)
8	5	2-Pyridone (2.5)	PCy_3 (5)	3 (12)
9	5	Bipy-6-OH (2.5)	PPh_3 (5)	38 (45)
10	5	Bipy-6-OH (2.5)	P^tBu_3 (5)	4 (9)
11	5	Bipy-6-OH (2.5)	XPhos (5)	80 (85)
12	**5**	**Bipy-6-OH (2.5)**	**$(PCy_3H)BF_4$ (5)**	**93 (97)** [c]
13	5	Bipy-6-OH (5)	PCy_3 (5)	78 (84) [c]
14	5	Bipy-6-OH (5)	PCy_3 (10)	31 (40) [d]
15	5	Bipy-6-OH (2.5)	PCy_3 (7.5)	46 (54) [d]
16	5	Bipy-6-OH (2.5)	PCy_3 (2.5)	35 (38) [d]
17	2.5	Bipy-6-OH (2.5)	$[Pd(PCy_3)_2]$ (2.5)	92 (95)
18	2.5	Bipy-6-OH (2.5)	**1** (2.5)	72 (75)
19	2.5	Bipy-6-OH (2.5)	**2** (1.25)	27 (35) [d]
20	2.5	Bipy-6-OH (2.5)	**2** (1.25) $(PCy_3H)BF_4$ (1.25)	98 (98) [c]

[a] Reaction conditions: p-$CF_3C_6H_4Br$ (0.34 mmol), Cs_2CO_3 (0.68 mmol), dry toluene (1.5 mL), dry DMA (1.5 mL), 100 °C. [b] Crude yields determined by ^{19}F NMR of the reaction mixture. The reduction of the arylbromide (ArH) and the homocoupling (Ar–Ar) are the observed byproducts. [c] After 3 h. [d] 80–90% yield after 24 h (see ESI†).



Scheme 4 Direct arylation of different arenes with the $Pd(OAc)_2$/bipy-6-OH/PCy_3 catalyst system.

The direct arylation of toluene using this catalyst system can be extended to other aryl bromides as coupling partners (Scheme 4). Electron-donating or electron-withdrawing functional groups can be present in the aryl halide (**3aa–3ae**, Scheme 4). Longer reaction times were used to ensure the complete conversion of the reactants when the reaction could not be followed by NMR of the crude mixture. The arylation of toluene is not regioselective, and a mixture of three isomers (*ortho*, *meta* and *para*) was obtained in all cases, with no strong preference for any position after considering the statistical factor. p-Bromobenzonitrile and p-bromobenzoic acid were also tested, but they did not lead to the cross-coupling product. Although electronically similar to other aryl bromides tested, the coordination ability of the substituent, specially the carboxylate moiety expected under catalytic conditions, may influence the reaction outcome. The *ortho* substitution in aryl bromide disfavored the reaction, and only 25% of a mixture of isomeric coupling products was obtained when o-$CF_3C_6H_4Br$ was reacted with toluene.

Interestingly, the reaction also works for aryl chlorides, which bear both electron-donating and electron-withdrawing groups (Scheme 4). This is remarkable since aryl chlorides are rarely active in direct arylation reactions of simple arenes with no directing groups.[12a,30] As a result, the reaction of p-bromochlorobenzene with toluene as arene gave a mixture of mono- and ditolyl products.

Different arenes were also tested. Ethyl benzoate, trifluorotoluene, and *N*,*N*-dimethylaniline gave moderate to good yields of the biaryl, the *meta* isomer being the major product (**3ca**, **3ef**, **3ha**, Scheme 4). The reaction is completely *meta* regioselective for pyridine (**3ka**). On the other hand, when anisole and fluorobenzene were reacted, the *ortho* biaryl product was preferred (**3da**, **3ga**). There is no clear correlation between the electronic properties of the arene and the regioselectivity of the reaction. The preference of pyridine for arylation in the *meta* position has been observed before,[11a,31] as well as the

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ortho substitution for fluorinated arenes.[32] In a few cases, good results were obtained using just 10 equivalents of the arene (anisole, pyridine).

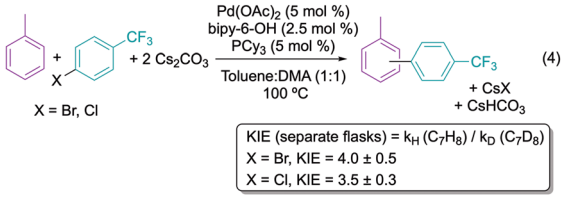
The C–H arylation did not take place with aniline as the arene, and the competitive C–N coupling product was obtained as the only product (amination reaction), in sharp contrast with the catalytic system with bipy-6-OH as the only ligand, which is capable of selectively producing *ortho*-arylated unprotected anilines.[33]

Mechanistic experiments

In order to shed light into the reaction mechanism, several experiments were carried out. First of all, we studied the species formed from the mixture of $Pd(OAc)_2$ and PCy_3. We observed the coordination of two phosphines to palladium acetate resulting in the complex $[Pd(OAc)_2(PCy_3)_2]$ as well as $[Pd(PCy_3)_2]$ with the concomitant oxidation of one phosphine (eqn (3) and Fig. S1, ESI†).[34] Therefore, Pd(0) species can be easily formed from the precatalytic mixture, consuming some of the phosphine added, which acts as a reducing agent. This is consistent with the preformed complex $[Pd(PCy_3)_2]$ also being efficient in the catalytic reaction (entry 17, Table 2).

$$Pd(OAc)_2 + 2\,PCy_3 \xrightarrow[25\,^{\circ}C]{\text{Toluene-d}_8} [Pd(OAc)_2(PCy_3)_2] + OPCy_3 + [Pd(PCy_3)_2] \quad (3)$$

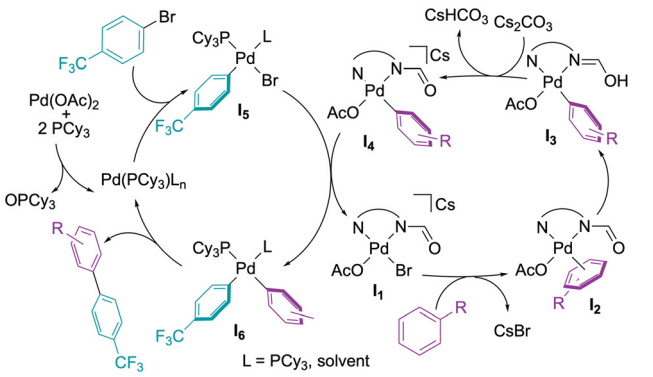
Kinetic experiments were carried out using the reaction between toluene and p-CF_3-C_6H_4Br as a model (eqn (4)). Using the variable time normalization analysis (VTNA) reported by Burés,[35] the results showed a first-order dependence on palladium in a concentration range of 2.8–5.6 mM (Fig. 1). The use of much lower catalyst concentrations led to a very slow reaction, so the hypothetical change in catalyst order from one to two, sometimes observed in some bimetallic processes at very low catalyst concentrations,[27,28] was not found. A zero-order dependence on the concentration of the aryl bromide or aryl chloride was observed (see ESI, section 1.5.2†). The kinetic isotope effect was determined, and large values were found for both p-CF_3-C_6H_4Br (KIE = 4.0 ± 0.5) and p-CF_3-C_6H_4Cl (KIE = 3.5 ± 0.3) when two separate experiments were carried out using toluene and toluene-d_8, consistent with C–H activation being the turnover limiting step (eqn (4) and section 1.5.1, ESI†).



