DOI: 10.1002/chem.201002093

Novel and Efficient Copper-Catalysed Synthesis of Nitrogen-Linked Medium-Ring Biaryls

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Abstract: Herein, a new copper-catalysed strategy for the synthesis of rare nitrogen-linked seven-, eight- and nine-membered biaryl ring systems is described. It is proposed that the reaction proceeds through a highly activated intramolecularly co-ordinated copper catalyst. The process is technically simple, proceeds under relatively mild conditions, displays a broad substrate scope and forms biologically valuable products that are difficult to synthesise by other methods. We envisage that this methodology will prove useful in a wide synthetic context, with possible applications in both target-oriented and diversity-oriented synthesis.

Keywords: antibiotics · biaryls · copper · medium-ring compounds · synthetic methods

Introduction

The importance of the N-aryl amine bond in organic and medicinal chemistry is exemplified by its presence in a large number of biologically active and pharmaceutically relevant compounds.[1] One therapeutically pertinent class of molecule incorporating this moiety is cyclic nitrogen-linked (N-linked) biaryls. Numerous compounds based around seven-membered N-linked biaryl scaffolds have been found to demonstrate extraordinary biological properties; eight-membered-ring derivatives are also known, but are relatively scarce (Figure 1). Indeed, there are very few reported examples of N-linked medium-ring biaryl compounds. This can be primarily attributed to the difficulties associated with medium-ring synthesis in general;[5] medium-ring biaryl scaffolds in particular are known to be especially challenging synthetic targets.[6] As a result, compounds based around N-linked medium-ring biaryls are currently under-represented in small molecule libraries.

Typical approaches to these ring systems suffer from drawbacks including a reliance on harsh conditions (and thus limited functional group tolerability), difficulties in substrate preparation, low yields, unpredictability and limited structural diversity in the resulting compounds.[7] Thus, there is a need for the development of new and efficient methodology of broad utility for the synthesis of N-linked medium-ring biaryls so that the biological usefulness of this structural moiety can be investigated and exploited further. Herein, we describe a novel strategy for the synthesis of seven-, eight- and nine-membered N-linked biaryl ring systems from acyclic precursors that is based around the ability of an activated intramolecular copper species to facilitate C-(aryl)–N bond formation and thus affect ring closure.

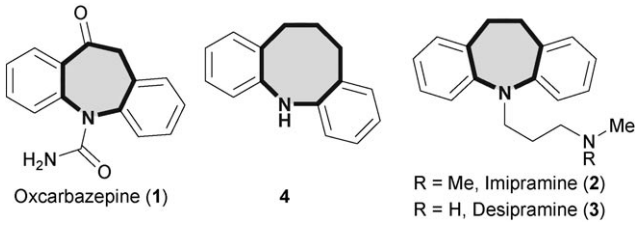

Figure 1. Some examples of biologically active compounds based around N-linked medium-ring biaryl scaffolds (highlighted in bold). Oxcarbazepine (**1**) is used in the treatment of epilepsy;[2] imipramine (**2**) and desipramine (**3**) are commonly used as anti-depressants[3] and compound **4** has been reported to have analgesic and anti-inflammatory effects.[4]

Results and Discussion

Palladium- and copper-mediated C(aryl)–N bond forming reactions are synthetically powerful processes that are used routinely in both academic and industrial settings.[8] Intramolecular N-arylations mediated by these metals have been

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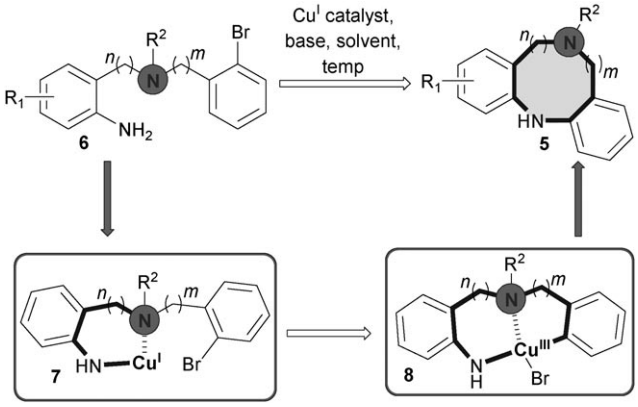
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201002093.

reported, primarily for the generation of five-, six- and, to a lesser extent, seven-membered rings.[9] Seven-membered N-linked biaryl systems are also commonly accessed by methods involving the direct metal-mediated N-arylation of acyclic precursors;[7d–g] however, there is much less precedence for the synthesis of eight- and nine-membered analogues by this approach despite its arguably being the most synthetically versatile and conceptually straightforward route towards such scaffolds. To this end we envisaged a new copper-catalysed strategy for the direct N-arylation of acyclic precursors based around internal chelation and activation of the copper metal.

