Catalytic Enantioselective Synthesis of Indanes by a Cation-Directed 5-Endo-Trig Cyclization

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Abstract

5-endo-trig cyclizations are generally considered to be kinetically unfavourable, as described by the Baldwin Rules. Consequently, observation of this mode of reaction under kinetic control is rare; this is usually ascribed to challenges in achieving appropriate approach trajectories for orbital overlap in the transition state. Here we describe a highly enantio- and diastereoselective route to complex indanes bearing all-carbon quaternary stereogenic centres via a 5-endo-trig cyclization catalysed by a chiral ammonium salt. Through computation the preference for the formally disfavoured 5-endo-trig Michael reaction over the formally favoured 5-exo-trig Dieckmann reaction is shown to result from thermodynamic contributions to the innate selectivity of the nucleophilic group, which outweigh the importance of approach trajectory as embodied by the Baldwin rules. Our experimental and theoretical findings demonstrate that geometric and stereoelectronic constraints may not be decisive in the observed outcome of irreversible ring closing reactions.

The indane architecture is a constituent of many natural product families and a key component of clinically relevant entities and biologically active molecules, yet relatively few catalytic enantioselective procedures for its synthesis have been disclosed.^[1-10] Previous synthetic strategies have typically relied on intramolecular 5-exo-trig Michael additions (Figure 1) to generate these carbocycles utilizing chiral imidazolidinones,^[5] cyclic isothioureas,^[6] *N*-heterocyclic carbenes,^[7-9] or proline derivatives.^[10] Thus far, the related 5-endo-trig disconnection has not been explored; this is probably due to the fact it is considered to be a stereoelectronically disfavoured cyclization as described in the Baldwin rules.^[11-14] From a mechanistic perspective, this transformation can also be considered as an anionic 6 π electrocyclization related to the classical pentadienyl anion cyclization.^[15,16]

■ Baldwin's rules for ring-closing reactions

■ Previous work: catalytic asymmetric intramolecular Michael addition

■ This work: catalytic enantioselective cation-directed 5-endo-trig cyclization

The rules proposed by Baldwin allow prediction of the relative facility of ring-closing reactions under kinetic control based upon the ability of the tethered nucleophile and electrophile to achieve the correct trajectory for bond formation. This is a consequence of the geometric constraints of the tethering atoms and the requirement for attack upon the $\pi^*_{C=Y}$ at the Bürgi-Dunitz angle. We reasoned that a catalytic enantioselective route to densely functionalized indanes could be achieved using a chiral counterion to control π -face selectivity in a 5-endo-trig

cyclization reaction. We rationalized that key to achieving this would be the installation of an electron-withdrawing group on the trigonal carbon to stabilize developing charge in the transition state resulting from the ring-forming step. Quenching of this anion with an appropriate electrophile would also give access to all-carbon quaternary stereocentres. Our previous investigations into the counterion-directed cyclization of delocalized anions to form indolines^[17,18] and indolenines^[19] has demonstrated that analogous transformations can proceed with high enantioselectivity.

