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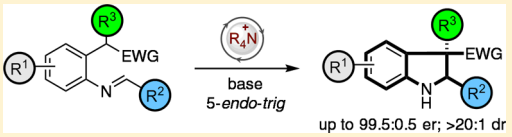
Cation-Controlled Enantioselective and Diastereoselective Synthesis of Indolines: An Autoinductive Phase-Transfer Initiated 5-*endo-trig* Process

Krishna Sharma,[†] Jamie R. Wolstenhulme,[†] Phillip P. Painter,[‡] David Yeo,[†] Francisca Grande-Carmona,[†] Craig P. Johnston,[†] Dean J. Tantillo,*[,‡] and Martin D. Smith*[,†]

[†]Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, United Kingdom
[‡]Department of Chemistry, University of California, Davis, California 95616, United States

Supporting Information

ABSTRACT: A catalytic enantioselective approach to the synthesis of indolines bearing two asymmetric centers, one of which is all-carbon and quaternary, is described. This reaction proceeds with high levels of diastereoselectivity (>20:1) and high levels of enantioselectivity (up to 99.5:0.5 er) in the presence of $CsOH{\cdot}H_2O$ and a quinine-derived ammonium salt. The reaction most likely proceeds via a delocalized 2-aza-pentadienyl anion that cyclizes either by a suprafacial electrocyclic mechanism, or through a kinetically controlled 5-*endo-trig* Mannich process. Density functional theory calculations are used to probe these two mechanistic pathways and lead to the conclusion that a nonpericyclic mechanism is most probable. The base-catalyzed interconversion of diastereoisomeric indolines in the presence of certain quaternary ammonium catalysts is observed; this may be rationalized as a cycloreversion−cyclization process. Mechanistic investigations have demonstrated that the reaction is initiated via a Mąkosza-like interfacial process, and kinetic analysis has shown that the reaction possesses a significant induction period consistent with autoinduction. A zwitterionic quinine-derived entity generated by deprotonation of an ammonium salt with the anionic reaction product is identified as a key catalytic species and the role that protonation plays in the enantioselective process outlined. We also propose that the reaction subsequently occurs entirely within the organic phase. Consequently, the reaction may be better described as a phase-transfer-*initiated* rather than a phase-transfer-*catalyzed* process; this observation may have implications for mechanistic pathways followed by other phase-transfer-mediated reactions.



INTRODUCTION

Asymmetric phase-transfer catalysis is a powerful technique that enables a wide range of transformations under mild conditions, often using inexpensive and environmentally benign reagents.[1] Since its invention, a wide range of asymmetric carbon−carbon bond forming reactions have been disclosed.[2] We have focused on extending the application of phase-transfer catalysis to new reaction manifolds and cascade processes.[3] With this in mind, we conceived an approach to the asymmetric catalysis of electrocyclic reactions based upon using a chiral counterion to achieve π-face selectivity in anionic cyclization manifolds.[4] This ideal led to the development of a method to generate indolines with a single asymmetric center[5] but also posed a series of questions: notably, whether the reaction was likely to be pericyclic, and also whether the transformation was a general process that would permit the synthesis of stereochemically more complex materials.[6,7] Herein we describe an extension of this approach to generate indolines bearing two asymmetric centers, one of which is quaternary and all-carbon and, through density functional theory (DFT) calculations, probe whether or not the reaction is pericyclic (Figure 1).

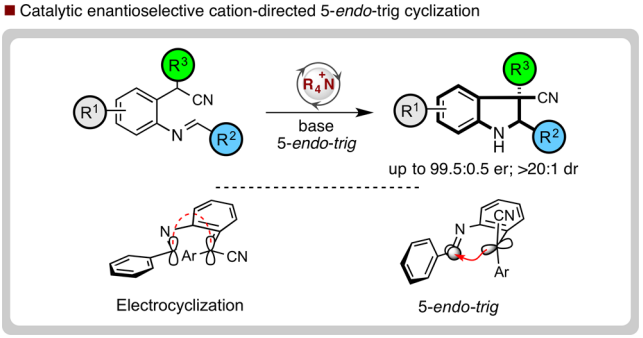


Figure 1. Outline of current study.

RESULTS AND DISCUSSION

A suitable substrate to probe the potential for diastereoselective cyclization was synthesized in three simple and scalable steps (Scheme 1).

Nucleophilic aromatic substitution of *o*-fluoronitrobenzene **1** with isopropyl 2-phenylacetate in the presence of NaH in DMF

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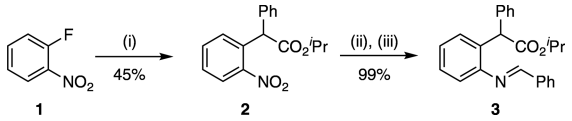
Scheme 1[a]



[a](i) $PhCH_2CO_2{}^iPr$, NaH, DMF, 0 °C to RT, (ii) H_2, Pd/C, MeOH, (iii) $MgSO_4$, PhCHO, toluene, rt.

afforded **2** in 45% yield. Quantitative reduction with hydrogen and palladium on carbon afforded an aniline intermediate, which was treated with benzaldehyde in the presence of magnesium sulfate to afford imine **3** in 99% isolated yield. With this intermediate in hand, we probed its reactivity and selectivity under basic conditions (Table 1). The system was unreactive with potassium carbonate or cesium carbonate in toluene in the presence of tetrabutylammonium chloride (TBAC). In contrast, ester **3** cyclized smoothly in 24 h with potassium *tert*-butoxide in THF, yielding indolines **4** and **5** in a ratio of 2.5:1, respectively (entry 3). We lowered the reaction temperature to 0 °C and after 1 h observed complete consumption of **3** to afford **4** (>20:1 dr, **4**:**5**, entry 4).[8]

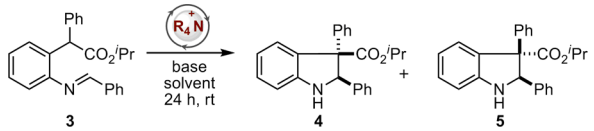
This result was in contrast to the outcome of a similar reaction in the presence of TBAC, which gave complete conversion but with a complete reversal of selectivity, generating indolines **4** and **5** in a ratio of <1:20, respectively (entry 5). This observation indicated the possibility that under certain reaction conditions interconversion of the two isomers was occurring. Broadly similar results were observed with solid KOH[9] in THF (entries 6 and 7), and this demonstrated the potential for a highly diastereoselective cyclization to afford indolines bearing two stereocenters. However, we rationalized that we were unlikely to attain an enantioselective transformation unless a switch to a less polar solvent could be achieved. Gratifyingly, solid KOH in toluene in the presence of TBAC led to 60% conversion and a <1:20 ratio of indolines (**4**:**5**, entry 9). Consequently, we focused on the use of this solvent and base combination to examine the potential for an asymmetric transformation. Using these conditions in the presence of *N*-benzylcinchonidinium chloride (entry 10) gave complete conversion, a 6:1 ratio of diastereoisomers, and high levels of enantioselectivity (96:4 er, major diastereoisomer). Reducing the temperature to −15 °C and a switch to solid $CsOH{\cdot}H_2O$ gave 97:3 er and >20:1 dr (entry 12).

