Downstream Paradigm in Enamine Catalysis: Comment on "On Stereocontrol in Organocatalytic α-Chlorinations of Aldehydes"

Ponath et al., (https://doi.org/10.26434/chemrxiv.14229875.v1)

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Introduction

A recent manuscript deposited on *ChemRxiv* entitled "On Stereocontrol in Organocatalytic α-Chlorinations of Aldehydes" (https://doi.org/10.26434/chemrxiv.14229875.v1)[1] by Ponath et al. states that the work is a "comprehensive analysis of the organocatalytic α-chlorination of aldehydes with *N*-chloroimides and different catalysts" aimed at resolving different mechanistic interpretations in the literature. Because this manuscript directly challenges a body of work published by us between 2011-2016 (Burés et al.),[2] we feel it is both appropriate and exigent for us to comment as well as contribute to this discourse with further results from our work. For proper context, we first disclose the background to this mechanistic discussion. The current *ChemRxiv* contribution of Ref. 1 follows on from a previous paper published in *Angew. Chemie* in 2018[3] by one of the senior authors (Christmann). Studying the same imidazolidinone catalyst systems as the current *ChemRxiv* contribution, Christmann and coworkers disputed our proposal of a "downstream intermediate" paradigm for stereocontrol in reactions using diarylprolinol ether catalysts. Figure 1 below left (redrawn from Figure 7, Ref. 3) shows the network that Christmann and coworkers incorrectly attributed to us, with what they termed a "secondary stereodetermining catalytic cycle" containing the aminal **B**.

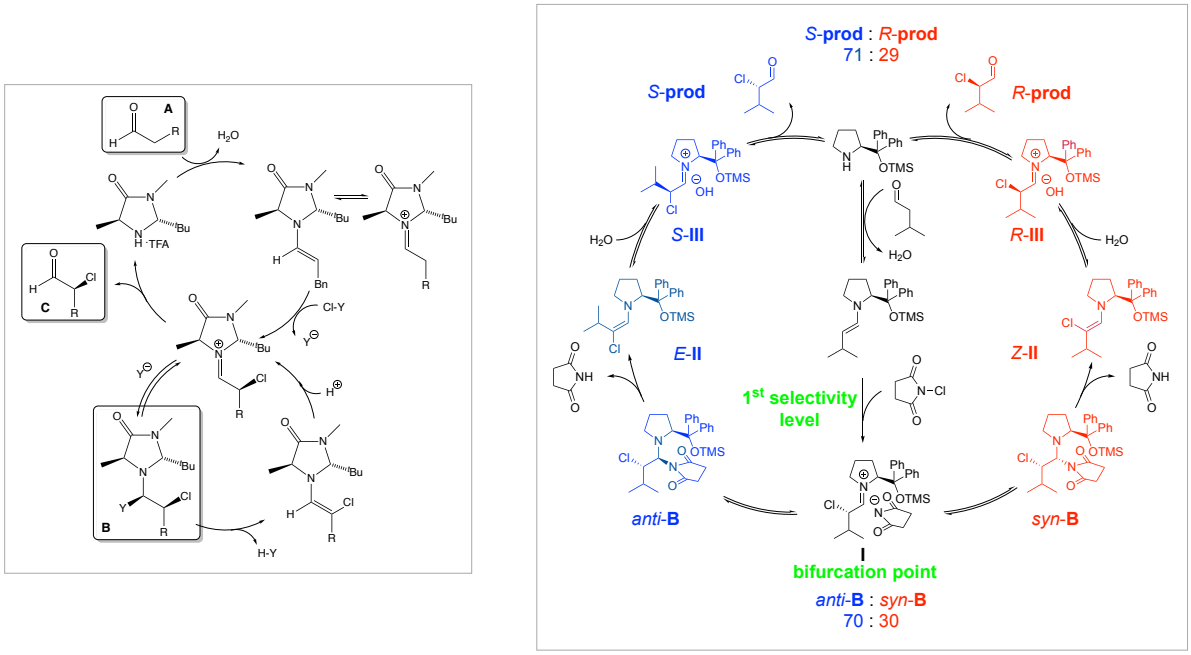
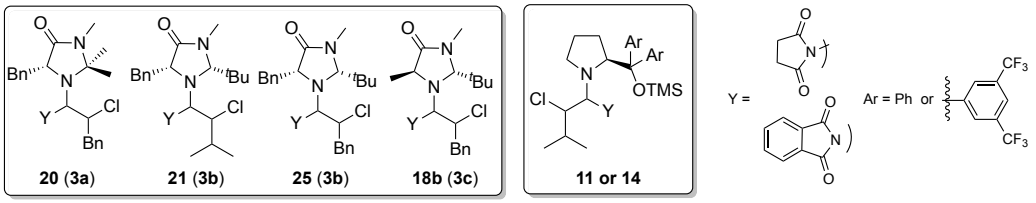


