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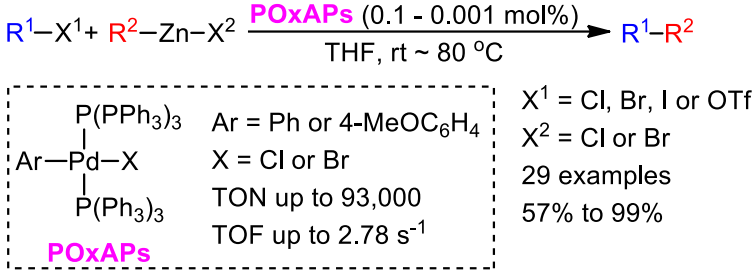
POxAP Precatalysts and the Negishi Cross-Coupling Reaction

Shuang-Qi Tang
Martine Schmitt
Frédéric Bihel*

Laboratoire d'Innovation Thérapeutique, Faculté de Pharmacie, UMR7200, Labex Médalis, CNRS, Université de Strasbourg, 74 Route du Rhin, 67412 Illkirch, France

fbihel@unistra.fr

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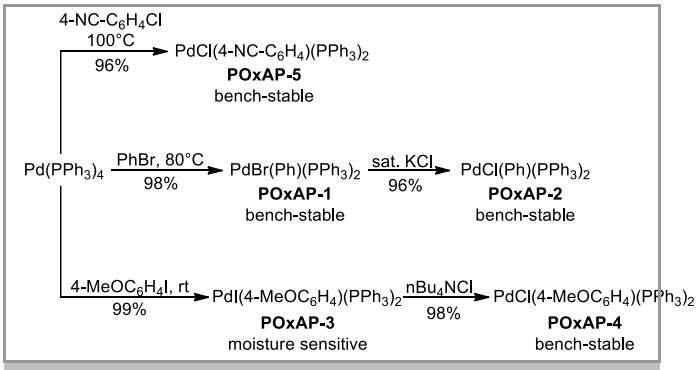
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Abstract Recently developed for Fukuyama reaction, POxAP precatalysts are also very efficient to catalyze Negishi cross-coupling reaction between organohalides and organozinc reagents. Using very low catalyst loading, POxAPs shows similar catalytic activities than classical precatalysts such as XPhos Pd G4 or PEPPSI-IPr, with TON about 90,000. Easily prepared and stable to air and moisture, POxAPs tolerate a wide range of functional groups in the Negishi CCR, and complete advantageously the arsenal of organic chemists in terms of Pd precatalysts.

Key words Negishi cross-coupling reaction, organohalide, organozinc, palladium, precatalyst, POxAP

Palladium-catalyzed cross-coupling reactions (CCR) have been widely recognized as a highly efficient and predictable tool for the construction of carbon-carbon (C-C) bond, enabling synthetic chemists to increase the complexity and diversity of their target molecules.[1] A major advance in CCR over the past two decades is likely the development of well-defined, bench-stable palladium precatalysts that do not require the addition of free ancillary ligands.[2] Indeed, specific ligands are often as expensive as palladium itself, and the traditional formation of the active Pd(0) by addition of excess ligand becomes particularly unattractive. By using well-defined and bench stable Pd(II) precatalyst, catalytic complex already contain one molar equivalent of ancillary ligand and can be easily and quickly transformed in active Pd(0) species, enabling reactions under milder conditions and with lower catalyst loadings. Although very efficient Pd(II) precatalysts have been already described in the literature, the development of alternative precatalysts could complete the tool box for CCR.

We have recently reported a novel family of precatalysts named POxAP (Post-Oxidative Addition Precatalyst) of generic formula $PdX(Ar)(PPh_3)_2$ (Scheme 1).[3] These palladium complexes are well-known in the literature, as they result from the first oxidative addition between a Pd(0) species and ArX in all Pd-catalyzed CCR involving aryl halides. However, they have been scarcely described *per se* as catalysts, with only three papers published in the 70s.[4,5] Fauvarque and Jutand reported a unique example in which the complex $PdI(Ph)(PPh_3)_2/PPh_3$ (10 mol%/20 mol%) was tested to couple $BrZnCH_2CO_2Et$ to PhI in a modest 54% yield.[5] Whereas iodinated POxAP (POxAP-3, Scheme 1) are moisture sensitive, brominated POxAP-1 or chlorinated POxAP-2, -4 & -5 appeared stable to air or moisture. In our hands, we have shown that all these POxAP precatalysts allowed the Fukuyama CCR between thioesters and organozinc reagents to be performed at room temperature with a 0.001% Pd loading and a turnover number (TON) of about 90,000.[3] We propose to describe in this article that POxAP precatalysts may also be useful for Negishi CCR between organozinc reagents and aryl halides.



