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Continuous flow Negishi cross-couplings employing silicasupported *Pd-PEPPSI-IPr* Precatalyst

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The synthesis of a triethoxysilyl functionalised *Pd-PEPPSI-IPr* complex prepared *via* azide-alkyne cycloaddition is described. The complex was immobilised onto silica gel and applied as a heterogeneous catalyst in the Negishi reaction. The catalyst was active in both batch and continuous flow operation and was particularly effective for the coupling of heteroaryl chlorides. Long-term continuous flow experiments demonstrated good catalyst activity over fifteen hours.

Introduction

Continuous flow organic synthesis has undergone rapid development in recent years owing to the considerable benefits afforded over conventional batch reaction processes. Flow reactors enable greater control of reaction variables, enhanced reaction efficiency,¹ and improved safety profiles for processes that have risk associated with them.² Additionally, the ability to number up and adjust scale without altering the reaction conditions is a distinct advantage inherent to flow chemistry.³

Palladium catalysed cross-coupling reactions are widely employed and extremely versatile reactions for the construction of carbon-carbon and carbon-heteroatom bonds.⁴ Given the importance of these reactions for the production of compounds in the pharmaceutical and fine chemical industries many attempts have been made to carry out these transformations in a continuous flow setup.⁵ Of the possible ways to achieve this goal the use of heterogeneous catalysts in the form of supported metal particles⁶ and films^{5d, 7} has been investigated, further, packed bed reactors have received significant attention.⁸ Combining these two branches of chemistry would enable recovery and re-use of the palladium catalyst and also simplify purification of the final product by reducing the level of metal present in the eluent stream due to metal/ligand particulates. Under batch conditions, Nheterocyclic carbene (NHC) ligands are now well-established alternatives to the phosphine ligands traditionally employed in palladium catalysed coupling reactions.⁹ This is due to the favourable electronic and steric parameters of NHC ligands that give rise to Pd-NHC complexes with high catalytic

activity.¹⁰ Of the various catalytic systems described in the literature, the Pd-PEPPSI (pyridine-enhanced precatalyst preparation, stabilisation and initiation) family of precatalysts has emerged as a highly active and 'user-friendly' catalyst system for numerous coupling reactions.¹¹ Currently, Pd-PEPPSI pre-catalysts are used as homogeneous catalysts, however several immobilisation strategies have recently been applied to NHC-Palladium complexes including Pd-PEPPSI derivatives. In general, covalent tethering techniques have been explored due to the formation of stable linkages between the support and catalyst.¹² A facile approach to immobilisation involves substitution of one of the N-aryl arms of the NHC ligand with an alkyl chain containing a tethering group (Figure 1).¹³ However, by removing some of the steric bulk around the palladium centre the stability and catalytic activity of the complex is diminished.¹⁴ Hashmi and co-workers have described the use of a gold-carbene complex connected to a silsesquioxane cage as a mimic of the surface attachment.¹⁵ Very active catalysts could be obtained in this way, although they remained soluble in the reaction medium. Immobilisation via functionalisation of the N-heterocyclic backbone has also been utilised to prepare heterogeneous NHC-metal catalysts with a range of metals (Figure 1),¹⁶ although examples featuring Pd-NHC complexes are rare.¹



Figure 1: Immobilisation strategies for solid supported NHC-metal complexes.

Another option that has been investigated is to functionalise the *para*-position of one or both of the *N*-aryl rings of the NHC

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ligand with a tethering group. This method enables preparation of symmetrical and unsymmetrical NHC ligands (about the C₂ axis), and has the benefit of retaining the requisite steric bulk around the metal centre. To this end, Claver and co-workers have recently reported the immobilisation of a range of palladium-acetylacetonate- NHC complexes through para-functionalisation.¹⁸ Installation of a triethoxysilyl tether was accomplished through a thiol-ene reaction and the complexes exhibited good activity and recyclability in Suzuki-Miyaura reactions under batch and continuous flow conditions. In an alternative approach, Kirschning and co-workers,¹⁹ reported a PEPPSI-IPr catalyst that was immobilised on a polyvinylpyridine support through the ligand trans to the NHC. Although a number of studies have addressed the use of heterogeneous palladium catalysts for Suzuki-Miyaura cross-couplings under flow conditions, until recently there was a lack of literature precedent concerning Negishi cross-couplings carried out as continuous flow processes. One of the challenges often encountered when performing Suzuki-Miyaura reactions in flow is the precipitation of insoluble salts during the course of the run. In contrast, Negishi couplings generally result in homogeneous mixtures providing an appropriate solvent system is selected for the reaction. Moreover, the Negishi reaction provides a facile means to install new sp³-carbon centres in organic molecules through sp²-sp³ and sp³-sp³ cross-couplings.^{9f-i, 11b,} 11h, 11q, 11r, 11w, 11z, 11aa, 11ad, 11aj, ²⁰ This is of increasing relevance to