Figure 1. Left: Catalytic cycle wrongly attributed to Burés et al.,[2] redrawn from Figure 7 in the earlier *Angew. Chemie* paper by Ponath et al., Ref. 3; Right: Catalytic cycle correctly attributed to Burés et al.[2] in the current *ChemRxiv* paper of Ref. 1, redrawn here showing the catalyst and chlorinating agent structures that were missing from the scheme given in Ref. 1.

Here we state categorically that Burés et al. never proposed a mechanism such as that shown in Figure 1 (left), which is a stark misrepresentation of the cycle that was proposed by us. In

addition, the kinetic modeling carried out by Christmann and coworkers based on their erroneous interpretation in fact violates the principle of microscopic reversibility.[4] This invalidates the conclusions drawn about our model from their kinetic analysis in Ref. 3. Figure 1, right, shows the network that Ponath et al. now correctly attribute to Burés et al. in the current *ChemRxiv* contribution, in which they make no mention that this scheme clearly departs in critical ways from what they published previously as our mechanism.

The authors revisit the topic of our mechanistic model in their current *ChemRxiv* contribution, seeking to replace their faulty kinetic analysis with other evidence that will allow them to sustain the conclusions of their former work. Ref. 1 relies less on kinetics and includes NMR spectroscopic results and calculations, mass spectroscopic results, and DFT calculations. Most of the *ChemRxiv* contribution of Ref. 1 is devoted to the MacMillan imidazolidinone catalyst systems – which were not studied in detail by Burés et al – and touches more briefly on the diarylprolinol ether systems that were the principal focus of our work.[2] Our discussion will comment on these investigations together with presentation of kinetic modeling results of our own in order to evaluate these mechanistic proposals. The focus of the debate is the identity and role of aminal intermediates such as those shown below (compound numbering from Ref. 1, number for imidazolidinone catalyst of origin in parentheses) that have been observed by Burés et al.[2c] and by the authors of Refs. 1 and 3. Are the aminals *syn* or are they *anti*, or are both observed? Do they lie on the catalytic cycle, as we suggest, or are they off-cycle species, as proposed by Refs. 1 and 3?



Imidazolidinone Catalyst Systems

DFT Studies. Ref. 1 presents DFT calculations of the chlorination of phenylpropionaldehyde **16** with NCS **6** using the MacMillan imidazolidinone catalyst **3c**.TFA (compound numbers from Ref. 1). The reaction coordinate from their Figures 3 and 4 is reproduced here in Figure 2, with what they propose as the productive pathway given in black and the pathway forming aminal intermediates in blue and magenta. These authors use this diagram in support of their thesis that the aminal intermediates **18b** are parasitic off-cycle species.

Concerns may be raised about the relevance of the DFT calculations in Ref. 1 that use computed barriers for "equimolar" reaction steps to make conclusions about the kinetics of catalytic reactions where the concentrations of various species differ widely and vary with time.[5] An additional issue lies in the way that the free energy profiles in Ref. 1 have been constructed by adding the free energies of individual species that were not present in the calculations. All along the reaction coordinate, the quoted relative energies are the sum of the components of neutral catalyst **3c**, TFA, and substrates **6** and **16**. This is likely to lead to significant errors, particularly where the added components are capable of explicit interactions with the other species. For example, a water molecule is included explicitly for **Int 2, TS3**, and **Int4a**, but not for **Int3**, **TS4**, or **Int4**. For **Int4**, the relative free energy value of -25.1 kcal/mol is obtained by simply adding the free energy of H_2O to the free energy of the calculated species (chloroiminium trifluoroacetate *and succinimide*). For **Int4a**, the free energy of succinimide is added to the calculated species (chloroiminium trifluoroacetate *and H_2O*) to give -29.3 kcal/mol. Thus, the difference in energy

between **Int4** and **Int4a** illustrates the sizeable discrepancies (4.2 kcal/mol in this case) that can arise when explicit interactions are ignored.

