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Pd/NHC-catalyzed cross-coupling reactions of nitroarenes†

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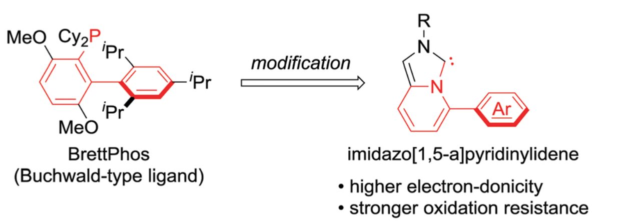
N-Heterocyclic carbene (NHC) ligands effective for the cross-coupling of nitroarenes were identified. A rational design of the NHC ligand structures enabled significant reduction of catalyst loadings compared with the previous system employing BrettPhos as a phosphine ligand. Experimental and theoretical studies to compare these ligands gave some insights into high activity of the newly developed NHC ligands.

Denitrative transformations of nitroarenes are advantageous in synthetic chemistry because they serve as an important class of chemical feedstocks readily available from simple nitration of aromatic compounds.[1] In addition, well-established functionalisations of nitroarenes including S_NAr/S_EAr/VNS and/or C–H functionalisation[2,3] to afford multi-substituted nitroarenes in a site-selective manner make denitrative transformations highly attractive to access a variety of substituted arenes. Conventionally, the replacement of the NO_2 group with various functional groups could be achieved in 3 steps including reduction, diazotisation, and Sandmeyer/cross-coupling reactions. Direct transformations of nitro groups have been therefore of high demand to upgrade the synthetic utility of nitroarenes. Some examples of such single-step transformations of Ar–NO_2 bonds have been reported but lacked generality in terms of scope of nitroarenes.[4] The difficulty in the use of nitroarenes for cross-coupling reactions is partly derived from reduction of the NO_2 group by low-valent metal catalysts.[5] Nevertheless, we previously reported that the combination of palladium as a metal center and BrettPhos[6a] as a supporting ligand enabled the unprecedented oxidative addition of Ar–NO_2 bonds to palladium(0) to enable the Suzuki–Miyaura coupling,[7a] Buchwald–Hartwig amination,[7b] and reductive denitration of nitroarenes.[7c] Although these coupling reactions opened a novel aspect in chemistry of nitroarenes, there still remained serious issues from a practical point of view such as high loadings of precious Pd (>5 mol%) and expensive Buchwald-type ligands[6] (10–20 mol%). Phosphine ligands could also be deactivated through oxidation by the NO_2 group.

To deviate from phosphine ligands, we turned our attention to the use of NHC ligands.[8] In 2005, the groups of Lassaletta and Glorius independently reported the use of imidazo[1,5-*a*]pyridinylidenes,[9a,b] which appeared to be a hybrid form of the Buchwald-type ligands and NHC ligands (Scheme 1). Subsequently, some derivatives were investigated and published.[9] Despite being structural mimics of the Buchwald-type ligands, they have rarely been applied to metal-catalysed reactions. We conceived the use of imidazo[1,5-*a*]pyridinylidene bearing an Ar group at the C5 position as a supporting ligand in the cross-coupling reactions of nitroarenes. NHC ligands generally possess higher electron-donicity and tolerance toward oxidation than phosphine ligands. We expected that the NHC ligands could facilitate the rate-determining oxidative addition of Ar–NO_2 bonds and elongate the catalyst lifetime by preventing ligand oxidation.

We examined the Suzuki–Miyaura coupling of 4-nitroanisole (**1a**) and phenylboronic acid (**2a**) in the presence of 1.0 mol% $Pd(acac)_2$ and 2.0 mol% **L1**[9i] (eqn (1)). In contrast to the use of BrettPhos, which resulted in only 6% of the desired product **3a**, the use of **L1** drastically improved the yield of **3a** to 60%.

Motivated by the preliminary result, we screened various imidazo[1,5-*a*]pyridinylidenes as ligands in the reaction of **1a**



Scheme 1 Design of imidazo[1,5-*a*]pyridinylidene ligands for the cross-coupling of nitroarenes.