(4)

The mechanistic scheme for this dual system has to explain the advantage of both ligands and account for the fact that the optimal metal-to-ligand mol ratio is Pd/bipy-6-OH/PCy_3 = 1 : 0.5 : 1. Moreover, considering the reduction to Pd(0) mentioned above, the actual phosphine amount present under catalytic conditions can be smaller. Also, the kinetic experiments show that the C–H activation step is turnover limiting and that the C–H cleavage is assisted by the cooperating bipy-6-O (*cf.* entries 1 and 3–5, Table 2). The dual system is active for aryl chlorides, whereas the monoligand (bipy-6-OH) system is not, even at the higher temperature used for the reaction (130 °C). This points to the involvement of PCy_3 in the oxidative addition step.

The plausible mechanistic pathway is represented in Scheme 5. It shows a bimetallic process through two different palladium complexes acting in a synergistic way: on one cycle, PCy_3 is coordinated to half of the palladium centers and on



Scheme 5 Reaction pathway for the Pd/bipy-6-OH/PCy_3 dual ligand system.

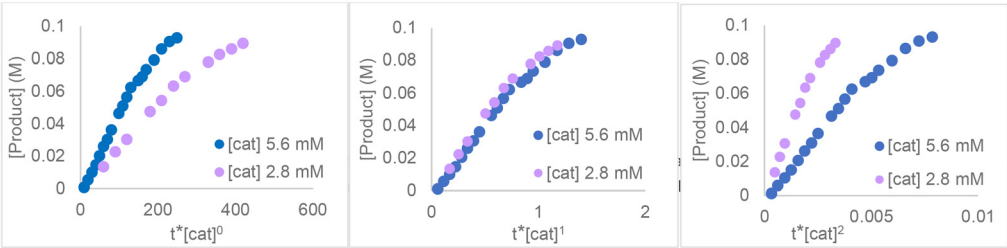


Fig. 1 Plots derived from the variable time normalization analysis (VTNA). Overlay of plots gives the order in the catalyst (power value in abscissa axis). [Cat] = $Pd(OAc)_2$/0.5 bipy-6-OH/PCy_3; the given concentration corresponds to the Pd precursor. See the ESI for details (section 1.5.2).†

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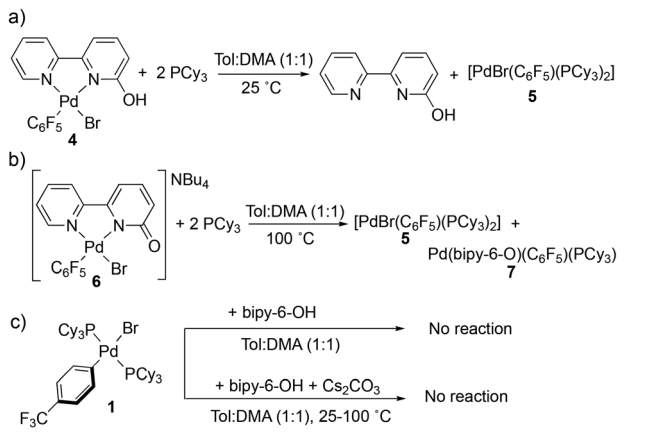
the other, a bipy-6-OH-containing complex. The oxidative addition of aryl bromide occurs on the phosphine complex. Meanwhile, the coordination and C–H activation of toluene takes place in the bipy-6-OH complex. After deprotonation of the ligand, which easily occurs in the presence of Cs_2CO_3, a transmetalation step between both metal centers places the organic groups coordinated to a phosphine complex that would undergo the reductive elimination step, leading to the final product and the Pd(0) complex that reenters the catalytic cycle.

We performed some independent stoichiometric experiments in order to probe this proposal. Ligand exchange experiments were carried out first, as shown in Scheme 6. We used isolable, well-defined model derivatives that show analogies to the complexes formed after the C–H activation process (complexes **4** and **6**) or as a result of the oxidative addition of the aryl halide (complex **1**). Complex **4**, as a model complex with a coordinated neutral ligand bipy-6-OH, was reacted with 2 equivalents of PCy_3 in the solvent mixture used in the catalytic experiments (toluene/DMA, 1 : 1 v/v). A complex with two coordinated PCy_3 (**5**) and free bipy-6-OH was formed after a few minutes at room temperature (Scheme 6a and Fig. S3–S7, ESI†).

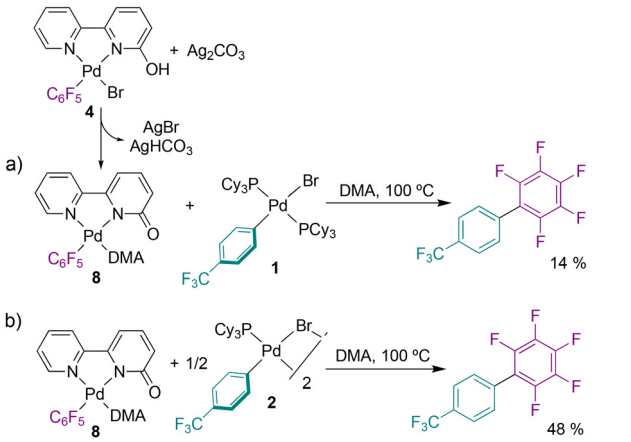
The same experiment was carried out using the preformed complex **6**, where the coordinating ligand is deprotonated and monoanionic (bipy-6-O). It has been shown previously that the coordination ability of the ligand is better when it is deprotonated.[11a] One hour after the addition of phosphine at room temperature, the formation of a new complex was observed, which we tentatively assigned to complex **7** (Scheme 6b). The reaction evolved to the formation of complex **5** after heating the mixture at 100 °C for 30 min (Fig. S8–S10, ESI†). This shows that the substitution of the bipy-6-O by PCy_3 is more difficult than in the case of bipy-6-OH; however, it is occurring under the catalytic conditions. The reverse reaction, the substitution of a coordinated PCy_3 by the bipyridone ligand, was also tested. Bipy-6-OH was added to complex **1** in toluene/DMA (1 : 1), and no changes in the reaction mixture were observed. The addition of cesium carbonate to deprotonate the ligand led to the same results both at room temperature and at 100 °C (Scheme 6c and Fig. S11, ESI†). These experiments clearly show that the coordination ability of the ligands present in the catalysis follows the trend PCy_3 > bipy-6-O > bipy-6-OH. Thus, an excess of phosphine will have a detrimental effect in the reaction by coordinating to palladium preferentially and decreasing the concentration of the bipy-6-O complexes, responsible for the turnover limiting step. This is observed in the catalytic experiments (*cf.* entries 1, 15 and 13, 14 in Table 2). When an excess of bipy-6-OH is added, the relative concentration of both types of complexes is not altered significantly, and the effect on the reaction rate is not important (*cf.* entries 1 and 13, Table 2).

