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Mechanism Selection for Regiocontrol in Base-Assisted, Palladium-Catalysed Direct C–H Coupling with Halides: First Approach for Oxazole- and Thiazole-4-Carboxylates

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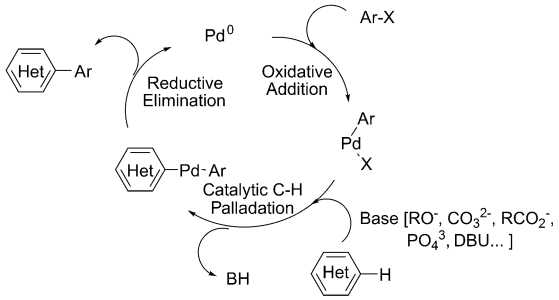
Dedicated to the memory of Keith Fagnou

Abstract: Both base-assisted non-concerted metallation–deprotonation (nCMD) and concerted metallation–deprotonation (CMD) have been identified as two potent operating mechanisms in palladium-catalysed direct C–H coupling of oxazole and thiazole-4-carboxylate esters with halides through base- and solvent-effect experiments. Novel C2- and C5-selective CMD direct arylation procedures in oxazole- and thiazole-4-carboxylate series were then designed by controlling the balance between electronic and steric factors. Notably, charge interactions between the palladium catalyst and substrate were identified as a parameter for controlling selectivity and reducing the impact of steric factors in the CMD reaction.

Keywords: azoles · C–H activation · coupling reactions · density functional calculations · reaction mechanisms

Introduction

Transition-metal-catalysed direct C–H functionalisation of arenes is an attractive alternative to commonly employed cross-coupling reactions by avoiding the preliminary preparation of the requisite organometallic and/or halogenated arenes.[1] Among the broadly useful catalytic cycles, including activation of the unreactive C–H bond, palladium(0)-catalysed direct C–H coupling with halides is the main methodology used for the direct C–H functionalisation of heterocycles (Scheme 1).[2] To date, four main mechanisms have been proposed (Scheme 2):[3] 1) electrophilic palladation (S_EAr type);[4] 2) concerted C–H activation, which includes direct C–H oxidation, σ-bond metathesis and base-assisted intra- or intermolecular concerted metallation–deprotonation (CMD),[5] 3) base-assisted and/or copper(I)-co-catalysed intra- or intermolecular non-concerted deprotonation–metallation (nCMD) related to the standard cross-coupling process;[6] and 4) carbopalladation (Heck type).[7] Of the widely reported catalytic C–H couplings on aromatic compounds in the past decade, the mechanism is often only postulated.[3]



Scheme 1. Reaction cycle for palladium-catalysed direct C–H coupling of (hetero)aromatics with halides. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Thus, complete systematic mechanistic investigation, first reported by Gevorgyan et al. for a series of indolizidines,[4h] remains very sparse for direct C–H coupling of heterocycles.[8] Moreover, to the best of our knowledge, no prior mechanistic determination has been made to design regiocontrolled direct C–H coupling reactions with halides. Indeed, electrophilic activation is expected at the most nucleophilic site; this could be localised by S_EAr halogenation reactions and through HOMO calculations. Interestingly, recently highlighted base-assisted external or internal CMD may target a C–H bond that exhibits both good nucleophilic

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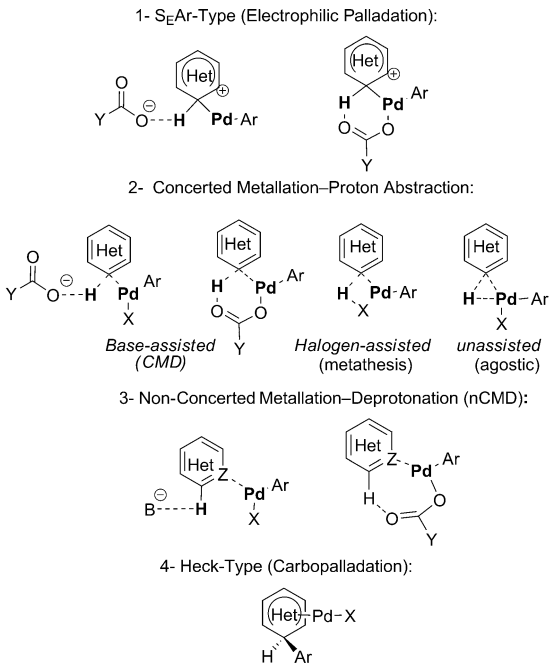


Scheme 2. Proposed C–H palladation pathways in palladium(0)-catalysed direct C–H coupling of (hetero)aromatics with halides depicted in Scheme 1 (Y = oxanion or *tert*-butyl group).

and acidic characteristics. Recent evaluation of the CMD transition state (TS) on various heterocycles by Gorelsky et al. revealed this trend.[5g] Moreover, these calculations also showed that, in many cases, the HOMO site (vs. the most acidic site) was privileged, and thus, CMD was a more viable mechanism and lower in energy than electrophilic metallation for many heterocycles, including highly electron-rich azoles.[5g] One of the most significant recent demonstrations is the exceptionally low energy barrier (6.11 kcal mol^{-1}) of the acetate-assisted CMD TS calculated for a Boc-2-aminothiazole-4-carboxylate (Boc = *tert*-butoxycarbonyl) model.[5f] Nevertheless, a strongly base-dependent reaction on the most acidic position, identified through deuterium incorporation experiments, has also been associated to an nCMD. It is suspected to be favoured by prior interaction of the catalyst to a heteroatom, leading to an acidity reinforcing effect.[2h] In contrast, a Heck-type mechanism is postulated to be less base-dependent than the previously described mechanisms. Therefore, it involves a crucial syn-β-elimination step, which is only facilitated when carbopalladation leads to an allylpalladium system that allows the inversion of the novel Csp^3–Pd centre.[7]

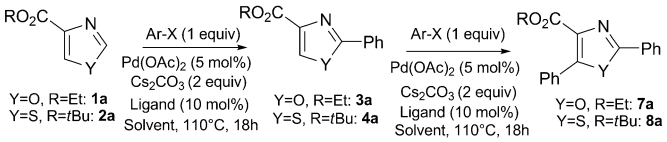
Herein, both nCMD and CMD have been identified as potent operating mechanisms in base-assisted, palladium(0)-catalysed direct C–H coupling of oxazole and thiazole-4-carboxylate esters with halides, which were then used to design novel C2- and C5-selective direct arylation procedures.

Results and Discussion

Our previously reported palladium-catalysed, C2-regiocontrolled direct arylation of ethyloxazole-4-carboxylate (**1a**) and *tert*-butylthiazole-4-carboxylate (**2a**) methodologies were based upon the selection of ligand/solvent pairs that were much more effective for C2 than for subsequent C5 direct phenylation (Table 1).[9a] Thus, 2-(dicyclohexylphosphino)biphenyl (Cy-John-Phos)/dioxane and P(*o*-tol)$_3$/toluene pairs (vs. P(*o*-tol)$_3$/DMF and Cy-John-Phos/DMF pairs; *o*-tol = *o*-tolyl) were selected for the coupling of **1a** (vs. **2a**) with iodo- and chloroaromatics, respectively. First mechanistic investigations were carried out with these selected ligand/solvent pairs. Competitive direct C2 phenylations between 5-phenyloxazole-4-carboxylates with 4-CN and 4-OMe substitutions (**5b** and **c**) revealed that the electron-withdrawing group (EWG) model reacts faster than the electron-donating group (EDG) model when using iodo- and chlorobenzene as the coupling partners (Table 2). Similar results were observed for competitive direct C5 phenylations between 2-phenyloxazole-4-carboxylates with a 4-CN and 4-OMe (**3b**,**c**) substitution using both iodo- and chlorobenzene and the same selected ligand/solvent pairs.[10a]*

These combined observations suggested that electrophilic palladation did not operate for palladium(0)-catalysed, C2-selective and subsequent C5 direct phenylation of **1a** and finally cast serious doubts on an S$_E$Ar-type mechanism (Scheme 2) in direct C–H coupling in the series of oxazole-4-carboxylates.[10b] Additional DFT geometry optimisation calculations showed that methyloxazole-4-carboxylate was less nucleophilic than the indolizidine reference com-

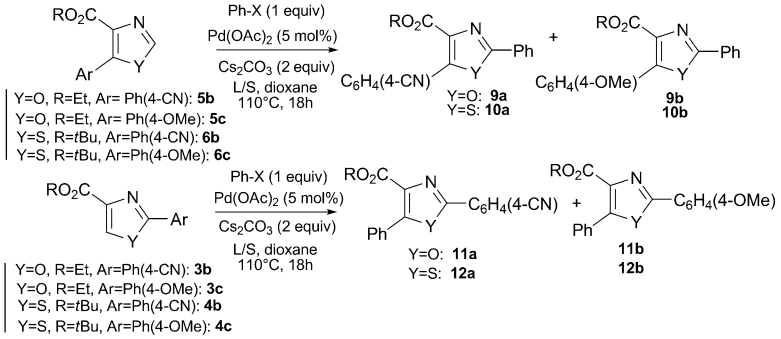
Table 1. Previous selection of ligand/solvent pairs for C2-selective direct arylation of **1a** and **2a**.[a]



Entry	Y	Solvent	ArX	L = P(*o*-tol)$_3$		L = Cy-John-Phos	
				2-Ph[b] [%]	2,5-diPh[b] [%]	2-Ph[b] [%]	2,5-diPh[b] [%]
1	O	dioxane	PhI	37	81	69	27
2			PhCl	78[d]	70[d]	79	70[c]
3	O	toluene	PhI	86	96	67	49
4			PhCl	71[c]	16	85	69[c]
5	S	DMF	PhI	82	7	68	17
6			PhCl	n.r.[d]	n.r.[d]	95[d]	6[d]

[a] Performed with **1a** (0.35 mmol) or **2a** (0.27 mmol). [b] Isolated yield. [c] Performed with electrophile (0.7 mmol). [d] Reaction failed with chlorobenzene and was then performed with 2-chloropyridine.

