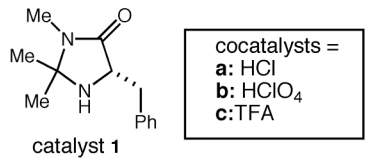
C h a p t e r 1

The Enantioselective Organocatalytic Indole Alkylation

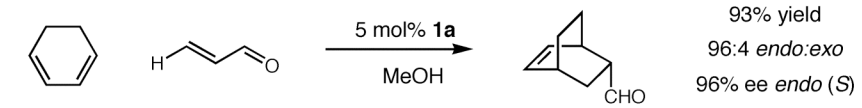
Introduction

The desire for new synthetic methodologies for the rapid construction of enantiomerically pure compounds has been a fruitful driving force for chemical research.[1] This line of research has produced a stunning array of technologies that practitioners of synthetic organic chemistry may use for the construction of molecules of interest. Concomitantly, single enantiomer compounds have become increasingly important for biomedical research.[2] The Food and Drug Administration's position on the marketing of racemic mixtures of drugs further increases the need for the development of general procedures for enantiocontrolled synthesis.[3]

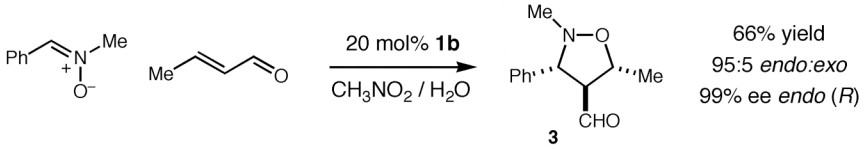
During our group's studies on LUMO-lowering organocatalysis, salts of imidazolidinone **1** were shown be effective catalysts. It has been shown that α,β-unsaturated aldehydes are useful substrates for the first examples of the organocatalyzed Diels-Alder reaction;[4] [3+2]-Nitrone cycloaddition;[5] and pyrrole Friedel-Crafts alkylation[6] (equations 1-3 respectively). These reactions produce the enantioenriched adducts **2**-**4** via catalysis by salts of imidazolidinone **1**. These studies demonstrated the viability of utilizing secondary amines for traditional and non-traditional Lewis acid catalyzed reactions. The rationale behind LUMO-lowering organocatalysis as a new paradigm in chemical synthesis has been discussed in depth elsewhere and will not be covered here.[7-12]



Equation 1.Diels-Alder Reaction



Equation 2. [3 + 2] Nitrone Cycloaddition



Equation 3. Pyrrole Friedel-Crafts Alkylation

Central to the success of α, β-unsaturated aldehydes as substrates for imidazolidinone catalysis is their ability to reversibly form a reactive iminium ion intermediate with a high level of geometry control (Figure 1). As the two iminium ion isomers **5** and **6** expose opposite enantiofaces of the substrate, selective geometry formation is one aspect that governs the enantioselectivity in an iminium catalyzed event. The iminium ion geometry is controlled by the size difference between the C2 and C5 positions of imidazolidinone **1**. The sterically larger two methyl groups (C2) dictate that the iminium geometry be formed over the smaller hydrogen and benzyl substituents at C5. An additional important feature of **1** is the selective π-facial coverage of one reactive face of the iminium ion species over another (Figure 2). As the two reactive iminium faces lead to opposite enantiomers of the product, selective π-facial coverage helps to dictate the enantioselectivity in an iminium catalyzed event. Steric control of the reactive

faces of iminium **7** is dictated by the size difference between the hydrogen and the benzyl substituent on the C5 position of the catalyst. Since the benzyl is the larger of the two substituents, reaction occurs from the same face as the hydrogen on C5 of the catalyst. Imidazolidinone catalyst **1**, utilized in the aforementioned organocatalyzed processes, has been shown to achieve all of these goals.

Figure 1. Importance of Iminium ion Geometry

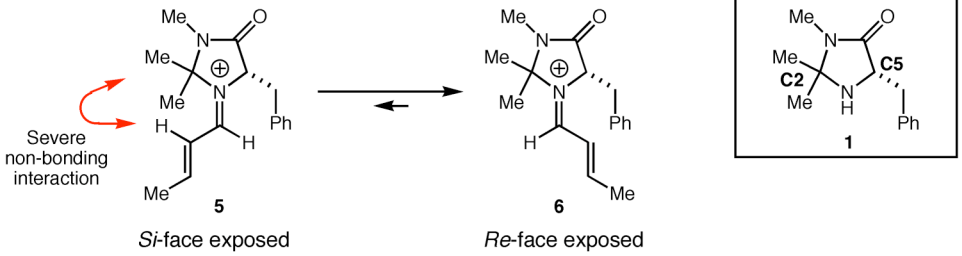
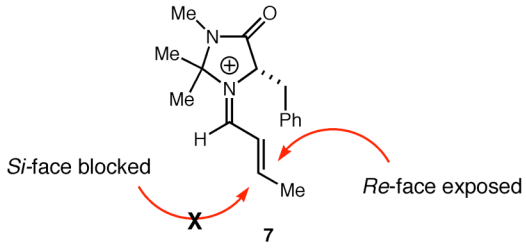


Figure 2. Importance of Selective iminium Facial Coverage

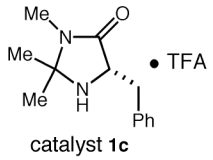


Initial Investigations of Indole Friedel-Crafts

After the successful development of the asymmetric pyrrole Friedel-Craft alkylation, attention in the MacMillan group turned to other π-nucleophiles. This thesis documents the development of an organocatalytic indole alkylation, and the subsequent discovery of a number of related methodologies. The indole framework has become widely identified as a "privileged" pharmacophore, being represented in over 3000 natural isolates and 82 medicinal agents of diverse therapeutic action.[2] It is surprising, however, that asymmetric entry into this structurally important core has been limited to the derivatization of enantiopure aminoacids and the optical resolution of racemic

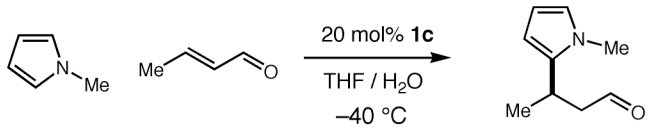
mixtures.[13] During the course of this investigation, the enantioselective metal-catalyzed addition of indoles to α,β-unsaturated ketoesters was disclosed by Jorgensen et. al.[14] Subsequent to the disclosure of this research, the enantioselective metal-catalyzed addition of indoles to α,β-unsaturated acyl phosphonates was disclosed by Evans et. al,[15]

Despite structural similarities, it has been long established that the pyrrole π-system is significantly more nucleophilic than that of the corresponding indole.[16] It was thus not surprising that conditions developed for the pyrrole alkylation (Equation 4) were not effective for the corresponding indole alkylation (Equation 5). It was found that the Friedel-Crafts alkylation of N-methylindole **8** with crotonaldehyde **9** progressed slowly with poor levels of chemical efficiency to provide indolylbutyraldehyde **10**.

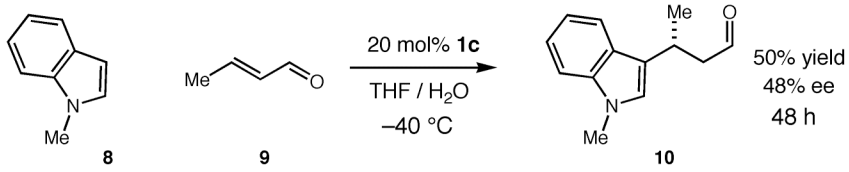


catalyst **1c**

Equation 4. Successful conditions to alkylate N-methylpyrrole: Nick Paras



Equation 5. Conditions do not translate to N-methylindole

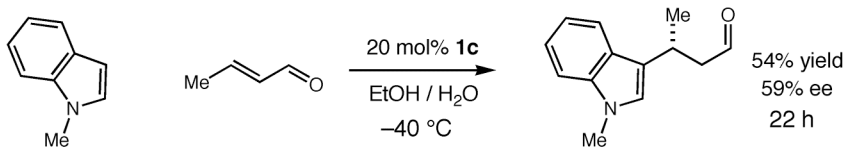


8 **9** **10**

Optimization of reaction parameters such as reagent equivalents, molarity, solvent and cosolvent effects, temperature, reaction time, effect of additives, catalyst structure, and cocatalyst acidity were performed to identify conditions for the indole alkylation. It was concluded that useful levels of enantioinduction with salts of imidizolidinone **1** could not be achieved (59% ee, Equation 6). This result shows that the indole alkylaton with

salts of **1** is slower, less selective and proceeds in lower yields than the corresponding pyrrole alkylation.

Equation 6. Optimal Conditions for N-methylindole Alkylation with Catalyst 1



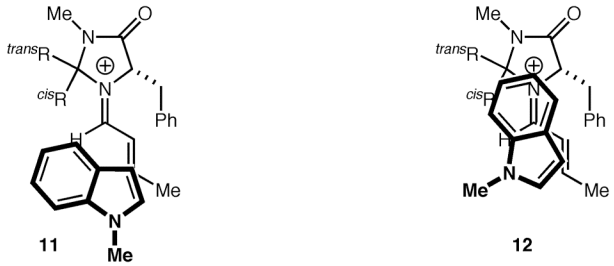
We embarked upon the search for a new, more reactive amine catalyst that would allow for the enantioselective catalytic alkylation of indoles and other less reactive nucleophiles to provide new reaction manifolds that were previously not possible. Three guiding principles that led the search for a new more reactive amine catalyst were:

- Improvement of the reaction rates.
- Retain control of the iminium ion geometry.
- Reinforce the well-defined chiral environment.

