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2,2,5,5-Tetramethyloxolane (TMO) as a Solvent for Buchwald-Hartwig Aminations

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ABSTRACT: Buchwald-Hartwig amination is one of the most important methods for the synthesis of *N*-arylamines and is widely employed for the synthesis of potential pharmaceuticals, natural products and other fine chemicals. The reaction usually uses a Pd(0) catalyst such as $Pd(dba)_2$ and (±)-BINAP in the presence of a base, and toluene is the most commonly used solvent. However, there are significant safety, toxicological and environmental hazards associated with the use of toluene. Herein, we demonstrate the successful application of 2,2,5,5-tetramethyloxolane (TMO), a solvent with a similar property profile to toluene, for Buchwald-Hartwig amination reactions for coupling a wide range of primary and secondary amines with aryl bromides. When

NaO*t*-Bu was used as the base, similar yields were obtained in toluene and TMO. In contrast, using Cs_2CO_3, TMO outperformed toluene significantly for electron deficient aryl bromides that could be susceptible to nucleophilic attack. To showcase the use of TMO as a solvent for Buchwald-Hartwig aminations, the synthesis of a key intermediate in the route to smoothened (SMO) receptor antagonist drug candidate SEN826 was successfully accomplished in TMO. Improved metrics and reduction in residual palladium in the isolated amines demonstrate further benefits in the substitution of toluene with TMO in Buchwald-Hartwig aminations.

INTRODUCTION

Palladium-catalysed cross-coupling reactions are arguably the most valuable methodology in the toolkit of a synthetic chemist, and are widely used in both industry and academia.[1–6] Of these, the Buchwald-Hartwig amination is of significant importance due to the prevalence of *N*-arylamines in numerous pharmaceuticals, natural products, agrochemicals and other fine chemicals.[1–3,7–17] Representative examples of pharmaceuticals (Imatinib) or potential pharmaceuticals (SEN826), fungicides (Mepanipyrim) and natural products (Mukoline) are shown in Figure 1A. In each case, the bond highlighted in green was crafted using Buchwald-Hartwig amination. A main focus of previous work on such aminations has been the development of suitable ligands, in an attempt to increase the substrate scope and the efficiency. From these studies, it has emerged that the combination of $Pd(dba)_2$ and (±)-BINAP is one of the most widely applicable catalyst systems for the coupling of (hetero)aryl bromides with primary or secondary amines.[18–20] Of note, investigation into the use of different solvents for Buchwald-Hartwig aminations has received little attention. The solvents most commonly used in Buchwald-Hartwig aminations are toluene, 1,4-dioxane and THF and, where solubility issues with more polar substrates have been encountered, NMP and DMF have been occasionally utilised.[2,21,23]

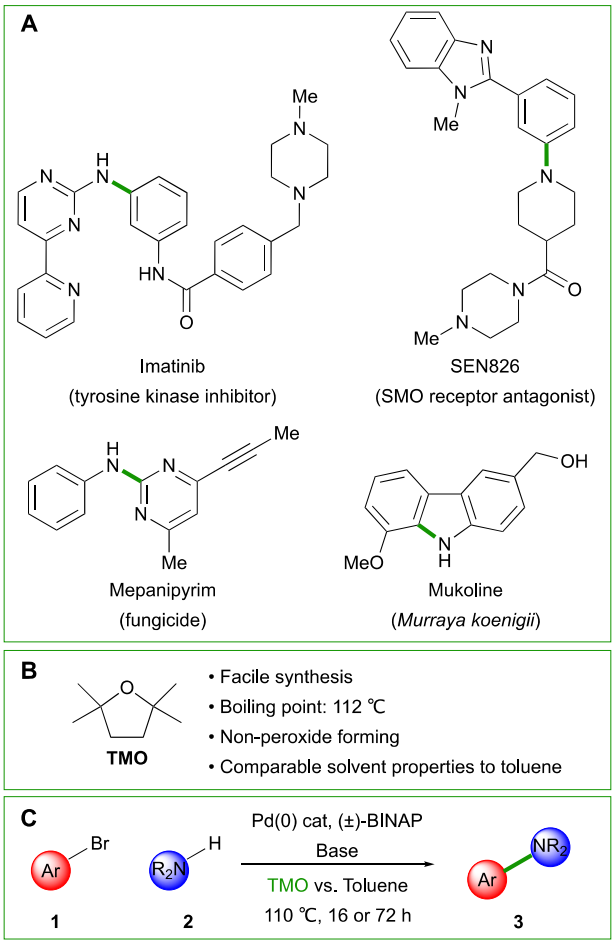


Figure 1. (**A**) Pharmaceuticals, agrochemicals and natural products synthesised *via* Buchwald-Hartwig aminations (bond formed highlighted in green). (**B**) 2,2,5,5-Tetramethyloxolane (TMO). (**C**) This work.

