ARTICLE IN PRESS

Tetrahedron Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The solid copper-mediated C–N cross-coupling of phenylboronic acids under continuous flow conditions

Jennifer Bao [a], Geoffrey K. Tranmer [a,b,*]

[a] *College of Pharmacy, Faculty of Health Science, University of Manitoba, Winnipeg, MB R3E 0T5, Canada*
[b] *Department of Chemistry, Faculty of Science, University of Manitoba, Winnipeg, MB R3T 2N2, Canada*

ARTICLE INFO

Article history:
Received 5 November 2015
Revised 17 December 2015
Accepted 26 December 2015
Available online xxxx

Keywords:
Solid copper-mediated
Arylboronic acid
N-arylation
Continuous flow
C–N coupling

ABSTRACT

We have developed two general methods for the C–N cross-coupling of phenylboronic acids with amines using solid copper flow reactors, in combination with an oxidant. We have developed one method for a C–N arylation reaction which employs a solid copper coil reactor, in combination with *tert*-butyl peroxybenzoate, to give products in moderate isolated yields. We have also developed a general method for the C–N cross coupling of phenylboronic acids using a column packed with solid copper powder, in combination with acetic acid and TEMPO, to give products in isolated yields in excess of 75+%. We have also applied our general copper powder method to generate a library of products which highlights the utility of solid copper flow reactors for C–N cross coupling reactions, generating 16 examples in good yields. Mechanistic implications and future directions are also discussed.

Arylboronic acids are important building blocks which have been used extensively in cross-coupling reactions.[1] The copper-mediated formation of C-heteratom bonds have also become an important synthetic transformation in recent years, and a large pool of potential reactions and coupling partners exist.[2] In particular, the C–N bond forming reaction involving the use of arylboronic acids under copper-mediated conditions[3,4] has been studied since the late 1990's and has served as a synthetically useful tool for the generation of heterocycles[5] and biologically active compounds.[6] In general, these reactions are performed at room temperature in the presence of a copper catalyst (usually $Cu(OAc)_2$) and a mild base, wherein a new C–N bond is formed between an arylboronic acid and an amine. These reactions can be carried out in air, which can offer some synthetic advantages over Buchwald-Hartwig cross-coupling reactions,[7] however, the copper-mediated coupling of arylboronic acids and amines can often require long reaction times (2 days).[8]

In recent years, flow chemistry[9] has become an increasingly important tool in modern organic synthesis, and considerable interest has centered upon the application of flow chemistry techniques toward solving complex chemical problems. Flow chemistry has proven to be superior to batch reaction processes in many ways, largely through the benefits derived from continuous multi-step processing.[10,11] The benefits realized through this technique have been applied to the flow synthesis of natural products,[12] the flow synthesis of heterocycles[13] and in the field of photochemistry where flow techniques have proven to be particularly advantageous.[14,15]

We recently reported on the application of flow chemistry techniques in combination with solid copper flow reactors for bench-top organic synthesis.[16] The rewards are observed in terms of increases in yield and safety, with solid copper flow reactors being used to perform Sonogashira C–C couplings, Ullmann couplings, 1,3-dipolar cycloadditions or macrocyclizations and the first reported use of copper tubing to promote C–N bond formation.[17] Overall, the use of solid copper as part of a flow reactor, either in the form of copper tubing or as copper powder/turnings, has proven to be synthetically versatile and has shown improvements and superiority over equivalent batch reactions. Even though the use of copper-mediated C–N bond formation has become increasingly important in synthetic chemistry, and the implementation of flow chemistry techniques has proven to give numerous synthetic benefits over batch reactions, to the best of our knowledge, the use of a solid copper reactor under continuous flow conditions has yet to be explored for the N-arylation of arylboronic acids. It has been the goal of our research group to investigate the use of solid copper flow reactors for the formation of new C–N bonds as a new paradigm for the synthesis of heterocycles. We plan to develop novel methods for the C–N functionalization of aryl- and alkylboronic acids using a solid copper flow reactor, combining the many benefits of flow chemistry with the use of a

---

* Corresponding author. Tel.: +1 204 474 8358; fax: +1 204 789 3744.
E-mail address: geoffrey.tranmer@umanitoba.ca (G.K. Tranmer).

http://dx.doi.org/10.1016/j.tetlet.2015.12.107
0040-4039/

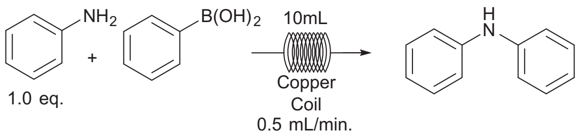
Please cite this article in press as: Bao, J.; Tranmer, G. K. *Tetrahedron Lett.* (2016), http://dx.doi.org/10.1016/j.tetlet.2015.12.107

cost-effective, readily available copper source that is easily scalable, producing a preferred flow technique for the generation of C–N bonds. Herein we report on the use of both copper tubing, and copper powder as a reusable catalyst to invoke the formation of new C–N bonds, through the cross coupling of arylboronic acids and amines.

