

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

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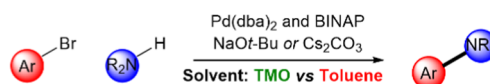
Supporting Information

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 NaOt-Bu was used as the base, similar yields were obtained in toluene and TMO.

In contrast, using Cs₂CO₃, 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.

KEYWORDS: Buchwald–Hartwig aminations, green metrics, palladium catalyst, solvent substitution, 2,2,5,5-tetramethyloxolane

2,2,5,5-Tetramethyloxolane (TMO) solvent for Buchwald–Hartwig aminations



TMO

- Low Toxicity
- Non-peroxide Forming
- Easily Synthesised
- Potential Replacement for Toluene

- 25 examples
- Similar yields in both solvents when using NaOt-Bu (44–98%)
- Improved yields in TMO (48–85%) compared to toluene (38–62%) when using Cs₂CO₃ base
- Evidence of reduced residual Pd in TMO reactions

INTRODUCTION

Palladium-catalyzed 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. The main focus of previous work on such aminations has been the development of suitable ligands, in an attempt to increase the substrate scope and 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

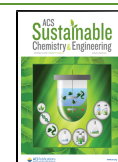
encountered, NMP and DMF have been occasionally utilized.^{2,21–24}

In recent years, the pharmaceutical and fine chemical industries have become interested in the use of safer and more sustainable chemicals, with the replacement of solvents of particular interest due to the large volumes in which they are utilized. 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 substance list.^{29,30} Toluene is suspected of causing damage to fertility, among other health hazards, while 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

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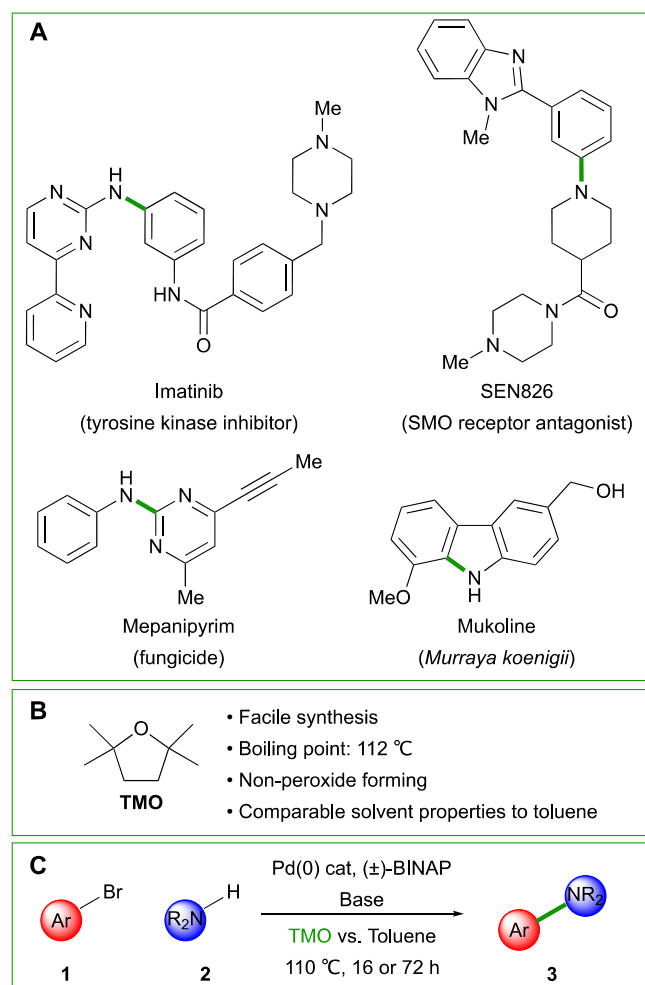


Figure 1. (A) Pharmaceuticals, agrochemicals, and natural products synthesized via Buchwald–Hartwig aminations (bond formed highlighted in green). (B) 2,2,5,5-Tetramethyloxolane (TMO). (C) This work.

