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Catalytic Asymmetric Diazoacetate Cyclopropanation of 1-Tosyl-3-vinylindoles. A Route to Conformationally Restricted Homotryptamines

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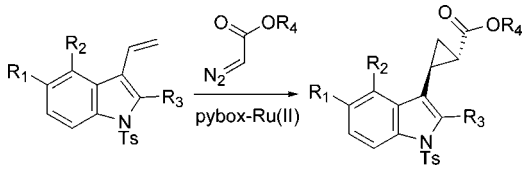
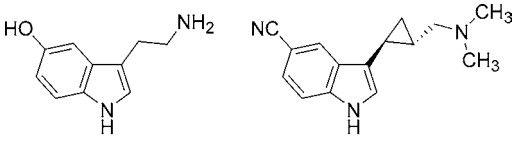
ABSTRACT



Substituted 1-tosyl-3-vinylindoles undergo catalytic asymmetric cyclopropanation with ethyl- and *tert*-butyldiazoacetate to afford N-protected *trans*-2-(indol-3-yl)-1-cyclopropanecarboxylic esters in good yield and high enantiomeric excess (81–88% ee). The resulting cycloadducts are demonstrated to be useful intermediates for the synthesis of conformationally restricted, homotryptamine-like analogues such as BMS-505130.

5-Hydroxytryptamine (serotonin) is a neurotransmitter that plays a key role in a variety of physiological functions in the central nervous system (CNS) and peripheral tissues.[1] Serotonin receptors, uptake sites, metabolism, and synthetic enzymes are implicated in the origin of many CNS disorders, including depression, anxiety, schizophrenia, social phobia, obsessive-compulsive, and panic disorders. Additionally, serotonin misregulation may be responsible for other peripheral disease states such as migranes, hypertension, eating disorders, emesis, irritable bowel, and sexual dysfunction. Consequently, the modulation of serotonin function via therapeutic agents continues to be an active and promising area of drug discovery research. Toward this end, conformational restriction of the aminoethyl side chain of 5-hydroxytryptamine has been a productive strategy used to optimize the potency and target selectivity of serotonin-like analogues.[2] This communication details synthetic chemistry efforts that have enabled rapid and efficient access to an interesting class of cyclopropane-derived, homotryptamine-like compounds, which include the selective serotonin reuptake inhibitor BMS-505130.[3]



While cyclopropanes are commonly used in drug design to impart conformational restriction to flexible molecules,[4]

(1) (a) Hoyer, D.; Hannon, J. P.; Martin, G. R. *Pharmacol., Biochem. Behav.* **2002**, *71*, 533. (b) Jones, B. J.; Blackburn, T. P. *Pharmacol., Biochem. Behav.* **2002**, *71*, 555.

(2) (a) Vangveravong, S.; Kanthasamy, A.; Lucaites, V. L.; Nelson, D. L.; Nichols, D. E. *J. Med. Chem.* **1998**, *41*, 4995. (b) Macor, J. E.; Blank, D. H.; Ryan, K.; Post, R. J. *Synthesis* **1997**, 443. (c) Ezquerra, J.; Pedregal, C.; Lamas, C.; Pastor, A.; Alvarez, P.; Vaquero, J. J. *Tetrahedron Lett.* **1996**, *37*, 683. (d) Macor, J. E.; Blank, D. H.; Post, R. *Tetrahedron Lett.* **1994**, *35*, 45. (e) Taylor, E. W.; Nikam, S.; Weck, B.; Martin, A.; Nelson, D. *Life Sci.* **1987**, *41*, 1961. (f) Schmitz, W. D.; Denhart, D. J.; Brenner, A. B.; Ditta, J. L.; Mattson, R. J.; Mattson, G. K.; Molski, T. F.; Macor, J. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1619.

