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Copper-Catalyzed Cyclization of Iodo-tryptophans: A Straightforward Synthesis of Pyrroloindoles

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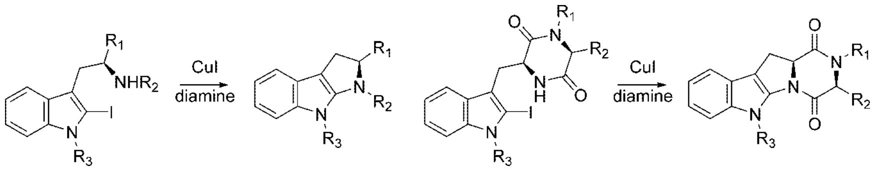
ABSTRACT



Pyrroloindoles are a key structural motif found in a wide number of biologically active alkaloids. Intramolecular copper-catalyzed coupling of readily accessible 2-iodo-tryptophan derivatives occurs in excellent yield, affording a wide range of polysubstituted, enantioenriched tetrahydropyrrolo[2,3-*b*]indoles. Diketopiperazines are also suitable substrates for this cyclization reaction, which affords a straightforward entry to tetra- to hepta-polycyclic systems.

The pyrrolo[2,3-*b*]indole skeleton is a key structural motif[1] that appears in the core structure of an impressive number of biologically active alkaloids such as the potent vasodilator amauromine **1**,[2] the insecticidal okaramine C **2**,[3] the anticancer agent phakellistatin 3 **3**,[4] as well as polycyclic compounds minfiensine **4**[5] and psychotrimine **5**[6] (Figure 1).[7] While intense research activity has been devoted to the preparation of hexahydropyrrolo[2,3-*b*]indoles (HPI), the affiliated system possessing an additional unsaturation, tetrahydropyrrolo[2,3-*b*]indoles (TPI) **6**, has received less attention. They proved, however, to be especially efficient and versatile intermediates for assembling various hetero-

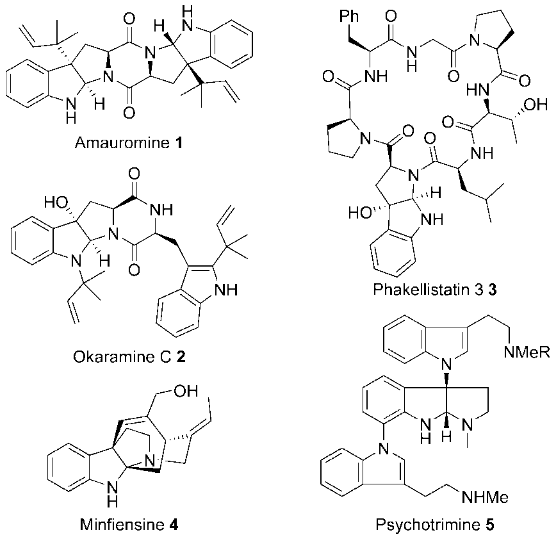


Figure 1. Representative hexahydropyrroloindole alkaloids.

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[1] For reviews, see: (a) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (b) Schmidt, M. A.; Movassaghi, M. *Synlett* **2008**, 313.

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[6] Takayama, H.; Mori, I.; Kitajima, M.; Aimi, N.; Lajis, N. H. *Org. Lett.* **2004**, *6*, 2945.

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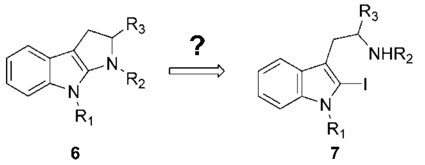
cyclic compounds, and the presence of the additional unsaturation is a key element for chemical diversity.[8] The current approach toward this polycyclic ring system mainly relies on Witkop's oxidative cycloaromatization of tryptophan derivatives.[9] While this method usually performs well with simple systems, its use with complex starting materials can be problematic, and aromatization, protecting group migration, and oxidation can dramatically lower yields.[10] An alternative and general route to prepare tetrahydropyrrolo[2,3-*b*]indoles is therefore required.

