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Cross Coupling

New Insights into the Reaction Capabilities of Ionic Organic Bases in Cu-Catalyzed Amination

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Abstract: The application of ionic organic bases in the copper-catalyzed amination reaction (Ullmann reaction) has been studied at room temperature, with sub-mol-% catalyst loadings, and with more challenging amines at elevated temperatures. The cation present in the base has been shown to have little effect on the reaction at standard catalyst and ancillary ligand loadings, whereas the choice of anion is crucial for good reactivity. A substrate scope carried out at room temperature with the best performing bases, TBAM and TBPM, showed both bases to be highly effective under these mild reaction conditions. Moreover, under sub-mol % catalyst loadings and room temperature conditions, TBPM gave good to excellent yields for a number of different amines and functionalized aryl iodides (14 examples). However, reactions involving more challenging amines gave little or no yield. By using more forceful conditions (120 °C) moderate to excellent yields of cross-coupled products containing more challenging amines was achievable using TBPM and to a lesser extent with TBAM. As part of this work a study on the stability of the organic bases at 120 °C was undertaken. TBAM is shown to decompose to give nBu$_3$N and mono-butylmalonate at higher temperatures, and this can be correlated to a decrease in performance in the coupling reaction. The phosphonium cations in TBPM did not undergo analogous reactivity but were shown instead to experience some degree of deprotonation at the α-CH$_2$ to generate phosphonium ylides. This however did not lead to a significantly degradation in the activity of the TBPM in the cross-coupling reaction.

Introduction

A substantial number of pharmaceuticals, organic materials, and natural products contain C–N bonds, with aryl amines serving as important building blocks in many organic synthesis endeavors. The preparation of these aryl amines commonly involves the activation of aryl halide precursors using a Pd-based catalytic system.[1–5] However, there is a rapidly growing interest in the equivalent Cu-catalyzed cross-coupling reaction (the Ullmann reaction) both from academia and industry.[6–11] Not only is copper significantly cheaper and less toxic than palladium, it also uses cheaper and lower molecular weight ligands such as 1,10-phenanthroline or amino acids.[12–19] Many recent advances in copper catalyzed amination have concerned the discovery of new ligand systems to improve the reactivity, particularly towards more challenging substrates such as aryl chlorides.[11] However, the base has also been shown to play a crucial role in the reaction, in some cases acting as a ligand as well as a base,[19–21] and playing a role in catalyst deactivation pathways.

We have recently been interested in the application of soluble organic bases for copper catalysis.[21,22] These were first reported by Liu et al. in 2009,[17] where they were shown to be able to efficiently promote Ullmann C–N cross coupling reactions with aryl iodide and bromide substrates at room temperature or 0 °C in the presence of 10 mol-% of copper and 20 mol-% ligand (*N*,*N*′-dimethylglycine or L-proline). We have recently reported upon the use of bis(tetra-(*n*-butyl)phosphonium) malonate (TBPM) for the C–N cross coupling reaction between piperidine and iodobenzene.[22] Unlike inorganic bases such as K_3PO_4, TBPM is completely soluble in the reaction medium DMSO. Hence by using TBPM we were able to mitigate mass transfer effects commonly observed with poorly soluble inorganic bases in organic solvents and therefore obtain in-situ kinetic data on these systems. This allowed us to suggest improvements to the understanding of the reaction mechanism and catalyst deactivation pathways.[21,22]

Despite these recent advances there are still very few reports concerning the study and optimization of room-temperature reactions in copper catalysis.[21,23–26] Following on from our work on room-temperature reaction systems with inorganic K_3PO_4 base using relatively high catalyst and ligand loadings (10 and 20 mol-% respectively),[21] we sought to investigate a range of organic ammonium and phosphonium bases for use in Ullmann catalytic systems. An initial organic base screening was first carried out in order to widen the scope of studied species. As a consequence, a room temperature reaction system using low catalyst and ligand loadings has now been developed, and studies on the stability and performance of the organic bases with challenging substrates at elevated temperatures are reported.

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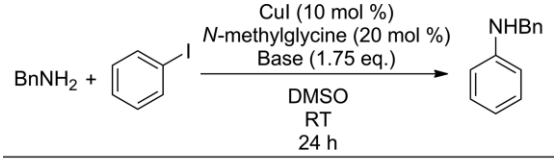
Results and Discussion

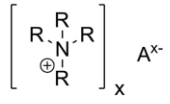
Organic Base Screening

Previous studies on the application of organic bases in copper-catalyzed couplings have mainly focused upon the use of phosphonium or ammonium cations with relative simple inorganic anions such as PO_4^{3-}, CO_3^{2-}, OAc^-, or $C_2O_4^{2-}$.[17] However the most efficacious systems were shown to be based on organic carboxylates such as malonate and adipate.[17] In addition, we have previously demonstrated how malonate anion in the base is also able to act as a ligand for the copper center in the coupling reaction, leading to improved kinetic reactivity than expected based on just pK_a considerations.[21,22] Given this we now report upon the preparation of a number of organic ammonium and phosphonium carboxylate bases and their application in the room temperature copper-catalyzed reaction (Table 1). As far as we are aware, with the exception of TBPM, TBAA and TBPA (**B5**, **B7** and **B9** respectively, Table 1),[17] all organic bases reported in Table 1 have not previously been employed in Ullmann C–N cross coupling reactions. However some have been used as ionic liquids or as catalysts for aminoxylation of aldehydes.[27–31] All organic bases were prepared by reacting either tetraalkylammonium hydroxide or tetraalkylphosphonium hydroxide with the corresponding acid. They were subsequently dried under high vacuum for 2 to 3 days.

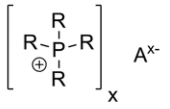
Table 1. Room temperature Ullmann coupling with organic bases.



