

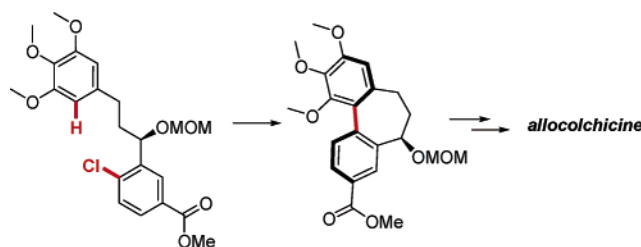
## Allocolchicinoid Synthesis via Direct Arylation

Mélissa Leblanc and Keith Fagnou\*

*Center for Catalysis Research and Innovation, Department of Chemistry,  
University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5**keith.fagnou@science.uottawa.ca*

Received March 18, 2005

## ABSTRACT



A formal enantioselective synthesis of allocolchicine and a synthesis of a C-ring analogue have been achieved by employing an intramolecular direct arylation of an aryl chloride to form the biaryl carbon–carbon bond and the seven-membered ring.

Microtubule depolymerizing agents such as colchicine **1** are promising leads in the search for new antitumor agents.<sup>1</sup> Unfortunately, their toxicity has limited their use in the treatment of human neoplasms and has prompted the search for derivatives with a greater therapeutic window. The allocolchicines, which are biphenyl analogues of the naturally occurring **1**, show promise in this respect. Unfortunately, the majority of synthetic approaches to allocolchicines commence with colchicine itself,<sup>2</sup> thus severely limiting the type and position of structural variation and hindering the development of more potent analogues.

The tricyclic core and seven-membered ring of allocolchicine **2** present special challenges. Indeed, the only previous asymmetric total synthesis of **2** first establishes the A- and

B-rings and then introduces the C-ring.<sup>3</sup> As part of a program examining the functionalization of unactivated substrates,<sup>4</sup> we chose to examine the suitability of direct arylation in the synthesis of **2**. We envisioned that an efficient enantioselective synthesis of **2** could be achieved by elaboration of commercially available **5** via two halide-selective cross-coupling reactions, an asymmetric ketone reduction and a palladium-catalyzed intramolecular direct arylation reaction (Scheme 1). Ring-C analogue **3**<sup>5</sup> could be prepared via an analogous route.

Such an approach would push catalytic direct arylation<sup>6–8</sup> onto challenging ground since it requires the formation of a

(3) Vorogushin, A. V.; Predeus, A. V.; Wulff, W. D.; Hansen, H. J. *J. Org. Chem.* **2003**, *68*, 5826.

(4) (a) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (b) Lafrance, M.; Blaquiere, N.; Fagnou, K. *Chem. Commun.* **2004**, *24*, 2874.

(5) Boyé, O.; Brossi, A.; Yeh, H. J. C.; Hamel, E.; Wegrzynski, B.; Toome, V. *Can. J. Chem.* **1992**, *70*, 1237.

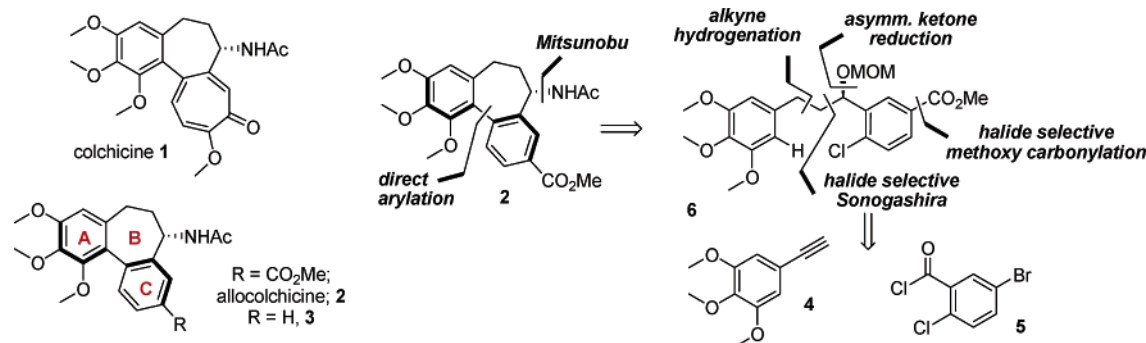
(6) For recent reviews, see: (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 211. (d) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(7) For intermolecular examples, see: (a) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. (b) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (c) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. (d) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698.