Results

Synthesis of the requisite cyclization precursors **1-3** was accomplished through a Stille coupling reaction between an *ortho*-substituted arene and vinyl stannane utilizing Pd(PPh₃)₄ or Pd₂dba₃/tri(2-furyl)phosphine with excess CuI in NMP.^[20] Preliminary investigation and optimization of the cyclization centered on three substrates to determine the feasibility of this methodology. In a screen of cyclization conditions, treatment of **1** with 10 mol% of (8*S*, 9*R*)-*N*-benzylcinchonidinium chloride **7** in toluene with either aqueous K₂CO₃ or solid Cs₂CO₃ returned only starting material (Table 1). However, switching to solid CsOH•H₂O was more promising, delivering a 3:1 (*anti*:*syn*) mixture of indanes **4** in 64:36 er (*anti*). Evaluation of alternative *cinchona* alkaloid catalysts bearing an electron-poor CF₃-substituted arene **8** or bulky anthracenyl group **9** demonstrated no improvement in enantioselectivity. Assessment of an architecturally distinct phase-transfer catalyst (*R*)-**10** first described by Lygo^[22] demonstrated a modest improvement in enantioselectivity with a 2-naphthyl substituted substrate **2** cyclizing in 71:29 er. Switching the base to 50% aqueous KOH delivered indane **6** in 86:14 er. Decreasing the polarity of the solvent medium was also advantageous with catalyst (*R*)-**10**. Dibenzazepine-based catalysts were clearly the most selective and hence we examined (*S*)-**11** and (*R,R*)-**12**, pioneered by Maruoka.^[21, 23-25] Utilizing 10 mol% of catalyst (*S*)-**11** with 50% aqueous KOH delivered the requisite indane in 66:34 er. However, using the *N*-spiro C₂-symmetric catalyst (*R,R*)-**12** in toluene at -15 °C with 50% aqueous KOH furnished indane **6** in 96:4 er. Pleasingly, the catalyst loading could be lowered to 2 mol% without significantly impacting the enantioselectivity of the reaction. No further enhancements in the levels of stereocontrol were observed on reduction of the temperature to -30 °C or by lowering the polarity of the solvent medium. We also examined the cyclization of a series of analogues of **1** with different electron-withdrawing groups on the vinyl group. Substrates bearing nitrile, amide, phosphonate and sulfone substituents cyclized in high yield and diastereoselectivity but with significantly poorer er than ester-containing substrates.

Table 1. Optimization of Cyclization Conditions.

1: R² = Ph
2: R² = 2-naphthyl
3: R² = 4-OMe-C₆H₄

4: R² = Ph
5: R² = 2-naphthyl
6: R² = 4-OMe-C₆H₄

Substrate	Cat. (%)	Base	Solvent	dr ^a	er ^b
1	7 (10)	K ₂ CO ₃ (aq.)	tol.	-	-
1	7 (10)	Cs ₂ CO ₃ (s)	tol.	-	-
1	7 (10)	CsOH•H ₂ O (s)	tol.	3 : 1	64 : 36
1	8 (10)	CsOH•H ₂ O (s)	tol.	2 : 1	55 : 45
1	9 (10)	CsOH•H ₂ O (s)	tol.	2 : 1	50 : 50
2	10 (10)	CsOH•H ₂ O (s)	tol.	3 : 1	71 : 29 ^c
3	10 (10)	KOH (aq.)	tol.	2 : 1	86 : 14 ^c
1	10 (10)	KOH (aq.)	tol./hex. ^d	1 : 3	89 : 11 ^c
1	10 (10)	KOH (aq.)	ⁱ Pr ₂ O	1 : 1	90 : 10 ^c
1	10 (10)	CsOH•H ₂ O (s)	tol.	3 : 1	80 : 20 ^c
3	11 (10)	KOH (aq.)	tol.	1 : 4	66 : 34 ^c
3	12 (10)	KOH (aq.)	tol.	1 : 4	96 : 4
3	12 (2)	KOH (aq.)	tol.	1 : 2	97 : 3
1	12 (2)	KOH (aq.)	tol.	1 : 2	96 : 4 ^e
1	12 (2)	KOH (aq.)	tol./hex. ^d	1 : 3	92 : 8

^aDetermined by ¹H NMR analysis of the crude reaction mixture; reported as *anti:syn*; ^ber for major diastereomer given as determined by chiral HPLC analysis. ^cOpposite absolute configuration. ^dSolvent ratio was 1 : 1. ^eReaction conducted at -30 °C.

With optimal phase-transfer conditions in hand, we probed the generality of the cyclization process by generating a small set of tetrasubstituted indanes. All substrates cyclized smoothly in good isolated yields with high levels of enantioselectivity (up to 98:2 er). However, despite the excellent levels of enantiocontrol, no consistent bias was observed for either diastereomer. Using CsOH·H₂O as a base gave predominantly the kinetic *syn*-isomer, whilst using KOH afforded predominantly the thermodynamic *anti*-isomer. Consequently, we rationalized that the poor diastereoselectivity observed could be due to reversible protonation α- to the ester under the basic phase-transfer conditions. We reasoned that trapping this nascent enolate with a suitable electrophile could lead to an irreversible carbon-carbon bond-forming event directed by the adjacent stereocenter. To test this premise, excess benzyl bromide in DMSO was added post-cyclization, affording **13** in 77% yield and 95:5 er, with complete diastereoselectivity (Table 2).

