

Cross-Coupling

Coupling of Reformatsky Reagents with Aryl Chlorides Enabled by Ylide-Functionalized Phosphine Ligands

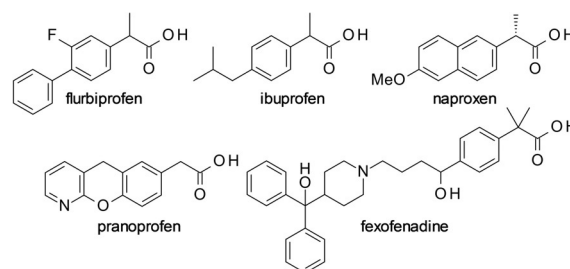
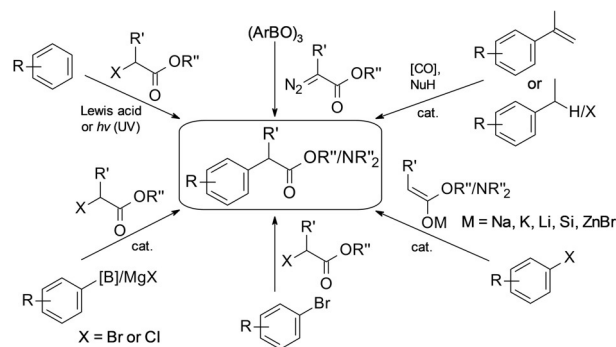
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Dedicated to Professor Pierre Dixneuf on the occasion of his 80th birthday

Abstract: The coupling of aryl chlorides with Reformatsky reagents is a desirable strategy for the construction of α -aryl esters but has so far been substantially limited in the substrate scope due to many challenges posed by various possible side reactions. This limitation has now been overcome by the tailoring of ylide-functionalized phosphines to fit the requirements of Negishi couplings. Record-setting activities were achieved in palladium-catalyzed arylations of organozinc reagents with aryl electrophiles using a cyclohexyl-YPhos ligand bearing an ortho-tolyl-substituent in the backbone. This highly electron-rich, bulky ligand enables the use of aryl chlorides in room temperature couplings of Reformatsky reagents. The reaction scope covers diversely functionalized arylacetic and arylpropionic acid derivatives. Aryl bromides and chlorides can be converted selectively over triflate electrophiles, which permits consecutive coupling strategies.

Introduction

The α -aryl ester unit is a key functionality in biologically active compounds and pharmaceuticals including the non-steroidal anti-inflammatory agents flurbiprofen, ibuprofen, naproxen and pranopfen, as well as the antihistamine fexofenadine (Figure 1).^[1] In addition, α -aryl esters and amides are valuable synthons en route to aryl alcohols, amines or nitriles.


 Figure 1. Examples of biologically active α -aryl alkylcarboxylates.

 Scheme 1. Synthetic entries to α -aryl alkylcarboxylates.

Several methods are available for the construction of α -aryl ester, but all of them have their individual limitations (Scheme 1). Uncatalyzed C–C bond-forming reactions between aryl electrophiles and enolates, for example, photochemical reactions,^[2] additions to benzyne,^[3] reactions with arylbismuth or aryllead reagents,^[4] and nucleophilic aromatic substitutions at electron-deficient arenes,^[5] suffer from limited substrate scope, toxic reagents, and/or harsh reaction conditions.

Friedel–Crafts alkylations of arenes with α -halo carbonyl compounds give a mixture of regioisomers.^[6] Reactions between arylboroxines with diazo esters are restricted by multistep-synthesis of starting materials.^[7] Catalytic carbonylation reactions are advantageous on large scales but experimentally difficult on lab scales.^[8] Couplings of phenylboronic acids or Grignard reagents^[9] are convenient but limited by the availability of the aryl nucleophile.

In the past decades, transition-metal-catalyzed α -arylations of carbonyl compounds have emerged as a powerful tool for the late-stage synthesis of α -arylesters,^[1a,5] but they call for strongly basic conditions.^[10] The increased acidity of the

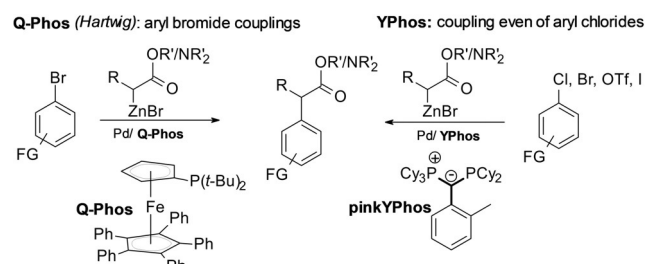
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<https://doi.org/10.1002/anie.202016048>.

