Chiral *N*-heterocyclic carbene ligands for asymmetric catalytic oxindole synthesis†‡

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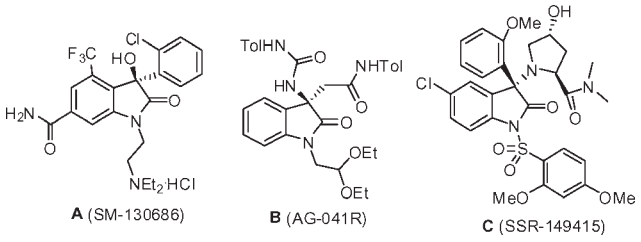
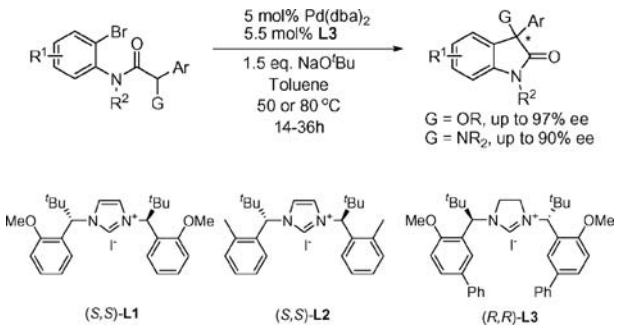
The Pd-catalysed asymmetric intramolecular α-arylation of amide enolates containing heteroatom substituents gives chiral 3-alkoxy or 3-aminooxindoles in high yield and with enantioselectivities up to 97% ee when a new chiral *N*-heterocyclic carbene ligand is used.

Oxindoles containing a quaternary benzylic center constitute a common structural motif in many natural products and biologically active compounds.[1] Among them, oxindoles with heteroatoms at the stereogenic center are a useful class of compounds in the field of medicinal chemistry, including the potent growth hormone secretagogue SM-130686 (**A**),[2] the clinical candidate AG-041R (**B**) as gastrin/CCK-B receptor antagonist[3] and SSR-149415 (**C**), a drug now in clinical trials for treatment of anxiety and depression.[4] Owing to the significance of this structural motif, the development of a catalytic asymmetric synthetic method for these compounds is highly valuable. Several examples of transition-metal-catalysed asymmetric preparation of 3-hydroxyoxindoles have been reported;[5] however, to the best of our knowledge, there is no example of the catalytic asymmetric synthesis of 3-aminooxindoles. Moreover, while the asymmetric palladium-catalysed α-arylation of amides, pioneered by Hartwig,[6] provides an efficient access to chiral 3-alkyl-3-aryloxindoles, there is no report on the application of this process to the synthesis of oxindoles with heteroatoms at the stereogenic center.



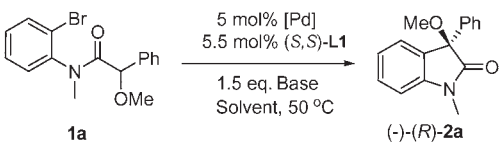
Recently, two of us (YJ and EPK) have reported the synthesis of new chiral *N*-heterocyclic carbene ligands (NHC's) and their successful application in the palladium-catalysed intramolecular α-arylation of amides, yielding chiral 3-alkyl-3-aryloxindoles with excellent enantiomeric purity (up to 95% ee).[7] Here we report the preliminary results on the enantioselective synthesis of chiral 3-alkoxyoxindoles and 3-aminooxindoles with high yield and enantioselectivity, using the new chiral NHC ligand **L3** (Scheme 1).[8]



Scheme 1 The Pd-catalysed asymmetric intramolecular α-arylation of amides to give chiral 3-alkoxy- or 3-amino-3-aryloxindoles.

Initially we carried out the reaction of substrate **1a** in the presence of 5 mol% $Pd(dba)_2$, 5.5 mol% (*S,S*)-**L1** and 1.5 eq.

Table 1 Optimization of the arylation of **1a** with (*S,S*)-**L1** as a ligand[a]



Entry	[Pd]	Solvent	Base	*t*/h	Yield[b] (%)	Ee[c] (%)
1	$Pd(dba)_2$	DME	^{t}BuONa	24	46	80
2	$Pd(dba)_2$	THF	^{t}BuONa	24	Trace	79
3	$Pd(dba)_2$	Toluene	^{t}BuONa	14	97	76
4	$Pd(dba)_2$	Dioxane	^{t}BuONa	24	43	77
5	$Pd(C_3H_5)Cl$	Toluene	^{t}BuONa	24	23	82
6	$Pd(OAc)_2$	Toluene	^{t}BuONa	24	43	77
7	$Pd_2(dba)_3$	Toluene	^{t}BuONa	14	63	75
8	$Pd(dba)_2$	Toluene	^{t}BuOK	24	35	82
9	$Pd(dba)_2$	Toluene	^{t}BuOLi	24	16	82
10	$Pd(dba)_2$	Toluene	NaHMDS	24	31	80
11	$Pd(dba)_2$	Toluene	NaOTMS	24	0	—
12[d]	$Pd(dba)_2$	Toluene	^{t}BuONa	24	0	—

[a] 0.2 mmol substrate, 4 mL solvent. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Without ligand.

