Tetrahedron 72 (2016) 6668–6677

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Readily available catalysts for demanding Suzuki–Miyaura couplings under mild conditions

Oleg M. Demchuk *, Katarzyna Kapłon, Liliana Mazur, Dorota Strzelecka, K. Michał Pietrusiewicz

Department of Organic Chemistry, Maria Curie-Sklodowska University, 33 Gliniana St., 20614 Lublin, Poland

ARTICLE INFO

Article history:
Received 7 June 2016
Received in revised form 17 August 2016
Accepted 30 August 2016
Available online 31 August 2016

Keywords:
Cross-coupling
C,P-complexation
Aqueous media
Suzuki–Miyaura coupling
Heck reaction
Catalyst structure

ABSTRACT

A straightforward synthesis of a sterically hindered and electron rich bidentate monophosphine biaryl ligand *Sym*-Phos of C,P-type of complexation was realised in a high yield starting from simple substrates in easily affordable conditions. In combination with a palladium source, the obtained ligand formed a highly active catalyst mediating sterically demanding Suzuki–Miyaura coupling reactions in aqueous media even at 60 °C and with no need to protect the reaction mixture by an inert gas.

1. Introduction

Sterically demanding Suzuki–Miyaura coupling reactions have been considered a significant challenge for the organic chemist and chemical industry.[1–4] Many tri- and tetra-*ortho* substituted (in relation to aryl–aryl bond) biaryls are associated with biologically active and natural compounds[5–10] and constitute a core of efficient ligands in homogenous catalysis,[11–16] as well as of functional materials.[17]

The palladium complexes of phosphorus ligands are typical catalysts for cross-coupling reactions.[18] The catalytic efficiency of such catalysts is closely associated with the basicity of the phosphorus atom and the steric hindrance created by its substituents. The electron density at phosphorus atom in the transition metal complexes is transmitted to the transition metals,[14,19] and increases their nucleophilicity and reactivity towards organohalides at the oxidative addition reaction step.[20–22] At the same time the presence of the bulky substituents on the phosphorus atom are also crucial.[23] The bulky groups at phosphorus atom in the ligand structure play a multi-fold role—they facilitate formation of the catalytically active low coordinating transition metal complexes with a single phosphorus ligand bonded, and accelerate the last reaction step of reductive elimination of the product. In certain cases the presence of the bulky substituents on the phosphorus atom are important to keep the ligand in the oxygen resistant conformation,[24] or conformation suitable for the high level of asymmetric induction.[15,25,26]

Results of the extensive number of complementary studies of many research groups indicate that the phosphorus ligands of less typical C,P-type of complexation (Fig. 1),[27,28] such ligands as Hayashi's MOP, Kočovský's MAP and Buchwald's *S*-Phos and similar,[27–31] are superior over the other types of phosphorus, nitrogen and sulfur ligands in challenging cross-coupling reactions.

Recent developments in synthetic organic chemistry allow sterically demanding couplings to take place thanks to the new and very efficient catalysts used. Such reactions are usually run in anhydrous conditions at high temperatures.[28,29,32–37] However, the substrate scope for the synthesis of tetra-*ortho*-substituted biaryls is not wide and usually limited to small alkyl and alkoxy substituted

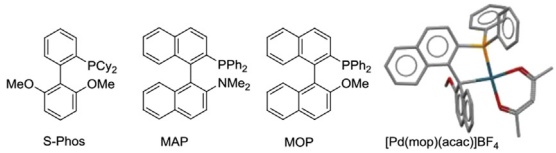


Fig. 1. Illustrative examples of C,P-ligands and complexes.

* Corresponding author. E-mail address: Oleh.Demchuk@UMCS.Lublin.pl (O.M. Demchuk).

http://dx.doi.org/10.1016/j.tet.2016.08.087
0040-4020/

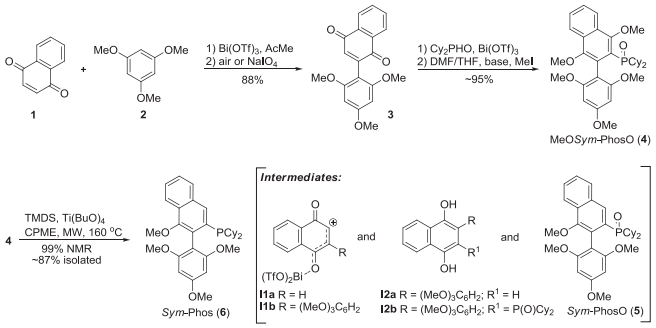
aromatics.[28] An additional challenge for the pharmaceutical and fine chemical industries is sustainable catalysis.[38,39] It could be very attractive to perform advanced Suzuki–Miyaura couplings in water at near to ambient temperatures. Water does not usually solubilise substrates nor products, but the inorganic 'by-products' of the reaction are soluble in water, and in combination with high yields of the reaction it makes the procedure of product isolation very simple. At the same time, the medium of the reaction could be used several times without purification (the reaction is not sensitive to inorganic salts present in the aqueous phase) and it could be used for the simplification of the process of recovering of used halogens.

The Suzuki–Miyaura coupling reactions, mediated by palladium complexes recently announced in a communication,[40,41] bulky and electron rich chelating monophosphorus biaryl ligand *Sym*-Phos (**6**), had been used to confront this challenge. Thus, herein we present the results of our comprehensive studies on the synthesis of sterically hindered biaryls performed in environmentally friendly conditions.[25,30,31,40,42] Assessed, in comparison with other excellent ligands, efficiency of palladium complexes of *Sym*-Phos in Suzuki–Miyaura and Heck coupling reaction in combination with the improved, notably simpler, fast, high-yielding and inexpensive synthesis could make *Sym*-Phos a ligand of choice in a variety of challenging cross-coupling reaction based syntheses.

2. Results and discussion

2.1. Synthesis of the *Sym*-Phos ligand

Approach to the synthesis of *Sym*-Phos (**6**) (Scheme 1) is based on a variation of the previously reported protocol we had applied in the synthesis of *Nap*-Phos ligand.[29] Taking into consideration that the most costly step of the *Nap*-Phos synthesis was naphthoquinone arylation realised by means of Suzuki–Miyaura coupling, in the optimised protocol leading to even more electron rich *Sym*-Phos ligand we used an alternative procedure of formal direct cross dehydrogenative coupling of naphthoquinone with 1,3,5-trimethoxy-benzene.[43] In such a way, the key intermediate **3** was obtained in 88% yield. The arylation reaction starts with the activation of **1** by coordination of oxophilic bismuth(III) (Scheme 1, intermediate **I1a**), and subsequently dihydroxynaphthalene **I2a** is formed according to the Friedel–Crafts mechanism. Next, intermediate **I2a** undergoes the spontaneous oxidation by **1**, used in excess, or atmospheric dioxygen to arylnaphthoquinone **3** (the 60% of **3** have spontaneously crystallised from the reaction mixture at this point). To accelerate the oxidation process, sodium periodate could be added to the reaction mixture when the arylation is completed (the 88% of **3** could be chromatographically isolated from the reaction mixture at this point). Next improvement was made at the phosphorylation step. The classical approach to Michael addition of secondary phosphine oxides to EWG substituted olefins is based on the activation of phosphorus nucleophile by the strong base driven deprotonation of phosphine oxide. Such an approach suffers from its air sensitivity and possibility of base promoted side reactions. To override this problem we have developed an alternative Lewis acid catalysed procedure, according to which the treatment of **3** with dicyclohexylphosphine oxide (Cy_2PHO) in the presence of $Bi(OTf)_3$ leads to the formation of intermediate **I2b**, which can be isolated by filtration. Without the isolation, **I2b** was subjected to the methylation reaction with dimethyl sulfate or methyl iodide run in the presence of sodium hydride and caesium carbonates in DMF giving MeO*Sym*-PhosO (**4**). Since **4** does not undergo the deoxygenation reaction in the presence of usual P=O reducing reagents,[29,44] the formed in situ titanium hydride reagent was applied in the synthesis of target *Sym*-Phos phosphine (**6**). The tandem conversion of MeO*Sym*-PhosO (**4**) to *Sym*-Phos (**6**) was realised in sealed pressure-resistant reactors under a microwave heating with the utilisation of reducing mixture $(Me_2SiH)_2O$ and $Ti(BuO)_4$ in CPME (cyclopentyl methyl ether) for 5 h at 160 °C in almost quantitative ^{31}P NMR yield. $(EtO)_3SiH$ or even $PhSiH_3$ could be used instead of TMDS; moreover, their utilisation resulted in some shortening of the reaction time. (Attention!) The significant amounts of flammable gases caused the rapid rise of the pressure inside the sealed reactors. Thus, in the cases of a full-scale synthesis the pressure was released after 1 h of reaction run. The pure phosphine **6** is crystallised from the chilled reaction mixture in 72% yield. An additional 15% of **6** could be chromatographically isolated from the residue. To omit the necessity to work with pressured microwave reactors, a two-steps produce leading from **4** to **6** in some lower yield could be also applied.[41] The demethoxylation of **4**, carried out under the reflux conditions in THF, in the presence of $PhSiH_3$ or $(Me_2SiH)_2O$ and $(i\text{-}PrO)_4Ti$, leads to **5** in reasonably high 75–80% yield. The deoxygenation of *Sym*-PhosO carried out in toluene at 100 °C by application of standard $HSiCl_3/Et_3N$ reductant furnish **6** in 85% isolated yield. The isolation of **6** include an alkalisation of the reaction mixture with 15% aqueous sodium hydroxide, filtration and washing with hot ethanol in a sealed vial. The *Sym*-Phos (**6**) is an air- and humidity resistant odour- and colourless phosphine, soluble in not polar organic solvents and weakly soluble in acetone and methanol. Exposed to air, diluted solutions of **6** undergo slow oxidation to form **5**.



