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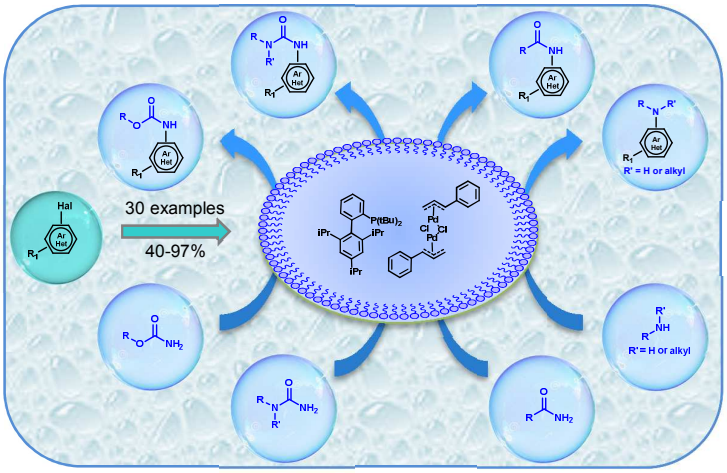
ABSTRACT

t-BuXPhos: a highly efficient ligand for Buchwald-Hartwig coupling in water

Patrick Wagner,[a] Maud Bollenbach,[a] Christelle Doebelin,[a] Frédéric Bihel,[a] Jean-Jacques Bourguignon,[a] Christophe Salomé,[a, b*] and Martine Schmitt [a*]

An efficient and versatile catalytic system for the Buchwald-Hartwig cross-coupling reaction in water is reported. In an aqueous micellar medium, the combination of *t*-BuXPhos with $[(cinnamyl)PdCl]_2$ showed excellent performance for coupling arylbromides or chlorides with a large set of amines, amides, ureas and carbamates. The method is functional-group tolerant, proceeds smoothly (30 to 50°C) and provides rapid access to the target compounds in good to excellent isolated yields. When applied to the synthesis of a known NaV1.8 modulator, this method led to a significant improvement of the E-factor in comparison with classical organic synthesis.



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An efficient and versatile 'green' catalytic system for the Buchwald-Hartwig cross-coupling reaction in water is reported. In an aqueous micellar medium, the combination of *t*-BuXPhos with $[(cinnamyl)PdCl]_2$ showed excellent performance for coupling arylbromides or chlorides with a large set of amines, amides, ureas and carbamates. The method is functional-group tolerant, proceeds smoothly (30 to 50°C) and provides rapid access to the target compounds in good to excellent isolated yields. When applied to the synthesis of a known NaV1.8 modulator, this method led to a significant improvement of the E-factor in comparison with classical organic synthesis.

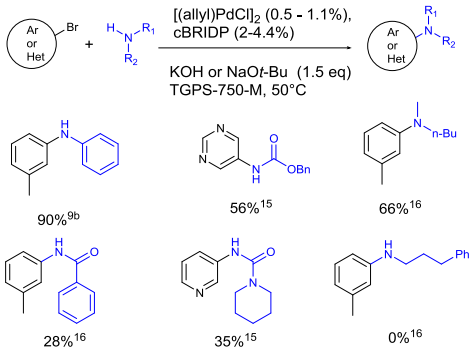
Introduction

As key structural cores of various bioactive natural or synthetic products and organic materials, nitrogen-containing heterocyclic compounds are of considerable biological and chemical significance.[1-3] In recent years, transition-metal assisted amination of aryl or heteroaryl halides has been developed as the most viable and direct method for the synthesis of a large variety of substituted arylamines.[4] Although these metal-catalysed cross-coupling reactions have been developed increasingly in organic synthesis, they, in general, are still poorly adapted to fit the principles of green chemistry.[5a-b]

Recent focus on the ″green-ness″ of a chemical process has resulted in the development of various synthetic procedures that can be carried out under ″green″ conditions in or on water.[5c-d] Conducting transition metal-catalysed cross-coupling chemistry in water, instead of organic solvents could have a number of potential benefits in terms of cost, environmental impact, safety, and impurity profiles.[6a-q] However, solubility of the reagents in water was an issue.[6r] To overcome this, the concept of micellar catalysis was introduced where the reactants are solubilized in the aqueous phase with help of surfactants. Several amphiphilic compounds were reported to form nanomicellar reactors in water, providing a convenient lipophilic medium in which cross-coupling reactions can take place.[7]

Since 2008, Lipshutz et al. have published a series of papers [8-15] demonstrating the viability of surfactant-promoted transition metal-catalysed chemistry in water. They have shown that polyoxyethanyl-α-tocopheryl succinate (TPGS-750-M), a non-ionic amphiphile, allows important cross-coupling reactions such as methathesis,[10] Suzuki–Miyaura,[11] Heck,[12] and Sonogashira reactions[13] to be carried out on water.