(1) (a) Hamel, E. *Med. Res. Rev.* **1996**, *16*, 207. (b) Shi, Q.; Morris-Natschke, S. L.; Lee, K.-H. *Curr. Pharm. Des.* **1998**, *4*, 219. (c) Lee, K.-H. *J. Biomed. Sci.* **1999**, *6*, 236. (d) Leoni, L. M.; Hamel, E.; Genini, D.; Shih, H.; Carrera, C. J.; Cottam, H. B.; Carson, D. A. *J. Natl. Cancer Inst.* **2000**, *92*, 217. (e) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 3230.

(2) For example, see: (a) Bergemann, S.; Brecht, R.; Buttner, F.; Guendard, D.; Gust, R.; Seitz, G.; Stubbs, M. T.; Thoret, S. *Bioorg. Med. Chem.* **2003**, *11*, 1269. (b) Davis, P. D.; Dougherty, G. J.; Blakey, D. C.; Galbraith, S. M.; Tozer, G. M.; Holder, A. L.; Naylor, M. A.; Nolan, J.; Stratford, M. R. L.; Chaplin, D. J.; Hill, S. A. *Cancer Res.* **2002**, *62*, 7247. (c) Shi, Q.; Chen, K.; Brossi, A.; Verdier, P.; Hamel, E.; McPhail, A. T.; Tropsha, A.; Lee, K.-H. *J. Org. Chem.* **1998**, *63*, 4018.

# Scheme 1. Intramolecular Direct Arylation as a Synthetic Strategy and Retrosynthetic Analysis



seven-membered ring via direct arylation, which is exceedingly rare.<sup>9,10</sup> Additionally, the use of **5** as the starting material necessitates the use of an aryl chloride as a coupling partner in the direct arylation. In contrast to other reaction classes,<sup>11</sup> aryl chlorides have been scantily examined in these processes,<sup>12</sup> and the majority of applications in synthesis have relied on aryl iodides<sup>13</sup> and triflates.<sup>14,15</sup>

In this letter we describe the realization of these goals. As a result of these efforts, we have uncovered an important link between the amount of dehalogenation, which occurs as an unwanted side reaction in challenging arylations, and the ligand-to-palladium ratio. These observations should prove to be useful in other challenging direct arylation reactions. Furthermore, the successful application of this method in synthesis of **2** should provide us and others with confidence to consider these transformations in the synthesis of other, even more complex molecules.

The synthesis of direct arylation substrate **6** is outlined in Scheme 2. A Sonogashira cross-coupling between alkyne **4**<sup>16</sup> and arene **5** in the presence of 1 mol % PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, 3 mol

% copper iodide, and 1.5 equiv of triethylamine in THF at room temperature occurs with excellent selectivity for the acyl chloride moiety, giving **7** in 92% yield leaving the aryl chloride and bromide functionalities intact for subsequent elaboration.<sup>17,18</sup> Of the methods for asymmetric ketone reduction examined, the combination of (*S*)-pinene and 9-BBN as the chiral reductant<sup>19</sup> followed by treatment with sodium hydroxide and hydrogen peroxide produced the best results. Using these conditions, we prepared alcohol **8** in 80% yield and 97% ee, and subsequent protection gave the methoxymethyl (MOM) ether **9** in 94% yield. Selective hydrogenation of the alkyne was performed with diimide generated in situ by the treatment of **9** with 4-toluenesulfonylhydrazide and sodium acetate in a DME/water mixture to give **10** in greater than 95% yield.<sup>20</sup>

A second halide-selective palladium-catalyzed reaction employing 5 mol % PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, methanol, and potassium carbonate under 5 atm of carbon monoxide in DMF at 95 °C<sup>21</sup> creates the ester functionality and provides **6** in 82% isolated yield, preserving the aryl chloride functionality for the key direct arylative carbon–carbon bond-forming step.

A similar pathway, employing arene **11**, was used to prepare the direct arylation precursor **15** lacking the ester functionality. As outlined in Scheme 2, a halide-selective Sonogashira followed by an (*S*)-pinene/9-BBN reduction, MOM protection, and diimide alkyne reduction under conditions similar to those employed in the preparation of **6** provided aryl bromide **15** in good yield and 97% ee.