(Yield %) Base:



B1: TBANM: R = ^{n}Bu, A$^-$ = N-methylglycinate **(0 %)**
B2: TBALP: R = ^{n}Bu, A$^-$ = L-prolinate **(0 %)**
B3: TMAM: R = Me, A^{2-} = malonate **(92 %)**
B4: TBAM: R = ^{n}Bu, A^{2-} = malonate **(98 %)**
B5: TBAA: R = ^{n}Bu, A^{2-} = adipate **(72 %)**



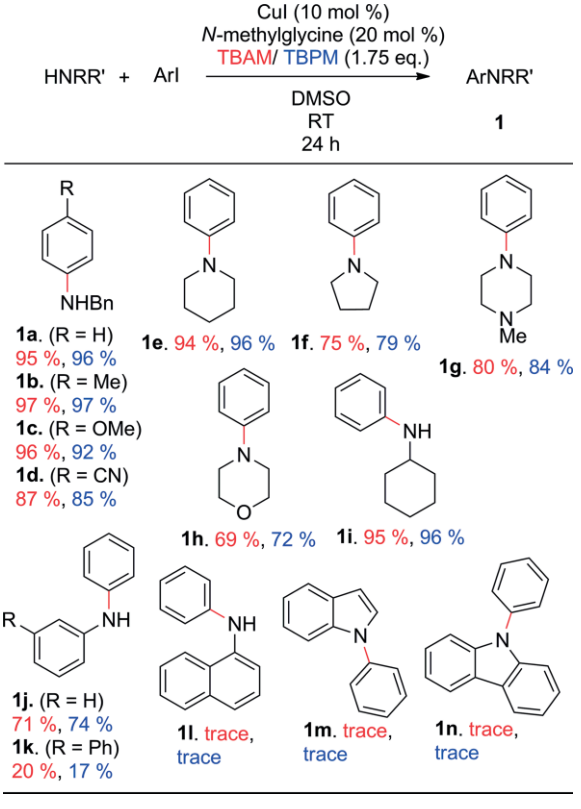
B6: TBPO: R = ^{n}Bu, A^{2-} = oxalate **(95 %)**
B7: TBPM: R = ^{n}Bu, A^{2-} = malonate **(98 %)**
B8: TBPS: R = ^{n}Bu, A^{2-} = succinate **(87 %)**
B9: TBPA: R = ^{n}Bu, A^{2-} = adipate **(59 %)**
B10: TBPP: R = ^{n}Bu, A^{2-} = phthalate **(88 %)**

Although *N*-methylglycine and L-proline as auxiliary ligands are known to promote high yields and reactivity in C–N cross coupling reactions,[21] the organic bases containing these ligands in deprotonated form, namely TBANM and TBALP (**B1** and **B2**, Table 1), both demonstrated no reactivity (Table 1). This could be indicative of *N*-methylglycinate and L-prolinate anions being poor bases for the cross-coupling reaction (pK_a of *N*-methylglycine and L-proline in H_2O are 2.23 and 1.19 respectively, while pK_a of oxalic, malonic, succinic, adipic and phthalic acids in H_2O are > 4.19).[32] We therefore turned our attention to dicarboxylate bases. In general, these bases gave moderate to excellent reactivity in the C–N cross coupling reaction. Inspection of the results obtained with TMAM, TBAM and TBPM (**B3**, **B4** and **B7** respectively, Table 1) suggests that the cation has little effect on reactivity under these conditions. However, the structure of the dicarboxylate plays a larger part in the observed reactivities with malonate giving the highest yield of product.

Substrate Scope with TBAM

The initial organic base screening results show both TBAM and TBPM (**B4** and **B7**, Table 1) to be the most effective bases in promoting C–N cross coupling reactions at room temperature (Table 1). Although TBPM (**B7**) has been reported before by Liu et al.,[17] TBAM (**B4**) has not previously been studied in this reaction. Advantages of using TBAM (**B4**) over TBPM (**B7**) include the lower cost of the tetraalkylammonium hydroxide precursor relative to its phosphonium counterpart. In addition, it was observed during the synthesis of ammonium bases that they are significantly less hygroscopic relative to phosphonium bases, with lower rates of water absorption (see ESI, Table S1). This allows better reaction performance to be obtained in the

Table 2. Room temperature Ullmann coupling with TBAM and TBPM across a range of subtrates.



C–N cross-coupling reaction as addition of just 10 mol-% of H_2O will lead to a reduction in yield from 98 % to 0 % with TBPM. No residual water was present in organic bases prepared in Table 1.

A substrate scope involving both TBAM and TBPM (red and blue respectively, Table 2) was carried out with 14 different primary/secondary amines and aryl halides. Both TBAM and TBPM gave similar yields (entries **1a** – **1j**, Table 2).[17]

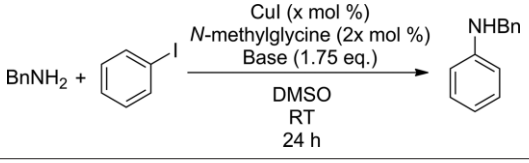
While aniline itself (**1j**, Table 2) was found to be a competent N-nucleophile under conditions shown in Table 2, further substitution to the aniline core proved to be deleterious (entries **1k** - **1n**, Table 2) – this is a previously reported issue for all Ullmann amination reactions.[21]

Room-Temperature Sub-Mol % Reactions

One of the main practical challenges facing the Ullmann reaction is the requirement for high copper catalyst loadings (< 5 mol-% is rare). Nevertheless, recent work carried out in the groups of Norrby, Ling, Jiang and Ma have shown that the use of sub-mol % Cu loadings in the Ullmann amination reaction is achievable in some situations.[33–39] However, these reactions still required either high loadings of auxiliary ligand (10–20 mol-% DMEDA),[33–37] or elevated reaction temperatures (50–135 °C).[33–36,38,39]

By exploiting the high activity observed with organic bases it was thought that it might be possible to achieve a room temperature sub-mol % Ullmann reaction system that does not require a large excess of auxiliary ligand relative to Cu. Thus, several ammonium and phosphonium bases were selected based on their performance in the initial base screening (Table 3), where sub-mol % catalyst loading (0.5 mol-%) was used in the reaction between benzylamine and phenyl iodide (Table 3). Much to our delight, TBPM proved to be a suitable base at a catalyst loading of 0.5 mol-% whereas other organic bases were less effective. A greater variation in reaction yield vs. base was observed at the lower catalysts loading of 0.5 mol-% CuI compared to 10 mol-% CuI. Extending the reaction time to 36 hours gave no noticeable improvement in reaction yield for all bases. Therefore, the difference in reactivity exhibited by different bases is most likely caused by catalyst deactivation under these conditions.

