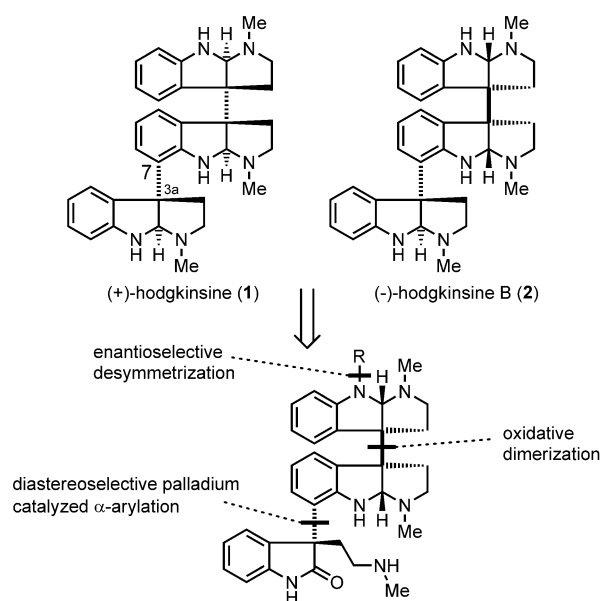


Catalytic Enantioselective Total Synthesis of Hodgkinsine B**

Robert H. Snell, Robert L. Woodward, and Michael C. Willis*

Hodgkinsine (**1**) and hodgekinsine B (**2**) belong to a large family of polypyrrolidinoindoline alkaloids which are present in a variety of flora and fauna.^[1] These alkaloids have been shown to exhibit a broad range of biological activities, including antibacterial,^[2] antifungal,^[2] antiviral,^[2] cytotoxic,^[2,3] and analgesic properties.^[4] The simplest member of this family, *meso*-chimonanthine (**5**), consists of two cyclotryptamine units fused at the C3a-position. The higher order oligomers, such as hodgekinsine (**1**) and hodgekinsine B (**2**), generally possess a chimonanthine-derived core decorated with additional cyclotryptamine units at the C7-position(s).^[5] The natural products **1** and **2** possess six stereocenters, of which four are contiguous and three quaternary, and feature a number of basic sites. These features, combined with their high degree of symmetry, make these natural products challenging targets for total synthesis. The synthesis of cyclotryptamine alkaloids in general has received considerable attention of late, with the publication of several elegant routes. Selected benchmarks include: the synthesis of *meso*- and (–)-chimonanthine (**5**),^[6a,b] hodgekinsine (**1**), hodgekinsine B (**2**),^[6c,d] and quadrigemine C^[6e] by Overman and co-workers, (+)-chimonanthine^[6f] and (+)-11,11'-dideoxyverticillin A^[6g] by Movassaghi and co-workers, and psychotrimine^[6h] and (+)-psychotetramine^[6i] by Baran and co-workers.

To date, the symmetry of the hodgekinsine core has not been fully exploited in a total synthesis.^[6c,d,7] Our own interest in desymmetrization reactions^[8] highlighted *meso*-chimonanthine (**5**) as an ideal building block to access such a strategy. We envisaged that the prochiral amines present in **5** (see Scheme 2) could be functionalized in a key symmetry-breaking operation. A subsequent palladium-catalyzed oxindole α -arylation, developed in our laboratory,^[9,10] should allow the installation of the final cyclotryptamine functionality at the C7-position (Scheme 1). Importantly, this type of desymmetrization/C7-functionalization strategy should also be adapt-



Scheme 1. Selected examples of cyclotryptamine alkaloids, together with retrosynthetic strategies for the synthesis of hodgekinsine (**1**) and hodgekinsine B (**2**).

able to the synthesis of other high order oligomers such as quadrigemine H.

