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# Applications of Organocatalytic Asymmetric Synthesis to Drug Prototypes—Dual Action and Selective Inhibitors of *n*-Nitric Oxide Synthase with Activity Against the 5-HT$_{1D/1B}$ Subreceptors

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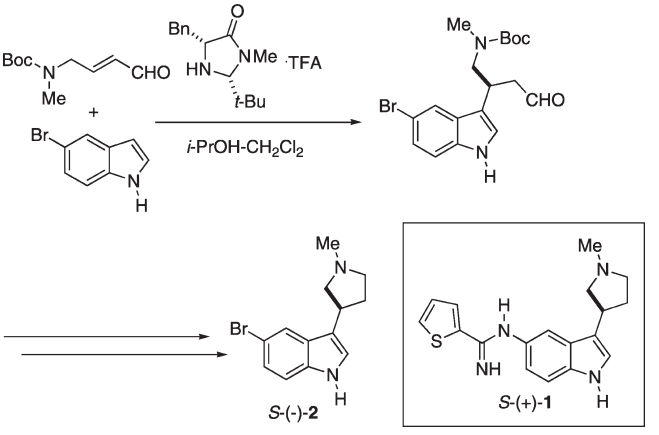
## ABSTRACT




**The scope of MacMillan's organocatalytic asymmetric conjugate addition reaction of indoles and electron-rich aromatics to α,β-unsaturated aldehydes has been extended to the use of 3-amino crotonaldehydes as substrates. The aromatics used include indoles as well as an aniline and a furan. The scope and effect of the groups on nitrogen (R, R′) has also been studied. The method has been applied to the concise synthesis of an advanced precursor to *S*-(+)-1, a drug prototype for the treatment of migraine headaches.**

In recent years, organocatalysis has played an increasingly prominent role in the design and synthesis of enantioenriched substances.[1] Asymmetric processes relying on the intermediacy of iminium ions[2] or enamines derived from aldehydes and ketones have gained widespread use in diverse C−C and C−heteroatom bond forming reactions. Such metal-free organocatalytic transformations present distinct advantages in many cases.[1] The recent scholarly contributions of MacMillan[2a−f] on the diverse applications of iminium ions derived from α,β-unsaturated aldehydes, for example, provide a conceptually elegant and operationally simple approach to the synthesis of a variety of chiral nonracemic compounds.

In connection with a project involving the synthesis of 3-pyrrolidinylindoles as core components of potential drug

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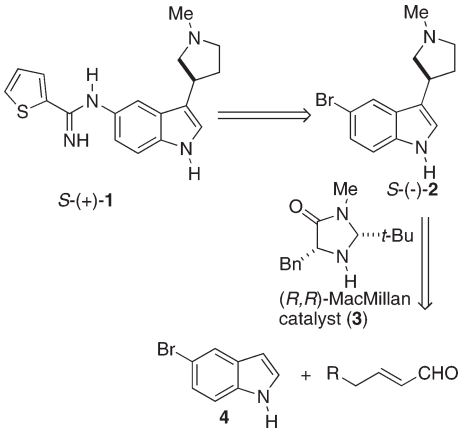
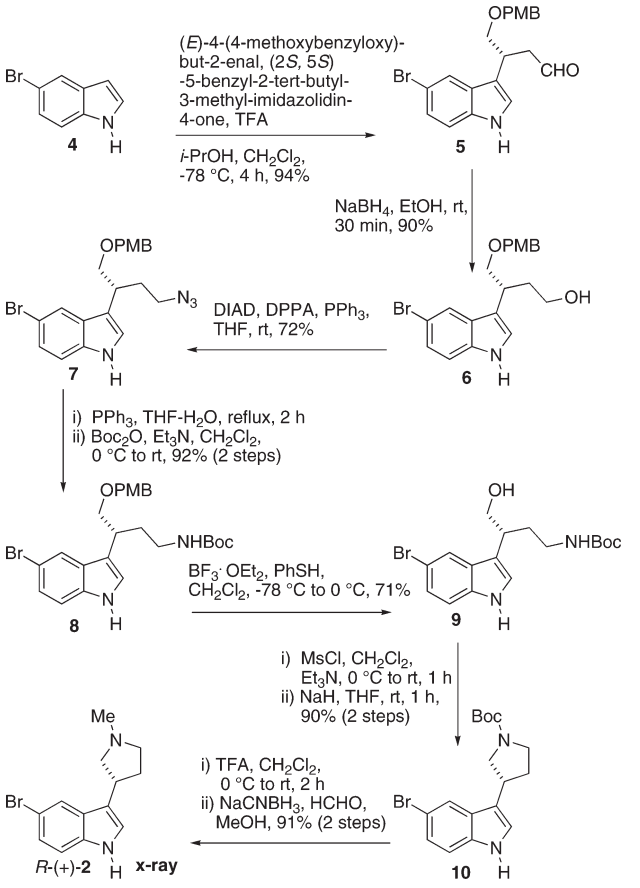