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 biocatalyzed synthesis of polyesters.^{31,32} TMO can be synthesized by the H- β -zeolite-catalyzed intramolecular dehydration of 2,5-dimethyl-2,5-hexanediol in very high yields (>95%) and selectivity ($\geq 99\%$). Several possible biobased routes to TMO have recently been assessed by green metrics and followed by preliminary lab-scale synthesis, with biocarbon content confirmed for a sample of the solvent produced from methyl levulinate.³³

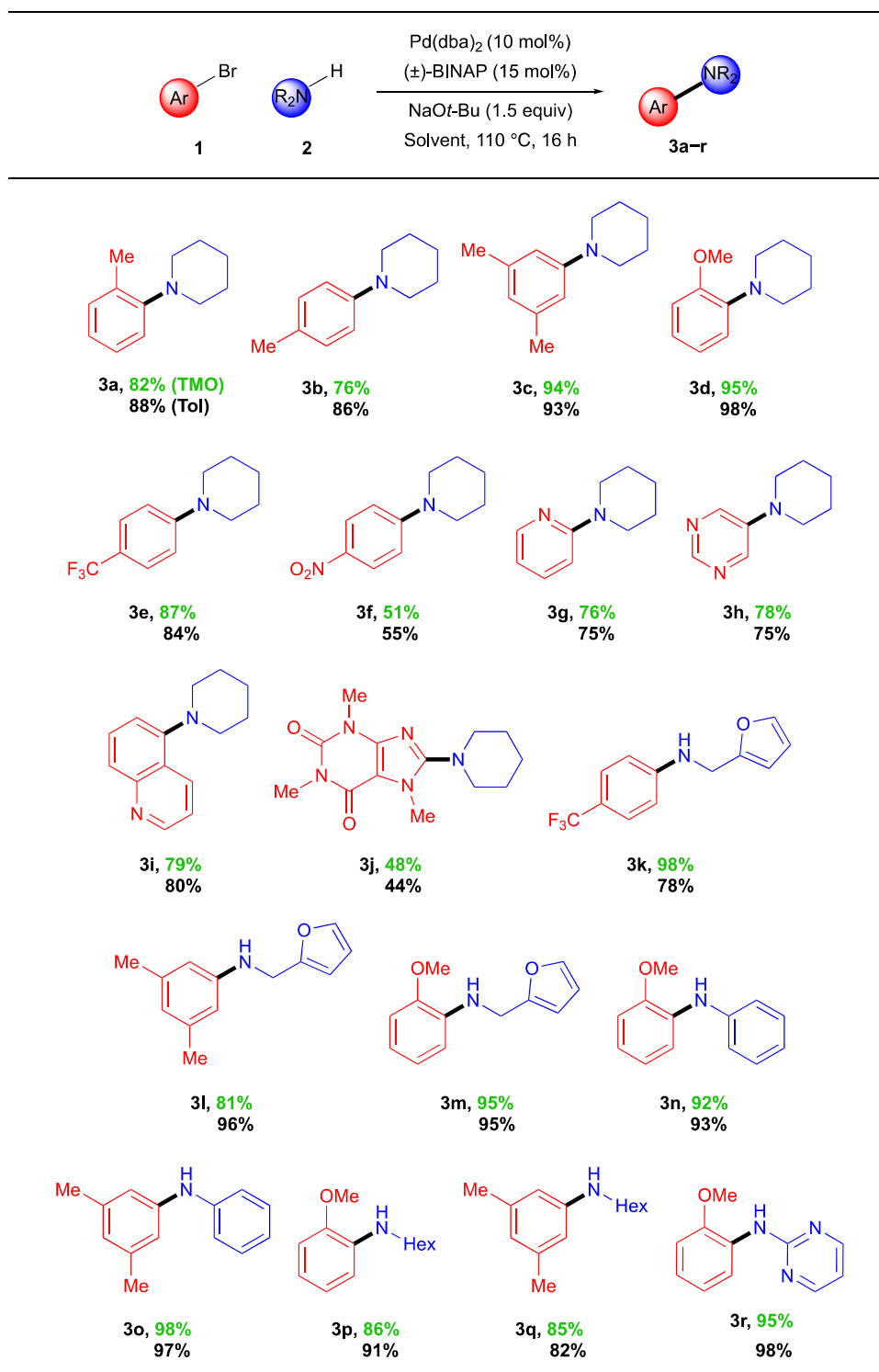
Herein, motivated by the desire to demonstrate that TMO can be applied to other widely employed reactions, we report that TMO is an excellent solvent for the Buchwald–Hartwig amination of aryl bromides **1** with amines **2** to give *N*-arylamines **3**, performing similar to, and sometimes better than, 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 the 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 $\text{Pd}(\text{dba})_2$ (10 mol %) in combination with (\pm)-BINAP (15 mol %) in toluene at 110 °C for 16 h with NaOt-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, the 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 the 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 monoarylation 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–q** 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.