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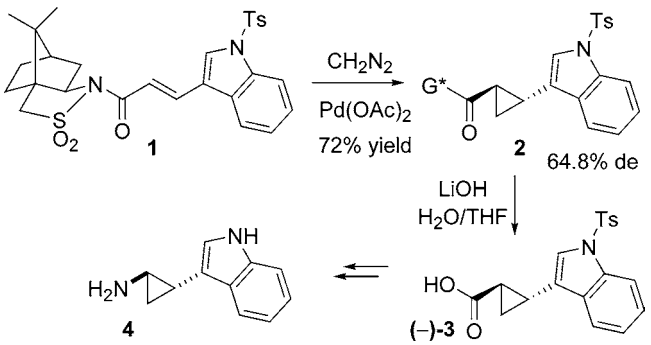
reports that describe the asymmetric syntheses of trans-1,2-disubstituted 3-indolylcyclopropanes are remarkably rare.[5] In 1995, Nichols and co-workers reported a diastereoselective palladium-catalyzed cyclopropanation of chiral *N*-enoyl sultams **1** using diazomethane (Scheme 1).[5a] The reaction

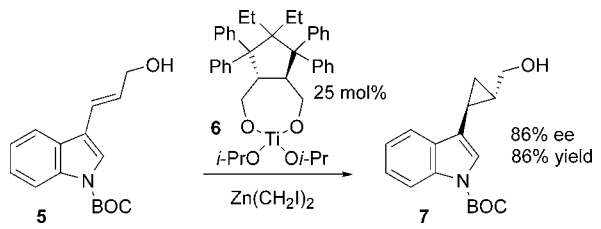
Scheme 1



afforded the corresponding cyclopropane **2** with 72% overall yield and 65% diastereomeric excess (de). The major diastereomer was separated and transformed into the rigid tryptamine analogue **4**.

Additionally, Charette and co-workers have described an enantioselective Simmons−Smith cyclopropanation of indolyl alcohol **5** using bis(iodomethyl)zinc and 0.25 equiv of the chiral titanium-TADDOLate ligand **6** (Scheme 2).[5b] The

Scheme 2

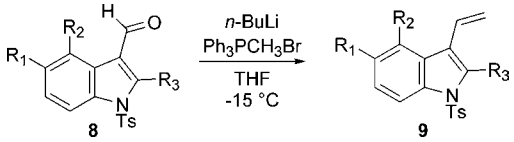


cyclopropylmethyl alcohol **7** was obtained in good yield and 86% enantiomeric excess (ee).

While the methods of Nichols and Charette are clearly effective, we desired a scalable synthesis that precluded the use of diazomethane and proceeded with greater catalytic efficiency than the Simmons−Smith method. Consequently, we choose to explore an alternative strategy involving catalytic asymmetric diazoacetate cyclopropanation.[6] In particular, the pybox−Ru(II) catalysts developed by Nishiyama and Itoh have been well documented to provide useful levels of enantio- and diastereocontrol in the formation of *trans*-cyclopropylesters from conjugated olefins.[7] Implementation of this strategy required the use of 3-vinylindoles as substrates. To the best of our knowledge, 3-vinylindoles have never been examined in asymmetric diazoacetate cyclopropanations.[8]

Our effort began with the synthesis of the requisite 3-vinylindoles. For this purpose, 1-tosylindole-3-carboxaldehydes were readily prepared in two steps from the parent indoles by Vilsmeir formylation and N-sulfonylation.[9] Wittig methylenation of the protected indole carboxaldehydes **8** provided the corresponding 1-tosyl-3-vinylindoles **9** in good yields (Table 1).[10] With the exception of **9e**, the vinylindoles

Table 1. Preparation of 3-Vinylindoles



entry	R_1	R_2	R_3	yield of **9**, %
a	H	H	H	86[a]
b	F	H	H	87
c	CN	H	H	71
d	OCH_3	H	H	82[a]
e	H	CH_3	H	92
f	H	H	CH_3	79

[a] Literature preparation; see ref 10.

were stable crystalline solids that could be stored at room temperature for several months without noticeable decomposition. The 4-methyl derivative **9e** slowly dimerized when stored in solution, as evidenced by LC mass spectra analysis.