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arylated product compared to the starting material often leads to undesired diarylation. In this respect, the use of mildly basic zinc enolates (Reformatsky reagents)^[11] was a major advance. These reagents are easily accessible from α -halo carbonyl compounds and zinc metal or zinc reagents, or directly from carbonyl compounds via deprotonation/transmetalation strategies.^[12] Hartwig et al. established the Pd-catalyzed Negishi coupling^[13] of aryl bromides with Reformatsky reagents as one of the most generally applicable synthetic concepts for the synthesis of functionalized α -aryl alkyl esters and amides (Scheme 2).^[14]



Scheme 2. Pd-catalyzed Negishi couplings of Reformatsky reagents.

The reaction critically depends on the use of extremely bulky, electron-rich Q-Phos ligands. However, even with this highly refined ligand system, the reaction is mostly limited to aryl bromide substrates. Only a small range of activated aryl chlorides were successfully converted at elevated temperatures, which led the authors to conclude that “studies are required to address the scope of the coupling (...) with chloroarenes.”^[15] This limitation is also found for metal-lathotoredox-catalyzed cross-coupling of aryl electrophiles with halocarboxylates.^[16]

The coupling of Reformatsky reagents with aryl chlorides^[17] still poses a substantial challenge, bringing even the most sophisticated catalyst systems to their performance limit.^[15] This is due to several additional challenges: (1) C- and O-metalated zinc enolates exist in equilibrium,^[12a] and competing C–O bond formation needs to be avoided. (2) The arylation product is more acidic than the starting material, and protonation equilibria might lead to diarylation by-products. (3) Uncatalyzed self-condensation of ester enolates proceeds rapidly,^[18] so that the oxidative addition of the aryl electrophile must occur rapidly to compete with this background reaction.^[19]

We recently established ylide-functionalized monophosphine ligands (YPhos) as steering ligands in catalysis.^[20] Palladium-YPhos complexes are easily generated from phosphonium salts, which are accessible in great structural diversity. The high donor strength induced by the ylide group in combination with bulky substituents at the phosphorous enables the synthesis of Pd catalysts with exceptional catalytic activity in Buchwald–Hartwig aminations,^[21] ketone arylations,^[22] and cross-couplings of organolithium and Grignard compounds.^[23] The bulky substituents at the ligand facilitate the formation of highly reactive monoligated Pd complexes, which allow oxidative additions of deactivated aryl chlorides at low temperatures.^[21a] These properties gave us confidence

that YPhos catalysts would go well beyond the limits of established ligand systems in the coupling of zinc enolates.

Results and Discussion

To test the potential of YPhos-Pd complexes as catalysts in Negishi couplings, we chose the coupling of Reformatsky reagent **2a** with 3-chloroanisole (**1a**) as a test reaction (Table 1). The reference in this area, Q-Phos-Pd systems, were found to be inactive at room temperature. Other high-performance ligands of the Buchwald or Fu-type, as well as CataCXium A ($\text{Ad}_2\text{P}^t\text{Bu}$), gave unsatisfactory yields, and standard alkyl- or arylphosphines were ineffective (Table 1, entries 1–3 and Table S1). No significant improvement was observed when using defined Pd complexes. Also, the simple YPhos ligand **L1** with a methyl group in the backbone was tested without success. However, the introduction of an aryl substituent at the ylidic carbon atom (**L2**) unleashed the desired reactivity. Fine-tuning of the ligand design revealed a high sensitivity of the catalyst performance towards the

Table 1: Coupling of aryl halides with Reformatsky reagent.^[a]