Buchwald et al. have proposed that copper-mediated C(aryl)–N bond-forming reactions between amines and aryl halides may proceed through a copper(I)/copper(III) couple.[10] Co-ordination of the copper(I) species to the amine is followed by oxidative addition to the aryl halide and subsequent reductive elimination yields the coupled product.[10] Based on this mechanism, we hypothesised that the copper-catalysed synthesis of N-linked medium-ring biaryls of general form **5** by direct C(aryl)–N bond formation may be facilitated by the presence of an auxiliary nitrogen atom in the acyclic precursors **6** (Scheme 1). The lone



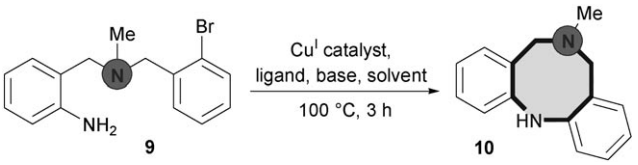
Scheme 1. Mechanistic blueprint for the copper(I)-catalysed N-linked biaryl cyclisation strategy. Possible ancillary ligands omitted for clarity. The auxiliary Ⓝ atom allows internal chelation to form the active intramolecular copper species and its geometry may facilitate ring closure.

pair of electrons on this atom could be involved in co-ordination to any copper-based intermediates. Thus, in combination with the aniline nitrogen, an internal diamine species is effectively present in the substrate. The use of chelating bidentate ligands, in particular diamine ligands, in copper-mediated cross-coupling reactions is known to be associated with high levels of catalyst reactivity.[1a,8f,g,i] The internal co-ordination of the diamine moiety of substrates of the form **6** to the copper(I) catalyst would thus be expected to yield a highly activated intramolecular form of copper, in which the metal is incorporated in a six-membered chelate (**7**, Scheme 1).

In addition, such chelation would be expected to bring the reactive copper metal into close proximity with the aryl halide bond, which may facilitate the subsequent oxidative addition step to generate intermediates of the form **8** (also termed the copper(I)-mediated aryl halide activation step). In analogous cyclisation substrates without an auxiliary nitrogen, oxidative addition across the aryl–halide bond requires the formation of medium-to-large ring systems. However, in the case of internally chelated systems of the form **7**, the oxidative addition step requires the formation of smaller ring sizes (as bicyclo metallocyclic species are generated) and, as such, are expected to be more kinetically facile.[11,12]

Initial optimisation studies focused upon the cyclisation of aniline derivative **9** to generate eight-membered N-linked biaryl **10** (Table 1). A variety of copper-catalysed amination

Table 1. Optimisation of reaction conditions for the intramolecular cyclisation reaction.[a]



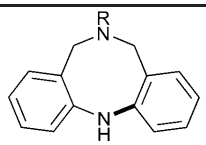
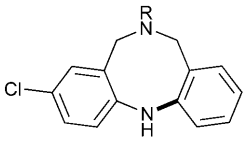
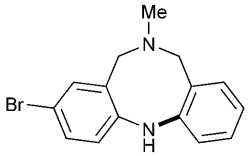
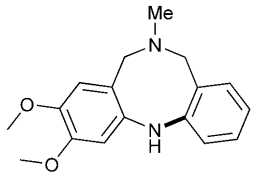
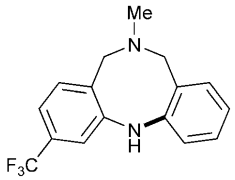
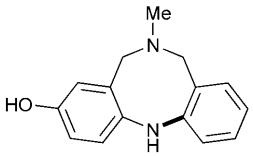
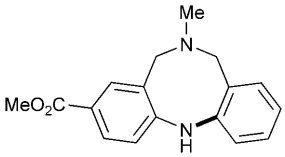
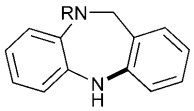
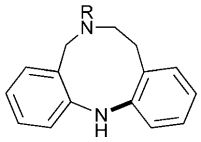
	Ligand	Base	Copper source	Solvent	Yield [%][b]
1	2,4-pentanedione	Cs_2CO_3	CuI	DMF	63
2[c]	2,4-pentanedione	Cs_2CO_3	CuI	DMF	55
3	2-acetylcyclohexanone	Cs_2CO_3	CuI	DMF	42
4[d]	2,4-pentanedione	Cs_2CO_3	CuI	ethanol	85
5	2,4-pentanedione	Cs_2CO_3	$Cu(OAc)_2$	DMF	72
6	2,4-pentanedione	K_3PO_4	CuI	DMF	43
7	ethylene glycol	Cs_2CO_3	CuI	ethylene glycol	91