Initially, we set out to explore the formation for C–N bonds using solid copper flow reactors and looked to the literature for representative methods. To our surprise, other than 'click' chemistry reactions, we could not find any precedence for the solid copper mediated formation of C–N bonds under continuous flow conditions. The solution phase copper-mediated N-arylation of arylboronic acids has been explored, however, using a continuous flow microreactor[18] rather than a solid copper reactor. The article describes a continuous flow procedure which utilizes classic copper-mediated batch conditions ($Cu(OAc)_2$, dichloromethane, base, room temperature) to perform the N-arylation of anilines. In this case however, a microfluidic reactor is used in which starting material is progressed at a rate of 0.2 mL/min, and requires 120 min of residence time for highest rates of conversion. The communication reported only 5 successful C–N coupling products, in moderate yields (56-73%), however, 1.0 equiv of copper acetate is required. We set out to develop an N-arylation reaction which utilized a reusable solid copper reactor as a method to invoke this transformation that was applicable to a wider range of amines, and would set the foundation for a generalized reaction that would not require the addition of any copper catalyst, but rely on the use of a solid copper flow reactor to perform the reaction in much more cost-effective, efficient and scalable manner.

Initially, we set out to optimize the reaction using a solid copper flow reactor through the use of either copper tubing, or a column packed with copper powder. Extensive optimization studies were carried out that varied the copper reactor, solvent, base, oxidant, organoboron reactant (arylboronic acids vs. aryl trifluoroborates) and amine coupling partner. We experienced solubility issues when trying to use aryl trifluoroborates as coupling partners, and as a result, focused our optimization studies solely on the use of arylboronic acids. A summary of the key optimization parameters is highlighted in Table 1. To perform our reactions, we used a Vapourtec R2 pumping module which is connected to an R4 reactor module which held our solid copper flow reactor. The Vapourtec R2 system contains two HPLC-style pumps connected to sample loops which were used to introduce our starting material. Initially, we utilized a 10 mL copper coil which is commercially available from Vapourtec as our solid copper source due to its synthetic utility and the ease in which it can be heated to high temperatures using a Vapourtec R4 reactor module. Our first reactions mimicked 'classic' Chan-Lam reaction conditions, using trimethylamine (TEA) as a base, and 1.0 equivalents (equiv) each of the aniline and boronic acid in dichloromethane (DCM) as solvent. It was only until the base was switched to pyridine that we were able to find desired product. After numerous test reactions, the highest isolated yield we were able to obtain was 24% when the reaction was performed at 13° C and 1.5 equiv of boronic acid was used, with pyridine, DCM and 2.0 equiv of myristic acid. Following several other test reactions, we were unable to surpass the 24% benchmark and decided to alter our optimization reactions to include the addition of an internal oxidant, as in Table 2.

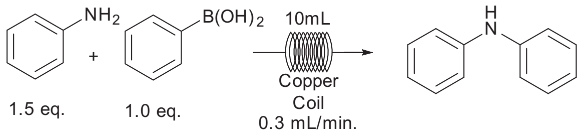
Table 1
Solid copper C–N arylation under classic conditions



Solvent	Base (5.0 equiv)	Temp (°C)	Boronic acid (equiv)	Yield[b]
DCM	Triethylamine	60	1.0	0
DCM	Pyridine	60	1.0	10
DCM	Pyridine	80	1.0	13
DCM	Pyridine	130	1.5[a]	24
Toluene	Pyridine	160	1.0	0

[a] 2.0 equiv of myristic acid used as additive.
[b] Isolated yields (%).

