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Synthetic Methods

Enantioselective Alkylation of 2-Oxindoles Catalyzed by a Bifunctional Phase-Transfer Catalyst: Synthesis of (−)-Debromoflustramine B

Ryan Craig, Emiliano Sorrentino, and Stephen J. Connon*[a]

Dedicated to Prof. A. Frank Hegarty on the occasion of his 75th birthday

Abstract: A new bifunctional phase-transfer catalyst that employs hydrogen bonding as a control element was developed to promote efficient enantioselective S_N2 reactions for the construction all-carbon quaternary stereocenters in high yield and excellent enantioselectivity (up to 97% *ee*) utilizing the alkylation of a malleable oxindole substrate. The utility of the methodology was demonstrated through a concise and highly enantioselective synthesis of (−)-debromoflustramine B.

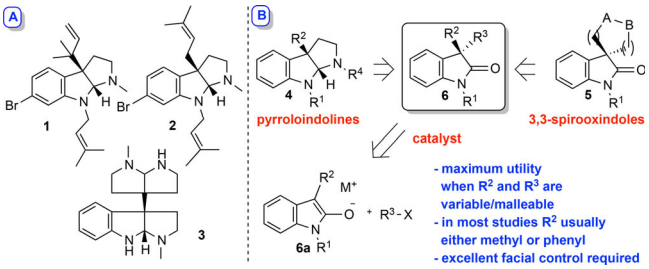

Figure 1. Pyrroloindoline natural isolates and catalytic asymmetric S_N2 chemistry as a route to pyrroloindolines and 3,3-spirooxindoles.

The 3,3-disubstituted 2-oxindole structural motif is present in a myriad of natural products/bioactive molecules and methods for their catalytic asymmetric synthesis are continually sought.[1] In addition, their facile transformation into pyrroloindoline compounds—an important subclass of alkaloids that can behave as (inter alia) muscle relaxants,[2] potassium channel-blockers,[3] and anti-cancer agents[4] (flustramine A (**1**), flustramine B (**2**) and chimonanthine (**3**) respectively, Figure 1 A) renders them potentially highly valuable synthetic building blocks.

Both classes of pyrroloindolines **4** and spirooxindoles **5** are conceivably available from key 3,3-disubstituted intermediates **6**, which could be prepared from an enantioselective S_N2 alkylation of enolate **6a**. For this strategy to have general utility the substituents at the 3-position (both existing in the substrate and added via reaction) should be as malleable as possible to facilitate onward manipulation. While considerable attention has been directed towards the total synthesis of natural pyrroloindolines,[5] including several catalytic asymmetric approaches[5,6] we were surprised to note that the simple, modular and direct approach offered by S_N2 chemistry had been scarcely applied in this context.[7,8]

Since the pioneering studies carried out by Dolling et al.,[9] phase-transfer catalysis (PTC) has become an efficient methodology for the asymmetric[10] S_N2-alkylation of enolates generated in situ. In 1991 Wong et al. reported the asymmetric cyanomethylation of *N*-methyl oxindole derivative **7** (Figure 2 A) promoted by catalyst **8** in moderate *ee*.[11]