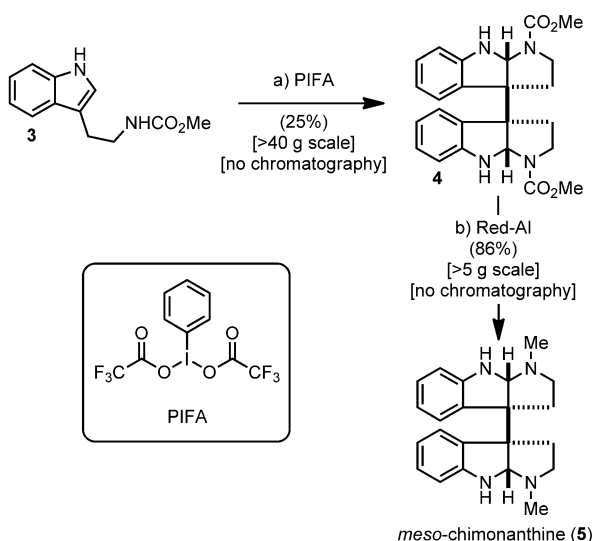
Key to our synthesis was the availability of *meso*-chimonanthine (**5**) in short order and on a large scale. Accordingly, we selected the hypervalent iodine-mediated oxidative dimerization strategy of Takayama and co-workers for the preparation of the core of *meso*-chimonanthine (**5**).^[11] This protocol forms the complex alkaloid in two steps from commercially available starting materials. However, in our hands, the method suffered from scalability and purification issues, requiring extensive flash chromatography to separate the regio- and diastereoisomers generated during the dimerization. We attributed the scalability problems to poor mass transfer, associated with the low solubility of PIFA.^[12] By simply employing vigorous overhead stirring we successfully scaled the reaction to greater than 40 g. To our delight, we also found that careful treatment of a supersaturated solution of the crude products with crystals of the desired *meso* isomer precipitated the product as a > 9:1 mixture of *meso*-**4** and undesired isomers (Scheme 2). Reduction of this *meso*-enriched mixture with Red-Al and subsequent recrystallization afforded *meso*-chimonanthine (**5**) on a multigram scale with no chromatographic steps.

The inherent reactivity of amines (compared to alcohols) has minimized their use as prochiral nucleophiles in desymmetrizing processes.^[8a,13,14] Nevertheless, Taguchi and co-workers^[13a,b] have demonstrated that simple *meso*-diamines (derivatized to sulfonamides) can be desymmetrized in high

[*] R. H. Snell, Dr. M. C. Willis
Department of Chemistry, University of Oxford
Chemistry Research Laboratory
Mansfield Road, Oxford, OX1 3TA (UK)
E-mail: michael.willis@chem.ox.ac.uk
Homepage: <http://mcwillis.chem.ox.ac.uk/MCW/Home.html>
Dr. R. L. Woodward
AstraZeneca Global Medicines Development
Macclesfield Works, Hurdsfield Industrial Estate
Macclesfield, Cheshire, SK10 2NA (UK)

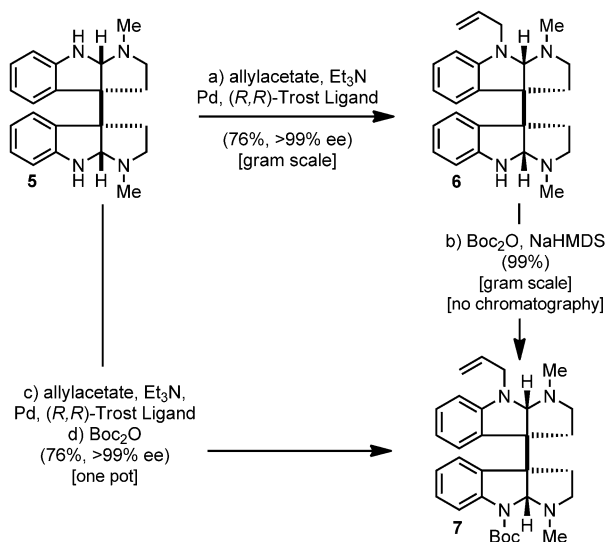
[**] This work was supported by the EPSRC, AstraZeneca, and the University of Oxford. The NMR spectroscopy and mass spectrometry services at the University of Oxford are also thanked for their assistance.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201103864>.