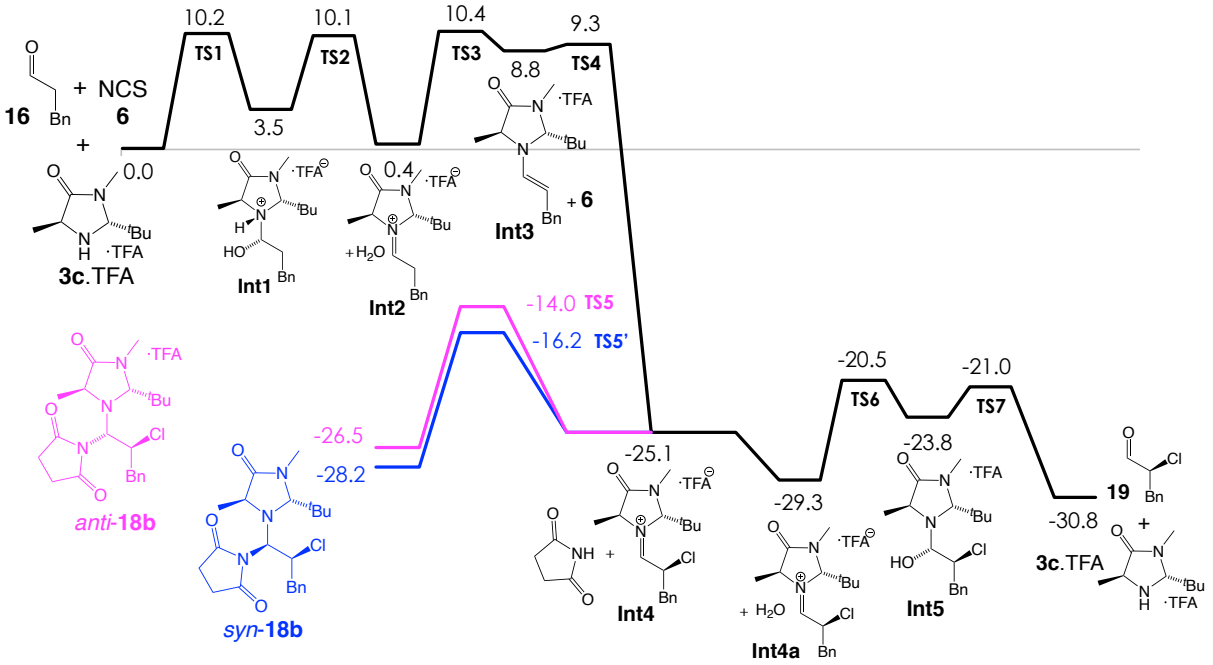


Figure 2. Reaction pathway redrawn from Ref. 1 from their DFT calculations of the chlorination of phenylacetaldehyde **16** with NCS **6** using the imidazolidinone catalyst **3c.**TFA (combining Figures 3 and 4 of Ref. 1). Black line: productive pathway; Blue line: off-cycle aminal species *syn*-**18b**. Magenta line: off-cycle aminal species *anti*-**18b**. Intermediate species free energies and transition state energies in kcal/mol.

The energy profiles in Figure 2 place the *syn* and *anti* aminals **18b** at slightly higher energy than the chloroiminium (1.1 and 2.8 kcal/mol, respectively, relative to **Int4a**) and to have barriers of formation significantly higher than the barrier for iminium hydrolysis (15.3 and 13.1 vs. 8.8 kcal/mol, relative to **Int4a**). These calculations run counter to the fact that aminals, and not chloroiminiums, are the experimentally observed intermediates in all the work under discussion.[1-3] In addition, neither Ref. 1 nor the earlier study of this system in Ref. 3 reports experimental kinetic studies to determine reaction orders in substrate concentrations, which could directly support or challenge the findings from the DFT calculations. Ultimately, in determining whether calculations provide a useful or realistic model, the question must be whether they fit with experimental observations.