More recently, they have expanded the range of application of surfactant-promoted chemistry to *N*-arylation reactions through the Buchwald-Hartwig reaction.[13-15] They demonstrated that Takasago's cBRIDP ligand in combination with $[(allyl)PdCl]_2$ generates a highly efficient catalytic system for the Buchwald reaction. However, further studies demonstrated that this catalytic system has some drawbacks. While cBRIDP displayed high yields for aniline derivatives[9b] and moderate to good yields for protected NH groups (carbamate, sulfonamides or ureas)[15-16] in Pd-mediated coupling reactions, it failed when other classes of amines were employed.[16] For example, we have previously demonstrated that benzamides are rather poor substrates under Lipshutz's conditions, leading to only 28% conversion in the presence of 3-bromotoluene after 16 h.[16] Moreover, while secondary amines were readily cross-coupled in the presence of cBRIDP, no reaction was observed with primary amines (Scheme 1).



Scheme 1 Scope of the Buchwald-Hartwig reaction in water using $[(allyl)PdCl]_2$ / cBRIDP as the catalytic system.

Improvements in Buchwald-Hartwig reactions have relied on the increased reactivity and stability of the metal catalyst using more effective ligands.[17-19] Despite significant research efforts, a single catalyst system that can couple a broad range of amines and amides with aryl- or heteroaryl halides is unknown. This led us to explore other reaction conditions in order to broaden the scope of the Buchwald-Hartwig reaction under micellar conditions. Herein, we present a full report of a catalyst system that allows the cross-

coupling of aryl and heteroaryl halides to a large set of amines, including primary and secondary amines, aryl and heteroarylamines, amides, urea, and azaheterocycles.

Results and discussion

In our initial screening experiments, 3-bromotoluene **1** and 4-methoxybenzamide **2** were used as the prototypical substrates to establish the most suitable reaction conditions (Figure 1) for our new catalyst system. We chose an amide as substrate because this functional group was found to be poorly reactive under previously reported conditions. In the first step, using an aqueous solution of TPGS-750-M (2 wt %), a set of fifteen ligands were evaluated in combination with $[(allyl)PdCl]_2$ in the presence of NaO*t*-Bu at 50°C. The use of Takasago's cBRIDP ligand gave about 20% of the desired amide **3b** (Figure 1, bar L_2). In comparison, the less bulky Cy-cBRIDP was much less active as no reaction was observed (bar L_1).

