Pyroles are common heterocycles that appear in natural products, pharmaceuticals, dyes, and organic materials. Representative pyrrole-containing natural products include lamellarin D, lycogarubin C, whereas drugs that contain a pyrrole include sunitinib and atorvastatin (Figure 1). In view of their importance, numerous strategies to prepare pyrroles have been developed. 

We and others have recently described nickel-catalyzed anti-carboinsertive cyclizations of alkynyl electrophiles that give various carbocyclic and heterocyclic products. Although these reactions utilized several types of electrophiles, amides have yet to be described, which is perhaps unsurprising given their relatively low electrophilicity. Nevertheless, the successful use of amides could provide a versatile synthesis of multisubstituted pyrroles, as shown in Scheme 1. Nickel-catalyzed addition of an arylboronic acid to the alkynamide would give alkynynickel species (E)-2. Although (E)-2 cannot cyclize onto the amide because of geometric constraints, reversible E/Z isomerization of (E)-2 would provide (Z)-2, which could now attack the amide to give nickel alkoxide 4. Incorporating an electron-withdrawing N-tosyl group into 1 was expected to increase the reactivity of the amide carbonyl to favor this nucelophilic addition. Protonation of 4, followed by elimination of water, would then provide a 2,3,4-trisubstituted pyrrole 3.

Our investigations began with the reaction of alkynamide 1a with PbB(OH)2 to give pyrrole 3aa, which was conducted in the presence of Ni(OAc)2·4H2O (10 mol%) in 2,2,2-trifluoroethanol (TFE) at 80 °C for 24 h (Table 1, entry 1). However, 3aa was not detected in this reaction. Next, various P,N-ligands (10 mol%) were added (entries 2–7). The achiral ligand L1 gave 3aa in 27% yield as determined by 1H NMR analysis, but significant quantities of 1a remained (entry 2). Chiral phosphinoxazolines L2–L6 were then examined (entries 3–7) and of these, (R)-Ph-PHOX (L2) gave 3aa in 90% NMR yield with no starting material remaining (entry 3).

With an effective ligand identified, the scope of the alkynamide was surveyed in reactions with PhB(OH)2 (Table 2). Here, racemic L2 was used and satisfactory results were obtained using a reduced catalyst loading of 5 mol%. These experiments gave pyroles 3aa–3ma in 46–99% yield. Regarding the alkynyl substituent, the reaction is compatible with a phenyl group (3aa), various para-
Table 1: Evaluation of reaction conditions

| Entry | Ligand | Yield of 1a [%] | Yield of 3aa [%] |
|-------|--------|-----------------|-----------------|
| 1     |        | >95             | <5              |
| 2     | L1     | 33              | 27              |
| 3     | L2     | -               | 90              |
| 4     | L3     | 18              | 52              |
| 5     | L4     | 13              | 70              |
| 6     | L5     | 10              | 63              |
| 7     | L6     | 11              | 52              |

* Reactions were conducted with 0.05 mmol of 1a. * Determined by 1H NMR analysis using 1,4-dimethoxybenzene as an internal standard.

and 3ca, meta- (3da), and ortho-substituted phenyl groups (3ea), and a 2-thienyl group (3fa). Replacement of the benzoyl group of the amide with various para-substituted benzenes is also possible (3ga and 3ha). N-Acyl groups with alkyl substituents are also tolerated. For example, pyrroles containing methyl (3ia), n-butyl (3ja), cyclopropyl (3ka), or cyclohexyl (3la) groups were formed in 54–92% yield, although for 3la, increasing the temperature to 120 °C was required for high conversion. The process is not limited to aromatic groups at the alkyne, as shown by the reaction of 1,3-ene 1m to give pyrrole 3ma in 99% yield. However, a substrate containing a methyl group on the alkyne only gave a complex mixture of products. Furthermore, the N-tosyl group is important for reactivity, as N-aryl alkynamides failed to cyclize.

The cyclization of carbomethoxy-containing substrate 1n failed under the standard conditions, and led only to decomposition by cleavage of the methyl oxalyl group. However, changing the solvent to THF and increasing the catalyst loading to 20 mol% successfully gave pyrrole 3na in 35% yield, along with 3-pyrroline 5na in 38% yield (eqn 1). Increasing the temperature to 120 °C improved the yield of 3na to 73%, and none of 5na was observed (eqn 2).

Table 3: Scope of boronic acids

* Reactions were conducted with 0.30 mmol of 1a in TFE (3 mL). Yields are of isolated products.

