DOI: 10.1002/adsc.200900499

Direct Preparation of 7-Allyl- and 7-Arylindolines

Daniele Leonori[a] and Iain Coldham[a,*]

[a] Department of Chemsitry, University of Sheffield, Brook Hill, Sheffield S3 7HF, U.K.
Fax: (+44)-(0)114-222-9346; phone: (+44)-(0)114-222-9428; e-mail: i.coldham@sheffield.ac.uk

Received: July 16, 2009; Published online: October 28, 2009

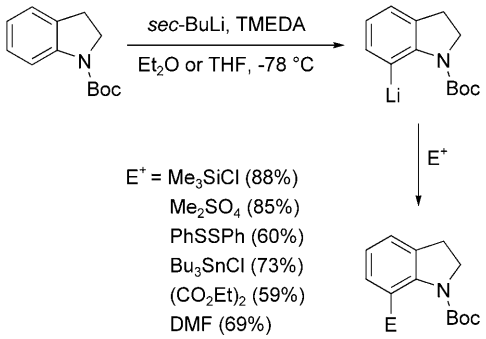
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900499.

Abstract: Addition of allyl halides to the organolithium species derived from lithiation of *N*-*tert*-butoxycarbonylindoline with *sec*-butyllithium (*sec*-BuLi) and tetramethylethylenediamine (TMEDA) occurs regioselectively by S_N2 allylation. In contrast, the organolithium species can be transmetalated to the mixed zinc cuprate that undergoes regioselective S_N2' allylations. Transmetalation to the organozinc chloride allows a Negishi-type cross-coupling reaction with aryl bromides using palladium catalysis with triphenylphosphine (PPh_3) as ligand. The chemistry was applied to a very short synthesis of 7-prenylindole and of the alkaloid vasconine.

Keywords: allylation; arylation; carbanions; indoles; lithium; metalation

Indoles and indolines are present in many natural products that have important biological properties.[1,2] A substituent in the aromatic ring and, in particular, at position 7 is a key feature of many Amaryllidaceae and other alkaloids (Figure 1).[3] A convenient way to access this position is to protect the indoline nitrogen atom with a Boc group (Boc = *tert*-butoxycarbonyl), and perform a regioselective lithiation using *sec*-BuLi and TMEDA.[4]

This reaction generates an aromatic organolithium compound that, after quench with an electrophile, gives 7-substituted *N*-Boc-indolines in good yields (Scheme 1).[4] However, the scope of electrophile used to date is narrow and does not allow direct access to indoles or indolines bearing 7-allyl or 7-aryl substituents, as required for many alkaloids. To expand the reactivity of this organolithium compound and provide a method to prepare these products, we decided to investigate the use of allylic and aryl halides as electrophilic coupling partners.



Scheme 1. 7-Lithiation of *N*-Boc-indoline.

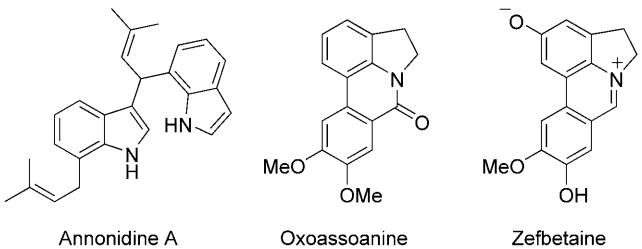


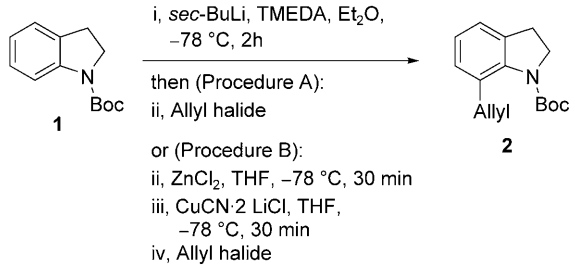
Figure 1. Some 7-substituted indole and indoline alkaloids.