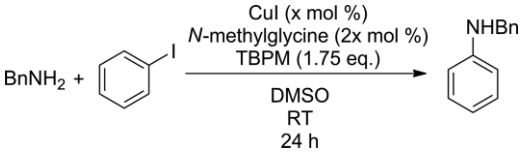
Table 3. C–N coupling reactions using 0.5 and 10 mol-% Cu loading.



Entry	Base	Yield [%] 0.5 mol-% CuI	Yield [%] 10 mol-% CuI
1	TMAM (**B3**)	68	92
2	TBAM (**B4**)	80	98
3	TBPO (**B6**)	76	95
4	TBPM (**B7**)	98	98
5	K_3PO_4 (**B11**)	35	98

Results in Table 3 reveal TBPM (**B7**) to give the best performance under sub-mol % catalyst loadings. Attempts to lower the catalyst loading even further with this base unfortunately led to a significant decrease in yield (Table 4). As before, extending the reaction time to 36 h gave no noticeable improvement in reaction performance with either 0.05 or 0.1 mol-% Cu loading.

Table 4. C–N coupling reactions with TBPM using different catalyst and ligand loadings.

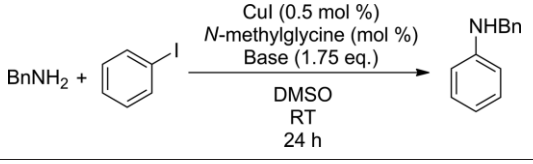


Entry	CuI (mol %)	Yield [%]
1	0	0
2	0.05	38
3	0.1	42
4	0.5	98
5	2.5	98
6	5	98
7	10	98

Attempts to optimize the sub-mol % reaction systems by varying reaction concentration (i.e. solvent volume) were carried out with TBAM, TBPM and K_3PO_4 (**B4**, **B7** and **B11** respectively). Although diluting the reaction gave a modest improvement in yield with TBAM and K_3PO_4 (**B4** and **B11**), the performance of these reactions was still sluggish relative to TBPM (**B7**) at similar catalyst loadings (Figures S1–S2). No improvements in yield on dilution were observed with TBPM (**B7**) at any of the studied Cu loadings (Figure S3).

Contrary to observations by Norrby and Ling for their systems,[33,37] using a large excess of ligand relative to the Cu catalyst in our system did not aid reactivity with either TBAM, TBPM or K_3PO_4 bases (**B4**, **B7** and **B11** respectively). In fact, using a large excess of ligand led to a decrease in reaction yield (Table 5). This is possibly due to catalyst deactivation – previous mechanistic studies have demonstrated how an excess of *N*-methylglycine can lead to catalyst deactivation and low turnover numbers.[21]

Table 5. C–N coupling reactions with different bases using different ligand loadings.

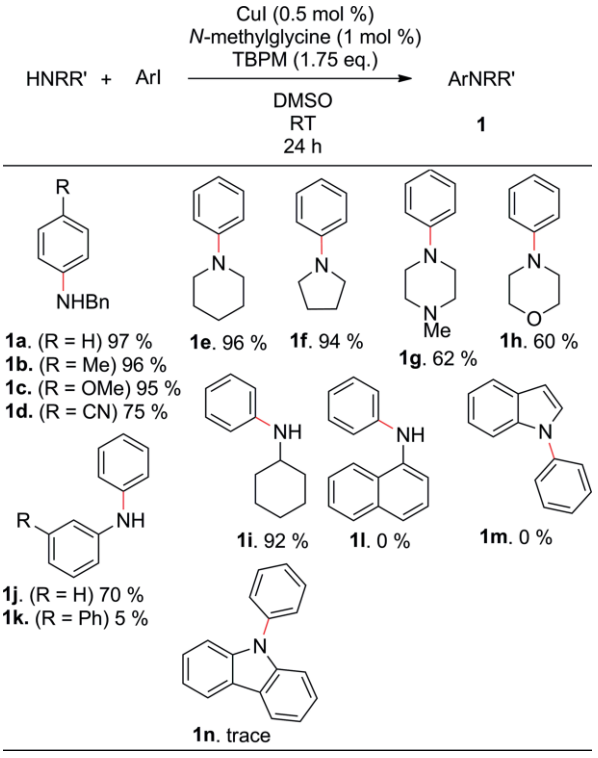


Entry	Base	Yield [%] 1 mol-% *N*-methylglycine	Yield [%] 20 mol-% *N*-methylglycine
1	TBAM (**B4**)	68	92
2	TBPM (**B7**)	80	98
3	K_3PO_4 (**B11**)	35	98

Based on these results TBPM (**B7**) was taken forward for further study as the most promising base under these conditions. A range of amines were aminated at room temperature with excellent reactivity observed (entries **1a** – **1j**, Table 6). The required reaction time varied depending on the substrate: the

syntheses of **1a** and **1e** were complete in approximately 5 and 7 hours respectively, while other substrates required 18–24 hours to reach maximum yield. Hence, all reactions were carried out for 24 hours.

Table 6. Coupling reaction between amines and aryl iodides using sub-mol % catalyst loadings.



As far as we are aware this is the first reported room-temperature copper-catalyzed sub-mol % catalytic system that can be carried out without the need for an excess of auxiliary ligand loading.[37] However, similar to entries **1k** - **1n** in Table 2, challenging amines exhibited little or no reactivity (entries **1k** - **1n**, Table 6). Attempts to carry out sub-mol % catalytic reactions with TBPM (**B7**) in other solvents such as acetonitrile, 2-propanol and toluene were also unsuccessful.

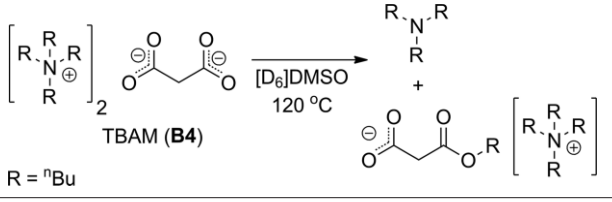
Reactions under sub-mol % catalyst loadings were generally limited to aryl iodide substrates. Substituting aryl iodides with more challenging aryl bromide and aryl chlorides led to a (in some cases significant) decrease in reaction yield (Tables S2 and S3, see ESI).