Scheme 1. Synthesis of *Sym*-Phos (**6**).

2.2. Palladium complexes of *Sym*-Phos

The *Sym*-Phos ligand is structurally similar to the highly efficient ligands of *S*-Phos (and their analogues), while at the same time it is significantly more electron rich and spatially developed. These additional features of *Sym*-Phos allow us to expect that it will be also highly efficient in cross-coupling reaction. The pre-catalysts based on *Sym*-Phos were obtained in reaction of latter with bis(acetonitrile)dichloropalladium(II) in DCM. Applying different stoichiometry of the reagents, [Pd(*sym*-phos)$_2$Cl$_2$] and [Pd(*sym*-phos)Cl$_2$] complexes were obtained selectively. The ^{31}P NMR (CD_2Cl_2) spectra of the complexes contained signals at 48 and 61 ppm, respectively. This allows to make an assumption that the palladium atom in a complex with a single ligand is more charged than in a complex with two coordinated ligands. Thus, in the bisphosphine complex, two phosphorus ligands may donate more electron density to the palladium atom than a single phosphorus ligands together with an aromatic system participating in C,P-complexation. The pure monophosphine complex had been re-crystallised from DCM-Et_2O solution. At the same time, the bisphosphine complex was less stable and in the solution in weakly coordinating solvents (such as CD_2Cl_2, $CDCl_3$) it always underwent a partial dissociation to free *Sym*-Phos and [Pd(*sym*-phos)Cl$_2$]. The ^1H and ^{31}P NMR spectra of [Pd(*sym*-phos)Cl$_2$] recorded at 22 °C in $CDCl_3$ contained additional minor signals of equal amounts of free phosphine and [Pd(*sym*-phos)Cl$_2$]. Addition of some excess of *Sym*-Phos allows to shift equilibrium in the direction of complete formation of [Pd(*sym*-phos)$_2$Cl$_2$].

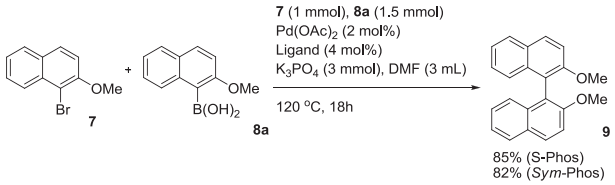
The nature of the 'special' electronic and chemical properties of obtained monophosphine complex was studied by means of X-ray crystallography (Fig. 2).[45] The mononuclear palladium(II) complex [Pd(*sym*-phos)Cl_2] crystallises in triclinic space group P-1 with two diethyl ether and two neutral [Pd(*sym*-phos)Cl_2] moieties (marked as I and II) in an asymmetric unit. One of the solvent molecules is disordered over two positions (O5A>C36A and O5B>C36B) with comparable occupancies of the appropriate atoms. The refinement of common occupancy factors (s.o.f.) gave the values 0.51(1):0.49(1).

The most visible conformational dissimilarities between I and II (Fig. 2) are in the geometry of the ligand and they are mostly due to rotation around the C3–C11 and C2–P1 bonds (see Supplementary data, Table S1). The molecules differ from each other in the relative orientation of the phenyl ring with respect to the naphthyl group, as evidenced by the dihedral angles between their best planes of 81.0(1)° and 86.2(1)°, respectively. Still another difference is in orientation of the 4-methoxy substituent (see Supplementary data, Fig. S1) which is rotated by 107.6(3)° (I) and −107.0(3)° (II) (see Supplementary data, Table S1) from the plane of the naphthyl group.

The structural data confirmed Pd(II)-arene interactions in the studied complex. The Pd atoms in both molecules adopt a distorted square-planar geometry. The distortion can be inferred by non-linearity of C11–Pd1–Cl2 and P1–Pd1–Cl1 bond angles (see Supplementary data, Table S1) which deviate quite significantly from the ideal 180°. The Pd1–Cl2 bonds *trans* to the phosphine-biaryl unit are slightly longer than Pd1–Cl1 ones *trans* to the trimetoxyphenyl group (Table S1). As expected, the C11–C(*ortho*) distances (1.447(4)–1.473(4) Å) are slightly longer than all remaining C–C bonds (1.365(4)–1.415(4) Å) in the phenyl ring, which indicate some delocalisation of the electron density in the system. Thus, the crystallographic analysis clearly indicates that palladium(II) complex of *Sym*-Phos adopt C,P-type of complexation geometry, in which palladium is chelating between the phosphorus and the first carbon atom of the phenyl ring. This coordination stabilises the monophosphorus complex, increases electron density at metal atom and makes it more resistant to weakly coordinating ligands (e.g., Cl^-, solvent or even second phosphine ligand).

2.3. Benchmark Suzuki–Miyaura coupling reactions run in organic solvent

The efficiency of the ligand **6** in palladium-catalysed cross-coupling reactions was tested in difficult Suzuki–Miyaura couplings. From historical perspective, synthesis of sterically hindered biaryls has been considered as especially challenging. Such reactions are usually run in anhydrous conditions at significantly higher temperature.[37] On the other hand, the utilisation of deactivated aromatic chlorides (those bearing EDG) in cross-coupling reaction is possible only in cases where highly active catalysts, based on electron rich ligands, are utilised. This is also why in our preliminary studies we applied such harsh conditions to collect data for direct comparison of the catalytic action of *Sym*-Phos based catalysts with the most efficient available on the market. Similarly like in the case of *S*-Phos complexes mediated reactions, under anhydrous conditions the catalysis by *Sym*-Phos complexes was realised with utilisation of palladium to phosphine ratio of 1:2. In a benchmark Suzuki–Miyaura coupling **7** with **8a** (Scheme 2), the utilisation of the catalyst based on electron rich and sterically hindered ligands *S*-Phos and *Sym*-Phos brought the 82 and 85% yields of **9**, respectively, while the reference catalysts based on Ph_3P, and $PhCy_2P$ (bulky as well as electron rich) did not allow to obtain **9** in significant yields.



Scheme 2. Benchmark Suzuki–Miyaura coupling reaction.

An active catalyst, derived from [Pd(*sym*-phos)$_2$$Cl_2$] complex, has proven to be highly efficient in demanding cases of Suzuki–Miyaura cross-couplings (Table 1). Thus, the [Pd(*sym*-phos)$_2$$Cl_2$] pre-catalyst, which is an air resistant compound and could be prepared separately from [Pd(C_6H_5CN)$_2$$Cl_2$] and *Sym*-Phos in DCM was used. Among tested anhydrous solvents, dioxane and toluene assured better yields, whereas CsF, K_3PO_4 and Cs_2CO_3 were the bases of choice in reactions run at 80–100 °C. Under these optimised conditions, a wide range of multiple ortho substituted sterically hindered and deactivated aryl chlorides and bromides as well as arylboronic acids underwent the coupling reactions to furnish the desired biaryl products in high isolated yields reaching 99%. Aryl bromide containing unprotected *ortho* amino group (which is usually not suitable for transition metal mediated catalytic processes) was also utilised in the reaction under the *Sym*-Phos complex catalysis and corresponding racemic biaryls were obtained in high yields (Table 1, entries 5, 6).

2.4. Water mediated Suzuki–Miyaura coupling reactions

Water is a natural green solvent, which could be used to mediate cross-coupling reactions. According to the mechanistic considerations, application of water may facilitate the transmetallation reaction step of the Suzuki–Miyaura coupling. At the same time, utilisation of water makes the isolation of the usually insoluble products more simple and overall process of biaryl synthesis less dangerous. As a benchmark reaction to evaluate the activity of *Sym*-Phos based catalysts in water mediated Suzuki–Miyaura reaction, the coupling furnishing 2,2′-dimethoxy-1,1′-binaphthyl (**9**) (Scheme 2) was chosen again. All the experiments were carried out without the application of protecting argon atmosphere in the presence of 2 mol % of palladium pre-catalyst of 1:2 palladium to ligand ratio.

It was important to use a proper palladium to ligand stoichiometry. In the tests where 1:1 and 1:3 ratios of Pd to *Sym*-Phos was applied, product **9** was obtained in significantly lower yields than in experiments with 1:2–2.5 ratio. This phenomenon could be rationalised with reference to philosophy of 'slow-release strategy'. According to it, the unstable active catalyst, bearing only one ligand and Pd(0) atom, should be slowly formed in the reaction, while a liberated ligand may undergo an oxidation by atmospheric oxygen.