Table 2
Optimization of solid copper coil C–N arylation



Solvent	Oxidant	Oxidant (equiv)	Temp (°C)	Yield[a]
THF	^{t}Bu-Peroxybenzoate	1.5	40	0
2-Propanol	^{t}Bu-Peroxybenzoate	1.5	40	0
DCM	^{t}Bu-Peroxybenzoate	1.5	40	50
MeOH	^{t}Bu-Peroxybenzoate	1.5	40	30
MeOH	^{t}Bu-Peroxybenzoate	0.5	40	11
MeCN	^{t}Bu-Peroxybenzoate	1.5	40	58
MeCN	^{t}Bu-Peroxybenzoate	0.5	40	26
MeCN	Di-^{t}butyl peroxide	1.5	40	0
MeCN	Di-^{t}butyl peroxide	1.5	100	0
MeCN	Hydrogen peroxide	1.5	40	0
MeCN	Benzoyl peroxide	1.5	40	21

[a] Isolated yields (%).

During this phase of the project, we were pleased to discover that the use of *tert*-butyl peroxybenzoate (1.5 equiv) gave superior yields in comparison to our previous efforts. The use of DCM, 1.5 equiv aniline, 1.0 equiv boronic acid, 40° C at a flow rate of 0.3 mL/min gave an isolated yield 50% for diphenylamine. The use of tetrahydrofuran (THF) or 2-propanol did not yield any product, while methanol gave a decreased yield of 30%. We found that acetonitrile (MeCN) gave the highest isolated yields (58%), and due to this result and the fact that we found it easier to work with at higher temperatures, we decided to select MeCN as our solvent of choice for this reaction. We also found that decreasing the equivalents of the oxidant to 0.5 gave a proportional decrease in yield. Several other oxidants were studied, however, only benzoyl peroxide was found to give the desired product, although in a smaller isolated yield of 21%. Further reactions were carried out for optimization purposes which varied solvent, base, oxidant and equivalence of oxidant, however, we were unable to find conditions that were superior to the 58% isolated yield provided by 1.5 equiv of *tert*-butyl peroxybenzoate (^{t}BPB) in MeCN at 40° C.[19]

Mechanistically, one could make the argument that these types of reactions can occur on the surface of the solid copper metal (heterogeneous), or proceed via dissolved copper (homogenous). It is certain, however, that copper metal must be present for the reactions to occur, and that a certain level of copper leaching is often observed when solid copper flow reactors are employed.[16] For our reactions, a copper coil reactor was initially used, and utilized for well over 100+ test-optimization reactions. At this point, a small amount of 'pitting' was observed on the inner surface of the openings of the copper coil reactor, indicating, at the very least, that some copper was leaching from the reactor. In the interest of safety, and as a means to employ a more cost-effective solid copper flow reactor, we continued our optimization reactions using a glass Omnifit column (6.6 × 150 mm) filled with solid copper powder, typically 5.5 cm of column height. We found the copper

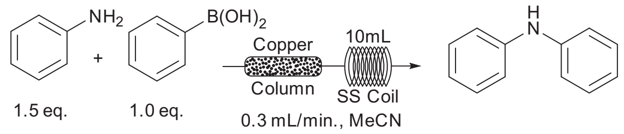
Please cite this article in press as: Bao, J.; Tranmer, G. K. *Tetrahedron Lett.* (2016), http://dx.doi.org/10.1016/j.tetlet.2015.12.107

powder to be much cheaper than the copper coil, was reusable, and was easily heated using the Vapourtec R4 reactor module, offering a more economical, convenient, and reusable solid copper reactor.

