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Coupling of *ortho*-substituted aryl chlorides with bulky amides†

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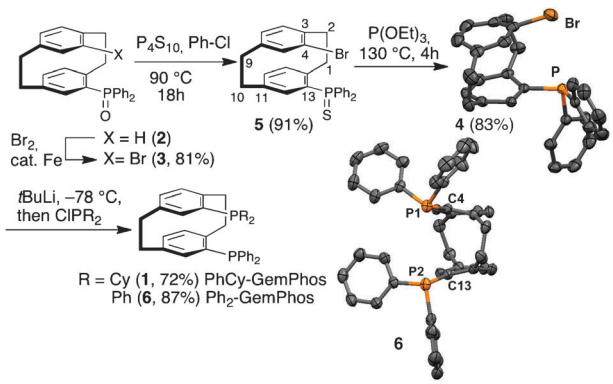
Voluminous amides were coupled with deactivated, sterically hindered aryl chlorides in excellent yields providing products, which have not been efficiently accessible by transition metal catalysis so far. Application of an unsymmetric bisphosphine ligand was critical for the high catalytic activity.

Nitrogen containing heterocycles are ubiquitous structural elements in molecule design for medicine, life science and crop protection, ensuring a constant demand for efficient syntheses.[1] The amination and the amidation of sp^2-hybridized halides are some of the most powerful methodologies for the introduction of nitrogen into complex molecules.[2] This can be achieved by transition metal catalysts, which exhibit high functional group tolerance, allowing the elegant assembly of complex molecules.[3] Very efficient catalysts have been reported, which depend on the nature of the halide (or pseudo-halide, *e.g.* triflate) for the C–N bond formation.[2b,4] Buchwald has demonstrated that carefully designed monodentate biaryl phosphine ligands are exceptionally potent to promote the coupling of mainly *meta*- and *para*-substituted aryl chlorides with amides.[3a,4c,5c,5e] Additionally, only few examples are described for the coupling of deactivated aryl chlorides with bulky amides.[5b,6] A copper mediated amidation of aryl chlorides with bulky amides was described providing the product in medium yield.[6b] However, here, we present a catalytic system, which is exceptionally potent for the coupling of *ortho*- and *ortho,ortho*-disubstituted aryl chlorides with sterically challenging amides accessing highly encumbered C–N bond formation products in excellent yields.

Bisphosphines display remarkable features in palladium mediated amidations:[5] First, the binding mode of the amidate ligand can be modulated (κ^1 *versus* κ^2).[5e,5f,5g] Second, unsymmetrically substituted bisphosphines can increase the rate of reductive elimination.[5d,5h] These two criteria were consulted for the synthesis of a novel bisphosphine embedded in the highly rigid [2.2]paracyclophane scaffold.[7] A new flexible high yielding synthesis towards pseudo-*geminally* substituted bisphosphine



Scheme 1 Synthesis of GemPhos derivatives **1** and **6**.[8]

derivatives, GemPhos, was developed (Scheme 1). The synthesis of GemPhos derivatives commences from racemic 4-[2.2]paracyclophanyl-diphenylphosphine oxide[7g,9] (**2**, Scheme 1), which underwent electrophilic bromination regiospecifically in 81% yield. The pseudo-*geminal* substitution pattern in **3** was unambiguously established by NMR spectroscopy (^{31}P NMR δ = 27.9 ppm) and crystal structure analysis.[8] Reduction of **3** was achieved by stepwise conversion first to the sulfide **5** (^{31}P NMR δ = 41.1 ppm) followed by sulfur metathesis with triethoxy phosphite[11] furnishing the phosphine **4** (^{31}P NMR δ = –9.7 ppm) in 61% over two steps (Scheme 1).[10] The bromophosphine **4** was converted either into the symmetrical bisphosphine **6** (Ph_2-GemPhos, 87% yield) or into the racemic, unsymmetrical bisphosphine **1** (PhCy-GemPhos, 72% yield) by metallation and treatment with the corresponding chlorophosphine. This high yielding synthesis (44% **1**, 53% **6** over four steps) required only one chromatographic purification (last step) and can be performed on a gram scale. The structural and electronic features of these extraordinary ligands were analyzed by NMR, IR spectroscopy and single crystal structure analysis (see ESI†).[8] The two bisphosphines were subjected to coordination to palladium(II). The dicationic square planar Pd-complexes were unambiguously characterized by NMR spectroscopy and X-ray crystal structure analysis[8] confirming the exclusive *cis*-coordinating nature of **1** and **6**. The efficiency of the bisphosphine ligands was first investigated in the palladium catalyzed C–N bond formation reaction of 4-chlorotoluene (**7a**) and benzamide (**8a**). The palladium species, which was obtained from the reaction of symmetrical bisphosphine **6** with all palladium sources, furnished ineffective catalysts. In contrast, the palladium complexes generated by the reaction of **1**