In recent years, the pharmaceutical and fine chemical industries have become interested in the use of safer and more sustainable chemicals, with replacement of solvents of particular interest due to the large volumes in which they are utilised. Attempts to replace the most environmentally damaging and harmful solvents have resulted in the introduction of new solvents and solvent selection guides.[25–28] The replacement of toluene by other solvents has recently garnered further importance as a result of the addition of toluene into the REACH restricted substances list.[29,30] Toluene is suspected of causing damage to fertility, amongst other health hazards, whilst also being

a hazardous air pollutant and harmful to aquatic life with long lasting effects.[30] 2,2,5,5-Tetramethyloxolane (TMO) (Figure 1B), a solvent recently developed in our group, has been found to have similar solvent properties to toluene, including a virtually identical boiling point (112 °C compared to 111 °C for toluene).[31] As a result, TMO was found to perform similarly to toluene in esterifications, Grignard reactions and the biocatalysed synthesis of polyesters.[31,32] TMO can be synthesised by the H-beta-zeolite catalysed intramolecular dehydration of 2,5-dimethyl-2,5-hexanediol in very high yields (>95%) and selectivity (≥99%). Several possible bio-based routes to TMO have recently been assessed by green metrics and followed by preliminary lab-scale synthesis, with bio-carbon content confirmed for a sample of the solvent produced from methyl levulinate.[33]

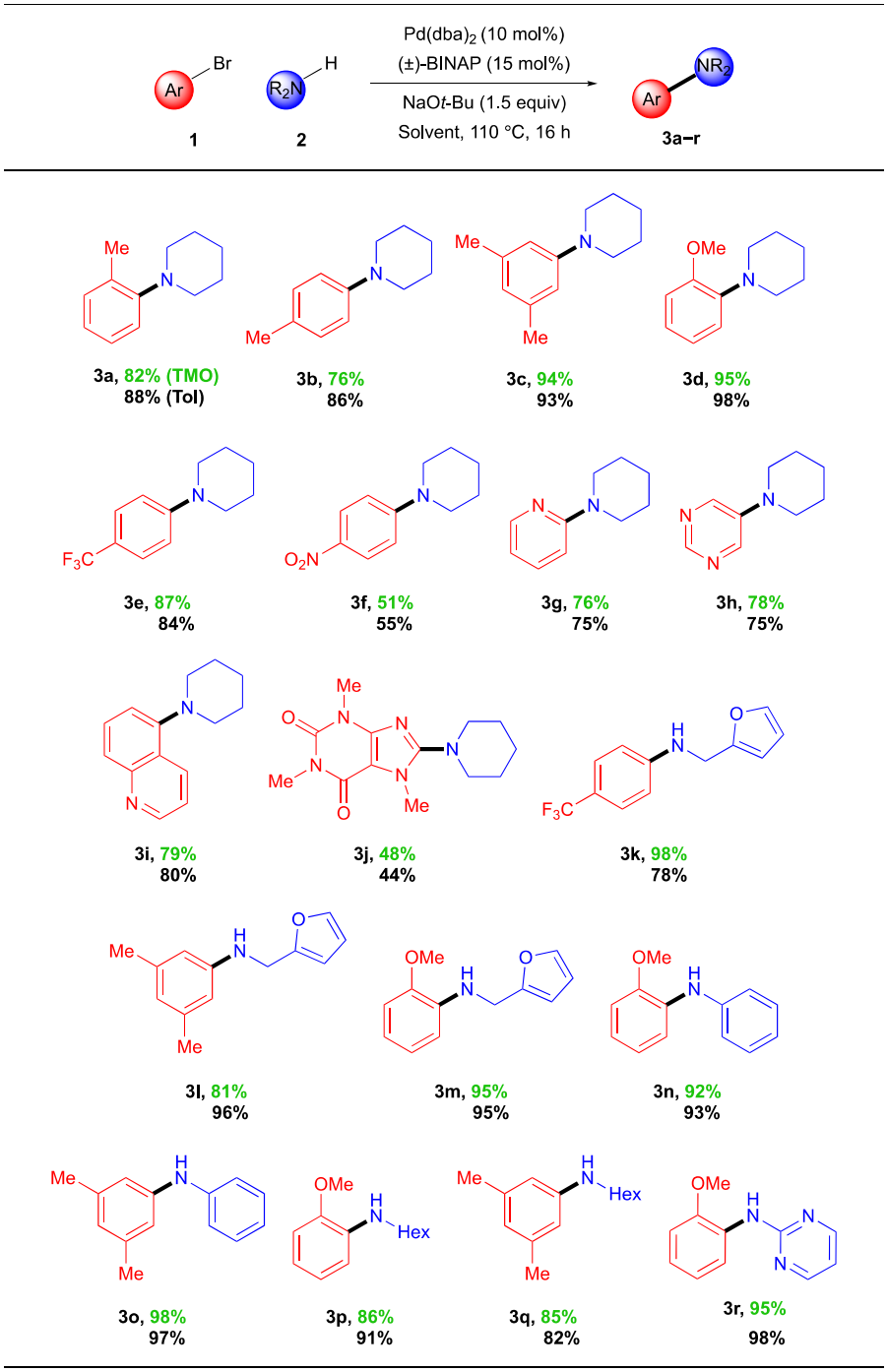
Herein, motivated by the desire to demonstrate that TMO can be applied to other widely employed reactions, we report that TMO is an excellent solvent for the Buchwald-Hartwig amination of aryl bromides **1** with amines **2** to give *N*-aryl amines **3**, performing similar to, and sometimes better than, toluene in a range of examples (Figure 1C). Aminations with both primary and secondary amines and aryl bromides possessing various electronic and steric properties, including heterocycles were successfully explored. To demonstrate the synthetic utility of TMO as a solvent, a Buchwald-Hartwig amination for the synthesis of a key intermediate used in the synthesis of the SMO (smoothened) receptor antagonist SEN826 was carried out. Significantly, our studies have revealed that reactions using Cs_2CO_3 as base performed better (in terms of yield) in TMO compared to those in toluene. Green metrics such as Process Mass Intensity and Resource Mass Efficiency further support the positive benefits of using TMO in Buchwald-Hartwig aminations. Additionally, TMO was shown to result in reduced palladium content in the final isolated compounds, leading to benefits in both elemental sustainability and regulatory grounds.