Table 2: Substrate Scope of Enantio- and Diastereoselective Synthesis of Pentasubstituted Indanes

dr determined by ¹H NMR analysis of the crude reaction mixture; er determined by chiral HPLC analysis; yields are for isolated material.
^aReaction solvent was toluene:CHCl₃ (9:1). ^b(*S,S*)-**12** was used as catalyst. ^cNo DMSO was added.

Both the 2-substituent on the indane and the nature of the trapping electrophile (at the 1-position) could be varied significantly without compromising diastereo- or enantioselectivity. *meta*-Chloro or *meta*-methoxy substituted arenes underwent cyclization-alkylation with 2-naphthyl bromide or *para*-bromobenzyl bromide to give indanes **15** and **16** in 96:4 er (66% yield) and 93:7 er (88% yield), respectively. Single crystal X-ray diffraction confirmed the relative configuration of **16** (see supplementary information). Cyclization-1,4-addition with methyl vinyl ketone did not require DMSO as an additive and the resulting indane **17** was obtained in 97:3 er (66% yield) and was shown to have an identical relative configuration to **16** by single crystal X-ray diffraction. Further exploration of the substrate tolerance probed various substituents on the aromatic ring of the indane motif and it was found that a methyl group at the 6-position **18-20** offered a modest increase in enantioselectivity (up to 99:1 er). In contrast, exchanging the methyl group for a methoxy group showed a slight decrease in enantioselectivity (**21**, **22**; 88:12 and 87:13 er respectively). The overall cyclization-alkylation protocol tolerates the introduction of a range of groups at the 1-position of the indane including propargylic **19**, prenyl **20** and allyl **21** substituents, all of which reacted to afford a single diastereoisomer. We noted that the presence of substituents at the 7-position of the indane proved detrimental to the enantioselectivity of the cyclization: a 7-methyl group resulted in near racemic cyclization, affording indane **23** in 52:48 er. Probing this outlying result through introduction of a CF₃ **24**, bromine **25**, or fluorine group **26** also gave similarly poor levels of asymmetric induction, approximately in line with the A-values for these groups. This is likely a consequence of a highly specific catalyst-substrate interaction and we have proposed a model which is consistent with this observation (see Figure 2).

In order to deliver structures with greater synthetic value we sought to introduce increased functional group orthogonality (Table 3).

Table 3. Enantio- and Diastereoselective Synthesis of Orthogonally Functionalized Indanes.

dr determined by ¹H NMR analysis of the crude reaction mixture. er determined by chiral HPLC analysis. Yields are for isolated material.
^aReaction solvent was toluene:CHCl₃ (9:1). ^bⁿBu₄NBr was added instead of DMSO.

Previous work had shown that non-symmetrical malonates were poorly diastereoselective substrates for related cyclizations.^[17] In order to differentiate between the malonate and Michael acceptor functionalities we chose to introduce a *tert*-butyl ester onto the vinyl component of the indane precursor. Cyclization-alkylation afforded benzyl- **27** and **28**, propargyl- **30** or allyl- **32** substituted indanes under optimum conditions with complete diastereoselectivity and up to 95:5 er. The absolute configuration of **28** was confirmed by X-ray crystallography (see supplementary information). Cyclization-1,4-addition with acrylonitrile to afford **29** and **31** was also effective, although this necessitated the presence of ⁿBu₄NBr in the 1,4-addition reaction, presumably as a consequence of the greater steric bulk of the *tert*-butyl ester compared to the isopropyl ester.

To demonstrate the orthogonality of these functional groups, chemoselective derivatizations were implemented (Figure 1). Deprotection of the *tert*-butyl ester in **29** was performed with TFA to afford **33**, whereas a selective reduction of the nitrile was conducted with nickel boride generated *in situ* to give **34**.^[26] Although there are few reports that demonstrate the chemoselective modification of an isopropyl ester in the presence of a *tert*-butyl ester, treatment of **27** with lithium aluminium hydride led to decarboxylation of the diisopropyl malonate group to afford a mixture of diastereoisomers at the 3-position of the indane, presumably *via* a nucleophilic addition-retro-Claisen type process. This intermediate could be alkylated with allyl bromide under phase-transfer conditions to generate indane **35** with three contiguous stereocenters, two of which are all-carbon and quaternary.