the pharmaceutical industry, where there is a renewed interest in targeting structurally complex drug candidates that contain more sp³ centres.²¹ In this regard, Alcazar *et al.*²² and McQuade and co-workers²³ have described the use of a silica-supported diphenylphosphine based Pd(II) catalyst, Silia*Cat* DPP-Pd, for flow Negishi reactions.²⁴ Good to excellent conversions were reported for a range of couplings between alkyl zinc species and aryl iodides, bromides and activated chlorides at 60 °C. The catalyst was found to be stable for a 4 - 13 h period.

Given our group's longstanding interest in the Negishi reaction^{11b, 11h, 11q, 11r, 11w, 11z, 11aa, 11ad, 11aj, 20a} we sought to immobilise a Pd-NHC complex on a silica support for use in continuous flow couplings. Herein, we report the synthesis and subsequent immobilisation of a triethoxysilyl functionalised *Pd-PEPPSI-IPr* complex prepared *via* azide-alkyne cycloaddition chemistry.²⁵ The efficacy of the solid supported pre-catalyst in Negishi cross-coupling reactions under both batch and flow conditions is also described.

Results and Discussion

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The synthesis of *PEPPSI* complex **9** began with preparation of TMS-protected alkyne functionalised imidazolium salt **5** using modifications to the method described by Furstner and coworkers for the preparation of unsymmetrical imidazolium salts.²⁶ 4-Iodo-2,6-diisopropylaniline (**2**) prepared from **1** by iodination,²⁷ underwent Sonogashira coupling with trimethylsilylacetylene²⁸ furnishing alkyne **3** in 71% yield over 2 steps (Scheme 1). Reaction of **3** with Furstner's oxazolinium



Scheme 1: Preparation of TMS-alkyne functionalised aniline (3)

adduct 4 afforded an intermediate hydroxylated imidazolium salt that subsequently underwent dehydration to yield imidazolium salt 5. With 5 in hand we next explored routes to palladium NHC complex 9 (Scheme 2). We opted for a mild approach whereby intermediate copper complex (7) was 'clicked' to an azide adorned with a triethoxysilyl group, before undergoing transmetallation with a Pd source. This protocol is appealing as the use of a strong base in the synthesis of metal complexes is avoided,²⁹ and crucially the copper-NHC intermediate can also be functionalised and immobilised on a silica support for use in continuous flow reactions. Initially, we examined the direct preparation of Cu-NHC complex (7) from perchlorate salt 5 using the method reported by Zhu and coworkers.³⁰ Under these conditions, the desired metallation was found to take place concomitant with deprotection of the TMS-alkyne to give 7 in moderate yield. The reaction suffered from poor reproducibility between batches and drastically reduced yields upon scale-up resulting from undesired Glaser-Hay coupling³¹ between two terminal alkyne units. Owing to the improved versatility of imidazolium salts having halide counter-ions we examined exchange of perchlorate for chloride using an anion exchange resin. Gratifyingly, filtration of 5 through DOWEX® ion-exchange resin resulted in clean conversion to imidazolium salt 6.32 Treatment of 6 with copper(I) oxide³³ yielded Cu-NHC 7 along with trace amounts of the TMS-protected alkyne analogue. The alkyne could be completely deprotected in a second step by reacting the crude Cu-NHC mixture with tetrabutylammonium fluoride in THF resulting in a 65% yield of 7 over two steps. It should be noted that no Glaser-Hay by-products were observed when the Cu₂O protocol was used to prepare 7, and no evidence of halide scrambling at the copper centre could be detected by ¹⁹F{¹H} NMR spectroscopy. Inspired by the report of Gautier et al.³⁴ that Cu-NHC complexes can act as both catalyst and substrate for azide-alkyne cycloadditions, we found that 7 underwent reaction with 3-azidopropyltriethoxysilane to give 8 in excellent yield. We next investigated transmetallation of 8 to a Pd(II) centre and soon realised that the triazole on the NHC backbone interfered with ligand transfer. After careful selection of the solvent and reaction conditions,