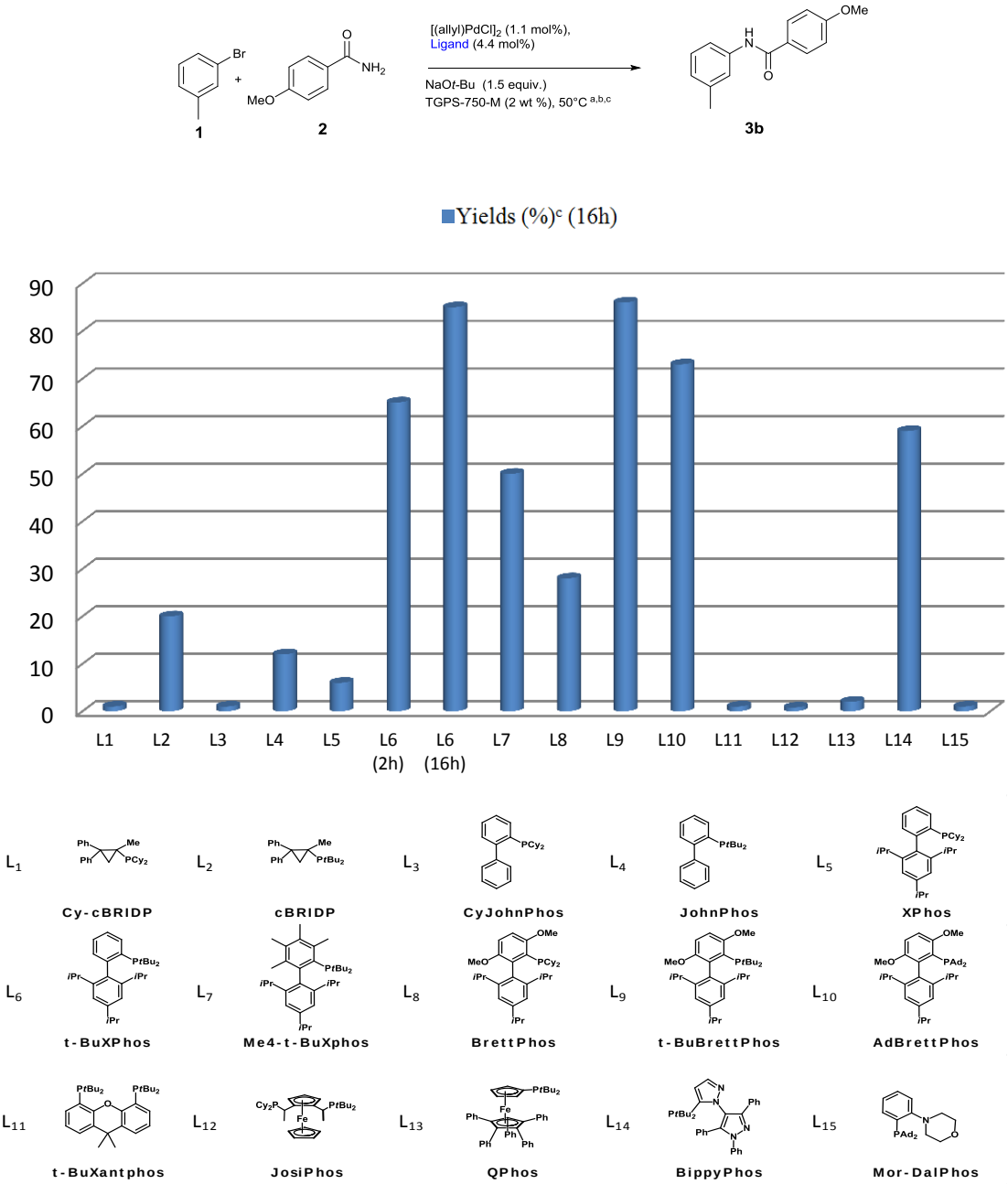


Figure 1 Impact of various ligands on the efficiency of the aryl amidation reaction in TPGS -750-M.
[a] Reaction conditions: $[(allyl)PdCl]_2$ (1.1 mol%), Ligand (4.4 mol %), NaO*t*-Bu (1.5 equiv.), TPGS-750-M (2 wt %), 3-bromotoluene (1 equiv.), 4-methoxybenzamide (1.2 equiv.), 50°C, 16h. [b] Average yield of 2 runs, [c] Yields were determined by HPLC/UV using caffeine as an internal standard.

Replacement of the cBRIDP by Johnphos showed weak coupling activity as only 12% of the expected *N*-arylated compound was obtained (bar L_4). As previously observed, replacement of the *t*-Bu group of the phosphine with cyclohexane was completely inefficient (compare bars L_1 with L_2, L_3 with L_4 and L_8 with L_9). On comparing JohnPhos-related ligands (bars L_3 to L_{10}), it was clear that the degree of substitution on the *ortho*-phenylbenzene plays an important role in the catalytic activity of the ligand. The use of *t*-BuXPhos led to 65% of **3b** after 2 h and 82% after 16 h (bars L_6). The presence of the four methyl group in tetra methyl-*t*-BuXPhos led to a less active ligand (only 50% of conversion after 16 h, bar L_7). A combination of electron-donating (OMe) and sterically hindered groups (*i*Pr) in *t*-BuBrettPhos afforded the most active ligand (85% of conversion, bar L_9). When *t*-BuBrettPhos was replaced by AdBrettPhos,[20] the isolated yield dropped from 85% to 73% (bars L_9 and L_{10}). With the heterobiaryl monophosphine ligand BippyPhos,[21] only 59% of the desired product was obtained (bar L_{14}). No reaction occurred with the use of mixed P, N donor ligand Mor DalPhos[22] (bar L_{15}). Bidentate phosphine ligands (*t*-BuXantphos, bar L_{11}) or ferrocene based ligands including JosiPhos[23] or QPhos [24] were found to be totally inefficient (bars L_{12} and L_{13}). Since there was not much difference in potency between *t*-BuBrettPhos and *t*-BuXphos (compare bars L_9 and L_6), we chose to use the cheaper *t*-BuXPhos for our reaction.

In the Buchwald-Hartwig reaction, the choice of the base can significantly influence the efficiency of the coupling.[18]

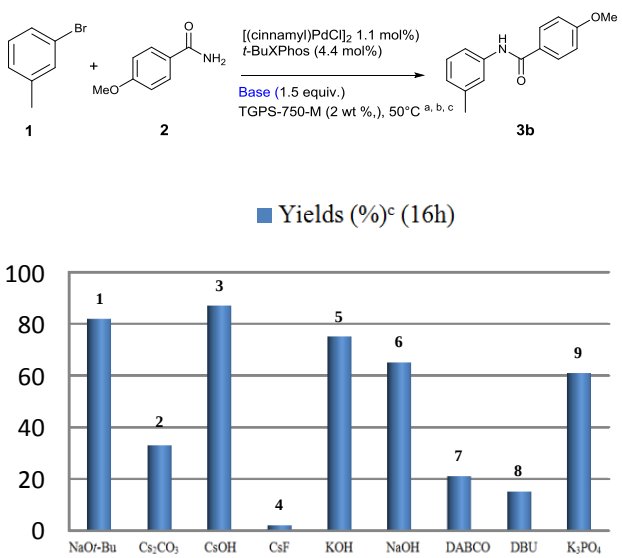
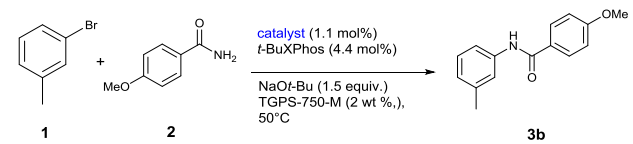


Figure 2 Impact of bases on amination in TPGS-750-M (2 wt %).
[a] Reaction conditions: [(cinnamyl)PdCl]$_2$ (1.1 mol%), *t*-BuXPhos (4.4 mol%), Base (1.5 equiv.), 3-bromotoluene (1 equiv.), 4-methoxybenzamide (1.2 equiv.), TPGS-750-M (2 wt %), 50°C, 16h. [b] Average yield of 2 runs, [c] Yields were determined by HPLC/UV using caffeine as an internal standard.