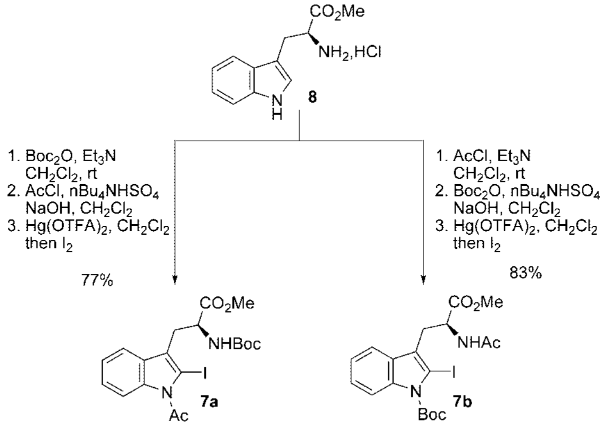
In this context and in continuation of our studies on copper-mediated cyclization of modified amino acids and peptides,[11] we envisioned an intramolecular amidation reaction to access substituted TPI **6** from readily available 2-iodotryptophan derivatives **7** (Scheme 1), and we report our results herein.

Scheme 1. Copper-Mediated Approach to Pyrroloindoles



To test the feasibility of the cyclization reaction, substrates **7a** and **7b**, whose amine groups were, respectively, protected as carbamate and amide, were prepared from L-tryptophan methyl ester **8**. The preparation of these substrates involved: (i) protection of the amino acid with Boc$_2$O or acetyl chloride, (ii) phase-transfer introduction of the indole protecting group, and (iii) regioselective C2-iodination of the indole (Scheme 2).[12] Using this short sequence, multigram quantities of each substrate could be easily prepared in excellent overall yields.

Scheme 2. Preparation of Iodinated Tryptophan Derivatives



With homochiral substrates **7a** and **7b** in hand, we next focused on the selection of optimal conditions for their cyclization to **6a** and **6b** using Buchwald's combination of diamines and copper iodide (Figure 2).[13] Screening all possible combinations of *N*,*N'*-dimethylethylenediamine and (±)-*trans*-cyclohexane-1,2-diamine as ligands, K$_2$CO$_3$ and K$_3$PO$_4$ as base and toluene, or 1,4-dioxane as solvent revealed a different reactivity of **7a** and **7b** toward various catalytic systems, which is most likely due to their different nucleophilicities. However, conversion as well as the amount of reduced products **9** and **10** could be quickly optimized in each case. While toluene and potassium phosphate were found to be superior for both substrates, *N*,*N'*-dimethylethylenediamine and (±)-*trans*-cyclohexane-1,2-diamine, respectively, gave the highest yields for the cyclization of carbamate **7a** and amide **7b**. Since extensive amounts of epimerization have been observed for related cyclization reactions,[14] we carefully checked the ee of tetrahydropyr-