To perform this reaction, a glass column was filled with copper powder and connected in-line with a 10 mL stainless steel coil which was used to incubate the reaction stream after it had passed through the solid copper powder. A summary of the optimization process is detailed in Table 3 and contains representative reactions that lead to the development of optimized reaction conditions. Initially, we replicated the optimized reaction conditions that were previously developed for use with a copper coil, which had previously resulted in a 58% isolated yield (1.5 equiv aniline, 1.0 equiv boronic acid, 1.5 equiv *tert*-butyl peroxybenzoate, MeCN). In this case, however, the reaction only offered a 21% isolated yield when the copper-filled column was used. The addition of base (TEA) did not result in an increased yield, while other oxidants such as hydrogen peroxide or benzoyl peroxide did not improve the yield. When a mixture of oxidants were used, ^{t}BPB:D^{t}BP (1.0:3.0), the yield increased to 51%, while acetic acid (CH_3CO_2H), in combination with di-*tert*-butyl peroxide (D^{t}BP; 1.0:3.0, respectively), gave 36% when 2.0 equiv of TEA was used. We found that the base was not required, giving 45% yield in the absence of TEA, while the reaction performed poorly under these conditions when MeOH, DCM and toluene were used, 12%, 22%, and 21%, respectively. An increase in the ratio of the oxidant (CH_3CO_2H:D^{t}BP; 1.0:4.0) gave 54% isolated yield, however, a decrease in the oxidant ratio (CH_3CO_2H:D^{t}BP; 1.0:1.5) gave a similar yield of 43%. After additional optimization reactions, we found that (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) served as the best oxidant and a CH_3CO_2H:TEMPO ratio of 1.0:1.5 provided for a yield of 51%. Our previous reactions required 1.5 equiv of the corresponding aniline, and we found that increasing this amount to 3.0 equiv of aniline resulted in our highest isolated yield to that date of 71%. Interestingly, an increase in the flow rate to 0.5 mL/min did result in a proportionate decrease in yield, indicating a sufficiently rapid reaction. Our highest yields were realized with we used an extra equivalent of acetic acid (2.0 equiv), resulting in a very good isolated yield of 79%. At this point we felt that we had sufficiently explored various reaction optimization conditions, and settled upon the use of 3.0 equiv aniline, 1.0 equiv boronic acid, CH_3CO_2H:TEMPO (1.0:1.5), and 0.3 mL/min in MeCN as our optimized reaction conditions[20] that we would apply to the synthesis of a library of products to examine the scope of this solid copper mediated continuous flow reaction.

The results of the library synthesis can be seen in Table 4, where each reaction was found to give appreciable amounts of desired product. In the cases where the yields were initially low, some reactions were performed again with 2.0 equiv of acetic acid (AA) which appeared to give the highest isolated yields, however, some reactions appeared to progress smoothly when 1.0 equiv of AA was used. In general, the reactions involving the use of phenylboronic acid appeared to perform the best, giving good isolated yields up to 79% and 82% (entry **1**, **3**) when 2.0 equiv of acetic acid were used. The reactions involving the use of 4-chlorophenylboronic acid appeared to perform poorly, giving only moderate isolated yields, down to a low of 25%, entry **14** even with 2.0 equiv of acetic acid. The reactions involving the use of *p*-tolylboronic acid appeared to progress smoothly in a range of 45–71% isolated yields. No general trends in the yields can be discerned at this point, other than morpholine giving the lowest yields, while the majority of the boronic acids had been consumed during the reactions giving high conversions. Several reactions were performed using the copper coil with our optimized reaction conditions, (2.0:1.5 of acetic acid:TEMPO) in place of the copper powder column. For these examples, entries **1**, **7**, and **12**, the yields were comparable or slightly higher than the copper powder column. Overall, the library results detail that we have developed a protocol using solid copper flow reactors that is capable of mediating the C–N arylation reaction of phenylboronic acids in moderate to good yields.[19] To date, there is still a need to improve the yields observed for these types of reactions and we expect to report our future findings in due course. However, we believe that these results serve as an excellent stepping stone from which to develop solid copper mediated C–N cross coupling reactions for the

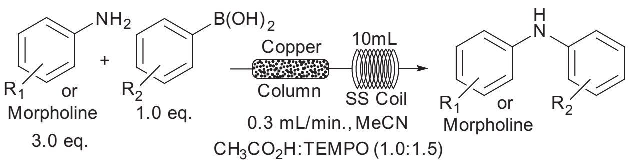
Table 3
Optimization of solid copper column C–N arylation



Base	Oxidant	Oxidant (equiv)	Solvent	Yield[a]
–	^{t}Bu-Peroxybenzoate	1.5 equiv	MeCN	21
2.0 equiv TEA	^{t}Bu-Peroxybenzoate	1.0 equiv	MeCN	23
2.0 equiv TEA	Hydrogen peroxide	1.0 equiv	MeCN	0
2.0 equiv TEA	Benzoyl peroxide	1.0 equiv	MeCN	18
2.0 equiv TEA	^{t}BPB:D^{t}BP	1.0:3.0	MeCN	51
2.0 equiv TEA	^{t}BPB:D^{t}BP	0.5:3.0	MeCN	30
2.0 equiv TEA	Acetic acid:D^{t}BP	1.0:3.0	MeCN	36
–	Acetic acid:D^{t}BP	1.0:3.0	MeCN	45
–	Acetic acid:D^{t}BP	1.0:3.0	MeOH	12
–	Acetic acid:D^{t}BP	1.0:3.0	DCM	22
–	Acetic acid:D^{t}BP	1.0:3.0	Toluene	21
–	Acetic acid:D^{t}BP	1.0:4.0	MeCN	54
–	Acetic acid:D^{t}BP	0.5:3.0	MeCN	30
–	Acetic acid:D^{t}BP	1.0:1.5	MeCN	43
–	Acetic acid:TEMPO	1.0:1.5	MeCN	51
3.0 equiv Aniline	Acetic acid:TEMPO	1.0:1.5	MeCN	71
3.0 equiv Aniline	Acetic acid:TEMPO	1.0:1.5	MeCN	70[b]
3.0 equiv Aniline	Acetic acid:TEMPO	2.0:1.5	MeCN	79

