Green Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Green Chem.*, 2014, **16**, 1480

Installation of protected ammonia equivalents onto aromatic & heteroaromatic rings in water enabled by micellar catalysis†

Nicholas A. Isley,‡ Sebastian Dobarco‡ and Bruce H. Lipshutz*

Received 23rd October 2013,
Accepted 13th December 2013

DOI: 10.1039/c3gc42188k

www.rsc.org/greenchem

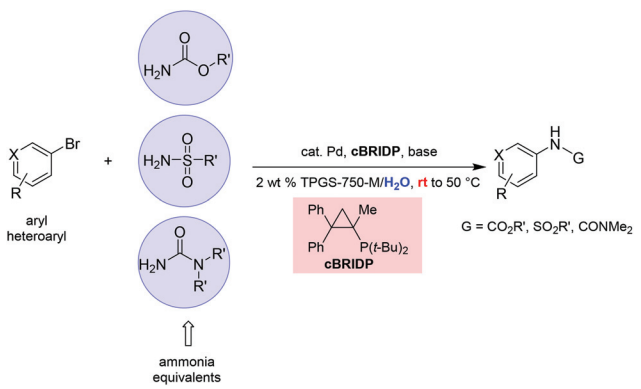
A single set of conditions consisting of a palladium catalyst, a commercially available ligand, and a base, allow for several types of C–N bond constructions to be conducted in water with the aid of a commercially available "designer" surfactant (TPGS-750-M). Products containing a protected NH_2 group in the form of a carbamate, sulfonamide, or urea can be fashioned starting with aryl or heteroaryl bromides, iodides, and in some cases, chlorides, as substrates. Reaction temperatures are in the range of room temperature to, at most, 50 °C, and result in essentially full conversion and good isolated yields.

Introduction

Palladium-catalyzed aminations of aromatic and heteroaromatic rings have seen tremendous growth over the past two decades. Such C–N bond formations, in particular *via* cross-coupling reactions, have been applied across a variety of disciplines.[1] These extensive studies tended to focus on the design of new classes of ligands, leading to the development of catalytic systems applicable to a broad scope of substrate types that can be used under impressively mild conditions.[2,3]

Anilines are valuable building blocks and play important roles as intermediates en route to dyes and pigments, rubber processing chemicals, agrochemicals, and pharmaceuticals.[4] Recently, several groups have described catalyst systems that utilize ammonia for the direct conversion of aryl halides to anilines.[5] Despite the virtues of using inexpensive ammonia, the synthesis of primary aryl amines from ammonia suffers from some important drawbacks, including high ligand loadings, and elevated pressures and temperatures oftentimes involved. As an alternative to ammonia, syntheses of primary aryl amines have typically been accomplished using ammonia surrogates.[5i,6] Of several ammonia equivalents, carbamates appear to be among the most valued coupling partners, especially in the case of multistep syntheses.[7] The first Pd-catalyzed amination using a carbamate as coupling partner was described in 1999 by Hartwig.[8] Since then, few examples utilizing carbamates as coupling partners for Pd-catalyzed C–N couplings have appeared.[9] Moreover, previous studies tended to focus almost exclusively on the use of *tert*-butyl carbamates as the coupling partner, and in most cases both high ligand loadings and temperatures were needed to achieve good yields.

Examples of sulfonamides and ureas as coupling partners in the literature are scarce, despite their synthetic utility as ammonia equivalents. The first report of sulfonamides as coupling partners was by Buchwald and co-workers a decade ago,[10a] with only a handful of reports having appeared since.[10] Likewise, there is a limited number of reports dealing with ureas serving in a similar capacity.[11]

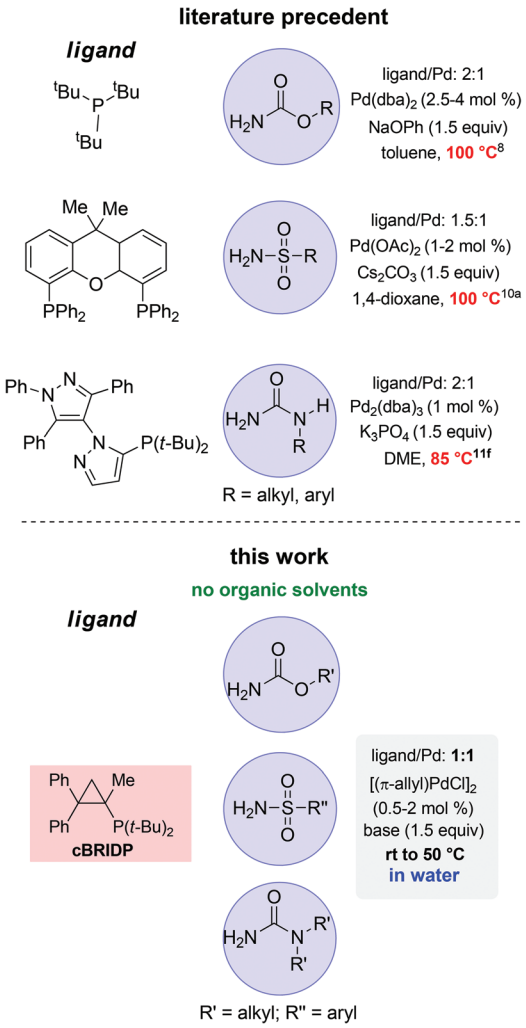


Surprisingly, despite literature rich with Pd-catalyzed C–N bond forming reactions, a single set of mild conditions applicable to primary carbamate-, sulfonamide-, and urea-based couplings has not been reported under which these three ammonia derivatives can be introduced. Indeed, the prognosis for finding such conditions is today viewed as virtually hopeless, as implied in a recent review outlining the dependence of amination reactions on the choice of palladium, ligand, base,

Department of Chemistry & Biochemistry, University of California, Santa Barbara, CA 93106, USA. E-mail: Lipshutz@chem.ucsb.edu

† Electronic supplementary information (ESI) available: Experimental procedures and details, copies of ^1H and ^{13}C spectra for all new compounds. See DOI: 10.1039/c3gc42188k

‡ N. A. I. and S. D. contributed equally to this work.



