Palladium-catalysed N-annulation routes to indoles: the synthesis of indoles with sterically demanding N-substituents, including demethylasterriquinone A1[†]

Anthony J. Fletcher,^a Matthew N. Bax^b and Michael C. Willis^{*a}

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Tandem palladium-catalysed aryl and alkenyl C–N bond formation allows the synthesis of a variety of indoles bearing sterically demanding N-substituents, including the natural product demethylasterriquinone A1.

The remarkable range of biological and medicinal properties displayed by indole-containing molecules has resulted in sustained interest in developing new syntheses of these important hetero-cycles.¹ N-Substituted indoles represent an important subclass² and, given the low nucleophilicity of indole nitrogen atoms, they can represent a significant synthetic challenge.³ This is particularly true when the N-substituent is sterically demanding, such as the reverse-prenyl group contained in the simple natural products 1⁴ and demethylasterriquinone A1 2 (Scheme 1).⁵

The majority of indole syntheses involve cyclisation of an acyclic precursor that contains the key N-atom. To adapt these syntheses to the preparation of N-substituted indoles requires that either the precursors must be modified (to include the substituent), or an efficient and selective functionalisation of an indole N-H must be achieved. This is often problematic; for example, syntheses of the simple natural product 1, and related structures, resort to functionalisation of indoline derivatives with modified, more reactive, alkylating reagents.⁶ This then necessitates re-oxidation to the indole oxidation level and modification of the appended group to achieve the target structure. A strategy that avoids these difficulties relies on introducing the N-atom, together with any N-substituent, at the final stage of the synthesis. In this communication we demonstrate how such a strategy, employing sequential inter- and intramolecular palladium-catalysed amination reactions, can be used to prepare a range of indoles bearing



Scheme 1 N-Functionalised indole natural products.

sterically demanding N-substituents, including the natural product demethylasterriquinone A1 (Scheme 2).

Recently, we have reported indole syntheses based on the general disconnection presented in Scheme 2 and have shown that they are effective for a variety of N-nucleophiles, including simple amines, anilines, amides, carbamates and sulfonamides.⁷ However, these protocols failed when we attempted to employ bulky amines such as *tert*-butylamine. Although disappointing, Pd-catalysed aryl amination and etherification reactions often display high levels of substrate specificity,⁸ and we reasoned that it should be possible to identify a catalyst system that was efficient for tandem coupling of sterically demanding N-nucleophiles with alkenyl-aryl dihalides (Table 1).

We selected the coupling of reverse-prenyl amine 3^9 with simple dihalogenated styrenes 4 as our test system; the attempted union of 3 and 4a employing a catalyst composed of Pd(OAc)₂ and BINAP using NaO'Bu as base resulted in no reaction (entry 1). We next turned our attention to the use of electron-rich biphenyl ligands 5, 6 and 7.¹⁰ Although ligands 5 and 6 were ineffective, the use of ligand 7 delivered indole 8 in 17% yield (entries 2-4). Increasing the temperature from 100 to 130 °C improved this to 37% (entry 5). Due to poor mass balance we suspected decomposition of the styrene substrate was occurring and reasoned that the alkenylchloride variant of the substrate would be more stable; thus, reaction of the Cl, Br-styrene 4b for a shorter reaction time delivered the indole 8 in a similar yield (entry 6). Unreacted starting material was also recovered, suggesting decomposition was no longer a problem. The bulky electron-rich phosphine P'Bu₃ has been shown to be a particularly effective ligand for a variety of palladium catalysed processes employing aryl chloride substrates,¹¹ and we were pleased to find that the use of this ligand with the Br, Cl-substrate delivered the required indole in 68% yield (entry 7). The final entry confirmed that the higher temperature was required to achieve an efficient reaction.

We next evaluated the range of sterically demanding N-nucleophiles that could be coupled to the Cl, Br-styrene (4b) using the optimised conditions (Table 2). The reaction proved to be efficient for a range of bulky alkyl amines with the substituted



Scheme 2 A palladium-catalysed N-annulation route to sterically demanding N-functionalised indoles.