To override the problem of the solubility of the substrates in water, small amounts of surfactants were added to the reaction mixture. In the preliminary experiments, a widely used surfactants

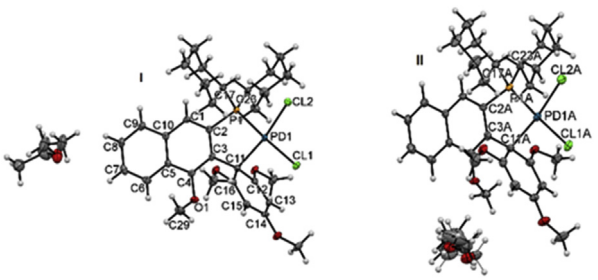
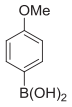
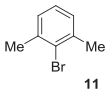
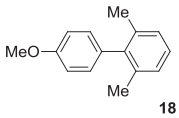
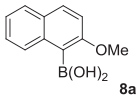
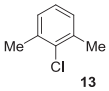
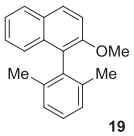
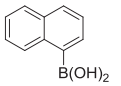
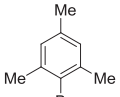
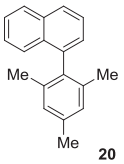
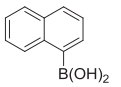
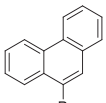
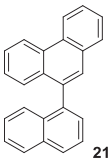
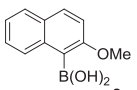
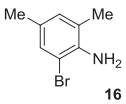
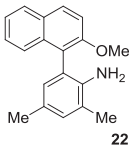
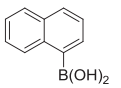
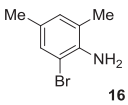
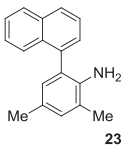
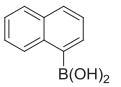
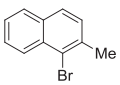
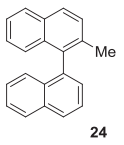
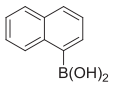
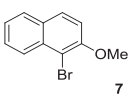
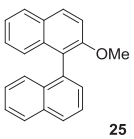


Fig. 2. Molecular structure of the diethyl ether solvate of [Pd(*sym*-phos)Cl_2]. Thermal ellipsoids are shown at the 50% probability level.

Table 1
Suzuki–Miyaura cross-coupling reaction run in anhydrous conditions

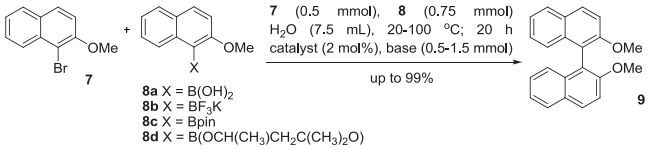
Entry	Substrates		Product	Yield, %
1	 **10**	 **11**	 **18**	90[a]
2	 **8a**	 **13**	 **19**	64[b]
3	 **12**	 **14**	 **20**	81[c]
4	 **12**	 **15**	 **21**	99[c]
5	 **8a**	 **16**	 **22**	82[c]
6	 **12**	 **16**	 **23**	99[c]
7	 **12**	 **17**	 **24**	99[d]
8	 **12**	 **7**	 **25**	99[d]

Conditions: Ar-Hal (1 mmol); Ar-B(OH)$_2$ (1.5 mmol).
[a] Dioxane (3 mL), 110 °C, 2 mol %, [Pd(*sym*-phos)$_2$Cl$_2$], CsF (3 mmol).
[b] Dioxane (3 mL), 110 °C, [Pd(*sym*-phos)$_2$Cl$_2$] (1.25%), K$_3$PO$_4$ (3 mmol), 16 h.
[c] Toluene (3 mL), 110 °C, K$_3$PO$_4$ (3 mmol), 2 mol % [Pd(*sym*-phos)$_2$Cl$_2$], 16 h.
[d] 2 mol % [Pd(*sym*-phos)$_2$Cl$_2$], DME (3 mL), Cs$_2$CO$_3$ (3 mmol), 4 h, 80 °C.

SDS, Triton X100 and Brij 97 were used. The reaction temperature, suitable base and appropriate amount of the surfactant were also optimised (Table 2).

The yield achieved in the case of utilisation of non-ionic surfactants was slightly higher (Table 2, entry 3 vs entry 4). Among 11 tested bases (K$_2$CO$_3$, K$_3$PO$_4$, Ca(OH)$_2$, NaOH, KOH, Ba(OH)$_2$, BaCO$_3$, CaCO$_3$, NaHCO$_3$, Cs$_2$CO$_3$, MgO), the most suitable proved to be Na$_2$CO$_3$ and K$_2$CO$_3$. Application of such derivatives of arylboronic acid as potassium trifluoroborates (Table 2, entries 1–4) pinacoloborates (Table 2, entry 19) as well as (4,4,6-trimethyl-[1,3,2]dioxaborinanes) instead of 2-methoxynaphthylboronic acid was also successful, and allowed the synthesis of 2,2-dimethoxy-1,1′-

Table 2
Optimisation of the conditions of water mediated couplings



Entry	8	Surfactant, %	Ligand	T, °C	Yield, %
1	**8b**	SDS (0.4)	*Sym*-Phos	20	34[a]
2	**8b**	SDS (0.4)	*Sym*-Phos	40	70[a]
3	**8b**	SDS (0.4)	*Sym*-Phos	60	89[a]
4	**8b**	Brij 97 (0.4)	*Sym*-Phos	60	92[a]
5	**8b**	SDS (0.3)	*Sym*-Phos	60	68[b]
6	**8b**	SDS (0.4)	*Sym*-Phos	90	28[a]
7	**8a**	None	*Sym*-Phos	60	69[a]
8	**8a**	Brij 97 (0.4)	*Sym*-Phos	60	81[a]
9	**8a**	Brij 97 (0.6)	*Sym*-Phos	60	80[a]
10	**8a**	Brij 97 (0.8)	*Sym*-Phos	60	88[a]
11	**8a**	Triton X100 (0.6)	*Sym*-Phos	60	83[a]
12	**8a**	SDS (0.3)	*Sym*-Phos	60	76[c]
13	**8a**	SDS (0.4)	*S*-Phos	60	63[c]
14	**8a**	SDS (0.4)	*S*-Phos	60	95[a]
15	**8b**	SDS (0.4)	*S*-Phos	60	95[a]
16	**8a**	SDS (0.4)	Ph$_3$P	100	>10[c]
17	**8b**	SDS (0.4)	Ph$_3$P	100	31[c]
18	**8a**	SDS (0.4)	PhCy$_2$P	60	0[c]
19	**8c**	Brij 97 (0.4)	*Sym*-Phos	60	91[a,d]
20	**8d**	Brij 97 (0.4)	*Sym*-Phos	60	99[a,d]

Conditions: **7** (0.5 mmol), **8** (0.75 mmol), Pd(OAc)$_2$ (2 mol %), ligand (4 mol %), H$_2$O (7.5 mL), 60 °C; 20 h, product isolated chromatographically.
[a] 1.5 mmol of Na$_2$CO$_3$ was used.
[b] 0.5 mmol of Na$_2$CO$_3$ was used.
[c] 1.5 mmol of K$_2$CO$_3$ was used.
[d] [Pd(*sym*-phos)$_2$Cl$_2$] pre-catalyst was used.

binaphthyl in up to 99% yield in the reactions run in 0.4% aqua solution of brij-97, in the presence of Na$_2$CO$_3$ and 2 mol % of PdCl$_2$(*sym*-phos)$_2$ pre-catalyst.

The optimal temperature of the reaction was determined. Low reaction temperature as 20 °C did not allow to achieve significant conversion (Table 2, entry 1). At the same time, it had been reported previously that use of such ligands as *Nap*-Phos and *S*-Phos at room temperature caused the significant progress of coupling reaction in relatively short time.[29] Thus, inactivity of *Sym*-Phos/Pd(OAc)$_2$ complexes at ambient temperature could be explained by the two simultaneously contributing factors—a slow activation of the pre-catalyst and slow coupling reaction of sterically hindered substrates at low temperature. On the other hand, at temperature as high as 90 °C resulted in the oxidation of the ligand (corresponding phosphine oxide **5** was found in the reaction mixture) and therefore lowering reaction yields (Table 2, entry 6). The optimal temperature, at which almost quantitative yields were obtained, was found to be 60 °C (Table 2, entry 4). In general, also in cross-coupling reactions run in water, *Sym*-Phos (**6**) and *S*-Phos appear to be notably efficient, while PhPCy$_2$ and Ph$_3$P proved to be not particularly useful.