Among common inorganic bases, CsOH in the presence of the catalytic system [Pd(allyl)Cl]$_2$ and *t*-BuXPhos appeared to be slightly more effective (85%, bar 3, Figure 2) than NaO*t*-Bu (82%, bar 1), while KOH, NaOH and K_3PO_4 gave slightly lower yields (bars 5, 6 and 9). Mineral bases such as Cs_2CO_3 and CsF led to poor yields (bars 2 and 4), as well as the use of organic bases such as DABCO and DBU (bars 7 and 8).

Finally, a brief study on the reactivity of several readily-available Pd catalysts was carried out. As shown in Table 1, when $PdCl_2$ or $Pd(OAc)_2$ was used in association with *t*-BuXphos in the presence of NaO*t*-Bu, no trace of the product was observed even after 16 h (entries 1 and 2). $Pd_2(dba)_3$ had the same reactivity as [(allyl)PdCl]$_2$ (80% and 85% yield, respectively. entries 4 and 3). [(Cinnamyl)PdCl]$_2$ was found to be the best catalyst for this reaction (92% yield, entry 5). Surprisingly, replacement of NaO*t*-Bu by CsOH led to a lower coupling as only 76% of **3b** (entry 6) was observed.

Table 1 Impact on Pd catalysts on amination in TPGS-750-M (2 wt %)



[a]

Entry	catalyst	Base	Yield (%) [a,b,c]
1	$PdCl_2$ [d]	NaO*t*-Bu	nr
2	$Pd(OAc)_2$ [d]	NaO*t*-Bu	nr
3	[(allyl)PdCl]$_2$	NaO*t*-Bu	85
4	$Pd_2(dba)_3$	NaO*t*-Bu	80
5	[(cinnamyl)PdCl]$_2$	NaO*t*-Bu	93
6	[(cinnamyl)PdCl]$_2$	CsOH	76

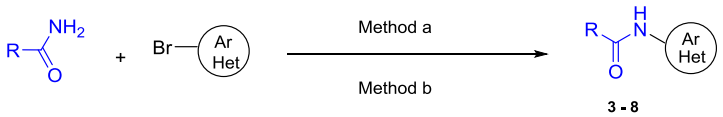
Reaction conditions: catalyst (1.1 mol%), *t*-BuXPhos (4.4 mol %), NaO*t*-Bu (1.5 equiv.), TPGS 750-M (2 wt %), 3-bromotoluene (1 equiv.), 4-methoxybenzamide (1.2 equiv.), 50°C, 16h. [b] Average yield of 2 runs, [c] Yields were determined by HPLC/UV using caffeine as an internal standard. [d] Reaction conditions: catalyst (2.2 mol%), *t*-BuXPhos (4.4 mol %), NaO*t*-Bu (1.5 equiv.), TPGS 750-M (2 wt %), ArBr (1 equiv.), 4-methoxybenzamide (1.2 equiv.), 50°C, 16h.

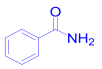
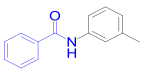
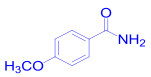
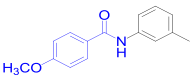
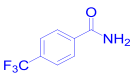
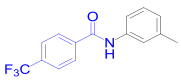
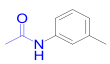
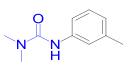
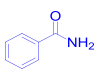
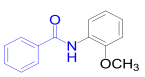
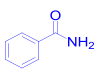
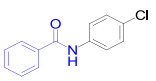
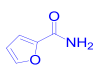
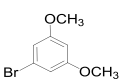
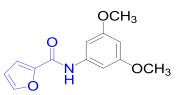
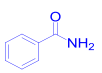
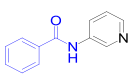
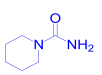
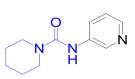
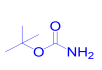
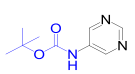
Based on all of these results [25], a combination of [(cinnamyl)PdCl]$_2$ (1.2 mol%), *t*-BuXPhos (4.4 mol%) and NaO*t*-Bu (1.5 equiv.) was selected as the catalyst system (Method a) of choice. Its efficacy in facilitating Buchwald-Hartwig coupling between a broad set of amines or amides and aryl coupling partners was evaluated.