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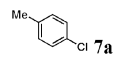
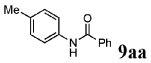
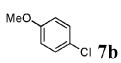
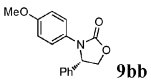
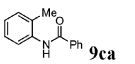
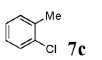
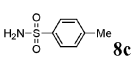
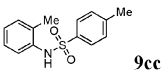
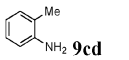
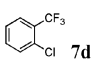
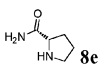
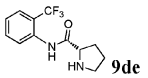
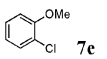
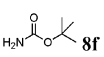
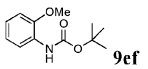
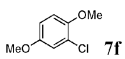
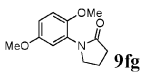
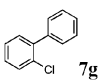
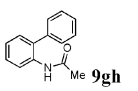
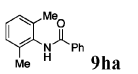
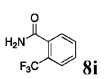
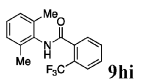
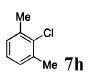
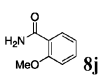
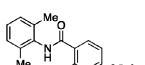
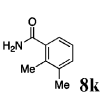
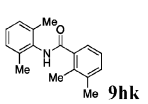
† Electronic supplementary information (ESI) available. CCDC 816638–816643. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc14844c

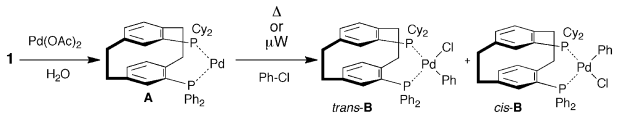
Table 1 Amidation of aryl chlorides

Entry	ArCl	Amide	Product	Yield/%[a]	
				[b]	μW[c]
1	 **7a**	 **8a**	 **9aa**	93	99
2	 **7b**	 **8b**	 **9bb**	58	72
3		 **8a**	 **9ca**	99	99
4	 **7c**	 **8c**	 **9cc**	78	76
5		$HN(SiMe_3)_2$ **8d**	 **9cd**	47	43[d]
6	 **7d**	 **8e**	 **9de**	94	92
7	 **7e**	 **8f**	 **9ef**	99	99
8	 **7f**	 **8g**	 **9fg**	99	94
9	 **7g**	 **8h**	 **9gh**	99	99
10		 **8a**	 **9ha**	96	94
11		 **8i**	 **9hi**	72	71
12	 **7h**	 **8j**	 **9hj**	87	89
13		 **8k**	 **9hk**	81	81

[a] Yield of product after column chromatography. [b] Conventional heating: 1 equiv. ArCl, 1 equiv. amide, 2–4 mol% $Pd(OAc)_2$, 6–12 mol% **1**, 4–16 mol% H_2O, 1.5 equiv. Cs_2CO_3, 125 °C to 150 °C, 18–24 h, 1 M in 1,4-dioxane. [c] Microwave irradiation: 1 equiv. ArCl, 1 equiv. amide, 2–4 mol% $Pd(OAc)_2$, 6–12 mol% **1**, 4–16 mol% H_2O, 1.5 equiv. Cs_2CO_3, 125 °C to 150 °C, 5 h, 1 M in 1,4-dioxane; (see ESI† for details; μW = microwave irradiation). [d] Lower yield due to its high vapour pressure.

