Organocatalysis

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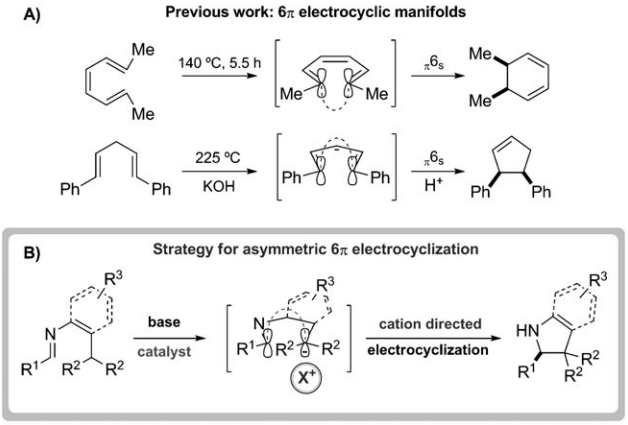
Catalytic Asymmetric 6π Electrocyclization: Enantioselective Synthesis of Functionalized Indolines**

*Eleanor E. Maciver, Sam Thompson, and Martin D. Smith**

Pericyclic reactions are a class of transformations that comprise sigmatropic rearrangements, group transfer reactions, cycloadditions and electrocyclic reactions. Since Woodward and Hoffmann delineated a rationale for the mechanism and stereochemistry of these reactions, they have become powerful synthetic tools.[1–3] Whilst sigmatropic rearrangements and cycloadditions are cornerstones of contemporary synthetic methodology, many electrocyclic reactions are not fully exploited. The high temperatures often required to initiate these transformations, and difficulties associated with assembling polyene precursors, often preclude their use in complex-molecule synthesis. There are no general methods for the asymmetric catalysis of electrocyclic reactions, and as a consequence opportunities for exerting stereocontrol in these manifolds are limited.[4,5] The archetypal 6π electrocyclic reaction—the hexatriene cyclization—proceeds suprafacially, and isoelectronic charged systems such as pentadienyl anion derivatives electrocyclize through the same mode (Scheme 1 A).[6,7]

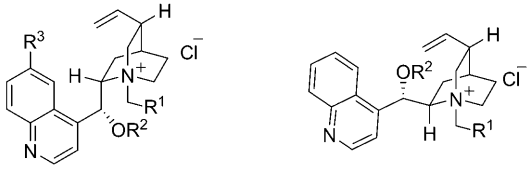


Scheme 1. Strategic approach to asymmetric electrocyclization.

We reasoned that exploring these anionic manifolds could provide an opportunity for exerting stereocontrol in an electrocyclic reaction. Here we describe this approach, and outline a catalytic asymmetric process for the generation of functionalized indolines.[8]

It has been demonstrated that the rates of electrocyclization of both 6π and 8π systems are dependant on the nature of the substituents in and around the extended π-system. Synergistic combinations of electron-withdrawing and donating groups have been demonstrated to significantly lower the barrier to cyclization.[9] Similarly, the presence and positioning of heteroatoms within the π-system is known to have profound effects on the propensity for cyclization.[10] In a series of pioneering investigations by Speckamp et al.[11] and others,[12] the [1,5]-electrocyclic reaction[13] of 2-aza-pentadienyl anions has been demonstrated to be a powerful and efficient process.[14] We rationalized that in order to control the absolute direction of rotation of the orbitals in the ring-closing process (the torquoselectivity),[15] we needed to block one π-face of the delocalized anionic component of the reaction and rely on the stereospecificity of the electrocyclic process to direct the stereochemical outcome (Scheme 1 B). One way to accomplish this would be to exploit tight ion-pairing in an organic solvent, using a chiral counterion to select one of the two faces of a pentadienyl anion or equivalent, and hence influence the enantioselectivity of the cyclization reaction. Asymmetric phase-transfer catalysis[16] relies on the tight-ion pairing principle, and has been demonstrated to be a powerful and practical approach to the generation of enantioenriched materials. As a consequence, we examined a series of cinchona alkaloid-derived quaternary ammonium salts **1**–**6** as chiral counterions for our approach to asymmetric electrocyclization (Scheme 2).[17]

We prepared a series of model benzaldimines **7**–**9** (as precursors to 2-aza-pentadienyl anions) in three efficient steps by using a modified literature procedure (Table 1).[18] In a preliminary reaction, we discovered that treatment of the trifluoromethyl-substituted benzaldimine **7** with 10 mol%



1 R^1 = Ph, R^2 = H, R^3 = H
2 R^1 = anthracenyl, R^2 = H, R^3 = H
3 R^1 = Ph, R^2 = allyl, R^3 = H
4 R^1 = Ph, R^2 = H, R^3 = OMe

5 R^1 = Ph, R^2 = H
6 R^1 = Ph, R^2 = allyl

Scheme 2. Catalysts examined in this study.