Scheme 1 Coupling overview of literature methods involving *different* conditions *vs*. micellar catalysis conditions.

solvent, and temperature all of which play a role in determining the level of success for any one given substrate/amine/catalyst/solvent combination (Scheme 1).[12] Herein, we report on the first general method for N-arylation/N-heteroarylation of carbamates, sulfonamides, and ureas using aryl/heteroaryl bromides, chlorides or iodides that relies on a *single source of palladium, ligand, and reaction medium*. These couplings can be performed at temperatures between ambient and 50 °C. The key to this general technology lies in the presence of small amounts of tailor-made nanomicelles, present in water only, that enable each type of C–N bond-forming reaction. Moreover, the nanoparticles can be recycled using an *in-flask* extraction procedure, thereby dramatically decreasing usage of organic solvent and associated organic waste, as quantified by E factors.[13]

Results and discussion

In a previous communication, the first Pd-catalyzed aminations of aryl bromides in nanomicelles composed of

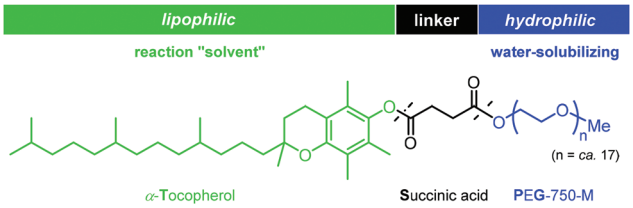


Fig. 1 Structural aspects to the 2nd generation designer surfactant TPGS-750-M.

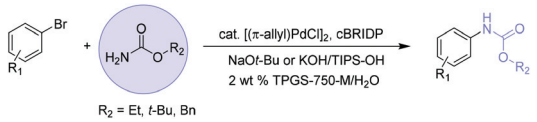
amphiphile PTS (polyethanyloxy α-tocopheryl subacate) were described, leading to unsymmetrical di- and triarylamines in water at room temperature.[14] The newly introduced, less expensive second-generation surfactant TPGS-750-M (Fig. 1),[15a] which varies from PTS in its four carbon succinate linker and contains MPEG-750 instead of PEG-600, was selected as the enabling technology for this study in water. Prior efforts had shown that reactions involving this new designer surfactant led to competitive or superior results as compared to those obtained using the first-generation surfactant PTS under otherwise identical conditions.[15b]

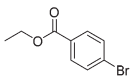
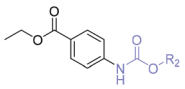
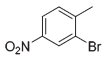
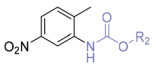
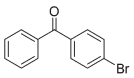
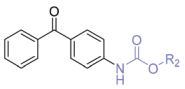
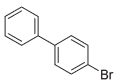
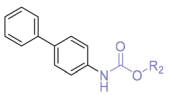
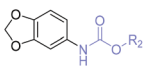
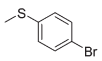
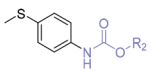
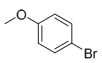
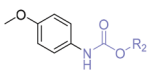
Our initial efforts focused on the application of these mild conditions to Pd-catalyzed couplings of aryl bromides with carbamates of ammonia. Recently, the first room temperature, Pd-catalyzed amination of aryl bromides in toluene using *tert*-butyl carbamate was reported by Hornberger and coworkers.[9f] Although the reactions were conducted at ambient temperatures, high catalyst loadings are needed to achieve good yields in reasonable times. Micellar conditions were found to effect the desired couplings employing the Pd catalyst [(π-allyl)PdCl]$_2$ (0.5 mol%) in the presence of Takasago's ligand cBRIDP[16] (2 mol%) in a 2 wt% TPGS-750-M/H_2O solution (1.0 M). The results under these conditions (Table 1) showed that the procedure was suitable for couplings of aryl bromides with a variety of carbamates, initially carried out at 50 °C.

The choice of base was found to be important, as noted previously in aminations with anilines as reaction partners.[14] Thus, alkoxide bases that are branched at carbon bearing oxygen afforded good results, such as *tert*-butoxide and triisopropylsilyloxide. Presumably this structural array decreases ionic character while increasing lipophilicity and solubility within the lipophilic core of TPGS-750-M nanomicelles, leading to smooth and complete reactions. Both NaO*t*-Bu and KOH/TIPS-OH were examined in all reactions, as listed in Table 1. An 'on-water' experiment was also conducted (*i.e.*, in the absence of any surfactant). Under otherwise identical optimized conditions, product **2** was formed in only 40%. Additionally, clumping of the substrate within the reaction vessel was observed, which is substantially minimized when 2 wt% TPGS-750-M is present in solution.

Insofar as carbamates are concerned, the Boc derivative of ammonia, an item of commerce,[7] was found to be the coupling partner of choice, mainly due to its general utility in synthesis. Complete conversions were observed within 24 h affording the desired products in typically high yields. The

Table 1 Scope of amidations of aryl bromides with carbamates[a]



Entry	Ar–Br	Carbamate (R_2)	Product	Time (h)	Yield[b] (%)
1–3		**1** = Et **2** = *t*-Bu **3** = Bn		24 24 24	99[c] 98[c] 77[c]
4–6		**4** = Et **5** = *t*-Bu **6** = Bn		24 24 24	97[d] 98[d] 99[d]
7–9		**7** = Et **8** = *t*-Bu **9** = Bn		24 24 24	98[c] 75[c] 80[c]
10–12		**10** = Et **11** = *t*-Bu **12** = Bn		48; 24[e] 48; 24[f] 48; 24[e]	84[d]; 92[d] 90[d]; 89[d] 83[d]; 90[d]
13–15		**13** = Et **14** = *t*-Bu **15** = Bn		24; 48[e] 24 24; 24[e]	30[c]; 86[d] 93[c] 50[c]; 91[d]
16–18		**16** = Et **17** = *t*-Bu **18** = Bn		24[f] 24[f] 24[f]	97[d] 94[d] 84[d]
19–21		**19** = Et **20** = *t*-Bu **21** = Bn		24 24 24	94[c] 99[c] 52[c]