Scheme 1 Simple access to POxAP precatalysts

Starting from $Pd(PPh_3)_4$, we were able to synthesize several POxAP precatalysts in gram scale in almost quantitative yields (Scheme 1). The temperature of the oxidative addition was directly linked to the nature of the halide (Cl > Br >> I). Geometry of these precatalysts are well defined as shown by the X-ray structure of POxAP-2 (Figure 1) which was fully consistent with the one published by Flemming.[6]

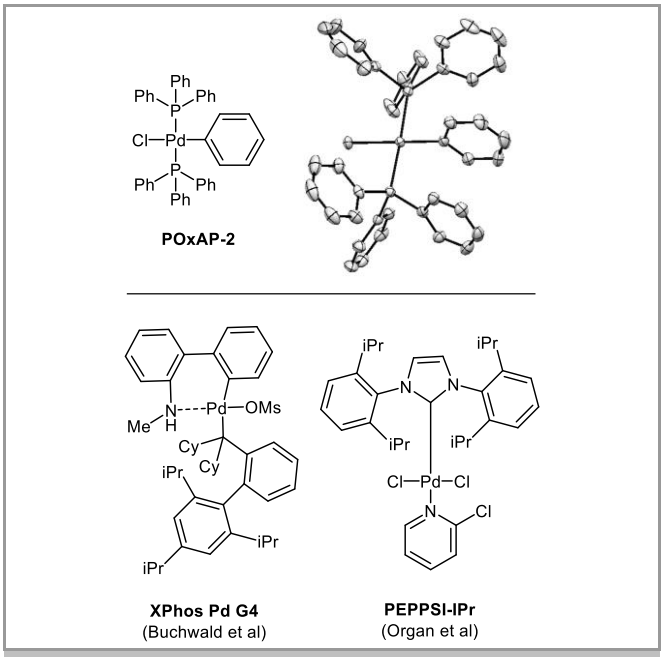
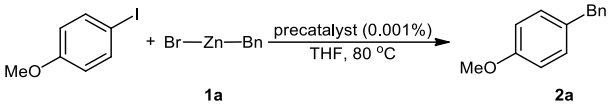


Figure 1 Upper panel: Crystallographically determined X-ray structure representation of POxAP-2. (CSD-JUWDEK);[6] Bottom panel: Structures of precatalysts XPhos Pd G4 and PEPPSI-IPr

As a starting point, we used standard Negishi CCR conditions to couple 4-$MeOC_6H_4I$ with BnZnBr in THF at 80 °C, but with a very low Pd loading (0.001 mol%) (Table 1 and Figure 2A). Under these conditions, $PdCl_2(PPh_3)_2$ appeared poorly efficient, affording the coupling product **2a** in 14% yield. In comparison, both POxAP-4 & -1 led to yields ranging from 89% to 93%, respectively. Both POxAPs were compared to XPhos Pd G4 and PEPPSI-IPr, two classical precatalysts for Negishi CCR (Figure 1). XPhos Pd G4 belongs to the 4th generation of palladacycle precatalysts developed by Buchwald et al.,[7] while PEPPSI-IPr is an organopalladium complex containing an N-heterocyclic carbene (NHC) ligand developed by Organ et al.[8] Both precatalysts are easy to prepare, stable under air or moisture, and are commonly used in various CCRs including Negishi CCR. [2] While these two classical precatalysts were found less efficient in the Fukuyama CCR,[3] they were found as expected very potent to catalyze the Negishi CCR shown in Table 1, affording compound **2a** in about 90% yield and TON of about 90,000. We were pleased to observe very similar values for POxAP-1 & -4. XPhos Pd G4 appeared to be the "fastest" precatalyst with an initial turnover frequency (TOF) of 3.89 s^{-1}, while POxAP-4 was significantly slower (1.11 s^{-1}) (Table 1 and Figure 2B). However, it is important to notice that these TOFs, measured during the first 30 minutes, highlight somehow the kinetic of formation of the catalytically-active Pd(0) species. Indeed, TOFs measured between 1 h and 3 h showed similar "cruising" rates, ranging from 1.4 to 1.8 s^{-1}, for the four precatalysts (Table 1 and Figure 2C).

Table 1 Kinetic study of precatalyst-catalyzed Negishi CCR[a]



1a 2a

Entry	Catalyst (0.001 mol %)	TON[b]	TOF (s^{-1}) Initial rate[c]	TOF (s^{-1}) Cruising rate[d]	Yield (%)[e]
1	$PdCl_2(PPh_3)_2$	14,000	0.56	0.28	14
2	POxAP-4	89,000	1.11	1.67	89
3	POxAP-1	93,000	2.78	1.67	93
4	XPhos Pd G4	92,000	3.89	1.81	92
5	PEPPSI iPr	87,000	2.22	1.39	87

[a] Reaction conditions: 1-iodo-4-methoxybenzene (0.2 mmol), 1a (0.3 mmol, 0.37 mL, 0.82 M in THF), precatalyst (0.001 mol %, 0.1 mL, 2×10^{-5} M in THF), 80 °C.
[b] TON was calculated by the yield at 40 h.
[c] Initial rate was measured between 0 and 30 min.
[d] Cruising rate was measured between 1 and 3 h.
[e] Yield of **2a** was determined from the average of two independent experiments after 40 h by HPLC/UV using caffeine as an internal standard.