A set of diverse amides was first investigated and the results are shown in Table 2. Yields are compared with those obtained using [(allyl)PdCl]$_2$ / cBRIDP system (Method b). Our initial attempt of reacting benzamide derivatives with 3-bromotoluene, under previous conditions (Method b), afforded the corresponding *N*-arylbenzamide **3a** and **3b**, albeit in low yield (< 30%). Interestingly, under our new conditions (Method a), all amides gave good conversion except for the highly soluble acetamide (entry 4, cpd **3d**). However, a higher yield of 54% was obtained when an excess (5 equiv.) of acetamide

was used. The reaction was still efficient with benzamide derivatives having either electron-withdrawing (entry 3, cpd **3c**) or electron-donating groups (entries 2 and 8, cpds **3b** and **6**). Additionally, under our optimized conditions, we were able to couple 3-bromotoluene with the *N*,*N*-dimethyl urea derivative (entry 5, cpd **3e**, 70%). The same reaction was previously attempted by Method b but no reaction was observed. In the case of arylbromides, electron-donating (entries 6 and 8, cpds **4** and **6**) or -withdrawing substituents (entry 7, cpd **5**) on the aromatic ring did not impair the reaction, and even with the bulky 2-bromoanisole, the reaction proceeded efficiently (entry 6, cpd **4**, 85% isolated yield).

Table 2: Expanded scope of amidation with aryl (heteroaryl)bromides.



Entry	Amide	Br-Ar	Product	Cpd N°	Yields (%) [a, b]	
					Method a	Method b [16]
1				3a	97	28
2				3b	92	25
3				3c	74	/
4				3d	9, 54 [d]	n.r.
5				3e	70	n.r.
6				4	85	/
7				5	89	/
8				6	89	/
9				7a	50 [e], 75 [c]	/
10				7b	54 [e], 69 [f]	35 [15]
11				8	40 [e], 77 [f]	23 [15]

Method a: Reaction conditions: $[(cinnamyl)PdCl]_2$ (1.2 mol%), *t*-BuXPhos (4.4 mol%), NaO*t*-Bu (1.5 equiv.), $RCONH_2$ (1.2 equiv), Ar(Het)Br (1 equiv.), TPGS-750-M (2 wt %), 50°C, 16h. **Method b**: Reaction conditions: $[(allyl)PdCl]_2$ (1.1 mol%), cBRIDP (4.4 mol%), NaO*t*-Bu (1.5 equiv.), $RCONH_2$ (1.2 equiv), Ar(Het)Br (1 equiv.), TPGS-750-M (2 wt %), 50°C, 16h. [a] Yields refer to isolated, chromatographically, purified materials. [b] Unpublished products were fully characterized by NMR and HR-MS data. [c] Reaction conditions: $[(cinnamyl)PdCl]_2$ (5 mol%), *t*-BuXPhos (10 mol%), NaO*t*-Bu (1.5 equiv.). [d] CH_3CONH_2 (5 equiv.), TPGS-750-M (5 wt %), 40h. [e] Reaction conditions: $[(cinnamyl)PdCl]_2$ (2 mol%), *t*-BuXPhos (4.4 mol%), NaO*t*-Bu (1.5 equiv.). [f] Reaction conditions: $[(cinnamyl)PdCl]_2$ (2 mol%), *t*-BuXPhos (8 mol%), NaO*t*-Bu (1.5 equiv.). n.r.: no reaction.

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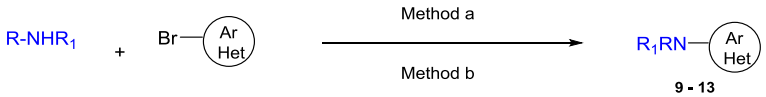
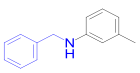
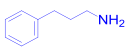
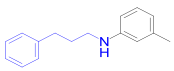
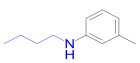
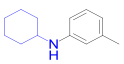
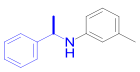
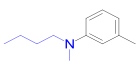
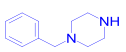
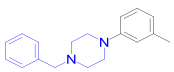
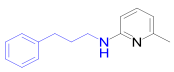
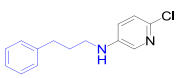
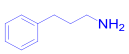
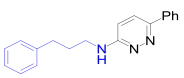
Next, we tested the efficacy of this catalytic system with heteroaromatic halides such as 3-bromopyridine or 5-bromopyrimidine. The reaction with benzamide, (entry 9), piperidyl carboxamide (entry 10) and *tert*-butyl carbamate (entry 11) gave the compounds **7a,7b** and **8** in good yields (75%, 69% and 77% respectively). In all cases, these yields were still higher than those reported in the literature.[15] Compared to the [(allyl)PdCl]$_2$ / cBRIDP system, the [(cinnamyl)PdCl]$_2$ / *t*-BuXPhos system provided much better efficacy with all the tested substrates.

Encouraged by these successful results, we extended the scope of our catalyst system to primary and secondary aliphatic amines. The results are shown in Table 3. In our initial studies with cBRIDP as ligand in combination with [(allyl)PdCl]$_2$ (Method b), no appreciable reaction was observed with primary aliphatic amines. In contrast, to our delight, with our new catalytic system (Method a) , the reaction worked very well with aryl (entries 1-5) and heteroaryl halides (entries 8-10) and the corresponding coupled products were obtained in 63-98% isolated yields. Reactions of linear primary amines occurred in high yields (> 80%, entries 1-3, 8-9) and even high conversion was obtained with the poorly soluble pyridazinone (entry 10, cpd **13**). However, in the latter case, a higher catalyst loading (5 mol%) with TPGS-750-M (5 wt%, 0.5M substrate concentration) was required (82%, isolated yield).