[a] Reactions were performed at a substrate concentration of 0.05 M by using catalyst (10 mol%), base (2 equiv), ligand (20 mol%; except in the case of entry 7, in which the ligand is the solvent). For the synthesis of substrate **9**, see the Supporting Information. [b] Yield of isolated product. [c] Reaction left for 24 h. [d] Reaction heated to 78 °C (reflux).

conditions based on those previously reported by Buchwald et al. were examined.[13] In all cases, the desired product was isolated. Pleasingly, an excellent yield of **10** was obtained by use of a combination of copper(I) iodide, Cs_2CO_3 and ethylene glycol (as both solvent and ligand, Table 1, entry 7) at a substrate concentration of 0.05 M. Under these conditions there was no evidence of competing intermolecular couplings, despite the relatively high concentration employed.[14] This implies that the intramolecular process is significantly more favourable. Furthermore, preliminary investigations established that two-component intermolecular coupling was not significant under the optimised cyclisation conditions.[15] These results highlight the importance of the auxiliary nitrogen atom in facilitating C–N bond formation under these conditions, which lends some degree of support to the mechanistic concept.

With optimised conditions in hand, the cyclisation of various other acyclic precursors was examined in order to explore the substrate scope of the methodology (Table 2). A range of electron donating and withdrawing substituents on the aniline-based ring portion were tolerated, allowing

Table 2. Synthesis of seven-, eight- and nine-membered N-linked biaryls.[a]

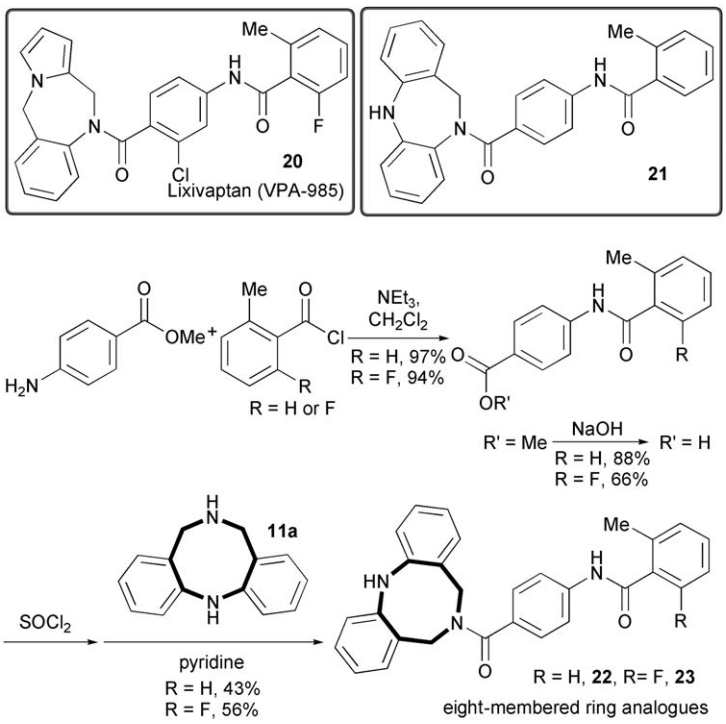
	Product		Yield [%]
1		R = H, **11a** R = Me, **11b** R = allyl, **11c** R = benzyl, **11d**	64 91 97 80
2		R = H, **12a** R = Me, **12b**	53 86
3		**13**	84
4		**14**	77
5		**15**	96
6		**16**	62
7		**17**	45[b]
8		R = H, **18a** R = Me, **18b**	82 94
9		R = H, **19a** R = Me, **19b**	82 93

[a] Conditions in all cases: CuI (10 mol%), Cs_2CO_3 (2 equiv), ethylene glycol (substrate concentration of 0.05 M), 100 °C, 3 h. The carbon–carbon bond formed during the cyclisation process is highlighted in bold. The syntheses of the acyclic precursors are described in the Supporting Information. [b] A 30% yield of the ethylene glycol *trans*-esterified derivative of the ring-closed product was also obtained.

access to a variety of eight-membered N-linked biaryl rings (**11**–**17**) in good-to-excellent yields. Halogen atoms could be successfully incorporated into the product scaffolds, with no evidence of competing intermolecular processes (Table 2, entries 2 and 3).