^aDepartment of Chemistry, University of Oxford, Chemical Research Laboratory, Mansfield Road, Oxford, UK OX1 3TA. E-mail: michael.willis@chem.ox.ac.uk; Fax: +44 (0)1865 285002; Tel: +44 (0)1865 285126

^bDepartment of Chemistry, University of Bath, Bath, UK BA2 7AY † Electronic supplementary information (ESI) available: Experimental procedures and data for all new compounds. See DOI: 10.1039/b712227f

Table 1An N-annulation route to indole 8^a



^{*a*} Conditions: styrene (1.0 equiv.), amine (3.0 equiv.), $Pd(OAc)_2$ (5 mol%), ligand (12 mol%), NaO'Bu (2.5 equiv.), PhMe, sealed tube. Br, Br-substrate used as a 5 : 1 ratio of Z : E isomers; Cl, Br-substrate as a 4.3 : 1 ratio. ^{*b*} Isolated yields. ^{*c*} Ligand used as HBF₄ salt. ^{*d*}



indoles being isolated in good yields in all cases (entries 1–5). α -Methyl benzylamine was also coupled effectively (entry 6), as were a range of *ortho*- and di-*ortho*-substituted anilines (entries 7–10). The formation of the adamantyl- and 2,6di(isopropyl)phenyl-substituted examples highlight that very hindered couplings are possible using this system (entries 5 and 9).

Variation of the styrene component was also possible (Table 3). All of the substrates shown in Table 3 were prepared from the corresponding benzaldehyde (or keto) derivative using simple Wittig chemistry. Introduction of 6-methyl-, 5,6-dioxalane- and 5-fluoro-substituents were all possible and coupling reactions with *tert*-amylamine delivered the indoles in good yields (entries 1–3). The use of a nitro-substituted styrene resulted in poor conversion, with only 34% of the indole being isolated (entry 4). Entry 5 demonstrated that the formation of 3-substituted indoles was also possible, with a trisubstituted Cl-alkene-substrate performing well. The low Z : E ratio of several of the substrates used in Table 3 confirms that both geometrical isomers of the substrates can be converted to the indole products;^{7b} in entry 5 the *E*-isomer of the substrate dominates.

With N-reverse-prenyl substituted indole (8) available in only two steps from *o*-bromobenzaldehyde it represents a useful subunit for synthesis. We elected to utilise indole 8 in a short synthesis of the natural product demethylasterriquinone A1 (Scheme 3).¹² The asterriquinones are a family of fungal natural products based on a central dihydroxy-quinone core appended with two indolyl units.¹³ The indoles are decorated in various positions with prenyland reverse-prenyl groups, and the quinone core can also feature bis(methyl)ethers. The asterriquinones display a range of biological functions,¹⁴ including antitumour activity and use as insulin mimetics. With indole 8 readily available, our approach to the



Table 2 Coupling of styrene 4b with sterically demanding

^{*a*} Conditions: styrene **4b** (1.0 equiv.), amine (3.0 equiv.), $Pd(OAc)_2$ (5 mol%), $HBF_4 \cdot P'Bu_3$ (12 mol%), NaO'Bu (2.5 equiv.), PhMe, 130 °C, 4 h, sealed tube. Substrate used as a 4.3 : 1 ratio. ^{*b*} Isolated yields.

Table 3 Coupling of Cl, Br-styrenes with tert-amylamine^a



^{*a*} Conditions: styrene (1.0 equiv.), *tert*-amylamine (3.0 equiv.), Pd(OAc)₂ (5 mol%), HBF₄·P'Bu₃ (12 mol%), NaO'Bu (2.5 equiv.), PhMe, 130 °C, 4 h, sealed tube. ^{*b*} Isolated yields.