Table 3: Expanded scope of amination with aliphatic amines



Entry	Amine	Br-Ar	Product	Cpd N°	Yields (%) [a, b]	
					Method a	Method b [16]
1				9a	94	25
2				9b	95	n.r.
3				9c	63[c], 96[d]	n.r.
4				9d	72	/
5				9e	71	/
6				10a	78	66
7				10b	73	80
8				11	92[e]	n.r.
9				12	64, 82[e]	/
10				13	82[f]	n.r.

Method a: Reaction conditions: [(cinnamyl)PdCl]$_2$ (1.1 mol%), *t*-BuXPhos (4.4 mol%), NaO*t*-Bu (1.5equiv.), Ar(Het)Br (1 equiv.), RNHR$_1$ (1.2 equiv.), TPGS-750-M (2 wt %), 50°C, 16h. **Method b**: Reaction conditions: [(allyl)PdCl]$_2$ (1.1 mol%), cBRIDP (4.4 mol%), NaO*t*-Bu (1.5equiv.), Ar(Het)Br (1 equiv.), RNHR$_1$ (1.2 equiv.), TPGS-750-M (2 wt %), 50°C, 16h.

[a] Yields refer to isolated, chromatographically purified materials. [b] Unpublished products were fully characterized by NMR and HR-MS data. [c] Formation of the diarylation adduct (<10%). [d] *n*-BuNH$_2$ (5equiv.). [e] Reaction conditions: [(cinnamyl)PdCl]$_2$ (2.2 mol%), *t*-BuXPhos (4.4 mol%), NaO*t*-Bu (1.5equiv.). [f] Reaction conditions: [(cinnamyl)PdCl]$_2$ (5 mol%), *t*-BuXPhos (4.4 mol%), NaO*t*-Bu (1.5equiv.), TPGS-750-M (5 wt %, 0.5M substrate concentration). n.r.: no reaction.

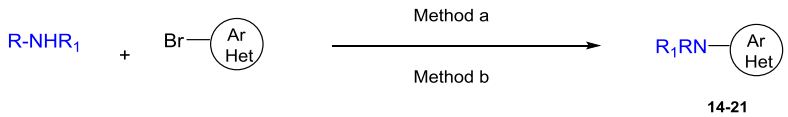
The steric hindrance of our catalytic system did not influence the reaction of bulky *α*-branched primary amines as illustrated from the cross coupling reaction with cyclohexylamine which resulted in 72% isolated yield (entry 4, cpd **9d**). In addition, the coupling of 3-bromotoluene with enantioenriched *α*-phenethylamine (99% ee) gave the *N*-arylated product **9e** in 71% yield with the retention of configuration (entry 5, α_D = -31°, c= 0.685).[26]

In addition to the remarkable reactivity of our catalyst system, no diarylation products were observed in most of the examples except with the highly water soluble butylamine (entry 3, cpd **9c**), where a small amount of the diarylation product (10%) was isolated. However, in the presence of an excess of butylamine (5 equiv.), the monoarylated compound **9c** was obtained quantitatively (96% isolated yield, entry 3). When an aryl (or heteroaryl) ring bearing both chlorine and bromine atoms was used as the substrate, no reaction was observed at the chlorine site (entry 7, Table 2 and entry 9, Table 3) revealing the chemoselectivity of this catalytic system even at a higher load.

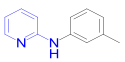
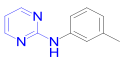
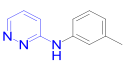
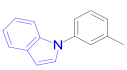
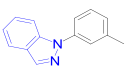
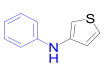
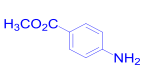
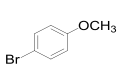
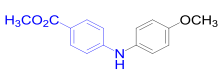
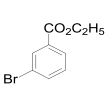
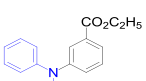
Acyclic and cyclic secondary amines (entries 6 and 7, cpds **10a** and **10b**) also gave good yields under our catalyst system. However, it has to be noted that the *N*–arylation reaction with these classes of amines have also been efficiently carried out with the first catalytic system (Method b).

To further explore our methodology, we attempted reactions with aromatic amines. The results are summarized in Table 4. The broad scope of the observed reactivity is exemplified by the fact that both aryl amines (entries 6 and 7) and heteroaryl amines (entries 1-3) could be cross-coupled in moderate to good yields.