Allyl halides represent an interesting class of electrophile, particularly due to the presence of 7-allylated indolines and indoles in natural products.[5] However the reaction of this type of electrophile with nucleophiles presents problems of regioselectivity due to competing S_N2 and S_N2' pathways. This can lead to mixtures of regioisomeric products when using unsymmetrical allyl electrophiles.

A general way to control the regiochemistry is to choose the nucleophilic partner carefully. Hard nucleophiles, such as organolithiums, tend to react directly at the sp^3 carbon (S_N2 attack) whereas softer nucleophiles, such as organocopper or organozinc reagents interact predominantly with the sp^2 carbon leading to S_N2' attack.[6]

We therefore investigated allylations of both the organolithium and the mixed zinc cuprate species, as il-

lustrated in Scheme 2. The organolithium compound was generated by treatment of *N*-Boc-indoline (**1**) with *sec*-BuLi/TMEDA (Procedure A),[4] while the



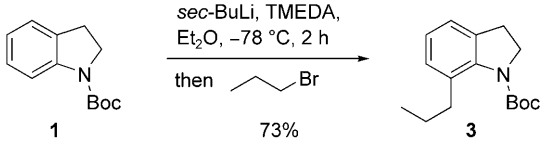
Scheme 2. Allylations of *N*-Boc-indoline (see Table 1).

zinc cuprate was prepared from the organolithium by direct addition of $ZnCl_2$ and then CuCN·2 LiCl (Procedure B).[7]

The reaction of these organometallic compounds has been investigated with a range of different allylic halides and the results are summarized in Table 1. These results show a different reactivity between the organolithium and the mixed zinc cuprate species. In particular, the organolithium compound was found to react by an S_N2 pathway, while the zinc cuprate reacts in an S_N2' fashion.

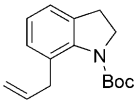
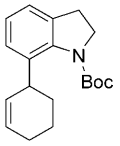
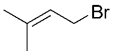
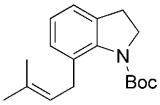
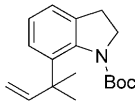
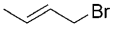
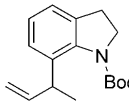
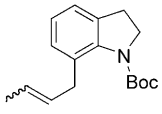
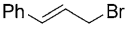
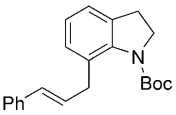
With symmetrical allylic bromides (allyl bromide and cyclohex-2-enyl bromide), the desired products **2a** and **2b** were obtained with good yields by either procedure (entries 1 and 8, 2 and 9). Prenyl bromide represents one of the best electrophiles and both regioisomers **2c** and **2g** were isolated in excellent yields (entries 3 and 10). Crotyl bromide or 3-chloro-1-butene could be used as the electrophile to prepare the products **2d** or **2e** (entries 4 and 11, 5 and 12). Cinnamyl bromide reacted with the organolithium but only starting material was obtained using procedure B (entries 6 and 13).

No examples are reported in the literature concerning the reactivity of *N*-Boc-7-lithioindoline toward alkyl halides, so we tested this reaction using bromopropane. We were pleased to find that a good yield of *N*-Boc-7-propylindoline (**3**) could be obtained using the direct addition of bromopropane to the organolithium (Scheme 3).

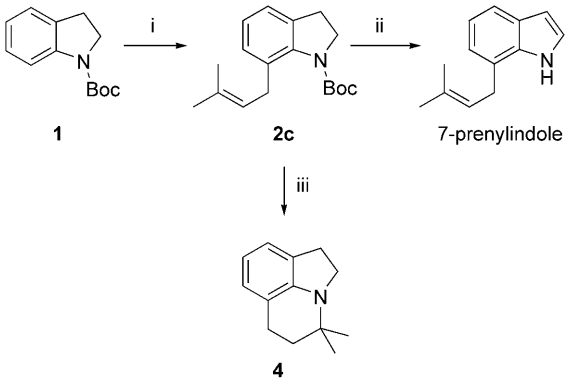


Scheme 3. Alkylation of *N*-Boc-7-lithioindoline.