Table 2. Competitive C2 (vs. C5) direct phenylation of 5- (vs. 2-)arylated oxazole- and thiazole-4-carboxylates with a 4-CN and 4-OMe substitution for S_EAr-type mechanism evaluation.[a]



	Y	ArX	Ligand/Solvent	**9a/9b (10a/10b)**[b]	**11a/11b (12a/12b)**[b]
1	O	PhI	P(*o*-tol)$_3$/toluene	–	2.5:1 (99)[c]
2			Cy-John-Phos/dioxane	10:1 (66)[c]	–
3	O	PhBr	P(*o*-tol)$_3$/toluene	3:1 (71)[c]	3:1 (92)[c]
4			Cy-John-Phos/dioxane	3:1 (65)[c]	2.5:1 (45)[e]
5	O	PhCl	P(*o*-tol)$_3$/toluene	n.r.	–
6			Cy-John-Phos/dioxane	3:1 (67)[c]	1.7:1 (46)[c]
7	S	PhI	P(*o*-tol)$_3$/DMF	2.5:1(41)[c]	n.r. (1.2:1)[f]
8		2-Cl-Py[d]	Cy-John-Phos/DMF	2.5:1(18)[c]	n.r.

[a] Performed on an equimolar mixture of **3b**,**c** or **5b**,**c** (0.70 mmol) with PhX (0.35 mmol) or **4b**,**c** or **6b**,**c** (0.54 mmol) with PhX (0.27 mmol). [b] Ratio determined by ^{1}H NMR spectroscopy. [c] Isolated yield of the major product. [d] 2Cl-Py = 2-chloropyridine. [e] Performed with 1,1′-bis(diphenylphosphino)ferrocene (dppf; 10 mol %). [f] Performed with 1,2-bis(diphenylphosphino)ethane (dppe; 10 mol %) in dioxane.

pound.[4h,5f] The HOMO was −2.7 eV lower in energy (E_{HOMO} = −7.56 vs. −4.9 eV for indolizidine) and partial charges derived from the same calculations were much more negative for indolizidine (−0.44) than for the oxazole-4-carboxylate model at both C2 and C5 positions (+0.470 and −0.018, respectively) (Figure 1).[11]

Considering the electron-attracting effect of the ester group reinforcing the acidity of the protons of the oxazole ring, the base-assisted metallation–deprotonation mechanisms were next evaluated.[12] For this purpose, deuterium

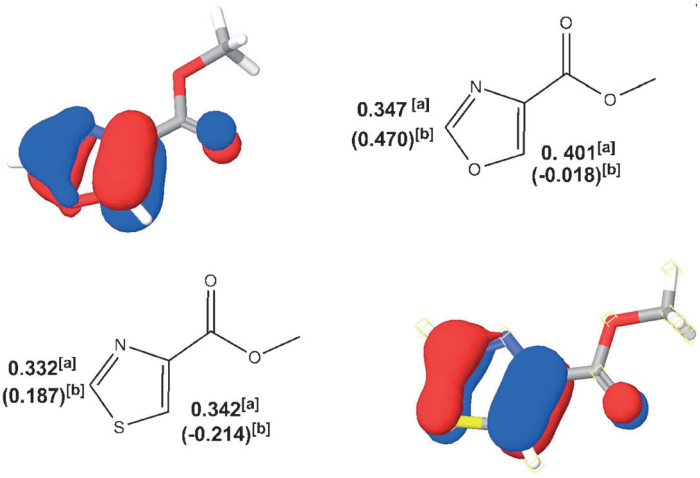
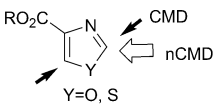


Figure 1. HOMO[a] and partial charges[b] for methyloxazole- and thiazole-4-carboxylates derived from DFT calculations.

incorporation experiments were systematically carried out by using potassium phosphate, potassium carbonate and DBU as bases; these were also evaluated in the direct coupling of **1a** with iodo- and chlorobenzene by using selected ligand/solvent pairs (Table 3, entries 3–8). First analysis revealed that positive deuterium incorporation experiments were systematically accompanied with good results for C2-selective direct phenylation of **1a** with iodo- and chlorobenzene in dioxane as well as in toluene (Table 3, entries 1–6).[13] This strong base-dependent effect discarded the S_EAr and Heck-type mechanisms yet again[7c] and was more consistent with an nCMD reaction (Scheme 2).

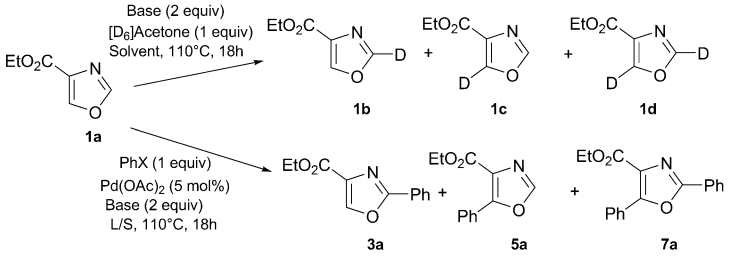
Therefore, the complete inefficiency of potassium carbonate base in the direct coupling of **1a** was only observed when using the iodobenzene/dioxane pair (Table 3, entry 7). Indeed, the reactivity slightly recovered when toluene was used as the solvent or with chlorobenzene as the electrophile, but notably with poor C2/C5 selectivity (Table 3, entries 7 and 8). These results immediately suggested an iodide inhibition effect often observed for CMD reactions.[14] Moreover, PivOH is a very useful additive for internal CMD (Scheme 2).[15] The significant increase in the reactivity of **1a** when using PivOH additive (30 mol %) in direct coupling reactions with iodo- and chlorobenzene (Table 3, entries 9 and 10) pointed to the CMD mechanism hypothesis. To summarise, a schematic representation of the two potent nCMD and CMD mechanisms involved in base-assisted, palladium-catalysed direct C–H coupling of **1a** with halides employing Pd(OAc)$_2$/phosphine/base catalysis and their operating sites is depicted in Scheme 3.

To validate these two potent operating mechanisms (Scheme 3), we designed new conditions for the highly selective C2 and C5 direct C–H couplings of **1a** with halides. One strategy to drive the arylation at the C2 position may favour the nCMD reaction by selecting a specific base/solvent pair useful for the key base-assisted deprotonation step, and concomitantly, by reducing the efficiency of the competitive CMD reaction by using iodide salts and/or an inadequate base.



Scheme 3. The potent nCMD and CMD operating mechanisms in base-assisted, palladium(0)-catalysed direct C–H coupling in the series of oxazole- and thiazole-4-carboxylates.

Table 3. H/D exchange and direct phenylations of **1a** with various bases.[a]



Entry	Base	H/D exchange[c]		X	**3a**[e] [%]	
		Dioxane	Toluene		Cy-John-Phos/dioxane	P(*o*-tol)$_3$/toluene
1	Cs_2CO_3	6:1 (73)[d]	4.3:1 (85)[d]	I	69	86
2				Cl	79	71[f]
3	K_3PO_4	1.2:1 (75)[d]	1:1 (85)[d]	I	88	82
4				Cl	63	35[g]
5	DBU	6.3:1 (72)[d]	5.8:1 (78)[d]	I	99	99
6				Cl	62	65[g]
7	K_2CO_3	ndi[a]	ndi[a]	I	n.r.	25 (1.6:1)[h]
8				Cl	24 (1:1)[h]	19 (1.9:1)[h,g]
9	K_2CO_3/PivOH[b]	1.8:1 (17)[d]	ndi[a]	I	n.r.	61
10				Cl	42 (3:1)[h]	21 (1.1:1)[h,g]

[a] Performed on a 0.35 mmol scale. ndi = no deuterium incorporation. [b] Pivalic acid (PivOH, 30 mol %). [c] Ratio of (**1b+1d**)/(**1c+1d**) determined by ^{1}H NMR spectroscopy. [d] Yield of (**1b+1d**) determined by ^{1}H NMR spectroscopy. [e] Isolated yield of the major product. [f] Performed with PhCl (2 equiv). [g] Reaction failed under initial conditions and was performed using Cy-John-Phos. [h] Ratio of **3a**/**5a** determined by ^{1}H NMR spectroscopy.

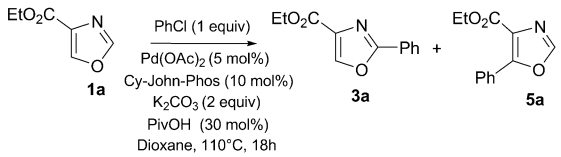
It was first demonstrated that the CMD direct phenylation of **1a** with chlorobenzene when using the K_2CO_3/PivOH pair occurred initially on both the C2 and C5 positions; this was completely quenched by using KI salt (0.5 equiv; Table 4, entries 1 and 2).

Then, the selectivity was further driven almost exclusively at the C2 position by using DMF as a co-solvent, which dramatically increased the solubility and the basicity of the potassium carbonate base, and thus, was useful for a C2-selective nCMD reaction (Table 4, entries 3–6). We also paid particular attention to the high efficiency of the DBU base, which allowed quantitative and exclusive C2 phenylation of **1a** using iodobenzene with both Cy-John-Phos/dioxane and P(*o*-tol)$_3$/toluene pairs (Table 3, entries 5 and 6), suggesting the total inefficiency of DBU as a base in CMD reactions. Additional experiments of direct phenylation of **1a** with iodobenzene in dioxane and toluene using DBU as the base and various ligands are presented in Table 5. Of the different classes of phosphines, Cy-John-Phos showed the best performance in dioxane and toluene, whereas the IMes/dioxane pair was only efficient when using iodobenzene (Table 5).

Remarkably, the methodology could be successfully applied to different aryl and heteroaryl iodides, bromides and chlorides as electrophiles (Table 6, entries 1–7).[16]

We were then interested in designing the conditions for the challenging CMD C5-selective direct arylation of **1a**. The Gibbs free energy of activation for palladium(0)-catalysed direct phenylation of **1a** at both C2 and C5 positions through an acetate-assisted internal CMD reaction was investigated by using DFT geometry optimisation calculations (B3LYP/6-31G**) and by following the model reported by Gorelsky et al.[5g] Thus, while DFT geometry optimisation calculations (Figure 1) revealed that the HOMO resided almost equally on the C2 and C5 positions, the resulting

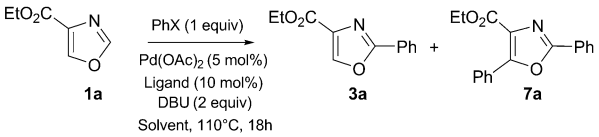
Table 4. Enhanced C2 selectivity of direct phenylation of **1a** with phenylchloride in dioxane when using DMF as a co-solvent.[a]



Entry	Additive	**3a**/**5a**[b]	**3a**[c] [%]
1	–	3:1	42
2	50 mol % KI	n.r.	–
3	5 % DMF	2:1	44
4	10 % DMF	4:1	44
5	50 % DMF	5:1	57 (11)[d]
6	100 % DMF	12:1	80 (16)[d]

[a] Performed on a 0.35 mmol scale. [b] Ratio determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Isolated yield of ethyl 2,5-diphenyloxazole-4-carboxylate (**7a**).