Organic Ammonium and Phosphonium Bases at Elevated Temperatures

Given the success of organic bases in these coupling protocols at low temperatures, we also wanted to explore their application at higher temperatures for the activation of more challenging substrates (such as entries **1k** – **1n**, Table 2 and Table 6). As the first step towards this the stability of the organic bases at higher temperatures was examined.

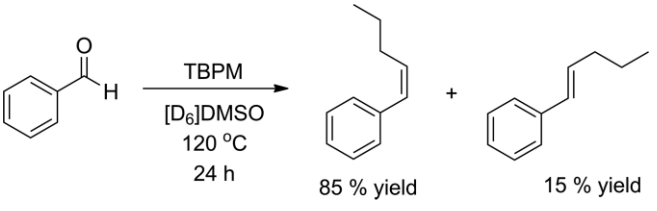
Variable ^{1}H NMR analysis (VT-^{1}H NMR in [D$_6$]DMSO, 30–120 °C) of TBAM (**B4**) showed no signs of base degradation within 0.5 h (Figure S4). However, when TBAM (**B4**) was heated to 120 °C for a more prolonged period of time (Table 7), ^{1}H and ^{13}C NMR analysis showed significant degradation of the TBAM (up to 26 % after 24 h) and generation of equimolar amounts of nBu$_3$N and mono-butylmalonate (Table 7 and Figures S4–S6). These products are most likely formed via a S$_N$2 attack of the malonate nucleophile on the tetrabutylammonium cation.[40] Unfortunately attempts to isolate a pure sample of tetra-*n*-butylammonium mono-butylmalonate were unsuccessful.

Table 7. Degredation of TBAM (B4) to form nBu$_3$N and mono-butylmalonate.



Entry	Time [h]	% degradation
1	0	0
2	1	Trace
3	4	22
4	24	26

VT-^{1}H NMR analysis (30–120 °C) was also carried out with the phosphonium salt analog TBPM (**B7**). A complete H/D exchange reaction occurred at the α-CH$_2$ of the phosphonium cation at > 50 °C (Figures S7 and S8). A similar exchange reaction has been reported by Chu et al. in phosphonium ionic liquids.[41] It has also been reported in the ionic liquid literature that under suitably basic conditions phosphonium cations can be deprotonated to generate phosphonium ylides, with H/D exchange at the α-CH$_2$ of the phosphonium cation most likely proceeding via such a ylide.[42–44] Since a basic malonate dianion is present in TBPM (**B7**), we wanted to determine if it too will exhibit similar reactivity. To this end, benzaldehyde was added to a solution of TBPM (**B7**) in [D$_6$]DMSO and allowed to stir at 120 °C for 24 hours. The formation of alkenes in the final reaction mixture (Scheme 1) confirmed the presence of such a phosphonium ylide intermediate. Carrying out the same reaction at room temperature did not result in the formation of alkenes.

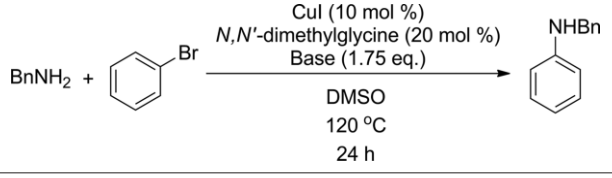


Scheme 1. Wittig reaction between benzaldehyde and TBPM.

In order to determine the effect of these undesired reaction pathways exhibited by TBAM and TBPM (**B4** and **B7**) on the cross-coupling reaction, a series of coupling experiments between benzylamine and bromobenzene was carried out at 120 °C (Table 8). The reaction mixture was pre-heated for 0, 1, 4 or 24 hours at 120 °C before the copper catalyst was injected. *N*,*N*′-dimethylglycine was used as the ligand as it has been shown that *N*-methylglycine can undergo competitive cross-

coupling with aryl halides at temperatures above 40 °C.[45] The reaction proceeded with complete conversion of bromobenzene for both TBAM and TBPM (**B4** and **B7**) when the reaction mixture was not pre-heated (0 h). However, pre-heating the reaction at 120 °C prior to the addition of the catalyst led to a decrease in yield for TBAM (**B4**) but not TBPM (**B7**). These results correlate with previous findings that mono-butylmalonate is unable to act as base in C–N cross coupling reactions.[22] However, phosphonium ylide formation is evidently a non-deleterious and benign background event (Table 8). To verify this, a reaction using identical reaction conditions in Table 8 was carried out in the presence of [D_6]DMSO and TBPM (**B7**). ^{1}H NMR analysis of the final reaction mixture clearly showed H/D exchange at the α-CH_2 of the phosphonium cation but 98 % yield of the cross-coupled product was still obtained.

Table 8. Cross-coupling reaction between benzylamine and bromobenzene in which the reaction was initiated using CuI after pre-heating the reaction mixture at 120 °C for 0, 1, 4 or 24 hours.



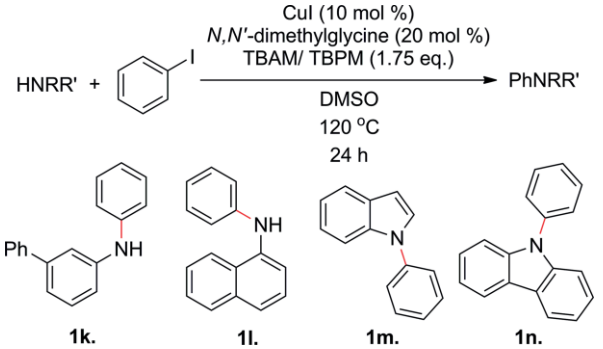
Delay in CuI addition [h]	0	1	4	24
Base	Yield [%]	Yield [%]	Yield [%]	Yield [%]
TBAM (**B4**)	98	90	40	30
TBPM (**B7**)	98	98	98	95

Most screening studies reported to date with organic base promoted transition metal-catalyzed processes (Cu, Pd or Ni) have focused on simple primary and secondary amines.[17,46–50] Coupling of more challenging amines with aryl halides under sub-mol % conditions either gave very poor reaction yields or were not reported during substrate scope studies.[33,35,39,51] Attempts to improve the reactivity of these challenging amines in sub-mol % copper-catalyzed reactions have yet to be reported.