The application of different amounts of surfactants also influenced the reaction yield. Without the surfactant addition, the substrates, products, and catalysts had coalesced to a single block which prevented reaction from proceeding further (Table 2, entry 7). Increasing the amount of the surfactant also increased the yields and at the same time decreased the product particle size. Thus, the optimal concentration of the surfactant (i.e., no significant yield increase observed in higher concentrations) was determined to be about 0.4–0.8%. The nature of the surfactant also influenced the yield of the coupling reaction. We chose to assess 11 surfactants of different nature: SDS, Brij 97, Triton x100, TPGS-750,[46] Pluronic P103, PEG-400, H$_3$C(CH$_2$)$_{15}$N(CH$_3$)$_3$Br, PEG-750M, SPAN 60 and SPAN 65, and the domestic liquid dishwashing detergent Ludwik®. In the case of reactive aromatic bromides, the nature of the

surfactant did not significantly influence the reaction yield. For example, in the coupling reaction of **12** with 1-bromo-4-methoxybenzene the yields of expected product were always above 95%. Thus, the search of the proper surfactant was performed with the utilisation more demanded chlorides. As a benchmark reaction used to assess the influence of surfactant structure on the reaction yield, was Suzuki–Miyaura coupling of 1-chloro-2-methoxybenzene (**26**) and 1-naphthylboronic acid (**12**). The coupling reactions were performed in an open vials in 2.5% aqueous solution of the tested surfactant in the presence of Na_2CO_3, $PdCl_2(C_6H_5CN)_2$ and *Sym*-Phos (**6**) ligand applied in ratio Pd to L of 1:2. The reaction product **27** did not crystallise from the reaction mixture and the extraction was therefore involved in the isolation process. The yields of the product were dependent both on the efficiency of the extraction and the chemical reaction yields. The efficiency of the extraction is related to the ability of aqueous and organic phase separation. It was divided into five groups: A—fast complete separation; B—some emulsion left after 1 h; C—emulsion occupies less than 25% of integrate volume after 1 h of phase separation; D—emulsion occupies more than 25% of integrate volume after 1 h of phase separation; E—emulsion occupies more than 50% of integrate volume after 1 h of phase separation (Fig. 3, Table 3).

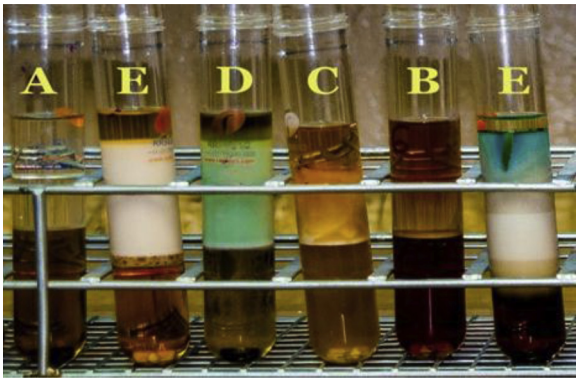
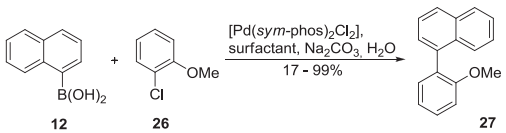


Fig. 3. Illustration of phase separation after 1 h of the extraction by DCM.

Table 3
Evaluation of surfactants in benchmark reaction leading to **27**



12 26 27

Entry	Surfactant	Efficiency layers separation[a]	Yield, %
1	None	A	62
2	Triton X-100	D	99[b]
3	SDS	E	28[b]
4	Ludwik®	E	95[b]
5	TPGS-750	B	64
6	Pluronic P103	B	17
7	$H_3C(CH_2)_{15}N^+(CH_3)_3\ Br^-$	E	22[b]
8	PEG 400	C	85
9	PEG 750M	C	90
10	SPAN 60	D	70[b]
11	SPAN 65	D	29[b]
12	Brij 95	C	97

Conditions: **26** (1 mmol), **12** (1.5 mmol), 1 mol % $[PdCl_2(sym\text{-phos})_2]$, 2.5% solution of surfactant in 15 mL of H_2O; Na_2CO_3 (3 mmol). All the reactions were repeated three times. The assessment of phase separation efficiency was made after 1 h of separation.

[a] Efficiency of separation of organic and inorganic layers were defined as next: A—fast complete separation; B—some emulsion left; C—emulsion occupy less than 25% of integrate volume; D—emulsion occupy more than 25% of integrate volume; E—emulsion occupy more than 50% of integrate volume Table Footnote.

[b] Yields were calculated based on GC–MS data.

Product **27** of the model reactions was isolated in these cases where organic phase was completely separated after the extraction, otherwise yields were calculated as a ratio of product to a substrate and by-products. The obtained results clearly indicate that the nature of the detergent significantly influenced the yield of Suzuki–Miyaura reaction, especially when deactivated aromatic chlorides are used as a coupling partner. The non-ionic surfactants usually facilitated the product formation (Table 3, entries 2, 4, 8, 9, 12). In the same time, especially in the case of unreactive aromatic chlorides, both cationic and anionic detergents have negative effect on the reaction yields (Table 3, entries 3, 7). This effect became less significant when more active aromatic bromides were used (Table 3, entries 3, 4).

The obtained results indicate that surfactant plays an active role in the reaction. It solves the solubility problem, arising from the use of insoluble in water reagents, and also it influences on catalytic cycle, probably by formation of nanomicelle encapsulated species which interact with the charged stern layer of micelle.

The utility of *Sym*-Phos were next demonstrated in the coupling reaction run in water in optimised conditions. The series of steric hindered biaryls had been obtained in high to excellent yields (Table 4).

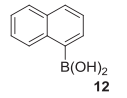
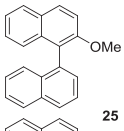
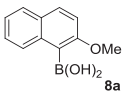
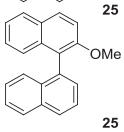
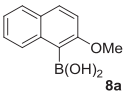
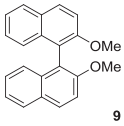
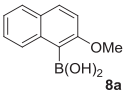
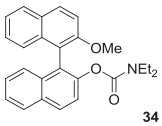
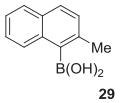
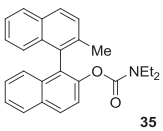
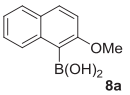
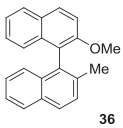
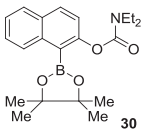
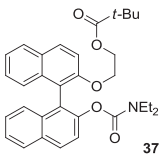
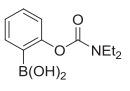
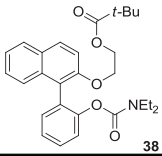
The reactions were carried out in the presence of SDS or Brij-97, Na_2CO_3, and 3 mol % of $[Pd(sym\text{-phos})_2Cl_2]$ pre-catalyst at 60 °C and allowed to obtain tri- and tetra-substituted biaryl products in 64%–99% yields. Application of argon protection atmosphere was not necessary, but it could have a positive effect on the reactions carried out at higher temperatures or with low catalyst loading. Interestingly, we did not observe the change in the reaction yield when, in case of synthesis **25**, we replaced bromide **7** with bromide **28** and boronic acid **12** with boronic acid **8a** (Table 4, entry 1 vs entry 2). The products of the benchmark reactions, obtained in mild and affordable conditions, are sterically hindered racemic but atropisomeric biaryls, which can find the practical applications in the synthesis of BINOL derivatives and some other chiral ligands and catalysts.[16]

Inspired by such promising results we have made the effort to reduce the amount of catalyst used as well as extended the substrate scope on EDG-inactivated, sterically hindered aromatic chlorides, triflates, and heterocyclic bromides (Table 5). The amount of catalyst reduced down to 0.5 mol % was used in the catalytic experiments protected this time by argon atmosphere. In the majority of the tested reactions we observed complete conversion of used halides. Nevertheless, in the cases of EDG-deactivated bis-*ortho* substituted chloride **13** and triflate **54**, as well as in the case of formation of some more hindered binaphthyls **55**, **19**, we found that significant amount of substrates remained after 16 h of the reaction. Taking the benefits from the use of argon protection atmosphere, we decided to increase the reaction temperature to 75 °C (Table 5, entries 12–17). This simplest change allowed to achieve excellent product yields also in such extremely difficult cases. Also, as indicated by entry 15, the utilisation of stable esters of arylboronic acids may be beneficial at higher temperatures. Finally, increasing the reactions scale from 1 to 10 mmol allows to reduce the amount of catalyst down to 0.27 mol % without deterioration of the reaction yield even in the case of unprotected 2-bromoaniline (**60**) (Table 5, entry 18).

