ChemComm

COMMUNICATION

A second-generation ligand for the enantioselective rhodium-catalyzed addition of arylboronic acids to alkenylazaarenes†

Cite this: DOI: 10.1039/c4cc00340c

Received 15th January 2014,
Accepted 24th January 2014

DOI: 10.1039/c4cc00340c

www.rsc.org/chemcomm

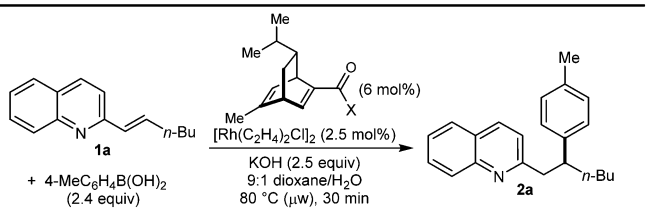
Iain D. Roy,[a] Alan R. Burns,[ab] Graham Pattison,[a] Boris Michel,[a] Alexandra J. Parker[c] and Hon Wai Lam*[ab]

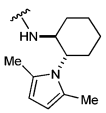
A 2,4,6-trialkylanilide-containing chiral diene has been identified as a superior ligand for the enantioselective rhodium-catalyzed arylation of alkenylazaarenes with arylboronic acids.

As part of a program aimed at the preparation of enantioenriched chiral azaarene-containing compounds,[1] we have focused upon an underexploited strategy in asymmetric synthesis, namely the utilization of the C=N moiety within certain azaarenes to activate adjacent functionality in enantioselective catalysis.[2–4] In this context, we have reported[1b] the enantioselective rhodium-catalyzed 1,4-arylation[5–8] of β-substituted alkenylazaarenes with arylboronic acids using a secondary amide-containing chiral diene[9–11] ligand **L1** (see Table 1, entry 1), which builds upon early studies by the groups of Lautens[12a] and Genet[12b] using vinylazaarenes. Although **L1** was highly effective, it was of interest to determine whether a ligand of this complexity, possessing stereochemical elements additional to those of the chiral diene component, was actually necessary for optimal results.[13] Herein, we report a simpler ligand that provides results superior to those obtained using **L1**, along with a more comprehensive evaluation of the scope of the reaction.

First, various analogues of **L1** were prepared and evaluated in the enantioselective addition of 4-methylphenylboronic acid to 2-alkenylquinoline **1a** (Table 1), a reaction that gave **2a** in 67% yield and 92% ee in our original study.[1b] The conditions employed were identical to those we described previously.[1b] Ligand **L2**, which lacks the pyrrole moiety on the cyclohexane, provided **2a** in high conversion but the enantioselectivity was slightly lower (entry 2) compared with that obtained using **L1** (entry 1). However, the dicyclohexylamide **L3** was noticeably inferior (entry 3). Ligands **L4** and **L5**, which contain one or two benzyl groups, respectively, provided reasonable results (entries 4 and 5), but the enantioselectivities were lower compared with **L1**. The dimethylamide **L6** gave high conversion but the reaction was poorly enantioselective (46% ee, entry 6). Next, ligands **L7–L9** containing anilide groups were studied (entries 7–9), and of these, the 2,4,6-triisopropylanilide **L9** provided the best results, giving **2a** in >95% conversion and 99% ee (entry 9).

Table 1 Ligand evaluation for arylation of **1a**[a]



Entry	Ligand	X	Conversion (%)	ee (%)
1[b]	**L1**		67% yield	92
2	**L2**	NHCy	>95	90
3	**L3**	NCy_2	28	59
4	**L4**	NHBn	>95	88
5	**L5**	NBn_2	81	85
6	**L6**	NMe_2	91	46
7	**L7**	NHPh	58	76
8	**L8**	$NH(2,4,6\text{-}Me_3C_6H_2)$	33	96
9	**L9**	$NH[2,4,6\text{-}(i\text{-}Pr)_3C_6H_2]$	>95	99