With these optimized conditions in-hand, we examined the reaction of a range of substrates, which cyclized smoothly with good to excellent diastereo- and enantioselectivity. The simple phenyl substrate cyclized at −15 °C to give indoline **4** in >20:1 dr and 97:3 er; selectivity could be augmented by running the reaction at −30 °C (>99:1 er and >20:1 dr) at the expense of conversion (10%). The *para*- and *ortho*-substituted imines were well-tolerated and generally cyclized with excellent enantioselectivity (up to 99:1 er for **12**) and with good diastereoselectivity. Substrates bearing *meta*-substituents on the imine arene underwent cyclization but were not as enantioselective (**10**, 71:29 er, and **11**, 88:12 er).

BENZONITRILE SUBSTRATES

We observed that some ester-containing substrates such as **9** underwent uncontrollable oxidation in the reaction mixture or on standing to generate indoles such as **17** (Table 2). While this undesired reactivity could possibly be controlled through further functionalization, we realized that this significantly compromised the potential utility of these building blocks, and decided that a change of substrate might offer an alternative stability profile. Consequently, we decided to investigate an alternative electron-withdrawing group, and focused on changing the isopropyl ester for a nitrile functional group. These substrates can be made by a strategically similar process outlined previously for the ester substrates (Scheme 2). An S_NAr reaction between a series of substituted fluoronitrobenzenes and phenylacetonitrile was mediated by aqueous NaOH in the presence of stoichiometric tetrabutylammonium hydrogen sulfate.[10] Reduction of the nitro group to the aniline generally occurred smoothly with zinc and ammonium chloride, and condensation with an aldehyde afforded imines **20**; these were often formed and used without formal purification.

Table 1. Exploration of Base-Catalyzed Synthesis of Indolines[a]



entry	solvent	base	catalyst	conversion [%]	dr (**4**:**5**)	er (major)
1	toluene	33% K_2CO_3 (aq)	$Bu_4N^+Cl^-$	none		
2	toluene	Cs_2CO_3	$Bu_4N^+Cl^-$	none		
3	THF	^{t}BuOK	none	>95	2.5:1	
4[b]	THF	^{t}BuOK	none	>95	>20:1	
5	THF	^{t}BuOK	$Bu_4N^+Cl^-$	>95	<1:20	
6[b]	THF	KOH	none	>95	2:1	
7	THF	KOH	$Bu_4N^+Cl^-$	>95	<1:20	
8	toluene	KOH	none	none		
9	toluene	KOH	$Bu_4N^+Cl^-$	60	<1:20	
10[b]	toluene	KOH	*N*-BnCD$^+$Cl$^-$	>95	6:1	96:4
11[b]	toluene	$CsOH{\cdot}H_2O$	*N*-BnCD$^+$Cl$^-$	>95	>20:1	96:4
12[c]	toluene	$CsOH{\cdot}H_2O$	*N*-BnCD$^+$Cl$^-$	>95	>20:1	97:3

[a]Conditions: 10 mol % catalyst, 2 equiv of base. dr established by examination of crude ^{1}H NMR spectra; er established by chiral stationary phase HPLC. [b]Reaction temperature was 0 °C. [c]Reaction temperature was −15 °C. *N*-BnCD$^+$Cl$^-$ = *N*-benzylcinchonidinium chloride **6**.

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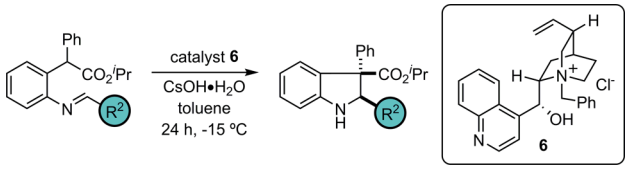
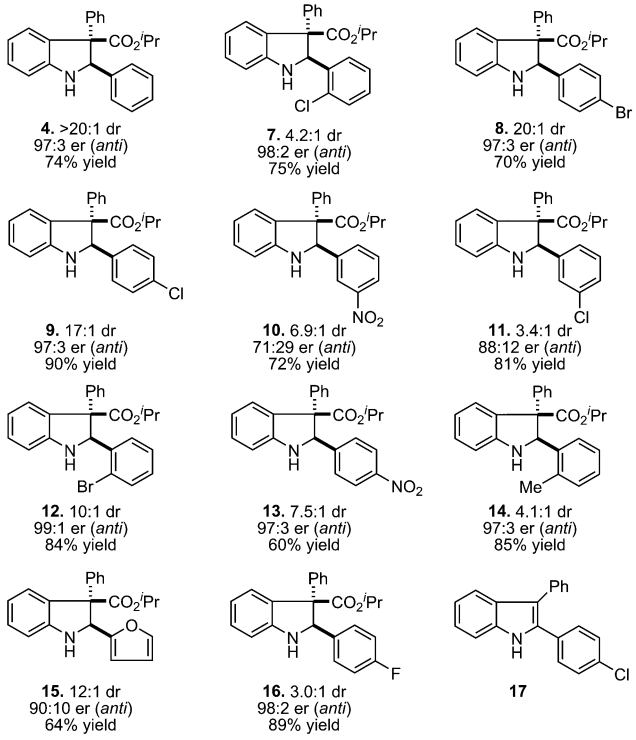
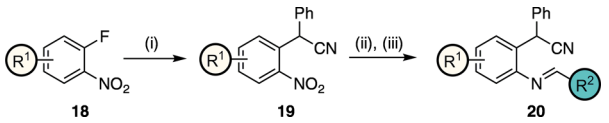
Table 2. Diastereo- and Enantioselective Synthesis of Indolines[a]





[a]Conditions: 50 mg of substrate, 2.5 mL of toluene, 2 equiv of CsOH·H_2O, 10 mol % catalyst. Reaction time: 24 h at −15 °C. dr established by examination of crude ^{1}H NMR spectra; er established by chiral stationary phase HPLC. Yields are for isolated material.

Scheme 2[a]

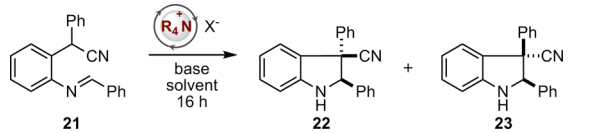


[a](i) $PhCH_2CN$, NaOH, $Bu_4N^+HSO_4^-$, toluene, RT; (ii) Zn, NH_4Cl, acetone/water, RT; (iii) $MgSO_4$, R^2CHO, toluene, RT.

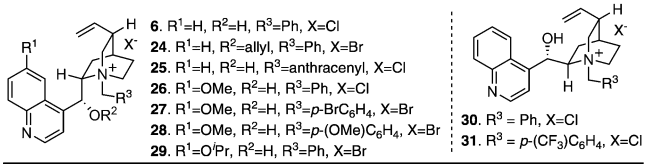
Under conditions that were successful for the previous ester system, the simple substrate **21** underwent smooth cyclization to yield a diastereoisomeric mixture of indolines in moderate er (72:28) and dr (3.6:1, **22**:**23**). Lowering the temperature to −50 °C led to an increase in dr to >20:1, but er and conversion were still disappointingly low (Table 3, entry 2). Consequently, we investigated a range of different base and catalyst combinations, which demonstrated that CsOH·H_2O, which facilitated complete conversion at a lower temperature than KOH, was optimum.