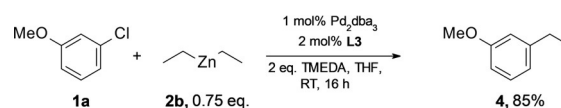
Entry	X	Ligand L	Additive	t [h]	3 [%]
1	Cl	Q-Phos	–	12	4
2	Cl	XPhos	–	12	16
3	Cl	^t Bu-XPhos	–	12	18
4	Cl	L1	–	12	traces
5	Cl	L2	–	12	35
6	Cl	L3	–	12	55
7	Cl	L4	–	12	30
8	Cl	L5	–	12	10
9	Cl	L6	–	12	16
10	Cl	L3	–	16	65
11	Cl	L3	LiCl	16	80
12	Cl	L3	LiBr	16	84
13	Cl	L3	Et ₃ N	16	62
14	Cl	L3	TMEDA	16	97
15	Cl	L3	DMPU	16	82
16 ^[b]	Cl	L3	TMEDA	16	95
17 ^[b,c]	Cl	L3	TMEDA	16	96 (95)^[d]
18 ^[b,c]	Br	L3	TMEDA	16	97
19 ^[b,c]	I	L3	TMEDA	16	90
20 ^[b,c]	OTf	L3	TMEDA	16	68

[a] Conditions: 0.25 mmol **1a**, 0.375 mmol **2a**, 2 mol % Pd_2dba_3 , 4 mol % **L**, 1.5 equiv. additive, 0.3 mL THF, RT, 16 h. [b] 2 equiv. of additive were used. [c] 1 mol % Pd_2dba_3 . [d] Yield of isolated product based on 0.5 mmol scale. Yields determined by GC analysis using *n*-tetradecane as internal standard.

ligand structure, with the *o*-tolyl group being the optimal substituent. Further increasing the steric demand and lowering the flexibility of the ligand structure by introduction of a mesityl group (**L4**) reduced the catalytic activity. Also, the more electron-rich *Pt*Bu₂ ligand (**L6**) led to lower yields suggesting that oxidative addition is not the critical step in the catalytic cycle. Based on this knowledge we also tested the newly designed ligand **L5** with an *ortho*-anisyl substituent (see the SI), which we hypothesized would facilitate transmetalation by pre-coordination of the zinc reagent. However, also this ligand led to no further improvement, thus emphasizing the challenges posed by this reaction.

Having identified the best ligand structure, we turned our attention towards a further improvement of the reaction conditions. The addition of solvents and additives is well known to modify the solution structure of zinc reagents and thereby influences their reactivity and stability.^[24] The zinc enolate has been reported to form stable dimers, which could be one reason for its low reactivity.^[24a,b] We thus employed TMEDA as an additive, since it has been reported to facilitate

the formation of mononuclear organometallic species.^[25] To our delight, this additive strongly increased the efficiency of the reaction, which we attribute to a higher concentration of mononuclear zinc species. For this reason, we tested various solvents, metal halides, and organic donor molecules (Table S2). THF was found to be the most effective solvent, TMEDA the best additive, also allowing a reduction of the catalyst loading to 1 mol %. Under optimized conditions, the reaction gave near-quantitative yields within 16 hours at room temperature. High yields were also achieved when starting from the corresponding aryl bromide (97 %), iodide (90 %), and triflate (68 %). The catalyst also effectively promotes the coupling of aryl chlorides with standard zinc reagents such as



Scheme 3. Pd-catalyzed Negishi couplings with diethylzinc.

Table 2: Coupling of aryl chlorides with Reformatsky reagent **2**.^[a]

$$\text{Ar(Het)}-\text{Cl} + \text{ZnBr}-\text{CH}(\text{CO}_2\text{R})\text{CH}_3 \xrightarrow[2 \text{ eq. TMEDA, THF, RT, 16 h}]{1 \text{ mol\% Pd}_2\text{dba}_3, 2 \text{ mol\% L3}} \text{Ar(Het)}-\text{CH}(\text{CO}_2\text{R})\text{CH}_3$$

1
2a or 2c
5–46

aryl chlorides

functional group tolerance

5, 97%

6, 90%

7, 86%

8, 86%

9, 53%

10, 85%^[b]

11, 94%

12, 90%

13, 98%

14, 85%

15, 68%

16, 64%

17, 75%

18, 90%

19, 93%

20, 90%

21, 82%

22, 98%^[b]

23, 38%^[b]

24, 21%^{[b][c]} (96%^{[b][c][d]})

25, 97%^[e]

steric hindrance

26, 98%

27, 96%

28, 94%

29, 83%

30, 52%

31, 42%

vinyl chlorides

30, 52%

31, 42%

heteroaryl chlorides

32, 65%

33, 92%

34, 96%

35, 55%

36, 93%^[f]