RESULTS AND DISCUSSION

SODIUM *tert*-BUTOXIDE BASE

To start, reaction conditions of $Pd(dba)_2$ (10 mol%) in combination with (±)-BINAP (15 mol%) in toluene at 110 °C for 16 h with NaO*t*-Bu were selected due to their widespread use.[18] Using these conditions, the Buchwald-Hartwig amination of 2-bromotoluene **1a** with piperidine in toluene gave tertiary amine **3a** in 88% yield (Scheme 1). Pleasingly, use of TMO delivered a comparable result, with tertiary amine **3a** being formed in 82% yield. This confirmed the potential of using TMO in this reaction and the scope was further explored (Scheme 1). Buchwald-Hartwig amination of aryl bromides **1** with electron withdrawing and electron donating substituents in the *ortho*-, *meta*- and *para*- positions with piperidine worked well. The reactions in TMO generated tertiary amines **3a-e** with good to excellent yields (76–95%), more or less identical to those achieved in toluene (84–98%) (Scheme 1). However, 1-bromo-4-nitrobenzene gave **3f** in lower yields (51% in TMO and 55% yield in toluene), although a higher yield was possible using Cs_2CO_3 in TMO (*vide infra*). Our attention then turned to reaction of heteroaryl bromides with piperidine. 2-Pyridinyl, 5-pyrimidinyl and the more sterically hindered 5-quinolinyl coupled products (**3g**, **3h** and **3i** respectively) were all obtained in good yields in TMO (76−79%). Even coupling of 8-bromocaffeine was possible, giving complex tertiary amine **3j** (48% yield). Primary amines were equally successful in TMO and toluene, with only mono-arylation occurring. As noted by Wolfe and Buchwald,[18] the steric hindrance associated with BINAP discourages a second *N*-arylation. Using furfurylamine, which is readily sourced from biomass and is a component of the *N*-aryl-furfurylamine moiety in the diuretic and hypertensive agent furosemide,[34] secondary amines **3k-m** were formed in 81−98% yield in TMO (compared to 78−96% in toluene). Aniline and *n*-hexylamine gave secondary amines **3n-3q** in 85−98% yield in TMO, with comparable yields in

toluene (82−97%). The coupling of heteroaryl amines in TMO was also possible with 2-aminopyrimidine and 2-bromoanisole giving secondary amine **3r** in 95% yield, compared to 98% in toluene.

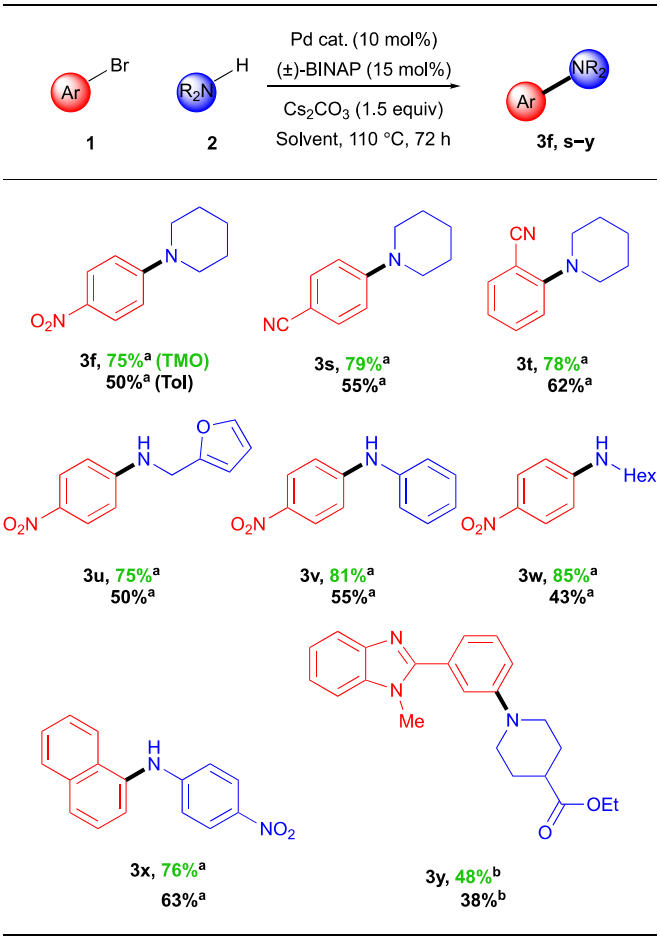


Scheme 1. Comparison of TMO and toluene as solvent for Buchwald-Hartwig amination with NaO*t*-Bu as base. Aryl bromide **1** (1.0 equiv, 1.0 mmol), amine **2** (1.1 equiv, 1.1 mmol), $Pd(dba)_2$ (0.10 equiv, 0.10 mmol), (±)-BINAP (0.15 equiv, 0.15 mmol), NaO*t*-Bu (1.5 equiv, 1.5 mmol),

solvent (5 mL). Purification by flash column chromatography. Yields in green (TMO solvent); Yields in black (toluene solvent).