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Scheme 2: Preparation of triethyoxysilyl-functionalised *Pd-PEPPSI* complex 9.

transmetallation to $PdCl_2(3-ClPy)_2^{35}$ proceeded in toluene at 110 °C to give triethyoxysilyl functionalised palladium complex 9 in moderate yield. Immobilisation onto the surface was carried out by reaction of 9 with high purity silica gel (Davisil™ grade 646) in toluene (Scheme 3). The supported catalyst was then subjected to continuous Soxhlet extraction with EtOAc for 24 hours, after which the silica support was passivated with hexamethyldisilazane. Characterisation of 10 by ICP elemental analysis gave a palladium content of 2.28 wt%, which corresponds to an effective catalyst loading of 0.21 mmol/g. The nitrogen content of 10, together with the Pd/N ratio give further information about the composition of the solid supported catalyst. The nitrogen loading was found to be 2.09 wt% giving a Pd/N atom ratio of 1:6.9, which is in close agreement with the calculated ratio of 1:6. We used SEM/EDX elemental analysis to view the silica particles after immobilisation and to verify the elemental compositions obtained by ICP analysis. EDX elemental analysis indicated a

palladium content of 2.17 wt%, and nitrogen content of 2.15 wt%, both of which are in excellent agreement with the results obtained by ICP analysis.

Evaluation of Catalytic activity

In order to evaluate the catalytic activity of 10 a series of Negishi coupling reactions were carried out under batch conditions. Initially, we chose to study the coupling of 2chloro-4-methylquinoline (11) with (6-ethoxy-6oxohexyl)zinc(II) bromide (12) using conditions developed previously in our group.^{11aj} We were pleased to find that **10** displayed excellent activity for the coupling at room temperature (Table 1, entry 1) although the reaction took 16 h to complete, compared to 2 h for the homogeneous PEPPSI complexes (Table 1, entries 2 and 3). However, by increasing the concentration with respect to aryl halide from 0.1 M (entry 1) to ~0.5 M (entry 4), full conversion with 10 was achieved in 2 h. In light of this high activity we next set about confirming that the observed efficacy in these reactions was not the result of something other than Pd-NHC complex 10, thus a number of control experiments were carried out (Table 1, entries 5-8 and

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Scheme 3: Immobilisation of *Pd-PEPPSI* complex (9) onto silica gel.

 ESI^{\dagger}). In all cases involving PdCl₂ only trace amounts of coupled product were observed, concurrent with the formation of palladium black. Furthermore, the use of 1-benzyl-4-(*p*-tolyl)-1*H*-1,2,3-triazole in combination with PdCl₂(MeCN)₂ (Table 1, entry 7) did not result in conversion to coupled product. Equally, a Pd(OAc)₂/ⁿBu₄NBr combination that is known to generate Pd-nanoparticles^{20c} displayed no catalytic activity. Collectively, these control experiments confirm the catalytic

Table 1: Initial screening of Pd complexes under batch conditions.

Entry ^a	[Pd] (mol %)	Time (h)	Yield ^d (%)	
	$ \begin{array}{c} BrZn + \int_{5}^{0} OEt \\ 12 \\ [Pd], LiBr \\ THF/DMI, THF/DMI, $			
	rt 11	13		
1	10 (2.0)	16	80	
2	9 (1.0)	2	90	
3	Pd-PEPPSI-IPr (1.0) 2	81	
4 ^b 10 (2.0)		2	85	
5	5 PdCl ₂ (5.0)		trace	
6	PdCl ₂ (MeCN) ₂ (5.0) 24	trace	
7	PdCl ₂ (MeCN) ₂ (5.0) + tr (5.0)	iazole ^c 24	trace	
8	Pd(OAc) (5.0) + ⁿ Bu₄NB	r (100) 24	trace	

^{*a*} Conditions: 2-chloro-4-methylquinoline (**11**, 0.5 mmol, ~0.1 M), LiBr (3.2 equiv.), RZnBr (1.8 equiv., 0.6 M in DMI), THF. ^{*b*} Conditions: 2-chloro-4-methylquinoline (**11**, 0.5 mmol, ~0.5 M), LiBr (3.2 equiv.), RZnBr (1.8 equiv., 0.6 M in DMI), THF. ^{*c*} triazole ligand = 1-benzyl-4-(p-tolyl)-1H-1,2,3-triazole. ^{*d*} isolated yield following purification on SiO₂ activity observed for **10** is derived from the Pd-NHC complex. Next, the recyclability of **10** in this reaction was studied over five cycles (Table 2).