with the palladium sources proved as highly active catalysts. The pre-formation of the catalyst according to a protocol by Buchwald[5c] and the application of 1,4-dioxane as solvent were critical for the efficient amidation of **7a**. The product *N*-4-toloyl benzamide (**9aa**) was obtained in high yield (93%) after stirring at 110 °C for 18 h. A commonly applied technique for a fast synthesis of amides and/or peptides employs microwave reactors.[12,13] Heating of **7a**, **8a** in a CEM microwave reactor with 2 mol% of activated catalyst/**1** to 150 °C for 5 h furnished product **9aa** in 99% yield (Table 1, entry 1). Subsequently, the scope for the coupling of aryl chlorides with a number of challenging amides using both conventional heating and microwave irradiation was explored (Table 1). Generally the reactions were promoted by the catalyst system $Pd(OAc)_2$/**1**/H_2O and furnished the products in good to excellent yields under both conventional heating and microwave irradiation. Coupling of deactivated **7b** with the bulky amide **8b** proceeded in 72% yield (entry 2, lit. 15%[14]). This observation encouraged us to investigate the amidation of sterically demanding coupling partners (entries 3 to 13). Indeed, the amidation of 2-chlorotoluene (**7c**) with **8a** afforded the C–N coupling product **9ca** in quantitative yield (entry 3, 99%, lit. 93%[15]). In particular, the poorly nucleophilic sulfone amide **8c** is a very challenging substrate for the amidation and has not yet been successfully applied in the C–N bond formation of *ortho*-substituted aryl chlorides. The amidation of **7c** proceeded smoothly with sulfone amide **8c** in 78% and 76% yields (entry 4). Even lithium hexamethyldisilazide (**8d**, LHMDS, entry 5) as an ammonia surrogate was successfully applied in the literature, unprecedented amidation of *ortho*-substituted **7c**.[15] The resulting aniline **9cd** was obtained in 43% and 47% yields.‡ Secondly, we investigated the influence of the nature of the *ortho*-substituents on the amidation reaction (entries 6 to 9). Electron withdrawing (**7d**), electron donating (**7e** and **7f**) and aryl groups (**7g**) are all well tolerated in combination with synthetically important nitrogen nucleophiles. The corresponding products **9** (entries 6 to 9, **9ef** 99%, lit. 10%[16]) were obtained in excellent yields. Even the combination of the highly electron-rich and sterically encumbered chloroarene **7f** with a weak nucleophile serendipitously furnished the aryl lactam **9fg** in quantitative yield. To our knowledge the amidation of the corresponding biaryl chlorides (*e.g.* **7g**) has not been reported yet.[17] The reaction of **7g** with acetamide **8h** furnished acetyl protected biaryl amine **9gh** in 99% yield and represents a significant development in the catalytic amidation of aryl chlorides. The efficient amidation of *ortho*,*ortho*-disubstituted aryl chlorides has not been reported so far.[16,18] The application of our catalytic system to the reaction of **7h** with **8a** furnished the amidation product in excellent yield (entry 10, 96% yield). Alkyl groups in the *ortho* position of the amides **8i–8k** increase the steric bulk making these substrates challenging coupling partners in the amidation of **7h**. Electron deficient (**8i**) and electron rich amides (**8j**) were applied in the amidation of the sterically encumbered aryl chloride **7h** (entries 11 and 12) furnishing the products **9hi** and **9hj** in high yields. The most bulky amide for the coupling with **7j** is the *ortho*,*meta*-substituted **8k**. The coupling furnished the tetra-substituted, highly sterically restricted amide **9hk** in 81% yield under both conventional heating and microwave irradiation demonstrating the scope for the developed system.

In order to determine whether the reactivity is a result of a possible monoligated phosphine–palladium complex we conducted NMR experiments (0.1 mmol scale). The incubation of $Pd(OAc)_2$, three equivalents of **1** and one equivalent of water furnished the palladium(0) bisphosphine complex (**A**) (Scheme 2, for $^{31}P\{^1H\}$ NMR spectra see ESI†). The $^{31}P\{^1H\}$ NMR spectrum exhibits four resonances, which were assigned to monooxidized



Scheme 2 Generation of Pd(0) (**A**) and Pd(II) (*cis*-**B**/*trans*-**B**) complexes (μW = microwave irradiation).

1 (45.6 ppm), Pd-bound phosphine (33.3 ppm and 26.2 ppm) and free phosphine (–3.5 ppm). The two resonances at 33.3 ppm and 26.2 ppm are split into doublets with a coupling constant of 12.2 Hz, which was attributed to the $^2J_{P-P}$ coupling in the chelated palladium(0) complex **A**. This complex was treated with one equivalent chlorobenzene and heated to 125 °C (4 h conventional heating; 2 h microwave irradiation). After the indicated time the two reactions were analyzed by $^{31}P\{^1H\}$ NMR spectroscopy revealing the formation of two diastereomeric Pd(II) complexes (*cis*/*trans*-**B**; 26.9 ppm, 18.9 ppm, 16.0 ppm and 15.2 ppm). The resonances are split into doublets with a $^2J_{P-P}$ coupling constant of 28.9 Hz and 28.4 Hz. These observations confirm the role of **1** as a bidentate ligand for Pd(0) (**A**) and for the oxidative addition products (*cis*/*trans*-**B**). It can be concluded that the chelating bisphosphine ligand **1** is responsible for the high reactivity in the C–N bond formation process observed.

In summary, the high yielding amidation of bulky, deactivated aryl chlorides with sterically encumbered amides was developed, providing substrates, which include ubiquitous *N*-protective groups (Ac, Boc, sulfone) and Evans-auxiliaries. The application of a rigid, unsymmetrical substituted bisphosphine was critical for the efficiency of the process. Mechanistic studies concentrating on the unusual activity of the bisphosphine/Pd complex are currently in progress.

Notes and references

‡ The low yield is attributed to the high volatility of the product.

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