Under these conditions, using *N*-benzyl cinchonidinium chloride as catalyst afforded indolines in a moderately improved dr and er (4:1 dr; 81:19 er, entry 4). Protecting the free hydroxyl group as an allyl ether (catalyst **24**) gave entirely

Table 3. Optimization of Benzonitrile Substrates[a]



Entry	Base	Catalyst	Temp. (°C)	dr (**22**:**23**)	er (major)
1*	KOH	**6**	0	3.6:1	72:28
2*	KOH	**6**	−50	>20:1	78:22
3	CsOH·H_2O	**6**	−50	4:1	74:26
4	CsOH·H_2O	**6**	−30	4:1	81:19
5	CsOH·H_2O	**24**	−30	3:1	50:50
6	CsOH·H_2O	**25**	−30	1:1	56:44
7	CsOH·H_2O	**26**	−30	14:1	89:11
8	CsOH·H_2O	**27**	−30	14:1	89:11
9	CsOH·H_2O	**28**	−30	10:1	85:15
10	CsOH·H_2O	**29**	−30	16:1	90:10
11	CsOH·H_2O	**30**	−30	4:1	20:80
12	CsOH·H_2O	**31**	−30	5:1	25:75
13§	CsOH·H_2O	**26**	−50	>20:1	95:5



[a]Conditions: 0.1 mmol imine, 1.3 mL toluene, 0.2 mmol base, 10 mol % catalyst. Reaction time: 2−48 h. dr established by examination of the crude ^{1}H NMR spectra; er established by chiral stationary phase HPLC. *1 mmol of base used. §5 mol % catalyst used.

racemic material, consistent with previous observations on the importance of Brønsted acidic groups in phase-transfer catalysis.[11] Use of catalyst **25**, which bears an *N*-anthracenyl group, did not lead to a significant improvement in enantio- or diastereoselectivity (1:1 dr; 56:44 er, entry 6). We also examined a series of quininium derivatives; catalyst **26** gave an improved er of 89:11 and dr of 14:1. Varying the nature of the *N*-substituent on the catalyst led to small changes in selectivity (entries 8−10) but no improvements. Pseudoenantiomeric catalysts **30** and **31** led to the predicted reversal of enantioselectivity, but no overall improvement, and these were not pursued further (entries 11 and 12). We focused on **26** as the optimum catalyst for the transformation, and lowering the temperature of the reaction to −50 °C and reducing catalyst loading to 5 mol % improved both diastereo- and enantioselectivity (>20:1 dr; 95:5 er, entry 13). With these optimal conditions in hand, we probed the generality of this transformation (Table 4).

Although intermediate imines could be isolated and purified, in practice we used imines without purification, and hence all yields are quoted over two steps from the corresponding anilines. In all cases the reaction is completely diastereoselective, affording the product in which the C-3 nitrile group is *syn*- to the C-2 substituent on the indoline. Nominally increasing the size of the aryl substituent (to 2-naphthyl **32**) led to a decrease in enantioselectivity (to 90:10 er), although substitution on the 4-position of the parent arene (as in **33**) leads to high er and dr. Electron-rich arenes such as 2-furyl (**34** and **35**) and *para*-methoxyphenyl **36** were well-tolerated, giving selectivities of up to 99:1 er. The relative stereochemistry of

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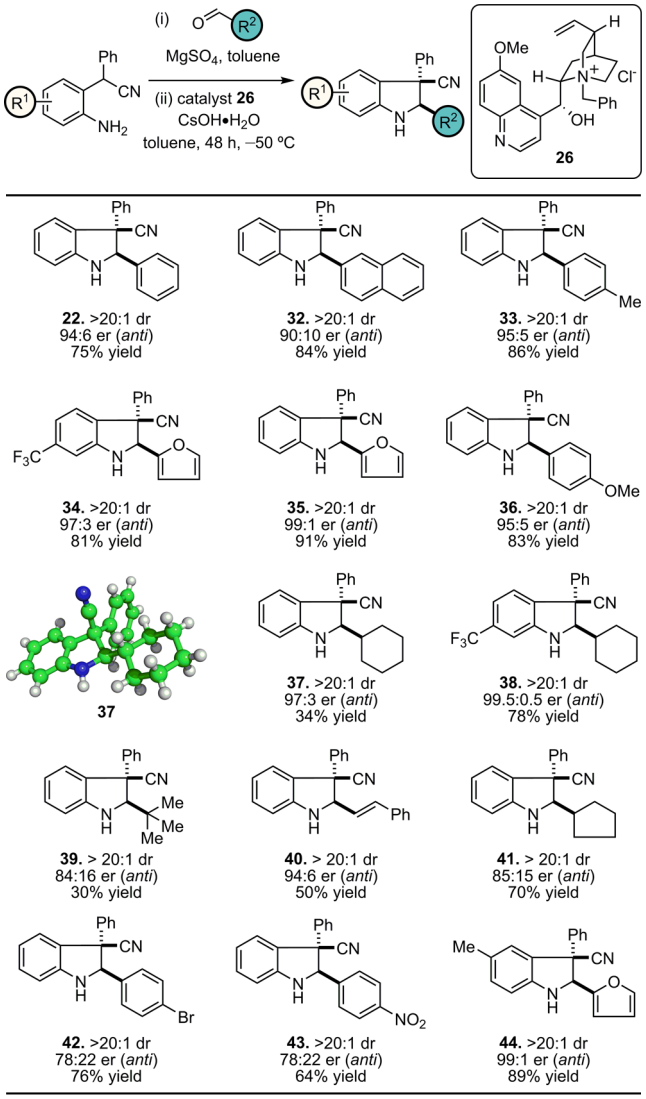
Table 4. Diastereo- and Enantioselective Synthesis of Indolines[a]



[a]Conditions: (i) aniline (1.0 equiv), aldehyde (1.1 equiv), $MgSO_4$ (5 equiv); (ii) 2.0 equiv of $CsOH{\cdot}H_2O$, 5 mol % catalyst; reaction time 48 h at −50 °C. dr established by examination of the crude ^1H NMR spectra; er established by chiral stationary phase HPLC. Yields are for isolated material.

IS DIASTEREOSELECTIVITY A CONSEQUENCE OF REVERSIBILTY UNDER CERTAIN CONDITIONS?

The observation that diastereoselectivity in the reaction of ester **3** varied with reaction temperature suggested to us that equilibration between the two diastereoisomers could be occurring under certain conditions. In order to probe this behavior, we examined the reactions of substrates **3** and **21** in the presence of chiral and achiral phase-transfer catalysts (Figure 2).