2.5. Benchmark Heck reactions

In all tested cases of Suzuki–Miyaura reaction, the utilisation of *Sym*-Phos based catalysts brings excellent yields of the coupling products, better or comparable with those observed when *S*-Phos ligand was used. This allows to suppose that *Sym*-Phos will be efficient also in other than Suzuki–Miyaura types of the cross-coupling reactions. The attempts to perform model Heck

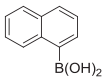
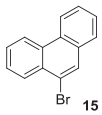
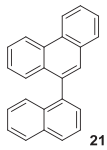
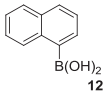
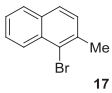
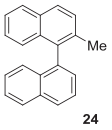
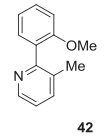
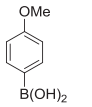
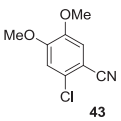
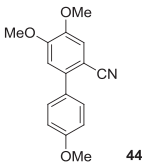
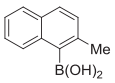
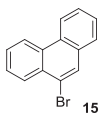
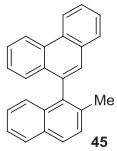
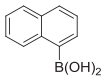
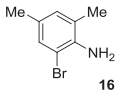
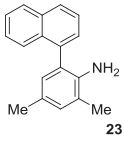
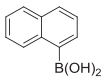
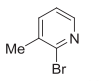
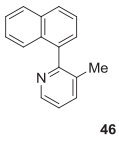
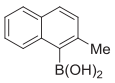
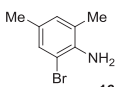
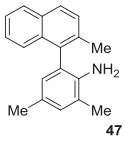
Table 4
Synthesis of steric hindered biaryls in water

Entry	Substrates	Product	Yield, %
1			97[a]
			96[b]
2			88[c]
3			94
4			82
5			67
6			63
7			67

Condition: Ar-X (1 mmol), Ar-B(OH)$_2$ (1.5 mmol), 2 mol% of [Pd(*sym*-phos)$_2$Cl$_2$], 15 mL of 0.4% brij 97 in H_2O, 16 h.
[a] 0.3% SDS was used instead of brij 97 solution.
[b] Reaction was run at 75 °C.
[c] 0.8% brij 97 was used.

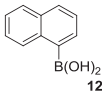
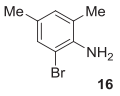
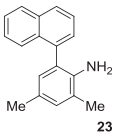
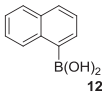
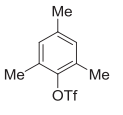
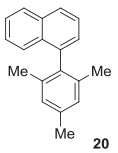
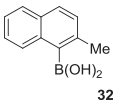
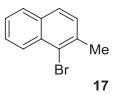
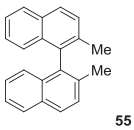
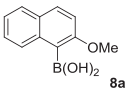
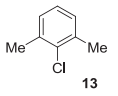
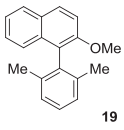
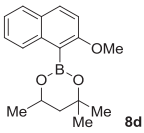
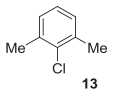
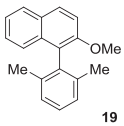
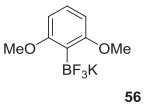
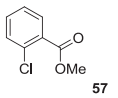
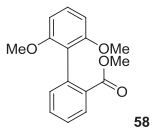
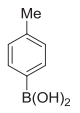
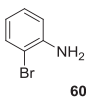
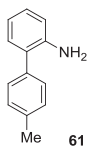
couplings of methyl acrylate with aromatic halides in water were undertaken next. The 2-bromo-1,4-dimethylbenzene, 2-iodo-1-ethyl-4-methylbenzene, 1-bromo-4-methylbenzene, and 1-bromo-4-methoxybenzene were selected to evaluate the usability of *Sym*-Phos in Heck reaction. The water mediated experiments were carried out in the previously optimised for Suzuki–Miyaura cross-coupling reactions conditions. Unfortunately, in all cases the unreacted aromatic halides were detected by means of GC–MS in almost initial amount. At the same time analogous Heck couplings run in DMA in the presence of Cy_2NMe and 2 mol% of [Pd(*sym*-phos)$_2$Cl$_2$] furnished desired products in high to excellent yields (Scheme 3).

Table 5
Substrate scope evaluation of the Suzuki coupling reaction

Entry	Substrates	Product	Yield, %
1	 		92
2	 		98
3	 		72
4	 		99
5	 		82
6	 		98
7	 		92
8	 		73
9			99
10			89
11			88

(*continued on next page*)

Table 5 (*continued*)

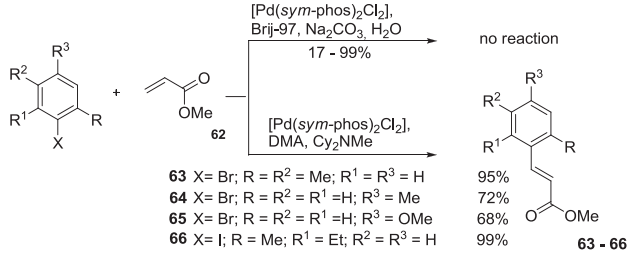
Entry	Substrates	Product	Yield, %
12	 **12**	 **16**	 **23**	99[a]
13	 **12**	 **54**	 **20**	99[a]
14	 **32**	 **17**	 **55**	85[a]
15	 **8a**	 **13**	 **19**	84[a]
16	 **8d**	 **13**	 **19**	93[a]
17	 **56**	 **57**	 **58**	76[a]
18	 **59**	 **60**	 **61**	99[b]

Condition: Ar-X (1 mmol), Ar-B(OH)$_2$ (2 mmol), 0.5 mol% of [Pd(*sym*-phos)$_2$Cl$_2$], 15 mL of 0.8% brij 97 in H_2O, 16 h, at 60 °C.

[a] Reaction was run at 75 °C.

[b] 59 (2 g, 14.7 mmol), 60 (1.72 g, 10 mmol), Na_2CO_3 (4.7 gm, 44 mmol), brij-97 (0.4%, 100 mL), [PdCl$_2$(*sym*-phos)$_2$] (34 mg, 0.27 mol%), 60 °C, 16 h.

In such a way, we have demonstrated that *Sym*-Phos ligand is also highly efficient in the Heck couplings reaction run under the usual for this type of coupling conditions. At the same time, low substrates conversion observed in water medium confirms the common opinion that efficient water mediated Heck coupling requires highly active substrates (usually non hindered iodides) or special micellar catalyst.[47,48]



Scheme 3. The model Heck coupling reaction.

3. Conclusions

In summary, we have designed and obtained highly efficient in Suzuki–Miyaura cross-coupling reactions, air stable, bulky, electron rich, chelating biaryl monophosphine ligand *Sym*-Phos of C,P-type of complexation. The palladium complexes of *Sym*-Phos were extremely active in both Suzuki–Miyaura and Heck cross-coupling reactions run under the anhydrous conditions as well as in the Suzuki–Miyaura cross-couplings run in aqueous media under the notably mild conditions. The variety of aromatic and heteroaromatic bromides, chlorides and triflates possessing deactivating EDG and substituents at bath *ortho* positions readily underwent catalysed palladium complexes of *Sym*-Phos cross-coupling reactions. As such, a wide range of coupling products were synthesised in good to excellent yields of 63–99%. It is anticipated, that some useful biaryl molecules could be produced by this method in the future. The effect of the base, surfactant and reaction temperature was also carefully studied. Further studies on exploration of active role of surfactants in cross-coupling reactions are in progress and will be reported in due course.

4. Experimental section

4.1. General

All reagents were purchased from Sigma–Aldrich, Strem, TCI and Alfa Aesar chemical companies and used without further purification. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F_{254} precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualisation of TLC plates was performed by means of UV light or either $KMnO_4$ or I_2 stains. NMR spectra were recorded on Bruker Avance 300, 400 or 500 MHz spectrometers, and chemical shifts are reported in ppm, and calibrated to residual solvent peaks at 7.27 ppm and 77.00 ppm for ^{1}H and ^{13}C in $CDCl_3$ or internal reference compounds. The following abbreviations are used in reporting NMR data: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Coupling constants (J) are in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). IR spectra were recorded on the Nicolet 8700A FTIR-ATR spectrometer. Wave numbers are in cm^{-1}. Products were purified by flash chromatography on silica gel 60 (230–400 mesh) using BUCHI chromatograph. MS spectra were recorded on Shimadzu LCMS IT-TOF spectrometer. The microwave heating was applied in SEM Discover Microwave Synthesizer. Commercially not available aryl bromide and arylboronic acid were obtained by known literature procedures. The details of synthesis as well as physical properties and NMR spectra of obtained products are available free of charge in Supplementary data.