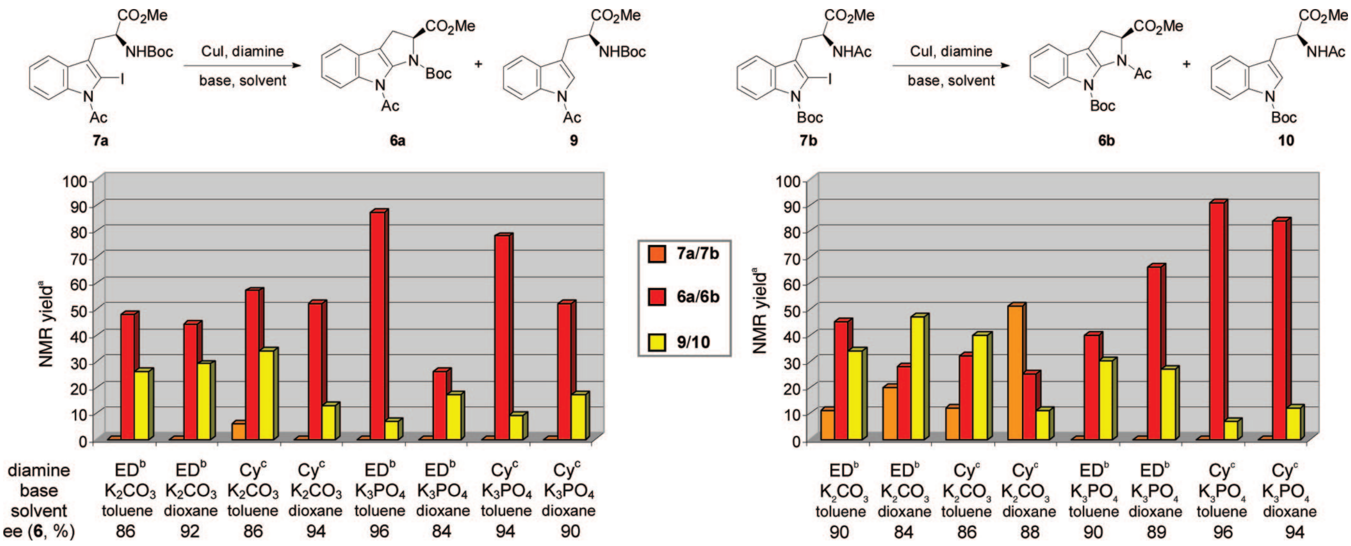


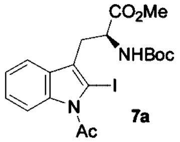
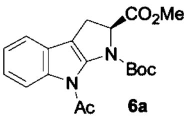
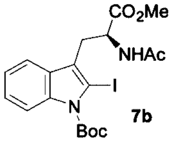
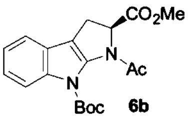
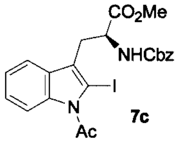
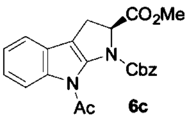
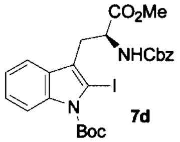
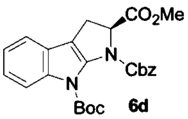
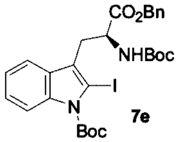
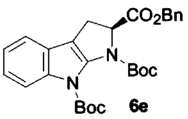
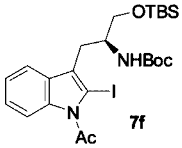
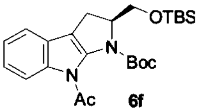
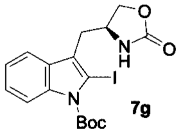
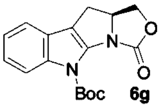
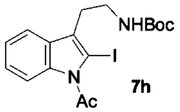
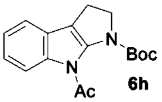
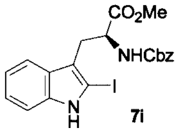
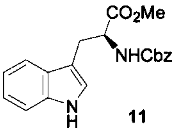
Figure 2. Optimization of cyclization conditions. a, Yields determined by ^{1}H NMR analysis of crude reaction mixtures using acetonitrile as internal standard. b, ED = *N*,*N'*-dimethylethylenediamine. c, Cy = (±)-*trans*-cyclohexane-1,2-diamine.

rolo[2,3-*b*]indoles **6a** and **6b**. We were delighted to find that the conditions used have only a small effect on our system since **6a** and **6b** could be isolated with 96% ee.

The scope of the reaction was next investigated with various 2-iodo-tryptophan derivatives using the optimized conditions: results are summarized in Table 1. In most cases, polycyclic products were obtained in good to excellent yields. Moreover, protecting groups on the nitrogen atoms have little influence as complete conversion was observed in all cases, and even substrate **7d** possessing two bulky carbamates cyclized smoothly (entry 4). However, the presence of two Boc groups (entry 5) or smaller substituents (tryptophanol, entries 6 and 7, or tryptamine derivatives, entry 8) did result in a more sluggish cyclization. Interestingly, yields did not significantly vary upon scaling up the reactions since substrates **6a**, **6b**, and **6d** were obtained in similar yields when the reaction was performed on milligram or multigram scales. It is noteworthy that the absence of a carbamate or an amide on the indole nitrogen has a dramatic impact on the reaction, since cyclization is completely inhibited with such substrates, and reduction is the preferred pathway (entry 9). This indicates that either a deprotonation of the indole inhibits the cyclization or that a strong *ortho* effect is operating.[15] The presence of a chelating group close to the iodide might stabilize the intermediate copper complex, therefore facilitating the overall cyclization process.