In order to address the very low conversions experienced with more challenging substrates at room temperature (entries **1k** - **1n**, Table 2), these reactions were now repeated at higher temperatures (Table 9, 120 °C). The reaction mixtures were not pre-heated prior to addition of the copper catalyst. This is to prevent undesired decomposition products from having an effect on the cross-coupling reaction, especially in the case of TBAM (**B4**, Table 7). All reactions gave a significant improvement in yield, with the most acidic substrates showing the greatest improvement (entries **1m** and **1n**, Table 9). As expected, TBPM (**B7**) exhibited better reactivity than TBAM (**B4**) at 120 °C (Table 9).

Given the promising results obtained with TBPM (**B7**) under these conditions, we also tried to carry out sub-mol % reactions with the same challenging substrates (**1k** – **1n**) at 120 °C with both TBPM and K_3PO_4 (**B7** and **B11**). While only a trace amount of product was obtained using K_3PO_4, we are pleased to report an improvement in reactivity using TBPM (**B7**) compared to

Table 9. Coupling reactions involving bulky secondary amines and iodobenzene at 120 °C with TBAM (B4) or TBPM (B7) using 10 mol-% CuI loadings.



Product	Yield [%] TBAM (**B4**)	Yield [%] TBPM (**B7**)
1k	30	41
1l	25	36
1m	77	98
1n	80	98

room temperature sub-mol % reactions, with isolated yields of 25, 24, 36 and 33 % (**1k** - **1n** respectively). To the best of our knowledge, this is the first report of challenging secondary amines (**1m** and **1n**) being used successfully in a transition-metal catalyzed (Cu, Pd or Ni) reaction using an organic ionic base.[17,46–50]

Conclusions

A range of organic ionic bases have been synthesized and evaluated for applications in the room temperature Ullmann amination reaction. Results obtained here have shown that the base cation has little effect on the reaction at standard catalyst and ancillary ligand loadings (10 and 20 mol-% respectively). The base anion however has a large effect on the observed reactivity, with malonate bases giving the highest product yields under these reaction conditions. A substrate scope carried out at room temperature with TBAM and TBPM (**B4** and **B7**) show both bases are excellent reagents for the Ullmann reaction under these mild room-temperature conditions, demonstrating similar yields over a range of primary and secondary amines.

Studies involving more challenging sub-mol-% catalyst loadings at room temperature were subsequently explored, with TBPM (**B7**) performing better than TBAM (**B4**) under these conditions. The cross-coupling reactions for a number of different amines and functionalized aryl iodides have been reported (14 examples), with good to excellent yields observed in most cases. The exception was reactions involving more challenging amines which gave little or no yield of the desired cross-coupled product. This is a commonly encountered problem for challenging amines. In order to address this, we have also explored the use of ionic organic bases under more forceful conditions (namely higher temperatures). The stability of the bases at these higher temperatures was first assessed. Heating TBAM (**B4**) at 120 °C led to the formation of nBu_3N and mono-butylmalonate and this was correlated to a decrease in performance of the base at these temperatures. The phosphonium cations in

TBPM (**B7**) did not undergo analogous reactivity but were shown instead be subject to deprotonation at the α-CH_2 to generate phosphonium ylides leading to H/D exchange in [D_6]DMSO. This however did not significantly degrade the activity of the base and using TBPM (**B7**) at 120 °C gave moderate to excellent yields of cross-coupled products with a range of structurally complex amines.

Experimental Section

General Information

All reactions were carried out under a nitrogen atmosphere and scrupulously dry conditions using standard Schlenk techniques or in a nitrogen-filled glovebox. Glassware used were dried in an oven at 120 °C prior to use. The quantities of the coupling product formed from the catalytic C-N coupling reactions between the amine and aryl iodide was determined using ^{1}H NMR, where naphthalene was used as an internal standard. Percentage yields reported were the mean of at least two independent runs.

All reagents and ligands were purchased commercially and were dried in a sealed vacuum tube (solids) or thoroughly degassed and dried using 4 Å molecular sieves (liquids). They were subsequently stored in a nitrogen-filled glovebox. Stock solutions were produced using volumetric flasks and liquid amounts were accurately added to the reaction vials using microliter pipettes.

^{1}H and ^{13}C NMR spectroscopy data were obtained at room temperature using Bruker AV-400 spectrometers (400 MHz for ^{1}H and 101 MHz for ^{13}C). Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS) and are referenced to the residual solvent resonances in ^{1}H and ^{13}C NMR spectra. Coupling constants (*J*) are given in Hz units. ^{1}H and ^{13}C NMR spectra were analyzed using MESTRELAB MestReNova software. CHN microanalyses were carried out at the London Metropolitan University.

General Procedure for the Preparation of organic bases as shown in Table 1

An equimolar amount of tetra-(*n*-alkyl)phosphonium or ammonium hydroxide in water was treated with the corresponding acid (25 mmol). The reaction mixture was left to stir at room temperature overnight in air. Water was removed via rotary evaporation and the product was subsequently dried under high vacuum at 40 °C for 24 h to remove any residual water. With the exception of bis(tetra-(*n*-butyl)phosphonium oxalate (TBPO), the evaporated residue was dissolved in anhydrous acetonitrile (50 mL) to give a mixture containing an insoluble solid. The mixture was filtered under gravity and the solvent was removed via rotary evaporation until a viscous liquid was obtained. The product was then dried under high vacuum at 40 °C for 3 days and stored in a nitrogen-filled glovebox. ^{1}H and ^{13}C NMR spectra of all organic bases can be found in the ESI.

TBANM (**B1**): Off white solid (76 % yield, 6.26 g). ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C, TMS) δ = 3.26–3.12 (m, 8H), 2.58 (s (broad), 1H), 2.18 (s, 2H), 1.67–1.50 (m, 8H), 1.41–1.26 (m, 8H), 0.94 (t, $^3J_{HH}$ = 7.3 Hz, 12H); ^{13}C NMR (101 MHz, [D_6]DMSO, 23 °C, TMS): δ = 173.07 (s), 57.97 (s (broad)), 57.87 (s), 37.39 (s), 23.54 (s), 19.68 (s), 13.96 (s); CHN analysis (%) for $C_{19}H_{41}N_2O_2$: C (69.25), H (12.54), N (8.50); found C (69.15), H (12.52), N (8.55).

