ChemComm

COMMUNICATION

Synthesis of multisubstituted pyrroles by nickel-catalyzed arylative cyclizations of *N*-tosyl alkynamides†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Simone M. Gillbard,[‡ab] Chieh-Hsu Chung,[‡ab] Somnath Narayan Karad,[ab] Heena Panchal,[ab] William Lewis[b] and Hon Wai Lam*[ab]

The synthesis of multisubstituted pyrroles by the nickel-catalyzed reaction of *N*-tosyl alkynamides with arylboronic acids is reported. These reactions are triggered by alkyne arylnickelation, followed by cyclization of the resulting alkenylnickel species onto the amide. The reversible *E*/*Z* isomerization of the alkenylnickel species is critical for cyclization. This method was applied to the synthesis of pyrroles that are precursors to BODIPY derivatives and a biologically active compound.

Pyrroles are common heterocycles that appear in natural products,[1] pharmaceuticals,[2] dyes,[3] and organic materials.[4] Representative pyrrole-containing natural products include lamellarin D[5,6] and lycogarubin C,[7] whereas drugs that contain a pyrrole include sunitinib[8] and atorvastatin[9] (Figure 1). In view of their importance, numerous strategies to prepare pyrroles have been developed.[10,11]

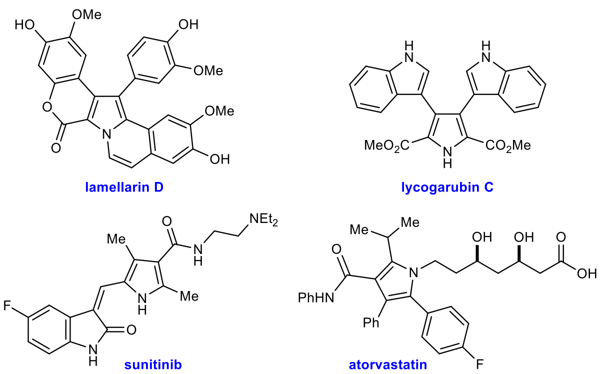
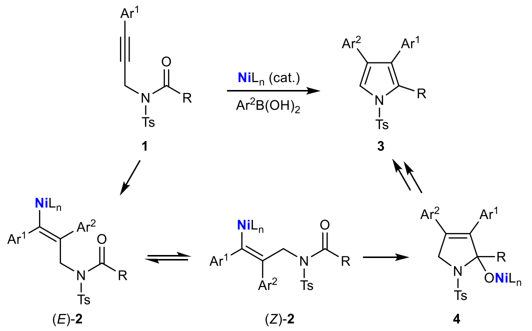


Figure 1 Representative pyrrole-containing natural products and drugs

We[12] and others[13] have recently described nickel-catalyzed *anti*-carbometallative cyclizations of alkynyl electrophiles that give various carbo- and heterocyclic products. Although these reactions utilized several types of electrophiles,[12,13] 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 **1** would give alkenylnickel 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 nucleophilic addition. Protonation of **4**, followed by elimination of water, would then provide a 2,3,4-trisubstituted pyrrole **3**.



Scheme 1 Proposed synthesis of pyrroles

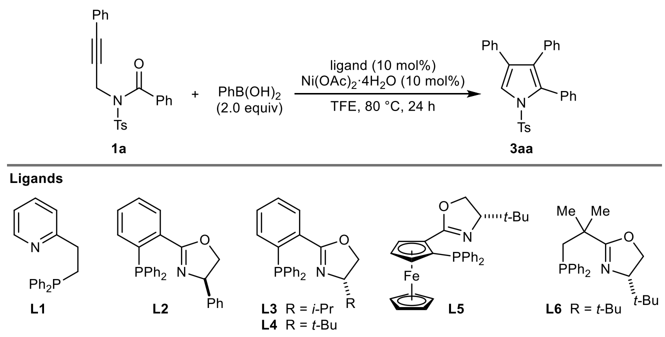
Our investigations began with the reaction of alkynamide **1a** with $PhB(OH)_2$ to give pyrrole **3aa**, which was conducted in the presence of $Ni(OAc)_2{\cdot}4H_2O$ (10 mol%) in 2,2,2-trifluoroethanol (TFE) at 80 °C for 24 h (Table 1, entry 1). However, **3aa** was not detected in this reaction. Next, various *P*,*N*-ligands (10 mol%) were added (entries 2–7). The achiral ligand **L1** gave **3aa** in 27% yield as determined by ^{1}H NMR analysis, but significant quantities of **1a** remained (entry 2). Chiral phosphinooxazolines **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 pyrroles **3aa**–**3ma** in 46–99% yield.[14] Regarding the alkyne substituent, the reaction is compatible with a phenyl group (**3aa**), various *para*- (**3ba**