Table 1. Formation of 7-allylindolines.

		Procedure A				Procedure B		
Electrophile	Entry	Product		Yield [%]	Entry	Product		Yield [%]
	1		**2a**	85	8		**2a**	78
	2		**2b**	53	9		**2b**	61
	3		**2c**	81	10		**2g**	83
	4		**2d**	41	11		**2e**	57
	5		**2e**	32	12		**2d**	51
	6		**2f**	47	13		–	–

We have applied this methodology to a very short and efficient synthesis of 7-prenylindole (Scheme 4).[8,9] 7-Prenylindole is a component of many natural products such as the annonidines[10] and



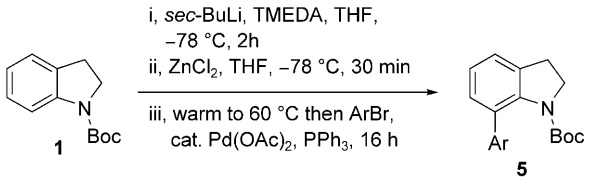
Scheme 4. Synthesis of 7-prenylindole. i) Procedure A (81%); ii) a) TFA, CH_2Cl_2, −10 °C, 45 min (100%); b) MnO_2, CH_2Cl_2, heat, 5 h (79%); iii) TFA, CH_2Cl_2, heat, 1 h (91%).

asterriquinones[11] and is itself a simple natural product.[8] As outlined in Scheme 4, lithiation of *N*-Boc-indoline (**1**) and addition of prenyl bromide (Procedure A) gave the desired indoline **2c**, in 81% yield. This was deprotected quantitatively using trifluoroacetic acid (TFA) at −10 °C and oxidised to the indole with manganese oxide.[9f] This completes a three-step synthesis of 7-prenylindole from commercially available starting material **1** in 64% overall yield. The deprotection should be carried out below 0 °C otherwise competitive cyclisation occurs to give the product **4** (which could be obtained in high yield upon heating).

The presence of 7-arylindoles in natural products then inspired us to investigate the use of aryl bromides as electrophiles. We envisaged that the 7-metalated indoline could be used in a cross-coupling reaction with an aryl halide.[12]

Related approaches to 7-arylindoles make use of a halogen atom at C-7 and, typically, a boronic acid as the other coupling partner.[13] The possibility of inverting this to have a metal atom in the indoline is attractive as it represents a more efficient and shorter overall process.[14]

We decided to investigate the conversion of the organolithium to the corresponding organozinc species followed by a Negishi-type cross-coupling reaction. We were pleased to find that this approach was successful, as outlined in Scheme 5 (General Procedure C). Thus, the organolithium (formed from **1** and *sec*-BuLi/TMEDA) was converted to the organozinc by slow addition of $ZnCl_2$. After warming to 60 °C, the aryl bromide, catalytic $Pd(OAc)_2$ and PPh_3 were added and the mixture was heated. This led to the 7-



Scheme 5. Direct metalation-coupling.

arylated compounds **5** in moderate to good yields (Figure 2).

The reaction was found to be general with different substituted aryl bromides and both electron-donating