Significantly, the reaction can be carried out on substrates bearing free hydroxyl and ester groups (Table 2, entries 6 and 7); these functionalities are valuable as they provide possible synthetic handles for post-cyclisation structure elaboration around the biaryl core. In addition, we found that the reaction conditions were tolerant of both allyl and benzyl protecting groups on the auxiliary nitrogen (Table 2, entry 1), and unprotected amine derivatives could also be smoothly converted into the corresponding product (Table 2, entries 1 and 2) providing an additional point for further synthetic manipulation of the cyclised products (see below). The methodology was also extended to the formation of seven- and nine-membered rings **18** and **19** from the corresponding acyclic precursors in good-to-excellent yields (Table 2, entries 8 and 9).

The modification of the central core of known bioactive compounds in an attempt to discover structurally novel derivatives (so-called scaffold hopping) plays a central role in modern medicinal chemistry.[16] In this context, given the relative scarcity of eight-membered N-linked biaryls (see above) a potentially valuable application of the new methodology is to form eight-membered ring analogues of known N-linked biaryl-based bioactive molecules and other related nitrogen-containing ring systems. To this end, we applied the methodology in the concise synthesis of analogues of compounds **20** (Lixivaptan or VPA-985) and **21** (Scheme 2).[17] These are both arginine vasopressin (AVP)

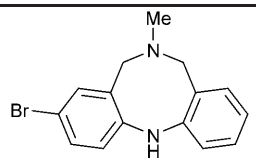
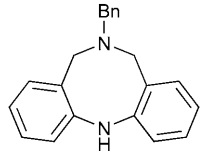
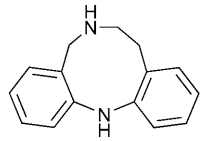
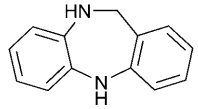


Scheme 2. Synthesis of eight-membered-ring analogues of arginine vasopressin (AVP) antagonists **20** and **21**.

antagonists with potential applications in the treatment of disorders characterised by excess renal reabsorption of free water, such as congestive heart failure and liver cirrhosis. Lixivaptan (**20**) is currently in clinical trials for the treatment of congestive heart failure.[18] Two analogues of these compounds **22** and **23** were synthesised; in both cases, the key step involved the regioselective mono-acylation of eight-membered N-linked biaryl **11a**, thus demonstrating the ability to conduct additional synthetic manipulations on the biaryl core of such compounds.

The biological activities of the compounds disclosed in this report are currently being evaluated and preliminary investigations have yielded some promising results. For example, inhibition of proliferation phenotypic assays have identified compounds capable of modulating the growth of the Gram-positive bacterium *Staphylococcus aureus* and the Gram-negative bacterium *Escherichia coli* (Table 3). *S. aureus* is well documented as an opportunistic human pathogen that is responsible for several serious infections including pneumonia, meningitis and scalded skin syndrome.[19] Strains of *E. coli* are known to cause a range of infections and diseases, including urinary tract infections, meningitis and diarrheal disease.[19] Several of the compounds also showed activity in phenotypic assays designed to identify possible antagonists of bacterial quorum sensing.[20] For example, compounds **11d**, **12b**, **13**, **18a** and **19a** inhibited violacein production in *Chromobacterium violaceum* biosensor strain CV026 at a concentration of 200 μM and compound **19a** inhibited prodigiosin production in *Serratia* ATCC 39006 biosensor strain SP19 at a concentration of 50 μM.[21] Several clinically relevant pathogens use quorum sensing systems to regulate processes associated with virulence.[22] Thus, the identification of small molecules that can antagonise quorum sensing pathways has attracted significant interest in recent years.[23] A full account of the results of our screening experiments will be reported in due course.

Table 3. Some examples of compounds from this study which display growth inhibitory activity against various bacterial strains. NS = no significant activity observed.

	Compounds		Growth inhibition [%][a] *E. coli*[b]	*S. aureus*[c]
1		**13**	NS	76
2		**11d**	54	40
3		**19a**	30	NS
4		**18a**	NS	48

[a] Percentage of growth inhibition at a compound concentration of 200 μM after 8 h of incubation at 37 °C. [b] *E. coli*. (strain ESS). [c] *S. aureus* (MSSA strain H) incubated in the presence of an enhanced oxygen atmosphere.