Table 4: Expanded scope of amination with heteroaromatic amines



14-21

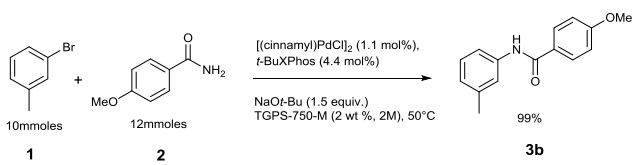
Entry	Amine	Br-Ar	Product	Cpd N°	Yields (%) [a, b]	
					Method a	Method b[16]
1				14	65, 89[c]	65
2				15	28, 82[c]	9
3				16	44[c],71[d]	/
4				17	87	70
5				18	14, 86[e]	9
6				19	95	/
7				20	86[f]	/
8				21	97[f]	84[14a]

Method a: Reaction conditions: [(cinnamyl)PdCl]$_2$ (1.1 mol%), *t*-BuXPhos (4.4 mol%), NaO*t*-Bu (1.5 equiv.), Ar(Het)Br (1 equiv.), RNHR$_1$ (1.2 equiv.), TPGS-750-M (2 wt %), 50°C, 16h. **Method b**: Reaction conditions: [(allyl)PdCl]$_2$ (1.1 mol%), cBRIDP (4.4 mol%), NaO*t*-Bu (1.5 equiv.), Ar(Het)Br (1 equiv.), RNHR$_1$ (1.2 equiv.), TPGS-750-M (2 wt %), 50°C, 16h. [a] Yields refer to isolated, chromatographically, purified materials. [b] Unpublished products were fully characterized by NMR and HR-MS data. [c] Reaction conditions: [(cinnamyl)PdCl]$_2$ (5 mol%), *t*-BuXPhos (4,4 mol%), NaO*t*-Bu (1.5 equiv.), [d] Reaction conditions: [(cinnamyl)PdCl]$_2$ (5 mol%), *t*-BuXPhos (10 mol%), NaO*t*-Bu (1.5 equiv.).[e] Reaction conditions: Pd$_2$(dba)$_3$ (5 mol%) used as catalyst, *t*-BuXPhos (4.4 mol%), NaO*t*-Bu (1.5 equiv.). [f] Method a, 3h at 30°C.

However, while keeping all other parameters constant, a higher loading of [(cinnamyl)PdCl]$_2$ catalyst (5 mol %) was required, to furnish **14** and **15** in satisfactory yields (entries 1 and 2). For instance, starting from 2-aminopyrimidine, only 28% of the corresponding *N*-arylated aminopyrimidine product **15** was obtained under the standard condition (entry 2). In the presence of [(cinnamyl)PdCl]$_2$ (5 mol %), the expected compound **15** was obtained in 82% yield. Under the same reaction conditions ([(cinnamyl)PdCl]$_2$ catalyst (5 mol %), *t*-BuXPhos (4.4 mol %)) the cross-coupling reaction of 3-aminopyridazine with 3-bromotoluene gave the expected product (**16**, entry 3) with only 44% of conversion. By increasing ligand to a 1:2 ratio (Pd/L), **16** was obtained in 75% yield. Compared to the first catalytic system (Method b) our new optimized conditions provided a better conversion in all the cases. As previously reported for primary aliphatic amines (Table 4), no diarylation product was detected by HPLC.

We also evaluated the tolerance of the reaction toward ester groups, which was well demonstrated with the synthesis of compounds **20** and **21** (entries 7 and 8**)**. Finally, as shown in Table 4, the amination process was successfully applied to indole and indazole (entries 4 and 5, cpds **17** and **18**). Indole afforded the target *N*-arylation product **17** in 87% isolated yield, while with indazole only 14% of the expected product was obtained. However, this reaction performed better with $Pd_2(dba)_3$ as the catalyst with 86% isolated yield (entry 5, cpd **18**).[27]

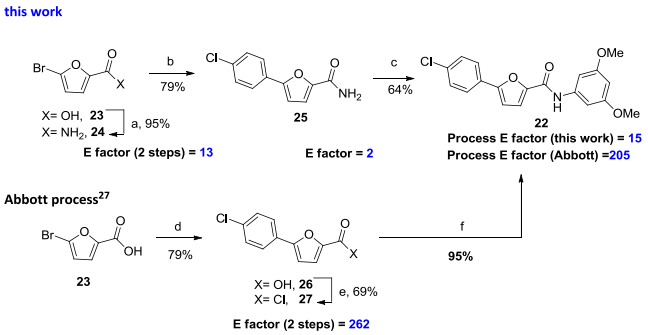
To demonstrate the efficacy of our catalyst system and thereby its potential industrial application as a ″green process″, the reaction was attempted on a multigram scale. The reaction with 10 mmol of 3-bromotoluene and 4-methoxybenzamide in TPGS-750-M (2 wt %, 2M substrate concentration) gave quantitative yield under our conditions (Scheme 2).



Scheme 2: Scale up for the preparation of **3b**.
Reaction conditions: [(cinnamyl)PdCl]$_2$ (1.1 mol%), *t*-BuXPhos (4.4 mol%), NaO*t*-Bu (1.5 equiv.), 3-bromotoluene (1 equiv.), 4-methoxybenzamide (1.2 equiv.), TPGS-750-M (2 wt %, 2M substrate concentration), 50°C, 16h.