[a] Reaction conditions: cat. [(π-allyl)PdCl]$_2$ (0.5 mol%), cBRIDP (2 mol%), base (1.5 equiv.), 1.0 M, 50 °C. [b] Isolated yields. [c] NaO*t*-Bu used as base. [d] KOH used as base with TIPS-OH (1.5 equiv.). [e] Reaction conditions: cat. [(π-allyl)PdCl]$_2$ (2 mol%), cBRIDP (4 mol%), base (1.5 equiv.), 1.0 M, 50 °C. [f] Reaction conditions: cat. [(π-allyl)PdCl]$_2$ (0.5 mol%), cBRIDP (2 mol%), base (1.5 equiv.), 0.5 M, 50 °C.

coupling between 4-bromobenzophenone and *tert*-butyl carbamate **8** (entry 8), however, appeared to be a notable exception. Indeed, the reaction did not reach full conversion, thereby giving the protected amine derivative in only 75% isolated yield after 24 h; the remaining mass was starting material. Couplings involving the analogous ethyl and benzyl carbamates proved in some cases to be more difficult, reacting more slowly than Boc-NH_2. Thus, the reaction between the 3,4-methylenedioxy-1-bromobenzene and ethyl carbamate using *tert*-butoxide as base (entry 13) gave the targeted compound **13** in only 30% yield after 24 hours. By changing the base to KOTIPS and increasing catalyst loading, a far better result was obtained; the desired product was isolated in 86% yield after 48 hours.

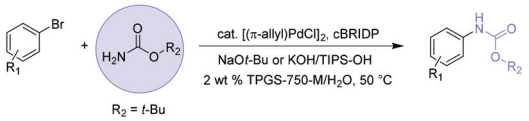
Slower rates of coupling were also generally observed for reactions involving benzyl carbamate as reaction partner. In all but two cases (entries 6 and 12), full conversion was not observed within 24 hours. Lower yields (50% and 52%, respectively) therefore, were obtained for couplings with 3,4-methylenedioxy-1-bromobenzene **15** (entry 15) and *p*-methoxybromobenzene **21** (entry 21). However, by increasing catalyst loading, the former educt could be fully converted to the desired product in good isolated yield after 24 hours.

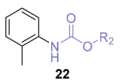
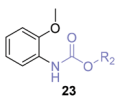
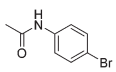
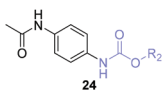
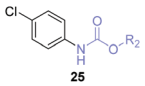
Reactivity differences between carbamates may be attributable to the same structural parameters that influence the effectiveness of the base: relative lipophilicity and the effective reduced polarity around the otherwise polar carbamate functional group. Also influencing reaction rates, as manifested in the case of bromobiphenyl (entries 10–12), is reaction concentration and associated level of stirring. That is, most reactions can be run at a global concentration of 1 M. However, in some cases the substrate has been observed to clump around the stir bar, impeding conversion. Complete conversion could be realized, however, by simply running the reactions at 0.5 M leading to good yields after 24 hours. Use of a reduced concentration also in the case of 4-bromothioanisole (entries 16–18) led to aminated derivatives in good yields within 24 hours.

Additional examples leading to Boc-protected anilines are illustrated in Table 2. Aryl bromides possessing substituents in *ortho* positions **22** and **23** (entries 1 and 2) were also tolerated well under these standard conditions, although a higher catalyst and ligand loading was required, affording the amidated products in 93–94% isolated yields.

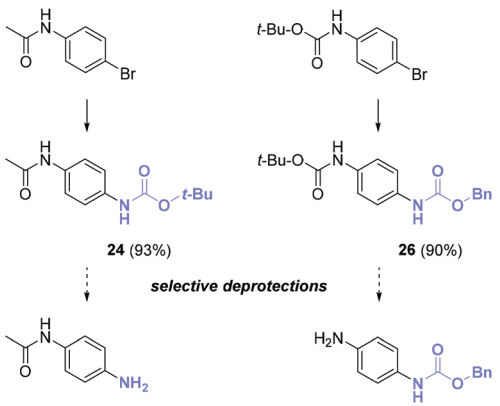
Opportunities for differentiation between amino residues on an aryl ring are represented by the examples in Scheme 2. Palladium-catalyzed cross couplings between 4-bromophenylacetamide with *t*-butyl carbamate, and between *t*-butyl 4-bromophenylcarbamate with benzyl carbamate, took place smoothly to afford the corresponding 1,4-diamine derivatives containing

Table 2 Expanded scope of amidations with aryl bromides and *tert*-butylcarbamate[a]



Entry	Ar–Br	Product	Base	Time[b] (h)	Yield (%)
1		 **22**	KOH/TIPS-OH	24	94
2		 **23**	KOH/TIPS-OH	24	93[c]
3		 **24**	NaO-*t*-Bu	30	93
4		 **25**	KOH/TIPS-OH	20	98[d]

[a] Reaction conditions: cat. [(π-allyl)PdCl]$_2$ (0.5 mol%), cBRIDP (2 mol%), base (1.5 equiv.), 1.0 M, 50 °C. [b] Time at which full conversion was observed by GC-MS and TLC. [c] Reaction conditions: cat. [(π-allyl)PdCl]$_2$ (2 mol%), cBRIDP (4 mol%), base (1.5 equiv.), 1.0 M, 50 °C. [d] Reaction conditions: cat. [(π-allyl)PdCl]$_2$ (2 mol%), cBRIDP (4 mol%), base (1.5 equiv.), 0.5 M, 50 °C.