The hexahydropyrrolo[2,3-*b*]indole core being an important constituent of various biologically active peptides, the ability to form the pyrroloindole skeleton within peptides is very attractive since it offers an interesting alternative to classical routes that involve its formation prior to peptide bond formation. The cyclization of iodinated dipeptides **12** and **14** was therefore considered (Scheme 3). Using *trans*-cyclohexane-1,2-diamine as ligand, the desired TPI-isoleucine **13** and TPI-phenylalanine **15** cyclized products were obtained in good yields and without noticeable epimerization.[16] These results demonstrate the possibility of a late stage cyclization and should pave the way for its use on more complex peptidic or cyclopeptidic systems.

Table 1. Scope and Limitations

entry	iodoindole	product	cond.[a]	yield[b]
1	 **7a**	 **6a**	A	87% (83%[c])
2	 **7b**	 **6b**	B	98% (95%[c])
3	 **7c**	 **6c**	A	93%
4	 **7d**	 **6d**	A	73% (71%[d])
5	 **7e**	 **6e**	A	62%
6	 **7f**	 **6f**	A	51%
7	 **7g**	 **6g**	B	55%
8	 **7h**	 **6h**	A	50%
9	 **7i**	 **11**	A	85%

[a] Conditions A: CuI (10 mol %), *N*,*N*′-dimethylethylenediamine (20 mol %), K_3PO_4 (2 equiv), toluene (0.1 mol·L^{-1}), 110 °C, 12−16 h. Conditions B: CuI (10 mol %), *trans*-cyclohexane-1,2-diamine (20 mol %), K_3PO_4 (2 equiv), toluene (0.1 mol·L^{-1}), 110 °C, 12−16 h. [b] Yield of pure, isolated product. [c] Reaction performed on gram scale. [d] Reaction performed on a 13 g scale.

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(7) For selected syntheses, see: (a) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953. (b) Roe, J. M.; Webster, R. A. B.; Ganesan, A. *Org. Lett.* **2003**, *5*, 2825. (c) Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628. (d) Hewitt, P. R.; Cleator, E.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 2415. (e) Lindel, T.; Bräuchle, L.; Golz, G.; Böhrer, P. *Org. Lett.* **2007**, *9*, 283. (f) Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 1485. (g) Shangguan, N.; Hehre, W. J.; Ohlinger, W. S.; Beavers, M. P.; Joullié, M. *J. Am. Chem. Soc.* **2008**, *130*, 6281. (h) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2008**, *130*, 5368. (i) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125.

(8) For examples, see: (a) Ohno, M.; Tanaka, S.; Shieh, T.-C.; Spande, T. F. *J. Org. Chem.* **1984**, *49*, 5069. (b) Kamenecka, T. M.; Danishefsky, S. J. *Chem. Eur. J.* **2001**, *7*, 41. (c) Okada, M.; Sato, I.; Cho, S. J.; Dubnau, D.; Sakagami, Y. *Tetrahedron* **2006**, *62*, 8907. (d) Cardoso, A. S.; Marques, M. M. B.; Srinivasan, N.; Prabhakar, S.; Lobo, A. M. *Tetrahedron* **2007**, *63*, 10211.

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(10) Bailey, P. D.; Cochrane, P. J.; Irvine, F.; Morgan, K. M.; Pearson, D. P. J.; Veal, K. T. *Tetrahedron Lett.* **1999**, *40*, 4593.

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(12) (a) Mingoia, Q. *Gazz. Chim. Ital.* **1930**, *60*, 509. (b) Snider, B. B.; Zeng, H. *J. Org. Chem.* **2003**, *68*, 545.

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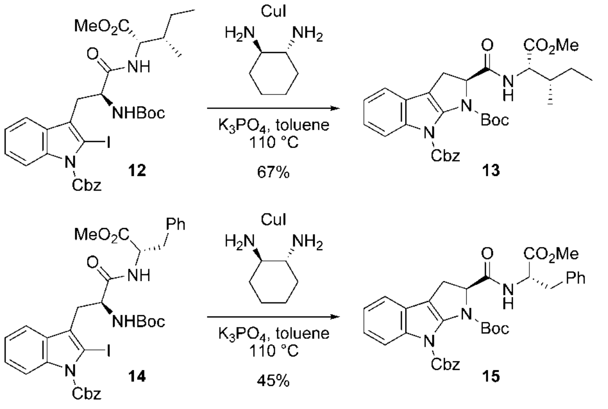
(14) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653.