Both synergistic catalytic cycles in Scheme 5 are connected by a transmetalation step, and the feasibility of the aryl exchange between palladium centers was tested by using two model complexes for both interconnecting cycles. The bipy-6-O complex **8** was prepared *in situ* by bromide abstraction and deprotonation of **4** using silver carbonate. After filtration of the insoluble silver byproducts, complex **1** was added to the solution of **8** and heated at 100 °C. The coupling product C_6F_5-C_6H_4-*p*-CF_3 was clearly observed by ^{19}F NMR (14%, referring to the total amount of pentafluorophenyl species) along with $[PdBr(C_6F_5)(PCy_3)_2]$ (**5**) as a result of the substitution of the bipy-6-O ligand by the free phosphine generated in the decomposition reaction (Scheme 7a and Fig. S12 in the ESI†).

A fraction of the added phosphine in the catalysis is consumed in the reduction of $Pd(OAc)_2$ to Pd(0), as shown in the experiment in eqn (3); because of this, the actual amount of PCy_3 under catalytic conditions would lead to a phosphine complex with a ratio of PCy_3/Pd < 2. Therefore, the palladium complex with only one coordinated PCy_3 (**2**) was tested as the transmetalation partner of **8**. The experiment was done in the same way as mentioned above, and complex **2** was added to the *in situ* generated **8**, then the mixture was heated at 100 °C. After 3 h, 48% of the coupling product was formed (Scheme 7b and Fig. S13, ESI†). The addition of cesium carbonate (also



Scheme 6 Ligand exchange experiments.



Scheme 7 Transmetalation experiments.

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present in the catalytic reactions) has no influence in the amount of C_6F_5-C_6H_4-*p*-CF_3 obtained (45%). These experiments show that a transmetalation step between a bipy-6-O palladium complex and a phosphine-containing Pd-derivative is possible, and it is a plausible elementary step in the catalytic cycle. An excess of phosphine disfavors this process, which is more efficient for monophosphine derivative **2**, and this contributes to the slow rate observed for the catalytic reactions upon the addition of higher amounts of phosphine (*cf.* entries 1, 15 and 13, 14 in Table 2). The inverse dependence of the transmetalation rate on the concentration of the ligand has been studied for other metal combinations such as Au/Pd or Sn/Pd in the context of Stille couplings.[36–38]

The nature of the intermediates in the C–H activation

When this dual bipy-6-OH/PCy_3 catalytic system is compared to that enabled by the cooperating bipy-6-OH only, there are some differences that are worth mentioning. The bipy-6-OH-only system shows no significant differences in reactivity for arenes with electron-withdrawing or electron-donating groups, and the regioselectivity observed favors the *meta* isomer in all cases.[29] In contrast, the dual system showed an effect of the electronic properties of the arene in the reaction rate as determined by the monitoring of the initial rate of the direct arylation of toluene, ethyl benzoate and anisole with *p*-CF_3-C_6H_4Br. The k_{obs} for each experiment are presented in Table 3; they show that the reaction is faster for arenes with electron-donating groups (anisole) than for arenes with electron-withdrawing groups (ethyl benzoate). In the former case, the *ortho*/*para* selectivity is favored. These data point to more electrophilic palladium intermediates involved in the C–H activation step for the dual system.

When bipy-6-OH is used as the only ligand, the oxidative addition of the aryl halide leads to aryl palladium intermediates such as **c4–c5** in Fig. 2, where the C–H activation takes place as has been tested experimentally in model complexes.[11a,29] In the dual system, this elementary step would happen in a palladium complex with the bipy-6-O coordinated, which is responsible for the C–H bond activation, and for example, an acetate (**c2**, Fig. 2a) instead of the more electron-rich complex **c5** with an aryl group that is involved in the monoligand catalytic cycle (Fig. 2b). DFT calculations of the C–H activation step on a simple model were carried out using the M06 functional and including solvation in the optimizations through the SMD implicit solvent method (DMA) at the experimental temperature (100 °C, see computational details in the ESI†). A total $\Delta\Delta G^{\ddagger}$ of 26.9 kcal mol^{-1}

Table 3 Rate constants for the arylation of arenes with different electronic properties with *p*-CF_3-C_6H_4Br [a]

Arene	Product	k_{obs} (M min^{-1})
Anisole	*p*-CF_3-C_6H_4-C_6H_4(OMe)	$3.6 \pm 0.3 \times 10^{-4}$
Toluene	*p*-CF_3-C_6H_4-C_6H_4Me	$2.7 \pm 0.1 \times 10^{-4}$
Ethyl benzoate	*p*-CF_3-C_6H_4-$C_6H_4CO_2Et$	$7.3 \pm 0.7 \times 10^{-5}$

[a] Reaction conditions shown in entry 1, Table 2.