4.2. 2-(2,4,6-Trimetoxyphenyl)naphthoquinone (3)

Obtained according to modified procedure which we reported previously.[41] A 100 mL round-bottom flask containing magnetic stir bar was charged with naphthoquinone (20 mmol, 3.16 g), 1,3,5-trimethoxybenzene (10 mmol, 1.68 g) and 25 mL acetone. The reaction mixture was stirred to dissolve the reactants and then Bi(OTf)$_3$ (0.05 mmol; 32.5 mg; 0.5%-mol) was added. The reaction mixture was refluxed under the vigorous stirring for 60 min. After this time $NaIO_3$ (9 mmol, 1.98 g) was added. The obtained mixture was next gently refluxed until complete oxidation of intermediate **I2a** (for about 24 h). Next, 50 g silica gel was added and solvent was evaporated off under the reduced pressure, the residue was placed

in short column and crude **3** was eluted with about 500 mL of chloroform. After evaporation of the solvent, the product was refluxed in 70 mL of methyl *tert*-butyl ether for 60 min, cooling down to rt, filtered, and dried under reduced pressure (1 mmHg) at 90 °C for 1 h. The product contains traces of naphthoquinone, whose complete removal is possible by prolonged gently heating under reduced pressure. Yield: 2.88 g (88%). Mp=182–183 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=3.74 (s, 6H, OCH_3), 3.87 (s, 3H, OCH_3), 6.21 (s, 2H, CH), 6.96 (s, 1H, CH), 7.73–7.75 (m, 2H, CH), 8.11–8.14 (m, 2H, CH). ^{13}C NMR (DEPT 135, 125.75 MHz, $CDCl_3$): δ=55.4 (COCH), 55.8 (OCH_3)$_3$, 90.8 (CH), 125.9 (CH), 126.8 (CH), 133.2 (CH), 133.4 (CH), 138.7 (CH). IR (neat): ν_{max}/cm^{-1} 3302, 3062, 3002, 2946, 2841, 1655, 1624, 1609, 1590, 1511, 1469, 1437, 1385, 1328, 1296, 1249, 1187, 1152, 1100, 1023, 1000, 925, 903, 869, 796, 772, 745, 716, 671, 565, 522. **HRMS (ESI):** *m*/*z*=325.1056 $[C_{19}H_{16}O_5+H]^+$, *m*/*z* (theor.)=325.1071, diff.=4.61 ppm.

4.3. MeO*Sym*-PhosO (4)

100 mL round-bottom flask containing magnetic stir bar was charged with **3** (3 mmol, 972 mg), dicyclophenylphosphine oxide (4.7 mmol, 1 g), 15 mL of THF, and $Bi(OTf)_3$ (0.12 mmol, 80 mg, 4 mol %). The reaction was stirred at 75 °C for 24 h. Next, the mixture was cooled down to room temperature, and equipped with U-shape bubbler filled with silicone oil. The reactor was evacuated and backfilled with argon, then Cs_2CO_3 (0.9 mmol; 0.3 g), tetrabutylammonium hydrogen sulfate (0.3 mmol, 0.1 g), and DMF (10 mL) were added. Under the vigorous stirring solid NaH (60% in Nujol, 17 mmol, 0.7 g) was added to a reactor in small portion to maintain slow liberation of hydrogen. Excessive foaming of the reaction mixture may be prevented by gentle vacuumating and backfilling with argon (via the bubbler). After the deprotonation is completed (approx. 2 h), the reaction mixture was cooled down to approx. 10 °C and CH_3I (16 mmol; 2.28 g; 1 mL) was slowly added. The reaction mixture was stirred next at room temperature for 24 h. After that, solvents were evaporated off under the reduced pressure, 50 mL of water was added and product **4** was extracted with methylene chloride (3×15 mL). A combined organic layer was dried over $MgSO_4$, filtered, and after the evaporation of solvent **4** was purified by column chromatography in hexane/ethyl acetate/methanol=5/3/0.2. Yield: 1.6 g (95%).

The synthesis was scaled up to 46 mmol scale. 500 mL round-bottom flask containing magnetic stir bar was charged with **3** (46 mmol, 15 g), dicyclophenylphosphine oxide (70 mmol, 15 g), 150 mL of DMF, and $Bi(OTf)_3$ (0.46 mmol, 300 mg, 1 mol %). The reaction was stirred at 95 °C for 48 h. Next, the mixture was cooled down to room temperature, and equipped with U-shape bubbler filled with silicone oil. The reactor was evacuated and backfilled with argon, then Cs_2CO_3 (15.4 mmol; 5 g), tetrabutylammonium hydrogen sulfate (3 mmol, 1 g). Under the vigorous stirring solid NaH (60% in Nujol, 150 mmol, 6 g) was added to a reactor in small portion to maintain slow liberation of hydrogen. Excessive foaming of the reaction mixture may be prevented by gentle vacuumating and backfilling with argon (via the bubbler). After the deprotonation is completed (approx. 3 h), the reaction mixture was cooled down to approx. 10 °C and CH_3I (370 mmol, 52.4 g, 23 mL) was slowly added. The reaction mixture was stirred next at room temperature for 24 h. After that, solvents were evaporated off under the reduced pressure, 150 mL of water was added and product **4** was extracted with methylene chloride (3×100 mL). A combined organic layer was dried over $MgSO_4$, filtered, and after the evaporation of solvent **4** was purified by column chromatography in hexane/ethyl acetate/methanol=5/3/0.2. After the evaporation of solvents from the collected eluant, diethyl ether (10 mL) was added to a crude product and formed crystalline **4** was filtered and dried under the reduced pressure. Yield: 21.4 g (82%).

Mp=109–110 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=1.17–2.18 (m, 22 H, Cy), 3.59 (s, 3H, OCH_3), 3.66 (s, 6H, OCH_3), 3.86 (s, 3H, OCH_3), 4.07 (s, 3H, OCH_3), 6.17 (s, 2H, CH), 7.52–7.58 (m, 2H, CH), 8.08 (d, *J*=8.20, 1H, CH), 8.16 (d, *J*=8.20, 1H, CH). ^{31}P NMR (202.45 MHz, $CDCl_3$): δ=49.60. ^{13}C NMR (75.52 MHz, $CDCl_3$): δ=26.4–27.3 (CH_2-Cy), 39.5 (CH-Cy), 40.4 (CH-Cy), 55.3 (OCH_3), 55.5 (OCH_3), 61.5 (OCH_3), 62.7 (OCH_3), 62.7 (OCH_3), 90.3 (CH), 123.9 (CH), 123.9 (CH), 124.0 (CH), 126.0 (CH), 127.4 (CH). IR (neat): ν_{max}/cm^{-1} 3467, 3406, 2924, 2850, 2168, 1611, 1591, 1505, 1467, 1449, 1412, 1341, 1271, 1223, 1204, 1182, 1155, 1126, 1072, 1041, 995, 963, 948, 887, 815, 780, 738, 699, 584, 529. **HRMS (ESI):** *m*/*z*=567.2881 $[C_{33}H_{43}O_6P+H]^+$, *m*/*z* (theor.)=567.2870, diff.=1.94 ppm.

4.4. 2-(Dicyclohexylphosphoryl)-3-(2,4,6-trimethoxyphenyl)-naphthalene-1,4-diol (I2b)

100 mL round-bottom flask containing magnetic stir bar was charged with **3** (10 mmol, 3.3 g), dicyclophenylphosphine oxide (20 mmol, 4.3 g), 80 mL of DMF, and $Bi(OTf)_3$ (0.30 mmol, 200 mg, 3 mol %). The reaction was stirred at 110 °C for 48 h. After that time the reaction was cooled down to ambient temperature and concentrated under the reduced pressure, than an equal volume of toluene was added. **I2b** was isolated by filtration as a white solid. Yield: 4.9 g (91%). Mp=dec 262–268 °C. ^{1}H NMR (500.13 MHz, $CDCl_3$): δ=13.52, (br s, 1H, OH), 8.40 (d, *J*=8.2, 1H, CH), 8.13 (d, *J*=9.0, 1H, CH), 7.54 (p, *J*=8.4, 2H, CH), 6.30 (s, 2H, CH), 4.58 (s, 1H, OH), 3.93 (s, 3H, CH_3), 3.71 (s, 6H, CH_3), 1.87–1.47 (m, 18H, Cy), 1.28–0.98 (m, 4H, Cy). ^{13}C NMR (75.53 MHz, $CDCl_3$): δ=25.8, 25.8, 26.2, 26.2, 26.5, 26.7, 26.9, 38.0, 38.8, 55.6, 56.0, 76.6, 77.0, 77.4, 91.4, 102.1, 103.3, 103.9, 110.8, 111.0, 122.0, 123.5, 125.7, 126.4, 126.6, 127.7, 141.2, 141.3, 158.6, 160.2, 163.0. ^{31}P NMR (202.45 MHz, $CDCl_3$): δ=66.98. IR (neat): ν_{max}/cm^{-1} 3492, 2986, 2931, 2900, 2858, 2839, 1601, 1575, 1495, 1464, 1401, 1384, 1365, 1335, 1275, 1203, 1179, 1145, 1156, 1122, 1097, 1083, 1063, 1032, 1019, 949, 887, 876, 848, 811, 789, 775, 747, 645, 538. **HRMS (ESI):** *m*/*z*=539.2579 $[C_{31}H_{39}O_6P+H]^+$, *m*/*z* (theor.)=539.2557, diff.=4.08 ppm.