We hypothesise that the success of the copper-catalysed N-linked medium-ring biaryl formation process is due to the presence of an appropriately positioned auxiliary nitrogen atom in the acyclic substrates (Scheme 1). It is believed that the lone pair of electrons on this nitrogen is involved in co-ordination to copper-based species generated during the reaction process, thereby facilitating cyclisation. Attempts to obtain a crystal structure of any of the copper-based intermediates have thus far been unsuccessful. However, the inability to cyclise substrates that are either lacking the auxiliary nitrogen (**24**, Figure 2) or have a carbonyl group incorporated adjacent to the auxiliary nitrogen (**25**–**27**, Figure 2) provides indirect evidence for the importance of the free nitrogen lone pair on the auxiliary nitrogen and thus the presence of a copper-based intermediate species co-ordinated to this atom.[24] The absence of any significant intermolecular coupling under the cyclisation conditions provides additional support for the important role played by the auxiliary nitrogen atom.[14]

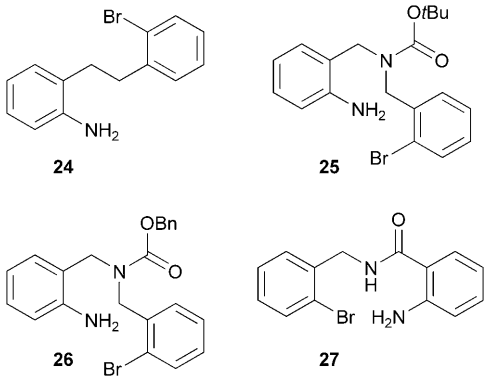


Figure 2. Substrates that do not undergo cyclisation under the reaction conditions. In **25**–**27** the auxiliary (benzylic) nitrogen atom forms part of an amide or carbamate functionality. As such, the lone pair of electrons of the auxiliary nitrogen can be delocalised into a carbonyl bond and thus is not as available for co-ordination to a copper species.

Conclusion

In summary, we have developed a new strategy for the synthesis of nitrogen-linked seven–nine-membered-ring biaryls, based on the premise of generating a highly active intramolecular form of copper. The process is technically simple, proceeds under relatively mild conditions, displays a broad

substrate scope, uses inexpensive copper catalysts and forms biologically valuable products that are difficult to synthesise by other methods. Furthermore, the strategy outlined in this report may conceivably be applied to the synthesis of a variety of other ring systems, including larger-sized cyclic N-linked biaryls, N-linked biaryls incorporating heterocycles and even ring systems involving different biaryl linking heteroatoms.[25] As such we envisage that this methodology will prove useful in a wide synthetic context, with possible applications in both target-oriented and diversity-oriented synthesis.[26]

Experimental Section

General experimental procedure for medium-ring biaryl synthesis: Ethylene glycol (2 mL per mmol substrate) was added to a mixture of the acyclic precursor (1 equiv), Cs_2CO_3 (2 equiv) and CuI (0.1 equiv). The reaction mixture was stirred at 100 °C for 3 h, cooled to room temperature and filtered through Celite. The solution was diluted with Et_2O (4.0 mL per mmol substrate) and the ethylene glycol was removed from the organic layer by washing with a large excess of water. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by using flash column chromatography on silica.

Analytical data for 5,6,7,12-tetrahydrodibenzo[*b*,*g*][1,5]diazocine (11a): $R_f = 0.16$ (SiO_2; MeOH/CH_2Cl_2, 1:9); ^{1}H NMR (500 MHz, CD_3OD): $\delta =$ 5.66–5.61 (m, 2H; aryl H), 5.57 (dd, $J = 7.5$, 1.5 Hz, 2H; aryl H), 5.40 (dd, $J = 8.0$, 1.0 Hz, 2H; aryl H), 5.33 (apparent td, $J = 7.5$, 1.0 Hz, 2H; aryl H), 2.40 (s, 4H; CH_2), 1.84–1.81 ppm (m, 2H; NH, CH_2NH); ^{13}C NMR (125 MHz, CD_3OD): $\delta = 143.80$, 130.57, 126.98, 121.36, 118.74, 116.57, 43.92 ppm; IR: $\tilde{\nu}_{max} =$ 3384 (m; N–H), 3288 (m; N–H), 3195 (m; aromatic C–H), 3028 (m; aromatic C–H), 2925 (m; C–H), 2852 (m; C–H), 1727 (m), 1606 (m; aromatic C=C), 1585 (m; aromatic C=C), 1470 (s), 1454 (m), 1332 (s), 1297 (m), 1253 cm^{-1} (m); HRMS (ESI+): *m/z* calcd for $C_{14}H_{15}N_2^+$: 221.1235 $[M+H]^+$; found: 221.1244 ($\Delta = 4.3$ ppm).

Acknowledgements

The authors thank Bayer Schering and the EU, EPSRC, BBSRC, MRC, Wellcome Trust and Newman Trust for funding.