Scheme 3 Synthesis of demethylasterriquinone A1.

synthesis of demethylasterriquinone A1 (DAQ A1) was based on achieving a direct nucleophilic addition of two molecules of indole 8 onto an activated quinone core. Although a number of literature protocols for the addition of a variety N-H indoles to activated quinones are known,¹⁵ examples featuring N-alkyl indoles are scarce.¹⁶ In the event, addition of indole 8 to 2,5-dichloroguinone could be promoted by HCl;17 subsequent treatment with DDQ delivered the mono-substituted indole 9 in 65% yield. Attempts to introduce a second indole unit using the same conditions were unsuccessful, resulting in the return of both reaction partners. Addition of a second indole unit to guinone 9 could be achieved under the action of Zn(OTf)2.18 Re-oxidation to the quinone oxidation level was again achieved with DDQ, providing bis(indole) 10 in 64% yield. Treatment of 10 with NaOH resulted in hydrolysis of the two quinone chloro-substituents and delivered demethylasterriquinone A1 in 98% yield.¹⁹ The stepwise addition of the two indole units paves the way for the preparation of nonsymmetrical members of the asterriquinone family and related structures.

In summary, we have demonstrated that indoles bearing sterically demanding *N*-alkyl substituents can be conveniently prepared using a tandem Pd-catalysed alkenyl-aryl-amination approach. Significant variation in both the acyclic substrate and amine are possible, allowing access to a variety of indole structures. The utility of the method has been demonstrated in a short synthesis of demethylasterriquinone A1.

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Notes and references

- Indole reviews: (a) R. J. Sundberg, *Indoles*, Academic Press, London, 1996; (b) G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045.
- 2 Selected examples: N-alkyl indoles: (a) L. F. Kuyper, D. P. Baccanari, M. L. Jones, R. N. Hunter, R. L. Tansik, S. S. Joyner, C. M. Boytos, S. K. Rudolph, V. Knick, H. R. Wilson, J. M. Caddell, H. S. Friedman, J. C. W. Comley and J. N. Stables, J. Med. Chem., 1996, **39**, 892; (b)