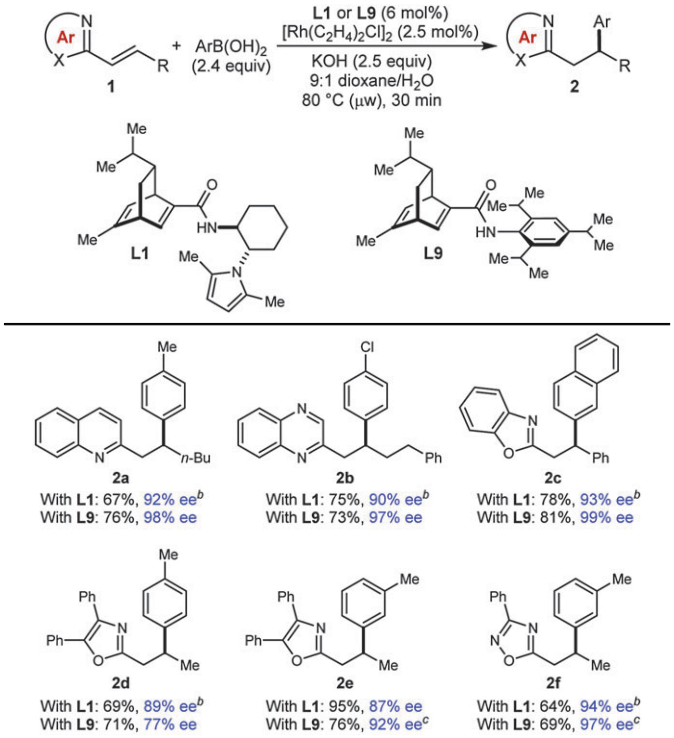
[a] Reactions were conducted using 0.10 mmol of **1a** (0.2 M). Conversions were determined by ^{1}H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by chiral HPLC analysis. [b] Ref. 1*b*.

Further confirmation of the superior enantioselectivities imparted by this new triisopropylanilide ligand **L9** was provided by repeating representative reactions described in our original study[1b] using **L9** in place of **L1** (Table 2). These results indicate that while in most cases the isolated yields of the products with both ligands are comparable, the enantioselectivities are higher using **L9** (**2a**, **2b**, **2c**, **2e**, and **2f**). One exception was the addition

[a] *EaStCHEM, School of Chemistry, University of Edinburgh, Joseph Black Building, The King's Buildings, West Mains Road, Edinburgh, EH9 3JJ, UK*
[b] *School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK. E-mail: hon.lam@nottingham.ac.uk; Tel: +44 (0)115-748-4677*
[c] *AstraZeneca Process Research and Development, Charter Way, Silk Road Business Park, Macclesfield, Cheshire, SK10 2NA, UK*

† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for new compounds, and crystallographic data. CCDC 976345 and 976346. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc00340c

Table 2 Comparison of ligand **L9** with **L1**[a]