[*] E. E. Maciver, Dr. S. Thompson, Dr. M. D. Smith
Chemistry Research Laboratory, University of Oxford
12 Mansfield Road, Oxford OX1 3TA (UK)
E-mail: martin.smith@chem.ox.ac.uk
Homepage: http://msmith.chem.ox.ac.uk

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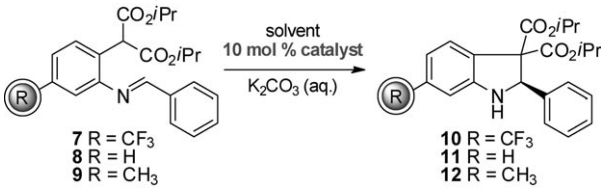
Table 1: Reaction optimization.[a]



R	Solvent	Cat.	*T*	Yield[b]	*ee* [%][c]
3-CF_3	$CHCl_3$/xylene	1	RT	85	(+) 86
3-CF_3	$CHCl_3$/xylene	1	RT	89	(+) 74
3-CF_3	hexane	1	RT	85	(+) 84
3-CF_3	toluene	1	RT	81	(+) 86
3-CF_3	THF	1	RT	81	(+) 80
3-CF_3	DCM	1	RT	88	(+) 76
3-CF_3	toluene	1	0 °C	81	(+) 89
3-CF_3	toluene	1	−15 °C	83	(+) 93
3-CF_3	toluene	1[d]	−15 °C	85	(+) 88
3-CF_3	toluene	1	−15 °C	99	(+) 97[e]
3-CF_3	toluene	2	−15 °C	96	(+) 85[e]
3-CF_3	toluene	3	−15 °C	95	(−) 36[e]
3-CF_3	toluene	4	−15 °C	97	(+) 98[e]
3-CF_3	toluene	5	−15 °C	96	(−) 63[e]
3-CF_3	toluene	6	−15 °C	95	(−) 5[e]
H	$CHCl_3$/xylene	1	−15 °C	70	(+) 93[e]
3-Me	$CHCl_3$/xylene	1	−15 °C	99	(+) 87[e]

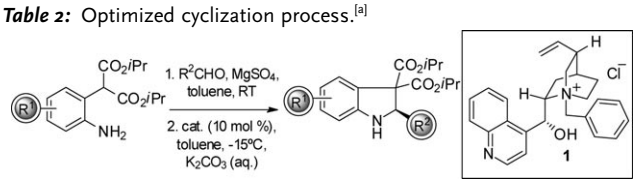
[a] 1 mmol Imine, 0.5 mL solvent, 0.2 mL 33% aq. K_2CO_3, 10 mol% catalyst. [b] Yield of isolated product. [c] *ee* measured by stationary phase chiral HPLC; (−) or (+) refers to the sign of optical rotation. [d] 1 mol% Catalyst. [e] Reaction conducted using imine purified by crystallization.

(8*S*,9*R*)-*N*-benzyl cinchonidinium chloride (**1**) in a biphasic system of aqueous potassium carbonate and xylene/$CHCl_3$ afforded cyclized product **10** in good yield (85%) and a promising *ee* of 86%. We found that yield and enantioselectivity were relatively insensitive to changes in solvent, but that a lower temperature (of −15 °C) gave an increased *ee* of 93%. Lowering the catalyst loading from 10 mol% to 1 mol% led to a reduction in enantioselectivity (to 88% *ee*), and hence we maintained it at the 10 mol% level in all subsequent reactions.

In the course of generating and purifying imine **7** by chromatography, we observed that this material was often contaminated with 2–3% of the racemic electrocyclized material, which could lead to erosion of the enantiomeric excess of the cyclized product. Rigorous purification of imine **7** by crystallization allowed removal of all traces of racemic indoline.[19] Subjecting this material to our optimized conditions afforded **10** in 99% isolated yield and an *ee* of 97–98%, a result we believe is representative of the selectivity of the asymmetric process.