With the direct arylation precursors in hand, the key cyclization step was investigated (Scheme 3). Initial optimization experiments were performed on aryl chloride **6**. Under previously reported conditions,<sup>4</sup> up to 92% conversion

(8) For intramolecular examples, see: (a) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460. (b) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 3739. (c) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2. See also ref 4.

(9) For examples with heterocyclic arene coupling partners, see: (a) Kozikowski, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, *32*, 3317. (b) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569.

(10) Examples of selective ring closure of a seven-membered-ring with nonheteroaromatic arenes are very rare. See ref 4a.

(11) Little, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(12) Successful reaction with aryl chlorides has been achieved in intermolecular reactions with electron-rich zinc pyrroles and intramolecularly in the formation of five-membered rings in moderate to good yield. See: (a) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981. (b) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310.

(13) For example, see: (a) Kitamura, M.; Ohmori, K.; Kawase, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1229. (b) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004. (c) Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187. (d) Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **2001**, 523.

(14) For example, see: (a) Futagami, S.; Ohashi, Y.; Imura, K.; Hosoya, T.; Ohmori, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 1063. (b) Harayama, T.; Akiyama, T.; Nakano, Y.; Shibaike, K.; Akamatsu, H.; Hori, A.; Abe, H.; Takeuchi, Y. *Synthesis* **2002**, 237.

(15) Examples employing aryl bromides are less common. See: (a) Cuny, G. D. *Tetrahedron Lett.* **2003**, *44*, 8149. (b) Bringman, G.; Ochse, M.; Gotz, R. *J. Org. Chem.* **2000**, *65*, 2069 and references therein.

(16) Lawrence, N. J.; Ghani, F. A.; Hepworth, L. A.; Hadfield, J. A.; McGown, A. T.; Pritchard, R. G. *Synthesis* **1999**, 9, 1656.

(17) Cox, R. J.; Ritson, D. J.; Dane, T. A.; Berge, J.; Charmant, J. P. H.; Kantacha, A. *Chem. Commun.* **2005**, 8, 1037.

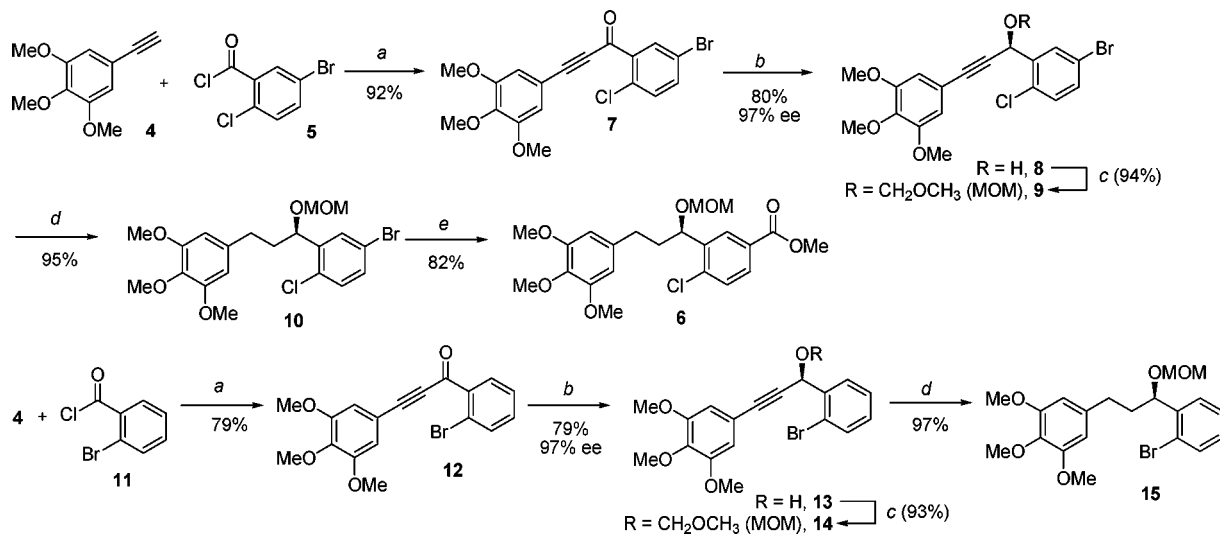
(18) (a) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, *11*, 777. (b) Negishi, E.-I.; Bagheri, V.; Chatterjee, S.; Luo, F.-T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *47*, 5181. For a recent review, see: Negishi, E.-I.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

(19) (a) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (b) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371.