Catalyst Development

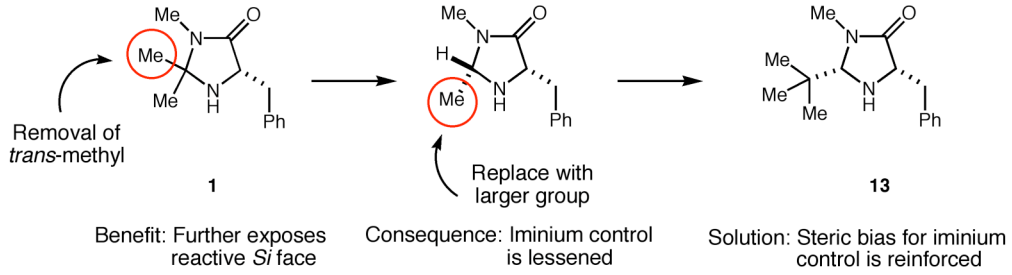
From studies on imidazolidinone catalysts such as **1**, various catalyst structure function proposals were made. A key rationale which united these structure function relationships was a theorized cation-π interaction between the nucleophilic indole and the conjugated iminium ion (Figure 3).[17] This proposed cation-π interaction is represented schematically as **12** in contrast to the more traditional Burgi-Dunitz angle approach of **11**. It is well precedented that indoles can participate in cation-π interactions, and as such, it was speculated that this stabilized transition state may explain some controversial results. As such, it was hypothesized that the *trans*-substituent (R^{trans}) of imidazolidinone **1** was deleteriously interacting with the indole thereby limiting the selectivity of the alkylation.

Figure 3. Proposed Interaction Between N-methylindole and Iminium Ion

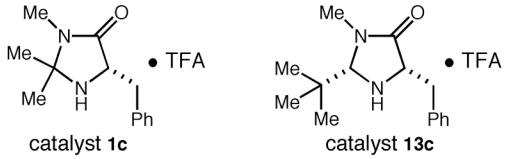


It was thus theorized that removal of the *trans*-methyl group from imidazolidinone **1** would lessen the steric encumbrance of the reactive face of the catalyst (Scheme 1). It was anticipated that removal of this methyl substituent would allow the indole to stabilize the transition state more effectively, and thus would improve the reaction rate. An additional benefit of this removal would be to lessen the steric hinderance about the participating nitrogen lone pair, which would increase the rate of iminium ion formation and hence increase the overall reaction rate. A possible drawback to this catalyst adjustment would be less control of iminium ion geometry caused by removal of the methyl group. To counteract this issue, replacement of the *cis*-methyl group with a sterically larger substituent was proposed. A *tert*-butyl group was chosen as the sterically large substituent, and it was hypothesized that this replacement would (A) increase the iminium ion geometry control and (B) provide further coverage of shielded *Si* face.

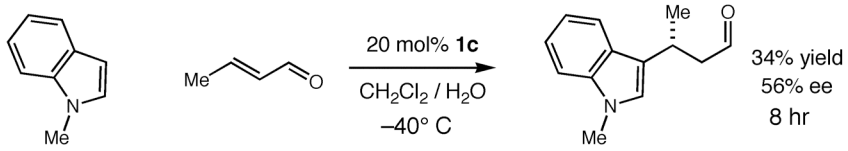
Scheme 1. Modular Reasoning for Catalyst Evolution



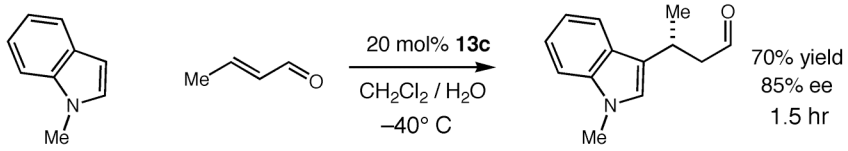
In collaboration with Christopher Borths, imidazolidinone **13** was prepared. As will be described in subsequent paragraphs, salts of imidazolidinone **13** were found to be useful for the enantioselective alkylation of indoles. Dr. Wen-Jing Xiao developed a high yielding, commercially utilized, method for the synthesis of **13**; this method is included in the supporting information. Previously the alkylation of indoles with catalyst **1c** proceeded with less than optimal results (equation 7). To our satisfaction, the same reaction with new catalyst **13c** under identical conditions yielded a highly efficient and selective indole alkylation that exhibits a remarkable increase in rate, enantioselectivity, and isolated yield (equation 8).



Equation 7. N-methylindole Alkylation Catalyzed by 1c



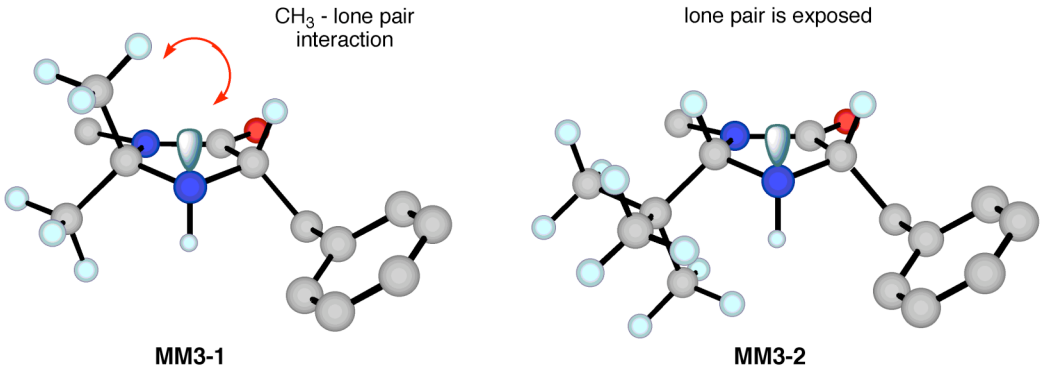
Equation 8. N-methylindole Alkylation Catalyzed by 13c



The rationalization for these improved results, and their relation to the aforementioned guiding principles, is given below. The first guideline in catalyst development was the requirement to increase reaction rates. Molecular modeling using Marcromodel was performed on both catalysts **1** and **13** at the MM3 level of theory. As shown in **MM3-1**, the nitrogen lone pair of imidizolidinone **1** is eclipsed by the *trans*-methyl substituent, whereas this eclipsing interaction is absent in **MM3-2** (figure 4).

Thus, as hypothesized, the lone pair of **MM3-2** is more free to participate in iminium ion formation. This may be a participating reason for the observed increase in reaction rates with salts of **13**.

Figure 4. Computational Models of 1 and 13

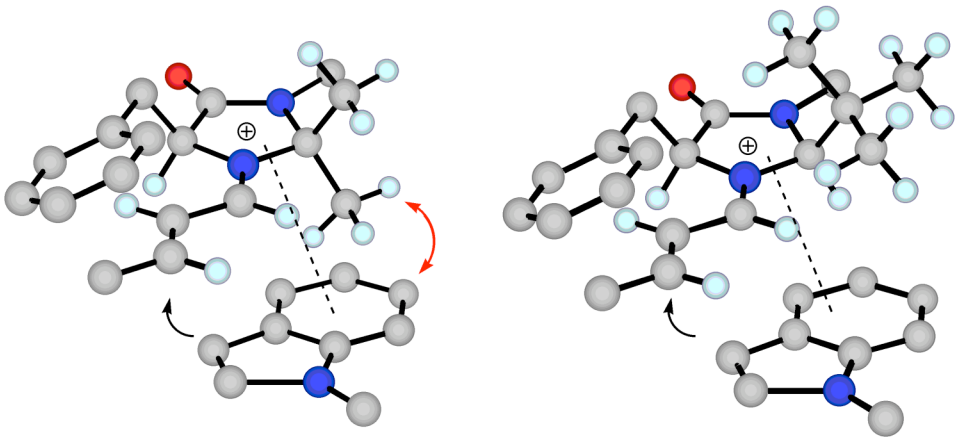


The control of iminium ion geometry was the next guideline we sought to adhere to. The size difference between a C2 position whose identity is two methyl groups (combined A-value of 3.48) versus a C2 position whose identity is a hydrogen and *tert*-butyl group (combined A-values of 4.90) is 1.52 kcal/mol. As mentioned earlier, the size difference between the C2 and C5 positions dictates the bias of the iminium ion formation. As such, the size of the C2 position was not deleteriously effected by the replacement, and the relative size difference between the C2 and C5 position was increased, thus leading to a reinforcement of the steric bias. This is in keeping with the second guiding principle as mentioned above.

Finally, the chiral environment which dictates *Re* or *Si* facial addition of the iminium ion can be considered. As shown in **MM3-3** (figure 5), attack of the iminium ion is dictated by the effective coverage of the *Si* versus the *Re* face. The difference between the facial coverage of the iminium ion derived from **1** is that of: the combined steric demand of a methyl and a benzyl group (combined A-values of 3.48) for the *Si* face versus the combined steric demand of a methyl and a hydrogen (combined A-values of

1.74) for the *Re* face. This results in the observed *Re* facial addition. Consideration of **MM3-4**, though reveals an improved relative difference between facial coverages. The difference between the facial coverage of the iminium ion derived from **13** is that of: the combined steric demand of a *tert*-butyl and a benzyl group (combined A-values of 6.64) for the *Si* face versus the combined steric demand of two hydrogens (combined A-values of 0) for the *Re* face. As can be seen, the *Si* face of the resultant iminium is completely blocked, thus allowing attack at the completely exposed *Re* face. Though these aforementioned A-values come from the conformational analysis of ring systems, it is believed that the analysis of their estimated size differences provides a useful tool for the understanding of the improved enantioselectivity of **13** versus **1**.