Asymmetric cyclopropanation of 1-tosyl-3-vinyl-1*H*-indole (**9a**) with ethyl diazoacetate using 5.0 mol % (*R*,*R*)-*trans*-Cl_2Ru(pybox-*ip*)(CH_2═CH_2) ((*R*)-**10**) provided a 9.2:1.0 mixture of *trans*- and *cis*-cyclopropylesters (Table 2, entry 1).[11] The pure trans product, **11a**, was isolated in 78% yield after a single purification using silica gel column chromatography.[12] Gratifyingly, compound **11a** was determined to

(3) Mattson, R.; Denhart, D.; Deskus, J.; Ditta, J.; Marcin, L.; Epperson, J.; Catt, J.; King, D.; Higgins, M. Preparation of cyclopropylindoles as selective serotonin reuptake inhibitors. PCT Int. Appl. WO 0279152, 2002.

(4) Rich, D. H. Stereochemical Aspects of Drug Action I: Conformational Restriction, Steric Hindrence, and Hydrophobic Collapse. In *Practice of Medicinal Chemistry*, 2nd ed.; Wermuth, C. G., Ed.; Elsevier: London, UK, 2003; pp 373−386.

(5) (a) Vangveravong, S.; Nichols, D. E. *J. Org. Chem.* **1995**, *60*, 3409. (b) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168.

(6) Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*, 7919.

(7) (a) Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247. (b) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223.

(8) Cyclopropanation of 1-benzenesulfonyl-3-vinylindole using ethyl diazoacetate and a chiral bisoxozoline Cu(II) complex has been reported; however, no details regarding the enantioselectivity of the reaction were provided. Raj, T. T.; Eftink, M. R. *Synth. Commun.* **1998**, *28*, 3787.

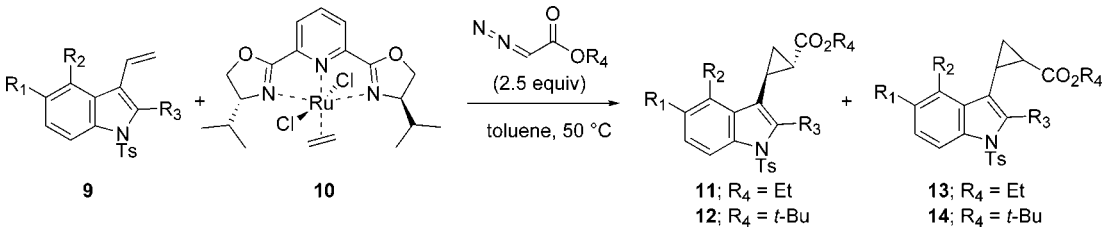
(9) Representative yields for the preparation of **8c** and **8e** were 49 and 70%, respectively. See Supporting Information for more details.

(10) Yang, C.-G.; Wang, J.; Tang, X.-X.; Jiang, B. *Tetrahedron: Asymmetry* **2002**, *13*, 383.

(11) Studies were limited to using Cl_2Ru(pybox-*ip*)(CH_2═CH_2), because of its widespread utility and ease of preparation. See ref 7a.

(12) In the ^{1}H NMR spectra, the trans product shows a downfield shift (∼0.5 ppm) of the −O$CH_2$$CH_3$ protons relative to the same protons of the cis product.