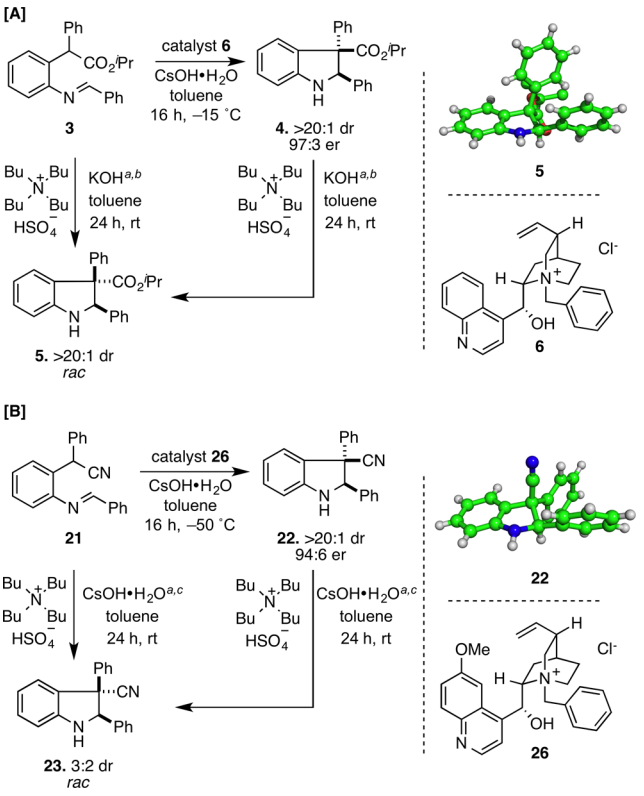


Figure 2. Catalyst dependent diastereoselectivity in ester and nitrile substituted benzhydryl systems. [a]10 mol % catalyst. [b]1 equiv of KOH. [c]1 equiv of $CsOH{\cdot}H_2O$. dr established by examination of the crude ^1H NMR spectra; er established by chiral stationary phase HPLC. The crystal structure data of **5**, **22**, **23**, and **37** have been deposited in the Cambridge Crystallographic Data Center (CCDC 1417302−1417305 respectively).

cyclohexyl substituted indoline **37** was confirmed by X-ray crystallography, illustrating the *syn* nature of the nitrile to the C-2 substituent. Both electron-withdrawing and -donating substituents are tolerated on the indolinyl arene without compromising selectivity; the trifluoromethyl substituted indoline bearing a cyclohexyl group in the 2-position **38** can be generated in 99.5:0.5 er. Alternative alkyl substituents proved to be more challenging, but indolines bearing a *tert*-butyl group (**39**, 84:16 er), an unsaturated side chain (**40**, 94:6 er), or a cyclopentyl group (**41**, 85:15 er) can also be accommodated. In the ester substituted system outlined earlier, electronegative substituents on the imine led to cyclization with very high levels of selectivity; this is in marked contrast to this system where electron-withdrawing groups such as 4-bromo **42** and 4-nitro **43** yield significantly lower levels of enantioselectivity (78:22 er). Alkyl substitution on the indoline (such as in **44**) is permitted without compromising selectivity (99:1 er).

Substrate **3** cyclizes upon treatment with solid KOH in toluene in the presence of tetra-*N*-butylammonium hydrogensulfate (TBAHS) to give indoline **5** in 78% yield as a single diastereoisomer. The stereochemical course of this reaction was probed through X-ray crystallography and NOE experiments, which are consistent with the C-2 arene and the C-3 ester being on opposite sides of the indoline nucleus (Figure 2A). Treatment of substrate **3** with *N*-benzylcinchonidinium chloride in toluene in the presence of $CsOH{\cdot}H_2O$ at −15 °C also led to the generation of a single indoline **4** with very high levels of diastereo- and enantioselectivity. However, NOE analysis demonstrated that this was the *opposite* diastereoisomer to that generated using an achiral phase-transfer catalyst (in which the C-2 arene and the C-3 ester were on the same side of the indoline core). Intriguingly, treatment of this material **4** (at 97:3 er and dr > 20:1) with tetra-*N*-butylammonium hydrogen sulfate and KOH in toluene at room temperature led to smooth

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interconversion to the opposite diastereoisomer **5** (and complete racemization). Similarly, we probed the variation in diastereoselectivity for the nitrile system (Figure 2B). This demonstrated that a single diastereoisomer is generated with the quinine-derived catalyst **26** (at −50 °C), but that a mixture of diastereoisomers (in which the opposite diastereoisomer predominates) is produced in the presence of a simple alkylammonium salt

We believe that this is only consistent with reversible ring closing and ring opening in the presence of TBAHS to ultimately yield the thermodynamically most stable product. It follows that diastereomer **4** is kinetically favored under these reaction conditions, and we propose that the cinchoninium salt leads to kinetic and effectively irreversible cyclization to indoline **4**. To probe this we followed the reaction with TBAHS and KOH by ^{1}H NMR spectroscopy. This confirmed that a low concentration of indoline **4** was present throughout the reaction, before being ultimately converted to indoline **5** over time. This is consistent with the proposed cyclization−cycloreversion mechanism, but does not explain why different diastereoisomers are produced with different catalysts. Differences in reactivity between structurally distinct ammonium salts in base-mediated phase-transfer reactions have been noted previously. In a comprehensive study, Denmark and co-workers demonstrated that ammonium charge accessibility and catalyst cross-sectional area were key factors in catalyst reactivity.[12] To understand the reaction mechanism further we decided to (i) explore the kinetic profile of the reaction of **21** with different phase-transfer catalysts, and (ii) perform quantum chemical calculations to probe reaction mechanisms and the relative thermodynamic stabilities of diastereoisomeric products such as **22** and **23**.

MECHANISM: KINETIC STUDIES

Our initial focus was on following the progress of the reaction with time; we found it to be technically challenging to follow the progress of the reaction under the optimized reactions conditions (at −50 °C), and the reaction is complete in fewer than 5 min at room temperature. Consequently we manipulated the reaction conditions (through dilution and a reduction in the amount of base) to enable the reaction to proceed to complete conversion at room temperature over a period of approximately 1 h (Figure 3).[13] We were able to demonstrate that the reaction proceeds, albeit slowly, in the absence of a phase-transfer catalyst, suggesting that the reaction is likely to be interfacial in nature with deprotonation occurring on the surface boundary between the solid base and toluene solution. The reaction was also mostly invariant with stirring rate until below 200 rpm, when the reaction rate dropped significantly, suggesting that this is when the reaction is intrinsically rate limited by mass transfer.[14] To establish a kinetic profile of the reaction, aliquots were removed from the reaction mixture, filtered through a prepacked pipet containing silica gel, eluted with a hexane/IPA mixture, and directly analyzed by HPLC; this enabled a plot of % conversion to indoline versus time to be produced (Figure 3). The reaction kinetic profile is clearly sigmoidal in shape and possesses a significant induction period that is superficially suggestive of autocatalysis or autoinduction.[15] The observation of autocatalysis in phase-transfer reactions is relatively rare.[16,17]

The order in catalyst was determined through variation of the catalyst concentration and monitoring reaction progress under the conditions above; this showed the order to be 0.56 (R^2 = 0.98). It has been demonstrated by Dolling et al.[18] that