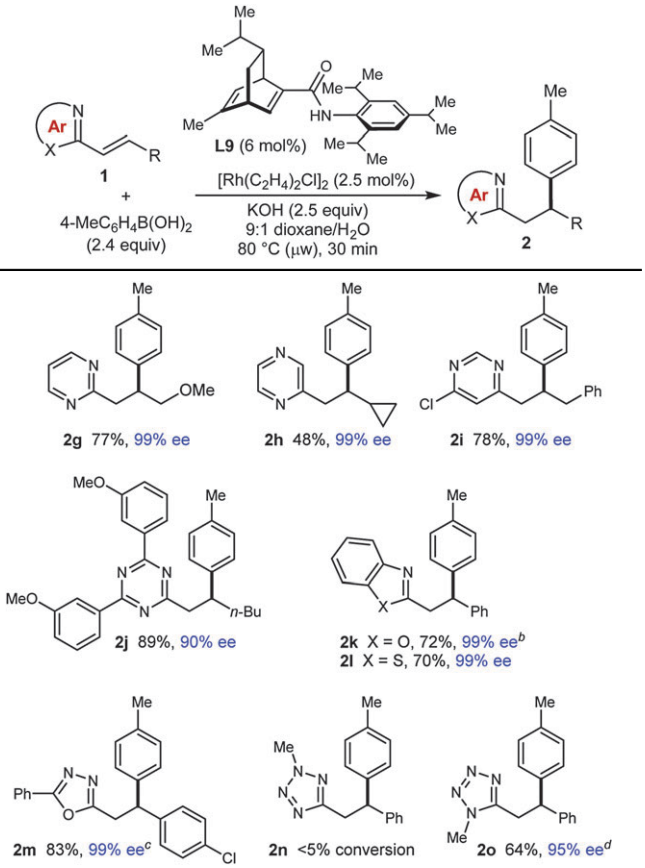


[a] Reactions were conducted using 0.50 mmol of alkenylazaarene (0.2 M). Yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis. [b] Results taken from ref. 1*b*. [c] Reaction conducted using 0.30 mmol of alkenylazaarene.

of 4-methylphenylboronic acid to a substrate containing a 4,5-diphenyloxazole as the activating group, which gave **2d** in 77% ee using **L9**, and this result is inferior to that obtained using ligand **L1** (89% ee). Interestingly, the inferiority of **L9** compared with **L1** with this substrate appeared to be restricted to the use of 4-methylphenylboronic acid; when 3-methylphenylboronic acid was employed, **L9** provided the product **2e** in a higher enantioselectivity. The reasons for these contrasting results are not currently known.

To explore the scope of the process with the second generation ligand **L9** more comprehensively, a range of previously reported and new alkenylazaarenes were reacted with 4-methylphenylboronic acid (Table 3). While substrates containing pyrimidine or benzoxazole, azaarenes that have already been demonstrated to be efficient activating groups in our original study,[1b] underwent arylation efficiently with excellent enantioselectivities as expected (**2g** and **2k**), further examples demonstrate that other azaarenes are also effective. These examples include π-deficient azaarenes such as pyrazine (**2h**), a chloropyrimidine (**2i**), and a 4,6-bis(aryl)-1,3,5-triazine (**2j**), as well as π-excessive azaarenes such as benzothiazole (**2l**), a 1,3,4-oxadiazole (**2m**), and a tetrazole (**2o**). A pyrazine-containing substrate was only moderately reactive, providing product **2h** in 48% yield, though in 99% ee. Although alkenyltetrazole **1l** was unreactive (none of **2n** was obtained), its regioisomer **1m** provided **2o** in 64% yield and 95% ee. The difference in reactivities between **1l** and **1m** can be understood by consideration of their conjugation patterns. Whereas the alkene is conjugated only with the C=N group of the tetrazole in **1l**, it is conjugated with both the C=N and N=N moieties in **1m**,

Table 3 Arylation of alkenylazaarenes with 4-methylphenylboronic acid[a]



[a] Reactions were conducted using 0.30 mmol of alkenylazaarene (0.2 M). Yields are of isolated material. Enantiomeric excesses were determined by chiral HPLC analysis. [b] Enantiomeric excess determined after hydrolysis to the secondary amide. [c] The stereochemistry of **2m** was determined by X-ray crystallography, CCDC 976346. [d] The structure of the alkenylazaarene substrate **1m** was determined by X-ray crystallography, CCDC 976345.

leading to a greater degree of activation (Fig. 1). With respect to the β-substituent on the alkene, the process is tolerant of simple alkyl groups (**2i** and **2j**), a cyclopropane (**2h**), an ether (**2g**), and aryl groups (**2k**, **2l**, **2m**, and **2o**).

A range of arylboronic acids are compatible with this process, as demonstrated by the results presented in Table 4. Arylboronic acids containing substituents such as methyl (entries 2 and 9), halogen (entries 3 and 10), or alkoxy (entries 4 and 10) groups reacted smoothly with various alkenylazaarenes in good yields and high enantioselectivities. Arylboronic acids containing strong electron-withdrawing groups such as ester, trifluoromethyl, or even nitro substituents were also effective (entries 5–7). A sterically encumbering *ortho*-substituent on the arylboronic acid was also tolerated (entry 2).