[a.] *The GlaxoSmithKline Carbon Neutral Laboratories for Sustainable Chemistry, University of Nottingham, Jubilee Campus, Triumph Road, Nottingham, NG7 2TU, United Kingdom*
[b.] *School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, United Kingdom*

† Electronic Supplementary Information (ESI) available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data for **3ah**. See DOI: 10.1039/x0xx00000x
‡ These authors contributed equally.

Table 1 Evaluation of reaction conditions[a]

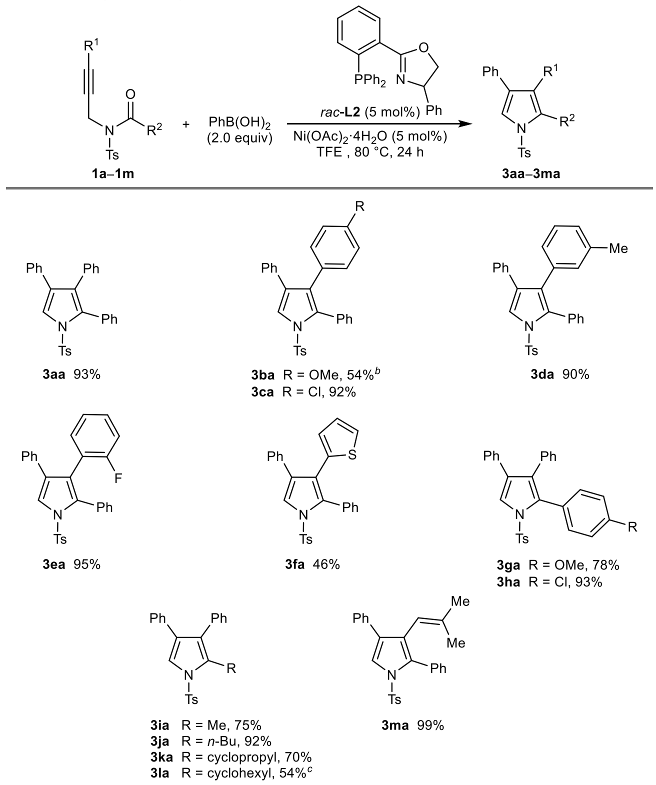


Entry	Ligand	Yield of **1a** [%][b]	Yield of **3aa** [%][b]
1	–	>95	<5
2	**L1**	33	27
3	**L2**	–	90
4	**L3**	18	52
5	**L4**	13	70
6	**L5**	10	63
7	**L6**	11	52

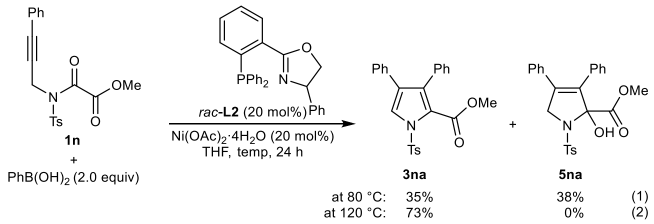
[a] Reactions were conducted with 0.05 mmol of **1a**. [b] Determined by ^{1}H NMR analysis using 1,4-dimethoxybenzene as an internal standard.

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**[15]). *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-enyne **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.

Table 2 Scope of alkynamides[a]