[1] a) R. A. Altman, S. L. Buchwald, *Nat. Protoc.* **2007**, *2*, 2474; see, for example: b) M. T. Bilodeau, A. E. Balitza, T. J. Koester, P. J. Manley, L. D. Rodman, C. Buser-Doepner, K. E. Coll, C. Fernandes, J. B. Gibbs, D. C. Heimbrook, W. R. Huckle, N. Kohl, J. J. Lynch, X. Mao, R. C. McFall, D. McLoughlin, C. M. Miller-Stein, K. W. Rickert, L. Sepp-Lorenzino, J. M. Shipman, R. Subramanian, K. A. Thomas, B. K. Wong, S. Yu, G. D. Hartman, *J. Med. Chem.* **2004**, *47*, 6363; c) B. M. Andresen, S. Caron, M. Couturier, K. M. DeVries, N. M. Do, K. Dupont-Gaudet, A. Ghosh, M. Girardin, J. M. Hawkins, T. M. Makowski, M. Riou, J. E. Sieser, J. L. Tucker, B. C. Vanderplas, T. J. N. Watson, *Chimia* **2006**, *60*, 554; d) I. E. Wrona, A. E. Gabarda, G. Evano, J. S. Panek, *J. Am. Chem. Soc.* **2005**, *127*, 15026.

[2] S. M. Grant, D. Faulds, *Drugs* **1992**, *43*, 873.

[3] a) P. Onali, S. Dedoni, M. C. Olianas, *J. Pharmacol. Exp. Ther.* **2010**, *332*, 255; b) M. Frankowska, A. Golda, K. Wydra, P. Gruca, M. Papp, M. Filip, *Eur. J. Pharmacol.* **2010**, *627*, 142; c) W. Schindler, F. Häfliger, *Helv. Chim. Acta* **1954**, *37*, 472; d) A. M. Jeannotte, J. G. McCarthy, A. Sidhu, *Neurosci. Lett.* **2009**, *467*, 86; e) A. Kumar, R. Garg, V. Gaur, P. Kumar, *Neurosci. Lett.* **2009**, *467*, 72.

[4] a) U. B. Olsen, NOVO NORDISK A/S, Novo Alle, DK-2880, Bagsværd, Denmark, WO9722342, **1997**; b) K. E. Andersen, U. B. Olsen, H. Petersen, F. C. Groenvald, U. Sonnewald, T. K. Joergensen, H. S. Andersen, NOVO NORDISK A/S, Novo Alle, DK-2880, Bagsværd, Denmark, WO9518793 (A1), **1995**; c) K. Kawashima, T. Saraie, Y. Kawano, T. Ishiguro, *Chem. Pharm. Bull.* **1978**, *26*, 942; d) J. R. Michel, J. L. Fouche, Rhône-Poulenc S.A., Paris, France, DE 1180751 (B), **1964**.

[5] The formation of medium rings from acyclic precursors is disfavoured by entropic and enthalpic factors and is thus both thermodynamically and kinetically challenging; G. Rousseau, *Tetrahedron* **1995**, *51*, 2777.

[6] a) X. B. Su, G. L. Thomas, W. R. J. D. Galloway, D. S. Surry, R. J. Spandl, D. R. Spring, *Synthesis* **2009**, 3880; b) X. B. Su, D. S. Surry, R. J. Spandl, D. R. Spring, *Org. Lett.* **2008**, *10*, 2593; c) D. S. Surry, X. B. Su, D. J. Fox, V. Franckevicius, S. J. F. Macdonald, D. R. Spring, *Angew. Chem.* **2005**, *117*, 1904; *Angew. Chem. Int. Ed.* **2005**, *44*, 1870.

[7] Selected examples of the formation of seven-membered and medium-sized N-linked biaryl ring systems: for intramolecular aryl–aryl (C–C bond) coupling (Ullmann-type chemistry) and intramolecular amide bond formation followed by reduction to form the amine, see: a) F.-W. Sum, J. Dusza, E. D. Santos, G. Grosu, M. Reich, X. Du, J. D. Albright, P. Chan, J. Coupet, X. Ru, H. Mazandarani, T. Saunders, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2195; for reductive phenylation and cyclisation of nitroarenes (C–N bond formation), see: b) C. A. Seymour, F. D. Greene, *J. Am. Chem. Soc.* **1980**, *102*, 6384; c) M. de Carvalho, A. E. P. M. Sorrilha, J. A. R. Rodrigues, *J. Braz. Chem. Soc.* **1999**, *10*, 415; for 7-membered N-linked biaryl systems generated by methods involving the direct metal-mediated N-arylation of acyclic precursors, see: d) M. Carril, R. SanMartin, F. Churruca, I. Tellitu, E. Dominguez, *Org. Lett.* **2005**, *7*, 4787; e) N. Carril, R. SanMartin, E. Dominguez, I. Tellitu, *Tetrahedron* **2007**, *63*, 690; f) L. Guo, B. Li, W. L. Huang, G. Pei, D. W. Ma, *Synlett* **2008**, 1833; g) B. J. Margolis, J. J. Swidorski, B. N. Rogers, *J. Org. Chem.* **2003**, *68*, 644.