[a] Isolated yields (%);
[b] Flow rate = 0.5 mL/min; Triethylamine (TEA); ^{t}Butyl peroxybenzoate (^{t}BPB); Di-^{t}butyl peroxide (D^{t}BP).

Table 4
C–N Arylation library using solid copper column



Entry	Amine	Boronic acid	Yield[a]
1	Aniline	Phenylboronic acid	71/79[b]/72[c]
2	2,4,6-Trimethylaniline	Phenylboronic acid	52[b]/68[c]
3	2-Methoxyaniline	Phenylboronic acid	66/82[b]
4	4-Chloroaniline	Phenylboronic acid	68/72[b]
5	4-Fluoroaniline	Phenylboronic acid	71[b]
6	2,4-Dimethylaniline	Phenylboronic acid	64/77[b]
7	Morpholine	Phenylboronic acid	51/57[b]/65[c]
8	Aniline	4-Methylphenylboronic acid	71/66[b]
9	2-Methoxyaniline	4-Methylphenylboronic acid	45/59[b]
10	4-Chloroaniline	4-Methylphenylboronic acid	59/57[b]
11	Morpholine	4-Methylphenylboronic acid	51[b]
12	Aniline	4-Chlorophenylboronic acid	39/51[b]/52[c]
13	2-Methylaniline	4-Chlorophenylboronic acid	38/47[b]
14	Morpholine	4-Chlorophenylboronic acid	25[b]
15	2,4-Dimethylaniline	4-Chlorophenylboronic acid	37[b]
16	2-Methylaniline	4-Methoxyphenylboronic acid	31[b]

[a] Isolated yields (%) with 1 equiv of acetic acid.
[b] 2.0 equiv of acetic acid.
[c] Isolated yields (%) using copper coil, (2.0:1.5) acetic acid:TEMPO.

Please cite this article in press as: Bao, J.; Tranmer, G. K. *Tetrahedron Lett.* (2016), http://dx.doi.org/10.1016/j.tetlet.2015.12.107

synthesis of heterocycles. We are continuing our efforts in this field and have proposed some areas where we believe improvements can be realized (vide infra). In particular, we hope to develop a protocol which uses commodity chemicals, such as solid copper, acetic acid and an oxidant, to mediated C–N cross coupling reactions which will be translated to a large scale continuous flow process.

In summary, we have developed two optimized procedures for the C–N cross coupling of phenylboronic acids under continuous flow conditions using both a copper coil and a copper column which contained solid copper powder. For our copper coil reaction, 1.5 equiv of *tert*-butyl peroxybenzoate was used as oxidant in MeCN, giving a moderate isolated yield of 58%. When a column filled with copper powder was used, the addition of acetic acid and TEMPO provide for the best reaction conditions, giving isolated yields in excess of 75%. Additionally, we were able to apply our optimized reaction conditions and generate a library of products which highlighted the utility of solid copper flow reactors for C–N cross coupling reactions, generating 16 examples. Our group plans to continue to explore the C–N arylation of phenylboronic acids using solid copper reactors in hopes of developing a new paradigm for the synthesis of heterocycles. Recently, gas addition modules have been developed which allow for the capability of generating a continuous gas-saturated solvent stream[21] that could be used in combination with a solid copper reactor to perform these types of reactions. We envision a continuous flow sequence that combines both a gas addition module, with a solid copper reactor to invoke a C–N bond forming reaction. We propose that the utilization of oxygen or air as an oxidant in the C–N arylation of boronic acids, would be able to improve upon the yields observed for this flow reaction, in combination with the knowledgebase of reaction conditions we have developed here. Currently, we are working with granting agencies to secure funds to purchase a commercially available gas addition module, or develop our own, and will present the results in due course. Additionally, we are examining the scalability, and various mechanistic aspects of this reaction, including the quantification of leaching copper and will similarly publish those results when we are confident whether a homogeneous, heterogeneous, or dual reaction mechanism is involved, including additional examples of substrate scope.