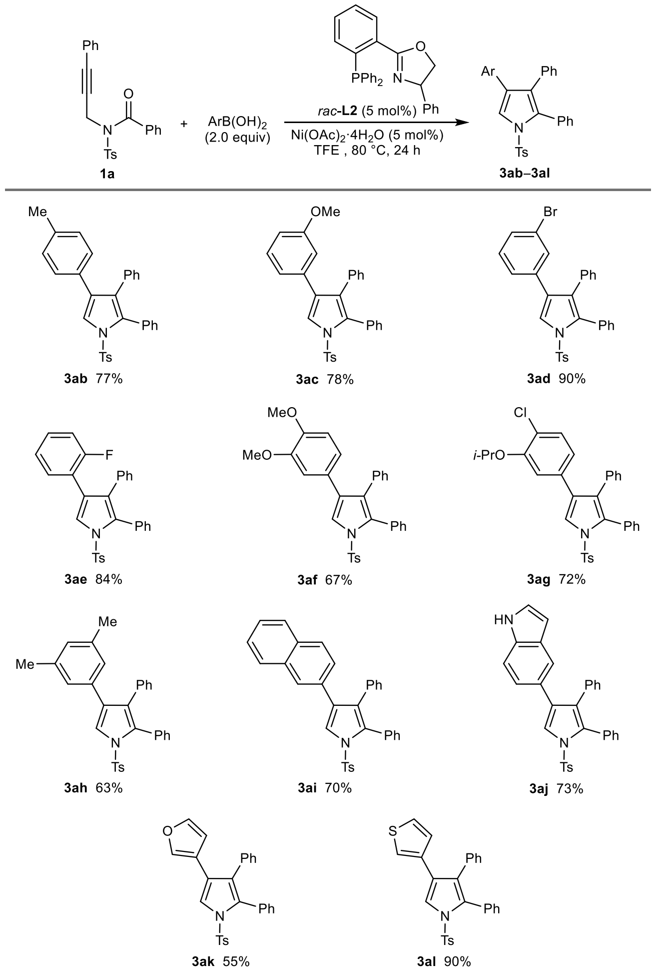


[a] Reactions were conducted with 0.30 mmol of **1a**–**1m** in TFE (3 mL). Yields are of isolated products. [b] An acyclic tetrasubstituted alkene was also isolated in 23% yield (see Supplementary Information). [c] Conducted at 120 °C.



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).

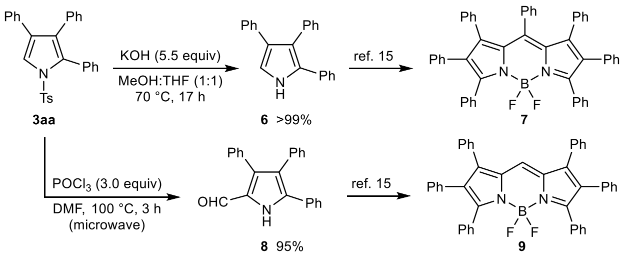
Table 3 Scope of boronic acids[a]



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

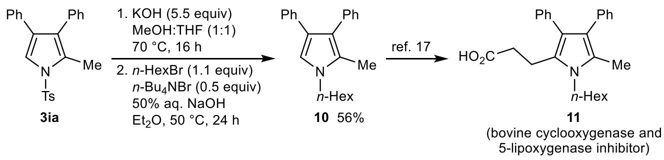
Pleasingly, this process is compatible with various(hetero)arylboronic acids, and pyrroles **3ab**–**3aj** were obtained in 63–90% yield from alkynyamide **1a** (Table 3). The scope includes *para*- (**3ab**), *meta*- (**3ac** and **3ad**), *ortho*- (**3ae**), and disubstituted phenylboronic acids (**3af**–**3ah**) 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-furanylboronic acid (**3ak**), and 3-thienylboronic acid (**3al**) are also tolerated. No reaction was observed when 4-pyridinylboronic 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).[3a,b,d] 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**.[16] Alternatively, treatment of **3aa** with $POCl_3$ 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**.[16]



Scheme 2 Synthesis of precursors to BODIPY derivatives

In a further application, removal of the tosyl group of **3ia** 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).[17] Pyrrole **10** was previously converted in two steps into **11**, a known inhibitor of bovine cyclooxygenase and 5-lipoxygenase.[17]



Scheme 3 Formal synthesis of bovine cyclooxygenase and 5-lipoxygenase 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 alkenylnickel 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 cyclooxygenase and 5-lipoxygenase.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the European Union's Horizon 2020 research and innovation programme [grant number 702386] through a Marie Skłodowska-Curie Individual Fellowship to S.N.K.; the University of Nottingham; and GlaxoSmithKline.

Notes and references

1 (*a*) I. S. Young, P. D. Thornton and A. Thompson, *Nat. Prod. Rep.*, 2010, **27**, 1801-1839. (*b*) H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264-287. (*c*) A. Fürstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582-3603.