* An acyclic tetrasubstituted alkene was also isolated in 23% yield (see Supplementary Information). * Conducted at 120 °C.
Pleasingly, this process is compatible with various (hetero)arylboronic acids, and pyrroles 3ab-3aj were obtained in 63–90% yield from alkynamide 1a (Table 3). The scope includes para-(3ab), meta-(3ac and 3ad), ortho- (3ae), and disubstituted phenylboronic acids (3af-3ah) with methyl (3ab and 3ah), halide (3ad, 3ae, and 3ag), or alkoxy groups (3ac, 3af, and 3ag). 2-Naphthylboronic acid (3ai) and various heteroarylboronic acids that include 5-indolylboronic acid (3aj), 3-furanboronic acid (3ak), and 3-thienylboronic acid (3al) are also tolerated. No reaction was observed when 4-pyridyldimethylboronic acid, methylboronic acid, or cyclopropylboronic acid were used.

To illustrate its utility, this methodology was applied to the preparation of pyrroles that have been used in the synthesis of 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY) derivatives (Scheme 2). Radical Removal of the tosyl group from 3aa with KOH in MeOH/TFH (1:1) at 70 °C gave pyrrole 6 in >99% yield, which has previously been converted into BODIPY derivative 7. Alternatively, treatment of 3aa with POCls in DMF at 100 °C in a microwave reactor resulted in formylation with concomitant removal of the tosyl group to give pyrrole 8, which has been used in the synthesis of BODIPY derivative 9.

**Scheme 2** Synthesis of precursors to BODIPY derivatives

In a further application, removal of the tosyl group of 3aa with KOH was followed by immediate alkylation with n-hexyl bromide as described previously to give pyrrole 10 in 56% yield over two steps (Scheme 3). Pyrrole 10 was previously converted in two steps into 11, a known inhibitor of bovine cytochrome oxygenase and 5-lipoxigenase.

**Scheme 3** Formal synthesis of bovine cytochrome oxygenase and 5-lipoxigenase inhibitor 11

In conclusion, we have developed a synthesis of diverse 2,3,4-trisubstituted pyrroles by the nickel-catalyzed reaction of N-tosyl alkynamides with arylboronic acids. These reactions rely upon the reversible E/Z isomerization of alkenylnicken species as a key step to enable cyclization to take place. This method was applied to the synthesis of pyrroles that are precursors to BODIPY derivatives, as well as an inhibitor of bovine cytochrome oxygenase and 5-lipoxigenase.
6455. (j) J. Y. Liao, P. L. Shao and Y. Zhao, *J. Am. Chem. Soc.*, 2015, 137, 628-631. (k) L. Zhu, Y. H. Yu, Z. F. Mao and X. L. Huang, *Org. Lett.*, 2015, 17, 30-33. (l) J. Xuan, X. D. Xia, T. T. Zeng, Z. J. Feng, J. R. Chen, L. Q. Lu and W. J. Xiao, *Angew. Chem., Int. Ed.*, 2014, 53, 5653-5656. (m) C. E. Kim, S. Park, D. Eom, B. Seo and P. H. Lee, *Org. Lett.*, 2014, 16, 1900-1903. (n) M. N. Zhao, Z. H. Ren, Y. Y. Wang and Z. H. Guan, *Chem. Eur. J.*, 2014, 20, 1839-1842. (o) S. Michlik and R. Kempe, *Nature Chem.*, 2013, 5, 140-144.

12 (a) C. Clarke, C. A. Incerti-Pradillos and H. W. Lam, *J. Am. Chem. Soc.*, 2016, 138, 8068-8071. (b) C. Yap, G. M. J. Lenagh-Snow, S. N. Karad, W. Lewis, L. J. Diorazio and H. W. Lam, *Angew. Chem., Int. Ed.*, 2017, 56, 8216-8220. (c) S. N. Karad, H. Panchal, C. Clarke, W. Lewis and H. W. Lam, *Angew. Chem., Int. Ed.*, 2018, 57, 9122-9125.

13 (a) T. Igarashi, S. Arai and A. Nishida, *J. Org. Chem.*, 2013, 78, 4366-4372. (b) X. Wang, Y. Liu and R. Martin, *J. Am. Chem. Soc.*, 2015, 137, 6476-6479. (c) M. Börjesson, T. Moragas and R. Martin, *J. Am. Chem. Soc.*, 2016, 138, 7504-7507. (d) X. Zhang, X. Xie and Y. Liu, *Chem. Sci.*, 2016, 7, 5815-5820. (e) G. R. Kumar, R. Kumar, M. Rajesh and M. S. Reddy, *Chem. Commun.*, 2018, 54, 759-762.

14 The reaction of alkyamine 1a with 1.5 equivalents of PhB(OH)2 under otherwise identical conditions to those shown in Table 2 gave pyrrole 3aa in 81% yield, with the mass balance being unreacted starting material.

15 The structure of 3ah was further confirmed by X-ray crystallography. CCDC 1861043.

16 A. Wakamiya, N. Sugita and S. Yamaguchi, *Chem. Lett.*, 2008, 37, 1094-1095.

17 G. Dannhardt and M. Lehr, *Arch. Pharm. (Weinheim)*, 1993, 326, 157-162.