Scheme 2 Potential for selective deprotections.

two differentiated amine groups (**24** and **26**) in good yields, allowing for potential selective deprotection.

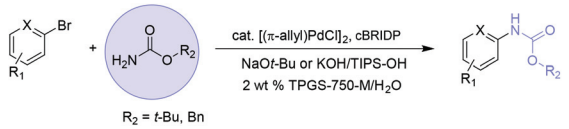
Both heteroaromatics 3-bromopyridine and 3-bromoquinoline reacted with Boc-NH$_2$ in water at 50 °C to afford the desired aminated products in high yields (Table 3). The corresponding Cbz derivatives were also obtained in both cases, but only the former went to completion and hence, gave a good isolated yield of the amine-protected pyridine. In the case of 5-bromopyrimidine, low levels of conversion, and hence, isolated yields were obtained with both carbamate partners **32** and **33** (Table 3, entries 6 and 7), suggesting that the adduct may have limited solubility within the lipophilic portion of these micellar nanoreactors.

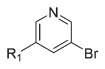
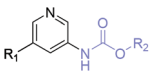
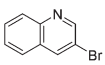
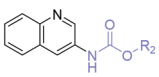
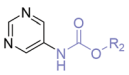
In several of the aryl bromides examined, it was possible to conduct these couplings under somewhat milder conditions of temperature. Dropping the temperature from the routinely employed 50 °C to 40 °C, and even to room temperature with selected aryl halides and *tert*-butyl carbamate led to excellent results, as shown in Table 4. Moreover, the length of time for these couplings was not elongated, and both GC-MS and TLC analyses showed them, in general, to be somewhat cleaner than those identical reactions having been run at 50 °C.

By way of comparison between these newly established aqueous conditions and those used previously involving organic solvents, Scheme 3 highlights the opportunities to achieve the desired couplings under *far milder*, *greener conditions* ("A") using these valuable coupling partners.

To further expand substrate scope, both methane- and toluene-sulfonamides, and a *N*,*N*-dialkylurea were examined as coupling partners in aqueous TPGS-750-M micelles at 50 °C, using either KOH/TIPS-OH or NaO*t*-Bu as base (Table 5). Both sulfonamides (entries 1–4) were successfully coupled with electron-rich, electron-poor, and sterically hindered aryl bromides. The KOH/TIPSOH combination appeared to be the better choice of base for introducing the tosylsulfonamide moiety, while NaO-*t*-Bu worked best for preparing aryl methylsulfonamides. *p*-Bromothioanisole did not react to full conversion, although based on the recovered starting material (brsm), the reaction is very clean (entry 4). A *N*,*N*-dimethylurea residue was successfully installed into both electron-rich and poor aryl bromides, albeit in modest yields. The starting material in these cases was successfully recovered as well (entries 5 and 6).

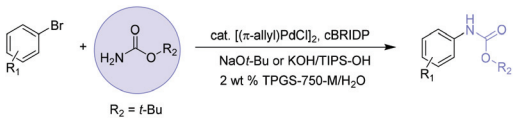
Table 3 Expanded scope of amidations with heteroarylbromides and carbamates[a]

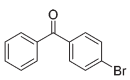
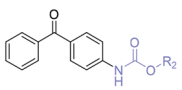
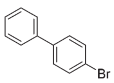
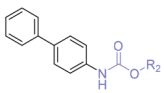
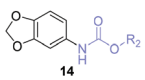
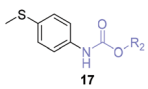
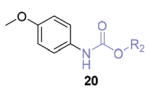
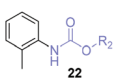
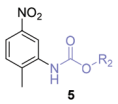
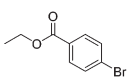
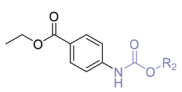


Entry	Ar–Br	Carbamate (R_2)	Product	Time (h)	Yield[b] (%)
1–3		**27** = *t*-Bu (R_1 = H) **28** = Bn (R_1 = H) **29** = *t*-Bu (R_1 = Br)		24 24 24	91 88 47
4–5		**30** = *t*-Bu **31** = Bn		24 24	90 60
6–7		**32** = *t*-Bu **33** = Bn		24 24	23 56

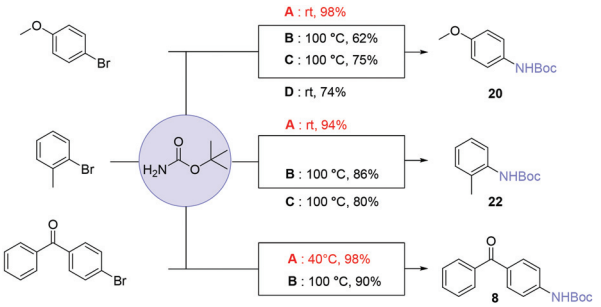
[a] Reaction conditions: cat. [(π-allyl)PdCl]$_2$ (2 mol%), cBRIDP (4 mol%), base (1.5 equiv.), 0.5 M, 50 °C. [b] Isolated yields.

Table 4 Amidations with aryl bromides with *tert*-butyl carbamate between room temperature and 40 °C[a]



Entry	Ar–Br	Product	Base	Time[b] (h)	Yield[c] (%)
1		 **8**	NaO*t*-Bu	24	98
2		 **11**	KOH/TIPS-OH	24[d]	94
3		 **14**	NaO*t*-Bu	30	90
4		 **17**	KOH/TIPS-OH	20[d]	96
5		 **20**	KOH/TIPS-OH	15	98[e]
6		 **22**	KOH/TIPS-OH	15	94[e]
7		 **5**	KOH/TIPS-OH	18	99[e]
8		 **2**	KOH/TIPS-OH	15	98[f]

[a] Reaction conditions: cat. [(π-allyl)PdCl]$_2$ (0.5 mol%), cBRIDP (2 mol%), base (1.5 equiv.), 1.0 M, 40 °C. [b] Time at which full conversion was observed by GCMS and TLC. [c] Isolated yields. [d] Reaction conditions: cat. [(π-allyl)PdCl]$_2$ (0.5 mol%), cBRIDP (2 mol%), base (1.5 equiv.), 0.5 M, 40 °C. [e] Reaction conditions: cat. [(π-allyl)PdCl]$_2$ (2 mol%), cBRIDP (4 mol%) 1.0 M, rt. [f] Reaction conditions: cat. [(π-allyl)PdCl]$_2$ (2 mol%), cBRIDP (4 mol%), 0.5 M, rt.