2 V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman and P. Sharma, *RSC Adv.*, 2015, **5**, 15233-15266.

3 (*a*) T. Kowada, H. Maeda and K. Kikuchi, *Chem. Soc. Rev.*, 2015, **44**, 4953-4972. (*b*) M. Kaur and D. H. Choi, *Chem. Soc. Rev.*, 2015, **44**, 58-77. (*c*) G. Ulrich, R. Ziessel and A. Harriman, *Angew. Chem., Int. Ed.*, 2008, **47**, 1184-1201. (*d*) A. Loudet and K. Burgess, *Chem. Rev.*, 2007, **107**, 4891-4932.

4 T. V. Vernitskaya and O. N. Efimov, *Russ. Chem. Rev.*, 1997, **66**, 489-505.

5 R. J. Andersen, D. J. Faulkner, C. H. He, G. D. Van Duyne and J. Clardy, *J. Am. Chem. Soc.*, 1985, **107**, 5492-5495.

6 For reviews of the lamellarins, see: (*a*) H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264-287. (*b*) D. Pla, F. Albericio and M. Alvarez, *MedChemComm*, 2011, **2**, 689-697. (*c*) D. Imbri, J. Tauber and T. Opatz, *Mar. Drugs*, 2014, **12**, 6142.

7 R. Fröde, C. Hinze, I. Josten, B. Schmidt, B. Steffan and W. Steglich, *Tetrahedron Lett.*, 1994, **35**, 1689-1690.

8 L. Sun, C. Liang, S. Shirazian, Y. Zhou, T. Miller, J. Cui, J. Y. Fukuda, J. Y. Chu, A. Nematalla, X. Y. Wang, H. Chen, A. Sistla, T. C. Luu, F. Tang, J. Wei and C. Tang, *J. Med. Chem.*, 2003, **46**, 1116-1119.

9 (*a*) B. D. Roth, C. J. Blankley, A. W. Chucholowski, E. Ferguson, M. L. Hoefle, D. F. Ortwine, R. S. Newton, C. S. Sekerke, D. R. Sliskovic and M. Wilson, *J. Med. Chem.*, 1991, **34**, 357-366. (*b*) J. J. Li, D. S. Johnson, D. R. Sliskovic and B. D. Roth, in *Contemporary Drug Synthesis*, John Wiley & Sons, Inc., 2004, pp. 113-124. (*c*) Z. Casar, *Curr. Org. Chem.*, 2010, **14**, 816-845.

10 (*a*) V. Estevez, M. Villacampa and J. C. Menendez, *Chem. Soc. Rev.*, 2014, **43**, 4633-4657. (*b*) V. Estevez, M. Villacampa and J. C. Menendez, *Chem. Soc. Rev.*, 2010, **39**, 4402-4421. (*c*) S. Thirumalairajan, B. M. Pearce and A. Thompson, *Chem. Commun.*, 2010, **46**, 1797-1812.

11 For recent, selected examples of the catalytic synthesis of pyrroles, see: (*a*) H. C. Chiu and I. A. Tonks, *Angew. Chem., Int. Ed.*, 2018, **57**, 6090-6094. (*b*) S. P. Midya, V. G. Landge, M. K. Sahoo, J. Rana and E. Balaraman, *Chem. Commun.*, 2018, **54**, 90-93. (*c*) M. Fleige and F. Glorius, *Chem. Eur. J.*, 2017, **23**, 10773-10776. (*d*) F. Kallmeier, B. Dudziec, T. Irrgang and R. Kempe, *Angew. Chem., Int. Ed.*, 2017, **56**, 7261-7265. (*e*) B. Emayavaramban, M. Sen and B. Sundararaju, *Org. Lett.*, 2017, **19**, 6-9. (*f*) P. Daw, S. Chakraborty, J. A. Garg, Y. Ben-David and D. Milstein, *Angew. Chem., Int. Ed.*, 2016, **55**, 14371-14375. (*g*) M. K. Majhail, P. M. Ylioja and M. C. Willis, *Chem. Eur. J.*, 2016, **22**, 7879-7884. (*h*) X. Q. Mou, Z. L. Xu, L. Xu, S. H. Wang, B. H. Zhang, D. Zhang, J. Wang, W. T. Liu and W. Bao, *Org. Lett.*, 2016, **18**, 4032-4035. (*i*) W. W. Tan and N. Yoshikai, *Chem. Sci.*, 2015, **6**, 6448-

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 alkynamide **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.