Figure 1: Chemoselective Derivatization of Indane Products. (a) orthogonal functional groups permit chemoselective derivatization (b) a reduction-retro-Dieckmann-alkylation process allows for chemo- and stereoselective ester functionalization

An asymmetric 5-*endo-trig* reaction

Following deprotonation adjacent to the malonate, there are two feasible mechanistic extremes: a 6π electrocyclization or an anionic 5-*endo-trig* cyclization (Figure 2). The electrocyclic pathway^[27-30] necessitates that the pentadienyl anion achieve near-planarity in order to maximize orbital overlap with the π -system. Alternatively, this process could involve a stereoelectronically challenging 5-*endo-trig* Michael reaction^[31-38] in which facial selectivity of addition to the α,β -unsaturated ester is directed by the chiral cation.^[39-42] To probe the electronic requirements of this cyclization we examined the reaction of a derivative **36** bearing a single anion-stabilizing group at the benzylic position (Figure 2). Treatment with KOH and tetrabutylammonium bromide in THF, or NaH in THF led to exclusive 5-*exo-trig* cyclization via a Dieckmann-like process to yield **37**. For comparison, we treated **3** under the same conditions and observed exclusive 5-*endo-trig* cyclization to give **6** (d.r. 3:1-5:1, *anti:syn*, Figure 2).

a. Mechanistic extremes: 5-*endo-trig* reaction or 6 π electrocyclization?

b. Different nucleophilic components lead to different chemoselectivity

c. Calculated substrate-catalyst complex and stereochemical model

Figure 2: Mechanistic possibilities and stereochemical model (a) There are two feasible mechanistic extremes for the reaction: an anionic 5-*endo-trig* reaction and a suprafacial 6 π electrocyclization (b) The mode of cyclization is dictated by substitution on the nucleophilic component of the reaction: an ester (as in **36**) leads exclusively to 5-*exo-trig* cyclization whilst a malonate (as in **3**) leads exclusively to 5-*endo-trig* cyclization (c) docking of the transition state for the cyclization reaction with the catalyst indicates that non-covalent interactions including C-H $\cdots$ O hydrogen bonds and C-H $\cdots$ π interactions are responsible for the observed enantioselectivity. This correctly predicts the absolute sense of enantioselectivity observed in the reaction and reproduces the trend in selectivity observed upon aromatic C₆ or C₇ substrate substitution.

We turned to quantum chemical calculations to understand why two anion-stabilizing groups, as exemplified by malonate **3**, are necessary for the formally Baldwin-disfavoured 5-*endo-trig* cyclization to occur. The results of these computations, performed at the CPCM-M06-2X/6-311++G(d,p) level of theory, are shown in Figure 3 and clearly illustrate that the exclusive preference of enolate **38** to undergo 5-*endo-trig* ring closure is kinetically controlled. 5-*endo-trig* TS **2** lies 8.7 kcal mol⁻¹ lower in free energy than 5-*exo-trig* TS **1** and there is no reversibility predicted after cyclization to 5-*endo*-adduct **40** has taken place. What makes the typically disfavoured pathway so facile in this case? The angle of approach to the C=C bond made by the nucleophilic carbon in TS **2** is more acute by 16° than computed for the TS for an intermolecular addition of a malonate anion to an α,β -unsaturated ester, the trajectory evidently affected by the small tether size although still obtuse (see supplementary information). However, the 5-*endo*-adduct provides a much greater thermodynamic driving force than the competing 5-*exo* pathway, which suffers from greater repulsive steric interactions. Analysis of activation barriers in terms of Marcus theory reveals that direct addition to the carbonyl has a smaller *intrinsic barrier*, ΔE_o , in both the intra- and intermolecular reactions, but it is the greater stability of the conjugate adduct that lowers the conjugate addition barrier and dictates regioselectivity.^[43-45] The geometrical constraint imposed upon the 5-*endo-trig* nucleophilic trajectory causes an increase in the intrinsic barrier from inter- to intramolecular reaction, from 12.1 to 17.5 kcal mol⁻¹. Evidently, this effect is outweighed by the comprehensive selectivity of the malonate anion to participate in conjugate addition, resulting in the overwhelming preference for 5-*endo-trig* cyclization. This is inherently a kinetic phenomenon, since ring closure is irreversible, but one whose roots lie in the stability of the 5-*endo*-adduct. We anticipate that the 5-*endo* closure will be observed in other reactions where the functional groups display a similarly strong kinetic preference for intermolecular 1,4-addition (at least by 5.4 kcal mol⁻¹).