**Figure 1.** Retrosynthetic analysis of *S*-(+)-**1**.

prototypes toward the treatment of migraine,[3] we explored a synthetic route that would circumvent the need for the separation of enantiomers by preparative supercritical fluid chromatography.[3] The target molecule **1** has been prepared in racemic form and demonstrated excellent dual activity against neuronal nitric oxide synthase (nNOS) and the 5-$HT_{1B/1D}$ receptor. Separation of the enantiomers revealed a 100-fold selectivity of the *S*-(+)-**1** isomer for inhibiting nNOS versus endothelial NOS (eNOS) and cytokine-inducible NOS (iNOS), which are other isoforms of NOS. Oral bioavailability and excellent efficacy with no evidence of undesireable coronary vasoconstriction (a liability with the triptan class of migraine medications) bodes well for the clinical development of this novel drug prototype.

The encouraging biological profile of (+)-**1** compelled us to develop a practical asymmetric synthesis of its immediate precursor **2**, based on MacMillan's Friedel−Crafts-type Michael reaction between indoles and α,β-unsaturated aldehydes[2a] in the presence of an imidazolidinone catalyst (Figure 1).

**Scheme 1.** First Generation Synthesis of *R*-(+)-**2**




Treatment of a mixture of 5-bromoindole **4** and (*E*)-4-(4-methoxybenzyloxy)-but-2-enal with 15−20 mol % of the MacMillan catalyst (*2S*,*5S*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (*ent*-**3**) in the presence of TFA and isopropanol, in dichloromethane at −78 °C, led to the adduct **5** in 94% yield as a single enantiomer (Scheme 1). Reduction of the aldehyde function with sodium borohydride to alcohol **6** and introduction of azide gave **7** in 72% yield.

Reduction of the latter, under Staudinger conditions, followed by protection of the resulting amino group led to the *N*-Boc derivative **8** in excellent overall yield. Cleavage of the *O*-PMB group to **9**, followed by mesylation and treatment of the product with sodium hydride afforded **10** in high yield.

Cleavage of the *N*-Boc group, followed by reductive amination with formaldehyde in the presence of sodium cyanoborohydride, gave the intended indole derivative (*R*)-(+)-**2** as a crystalline solid, whose structure and absolute stereochemistry was ascertained by single crystal X-ray crystallography and is consistent with the stereochemical outcome of the asymmetric Michael reaction (**4**→**5**) using the (*2S*,*5S*)-catalyst (*ent*-**3**).[4] The high enantiopurity