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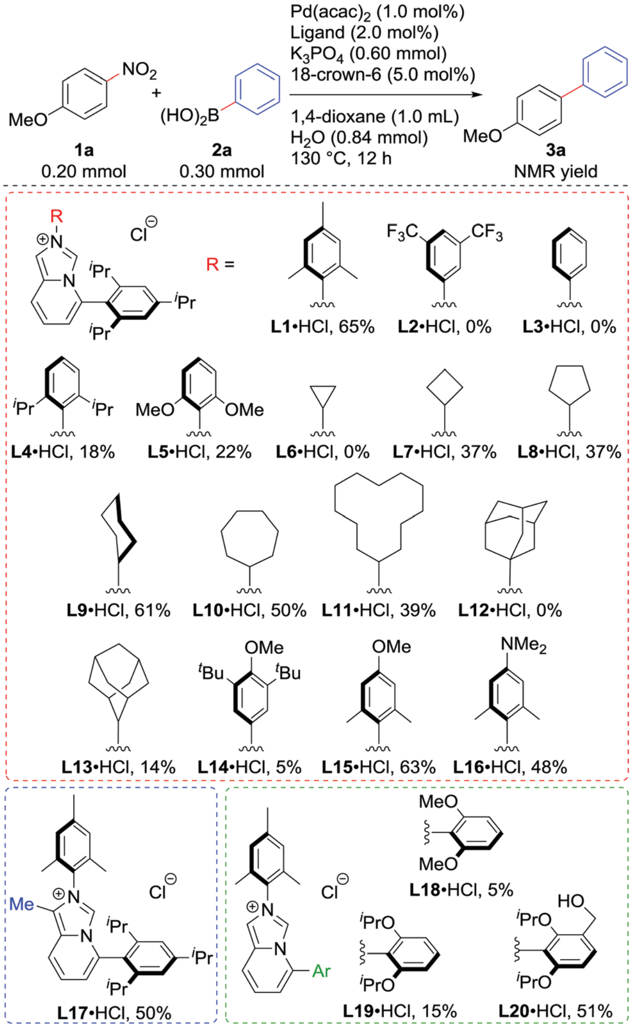
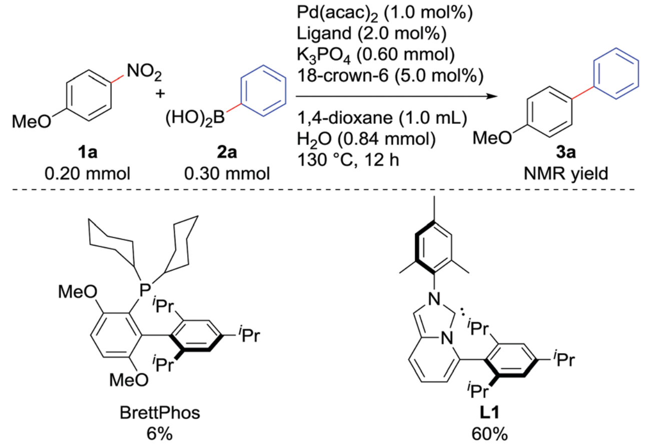


Scheme 2 Optimisation of ligand structures.

with **2a** using 1.0 mol% Pd (Scheme 2). The HCl adduct of **L1** could be used directly without any loss of the yield.[10] Regarding the substituent on nitrogen, electron-withdrawing 3,5-bistrifluoromethyphenyl in **L2** and even the phenyl group in **L3** were not suitable at all, while sterically hindered 2,6-diisopropylphenyl in **L4** and 2,6-dimethoxyphenyl in **L5** deteriorated the catalytic activity as well, though they were electron-donating. Cycloalkyl substituents seemed good for this system, except for the cyclopropyl group in **L6**, which could react with Pd(0).[11] **L9** showed the best performance among these, producing **3a** in 61% yield. The bulky adamantyl groups in **L12** and **L13**, and 3,5-di-*tert*-butyl-4-methoxyphenyl in **L14** retarded the reaction. **L15** and **L16**, which were expected to be more electron-donating than **L1**, unfortunately failed to improve the catalytic activity. Similarly, introducing an electron-donating methyl substituent on the backbone in **L17** did not bring any positive effects. By analogy with the Buchwald-type phosphines, the properties of the C5-aryl group were found to be important. **L18** and **L19** were less active than **L1** in line with the competition of the Buchwald phosphines (SPhos and RuPhos respectively *vs.* XPhos or BrettPhos) in our previous report.[7a] To our surprise, NHC bearing a hydroxymethyl group **L20** marked higher yield of **3a** than **L19**.[12]