With a practical procedure in hand, we examined the efficacy of cinchona alkaloid-derived ammonium salts **1**–**6** in the cyclization reaction, which demonstrated that cinchonidinium catalysts **1** and **4** were the most effective. Employing best catalyst **1**, excellent results were also achieved with recrystallized imines **8** (R = H, 70% yield, 93% *ee*) and **9** (R = Me, 99% yield, 87% *ee*), which cyclize significantly slower than the trifluoromethyl-substituted system **7**. These results demonstrate that this transformation is tolerant of electronically different groups on the aniline portion of the molecule. Whilst preparation and purification of intermediate imines through crystallization affords the highest yields and enantioselectivities in the subsequent cyclization, this is not always a convenient procedure. As such, we investigated the feasibility of a procedure that avoids purification of the intermediate imine and uses this crude material in the subsequent cyclization step. Treatment of aniline derivatives with a slight excess of aldehyde affords imines in essentially quantitative conversion, and inconsequential amounts of cyclized material. Subjecting these materials to our optimized cyclization conditions afforded indolines in excellent yields and enantioselectivities over the two steps. For compound **10** (Table 2), this leads to material in 87% yield and 94% *ee* over the two steps, which compares well with the result using purified imine.

Table 2: Optimized cyclization process.[a]



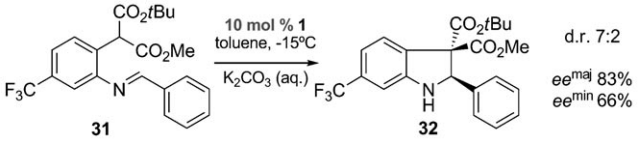
Cmpd.	R^1	R^2	Yield[b]	*ee* [%][c]
10	3-CF_3	Ph	87	94
13	3-CF_3	*m*-ClC_6H_4	84	86
14	3-CF_3	*p*-ClC_6H_4	69	93
15	3-CF_3	*p*-$(NO_2)C_6H_4$	75	98
16	3-CF_3	*m*-$(OMe)C_6H_4$	76	92
17	3-CF_3	*p*-BrC_6H_4	80	93
18	3-CF_3	2-naphthyl	92	92
19	3-CF_3	piperonyl	90	85
20	3-CF_3	*o*-ClC_6H_4	78	91
21	3-CF_3	*o*-$(NO_2)C_6H_4$	89	76
22[d]	H	*p*-BrC_6H_4	70	90
23[d]	H	2-furyl	68	86
24[d]	H	*p*-$(NO_2)C_6H_4$	89	89
25[e]	H	isopropyl	52	73
26[e]	H	cyclohexyl	94	90
27	2-F	*p*-BrC_6H_4	65	91
28	3-F	*p*-BrC_6H_4	67	91
29	3-F	Ph	60	91
30	4-F	*p*-BrC_6H_4	72	89

[a] 1 mmol Imine, 0.5 mL solvent, 0.2 mL 33% aq. K_2CO_3. [b] Yield of isolated product. [c] *ee* measured by stationary phase chiral HPLC. [d] Solvent: toluene/$CHCl_3$, 5:1 (v/v). [e] $CsOH{\cdot}H_2O$, toluene, −55 °C.

This procedure is most effective for substituents in the *para*-position of the aldehyde (**14**, **15**, **17**, **22** and **24**) affording materials in 90–98% *ee*, whilst *meta*-substituted aldehydes form indolines (**13** and **16**) with slightly lower enantioselectivity. *Ortho*-substitution is well tolerated (**20**), though may be sensitive to the size of the substituent in this position (**21**). In general, the procedure is tolerant of both electron-withdrawing and donating groups, with electron-rich aldehydes (**19** and **23**) cyclizing with slightly reduced enantioselectivities in comparison to electron-poor substituents (such as in **15**) that cyclize in up to 98% *ee*. Alkyl imines are also effective substrates, and cyclize in the presence of solid caesium

hydroxide and catalyst **1** at −55 °C to afford cyclohexyl derivative **26** in 90 % *ee* and isopropyl material **25** in 76 % *ee*. These solid–liquid phase transfer conditions were more effective for alkyl imines than the aqueous conditions used for aryl imines. We have also investigated substitution at a range of positions on the aniline ring (**27**–**30**), all of which cyclize effectively with high *ee*. The absolute configuration of *p*-bromo indoline **22** was established by X-ray crystallography. On this basis, we propose that the sense of induction offered by catalyst **1** in the cyclization process is the same for all compounds described in Table 2.