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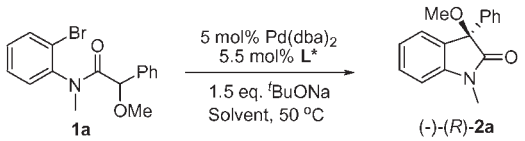
† This article is dedicated to Prof. Andy Holmes on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available: Experimental details for the preparation of the reported compounds. See DOI: 10.1039/b810858g

Table 2 Screening of ligands for the arylation reaction of **1a**[a]

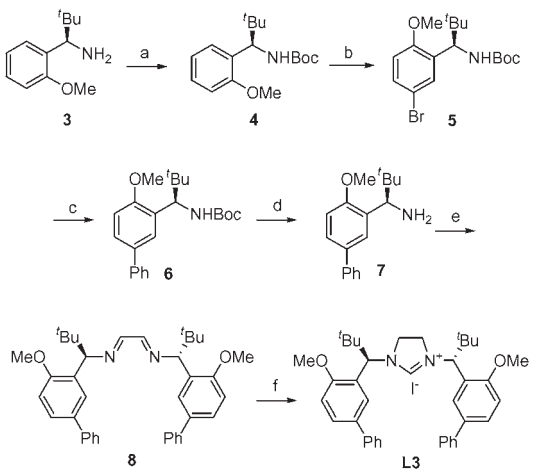


Entry	L*	Solvent	*t*/h	Yield[b] (%)	Ee[c] (%)
1	(*S*,*S*)-**L1**	Toluene	14	97	76
2	(*S*,*S*)-**L2**	Toluene	36	71	82
3	(*S*,*S*)-**L2**	DME	24	29	90
4	(*R*,*R*)-**L3**	Toluene	14	99[d]	92
5[e]	(*R*,*R*)-**L3**	Toluene	96	91[d]	97

[a] 0.2 mmol substrate, 4 mL solvent. [b] Isolated yield. [c] Determined by chiral HPLC. [d] (+)-(*S*)-**2a**. [e] At 25 °C.

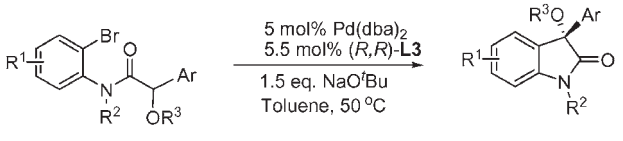
^{t}BuONa at 50 °C in DME, the same conditions which previously led to good results for synthesis of 3-alkyl-3-aryloxindoles.[7] The reaction proceeded smoothly to give oxindole **2a** in moderate yield (46%) and good enantioselectivity (80%) after 24 h (Table 1, entry 1). Among the solvents examined, toluene gave the highest yield although we noted a small erosion in asymmetric induction (Table 1, entry 3). Different palladium sources, such as $Pd(C_3H_5)Cl$, $Pd(OAc)_2$ and $Pd_2(dba)_3$, were tested next and $Pd(dba)_2$ was found to be the most effective (Table 1, entries 5–7). Product yields were lower when ^{t}BuOK, ^{t}BuOLi or NaHMDS were used in place of ^{t}BuONa (Table 1, entries 8–10). NaOTMS did not promote this arylation reaction (Table 1, entry 11) and no product was observed either when the reaction was carried out in the absence of the NHC ligand (Table 1, entry 12).