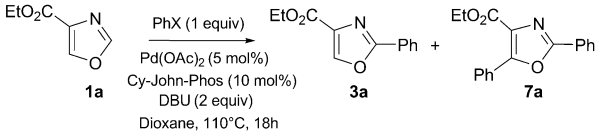
Table 5. Palladium(0)-catalysed C2-selective direct phenylation of **1a** with iodo- and chlorobenzene using DBU as the base and various ligands in dioxane and toluene.[a]

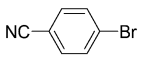
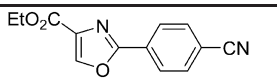
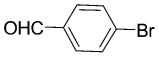
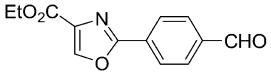
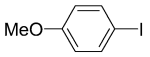
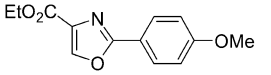
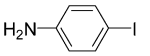
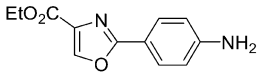
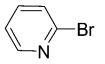
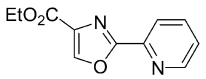
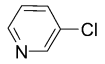
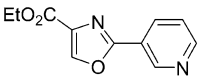
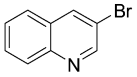
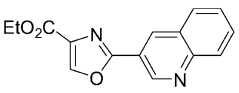


Entry	L	X	**3a**/**7a**[b]	**3a**[c] [%]
1	PCy_3	I	2:1 (2.5:1)[d]	66 (68)[d]
2		Cl	4:1 (1:1)[d]	67 (48)[d]
3	P*t*Bu$_3$	I	15:1 (3:1)[d]	94 (73)[d]
4		Cl	5:1 (0.6:1)[d]	68 (32)[d]
5	Cy-John-Phos	I	100:0 (100:0)[d]	97 (95)[d]
6		Cl	100:0 (100:0)[d]	65 (62)[d]
7	X-Phos	I	2:1 (7.5:1)[d]	68 (88)[d]
8		Cl	n.r. (0.3:1)[d]	n.r. (15)[d]
9	IMes	I	9:1 (11:1)[d]	62 (23)[d]
10		Cl	n.r.	n.r.

[a] Performed on a 0.35 mmol scale. Cy = cyclohexyl, X-Phos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene. [b] Ratio determined by ^{1}H NMR spectroscopy. [c] Isolated yield. [d] Toluene as the solvent.

Table 6. Palladium(0)-catalysed C2-selective direct arylation of **1a** with aryl halides using DBU base and the Cy-John-Phos ligand.[a]

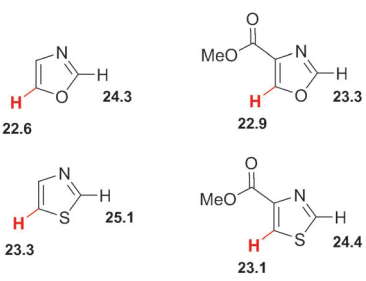


Entry	(Het)ArX	Product		Yield [%][b]
1			**3b**	96 (95)[c]
2			**3d**	66 (81)[c]
3			**3c**	88
4			**3e**	55 (65)[c]
5			**3f**	96 (92)[c]
6			**3g**	86
7			**3h**	92 (96)[c]

[a] Performed on a 0.35 mmol scale. [b] Isolated yields. [c] Performed in toluene.

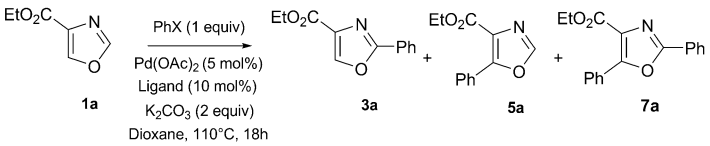
Gibbs free energy barriers for TS-2 and TS-5 (Scheme 4)[17] indicated that the C5 position was favourable for internal CMD because TS-5 was slightly more stable than TS-2 (0.4 kcal mol^{-1} lower in energy).

In contrast, CMD direct phenylation of **1a** with iodo- and chlorobenzene under $Pd(OAc)_2/K_2CO_3$/PivOH catalysis occurred selectively at the C2 position when using P(*o*-tol)$_3$/toluene and Cy-John-Phos/dioxane pairs, respectively (Table 3, entries 9 and 10). Recent observations on direct arylation of pyridine *N*-oxide proceeding through CMD revealed that the selectivity depended on a subtle balance between electronic and steric factors.[5n] Over a broad screening of phosphines, it was found that only P*t*Bu$_3$ drove the K_2CO_3-assisted direct arylation of **1a** in dioxane at the C2 position (Table 7, entries 1–3), while C5 selectivity was obtained by using several slightly to significantly less steric and electron-donating ligands, including John-Phos, PCy$_3$ and P(*p*-FPh)$_3$ (Table 7, entries 4–14), which offered the best C5-selectivity/completion performances.[18a]



Scheme 4. Free Gibbs energy of activation ($\Delta G^{\ddagger}_{298K}$, kcal mol^{-1}) calculated at the C2 (TS-2) and C5 (TS-5) positions for palladium(0)-catalysed direct phenylation of oxazole, thiazole, methyloxazole- and thiazole-4-carboxylates through an acetate-assisted internal CMD reaction.[17]

Table 7. Palladium(0)-catalysed direct phenylation of **1a** with phenylhalides using K_2CO_3 base with various phosphines.[a]



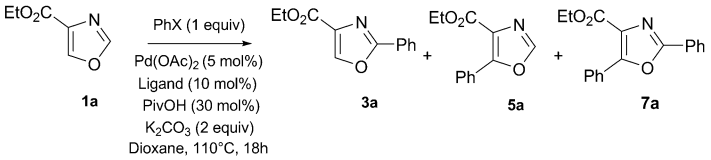
Entry	L	X	Conversion[b] [%]	**3a** /**5a**[c]	Mono /**7a**[c]	Yield[d] [%]
1	P*t*Bu$_3$	I	34	3.5:1	100:1	25
2	P*t*Bu$_3$	Br	60	18:1	30:1	55
3	P*t*Bu$_3$	Cl	78	3:1	2:1	42
4	JPhos	I	27	1:1	100:1	14
5	JPhos	Br	77	1:7	2:1	52
6	JPhos	Cl	81	1:17	2:1	51
7[e]	JPhos	Br	72	1:5	2:1	43[g]
8	PCy$_3$	I	n.r.	–	–	–
9	PCy$_3$	Br	81	1:12	3:1	59
10	PCy$_3$	Cl[f]	73	1:8	1.5:1	41
11[e]	PCy$_3$	Br	71	1:10	1.5:1	39[g]
12	P(FPh)$_3$	I	n.r.	–	–	–
13	P(FPh)$_3$	Br	79	1:24	1.7:1	48
14	P(FPh)$_3$	Cl[f]	n.r.	–	–	–
15	dppf	Br	82	1:12	5:1	57
16	dppe	Br	80	1:17	2.3:1	52
17	dppb	Br	82	1:18	2:1	53
18	–	Br	n.r.	–	–	–
19	–	Br	71	1:4	2:1	40

[a] Performed on a 0.35 mmol scale for **1a**. JPhos = 2-(di-*tert*-butylphosphino)biphenyl, dppb = 1,4-bis(diphenylphosphino)butane. [b] Completion of starting material determined by NMR spectroscopy. [c] Ratio determined by NMR spectroscopy. [d] Isolated yield of the major product. [e] Reaction performed with *tert*-butyloxazole-4-carboxylate **13**. [f] Reaction performed with 4-cyanochlorobenzene. [g] Isolated yield of *tert*-butyl 5-phenyloxazole-4-carboxylate **14a**.

Although bromo- and chlorobenzene gave better completion of the reactions than iodobenzene, the same trend in selectivity was observed independent of the nature of the halogen for all of the ligands screened, suggesting internal CMD, which implied [Pd(OCO$_2^{2-}$)(L)Ph] as the sole active palladium catalysts.[19] The C2/C5 selectivity thus depends on the electronic and steric effects of the ligand and the base. However, DFT calculations showed that HOMO levels at both C2 and C5 positions were similar, whereas the C5 position displays a more negative partial charge (−0.018) than the C2 position (+0.470) (Figure 1).[11] Thus, according to our prior observations that C5 selectivity increased when using less steric and electron-donating ligands, charge interaction appeared to be the main factor for enhancing C5 re-

activity through internal CMD and by reducing the impact of steric hindrance. To demonstrate further, C5 selectivity was also retained through direct coupling of the more sterically hindered and electron-rich *tert*-butyloxazole-4-carboxylate (**13**) with bromobenzene when using selected PCy_3 and John-Phos ligands (Table 7, entries 7 and 11). Moreover, similar C5 selectivity was observed by using the more sterically hindered and active PivOK base in the internal CMD reaction with tri(aryl)alkylphosphines, including PCy_3 and P(*p*-FPh)$_3$, which offered the best selectivity/completion performances (Table 8, entries 5–8).[18a,b] Under these conditions, the C2 position was only favoured by using the steric P*t*Bu$_3$ (Table 8, entries 1 and 2) and Buchwald ligands, including John-Phos, which displayed the best selectivity/completion performance (Table 8, entries 3 and 4).[18a,b] Having

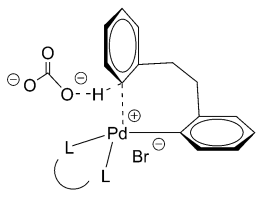
Table 8. Palladium(0)-catalysed direct phenylation of **1a** with halobenzenes using K_2CO_3 as the base with phosphine ligands and PivOH additive.[a]



Entry	L	X	Conversion[b] [%]	**3a**/**5a**[c]	Mono/**7a**[c]	Yield[d] [%]
1	P*t*Bu$_3$	Br	100	100:1	3.5:1	78
2	P*t*Bu$_3$	Cl	97	27:1	5.7:1	80
3	JPhos	Br	100	100:1	5:1	83
4	JPhos	Cl	84	10:1	3:1	58
5	PCy_3	Br	82	1:15	2:1	55
6	PCy_3	Cl[e]	78	1:9	1.5:1	45
7	P(FPh)$_3$	Br	80	1:24	1.5:1	48
8	P(FPh)$_3$	Cl[e]	n.r.	–	–	–