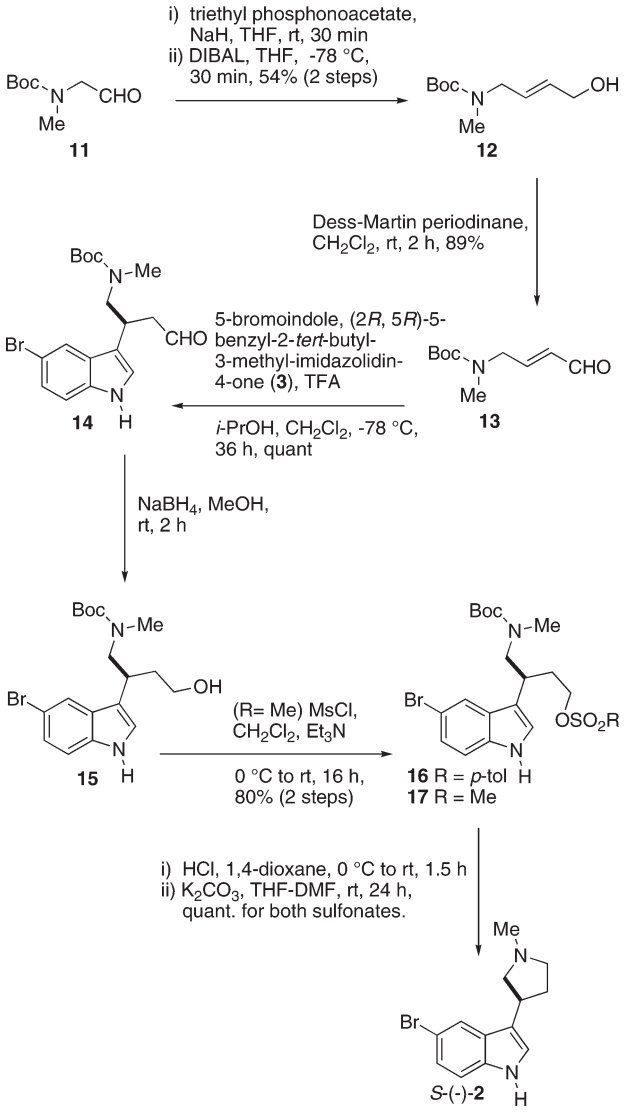
(1) For recent monographs see: (a) Dalko, P. I. *Asymmetric Organocatalysis: Reactions and Experimental Procedures*; Wiley-VCH: New York, 2007. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Asymmetric Synthesis*; Wiley-VCH:, Weinheim, Germany, 2005. For reviews see: (a) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (b) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (c) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (d) Barbas, C. F., III *Angew. Chem., Int. Ed.* **2008**, *47*, 42. (e) Mukherjee, S.; Yang, J. W.; Hoffman, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (f) Pelissier, H. *Tetrahedron* **2007**, *63*, 9267. (g) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

(2) Selected examples: Indole alkylation: (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (b) 1,3-Dipolar cycloaddition: Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (c) Intramolecular Diels−Alder: Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616. (d) Diels-Alder: Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (e) 1,4-Addition of electron rich benzenes: Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894. (f) Heterocycle 1,4-addition-α-chlorination cascade: Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (g) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892. (h) 2-Oxindole alkylation: Bravo, N.; Mon, I.; Companyó, X.; Alba, A.-N.; Moyano, A.; Rios, R. *Tetrahedron Lett.* **2009**, *50*, 6624. (i) Intramolecular aza-Micheal: Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283. (j) Bartoli, G.; Bosco, M.; Corlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403.

(3) Maddaford, S.; Ramnauth, J.; Rakhit, S.; Patman, J.; Renton, P.; Annedi, S. U.S. Patent 7375219, 2008.

(4) See the Supporting Information.