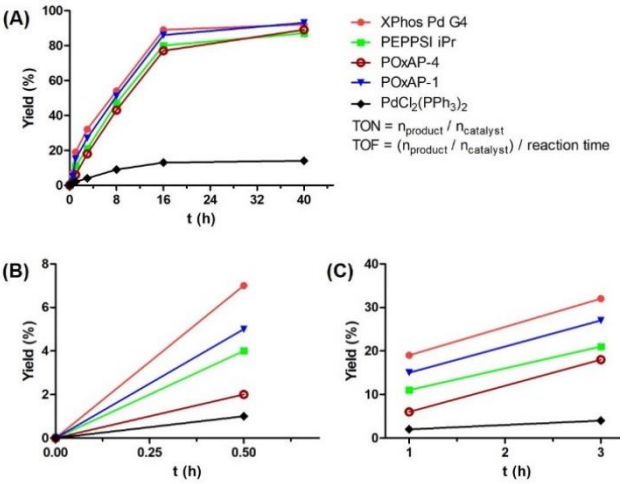
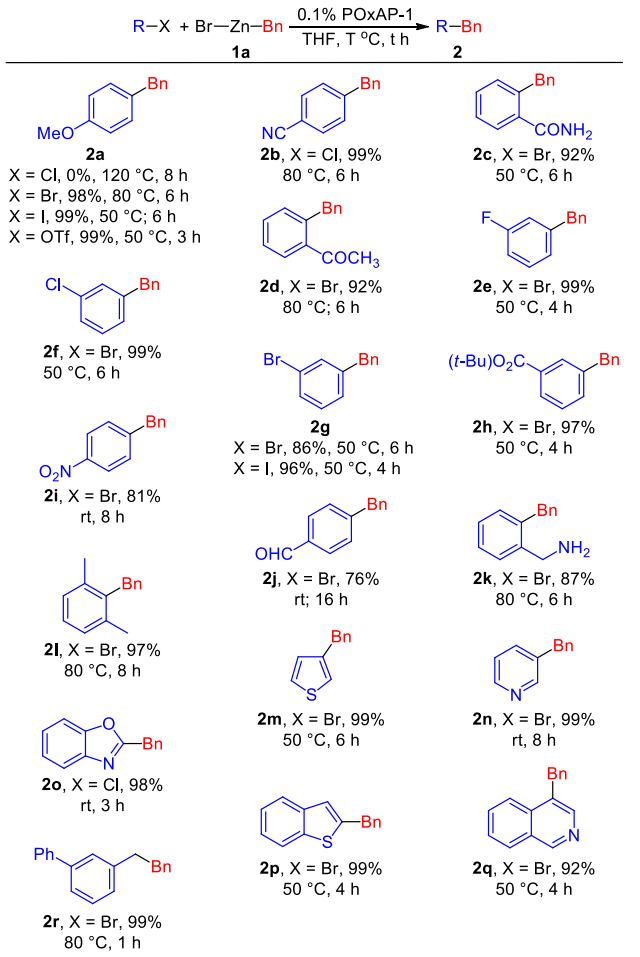


Figure 2 (A) Kinetic curves (0-40 h) of precatalyst-catalyzed Negishi CCR in Table 1; (B) Initial rate curves (0-30 min); (C) Cruising rate curves (1-3 h)

After establishing the potency of POxAPs to catalyze Negishi CCR in a model reaction, we established the scope of POxAP-1 to cross-couple various aryl halides (Scheme 2) as well as various organozinc reagents (Scheme 3).

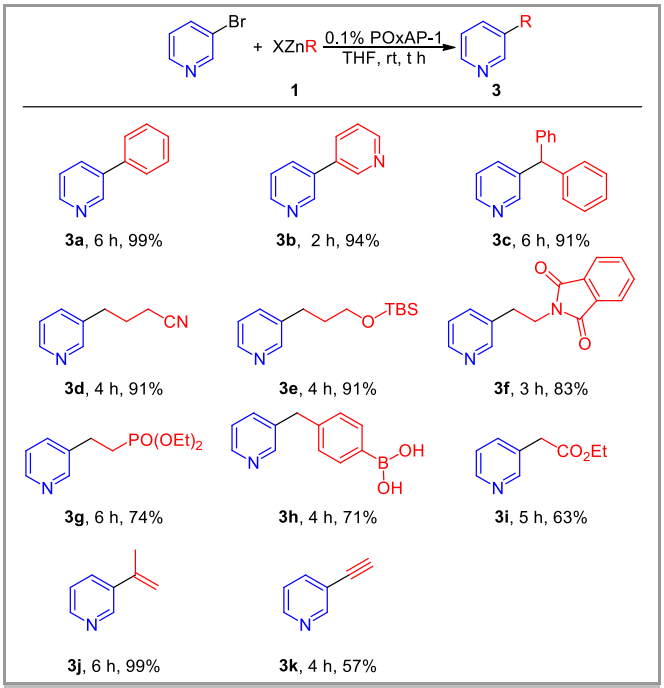
First, a diverse set of (hetero)aryl halides was investigated in presence of benzylzinc bromide (**1a**) with 0.1 mol% precatalyst loading (Scheme 2). Optimal reaction time and temperature were determined for each substrate in order to characterize the influence of substituents on reaction. As a standard, 1-benzyl-4-methoxybenzene (**2a**) was obtained in 98% yield (80 °C, 6 h) from the coupling reaction of 1-bromo-4-methoxybenzene with **1a**. Replacement of bromine by iodine or triflate facilitated the reaction, giving **2a** in nearly quantitative yield at lower temperature (50 °C) after 6 or 3 h, respectively. In contrast, 4-methoxy-chlorobenzene was less reactive and even at 120 °C, no reaction was observed. Interestingly, after replacing the electron-donating methoxy group by an electron-accepting cyano group, the corresponding aryl chloride became reactive enough to afford the expected product **2b** in 99% yield, after 6 h at 80 °C. Overall, aryl halides bearing electron-withdrawing substituents were generally coupled at lower temperatures (50 °C) than those bearing electron-donating groups (80 °C). This is perfectly