[a] Performed on a 0.35 mmol scale for **1a**. [b] Conversion of starting material determined by ^{1}H NMR spectroscopy. [c] Ratio determined by ^{1}H NMR spectroscopy. [d] Isolated yield. [e] Reaction performed with 4-cyanochlorobenzene.

highlighted charge interaction as the main factor in controlling electronic/steric balance through competitive C2/C5 CMD reactions when C2/C5 HOMOs are similar, we turned our attention to recent observations by Echavarren et al. on the great efficiency of bidentate ligands to generate a highly electrophilic arylpalladium complex suitable for external CMD (Scheme 5).[5h] Naturally, PivOH is a useful additive because by acting only as an external base and/or a ligand, it may decrease the reactivity by reducing the electrophilic character of the bidentate, active arylpalladium complex. Pleasingly, the first set of K_2CO_3-assisted direct phenylation of **1a** with bromobenzene using three bidentate ligands in dioxane gave the expected results, providing C5-phenylated **5a** as the major product (Table 7, entries 15–17) and dppf offered the best selectivity/completion performance. Nevertheless, due to the high electrophilic character of the active, bidentate palladium complex, additional competitive direct C5 phenylation between 2-phenyloxazole-4-carboxylates with 4-CN and 4-OMe (**3b**,**c**) substitution was immediately achieved with the dppf ligand. It also revealed that the EWG model reacted faster than the EDG model when using bromobenzene as a coupling partner, excluding a competitive S_EAr-type mechanism (Table 2, entry 4).[5]

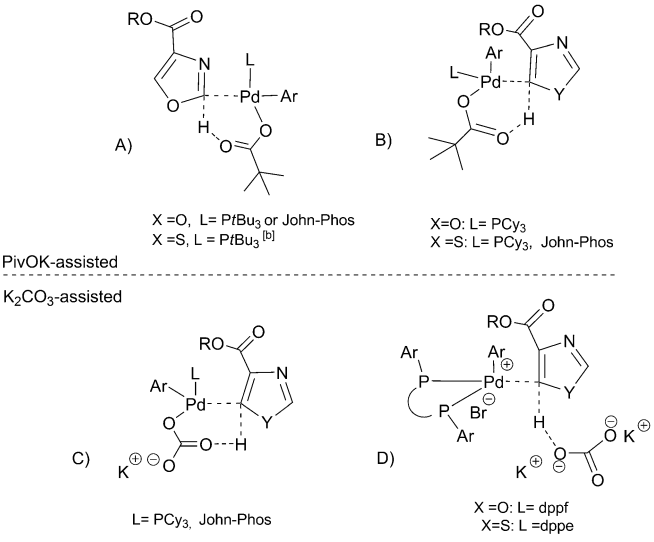


Scheme 5. The model developed by Echavarren et al. for carbonate-assisted external CMD reactions using bidentate ligands and arylbromide electrophiles.[5h]

It should be noted that direct arylation of **1a** was also successfully achieved without ligand and only in the presence of the PivOH additive and occurred selectively at the C5 position to provide **5a** in 40% yield (Table 7, entries 18 and 19).[20] Importantly, we also noted that the selectivity could be highly improved by reducing the temperature of the reaction, but the extent of completion dramatically decreased in the majority of cases, even when carrying out the direct phenylation over a 36 h period.[18c]

The novel C2- and C5-selective CMD direct arylation procedures using bromide and chloride electrophiles are summarised in Scheme 6. Thus, C2- and C5-selective direct arylation was optimally achieved under PivOK-assisted internal CMD using P*t*Bu$_3$ or John-Phos (Scheme 6A) and PCy_3 (Scheme 6B). Interestingly, C5-selective direct coupling was also optimally realised through K_2CO_3-assisted internal CMD using PCy_3 or John-Phos (Scheme 6C) as well as through K_2CO_3-assisted external CMD using dppf (Scheme 6D).

With these successful achievements in setting up C2- and C5-selective direct arylation methodologies for the series of



Scheme 6. Selective C2 and C5 CMD direct C–H coupling procedures in a series of oxazole-4-carboxylate and thiazole-4-carboxylate in dioxane using bromides and chlorides: A) PivOK-assisted C2 selective internal CMD (Y = O, R = Et or Y = S, R = *t*Bu); B) PivOK-assisted C5 selective internal CMD (Y = O, R = Et or Y = S, R = Me); C) K_2CO_3-assisted C5 selective internal CMD (Y = O, R = Et or Y = S, R = Me); and D) K_2CO_3-assisted C5 selective external CMD (Y = O, R = Et or Y = S, R = Me).

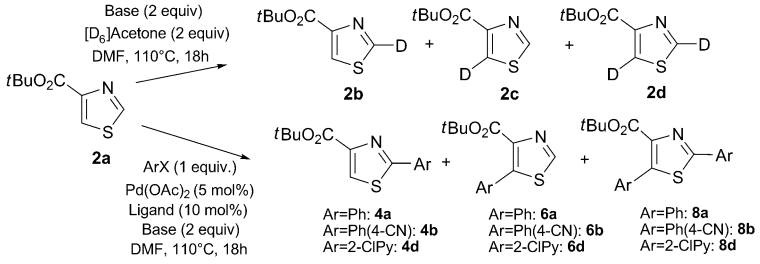
oxazole-4-carboxylate series upon prior determination of both nCMD and CMD operating mechanisms (Scheme 3), we turned to examining structurally related **2a**. Competitive C2 direct phenylation between 5-phenylthiazole-4-carboxylates with 4-CN and 4-OMe (**6b,c**) substitution was achieved by using the P(*o*-tol)$_3$/DMF and Cy-John-Phos/DMF pairs previously designed for C2-selective direct arylation of **2a** with iodo- and 2-chloropyridine, respectively (Table 1, entries 5 and 6).[9b] These experiments revealed that the EWG model reacted faster than the EDG model with iodobenzene and 2-chloropyridine (Table 2, entries 7 and 8), which led to discarding the S_EAr-type mechanism for the reaction at the C2 position. Further identical deuterium incorporation experiments associated with direct phenylation reactions using potassium phosphate, potassium carbonate, and DBU were executed. The results depicted in Table 9 are consistent with the two operating mechanisms proposed for direct C–H coupling with halides in the series of oxazole-4-carboxylate (Scheme 3). Indeed, a strong base effect on the efficiency and C2 selectivity of the direct phenylation was also underlined, but the C2-selective nCMD reaction now appeared naturally dependent on most basic conditions (Table 9) due to the better nucleophilic character and acidic property of the thiazole ring. Indeed, DFT geometry optimisation calculations on methyl thiazole-4-carboxylate clearly showed that the HOMO was slightly higher in energy (−7.44 eV) and notably the charge density at C5 (−0.214 eV) was much more negative than that for the oxazole model (−7.56 and −0.018 eV, respectively).[11] Thus, typically highly efficient C2-selective direct phenylation of **2a** with iodobenzene and 2-chloropyridine was only observed by using caesium carbonate as the base, which displayed the best basic properties with respect to pK_a and solubility (Table 9, entries 1 and 2).[21] K_3PO_4 was less efficient and DBU was now useless (Table 9, entries 3–6).

In contrast to that observed in the oxazole-4-carboxylate series (Table 3, entries 7 and 8), the reactivity was much improved when using less basic K_2CO_3 with or without PivOH additive, producing **6a** as the major product in 49 and 47% yields using iodobenzene (Table 9, entries 7 and 9). These results highlighted the good performance of the CMD reaction with the P(*o*-tol)$_3$ ligand.

To further validate nCMD and CMD as two dominant operating mechanisms in base-assisted direct substitutive arylation of **2a** (Scheme 3), the CMD direct phenylation of **2a** with iodobenzene using K_2CO_3 as the base with Cy-John-Phos was spectacularly driven from the C5 position to C2 by using CsI additive and allowing the in situ production of caesium carbonate, which as useful for the nCMD reaction (Table 10). Additional experiments of direct phenylation of **2a** were then executed using previously optimised ligands for the CMD reaction in the oxazole-4-carboxylate series in dioxane (Table 11).

Pleasingly, fair reactivity was recovered when using chlorides, suggesting better performance of the oxidative addition step in dioxane (Table 11, entries 3, 4, 9, 10, 14 and 15) than in DMF (Table 1, entry 6). Interestingly bromides were also successfully coupled and gave better results than iodides.[18b] Notably C5 selectivity was dramatically reinforced by using PCy_3 and John-Phos ligands independent of the use of PivOH additive (Table 11, entries 5–15). The C5 selectivity was consistent with DFT calculations of Gibbs free energy barriers investigated for C2 and C5 direct phenylation of methyl thiazole-4-carboxylate through acetate-assisted internal CMD (Scheme 4).[17] Indeed, results indicated a 1.8 kcal mol^{-1} difference in energy in favour of TS-5. However, the Gibbs free energy values of both TS-2 and TS-5 gave an advantage to the oxazole-4-carboxylate series, which appeared to be a better compromise for the CMD reaction when considering both nucleophilic and acidic properties. In contrast, a significantly higher C5 selectivity was observed for the screening of ligands through K_2CO_3- and PivOK-assisted CMD direct arylation of **2a** (Table 11) than that observed for **1a** (Tables 7 and 8), despite increased steric hindrance at the C5 position when using *tert*-butyl protection. In fact, selectivity could be only reversed from the C5 to the C2 position by specifically using the most

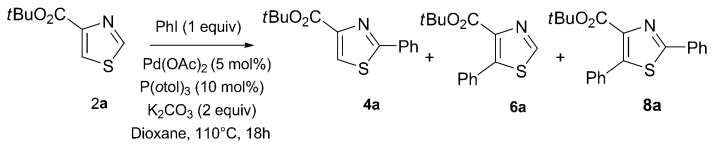
Table 9. Deuterium incorporation experiments associated with C2 direct phenylation of **2a** using various bases.[a]



Entry	Base	H/D exchange[c]	ArX	**4**/**6**/**8**[g]	Yield[h] [%]
1	Cs_2CO_3	1.1:1 (49)[d]	PhI[e]	100:1:1	82
2			2-PyCl[f]	100:1:1	92
3	K_3PO_4	1:1 (51)[d]	PhI[e]	1.2:1:–	32
4			2-PyCl[f]	100:1:1	65
5	DBU	1.1:1 (45)[d]	PhI[e	1.1:4:1	27
6			2-PyCl[f]	–	n.r. (n.r.)[i]
7	K_2CO_3	1.2:1 (69)[d]	PhI[e]	–:5.2:1	47
8			2-PyCl[f]	–	n.r. (n.r.)[i]
9	K_2CO_3	1.1:1 (65)[d]	PhI[e]	–:2.2:1	49
10	PivOH[b]		2-PyCl[f]	–	n.r. (n.r.)[i]

[a] Performed on a 0.27 mmol scale for **2a**. [b] 30 mol% PivOH additive. [c] Ratio of (**2b**+**2d**)/(**2c**+**2d**) determined by ^{1}H NMR spectroscopy. [d] Yield of (**2b**+**2d**) determined by ^{1}H NMR spectroscopy. [e] Performed with P(*o*-tol)$_3$ ligand (10 mol%). [f] Performed with Cy-John-Phos ligand (10 mol%). [g] Ratio determined by ^{1}H NMR spectroscopy. [h] Isolated yield of the major product. [i] Performed by using 4-cyanochlorobenzene.