4.5. *Sym*-Phos (6)

An argonated 10 mL microwave reactor containing magnetic stir bar was charged with MeO-*Sym*-PhosO (1 mmol, 567 mg), 4 mL of CPME, and TMDS (6 mmol, 1 mL) and $Ti(OBu)_4$ (1 mmol, 0.34 mL). The reactor was closed by snap cap and stirred under microwave heating at 130 °C for 30 min (note: reaction generate a significant pressure inside the reactor!). Next, the reaction was cooled down to ambient temperature, and formed gases were liberated. After that, the reaction mixture was subjected to microwave heating to maintain 160 °C for 5 h of stirring. Reaction mixture was then chilled down to −10 °C, formed crystalline precipitate was filtered, and washed with methanol to yield 376 mg (72%) of pure **6**. The filtrate was concentrated under the reduced pressure, mixed with 15 mL of pentane, formed participate was filtered and subjected to a column chromatography in hexane/acetone=6/1, this brought an additional 80 mg (15%) of **6**. Mp=186–188 °C. Solubility in CH_3CN—4 mg/mL, in MeOH—less than 1 mg/mL. ^{1}H NMR (300.33 MHz, benzene-d_6): δ=1.09–1.87 (m, 22H, Cy), 3.66 (s, 6H, OCH_3), 3.60 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.22 (s, 2H, CH), 7.48–7.51 (m, 2H, CH), 7.81–7.82 (m, 1 H, CH), 7.89–7.91 (m, 1H, CH), 8.14–8.16 (m, 1H, CH). ^{31}P NMR (121.57 MHz, benzene-d_6): δ=−8.87. ^{13}C NMR (DEPT 135, 125.75 MHz, benzene-d_6): δ=27.1–30.5 (CH_2-Cy), 34.8 (CH-Cy), 35.1 (CH-Cy), 54.6 (OCH_3-Ph), 55.0 (OCH_3-Ph), 55.2 (OCH_3-Ph), 60.9 (OCH_3), 90.7 (CH), 123.1 (CH), 126.1 (CH), 128.2 (CH), 128.3 (*C*H), 128.6 (*C*H), 128.8 (*C*H). IR (neat): ν_{max}/cm^{-1} 3004, 2921, 2845, 1604, 1586, 1502, 1485, 1447, 1408,

1354, 1330, 1315, 1263, 1222, 1198, 1177, 1154, 1120, 1106, 1068, 1047, 1032, 993, 949, 887, 849, 817, 758, 746, 635, 532. **HRMS (ESI):** *m*/*z*=521.2819 $[C_{32}H_{41}O_4P+H]^+$, *m*/*z* (theor.)=521.2815, diff.=0.77 ppm. *The alternative two steps synthesis of* **6** *is presented in* Supplementary data.

4.6. [Pd(*sym*-phos)Cl_2]

Sym-Phos (26 mg, 0.05 mmol) and $PdCl_2(CH_3CN)_2$ (13 mg, 0.05 mmol), and stirring bar were placed in 5 mL tube. The tube was argonated by vacuum/argon sequence for three times, and 2 mL of CH_2Cl_2 was added. The tube was closed and sonified at 50 °C for 30 min. Continuously stirring solution was cooled down to rt and diethyl ether had been slowly added to opalescence point. Solution was heated up and left in ambient conditions for a slow crystal growth. Yield: 34.8 mg (89%). Mp=dec 240–250 °C. The ^{1}H and ^{31}P NMR spectra were recorded at 22 °C. ^{31}P NMR (202 MHz, $CDCl_3$/CD_3OH): δ=63.26. ^{1}H NMR (500 MHz, $CDCl_3$/CD_3OH): δ=^{1}H NMR (500 MHz, $CDCl_3$): δ=7.87–7.91 (m, 2H); 7.77 (d, *J*=8.8 Hz, 1H); 7.47–7.51 (m, 2H); 6.01 (s, 2 H); 3.96 (s, 3H); 3.91 (br s, H_2O); 3.63 (s, 6H); 3.44 (s, 3H); 3.38 (q, *J*=6.9 Hz, 4H, Et_2O); 2.53 (bq, *J*=12 Hz, 2H); 2.23 (m, 2H); 1.83 (m, 2H); 1.57–1.69 (m, 10H); 1.18–1.26 (m, 6H); 1.09 (t, *J*=6.9 Hz, 6H, Et_2O). ^{13}C NMR (126 MHz, $CDCl_3$/CD_3OH): δ=178.0, 175.1, 153.1, 1530, 140.8, 137.1, 135.0, 134.9, 129.4, 129.4, 128.9, 127.8, 127.8, 127.0, 122.5, 92.4, 77.7, 77.3, 73.3, 65.8, 61.8, 57.0, 55.8, 38.4, 38.1, 28.8, 28.3, 28.3, 27.0, 27.0, 26.9, 26.9, 25.7, 14.8. IR (neat): ν_{max}/cm^{-1} 2922, 2851, 1597, 1529, 1472, 1444, 1402, 1356, 1326, 1266, 1229, 1207, 1179, 1157, 1116, 1063, 1015, 989, 909, 892, 822, 803, 763, 736, 678, 654, 517. **HRMS (ESI):** *m*/*z*=661.1489 $[C_{32}H_{41}O_4PClPd]^+$, *m*/*z* (theor.)=661.1460, diff.=4.39 ppm.

4.7. Single-crystal X-ray data and refinement details for $PdCl_2$(*sym*-phos)

$C_{32}H_{41}O_4PPdCl_2\cdot C_4H_{10}O$, triclinic, space group *P*-1, *a*=11.7498(3) Å, *b*=16.3333(7) Å, *c*=19.488(1) Å, α=85.623(4)°, β=75.914(3)°, γ=85.728(3)°, *V*=3611.0(3) Å^3; Z′=2; d_{calcd}=1.420 g cm^{-3}; μ=0.746 mm^{-1}; GooF=1.052; data/restraints/parameters: 16,471/0/868 [R_{int}=0.044]; final *R* indices (*I*>2(*I*)): R_1=0.0407, wR_2=0.0817; *R* indices (all data): R_1=0.0655, wR_2=0.0938; $\Delta\rho_{min/max}$ 0.74/0.59 e Å^{-3}. The crystallographic measurements were performed on an Oxford Diffraction Xcalibur CCD diffractometer with the graphite-monochromatised Mo K_α radiation (λ=0.71073 Å) at 100(2) K. Data sets were collected using the ω scan technique, with an angular scan width of 1.0°. The programs CrysAlis CCD and CrysAlis Red[49] were used for data collection, cell refinement and data reduction. A multi-scan absorption correction was applied. The structure was solved by direct methods using SHELXS-97[50] and refined by the full-matrix least-squares on F^2 using the SHELXL-97.[50] All non-H atoms were refined with anisotropic displacement parameters. H atoms were positioned geometrically and refined using the riding model with U_{iso}(H)=1.2–1.5U_{eq}(C) and C–H bond distances in the range 0.93–0.98 Å. **CCDC-1448447** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.8. [Pd(*sym*-phos)$_2$$Cl_2$]

Sym-Phos (110 mg, 0.22 mmol) and $PdCl_2(CH_3CN)_2$ (26 mg, 0.1 mmol), and stirring bar were placed in 5 mL Schlenk tube. The tube was argonated by vacuum/argon sequence for three times, and 3 mL of CH_3CN was added. The tube was closed and sonified at 20 °C for 10 min and at 40 °C for 30 min. Solvent was evaporated all under the reduces pressure and residue was sonified in Et_2O at 40 °C for 30 min under argon atmosphere. Formed fine yellow powder was filtered and dried in vacuum. Yield 100 mg (83%). Mp=dec 256–258 °C. Anal. C: 62.62; H: 6.82; Calcd for $C_{64}H_{84}Cl_2O_8P_2Pd$ C: 62.97; H: 6.94. The ^{1}H and ^{31}P NMR spectra recorded at 22 °C in $CDCl_3$ contained additional minor signals of equal amounts free phosphine and [Pd(*sym*-phos)Cl_2]. The addition of same excess of phosphine allows to shift equilibrium in direction of complete formation of [Pd(*sym*-phos)$_2$$Cl_2$]. ^{31}P NMR (202 MHz, $CDCl_3$): δ=48.11. ^{1}H NMR (500 MHz, $CDCl_3$): δ=^{1}H NMR (500 MHz, $CDCl_3$): δ=9.63 (t, *J*=7.9 Hz, 1H); 8.27 (bd, *J*=7.9 Hz, 1H); 8.17 (bd, *J*=7.9 Hz, 1H); 7.37–7.43 (m, 1H); 7.33–7.36 (m, 1H); 6.26 (s, 2H); 3.56 (s, 3H); 3.53 (s, 3H); 3.34 (s, 6H); 2.82 (m, 2H); 2.51 (m, 2H); 2.37 (m, 2H); 2.21 (m, 2H); 1.90–2.10 (m, 4H); 1.71–1.86 (m, 8H); 1.31–1.40 (m, 4H). ^{13}C NMR (125.75 MHz, CD_2Cl_2, at 0 °C): 161.5, 158.8, 153.7, 153.7, 153.7, 137.2, 137.1, 137.0, 132.2, 132.2, 132.1, 128.7, 128.1, 127.6, 127.1, 126.3, 122.3, 106.6, 90.1, 61.0, 55.5, 55.0, 33.6, 33.5, 33.5, 30.7, 28.6, 27.6, 27.5, 27.5, 26.3. IR (neat): ν_{max}/cm^{-1} 2922, 2848, 1606, 1584, 1503, 1446, 1413, 1344, 1303, 1267, 123, 1207, 1189, 1159, 1124, 1108, 1074, 1036, 994, 916, 957, 889, 850, 811, 746, 669, 631, 584, 505. **HRMS (ESI**): compounds dissociate under ionisation conditions to form [Pd(*sym*-phos)Cl_2] (*m*/*z*=661 Da) and *Sym*-phos (*m*/*z*=521 Da).