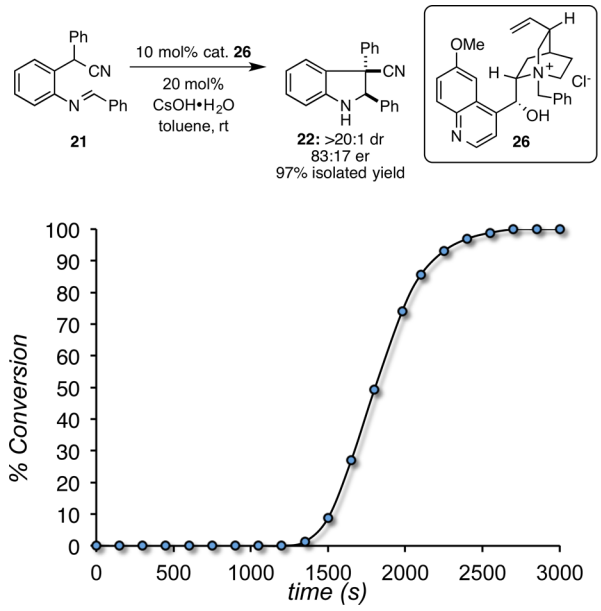
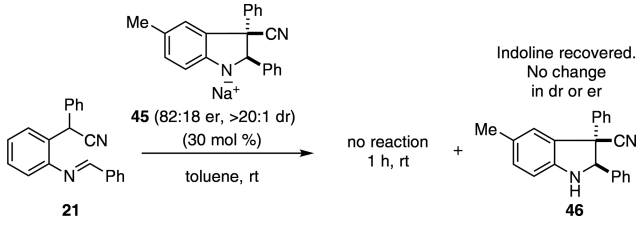


Figure 3. Plot of conversion to product versus time. T_0 corresponds to the time when base was added to the reaction mixture.

catalysts such as **26** exist as monodeprotonated dimeric species under basic reaction conditions. These authors suggested that the dimeric species is significantly more soluble in the organic phase than the monomeric derivative. This is consistent with the catalyst existing in a dimeric form in its resting state prior to rapid and reversible dissociation to an active monomeric form; this also implies that a process other than dimer dissociation is responsible for the induction period.[19] We also examined the reaction in the presence of a C-9 *O*-alkylated catalyst to see whether the presence of a free OH group was a prerequisite for reactivity. This catalyst effected cyclization at a significantly slower rate than catalyst **26**, and both reactions also possessed an induction period.[20] We considered that it was plausible that the product of the cyclization reaction, an indolinyl anion, could be accelerating the reaction through the production of a more organic soluble base. Once generated, this material would possess an appropriate pK_a value to deprotonate the benzhydryl position in **21** and, in concert with the quininium-derived cation, effect asymmetric cyclization. To probe this, we generated the sodium anion of 4-methyl indoline derivative **45** (>20:1 dr, 82:18 er) and added a substoichiometric amount to a solution of imine **21** in toluene at room temperature. Under these conditions we observed essentially no cyclization to product over a 1 h time scale, and 4-methyl indoline **46** was recovered unchanged from the reaction mixture (Scheme 3).

Consequently, we performed a related experiment whereby the 4-methyl indolinyl sodium salt **45** and ammonium salt **26** were premixed and then added to a stirring solution of imine **21**

Scheme 3



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in toluene. We were able to follow the conversion of imine **21** to indoline **22** by sampling rapidly during the first 10 min of the reaction (Figure 4).

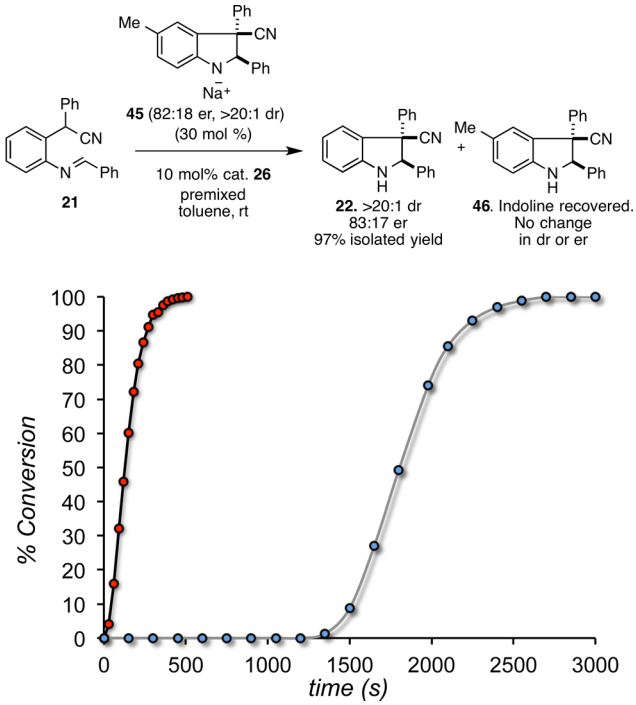
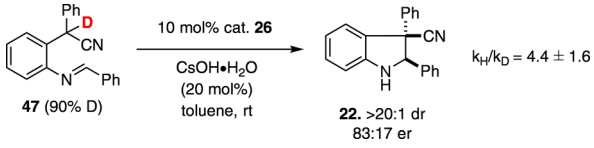


Figure 4. Plot of conversion to product versus time. Red markers indicate reaction progress in the presence of preformed indolinyl anion/ammonium salt mixture. T_0 corresponds to the time when the preformed indolinyl anion/ammonium salt mixture was added to substrate. Blue markers are data from Figure 3 (for comparison).

Under these conditions the kinetic profile of the reaction was significantly different, and there was effectively no induction period. This is suggestive that the reaction proceeds rapidly only when there is sufficient concentration of the indolinyl anion paired with the ammonium counterion in the organic phase.[21] However, this does not inform us whether the role of this anion is to deprotonate the imine substrate **21** prior to cyclization or whether another species is involved in this process. To investigate the deprotonation of imine **21** we prepared the deuterated substrate **47** (90% D)[22] and treated this under the optimized cyclization conditions (Scheme 4). This demonstrated that there is a significant kinetic isotope effect, consistent with deprotonation being the turnover-limiting step in the reaction.[23]

We must reconcile this with (i) the observation that the reaction can reverse under certain conditions, and (ii) the requirement for an effectively irreversible reaction in the presence of catalyst **26**. This suggests that the indolinyl anion

Scheme 4[a]



[a]dr established by examination of the crude ^{1}H NMR spectrum; er established by chiral stationary phase HPLC.

cannot be an autocatalyst as this is incompatible with being involved in both the turnover-limiting deprotonation and a low barrier protonation. Consequently, we proposed the indolinyl anion cyclization product could speed up the reaction by deprotonating **26** to generate a zwitterionic species which could accelerate a kinetically meaningful step in the reaction sequence.[24] To investigate this we treated ammonium salt **26** with a stoichiometric amount of CsOH·H_2O in toluene, and after stirring at rt for (i) 30 min and (ii) 6 h, we added substrate **21** and followed conversion to indoline **22** via HPLC (Figure 5).