Table 2. Catalytic Asymmetric Cyclopropanation of *N*-Tosyl-3-vinylindoles



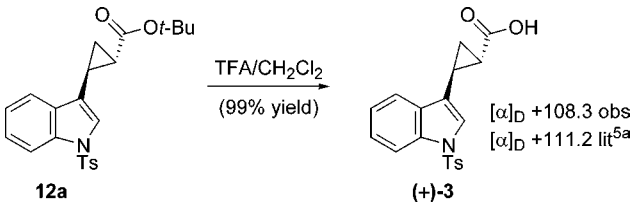
entry	substrate	R_1	R_2	R_3	R_4	catalyst **10**, mol %	trans/cis product ratio[a]	% yield (trans product)	% ee trans product[b] (stereochemistry)
1	**9a**	H	H	H	Et	*R*, 5.0	9.2/1.0	78 (**11a**)	85.0 (*S*,*S*)
2	**9a**	H	H	H	Et	*R*, 2.5	8.5/1.0	75 (**11a**)	84.0 (*S*,*S*)
3	**9a**	H	H	H	*t*-Bu	*R*, 5.0	19/1.0	85 (**12a**)	88.4 (*S*,*S*)
4	**9a**	H	H	H	*t*-Bu	*S*, 5.0	nd	80 (**12a′**)	86.6 (*R*,*R*)
5	**9b**	F	H	H	Et	*R*, 2.5	8.3/1.0	84 (**11b**)	84.4 (*S*,*S*)
6	**9c**	CN	H	H	Et	*R*, 2.5	9.2/1.0	82 (**11c**)	86.2 (*S*,*S*)
7	**9d**	OCH_3	H	H	*t*-Bu	*R*, 5.0	22/1.0	76 (**12d**)	86.0 (*S*,*S*)[c]
8	**9e**	H	CH_3	H	Et	*R*, 2.5	16/1.0	73 (**11e**)	81.2 (*S*,*S*)
9	**9f**	H	H	CH_3	Et	*R*, 2.5	3.3/1.0	75 (**11f**)	83.2 (*S*,*S*)

[a] Ratios determined by ^{1}H NMR integration of crude reaction mixtures or through isolated yields of purified diastereomers. [b] Determined by chiral HPLC analysis. [c] Enantiomeric excess determined by chiral HPLC analysis after conversion to corresponding methyl ester.

be enantiomerically enriched to the extent of 85% ee by chiral HPLC analysis.[13] A decrease in catalyst loading to 2.5 mol % for the same reaction had little or no effect on the yield or enantiomeric purity in the formation of **11a** (entry 2). Asymmetric cyclopropanation of **9a** using *tert*-butyl diazoacetate provided the corresponding *tert*-butyl ester **12a** in good yield (85%), excellent diastereoselectivity (19:1.0, trans/cis), and high enantioselectivity (88% ee) (entry 3).[14] As illustrated by entries 3 and 4, either enantiomer of the cycloadduct can be readily accessed, since both antipodes of the chiral catalyst are available in a single step from commercial materials.[7a] A variety of 2-, 4-, and 5-monosubstituted 1-tosyl-3-vinylindoles were examined in the cyclopropanation. Substrates with electron-withdrawing (−F, −CN) or electron-donating substituents (−OMe) at the 5-position were found to be suitable, providing useful levels of diastereo- and enantioselectivity (84−86% ee) (Table 2, entries 5−7). Most notably, the use of *tert*-butyl diazoacetate afforded a remarkably high level of trans/cis selectivity (22/1.0) in the formation of **12d** (entry 7). Vinylindoles **9e** and **9f**, with adjacent methyl group substitution, provided products **11e** and **11f** with similar levels of enantioselectivity (81−83% ee) but dramatically different trans/cis selectivity (16/1 and 3.3/1, respectively). According to the model proposed by Nishiyama,[7] which supports a concerted reaction mechanism for carbene transfer, the erosion in diastereoselectivity would be attributed to a lack of prochiral face selection by the vinylindole for the *re*- and *si*-faces of the ocatahedral $RuCl_2$(Pybox) complex. In the case of **9f**, the poor diastereoselectivity could be manifested in a switch of the reactive olefin conformation from s-cis for **9e** to s-trans for **9f**. The olefin conformation would be strongly influenced by the adjacent methyl substituents in these substrates.

To ascertain the absolute stereochemistry of **12a**, a portion was readily converted to the known carboxylic acid (+)-**3** using trifluoroacetic acid in dichloromethane (Scheme 3).