The on-cycle model of Burés et al. (Figure 1, right, and Figure 3) was based on a battery of experimental kinetic and spectroscopic data in several reactions catalyzed by diarylprolinol ethers.[2h] In the α-chlorination of aldehydes, we characterized two aminal species[2c] through a suite of 2D NMR techniques that defined the connectivity of Cl and Y but could not assign the relative stereochemistry; however, it was observed that the ratio of the two species matched the observed product e.r. in every example. In developing a rationale for how these species might lead directly to product, we suggested that if an *anti* aminal is the major species, an antiperiplanar elimination would lead to the *E*-chloroenamine and then on through a stereospecific enamine protonation to the major *S*-product (Figure 3). Such a pathway was supported by our observation of the proposed product enamines in the related selenylation reaction in CD_2Cl_2 (X = SePh, Y = phthalimide),[2g] where we found that their relative rate of hydrolysis correlated well with product e.r.[6]

It is important to note, as shown in Figure 3, that the key points of the on-cycle model would still hold if the major species were a *syn*-aminal rather than an anti-aminal, and a *syn*-elimination process took place. One could imagine a *syn*-elimination in which deprotonation of the developing chloroiminium ion by the departing succinimide is rapid compared to bond rotation (particularly if that group is not protonated), giving the *E*-chloroenamine from the *syn*-aminal and the *Z*-chloroenamine from the *anti*-aminal. Such a scenario provides the opposite fate for the two aminal species compared to *anti*-elimination. This *syn*-elimination mechanism was in fact proposed by us in Ref. 2g as an alternate rationalization of our observations.[7] As shown in Figure 3, both *syn*- and *anti*-eliminations remain viable scenarios that support the correlation between d.r. values of the observed aminals or product enamines and reaction product e.r. In addition, in the selenylation reaction, the observed differences in the relative concentration and reactivity of *E*- and *Z*-product enamines in different solvents successfully accounts for the unusual solvent-induced reversal in product stereochemistry that is difficult to explain by the shielding model alone.[2g,6]