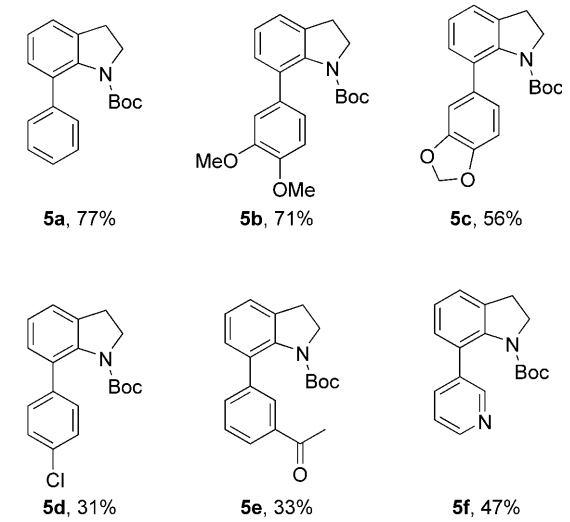
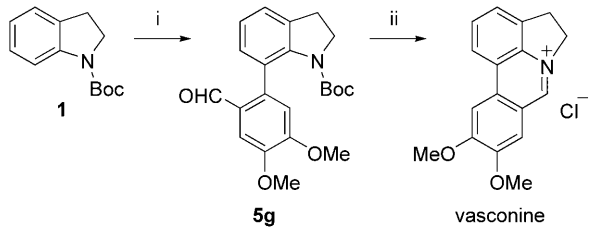


Figure 2. Structures and yields of 7-arylindolines **5a–f**.

and electron-withdrawing groups were tolerated. Thus, bromobenzene and alkoxy-substituted aryl bromides gave the products **5a–c**. The electron-poor substrates 1-bromo-4-chlorobenzene and 3-bromoacetophenone gave the products **5d** and **5e**, albeit with lower yields. The chemistry was amenable to the use of heteroaromatic bromides as shown using 3-bromopyridine, which gave the indoline **5f**. This methodology represents an improvement over previous methods to 7-aryl indolines[13,14] in terms of yields, substrate scope and number of steps.

Finally, we illustrate the use of this chemistry for a very short synthesis of vasconine,[15] a natural product isolated from *Narcissus vasconicus*[16] and a member of the Amaryllidaceae alkaloid family.[3] Our synthesis began with the Negishi cross-coupling between the organozinc reagent formed *in situ* and the commercial 6-bromoveratraldehyde. This gave the desired product **5g** in 41% yield (Scheme 6). Deprotection of the Boc group and concomitant cyclisation with anydrous HCl gave vasconine. This represents an efficient two-step synthesis of this tetracyclic alkaloid (and a formal syn-



Scheme 6. Synthesis of vasconine. i) *sec*-BuLi, TMEDA then $ZnCl_2$ then $Pd(OAc)_2$, PPh_3, 6-bromoveratraldheyde, 60 °C, 41%; ii) HCl, $CHCl_3$, room temperature, 89%.

thesis of the alkaloids assoanine and oxoassoanine).[14b]

In conclusion, we have extended the reactivity of *N*-Boc-7-lithioindoline particularly using allylic and aryl bromides. This organolithium can be generated easily from commercially available *N*-Boc-indoline **1** and reacts in good yield with allylic bromides in an S_N2 fashion. Conversion of the organolithium to a mixed organozinc cuprate alters the reactivity to promote an S_N2' mechanism. Conversion to an organozinc species allows Negishi-type cross-coupling with aryl bromides. These reactions have been applied to very short syntheses of the natural products 7-prenylindole and vasconine.

Experimental Section

Lithiation of *N*-Boc-Indoline – General Procedure A

sec-BuLi (1.2 equiv., 1.40 M) was added to a stirred 0.25 M solution of *N*-Boc-indoline **1** (1 equiv.) and TMEDA (1.2 equiv.) in Et_2O at −78 °C. After 2 h, the electrophile (3.0 equiv.) was added dropwise if liquid or as a 1.0 M solution in Et_2O if solid. The mixture was allowed to warm to room temperature overnight. The reaction was quenched by dropwise addition of a 10% solution of NH_4OH. Ether was added, and the mixture was stirred for 20 min. The organic layer was washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography to give the 7-substituted *N*-Boc-indoline.