consistent with structure-activity relationships in Negishi CCR reported by Mayr et al., in which they showed that this CCR is accelerated by the presence of electron-acceptor on aryl halides.[9] As expected, precatalyst POxAP-1 did not alter the high tolerance of the Negishi CCR for a large variety of functional groups, including cyanide (**2b**), amide (**2c**), ketone (**2d**), aldehyde (**2j**) and free amine (**2k**). Even the reaction with the bulky *o*, *o'*-dimethylbromobenzene efficiently provided the target compound (**2l**) in nearly quantitative yield. Taken into account the difference of reactivity between halides (I > Br >> Cl >> F), chemoselective couplings were obtained in quantitative yields when starting from aryl bearing 2 different halides (**2e**-**g**). Heteroaryl halides, including N, O or S heteroatoms, appeared very reactive and led to coupling products at temperatures below 50 °C (**2m**-**q**). Finally, we tested the capability to couple an alkyl group (3-phenyl-benzylbromide) with 0.1 mol% Pd loading, and product **2r** was recovered in quantitative yield after only 1 h at 80 °C.



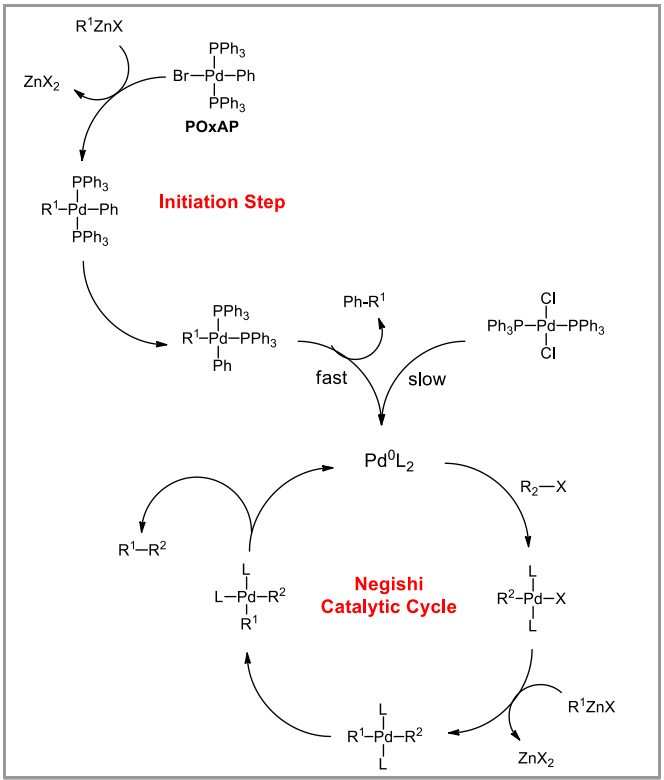
Scheme 2 $PdBr(Ph)(PPh_3)_2$-catalyzed Negishi CCR of halide and benzylzinc bromide (**1a**). Reaction conditions: halide (1 mmol), POxAP-1 (0.1 mol %, 1 mL, 10^{-3} M in THF), **1a** (1.5 mmol, 1.9 mL, 0.8 M in THF).

Next, we turned our attention to probe the scope of a diverse set of organozinc reagents (Scheme 3). 3-bromopyridine was used as model substrate and coupled at room temperature in presence of POxAP-1 (0.1 mol%). Phenylzinc chloride or 3-pyridylzinc chloride led to corresponding biaryls in excellent yields (**3a**-**b**), as well as alkylzinc halides (**3c**-**i**) or alkenylzinc chloride (**3j**). Ethynylzinc chloride reagent led to compound **3k** in a modest 57% yield, due to the formation of the side product 1,2-di(pyridin-3-yl)ethyne (11% yield) resulting from the double coupling reaction on the triple bond.[10] Again, POxAP-catalyzed Negishi CCR is very tolerant, allowing the presence of functional groups such as cyanide (**3d**, 91%), sylilated alcohol (**3e**, 91%), phthalimide (**3f**, 83%), or alkylated phosphonate (**3g**, 74%). Starting from organozinc bromomethyl-phenylboronic propane-1,3-diol ester, the reaction afforded after purification the free boronic acid derivative (**3h)** in good yield (71%). With ester group, the coupling product **3i** was obtained in 63% yield, and the product of homocoupling 3,3'-bipyridine was isolated in 14% yield.[11]



Scheme 3 $PdBr(Ph)(PPh_3)_2$-catalyzed Negishi CCR of 3-bromopyridine and organozinc reagents (**1**). Reaction conditions: 3-bromopyridine (1 mmol), POxAP-1 (0.1 mol %, 1 mL, 10^{-3} M in THF), **1** (1.5 mmol in THF), rt.