Figure 5. Computational Models of Iminium Derived from 1 and 13



MM3-3

Effective *Si*-face coverage
Re-face CH_3-substrate interaction
Diminished substrate addition rate

MM3-4

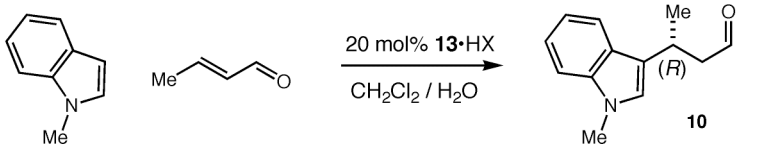
Increased *Si*-face coverage
Re-face addition unhindered
Increased substrate addition rate

Optimization of the enantioselective indole Friedel-Crafts alkylation of N-methylindole with salts of **13** was subsequently undertaken. The results are described below.

Enantioselective N-methylindole Alkylation with (E)-Crotonaldehyde Using 13

Optimization of reaction parameters such as reagent equivalents, concentration, solvent / cosolvent effects, temperature, reaction time, effect of additives, and cocatalyst acidity were performed to identify conditions for the enantioselective alkylation of N-methylindole with (*E*)-crotonaldehyde, using salts of **13**. As revealed in Table 1, it was found that salts of **13** provided the benzylic substituted indole (*R*)-**10** with high levels of enantioselectivity and reaction efficiency (entries 1-3, ≥70% yield, ≥85% ee). An enantioselectivity/temperature profile documents that optimal enantiocontrol is available at –83° C with catalyst **13c** (entry 5, 84% yield, 92% ee). A survey of solvent additives reveals that the use of *i*-PrOH (15% v/v in CH_2Cl_2) has a dramatic influence on reaction rate without loss in enantiocontrol (entry 6, 92% ee, 19 h). The superior levels of asymmetric induction and efficiency exhibited by **13c** to afford the substituted indole (*R*)-**10** in 92% ee and 82% yield prompted further exploration of the scope of this reaction.

Table 1. Effect of Cocatalyst and Temperature on the Alkylation of N-methylindole with (*E*)-Crotonaldehyde with Catalyst 13



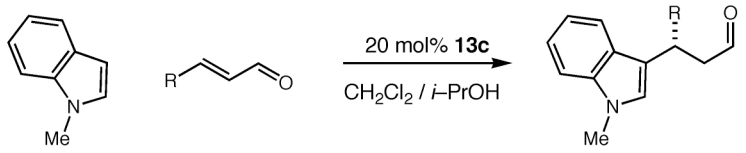
entry	catalyst	cocatalyst (HX)	temp (°C)	time (h)	% yield	% ee[a,b]
1	**13c**	TFA	−40	1.5	70	85
2	**13d**	*p*-TSA	−40	4	98	88
3	**13e**	2-NO_2PhCO_2H	−40	22	88	88
4	**13d**	*p*-TSA	−83	48	15	80
5	**13c**	TFA	−83	31	84	92
6	**13c**	TFA	−83	19	82	92[c]

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration assigned by chemical correlation to a known compoun. [c] Reaction conducted with CH_2Cl_2—*i*-PrOH (85:15 v/v) as solvent

Substrate Scope

Having identified an optimal catalyst and conditions for the indole alkylation the range of aldehydes that are amenable to this new process was examined (Table 2). The reaction appears quite tolerant with respect to the steric contribution of the olefin substituent (R = Me, Pr, *i*-Pr, CH_2OBz, entries 1-4, ≥74% yield, ≥92% ee). As revealed in entries 5 and 6, the reaction can accommodate electron-deficient aldehydes that do not readily participate in iminium formation (R=CO_2Me, 89% yield, 91% ee) as well as stabilized iminium ions that might be less reactive toward Friedel-Crafts alkylation (R=Ph, 84% yield, 90% ee). To demonstrate the preparative utility of this methodology, the addition of N-methylindole to crotonaldehyde was performed on a 25 mmol scale with catalyst **13c** to afford (R)-**10** in 92% ee and 81% yield.

Table 2. Organocatalyzed Alkylation of N-methylindole with Representative α,β-unsaturated Aldehydes



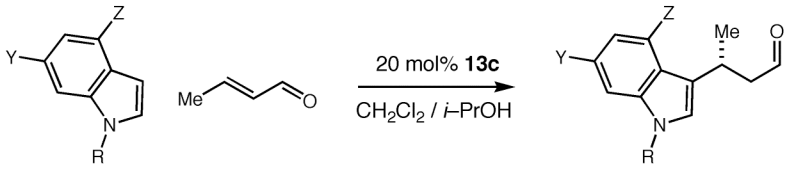
entry	R	temp (°C)	time (h)	% yield	% ee[a]
1	Me	−83	19	82	92[b]
2	Pr	−60	6	80	93
3	*i*-Pr	−50	32	74	93
4	CH_2OBz	−83	18	84	92[b]
5	Ph	−55	45	84	90
6	CO_2Me	−83	21	89	91

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration assigned by chemical correlation to a known compound.

This imidazolidinone-catalyzed conjugate addition is also general with respect to indole architecture (Table 3). Variation in the nitrogen protecting group (R = H, Me, CH_2Ph, allyl, entries 1–4) is possible without significant loss in yield or enantioselectivity (≥70% yield, 89–92% ee). Incorporation of alkyl and alkoxy substituents at the C4 indole position reveals that electronic and steric modification of the indole ring can be

accomplished with little influence on reaction selectivity (entries 5 and 6, ≥90% yield, 94% ee). As revealed in entry 7, we have successfully utilized electron-deficient nucleophiles in the context of a 6-chloro substituted indole (73% yield, 97% ee). Such halogenated indole adducts should prove to be valuable synthons for use in conjunction with organometallic technologies (e.g. Buchwald or Hartwig, Stille couplings).[18-20]

Table 3. Enantioselective Organocatalyzed Alkylation of Representative Indoles with (*E*)-Crotonaldehyde

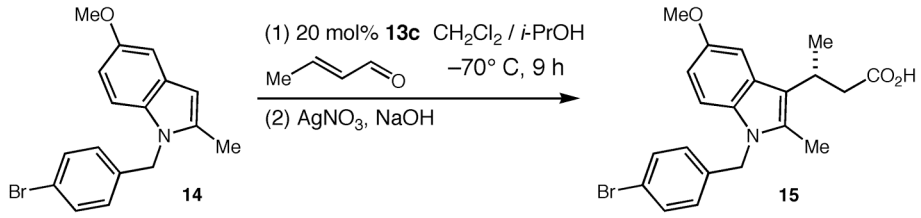


	indole substituents						
entry	R	Y	Z	temp (°C)	time (h)	% yield	% ee[a]
1	Me	H	H	−87	19	82	92[b]
2	H	H	H	−60	22	72	91[b]
3	allyl	H	H	−72	20	70	92
4	CH_2Ph	H	H	−60	120	80	89[b]
5	H	H	Me	−60	3	94	89[c]
6	Me	H	OMe	−87	19	90	89[c]
7	H	Cl	H	−60	13	73	89[c]

[a] Product ratios determined by chiral HPLC. [b] Absolute configuration assigned by chemical correlation to a known compound. [c] Reaction conducted with (E)-$BzOCH_2CH{=}CHCHO$

A demonstration of the utility of this organocatalytic alkylation is presented in the synthesis of indolobutyric acid **15** (Equation 10), a COX-2 inhibitor developed during the Merck rofecoxib campaign.[21] As outlined in Equation 10, organocatalytic alkylation of the 5-methoxy-2-methylindole **14** with crotonaldehyde followed by oxidation of the formyl moiety provides the COX-2 inhibitor **15** in 87% ee and 82% yield over two steps. This operationally trivial procedure reveals that complex enantioenriched drug leads can be readily accessed using this new organocatalytic protocol.

Equation 9. Synthesis of a Selective COX-2 Inhibitor



87% ee, 82% overall yield over two steps

Stereochemical Rationale

The observed sense of induction and absolute configuration of the products from this organocatalyzed indole alkylation are in complete accord with the rationale that was given in Figure 2.

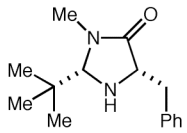
Limitations And Considerations

It has been found that neither **1** nor **13** successfully reacts with α-substituted-α,β-unsaturated aldehydes. To access this motif would require the development of a new catalyst. Electron withdrawing groups on the indole nitrogen (such as TMS) cause the alkylation to not proceed. This issue can be overcome by the fact that the unprotected indole reacts in a facile manner, thus allowing for the introduction of NH substitution. It should be noted that when attempting to alkylate NH indole, careful regulation of reagent stoichiometry must be kept to avoid bis-1,3-dialkylation from occurring. Steric encumbrance at the indole C2 position impedes the reaction rates and enantioselectivities of this organocatalytic alkylation. Though reactions with C2 substituted indoles proceed slowly with **13**, reaction efficiency can be improved by utilizing a tryptophan derived imidazolidinone (this catalyst is discussed further in Chapter 2).

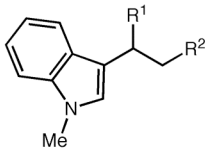
Extensions of This Chemistry

Subsequent to the disclosure of this work, the commercialization of **13**, as well as selected indole adducts, was undertaken by Materia. As shown in Figure 6, selected compounds as discussed in this thesis are now commercially available from Aldrich.