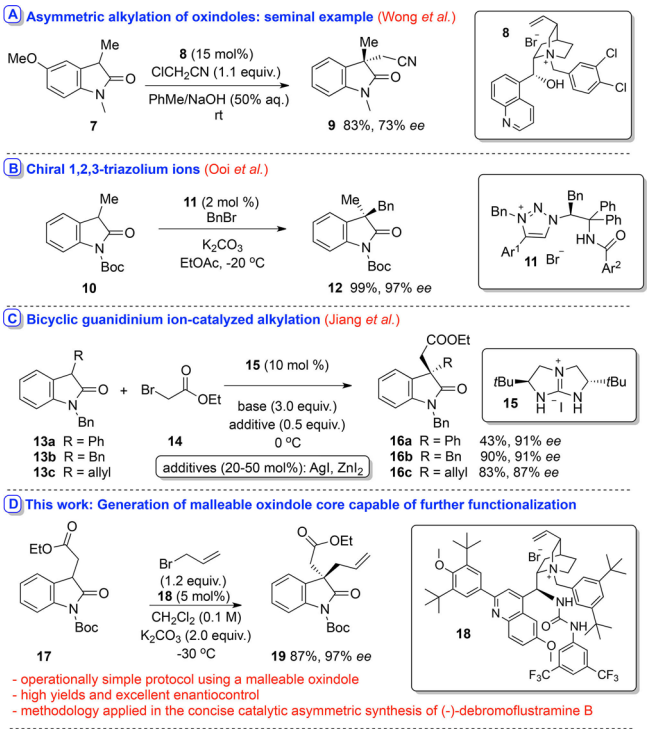

Figure 2. PTC of the S_N2 alkylation of 2-oxindoles.

[a] *R. Craig, Dr. E. Sorrentino, Prof. S. J. Connon*
Synthesis and Solid State Pharmaceutical Centre
Trinity Biomedical Sciences Institute, School of Chemistry
The University of Dublin, Trinity College
Dublin 2 (Ireland)
E-mail: connons@tcd.ie

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A significantly more enantiocontrolled alkylation of oxindole **10** (Figure 2B) was carried out by Ooi et al. in 2011,[12] using a chiral 1,2,3-triazolium ion-based phase-transfer catalyst **11**. Jiang et al. in 2013,[13] employed a bicyclic guanidinium ion **15** (Figure 2C) as a catalyst–in conjunction with a Lewis acid co-catalyst–to promote the alkylation of 3-substituted-2-oxindoles **13a–c** with activated alkyl bromides such as **14**. In the main, highly selective examples of these PTC-catalyzed alkylations reactions often involve oxindoles incorporating a simple methyl-, benzyl or aryl-substituent at position 3, which leaves the product less than ideally placed for further structural modification.

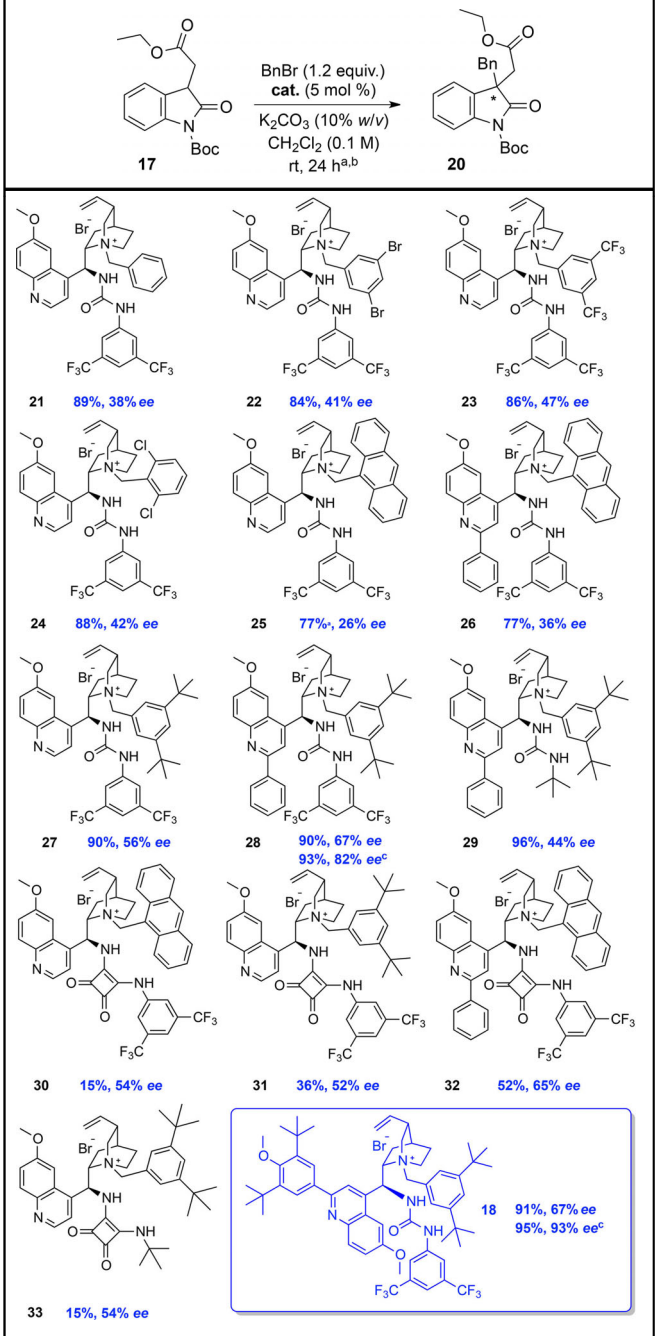
Herein we describe the highly enantioselective alkylation of ester-substituted 2-oxindole **17**[14] using a newly developed bulky, cinchona alkaloid-derived bifunctional phase-transfer catalyst **18** and the application of the methodology in the total synthesis of (−)-debromoflustramine B (Figure 2D).