- J. W. Huffman, R. Mabon, M.-J. Wu, J. Lu, R. Hart, D. P. Hurst, P. H. Reggio, J. L. Wiley and B. R. Martin, *Bioorg. Med. Chem.*, 2003, **11**, 539; (c) B. P. Smart, R. C. Oslund, L. A. Walsh and M. H. Gelb, *J. Med. Chem.*, 2006, **49**, 2858; *N*-arylated indoles: (d) G. Spadoni, C. Balsamini, A. Bedini, G. Diamantini, B. Di Giacomo, A. Tontini, G. Tarzia, M. Mor, P. V. Plazzi, S. Rivara, R. Nonno, M. Pannacci, V. Lucini, F. Frachini and B. M. Stankov, *J. Med. Chem.*, 1998, **41**, 3624; (e) K. Andersen, T. Liljefors, J. Hyttel and J. Perregaard, *J. Med. Chem.*, 1996, **39**, 3723; (f) C. A. Harbert, J. J. Plattner and W. M. Welch, *J. Med. Chem.*, 1980, **23**, 635.
- 3 J. A. Joule, in *Science of Synthesis*, ed. E. J. Thomas, Thieme, Stuttgart, 2000, vol. 10, ch. 13, p. 361.
- 4 L. M. Levy, G. M. Cabrera, J. E. Wright and A. M. Seldes, *Phytochemistry*, 2000, 54, 941.
- 5 Y. Yamamoto, K. Nishiyama and N. Kiriyama, *Chem. Pharm. Bull.*, 1976, 24, 1853.
- 6 (a) G. D. Sala, D. Capozzo, I. Izzo, A. Giordano, A. Iommazzo and A. Spinella, *Tetrahedron Lett.*, 2002, **43**, 8839; (b) F. Yokokawa, H. Sugiyama, T. Aoyama and T. Shioiri, *Synthesis*, 2004, 1476; (c) P. S. Baran, C. A. Guerrero and E. J. Corey, *J. Am. Chem. Soc.*, 2003, **125**, 5628; (d) J. M. Roe, R. A. B. Webster and A. Ganasan, *Org. Lett.*, 2003, **5**, 2825; (e) D. B. Hansen, A. S. Lewis, S. J. Gavalas and M. M. Joullié, *Tetrahedron: Asymmetry*, 2006, **17**, 15.
- 7 (a) M. C. Willis, G. N. Brace and I. P. Holmes, Angew. Chem., Int. Ed., 2005, 44, 403; (b) M. C. Willis, G. N. Brace, T. J. K. Findlay and I. P. Holmes, Adv. Synth. Catal., 2006, 348, 851.
- 8 For reviews of Pd-catalysed C–N and C–O cross-coupling of aryl halides, see: (a) J. F. Hartwig, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. I. Negishi, Wiley-Interscience, New York, 2002, vol. 1, p. 1051; (b) J. F. Hartwig, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. E. I. Negishi, Wiley-Interscience, New York, 2002, vol. 1, p. 1097; (c) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131; (d) D. Prim, J.-M. Campagne, D. Joseph and B. Andrioletti, *Tetrahedron*, 2002, **58**, 2041.
- 9 Amine 3 was prepared in multigram quantities by thermal [3,3]rearrangement of the corresponding trichloroacetimidate derivative, followed by NaOH mediated hydrolysis. Based on the procedure of Itoh *et al.*: H. Nagashima, H. Wakamatsu, N. Ozaki, T. Ishii, M. Watanabe, T. Tajima and K. Itoh, *J. Org. Chem.*, 1992, **57**, 1682.
- 10 S. D. Walker, T. E. Barder, J. R. Martinelli and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2004, **43**, 1871; X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 6653.
- A. F. Littke, C. Dai and G. C. Fu, J. Am. Chem. Soc., 2000, 122, 4020;
 M. R. Netherton and G. C. Fu, Org. Lett., 2001, 3, 4295.
- 12 For an earlier synthesis of demethylasterriquinone A1, see: M. C. Pirrung, Z. Li, K. Park and J. Zhu, J. Org. Chem., 2002, 67, 7919.
- K. Arai and Y. Yamamoto, *Chem. Pharm. Bull.*, 1990, **38**, 2929.
 A. Kaji, R. Saito, M. Nomura, K. Miyamoto and N. Kiriyama, *Anticancer Res.*, 1997, **17**, 3675; B. Zhang, G. Salituro, D. Szalkowski, Z. Li, Y. Zhang, I. Royo, D. Vilella, M. T. Díez, F. Pelaez, C. Ruby, R. L. Kendall, X. Mao, P. Griffin, J. Calaycay, J. R. Zierath, J. V. Heck, R. G. Smith and D. E. Moller, *Science*, 1999, **284**, 974.
- 15 G. D. Harris, Jr., A. Nguyen, H. App, P. Hirth, G. McMahon and C. Tang, *Org. Lett.*, 1999, **1**, 431; J. S. Yadav, B. V. S. Reddy and T. Swamy, *Tetrahedron Lett.*, 2003, **44**, 9121; J. S. Yadav, B. V. S. Reddy and T. Swamy, *Synthesis*, 2004, 106; H.-B. Zhang, L. Liu, Y.-J. Chen, D. Wang and C.-J. Li, *Eur. J. Org. Chem.*, 2006, 869.
- 16 S. Koulouri, E. Malamidou-Xenikaki and S. Spyroudis, *Tetrahedron*, 2005, 61, 10894. Also see ref. 12.
- M. C. Pirrung, K. Park and Z. Li, Org. Lett., 2001, 3, 365; M. C. Pirrung,
 L. Deng, Z. Li and K. Park, J. Org. Chem., 2002, 67, 8374.
- 18 M. C. Pirrung, Y. Liu, L. Deng, D. K. Halstead, Z. Li, J. F. May, M. Wedel, D. A. Austin and N. J. G. Webster, *J. Am. Chem. Soc.*, 2005, **127**, 4609; M. C. Pirrung, Z. Li, E. Hensley, Y. Liu, A. Tanksale, B. Lin, A. Pai and N. J. G. Webster, *J. Comb. Chem.*, 2007, DOI: 10.1021/ cc070062m.
- 19 M. C. Pirrung, K. Fujita and K. Park, J. Org. Chem., 2005, 70, 2537.