TBALP (**B2**): Off white solid (77 % yield, 6.86 g). ^{1}H NMR (400 MHz, [D_3]Acetonitrile, 23 °C, TMS) δ = 3.19–3.13 (m, 8H), 3.11–3.08 (m, 1H), 3.05–2.98 (m, 1H), 2.61–2.52 (m, 1H), 1.89–1.79 (m, 1H), 1.70–1.59 (m, 9H), 1.58–1.45 (m, 1H), 1.43–1.31 (m, 8H), 0.99 (t, $^3J_{HH}$ = 7.3 Hz, 12H); ^{13}C NMR (101 MHz, [D_3]Acetonitrile, 23 °C, TMS): δ = 177.15 (s), 63.55 (s), 58.33 (s), 47.50 (s), 31.76 (s), 26.49 (s), 23.37 (s), 19.36 (s), 12.82 (s); CHN analysis (%) for $C_{21}H_{43}N_2O_2$: C (70.93), H (12.19), N (7.88); found C (70.98), H (12.23), N (7.98). This compound has been previously reported.[27]

TMAM (**B3**): White solid (90 % yield, 5.63 g). ^{1}H NMR (400 MHz, D_2O, 23 °C, TMS) δ = 3.09 (s, 24H), 3.01 (s, 2H); ^{13}C NMR (101 MHz, D_2O, 23 °C, TMS): δ = 177.16 (s), 55.18 (s), 47.17 (s); CHN analysis (%) for $C_{11}H_{24}N_2O_4$: C (53.21), H (9.74), N (11.28); found C (53.31), H (9.92), N (11.35).

TBAM (**B4**): Sticky white solid (91 % yield, 13.4 g). ^{1}H NMR (400 MHz, [D_3]Acetonitrile, 23 °C, TMS) δ = 3.19–3.06 (m, 16H), 2.58 (s (broad), 2H), 1.65–1.50 (m, 16H), 1.40–1.24 (m, 16H), 0.93 (t, $^3J_{HH}$ = 7.3 Hz, 24H); ^{13}C NMR (101 MHz, [D_3]Acetonitrile, 23 °C, TMS): δ = 175.01 (s), 59.18 (s), 53.33 (s (broad)) 24.35 (s), 20.31 (s), 13.84 (s); CHN analysis (%) for $C_{35}H_{74}N_2O_4$: C (71.74), H (12.56), N (4.78); found C (71.67), H (12.65), N (4.62). This compound has been previously reported.[31]

TBAA (**B5**): White solid (85 % yield, 13.3 g). ^{1}H NMR (400 MHz, [D_3]Acetonitrile, 23 °C, TMS) δ = 3.19–3.06 (m, 16H), 1.83 (m, 4H), 1.59 (m, 16H), 1.42–1.26 (m, 20H), 0.95 (t, $^3J_{HH}$ = 7.4 Hz, 24H); ^{13}C NMR (101 MHz, [D_3]Acetonitrile, 23 °C, TMS): δ = 177.37 (s), 59.28 (s), 40.73 (s), 29.03 (s), 24.34 (s), 20.33 (s), 13.82 (s); CHN analysis (%) for $C_{38}H_{79}N_2O_4$: C (72.67), H (12.68), N (4.46); found C (72.57), H (12.64), N (4.42). This compound has been previously reported.[17]

TBPO (**B6**): White solid (91 % yield, 13.8 g). ^{1}H NMR (400 MHz, [D_3]Acetonitrile, 23 °C, TMS) δ = 2.28–2.20 (m, 16H), 1.58–1.43 (m, 32H), 0.96 (t, $^3J_{HH}$ = 7.0 Hz, 24H); ^{13}C NMR (101 MHz, [D_3]Acetonitrile, 23 °C, TMS): δ = 175.43 (s), 23.55 (d, $^3J_{CP}$ = 15.7 Hz), 23.16 (d, $^2J_{CP}$ = 4.5 Hz), 18.01 (d, $^1J_{CP}$ = 47.9 Hz), 12.70 (s); CHN analysis (%) for $C_{34}H_{72}O_4P_2$: C (67.29), H (11.96); found C (67.15), H (12.09). This compound has been previously reported.[28]

TBPM (**B7**): White solid (93 % yield, 14.5 g). ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C, TMS): δ = 2.41 (s (broad), 2H), 2.15–2.27 (m, 16H), 1.35–1.54 (m, 32H), 0.92 (t, $^3J_{HH}$ = 6.9 Hz, 24 H); ^{13}C NMR (101 MHz, [D_6]DMSO, 23 °C, TMS): δ = 173.20 (s), 50.20 (s(broad)), 23.35 (d, $^3J_{CP}$ = 15.6 Hz), 22.65 (d, $^2J_{CP}$ = 4.4 Hz), 17.29 (d, $^1J_{CP}$ = 47.6 Hz), 13.26 (s); CHN analysis (%) for $C_{35}H_{74}O_4P_2$: C (67.10), H (12.01); found C (67.60), H (12.12). This compound has been previously reported.[17]

TBPS (**B8**): White solid (80 % yield, 12.7 g). ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C, TMS): δ = 2.26–2.15 (m, 16H), 1.81 (s, 4H), 1.53–1.35 (m, 32H), 0.92 (t, $^3J_{HH}$ = 7.0 Hz, 24H); ^{13}C NMR (101 MHz, [D_6]DMSO, 23 °C, TMS): δ = 176.64 (s), 38.41 (s), 23.84 (d, $^3J_{CP}$ = 15.6 Hz), 23.14 (d, $^2J_{CP}$ = 4.4 Hz), 17.81 (d, $^1J_{CP}$ = 47.6 Hz), 13.75 (s); CHN analysis (%) for $C_{36}H_{75}O_4P_2$: C (68.21), H (11.93); found C (68.25), H (12.01). This compound has been previously reported.[29]

TBPA (**B9**): White solid (92 % yield, 15.2 g). ^{1}H NMR (400 MHz, [D_6]DMSO, 23 °C, TMS) δ = 2.27–2.14 (m, 16H), 1.73–1.64 (m, 2H), 1.53–1.36 (m, 32H), 1.31–1.24 (m, 2H), 0.92 (t, *J* = 7.0 Hz, 24H); ^{13}C NMR (101 MHz, [D_3]Acetonitrile, 23 °C, TMS): δ = 177.21 (s), 40.87 (s), 29.14 (s), 24.58 (d, $^3J_{CP}$ = 15.6 Hz), 24.02 (d, $^2J_{CP}$ = 4.6 Hz), 18.91 (d, $^1J_{CP}$ = 48.0 Hz), 13.65; CHN analysis (%) for $C_{38}H_{80}O_4P_2$: C (68.84), H (12.16); found C (68.80), H (12.10). This compound has been previously reported.[17]