Initial efforts were focused on the development of new cinchona alkaloid-based phase transfer catalysts capable of hydrogen bonding as a control element.[15] We began by investigating the alkylation of the potentially malleable oxindole **17** with benzyl bromide in the presence of an aqueous solution of potassium carbonate and dichloromethane, to yield **20** with the formation of a quaternary carbonaceous stereocenter (Table 1). In the absence of the phase transfer catalyst no reaction is observed under these conditions.[16] Catalysis by the urea-substituted ammonium salt **21** (first prepared by Dixon et al.[15b]) proceeded smoothly and with moderate enantiocontrol. The introduction of electron-withdrawing substituents on the benzyl unit in the 3,5- or 2,6-positions led to marginal increases in enantiocontrol (i.e., catalysts **22**–**24**). Exchange of the phenyl unit of the benzyl substituent with an anthracenyl group (i.e., **25**) diminished product *ee*, although this could be ameliorated somewhat through the introduction of a phenyl group at C-2 of the catalyst's quinoline moiety (i.e., catalyst **26**). Interestingly, returning to the N-benzyl motif and installing two bulky *tert*-butyl substituents allowed the formation of **20** with improved selectivity, and again incorporation of a C-2 phenyl unit proved advantageous (i.e., catalysts **27**–**28**). The role that the C-2 aryl unit plays in improving the enantioselectivity of the process is unclear at present. Recently, we reported the results of calculations which demonstrated that this unit can participate (via the *o*-hydrogen atom on phenyl substituent) in attractive O-H-C interactions with a squaramide-bound enolate in a bifunctional cinchona-alkaloid derived catalyst system; however a precise explanation of the role of the phenyl unit in this process awaits further study.[16]

The importance of the *N*-3,5-bis-triflurometylphenyl moiety is illustrated by the poor performance of catalyst **29**, in which this group has been exchanged with a *tert*-butyl substituent. Next we examined the use of squaramide derivatives. Initial results were promising: the squaramide analogue of **25** (i.e., **30**) promoted the reaction with superior *ee* (54 vs. 26%) albeit with a slow reaction rate. Similar catalyst modifications to those carried out in the urea series were then made (i.e., catalysts **31**–**33**)–and while levels of enantiomeric excess rivalled the best urea based catalysts, the reactions were prohibitively slow. The contribution from the urea *N*-3,5-bis-triflurometylphenyl moiety, the marked difference in rate between the urea- and squaramide-catalyzed reactions and the lack of enantiocontrol when neither are present[17] strongly implicates the hydrogen-bond donating unit as being a key driver of the catalysis.

