



A novel ditopic ring-expanded *N*-heterocyclic carbene ligand-assisted Suzuki-Miyaura coupling reaction in aqueous media



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ABSTRACT

A series of seven-membered ditopic ring-expanded *N*-heterocyclic carbene (dre-NHC) precursors, bearing sterically demanding and electron-rich aryl groups, were synthesised in moderate yields *via* the reaction of 1,2,4,5-tetrakis(bromomethyl)benzene with the corresponding *N,N'*-diarylformamidines in the presence of K₂CO₃ in acetonitrile under an air atmosphere. All new compounds were characterised by HRMS, NMR spectroscopy, and microanalysis, as well as X-ray crystallography for compound **1c**. The development of an efficient catalytic system for the Suzuki-Miyaura coupling reaction of aryl chlorides with various boronic acids was also investigated using the *in situ* generated dre-NHC ligands.

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Introduction

The palladium-catalysed Suzuki-Miyaura cross-coupling reaction between organoboron compounds and aryl halides is one of the most powerful methods¹ for the synthesis of biaryl compounds, which are often important chemicals in pharmaceuticals, organic chemistry and fine materials.^{2,3} The reputation of the Suzuki reaction stems from its use of low-cost and non-toxic chemicals, wide substrate tolerance, mild reaction conditions, and easy separation of products from the reaction media.^{4,5} The use of non-flammable, inexpensive and abundant green solvents, such as water or water solutions, is an important area of research for the Suzuki reaction.^{6–8} However, low substrate solubility or catalyst stability in water are potential issues. To overcome these problems, several additives have been successfully utilised.^{9–12} The employment of hydrophilic ligands, such as *N*-heterocyclic carbenes (NHCs) or phosphine ligands, is another method of improv-

ing the efficiency of Suzuki catalysis in water. However, despite the wide applications of phosphine ligands, they have limitations for use in the Suzuki reaction due to several disadvantages, including toxicity, sensitivity to air and moisture, and difficult separation from the products. As a result, NHCs have emerged as an alternative to phosphine ligands.^{13–19} The unique steric and electronic properties of NHCs as well as their specific coordination chemistry (strong σ -donor and weak π -acceptor properties) contribute to the generation of highly active and stable metal centres in the key catalytic steps of the Suzuki reaction. The accepted mechanism for the Pd-catalysed cross-coupling reaction²⁰ consists of three distinct parts: (i) oxidative addition of aryl halides to the active catalyst species, (ii) transmetalation of phenylboronic acid derivatives to the metal halides, and (iii) reductive elimination of the product from the active catalyst. For the oxidative addition step, electron-rich ligands improve insertion into the strong carbon-halogen bond of the aryl halide. Meanwhile, the steric bulk of the ligand is believed to increase the rate of reductive elimination to regenerate the active catalyst. Despite the bulky ligand increasing the reductive elimination rate, the rate of the oxidative addition step can be dramatically affected by the increasing steric effect of the

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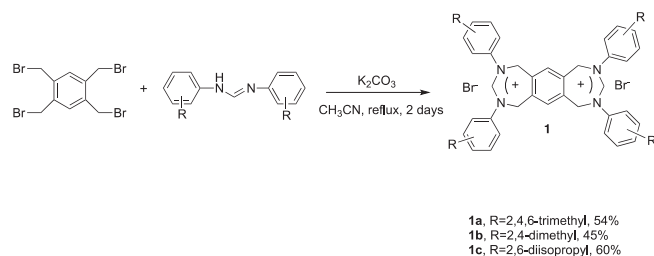
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ligand. According to these points, a balance between the steric and electronic properties of the ligand is an essential requirement.²⁰

So far, studies have focused on the synthesis and catalytic applications of classic NHC ligands. Recently, ring expanded *N*-heterocyclic carbenes (re-NHCs) have attracted attention due to their tuneable sterics and strong σ -donating nature, compared to classic NHCs, which make them desirable ligands for a range of transition metals and catalytic transformations.^{21–26} Despite these important features, re-NHCs have not been sufficiently investigated with regards to catalytic applications and complex syntheses. Preliminary investigations by the groups of Stahl and Cavell reported the syntheses of sterically and electronically unique six, seven and eight-membered re-NHCs, as well as their complexes and applications in catalysis.^{22–27} According to their results, large rings and N–C_{NHC}–N bond angles offer steric and electronic advantages in some applications when compared to conventional five-membered derivatives. The key facets of these ligands are the highly basic carbon and steric pressure related to the expanded ring and metal centre.²⁸ Re-NHCs have demonstrated excellent activity in C–C coupling,²⁹ hydrosilylation,³⁰ hydrogenation,³¹ and transfer hydrogenation reactions.³² In order to better understand the behaviour of these ligands, herein, we report more sterically demanding dre-NHC ligands and *in-situ* generation of the active catalyst for the Suzuki–Miyaura coupling reaction (Fig. 1).