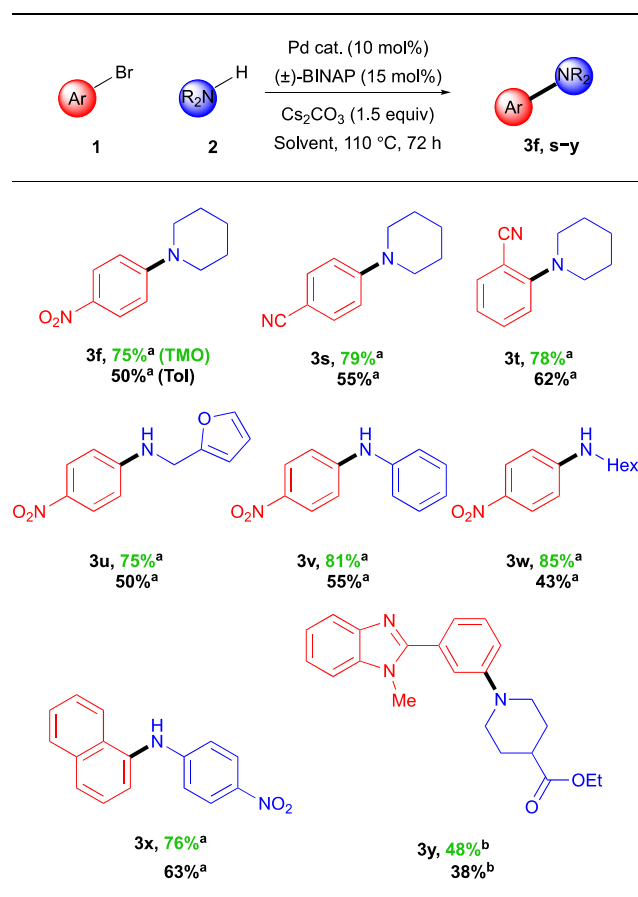
Cesium Carbonate Base. Wolfe and Buchwald have advocated the use of Cs_2CO_3 , a weaker base than NaOt-Bu , for the coupling of base- and nucleophile-sensitive aryl bromides such as those containing nitro and nitrile substituents.^{18,35} Therefore, some representative examples were explored in TMO and toluene using 10 mol % $\text{Pd}(\text{dba})_2$ and 15 mol % (\pm)-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 NaOt-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

Scheme 1. Comparison of TMO and Toluene as Solvent for Buchwald–Hartwig Amination with NaOt-Bu as the Base^a

^aAryl 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), NaOt-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).

to 72 h and a good yield of tertiary amine **3f** (75%) was obtained. Using Cs₂CO₃ and a 72 h reaction time in TMO, other base- or nucleophile-sensitive aryl bromides were investigated and amines **3s–x** were isolated in 75–85% yield. In contrast, consistently lower yields of amines **3f** and **3s–x** (43–63% yield) were obtained in toluene under otherwise

identical reaction conditions. This may be related to the solubility of Cs₂CO₃. It has been noted that Cs₂CO₃ 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 Cs₂CO₃ 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 Cs₂CO₃ as the Base^{a,b}


^aAryl 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), Cs₂CO₃ (1.5 equiv, 1.50 mmol), solvent (5 mL). Purification by flash column chromatography. ^bAryl 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), Cs₂CO₃ (3.0 equiv, 3.0 mmol), solvent (5 mL). Purification by recrystallization. Yields in green (TMO solvent); yields in black (toluene solvent).

We hypothesized that a small increase in the solubility of Cs₂CO₃ in TMO compared to toluene could account for the higher-yielding reactions in TMO. ICP-MS analysis (see the Supporting Information, Section S4) of each solvent after

stirring with Cs₂CO₃ under reaction conditions (72 h, 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 the 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 the drug candidate SEN826 (Figure 1A), an SMO (smoothened) receptor antagonist. In the synthesis by Betti et al.,¹⁶ the Buchwald–Hartwig coupling reaction was carried out in toluene and employed Cs₂CO₃ 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 Cs₂CO₃ examples (Scheme 2). In both reactions, amine **3y** was isolated by recrystallization avoiding large amounts of solvent used in flash column chromatography.