[8] a) E. R. Strieter, D. G. Blackmond, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4120; for reviews on metal-mediated cross-coupling reactions: for palladium, see: b) J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2154; *Angew. Chem. Int. Ed.* **1998**, *37*, 2046; c) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805; d) J. F. Hartwig, *Acc. Chem. Res.* **1998**, *31*, 852; e) C. G. Frost, P. Mendonça, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2615; for copper, see: f) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400; g) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337; h) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054; i) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2010**, *1*, 13.

[9] Selected examples of the formation of medium ring systems by metal-mediated intramolecular N-arylation: for palladium, see: a) G. Cuny, M. Bois-Choussy, J. P. Zhu, *J. Am. Chem. Soc.* **2004**, *126*, 14475; for zinc, see: b) R. Omar-Amrani, A. Thoma, E. Brenner, R. Schneider, Y. Fort, *Org. Lett.* **2003**, *5*, 2311.

[10] E. R. Strieter, B. Bhayana, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 78.

[11] This may be a particularly relevant consideration as the Cu^I-mediated aryl halide activation step is known to be rate determining in the copper-catalysed N-arylation of amides (see ref. [10]).

[12] Recently, Sperotto et al. have described the use of well-defined aminoarenethiolato-copper(I) (pre-)catalysts in C–N coupling reactions, in which a copper atom and a chelating amino 'arm' are present within the catalyst structure itself (cf. our work in which the chelating amino moiety is incorporated into the substrate), see: E. Sperotto, G. P. M. Van Klink, J. D. De Vries, G. Van Koten, *Tetrahedron* **2010**, *66*, 3478. The (pre-)catalysts of Sperotto et al. where found to be soluble in common organic solvents. It may be the case that the chelating nitrogen-type arrangement present in the acyclic substrates used in our report helps to enhance the solubility of the copper(I) catalyst, facilitating reactivity.