POxAPs result from the first oxidative addition between a Pd(0) species and ArX, and so they respect the criteria of Pd-based OACs (Oxidative Addition Complexes) recently described by Ingoglia and Buchwald.[12] Consequently, we proposed a catalytic cycle for the current POxAP-catalyzed Negishi CCR in Scheme 4. In the presence of organozinc reagent R^1ZnX, POxAP follows an initiation step and provides PhR^1 as well as a reactive Pd(0) entity, which is then available for a subsequent Negishi catalytic cycle. A proof of the proposed mechanism was determined in the Fukuyama CCR,[3] where we were able to detect 3-phenylpyridine (Ph-R^1) by mass spectroscopy, whose formation could be explained by an initiation step between POxAP-1 and pyridin-3-ylzinc bromide followed by a reductive elimination. This mechanism is also consistent with the fact that POxAP-1 and -4 showed differences in initial rates (Table 1, t < 30 min, TOF = 2.8 vs & 1.1 s^{-1}, respectively, but exhibit identical "cruising" rate (Table 1, 1 h < t < 3 h, TOF = 1.67 & 1.67 s^{-1}, respectively), as both POxAPs lead to the same reactive Pd(0) entity after the initiation step.



Scheme 4 Mechanism of POxAP-catalyzed Negishi CCR

In summary, we have demonstrated that POxAP precatalysts are very efficient in Negishi CCR, with comparable activities to classical precatalysts XPhos Pd G4 or PEPPSI-IPr. With 0.1% POxAP-1 ($PdBr(Ph)(PPh_3)_2$), 1 mmol aryl halide could be coupled with diverse organozinc reagents within 1 to 16 h, furnishing the corresponding products in high yields. Moreover, POxAP-1-catalyzed Negishi CCR has a good chemoselectivity (OTf ≈ I > Br > Cl >> F), as well as an extensive functional groups tolerance, such as nitro, amino, amide, ketone, aldehyde, alkene, alkyne, cyano, carboxylate, TBS-alcohol, phthalimide, phosphonate and borate. Easily prepared and stable to air and moisture, POxAPs complete the toolbox of organic chemists in terms of precatalysts exhibiting very high catalytic activities in the formation of C-C bond starting from organozinc reagents. These POxAPs will be next evaluated for their capabilities to catalyze other CCRs.

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All commercial reagents were used without additional purification. POxAPs were prepared according to the previous reported methods.[3] All the glassware were properly dried in an oven before use. ^1H (400 or 500 MHz) and ^{13}C (101 or 126 MHz) NMR spectra were recorded on Bruker Avance Spectrometer and internally referenced to the residual solvent signals (^1H NMR: $CDCl_3$, δ = 7.26; ^{13}C NMR: $CDCl_3$, δ = 77.16). All chemical shift values δ and coupling constants *J* are quoted in ppm and in Hz, respectively. HPLC were performed using a Dionex UltiMate 3000 using the following parameters: Flow rate of 0.5 mL/min, column temperature: 30 °C, solvent system: A (MeOH) and B (0.05% of TFA in H2O), t = 0 min to 1 min: 50 to 60% of B, then t = 1 min to t = 10 min: 60 to 100% of B and t = 10 min to t = 15 min: 100% of B.

Preparation of organozinc reagents

Typical procedure 1 (TP1)

Organozinc reagents were prepared as described by Knochel et al.[13] An oven-dried 20 mL microwave vial equipped with a magnetic stirrer was charged with zinc (1.5 equiv, 491 mg, 7.5 mmol) and LiCl (1.5 equiv, 318 mg, 154 µL, 7.5 mmol). The vial was properly capped and heated using a heat gun (350 °C, 10 min) under reduced pressure, then cooled to rt, degassed and backfilled with argon thrice. THF (5.2 mL for liqiud halides and 4.2 mL for solid halides) was added followed by 1,2-dibromoethane (5 %, 21.6 µL, 0.25 mmol) and chlorotrimethylsilane (5 %, 32 µL, 0.25 mmol). The suspension was heated (50 °C, 2 min) until the suspension became clear and grey precipitates formed. After cooling to rt, the corresponding halide (1 equiv, 5 mmol) was added dropwise at -10 °C (solid halides were dissolved in 1 mL THF before adding). The resulted solution was stirred at 0 °C for 30 min, then at the given temperature for the given time to afford corresponding organozinc reagent. The concentration and yield of the organozinc reagent were determined by iodometric titration of the supernatant solution according to the following formulas[14]

$C = m/254/V_{organozinc}$

$Yield = (C \times V_{total})/5$

m: weight of iodine (mg)

$V_{organozinc}$: volume of organozinc reagent comsumed for titration (mL)

V_{total}: total volume of organozinc reagent (mL)

Typical procedure 2 (TP2)

Organozinc reagents were prepared as described by Knochel et al.[15] An oven-dried 20 mL microwave vial equipped with a magnetic stirrer was charged with $ZnCl_2$ (1.5 equiv, 1.02 g, 7.5 mmol) and LiCl (1.5 equiv, 318 mg, 154 µL, 7.5 mmol). The vial was properly capped and heated using a heat gun (550 °C, 15 min) under reduced pressure, then cooled to rt, degassed and backfilled with argon thrice. THF (5 mL for 1 M and 7.5 mL for 2 M Grignard reagents) was added and the mixture was ultrasonicated until it became a clear solution (skip this step if the concentration of Grignard reagent is 0.5 M). The corresponding organomagnesium bromide (1 equiv, 5 mmol) was slowly added to aforementioned solution at 0 °C (final volumn = 10 mL) and a white precipitate was observed. The resulting mixture was stirred at rt for additional 3 h to afford the corresponding organozinc reagent (0.5 M), which was used directly without titration.