We have also investigated the cyclization of a non-symmetrical malonate derivative to assess diastereoselectivity in the generation of all-carbon quaternary asymmetric centres. The *rac*-malonate imine derivative **31** (used without purification) cyclized under aqueous biphasic conditions at 0 °C to afford **32** in 81 % yield as a 7:2 mixture of diastereoisomers (Scheme 3).

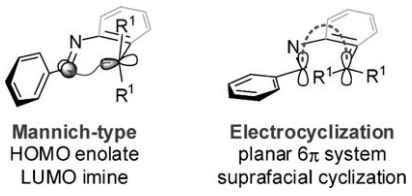


Scheme 3. Diastereo- and enantioselective cyclization. Conditions: 1 mmol imine, 0.5 mL solvent, 0.2 mL 33 % aq. K_2CO_3.

NOE studies confirmed the methyl ester to be *cis* to the arene in the major diastereoisomer, demonstrating that this process is tolerant of sterically different groups at the C-2 position.[19]

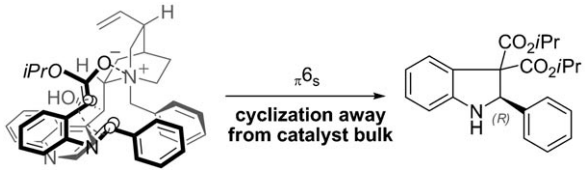
Reversibility studies are consistent with the reaction being under kinetic control over the timescale of the asymmetric transformation.[19] From a mechanistic perspective, there are two viable pathways for the cyclization reaction. An intramolecular Mannich reaction[20] under kinetic control would formally constitute a 5-(*enolexo*)-*endo* trig reaction, which is stereoelectronically demanding as delineated by the Baldwin rules.[21,22] To enable any possibility of orbital overlap between the enolate HOMO and the imine LUMO, the (*E*)-imine and the malonate portion of the system must lie essentially perpendicular to the plane of the arene, but this places the reacting centres somewhat distant (Scheme 4).

To facilitate an asymmetric transformation through this pathway, the catalyst must distinguish between the two prochiral faces of the imine, and it is not clear how this can be easily achieved;[23] tight-ion pairing involving the ammonium cation is generally considered the dominant feature of asymmetric phase-transfer processes. For the electrocyclic process to occur, deprotonation must lead to an essentially planar delocalized 6π anion, which cyclizes suprafacially in accord with the symmetry-related barrier rationalized by the Woodward–Hoffmann rules.



Scheme 4. Mechanistic possibilities for cyclization ($R^1 = CO_2iPr$).

The sense of stereoinduction in the electrocyclic mechanism may be tentatively rationalized using a modification of the tight-ion pair model for asymmetric phase transfer mediated alkylation proposed by Corey.[24] In this model, the enolate oxygen is closely associated with the bridgehead ammonium cation, of which only one face is accessible (Scheme 5).



Scheme 5. Stereochemical model for asymmetric electrocyclization (only one ester group is depicted for clarity).

Non-covalent interactions between the substrate, and both the quinoline and *N*-aryl units offer another binding surface. This effectively blocks one face of the substrate, with the torquoselectivity a consequence of rotation to place the pendant aryl substituent on the indoline away from the steric bulk of the catalyst. *O*-Allylated catalysts **6** and **3** afforded indolines with much lower *ee*, suggesting that the free alcohol plays a role in maintaining high levels of enantioselectivity in the cyclization reaction. Whether this is a steric effect or a result of the specific change in functional group is unclear at present.[25] The two mechanistic possibilities outlined for this transformation cannot be distinguished by the stereochemical outcome of the reaction, as the markers that can betray the stereospecificity of pericyclic transformations are absent in all examples outlined in this study.[19] Similarly, the intimate details of how small variations in catalyst structure affect the sense and effectiveness of asymmetric induction cannot be rationalized at present; studies in this area are ongoing.

In conclusion, we have developed an asymmetric synthesis of functionalized indolines that may constitute one of the few catalytic asymmetric electrocyclic processes yet described. This transformation offers a glimpse of the potential of asymmetric electrocyclic reactions, and we anticipate that this approach can be expanded to encompass other reaction manifolds.

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Keywords: asymmetric catalysis · electrocyclization · organocatalysis · phase transfer · torquoselectivity

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