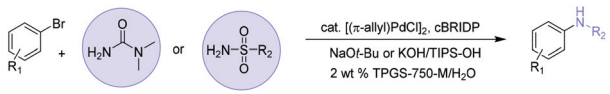
Scheme 3 Comparison of known traditional conditions *vs.* micellar conditions for carbamoylations. A: cat. $[(\pi\text{-allyl})PdCl]_2$ (0.5 mol%), cBRIDP (2 mol%), base (1.5 equiv.), 2 wt% TPGS-750-M/H_2O (0.3 mL, 1.0 M). B: cat. $Pd(dba)_2$ & ligand (2 : 1 ratio), Ar–Br (1 equiv.), carbamate (1.5 equiv.), toluene, 100 °C.[8] C: 3 mol% $Pd(OAc)_2$, 9 mol% Xphos, Ar–Br (1 equiv.), carbamate (1.2 equiv.), Cs_2CO_3 (1.4 equiv.), dioxane, 100 °C.[9g] C: 3 mol% $Pd_2(dba)_3$, $CHCl_3$, 9 mol% X-phos, Ar–Br (1 equiv.), carbamate (1.2 equiv.), NaO-*t*-Bu (1.4 equiv.), toluene, rt.[9f]

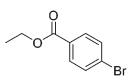
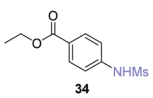
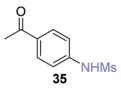
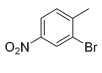
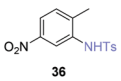
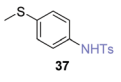
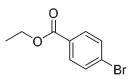
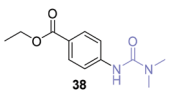
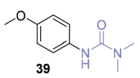
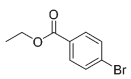
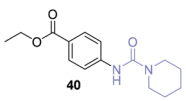
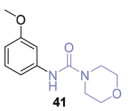
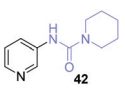
Lastly, piperidyl carboxamide **40** and **42** (entries 7, 9) was also installed in modest yields, as was the related morpholino derivative **41** (entry 8). The relatively low isolated yields are due to the difficulty in separating the products from the urea used in each coupling; C–N bond formation itself is efficient.

Potential applications of this coupling technology include the structural core characteristic of several natural products of topical interest,[17] a few of which are shown in Scheme 4. Using 2,2′-dibromo-1-1′-biphenyl together with the *t*-butylcarbamate of ammonia yielded Boc-protected carbazole **43**, reflecting double amination.

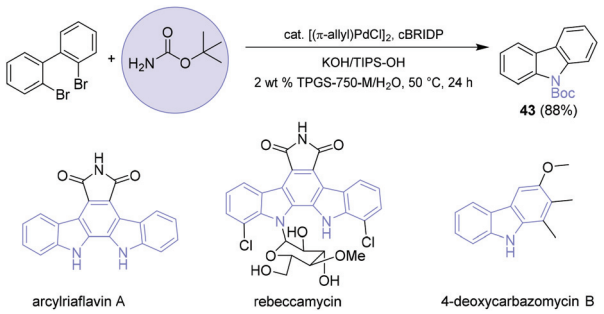
The potential for this methodology to be used in a one-pot sequence where water serves as the bulk reaction medium was also explored (Scheme 5). An initial amination of commercially available 1-iodo-4-bromobenzene yielded the desired product **45** (82%), which was followed by a second amination to **26** or **44**. Alternatively, formation of **20** followed by bromination in

Table 5 Sulfonamides and ureas used as coupling partners with aryl bromides[a]

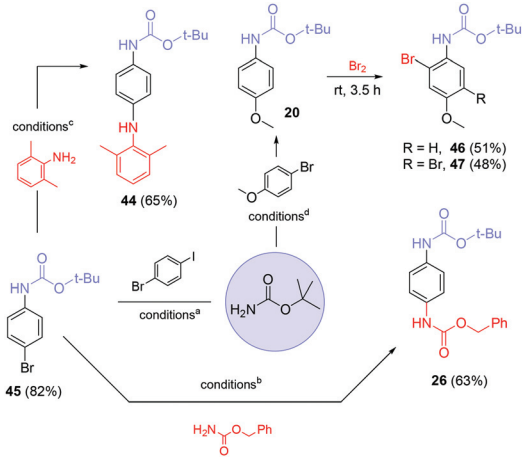


Entry	Ar–Br	Product	Base	Time (h)	Yield[b] (%)
1		 **34**	NaO*t*-Bu	24	87
2		 **35**	NaO*t*-Bu	24	85
3		 **36**	KOH/TIPS-OH	24	93
4		 **37**	KOH/TIPS-OH	24	47% (91 brsm[c])
5		 **38**	NaO*t*-Bu	24	61
6		 **39**	KOH/TIPS-OH	24	41
7		 **40**	KOH/TIPS-OH	24	69
8		 **41**	KOH/TIPS-OH	24	50
9		 **42**	KOH/TIPS-OH	24	35

[a] Reaction conditions: cat. $[(\pi\text{-allyl})PdCl]_2$ (2 mol%), cBRIDP (4 mol%), base (1.5 equiv.), 0.5 M, 50 °C. [b] Isolated yields. [c] Based on recovered starting material.



Scheme 4 Applications toward natural product synthesis in *water*.