Figure 6. Newly Commercialized Adducts Derived from this Work



Aldrich catalog #
569771-2G



R^1	R^2	Enantiomer	Aldrich catalog #
Me	CN	(*R*)	591661-1G
Me	CN	(*S*)	591785-1G
Me	CH_2OH	(*R*)	591890-1G
Me	CH_2OH	(*S*)	592005-1G
Me	CHO	(*R*)	591882-1G
Me	CHO	(*S*)	591343-1G
Ph	CHO	(*S*)	591017-1G
Ph	CO_2H	(*S*)	590800-1G
Ph	CN	(*R*)	591122-1G
Ph	CN	(*S*)	591246-1G

Amine catalyst **13**, and variations thereof, has been found to be effective for a wide range of reactions. Much of this work has been reported elsewhere, and / or is still being developed, and thus will not be discussed here.

Conclusions

In summary we have documented the development of a new organic catalyst for the LUMO-lowering activation of α, β-unsaturated aldehydes in the context of the first organocatalyzed enantioselective indole Friedel-Crafts alkylation. This work demonstrates the generality of the organocatalytic approach to LUMO-lowering catalysis. Future extension of this work will focus on broadening the substrate scope of this new process.

Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[2] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by $KMnO_4$ stain.

^1H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Irvine Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on

[1]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

[2]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

Hewlett-Packard 1100 Series chromatographs using either a Chiralcel OD-H column (25 cm) and OD guard (5 cm) or a Chiralcel AD column (25 cm) and AD guard (5 cm) as noted.

General Procedure: An amber 2-dram vial equipped with a magnetic stir bar and containing (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one was charged with methylene chloride, isopropyl alcohol, and associated acid, then placed in a bath of the appropriate temperature. The solution was stirred for 5 min before addition of the α,β-unsaturated aldehyde. After stirring for an additional 10 min the indole substrate was added in one portion. The resulting suspension was stirred at constant temperature until complete consumption of the indole was observed as determined by TLC. The reaction mixture was then transferred cold through a silica gel plug into a flask and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (solvents noted) to afford the title compounds. The enantioselectivity was determined by subjecting approximately 10 mg of the title compound to an excess of sodium borohydride and 1 mL of absolute ethanol. After 15 min, the remaining sodium borohydride was quenched with saturated aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The organic layer was separated, filtered through a silica gel plug and subjected to HPLC analysis.

(2*S*,5*S*)-5-Benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one (13). To a solution of ethanolic $MeNH_2$ (8.0 M, 50 ml) was added (*S*)-phenylalanine methyl ester (23.0 g, 130 mmol). The resulting solution was stirred at room temperature until the amino ester

was judged to be consumed by TLC analysis. The resulting solution was then concentrated to provide (*S*)-phenylalanine *N*-methyl amide (18 g, 82% yield) as a white solid. To a flask containing (*S*)-phenylalanine *N*-methyl amide (8.9 g, 50 mmol) was added THF (100 mL), trimethylacetaldehyde (5.4 g, 50 mmol), $FeCl_3$ (1.7 g, 10 mmol) and 4 Å MS (5.0 g). The resulting mixture was stirred at room temperature for 36 h, then washed with H_2O (3 x 100 mL). The combined organics were concentrated and the resulting residue was treated with HCl (27 mL, 1*N* in ether). The resulting hetereogenous mixture was filtered to removed the undesired *trans* isomer•HCl salt and the resulting solution was concentrated. The residue was recrystallized (9:1 pentane / CH_2Cl_2) to provide the product as a crystalline solid (2.88 g, 23% yield, >99% ee). IR (film) 3343, 2958, 1605, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H, ArH), 4.04 (s, 1H, NCHN), 3.72-3.65 (m, 1H, C**H**CH_2), 3.13 (dd, *J* = 4.1, 13.7 Hz, 1H, CH_2), 2.92 (dd, *J* = 7.7, 13.7 Hz, 1H, CH_2), 2.90 (s, 3H, NCH_3), 0.82 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 138.0, 129.8, 128.7, 126.8, 82.7, 77.8, 77.4, 76.9, 59.7, 38.6, 35.4, 31.0, 25.7; $[\alpha]_D$ = –39.6 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC using a Chiralpak OD-H and OD guard column (3.0% *i*-PrOH / hexanes, 1 mL/min); (5*S*) isomer t_r = 16.7 min, (5*R*) isomer t_r = 20.1 min.

(*R*)-3-(1-Methyl-1*H*-indol-3-yl)-butanal. Prepared according to the general procedure from crotonaldehyde (125 μL, 1.50 mmol), 1-methyl-1*H*-indole (64 μL, 0.50 mmol), TFA (7.7 μL, 0.10 mmol) and (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol) in CH_2Cl_2 (0.85 mL) and 2-propanol (0.15 mL) at –83 °C for 19 h to provide the title compound as a colorless oil (83 mg, 82%

yield, 92% ee) after silica gel chromatography in benzene. IR (film) 3054, 2960, 2824, 2722, 1720, 1616, 1550, 1474, 1374, 1329, 1241, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (dd, *J* = 2.1, 2.1 Hz, 1H, CHO), 7.63 (d, *J* = 7.8 Hz, 1H, ArH), 7.32-7.21 (m, 2H, ArH), 7.12 (ddd, *J* = 1.5, 7.4, 8.1 Hz, 1H, ArH), 6.84 (s, 1H, NCH), 3.75 (s, 3H, NCH_3), 3.68 (dt, *J* = 6.9, 13.8 Hz, 1H, ArCH), 2.88 (ddd, *J* = 2.7, 6.9, 16.2 Hz, 1H, C**H**$_2$CO); 2.71 (ddd, *J* = 2.7, 6.9, 16.2 Hz, 1H, C**H**$_2$CO); 1.44 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 137.2, 126.6, 125.2, 121.8, 119.1, 118.9, 118.8, 109.5, 51.2, 32.8, 26.0, 21.9; HRMS (CI) exact mass calcd for ($C_{13}H_{15}NO$) requires *m/z* 201.1154, found *m/z* 201.1152. $[\alpha]_D$ = –4.2 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AD and AD guard column (2% ethanol / hexanes, 1 mL/min); *S* isomer t_r = 25.2 min and *R* isomer t_r = 27.8 min.

(*R*)-3-(1-Methyl-1*H*-indol-3-yl)-hexanal. Prepared according to the general procedure from 2-hexenal (174 μL, 1.50 mmol), 1-methyl-1*H*-indole (64μL, 0.50 mmol), TFA (7.7 μL, 0.10 mmol) and (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol) in CH_2Cl_2 (0.85 mL) and 2-propanol (0.15 mL) at –60 °C for 6 h to provide the title compound as a colorless oil (92 mg, 80% yield, 93% ee) after silica gel chromatography in 5% EtOAc / hexanes. IR (film) 2959, 2923, 2870, 1720, 1483, 1470, 1425, 1376, 1327, 1244, 1159, 1132, 1016, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (dd, *J* = 2.1, 2.1 Hz, 1H, CHO), 7.67 (d, *J* = 8.4 Hz, 1H, ArH), 7.35-7.24 (m, 2H, ArH), 7.12 (ddd, *J* = 1.5, 7.2, 8.1 Hz, 1H, ArH), 6.87 (s, 1H, NCH), 3.76 (s, 3H, NCH_3), 3.55 (m, 1H, ArCH), 2.83 (m, 2H, C**H**$_2$CO), 1.79 (m, 2H, CHC**H**$_2$$CH_2$), 1.34 (dt,

J = 7.2, 22.8 Hz, 2H, CHC**H**$_2$CH$_3$), 0.92 (dd, *J* = 7.2, 7.2 Hz, 3H, CH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 137.2, 127.0, 126.0, 121.6, 119.2, 118.7, 117.0, 109.4, 49.7, 38.5, 32.8, 31.4, 20.8, 14.2; HRMS (CI) exact mass calcd for ($C_{15}H_{19}NO$) requires *m/z* 229.1467, found *m/z* 229.1464. $[\alpha]_D = -1.7$ (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AS and AS guard column (2% ethanol / hexanes, 1 mL/min); *S* isomer t_r = 16.1 min and *R* isomer t_r = 18.1 min.

(*S*)-4-Methyl-3-(1-methyl-1*H*-indol-3-yl)-pentanal. Prepared according to the general procedure from 4-methyl-2-pentenal (175 μL, 1.50 mmol), 1-methyl-1*H*-indole (64μL, 0.50 mmol), TFA (7.7 μL, 0.10 mmol) and (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol) in CH_2Cl_2 (0.90 mL) and 2-propanol (0.10 mL) at −50 °C for 32 h to provide the title compound as a colorless oil (85 mg, 74% yield, 93% ee) after silica gel chromatography in 10% EtOAc / hexanes. IR (film) 3052, 2958, 2870, 2834, 2716, 1723, 1609, 1546, 1482, 1469, 1423, 1373, 1328, 1246, 1160, 1138, 1015, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (dd, *J* = 2.4, 2.4 Hz, 1H, CHO), 7.63 (dt, *J* = 0.9, 8.1 Hz, 1H, ArH), 7.33-7.22 (m, 2H, ArH), 7.13 (ddd, *J* = 1.5, 6.9, 8.1 Hz, 1H, ArH), 6.82 (s, 1H, NCH), 3.75 (s, 3H, NCH_3), 3.40 (dt, *J* = 6.6, 7.8 Hz, 1H, ArCH), 2.81 (d, *J* = 2.4 Hz, 1H, C**H**$_2$CO); 2.79 (d, *J* = 2.4 Hz, 1H, C**H**$_2$CO); 2.10 (ddd, *J* = 6.6, 13.2, 19.8 Hz, 1H, C**H**$(CH_3)_2$, 0.96 (d, *J* = 2.1, 3H, CH(C**H**$_3)_2$, 0.94 (d, *J* = 2.1 Hz, 3H, CH(C**H**$_3)_2$; ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 137.0, 127.6, 126.7, 121.6, 119.4, 118.8, 115.6, 109.3, 46.1, 38.0, 32.9, 32.9, 20.6, 20.4; HRMS (CI) exact mass calcd for ($C_{15}H_{19}NO$) requires *m/z* 229.1467, found *m/z* 229.1465. $[\alpha]_D = +15.8$ (c = 1.0,

$CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AS and AS guard column (4% ethanol / hexanes, 1 mL/min); *R* isomer t_r = 13.4 min and *S* isomer t_r = 16.7 min.