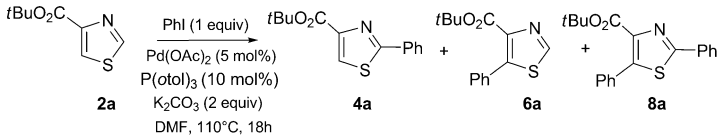
Table 10. Additional experiments to probe the kinetically favoured Cs_2CO_3-assisted nCMD in DMF.



Entry	Solvent	Base	Additive [equiv]	**4a**/**6a**/**8a**[b]	**4a**[c] [%]	**6a**[c] [%]
1	DMF	K_2CO_3	–	0:5:1		47
2	DMF	K_2CO_3	CsI (0.5)	1:2.5:1.8	9	22
3	DMF	K_2CO_3	CsI (1)	1:1:1	17	15
4	DMF	K_2CO_3	CsI (1.5)	8:1:1.3	36	8
5	DMF	K_2CO_3	CsI (2)	100:0:0	79	–
6	DMF	Cs_2CO_3	–	100:0:0	82	–

[a] Performed on a 0.27 mmol scale for **2a**. [b] Ratio determined by ^{1}H NMR spectroscopy. [c] Isolated yield.

Table 11. Palladium-catalysed direct phenylation of **2a** with halobenzenes using K_2CO_3 as the base and phosphine ligands.



Entry	L	PivOH [%]	X	Conversion[b] [%]	**4a**/**6a**[c]	Mono/**8a**[c]	Yield[d] [%]
1	P*t*Bu$_3$	–	Br	68	1:3	1:1	29
2	P*t*Bu$_3$	0.3	Br	72	5.5:1	1:1	33
3	P*t*Bu$_3$	–	Cl	68	1:1	1:1.5	19
4	P*t*Bu$_3$	0.3	Cl	77	16:1	1.7:1	47
5	JPhos	–	Br	71	1:8	1:1	32
6	JPhos	0.3	Br	68	1:9.5	1.4:1	38
7[e]	JPhos	–	Br	79	1:29	3:1	58[g]
8[e]	JPhos	0.3	Br	77	1:18	3:1	54[g]
9	JPhos	–	Cl	74	1:26	2.6:1	52
10	JPhos	0.3	Cl	69	1:6	1:1	30
11	PCy$_3$	–	Br	55	1:47	6:1	47
12	PCy$_3$	0.3	Br	85	1:61	2.5:1	61
13[e]	PCy$_3$	0.3	Br	86	1:65	3.5:1	65[g]
14	PCy$_3$	–	Cl[f]	78	1:5	3.2:1	45
15	PCy$_3$	0.3	Cl[f]	80	1:5	2.2:1	48
16	dppf	–	Br	77	1:32	5.8:1	64
17	dppe	–	Br	81	1:33	4.6:1	65
18	dppb	–	Br	83	1:34	5.2:1	61
19	–	–	Br	n.r.	–	–	–
20	–	0.3	Br	n.r.	–	–	–

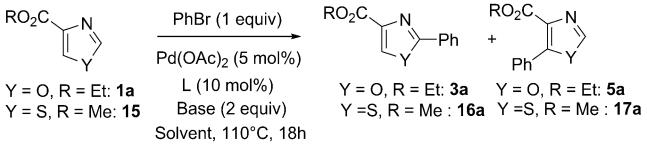
[a] Performed on a 0.27 mmol scale for **2a**. [b] Conversion of starting material determined by ^{1}H NMR spectroscopy. [c] Ratio determined by ^{1}H NMR spectroscopy. [d] Isolated yield. [e] Reaction performed with **15**. [f] Reaction performed with 4-cyanochlorobenzene. [g] Isolated yield of **16a**.

electron-rich and sterically hindered P*t*Bu$_3$/PivOH pair (Table 11, entries 2 and 4). All of these observations demonstrated again that the charge interaction was the main factor controlling selectivity in base-assisted internal CMD. Indeed, although DFT calculations showed almost identical C2/C5 HOMO and a similar C2/C5 charge gap (0.488 vs. 0.401; Figure 1), the C5 position of the thiazole model displayed a lower negative charge than that of the oxazole (−0.214 vs. −0.018). Significantly better results were thus naturally observed with **15** because the partial charge was less dramatically reduced than the steric hindrance at the C5 position (Table 11, entries 7, 8 and 13). Thus, as expected, further external CMD direct arylation of **2a** with bromobenzene using bidentate ligands was also highly selective at the C5 position (Table 11, entries 16–18). The competitive S_EAr-type mechanism was yet again discarded through additional competitive direct C5 phenylation between 2-phenylthiazole-4-carboxylates with 4-CN and 4-OMe (**4b**,**c**) substitution, which revealed that EWG model was slightly more reactive than the EDG model (Table 2, entry 7).[5] Also notable was that, in contrast to observations for the oxazole-4-carboxylate series, direct arylation of **2a** failed without ligand even in the presence of PivOH additive (Table 11, entries 19 and 20).[20] The novel procedures designed for C2- and C5-selective CMD direct arylation of **2a** with bromides and chlorides in dioxane are summarised in Scheme 6. Thus, C2-selective direct arylation was optimally achieved for PivOK-assisted CMD using P*t*Bu$_3$ and *tert*-butyl protection (Scheme 6A). Therefore, C5-selective direct arylation was optimally realised under both K_2CO_3- and PivOK-assisted internal CMD using both PCy$_3$ and John-Phos (Scheme 6B and C) with methyl protection. C5 selectivity could be also attained under K_2CO_3-assisted external CMD using bromides and dppe ligand with methyl protection.

At this stage, the C2- and C5-selective CMD direct arylation procedures for the oxazole and thiazole-4-carboxylate series (Scheme 6) were evaluated with various bromides and chlorides (Table 12). Interestingly, both C2- and C5-selective direct arylation could be successfully achieved by using arylbromides and chlorides with little influence by the substitution. Notably, anilines were successfully coupled (Table 12, entries 5 and 14) and several heteroaryl halides were effective coupling partners (Table 12, entries 6–9, 15–18). Good conversions were generally observed (>80%), but the yield of 2- or 5-arylated oxazole and thiazole-4-carboxylates was reduced by a significant subsequent production of diarylated product. It should also be noted that results of C2-selective direct arylation of **1a** and **2a** were significantly lower when using K_2CO_3- or PivOK-assisted CMD procedures than those previously reported for Cs_2CO_3-assisted nCMD reactions.[9b–c] Moreover, phenyltosylate was an inefficient coupling partner under these optimised conditions.[22]

As the final part of this study, we focused on additional mechanism information. Indeed, the specific C2 selectivity of the nCMD reaction was observed in the series of oxazole and thiazole-4-carboxylates along with incorporation of deuterium at both C2 and C5 positions (Tables 7 and 9). These observations discarded the cross-coupling mechanism often

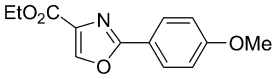
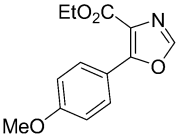
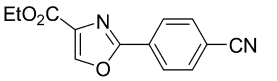
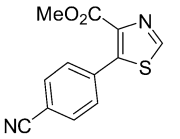
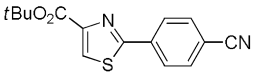
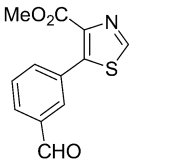
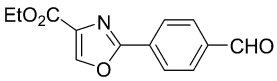
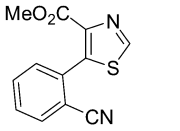
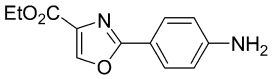
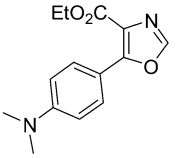
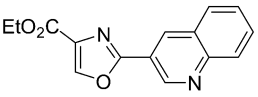
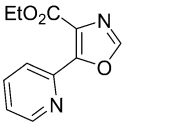
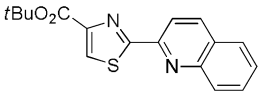
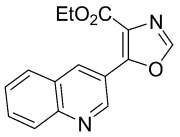
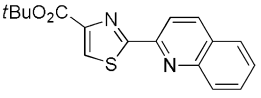
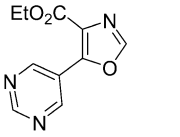
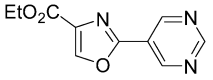
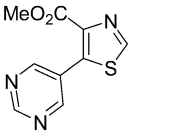
Table 12. Palladium(0)-catalysed CMD direct C2- and C5-selective arylation with bromides and chlorides for the series of oxazole and thiazole-4-carboxylates.