Metric Assessment. An assessment using the CHEM21 Metric Toolkit (see the Supporting 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”, which considers materials used for the reaction and work-up and “PMI reaction”, which only covers the reagents required for the reaction itself.

Arylated amines **3a**, **3f**, **3h**, and **3k** were formed in the presence of NaOt-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 to 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–k**, the influence of yield and AE on PMI

Table 1. Metric Assessment for a Selection of Buchwald–Hartwig Aminations Performed in TMO or Toluene Solvent^a

solvent	3a		3f		3h		3k		3v		3y—final step*	
	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	

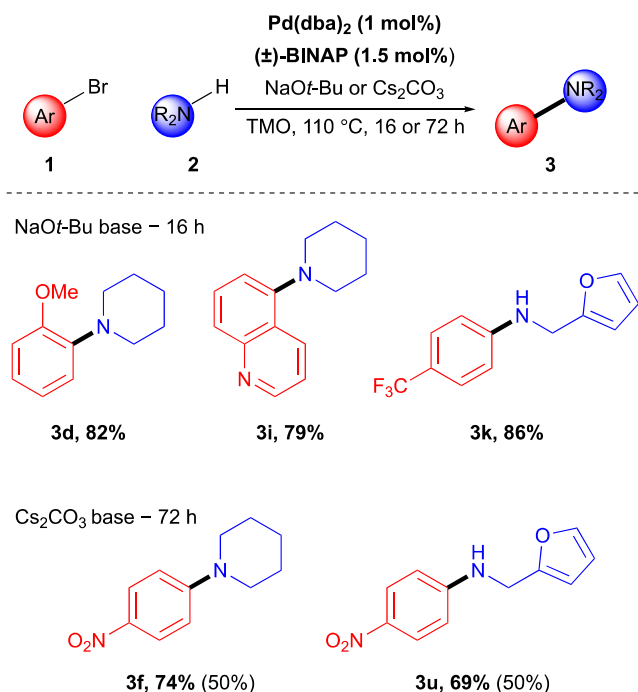
^aMetrics calculated using the CHEM21 Metrics Toolkit, spreadsheet for calculations available in the supporting information. Tol = toluene; PMI = process mass intensity; RME = reaction mass efficiency; AE = atom economy; a = “PMI overall” includes contributions from work-up; b = “PMI reaction” only covers 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.

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 the 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 synthesized 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.

Palladium Sustainability Considerations. Palladium is a metal of wide utility as a catalyst, finding use in catalytic converters, 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 that 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 reuse are 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 $\text{Pd}(\text{dba})_2$ and (\pm) -BINAP loading in TMO (Scheme 3) was explored initially when employing NaOt-Bu as the base. The

Scheme 3. Reduction in Palladium Loading in Reactions with TMO as Solvent.^a



^aAryl Bromide **1** (1.0 equiv, 1.0 mmol), Amine **2** (1.1 equiv, 1.1 mmol), $\text{Pd}(\text{dba})_2$ (0.01 equiv, 0.01 mmol), (\pm) -BINAP (0.015 equiv, 0.015 mmol), NaOt-Bu (1.5 equiv, 1.5 mmol) or Cs_2CO_3 (1.5 equiv, 1.50 mmol), TMO solvent (5 mL), 110 °C, 16 h (NaOt-Bu Base) or 72 h (Cs_2CO_3 base). Purification by flash column chromatography. For **3f** and **3u**, values in parentheses () are for identical reactions but using 5 mL of toluene as the solvent.

$\text{Pd}(\text{dba})_2$ and (\pm) -BINAP ratio was maintained at 1:1.5 throughout, and 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 $\text{Pd}(\text{dba})_2$, 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 $\text{Pd}(\text{dba})_2$ 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 $\text{Pd}(\text{dba})_2$ and (\pm) -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.

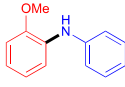
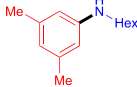
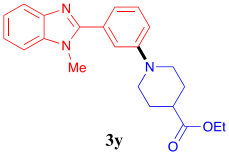
Reduction in the loading of $\text{Pd}(\text{dba})_2$ and (\pm) -BINAP in TMO was particularly successful with the Cs_2CO_3 base reactions. A 74% yield of tertiary amine **3f** was obtained using only 1 mol % of Pd, comparable to the 75% yield obtained with 10 mol %. The use of toluene as the solvent 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 of 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 the Supporting 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 reducing Pd contamination in the isolated product.