(*S*)-3-(1-Methyl-1*H*-indol-3-yl)-3-phenyl-propanal. Prepared according to the general procedure from cinnamaldehyde (190 μL, 1.50 mmol), 1-methyl-1*H*-indole (64μL, 0.50 mmol), TFA (7.7 μL, 0.10 mmol) and (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol) in CH_2Cl_2 (0.85 mL) and 2-propanol (0.15 mL) at −55 °C for 45 h to provide the title compound as a colorless oil (110 mg, 84% yield, 90% ee) after silica gel chromatography in 10% EtOAc / hexanes. IR (film) 3051, 3026, 2945, 2888, 2822, 2733, 1722, 1616, 1604, 1547, 1474, 1429, 1376, 1331, 1245, 1225, 1156, 1131, 1013, 765, 740, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (dd, *J* = 2.4, 2.4 Hz, 1H, CHO), 7.43 (dt, *J* = 0.9, 8.1 Hz, 1H, ArH), 7.36-7.28 (m, 7H, ArH), 7.04 (ddd, *J* = 1.2, 6.9, 8.1 Hz, 1H, ArH), 6.88 (s, 1H, NCH), 4.88 (t, *J* = 7.5 Hz, 1H, ArCH), 3.76 (s, 3H, NCH_3), 3.22 (ddd, *J* = 2.7, 8.4, 16.5 Hz, 1H, C**H**$_2$CO); 3.10 (ddd, *J* = 2.7, 8.4, 16.5 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 143.5, 137.3, 128.6, 127.6, 126.8, 126.6, 126.4, 121.9, 119.4, 119.0, 116.6, 109.3, 50.0, 37.4, 32.9; HRMS (CI) exact mass calcd for ($C_{15}H_{17}NO$) requires *m*/*z* 263.1310, found *m*/*z* 263.1306. $[\alpha]_D$ = +30.9 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AD and AD guard column (3% ethanol / hexanes, 1 mL/min); *S* isomer t_r = 48.5 min and *R* isomer t_r = 38.9 min.

(*R*)-4-Benzyloxy-3-(1-methyl-1*H*-indol-3-yl)-butanal. Prepared according to the general procedure from 4-benzyloxy-but-2-enal (286 mg, 1.50 mmol), 1-methyl-1*H*-indole (64 μL, 0.50 mmol), TFA (7.7 μL, 0.10 mmol) and (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol) in CH_2Cl_2 (0.85 mL) and 2-propanol (0.15 mL) at −83 °C for 18.5 h to provide the title compound as a colorless oil (134 mg, 84% yield, 96% ee) after silica gel chromatography in 50% Et_2O / hexanes. IR (film) 3056, 2957, 2894, 2830, 2722, 1717, 1618, 1600, 1582, 1550, 1478, 1451, 1370, 1331, 1309, 1272, 1223, 1173, 1110, 1070, 1024, 772, 740, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (dd, *J* = 2.1, 2.1 Hz, 1H, CHO), 8.04 (d, *J* = 7.2 Hz, 2H, ArH), 7.75 (d, *J* = 8.1 Hz, 1H, ArH), 7.61-724 (m, 5H, ArH), 7.17 (ddd, *J* = 1.5, 6.6, 8.1 Hz, 1H, ArH), 6.96 (s, 1H, NCH), 4.73 (dd, *J* = 5.1, 11.1 Hz, 1H, C**H**$_2$O), 4.42 (dd, *J* = 8.7, 11.1 Hz, 1H, C**H**$_2$O), 4.12 (m, 1H, ArCH), 3.76 (s, 3H, NCH_3), 3.06 (ddd, *J* = 2.1, 6.3, 16.8 Hz, 1H, C**H**$_2$CO); 2.96 (ddd, *J* = 2.7, 8.4, 16.8 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5, 166.4, 137.1, 133.1, 129.9, 129.6, 128.5, 126.8, 126.4, 122.1, 119.3, 119.0, 112.9, 109.6, 68.1, 46.5, 33.0, 31.2; HRMS (CI) exact mass calcd for ($C_{20}H_{19}NO$) requires *m/z* 321.1365, found *m/z* 321.1354. $[\alpha]_D$ = −2.0 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AS and AS guard column (4% ethanol / hexanes, 1 mL/min); *S* isomer t_r = 42.9 min and *R* isomer t_r = 53.2 min.

(R)-2-(1-Methyl-1*H*-indol-3-yl)-4-oxo butyric acid methyl ester. Prepared according to the general procedure from methyl 4-oxo-butenoate (171 mg, 1.50 mmol), 1-methyl-1*H*-indole (64μL, 0.50 mmol), TFA (7.7 μL, 0.10 mmol) and (2*S*, 5*S*)-5-

benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol) in CH_2Cl_2 (0.90 mL) and 2-propanol (0.10 mL) at −85 °C for 21 h to provide the title compound as a colorless oil (109 mg, 89% yield, 91% ee) after silica gel chromatography in 5% acetone / 47.5% CH_2Cl_2 / 47.5% hexanes. IR (film) 2937, 2833, 2729, 1732, 1623, 1545, 1477, 1436, 1379, 1332, 1228, 1171, 1042, 1016, 980, 773, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H, CHO), 7.67 (d, *J* = 8.4 Hz, 1H, ArH), 7.33-7.23 (m, 2H, ArH), 7.15 (ddd, *J* = 1.2, 7.6, 7.8 Hz, 1H, ArH), 6.98 (s, 1H, NCH), 4.44 (dd, *J* = 5.4, 9.3 Hz, 1H, ArH), 3.76 (s, 3H, NCH_3), 3.69 (s, 3H, OCH_3), 3.47 (dd, *J* = 9.3, 18.6 Hz, 1H, C**H**$_2$CO); 2.94 (dd, *J* = 5.1, 18.3 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 173.8, 137.0, 126.9, 126.5, 122.1, 119.5, 119.1, 110.8, 109.6, 52.5, 46.8, 36.5, 33.0; HRMS (CI) exact mass calcd for ($C_{14}H_{15}NO_3$) requires *m/z* 245.1052, found *m/z* 245.1048. $[\alpha]_D$ = −123.6 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AS and AS guard column (3% 2-propanol / hexanes, 1 mL/min); *S* isomer t_r = 71.7 min and *R* isomer t_r = 76.3 min.

(*R*)-3-(1*H*-Indol-3-yl)-butanal. Prepared according to general procedure from crotonaldehyde (100 μL, 1.25 mmol), indole (146 mg, 1.25 mmol), 2,4-dinitrobenzoic acid (53 mg, 0.25 mmol) and (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (62 mg, 0.25 mmol) in CH_2Cl_2 (2.25 mL) and 2-propanol (0.25 mL) at −60 °C for 19 h at which time an additional 30 μL (0.36 mmol) of crotonaldehyde was added. The reaction was allowed to continue stirring for an additional 3 h to provide the title compound as a colorless oil (168 mg, 72% yield, 91% ee) after silica gel chromatography in 20% EtOAc

/ hexanes. Upon exposure to light the oil changes to a bright pink color. IR (film) 3408, 2962, 2875, 2833, 2729, 1716, 1617, 1451, 1420, 1337, 1223, 1099, 1010, 772, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (dd, *J* = 2.1, 2.1 Hz, 1H, CHO), 8.15 (s, 1H, NH), 7.68 (dt, *J* = 0.6, 7.8 Hz, 1H, ArH), 7.35 (dt, J = 1.5, 7.8 Hz, 1H, ArH), 7.27-7.15 (m, 2H, ArH), 6.94 (d, *J* = 2.4 Hz, 1H, NCH), 3.68 (dt, *J* = 7.2, 21 Hz, 1H, ArCH), 2.91 (ddd, *J* = 2.4, 6.9, 16.2 Hz, 1H, C**H**$_2$CO); 2.73 (ddd, *J* = 2.1, 7.2, 16.2 Hz, 1H, C**H**$_2$CO); 1.47 (d, *J* = 6.9 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 136.5, 126.1, 122.1, 120.7, 120.1, 119.3, 118.9, 111.4, 50.9, 26.0, 21.6; HRMS (CI) exact mass calcd for ($C_{12}H_{13}NO$) requires *m/z* 187.0997, found *m/z* 187.0093. $[\alpha]_D$ = −2.2 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel OD−H and OD guard column (10% ethanol / hexanes, 1 mL/min); *S* isomer t_r = 20.2 min and *R* isomer t_r = 17.6 min.