Y = O, R = Et: **1a**; Y = S, R = Me: **15**

Y = O, R = Et: **3a**; Y = S, R = Me : **16a**

Y = O, R = Et: **5a**; Y = S, R = Me : **17a**

Entry	Product	X	Method[c]	2-Ar/2,5-diAr[d]	Yield[e] [%]	Entry	Product	X	Method[c]	5-Ar/2,5-diAr[d]	Yield[e] [%]
1	 **3c**	Br	A_1	8:1	66	10	 **5c**	Br	C_2	2.5:1	54
2	 **3b**	Cl	A_1	4:1	49	11	 **17b**	Cl	B_1	3:1	61
3	 **4b**	Cl	A_1	2.5:1	52	12	 **17c**	Br	B_2	8:1	65
4	 **3d**	Br	A_1	7:1	74	13	 **17d**	Br	D_2	3:1	37
5	 **3e**	Cl	A_2	3:1	39	14	 **5d**	Br	D_1	2:1	33[f]
6	 **3f**	Cl	A_1	5:1	60	15	 **5e**	Cl	C_2	2:1	39
7	 **3h**	Br	A_1	3:1	48	16	 **5f**	Br	C_2	4:1	37
8	 **4e**	Cl	A_1	3:1	38	17	 **5g**	Br	C_2	3:1	51
9	 **3i**	Br	A_1	4:1	53	18	 **17e**	Br	B_1	3.5:1	57

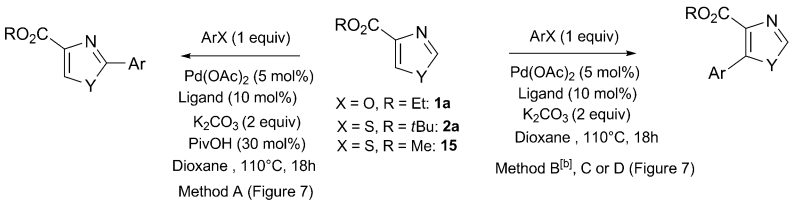
[a] Performed with **1a** (0.35 mmol) or **2a** or **15** (0.27 mmol). [b] PivOH (30 mol%). [c] Reaction performed by using methods depicted in Scheme 6 with the following definitions: A_1: P*t*Bu$_3$; A_2: John-Phos; B_1: PCy$_3$, B_2: John-Phos; C_1: PCy$_3$, C_2: John-Phos; D_1: dppf, D_2: dppe = 1,2-bis(diphenylphosphino)-ethane. [d] Ratio determined by ^{1}H NMR spectroscopy. [e] Isolated yields. [f] When 2- and 4-chloroaniline were used as electrophiles, compounds **3e** and **3j** were obtained in 11 and 41% yield, respectively.

evoked in the oxazole and thiazole series, notably implying ring-opening tautomers.[2h,23] In fact, the crucial proton abstraction force of the base associated with specific C2 selectivity under nCMD reaction conditions are more in accord-

ance with a prior nitrogen-chelating palladium catalyst route, which would enhance the acidity of the proton and notably might prevent the formation of the ring-opening tautomer after the deprotonation step.[24] A similar prior interaction was already suggested for palladium(0)-catalysed direct arylation of azoles under strongly basic conditions when using a copper(I) co-catalyst.[2h,6,23] Although more data are now necessary to determine the deprotonation/transmetallation pathway, it could be related to a base-assisted electrophilic substitution process[25] with the possible formation of a stabilised carbene, as previously suggested by Bellina et al. (Scheme 7).[2h]

Moreover, having highlighted both nCMD and CMD as potent operating mechanisms in base-assisted direct coupling of the oxazole and thiazole-4-carboxylate series, we finally evaluated the ligands and the proton-abstraction force of the base by controlling both processes in the case of competition.[18d] The results of Cs_2CO_3-assisted direct arylations of **1a** revealed that the C5-selective CMD reaction (vs. the C2-selective nCMD reaction) was kinetically favoured only when using PCy_3 (vs. John-Phos and dppf ligands; Table 13, entries 1–3). However, as expected, C2 selectivity was recovered when using the PCy_3 ligand under the increased basicity effect of DMF (Table 13, entry 4). While K_2CO_3-assisted C5-selective CMD was highly favoured in dioxane when using the PCy_3 ligand (Table 7, entry 9), C2-selective direct arylation was naturally partially recovered in DMF (Table 12, entry 5). For the thiazole-4-carboxylate series, all bases were effective in deuterium incorporation experiments with **2a** due to the increased basicity effect in DMF (Table 8), which revealed possible nCMD/CMD competition for all carbonate bases in DMF. Thus, it was previously observed that K_2CO_3- and PivOK-assisted (vs. Cs_2CO_3 assisted) C5-selective CMD (vs. C2-selective nCMD) were kinetically favoured when using the P(*o*-tol)$_3$ ligand and iodobenzene (Table 9, entries 7 and 9). Further additional K_2CO_3-assisted reactions in DMF using the PCy_3, John-Phos and dppe ligands were successfully executed, but a lower C5 selectivity was observed (Table 13, entries 6–8). However, when using the PCy_3 ligand, for instance, the C2 selectivity was completely recovered when replacing K_2CO_3 with Cs_2CO_3 (Table 13, entry 9).

Table 13. Competitive nCMD versus CMD direct arylation with phenylbromide in the oxazole- and thiazole-4-carboxylate series.

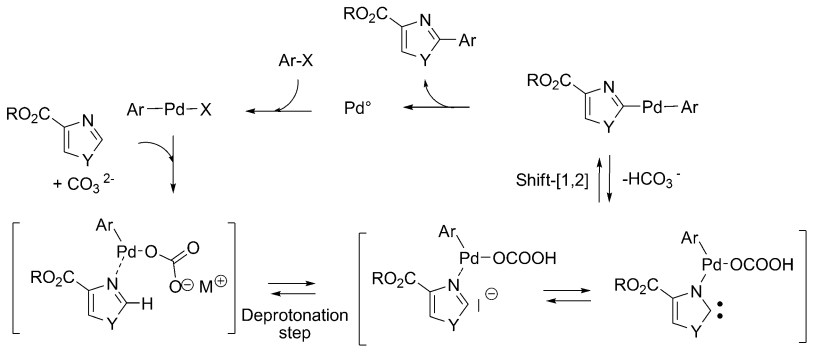


Entry	Reagent	L	Solvent	Base	2-Ph/5-Ph[b]	MP[c]	Yield[d] [%]
1	**1a**	PCy_3	dioxane	Cs_2CO_3	1:50	**5a**	48
2	**1a**	JP	dioxane	Cs_2CO_3	9:1	**3a**	71
3	**1a**	dppf	dioxane	Cs_2CO_3	5:1	**3a**	55
4	**1a**	PCy_3	DMF	Cs_2CO_3	100:1	**3a**	62
5	**1a**	PCy_3	DMF	K_2CO_3	1:1	**3a**	41
6	**15**	PCy_3	DMF	K_2CO_3	1:2	**17a**	40
7	**15**	JP	DMF	K_2CO_3	1:2	**17a**	41
8	**15**	dppe	DMF	K_2CO_3	1:2.5	**17a**	43
9	**15**	PCy_3	DMF	Cs_2CO_3	100:1	**16a**	75

[a] Performed with **1a** (0.35 mmol) and **15** (0.27 mmol). [b] Ratio determined by ^{1}H NMR spectroscopy. [c] Major product. [d] Isolated yield.

Conclusion

After discarding the S_EAr-type mechanism, both nCMD and CMD mechanisms were clearly identified in base-assisted, palladium-catalysed direct C–H coupling of oxazole and thiazole-4-carboxylate esters with halides through base, iodide, pivalate and solvent effect experiments with previously determined ligand/solvent pairs for selective C2 arylation.[9a,b] This mechanistic study was then successfully applied to design novel, efficient K_2CO_3- and PivOK-assisted C2- and C5-selective CMD procedures with bromide and chloride electrophiles in both series. The best yield/selectivity performance was obtained when P*t*Bu$_3$, PCy_3 and John-Phos were used for internal CMD and dppf and dppe were used for external CMD. This report gives new evidence for the involvement of a strongly base-dependent nCMD reaction in competition with the CMD reaction in base-assisted, palladium-catalysed direct C–H coupling methodology with halides. Competitive reactions revealed clearly that the competition between nCMD and CMD reactions was mainly reinforced by modulation of intrinsic basicity (Cs^+ vs. K^+), but unexpected electronic ligand effects were important for controlling the subtle nCMD/CMD competi-



Scheme 7. Proposed strongly base-assisted, palladium(0)-catalysed nCMD reaction for the oxazole- and thiazole-4-carboxylate series.

tion. Moreover, the charge interaction between the carbon possessing the most partial negative charge and the electropositive arylpalladium(II) catalyst appeared to be a determining factor in controlling the selectivity at the most hindered position when HOMO levels were almost identical for the CMD reaction. This is a different view from the current selection of the most electropositive site of the substrate, which allows the stabilisation of the developed negative charge of the internal CMD transition state.[5n] This new approach in selectivity is being evaluated for other azole series.[26]

Experimental Section

General: Compounds **1a** and **2a** were prepared according to our previously reported procedure.[9a] P*t*Bu$_3$·HBF$_4$, PCy$_3$·HBF$_4$, tributylphosphine, triphenylphosphine, tri(4-fluorophenyl)phosphine, tri-*o*-tolylphosphine, Cy-John-Phos, SPhos, John-Phos, dppf, dppe, dppb, starting materials **18**, **24** and halides were purchased from major chemical suppliers and were used as received.

General computational details: Atomic charges using electrostatic potentials were computed at the B3LYP/6-31G** level of theory using Jaguar as a part of the Maestro package implemented on a PC-Linux computer. Transition states were located without any constraint starting from a reasonable CMD structure after optimisation at the B3LYP level of theory as implemented in the Gaussian 03 package.[27] The basis set was DGZVP for palladium and TZVP for all other atoms. Free energies of the reagents and transition states were determined after a frequency calculation to perform a temperature correction and to compute the eigenvalues of the Hessian.

General procedure for DBU-assisted, C2-selective direct arylation of 1a: Compound **1a** (50 mg, 0.35 mmol) was placed in a sealed tube (10 mL) with DBU (106 μL, 0.70 mmol), Pd(OAc)$_2$ (4.5 mg, 0.018 mmol) and Cy-John-Phos ligand (12.3 mg, 0.035 mmol). A solution of aryl halide (0.35 mmol) in dry dioxane (1 mL) was added and the resulting mixture was purged with nitrogen. The mixture was stirred at 110 °C for 18 h. After filtration through Celite and concentration in vacuo, the crude product was purified by flash column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate as the eluent.