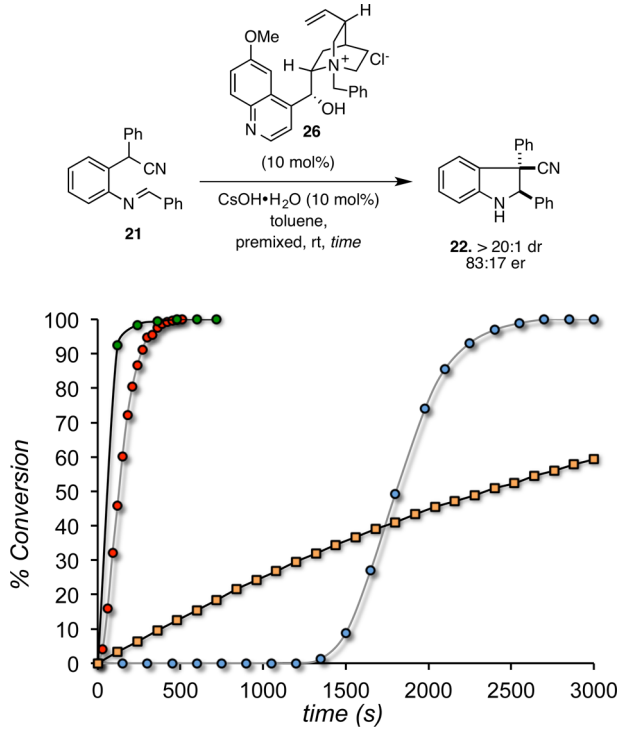


Figure 5. Plot of conversion to product versus time. Green circles indicate reaction progress after 6 h prestirring; orange squares indicate reaction progress after 30 min prestirring. T_0 corresponds to the time when substrate was added to the reaction. Blue and red markers are data from Figures 3 and 4, respectively (for comparison).

Prestirring for 30 min, a period comparable with the observed induction period in Figure 3, led to the conversion plot above (Figure 5, orange squares). This reduced the induction period to essentially zero, but the maximum rate of reaction was significantly slower than that observed in Figure 3. As a result, we prestirred for a longer period of 6 h before adding substrate **21** (green circles). Under these conditions the reaction proceeds rapidly to complete conversion (in under 4 min) with identical enantioselectivity and a maximum rate of reaction comparable to that observed in Figures 3 and 4, but with no induction period. We attribute the lower rate of reaction with a shorter prestirring period to a lower concentration of active catalyst. We thus propose that the overall process can be described by the catalytic cycle below (Figure 6). We suggest that the catalyst resting state is likely to be dimeric by virtue of our observation that its order is 0.56, consistent with the proposal of Dolling.[18] Our observation that prestirring catalyst and base for a time comparable with the induction period does not reproduce the maximal rate is

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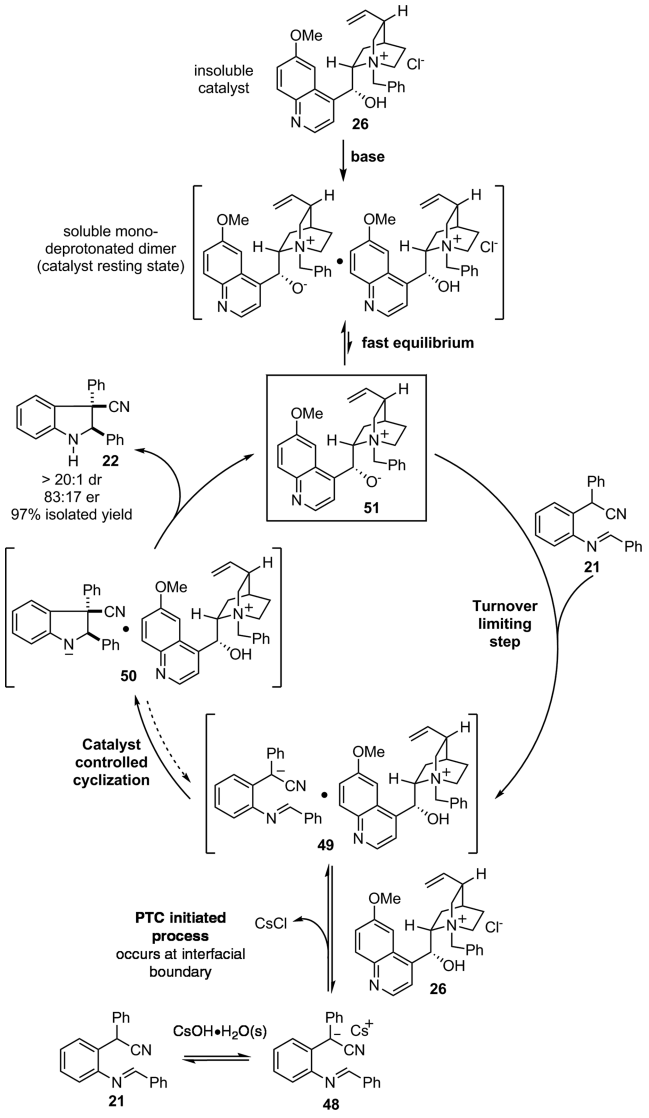

Figure 6. Proposed catalytic cycle (for reaction at RT, 10 mol % catalyst, 20 mol % $CsOH{\cdot}H_2O$).

suggestive that this may not be the only route for the formation of the active catalyst. An alternative route involves initial deprotonation, likely by an interfacial process, of the organic soluble imine **21** by solid cesium hydroxide to form a cesium cyanocarbanion **48**.

This anion is relatively unreactive toward cyclization in the interfacial region until it undergoes ion exchange with the ammonium salt to afford **49**, whereby this substrate·ammonium complex migrates to the organic phase and undergoes cyclization controlled by the chiral cation to generate an enantioenriched indolinyl anion paired with the chiral ammonium salt **50**. This indolinyl anion can then deprotonate the alcohol functional group on the cinchona-derived ammonium salt, leading to the generation of the product **22** and the zwitterion **51**. In order to achieve high levels of enantioselectivity, the presence of a Brønsted acid in the organic phase is essential to facilitate rapid trapping of the indolinyl anion. Zwitterion **51** can then function as a Brønsted base and deprotonate another molecule of imine **21** in the turnover-limiting step leading to **49** and **22** (but this time in the organic phase) and continuing the cycle. The induction period is thus a reflection of the requirement to generate a sufficient concentration of species **51** in the organic phase.[25] Consequently, the reaction can be considered as an interfacial phase-transfer reaction, but this may not be the most accurate description of the overall process. Once initiated, we believe the reaction proceeds entirely in the homogeneous organic phase, with the zwitterion **51** being responsible for turnover. As such, the reaction may be better described as a phase-transfer *initiated* and counterion-directed cyclization than a phase-transfer-catalyzed process. This mechanism could potentially operate in a range of phase-transfer reactions where the pK_a of an anion formed by nucleophilic addition is able to deprotonate a pro-nucleophile and allow the reaction to turn over. This is entirely consistent with the principle of cocatalysis outlined by Mąkosza.[26] On the basis of this model, we can also speculate on how differences in catalyst structure (between simple alkylammonium salts and quinine-derived salts) lead to the observed differences in kinetic and thermodynamic product distribution. In the presence of a catalyst that does not contain an alcohol functional group (such as tetrabutylammonium hydrogen sulfate or *O*-allylated cinchonidinium derivative **24**), we observed that (i) the rate of formation of product **22** is significantly lower, and (ii) the reaction leads to a different diastereoisomeric outcome than when catalyst **26** is used. On the basis of our proposed mechanism (Figure 6) we suggest that the observed difference in diastereoselectivity arises by a process that occurs entirely in the organic phase, and hence, we can neglect ion transport and interfacial processes. This assumes that the ammonium salts are concentrated in the organic phase, and hence solubility and lipophilicity are less important than they are in processes where genuine transfer between phases is a prerequisite for the bulk of the reaction to occur. In the absence of a proton source in toluene, we believe the indolinyl anion could sequester the catalyst and slow turnover. This has been observed in the nitroarylation of acetonitriles, which requires a stoichiometric quantity of phase-transfer agent to proceed to completion.[10] Where formation of a zwitterion is not possible (as with catalyst **24**), the system could be forced into an alternative autocatalytic cycle where the indolinyl anion must deprotonate imine **21** directly; it could be expected that this would be slower than deprotonation of an alcohol, which is reflected in the overall lower rate. This longer-lived indoline anion is then subject to cycloreversion and racemization, consistent with the complete lack of enantioselectivity demonstrated by **24**.[27]