(20) Hart, D. J.; Hong, W.-P.; Hsu, L.-Y. *J. Org. Chem.* **1997**, *62*, 4665.

(21) Adapted from: (a) Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7595. (b) Back, T. G.; Parvez, M.; Wulff, J. E. *J. Org. Chem.* **2003**, *68*, 2223.

**Scheme 2.** Synthesis of Direct Arylation Substrates **6** and **15**<sup>a</sup>



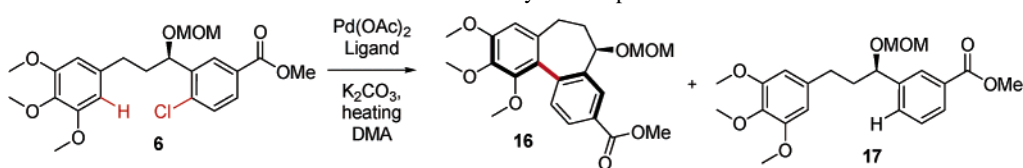
of the starting material could be obtained. Unfortunately, the desired biaryl **16** was generated along with an unacceptable amount of a hydrodechlorinated byproduct **17** (approximately 20%). This prompted a reinvestigation of all the reaction parameters. The majority of these efforts gave inferior conversions and/or direct arylation-to-reduction ratios. We also found that the use of equimolar quantities of  $(\text{IPr})\text{Pd}(\text{OAc})_2(\text{OH}_2)$  and  $\text{IPr}\cdot\text{HCl}$  (1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride) failed to induce selective ring closure.<sup>22</sup>

After significant experimentation, a promising trend was uncovered. With ligand **18**,<sup>23</sup> it was noted that the amount

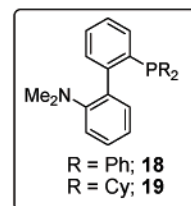
of reduced byproduct **17** is dependent on the ratio of palladium to ligand used. For example, when 4 equiv of ligand **18** is used relative to  $\text{Pd}(\text{OAc})_2$ , the reduced product **17** predominates with a ratio of 0.3:1 (entry 1). Conversely, when a 1:1 Pd:ligand ratio is employed, the ratio improves slightly to 5:1 in favor of **16** (entry 3). Unfortunately, this improvement comes at the expense of overall conversion since only 15% conversion is obtained when a 1:1 ligand **18** to palladium ratio is used.

To improve the low conversion, this trend was investigated with different ligands. We were gratified to find that with dicyclohexylphosphino biphenyl ligand **19**, the ratio of

**Scheme 3.** Direct Arylation Optimization<sup>a</sup>



Entry	Ligand	Ligand:Pd	Temp. (°C)	% Conv. <sup>b</sup>	16:17 <sup>b</sup>
1	<b>18</b>	4:1	130	88	0.3:1
2	<b>18</b>	2:1	130	92	4:1
3	<b>18</b>	1:1	130	15	5:1
4	<b>19</b>	4:1	130	77	8:1
5	<b>19</b>	2:1	130	94	3:1
6	<b>19</b>	1:1	130	64	12:1
7	<b>19</b>	1:1	145	94	14:1