Compound 3b: White solid (81 mg, 96 %); m.p. 123–124 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.40 (t, J = 7.1 Hz, 3H), 4.43 (q, J = 7.1 Hz, 2H), 7.77 (d, J = 8.7 Hz, 2H), 8.22 (d, J = 8.7 Hz, 2H), 8.32 ppm (s, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.3, 62.3, 114.0, 115.0, 118.0, 127.5, 129.0, 130.6, 132.3, 132.8, 144.6, 153.6, 161.6 ppm; IR (KBr): $\tilde{\nu}$ = 1551, 1572, 1654, 1717, 2230, 3100 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{10}N_2O_3$ (242.2): C 64.46, H 4.16, N 11.56; found: C 64.63, H 4.10, N 11.54. Analytical data are consistent with those reported in the literature.[9a]

Compound 3c: White solid (76 mg, 88 %); m.p. 102–103 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.40 (t, J = 7.0 Hz, 3H), 3.86 (s, 3H), 4.42 (q, J = 7.0 Hz, 2H), 6.97 (d, J = 8.9 Hz, 2H), 8.05 (d, J = 8.9 Hz, 2H), 8.22 ppm (s, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.4, 55.4, 61.3, 114.2, 119.1, 128.7, 134.5, 143.2, 161.5, 161.9, 162.6 ppm; IR (KBr): $\tilde{\nu}$ = 1503, 1617, 1735, 2996, 3148 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{13}NO_4$ (247.2): C 63.15, H 5.30, N 5.67; found: C 63.05, H 4.97, N 5.48. Analytical data are consistent with those reported in the literature.[9a]

Compound 3d: White solid (57 mg, 66 %); m.p. 126–127 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.37 (t, J = 7.2 Hz, 3H), 4.40 (q, J = 7.2 Hz, 2H), 7.95 (d, J = 8.3 Hz, 2H), 8.24 (d, J = 8.3 Hz, 2H), 8.31 (s, 1H), 10.04 ppm (s, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.4, 61.6, 127.4, 130.1, 131.3, 135.2, 137.8, 144.5, 161.1, 161.2, 191.5 ppm; IR (KBr): $\tilde{\nu}$ = 1584, 1613, 1704, 1726, 2848, 2991, 3151 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{11}NO_4$ (245.2): C 63.67, H 4.52, N 5.71; found: C 63.64, H 4.39, N 5.67. Analytical data are consistent with those reported in the literature.[9a]

Compound 3e: White solid (45 mg, 55 %); m.p. 152–153 °C; ^{1}H NMR CDCl$_3$, 300 MHz): δ = 1.38 (t, J = 7.2 Hz, 3H), 4.04 (s, 2H), 4.39 (q, J = 7.2 Hz, 2H), 6.69 (d, J = 8.7 Hz, 2H), 7.88 (d, J = 8.7 Hz, 2H), 8.17 ppm (s, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.4, 61.2, 114.6, 116.5, 128.6, 134.3, 142.9, 149.3, 161.8, 163.2 ppm; IR (KBr): $\tilde{\nu}$ = 1500, 1611, 1626, 1725, 2982, 3166, 3223, 3361, 3456 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{12}N_2O_3$ (232.2): C 62.06, H 5.21, N 12.06; found: C 62.16, H 4.92, N 12.04. Analytical data are consistent with those reported in the literature.[9a]

Compound 3f: White solid (73 mg, 96 %); m.p. 95–96 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.37 (t, J = 7.2 Hz, 3H), 4.40 (q, J = 7.2 Hz, 2H), 7.39 (ddd, J = 1.5, 4.8, 7.7 Hz, 1H), 7.82 (td, J = 1.5, 7.7 Hz, 1H), 8.26 (d, J = 7.7 Hz, 1H), 8.34 (s, 1H), 8.71 ppm (d, J = 4.8 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.4, 61.5, 122.9, 125.5, 134.9, 137.2, 144.8, 145.2, 150.1, 161.0, 161.1 ppm; IR (KBr): $\tilde{\nu}$ = 1561, 1591, 1744, 2986, 3076, 3127 cm^{-1}; elemental analysis calcd (%) for $C_{11}H_{10}N_2O_3$ (218.2): C 60.47, H 4.62, N 12.84; found: C 60.60, H 4.36, N 12.93. Analytical data are consistent with those reported in the literature.[9a]

Compound 3g: White solid (67 mg, 86 %); m.p. 93–94 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.38 (t, J = 7.1 Hz, 3H), 4.41 (q, J = 7.1 Hz, 2H), 7.40 (td, J = 4.9, 8.0 Hz, 1H), 8.31 (s, 1H), 8.37 (dd, J = 1.3, 8.0 Hz, 1H), 8.70 (dd, J = 1.3, 4.9 Hz, 1H), 9.30 ppm (d, J = 1.3 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.4, 61.6, 122.8, 123.7, 134.2, 135.0, 144.3, 148.1, 151.9, 160.2, 161.1 ppm; IR (KBr): $\tilde{\nu}$ = 1575, 1729, 2855, 2930, 2965, 2998, 3147 cm^{-1}; elemental analysis calcd (%) for $C_{11}H_{10}N_2O_3$ (218.2): C 60.55, H 4.62, N 12.84; found: C 60.42, H 4.66, N 12.76. Analytical data are consistent with those reported in the literature.[9a]

Compound 3h: White solid (86 mg, 92 %); m.p. 149–150 °C; ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 1.43 (t, J = 7.2 Hz, 3H), 4.46 (q, J = 7.2 Hz, 2H), 7.62 (td, J = 1.3, 8.3 Hz, 1H), 7.80 (td, J = 1.3, 8.3 Hz, 1H), 7.91 (d, J = 8.3 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 8.36 (s, 1H), 8.89 (d, J = 2.0 Hz, 1H), 9.59 ppm (d, J = 2.0 Hz, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 14.4, 61.6, 119.7, 127.1, 127.8, 128.6, 129.5, 131.4, 134.7, 135.1, 144.2, 147.8, 148.8, 160.5, 161.1 ppm; IR (KBr): $\tilde{\nu}$ = 1557, 1625, 1728, 2980, 3130, 3449.6 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{12}N_2O_3$ (268.3): C 67.16, H 4.51, N 10.44; found: C 67.25, H 4.39, N 10.29. Analytical data are consistent with those reported in the literature.[9a]

General procedure for PivOK-assisted, C2-selective direct arylation of 1a: Compound **1a** (50 mg, 0.35 mmol) was placed in a sealed tube (10 mL) with potassium carbonate (96 mg, 0.70 mmol), PivOH (11 mg, 0.12 mmol), Pd(OAc)$_2$ (4.5 mg, 0.018 mmol) and ligand (0.035 mmol). A solution of aryl halide (0.35 mmol) in dry dioxane (1 mL) was added and the resulting mixture was purged with argon. The mixture was stirred at 110 °C for 18 h. After filtration through Celite and concentration in vacuo, the crude product was purified by flash column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate as the eluent.

Compound 3b: By following the above procedure with 4-chlorocyanobenzene (48 mg) and P*t*Bu$_3$·HBF$_4$ (10.1 mg), compound **3b** was obtained as a white solid (42 mg, 49 %). Analytical data are identical to those previously reported.

Compound 3c: By following the above procedure with 4-bromoanisole (44 μL) and P*t*Bu$_3$·HBF$_4$ (10.1 mg), compound **3c** was obtained as a white solid (57 mg, 66 %). Analytical data are identical to those previously reported.

Compound 3d: By following the above procedure with 4-bromobenzaldehyde (49 mg) and P*t*Bu$_3$·HBF$_4$ (10.1 mg), compound **3d** was obtained as a white solid (51 mg, 74 %). Analytical data are identical to those previously reported.

Compound 3e: By following the above procedure with 4-chloroaniline (45 mg) and John-Phos ligand (10.4 mg) then standard workup followed by flash chromatography, compound **3e** was obtained (21 mg, 39 %). Analytical data are identical to those previously reported.

Compound 3f: By following the above procedure with 2-chloropyridine (33 μL, 0.35 mmol) and P*t*Bu$_3$·HBF$_4$ (10.1 mg, 0.035 mmol), compound **3f**

was obtained as a white solid (44 mg, 60%). Analytical data are identical to those previously reported.

Compound 3h: By following the above procedure with 3-bromoquinoline (48 μL) and P*t*Bu$_3$·HBF$_4$ (10.1 mg), compound **3h** was obtained as a white solid (43 mg, 48%). Analytical data are identical to those previously reported.

Compound 3i: By following the above procedure with 5-bromopyrimidine (56 mg) and P*t*Bu$_3$·HBF$_4$ (10.1 mg), compound **3i** was obtained as a white solid (40 mg, 53%). M.p. 137–138°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.39 (t, J=7.2 Hz, 3H), 4.42 (q, J=7.2 Hz, 2H), 4.26 (q, J=7.2 Hz, 2H), 8.36 (s, 1H), 9.30 (s, 1H), 9.39 ppm (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.4, 61.8, 121.4, 135.3, 144.8, 157.7, 160.1, 160.8 ppm; IR: $\tilde{\nu}$=3127, 2991, 1723, 1606, 1575 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_9N_3O_3$ (219.2): C 54.79, H 4.14, N 19.17; found: C 54.77, H 4.13, N 19.18.

General procedure for PivOK-assisted, C2-selective direct arylation of 2a: Compound **2a** (50 mg, 0.27 mmol) was placed in a sealed tub (10 mL) with potassium carbonate (75 mg, 0.54 mmol), PivOH (9 mg, 0.08 mmol), Pd(OAc)$_2$ (3 mg, 0.014 mmol) and P*t*Bu$_3$·HBF$_4$ (7.8 mg, 0.027 mmol). A solution of aryl halide (0.27 mmol) in dry dioxane (1 mL) was added and the resulting mixture was purged with nitrogen. The mixture was stirred at 110°C for 18 h. After filtration through Celite and concentration in vacuo, the crude product was purified by flash column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate as the eluent.

Compound 4b: By following the above procedure with 4-chlorobenzonitrile (37 mg), compound **4b** was obtained as a white solid (27 mg, 52%). M.p. 192–193°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.62 (s, 9H), 7.74 (dd, J=8.4, 1.2 Hz, 2H), 8.11 (s, 1H), 8.13 ppm (dd, J=8.4, 1.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=28.3, 82.6, 114.0, 118.4, 127.4, 132.9, 136.7, 150.2, 160.2, 166.0 ppm; IR (KBr): $\tilde{\nu}$=3133, 2976, 2230, 1712 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{14}N_2O_2S$ (286.3): C 62.92, H 4.93, N 9.78, S 11.20; found: C 62.85, H 4.98, N 9.72, S 11.25. Analytical data are consistent with those reported in the literature.[9b]

Compound 4e: By following the above procedure using 2-chloroquinoline (44 mg), compound **4e** was obtained as a white solid (21 mg, 38%). M.p. 160–161°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.64 (s, 9H), 7.55 (td, J=8.0, 1.3 Hz, 1H), 7.73 (td, J=8.0, 1.3 Hz, 1H) 7.83 (d, J=8.0 Hz, 1H), 8.11 (d, J=8.6 Hz, 1H), 8.18 (s, 1H), 8.25 (d, J=8.6 Hz, 1H), 8.45 ppm (d, J=8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=28.3, 82.2, 118.2, 127.5, 127.9, 129.0, 129.4, 129.5, 130.2, 137.2, 147.8, 149.7, 150.6, 160.6, 170.1 ppm; IR (KBr): $\tilde{\nu}$=1716, 2931, 2980, 3002, 3061, 3133 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{16}N_2O_2S$ (312.4): C 65.36, H 5.16, N 8.97, S 10.26; found: C 65.23, H 5.18, N 8.93, S 10.31. Analytical data are consistent with those reported in the literature.[9b]

General procedure for K_2CO_3-assisted, C5-selective direct arylation of 1a: Compound **1a** (50 mg, 0.35 mmol) was placed in a sealed tube (10 mL) with potassium carbonate (96 mg, 0.70 mmol), Pd(OAc)$_2$ (4.5 mg, 0.018 mmol) and ligand (0.035 mmol). A solution of aryl halide (0.35 mmol) in dry dioxane (1 mL) was added and the resulting mixture was purged with nitrogen. The mixture was stirred at 110°C for 18 h. After filtration through Celite and concentration in vacuo, the crude product was purified by flash column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate as the eluent.