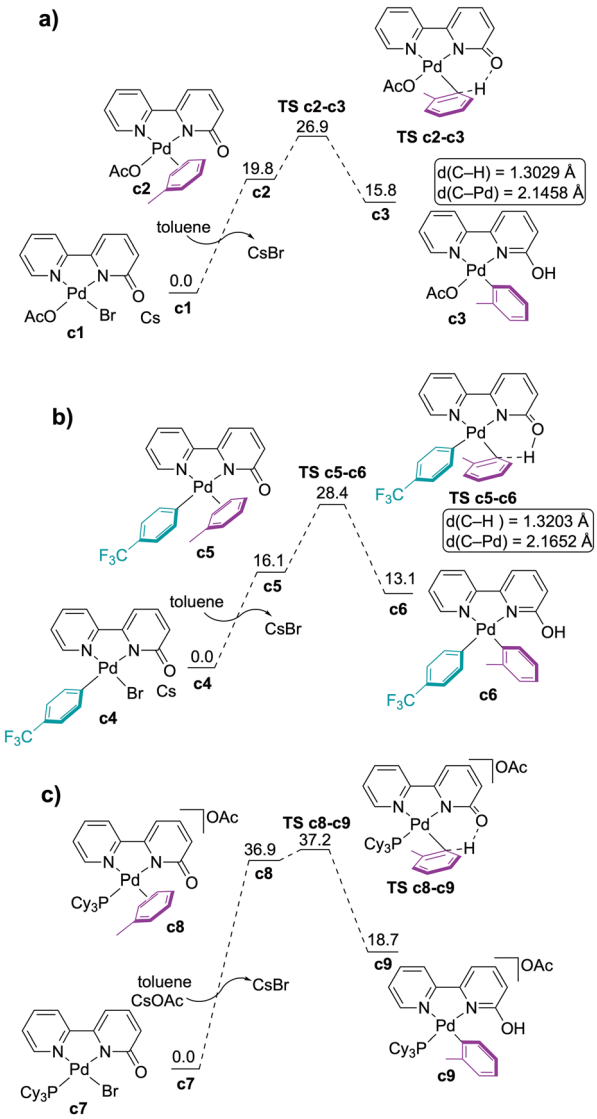

Fig. 2 DFT profiles for the C–H activation in: (a) the dual bipy-6-OH/PCy_3 catalytic system; (b) the catalytic system that uses bipy-6-OH only; (c) a complex with both bipy-6-O and phosphine ligands coordinated to palladium. Energies in kcal mol^{-1}.

was found *via* **c2** (Fig. 2a). The calculated $\Delta\Delta G^{\ddagger}$ for the C–H activation *via* intermediate **c5** was found to be higher (28.4 kcal mol^{-1}, Fig. 2b). This accounts for the difference in activity of both systems.[39] The intermediate complex **c2** with a coordinated acetate is the most plausible intermediate *vs.* a bromide-ligated derivative [Pd(bipy-6-O)Br(toluene)] since, given the higher solubility of cesium acetate *vs.* cesium bromide in the solvent used, the equilibrium **c1–c2** is expected to be less disfavored when CsBr is formed. A hypothetical C–H activation in a cationic complex with both bipy-6-O and PCy_3 coordinated to palladium was also calculated, but the total $\Delta\Delta G^{\ddagger}$ found rises to 37.2 kcal mol^{-1}, which makes the involvement of such species unlikely (Fig. 2c).

Comparing both transition states in Fig. 2a and b, it can be seen that the C–H and C–Pd bond distances for **TS c2–c3** are

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slightly shorter than those in **TS c4–c5**, indicating that the mechanism for C–H activation has an *electrophilic* CMD character (*e*CMD, also known as BIES, base-assisted internal electrophilic substitution),[40,41] where the transition state is characterized by more advanced metal–carbon bonding and less C–H bond cleavage, as discussed by Wang and Carrow.[41] This is in agreement with the higher rate observed for electron-rich arenes.

Thus, because the oxidative addition step is happening in a phosphine complex and not in the bipy-6-O complex (Scheme 5), the nature of the intermediates in the turnover limiting C–H activation step is modified, lowering the overall barrier of the reaction and making the whole system more active.

Conclusions

The mixture of a cooperating bipyridone ligand, capable of assisting the C–H activation step (bipy-6-OH), and a phosphine (PCy_3) in combination with $Pd(OAc)_2$ in a suitable mol ratio forms a very active catalyst for the challenging direct arylation of simple arenes. The dual ligand combination is more active than the monoligand Pd/bipy-6-OH catalyst, and the reactions can be carried out under milder conditions (short reaction times and a decrease in temperature by 30 °C). Besides the common aryl iodides or bromides, the system is also capable of arylating simple arenes using aryl chlorides. This expands the utility of this reaction to a wider range of reactants.

The increase in activity of the dual system occurs by a novel combined metal–ligand cooperation (MLC) for C–H activation and a synergistic Pd–Pd mechanism. Two catalytic cycles operate: (a) a Pd/PCy_3 system where the ArX oxidative addition and the biaryl reductive elimination take place, and (b) a Pd/bipy-6-OH system where the C–H activation occurs *via* MLC with no involvement of the phosphine ligand. Both cycles are connected by transmetalation of an aryl group from one Pd to another Pd center (Scheme 5). The presence of the phosphino palladium species acts in fact as a Pd-aryl reservoir and, as a result, a change in the nature of the species responsible for the C–H activation of the arene occurs. This species bears a more electrophilic metal center and leads to a lower barrier for C–H activation, the turnover limiting step, producing an overall acceleration effect. Thus, the beneficial effect of the additional ligand is not a direct involvement in the turnover limiting step of the reaction *via* coordination to the key intermediate, but the opening of a different pathway which indirectly influences the nature of the intermediate where the C–H cleavage takes place.

Experimental

General considerations

^1H, $^{13}C\{^1H\}$, $^{31}P\{^1H\}$ and ^{19}F NMR spectra were recorded on Agilent MR-500, Agilent MR-400 or Bruker AV-400 spectrometers at the LTI/UVa. Chemical shifts (in δ units, ppm) were referenced to $SiMe_4$ (^1H and ^{13}C), $CFCl_3$ (^{19}F) and H_3PO_4 (85%, ^{31}P). The spectral data were recorded at 298 K unless otherwise noted. HRMS analyses were carried out on a Bruker Maxis Impact mass spectrometer at the LTI/UVa. Elemental analyses were carried out in a Thermo Scientific FLASH 2000 microanalyzer (at the Parque Científico Tecnológico/UBU).

Solvents were distilled from appropriate drying agents under nitrogen and stored over 3 Å or 4 Å molecular sieves (toluene) or used directly from storage with the drying agent (anisole, ethyl benzoate, α,α,α-trifluorotoluene, fluorobenzene and *N*,*N*-dimethylaniline). DMA, pinacolone, toluene-d_8 and pyridine were purchased as anhydrous and stored under nitrogen over 3 Å or 4 Å molecular sieves. In the case of DMA, used as co-solvent in the catalytic reactions, the drying procedure was as follows: it was stored over molecular sieves for a week and then transferred to a flask with freshly activated molecular sieves and kept for another week prior to use.