CAESIUM CARBONATE BASE

Wolfe and Buchwald have advocated the use of Cs_2CO_3, a weaker base than NaO*t*-Bu, for the coupling of base- and nucleophile-sensitive aryl bromides such as those containing nitro and nitrile substituents.[18,35] Therefore, some representative examples were explored in TMO and toluene using 10 mol% $Pd(dba)_2$ and 15 mol% (±)-BINAP under typical Cs_2CO_3 reaction conditions (Scheme 2). The coupling of 1-bromo-4-nitrobenzene with piperidine using Cs_2CO_3 in TMO gave tertiary amine **3f** in only 30% yield after 16 h (compared to 51% with NaO*t*-Bu). However, it was noted that the crude reaction mixture from the Cs_2CO_3 reaction contained unreacted starting materials. Hence, the reaction time with Cs_2CO_3 based was increased to 72 h and a good yield of tertiary amine **3f** (75%) was obtained. Using Cs_2CO_3 and a 72 h reaction time in TMO, other base- or nucleophile-sensitive aryl bromides were investigated and amines **3s**−**3x** were isolated in 75−85% yield. In contrast, consistently lower yields of amines **3f** and **3s**−**3x** (43−63% yield) were obtained in toluene under otherwise identical reaction conditions. This may be related to the solubility of Cs_2CO_3. It has been noted that Cs_2CO_3 is virtually insoluble in toluene and it has been proposed that the deprotonation step occurs at the solid/liquid phase boundary.[21,36,37] In addition, with Cs_2CO_3 in toluene, amine deprotonation is believed to be rate-determining.[36]



Scheme 2. Comparison of TMO and toluene as solvent for Buchwald-Hartwig amination with Cs_2CO_3 as base. [a] Aryl bromide **1** (1.0 equiv, 1.0 mmol), amine **2** (1.1 equiv, 1.1 mmol), $Pd(dba)_2$ (0.10 equiv, 0.10 mmol), (±)-BINAP (0.15 equiv, 0.15 mmol), Cs_2CO_3 (1.5 equiv, 1.50 mmol), solvent (5 mL). Purification by flash column chromatography. [b] Aryl bromide **1** (1.0 equiv, 1.0 mmol), amine **2** (1.1 equiv, 1.1 mmol), $Pd(OAc)_2$ (0.05 equiv, 0.05 mmol), (±)-BINAP (0.075 equiv, 0.075 mmol), Cs_2CO_3 (3.0 equiv, 3.0 mmol), solvent (5 mL). Purification by recrystallisation. Yields in green (TMO solvent); Yields in black (toluene solvent).

We hypothesised that a small increase in the solubility of Cs_2CO_3 in TMO compared to toluene could account for the higher yielding reactions in TMO. ICP-MS analysis (see Supplementary

Information, section S4) of each solvent after stirring with Cs_2CO_3 under reaction conditions (72 hours, 110 °C) confirmed that in toluene the Cs concentration was below quantifiable levels (<0.6 ppb). In TMO, the Cs concentration was quantified at 484 ppb. Several orders of magnitude higher concentrations of Cs logically account for the observed difference in performance of the two solvents with this particular base, especially if amine deprotonation is the rate-determining step.[21,36]

To further demonstrate the utility of carrying out Buchwald-Hartwig aminations in TMO, our methodology was extended to the synthesis of tertiary amine **3y** which is an intermediate in the synthesis of drug candidate SEN826 (Figure 1A), a SMO (smoothened) receptor antagonist. In the synthesis by Betti *et al.*[16] the Buchwald-Hartwig coupling reaction was carried out in toluene and employed Cs_2CO_3 presumably due to the nucleophile-sensitive ester group. In our hands, a higher yield of amine **3y** was obtained in TMO (48%) than in toluene (38%), consistent with the other Cs_2CO_3 examples (Scheme 2). In both reactions, amine **3y** was isolated by recrystallisation avoiding large amounts of solvent use in flash column chromatography.

METRIC ASSESSMENT

An assessment using the CHEM21 Metric Toolkit (see supplementary file *CHEM21 Metric Toolkit Results*) was performed on a selection of the reactions above to ascertain the relative greenness of this methodology.[38] The results are summarized in Table 1. For this study, we compared Atom Economy (AE), Reaction Mass Efficiency (RME) and Process Mass Intensity (PMI). PMI was additionally split into "PMI overall" that considers materials used for the reaction and work-up, and "PMI reaction" that only covers the reagents required for the reaction itself.