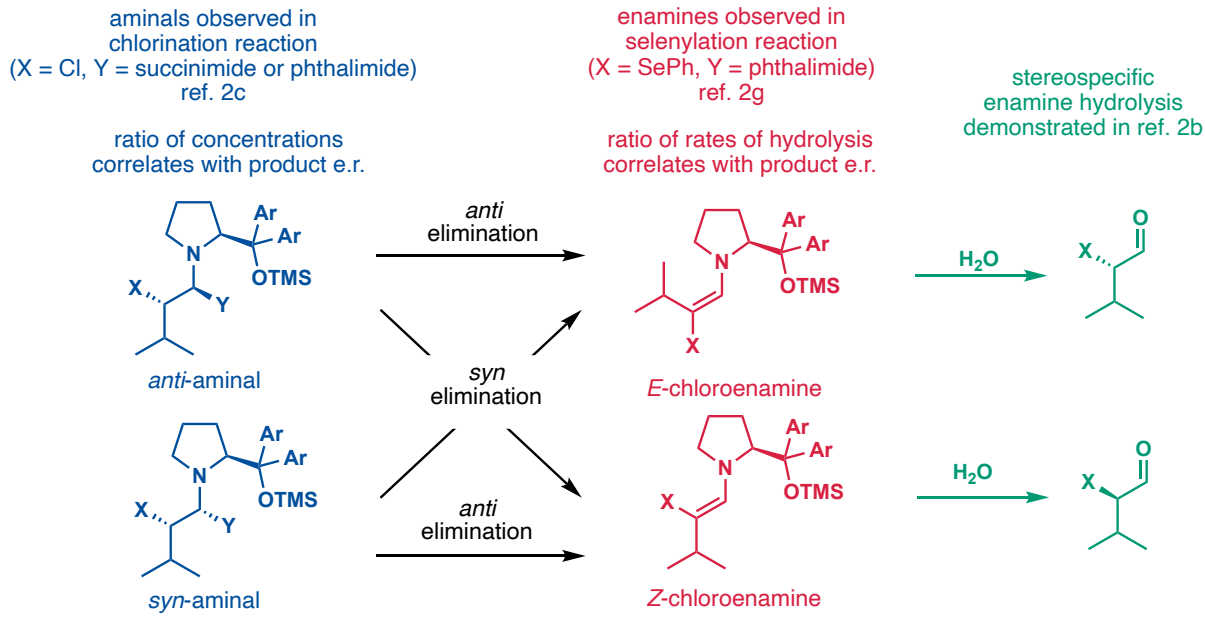


Figure 3. Proposed mechanistic relationships between observed downstream intermediates and product enantiomers observed by Burés et al. in chlorination and selenylation reactions.

The authors of Ref. 1 show that, in the case of imidazolidinone catalyst **3a** in the α-chlorination reaction, the major aminal species **20** is in fact *syn*. Contrary to the scenario presented above and in our previous work,[2g,7] they suggest that this finding precludes our on-cycle model. They do not report a computational search for the concerted *syn*-elimination process discussed above; they do calculate a stepwise E1 process for aminal **18b** formed with catalyst **3c** (a process that is indeed *syn*-overall and converts the *syn*-aminal to an *E*-enamine) with a barrier of 28.2 kcal/mol. Even if this is the lowest energy elimination pathway, it is possible to argue that its barrier would be expected to be lower if the catalyst were changed from the imidazolidinones to diarylprolinol ethers. In TS-E1 shown in Figure 4a of Ref. 1, there is a developing interaction between the Bn group and the *t*Bu group of the catalyst **3c**, which will contribute to the barrier. In this catalyst class, a similar interaction with a catalyst substituent (Me) would be present starting from the other enamine rotamer, because of the "C2" nature of the catalyst. On the other hand, for the diarylprolinol ether catalysts, the s-*trans* enamine rotamer would not suffer from this clash, and the elimination barrier might be expected to be significantly lower.

The next step towards the product in the on-cycle mechanism is the stereospecific protonation of the product enamines. The authors of Ref. 1 state that this stereospecific protonation "was not further detailed" by Burés et al. in Ref. 2c. It should be noted, however, that stereospecific enamine reactions were indeed demonstrated by us in Ref. 2c using EXSY-NMR experiments,[8] and kinetic stereospecificity between aldehyde and enamine stereoisomers with pyrrolidine-based catalysts was the subject of Ref. 2b, which is not cited in Ref. 1.

Kinetics. The authors of Ref. 1 venture tentatively back to kinetic analysis to argue against the case for aminal species to be present on-cycle. Monitoring the temporal profile of the reaction by ^{1}H NMR spectroscopy, they show that the rate of buildup of aminal intermediates is slower than that of product formation (Figure 4, left, redrawn from Figure 6, Ref. 1). They then conclude that this observation "*eliminates the possibility of the catalyst being turned over through the thermodynamically most stable aminal.*" A similar statement was made in the faulty kinetic analysis of Ref. 3. Catalytic reaction simulations easily prove this claim to be false. As shown in Figure 4, right, an on-cycle model can exhibit faster formation of the product compared to the aminal, the very outcome that the authors of Ref. 1 concluded is impossible. Either model can predict either result depending simply on the rate constants governing each elementary step. An illustration of how this prediction is mathematically defined is given in Table 1 for a simplified reaction network.[9]