Scheme 2. Chromatography-free synthesis of *meso*-chimonanthine (**5**). Reagents and conditions: a) **3** (1.00 equiv), PIFA (0.65 equiv), $\text{CF}_3\text{CH}_2\text{OH}$, -30°C , 5.5 h. b) **4** (1.00 equiv), Red-Al (10.00 equiv), PhMe, reflux, 16 h. Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride.

yields and enantiopurity by means of a Trost allylation.^[15,16] Despite the complexity of our substrate, we envisaged that this method could be adapted to meet our needs. With *meso*-chimonanthine (**5**) in hand, we subjected it to the desymmetrization conditions of Taguchi and co-workers. The initial results were very encouraging and showed that the desymmetrized product **6** could be isolated with 99% *ee* (Scheme 3).

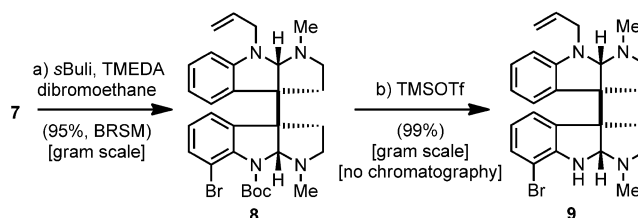


Scheme 3. Desymmetrization of *meso*-chimonanthine (**5**). Reagents and conditions: a) **5** (1.0 equiv), allyl acetate (1.2 equiv), Et_3N (2.0 equiv), $[(\text{allyl})\text{PdCl}]_2$ (2.5 mol%, Pd), (R,R)-DACT-phenyl Trost ligand (3.8 mol%), PhMe, 0°C , 1.5 h. b) **6** (1.0 equiv), Boc_2O (1.3 equiv), NaHMDS (2.2 equiv), THF, RT, 2 h. c) **5** (1.0 equiv), allyl acetate (1.2 equiv), Et_3N (3.0 equiv), $[(\text{allyl})\text{PdCl}]_2$ (5 mol%, Pd), (R,R)-DACT-phenyl Trost ligand (6 mol%), PhMe, 50°C , 45 min. d) Boc_2O (1.1 equiv), RT, 16 h. Boc = *tert*-butoxycarbonyl, (R,R)-DACT-phenyl Trost ligand = (1R,2R)-(+)-1,2-diaminocyclohexane-*N,N'*-bis(2-diphenylphosphinobenzoyl), HMDS = hexamethyldisilazane.

This was particularly impressive considering the complexity of the nucleophile—*meso*-chimonanthine—which is arguably the most challenging substrate used in this type of allylation to date.

Unfortunately, the reaction was somewhat capricious with respect to yield and scalability, often yielding none of the desired product. Fortunately, a brief investigation highlighted the use of Et_3N (instead of KO^tBu), as an effective means of increasing the robustness of the reaction. High yields were obtained on a multigram scale (ca. 3 g), and the product **6** was obtained as essentially a single enantiomer. The only significant by-product was bisallylated material,^[17] which could be removed by flash chromatography. Pleasingly, we were able to install an *ortho*-directing group in “one pot” by addition of Boc_2O to the crude reaction mixture resulting from the allylation event. This reaction could also be accomplished by a “two-pot” protocol, at an accelerated rate, by using NaHMDS.