Table 2: Recycling of 10 under batch conditions.										
	Cycle	1	2	3	4	5				
	Time (h)	16	16	24	24	24	30	-		
	Conversion (%) ^a	>99	98	>99	>99	72	83			

Conditions: 2-chloro-4-methylquinoline (**11**, 0.5 mmol, ~0.1 M), THF (2.5 mL), LiBr (139 mg, 1.6 mol, 3.2 equiv.), RZnBr (**12**, 1.25 mL, 0.65 M in DMI, 0.8 mmol), **10** (60 mg, 2.5 mol%). ^{*a*} Conversion determined by ¹H NMR spectroscopy of the crude reaction mixtures.

The coupling was performed under the same conditions as those described for the preliminary screening (see Table 1), except a 2.5 mol% loading of supported catalyst was used. After each cycle, **10** was collected by filtration, washed with dichloromethane and Et_2O and then dried under vacuum. Conversion of starting material to product was determined by ¹H NMR spectroscopy. It was found that this recycled complex maintained high activity over five successive reactions, although the observed reaction rate slowed after the second cycle. In these cases, extending the reaction time from 16 h to 24 h was sufficient to restore quantitative conversion to coupled product. The oxidation state of palladium during the recycling process is currently unknown however it is possible that the silica support stabilises the Pd centre, perhaps through formation of an oxo-palladium species.

Substrate scope under batch and continuous flow conditions

The use of 10 in packed bed reactors for continuous flow Negishi couplings was then evaluated. In light of our batch experience, we again chose the coupling of 2-chloro-4methylquinoline (11) with (6-ethoxy-6-oxohexyl)zinc(II) bromide (12) as the model reaction. The flow reactor was comprised of a FEP (fluorinated ethylene propylene) tube (0.159 cm ID x 8 cm) packed with 70 mg of 10. Connected to the reactor outlet was a length of FEP tubing (0.025 cm ID x 20 cm) that fed directly into a quench solution of saturated NaHCO₃/H₂O. Flow screening was conducted using the same reagent stoichiometry and solvent system as for the batch reactions detailed in Table 1. A stock solution of aryl halide, organozinc and LiBr in THF/DMI (2:1) was passed through the catalyst bed at room temperature at a flow rate of 20 $\mu\text{L/min}$ giving a residence time (t_R) of ~9 min. Using these conditions coupled product 13 could be obtained in high yield on a 2.4 mmol scale (Scheme 4). Substrate scope was then examined and various functional groups were well tolerated including nitriles, esters, ketones and alkenes (Scheme 4, 13, 14, 16-19). Further, N-heteroaryl chlorides could be coupled uneventfully in excellent yield (13, 17, 20). Typically, cross-couplings involving 2-chloropyridyl-like species can be difficult to affect with commercially available immobilised catalysts.²² Even deactivated substrates such as 2-chloro-6-methoxypyridine (18) underwent reaction in high yield upon reduction of the

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Scheme 4: Substrate scope with **10** in continuous flow couplings displaying isolated yields. General Conditions for couplings in flow: aryl halide (~0.1 M), THF, organozinc in DMI (1.8 equiv.), LiBr (3.2 equiv.), **10** (70 mg, 0.21 mmol/g, 0.015 mmol), rt, 20 μ L/min residence time ~ 35 mins.

flow rate to 15 μ L/min (t_R = ~12 min). Unfortunately, the coupling of an N-Boc-protected indole led to low product recovery under these flow conditions (15). It should be noted that during the course of these studies we found that coupling of 4-bromobenzonitrile with (6-ethoxy-6-oxohexyl)zinc(II) bromide (to generate 14) could be effected with simple palladium halide salts, perhaps through a metal promoted S_nAr reaction. With these results in hand, we conducted further screening of 10 in continuous flow Negishi couplings using commercially available organozinc reagents. Supported precatalyst 10 (350 mg) was packed into an Omnifit column (0.3 cm x 10 cm) possessing a larger void volume than the previously used system (i.e., 500 μ L vs. 171 μ L). A stock solution of aryl halide and organozinc reagent in THF/DMI (3:2) (0.15 M) was pumped through the reactor at 50 μ L/min ($t_{\rm R}$ = ~10 min) at rt. The products were purified by reverse phase HPLC and isolated as TFA salts. Single columns could be used to generate small libraries of compounds by simply washing the column after each run with a small volume of solvent and changing the organozinc being used (Scheme 5). 2-Chloro-4methylquinoline and 2-chloro-7-methoxy-4-methylquinoline could be coupled with a variety of organozinc reagents in good to excellent yield. Again, various functionalities were well tolerated in the reaction.