The haloaryl derivatives, cesium carbonate, palladium acetate, PR_3 (R = Cy, Ph, ^{t}Bu), $(PCy_3H)BF_4$, X-Phos, 2,2′-bipyridine, *N*-acetylglycine, and 2-pyridone are commercially available and were purchased and used as received unless otherwise noted. [2,2′-Bipyridin]-6(1*H*)-one (bipy-6-OH),[11a] [2,2′-bipyridin]-4(1*H*)-one (bipy-4-OH),[11a] $[Pd(bipy\text{-}6\text{-}OH)Br(C_6F_5)]$ (**4**),[11a] $(NBu_4)[Pd(bipy\text{-}6\text{-}O)Br(C_6F_5)]$ (**6**),[11a] $[Pd(C_6H_4\text{-}p\text{-}CF_3)I(TMEDA)]$,[42] and $[Pd_2dba_3].CHCl_3$,[43] were prepared according to the procedures in the literature.

Catalytic reactions

General procedure for the direct arylation of arenes. $Pd(OAc)_2$ (3.8 mg, 0.017 mmol), bipy-6-OH (1.5 mg, 0.0085 mmol) and cesium carbonate (222 mg, 0.68 mmol) were introduced in a Schlenk flask under a nitrogen atmosphere. The corresponding aryl halide (0.34 mmol), PCy_3 (4.7 mg, 0.017 mmol) dissolved in the corresponding arene (1.5 mL) and DMA (1.5 mL) were added to the flask. The mixture was stirred at 100 °C and checked by ^{19}F NMR at the indicated time. When total conversion was observed, the solvent was evaporated *in vacuo*, and the organic product was extracted with a mixture of *n*-hexane (8 mL) and ethyl acetate (2 mL). The extract was filtered through kieselgur and evaporated to dryness. The products were checked by NMR and GC-MS. Crude yields and isomer ratios were determined by ^{19}F NMR of the crude mixture or ^1H NMR for samples without fluorine.

Synthesis of palladium complexes

$[PdBr(C_6H_4\text{-}p\text{-}CF_3)(PCy_3)_2]$ (1). $[PdBr(C_6H_4\text{-}p\text{-}CF_3), TMEDA]$ (76.1 mg, 0.17 mmol) and dry dichloromethane (2 mL) were introduced into a N_2-flushed flask. PCy_3 (95.3 mg, 0.34 mmol) was added, and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed, and cold Et_2O was added to the residue. A yellow solid appeared. The solid was filtered, washed with cold Et_2O and air dried. Yield: 115.7 mg (76%). ^1H NMR (500.13 MHz, δ, $CDCl_3$): 7.55 (d, J = 8.3 Hz, 2H,

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H^{meta}), 7.16 (d, J = 8.3 Hz, 2H, H^{ortho}), 2.10–0.96 (m, 66H, H^{PCy3}). $^{13}C\{^1H\}$ NMR (125.78 MHz, δ, $CDCl_3$): 161.9 (C^{ipso}), 138.2 (C^{meta}), 124.9 (C^{CF3})*, 124.5 (C^{para}), 122.5 (C^{ortho}), 34.2 (*pseudo*-t, $^1J_{P-C}$ = 9.6 Hz, CH PCy_3), 30.1 (s, CH_2 PCy_3), 27.6 (*pseudo*-t, $^2J_{P-C}$ = 5.2 Hz, CH_2 PCy_3), 26.5 (s, CH_2 PCy_3). ^{19}F NMR (470.168 MHz, δ, $CDCl_3$): −62.06 (s, CF_3). $^{31}P\{^1H\}$ NMR (202.31 MHz, δ, $CDCl_3$): 19.8. *The chemical shift was determined by ^{13}C–^{19}F HSQC. HRMS (ESI-TOF): calcd for $C_{43}H_{70}F_3P_2Pd$ $(M - Br)^+$ 811.395, found 811.3946.

$[Pd(\mu\text{-}Br)(C_6H_4\text{-}p\text{-}CF_3)(PCy_3)]_2$ (2). Following a similar synthesis described in the literature,[44] $[Pd(C_6H_4\text{-}p\text{-}CF_3)(\mu\text{-}OAc)(PCy_3)]_2$ (100 mg, 0.08 mmol) was dissolved in CH_2Cl_2 (1 mL), and NBu_4Br (69 mg, 0.21 mmol) was added to the mixture while stirring. Acetone (10 mL) and water (0.2 mL) were added to the solution. A white solid appeared. The mixture was stirred at room temperature for 3 h. The suspension was filtered, and the solid was washed with water and acetone and air-dried. Yield: 70 mg (67%). ^1H NMR (500.13 MHz, δ, $CDCl_3$): 7.55 (d, J = 7.6 Hz, 2H, H^{ortho}), 7.18 (d, J = 7.6 Hz, 2H, H^{meta}), 2.0–0.93 (m, 33H, H^{PCy3}). $^{13}C\{^1H\}$ NMR (125.78 MHz, δ, $CDCl_3$): 157.4 (C^{ipso}), 136.3 (C^{ortho}), 125.2 (C^{para})*, 124.8 (C^{CF3})*, 122.9 (C^{meta}), 35.1 (d, J_{P-C} = 22 Hz, C^{ipso}, PCy_3), 30 (s, C^{meta}, PCy_3), 27.4 (d, J_{P-C} = 11 Hz, C^{ortho}, PCy_3), 26.3 (s, C^{para}, PCy_3). ^{19}F NMR (470.168 MHz, δ, $CDCl_3$): −61.95 (s, CF_3). $^{31}P\{^1H\}$ NMR (202.31 MHz, δ, $CDCl_3$): 37.74. *The chemical shift was determined by ^{13}C–^{19}F HSQC and HMBC. Anal. calc. for $C_{50}H_{74}Br_2F_6P_2Pd_2$: C, 49.08%; H, 6.10%; found: C, 49.07%; H, 6.11%.

Additional experimental information, characterization and kinetic data, spectra for the compounds and computational details (pdf), as well as cartesian coordinates for the calculated species (xyz file) can be found in the ESI.†

Author contributions

C. P. and M. G. Z. conducted the investigation under A. C. A.'s supervision. A. C. A. wrote the manuscript, and C. P. prepared the ESI.† All authors contributed to the conceptualization of the project and the review and editing of the manuscript.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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References

1 (*a*) Y. Yang, J. Lan and J. You, Oxidative C–H/C–H Coupling Reactions between Two (Hetero)arenes, *Chem. Rev.*, 2017, **117**, 8787–8863; (*b*) W. Zhu and T. B. Gunnoe, Advances in Group 10 Transition-Metal-Catalyzed Arene Alkylation and Alkenylation, *J. Am. Chem. Soc.*, 2021, **143**, 6746–6766; (*c*) W. Ali, G. Prakash and D. Maiti, Recent development in transition metal-catalysed C–H olefination, *Chem. Sci.*, 2021, **12**, 2735–2759; (*d*) T. Dalton, T. Faber and F. Glorius, C–H Activation: Toward Sustainability and Applications, *ACS Cent. Sci.*, 2021, **7**, 245–261.

