ORGANIC LETTERS

2006
Vol. 8, No. 8
1745−1747

Enantioselective Synthesis of a PKC Inhibitor via Catalytic C–H Bond Activation

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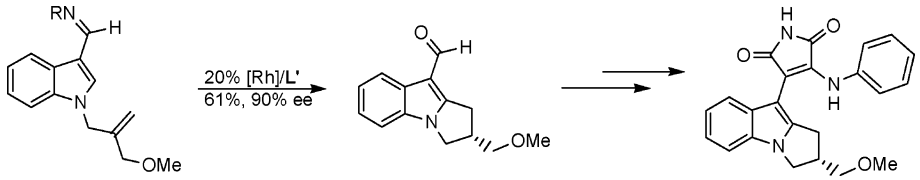
Received February 26, 2006

ABSTRACT



The syntheses of two biologically active molecules possessing dihydropyrroloindole cores (1 and 2) were completed using rhodium-catalyzed imine-directed C–H bond functionalization, with the second of these molecules containing a stereocenter that can be set with 90% ee during cyclization using chiral nonracemic phosphoramidite ligands. Catalytic decarbonylation and direct indole/maleimide coupling provide efficient access to 2.

The dihydropyrroloindole core, like its parent molecule, is a recurring motif in drug candidates and natural products.[1] For example, compounds **1** and **2** (Figure 1) have been shown to have significant physiological effects; the former targets the serotonin receptor (5-HT_{2C}),[2] and the latter is a protein kinase C inhibitor selective for isozyme β.[3] These activities are potentially useful in the treatment of obesity and its established corollary, diabetes. We recognized an opportunity to rapidly synthesize biologically active dihydropyrroloindoles such as **1** and **2** using intramolecular catalytic C−H bond functionalization and our recently developed enantioselective variant,[4] and this paper reports the achievement of these goals. Although there is growing interest in the application of C−H activation in organic synthesis,[5,6] examples of this important transformation in the synthesis of biologically active molecules, particularly catalytic enantioselective variants, are rare.

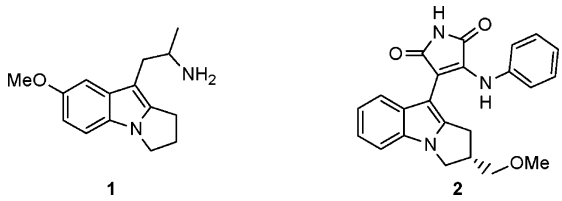


Figure 1. Biologically active dihydropyrroloindoles.

(1) For recent examples, see: (a) Bentley, J. M.; Bickerdike, M. J.; Hebeisen, P.; Kennett, G. A.; Lightowler, S.; Mattei, P.; Mizrahi, J.; Morley, T. J.; Plancher, J.-M.; Richter, H.; Roever, S.; Taylor, S.; Vickers, S. P. Preparation of cycloalkyl fused indole derivatives and their use as 5-HT_{2B} and 5-HT_{2C} receptor ligands. Int. Pat. Appl. WO 02/051844 A1, July 4, 2002. (b) Wang, Z.; Dufresne, C.; Guay, D.; Leblanc, Y. Dihydropyrrolo-[1,2-*a*]indole and Tetrahydropyrido[1,2-*a*]indole Derivatives as Prostaglandin D2 Receptor Antagonists. Int. Pat. Appl. WO 02/094830 A2, Nov 28, 2002. For a review on the mitomycinoids, see: (c) Danishefsky, S. J.; Schkeryantz, J. M. *Synlett* **1995**, 475−490.