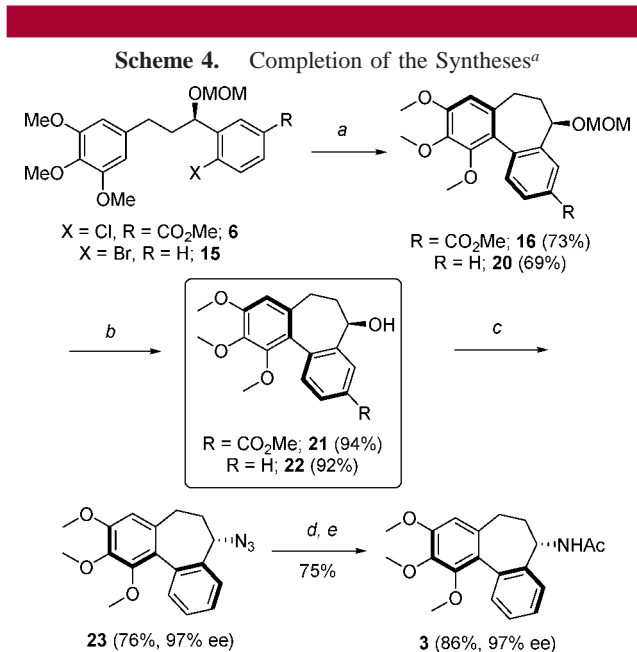


<sup>a</sup> Conditions: **6**,  $\text{Pd}(\text{OAc})_2$  (10 mol %), ligand (10–40 mol %),  $\text{K}_2\text{CO}_3$  (2 equiv) dissolved in DMA and heated to the indicated temperature for 14–16 h. <sup>b</sup> Determined by NMR of the crude reaction mixture.

**16:17** could be improved from 3:1 (entry 5) to 12:1 (entry 6) by changing from a 2:1 ligand:Pd ratio to a 1:1 ligand:Pd ratio. Importantly, with ligand **19**,<sup>24</sup> an improved but still moderate conversion to product was achieved, 64% (entry 6). Fortunately, this could be significantly improved by increasing the reaction temperature to 145 °C. Under these new conditions, up to 94% conversion can be obtained by employing a 1:1 ligand **19**:Pd ratio, and by heating the mixture at 145 °C, a synthetically acceptable ratio of **16:17** of 14:1 is obtained, providing **16** in 73% isolated yield as a 10:1 mixture of atropisomers (Scheme 4).<sup>25</sup> Deprotection of the MOM ether by treatment with HCl in methanol provides alcohol **21** in 94% yield and 97% ee, which can be converted to **2** as described by Wulff.<sup>3</sup>

We were also gratified to find that these new direct arylation conditions could be applied to the cyclization of aryl bromide **15** to give ring-C variant **20**. MOM deprotection to give **22** and subsequent Mitsunobu inversion of the alcohol by treatment with Zn(N<sub>3</sub>)<sub>2</sub>·pyridine, diisopropyl diazodicarboxylate and triphenylphosphine in toluene at room temperature provides azide **23** in 76% yield with perfect preservation of the enantiomeric excess, 97% ee. Azide reduction with LiAlH<sub>4</sub> in THF and formation of the acetamide by treatment with acetic anhydride and catalytic DMAP provides allocolchicine ring-C analogue **3** in 75% yield for the two steps.

In conclusion, we have achieved an enantioselective formal synthesis of allocolchicine **2** by making use of two halide selective functionalizations, an asymmetric ketone reduction and an intramolecular direct arylation of an aryl chloride. The success of this final step required a reinvestigation of the



<sup>a</sup> Conditions: (a) 10 mol % Pd(OAc)<sub>2</sub>, 10 mol % ligand **19**, K<sub>2</sub>CO<sub>3</sub>, DMA, 145 °C; (b) MeOH, HCl, reflux, 1 h; (c) Zn(N<sub>3</sub>)<sub>2</sub>·pyridine, DIAD, PPh<sub>3</sub>, PhMe, rt; (d) LiAlH<sub>4</sub>, THF, rt; (e) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP (cat), DCM. DIAD = diisopropyl diazodicarboxylate.

reaction conditions and uncovered an important link between the ratio of ligand to palladium employed and the amount of undesired hydrodehalogenated byproduct that was produced. This strategy was also employed in an asymmetric total synthesis of ring-C analogue **3**.

**Acknowledgment.** We thank the NSERC, CFI, OIT, and the University of Ottawa for financial support.

**Supporting Information Available:** Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0505959

(22) Campeau, L.-C.; Thansandote, P.; Fagnou, K. *Org. Lett.* **2005**, *7*, 1857. We attribute the diminished reactivity of the IPr carbene catalyst to the enhanced steric bulk of the NHC ligand, which may be incompatible in direct arylation ring closures that produce biaryls with three ortho substituents.

(23) Harris, M. C.; Geis, O.; Buchwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019.

(24) Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334.

(25) Allocolchicines are known to exist as a mixture of interconverting atropisomers whose equilibrium ratio is solvent dependent. For example, see refs 5 and 2c.