2 (*a*) L. C. Campeau and K. Fagnou, Palladium-catalyzed direct arylation of simple arenes in synthesis of biaryl molecules, *Chem. Commun.*, 2006, 1253–1264; (*b*) R. Vicente, A. R. Kapdi and L. Ackermann, Transition-Metal-Catalyzed Direct Arylation of (Hetero)Arenes by C–H Bond Cleavage, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (*c*) A. L. Mayhugh, P. Yadav and C. K. Luscombe, Circular Discovery in Small Molecule and Conjugated Polymer Synthetic Methodology, *J. Am. Chem. Soc.*, 2022, **144**, 6123–6135.

3 (*a*) J. F. Hartwig and M. A. Larsen, Undirected, Homogeneous C–H Bond Functionalization: Challenges and Opportunities, *ACS Cent. Sci.*, 2016, **2**, 281–292; (*b*) P. Wedi and M. van Gemmeren, *Angew. Chem., Int. Ed.*, 2018, **57**, 13016–13027; (*c*) S. Kancherla, K. B. Jorgensen and M. A. Fernández-Ibáñez, Recent Developments in Palladium-Catalysed Non-Directed C–H Bond Activation in Arenes, *Synthesis*, 2019, 643–663.

4 (*a*) S. R. Neufeldt and M. S. Sanford, Controlling Site Selectivity in Palladium- Catalyzed C–H Bond Functionalization, *Acc. Chem. Res.*, 2012, **45**, 936–946; (*b*) A. Tomberg, M. E. Muratore, M. J. Johansson, I. Terstiege, C. Sköld and P. O. Norrby, Relative Strength of Common Directing Groups in Palladium-Catalyzed Aromatic CH Activation, *iScience*, 2019, **20**, 373–391; (*c*) S. Rej, Y. Ano and N. Chatani, Bidentate Directing Groups: An Efficient Tool in C–H Bond Functionalization Chemistry for the Expedient Construction of C–C Bonds, *Chem. Rev.*, 2020, **120**, 1788–1887; (*d*) G. Meng, N. Y. S. Lam, E. L. Lucas, T. G. Saint-Denis, P. Verma, N. Chekshin and J.-Q. Yu, Achieving Site-Selectivity for C–H Activation Processes Based on Distance and Geometry: A Carpenter's Approach, *J. Am. Chem. Soc.*, 2020, **142**, 10571–10591.

5 (*a*) J. Luo, S. Preciado and I. Larrosa, Overriding Ortho–Para Selectivity via a Traceless Directing Group Relay Strategy: The Meta-Selective Arylation of Phenols, *J. Am. Chem. Soc.*, 2014, **136**, 4109–4112; (*b*) F.-L. Zhang, K. Hong, T.-J. Li, H. Park and J.-Q. Yu, Functionalization of

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C(sp3)–H bonds using a transient directing group, *Science*, 2016, **351**, 252–256; (*c*) N. Goswami, T. Bhattacharya and D. Maiti, Transient directing ligands for selective metal-catalysed C–H activation, *Nat. Rev. Chem.*, 2021, **5**, 646–649; (*d*) C. Jacob, B. U. W. Maes and G. Evano, Transient Directing Groups in Metal Organic Cooperative Catalysis, *Chem. – Eur. J.*, 2021, **27**, 13899–13952.

6 J. Dhankhar, E. González-Fernández, C.-C. Dong, T. K. Mukhopadhyay, A. Linden and I. Coric, Spatial Anion Control on Palladium for Mild C−H Arylation of Arenes, *J. Am. Chem. Soc.*, 2020, **142**, 19040–19046.

7 T. Higashi, S. Kusumoto and K. Nozaki, Cleavage of Si−H, B−H, and C−H Bonds by Metal−Ligand Cooperation, *Chem. Rev.*, 2019, **119**, 10393–10402.

8 K. Wu, N. Lam, D. A. Strassfeld, Z. Fan, J. X. Qiao, T. Liu, D. Stamos and J.-Q. Yu, Palladium(II)-Catalyzed C H Activation with Bifunctional Ligands: From Curiosity to Industrialization, *Angew. Chem., Int. Ed.*, 2024, **63**, e202400509.

9 (*a*) Q. Shao, K. Wu, Z. Zhuang, S. Qian and J.-Q. Yu, From $Pd(OAc)_2$ t o Chiral Catalysts: The Discovery and Development of Bifunctional Mono-N-Protected Amino Acid Ligands for Diverse C−H Functionalization Reactions, *Acc. Chem. Res.*, 2020, **53**, 833–851; (*b*) C. A. Salazar, J. J. Gair, K. N. Flesch, I. A. Guzei, J. C. Lewis and S. S. Stahl, Catalytic Behavior of Mono-N-Protected Amino-Acid Ligands in Ligand-Accelerated C!H Activation by Palladium(II), *Angew. Chem., Int. Ed.*, 2020, **59**, 10873–10877; (*c*) S. Porey, X. Zhang, S. Bhowmick, V. K. Singh, S. Guin, R. S. Paton and D. Maiti, Alkyne Linchpin Strategy for Drug:Pharmacophore Conjugation: Experimental and Computational Realization of a Meta-Selective Inverse Sonogashira Coupling, *J. Am. Chem. Soc.*, 2020, **142**, 3762–3774.

10 P. Wang, P. Verma, G. Xia, J. Shi, J. X. Qiao, S. Tao, P. T. W. Cheng, M. A. Poss, M. E. Farmer, K.-S. Yeung and J.-Q. Yu, Ligand-accelerated non-directed C–H functionalization of arenes, *Nature*, 2017, **551**, 489–493.