benzylzinc(II) bromide (1a)

1a was prepared from 0.6 mL (bromomethyl)benzene at rt in 16 h according to typical procedure TP1 (96%, 0.8 M).

phenylzinc(II) chloride (1b)

1b was prepared from 5 mL phenylmagnesium bromide (1 M in THF) at rt in 3 h according to typical procedure TP2 (100%, 0.5 M).

pyridin-3-ylzinc(II) chloride (1c)

1c was prepared from 0.48 mL 3-bromopyridine according to a previous reported method (64%, 0.3 M).[3]

benzhydrylzinc(II) bromide (1d)

1d was prepared from 1.23 g (bromomethylene)dibenzene at -10 in 3 h according to typical procedure TP1 (70%, 0.55 M).

(3-cyanopropyl)zinc(II) bromide (1e)

1e was prepared from 0.5 mL 4-bromobutanenitrile at 80 °C in 16 h according to typical procedure TP1 (74%, 0.62 M).

(3-((*tert*-butyldimethylsilyl)oxy)propyl)zinc(II) bromide (1f)

1f was prepared from 1.16 mL (3-bromopropoxy)(*tert*-butyl)dimethylsilane at 80 °C in 16 h according to typical procedure TP1 (86%, 0.66 M).

(2-(1,3-dioxoisoindolin-2-yl)ethyl)zinc(II) bromide (1g)

1g was prepared from 1.34 g 2-(2-bromoethyl)isoindoline-1,3-dione at 80 °C in 20 h according to typical procedure TP1 (81%, 0.58 M).

(2-(diethoxyphosphoryl)ethyl)zinc(II) bromide (1h)

1h was prepared from 1.53 mL diethyl (2-bromoethyl)phosphonate at 50 °C in 6 h according to typical procedure TP1 (97%, 0.69 M).

(4-(1,3,2-dioxaborinan-2-yl)benzyl)zinc(II) bromide (1i)

1i was prepared from 1.27 g 2-(4-(bromomethyl)phenyl)-1,3,2-dioxaborinane at rt in 16 h according to typical procedure TP1 (84%, 0.64 M).

(2-ethoxy-2-oxoethyl)zinc(II) bromide (1j)

1j was prepared from 0.55 mL ethyl 2-bromoacetate at 40 °C in 5 h according to typical procedure TP1 (88%, 0.73 M).

prop-1-en-2-ylzinc(II) chloride (1k)

1k was prepared from 10 mL prop-1-en-2-ylmagnesium bromide (0.5 M in THF) at rt in 3 h according to typical procedure TP2 (100%, 0.5 M).

ethynylzinc(II) chloride (1l)

1l was prepared from 10 mL ethynylmagnesium bromide (0.5 M in THF) at rt in 3 h according to typical procedure TP2 (100%, 0.5 M).

General procedure of $PdBr(Ph)(PPh_3)_2$-catalyzed Negishi CCR

An oven-dried 20 mL microwave vial equipped with a magnetic stirrer was charged with halide (1 equiv, 1 mmol) and $PdBr(Ph)(PPh_3)_2$ (0.1 mol %, 1 mL, 10^{-3} M in THF, 1 mL). The vial was properly capped and degassed/backfilled with argon thrice. Then, the solution of organozinc reagent (1.5 equiv, 1.5 mmol) in THF was slowly added to the mixture at rt. The reaction temperature and time were listed in Scheme 2 and 3. After completion, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (10 mL) thrice. The combined organic phases were concentrated in vacuo and purified by reverse phase chromatography ($MeOH/H_2O$) to afford the coupled products.

1-benzyl-4-methoxybenzene (2a)

Eluent: $MeOH/H_2O$ (50:50); colorless oil; yield: 196 mg (0.99 mmol, 99%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.3 Hz, 2H), 7.25 – 7.17 (m, 3H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.96 (s, 2H), 3.81 (s, 3H).

These data are consistent with the previously reported characterization.[16]

4-benzylbenzonitrile (2b)

Eluent: $MeOH/H_2O$ (40:60); colorless oil; yield: 191 mg (0.99 mmol, 99%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.50 (m, 2H), 7.29 – 7.17 (m, 5H), 7.13 – 7.08 (m, 2H), 3.98 (s, 2H).

These data are consistent with the previously reported characterization.[17]

2-benzylbenzamide (2c)

Eluent: $MeOH/H_2O$ (40:60); white solid; yield: 194 mg (0.92 mmol, 92%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.37 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 – 7.22 (m, 4H), 7.22 – 7.16 (m, 3H), 5.68 (br, 2H), 4.25 (s, 2H).

These data are consistent with the previously reported characterization.[18]

1-(2-benzylphenyl)ethanone (2d)

Eluent: $MeOH/H_2O$ (40:60); colorless oil; yield: 193 mg (0.92 mmol, 92%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.30 (td, *J* = 7.5, 1.4 Hz, 1H), 7.20 (td, *J* = 7.6, 1.2 Hz, 1H), 7.17 – 7.12 (m, 3H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 2H), 4.18 (s, 2H), 2.36 (s, 3H).