Given the inferiority of squaramides in this process, focus returned to the urea based systems. Catalyst **18**, which compris-

Table 1. Catalyst evaluation.



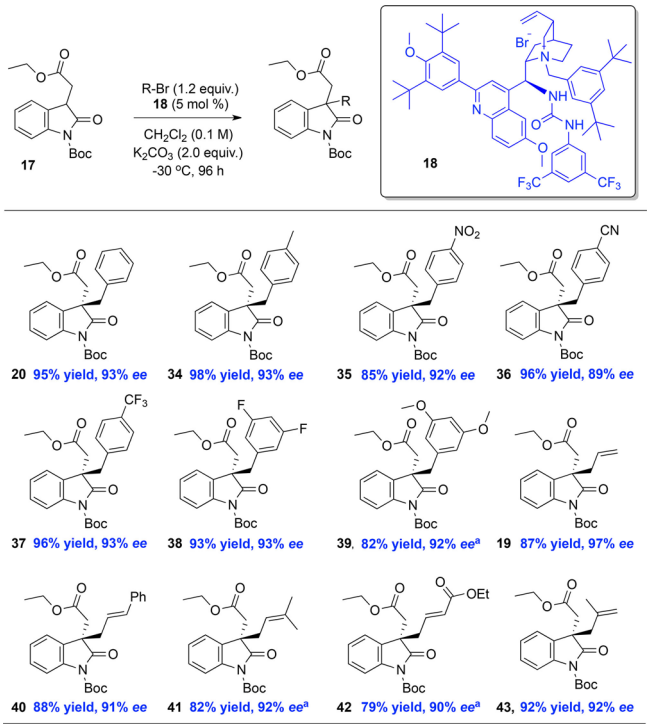
[a] Conversion determined by ^{1}H NMR spectroscopy using *para*-iodoanisole as an internal standard. [b] *ee* determined by chiral HPLC analysis after isolation by column chromatography. [c] CH_2Cl_2 (1.0 M), K_2CO_3 (s) (2.0 equiv), −30 °C.

es the superior ammonium N-alkyl and urea N-aryl substituents previously identified, together with and a C-2 aryl unit of considerably increased bulk and lipophilicity, could promote the reaction with 91% yield and 67% *ee*, but was also amenable to operation at lower temperatures. Use of this catalyst under modified conditions involving solid powdered K_2CO_3 at −30 °C allowed the isolation of **20** in excellent yield and enantiomeric excess.

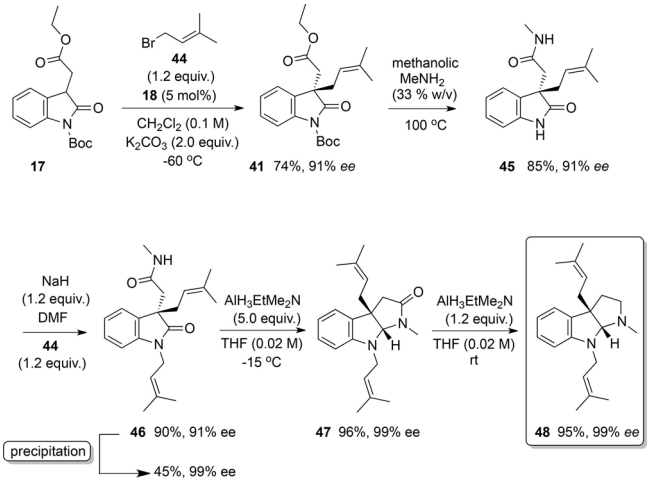
With a suitable catalyst now in hand, attention turned to the issue of substrate scope. Catalyst **18** could promote the efficient alkylation of **20** at 5 mol% levels with benzyl bromides (including analogues equipped with either electron-donating or electron withdrawing substituents–that is, products **34**–**39**) with excellent *ee* (Scheme 1). Gratifyingly, enantiocontrol was not diminished upon construction of quaternary stereocenters bearing allylic substituents–with enantiomeric excesses in the 90–97% range. Terminal (i.e., **19**), conjugated (**40**), trisubstituted (**41**), α,β-unsaturated (**42**) and disubstituted (**43**) olefin products could be easily prepared; with the densely functionalized oxindole **42** serving as a particularly prominent example of how highly malleable materials can be quickly and enantioselectively assembled in one pot using this methodology.

