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Selective and General Exhaustive Cross-Coupling of Di-Chloroarenes With a Deficit of Nucleophile Mediated by a Pd-NHC Complex

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We report the first example of a general, exhaustive Pd-mediated cross-coupling of polychloroarenes in the presence of a deficit of nucleophile, mediated by the highly active PEPPSI-IPent catalyst. Our results indicate that this catalyst system may be applicable to the pseudo-living polymerisation of chloroarene monomers.

Transition metal-mediated catalyst transfer polycondensations, introduced independently by Yokozawa and McCullough in 2004,¹ allow the pseudo-living synthesis of conjugated polymers with enhanced properties through fine control over molecular weight, polydispersity and in the case of copolymers, block size.^{2,3} This is as a result of a mechanism in which the catalyst oxidatively adds to the C-X group of the growing polymer chain after reductive elimination faster than the two can separate resulting in a chain growth process.⁴ Prior to this breakthrough, transition metal cross-coupling polymerisations typically resulted in poor control over polymer properties as they proceeded via a step growth mechanism.⁵

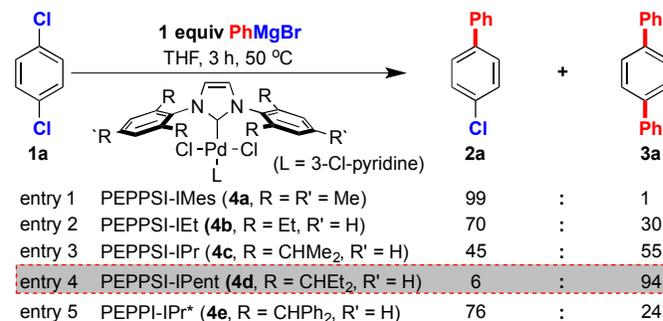
The first complexes identified as operating via a catalyst transfer mechanism were based on Ni and these catalysts continue to dominate the field.³ However, in 2005 Dong and Hu applied McCullough's proposal^{1b} that a catalyst's ability to mediate a pseudo living polymerization could be assessed by examining its reactivity with dihaloarenes in the presence of a deficit of nucleophile in order to identify Pd(0)/P^tBu₃⁶ as a promising candidate:⁷ this Pd catalyst selectively mediated the exhaustive functionalization of dibromo- and diiodo-benzenes, suggesting that the catalyst and substrate do not separate after reductive elimination. This prediction has since been vindicated through the synthesis of poly-thiophenes, -phenylenes and -fluorenes with controlled M_w as well as dendrimers and polymer brushes by surface initiated polymerization.⁸

We recently employed McCullough's exhaustive functionalization approach to identify PEPPSI-IPr (**4c**), a versatile NHC-ligated⁹ Pd catalyst developed by Organ and co-workers,^{10,11} as a promising candidate to mediate catalyst transfer polymerisations of iodo- and bromo-monomers.¹² Subsequent work by McNeil and co-workers confirmed that PEPPSI-IPr is indeed capable of mediating a catalyst-transfer

polycondensation, producing block copolymers with narrow molecular weight distribution in a pseudo-living manner.¹³

Despite these successes, to date the vast majority of catalyst transfer polycondensations mediated by either Ni or Pd for the synthesis of conjugated polymers employ monomers of the form X-Ar-M where X = Br or I.³ In contrast only limited examples of the successful pseudo-living polymerization of cheaper and more readily available chloroarene monomers have been reported using a C-H functionalization strategy in the presence of a Ni catalyst.¹⁴ Indeed, both the Pd(0)/P^tBu₃ and PEPPSI-IPr catalyst systems fail to achieve exhaustive functionalization of dichloroarenes,^{7,12} and only two reports, each of which disclose a single example, demonstrate this behavior mediated by Ni.¹⁵

Given the high reactivity of NHC-ligated Pd complexes with aryl chlorides, and the known effect of NHC ligand structure on the behavior of these catalysts, we set out to determine if modification of the ligand in the PEPPSI system would allow the exhaustive substitution of aryl chlorides. Here we explore in detail the first general example of such a selective process mediated by a Pd catalyst, opening the door to their use in the synthesis of structurally defined conjugated polymers.