(*R*)-3-(1-Allyl-1*H*-indol-3-yl)-butanal. Prepared according to general procedure from crotonaldehyde (125 μL, 1.50 mmol), 1-allyl-1*H*-indole (78.5 mg, 0.500 mmol), TFA (7.7 μL, 0.10 mmol) and (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol) in CH_2Cl_2 (0.90 mL) and 2-propanol (0.10 mL) at −72 °C for 21 h to provide the title compound as a colorless oil (80 mg, 70% yield, 92% ee) after silica gel chromatography in 7% EtOAc / hexanes. IR (film) 3041, 2966, 2919, 2822, 2834, 2712, 1722, 1469, 1375, 1328, 1309, 1262, 192, 1018, 995, 929, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (dd, *J* = 2.1, 2.1 Hz, 1H, CHO), 7.64 (dt, *J* = 0.9, 7.8 Hz, 1H, ArH), 7.33-7.20 (m, 2H, ArH), 7.13 (ddd, *J* = 0.9, 6.9, 7.8 Hz, 1H, ArH), 6.89 (s, 1H, NCH), 5.98 (ddd, *J* = 5.4, 9.9, 22.5 Hz, 1H, CH_2C**H**CH_2), 5.20 (dd, *J* = 1.5, 10.2 Hz, 1H,

CH_2CHCH_2), 5.10 (dt, *J* = 1.5, 17.1 Hz, 1H CH_2CHCH_2), 4.68 (d, *J* = 5.4 Hz, 2H NCH_2), 3.69 (dt, *J* = 6.9, 21.3 Hz, 1H, ArCH), 2.88 (ddd, *J* = 2.4, 6.6, 16.2 Hz, 1H, CH_2CO); 2.71 (ddd, *J* = 2.1, 7.2, 16.2 Hz, 1H, CH_2CO); 1.44 (d, *J* = 6.9 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 136.7, 133.5, 126.8, 124.1, 121.8, 119.3, 119.2, 119.0, 117.4, 109.8, 51.1, 48.9, 26.1, 21.8; HRMS (CI) exact mass calcd for ($C_{15}H_{17}NO$) requires *m/z* 227.1310, found *m/z* 227.1309. $[\alpha]_D$ = –4.4 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AD and AD guard column (2% ethanol / hexanes, 1 mL/min); *S* isomer t_r = 38.7 min and *R* isomer t_r = 42.2 min.

(*R*)-3-(1-Benzyl-1*H*-indol-3-yl)-butanal. Prepared according to the general procedure from crotonaldehyde (125 μL, 1.50 mmol), 1-benzyl-1*H*-indole (104 mg, 0.500 mmol), 2,4-dinitrobenzoic acid (21.2 mg, 0.100 mmol) and (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol) in CH_2Cl_2 (0.90 mL) and 2-propanol (0.10 mL) at –60 °C for 41 h, at which time an additional 125 μL (1.50 mmol) of crotonaldehyde was added. The reaction was continued for an additional 70 h, at which time an additional 42 μL (0.50 mmol) of crotonaldehyde was added. The reaction was continued at this temperature for an additional 5 h, at which time the temperature was raised to –40 °C for 2 h, then –10 °C for an additional 2 h to provide the title compound as a colorless oil (110 mg, 80% yield, 89% ee) after silica gel chromatography in 15% EtOAc / hexanes. IR (film) 3062, 3030, 2965, 2925, 2877, 2820, 2724, 1722, 1613, 1589, 1549, 1496, 1480, 1468, 1452, 1392, 1372, 1356, 1331, 1303, 1251, 1203, 1174, 1017 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (dd, *J* = 2.4, 2.4 Hz,

1H, CHO), 7.66 (dt, *J* = 0.6, 7.5 Hz, 1H, ArH), 7.33-7.08 (m, 8H, ArH), 6.92 (s, 1H, NCH), 5.28 (s, 2H, NCH_2), 3.70 (dt, *J* = 6.9, 21 Hz, 1H, ArCH), 2.89 (ddd, *J* = 2.4, 6.6, 16.5 Hz, 1H, C**H**$_2$CO); 2.72 (ddd, *J* = 1.8, 7.8, 15.9 Hz, 1H, C**H**$_2$CO); 1.44 (d, *J* = 6.9 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 137.5, 131.9, 128.8, 127.6, 126.9, 126.8, 124.6, 122.0, 119.6, 119.3, 119.2, 110.0, 51.2, 50.1, 26.1, 21.0; HRMS (CI) exact mass calcd for ($C_{19}H_{19}NO$) requires *m/z* 277.1467, found *m/z* 277.1464. $[\alpha]_D$ = +3.5 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AD and AD guard column (2% 2-propanol / hexanes, 1 mL/min); *S* isomer t_r = 26.5 min and *R* isomer t_r = 29.5 min.

(*R*)-4-Benzyloxy-3-(4-methoxy-1-methyl-1*H*-indol-3-yl)-butanal. Prepared according to the general procedure from 4-benzyloxy-but-2-enal (285 mg, 1.50 mmol), 4-methoxy-1-methyl-1*H*-indole (80.5 mg, 0.500 mmol), TFA (7.7 μL, 0.10 mmol) and (2S, 5S)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol) in CH_2Cl_2 (0.90 mL) and 2-propanol (0.10 mL) at −87 °C for 19.5 h to provide the title compound as a colorless oil (158 mg, 90% yield, 94% ee) after silica gel chromatography in 20% EtOAc / hexanes giving. IR (film) 3081, 2961, 2850, 2730, 1719, 1608, 1582, 1548, 1501, 1466, 1454, 1424, 1381, 1334, 1321, 1274, 1261, 1180, 1116, 1073, 1026, 782, 714 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (dd, *J* = 2.4, 2.4 Hz, 1H, CHO), 8.03-8.01 (m, 2H, ArH), 7.59-7.53 (m, 1H, ArH), 7.47-7.41 (m, 2H, ArH), 7.16 (t, *J* = 8.4 Hz, 1H, ArH), 6.92 (dd, *J* = 0.6, 8.4 Hz, 1H, ArH), 6.83 (s, 1H, NCH), 6.52 (d, *J* = 7.5 Hz, 1H, ArH), 4.71 (dd, *J* = 5.1, 10.5 Hz, 1H, C**H**$_2$O), 4.50 (dd, *J* = 8.4, 10.5 Hz, 1H, C**H**$_2$O),

4.35 (m, 1H, ArCH), 3.94 (s, 1H, OCH_3), 3.71 (s, 3H, NCH_3), 2.98 (d, *J* = 2.4 Hz, 1H, C**H**$_2$CO); 2.96 (d, *J* = 2.7 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 166.3, 154.2, 133.0, 130.3, 129.6, 128.6, 128.4, 125.4, 122.9, 116.8, 113.6, 102.8, 99.4, 68.8, 55.3, 47.3, 33.2, 32.2; HRMS (CI) exact mass calcd for ($C_{21}H_{21}NO_4$) requires *m/z* 351.1471, found *m/z* 351.1466. $[\alpha]_D$ = −13.9 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AD and AD guard column (4% ethanol / hexanes, 1 mL/min); *S* isomer t_r = 58.7 min and *R* isomer t_r = 47.5 min.

(*R*)-4-Benzyoxy-3-(4-methyl-1*H*-indol-3-yl)-butanal. Prepared according to the general procedure from benzoic acid 4-benzyloxy-but-enal (143 mg, 0.750 mmol), 4-methyl-1*H*-indole (80.5 mg, 0.500 mmol), 2,4-dinitrobenzoic acid (21.2 mg, 0.100 mmol) and (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol) in CH_2Cl_2 (0.90 mL) and 2-propanol (0.10 mL) at −60 °C for 2.5 h to provide the title compound as a colorless oil (150 mg, 94% yield, 94% ee) after silica gel chromatography in 15% EtOAc / hexanes. IR (film) 3406, 2947, 2923, 2843, 2738, 1717, 1620, 1604, 1584, 1451, 1411, 1383, 1344, 1315, 1271, 1178, 1114, 1066, 1226, 969 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (dd, *J* = 2.1, 2.1 Hz, 1H, CHO), 8.14 (s, 1H, NH), 8.02 (dt, *J* = 1.5, 7.2 Hz, 2H, ArH), 7.58 (tt, *J* = 1.5, 6.6 Hz, 1H, ArH), 7.45 (tt, *J* = 1.2, 6.9 Hz, 2H, ArH), 7.24-7.08 (m, 3H, ArH, NCH), 6.91 (dt, *J* = 0.9, 7.2 Hz, 1H, ArH), 4.74 (dd, *J* = 4.2, 10.5 Hz, 1H, C**H**$_2$O), 4.52-4.43 (m, 1H, ArCH), 4.32 (dd, *J* = 8.4, 10.8 Hz, 1H, C**H**$_2$O), 3.05 (ddd, *J* = 2.1, 6.9, 16.8 Hz, 1H, C**H**$_2$CO); 2.95 (ddd, *J* = 2.1, 7.8, 16.8 Hz, 1H, C**H**$_2$CO), 2.82 (s, 3H, $ArCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 166.3, 136.5,

133.2, 130.5, 130.0, 129.7, 128.5, 125.1, 122.6, 122.1, 121.7, 115.8, 109.4, 68.9, 47.8, 31.7, 21.0; HRMS (CI) exact mass calcd for ($C_{20}H_{19}NO_3$) requires *m/z* 321.1365, found *m/z* 321.1353. $[\alpha]_D$ = –26.6 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AD and AD guard column (10% ethanol / hexanes, 1 mL/min); *S* isomer t_r = 47.8 min and *R* isomer t_r = 42.4 min.