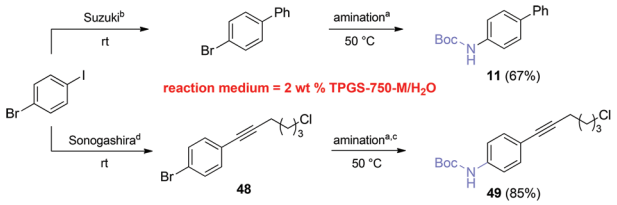


Scheme 5 1-Pot tandem reactions in water. Conditions: a. cat. [(allyl)-$PdCl]_2$ (0.5 mol%), cBRIDP (2 mol%), carbamate (1.1 equiv.), KOH/TIPSOH (1.5 equiv.), rt, 14 h. b. cat. $[(allyl)PdCl]_2$ (0.5 mol%), cBRIDP (2 mol%), carbamate (1.2 equiv.), KOH/TIPSOH (1.5 equiv.), 50 °C, 24 h. c. cat. $[(allyl)PdCl]_2$ (0.5 mol%), cBRIDP (2 mol%), arylamine (1.2 equiv.), KOH/TIPSOH (1.5 equiv.), 50 °C, 24 h. d. cat. $[(allyl)PdCl]_2$ (0.5 mol%), cBRIDP (2 mol%), carbamate (1.2 equiv.), KOH/TIPSOH (1.5 equiv.), rt, 20 h.

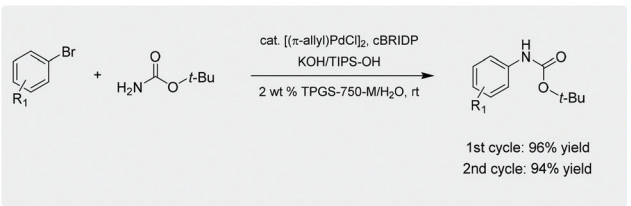
the same pot, all in water, afforded a mix of mono- and di-brominated products **46** and **47** (Scheme 5). Yet another sequence also performed in water involves an initial cross-coupling, *e.g.*, a Suzuki–Miyaura or Sonogashira reaction in aqueous nanoparticles of TPGS-750-M, followed by an amination reaction to **11** and **49** (Scheme 6).

The potential for recycling of the aqueous media associated with these couplings has also been examined. An *in-flask* extraction was performed using a minimal amount of EtOAc (Scheme 7). The aqueous reaction medium could then be re-used, as the surfactant is engineered to remain in the water. The first recycle led to poor conversion, whether at ambient temperature or with applied heat; even additional catalyst and ligand did not help drive the reaction to completion. The pH of the surfactant solution was found to be high (~11) following addition of the required amount of base, perhaps slowing the reaction rate. When KOH was added portion-wise over the course of the reaction, full conversion was achieved.

One major advantage associated with aqueous micellar technology is the opportunity to drastically reduce the amount



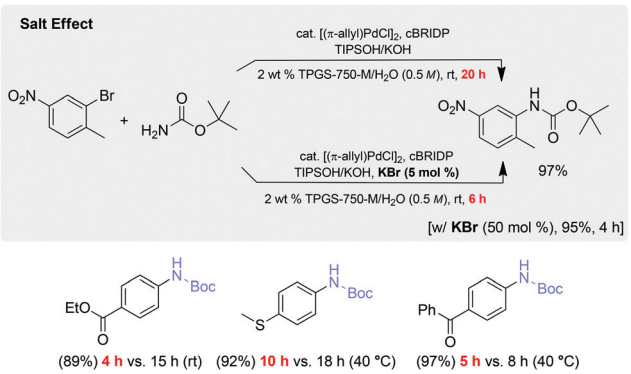
Scheme 6 1-Pot cross-coupling tandem reactions in water. Conditions: a. cat. $[(allyl)PdCl]_2$ (0.5 mol%), cBRIDP (2 mol%), carbamate (1.2 equiv.), KOH/TIPSOH (1.5 equiv.), 0.5 M. b. $Pd(dtbpf)Cl_2$ (2 mol%), phenylboronic acid (1.1 equiv.), KOH (3 equiv.), 0.5 M. c. Filteration required prior to amidation. d. $Pd(OAc)_2$ (3 mol%), cBRIDP (6 mol%), alkyne (1.1 equiv.), Et_3N (3 equiv.), 0.5 M.



E Factors

based on:	1st cycle	2nd cycle
total organic solvent	**2.7**	**2.9**
aqueous workup included	**7.0**	**2.9**

Scheme 7 Impact on E factors from recycling of aqueous TPGS-750-M.



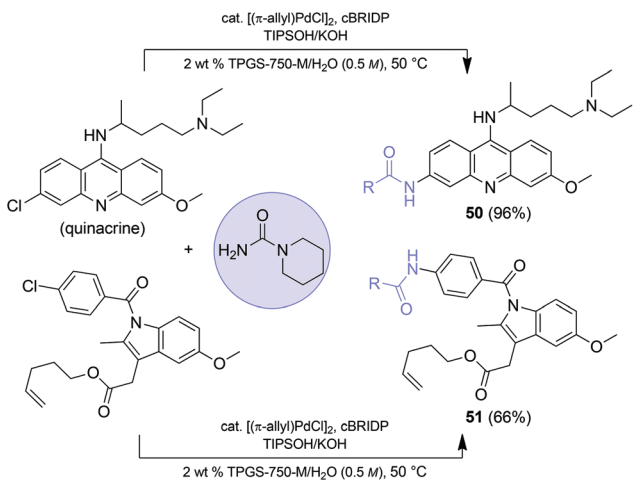
Scheme 8 Effect of added KBr in aminations.

of organic, as well as aqueous waste, as manifested by the associated E factors.[18] Using limited amounts of EtOAc, *in-flask* extraction can be performed; no additional water need be added. The overall amounts of organic waste and waste water produced using these procedures are reduced dramatically resulting in E factors, whether based solely on organic solvent, or including water in the overall calculation (Scheme 8), that compare quite favorably with those for solvent alone typically seen among fine chemical (E factors 5–25) and large pharmaceutical companies (E factors 25–100).[18]