Figure 3: Computed Free Energy Profiles for Ring Closure (a) 5-endo-trig cyclization of malonate **38** is kinetically favoured (b) 5-exo-trig cyclization of ester **41** is kinetically favoured. CPCM-M06-2X/6-311++G(d,p) free energies are quoted in kcal mol⁻¹.

Calculations performed for the cyclization of **41** with only a single anion-stabilizing group confirm the opposite selectivity is to be expected: 5-endo-trig closure is kinetically disfavoured relative to the 5-exo-trig closure, consistent with what is observed experimentally (Figure 3). The free energy difference of 9.6 kcal mol⁻¹ between TS **3** and TS **4** is again unequivocal, but now it is the *exo-trig* reaction predicted by Baldwin's rules that is favoured! The thermodynamics of the 5-endo-trig cyclization are unaltered and similarly exergonic for both enolates **38** and **40**, but the activation barrier of TS **4** is prohibitively large. There is only a small variation in the obtuse trajectory of attack^[52] (5-endo; 96.5° for TS **2** vs 92.4° for TS **4**) of either substrate, so what are the origins of the 8.7 kcal mol⁻¹ increase in the 5-endo-trig barrier height? Analysis of the activation barriers through Marcus theory indicate that the intrinsic barrier, ΔE_0 , of TS **4** is greatly increased relative to an intermolecular conjugate addition by more than 12 kcal mol⁻¹. We attribute this to the ground state conformation of **41**, which is planar and benefits from delocalization of the negative charge around the extended π -system, and which must be disrupted by an out-of-plane rotation of both enolate and enoate groups to achieve 5-endo TS **4**. Out-of-plane rotation of the enolate is smaller in TS **3** by 20°, while bond formation is more advanced, favouring the *exo*-pathway. The computed barrier to rotation about the C₃-C₄ single bond is computed to be 13.5 kcal mol⁻¹, close to the increase in intrinsic barrier height. The temporary loss of delocalization in the TS, which is regained in the product, causes a significant rise in the activation barrier. Similarly, the unusual 5-endo-trig preference of enolate **38** result can now be understood in terms of its non-planarity: there is less delocalization to disturb in rotating the anionic group in **38** to achieve the geometry required for cyclization, and the inherent selectivity for conjugate addition prevails.^[46] Computed effects of aromatic substitution on the barrier heights via TS **2** and TS **4** are entirely consistent with this interpretation.

An intramolecular conjugate addition or an electrocyclicization?

Baldwin himself suggested that conventional rules for closure “*may not apply to concerted electrocyclic processes in which geometric changes other than inversions are often observed*”.^[11] What we propose is in fact quite the opposite: it is the absence of electrocyclic character in TS **2** that makes the 5-endo-trig cyclization so facile. The non-planar geometry of TS **2** is quite unlike the planar TS obtained for the disrotatory 6 π -electrocyclic ring closure of the pentadienyl anion, or those characteristic of a *pseudopericyclic* mechanism.^[47] The intrinsic reaction coordinate (IRC) indicates very little rotation of the malonate group and the induced diatropic (aromatic) ring current expected for a pericyclic reaction is absent. A positive NICS(0)_{zz} value of 13.2 ppm is computed at the centre (and is similarly positive 1 Å above/below the plane) of TS **2**, in contrast to a value of -17.3 ppm obtained for the pentadienyl anion electrocyclicization, so TS aromaticity does not contribute towards the observed 5-endo-trig reactivity. Structural and energetic similarities between intra- and intermolecular malonate conjugate addition lead us to the conclusion that TS **2** embodies a 5-endo-trig nucleophilic cyclization. Indeed, such a mechanism was

originally posited by Huisgen for 1,5-electrocyclizations.^[48] In contrast, **TS 4** displays some of the characteristics evident of a electrocyclization: disrotatory closure is apparent along the IRC and the NICS(1)_{ZZ} values either side of the ring plane are negative (ca. -10 ppm). Greater involvement of the π -system in **TS 4** is consistent with a more planar enolate conformation, in which the dihedral angle $\phi_{C=C-C=C}$ is 54°, compared with 89° in **TS 2**.