Scheme 5: Substrate scope with **10** using commercially available organozinc reagents, displaying isolated yields. Conditions: **10** (350 mg, 0.21 mmol/g, 0.0735 mmol), aryl chloride (1.12 mmol, 1.0 equiv.), DMI (3.0 mL), RZnBr (0.5 M in THF, 4.5 mL, 2.25 mmol, 2.0 equiv.), rt, 50 μ L/min, t_R = ~10 min.

Long-term activity of catalyst and heterogeneity tests

The long-term activity of 10 was assessed using the model reaction leading to 13 (see Figure 2). Fresh reagents were pumped into the reactor and the conversion to product monitored over a prolonged period of time. Using a flow rate of 20 μ L/min ($t_{\rm R}$ = ~9 min) we observed a gradual decrease in conversion over a period of 15 hours. Intrigued by this slow loss in activity, a series of heterogeneity tests were performed on the supported catalyst. First, we carried out a filtration test³⁶ whereby coupling is initiated, the catalyst is removed by filtration, and then the filtrate is subsequently monitored for further catalytic activity. Any continued conversion within the filtrate indicates leaching of a soluble palladium catalyst into solution. In the first experiment a ca. 20% increase in conversion was observed over 24 h in the filtrate following removal of 10. We wondered whether the observed activity in the filtrate might be due, at least in part, to washing off noncovalently bound 9, rather than leaching from 10 per se. Therefore, THF (3 mL) was flowed through a packed bed of 10 into a vial containing aryl halide, organozinc reagent, and LiBr in DMI. After 36 h at room temperature, conversion in the vial reached 52 % signifying that some unbound palladium complex had been liberated from the support. To address this issue, 10 was subjected to Soxhlet extraction with THF at reflux. Subsequently, THF was pumped through a bed of the

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Figure 2: Long-term Negishi coupling at 20 μ L/min residence time ~ 9 mins. Conditions: 2-chloro-4-methylquinoline (**11**, 2.4 mmol, ~0.1 M), THF, organozinc in DMI (1.8 equiv.), LiBr (3.2 equiv.), **10** (70 mg, 0.21 mmol/g, 0.015 mmol), 20 μ L/min residence time ~ 9 mins. Product ratio determined by ¹H NMR spectroscopy.

newly extracted material into a vial containing the reagents. In this case no catalytic activity could be detected after 36 h demonstrating that the additional extraction of 10 with THF had removed the unbound complex. Moreover, the THFextracted material had essentially the same catalytic activity in flow couplings as the non-extracted catalyst. After repeating the filtration test with freshly extracted **10** we observed a ca. 10% increase in conversion in the filtrate over 36 h (compared to 100% conversion without filtration of 10 in 16 h and 100% conversion in 2 h for 9). In addition to these studies, reaction streams from continuous flow couplings were left overnight without the addition of a quench solution and analysis revealed only a small (ca. 2%) increase in conversion. These results, combined with the short reaction time observed for homogeneous Pd-NHC complex (9) suggest that after extraction with THF only a small amount of active palladium catalyst leaches from the support during the reaction cycle. Finally, the level of palladium leaching was determined by ICP-AES analysis for the continuous flow synthesis of 13. Supported precatalyst 10 (70 mg total, 1.6 mg of Pd) was used in the experiment and samples were analysed for metal



Figure 3: Percentage palladium remaining on support during flow reaction. Conditions: 2-chloro-4-methylquinoline (2.4 mmol, ~0.1 M), organozinc in DMI (1.8 equiv.), LiBr (3.2 equiv.), **10** (70 mg, 0.21 mmol/g, 0.015 mmol), 20 μ L/min residence time ~ 9 mins.