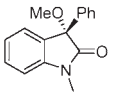
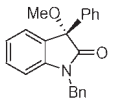
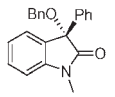
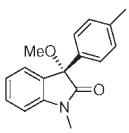
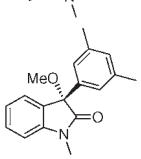
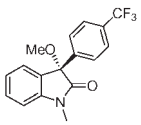
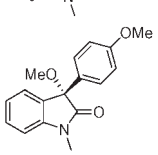
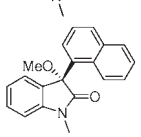
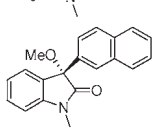
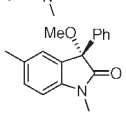
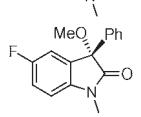
While yields were very good, product enantioselectivity did not reach the level we strove for. We thus turned to other chiral NHC ligands. The reaction with (*S*,*S*)-**L2**, the best performer



Scheme 2 Synthesis of the new chiral *N*-heterocyclic carbene ligand precursor (*R*,*R*)-**L3**. *Reagents and conditions:* (a) Boc_2O, NEt_3, CH_2Cl_2; (b) NBS, 1 N HCl–acetone, 91% (over 2 steps); (c) 2.5 mol% $Pd(dba)_2$, 5 mol% P^tBu_3, $PhB(OH)_2$, K_2CO_3, DME–H_2O, 96%; (d) CF_3CO_2H, H_2O, 92%; (e) glyoxal, Na_2SO_4, CH_2Cl_2, 71%; (f) (i) $NaBH_4$, MeOH; (ii) NH_4BF_4, $HC(OEt)_3$; (iii) NaI, acetone, 88% (over 3 steps).

Table 3 Substrate scope of chiral 3-alkoxy-3-aryloxindoles

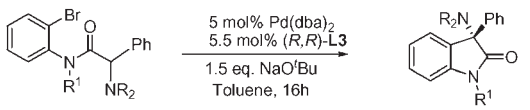


Entry	Product[a]		*t*/h	Yield[b] (%)	Ee[c] (%)
1		(+)-**2a**	14 96	99 91	92 97[d]
2		(+)-**2b**	16	93	85
3		(+)-**2c**	16	94	79
4		(+)-**2d**	16	99	91
5		(+)-**2e**	18	89	96
6		(+)-**2f**	36	45	82
7		(+)-**2g**	20	90	91
8		(-)-**2h**	18	99	86
9		(+)-**2i**	16	92	90
10		(+)-**2j**	16	95	93
11		(+)-**2k**	20	76	93

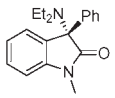
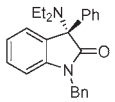
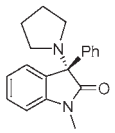
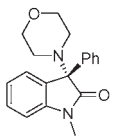
[a] 0.2 mmol substrate, 4 mL solvent. The absolute configuration shown (*S*) is that determined for (+)-**2a**. Assignment for **2b–2k** is made by analogy and is tentative. [b] Isolated yield. [c] Determined by chiral HPLC. [d] At 25 °C.

in our earlier work,[7] proceeded smoothly and the arylation product was obtained in 71% yield and 82% ee (Table 2, entry 2). The same reaction carried out in DME gave the product in

Table 4 Substrates scope of arylation to give chiral 3-aminooxindoles



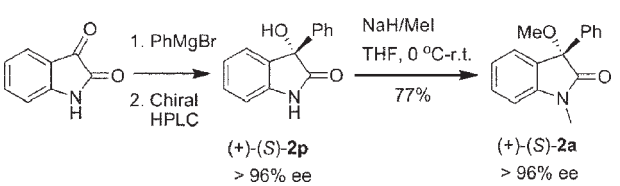
1l-o (*S*)-**2l-o**

Entry	Product[a]		T/°C	Yield[b] (%)	Ee[c] (%)
1		(−)-**2l**	80	93	75
2		(−)-**2m**	80	94	80
3		(−)-**2n**	50	96	90
4		(−)-**2o**	50	88	85

[a] 0.2 mmol substrate, 4 mL solvent. The absolute configuration shown (*S*) is that determined for (+)-**2a**. Assignment for **2l–2o** is made by analogy and is tentative. [b] Isolated yield. [c] Determined by chiral HPLC.

90% ee but with only 29% yield (Table 2, entry 3). The results could not be improved in spite of many efforts to optimize the reaction. Since **L1** yielded the product more efficiently than **L2** (Table 2, entries 1 and 2), modification of the former was investigated. Of all modifications carried out we here detail only the one (**L3**) that solved our problem in the end. **L3** was obtained from the chiral amine (*R*)-**3** in a high-yielding eight step procedure (Scheme 2). We were pleased to find that **L3** is a very effective ligand for the arylation reaction, yielding oxindole **2a** quantitatively in 92% ee after 14 h (Table 2, entry 4). Lowering the reaction temperature to 25 °C led to a further increase of the ee to 97%, albeit that a longer reaction time was required (Table 2, entry 5).