TBPP (**B10**): White solid (85 % yield, 14.5 g). ^{1}H NMR (400 MHz, [D_3]Acetonitrile, 23 °C, TMS) δ = 7.21–7.16 (m, 2H), 6.98–6.88 (m, 2H), 2.23–2.14 (m, 16H), 1.52–1.36 (m, 32H), 0.91 (t, $^3J_{HH}$ = 7.1 Hz, 24H); ^{13}C NMR (101 MHz, [D_3]Acetonitrile, 23 °C, TMS): δ = 174.29

(s), 127.85 (s), 125.31 (s), 24.55 (d, $^3J_{CP}$ = 15.6 Hz), 24.09 (d, $^2J_{CP}$ = 4.5 Hz), 18.93 (d, $^1J_{CP}$ = 47.8 Hz), 13.68 (s); CHN analysis (%) for $C_{40}H_{75}O_4P_2$: C (70.45), H (11.09); found C (70.57), H (11.22). This compound has been previously reported.[30]

General reaction procedure for the reaction between benzylamine and aryl halides as shown in Table 1, Table 3, Table 4, Table 5, Table 8 and Figures S1–S3 (ESI)

In a nitrogen-filled glovebox, benzylamine (164 μL, 1.50 mmol), aryl halide (1.00 mmol), base (1.75 mmol), ligand, naphthalene (internal standard) and DMSO (required amount to make up to 500 μL total volume unless otherwise stated) were added to a reaction vial with a magnetic stirring bar. Copper(I) iodide (0.100 M solution in DMSO) was added to initiate the reaction. The vial was sealed using an open top cap with a 6 mm septum and the reaction stirred at room temperature for 24 hours. The reaction mixture was diluted with $CDCl_3$ (1 mL) and washed with three portions of distilled water (3 × 1 mL). The resulting solution was dried using $MgSO_4$ and filtered into a NMR tube for ^{1}H NMR analysis.

General reaction procedure for the reaction between benzaldehyde and TBPM as shown in Scheme 1

In a nitrogen-filled glovebox, benzaldehyde (104 μL, 1.00 mmol), TBPM (0.621 g, 1.00 mmol), naphthalene (100 μL of 1.00 M solution in DMSO, 0.100 mmol) and DMSO (2 mL) were added to a reaction vial with a magnetic stirring bar. The vial was sealed using an open top cap with a 6 mm septum and was taken out of the glovebox and placed in a temperature-controlled sand bath where it was left to stir for 24 hours at 120 °C. The reaction mixture was diluted with $CDCl_3$ (1 mL) and washed with three portions of distilled water (3 × 1 mL). The resulting solution was dried using $MgSO_4$ and filtered into a NMR tube for ^{1}H NMR analysis.

General reaction procedure for the reaction between amines and aryl iodides with TBAM/TBPM as shown in Table 2, Table 6 and Table 9

In a nitrogen-filled glovebox, amine (1.50 mmol), aryl iodide (1.00 mmol), base (1.75 mmol), ligand and DMSO (required amount to make up to 500 μL total volume) were added to a reaction vial with a magnetic stirring bar. Copper(I) iodide (0.100 M solution in DMSO) was added to initiate the reaction. The vial was sealed using an open top cap with a 6 mm septum and stirred at room temperature or in a temperature-controlled sand bath (120 °C) where it was left to stir for 24 hours. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried using $MgSO_4$ and concentrated in vacuo. All products were isolated after purification using silica gel chromatography. ^{1}H and ^{13}C NMR spectra of all C-N cross coupled products can be found in the ESI.

1a: White solid. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.50–7.40 (m, 4H), 7.39–7.34 (m, 1H), 7.27 (t, $^3J_{HH}$ = 7.6 Hz, 2H), 6.81 (t, $^3J_{HH}$ = 7.3 Hz, 1H), 6.72 (d, $^3J_{HH}$ = 7.9 Hz, 2H), 4.40 (s, 2H), 4.09 (s (broad), 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 148.24 (s), 139.54 (s), 129.33 (s), 128.70 (s), 127.57 (s), 127.29 (s), 117.63 (s), 112.93 (s), 48.39 (s). This compound has been previously reported.[52]

1b: Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.50–7.40 (m, 4H), 7.40–7.34 (m, 1H), 7.08 (d, $^3J_{HH}$ = 7.1 Hz, 2H), 6.65 (d, $^3J_{HH}$ = 6.7 Hz, 2H), 4.39 (s, 2H), 3.96 (s (broad), 1H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 146.00 (s), 139.75 (s), 129.82 (s), 128.66 (s), 127.56 (s), 127.21 (s), 126.78 (s), 113.06 (s), 48.69 (s), 20.49 (s). This compound has been previously reported.[53]

1c: Yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.44–7.34 (m, 4H), 7.34–7.26 (m, 1H), 6.84–6.78 (m, 2H), 6.68–6.60 (m, 2H), 4.32 (s, 2H), 3.82 (s (broad), 1H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 152.20 (s), 142.46 (s), 139.68 (s), 128.60 (s), 127.56 (s), 127.18 (s), 114.92 (s), 114.11 (s), 55.83 (s), 49.27 (s). This compound has been previously reported.[53]

1d: White solid. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.45–7.31 (m, 7H), 6.62 (d, $^3J_{HH}$ = 6.6 Hz, 2H), 4.83 (s (broad), 1H), 4.41 (d, $^3J_{HH}$ = 5.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 151.24 (s), 137.92 (s), 133.72 (s), 128.88 (s), 127.67 (s), 127.31 (s), 120.57 (s), 112.45 (s), 98.80 (s), 47.43 (s). This compound has been previously reported.[53]

1e: Orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.41 (q, $^3J_{HH}$ = 7.4 Hz, 2H), 7.11 (t, $^3J_{HH}$ = 7.1 Hz, 2H), 6.99 (t, $^3J_{HH}$ = 7.0 Hz, 1H), 3.31 (t, $^3J_{HH}$ = 3.3 Hz, 4H), 1.94–1.80 (m, 4H), 1.79–1.67 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 152.42 (s), 129.14 (s), 119.32 (s), 116.68 (s), 50.83 (s), 26.07 (s), 24.52 (s). This compound has been previously reported.[54]