content after 4.5, 7.5, 10.5 and 13.5 h of continuous operation. It was found that palladium leaching reaches ~40 % of total palladium content after 13.5 h corresponding to ~0.62 mg of Pd in the reaction stream (Figure 3). We observed a high initial leaching of Pd in the first hours of the experiment (82 ppm, 28%, 0.44 mg, in 4.5 h), followed by a lower level of constant leaching over a further 10 h. To confirm the leaching was not due to degradation of the silica support the stream was analysed for the presence of silicon. Low levels of silicon (< 8 ppm) were detected in all samples illustrating that the support remains intact during the reaction. The leached palladium species displayed poor catalytic activity as detailed above, thus it is reasonable to assume that the initial level of leaching observed is due to decomposition of the catalyst that releases Pd into the flow stream. The level of palladium leaching detected may be greatly influenced by the reaction conditions. For example, the N-heterocycles in this study may facilitate greater leaching from the support due to coordination of the nitrogen to the Pd centre, thus 'stripping' it off the support. Additionally, the use of excess organozinc reagent (1.8 equiv.) could facilitate catalyst decomposition. In a control experiment, an organozinc solution was passed through a packed bed of 10 into a vial containing aryl chloride in THF. In this case the catalyst immediately darkened and significant quantities of palladium black were found in the reaction stream. No cross-coupling product was detected in the vial over a period of 48 h demonstrating a change in catalyst structure to something that is inactive. A further batch reaction was carried out with the recovered supported catalyst (10) from the organozinc wash. The material was found to have a significantly diminished catalytic activity (~30% conversion in 26 h), thus signalling that partial decomposition of the active catalyst occurred in the presence of excess organozinc reagent. Therefore, reducing the number of equivalents of organozinc reagent used in these couplings may improve the lifetime of the catalyst under continuous flow conditions.

Conclusions

Reliable methods have been developed for the preparation and immobilisation onto silica of triethoxysilyl functionalised Pd-PEPPSI-IPr complex 9 onto silica gel. The resultant supported catalyst (10) was found to be active in Negishi crosscoupling reactions under batch and continuous flow conditions at room temperature. In batch the catalyst could be recycled at least five times with minimal loss in activity. Conversely, 10 could also be used in packed-bed reactors, giving moderate to excellent vields of coupled product with various functionalised alkylzinc reagents and aryl halides. In particular, N-heteroaryl chlorides proved to be excellent coupling partners. Precatalyst 10 displayed good activity after fifteen hours of continuous flow operation, although a slow decrease in conversion was observed over the course of the experiment. Leaching experiments and heterogeneity tests indicated loss of palladium from the support during cross coupling, however the leached material displayed low levels of catalytic activity.

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Experimental Section

Synthesis of IPr-triazole-CuCl (8)

Under argon, a vial was charged with 1-(2,6diisopropylphenyl)-3-(2,6-diisopropylphenyl-4-

ethynylphenyl)imidazol-2-ylidene]copper(I) chloride (4.6 g, 9.0 mmol) and sealed with a septum. MeCN (100 mL) and (3azidopropyl)triethoxysilane³⁷ (3.3 g, 13.3 mmol) were added and the mixture stirred for 16 h at 35 °C. After cooling to rt the solvent was removed in vacuo and the residue filtered through a plug of SiO₂ using CH₂Cl₂/EtOAc (1:1) as eluent. The filtrate was concentrated to ~5 mL and pentane added to induce precipitation of 8 as an off-white solid that was collected by filtration (5.9 g, 86 %). ¹H NMR (400 MHz, (CDCl₃): δ 7.89 (s, 1H), 7.73 (s, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.15 (s, 2H), 4.46 (t, J = 7.1 Hz, 2H), 3.84 (q, J = 7.1 Hz, 6H), 2.52 - 2.65 (m, 4H), 2.12 (t, J = 8.1 Hz, 2H), 1.35 (d, J = 6.1 Hz, 6H), 1.31 (d, J = 7.1 Hz, 6H), 1.28 (d, J = 7.1 Hz, 6H), 1.21 - 1.26 (m, 15H), 0.68 (t, J = 8.1 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ 179.9, 146.4, 145.8, 145.1, 134.0, 133.6, 132.5, 130.1, 123.7, 123.0, 123.0, 121.1, 120.3, 58.1, 52.1, 28.4, 28.3, 24.4, 24.3, 23.8, 23.4, 23.4, 17.9, 7.0. HRMS calculated for $C_{38}H_{58}CICuN_5O_3Si[M^++H]^+: 758.3288$, found: 758.3295.