Scheme 3



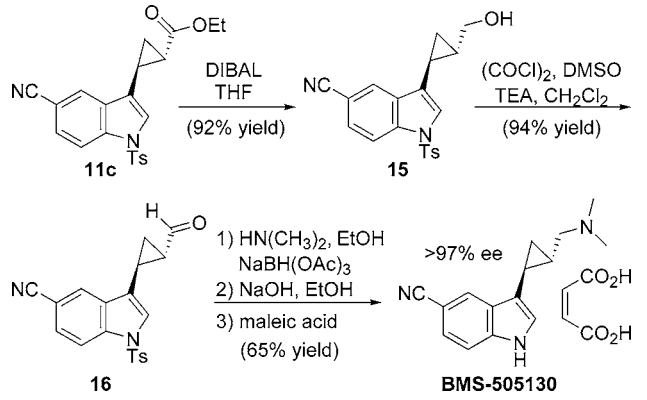
Optical rotation for compound (+)-**3** confirmed the 1*S*,2*S* stereochemical designation.[5a] The remaining products **11a**−**f** and **12d** were assigned as 1*S*,2*S* by analogy. The sense of asymmetric induction for the (*R*,*R*)-pybox−Ru(II)-catalyzed cyclopropanation of 1-tosyl-3-vinylindoles is consistent with literature reports involving reactions of ethyl diazoacetate with styrene.[7]

The enantiomerically enriched indolylcyclopropyl esters **11** and **12** were prepared as part of a medicinal chemistry program focused on the synthesis of conformationally restricted homotryptamine-like analogues. Toward this end, the ethyl ester **11c** was cleanly reduced in 92% yield, using diisobutylaluminum hydride, to the primary alcohol **15** (Scheme 4). The alcohol was oxidized, using Swern conditions, to the corresponding aldehyde **16** in 94% yield.

(13) Enantiomeric excess of the cis diastereomer was not determined, since an analytical method for its chiral HPLC separation was not developed.

(14) In the case of styrene, the use of bulky diazoesters has been documented to improve both the diastereo- and enantioselectivity of the reaction. See ref 7b.

Scheme 4



Attempts to access the aldehyde via partial reduction of the ester using DIBAL at low temperatures were unsuccessful. Aldehyde **16** was subjected to a two-step, one-pot reaction sequence involving reductive amination with dimethylamine, followed by in situ *N*-tosyl cleavage using sodium hydroxide. After aqueous workup, the crude product was easily purified by crystallization as the maleate salt. The analytically pure, maleate salt of BMS-505130 was obtained in 65% overall yield from intermediate **16**. Importantly, the crystallization process enriched the final product to >97% ee as determined by chiral HPLC analysis. While the in vivo characterization of BMS-505130 as a selective serotonin reuptake inhibitor is the subject of a separately published report,[15] it is noteworthy that BMS-505130 (hSERT K_i 0.18 nM)[15] demonstrated a 10-fold improvement in binding potency to the serotonin transporter versus the more flexible analogue, 5-cyano-3-[3-(dimethylaminopropyl)]indole (hSERT K_i 2.0 nM).[2f]

In summary, 1-tosyl-3-vinylindoles were found to be excellent substrates for the pybox-Ru(II)-catalyzed asymmetric diazoacetate cyclopropanation. Good diastereoselectivity and high enantioselectivity were observed for a variety of substituted 3-vinylindoles. Trans/cis diastereoselectivity was notably improved when using *tert*-butyl as opposed to ethyl diazoacetate. Enantioselectivity was slightly better with 5-substituted 3-vinylindoles versus 2- or 4-substituted substrates. The utility of the method was demonstrated by conversion of an enantiomerically enriched cycloadduct into the potent SSRI BMS-505130.[16] A full account describing the biological activity of BMS-505130 and the structure−activity relationship of many other indole cyclopropylmethylamines is forthcoming.[17]

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Supporting Information Available: Full experimental and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050790N

(15) Taber, M. T.; Wright, R. M.; Molksi, T. F.; Clark, W. J.; Brassil, P. J.; Denhart, D. J.; Mattson, R. J.; Lodge, N. J. *Pharmacol., Biochem. Behav.* **2005**, *80*, 521.

(16) A manuscript detailing a highly optimized synthesis of BMS-505130 on a kilogram scale using the catalytic asymmetric diazoacetate cyclopropanation is currently in preparation.

(17) Mattson, R. J.; Denhart, D. J.; Marcin, L. R.; Higgins, M. A.; Ditta, J. L.; Deskus, J. A.; Catt, J. D.; Sloan, C. P.; Beno, B. R.; Gao, Q.; Molski, T. F.; Mattson, G. K.; Taber, M. T.; Lodge, N. J. Manuscript submitted.