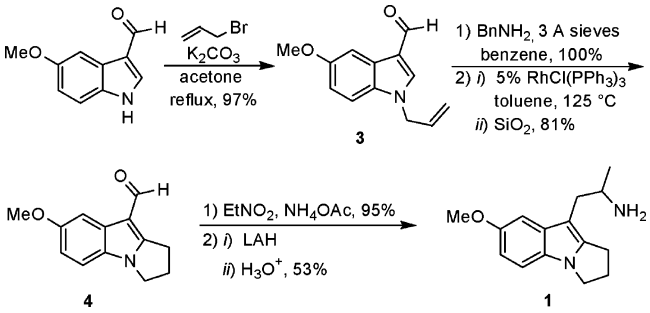
(2) Adams, D. R.; Bentley, J. M.; Roffey, J. R. A.; Hamlyn, R. J.; Gaur, S.; Duncton, M. A. J.; Davidson, J. E. P.; Bickerdike, M. J.; Cliffe, I. A.; Mansell, H. L. Pyrroloindoles, Pyridoindoles, and Azopinoindoles as 5-HT_{2C} Agonists. US Patent 6,433,175 B1, Aug 13, 2002.

(3) Inaba, T.; Tanaka, M.; Sakoda, K. Disubstituted Maleimide Compounds and Medicinal Utilization Thereof. Eur. Pat. Appl. 1,120,414 A1, Aug 1, 2001.

(4) (a) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692−9693. (b) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192−7193.

10.1021/ol060485h CCC: $33.50
Published on Web 03/15/2006

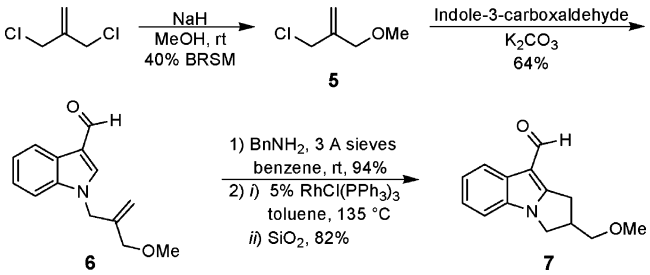
Scheme 1. Synthesis of Compound **1**



The synthesis of compound **1** (Scheme 1) began with the reaction of 5-methoxyindole-3-carboxaldehyde with excess allyl bromide to give the *N*-alkylated indole (**3**) in 97% yield. Aldehyde **3** was then condensed with benzylamine in quantitative yield. Subsequent treatment of the *N*-benzyl imine with 5 mol % of $RhCl(PPh_3)_3$ (Wilkinson's catalyst) at 125 °C for 1.5 h followed by imine hydrolysis on silica gel afforded tricyclic aldehyde **4** in 81% yield. We completed our synthesis according to the previously reported procedures;[2] a Henry reaction on **4** followed by a $LiAlH_4$ reduction of the resulting nitroalkene afforded the final product in five steps and in 40% overall yield.

In the synthesis of compound **2** (Figure 1), alkylation of indole-3-carboxaldehyde with allyl chloride **5** provided aldehyde **6** (Scheme 2), which was then condensed with

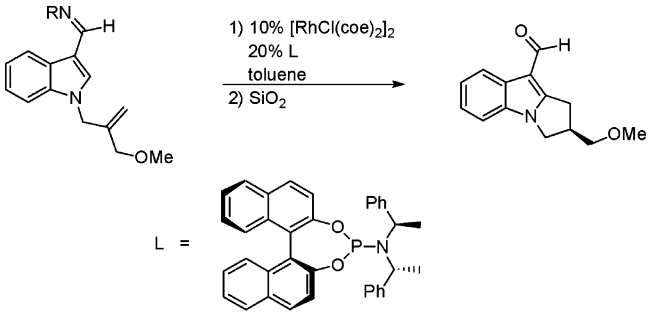
Scheme 2. Cyclization with Achiral Catalyst

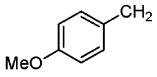
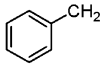
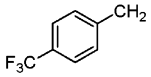
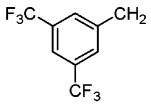
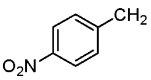


benzylamine. We were gratified to discover that the *N*-benzyl imine product, possessing an allylic methyl ether tether, is a viable substrate for our directed C−H bond activation reaction, cyclizing in 82% yield with 5 mol % of $RhCl(PPh_3)_3$ at 135 °C.