These data are consistent with the previously reported characterization.[19]

1-benzyl-3-fluorobenzene (2e)

Eluent: $MeOH/H_2O$ (60:40); colorless oil; yield: 184 mg (0.99 mmol, 99%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 2H), 7.22 – 7.17 (m, 2H), 7.16 – 7.12 (m, 2H), 6.93 (d, *J* = 7.3 Hz, 1H), 6.88 – 6.80 (m, 2H), 3.93 (s, 2H).

These data are consistent with the previously reported characterization.[20]

1-benzyl-3-chlorobenzene (2f)

Eluent: $MeOH/H_2O$ (60:40); yellow oil; yield: 200 mg (0.99 mmol, 99%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.3 Hz, 2H), 7.17 – 7.09 (m, 6H), 7.00 (d, *J* = 7.1 Hz, 1H), 3.88 (s, 2H).

These data are consistent with the previously reported characterization.[21]

1-benzyl-3-bromobenzene (2g)

Eluent: $MeOH/H_2O$ (60:40); yellow oil; yield: 237 mg (0.96 mmol, 96%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 4H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.19 – 7.09 (m, 4H), 3.95 (s, 2H).

These data are consistent with the previously reported characterization.[22]

***tert*-butyl 3-benzylbenzoate (2h)**

Eluent: $MeOH/H_2O$ (70:30); colorless oil; yield: 260 mg (0.97 mmol, 97%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.88 (m, 1H), 7.88 – 7.84 (m, 1H), 7.37 – 7.34 (m, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.19 (m, 3H), 4.04 (s, 2H), 1.61 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.94, 141.33, 140.70, 133.14, 132.31, 130.00, 129.00, 128.66, 128.45, 127.38, 126.35, 81.05, 41.85, 28.31.

GC-MS: m/z = 268.146.

1-benzyl-4-nitrobenzene (2i)

Eluent: $MeOH/H_2O$ (40:60); colorless oil; yield: 173 mg (0.81 mmol, 81%).

^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.36 – 7.32 (m, 4H), 7.28 – 7.26 (m, 1H), 7.20 (s, 2H), 4.10 (s, 2H).

These data are consistent with the previously reported characterization.[23]

4-benzylbenzaldehyde (2j)

Eluent: $MeOH/H_2O$ (40:60); white solid; yield: 149 mg (0.76 mmol, 76%).

^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.18 (m, 4H), 7.16 – 7.12 (m, 1H), 7.11 – 7.05 (m, 2H), 3.96 (s, 2H).

These data are consistent with the previously reported characterization.[24]

(2-benzylphenyl)methanamine (2k)

Eluent: $MeOH/H_2O$ (40:60); white solid; yield: 172mg (0.87 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.1 Hz, 1H), 7.28 – 7.16 (m, 6H), 7.13 (t, *J* = 7.6 Hz, 2H), 4.06 (s, 2H), 3.81 (s, 2H).

These data are consistent with the previously reported characterization.[25]

2-benzyl-1,3-dimethylbenzene (2l)

Eluent: MeOH/H_2O (70:30); colorless oil; yield: 190 mg (0.97 mmol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.27 (m, 5H), 7.26 – 7.23 (m, 1H), 7.20 (d, *J* = 7.2 Hz, 2H), 4.25 (s, 2H), 2.43 (s, 6H).

These data are consistent with the previously reported characterization.[26]

3-benzylthiophene (2m)

Eluent: MeOH/H_2O (60:40); yellow oil; yield: 172 mg (0.99 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.31 – 7.23 (m, 4H), 6.98 – 6.94 (m, 2H), 4.03 (s, 2H).

These data are consistent with the previously reported characterization.[27]

3-benzylpyridine (2n)

Eluent: MeOH/H_2O (40:60); yellow oil; yield: 167 mg (0.99 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 – 8.49 (m, 1H), 8.48 – 8.44 (m, 1H), 7.46 (dt, *J* = 7.7, 1.8 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.25 – 7.16 (m, 4H), 3.98 (s, 2H).

These data are consistent with the previously reported characterization.[28]

2-benzylbenzo[*d*]oxazole (2o)

Eluent: MeOH/H_2O (50:50); yellow oil; yield: 205 mg (0.98 mmol, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 1H), 7.40 – 7.34 (m, 1H), 7.33 – 7.24 (m, 4H), 7.23 – 7.16 (m, 3H), 4.19 (s, 2H).

These data are consistent with the previously reported characterization.[29]

2-benzylbenzo[*b*]thiophene (2p)

Eluent: MeOH/H_2O (50:50); white solid; yield: 222 mg (0.99 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.9 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.16 (m, 7H), 6.95 (s, 1H), 4.17 (s, 2H).

These data are consistent with the previously reported characterization.[30]

4-benzylisoquinoline (2q)

Eluent: MeOH/H_2O (50:50); yellow solid; yield: 202 mg (0.92 mmol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.47 (s, 1H), 7.99 (dd, *J* = 25.5, 8.1 Hz, 2H), 7.69 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.62 (ddd, *J* = 7.9, 6.7, 1.0 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.27 – 7.21 (m, 3H), 4.43 (s, 2H).