Arylated amines **3a**, **3f**, **3h** and **3k** were formed in the presence of NaO*t*-Bu as the base and for these reactions RME and PMI metrics were predominately dictated by yield when comparing TMO to toluene. Amine **3a** was obtained in a higher yield in toluene and therefore PMI and RME were marginally improved relative to TMO. Amines **3f**, **3h** and **3k** are all examples where TMO produced higher isolated yields and therefore PMI and RME are higher than in toluene. AE, a measure of the amount of the reactants' atoms that end-up in the product, is unaffected by yield and molar excesses. In our selected Buchwald-Hartwig aminations, AE ranged from 67-82% because of the atomic losses due to the Br salt produced. Higher AEs were seen when larger reactants are coupled, with the synthesis of amine **3y** giving the highest value of 81.8%. Across the amines **3f-3k**, the influence of yield and AE on PMI can be seen. For example, amine **3h** in TMO and amine **3k** in toluene have relatively similar yields (77% vs 78% respectively) but the higher AE for amine **3k** (74.9%) transfers into a better PMI. Amine **3v** was prepared using Cs_2CO_3 as base, and in this instance the much higher yields observed in TMO (81% vs 55%, TMO vs toluene) translated into significantly improved PMI (90.4 vs 136.5) and RME (56.9 vs 38.5). Amine **3y** was also synthesised using Cs_2CO_3 as the base, and although yields in both solvents were below 50%, the higher AE transferred into reasonable PMIs and RMEs.

Table 1. Metric assessment for a selection of Buchwald-Hartwig aminations performed in TMO or toluene solvent

	3a		**3f**		**3h**		**3k**		**3v**		**3y** – final step*	
Solvent	**Tol**	**TMO**	**Tol**	**TMO**	**Tol**	**TMO**	**Tol**	**TMO**	**Tol**	**TMO**	**Tol**	**TMO**
Yield / %	87	82	50 (47)	75 (74)	75	77	78	99 (86)	55	81	38	48
PMI overall[a]	101.7	106.8	154.7 (160)	100.9 (102)	126.4	120.1	82.7	64.4 (73.4)	136.3	90.4	118.0	90.3

PMI reaction[b]	32.1	32.3	51.3 (50)	32.2 (32)	39.8	36.2	26.3	19.7 (21.9)	45.2	28.9	42.8	32.0
RME	57.7	54.0	34.4 (32.4)	51.8 (50.7)	48.6	50.2	56.9	71.7 (62.3)	38.5	56.9	30.2	37.9
AE / %	68.4		71.8		66.9		74.9		72.8		81.8	

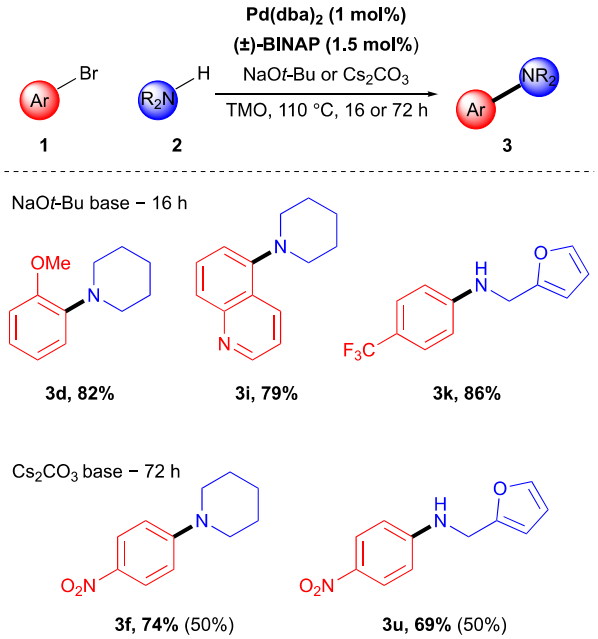
Metrics calculated using the CHEM21 Metrics Toolkit, spreadsheet for calculations available in the supplementary information. Tol = toluene; PMI = Process Mass Intensity; RME = Reaction Mass Efficiency; AE = Atom Economy; a = "PMI overall" includes contributions from work-up; b = "PMI reaction" only covers the reagents used for the reaction itself (reactants, solvent, catalyst, base) and omits work-up chemicals; for **3f** and **3k** the values in parentheses ( ) are for reactions performed with the loading of $Pd(dba)_2$ reduced to 1 mol% and (±)-BINAP reduced to 1.5 mol%; for **3y** the metrics assessment only covers the final Buchwald-Hartwig coupling step and this used the lower 5 mol% loading of $Pd(OAc)_2$ with a 7.5 mol% loading of (±)-BINAP. *Synthesis of **3y** used the lower 5 mol% loading of $Pd(OAc)_2$ with a 7.5 mol% loading of (±)-BINAP.