37, 58%

38, 94%^[f]

natural products or drug motifs

39, 84%, menthol derivative

40, 90%, loratadine

41, 42%, chloroxylenol derivative

42, 70%, arbutin derivative

43, 79%, clofibric acid derivative

44, 74%, estrone derivative

45, 89%, cholesterol derivative

46, 89%, indometacin derivative

[a] Conditions: 0.5 mmol **1**, 0.75 mmol **2a** or **2c**, 1 mol % Pd₂dba₃, 2 mol % **L3**, 2 equiv. TMEDA, 0.3 mL THF, RT, 16 h, yields of isolated product.

[b] 0.5 mol % Pd₂dba₃ and 1 mol % **L3**. [c] 2.2 equiv. **2c**. [d] No aryl chloride but aryl bromide. [e] 3 equiv. **2c**. [f] 40 h reaction time.

diethyl zinc producing the desired product **4** in 85 % yield (Scheme 3).

A wide variety of aryl and heteroaryl as well as vinyl chlorides was successfully coupled with Reformatsky reagent **2a** in good yields (Table 2). Suitable substrates range from electron-deficient (pyrazinyl) to extremely electron-rich (*p*-*N,N*-dimethylamino-phenyl) aryl- or heteroaryl chlorides, and the scope covers sterically highly demanding groups (*o,o*-dimethylphenyl) as well as coordinating pyridine or thiophene heterocycles. A wealth of functional groups is tolerated, including trifluoromethyl, fluoro, ester, trimethylsilyl, nitrile, mesylate, and even pinacol boronate (Table 2, **14–17**, **20**, **22**). The efficiency of the coupling is higher for sterically demanding *tert*-butyl than for ethyl ester substrates, so that they are recommended for particularly challenging aryl chlorides. The performance limit of the system is reached for 4-chlorophenol, which is likely to be deprotonated by the enolate leading to an extremely electron-rich chlorophenolate reluctant to undergo oxidative addition. Still, 4-chlorophenol was coupled to give **23** in a yield of 38 %. The coupling of 4-chloroaniline gave only unsatisfactory results, but 4-bromoaniline gave compound **24** in near-quantitative yield despite its free NH group (Table 2). The tolerance of these functionalities is remarkable, especially when considering that Pd-YPhos systems are powerful catalysts also for C–N bond formations. The established reaction protocol also allowed successful coupling of more complex structures, thus demonstrating its potential in late-stage functionaliza-

tion.^[4,9d,10g,26] For example, derivatives of menthol, cholesterol, loratadine or clofibric acid as well as estrone and arbutin could be converted in good to high yields (Table 2, **39–46**).

We next investigated the scope of the transformation with regard to the zinc reagents (Table 3). Not only linear, but also branched zinc enolates **2d** were successfully coupled, which is of substantial interest given the importance of the phenylpropenyl substructure. At this stage, the coupling of α,α -disubstituted Reformatsky reagents gave only unsatisfactory yields (see SI). Starting from commercially available 2-bromo-6-methoxynaphthalene, the naproxen ester **50** was obtained in almost quantitative yield. Amide enolates, even with Weinreb-type reactivity, which are easily prepared from Zn(TMP)₂ or lithium enolates,^[14b,27] were also successfully coupled (Table 3, **51–53**). The YPhos-Pd catalyst also allows the room-temperature Negishi cross-coupling^[28] of primary or secondary alkyl-, benzyl-, and arylzinc reagents. Best results were obtained when using Pd[COD]Cl₂ rather than Pd₂dba₃ as the Pd source (conditions **B**). At this stage, we have no explanation why Pd[COD]Cl₂, which is almost ineffective as the Pd source in the coupling of zinc enolates, is a superior Pd precursor for other organozinc reagents. To our delight, almost no rearrangement to linear products was observed.

Secondary alkylzinc reagent **2i** was converted with 25:1 selectivity in favor of the branched isomer (**56**); for the benzylic reagent **2n**, solely branched product was observed (**61**).

Since the preliminary studies (Table 1) indicated that the YPhos-Pd complex also convert bromides and triflates to the coupling products, we next examined a possible discrimination between the different electrophiles. To this end, we performed competition experiments in which two electrophiles were treated with zinc reagents (Scheme 4, Tables S3–S12).