**Scheme 2.** Second Generation Synthesis of *S*-(−)-**2**

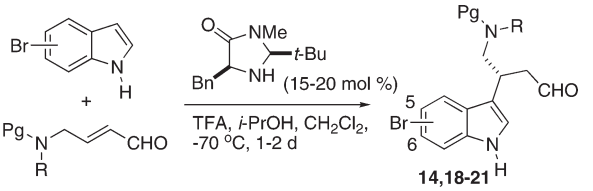



(92% ee) of the Michael adduct **5** was determined from analysis of the Mosher ester derived from the alcohol **6**.[4]

Having successfully completed the synthesis of the (*R*)-(+)-**2** isomer, we sought to provide access to the more biologically active enantiomer (+)-**1** from the (*S*)-(−)-**2** precursor. It occurred to us that the inclusion of the *N*-Boc and *N*-methyl groups in the starting α,β-unsaturated aldehyde would obviate the need to introduce an azide as already shown in Scheme 1, thus shortening the synthesis. However, to the best of our knowledge, there is only one example of the application of the MacMillan iminium-based organocatalytic Michael-type addition reaction onto a nitrogen-containing α,β-unsaturated aldehyde,[5] and no examples with indoles.[6]

The synthesis of the desired (*S*)-(−)-**2** is outlined in Scheme 2. Treatment of *N*-Boc,*N*-methyl acetaldehyde **11** with triethylphosphonoacetate under standard conditions, followed by DIBAL reduction, led to allylic alcohol **12**, which was oxidized to the aldehyde **13** with the Dess−Martin periodinane reagent in excellent yield. Treatment of **13** with 15−20 mol % of the (*R*,*R*)-MacMillan catalyst (**3**), followed by addition of 5-bromoindole (**4**), afforded the adduct **14** in quantitative yield. Reduction to the alcohol and mesylation to **16**, followed by cleavage of the *N*-Boc group and treatment of the product with potassium carbonate in a mixture of THF and DMF as solvent, led to the target compound (*S*)-(−)-**2** in excellent yield. Stereochemical purity (94:6 er) was established by chiral HPLC analysis. The value obtained with the nitrogen containing aldehyde **13** was not significantly lower than that obtained in Scheme 1 with (*E*)-4-(4-methoxybenzyloxy)but-2-enal (96:4).

**Table 1.** Organocatalytic MacMillan Indole Alkylation with Nitrogen Containing Aldehydes




| entry | product | Pg | R | Br position | yield[a] (%) | er[b] | time (d) |
|---|---|---|---|---|---|---|---|
| 1 | **14** | Boc | Me | 5 | quant | 94:6 | 1 |
| 2 | **18** | Bus[f] | Me | 5 | 89[c] | 96:4 | 1 |
| 3 | **19** | $CO_2Me$ | Me | 5 | 97 | 95.5:4.5 | 1 |
| 4 | **20** | Boc | PMB | 5 | 80 | 96:4 | 2 |
| 5 | **21** | Boc | PMB | 6 | 65 (83[d]) | 90.5:9.5 | 2 |
| 6 | | Boc | H | 5 | nil[e] | | 1 |

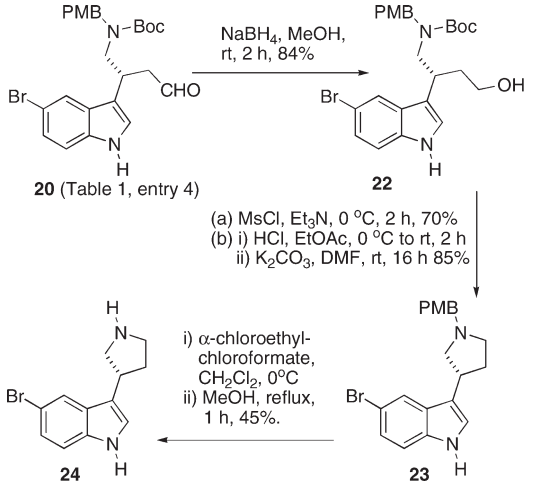
[a] Isolated yield of pure product unless otherwise indicated. [b] On the basis of chiral HPLC analysis of the corresponding alcohols obtained by $NaBH_4$ reduction. The opposite enantiomer was obtained by running the reaction again with the enantiomeric MacMillan catalyst. [c] 61% pure isolated material and 28% which was not separated from starting aldehyde as determined by $^1H$ NMR. [d] Corrected for recovered 6-bromoindole. [e] The aldehyde was converted to *N*-Boc-pyrrole, which was the only isolated product. [f] Bus = *tert*-butylsulfonyl.