Lithiation-Transmetalation (to Zinc Cuprate) of *N*-Boc-Indoline – General Procedure B

sec-BuLi (1.2 equiv., 1.40 M) was added to a stirred 0.25 M solution of *N*-Boc-indoline **1** (1 equiv.) and TMEDA (1.2 equiv.) in Et_2O at −78 °C. After 2 h, a 0.8 M solution of $ZnCl_2$ (1.3 equiv.) in THF was added over 10 min. After 30 min a 0.3 M solution of CuCN (1.2 equiv.) and LiCl (2.4 equiv.) in THF was added rapidly. The yellow mixture was stirred at −78 °C for 30 min and the electrophile (3.0 equiv.) was added dropwise if liquid or as a 1.0 M solution in Et_2O if solid. The mixture was allowed to warm to room temperature overnight. The reaction was quenched by dropwise addition of a 10% solution of NH_4OH. Ether was added, and the mixture was stirred for 20 min. The organic layer was washed with brine, dried (Na_2SO_4) filtered and evaporated. The residue was purified by column chromatography to give the 7-substituted *N*-Boc-indoline.

Lithiation-Transmetalation-Cross Coupling of *N*-Boc-Indoline – General Procedure C

sec-BuLi (1.2 equiv., 1.40 M) was added to a stirred 0.25 M solution of *N*-Boc-indoline **1** (1 equiv.) and TMEDA (1.2 equiv.) in THF at −78 °C. After 2 h, a 0.8 M solution of $ZnCl_2$ (1.3 equiv.) in THF was added over 10 min. After 30 min the mixture was warmed to 25 °C. After 30 min the mixture was warmed to 60 °C and the aryl bromide (1.3 equiv.), $Pd(OAc)_2$ (10 mol%) and PPh_3 (20 mol%) were added in one portion. After stirring at 60 °C overnight, the mixture was cooled to room temperature and 10% NH_4OH (10 mL) was added. Ether (10 mL) was added, and the mixture was stirred for 20 min. The organic layer was washed with brine, dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography to give the 7-aryl-*N*-Boc-indoline.

For experimental data and NMR spectra, see Supporting Information.

Acknowledgements

We thank the EPSRC (grant EP/E012272/1) and the University of Sheffield for support of this work.

References

[1] a) G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045; b) M. Ishikura, K. Yamada, K. *Nat. Prod. Rep.* **2009**, DOI: 10.1039/b820693 g.

[2] a) S. De Lombaert, L. Blanchard, L. B. Stamford, D. M. Sperbeck, M. D. Grim, T. M. Jenson, H. R. Rodriguez, *Tetrahedron Lett.* **1994**, *35*, 7513; b) M. Prakesch, K. Bijian, V. Campagna-Slater, S. Quevillon, R. Joseph, C.-Q. Wei, E. Sesmilo, A. Reayi, R. R. Poondra, M. L. Barnes, D. M. Leek, B. Xu, C. Lougheed, M. Schapira, M. Alaoui-Jamali, P. Arya, *Bioorg. Med. Chem.* **2008**, *16*, 9596.

[3] a) J. R. Lewis, *Nat. Prod. Rep.* **1994**, *11*, 329; b) O. Hoshino, *The Amaryllidaceae Alkaloids*, in: *The Alkaloids*, (Ed.: G. A. Cordell), Academic Press, San Diego, **1998**, Vol. 51; p 323.

[4] a) M. Iwao, T. Kuraishi, *Heterocycles* **1992**, *34*, 1031; b) A. I. Meyers, G. Milot, *J. Org. Chem.* **1993**, *58*, 6538; c) P. Beak, W. K. Lee, *J. Org. Chem.* **1993**, *58*, 1109; d) M. Iwao, T. Kuraishi, *Org. Synth.* **1998**, *9*, 124; e) V. Diep, J. J. Dannenberg, R. W. Franck, *J. Org. Chem.* **2003**, *68*, 7907; f) A. B. Smith, L. Kürti, A. H. Davulcu, Y. S. Cho, K. Ohmoto, *J. Org. Chem.* **2007**, *72*, 4611.