Enolates, alkyl- and arylzinc reagents all gave excellent selectivities in favor of aryl bromides over triflates. A similar selectivity pattern was also observed for Q-Phos, whereas X-Phos was significantly less selective (see Table S13). Remarkably, even aryl chlorides were coupled preferentially over triflates despite their lower inherent leaving group ability.^[29]

Table 3: Coupling of aryl chlorides with zinc reagents.

1	2	Cond. A: 1 mol% Pd ₂ dba ₃ , 2 mol% L3, TMEDA, THF, RT, 16 h	Cond. B: 3 mol% Pd[COD]Cl ₂ , 3 mol% L3, THF, RT, 16 h	47–62
		Cond. A: FG = <i>m</i> -OMe, 47 , 89%		
		= <i>p</i> -OMe, 48 , 89%		
		= <i>p</i> -NO ₂ , 49 , 84%		
		Cond. A: 50 , 98% ^[a]		
		Cond. A: 51 , 45% (86% ^[b] , 56% ^[c])		
		Cond. A: 52 , 57% ^[c]		
		Cond. A: 53 , 64% ^[c]		
		Cond. B: 54 , 93%		
		Cond. B: 55 , 72%		
		Cond. B: 56 , 87% b:l = 25:1		
		Cond. B: 57 , 94%		
		Cond. B: 58 , 68%		
		Cond. B: 59 , 80%		
		Cond. B: 60 , 70%		
		Cond. A: 61 , 75%		
		Cond. A: 62 , 81%		

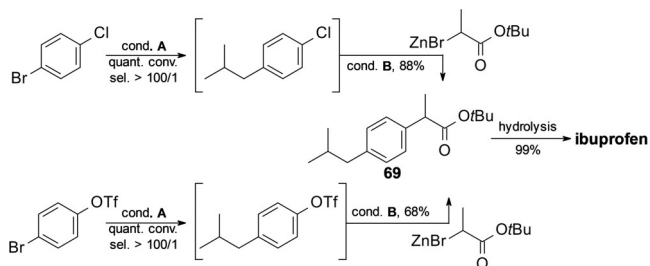
Conditions **A**: 0.5 mmol **1**, 0.75 mmol **2**, 1 mol% Pd₂dba₃, 2 mol% L3, 0.3 mL THF, 2 equiv. TMEDA, RT, 16 h, yields of isolated product. Conditions **B**: 0.5 mmol **1**, 0.75 mmol **2**, 3 mol% Pd[COD]Cl₂, 3 mol% L3, 0.3 mL THF, RT, 16 h, yields of isolated product. [a] No aryl chloride but aryl bromide. [b] Using (Et₃NCOCH₂)₂Zn, 2 mol% Pd₂dba₃, 4 mol% L3, and 1.5 equiv. LiBr. [c] Zinc reagent was prepared by lithium enolate with zinc chloride, 0.5 mmol **1**, 0.6 mmol amide **2**, 1 mol% Pd₂dba₃, 2 mol% L3, 1 mL THF.

R-Zn-Hal	X	Y	1 mol% Pd ₂ dba ₃ , 2 mol% L3, optimized cond.	R	R
R = CH ₂ COOEt	Cl	<i>t</i> -Bu		6%	78%
R = isobutyl	Cl	<i>t</i> -Bu		n.d.	98%
R = phenyl	Cl	<i>t</i> -Bu		13%	89%
R = CH ₂ COOEt	OTf	<i>t</i> -Bu		n.d.	85%
R = isobutyl	OTf	<i>t</i> -Bu		n.d.	98%
R = phenyl	OTf	<i>t</i> -Bu		2%	82%
R = CH ₂ COOEt	OTf	Cl		6%	68%
R = isobutyl	OTf	Cl		11%	88%
R = phenyl	OTf	Cl		11%	67%

Scheme 4. Selectivity of Br/Cl, Br/OTf, and Cl/OTf coupling with different zinc reagents. Conditions: 0.25 mmol (1 equiv.) aryl electrophiles, 1.1–1.5 equiv. zinc reagent **2**, 1 mol% Pd₂dba₃, 2 mol% L3, 2 equiv. additive, 0.3 mL THF, RT or 0°C, 16 h. Yields determined by GC analysis using *n*-tetradecane or methyl decanoate as internal standard. For detailed conditions see SI Table S3–S12.