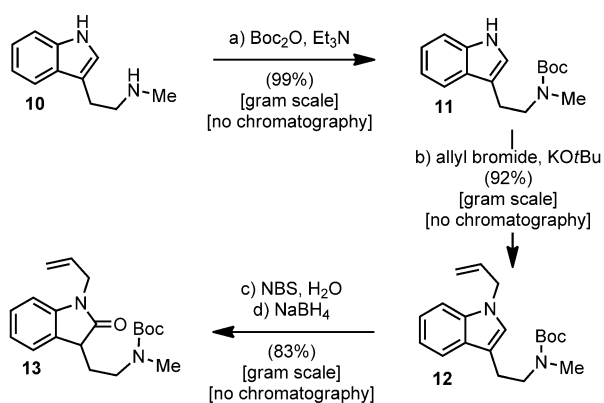
With a directing group in place, we used the directed *ortho*-lithiation protocol of Snieckus^[18] to install a bromine atom at the C7-position; this occurred in 53% yield (75% based on recovered starting material (BRSM); Scheme 4).



Scheme 4. Synthesis of 7'-Br-*N*-allylchimonanthine (**9**). Reagents and conditions: a) **7** (1.0 equiv), TMEDA (3.0 equiv), *s*BuLi (2.5 equiv), dibromoethane (4.0 equiv), Et_2O , -78 – 0°C , 1.5 h. b) **8** (1.0 equiv), TMSOTf (2.5 equiv), CH_2Cl_2 , RT, 16 h. TMEDA = *N,N,N',N'*-tetramethylethylenediamine, TMS = trimethylsilyl, OTf = trifluoromethanesulfonyl.

The recovered **7** was resubjected to the reaction conditions to produce an additional crop of halogenated material in 61% yield (95% BRSM). This procedure allowed access to multigram quantities of the C7-functionalized product. The directing group was efficiently cleaved by TMSOTf in a quantitative yield, and again this was carried out on a gram scale without chromatographic purification to yield 7'-bromo-*N*-allylchimonanthine (**9**) in 95% yield (BRSM) over two steps.^[19]

The stage was then set for the installation of the final cyclotryptamine fragment. A suitable oxindole coupling partner **13** was prepared in a three-step, chromatography-free, route in 76% yield from commercially available methyltryptamine (**10**; Scheme 5). During this procedure, we were unable to use conventional indole oxidation conditions (conc. HCl/DMSO) because of the acid-sensitive Boc functionality.^[20] Instead, we generated the 3-bromooxindole^[21] and then chemoselectively cleaved the bromine substituent at workup with NaBH_4 . Attempts to generate the oxindole directly by this method (without the reductive



Scheme 5. Synthesis of oxindole **13**. Reagents and conditions: a) **10** (1.0 equiv), Boc_2O (1.2 equiv), Et_3N (3.0 equiv), THF, RT, 1.5 h. b) **11** (1.0 equiv), KOtBu (1.2 equiv), allylbromide (1.5 equiv), THF, RT, 2 h. c) **12** (1.0 equiv), NBS (2.4 equiv), H_2O (4.0 equiv), $t\text{BuOH/THF}$ (1:1), RT, 30 min. d) NaBH_4 (6.0 equiv). NBS = *N*-bromosuccinimide.

workup) gave diminished yields accompanied by a mixture of products.

Oxindole **13** was coupled with aryl bromide **9** to form the required C3a–C7 linkage and establish the final congested quaternary stereocenter, thereby affording **14** as a single diastereoisomer in 77% yield (Scheme 6).^[22] This result is particularly noteworthy considering the complexity of the aryl halide substrate, which possesses *ortho* substituents and multiple functional groups.^[9,23] Removal of the Boc group with TMSOTf and subsequent exposure of the crude product to Na/NH_3 ^[6c,24] delivered the natural product, hodgkinsine B (**2**), in 32% yield.^[25] The yield of this sequence could be increased to 65% through a three-stage protocol by using LiAlH_4 to effect the reductive amination prior to de-allylation with Na/NH_3 (Scheme 6).