PALLADIUM SUSTAINABILITY CONSIDERATIONS

Palladium is a metal of wide utility as a catalyst, finding use in catalytic convertors, hydrogenation/dehydrogenation reactions and for an array of cross-coupling reactions, Buchwald-Hartwig amination being one such example. Palladium is a precious metal, and as such its relatively low natural abundance means it has medium to long-term supply risks.[39,40] Palladium's usefulness in catalysis, coupled with concerns over diminishing global supplies, means that it is widely viewed as a critical element, and therefore one where a more sustainable approach to its use is necessary.[41,42]

Where substitution of a critical element has proven impossible, and where recovery and re-use is currently uneconomical, the next most sustainable approach is to develop improved catalytic

systems that permit lower quantities of the critical element required. Reduction in the $Pd(dba)_2$ and (±)-BINAP loading in TMO (Scheme 3) was explored initially when employing NaO*t*-Bu as a base. The $Pd(dba)_2$ and (±)-BINAP ratio was maintained at 1:1.5 throughout, thus any changes in Pd loading correspond to an equivalent change in ligand loading. The yield of amine **3d** remained high (82%) using 1 mol% of $Pd(dba)_2$, comparing well to the yield of 95% when 10 mol% Pd was used, but a lower yield (50%) was obtained when further reducing the catalyst loading to 0.5 mol% Pd. For amine **3i**, lowering the $Pd(dba)_2$ loading from 10 to 1 mol% did not reduce the isolated yield, which remained at 79%. For amine **3k**, a reduction in Pd loading lowered the isolated yield from 98% to 82%. However, this remained marginally higher than the 78% yield obtained using the highest catalyst loading with toluene as the solvent. Despite the lower mass of $Pd(dba)_2$ and (±)-BINAP, the reduction in amine **3k** yield with the 1 mol% loading negatively affected the metrics (Table 1, value in parentheses); PMI increased by 9 and RME was reduced by 9.4. This highlights the significant contribution still made by yield in process efficiency.



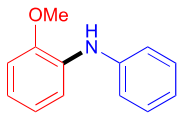
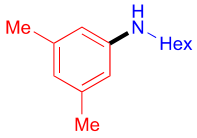
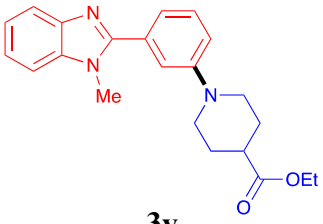
Scheme 3. Aryl bromide **1** (1.0 equiv, 1.0 mmol), amine **2** (1.1 equiv, 1.1 mmol), $Pd(dba)_2$ (0.01 equiv, 0.01 mmol), (±)-BINAP (0.015 equiv, 0.015 mmol), NaO*t*-Bu (1.5 equiv, 1.5 mmol) or Cs_2CO_3 (1.5 equiv, 1.50 mmol), TMO solvent (5 mL), 110 °C, 16 hours (NaO*t*-Bu base) or 72 hours (Cs_2CO_3 base). Purification by flash column chromatography. For **3f** and **3u,** values in parentheses ( ) are for identical reactions but using 5 mL toluene as solvent.

Reduction in the loading of $Pd(dba)_2$ and (±)-BINAP in TMO was particularly successful with the Cs_2CO_3 base reactions. A 74% yield of tertiary amine **3f** was obtained using only 1 mol% of Pd, comparable to the 75% yield obtained with 10 mol%. Use of toluene as solvent for amine **3f** also showed a minimal change in yield on reducing catalyst loading, going from 50% (10 mol%) to 47% (1 mol%). Despite this impressive tolerance to catalyst loading reduction, there was minimal change in the metrics for amine **3f** (Table 1, values in parentheses), with barely noticeable shifts in PMI as a result of the catalyst only contributing a very small mass to the overall reagent load. When reducing the catalyst loading further to 0.5 mol% Pd, the yield of amine **3f** was considerably lower (21%). For amine **3t** the switch to the lower 1 mol% Pd loading slightly reduced the yield from 75% to 69%. In the case of both amines **3f** and **3u** the equivalent reactions in toluene at 1 mol% Pd loading (Scheme 3, values in parentheses) were only 50%, reiterating the benefits in using TMO over toluene on elemental sustainability grounds.

The residual Pd that can be present in isolated compounds is problematic, especially when intended for applications in the pharmaceutical industry, and so ICP-MS analysis of isolated samples of amines **3n**, **3q** and **3y** (produced in both solvents) was conducted to establish the Pd content (Table 2, further details in Supplementary Information, section S4). In all three compounds, the detected levels of residual Pd were lower when produced in TMO than in toluene. For amines **3n** and **3q**, the values are below the pharmaceutical regulatory maximum of 5 ppm,[43,44]

while for amine **3y** they are considerably higher and these samples would require further purification before use in a drug development setting. Nevertheless, these preliminary data indicate that TMO offers a tangible benefit in improving the sustainable use of Pd for Buchwald-Hartwig amination by both allowing lower catalyst loadings and reduced Pd contamination in the isolated product.

Table 2. ICP-MS determined residual ppb Pd content for isolated samples of compounds **3n**, **3q** and **3y** prepared in either TMO or toluene

	 **3n**	 **3q**	 **3y**
Pd content when synthesised in TMO / ppm	0.7861	2.4204	38.0947
Pd content when synthesised in toluene / ppm	1.4267	3.6600	46.7501

Details for sample preparation and ICP-MS procedure can be found in the experimental methods section and the supplementary information.