Results and discussion

According to Scheme 1, compounds **1a–c** were synthesised in moderate yields *via* the reaction of 1,2,4,5-tetrakis(bromomethyl) benzene with the corresponding *N,N'*-diarylformamidines in the presence of K₂CO₃ in acetonitrile under an air atmosphere.³³ Well-known seven-membered NHCs have been reported by Cavell and co-workers.^{23–26,28–32} Upon formation of the seven membered dre-NHC precursors **1a–c**, ¹H NMR spectroscopy revealed the appearance of the characteristic formamidinium salt NCHN proton at 8.37, 8.29, and 8.42 ppm, respectively. The ¹H NMR shifts of **1a–c** were consistent with previously reported seven-membered NHC salts.²³ The methylene protons (NCH₂) of salts **1a–c** were visible as very broad singlets (between 4.0 and 6.5 ppm) at ambient temperature in CDCl₃ and DMSO-*d*₆. The imino carbons of **1a–c** (NCHN)



Scheme 1. Synthesis of dre-NHC compounds **1a–c**.

were detected as typical singlets in the ¹H-decoupled mode at 158.5, 157.4, and 156.7 ppm, respectively. All dre-NHC precursors were soluble in water and exhibited high stability in air and aqueous solutions.

Several catalytic systems have been reported for the aqueous Suzuki–Miyaura coupling reactions of aryl chlorides. However, most of these require at least 1 mol% of the Pd precursor and high reaction temperatures.^{34,35} Our group has previously reported a series of aqueous coupling protocols for aryl chlorides.^{36–39} In the present study, the activity of the *in-situ* generated dre-NHC/Pd catalyst system was investigated.³³

For this purpose, several inexpensive and readily water soluble alkaline metal bases, e.g. Na₂CO₃, K₂CO₃ and Cs₂CO₃, were examined. K₂CO₃ showed excellent catalytic activity in the DMF/H₂O solvent mixture (Table 1, entries 9–11). The use of a single solvent medium, such as H₂O, *i*-PrOH, dioxane or DMF, afforded lower yields (Table 1, entries 1–8). The solvents ratio was also examined (Table 1, entries 9–11); the best result was obtained using DMF/H₂O (1:1) (Table 1, entry 10).

The reaction of various phenylboronic acids with aryl chlorides was examined (Table 2; see ESI for the full version of Table 2). High yields were obtained with low catalyst loadings in the case of *p*-activated substrates, such as *p*-chloroacetophenone and *p*-chloroaldehyde (Table 2, entries 1–8, 26–28). Additionally, we examined the effect of temperature and reaction time (Table 2, entries 3–14, 26–28). Unactivated aryl chlorides required higher

Table 1

Effect of solvent and base on the model Suzuki coupling reaction of *p*-chloroacetophenone with phenylboronic acid, catalysed by the Pd(OAc)₂/**1a** catalyst system.

Entry	Solvent	Base	Conversion [%] ^a
1	Dioxane	Na ₂ CO ₃	64
2	Dioxane	K ₂ CO ₃	75
3	Dioxane	Cs ₂ CO ₃	35
4	<i>i</i> -PrOH	Na ₂ CO ₃	60
5	<i>i</i> -PrOH	K ₂ CO ₃	62
6	<i>i</i> -PrOH	Cs ₂ CO ₃	63
7	DMF	K ₂ CO ₃	79
8	H ₂ O	K ₂ CO ₃	37
9	DMF/H ₂ O (2:1)	K ₂ CO ₃	84
10	DMF/H ₂ O (1:1)	K ₂ CO ₃	>99
11	DMF/H ₂ O (1:2)	K ₂ CO ₃	88
12	DMF/H ₂ O (1:1)	Na ₂ CO ₃	80
13	DMF/H ₂ O (1:1)	Cs ₂ CO ₃	65

^a Reagents and conditions: Pd(OAc)₂ (0.5 mol%), **1a** (0.5 mol%), 4-chloroacetophenone (1 mmol), PhB(OH)₂ (1.5 mmol), base (1.5 eq.), solvent (6 mL) 80 °C, 1 h. GC yield calibrated against an internal standard (undecane).

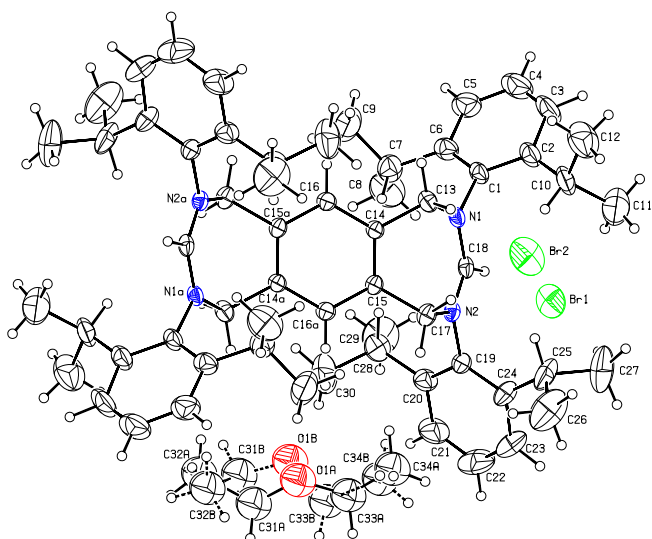


Fig. 1. ORTEP view of **1c**. Thermal ellipsoids are drawn at the 40% probability level and H-atoms are shown as small circles of arbitrary radii. The labeling of symmetry related atoms is omitted for clarity and symmetry related Br-ions and diethyl ether are not shown.

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