We also applied our methodology in a three-step synthesis of 5-aryl-2-furfuramide **22**, a potent and selective blocker of the $NaV_{1.8}$ sodium channel, which has proved its efficacy in models of neuropathic and inflammatory pain. [28]

Starting from an easily available 5-bromo-2-furfuramide **24**, two consecutive palladium-catalysed reactions were carried out in aqueous TPGS-750-M as illustrated in Scheme 3. A Suzuki-Miyaura cross-coupling reaction of amide **24** with 4-chloro-phenylboronic acid in the presence of $PdCl_2$(dtbpf) catalyst led to the corresponding 5-aryl furfuramide **25**. After isolation, a subsequent Buchwald-Hartwig reaction provided the targeted product **22** in 48% yield over three steps. The overall yield of our eco-friendly green procedure is comparable to the reported yield of Abbott process.[27] (48% vs ~51%).

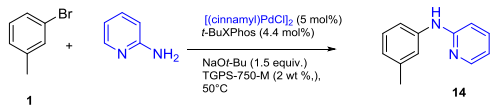


Scheme 3. Synthetic routes for the preparation of **22**: Conventional literature procedure vs green procedure.
Reagents and conditions: (a) 5-bromofuroic acid (1equiv.) 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI, 1.2 equiv.), Hydroxy-benzotriazol-ammonia salt (HOBt·NH_3, 1.5equiv.), DMF, 2h, rt. (b) 1,1′-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) ($PdCl_2$(dtbpf), 2 mol%), NEt_3 (3 equiv.), *p*-Cl-Ph-B(OH)$_2$ (2 equiv.), TPGS-750-M (2 wt %), 16h, 50°C (c) [(cinnamyl)PdCl]$_2$ (1.1 mol%), *t*-BuXPhos (4.4 mol%), NaO*t*-Bu (1.5 equiv.), 1-bromo-3,5-dimethoxybenzene (1.2 equiv.), **25** (1 equiv.), TPGS-750-M (2 wt %), 50°C,16h. (d) iPrOH, $PdCl_2(PPh_3)_2$, Na_2CO_3,.4-Cl-Ph-B(OH)$_2$, rt; (e) $(COCl)_2$, CH_2Cl_2, DMF cat, rt; (f) 3,5 dimethoxyaniline, Et_3N, CH_2Cl_2, rt.

To quantify the ″green-ness″ of our catalyst system, we evaluated the environmental (E) factor [29] and atom economy [30] of our system. These are two green chemistry metrics that measure the efficiency in a chemical process when a green chemistry improvement has been made to the process. The E-factor quantifies the mass ratio of organic reactants and solvents used to produce the final compound. The E-factor for our synthetic pathway was 15 (13 for steps 1 and 2, and 2 for step 3, solvents used for purification were not taken into account), which is a significant improvement over the E-factor for the Abbott company process (205 and 262 for steps 1 and 2, and 115 for step 3).

Atom economy is another important factor widely used to evaluate the "green-ness" of chemical transformations. Under micellar conditions, calculation of the percentage of atom economy gave a value of 38 compare to 30% for the Abbott company process. These results show that the new efficient catalytic system, optimized for the *N*-arylation of amide derivatives, could be of interest to medicinal chemist and pharmaceutical companies willing to develop a more eco-friendly process for drug synthesis.

Lastly, we turn our attention onto the recycling of the media in presence of a high loading of Pd. So, recycling of TPGS-750-M in presence of $[(Cinnamyl)PdCl]_2$ (5 mol %) was examinated. The Buchwald reaction of 3- bromotoluene **1** and 2-aminopyridine was studied, where each cycle was followed by a standart in-flask extraction of the product using minimal amount of Et_2O (2 times, 1ml), after which fresh substrates and catalyst were introduced as previously described by Lipshutz.[13] As illustrated in Table 5, after 4 four recycles a 76% yield of **14** was observed.



cycles			
1	2	3	4
87%	87	82%	76%

Figure 3: Recycling of TPGS-750-M

Yields were determined by ^1H NMR experiments using caffeine as an internal standard

Conclusions

We developed a general and high yielding method for accomplishing Buchwald-Hartwig coupling reactions of aryl or heteroaryl halides under green conditions. With this versatile catalyst system ($[(cinnamyl]PdCl]_2$/*t*-BuXPhos), the cross-coupling reaction was extended to several aryl and amine coupling partners. The reaction protocols are extremely flexible and were successfully applied to aliphatic, cyclic, acyclic, and aromatic amines and also to benzamide derivatives.

This is in striking contrast to the previously reported catalyst system (Takasago's cBRIDP ligand in combination with $[(allyl)PdCl]_2$) that shows dramatically lower activities for Buchwald-Hartwig reactions with aliphatic primary amines or benzamide derivatives. All the reactions were carried out in water at a low temperature (50°C), and the amides were cleanly formed and could be isolated in good to excellent yields. Because of the mild reaction conditions, this reaction can tolerate a wide variety of functional groups like esters and halides and no racemization was observed in the presence of a chiral centre. Moreover the system allows the recycling of the aqueous micellar media increasing the greenness of the method. Finally, we hope that our new green catalytic system will allow medicinal chemist and pharmaceutical companies to synthesize new drugs in environment-friendly conditions.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [^1H and ^{13}C spectra, calculations of the E factors and % atom economy]. See DOI: 10.1039/b000000x/

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