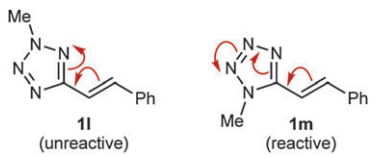
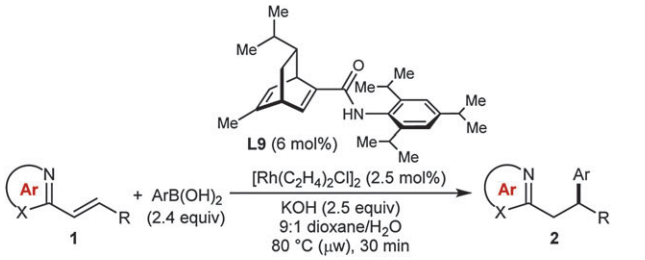
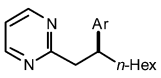
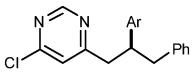
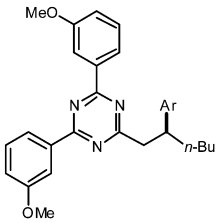
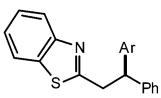
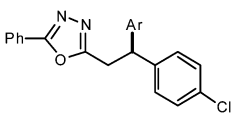


Fig. 1 Difference in conjugation between alkenyltetrazoles **1l** and **1m**.

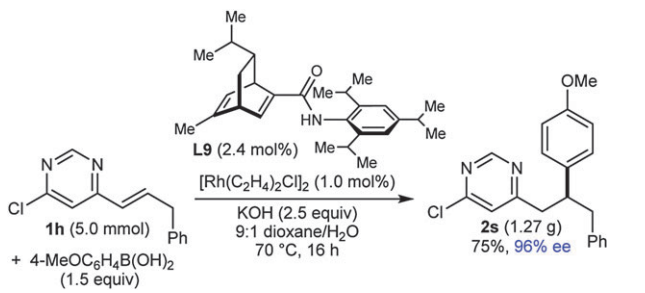
Table 4 Arylation of alkenylazaarenes with various arylboronic acids[a]



Entry	Product		Yield[b] (%)	ee[c] (%)
1		**2p** Ar = Ph	89	99
2		**2q** Ar = 2-MeC$_6$H$_4$	>95	97
3		**2r** Ar = 4-FC$_6$H$_4$	78	99
4		**2s** Ar = 4-MeOC$_6$H$_4$	82	98
5		**2t** Ar = 3-EtO$_2$C$_6$H$_4$	62	93[d]
6		**2u** Ar = 3,5-(F$_3$C)$_2$C$_6$H$_3$	92	96[e]
7		**2v** Ar = 4-O$_2$NC$_6$H$_4$	85	94
8		**2w** Ar = 2-naphthyl	62	98
9		**2x** Ar = 3,5-Me$_2$C$_6$H$_3$	85	99
10		**2y** Ar = 3-Cl-4-i-PrOC$_6$H$_3$	63	99

[a] Reactions were conducted using 0.30 mmol of alkenylazaarene (0.2 M). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Enantiomeric excess determined on a derivative obtained after treatment of **2t** with LiOH in THF/MeOH/H_2O. [e] Enantiomeric excess determined after demethylation of the methoxy groups using BBr_3.

This process can also be conducted on a larger scale using lower loadings of the arylboronic acid and catalyst. For example, arylation of alkenylpyrimidine **1h** on a 5.0 mmol scale with 4-methoxyphenylboronic acid (1.5 equiv.), using thermal heating at 70 °C in the presence of 2.0 mol% of the rhodium–chiral diene complex, provided **2s** in 75% yield (1.27 g) and 96% ee (eqn (1)).