1f: Orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.28 (t, $^3J_{HH}$ = 7.3 Hz, 2H), 6.71 (t, $^3J_{HH}$ = 6.7 Hz, 1H), 6.64 (d, $^3J_{HH}$ = 6.6 Hz, 2H), 3.34 (t, $^3J_{HH}$ = 3.4 Hz, 4H), 2.06 (t, $^3J_{HH}$ = 3.0 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 147.99 (s), 129.15 (s), 115.46 (s), 111.72 (s), 47.65 (s), 25.49 (s). This compound has been previously reported.[55]

1g: Orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.30 (t, $^3J_{HH}$ = 7.3 Hz, 2H), 6.97 (d, $^3J_{HH}$ = 7.0 Hz, 2H), 6.89 (t, $^3J_{HH}$ = 6.9 Hz, 1H), 3.26 (q, $^3J_{HH}$ = 3.3 Hz, 4H), 2.63 (q, $^3J_{HH}$ = 2.6 Hz, 4H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 151.23 (s), 129.13 (s), 119.75 (s), 116.09 (s), 55.14 (s), 49.04 (s), 46.12 (s). This compound has been previously reported.[56]

1h: Orange oil. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.38–7.28 (m, 2H), 7.02–6.89 (m, 3H), 3.94–3.86 (m, 4H), 3.30–3.12 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 151.30 (s), 129.21 (s), 120.08 (s), 115.74 (s), 66.97 (s), 49.39 (s). This compound has been previously reported.[57]

1i: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.22 (t, $^3J_{HH}$ = 7.2 Hz, 2H), 6.72 (t, $^3J_{HH}$ = 7.3 Hz, 1H), 6.65 (t, $^3J_{HH}$ = 6.7 Hz, 2H), 3.51–3.44 (s (broad), 1H), 3.32 (tt, $^3J_{HH}$ = 10.1, 3.8 Hz, 1H), 2.17–2.08 (m, 2H), 1.87–1.78 (m, 2H), 1.77–1.67 (m, 1H), 1.51–1.14 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 147.45 (s), 129.29 (s), 116.87 (s), 113.20 (s), 51.74 (s), 33.54 (s), 26.01 (s), 25.09 (s). This compound has been previously reported.[58]

1j: Orange solid. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.30 (t, $^3J_{HH}$ = 7.8 Hz, 4H), 7.11 (d, $^3J_{HH}$ = 7.9 Hz, 4H), 6.97 (t, $^3J_{HH}$ = 7.3 Hz, 2H), 5.72 (s (broad), 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 143.13 (s), 129.35 (s), 121.00 (s), 117.82 (s). This compound has been previously reported.[59]

1k: White solid. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.63–7.57 (m, 2H), 7.51–7.43 (m, 2H), 7.40–7.27 (m, 5H), 7.22–7.13 (m, 3H), 7.12–7.07 (m, 1H), 7.01–6.96 (m, 1H), 5.83 (s (broad), 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 206.81 (s), 143.64 (s), 143.06 (s), 142.55 (s), 141.18 (s), 129.71 (s), 129.40 (s), 128.69 (s), 127.34 (s), 127.12 (s), 121.18 (s), 119.94 (s), 118.08 (s), 116.62 (s), 116.48 (s). This compound has been previously reported.[60]

1l: Orange solid. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 8.07–8.03 (m, 1H), 7.91–7.88 (m, 1H), 7.60 (dd, $^3J_{HH}$ = 7.5, 1.9 Hz, 1H), 7.54–7.49 (m, 2H), 7.44–7.37 (m, 2H), 7.32–7.25 (m, 2H), 7.02 (d, $^3J_{HH}$ = 7.0 Hz, 2H), 6.94 (t, $^3J_{HH}$ = 7.4 Hz, 1H), 5.97 (s (broad), 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 144.80 (s), 138.80 (s) 134.71 (s), 130.86 (s), 129.34 (s), 128.54 (s), 126.10 (s), 126.02 (s), 125.67 (s), 122.98 (s), 121.80 (s), 120.49 (s), 117.40 (s), 115.90 (s). This compound has been previously reported.[61]

1m: White solid. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 7.82 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 7.70 (d, $^3J_{HH}$ = 7.6 Hz, 1H), 7.62–7.61 (m, 4H), 7.48–7.43 (m, 2H), 7.35–7.28 (m, 2H), 6.81 (d, $^3J_{HH}$ = 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 139.70 (s), 135.81 (s), 129.59 (s), 127.93 (s), 126.43 (s), 124.38 (s), 122.33 (s), 121.10 (s), 120.33 (s), 110.48 (s), 103.55 (s). This compound has been previously reported.[62]

1n: White solid. ^{1}H NMR (400 MHz, $CDCl_3$, 23 °C, TMS): δ = 8.33–8.28 (m, 2H), 7.73–7.68 (m, 4H), 7.61–7.54 (m, 5H), 7.48–7.40 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, 23 °C, TMS): δ = 141.09 (s), 137.90 (s), 129.97 (s), 127.54 (s), 127.27 (s), 126.07 (s), 123.56 (s), 120.44 (s), 120.07 (s), 109.91 (s). This compound has been previously reported.[63]

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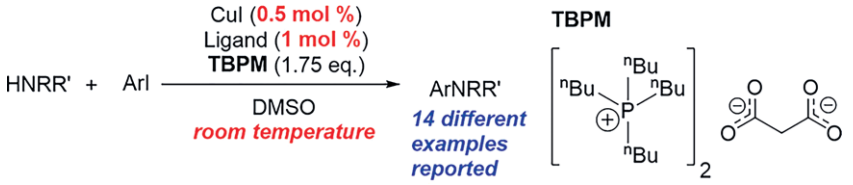
Cross Coupling



Room-temperature sub-mol % Ullmann amination has been realized, promoted by the organic ionic base TBPM (14 examples). In addition, the stability and application of ammonium and phosphonium based organic ionic bases at higher temperatures was investigated, leading to a new protocol for the activation of structurally complex amines.

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