In summary, we have completed a total synthesis of hodgkinsine B with just six isolated intermediates in its longest linear sequence, and, in total, only four chromatographic operations. To the best of our knowledge, chimonanthine represents the most complex *N* nucleophile used as an allylic-substitution desymmetrization substrate. Our desymmetrization/ α -arylation approach demonstrated here should also be applicable to other high-order cyclotryptamine

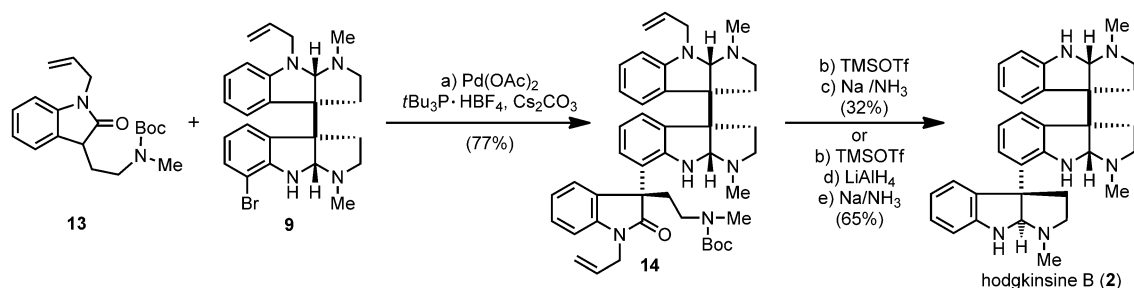
oligomers. In particular, readily available enantiomerically enriched *N*-allylchimonanthine (**7**) represents an attractive building block to access the polypyrrolidinoindoline alkaloids.

Received: June 7, 2011

Published online: August 24, 2011

Keywords: alkaloids · asymmetric catalysis · natural products · palladium catalysis · total synthesis

- [1] a) E. F. L. J. Anet, G. K. Hughes, E. Ritchie, *Aust. J. Chem.* **1961**, *14*, 173; b) K. P. Parry, G. F. Smith, *J. Chem. Soc. Perkin Trans. 1* **1978**, 1671; c) T. Tokuyama, J. W. Daly, *Tetrahedron* **1983**, *39*, 41; d) L. Verotta, T. Pilati, M. Tatò, E. Elisabetsky, T. A. Amador, D. S. Nunes, *J. Nat. Prod.* **1998**, *61*, 392; e) V. Jannic, F. Guérille, O. Laprévotte, L. Serani, M. Martin, T. Sévenet, P. Potier, *J. Nat. Prod.* **1999**, *62*, 838; f) L. Verotta, F. Peterlongo, E. Elisabetsky, T. A. Amador, D. S. Nunes, *J. Chromatogr. A* **1999**, *841*, 165.
- [2] H. A. Saad, S. H. El-Sharkawy, W. t. Shier, *Planta Med.* **1995**, *61*, 313.
- [3] Y. Adjibadé, H. Saad, B. Kuballa, J. P. Beck, T. Sévenet, P. Cabalion, R. Anton, *J. Ethnopharmacol.* **1990**, *29*, 127.
- [4] a) T. A. Amador, L. Verotta, D. S. Nunes, E. Elisabetsky, *Planta Med.* **2000**, *66*, 770; b) L. Verotta, F. Orsini, M. Sbaccchi, M. A. Scheidler, T. A. Amador, E. Elisabetsky, *Bioorg. Med. Chem.* **2002**, *10*, 2133; c) D. D. Porto, A. T. Henriques, A. G. Fett-Neto, *The Open Bioactive Compounds J.* **2009**, *2*, 29; d) J. Sanz-Biset, J. Campos-de-la-Cruz, M. A. Epiquién-Rivera, S. Cañigüeral, *J. Ethnopharmacol.* **2009**, *122*, 333.
- [5] For reviews, see a) G. A. Cordell, J. E. Saxton, *The Alkaloids* **1981**, *20*, 10; b) A. Steven, L. E. Overman, *Angew. Chem.* **2007**, *119*, 5584; *Angew. Chem. Int. Ed.* **2007**, *46*, 5488; c) P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Álvarez, *Chem. Eur. J.* **2011**, *17*, 1388; d) M. A. Schmidt, M. Movassaghi, *Synlett* **2008**, 313.
- [6] a) J. T. Link, L. E. Overman, *J. Am. Chem. Soc.* **1996**, *118*, 8166; b) L. E. Overman, D. V. Paone, B. A. Stearns, *J. Am. Chem. Soc.* **1999**, *121*, 7702; c) J. J. Kodanko, L. E. Overman, *Angew. Chem.* **2003**, *115*, 2632; *Angew. Chem. Int. Ed.* **2003**, *42*, 2528; d) J. J. Kodanko, S. Hiebert, E. A. Peterson, L. Sung, L. E. Overman, V. M. Linck, G. C. Goerck, T. A. Amador, M. B. Leal, E. Elisabetsky, *J. Org. Chem.* **2007**, *72*, 7909; e) A. D. Lebsack, J. T. Link, L. E. Overman, B. A. Stearns, *J. Am. Chem. Soc.* **2002**, *124*, 9008; f) M. Movassaghi, M. A. Schmidt, *Angew. Chem.* **2007**, *119*, 3799; *Angew. Chem. Int. Ed.* **2007**, *46*, 3725; g) J. Kim, J. A. Ashenhurst, M. Movassaghi, *Science* **2009**, *324*, 238; h) T. Newhouse, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 10886; i) K. Foo, T. Newhouse, I. Mori, H. Takayama, P. S. Baran, *Angew. Chem.* **2011**, *123*, 2768; *Angew. Chem. Int. Ed.* **2011**, *50*, 2716.