(1)

To make this system more efficient, we made an attempt to use (**L1**)Pd complexes as catalyst precursors (Table 1). (**L1**)Pd(acac)Cl was prepared and examined first, but the yield was similar to the case where $Pd(acac)_2$ and **L1**·HCl were independently used. Another complex (**L1**)Pd(allyl)Cl proved to be effective to afford **3a** in 76%.

We then carried out some analyses to verify the properties of **L1**. Fig. 1 shows the time-course of the Suzuki–Miyaura coupling of **1a** with **2a** catalysed by 5.0 mol%Pd/BrettPhos and 1.0 mol%Pd/**L1**. The former system turned out to be deactivated within 3 h,[13] whereas the coupling proceeded with the latter system much faster and the yield of **3a** kept increasing even after 4 h. These reaction profiles obviously revealed two significant effects associated with **L1**: rate-acceleration and longer catalyst lifetime. The higher reaction rate was also

Table 1 Optimisation of catalyst precursors

Pd/**L1**	Yield (%)
$Pd(acac)_2$ (1.0 mol%) + **L1**·HCl (2.0 mol%)	65
(**L1**)Pd(acac)Cl (1.0 mol%)	61
(**L1**)Pd(allyl)Cl (1.0 mol%)	76

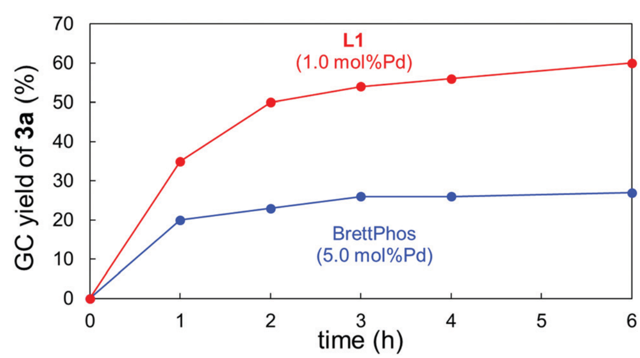
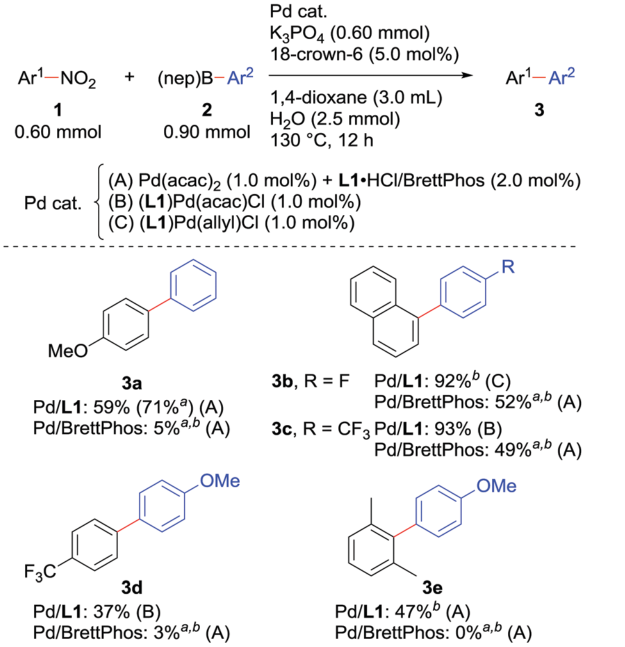
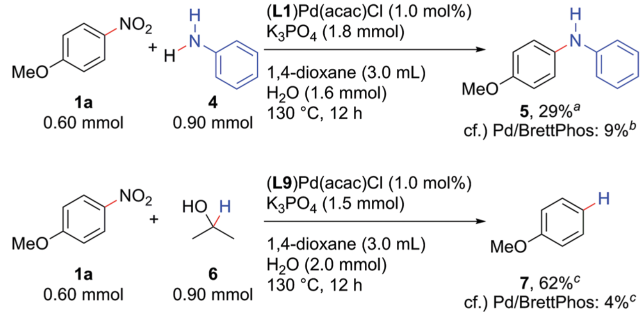


Fig. 1 Time-courses of the coupling of 4-nitroanisole (**1a**) and phenylboronic acid (**2a**).