11 (*a*) V. Salamanca, A. Toledo and A. C. Albéniz, [2,2′-Bipyridin]-6(1*H*)–one, a Truly Cooperating Ligand in the Palladium-Mediated C−H Activation Step: Experimental Evidence in the Direct C–3 Arylation of Pyridine, *J. Am. Chem. Soc.*, 2018, **140**, 17851–17856; (*b*) Y.-J. Wang, C.-H. Yuan, D.-Z. Chu and L. Jiao, Regiocontrol in the oxidative Heck reaction of indole by ligand-enabled switch of the regioselectivity-determining step, *Chem. Sci.*, 2020, **11**, 11042–11054; (*c*) Z. Wang, L. Hu, N. Chekshin, Z. Zhuang, S. Qian, J. X. Qiao and J.-Q. Yu, Ligand-controlled divergent dehydrogenative reactions of carboxylic acids via C–H activation, *Science*, 2021, **374**, 1281–1285.

12 Some examples (no silver salts used as additives): (*a*) L. C. Campeau, M. Parisien, A. Jean and K. Fagnou, Catalytic Direct Arylation with Aryl Chlorides, Bromides, and Iodides: Intramolecular Studies Leading to New Intermolecular Reactions, *J. Am. Chem. Soc.*, 2006, **128**, 581–590; (*b*) T. Yan, L. Zhao, M. He, J.-F. Solulé, C. Bruneau and H. Doucet, Reactivity of 3-Substituted Fluorobenzenes in Palladium- Catalysed Direct Arylations with Aryl Bromides, *Adv. Synth. Catal.*, 2014, **356**, 1586–1596; (*c*) C. Arroniz, J. G. Denis, A. Ironmonger, G. Rassias and I. Larrosa, An organic cation as a silver(I) analogue for the arylation of sp^2 and sp^3 C–H bonds with iodoarenes, *Chem. Sci.*, 2014, **5**, 3509–3514.

13 Y.-N. Wang, X.-Q. Guo, X.-H. Zhu, R. Zhong, L.-H. Cai and X.-F. Hou, $Pd(OAc)_2$ c atalyzed direct arylation of electron-deficient arenes without ligands or with monoprotected amino acid assistance, *Chem. Commun.*, 2012, **48**, 10437–10439.

14 L. C. Campeau, S. Rousseaux and K. Fagnou, A Solution to the 2-Pyridyl Organometallic Cross-Coupling Problem: Regioselective Catalytic Direct Arylation of Pyridine N-Oxides, *J. Am. Chem. Soc.*, 2005, **127**, 18020–18021.

15 X.-X. Wang and L. Jiao, Dual Ligand Enabled Pd-Catalyzed *Ortho*-Alkylation of Iodoarenes, *J. Am. Chem. Soc.*, 2024, **146**, 25552–25561.

16 S. Kaltenberger and M. van Gemmeren, Controlling Reactivity and Selectivity in the Nondirected C–H Activation of Arenes with Palladium, *Acc. Chem. Res.*, 2023, **56**, 2459–2472.

17 (*a*) H. Chen, P. Wedi, T. Meyer, G. Tavakoli and M. van Gemmeren, Dual Ligand–Enabled Nondirected C−H Olefination of Arenes, *Angew. Chem., Int. Ed.*, 2018, **57**, 2497–2501; (*b*) P. Wedi, M. Farizyan, K. Bergander, C. Mück-Lichtenfeld and M. van Gemmeren, Mechanism of the Arene–Limited Nondirected C−H Activation of Arenes with Palladium, *Angew. Chem., Int. Ed.*, 2021, **60**, 15641–15649.

18 H. Chen, A. Mondal, P. Wedi and M. van Gemmeren, Dual Ligand-Enabled Nondirected C–H Cyanation of Arenes, *ACS Catal.*, 2019, **9**, 1979–1984.

19 A. Mondal, H. Chen, L. Flämig, P. Wedi and M. van Gemmeren, Sterically Controlled Late-Stage C–H Alkynylation of Arenes, *J. Am. Chem. Soc.*, 2019, **141**, 18662–18667.

20 (*a*) H. S. Park, Z. Fan, R.-Y. Zhu and J.-Q. Yu, Distal γ-C(sp^3)−H Olefination of Ketone Derivatives and Free Carboxylic Acids, *Angew. Chem., Int. Ed.*, 2020, **59**, 12853–12859; (*b*) M. Tomanik and J.-Q. Yu, Palladium-Catalyzed Stitching of 1,3-C(sp^3)-H Bonds with Dihaloarenes: Short Synthesis of (±)-Echinolactone D, *J. Am. Chem. Soc.*, 2023, **145**, 17919–17925.

21 G. Meng, Z. Wang, H. S. S. Chan, N. Chekshin, Z. Li, P. Wang and J.-Q. Yu, Dual-Ligand Catalyst for the Nondirected C–H Olefination of Heteroarenes, *J. Am. Chem. Soc.*, 2023, **145**, 8198–8208.

22 B. Yin, M. Fu, L. Wang, J. Liu and Q. Zhu, Dual Ligand-Promoted Palladium-Catalyzed Nondirected C–H Alkenylation of Aryl Ether, *Chem. Commun.*, 2020, **56**, 3293–3296.

23 (*a*) S. K. Sinha, S. Panja, J. Grover, P. S. Hazra, S. Pandit, Y. Bairagi, X. Zhang and D. Maiti, Dual Ligand Enabled Nondirected C–H Chalcogenation of Arenes and

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Heteroarenes, *J. Am. Chem. Soc.*, 2022, **144**, 12032–12042; (*b*) S. Porey, Y. Bairagi, S. Guin, X. Zhang and D. Maiti, Nondirected C–H/C–F Coupling for the Synthesis of α–Fluoro Olefinated Arenes, *ACS Catal.*, 2023, **13**, 14000–14011.

24 (*a*) I. Beckers, A. Bugaev and D. De Vos, Dual Ligand Approach Increases Functional Group Tolerance in the Pd-Catalysed C–H Arylation of N-Heterocyclic Pharmaceuticals, *Chem. Sci.*, 2023, **14**, 1176–1183; (*b*) I. Beckers and D. De Vos, Rational Ligand Modification Maximizes Turnover Rate in a Model Pd-Catalyzed C–H Arylation, *iScience*, 2023, **26**, 105790.

25 (*a*) U. B. Kim, D. J. Jung, H. J. Jeon, K. Rathwell and S.-G. Lee, Synergistic Dual Transition Metal Catalysis, *Chem. Rev.*, 2020, **120**, 13382–13433; (*b*) G. Y. Wang, Z. Ge, K. Ding and X. Wang, Cooperative Bimetallic Catalysis via One-Metal/Two-Ligands: Mechanistic Insights of Polyfluoroarylation-Allylation of Diazo Compounds, *Angew. Chem., Int. Ed.*, 2023, **62**, e202307973.

