Acyclic diaminocarbenes: simple, versatile ligands for cross-coupling reactions†

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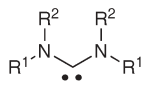
Acyclic diaminocarbenes are found to be useful ligands for palladium catalyzed Suzuki–Miyaura, Sonogashira and Heck cross-coupling reactions of aryl/alkenyl bromides and chlorides.

The major driving force behind the impressive growth in transition metal catalysis has been the continual development of new ligands.[1] Recently, a new class of ligands—N-heterocyclic carbenes (NHC)—has been introduced into the field of catalysis.[2,3] In particular, the application of NHC in a variety of cross-coupling reactions has proved very fruitful.[4–6] Several of the more widely used NHC (**2–4**) are shown below.

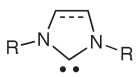
Acyclic diaminocarbenes (ADC) (**1**),[7,8] on the other hand, have not attracted the same degree of attention as NHC despite several appealing characteristics. These include the simple, straightforward preparation of the formamidinium salt precursors,[9] and the more basic nature of the resulting carbenes.[8i,j] We were thus interested in investigating a series of ADC (*vide infra*) in a select number of palladium catalyzed cross-coupling reactions.[10]

ADC

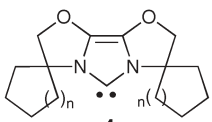


1a: $R^1 = R^2 = i$-Pr
1b: $R^1 = t$-Bu, R^2 = Me
1c: $R^1 = R^2 = (CH_2)_4$
1d: $R^1 = R^2 = (CH_2)_5$

NHC



2: R = 2,6-diisopropylphenyl
3: R = 2,4,6-trimethylphenyl



4

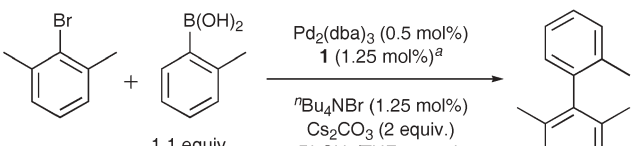
We chose to evaluate the utility of ADC **1a–d** as ligands in the Suzuki–Miyaura reaction between 2-bromo-1,3-dimethylbenzene and 2-methylphenylboronic acid (Table 1).[11] Several reaction parameters were initially varied including the palladium source, base, solvent, and other additives.[12] After extensive screening, the following set of standard reaction conditions were established with respect to the aryl/alkenyl halide: 0.5 mol% $Pd_2(dba)_3$, 1.25 mol% **1**, 1.25 mol% $^nBu_4NBr$,[13] 1.1 equiv. $ArB(OH)_2$ and 2 equiv. Cs_2CO_3 in toluene–THF. The requisite ADC were synthesized *in situ* through deprotonation (LDA) of the corresponding formamidinium salts,[9] as originally reported by Alder *et al.*[7] Bis(diisopropylamino)carbene (**1a**) was found to be the ligand of choice affording the desired tri-*ortho*-substituted biaryl (**5a**) in 89% isolated yield.[14] There was very little difference in efficacy when isolated carbene **1a** (entry 3) was used in place of the *in situ* generated variant (entry 2).

The room temperature Suzuki–Miyaura reaction was extended to a variety of other substrates, the results of which are shown in Table 2. The coupling was effective for sterically hindered aryl bromides (entries 5–7), heterocyclic bromides (entries 2,3) and alkenyl bromides (entries 8,9). The scope of the reaction was also established with a number of sterically demanding (entries 1–4) and electron rich boronic acids (entry 9). The nature of the boronic acid was also expanded to include alkenyl (entries 5,6) and heterocyclic variants (entry 7).

A significant improvement to the process was to enable the use of aryl chlorides in the Suzuki–Miyaura reaction. Initial optimization studies involving 2-chloro-1,3-dimethylbenzene and 2-methylphenylboronic acid revealed that the coupling reaction, when conducted under the conditions reported in Table 2, proceeded rather sluggishly (22% isolated yield of **5a**). Fortunately, elevating the reaction temperature from rt to 45 °C resulted in a much more facile reaction (80% isolated yield of **5a**). A variety of aryl chlorides and boronic acids were then subjected to the cross-coupling reaction using ADC ligand **1a** (Table 3). As before, the desired products were obtained in good yields.