The aforementioned conditions were then applied to other alkoxy substrates as depicted in Table 3. The chiral oxindoles were obtained in good yields and with high enantioselectivity. Exceptions are reactions with substrates containing electron-withdrawing aryl substituents (**1f** and **1k**), for which reactions



Scheme 3 Determination of the absolute configuration of **2b**.

were sluggish (Table 3, entries 6 and 11). Also, although the yields remained high, oxindoles **2b** and **2c**, containing the easily removable benzyl group, were obtained with lower ee values (Table 3, entries 2 and 3).

Amides containing amino groups could also be arylated to oxindoles. Since substrates **1l** and **1m** proved less reactive than **1a–k**, a higher temperature (80 °C) was required to achieve full conversion. This resulted in lower enantioselectivities (Table 4, entries 1 and 2). Interestingly, reactions of substrates **1n** and **1o** can be carried out at 50 °C to give higher ee values (Table 4, entries 3 and 4), probably because the pyrrolidine and morpholine groups in substrates **1n** and **1o** are less sterically hindered than the dialkylamines in substrates **1l** and **1n**.

It remained to determine the absolute configuration of the products. This was done for (+)-(*S*)-**2a**. Addition of PhMgBr to isatin afforded *rac*-**2p** (Scheme 3).[9a,c] A highly enantiomerically enriched sample (>96% ee) was obtained by chiral HPLC (Chiracel OD column (*i*PrOH–*n*Hex = 10 : 90, 2.0 mL min^{-1}, 254 nm). Its $[\alpha]_D^{25}$ of +18.4 (c = 1.0, in MeOH) identified it as the (*S*)-enantiomer.[9b] Methylation afforded (*S*)-**2a** with an $[\alpha]_D^{25}$ of +81.2 (c = 0.5, in acetone).

In summary, we have developed an asymmetric Pd/NHC-catalysed intramolecular α-arylation of amide enolates containing heteroatom substituents to furnish optically active 3-alkoxy or 3-aminooxindoles in high yields and enantioselectivities. This protocol will be useful in the synthesis of biologically active chiral oxindoles.

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Notes and references

1 (*a*) K. C. Nicolaou, J. L. Hao, M. V. Reddy, P. B. Rao, G. Rassias, S. A. Synder, X. H. Huang, D. Y. K. Chen, W. E. Brenzovich, N. Giuseppone, P. Giannakakou and A. O'Brate, *J. Am. Chem. Soc.*, 2004, **126**, 15316; (*b*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209.
2 T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi and R. Nagata, *J. Med. Chem.*, 2001, **44**, 4461.
3 M. Ochi, K. Kawasaki, H. Kataoka and Y. Uchio, *Biochem. Biophys. Res. Commun.*, 2001, **283**, 1118.
4 (*a*) K. Bernard, S. Bogliolo and J. Ehrenfeld, *Br. J. Pharmacol.*, 2005, **144**, 1037; (*b*) G. Gilles and S. L. Claudine, *Stress*, 2003, **6**, 199.
5 (*a*) R. Shintani, M. Inoue and T. Hayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 3353; (*b*) T. Ishimaru, N. Shibata, J. Nagai, S. Nakamura, T. Toru and S. Kanemasa, *J. Am. Chem. Soc.*, 2006, **128**, 16488.
6 (*a*) S. Lee and J. F. Hartwig, *J. Org. Chem.*, 2001, **66**, 3402; (*b*) F. Glorius, G. Altenhoff, R. Goddard and C. Lehmann, *Chem. Commun.*, 2002, 2704; (*c*) T. Arao, K. Kondo and T. Aoyama, *Chem. Pharm. Bull.*, 2006, **54**, 1743; (*d*) T. Arao, K. Kondo and T. Aoyama, *Tetrahedron Lett.*, 2006, **47**, 1417.
7 E. P. Kündig, T. M. Seidel, Y.-X. Jia and G. Bernardinelli, *Angew. Chem., Int. Ed.*, 2007, **46**, 8484.
8 For the racemic version of this reaction, see: (*a*) S. P. Marsden, E. L. Watson and S. A. Raw, *Org. Lett.*, 2008, **10**, 2905; (*b*) J. M. Hillgren and S. P. Marsden, *J. Org. Chem.*, 2008, 73, doi: 10.1021/jo8010842.
9 (*a*) J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 1957, 4789; (*b*) S. Barroso, G. Blay, L. Cardona, I. Fernández, B. García and J. R. Pedro, *J. Org. Chem.*, 2004, **69**, 6821; (*c*) P. Magnus and R. Turnbull, *Org. Lett.*, 2006, **8**, 3497.