CONCLUSIONS

2,2,5,5-Tetramethyloxolane (TMO) was successfully applied as the solvent in a range of palladium-catalyzed 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 the base. ICP-MS analysis indicates that the reason for this enhanced performance in TMO may be due to the greater

Table 2. ICP-MS Determined Residual ppb Pd Content for Isolated Samples of Compounds 3n, 3q, and 3y Prepared in Either TMO or Toluene^a

			
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

^aDetails for sample preparation and the ICP-MS procedure can be found in the [Experimental Section](#) and the [Supporting Information](#).

solubilization 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 the 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 SECTION

¹H NMR (400 MHz) and ¹³C (101 MHz) NMR spectra were recorded on a Joel ECX-400 instrument. Chemical shifts (δ in ppm) were referenced to residual solvent peaks (CDCl₃ 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, td, m, and br abbreviations correspond to singlet, doublet, triplet, quartet, quintet, double doublets, double double doublets, triple doublets, multiplets, and broad, respectively. ¹³C 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 Daltonics microOTOF spectrometer. Flash column chromatography was carried out using Sigma-Aldrich silica gel (220–440 mesh). Thin-layer chromatography was carried out using Merck F₂₅₄ aluminum-backed silica plates and the plates were visualized by UV (254 nm) or stained using aqueous acidic KMnO₄. Celite 545 purchased from Sigma-Aldrich was used for filtration. Petrol ether refers to the fraction of petroleum ether boiling in the range of 40–60 °C. EtOAc refers to ethyl acetate, Et₂O 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 Cs₂CO₃ refers to cesium 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- β -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 an oxygen-free Ar or N₂ 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. Cs₂CO₃ and methyl iodide were 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 [Supporting Information](#).

General Procedure with NaO-*t*Bu as the Base. A round-bottom 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 N₂ 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 Et₂O (10 mL), and the solids were removed by filtration through Celite. The solids were washed with Et₂O (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 Cs₂CO₃ as the Base. A round-bottom 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 Cs₂CO₃ (0.488 g, 1.50 mmol, 1.50 equiv) was evacuated and placed under a N₂ 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 Et₂O (5 mL), and the solids were removed by filtration through Celite. The solids were washed with Et₂O (2 × 5 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 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 the base (1.50 mmol, 1.50 equiv, NaO-*t*Bu or Cs₂CO₃) was evacuated and placed under a N₂ 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 Et₂O (5 mL), and the solids were removed by filtration through Celite. The solids were washed with Et₂O (2 × 5 mL), and the filtrate was evaporated under reduced pressure to afford the crude product, each subsequently purified by flash column chromatography.

Full details for procedure, isolation, and characterization for each compound synthesized can be found in the [Supporting 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 CaH₂ and stored under 3 Å molecular sieves under a N₂ atmosphere), 1.5 mmol of Cs₂CO₃ was placed into 5 mL of each solvent and stirred at 110 °C for 72 h. The suspensions were filtered (Whatman PTFE syringe filters) to remove undissolved Cs₂CO₃ and submitted for ICP-MS analysis. For residual Pd content, a portion of the isolated samples as prepared in the experimental section in the [Supporting Information](#) was 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) were 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% H₂O₂. The digestion vessels were sealed and placed into a microwave, with a thermocouple in one digestion vessel to monitor the temperature of the liquid. The samples were ramp-heated to 200 °C over a period of 30 min, followed by 15 min maintained heating at 200 °C. Upon cooling, the contents of each digestion vessel were diluted with distilled water to 100 mL in a conical flask; separate dilution factors for each sample are given in the [Supporting Information](#). Ten 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

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.1c06292>.

General experimental conditions, methods of analysis and the list of reagents; detailed experimental procedures and characterization for all compounds, ¹H- and ¹³C-NMR spectra for each compound; investigation into reducing the loading of the catalyst when using TMO as the solvent; study of alternative solvents for work-up; ICP-MS analysis ([PDF](#))

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 ([XLSX](#))

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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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Notes

The authors declare no competing financial interest.

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