Synthesis of Pd-PEPPSI-IPr-triazole (9)

Under argon, a two-necked round bottom flask equipped with a condenser was charged with IPr-triazole-CuCl (8, 1.3 g, 1.8 mmol) followed by $Cl_2Pd(3-CIPy)_2^{35}$ (0.85 g, 2.12 mmol, 1.2 equiv.) and toluene (100 mL) after which the suspension was stirred at 110 °C for 48 h. After cooling to rt, Et₂O (100 mL) was added and the suspension filtered through a pad of Celite® using Et₂O as eluent. The solvent was removed under reduced pressure and the residue extracted with boiling hexanes (100 mL). The solvent was removed to give a yellow solid. In order to remove any remaining copper species the crude product was dissolved in CH₂Cl₂/EtOAc (95:5) and passed through a plug of SiO2. Removal of the solvent in vacuo afforded Pd-PEPPSI-IPr-triazole (9) as a yellow solid (1.02 g, 61 %). (Alternatively the complex could by purified by column chromatography on SiO₂ (5 to 15% EtOAc/CH₂Cl₂). ¹H NMR (600 MHz, CDCl3): δ 8.59 (d, J = 2.7 Hz, 1H), 8.49-8.54 (m, 1H), 7.87 (s, 1H), 7.80 (s, 2H), 7.54 (d, J = 8.1 Hz, 1H), 7.48-7.52 (m, 1H), 7.36 (d, J = 7.6 Hz, 2H), 7.16 (d, J = 2.2 Hz, 2H), 7.06 (dd, J = 8.1, 5.4 Hz, 1H), 4.44 (t, J = 7.0 Hz, 2H), 3.83 (q, J = 7.0 Hz, 6H), 3.11-3.24 (m, 4H), 2.05-2.13 (m, 2H), 1.53 (d, J = 6.5 Hz, 6H), 1.48 (d, J = 6.5 Hz, 6H), 1.23 (t, J = 6.8 Hz, 9H), 1.16 (d, J = 7.0 Hz, 6H), 1.13 (d, J = 7.0 Hz, 6H), 0.60-0.71 (m, 2H). ${}^{13}C{}^{1}H{}$ NMR (151MHz, CDCl₃): δ 153.7, 150.4, 149.4, 147.5, 147.3, 146.7, 137.4, 135.0, 134.8, 132.5, 132.0, 130.4, 125.2, 125.1, 124.3, 124.1, 121.6, 120.2, 58.6, 52.5, 28.9, 28.7, 26.3, 26.2, 24.3, 23.2, 23.2, 18.3, 7.5. HRMS calculated for C₄₃H₆₂Cl₃N₆O₃PdSi [M+H]⁺: 949.2747, found: 949.2742.

Synthesis of solid supported Pd-PEPPSI-IPr (10)

Silica gel (20 g) was first suspended in H_2O (100 mL) and HCl (conc., 20 mL) was added. The suspension was then heated to 90 °C for 5 h. After cooling to rt the silica gel was collected by

filtration and washed thoroughly with $\rm H_2O$ (2 L) and acetone (2 L) before being dried in vacuo at 80 $^{\circ}\rm C.^{38}$

In air, a vial was charged with SiO₂ (14.2 g), **9** (4.7 g, 4.9 mmol) mmol) and toluene the resultant suspension was rotated in a rotisserie oven for 24 h at 100 °C. After cooling to rt the silica was collected by filtration, washed with CH_2Cl_2 (100 mL) and subjected to Soxhlet extraction using EtOAc for 24 h. The silica was collected by filtration, washed with EtOAc (50 mL) and CH_2Cl_2 (100 mL) and then dried *in vacuo*. The supported complex was suspended in a mixture of toluene (20 mL) and hexamethyldisilazane (20 mL) and rotated for 24 h at rt. The supernatant liquid was decanted and the silica washed with CH_2Cl_2 (2 x 50 mL), EtOAc (2 x 50 mL) and EtOAc/MeOH (2:1) before being dried *in vacuo* (17.3 g of silica obtained after drying). Analysis found: C 12.11; H 1.90; N 2.09; Pd 2.28; Cl 2.00; Si 37.4.

General procedure for the preparation of alkylzinc reagents³⁹

In a glovebox, a flame-dried round bottom flask was charged with zinc dust (3.9 g, 60 mmol, 1.5 equiv.). The flask was removed from the glovebox and I₂ (0.5 g, 2 mmol, 0.05 equiv.) was added before it was purged with argon (3x). DMI (40 mL) was added portion-wise and the resultant suspension stirred at rt until the colour of I₂ disappeared (ca. 5 min). The alkyl bromide (7.1 mL, 40 mmol) was added and the mixture heated to 80 °C for 16 h at which time it was cooled to rt. and allowed to stand without stirring for 10 h. The concentration of the organozinc solution was determined by iodometric titration of the resulting supernatant using Knochel's procedure.⁴⁰