(15) For an ortho effect with trifluoroacetamides, see: (a) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276. (b) Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050. (c) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 2598. (d) Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844.

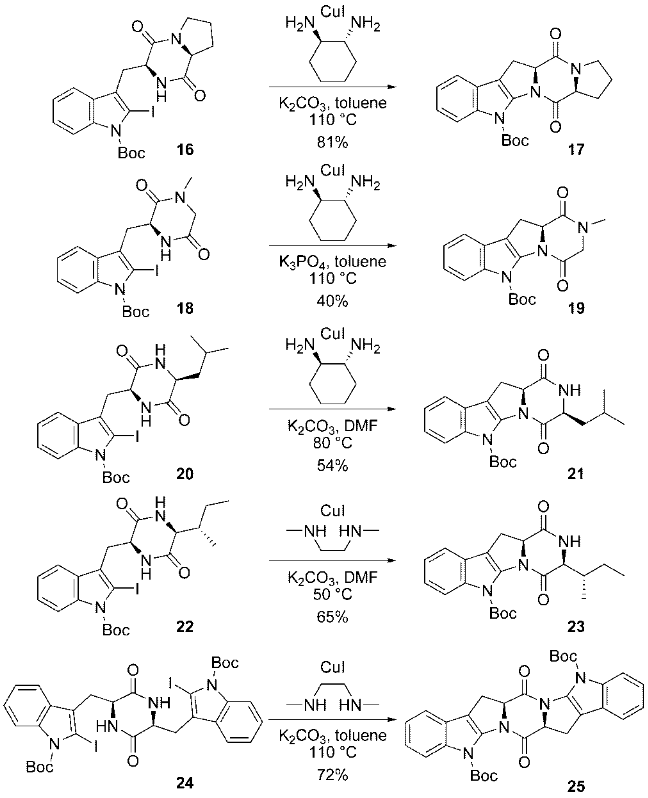
(16) Compounds obtained as single diastereoisomers by ^{1}H NMR analysis of crude reaction mixtures.

Scheme 3. Cyclization of Iodinated Dipeptides



To expand the scope of the cyclization and to address its regioselectivity with systems possessing several amides, together with providing a straightforward entry to the polycyclic skeleton of natural products such as the okaramines or brevienamides, the cyclization of various iodinated, tryptophan-derived, diketopiperazines was finally undertaken (Scheme 4). Such substrates were found to cyclize smoothly, providing tetra- or pentacyclic products **17**,[16] **19**,[16] **21**, and **23**, whose structures were ascertained by X-ray diffraction analysis in the first two cases. For substrates **20** and **22**, the use of DMF as solvent, for solubility reasons, however, led to the formation of minor amounts (ca. 5%) of epimerized side products that could easily be separated by column chromatography.

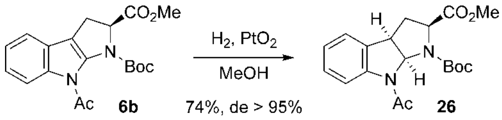
Scheme 4. Cyclization of Iodinated Diketopiperazines



Interestingly, and to test the cyclization reaction further, the double cyclization of bisiodinated diketopiperazine **24** was attempted. This substrate was found to cyclize smoothly to heptacyclic compound **25**[16] which was isolated in 72% yield as a single diastereoisomer (Scheme 4). It is noteworthy that this compound possesses the core structure of hexahydropyrroloindole alkaloids such as amauromine and gypsetin.

One "post-ring forming" reaction was finally attempted. Treatment of **6b** with Adam's catalyst diastereoselectively reduced the indole ring to give **26** whose stereochemistry was ascertained by X-ray analysis (Scheme 5).

Scheme 5. "Post-Ring Forming" Hydrogenation



In conclusion, we have developed an efficient copper-catalyzed procedure giving rapid access to a wide range of enantiopure pyrrolo[2,3-*b*]indoles from readily available 2-iodo-tryptophan derivatives. Further applications of this method are underway and will be reported in due course.

Acknowledgment. The authors thank the CNRS and the ANR (project ProteInh) for financial support. M.T. acknowledges the Ministère de la Recherche and A.C. the Institut du Cancer for graduate fellowships.

Supporting Information Available: Experimental procedures, characterization, copies of ^1H and ^{13}C NMR spectra for all new compounds, and X-ray structures of **17**, **19**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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