■ MECHANISM: QUANTUM CALCULATIONS

We decided to apply computation to address another key mechanistic issue: are these reactions pericyclic or not? Using DFT calculations[28] we first examined the reaction of a malonate-derived substrate ($R^1 = R^2 = CO_2Me$). The ring-closure can be formulated as either a 6π electrocyclization or a 5-*endo-trig* ring-closure where a malonate anion nucleophile attacks an imine electrophile, analogous to a Mannich reaction.[29]

The imine in the reactant can adopt either an *E*- or *Z*-geometry, and distinct transition state structures for indoline formation were found for both (Figure 7). Although activation barriers for ring-closure from either the *E*- or *Z*-reactant differ by less than 1 kcal mol^{-1}, the transition state structure for reaction of the *E*-imine is 5 kcal mol^{-1} lower than that for reaction of the *Z*-imine, a consequence of the fact that the *E*-reactant is 6 kcal mol^{-1} lower in energy than its *Z*-isomer. In

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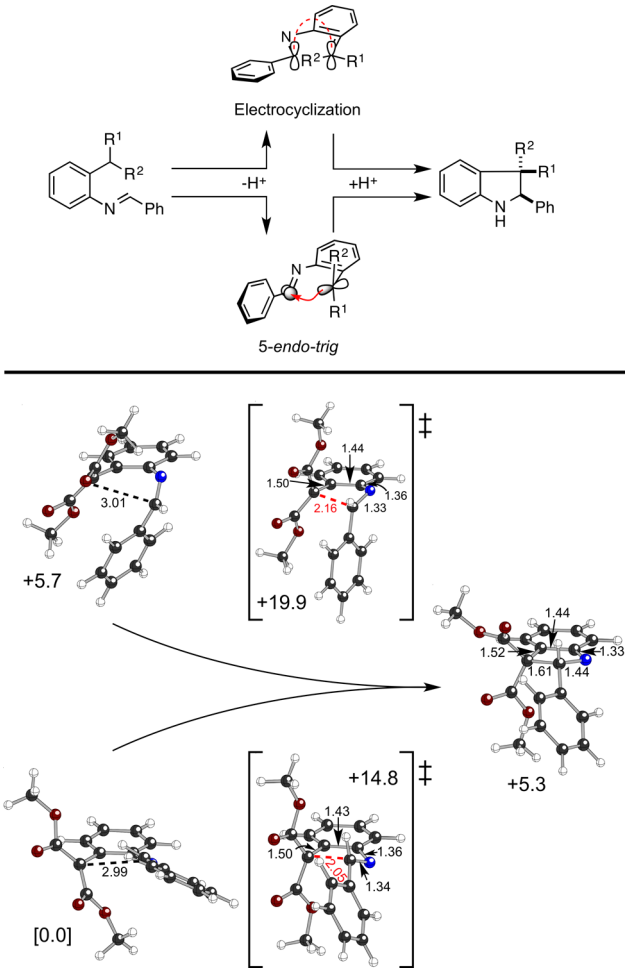

Figure 7. Structures and relative free energies (M06-2X/6-31+G(d,p); selected distances in Å) of stationary points involved in ring-closure of *Z*-imine (top) and *E*-imine (bottom).

both cases, visual inspection of the transition state structure geometries does not readily reveal if they are best described as pericyclic, so NICS (nucleus independent chemical shift) calculations[30] were used to probe aromaticity changes along the associated reaction coordinates.[31] Points at both the center of the benzene ring and the center of the forming 5-membered ring were examined (blue spheres in Figure 8). On the basis of the NICS criteria, the arene in both systems becomes less aromatic as cyclization occurs. This indicates significant delocalization of the product anion into the benzene ring, which disrupts aromaticity, but not reactant anion delocalization, consistent with the twisting of reactant geometries to avoid steric clashes.

NICS values for the forming ring indicate a decrease of aromaticity throughout the reaction for the *E*-reactant (following a region where there is little variation in NICS value), but an increase and then decrease of aromaticity (i.e., a decrease then increase in NICS value) along the reaction coordinate for the *Z*-isomer. The former is consistent with a Mannich-type process, but the latter is what one would expect for a pericyclic reaction where aromaticity is maximal near the delocalized transition state structure.[32] The malonate group in the transition state structure for cyclization of the *Z*-reactant is also twisted into a geometry expected for disrotation, while that for cyclization of the *E*-reactant is essentially perpendicular to the benzene π-system, thereby shutting down the delocalization expected for a pericyclic reaction. These results are consistent with the *E*-isomer reacting via the Mannich-type pathway and the *Z*-isomer reacting via a pericyclic-like reaction.[33] The lack of cyclic delocalization during cyclization for the former is connected to the *E*-imine geometry, which alters the position of the imine substituent, providing a better geometry for π-stacking in the transition state structure; this, however, appears to come at the cost of reducing conjugation.[34] Experimentally, the cyclization almost certainly involves closure of *E*-imines.[35] We subsequently examined the cyclization of anions **52** and **57** (derived from **21** and **3**, respectively) in an attempt to understand why we observe interconversion between different diastereoisomers (Figure 9). Starting with cyanocarbanion **52** (Figure 9A), we identified transition state structures for the cyclization to indolinyl anions **53** and **54**. The transition state structure (TS2) for cyclization to **54** is 2.1 kcal mol^{-1} lower than that for formation of **53** (TS 1): a consequence of the fact that minimum **56** is lower in energy than **55**. A similar picture emerges for the cyclization of ester enolate **57**, and in both cases, transition state structures with both phenyl groups near each other are predicted to be lower in energy than those with distal phenyl groups. The proximity of the aryl groups in the

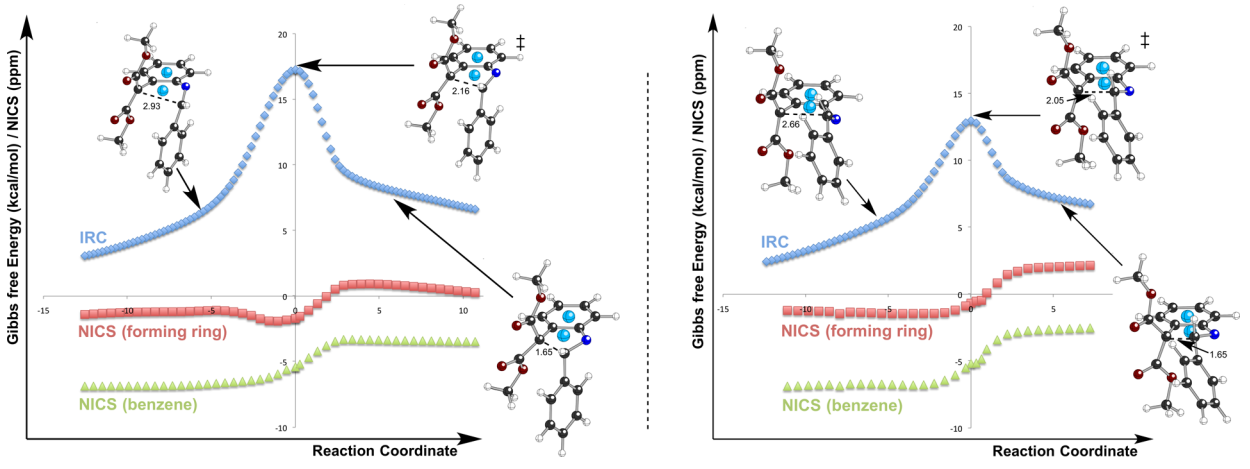

Figure 8. Intrinsic reaction coordinate (blue) and NICS values (red and green; blue spheres on structures indicate points at which NICS values were calculated) for ring-closure of *Z*-(left) and *E*-(right) imines; M06-2X/6-31+G(d,p) (forming C−C bond distances in Å).