Scheme 6. Total synthesis of hodgkinsine B (**2**). Reagents and conditions: a) **9** (1.0 equiv), **13** (1.7 equiv), Cs_2CO_3 (6.0 equiv), $\text{Pd}(\text{OAc})_2$ (5 mol %), $t\text{Bu}_3\text{P}\cdot\text{HBF}_4$ (10 mol %), PhMe, 100°C , 2 h. b) **14** (1.0 equiv), TMSOTf (2.2 equiv), CH_2Cl_2 , RT, 16 h. c) Na (100 equiv), $\text{NH}_3(l)$, THF, -78°C , 2 h, NH_4Cl quench. d) LiAlH_4 (3.7 equiv), THF, reflux, 1.5 h. e) Na (60 equiv), $\text{NH}_3(l)$, THF, -78°C , 2 h, NH_4Cl quench.

- [7] Kodanko and Overman employed a desymmetrization approach in their synthesis of quadrigemine C; see Ref. [6c].
- [8] a) M. C. Willis, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1765; b) M. C. Willis, L. H. W. Powell, C. K. Claverie, S. J. Watson, *Angew. Chem.* **2004**, *116*, 1269; *Angew. Chem. Int. Ed.* **2004**, *43*, 1249; c) S. J. Byrne, A. J. Fletcher, P. Hebeisen, M. C. Willis, *Org. Biomol. Chem.* **2010**, *8*, 758.
- [9] a) M. J. Durbin, M. C. Willis, *Org. Lett.* **2008**, *10*, 1413; b) R. A. Altman, A. M. Hyde, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 9613; c) A. M. Taylor, R. A. Altman, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 9900; d) C. Mai, M. F. Sammons, T. Sammakia, *Org. Lett.* **2010**, *12*, 2306.
- [10] For recent reviews on catalytic carbonyl α -arylation, see a) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082; b) C. C. C. Johansson, T. J. Colacot, *Angew. Chem.* **2010**, *122*, 686; *Angew. Chem. Int. Ed.* **2010**, *49*, 676.
- [11] a) H. Ishikawa, H. Takayama, N. Aimi, *Tetrahedron Lett.* **2002**, *43*, 5637; b) H. Takayama, Y. Matsuda, K. Masubuchi, A. Ishida, M. Kitajima, N. Aimi, *Tetrahedron* **2004**, *60*, 893; c) Y. Matsuda, M. Kitajima, H. Takayama, *Heterocycles* **2005**, *65*, 1031.
- [12] a) A. Varvoglis, *Tetrahedron* **1997**, *53*, 1179; b) T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka, Y. Kita, *Tetrahedron* **2009**, *65*, 10797.
- [13] a) O. Kitagawa, K. Yosumoto, M. Kohriyama, Y. Dobashi, T. Taguchi, *Org. Lett.* **2004**, *6*, 3605; b) O. Kitagawa, S. Matsuo, K. Yosumoto, T. Taguchi, *J. Org. Chem.* **2006**, *71*, 2524; c) M. Anstiss, J. M. Holland, A. Nelson, J. R. Titchmarsh, *Synlett* **2003**, 1213; d) M. Anstiss, A. Nelson, *Org. Biomol. Chem.* **2006**, *4*, 4135; e) K. Takenaka, N. Itoh, H. Sasai, *Org. Lett.* **2009**, *11*, 1483; f) L. Porosa, R. D. Viirre, *Tetrahedron Lett.* **2009**, *50*, 4170.