Acknowledgments

The authors offer a debt of gratitude for financial aid from the Manitoba Medical Service Foundation, The Dr. Paul H.T. Thorlakson Foundation and the College of Pharmacy at the University of Manitoba.

References and notes

1. Suginome, M.; Ohmura, T. Arylboronic acid cross coupling reactions. In *Science of Synthesis, Cross Coupling and Heck-Type Reactions*, Molander, G. A., Ed.; Thieme: Wienheim, 2013; Vol. 1, pp 147–201.
2. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
3. Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936.
4. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941–2944.
5. Sanjeeva Rao, K.; Wu, T.-S. *Tetrahedron* **2012**, *68*, 7735–7754.
6. Fischer, C.; Koenig, B. *Beilstein J. Org. Chem.* **2011**, *7*, 59–74.
7. Janey, J. M. Buchwald-Hartwig amination. In *Name Reactions for Functional Group Transformations*; Li, J. J., Corey, E. J., Eds.; John Wiley & Sons Inc: Hoboken, NJ, 2007; pp 564–609.
8. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, 0674–0676.
9. McQuade, D. T.; Seeberger, P. H. *J. Org. Chem.* **2013**, *78*, 6384–6389.
10. Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675–680.
11. Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17–57.
12. Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849–8869.
13. Baumann, M.; Baxendale, I.; Ley, S. *Mol. Divers* **2011**, *15*, 613–630.
14. Knowles, J. P.; Elliott, L. D.; Booker-Milburn, K. I. *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052.
15. Gilmore, K.; Seeberger, P. H. *Chem. Rec.* **2014**, *14*, 410–418.
16. Bao, J.; Tranmer, G. K. *Chem. Commun.* **2015**, *51*, 3037–3044.
17. Zhang, Z.; Jamison, T. F.; Patel, S.; Mainolfi, N. *Org. Lett.* **2011**, *13*, 280–283.
18. Singh, B. K.; Stevens, C. V.; Acke, D. R. J.; Parmar, V. S.; Van der Eycken, E. V. *Tetrahedron Lett.* **2009**, *50*, 15–18.
19. General procedure for copper coil reactor: A 10mL copper coil available from Vapourtec Ltd was placed in a Vapourtec R4 reactor module and heated to 40° C. Using a Vapourtec R2C+ flow chemistry system, a 2 mL solution in acetonitrile containing arylboronic acid (0.8 mmol) and amine (1.2 mmol) was placed in 2 mL sample loop A and a 2 mL solution containing *tert*-butyl peroxybenzoate (1.2 mmol) in acetonitrile was placed in 2 mL sample loop B. The reactants were progressed through the copper coil reactor (0.30 mL/min), with each sample loop/pump set at 0.15 mL/min., and a 250 psi back-pressure regulator and collected in a 100 mL RB flask. The solvent evaporated and the product purified using a Teledyne Combiflash Rf and silica gel column chromatography in ethyl acetate:hexane (typically 1:19) to yield an isolated product.
20. General procedure for copper column reactor: An Omnifit glass column (6.6 × 150 mm) was filled with copper powder (5.5 cm height) and connected to a 10 mL stainless steel reactor coil and both were heated to 100° C using a Vapourtec R4 reactor module. Using a Vapourtec R2C+ flow chemistry system, a 2 mL solution containing arylboronic acid (0.8 mmol) and amine (2.4 mmol) in acetonitrile was placed in 2 mL sample loop A and 2 mL solution containing TEMPO (1.2 mmol) and acetic acid (1.6 mmol) in acetonitrile was placed in 2 mL sample loop B. The reactants were progressed through the copper column and SS coil reactor (0.30 mL/min), with each sample loop/pump set at 0.15 mL/min, and a 250 psi back-pressure regulator and collected in a 100 mL RB flask. The solvent removed and product purified with a Teledyne Combiflash Rf and silica gel column chromatography in ethyl acetate:hexane (typically 1:19) to yield an isolated product.
21. Mallia, C. J.; Baxendale, I. R. The use of gases in flow synthesis *Org. Process Res. Dev.* **2015**. http://dx.doi.org/10.1021/acs.oprd.5b00222. article ASAP Aug 4th, 2015.

Please cite this article in press as: Bao, J.; Tranmer, G. K. *Tetrahedron Lett.* (2016), http://dx.doi.org/10.1016/j.tetlet.2015.12.107