To demonstrate the potential utility of the catalytic process we carried out a concise and highly enantioselective catalytic asymmetric synthesis of (−)-debromoflustramine B (Scheme 2). Only four catalytic asymmetric total synthesis of flustramine Bs have been reported,[7e–h] none of which rely on a simple S_N2-based approach. The alkylation of **17** with 3,3-dimethylallyl bromide (**44**) furnished the requisite oxindole **41** bearing the necessary architecture capable of cyclizing to form the pyrroloindoline core in good yield and excellent enantiocontrol. The aminolysis of adduct **41** to amide **45** proceeded smoothly with concurrent Boc-deprotection and no diminution of *ee*. Efficient N-alkylation of the oxindole **45** with **44** afforded **46**, which could either be carried forward, or precipitated using diethyl ether to provide product with an enantiomeric excess of 99%. This amide participated in an alane-*N*,*N*-dimethylethylamine complex-mediated reductive cyclization to form the tricyclic product **47** in excellent yield. Reduction of the lactam with the same alane-complex provided the natural product **48** in 94% yield and near optical purity.[18]

In conclusion we have described a highly enantioselective S_N2 alkylation of a malleable 3-substituted oxindole. The reaction is catalyzed by a novel cinchona alkaloid derived phase-transfer catalyst; generating products incorporating a new quaternary carbonaceous stereocenter with excellent levels of enantiopurity. Optimization studies identified the catalyst's urea-based hydrogen bond donating group, a bulky N-benzyl substituent and a C-2-aryl unit installed at the quinoline ring as key units for the facilitation of effective catalysis. The process generates a range of functionalized benzylated and allylated 2-oxindole units equipped with functionality highly amenable to onward manipulation–exemplified by the concise enantioselective synthesis of (−)-debromoflustramine B. Studies to further exploit the synthetic potential of bifunctional phase transfer catalysis are underway.



Scheme 1. Substrate scope: the electrophilic component. [a]Reactions carried out at −70 °C, 168 h.



Scheme 2. Synthesis of (−)-debromoflustramine B (**48**).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkylation · enolates · oxindoles · phase-transfer catalysis · pyrroloindoline

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[17] Likewise, catalysis in the presence of *N*-benzyl cinchonidium bromide provided the product in 34% yield and 19% *ee* after 24 h.

[18] Attempts to execute both these steps in one pot led to consistently lower product yield.

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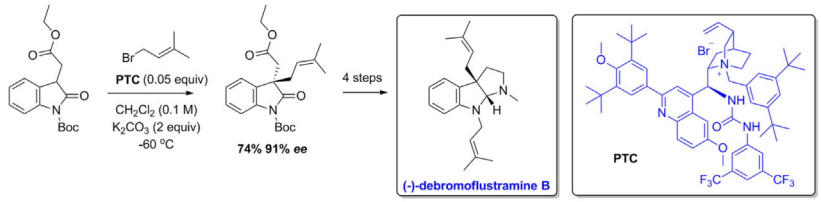

A highly enantioselective alkylation of 3-substituted oxindoles with a broad range of electrophiles was developed using a novel, bulky bifunctional phase transfer catalyst. The methodology was applied to the catalytic asymmetric total synthesis of (−)-debromoflustramine B.

Synthetic Methods

*R. Craig, E. Sorrentino, S. J. Connon**

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Enantioselective Alkylation of 2-Oxindoles Catalyzed by a Bifunctional Phase-Transfer Catalyst: Synthesis of (−)-Debromoflustramine B