(*R*)-4-Benzyloxy-3-(6-chloro-1*H*-indol-3-yl)-butanal. Prepared according to the general procedure from 4-benzyloxy-but-2-enal (143 mg, 0.750 mmol), 6-chloro-1*H*-indole (75.8, 0.500 mmol), 2,4-dinitrobenzoic acid (21.2 mg, 0.100 mmol) and (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (24.6 mg, 0.100 mmol) in CH_2Cl_2 (0.90 mL) and 2-propanol (0.10 mL) at –60 °C for 12.75 h to provide the title compound as a colorless oil (124 mg, 73% yield, 97% ee) after silica gel chromatography in CH_2Cl_2. IR (film) 3383, 2953, 2930, 2834, 2734, 1718, 1623, 1603, 1548, 1453, 1403, 1378, 1273, 1184, 1104, 1069, 1019, 909, 804, 774, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (dd, *J* = 1.8, 1.8 Hz, 1H, CHO), 8.15 (s, 1H, NH), 8.02-7.99 (m, 2H, ArH), 7.65 (dd, *J* = 0.6, 8.7 Hz, 1H, ArH), 7.58 (tt, *J* = 1.5, 6.6 Hz, 1H, ArH), 7.48-7.42 (m, 2H, ArH), 7.37 (d, *J* = 1.8 Hz, 1H NCH), 7.12 (dt, *J* = 2.1, 8.7 Hz, 2H, ArH), 4.70 (dd, *J* = 5.1, 10.8 Hz, 1H, C**H**$_2$O), 4.42 (dd, J = 8.4, 11.1 Hz, 1H, C**H**$_2$O), 4.08 (m, 1H, ArCH), 3.06 (ddd, *J* = 1.8, 6.3, 16.8 Hz, 1H, C**H**$_2$CO); 2.95 (ddd, *J* = 2.1, 7.8, 16.5 Hz, 1H, C**H**$_2$CO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 166.5, 136.7, 135.4, 133.2, 129.9, 129.6, 128.5. 125.1, 122.3, 120.7, 119.8, 115.0, 111.4, 67.8, 46.5, 31.0; HRMS (CI) exact mass calcd for ($C_{19}H_{16}ClNO_3$) requires *m/z* 341.0819, found *m/z* 341.0814. $[\alpha]_D$ = –3.3 (c = 1.0, $CHCl_3$).

The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel AD and AD guard column (10% ethanol / hexanes, 1 mL/min); *S* isomer t_r = 38.8 min and *R* isomer t_r = 43.3 min.

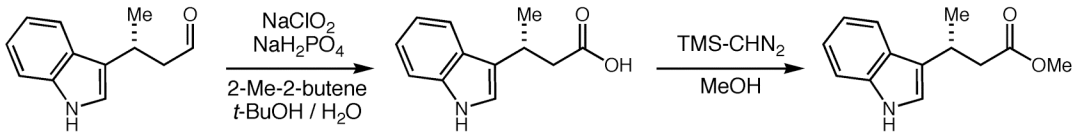
(*R*)-3-[1-(4-Bromo-benzyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-butanal. To 1-(4-bromo-benzyl)-5-methoxy-2-methyl-1*H*-indole (110 mg, 0.333 mmol) in a 2-dram amber vial was added CH_2Cl_2 (0.60 mL), 2-propanol (0.066 mL), dichloroacetic acid (5.5 μL, 0.066 mmol) and (2*S*, 5*S*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (16.4 mg, 0.066 mmol). This solution was stirred for 10 min at room temperature, then placed in a −70 °C bath for an additional 10 min. At this time, crotonaldehyde (82 μL, 1.0 mmol) was added and the reaction was stirred at −70 °C for 9 h. The reaction mixture was then transferred cold through a silica plug into a flask and concentrated *in vacuo*. The resulting residue provided the title compound as a colorless oil (111 mg, 84% yield, 87% ee) after silica the pure product as a colorless oil after silica gel chromatography in 20% EtOAc / hexanes. IR (film) 2930, 2823, 2730, 1722, 1618, 1581, 1530, 1483, 1452, 1405, 1229, 1156, 1073, 1037, 1011, 902, 798, 476 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (dd, *J* = 1.8, 1.8 Hz, 1H, CHO), 7.38 (dt, *J* = 2.4, 9.0 Hz, 2H, ArH), 7.12 (d, *J* = 2.1 Hz, 1H, ArH), 7.05 (d, *J* = 9.0, 1H, ArH), 6.79-6.75 (m, 3H, ArH), 5.19 (s, 2H NCH_2), 3.88 (s, 3H, OCH_3), 3.66 (dt, *J* = 7.2, 22.2 Hz, 1H ArCH), 3.02 (ddd, *J* = 1.8, 8.1, 16.5 Hz, 1H, C**H**$_2$CO); 2.85 (ddd, *J* = 2.1, 6.6, 16.5 Hz, 1H, C**H**$_2$CO); 2.30 (s, 3H, ArCH_3) 1.48 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 153.6, 137.0, 132.7, 132.0, 131.9, 127.6, 126.6, 121.1, 114.5, 110.0, 109.8, 102.3, 56.2, 50.6, 46.2, 26.4, 21.4, 10.9; HRMS (CI) exact mass calcd for ($C_{21}H_{22}BrNO_2$) requires *m/z* 399.0834, found *m/z*

399.0833. $[\alpha]_D$ = –20.8 (c = 1.0, $CHCl_3$). The enantiomeric ratio was determined by HPLC analysis of the alcohol, obtained by $NaBH_4$ reduction of the aldehyde, using a Chiracel OD–H and OD guard column (4% ethanol / hexanes, 1 mL/min); *S* isomer t_r = 45.1 min and *R* isomer t_r = 35.9 min.

(*R*)-3-[1-(4-Bromo-benzyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-butyric acid. A solution of (*R*)-3-[1-(4-Bromo-benzyl)-5-methoxy-2-methyl-1*H*-indol-3-yl]-butanal (110 mg, 0.250 mmol) and silver nitrate (59.7 mg, 0.275 mmol) in 1.3 ml absolute ethanol was treated with a solution of 5N NaOH in ethanol (1:5, 0.9 mL, 0.75 mmol NaOH). After 45 min this was treated with 10ml water, acidified to pH 3 and extracted with $CHCl_3$ (5x20 mL) rinsing each extract with brine. The combined organics were dried over Na_2SO_4 and concentated *in vacuo* to provide the title compound as a pale yellow solid (101 mg, 97% yield). IR (film) 3425, 2961, 2934, 2833, 1706, 1483, 1451, 1405, 1228, 1156, 1010, 796, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 9.0 Hz, 2H, ArH), 7.11 (d, *J* = 2.4 Hz, 1H, ArH), 7.04 (d, *J* = 8.7, 1H, ArH), 6.77-6.73 (m, 3H, ArH), 5.18 (s, 2H NCH_2), 3.86 (s, 3H, OCH_3), 3.56 (dt, *J* = 7.2, 21.9 Hz, 1H ArCH), 2.86 (d, *J* = 3.6 Hz, 1H, C**H**$_2$CO); 2.83 (d, *J* = 3.3 Hz, 1H, C**H**$_2$CO); 2.27 (s, 3H, $ArCH_3$) 1.49 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 153.7, 137.3, 133.8, 133.0, 132.0, 127.7, 126.7, 121.2, 118.8, 114.6, 110.1, 109.9, 102.4, 56.3, 46.3, 41.5, 28.6, 21.1, 10.9; HRMS (CI) exact mass calcd for ($C_{21}H_{23}BrNO_3$) (M+1) requires *m/z* 416.0861, found *m/z* 416.0867. $[\alpha]_D$ = –30.9 (c = 1.0, $CHCl_3$).

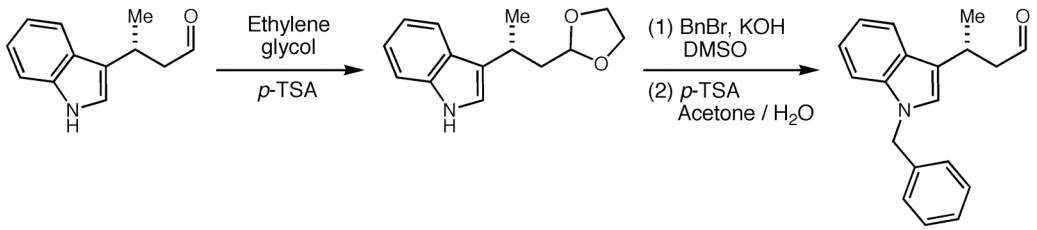
Determination of absolute stereochemistry

Figure 7. Derivatization of (*R*)-3-(1*H*-indol-3-yl)-butanal to Known Ester



Determination of the absolute stereochemistry of (*R*)-3-(1*H*-indol-3-yl)-butanal by correlation to (*S*)-3-(1*H*-indol-3-yl)-butyric acid methyl ester. 3-(1*H*-Indol-3-yl)-butanal (130 mg, 0.690 mmol) was dissolved in *tert*-butyl alcohol (27 mL) and 2-methyl-2-butene (4.7 mL) and subsequently was stirred for 10 min. To this solution was added an aqueous solution (4.7 mL) of $NaClO_2$ (75 mg, 0.83 mmol) and NaH_2PO_4 (115 mg, 0.830 mmol) in one portion. The reaction mixture was stirred at room temperature for 12 h. The organics were removed by concentrating *in vacuo*. The residue was diluted with 10 mL of H_2O, and adjusted to a neutral pH with 1M HCl. Extraction with EtOAc (3x10 mL), drying over Na_2SO_4, and concentration *in vacuo* provided 3-(1*H*-indol-3-yl)-butanoic acid. TMS-diazomethane was added dropwise to a solution of the crude 3-(1*H*-indol-3-yl)-butanoic acid in methanol (7 mL) until a yellow color persisted. The residual TMS-diazomethane was quenched by the dropwise addition of acetic acid until the yellow color disappeared. The reaction was then treated with an excess of saturated aqueous sodium bicarbonate, extracted with Et_2O (3 x 20 mL), dried over Na_2SO_4 and purified by silica gel chromatography in 20% EtOAc / hexanes to provide (*R*)-3-(1*H*-indol-3-yl)-butyric acid methyl ester. $[\alpha]_D = -7.6$ (c = 1.0, benzene); reported rotation for (*S*)-3-(1*H*-indol-3-yl)-butyric acid methyl ester $[\alpha]_D = +10.9$ (c = 2.12, benzene).