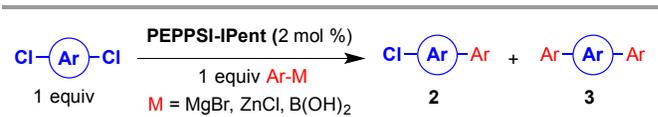
Scheme 1. Effect of catalyst structure on the chemoselective reaction of 1,4-dichlorobenzene. Couplings were performed with 0.02 equiv of **4** and 1 equiv of PhMgBr relative to **1a**. Ratio **2a** : **3a** was determined by ¹H NMR and GCMS.

Given that variation in the structure of the NHC ligand is known to significantly alter the Pd-catalyst behaviour,^{10d} we studied the Kumada reaction between 1,4-dichlorobenzene and PhMgBr mediated by a series of PEPPSI-type precatalysts (Scheme 1). Variation of the NHC ligand led to increasing selectivity for di-substitution in the order IMes (**4a**) < IEt (**4b**) < IPr (**4c**) < IPent (**4d**), which parallels the trend in in both ligand steric demand and catalyst activity (entries 1-4).¹⁶ Gratifyingly, PEPPSI-IPent displayed extremely high selectivity for the di-arylation (94:6) of 1,4-dichlorobenzene. Surprisingly, although PEPPSI-IPr* (entry 5, **4e**) is extremely bulky and known to display similar reactivity to **4d**,¹⁷ it displays similar selectivity to less sterically demanding and reactive **4b**, indicating that high catalyst reactivity and ligand bulk are not sufficient requirements for exhaustive cross-coupling. Having identified PEPPSI-IPent as a promising candidate for selective poly-substitution, we set out to examine the scope and limitations of this process.

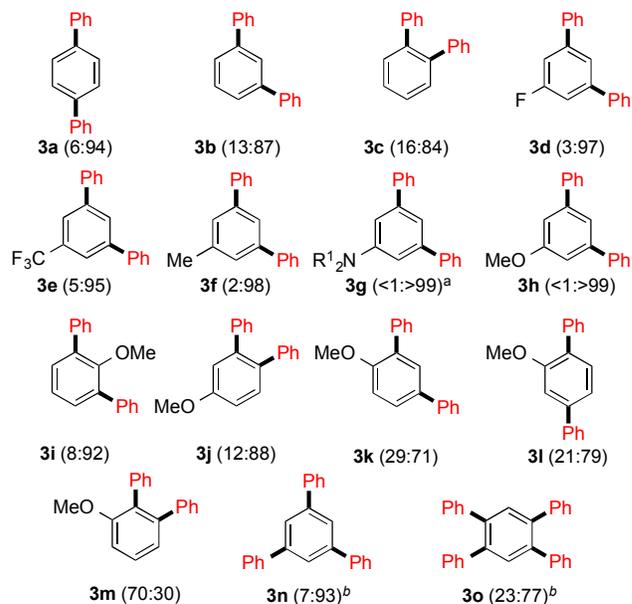
Variation in the relative orientation of the C-Cl moieties (Scheme 2a, **3a-c**) led to small changes in the reaction outcome with the selectivity falling to 16:84 in the case of sterically hindered 1,2-dichlorobenzene. Conversely, in a series of substituted *m*-dichlorobenzenes (**3d-h**), electron-withdrawing (**3d-e**) and electron-donating (**3f-h**) substituents both led to high di-selectivity. On the other hand, examination of a series of regioisomers of dichloroanisole (**3h-m**) demonstrated that the relative position of the substituents has an appreciable effect on the reaction selectivity; while highly symmetrical **3h** and **3i** were obtained with high selectivity, when the MeO substituent was placed *ortho* to only one of the C-Cl bonds, di-selectivity was significantly reduced (**3k**, 29:71 and **3l**, 21:79) or even reversed (**3m**, 70:30). Finally, even arenes substituted with 3 and 4 C-Cl bonds were found to lead to exhaustive substitution with very high selectivities of 7:93 (**3n**) and 23:77 (**3o**), respectively, indicating that this effect is not limited to dichloroarenes.