(1)

In summary, a more in-depth evaluation of chiral diene ligands for the enantioselective addition of arylboronic acids to alkenylazaarenes has resulted in the identification of a second-generation ligand **L9** containing a 2,4,6-triisopropylanilide moiety that is superior to our first generation ligand **L1**. Not only does this new chiral diene result in generally superior enantioselectivities, it is simpler in structure. A more thorough assessment of the scope of the process demonstrated that the effectiveness of ligand **L9** is fairly general across a range alkenylazaarenes and arylboronic acids. Further experimental and theoretical[14] investigations of anilide-containing chiral dienes in asymmetric catalysis are planned, and will be reported in due course.

This work was supported by the EPSRC, Pfizer, and the University of Edinburgh. The EPSRC is gratefully acknowledged for the award of a Leadership Fellowship to H.W.L. We thank Dr Gary S. Nichol and Stewart Franklin at the University of Edinburgh for X-ray crystallography and technical assistance, respectively. We thank the EPSRC National Mass Spectrometry Facility for providing high-resolution mass spectra.

Notes and references

1 (*a*) L. Rupnicki, A. Saxena and H. W. Lam, *J. Am. Chem. Soc.*, 2009, **131**, 10386–10387; (*b*) G. Pattison, G. Piraux and H. W. Lam, *J. Am. Chem. Soc.*, 2010, **132**, 14373–14375; (*c*) A. Saxena, B. Choi and H. W. Lam, *J. Am. Chem. Soc.*, 2012, **134**, 8428–8431; (*d*) C. Fallan and H. W. Lam, *Chem.–Eur. J.*, 2012, **18**, 11214–11218; (*e*) D. Best, S. Kujawa and H. W. Lam, *J. Am. Chem. Soc.*, 2012, **134**, 18193–18196; (*f*) A. J. Simpson and H. W. Lam, *Org. Lett.*, 2013, **15**, 2586–2589.

2 D. Best and H. W. Lam, *J. Org. Chem.*, 2014, **79**, DOI: 10.1021/jo402414k, ASAP. Q5

3 For Ni-catalyzed additions of organometallics to 4-alkenylpyridines with low enantioselectivities (≤15% ee), see: I. N. Houpis, J. Lee, I. Dorziotis, A. Molina, B. Reamer, R. P. Volante and P. J. Reider, *Tetrahedron*, 1998, **54**, 1185–1195.

4 For catalytic asymmetric Michael additions of nitroalkanes and anthrone to 4-nitro-5-styrylisoxazoles, see: (*a*) A. Baschieri, L. Bernardi, A. Ricci, S. Suresh and M. F. A. Adamo, *Angew. Chem., Int. Ed.*, 2009, **48**, 9342–9345; (*b*) H.-W. Sun, Y.-H. Liao, Z.-J. Wu, H.-Y. Wang, X.-M. Zhang and W.-C. Yuan, *Tetrahedron*, 2011, **67**, 3991–3996.

5 A seminal reference: M. Sakai, H. Hayashi and N. Miyaura, *Organometallics*, 1997, **16**, 4229–4231.

6 The first enantioselective example: Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai and N. Miyaura, *J. Am. Chem. Soc.*, 1998, **120**, 5579–5580.

7 For reviews, see: (*a*) T. Hayashi and K. Yamasaki, *Chem. Rev.*, 2003, **103**, 2829–2844; (*b*) K. Yoshida and T. Hayashi, in *Modern Rhodium-Catalyzed Organic Reactions*, ed. P. A. Evans, Wiley-VCH, Weinheim, 2005, ch. 3, pp. 55–77; (*c*) H. J. Edwards, J. D. Hargrave, S. D. Penrose and C. G. Frost, *Chem. Soc. Rev.*, 2010, **39**, 2093–2105; (*d*) P. Tian, H.-Q. Dong and G.-Q. Lin, *ACS Catal.*, 2011, **2**, 95–119.

8 For a review of Rh-catalyzed carbon–carbon bond-forming reactions of organometallic compounds, see: K. Fagnou and M. Lautens, *Chem. Rev.*, 2003, **103**, 169–196.