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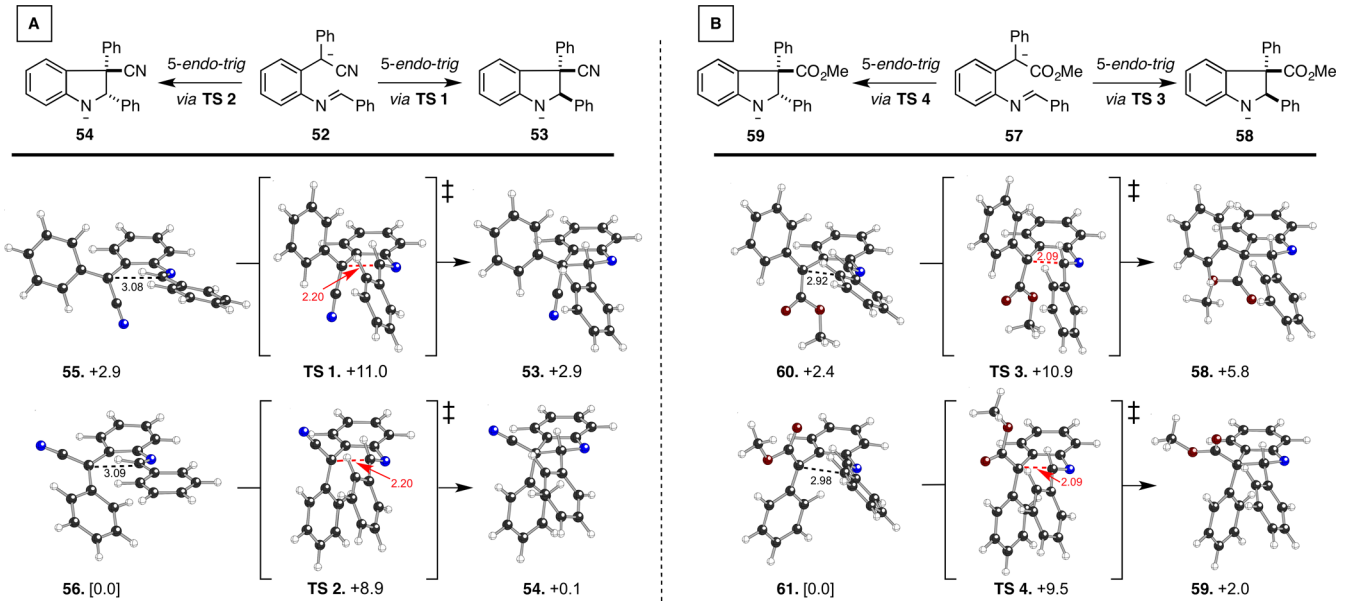

Figure 9. Structures and relative free energies (M06-2X/6-31+G(d,p); distances in Å) of stationary points involved in ring-closure of (A) conformers **55** and **56** of anion **52** (from **21**) and (B) conformers **60** and **61** of anion **57** (derived from methyl ester derivative of **3**).

lower energy transition state structure is consistent with π-stacking playing an important role in diastereoselection. These results are consistent with the experimental observations for reactions in the presence of achiral phase-transfer catalysts, and may also reflect the ability of chiral catalysts such as **26** to overwhelm the inherent stereochemical preference of the cyclization.

We have recently described a 5-*endo-trig* cyclization to form indanes[6] that has some similarities with this reaction. Although in this case there is no obvious alternative (5-*exo-trig*) pathway, the ease with which this nominally disfavored cyclization occurs under kinetic control is noteworthy. Calculations performed for the cyclization of cyanocarbanion **52** demonstrate that, in the minimum, the cyano group and both arenes do not lie in a plane, so this anion is not delocalized into the nitrogen substituted arene. The transition states for the formation of diastereoisomers **53** and **54** have angles of attack onto the imine of 96° (TS 1) and 98° (TS 2), respectively. These are significantly smaller than the Bürgi–Dunitz angle and are consistent with previous observations that approach trajectory may not be decisive in irreversible ring closing reactions.[6]

In all cases, these reactions are predicted to be close to thermoneutral or are slightly endergonic, which is consistent with the ease with which the process reverses under certain conditions. This is also consistent with the observation that high enantioselectivity requires a catalyst bearing an alcohol to facilitate a low barrier and essentially irreversible protonation event to drive the reaction forward.

CONCLUSIONS

We have demonstrated an approach to the diastereo- and enantioselective synthesis of indolines bearing two stereocenters via a Mannich-like 5-*endo-trig* process. Kinetic analysis has shown that this is an autoinductive process that is merely *initiated* by phase-transfer catalysis, rather than a true phase-transfer process. Once sufficient concentration of the reactive catalyst—a quinine-derived zwitterion—is produced, the reaction occurs entirely within the organic liquid phase. The enantioselective reaction is facilitated by a protonation event that necessitates the presence of an alcohol; catalysts not bearing this functional group are kinetically less proficient and nonselective. These observations may have implications for the mechanisms of other phase-transfer-mediated reactions and the design of new phase-transfer catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08834.

Full synthetic details, ^{1}H and ^{13}C NMR spectra, and additional details on computations (PDF)
Data used to generate figures (XLSX)
Crystallographic data (CIF)

AUTHOR INFORMATION

Corresponding Authors

*djtantillo@ucdavis.edu
*martin.smith@chem.ox.ac.uk

Notes

The authors declare no competing financial interest.

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(8) This transformation is sensitive to the quality of the potassium *tert*-butoxide employed; newly sublimed and anhydrous material is optimal.

(9) Both KOH and $CsOH{\cdot}H_2O$ are deliquescent solids, and it is challenging to ascertain the amount of adventitious water that these materials absorb from the air. We did not take special precautions (such as a glovebox) to exclude moisture during weighing of these materials for reaction.

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(13) We make the assumption that the reaction mechanism under these modified conditions does not change from that operating under the optimized conditions.

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(33) The IUPAC definition of an electrocyclization is "a molecular rearrangement that involves the formation of a σ-bond between the termini of a fully conjugated linear π-electron system and a decrease by one in the number of π-bonds". Although this definition is consistent with the transformation of **21** to **22**, the lack of both aromaticity and disrotation in the transition structure are key features that indicate the reaction is better described as nonpericyclic.

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