In order to ascertain the effect of nucleophile structure on the observed product selectivity we studied the reaction of **1a** with a range of substituted Grignard reagents and other nucleophiles (Scheme 2b). Both electron-rich and electron-poor ArMgBr nucleophiles led to di-aryl adducts with high selectivities (**3p-r**). On the other hand, the use of a heteroaryl thienyl Grignard led to complete loss of selectivity (**3s**). Interestingly, high di-arylation selectivity was restored for the electron-rich 3,5-dichloroanisole even with thienyl Grignard (**3t**). Remarkably, the observed di-selectivity is not limited to the Kumada coupling: the coupling of PhB(OH)₂ or PhZnCl with **1a** both proceed with high selectivity (3:97 and 11:89 respectively).

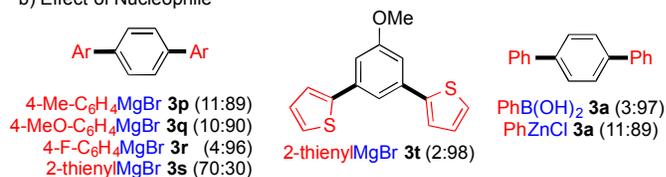
Finally, we extended our study to a number of dichloroarene derivatives of monomers commonly used in the synthesis of conjugated organic polymers (Figure 1). Gratifyingly, models of common p-type monomers including 1,4-dimethoxybenzene (**3u**), fluorene (**3w** and **3x**) and carbazole (**3y**) all displayed high selectivity for di-substitution when reacted with PhMgBr. This selectivity was maintained when 2-thienyl Grignard was used as the nucleophile (**3v**). Disappointingly, electron-deficient dichloro-fluorenone (**3z**), dichlorothiophene (**3aa**) and dichloro-EDOT (**3ab**), were either unselective (**3z**) or gave rise to the product of mono-substitution (**3aa** and **3ab**). In all cases examined, Kumada couplings proved superior, with Negishi and Suzuki couplings providing slightly lower selectivities (see SI for details).



a) Effect of substituents on the exhaustive cross-coupling with PhMgBr



b) Effect of Nucleophile



Scheme 2. Scope of the exhaustive cross-coupling of poly-chloroarenes mediated by PEPPSI-IPent (**4d**). Couplings were performed with 0.02 equiv of **4d** and 1 equiv of ArM relative to the electrophile. Unless otherwise stated M = MgBr. Cross-coupling yields (based on the organometallic component) generally exceeded 70%; see SI for details. Ratio of **2** : **3** determined by GCMS. ^a R¹ = - (CH₂)₂O(CH₂)₂- ^bSum of other arylation products vs exhaustive arylation.

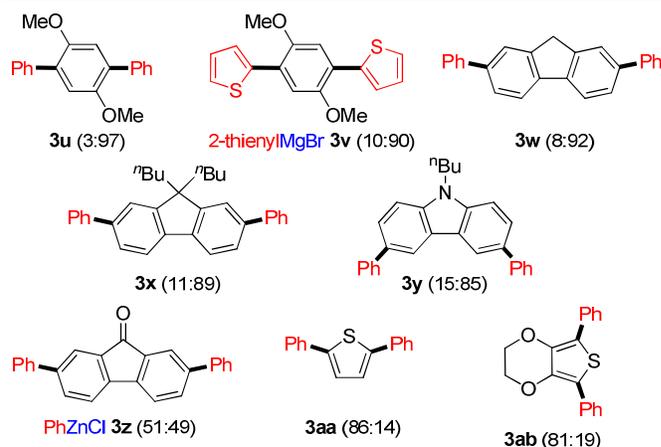


Figure 1. Scope of Exhaustive Cross-Coupling of Monomer-Like Di-Chloroarenes Mediated by PEPPSI-IPent (**4d**). Couplings were performed with 0.02 equiv of **4d** and 1.0 equiv of ArM relative to the electrophile. Cross-coupling yields (based on the organometallic component) generally exceeded 70%; see SI for details. Ratio of **2** : **3** was determined by GCMS.

In conclusion, we have demonstrated the first general, Pd-mediated catalyst system for the exhaustive cross-coupling on poly-chloroarenes under a defect of the nucleophilic coupling partner applicable to a wide range of substrates. Our results suggest that PEPPSI-IPent (**4d**) could be used to perform chain-growth polymerization of chloroarene-based monomers, including several monomers of interest for the synthesis of π -conjugated polymers. Based on our results however, further catalyst development is required for the pseudo-living polymerization of electron deficient or thiophene monomers.

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Notes and references

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