It was known from previous work in our group that although aromatic ketimines are excellent substrates for the rhodium-chiral phosphoramidite-mediated enantioselective cyclization reaction,[4b] the corresponding aldimines are much poorer substrates and provide products in very low yields. After initial attempts with other phosphorus ligands yielded unsatisfactory ee's (<15%), we returned to the phosphoramidite ligands and found that by changing the metal/ligand ratio from 1:1.5 to 1:1, we were able to observe product. We chose to optimize the reaction using ligand **L** (Table 1), which gave the best ee (73%) and the least starting material decomposition.

Table 1. Directing Groups Evaluated in Asymmetric Cyclization



entry	R	temp (°C)	time (h)	%P[a] (%ee)[b]	%SM
1		105	16.5	28(80)	41
2		105	24	31(84)	39
3		105	16.5	44(86)	25
4		105 90	22 24	57(86) 65(90)	0 0
5		105	18	43(33)	0
6		105	18	22(56)	66

[a] Yields based on ^1H NMR integration relative to 2,6-dimethoxytoluene internal standard. Rhodium insertion into the aldimine C−H bond accounts for a significant amount of the remaining material. [b] ee's determined by chiral HPLC after hydrolysis.

Because we believe that reductive elimination is the rate-limiting step in our catalytic cycle,[7] and because it is well-established that placing electron-withdrawing groups on a metal-bound ketone can reduce the barrier to reductive elimi-

(5) For examples of the application of C−H bond activation in target-oriented synthesis, see: (a) Harris, P. W. R.; Woodgate, P. D. *J. Organomet. Chem.* **1997**, *530*, 211−223. (b) Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122*, 6321−6322. (c) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856−11857. (d) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950−12951. (e) Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1301−1303. (f) Pastine, S. J.; Sames, D. *Org. Lett.* **2003**, *5*, 4053−4055. (g) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496−13497.

(6) For examples of the application of rhodium-carbenoid insertions into C−H bonds in target-oriented synthesis, see: (a) Taber, D. F.; Song, Y. *J. Org. Chem.* **1997**, *62*, 6603−6607. (b) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233−236. (c) Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951−4953 and references therein.

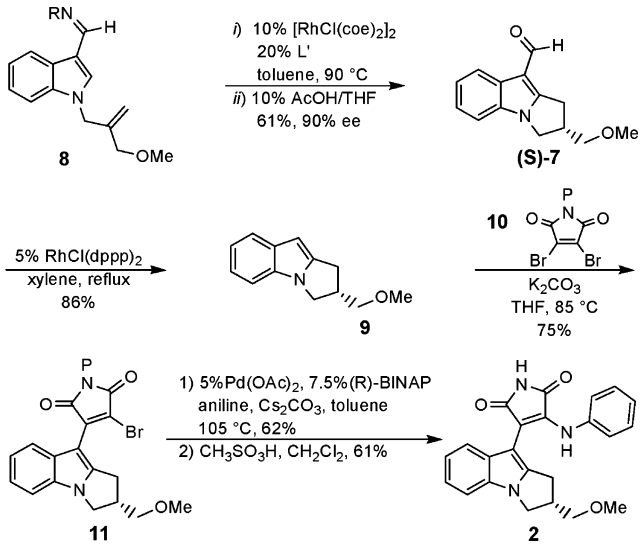
(7) (a) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62−83. (b) Jun, C. H.; Moon, C. W.; Hong, J. B.; Lim, S. G.; Chung, K. Y.; Kim, Y. H. *Chem. Eur. J.* **2002**, *8*, 485−492.

nation from the metal center,[8] we decided to modify the *N*-benzyl imine in an effort to increase the efficiency of the cyclization.