CONCLUSION

2,2,5,5-Tetramethyloxolane (TMO) was successfully applied as the solvent in a range of palladium catalysed Buchwald-Hartwig amination reactions. A broad substrate scope was demonstrated by the combination of different (hetero)aryl bromides and amines. Significantly, higher yields were obtained in TMO compared to toluene when Cs_2CO_3 was used as a base. ICP-MS analysis indicates that the reason for this enhanced performance in TMO may be due to the greater solubilisation of

Cs^+ ions. Reduction of Pd catalyst loading, from the original 10 mol% down to 1 mol%, was found possible for the TMO reactions screened with minimal loss of yield. Furthermore, the preparation of a key intermediate in the synthesis of drug candidate SEN826 was accomplished in TMO. Preliminary ICP-MS results also indicate an added benefit of using TMO as the solvent as this led to reduced residual Pd content in the selected isolated compounds screened. A metric assessment indicated that TMO enhanced RME and PMI for several reactions, primarily dictated by the higher yields for some substrates. Given the hazards presented by toluene, TMO can now be considered as an appealing alternative to toluene and other available ethers and bio-based solvents for Buchwald-Hartwig aminations. This study highlights the significant potential offered by TMO as a solvent for important cross-coupling reactions in the synthesis of bioactive compounds, particularly with the additional benefits seen in base sensitive substrates and the reduced Pd content in the final isolated compounds.

EXPERIMENTAL METHODS

^{1}H NMR (400 MHz) and ^{13}C (101 MHz) NMR spectra were recorded on a Joel ECX-400 instrument. Chemical shifts (δ in ppm) were referenced to residual solvent peaks ($CDCl_3$ at δ_H 7.26 ppm, δ_C 77.0 ppm and DMSO-d_6 at δ_H 2.50 ppm, δ_C 39.52 ppm). Coupling constants (*J* values) are given in Hz and s, d, t, q, quin, dd, ddd and td, m and br abbreviations corresponds to singlet, doublet, triplet, quartet, quintet, double doublets, double double doublets, triple doublets, multiplets and broad respectively. ^{13}C NMR spectra were assigned using DEPT 135 experiments. Melting points were measured on a Stuart SMP20 melting point apparatus. Electrospray high resolution mass spectra were recorded on a Bruker Daltronics microOTOF spectrometer. Flash column chromatography was carried out using Sigma-Aldrich silica gel (220-440 mesh). Thin layer chromatography was carried out using Merck F_{254} aluminium-backed silica plates and were

visualised by UV (254 nm) or stained using aqueous acidic $KMnO_4$. Celite® 545 purchased from Sigma-Aldrich was used for filtration. Petrol Ether refers to the fraction of petroleum ether boiling in the range 40–60 °C. EtOAc refers to ethyl acetate, Et_2O refers to diethyl ether, TMO refers to 2,2,5,5-tetramethyloxolane, (±)-BINAP refers to racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, $Pd(dba)_2$ refers to bis(dibenzylideneacetone)palladium(0), NaO-*t*Bu refers to sodium *tert*-butoxide and Cs_2CO_3 refers to caesium carbonate.

TMO was synthesized following a literature procedure,[31] by the ring closure dehydration of 2,5-dimethyl-2,5-hexanediol (purchased from Sigma-Aldrich) in the presence of a H-beta-zeolite catalyst (CZB 150). TMO and toluene were dried over 3 Å molecular sieves purchased from Alfa Aesar and calcined at 300 °C prior to use. All reactions were carried out under oxygen-free Ar or N_2 atmosphere. $Pd(dba)_2$, (±)-BINAP, NaO-*t*Bu, piperidine, furfurylamine, aniline, hexylamine, 1,2-phenylenediamine, 3-bromobenzaldehyde, sodium bisulfite, 4-bromotoluene, 2-bromotoluene, 1-bromo-3,5-dimethylbenzene, 4-bromobenzotrifluoride, 1-bromo-4-nitrobenzene, 2-bromobenzonitrile and 2-bromopyridine were all purchased from Sigma-Aldrich. 4-bromobenzonitrile was purchased from Alfa Aesar. Cs_2CO_3 and methyl iodide was purchased from Acros Chemicals and 2-bromotoluene was purchased from BDH Chemicals and were all used without further purification. HCZB 150E was a gift from Clariant and was calcined at 300 °C prior to use. Details for the synthesis and characterization for 2-(3-bromophenyl)-1H-benzimidazole and 2-(3-Bromophenyl)-1-methylbenzimidazole, precursors to amine **3w**, can be found in the supplementary information.

General procedure with NaOt-Bu as base: A round bottomed flask (25 mL) charged with $Pd(dba)_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.093 g, 0.15 mmol, 0.15 equiv) and a NaO*t*-Bu (0.144 g, 1.50 mmol, 1.50 equiv) was evacuated and placed under a N_2 atmosphere. A

solution of aryl bromide (1.00 mmol, 1.00 equiv) in dry toluene or dry TMO (5 mL) was added followed by the amine (1.10 mmol, 1.10 equiv). The resulting mixture was stirred and heated at 110 °C for 16 h. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (10 mL) and the solids were removed by filtration through Celite®. The solids were washed with Et_2O (2 × 10 mL) and the filtrate was evaporated under reduced pressure to afford the crude product, each of which was purified by flash column chromatography.