Caveats to Baldwin's rules have been previously described by Alabugin as resulting from unusual bond lengths, thermodynamic contributions, cationic cyclizations, alkynes and sigmatropic shifts masquerading as *endo*-cyclizations.^[50-52] In contrast, the *5-endo-trig* cyclization of compounds such as **3** is the result of the inherent kinetic regioselectivity of the reacting chemotypes. The sterically enforced non-planar enolate geometry ensures that the adjoining benzene ring serves as a tether for the intramolecular *5-endo-trig* cyclization, without raising the activation barrier through reactant stabilization. These factors outweigh considerations of the trajectory of approach, since this is essentially the same for both types of substrate considered.

A predictive model for stereinduction

Stereinduction due to catalyst (*R,R*)-**12** results from close ion-pairing with **TS 2**. In the most favourable B97D/6-31G(d) optimized geometries obtained for each enantiomeric TS in complex with the catalyst, the substrate is effectively "anchored" by the same three-point interaction.^[53] The most stable TS located leads to the major enantiomer obtained experimentally and is shown in Figure 2. Non-bonding interactions dominated by electrostatics are present between the ammonium α -hydrogen atoms ($q_{NPA} = +0.3e$) and the two negatively charged oxygen atoms ($q_{NPA} = -0.7e$) of the malonate and Michael acceptor groups in the TS. The involvement of a catalytic "oxyanion hole" formed from non-classical C-H $\cdots$ O hydrogen bonds is supported by natural bond orbital (NBO) calculations, which show a cumulative $n_O \rightarrow \sigma^*_{CH}$ delocalization energy of 18.5 kcal mol⁻¹ in the most favourable TS shown in Figure 2. This is consistent with other computational and experimental observations on the importance of C-H $\cdots$ O interactions in ammonium and phosphonium salts.^[54-56] A third interaction point, also largely electrostatic in origin, results from the projection of one of the catalyst's α -hydrogens towards the anionic substrate's benzene ring, lying 2.52 Å above the ring centre giving rise to a cation- π interaction. These calculations correctly predict the absolute sense of enantioselectivity and reproduce the trend in selectivity observed upon aromatic C₆ or C₇ substitution. The dramatic erosion in selectivity observed upon C₇ substitution is also rationalized since the hydrogen at this position is projected into the face of one of the catalyst's naphthyl groups. In accord with experimental observations, a progressively larger substituent at this position (e.g. the series H < F < CF₃) is computed to lead to a more pronounced erosion in enantioselectivity (see supplementary information).

Conclusion

A chiral cation is able to facilitate a highly enantio- and diastereoselective *5-endo-trig* Michael reaction to generate complex indanes bearing all-carbon quaternary stereocentres. The ease with which this kinetically controlled but formally disfavoured reaction occurs led us to apply quantum calculation to probe the mechanism. This demonstrated that geometric/stereoelectronic constraints may not be decisive in the observed outcome of irreversible ring closing reactions, and we anticipate that further study of other kinetically controlled *5-endo-trig* processes^[17] will provide new insight into the factors that control ring closing reactions.

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Authorship

M.D.S. conceived and designed the study; C.P.J. and A.K. performed the synthetic experiments; R.S.P conceived and designed the computational study; T.S., K.E.J. and S.I.O. performed the computational study; M.D.S, C.P.J. and R.S.P. co-wrote the paper.

Additional Information

Supplementary information, details of all computational methods, X-ray data (CIF) for compounds **4**, **16**, **17** and **28** (CCDC numbers 943254, 943256 and 943255 and 1015607 respectively) and chemical compound information are available in the [online version](#) of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to MDS.

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