As expected, placing a trifluoromethyl group at the para position increased the yield significantly, from 31% to 44% at 105 °C (Table 1, entry 3), while a methoxy group at the same position caused the yield to drop slightly to 28% (entry 1). Placing trifluoromethyl groups at both meta positions caused another significant increase in yield, this time giving the cyclized product in 57% yield with 86% ee (entry 4). We attribute this yield increase partly to the more electron-withdrawing nature of the substituent and partly to the fact that, unlike most of the other substrates, the bis(trifluoromethyl)benzyl imine can be readily purified by recrystallization from pentane. Decreasing the reaction temperature to 90 °C afforded the desired product in 65% yield and 90% ee. The methylene moiety of the benzyl group appears to be critical in the transfer of chirality from catalyst to product; although the imine derived from aniline gives a much higher yield than does the unsubstituted *N*-benzyl imine, the ee drops precipitously (entry 5).

As a result of the directing group studies, we chose to use bis(trifluoromethyl)benzyl imine **8** (Scheme 3) in our synthesis; this molecule was made from **6** and the commercially available 3,5-bis(trifluoromethyl)benzylamine in 85% yield after recrystallization. Although other phosphoramidite ligands were tested with this new substrate, ligand **L** was found to give both the highest ee and the highest yield. Imine **8** was then cyclized using 10% mol % of $[RhCl(coe)_2]_2$ and 20% mol % of the enantiomer of ligand **L** (ligand **L′**) and hydrolyzed with 10% acetic acid in THF to afford the final product in 61% isolated yield and 90% ee.

Scheme 3. Enantioselective Cyclization and Synthesis of Compound **2**



R = 3,5-bis(trifluoromethyl)benzyl, P = 2,4-dimethoxybenzyl

To determine the absolute stereochemistry of the cyclized product, compound **7** was condensed with 4-bromo-2-nitrophenylhydrazine, and X-ray quality crystals of the resulting hydrazone (**12**, see the Supporting Information) were grown. This compound was shown by anomalous dispersion to have an (*S*)-configuration as a result of the (*R*)-BINOL-based ligand used in the cyclization; this is consistent with previous work done on this type of system.[4b]

To perform the catalytic decarbonylation, literature conditions for indole-2-carboxaldehydes were applied to our substrate (**S-7**),[9] giving the desired decarbonylated product (**9**) in 86% yield. Although initial attempts at 3-lithiation of **9** proved unsuccessful, the direct substitution of indole **9** into maleimide **10**, a transformation which has not been reported for an *N*-alkylated indole, gave **11** in good yield in THF at 85 °C over 5.5 days. To complete the synthesis, **11** was cross-coupled with aniline[10] and subsequently deprotected with methanesulfonic acid,[11] providing compound **2** in eight linear steps.

In conclusion, we have demonstrated the use of catalytic directed C−H bond activation in the synthesis of two biologically active tricyclic indoles, the second of which contains a stereocenter that can be set with high ee (90%) by the use of enantioselective catalysis. The C−H activation methods described in this publication should be applicable to the efficient syntheses of a variety of analogues of **1** and **2** as well as to the synthesis of other biologically active dihydropyrroloindoles.

Acknowledgment. This work was supported by the NIH GM069559 (to J.A.E.) and the Director and Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division, U.S. Department of Energy, under Contract No. DE-AC02-05CH11231 (to R.G.B.). We thank Dr. Allen Oliver and Dr. Fred Hollander of the UC Berkeley CHEXRAY facility for carrying out the X-ray diffraction studies.

Supporting Information Available: Complete experimental details and spectral data for all compounds described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Meyer, M. D.; Kruse, L. I. *J. Org. Chem.* **1984**, *49*, 3195−3199.

(10) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144−1157. Although $Pd(OAc)_2$ proved to be an excellent catalyst precursor for the cross-coupling of a maleimide subtrate, $Pd_2(dba)_3$ gave 0% conversion under identical conditions.

(11) Shen, L.; Prouty, C.; Conway, B. R.; Westover, L.; Xu, J. Z.; Look, R. A.; Chen, X.; Beavers, M. P.; Roberts, J.; Murray, W. V.; Demarest, K. T.; Kuo, G. H. *Bioorg. Med. Chem.* **2004**, *12*, 1239−1255.