This points towards a strong preference of YPhos-Pd catalysts for soft nucleophiles. The 10:1 selectivity of aryl bromides over chlorides is also on a preparatively useful level.

We used the synthesis of ibuprofen as a showpiece to demonstrate the synthetic utility of the distinct selectivity pattern of the YPhos-Pd catalyst. Consecutive treatment of *p*-bromochlorobenzene or *p*-bromophenyl triflate with isobutyl zinc **2g**, then with enolate **2d** in the presence of YPhos-Pd gave the desired product **69** in high selectivity and good yield (Scheme 5).



Scheme 5. Synthesis of ibuprofen. Cond. A: 1.3 equiv. **2g**, 1 mol% Pd₂dba₃, 2 mol% **L3**, 2 equiv. ZnBr₂, 0.3 mL THF, RT, 16 h. Cond. B: 1.3 equiv. **2d**, 1 mol% Pd₂dba₃, 2 mol% **L3**, 0.3 mL THF, 2 equiv. TMEDA, RT, 16 h. Hydrolysis: 5 equiv. TFA, 5.5 mL DCM, RT, 12 h.

Conclusion

A sterically demanding YPhos-Pd catalyst has been shown to be highly efficient in the Negishi cross-coupling of aryl chlorides. Already the first catalyst generation goes well beyond the state of the art in the challenging coupling of Reformatsky reagents. Screening of a series of different phosphines revealed that the ligand structure crucially affects the catalyst efficiency resulting in drastic changes even with seemingly small variations in the ligand architecture. The developed reaction protocol showed a high tolerance towards a variety of functional groups, which also allowed for the coupling of a large substrate scope including the functionalization of complex molecular structures. Furthermore, high selectivities were achieved with secondary alkyl zinc reagents as well as for the discrimination between chloro, bromo and triflate electrophiles, thus enabling the consecutive functionalization with different nucleophiles. Overall, the reported protocol substantially increases the breadth of application of zinc reagents in palladium-catalyzed coupling reactions and thus opens new possibilities for Negishi couplings also in the functionalization of complex structures.

Experimental Section

For the coupling of zinc enolates or aryl zinc reagents, a 20 mL vial was charged with Pd₂dba₃ (5.00 mg, 1 mol%, 21 wt % Pd), **L3** (5.80 mg, 2 mol%), and closed with a septum cap. Under exclusion of air and water, THF (0.3 mL) was added, and the resulting mixture was stirred at room temperature for 1 h. Aryl chloride **1** (0.50 mmol) and zinc reagent **2** (0.75 mmol, 1.5 equiv.), and TMEDA (117 mg, 1.00 mmol, 2 equiv.) were added via syringe and the resulting mixture was stirred at room temperature for 16 h.

For the coupling with alkyl zinc reagents, the 20 mL vial was charged with Pd[COD]Cl₂ (4.33 mg, 3 mol%), and **L3** (8.71 mg, 3 mol%) and closed with a septum cap. Under exclusion of air and water, THF (0.3 mL) was added, and the resulting mixture was stirred at room temperature for 1 h. Aryl chloride **1a** (0.50 mmol), and zinc reagent **2** (0.75 mmol, 1.5 equiv.) were added via syringe under argon atmosphere. The resulting mixture was stirred at room temperature for 16 h.

After the reactions were complete, they were quenched with water (20 mL) and extracted with Et₂O (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over MgSO₄, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (SiO₂, pentane/Et₂O or Cy/EtOAc).

Acknowledgements

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy—EXC-2033-390677874—RESOLV and SFB TRR88 “3MET” and by the European Research Council (Starting Grant: YlideLigands 677749). We thank UMICORE for donating chemicals, BMBF and the state of NRW (Center of Solvation Science “ZEMOS”), as well as the CSC (fellowship to Z.H.) and the Alexander von Humboldt Foundation (fellowship to X.-J.W.) for financial support and M. Wüstefeld for HRMS measurements. Open access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors have filed patent WO2019030304 in collaboration with UMICORE AG & Co. KG, covering YPhos ligands and complexes.

Keywords: aryl chlorides · cross-coupling · phosphine ligands · Reformatsky reagent · selectivity

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Manuscript received: December 2, 2020

Accepted manuscript online: January 11, 2021

Version of record online: January 28, 2021