General procedure for Negishi coupling reactions in batch

Under argon, a vial was charged with 10 (50 mg, 0.21 mmol/g loading, 2 mol%) and LiBr (139 mg, 1.6 mmol). THF (2.5 mL) was added followed by the organozinc reagent (1.25 mL, 0.65M in DMI, 0.8 mmol). After stirring for 2 min the aryl halide (0.5 mmol) was added and the reaction vial rotated in a rotisserie oven at 10 rpm under a static argon atmosphere for 16 h. Alternatively, if the aryl halide was a solid at rt, it was introduced into the reaction vial prior to the addition of THF. After this time, the reaction mixture was filtered in air and the heterogeneous catalyst washed with CH₂Cl₂ (2 x 20 mL) and Et. ₂O (2 x 20 mL), after which it was dried under vacuum. The reaction mixture was diluted with Et₂O (20 mL), and then washed successively with sat. aq. NaHCO₃ (25 mL), water (25 mL) and brine (25 mL). After drying over anhydrous MgSO₄ the solution was filtered and the solvent removed in vacuo. The residue was then purified by flash chromatography on silica gel.

General procedure for Negishi couplings in continuous flow

An FEP (fluorinated ethylene propylene) tube (0.159 cm ID x 8 cm) was packed with 70 mg of **10** and a small wad of cotton placed at the ends of the reactor to hold the supported catalyst in place. Connected to the reactor outlet was a length of FEP tubing (0.025 cm ID x 20 cm) that fed directly into a

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quench solution of saturated NaHCO₃/H₂O (1:1). The total reactor volume was 171 µL. The tubing containing the catalyst 5. was washed with THF (3 mL) pumped through the reactor at 20 µL/min. Under argon, a round bottom flask was charged with 2-chloro-4-methylquinoline (428 mg, 2.4 mmol) and LiBr (670 mg, 7.7 mmol, 3.2 equiv.). THF (13.6 mL) was added followed by (6-ethoxy-6-oxohexyl)zinc(II) bromide (6.8 mL, 0.66 M in DMI, 4.5 mmol, 1.8 equiv.) and the mixture stirred until the solids had dissolved. Contents of the flask were drawn into a 30 mL syringe and placed on a New-Era NE-1000 pump set to infuse at a rate of 20 µL/min. The reaction mixture was passed through the packed bed catalyst at rt and deposited in the stirred quench solution; after ca. 1 h had passed allowing for steady state, 19 mL was subsequently collected. The mixture was extracted with Et₂O (3 x 50 mL), the organic phase washed with brine (100 mL) and the organic 6. layer dried over anhydrous MgSO₄. The suspension was filtered and the solvent removed in vacuo. The residue was then purified by flash chromatography on silica gel (0 to 20% EtOAc in hexanes) to give 13 as a clear oil (560 mg, 88%). $R_f =$ 0.34 (20% EtOAc/hexanes). ¹H NMR (400 MHz, (CD₃)₂CO): δ 8.01 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.24 (s, 1H), 4.06 (q, J = 7.1 Hz, 2H), 2.89 (t, J = 7.6 Hz, 2H), 2.67 (s, 3H), 2.29 (t, J = 7.6 Hz, 2H), 1.83 (quint, J = 7.6 Hz, 2H), 1.66 (quint, J = 7.6 Hz, 2H), 1.42 (quint, J = 7.6 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H). ¹³C{¹H} NMR (101 MHz, (CD₃)₂CO): δ 173.7, 163.1, 149.0, 144.9, 130.5, 129.7, 127.8, 126.3, 124.8, 123.0, 60.5, 39.4, 34.7, 29.9, 29.7, 25.7, 18.7, 14.7. ¹H NMR (400 MHz, CDCl₃): δ 8.01 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6Hz, 1H), 7.11 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 2.9 (t, J = 8.1 Hz, 2H), 2.64 (s, 3H), 2.28 (t, J = 7.1 Hz, 2H), 1.81 (quint, J = 7.8 Hz, 2H), 1.68 (quint, J = 7.6 Hz, 2H), 1.43 (quint, J = 7.6 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H). ${}^{13}C{}^{1}H{}$ NMR (101 MHz, CDCl₃): δ 173.7, 162.3, 8. 147.6, 144.1, 129.2, 128.9, 126.7, 125.3, 123.5, 121.9, 60.1, 38.9, 34.2, 29.5, 28.9, 24.8, 18.6, 14.1. HRMS (ESI) calculated for C₁₈H₂₄NO₂ [M+H]⁺: 286.1802, Found: 286.1793. 9.

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