Compound 5c: By following the above procedure with 4-bromoanisole (44 μL) and John-Phos ligand (10.4 mg), compound **5c** was obtained as a white solid (47 mg, 54%). M.p. 70–71°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.41 (t, J=7.2 Hz, 3H), 3.86 (s, 3H), 4.41 (q, J=7.2 Hz, 2H), 7.00 (d, J=9.0 Hz, 2H), 7.85 (s, 1H), 8.07 ppm (d, J=9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.4, 55.5, 61.4, 113.9, 119.3, 125.4, 130.3, 148.5, 155.9, 161.3, 162.3 ppm; IR (KBr): $\tilde{\nu}$=3139, 2975, 1694, 1608, 1504, 1182, 1077, 847, 790, 643, 617, 547 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{13}NO_4$ (247.2): C 63.15, H 5.30, N 5.67; found: C 62.84, H 5.61, N 6.02.

Compound 5d: By following the above procedure with 4-bromo-*N*,*N*-dimethylaniline (70 mg) and dppf ligand (19.4 mg), compound **5d** was obtained as a pale brown solid (30 mg, 33%). M.p. 83–84°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.41 (t, J=7.2 Hz, 3H), 3.03 (s, 6H), 4.41 (q, J=7.2 Hz, 2H), 6.74 (d, J=9.0 Hz, 2H), 7.79 (s, 1H), 8.03 ppm (d, J=9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.3, 39.9, 60.9, 111.1, 113.8, 123.6, 129.6, 147.6, 151.3, 156.7, 162.3 ppm; IR (KBr): $\tilde{\nu}$=3125, 2899, 1705, 1608, 1516, 1371, 1181, 1070, 1029, 944, 785, 641 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{16}N_2O_3$ (260.3): C 64.60, H 6.20, N 10.76; found: C 64.82, H 6.34, N 10.84.

Compound 5e: By following the above procedure with 2-chloropyridine (33 μL) and John-Phos ligand (10.4 mg), compound **5e** was obtained as a white solid (30 mg, 39%). M.p. 76–77°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.40 (t, J=7.2 Hz, 3H), 4.42 (q, J=7.2 Hz, 2H), 7.36 (ddd, J=7.8, 4.8, 1.3 Hz, 1H), 7.83 (td, J=7.8, 1.3 Hz, 1H), 8.00 (s, 1H), 8.43 (d, J=7.8 Hz, 1H), 8.75 ppm (d, J=4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.3, 61.8, 124.7, 125.3, 128.8, 136.8, 145.8, 149.9, 150.2, 153.7, 161.8 ppm; IR: $\tilde{\nu}$=3094, 2975, 1713, 1571, 1528 cm^{-1}; elemental analysis calcd (%) for $C_{11}H_{10}N_2O_3$ (218.2): C 60.55, H 4.62, N 12.84; found: C 58.46, H 4.91, N 12.38.

Compound 5f: By following the above procedure with 3-bromoquinoline (48 μL) and John-Phos ligand (10.4 mg), compound **5f** was obtained as a yellow solid (35 mg, 37%). M.p. 111–112°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.43 (t, J=7.2 Hz, 3H), 4.46 (q, J=7.2 Hz, 2H), 7.61 (td, J=7.2, 0.7 Hz, 1H), 7.79 (td, J=7.2, 0.7 Hz, 1H), 7.94 (d, J=8.2 Hz, 1H), 8.03 (s, 1H), 8.14 (d, J=8.2 Hz, 1H), 9.08 (d, J=1.9 Hz, 1H), 9.42 ppm (d, J=1.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.6, 62.1, 120.5, 127.3, 127.8, 128.5, 129.1, 129.7, 131.5, 136.9, 148.6, 149.1, 150.0, 153.5 162.1 ppm; IR: $\tilde{\nu}$=3430, 3327, 2975, 1704, 1569 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{12}N_2O_3$ (268.3): C 67.16, H 4.51, N 10.44; found: C 66.87, H 4.77, N 10.15.

Compound 5g: By following the above procedure with 5-bromopyrimidine (56 mg) and John-Phos ligand (10.4 mg), compound **5g** was obtained as a white solid (39 mg, 51%). M.p. 89–90°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.42 (t, J=6.9 Hz, 3H), 4.45 (q, J=6.9 Hz, 2H), 8.04 (s,1H), 9.28 (s, 1H), 9.42 ppm (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.5, 62.4, 122.3, 125.6, 129.7, 150.2, 150.8, 156.3, 159.6, 161.6 ppm; IR: $\tilde{\nu}$=3110, 2986, 1713, 1572, 1313, 1078 cm^{-1}; elemental analysis calcd (%) for $C_{10}H_9N_3O_3$ (219.2): C 54.79, H 4.14, N 19.17; found: C 54.73, H 4.21, N 18.60.

General procedure for K_2CO_3-assisted, C5-selective direct arylation of 15: Compound **15** (38 mg, 0.27 mmol) was placed in a sealed tube (10 mL) with potassium carbonate (75 mg, 0.54 mmol), Pd(OAc)$_2$ (3 mg, 0.014 mmol) and dppe ligand (11 mg, 0.027 mmol). A solution of aryl halide (0.27 mmol) in dry dioxane (1 mL) was added and the resulting mixture was purged with nitrogen. The mixture was stirred at 110°C for 18 h. After filtration through Celite and concentration in vacuo, the crude product was purified by flash column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate as the eluent.

Compound 17d: By following the above procedure with 2-bromobenzonitrile (49 mg), compound **17d** was obtained as a white solid (24 mg, 37%). M.p. 98–99°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.86 (s, 3H), 7.51 (dd, J=0.6, 7.5 Hz, 1H), 7.56 (td, J=1.2, 7.8 Hz, 1H), 7.66 (td, J=1.2, 7.8 Hz, 1H), 7.79 (dd, J=0.9, 7.8 Hz, 1H), 8.91 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=52.7, 113.9, 117.3, 129.8, 131.3, 132.5, 133.2, 134.0, 141.6, 143.3, 153.1, 161.8 ppm; IR: $\tilde{\nu}$=3074, 2232, 1710 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_8N_2O_2S$ (244.3): C 59.00; H 3.30, N 11.47, S 13.13; found: C 59.00, H 3.37, N 11.22, S 13.33.

General procedure for PivOK-assisted, C5-selective direct arylation of 15: Compound **15** (38 mg, 0.27 mmol) was placed in a sealed tube (10 mL) with potassium carbonate (75 mg, 0.54 mmol), PivOH (9 mg, 0.08 mmol), Pd(OAc)$_2$ (3 mg, 0.014 mmol) and ligand (0.027 mmol). A solution of aryl halide (0.27 mmol) in dry dioxane (1 mL) was added and the resulting mixture was purged with nitrogen. The mixture was stirred at 110°C for 18 h. After filtration through Celite and concentration in vacuo, the crude product was purified by flash column chromatography on silica gel using a mixture of petroleum ether/ethyl acetate as the eluent.

Compound 17b: By following the above procedure with 4-chlorobenzonitrile (37 mg) and PCy$_3$·HBF$_4$ (9.9 mg), compound **17b** was obtained as a yellow solid (43 mg, 61%). M.p. 139–140°C; ^{1}H NMR ($CDCl_3$,

300 MHz): $\delta = 3.88$ (s, 3H), 7.64 (dd, $J = 6.6$, 2.1 Hz, 2H), 7.72 (dd, $J = 6.6$, 2.1 Hz, 2H), 8.85 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 52.6$, 113.2, 118.3, 130.9, 132.0, 134.8, 141.7, 144.5, 152.4, 161.9 ppm; IR: $\tilde{\nu} =$ 3069, 2959, 2224, 1708 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_8N_2O_2S$ (244.3): C 59.00, H 3.30, N 11.47, S 13.13; found: C 58.78, H 3.33, N 11.06, S 13.59.

Compound 17c: By following the above procedure with 3-bromobenzaldehyde (32 μL) and John-Phos ligand (8 mg), compound **17c** was obtained as a white solid (43 mg, 65%). M.p. 134–135 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.87$ (s, 3H), 7.63 (t, $J = 7.8$ Hz, 1H), 7.80 (ddd, $J = 7.8$, 1.2, 1.8 Hz, 1H), 7.96 (dt, $J = 7.8$, 1.2 Hz, 1H), 8.01–8.02 (m, 1H), 8.83 (s, 1H), 10.06 ppm (s, 1H) ; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 52.6$; 129.1, 130.7, 131.1, 131.2, 136.0, 136.4, 141.4, 145.5, 151.9, 162.2, 191.6 ppm; IR: $\tilde{\nu} = 3066$, 2824, 1719, 1691 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_9NO_3S$ (247.3): C 58.29, H 3.67, N 5.66, S 12.97; found: C 58.31, H 3.66, N 5.59, S 13.14.

Compound 17e: By following the above procedure with 5-bromopyrimidine (43 mg) and $PCy_3{\cdot}HBF_4$ (9.9 mg), compound **17e** was obtained as a white solid (59 mg, 57%). M.p. 178–179 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.89$ (s, 3H), 8.91 (s, 2H), 8.93 (s, 1H), 9.27 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 52.9$, 153.1, 157.1, 158.9, 161.2 ppm; IR: $\tilde{\nu} = 3072$, 2921, 1704, 1551, 1233 cm^{-1}; elemental analysis calcd (%) for $C_9H_7N_3O_2S$ (221.2): C 48.86, H 3.19, N 18.99, S 14.49, found: C 48.36, H 3.38, N 18.70, 13.71.

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