[5] a) M. C. Pirrung, Z. Li, K. Park, J. Zhu, *J. Org. Chem.* **2002**, *67*, 7919; b) M. C. Pirrung, L. Deng, Z. Li, K. Park, *J. Org. Chem.* **2002**, *67*, 8374; c) M. C. Pirrung, Y. Liu, L. Deng, D. K. Halstead, Z. Li, J. F. May, M. Wedel, D. A. Austin, N. J. G. Webster, *J. Am. Chem. Soc.* **2005**, *127*, 4609.

[6] a) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1984**, *25*, 3063; b) N. Yoshikai, S.-L. Zhang, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 12862.
[7] a) J. P. N. Papillon, R. J. K. Taylor, *Org. Lett.* **2002**, *4*, 119; b) P. Knochel, M. C. P. Yeh, S. C. Berk, J. Talbert, *J. Org. Chem.* **1988**, *53*, 2390; c) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.
[8] a) V. Benesova, V. Herout, F. Strom, *Collect. Czech. Chem. Commun.* **1969**, *34*, 1810; b) F. Delle Monache, G. Delle Monache, M. A. De Moraes e Souza, M. S. Cavalcanti, A. Chiappeta, *Gazz. Chim. Ital.* **1989**, *119*, 435; c) F. Nagashima, Y. Sari, M. Tori, Y. Ishikawa, S. Huneck, *Phytochemistry* **1993**, *34*, 1341.
[9] For other preparations of 7-prenylindole, see: a) M. Somei, T. Funamoto, T. Ohta, *Heterocycles* **1987**, *26*, 1783; b) H. Muratake, M. Natsume, *Heterocycles* **1989**, *29*, 771; c) Y. Kondo, S. Kojima, T. Sakamoto, *Heterocycles* **1996**, *43*, 2741; d) C. G. Hartung, A. Fecher, B. Chapell, V. Snieckus, *Org. Lett.* **2003**, *5*, 1899; e) M. C. Pirrung, M. Wedel, Y. Zhao, *Synlett* **2002**, 143; f) X. Xiong, M. C. Pirrung, *J. Org. Chem.* **2007**, *72*, 5832.
[10] H. Achenbach, C. Renner, *Heterocycles* **1985**, *23*, 2075.
[11] S. Shimizu, Y. Yamamoto, S. Koshimura, *Chem. Pharm. Bull.* **1982**, *30*, 1896.
[12] a) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.
[13] a) U. V. Mentzel, D. Tanner, J. E. Tønder, *J. Org. Chem.* **2006**, *71*, 5807; b) J. C. Torres, A. C. Pinto, S. J. Garden, *Tetrahedron* **2004**, *60*, 9889; c) ref.[9d].
[14] For related processes, see ref.[4f] and: a) R. H. Hutchings, A. I. Meyers, *J. Org. Chem.* **1996**, *61*, 1004; b) J. S. Parnes, D. S. Carter, L. J. Kurz, L. A. Flippin, *J. Org. Chem.* **1994**, *59*, 3497; c) L. M. Stark, X.-F. Lin, L. A. Flippin, *J. Org. Chem.* **2000**, *65*, 3227; d) M. Iwao, H. Takehara, S. Obata, M. Watanabe, *Heterocycles* **1994**, *38*, 1717; e) T. Harayama, A. Hori, H. Abe, Y. Takeuchi, *Tetrahedron* **2004**, *60*, 1611; f) M. D. Ganton, M. A. Kerr, *Org. Lett.* **2005**, *7*, 4777.
[15] For other syntheses of vasconine, see: a) ref.[14b]; b) A. M. Rosa, A. M. Lobo, P. S. Branco, S. Prabhakar, M. Sá-da-Costa, *Tetrahedron* **1997**, *53*, 299.
[16] J. Bastida, C. Codina, F. Viladomat, M. Rubiralta, J.-C. Quirion, B. Weniger, *J. Nat. Prod.* **1992**, *55*, 122.