We next explored the efficacy of **1a** in the Sonogashira reaction.[15] The optimized copper-free protocol, which turned out to be similar to one previously reported by Soheili *et al.*,[16] is as follows: halide (1 equiv.), alkyne (1.1 equiv.), $[Pd(allyl)Cl]_2$

Table 1 Suzuki–Miyaura coupling of 2-bromo-1,3-dimethylbenzene with 2-methylphenylboronic acid using ADC **1a–d** as ligands



5a

Entry	ADC (**1**)	Yield (%)[b]
1	—	<3%[c]
2	**1a**	89
3	**1a**[d]	90
4	**1b**	88
5	**1c**	49
6	**1d**	40

[a] Prepared *in situ via* deprotonation (LDA) of the corresponding formamidinium salt. [b] Isolated yield (average of two runs). [c] Estimated yield based on crude ^1H NMR spectra. [d] Isolated **1a** was used.

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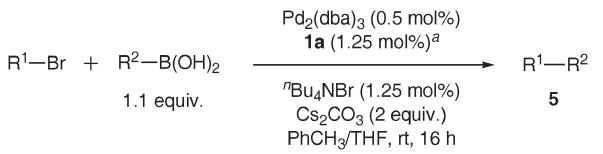
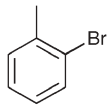
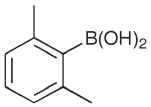
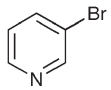
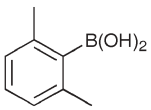
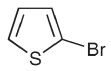
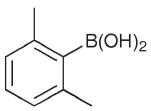
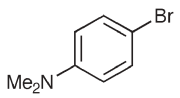
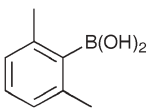
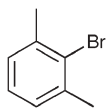
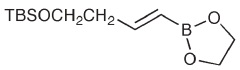
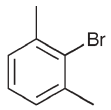
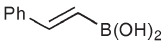
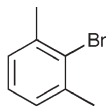
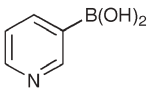
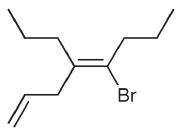
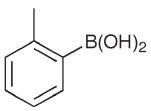
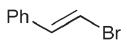
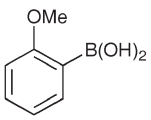
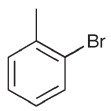
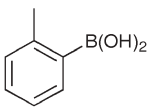
† Electronic Supplementary Information (ESI) available: Optimization studies and characterization data. See DOI: 10.1039/b516398f

Table 2 Room temperature Suzuki–Miyaura coupling of aryl/alkenyl bromides using ADC ligand **1a**

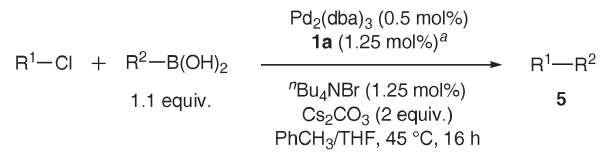


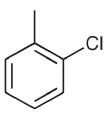
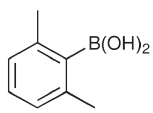
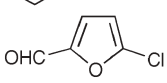
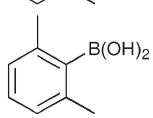
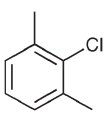
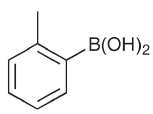
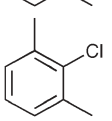
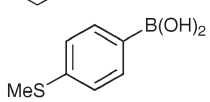
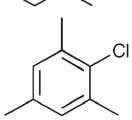
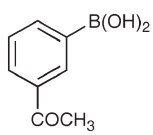
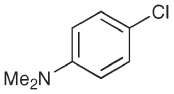
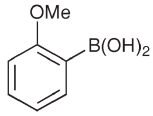
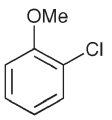
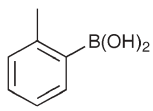
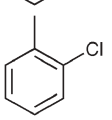
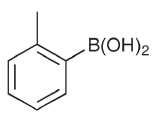
Entry	R^1–Br	R^2–$B(OH)_2$	Yield (%)[b]
1			86 (**5a**)
2			85 (**5b**)
3			89 (**5c**)
4			79 (**5d**)
5			93 (**5e**)
6			89 (**5f**)
7			91 (**5b**)
8			88 (**5g**)
9			93 (**5h**)
10			95 (**5i**)

[a] Prepared *in situ via* deprotonation (LDA) of the corresponding formamidinium salt. [b] Isolated yield (average of two runs).