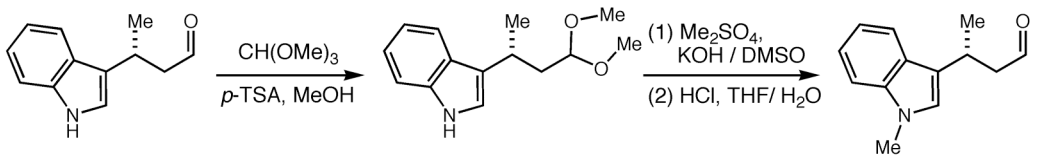
Figure 8. Derivatization of (*R*)-3-(1*H*-indol-3-yl)-butanal to Benzyl Analog



Determination of the absolute stereochemistry of (*R*)-3-(1-Benzyl-1*H*-indol-3-yl)-butanal by correlation to (*R*)-3-(1*H*-indol-3-yl)-butanal. (*R*)-3-(1*H*-Indol-3-yl)-butanal (89.5 mg, 0.479 mmol) was treated with ethylene glycol (130 μL, 2.4 mmol) and a catalytic amount of *p*-TSA in CH_2Cl_2 (2 mL). The reaction was stirred at room temperature for 12 h, at which time the organics were removed *in vacuo*. The solution was diluted with H_2O (10 mL) and extracted with Et_2O (3x20 mL). The collected organics where washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to provide (*R*)-3-(2-[1,3]dioxolan-2-yl-1-methyl-ethyl)-1*H*-indole (15.7 mg, 0.0680 mmol) after silica gel chromatography in 20% EtOAc / hexanes. This residual material was then exposed to 1 mL of DMSO, finely crushed KOH (15.3 mg, 0.272 mmol), and benzyl bromide (12 μL, 0.13 mmol) at 0 °C, then the solution was allowed to warm to room temperature and stirred for 12 h. The reaction was then treated with water (10ml), and extracted with Et_2O (2 x 20 mL). The aqueous layer was acidifid to pH 4, extracted with Et_2O 3x20ml), dried over Na_2SO_4 and concentrated *in vacuo* to provide 14.7 mg of (*R*)-1-benzyl-3-(2-[1,3]dioxolan-2-yl-1-methyl)-1*H*-indole after preparative TLC (20% EtOAc / hexanes). The benzylated product was then refluxed with a catalytic amount of *p*-TSA in H_2O (1 mL) / acetone (2 mL) overnight. The reaction mixture was diluted with H_2O (5 mL), and extracted with Et_2O (3 x 10 mL). The collected organics were washed with

brine, dried over Na_2SO_4 and concentrated *in vacuo* to provide (*R*)-3-(1-benzyl-1*H*-indol-3-yl)-butanal (5.5 mg, 0.020 mmol) after preparative TLC. $[\alpha]_D$ = +3.8 (c = 1.0, $CHCl_3$); reported rotation for (*R*)-3-(1-benzyl-1*H*-indol-3-yl)-butanal $[\alpha]_D$ = +3.5 (c = 1.0, $CHCl_3$).

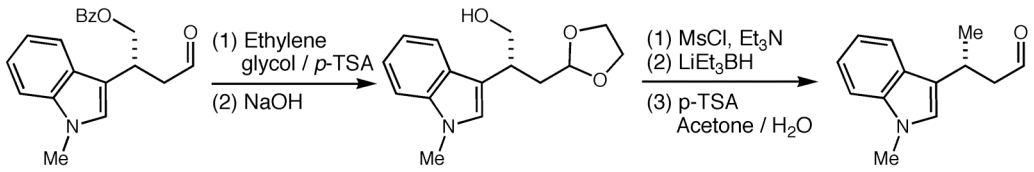
Figure 9. Derivatization of (*R*)-3-(1*H*-indol-3-yl)-butanal to Methyl Analog



Determination of the absolute stereochemistry of (*R*)-3-(1-methyl-1*H*-indol-3-yl)-butanal by correlation to (*R*)-3-(1*H*-indol-3-yl)-butanal. (*R*)-3-(1*H*-Indol-3-yl)-butanal (236 mg, 1.26 mmol) was dissolved in methanol (15 mL) and treated with trimethyl orthoformate (275 μL, 2.50 mmol) and a catalytic amount of *p*-TSA. The reaction was stirred at room temperature for 3 h, at which time H_2O (10 mL) was added and the reaction was extracted with ether (3x20 mL). The collected organics were rinsed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to provide 3-(3,3-dimethoxy-1-methyl-propyl)-1*H*-indole (228 mg, 1.17 mmol). 3-(3,3-dimethoxy-1-methyl-propyl)-1*H*-indole (39.9 mg, 0.171 mmol) was dissolved in a KOH (38.4 mg, 0.684 mmol) / DMSO (2 mL) solution and allowed to stir at 0 °C for 10 min, at which time dimethyl sulfate (32.5 μL, 0.340 mmol) was added and the reaction was allowed to warm to room temperature. The reaction was left to stir at room temperature until it appeared done by TLC. The reaction was quenched with H_2O (1 mL) and brought to a neutral pH with dropwise addition of 1M HCl. The solution was extracted with Et_2O (3 x 5 mL), and the collected organics were rinsed with brine, dried over Na_2SO_4, and concentrated *in vacuo*

to provide 3-(3,3-dimethoxy-1-methyl-propyl)-1-methyl-indole. This crude residual material was dissolved in THF (5 mL) and 1M HCl (1 mL) to give (*R*)-3-(1-methyl-1*H*-indol-3-yl)-butanal (1.9 mg, 0.0094 mmol) after preparative TLC (25% EtOAC / hexanes). $[\alpha]_D = -4.1$ (c = 1.0, $CHCl_3$); reported rotation for (*R*)-3-(1-methyl-1*H*-indol-3-yl)-butanal $[\alpha]_D = -4.2$ (c = 1.0, $CHCl_3$).

Figure 10. Deoxygenation of (*R*)-4-benzyloxy-3-(1-methyl-1*H*-indol-3-yl)-butanal



Determination of the absolute stereochemistry (R)-4-benzyloxy-3-(1-methyl-1*H*-indol-3-yl)-butanal by correlation to (*R*)-3-(1*H*-indol-3-yl)-butanal. (R)-Benzoic acid 2-(1-methyl-1*H*-indol-3-yl)-4-oxo-butyt ester (1.65g, 5.10 mmol) was dissolved in CH_2Cl_2 (50 mL). This solution was treated with *p*-TSA (20 mg) and ethylene glycol (1.4 mL, 26 mmol). The reaction was stirred at room temperature overnight, at which time the organics were removed *in vacuo*. The solution was diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The collected organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to provide (*R*)-benzoic acid 3-[1,3]dioxolan-2-yl-2-(1-methyl-1*H*-indol-3-yl)-propyl ester. The unpurified product was dissolved in MeOH/THF (18 mL / 18 mL) and allowed to stir at room temperature for 10 min. To this was added a 4% NaOH / MeOH (18 mL) solution. The reaction was allowed to stir at room temperature for 1 h. The solution was diluted with H_2O (10 mL) and extracted with Et_2O (3 x 20 mL). The collected organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to provide (R)-3-[1,3]dioxolan-2-yl-2-(1-methyl-1*H*-indol-3-

yl)-propan-1-ol (600 mg, 2.30 mmol) after silica gel chromatography (50% Et_2O / hexanes). (R)-3-[1,3]Dioxolan-2-yl-2-(1-methyl-1*H*-indol-3-yl)-propan-1-ol (69.5 mg, 0.267 mmol) was dissolved in CH_2Cl_2 (8 mL) and Et_3N (56 μl, 0.40 mmol). The reaction was cooled to 0 °C and treated with methanesulfonyl chloride (31 μl, 0.40 mmol). The reaction stirred for 1.5 h at this temperature then was allowed to warm to room temperature and stirred for an additional 10 min. The solution was diluted with H_2O (5 mL) and extracted with Et_2O (3x10 mL). The collected organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to provide (*R*)-methanesulfonic acid 3-[1,3]dioxolan-2-yl-2-(1-methyl-1*H*-indol-3-yl)-propyl ester. Deoxygenation was performed following the method of Holder and Matturro[i]. The unpurified material was dissolved in THF (2.7 mL) and the system was purged with an inert nitrogen atmosphere. Lithium triethylborohydride (560 μl, 1M solution in THF) was added in one portion and the reaction was allowed to reflux for 1 h under an nitrogen. The system was allowed to come to room temperature and was then cooled to 0 °C via an ice bath. Excess hydride was quenched by the dropwise addition of H_2O. Organoboranes were oxidized by adding 190 μl of a 3N NaOH solution followed by slow dropwise addition of 115 μl of 50% H_2O_2. The ice bath was removed and the reaction mixture was allowed to reflux for an additional hour. After cooling to room temperature, the mixture was diluted with 2.7 mL H_2O and extracted with pentane. The collected pentane layers were washed with H_2O, dried with $MgSO_4$, and concentrated *in vacuo* to provide (R)-3-(2-[1,3]dioxolan-2-yl-1-methyl-ethyl)-1-methyl-1*H*-indole. The unpurified material was dissolved in 8 ml acetone and 2 ml H_2O , treated with PPTS and warmed to reflux for 24 h. The reaction was diluted with H_2O (5 mL) and extracted with Et_2O (3 x 10 mL). The collected

organics were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to provide (*R*)-3-(1-methyl-1*H*-indol-3-yl)-butanal after preparative TLC (benzene). $[\alpha]_D$ = –4.6 (c = 1.0, $CHCl_3$); reported rotation for (*R*)-3-(1-methyl-1*H*-indol-3-yl)-butanal $[\alpha]_D$ = –4.2 (c = 1.0, $CHCl_3$).

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