4.9. General procedure for Suzuki–Miyaura coupling run in organic solvent

A dried and argonated Schlenk tube containing a magnetic stir bar was charged with aryl halide (1 mmol), arylboronic acid (1.5 mmol), 3 mL of appropriate solvent, base (3 mmol), and catalyst (see Table 1). The flask was evacuated, backfilled with argon and placed in to the oil bath (kept at appropriate temperature) on a magnetic stirrer for 16 h. After that 20 mL of water was added to the reaction mixture and product was extracted with methylene chloride (3×10 mL), combined organic layer was dried over $MgSO_4$, filtered, solvent was evaporated and the product was isolated by column chromatography. Yields: 64–99%.

4.10. General procedure for Heck coupling run in organic solvent

A dried and argonated Schlenk tube containing a magnetic stir bar was charged with aryl halide (1 mmol), methyl acrylate (2 mmol), 4 mL of DMA, 400 μL of Cy_2NMe (3 mmol), and catalyst (2 mol %). The flask was evacuated, backfilled with argon and placed in to the oil bath (kept at 100 °C) on a magnetic stirrer for 16 h. After that 20 mL of water was added to the reaction mixture and product was extracted with Et_2O (3×10 mL), combined organic layer was dried over $MgSO_4$, filtered, solvent was evaporated and the product was isolated by column chromatography. Yields: 68–99%.

4.11. General procedure for Suzuki–Miyaura run in water

Preparation of catalyst: 10 mL flask was charged with a stirrer, $Pd(OAc)_2$ (0.02 mmol, 2 mol %), ligand (*Sym*-Phos, PPh_3, $PhPCy_2$, *S*-Phos) (0.04 mmol, 4 mol %) and 1 mL of THF. The flask was evacuated, backfilled with argon, and the reaction mixture was stirred for 10 min at ambient temperature. Such prepared catalyst was used in the coupling reactions. Similarly were prepared catalysts based on $PdCl_2$ complexes. *Reaction setup*. A round-bottom flask containing magnetic stir bar was charged with 15 mL of 0.3% aqueous solution of SDS and base (3 mmol). Then aryl halide (1 mmol) dissolved in a minimum amount of THF, arylboronic acid or its derivative (1.5 mmol) and the pre-catalyst (see above) were added. The flask was placed in to the oil bath (kept at 60 °C) and reaction mixture was stirred for next 16 h. The product was filtered or extracted with methylene chloride or (3×10 mL), then combined organic layer was

dried over $MgSO_4$, filtered, solvent was evaporated and the product was isolated by column chromatography. Yields: 63–99%.

Acknowledgements

The financial support from the Polish National Science Centre grant number 2012/05/B/ST5/00362 is gratefully acknowledged. The research sample of CPME (cyclopentyl methyl ether) was granted by ZEON EUROPE GmbH.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.08.087.

References and notes

1. de Meijere, A.; Bräse, S.; Oestreich, M. *Metal Catalyzed Cross-coupling Reactions and More, 3 Volume Set*; Wiley, 2013.
2. Ackermann, L. *Modern Arylation Methods*; Wiley-VCH: Weinheim, 2009.
3. Johansson, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem.* **2012**, *124*, 5150–5174.
4. Burke, A. J.; Marques, C. S. *Catalytic Arylation Methods: From the Academic Lab to Industrial Processes*; Wiley, 2015.
5. Cepanec, I. *Synthesis of Biaryls*; Elsevier: Oxford, 2004.
6. Boldi, A. M. *Curr. Opin. Chem. Biol.* **2004**, *8*, 281–286.
7. Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563–639.
8. Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193–3207.
9. Chang, J.; Reiner, J.; Xie, J. *Chem. Rev.* **2005**, *105*, 4581–4609.
10. Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427.
11. Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857–898.
12. Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801–1836.
13. Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155–3212.
14. Demchuk, O. M.; Łastawiecka, E.; Pietrusiewicz, K. M. *Miesięcznik CHEMIK* **2013**, *67*, 325–340.
15. Demchuk, O. M.; Łastawiecka, E.; Pietrusiewicz, K. M. *Miesięcznik CHEMIK* **2012**, *66*, 758–770.
16. Zhou, Q.-L. *Privileged Chiral Ligands and Catalysts*; Wiley-VCH: Weinheim, Germany, 2011.
17. Zhou, Y.; He, Q.; Yang, Y.; Zhong, H.; He, C.; Sang, G.; Liu, W.; Yang, C.; Bai, F.; Li, Y. *Adv. Funct. Mater.* **2008**, *18*, 3299–3306.
18. Molander, G. A. *Handbook of Reagents for Organic Synthesis, Catalyst Components for Coupling Reactions*, 1 ed.; Wiley, 2013.
19. Demchuk, O. M.; Arlt, D.; Jasiński, R.; Pietrusiewicz, K. M. *J. Phys. Org. Chem.* **2012**, *25*, 1006–1011.
20. Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254–278.
21. Braga, A. A. C.; Ujaque, G.; Maseras, F. *Organometallics* **2006**, *25*, 3647–3658.
22. Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *Organometallics* **2007**, *26*, 2183–2192.
23. Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314–3332.
24. Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096–5101.
25. Demchuk, O. M.; Kapłon, K.; Kącka, A.; Pietrusiewicz, K. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2016**, *191*, 180–200 and publications cited there.
26. Shen, X.; Jones, G. O.; Watson, D. A.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 11278–11287.
27. (a) Dotta, P.; Kumar, P. G. A.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2003**, *22*, 5345–5349; (b) Vyskočil, Š.; Smrčina, M.; Kočovský, P. *Tetrahedron Lett.* **1998**, *39*, 9289–9292; (c) Vyskočil, Š.; Smrčina, M.; Hanuš, V.; Polášek, M.; Kočovský, P. *J. Org. Chem.* **1998**, *63*, 7738–7748; (d) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354–362.
28. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
29. Demchuk, O. M.; Yoruk, B.; Blackburn, T.; Snieckus, V. *Synlett* **2006**, 2908–2913.
30. Demchuk, O. M.; Jasiński, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2016**, *191*, 245–253 and publications cited there.
31. Mauger, C. C.; Mignani, G. A. *Aldrichimica Acta* **2006**, *39*, 17–24.
32. Zhao, Q.; Li, C.; Senanayake, C. H.; Tang, W. *Chem.—Eur. J.* **2013**, *19*, 2261–2265.
33. Altman, R. A.; Buchwald, S. L. *Nat. Protoc.* **2007**, *2*, 3115–3121.
34. Ruiz-Castillo, P.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 3085–3092.
35. Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201–2203.
36. Chartoire, A.; Lesieur, M.; Falivene, L.; Slawin, A. M. Z.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P. *Chem.—Eur. J.* **2012**, *18*, 4517–4521.
37. Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876.
38. Dunn, P. J.; Hii, K. K.; Krische, M. J.; Williams, M. T. *Sustainable Catalysis: Challenges and Practices for the Pharmaceutical and Fine Chemical Industries*; Wiley: Hoboken, New Jersey, 2013.
39. Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411–420.
40. Demchuk, O. M.; Kielar, K.; Pietrusiewicz, K. M. *Pure Appl. Chem.* **2011**, *83*, 633–644.
41. Kielar, K.; Demchuk, O. M. *Miesięcznik CHEMIK* **2012**, *66*, 585–589.
42. Kielar, K.; Demchuk, O. M.; Pietrusiewicz, K. M. *ISRN Org. Chem.* **2011**, *2*, 1–12.
43. Kapłon, K.; Demchuk, O. M.; Wieczorek, M.; Pietrusiewicz, K. M. *Curr. Chem. Lett.* **2014**, *3*, 23–36.
44. Demchuk, O. M.; Jasinski, R.; Pietrusiewicz, K. M. *Heteroat. Chem.* **2015**, *26*, 441–448.
45. CCDC-1448447 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
46. (a) Lipshutz, B. H.; Ghorai, S.; Abela, A. R.; Moser, R.; Nishikata, T.; Duplais, C.; Krasovskiy, A.; Gaston, R. D.; Gadwood, R. C. *J. Org. Chem.* **2011**, *76*, 4379–4391; (b) Isley, N. A.; Gallou, F.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2013**, *135*, 17707–17710.
47. Nabid, M. R.; Bide, Y. *Appl. Catal., A* **2014**, *469*, 183–190.
48. Iranpoor, N.; Rahimi, S.; Panahi, F. *RSC Adv.* **2015**, *5*, 49559–49567.
49. CrysAlis PRO; Agilent Technologies Ltd: Yarnton, Oxfordshire, 2013.
50. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.