26 Y. Tan, F. Barrios-Landeros and J. F. Hartwig, Mechanistic Studies on Direct Arylation of Pyridine N-Oxide: Evidence for Cooperative Catalysis between Two Distinct Palladium Centers, *J. Am. Chem. Soc.*, 2012, **134**, 3683–3686.

27 (*a*) J. Kim and S. H. Hong, Ligand-Promoted Direct C–H Arylation of Simple Arenes: Evidence for a Cooperative Bimetallic Mechanism, *ACS Catal.*, 2017, **7**, 3336–3343; (*b*) D. Kim, G. Choi, W. Kim, D. Kim, Y. K. Kang and S. H. Hong, The site-selectivity and mechanism of Pd-catalyzed C(sp2)–H arylation of simple arenes, *Chem. Sci.*, 2021, **12**, 363–373.

28 D. Wang, Y. Izawa and S. S. Stahl, Pd-Catalyzed Aerobic Oxidative Coupling of Arenes: Evidence for Transmetalation between Two Pd(II)-Aryl Intermediates, *J. Am. Chem. Soc.*, 2014, **136**, 9914–9917.

29 V. Salamanca and A. C. Albéniz, Faster Palladium-Catalyzed Arylation of Simple Arenes in the Presence of a Methylketone: Beneficial Effect of an a Priori Interfering Solvent in C–H Activation, *Org. Chem. Front.*, 2021, **8**, 1941–1951.

30 For some intramolecular examples and chelate-assisted direct arylation:(*a*) H. A. Chiong, Q.-N. Pham and O. Daugulis, Two Methods for Direct ortho-Arylation of Benzoic Acids, *J. Am. Chem. Soc.*, 2007, **129**, 9879–9884; (*b*) S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou and O. Baudoin, Intramolecular Palladium-Catalyzed Alkane C–H Arylation from Aryl Chlorides, *J. Am. Chem. Soc.*, 2010, **132**, 10706–10716.

31 M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris and J.-Q. Yu, Ligand-Promoted C3-Selective Arylation of Pyridines with Pd Catalysts: Gram-Scale Synthesis of (±)-Preclamol, *J. Am. Chem. Soc.*, 2011, **133**, 19090–19093.

32 E. Clot, O. Eisenstein, N. Jasim, S. A. Macgregor, J. E. Mcgrady and R. N. Perutz, C-F and C–H Bond Activation of Fluorobenzenes and Fluoropyridines at Transition Metal Centers: How Fluorine Tips the Scales, *Acc. Chem. Res.*, 2011, **44**, 333–348.

33 C. Pinilla, V. Salamanca, A. Lledós and A. C. Albéniz, Palladium-Catalyzed *Ortho*, C–H Arylation of Unprotected Anilines: Chemo- and Regioselectivity Enabled by the Cooperating Ligand [2,2′-Bipyridin]-6(1*H*)–one, *ACS Catal.*, 2022, **12**, 14527–14532.

34 H. Hattori, Y. Ogiwara and N. Sakai, Formation, Characterization, and Reactivity of Acyl Palladium Complexes in $Pd(OAc)_2$/P Cy_3-Catalyzed Transformation of Acyl Fluorides, *Organometallics*, 2022, **41**, 1509–1518.

35 (*a*) J. Burés, Variable Time Normalization Analysis: General Graphical Elucidation of Reaction Orders from Concentration Profiles, *Angew. Chem., Int. Ed.*, 2016, **55**, 16084–16087; (*b*) J. Burés, A Simple Graphical Method to Determine the Order in Catalyst, *Angew. Chem., Int. Ed.*, 2016, **55**, 2028–2031.

36 P. Villar, M. H. Pérez-Temprano, J. A. Casares, R. Álvarez and P. Espinet, Experimental and DFT Study of the [AuAr($AsPh_3$)]-Catalyzed cis/trans Isomerization of [$PdAr_2(AsPh_3)_2$] (Ar = C_6F_5 or $C_6Cl_2F_3$): Alternative Mechanisms and Its Switch upon Pt for Pd Substitution, *Organometallics*, 2020, **39**, 2295–2303.

37 A. L. Casado and P. Espinet, Mechanism of the Stille Reaction. 1. The Transmetalation Step. Coupling of R^1I and R^2SnBu_3 Catalyzed by *trans*-[PdR^1IL_2] (R^1 = $C_6Cl_2F_3$; R^2 = Vinyl, 4-Methoxyphenyl; L = $AsPh_3$), *J. Am. Chem. Soc.*, 1998, **120**, 8978–8985.

38 A. L. Casado and P. Espinet, Quantitative Evaluation of the Factors Contributing to the "Copper Effect" in the Stille Reaction, *Organometallics*, 2003, **22**, 1305–1309.

39 S. Kozuch and J. M. L. Martin, The Rate-Determining Step is Dead. Long Live the Rate- Determining State!, *ChemPhysChem*, 2011, **12**, 1413–1418.

40 (*a*) W. Ma, R. Mei, G. Tenti and L. Ackermann, Ruthenium(II)-Catalyzed Oxidative CH Alkenylations of Sulfonic Acids, Sulfonyl Chlorides and Sulfonamides, *Chem. – Eur. J.*, 2014, **20**, 15248–15251; (*b*) T. Rogge, J. C. A. Oliveira, R. Kuniyil, L. Hu and L. Ackermann, Reactivity-Controlling Factors in Carboxylate-Assisted C–H Activation under 4d and 3d Transition Metal Catalysis, *ACS Catal.*, 2020, **10**, 10551–10558.

41 L. Wang and B. P. Carrow, Oligothiophene Synthesis by a General C–H Activation Mechanism: Electrophilic Concerted Metalation–Deprotonation (eCMD), *ACS Catal.*, 2019, **9**, 6821–6836.

42 M. Yamashita, J. V. Cuevas Vicario and J. F. Hartwig, Trans Influence on the Rate of Reductive Elimination. Reductive Elimination of Amines from Isomeric Arylpalladium Amides with Unsymmetrical Coordination Spheres, *J. Am. Chem. Soc.*, 2003, **125**, 16347–16360.

43 Y. Ishii, S. Hasegawa, S. Kimura and K. Itoh, Novel trinuclear palladium(0) complexes: Tris(tribenzylideneacetylacetone)-tripalladium(solvent) complexes and their reactions, *J. Organomet. Chem.*, 1974, **73**, 411–418.

44 V. V. Grushin, Thermal Stability, Decomposition Paths, and, Ph/Ph Exchange Reactions of [$(Ph_3P)_2Pd$ (Ph)X] (X = I, Br, Cl, F, and HF_2), *Organometallics*, 2000, **19**, 1888–1900.