General procedure with Cs_2CO_3 as base: A round bottomed flask (25 mL) charged with $Pd(dba)_2$ (0.058 g, 0.10 mmol, 0.10 equiv), (±)-BINAP (0.093 g, 0.15 mmol, 0.15 equiv) and Cs_2CO_3 (0.488 g, 1.50 mmol, 1.50 equiv) was evacuated and placed under a N_2 atmosphere. A solution of aryl bromide (1.00 mmol, 1.00 equiv) in dry toluene or dry TMO (5 mL) was added followed by the amine (1.10 mmol, 1.10 equiv). The resulting mixture was stirred and heated at 110 °C for 72 h. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL) and the solids were removed by filtration through Celite®. The solids were washed with Et_2O (2 × 5 mL) and the filtrate evaporated under reduced pressure to afford the crude product, each of which was purified by flash column chromatography.

General procedure for 1 mol% catalyst loading: A round bottom flask (25 mL) charged with $Pd(dba)_2$ (0.006 g, 0.01 mmol, 0.01 equiv), (±)-BINAP (0.009 g, 0.015 mmol, 0.015 equiv) and base (1.50 mmol, 1.50 equiv, NaO*t*-Bu or Cs_2CO_3) was evacuated and placed under a N_2 atmosphere. A solution of aryl bromide (1.00 mmol, 1.00 equiv) in dry toluene or dry TMO (5 mL) was added followed by the amine (1.10 mmol, 1.10 equiv). The resulting mixture was stirred and heated at 110 °C for 16 – 72 h). The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (5 mL) and the solids were removed by filtration through Celite®.

The solids were washed with Et_2O (2 × 5 mL) and the filtrate evaporated under reduced pressure to afford the crude product, each subsequently purified by flash column chromatography.

Full details for procedure, isolation and characterisation for each compound synthesised can be found in the supplementary information.

ICP-MS Analysis. For Cs-content by ICP-MS the samples were prepared as follows: under inert conditions (both solvents dried, toluene from a dry solvent still and TMO distilled over CaH_2 and stored under 3 Å molecular sieves under N_2) 1.5 mmol of Cs_2CO_3 was placed into 5 mL of each solvent and stirred at 110 °C for 72 hours. The suspensions were filtered (Whatman PTFE syringe filters) to remove undissolved Cs_2CO_3 and submitted for ICP-MS analysis. For residual Pd-content a portion of the isolated samples as prepared in the experimental section in the supplementary information were used with no further purification. Prior to sample preparation, all glassware and digestion vessels used were cleaned by refluxing conc. nitric acid at 180°C to ensure that they were free of trace metal contamination. Each sample, and a blank (no sample) was accurately weighed and placed into separate digestion vessels followed by addition to each vessel of 8 mL of conc. nitric acid (trace metal grade) and 2 mL of 30% H_2O_2. The digestion vessels were sealed and placed into a microwave, with a thermocouple in one digestion vessel in order to monitor the temperature of the liquid. The samples were ramp-heated to 200°C over a period of 30 minutes, followed by 15 minutes maintained heating at 200°C. Upon cooling the contents of each digestion vessel was diluted with distilled water to 100 mL in a conical flasks, separate dilution factors for each sample are given in the supplementary information. 10 mL of each sample was placed in a 15 mL sterilized centrifuge tube for ICP-MS analysis. Prior to sample analysis, calibration curves for Pd and Cs were prepared. Samples, alongside the blank, were then analyzed using an Agilent 7700 series ICP-MS, the results for each element fitted against the calibration

curve. The result recorded was multiplied by the sample-specific dilution factor, to produce the concentration for each element in the samples received.

ASSOCIATED CONTENT

Supporting Information. General experimental conditions, methods of analysis and list of reagents; detailed experimental procedures and characterisation for all compounds, ^{1}H- and ^{13}C-NMR spectra for each compound; investigation into reducing the loading of catalyst when using TMO as solvent; study of alternative solvents for work-up; ICP-MS analysis. A spreadsheet using the CHEM21 Metrics Toolkit for assessment of the preparation of several samples is available as a standalone file (*CHEM21 Metric Toolkit Results*), with separate tabs for each reaction. See DOI: 10.1039/x0xx00000x

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Author Contributions

B.R.T. planned and performed the experiments. T.J.F., J.S., J.M. and P.O'B supervised the work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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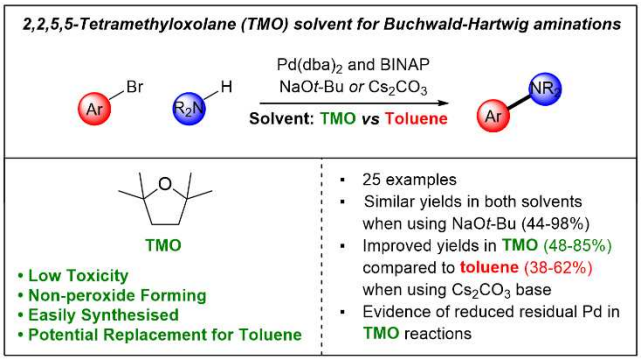

SYNOPSIS

TMO is a suitable replacement solvent for toluene in Buchwald-Hartwig aminations, the former outperforms the latter for reactions using Cs_2CO_3 base