Scheme 3 Scope of the Suzuki–Miyaura coupling of nitroarenes. [a] NMR yields determined using 1,3,5-trimethoxybenzene as an internal standard. [b] Ar^2–$B(OH)_2$ was used instead of Ar^2–B(nep).



Scheme 4 The Buchwald–Hartwig amination and reductive denitration of nitroarenes. [a] Isolated yield. [b] NMR yield determined using 1,3,5-trimethoxybenzene as an internal standard. [c] GC yields determined using n-$C_{13}H_{28}$ as an internal standard.

supported by DFT calculations. The activation barrier for the rate-limiting oxidative addition of **1a** to (**L1**)Pd^0 was calculated to be 27.2 kcal mol^{-1}, which was smaller than that of (BrettPhos)Pd^0 (30.1 kcal mol^{-1}).[14] This difference was likely to derive from their HOMO energies. The higher HOMO level of (**L1**)Pd^0 could enable the faster oxidative addition of the Ar–NO_2 bond (see the ESI† for details). Experimentally, a large difference of $\%V_{Bur}$[15] between (BrettPhos)AuCl and (**L1**)AuCl was noted (59.5% *vs.* 51.9%,[9i] respectively), illustrating that **L1** occupied less space around the Pd center, possibly allowing easier access of the substrate to Pd than with BrettPhos. Furthermore, the rigid skeleton of **L1** could inhibit its flip in the coordination sphere, unlike BrettPhos which could show two different coordination modes. This rigidity could partly contribute to the robustness of the (**L1**)Pd system in collaboration with reluctance of oxidation by nitroarenes.

We also checked the reactivity of the new catalyst to several other substrate sets (Scheme 3). The use of boronic acid neopentylglycol ester in combination with a catalyst derived from $Pd(acac)_2$ and **L1**·HCl slightly improved the yield of **3a**. Couplings of nitronaphthalene and F-containing arylboronic acids proceeded very smoothly to give **3b** and **3c**. A nitroarene bearing an electron-withdrawing trifluoromethyl group could be reacted, though the yield of biaryl **3d** was relatively low as observed in our original report.[7a] In all the cases, the new catalytic system performed much better than 1.0 mol% Pd/BrettPhos. Moreover, 2,6-dimethylnitrobenzene, which was too sterically demanding to cross-couple under the previous conditions, afforded biaryl **3e** by the Pd/**L1** catalyst, possibly due to the reduced $\%V_{Bur}$ of **L1** compared with BrettPhos.

The Pd/NHC system developed herein catalysed not only the Suzuki–Miyaura coupling, but also the Buchwald–Hartwig amination and reductive denitration of nitroarenes (Scheme 4). Aniline (**4**) could be coupled with **1a** to afford diarylamine **5** by using 1.0 mol% (**L1**)Pd(acac)Cl as a catalyst precursor. Denitration of **1a** proceeded well with (**L9**)Pd(acac)Cl, delivering anisole (**7**) in 62% yield. Both reactions again afforded the products in yields much higher than those catalysed by 1 mol% Pd/BrettPhos.

In conclusion, we have developed new reaction conditions employing imidazo[1,5-*a*]pyridinylidene as NHC ligands for the cross-coupling reactions of nitroarenes. The Pd/NHC catalysts showed much higher activity than the Pd/BrettPhos system. Some insights into the reasons for the improved performance by the Pd/NHC catalyst are shown in terms of experimental and theoretical studies. Further applications of the Pd/NHC catalyst to other reactions are in progress.

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Conflicts of interest

There are no conflicts to declare.

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