These data are consistent with the previously reported characterization.[31]

3-phenethyl-1,1'-biphenyl (2r)

Eluent: MeOH/H_2O (80:20); colorless oil; yield: 255 mg (0.99 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.56 (m, 2H), 7.48 – 7.42 (m, 3H), 7.41 – 7.29 (m, 5H), 7.25 – 7.17 (m, 4H), 2.99 (t, *J* = 2.5 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.37, 141.86, 141.50, 141.43, 128.89, 128.84, 128.64, 128.51, 127.57, 127.54, 127.33, 126.10, 124.98, 38.19, 38.15.

GC-MS: m/z = 258.139.

3-phenylpyridine (3a)

Eluent: MeOH/H_2O (40:60); yellow oil; yield: 153 mg (0.99 mmol, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.59 (d, *J* = 3.9 Hz, 1H), 7.86 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.49 – 7.45 (m, 2H), 7.43 – 7.37 (m, 1H), 7.35 (dd, *J* = 7.9, 4.7 Hz, 1H).

These data are consistent with the previously reported characterization.[32]

3,3'-bipyridine (3b)

Eluent: MeOH/H_2O (30:70); white solid; yield: 147 mg (0.94 mmol, 94%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.86 (d, *J* = 1.9 Hz, 2H), 8.67 (dd, *J* = 4.8, 1.6 Hz, 2H), 7.92 – 7.87 (m, 2H), 7.42 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 2H).

These data are consistent with the previously reported characterization.[33]

3-benzhydrylpyridine (3c)

Eluent: MeOH/H_2O (60:40); colorless oil; yield: 223 mg (0.91 mmol, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.44 (d, *J* = 2.3 Hz, 1H), 7.40 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.33 – 7.28 (m, 4H), 7.26 – 7.20 (m, 3H), 7.13 – 7.09 (m, 4H), 5.56 (s, 1H).

These data are consistent with the previously reported characterization.[34]

4-(pyridin-3-yl)butanenitrile (3d)

Eluent: MeOH/H_2O (40:60); brown oil; yield: 133 mg (0.91 mmol, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 – 8.51 (m, 2H), 7.64 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.35 (dd, *J* = 7.8, 5.0 Hz, 1H), 2.81 (t, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.02 – 1.95 (m, 2H).

These data are consistent with the previously reported characterization.[35]

3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)pyridine (3e)

Eluent: MeOH/H_2O (60:40); yellow oil; yield: 229 mg (0.91 mmol, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, *J* = 1.9 Hz, 1H), 8.40 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.50 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.19 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.61 (t, *J* = 6.1 Hz, 2H), 2.70 – 2.65 (m, 2H), 1.85 – 1.77 (m, 2H), 0.90 (s, 6H), 0.89 (s, 9H).

These data are consistent with the previously reported characterization.[36]

2-(2-(pyridin-3-yl)ethyl)isoindoline-1,3-dione (3f)

Eluent: MeOH/H_2O (50:50); white solid; yield: 209 mg (0.83 mmol, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 – 8.38 (m, 2H), 7.82 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.70 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.52 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.17 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.74 (t, *J* = 7.1 Hz, 2H), 2.73 – 2.63 (m, 2H), 2.06 – 1.99 (m, 2H).

These data are consistent with the previously reported characterization.[37]

diethyl (2-(pyridin-3-yl)ethyl)phosphonate (3g)

Eluent: MeOH/H_2O (40:60); yellow oil; yield: 180 mg (0.74 mmol, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 – 8.44 (m, 2H), 7.55 – 7.50 (m, 1H), 7.22 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.12 – 4.05 (m, 4H), 2.96 – 2.87 (m, 2H), 2.08 – 2.00 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 6H).

These data are consistent with the previously reported characterization.[38]

(4-(pyridin-3-ylmethyl)phenyl)boronic acid (3h)

Eluent: MeOH/H_2O (40:60); white solid; yield: 151 mg (0.71mmol, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.58 (m, 2H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.65 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.25 (d, *J* = 7.7 Hz, 2H), 4.07 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.29, 145.41, 140.38, 138.02, 137.87, 134.23, 129.89, 128.15, 124.11, 116.07, 39.31.

LC-MS: m/z = 214.051.

mp: 148 °C

ethyl 2-(pyridin-3-yl)acetate (3i)

Eluent: MeOH/H_2O (40:60); yellow oil; yield: 104 mg (0.63 mmol, 63%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 – 8.47 (m, 2H), 7.61 (dt, *J* = 7.8, 2.1 Hz, 1H), 7.23 (dd, *J* = 8.1, 4.9 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.59 (s, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).

These data are consistent with the previously reported characterization.[39]

3-(prop-1-en-2-yl)pyridine (3j)

Eluent: MeOH/H_2O (50:50); yellow solid; yield: 118 mg (0.99 mmol, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (d, *J* = 2.4 Hz, 1H), 8.50 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.73 (dt, *J* = 8.1, 2.0 Hz, 1H), 7.28 – 7.22 (m, 1H), 5.42 (s, 1H), 5.18 (s, 1H), 2.16 (s, 3H).

These data are consistent with the previously reported characterization.[40]

3-ethynylpyridine (3k)

Eluent: MeOH/H_2O (50:50); white solid; yield: 59 mg (0.57 mmol, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.57 (d, *J* = 4.8 Hz, 1H), 7.77 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.29-7.23 (m, 1H), 3.22 (s, 1H).

These data are consistent with the previously reported characterization.[41]

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Supporting Information

YES (this text will be updated with links prior to publication)

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NO (this text will be deleted prior to publication)

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