[13] a) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 793; b) F. Y. Kwong, A. Klapars, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 581.
[14] Medium ring formations from acyclic precursors typically require the use of dilute reaction conditions in order to maintain a low (effective) concentration of the reacting compound and thereby minimise competing intermolecular reactions; see ref. [5] and a) P. Ruggli, *Justus Liebigs Ann. Chem.* **1912**, *392*, (1), 92; b) K. Ziegler, H. Eberle, H. Ohlinger, *Justus Liebigs Ann. Chem.* **1933**, *504*, (1), 94. Some preliminary experiments (using $Cu^{I}I$ (10 mol%), acetylacetone (20 mol%), Cs_2CO_3 (2 equiv), DMF, 100 °C, 3 h) showed that cyclisation could be carried out at higher concentrations without any significant impact upon the isolated yield of the cyclised product: i) 0.05 M, 91%, ii) 0.1 M, 85%, iii) 0.2 M, 84%, iv) 0.5 M, 71% and v) 1 M, 51%. Only at a concentration of 1 M was any significant intermolecular coupling observed.
[15] Control experiments were carried out to see if intermolecular coupling between aniline and 4-bromobiphenyl- or 4-methoxybromobenzene would occur under the optimised cyclisation conditions. At a total substrate concentration of 0.05 M (the substrate concentration used for cyclisation), there was no evidence of any intermolecular coupling after 3 h. The fact that cyclisation was observed at this concentration highlights the importance of the auxiliary nitrogen atom in facilitating C–N bond formation under these conditions and lends some support to our mechanistic hypothesis outlined in Scheme 1. No intermolecular coupling between aniline and 4-bromobiphenyl- or 4-methoxybromobenzene was observed at a total substrate concentration of 0.15 M.
[16] a) H.-J. Böhm, A. Flohr, M. Stahl, *Drug Discovery Today: Technol.* **2004**, *1*, 217; b) H. Zhao, *Drug Discovery Today* **2007**, *12*, 149.
[17] See ref. [7a] and a) F. Wong, A. T. Blei, L. M. Blendis, P. J. Thuluvath, *Hepatology* **2003**, *37*, 182; b) J. D. Albright, M. F. Reich, E. G. D. Santos, J. P. Dusza, F.-W. Sum, A. M. Venkatesan, J. Coupet, P. S. Chan, X. Ru, H. Mazandarani, T. Bailey, *J. Med. Chem.* **1998**, *41*, 2442.
[18] Study to evaluate the effects of oral administration of Lixivaptan in patients with congestive heart failure: http://clinicaltrials.gov/ct2/show/NCT01055912; accessed 4th April 2010.
[19] P. R. Murray, E. J. Baron, M. A. Pfaller, F. C. Tenover, R. H. Yolken, *Manual Of Clinical Microbiology*, 7th ed., ASM Press Washington, D. C., **1999**.
[20] Quorum sensing is the intercellular signalling mechanism, mediated by small molecules that numerous species of bacteria use to co-ordinate their gene expression in a cell-density dependent manner; a) W. C. Fuqua, S. C. Winans, E. P. Greenberg, *J. Bacteriol.* **1994**, *176*, 269; b) B. L. Bassler, R. Losick, *Cell* **2006**, *125*, 237; c) C. Fuqua, M. R. Parsek, E. P. Greenberg, *Annu. Rev. Genet.* **2001**, *35*, 439.
[21] The bacterial strains CV026 and SP19 are mutants in which the production of the pigments violacein (purple) and prodigiosin (red), respectively, is under quorum sensing control and is dependent upon the exogenous addition of the corresponding native acyl homoserine lactone or a functional equivalent. Antagonists of quorum sensing can be identified through the inhibition of pigment production under these conditions. For more details see the Supporting Information and S. Poulter, T. M. Carlton, X. Su, D. R. Spring, G. P. C. Salmond, *Environ. Microbiol. Rep.* **2010**, *2*, 322.
[22] For example, in many bacterial species biofilm formation and the production and secretion of virulence factors are regulated by quorum sensing: a) P. Williams, K. Winzer, W. C. Chan, M. Camara, *Philos. Trans. R. Soc., B* **2007**, *362*, 1119; b) S. R. Chhabra, B. Philipp, L. Eberl, M. Givskov, P. Williams, M. Camara in *Chemistry of Pheromones and Other Semiochemicals II, Vol. 240* (Ed.: S. Schulz), Springer, Heidelberg, **2005**, p. 279.
[23] For recent discussions, see: a) M. E. Pomianek, M. F. Semmelhack, *ACS Chem. Biol.* **2007**, *2*, 293; b) N. Ni, M. Li, J. Wang, B. Wang, *Med. Res. Rev.* **2009**, *29*, 65; c) S. R. Chhabra, C. Harty, D. S. W. Hooi, M. Daykin, P. Williams, G. Telford, D. I. Pritchard, B. W. Bycroft, *J. Med. Chem.* **2003**, *46*, 97; d) T. Hjelmgaard, T. Persson, T. B. Rasmussen, M. Givskov, J. Nielsen, *Bioorg. Med. Chem.* **2003**, *11*, 3261; e) G. D. Geske, J. C. O'Neil, D. M. Miller, M. E. Mattmann, H. E. Blackwell, *J. Am. Chem. Soc.* **2007**, *129*, 13613.
[24] There was no evidence for the formation of any cyclised products when substrates **24**–**28** were subjected to the standard cyclisation conditions (by ^{1}H NMR and LCMS or HRMS analysis). In addition to the chelation argument discussed in the main text, another possible explanation as to why cyclisation was not possible by using substrates with a carbonyl group incorporated adjacent to the auxiliary nitrogen is that delocalisation of the nitrogen lone pair creates a more rigid system which cannot adopt a conformation suitable for ring closure. Whilst this possibility cannot be discounted outright, in light of other observations, such as the result with compound **24**, it is likely that the auxiliary nitrogen lone pair plays an important role in the progress of the cyclisation process.
[25] Preliminary work has shown that under slightly modified reaction conditions it is possible to form an O-linked biaryl ring system by using a phenol derivative containing an auxiliary nitrogen atom; see the Supporting Information for full details.
[26] For recent reviews on diversity-oriented synthesis (DOS), see: a) S. L. Schreiber, *Nature* **2009**, *457*, 153; b) W. R. J. D. Galloway, D. R. Spring, *Expert Opin. Drug Discovery* **2009**, *4*, 467; c) E. Nielsen, S. L. Schreiber, *Angew. Chem.* **2008**, *120*, 52; *Angew. Chem. Int. Ed.* **2008**, *47*, 48; d) W. R. J. D. Galloway, A. Bender, M. Welch, D. R. Spring, *Chem. Commun.* **2009**, 2446; e) C. Cordier, D. Morton, S. Murrison, A. Nelson, C. O'Leary-Steele, *Nat. Prod. Rep.* **2008**, *25*, 719.

Received: July 22, 2010
Revised: October 21, 2010
Published online: February 2, 2011