During the course of these reactions using aryl bromides as partners, the levels of KBr are presumably being built-up; the effect of this salt on subsequent reactions that involve recycling of these aqueous solutions was unclear. A control experiment was conducted in which additional KBr was added. Remarkably, the reaction rate dramatically increased (Scheme 8); a near *four-fold* acceleration was observed with a mere 5 mol% of KBr. A series of kalium salts was then screened to elucidate the role of potassium bromide (see ESI†). The loading of the salt had a non-linear effect on the reaction rate; an increase to 50 mol% afforded the fastest reaction times. When the anionic counterion to potassium was changed (*e.g.* to Cl or F), similar reaction rates were observed. With other salts (*e.g.* NaBr, LiBr) slower reactions were observed compared to those in the presence of KBr.

DLS measurements were performed to determine if KBr altered the particle size of TPGS-750-M in solution. Typically, TPGS-750-M in water consists of *ca.* 60 nm spherical micelles.[15] With KOH normally present (1.5 equiv.), the particle size increases significantly to *ca.* 210 nm. As the amount of KBr is increased the average particle size *decreases* to 20–100 nm. From previous studies, salt additives (usually NaCl) increase the average micelle diameter.[15] Unexpectedly, in the presence of 50 mol% of KBr, particles with sizes averaging *ca.* 78 nm and 295 nm are present. With additional KBr (100 mol%) the two distinct sized particles are lost, with the particle size range the same as that found with the standard solution containing only KOH and TPGS-750-M (*ca.* 210 nm).

Lastly, to further demonstrate the potential for this mild, green chemistry to be used in more highly functionalized cases, both quinacrine (an antiprotozoal and anti-rheumatic), and indomethacin (a non-steroidal anti-inflammatory), as its pentenyl ester, were converted to their urea derivatives under these standard micellar conditions, **50** and **51**, respectively (Scheme 9). It is worthy of note that both are aryl chlorides, suggesting that such reaction partners are also amenable to introduction of ammonia equivalents.



Scheme 9 Functionalized aryl chlorides as coupling partners with a urea.

Conclusions

New technologies have been developed that lead to installation of carbamates, sulfonamides, and ureas onto a diverse set of aryl/heteroaryl bromides, chlorides, and iodides using a single set of conditions, all reactions being conducted at ambient or near ambient temperatures. Each is enabled by a commercially available, designer surfactant, TPGS-750-M, used in small amounts (2 wt%), with water and only water as the bulk reaction medium. The processes themselves take place within the nanoreactors formed spontaneously in an aqueous medium. These reactions are quite easy to run in that the reagents are added to the reaction vessel, in no particular order, and the contents then stirred vigorously to afford the desired products in usually high yields. Additionally, the reaction media can be readily recycled, drastically reducing the associated E factors with a simple *in-flask* extraction using a minimum amount of a single, recoverable organic solvent. Lastly, with as little as 5 mol% of KBr present, reaction rates can be increased significantly. Applications of KBr-accelerated cross-couplings are underway.

Conflict of interest

The authors declare no competing financial interest.

Acknowledgements

Financial support provided by the NIH (GM 86485) is warmly acknowledged with thanks. We also greatly appreciate the catalysts and ligands generously provided for this study by Johnson Matthey (Dr Thomas Colacot).

Notes and references

1 (*a*) J. F. Hartwig, *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E.-I. Negishi and A. de Meijere, Wiley, New York, NY, 2002, vol. 1, p. 1051; (*b*) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131.

2 (*a*) Q. Dai, W. Gao, D. Liu, L. M. Kapes and X. Zhang, *J. Org. Chem.*, 2006, **71**, 3928–3934; (*b*) R. E. Tundel, K. W. Anderson and S. L. Buchwald, *J. Org. Chem.*, 2006, **71**, 430–433; (*c*) J. P. Wolfe, S. Wagaw and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 7215–7216; (*d*) M. S. Driver and J. F. Hartwig, *J. Am. Chem. Soc.*, 1996, **118**, 7217–7218; (*e*) J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1144–1157; (*f*) N. Marion, O. Navarro, J. G. Mei, E. D. Stevens, N. M. Scott and S. P. Nolan, *J. Am. Chem. Soc.*, 2006, **128**, 4101–4111; (*g*) C. A. Fleckenstein and H. Plenio, *Chem. Soc. Rev.*, 2010, **39**, 694–711; (*h*) X. Xie, T. Y. Zhang and Z. Zhang, *J. Org. Chem.*, 2006, **71**, 6522–6529; (*i*) J. F. Hartwig, *Acc. Chem. Res.*, 2008, **41**, 1534–1544; (*j*) N. Marion and S. P. Nolan, *Acc. Chem. Res.*, 2008, **41**, 1440–1449.

3 (*a*) M. Kienle, S. R. Dubbaka, K. Brade and P. Knochel, *Eur. J. Org. Chem.*, 2007, 4166–4176; (*b*) J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin and S. L. Buchwald, *J. Org. Chem.*, 2000, **65**, 1158–1174; (*c*) Q. Shen, T. Ogata and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 6586–6596.

4 (*a*) K. Weissermel and H. J. Arpe, *Industrial Organic Chemistry*, Wiley-VCH, Weinheim, 1997; (*b*) S. A. Lawrence, *Amines: Synthesis Properties, and Application*, Cambridge University Press, Cambridge, 2004; (*c*) Z. Rappoport, *Patai, Series: The Chemistry of Anilines, Part 1*, Wiley-VCH, Southern Gate, Chichester, 2007.