- [14] For examples of achiral N nucleophiles in desymmetrizing palladium-catalyzed asymmetric allylic alkylations, see a) B. M. Trost, A. Aponick, *J. Am. Chem. Soc.* **2006**, *128*, 3931; b) B. M. Trost, D. E. Patterson, *Chem. Eur. J.* **1999**, *5*, 3279; c) B. M. Trost, D. E. Patterson, *J. Org. Chem.* **1998**, *63*, 1339; d) G. Muchow, J. M. Brunel, M. Maffet, O. Pardigon, G. Buono, *Tetrahedron* **1998**, *54*, 10435; e) B. M. Trost, Z. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 3037.
- [15] During our investigations, a report was published on the kinetic resolution of indolines through a Trost allylation: X. L. Hou, B. J. Zheng, *Org. Lett.* **2009**, *11*, 1789.
- [16] For reviews of asymmetric allylic alkylation, see a) Z. Lu, S. Ma, *Angew. Chem.* **2008**, *120*, 264; *Angew. Chem. Int. Ed.* **2008**, *47*, 258; *Angew. Chem. Int. Ed.* **2008**, *47*, 258; b) B. M. Trost, V. L. Van Ranken, *Chem. Rev.* **1996**, *96*, 395; c) B. M. Trost, *Pure Appl. Chem.* **1996**, *68*, 779.
- [17] A secondary kinetic resolution step, leading to formation of the bisallyl product, was shown to be partly responsible for the high enantioselectivity of the reaction.
- [18] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879.
- [19] This strategy for installing a halogen at the C7-position was also used by Steven and Overman in their syntheses of polypyrrolidinoindoline alkaloids; see Ref. [5b].
- [20] K. Szabó-Pusztay, L. Szabó, *Synthesis* **1979**, 276.
- [21] J. R. Fuchs, R. L. Funk, *Org. Lett.* **2005**, *7*, 677.
- [22] The mass balance of the reaction was made up of dehalogenated starting material **6**, presumably formed through a transfer hydrogenation mechanism.
- [23] Earlier reports on the arylation of oxindoles have noted the difficulty in employing *ortho*-substituted aryl halide substrates; see Ref. [9c].
- [24] a) S. Escoubet, S. Gastaldi, M. Bertand, *Eur. J. Org. Chem.* **2005**, 3855; b) P. L. Julian, J. Pikl, *J. Am. Chem. Soc.* **1935**, *57*, 539.
- [25] It was noted in a review by Steven and Overman that yields for this type of transformation could be increased by the presence of *t*BuOH (see Ref. [5b]); however, when applied to our system there was no beneficial effect.