9 For seminal references describing chiral dienes in asymmetric catalysis, see: (*a*) T. Hayashi, K. Ueyama, N. Tokunaga and K. Yoshida, *J. Am. Chem. Soc.*, 2003, **125**, 11508–11509; (*b*) C. Fischer, C. Defieber, T. Suzuki and E. M. Carreira, *J. Am. Chem. Soc.*, 2004, **126**, 1628–1629.

10 For reviews of chiral diene ligands, see: (*a*) R. Shintani and T. Hayashi, *Aldrichimica Acta*, 2009, **42**, 31–38; (*b*) J. B. Johnson and T. Rovis, *Angew. Chem., Int. Ed.*, 2008, **47**, 840–871; (*c*) C. Defieber, H. Grutzmacher and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2008, **47**, 4482–4502.

11 For selected, recent examples of chiral dienes in catalytic asymmetric 1,4- and 1,6-addition reactions, see: (*a*) C. Shao, H.-J. Yu, N.-Y. Wu, P. Tian, R. Wang, C.-G. Feng and G.-Q. Lin, *Org. Lett.*,

2011, **13**, 788–791; (*b*) K. Sasaki and T. Hayashi, *Tetrahedron: Asymmetry*, 2012, **23**, 373–380; (*c*) T. Nishimura, A. Noishiki and T. Hayashi, *Chem. Commun.*, 2012, **48**, 973–975; (*d*) Y.-C. Chung, D. Janmanchi and H.-L. Wu, *Org. Lett.*, 2012, **14**, 2766–2769; (*e*) K. Sasaki, T. Nishimura, R. Shintani, E. A. B. Kantchev and T. Hayashi, *Chem. Sci.*, 2012, **3**, 1278–1283; (*f*) T. Nishimura, Y. Takiguchi and T. Hayashi, *J. Am. Chem. Soc.*, 2012, **134**, 9086–9089; (*g*) Z.-T. He, Y.-B. Wei, H.-J. Yu, C.-Y. Sun, C.-G. Feng, P. Tian and G.-Q. Lin, *Tetrahedron*, 2012, **68**, 9186–9191; (*h*) H.-J. Yu, C. Shao, Z. Cui, C.-G. Feng and G.-Q. Lin, *Chem.–Eur. J.*, 2012, **18**, 13274–13278; (*i*) J. Keilitz, S. G. Newman and M. Lautens, *Org. Lett.*, 2013, **15**, 1148–1151; (*j*) M. M. Hansmann, A. S. K. Hashmi and M. Lautens, *Org. Lett.*, 2013, **15**, 3226–3229; (*k*) A. A. Friedman, J. Panteleev, J. Tsoung, V. Huynh and M. Lautens, *Angew. Chem., Int. Ed.*, 2013, **52**, 9755–9758.

12 For Rh-catalyzed additions of arylboronic acids to vinylazaarenes resulting in achiral products, see: (*a*) M. Lautens, A. Roy, K. Fukuoka, K. Fagnou and B. Martín-Matute, *J. Am. Chem. Soc.*, 2001, **123**, 5358–5359; (*b*) R. Amengual, V. Michelet and J.-P. Genêt, *Tetrahedron Lett.*, 2002, **43**, 5905–5908.

13 For application of a simpler amide-containing chiral diene **L5** in enantioselective rhodium-catalyzed arylations of electron-deficient alkenylarenes, including a 5-nitro-2-alkenylpyridine, see: A. Saxena and H. W. Lam, *Chem. Sci.*, 2011, **2**, 2326–2331.

14 For computational studies of chiral diene ligands, see ref. 11*e* and: (*a*) E. A. B. Kantchev, *Chem. Commun.*, 2011, **47**, 10969–10971; (*b*) S. Gosiewska, J. A. Raskatov, R. Shintani, T. Hayashi and J. M. Brown, *Chem.–Eur. J.*, 2012, **18**, 80–84; (*c*) Y. Luo, N. G. Berry and A. J. Carnell, *Chem. Commun.*, 2012, **48**, 3279–3281; (*d*) E. A. B. Kantchev, *Chem. Sci.*, 2013, **4**, 1864–1875.