(1.5 mol%), **1a** (4 mol%), Cs_2CO_3 (2 equiv.), $PhCH_3$–THF, rt, 16 h. A variety of aryl halides were subjected to the conditions reported above, the results of which are shown in Table 4. The room temperature Sonogashira reaction worked well with both aromatic (entries 1,2,4–6) and aliphatic alkynes (entries 3,7). A range of sterically hindered- (entry 1), electron rich- (entries 2–4) and heterocyclic aryl bromides (entries 6,7) were employed as coupling partners. The resulting products were consistently obtained in good isolated yields.

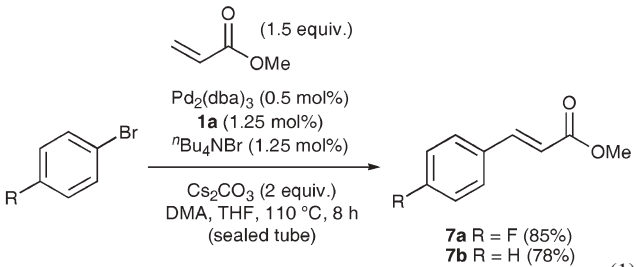
Table 3 Suzuki–Miyaura coupling of aryl/alkenyl chlorides using ADC ligand **1a**



Entry	R^1–Cl	R^2–$B(OH)_2$	Yield (%)[b]
1			81 (**5a**)
2			89 (**5j**)
3			80 (**5a**)
4			86 (**5k**)
5			88 (**5l**)
6			85 (**5m**)
7			92 (**5n**)
8			89 (**5i**)

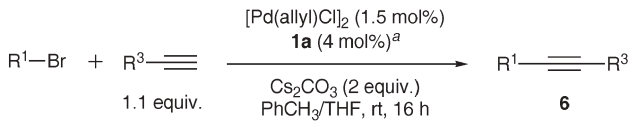
[a] Prepared *in situ via* deprotonation (LDA) of the corresponding formamidinium salt. [b] Isolated yield (average of two runs).

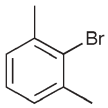
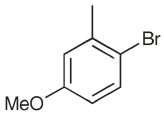
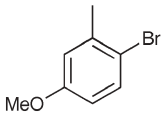
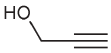
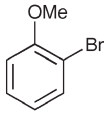
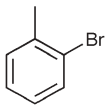
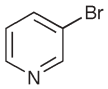
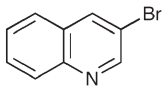
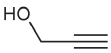
Finally, we also briefly examined the applicability of ADC **1a** in intermolecular Heck reactions.[17] Aryl bromides were readily coupled to an electron deficient alkene in good yields under a modified set of conditions (eqn (1)).[12] The corresponding aryl chlorides, however, were poor substrates for the Heck reaction (35% and 29% isolated yields of **7a** and **7b** respectively) under the conditions shown in eqn (1).[12]



(1)

Table 4 Room temperature Sonogashira coupling of aryl bromides using ADC ligand **1a**



Entry	R^1–Br	R^3	Yield (%)[b]
1			80 (**6a**)
2			87 (**6b**)
3			80 (**6c**)
4			91 (**6d**)
5			89 (**6e**)
6			90 (**6f**)
7			81 (**6g**)

[a] Prepared *in situ via* deprotonation (LDA) of the corresponding formamidinium salt. [b] Isolated yield (average of two runs).

In summary, we have demonstrated that ADC are useful ligands for the Suzuki, Sonogashira and Heck reactions, affording the desired products in good to excellent yields.

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