5 (*a*) H. Xu and C. Wolf, *Chem. Commun.*, 2009, 1715; (*b*) L. Jiang, X. Lu, H. Zhang, Y. Jiang and D. Ma, *J. Org. Chem.*, 2009, **74**, 4542–4546; (*c*) D. Wang, Q. Cai and K. Ding, *Adv. Synth. Catal.*, 2009, **351**, 1722–1726; (*d*) M. K. Elmkaddem, C. Fischmeister, C. M. Thomas and J.-L. Renaud, *Chem. Commun.*, 2010, **46**, 925–927; (*e*) J. R. Lundgren, D. B. Peters, G. P. Alsabeh and M. Stradiotto, *Angew. Chem., Int. Ed.*, 2010, **49**, 4071–4074; (*f*) D. S. Surry and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 10354–10355; (*g*) G. D. Vo and J. F. Hartwig, *J. Am. Chem. Soc.*, 2009, **131**, 11049–11061; (*h*) A. Dumrath, C. Lübbe, H. Neumann, R. Jackstell and M. Beller, *Chem.–Eur. J.*, 2011, **17**, 9599–9604; (*i*) Q. Shen and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 10028–10029.

6 (*a*) J. P. Wolfe, J. Åhman, J. P. Sadighi, R. A. Singer and S. L. Buchwald, *Tetrahedron Lett.*, 1997, **38**, 6367; (*b*) S. Bhagwanth, G. M. Adjabeng and K. R. Hornberger, *Tetrahedron Lett.*, 2009, **50**, 1582–1585; (*c*) S. Jaime Figueroa, Y. Liu, J. M. Muchowski and D. G. Putman, *Tetrahedron Lett.*, 1998, **39**, 1313; (*d*) S. Lee, M. Jorgensen and J. F. Hartwig, *Org. Lett.*, 2001, **3**, 2729; (*e*) X. Huang and S. L. Buchwald, *Org. Lett.*, 2001, **3**, 3417; (*f*) D.-Y. Lee and J. F. Hartwig, *Org. Lett.*, 2005, **7**, 1169.

7 D. Chaturvedi, *Tetrahedron*, 2012, **68**, 15–45.

8 J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy and L. M. Alcazar-Roman, *J. Org. Chem.*, 1999, **64**, 5575–5580.

9 (*a*) J. Yin and S. L. Buchwald, *Org. Lett.*, 2000, **2**, 1101–1104; (*b*) A. Kuwahara, K. Nakano and K. Nozaki, *J. Org. Chem.*, 2005, **70**, 413–419; (*c*) A. S. Dallas and K. V. Gothelf, *J. Org. Chem.*, 2005, **70**, 3321–3323; (*d*) F. Shi, M. R. Smith III and R. E. Maleczka, *Org. Lett.*, 2006, **8**, 1411–1414; (*e*) A. A. Trabanco, J. A. Vega and M. Alejandro Fernandez, *J. Org. Chem.*, 2007, **72**, 8146–8148; (*f*) S. Bhagwanth, A. G. Waterson, G. M. Adjabeng and K. R. Hornberger, *J. Org. Chem.*, 2009, **74**, 4634–4637; (*g*) L. Qin, H. Cui, D. Zou, J. Li, Y. Wu, Z. Zhu and Y. Wu, *Tetrahedron Lett.*, 2010, **51**, 4445–4448.

10 (*a*) J. Yin and S. L. Buchwald, *Org. Lett.*, 2000, **2**, 1101–1104; (*b*) J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 6043–6048; (*c*) G. Burton, P. Cao, G. Li and R. Rivero, *Org. Lett.*, 2003, **5**, 4373–4376; (*d*) M. K. Muthayala, B. S. Chhikara, K. Parang and A. Kumar, *ACS Comb. Sci.*, 2012, **14**, 60–65.

11 (*a*) G. A. Artamkina, A. G. Sergeev and I. P. Beletskaya, *Tetrahedron Lett.*, 2001, **42**, 4381; (*b*) A. G. Sergeev, G. A. Artamkina and I. P. Beletskaya, *Tetrahedron Lett.*, 2003, **44**, 4719; (*c*) A. Abad, C. Agulló, A. C. Cuñat and C. Vilanova, *Synthesis*, 2005, 915; (*d*) M. McLaughlin, M. Palucki and I. W. Davies, *Org. Lett.*, 2006, **8**, 3311; (*e*) M. C. Willis, R. H. Snell, A. J. Fletcher and R. L. Woodward, *Org. Lett.*, 2006, **8**, 5089; (*f*) B. J. Kotecki, D. P. Fernando, A. R. Haight and K. A. Lukin, *Org. Lett.*, 2009, **11**, 947–950.

12 D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27.

13 R. A. Sheldon, I. W. C. E. Arends and U. Hanefeld, *Green Chemistry and Catalysis*, Wiley-VCH, Weinheim, Germany, 2007.

14 W. D. Chung, B. Rich and B. H. Lipshutz, *Adv. Synth. Catal.*, 2009, **351**, 1717–1721.

15 (*a*) B. H. Lipshutz and S. Ghorai, *Aldrichimica Acta*, 2012, **45**, 3; (*b*) B. H. Lipshutz, S. Ghorai, R. A. Abela, R. Moser, T. Nishikata, C. Duplais and A. Krasovskiy, *J. Org. Chem.*, 2011, **76**, 4379–4391.

16 K. Suzuki and H. T. Kobayashi, *Adv. Synth. Catal.*, 2008, **350**, 652–656.

17 (*a*) A. W. Schmidt, K. R. Reddy and H.-J. Knölker, *Chem. Rev.*, 2012, **112**, 3193–3328; (*b*) S. Guo, S. K. Tipparaju, S. D. Pegan, B. Wan, S. Mo, J. Orjala, A. D. Mesecar, S. G. Franzblau and A. P. Kozikowski, *Bioorg. Med. Chem.*, 2009, **17**, 7126–7130.

18 B. H. Lipshutz, N. A. Isley, J. C. Fennewald and E. D. Slack, *Angew. Chem., Int. Ed.*, 2013, **52**, 10952–10958.