The successful utilization of γ-*N*-Boc/*N*-Me α,β-unsaturated aldehyde **13** in the Michael-type reaction with 5-bromoindole (**4**) led us to explore the same reaction with other *N*-substituents. The results shown in Table 1 (above) indicate that a variety of *N*-subtituents can be used in the original reaction with excellent enantioselectivities which did not seem to vary significantly with less bulky protecting groups on nitrogen (entry 3), or when groups with stronger electron-withdrawing capability were introduced (entry 2). However, when the bulkier bis-protected substrates (entries 4 and 5) were used, longer reaction times were necessary. Due to the failure of the NH containing aldehyde (entry 6) to participate in the indole alkylation reaction, we sought an alternate route to compound **26** (Scheme 3), which is a presumed intermediate in the synthesis of *R*-(+)-**2** from **10** (Scheme 1).

(5) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328.

(6) For indole 1,2-addition onto an activated iminium see: Peterson, E. A.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6328.

**Scheme 3.** Second Generation Approach to a Substrate Suitable for Indole-3-pyrrolidine Synthesis



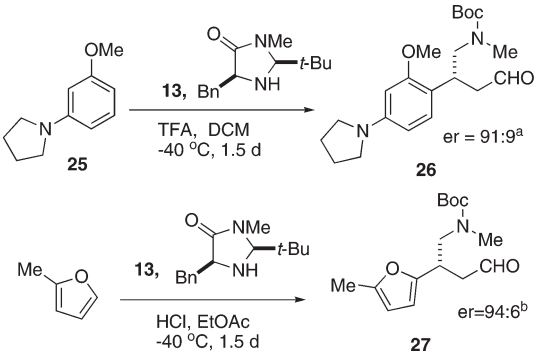

Starting from **20** (Table 1, entry 4), we first reduced the aldehyde to the primary alcohol (**20** → **22**). Conversion to the mesylate and removal of the Boc group furnished the pyrrolidine **23**.

Removal of the PMB protecting group was easily accomplished by using α-chloroethylchloroformate[7] to furnish **24**. This would be a useful intermediate in generating a variety of *N*-alkyl analogues by reductive amination with a library of aldehydes or ketones.

MacMillan has reported similar organocatalytic Friedel–Crafts-type alkylations of electron-rich aromatics,[2e] and furans[2f] with α,β-unsaturated aldehydes. We decided to test these with the nitrogen-containing aldehyde **13** (Scheme 4) and found that it participated in these reactions as well. The substrates used were anisole **25** and 2-methylfuran, which gave adducts **26** and **27** in enantiomeric excesses of 82% and 88%, respectively.

(7) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, 195.

**Scheme 4.** Synthesis of Enantioenriched Phenethylamines and 2-Ethylaminofurans




[a] Determined by HPLC analysis of the correspnding alcohols. [b] Determined by $^1$H NMR analysis of the Mosher esters prepared by $NaBH_4$ reduction, preparation of the Mosher esters ((+)- and (−)-MTPA-Cl, $Et_3N$), and removal of the Boc group (HCl, EtOAc, dioxane). 8−10% organocatalyst was used in these reactions.

In conclusion, the extension of MacMillan's organocatalytic aromatic alkylation to hitherto unexplored 3-amino crotonaldehydes has been realized and has found application in a concise synthesis of *S*-(−)-**2**, a late stage intermediate in the synthesis of the dual action migraine drug prototype *S*-(+)-**1**. We expect that this methodology will also find application in alkaloid synthesis and in the synthesis of other nitrogen-containing compounds of medicinal interest.

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**Supporting Information Available.** Experimental procedures and spectral data for compounds **5**−**27**. This material is available free of charge via the Internet at http://pubs.acs.org.