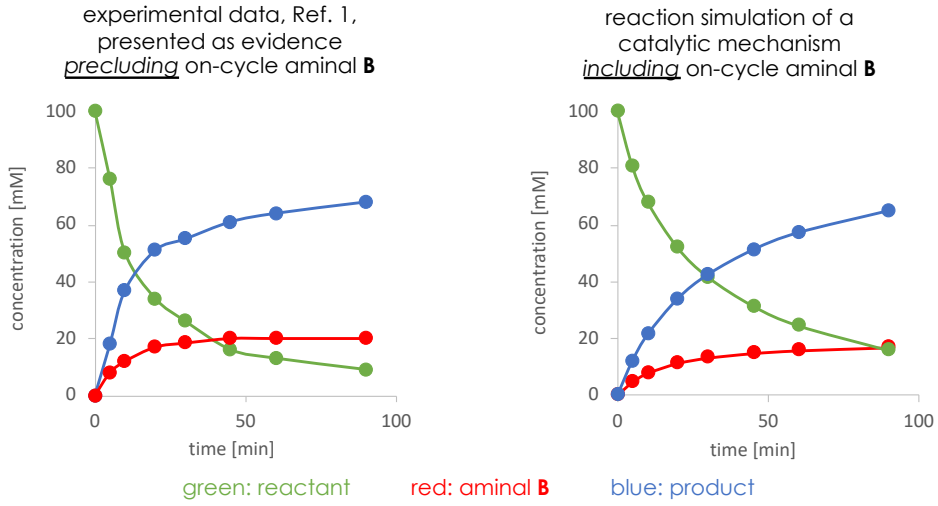
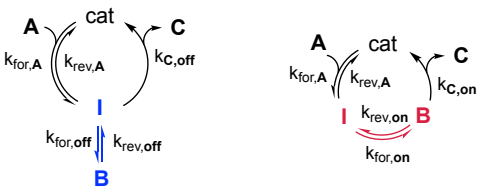


Figure 4. Comparison of temporal kinetic profiles: a) experimental NMR concentration data from the reaction of **16** with **6** catalyzed by **3c**.TFA, redrawn from Figure 6, Ref. 1; b) kinetic simulation of a reaction with a mechanism including formation of a downstream, on-cycle aminal species **B**.

Table 1. Comparison of rates of product **C** and aminal **B** formation in the off-cycle and on-cycle models for a simplified reaction network.

to B (on cycle)…
…or not to B (on cycle)?



mechanism	Off-cycle model	On-cycle model
rate of product **C** formation	$r_{C,off} = k_{C,off}[I]$	$r_{C,on} = k_{C,on}[B]$
rate of aminal **B** formation	$r_{B,off} = k_{for,off}[I] - k_{rev,off}[B]$	$r_{B,on} = k_{for,on}[I] - k_{rev,on}[B] - k_{C,on}[B]$
condition for rate of aminal formation r_B to exceed rate of product formation r_C	$k_{C,off} < k_{for,off} - \left(k_{rev,off} \cdot \frac{[B]}{[I]}\right)$	$2k_{C,on} < \left(k_{for,on} \cdot \frac{[I]}{[B]}\right) - k_{rev,on}$

It should be noted also that comparison of these relative rates will apply only in the very beginning of the reaction prior to establishment of steady-state, since under steady-state conditions the rate of formation of aminal **B** is in equilibrium with its rate of consumption in the off-cycle case. This is where one advantage of reaction calorimetric studies over standard NMR spectroscopic techniques becomes evident, as illustrated in Figure 5. This technique accurately captures the instant the reaction commences, and it provides continuous monitoring of subsequent instantaneous rates with high data density (100 data points are collected in Figure 5 by the time the first data point is collected in Figure 4). Specialized NMR techniques would be required to accurately monitor the very initial stages of the reaction shown in Figure 4, left, where the first data point is collected at ca. 20% conversion to product, likely already under steady state operation.[10] The inability to precisely capture time zero and the lack of high data density at very early reaction times make the kinetic arguments of Ref. 1 ineffectual.[11]

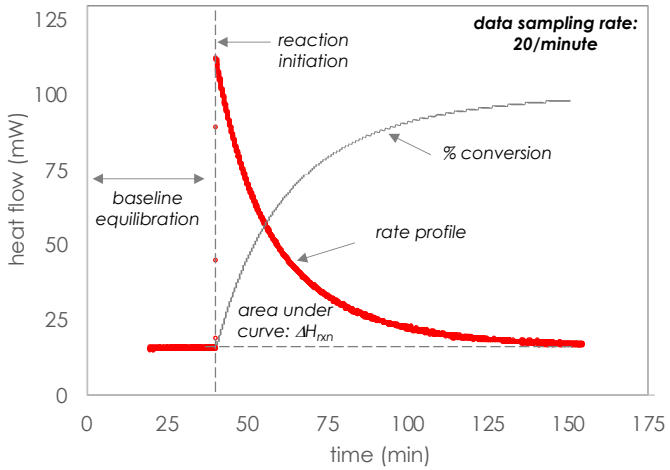


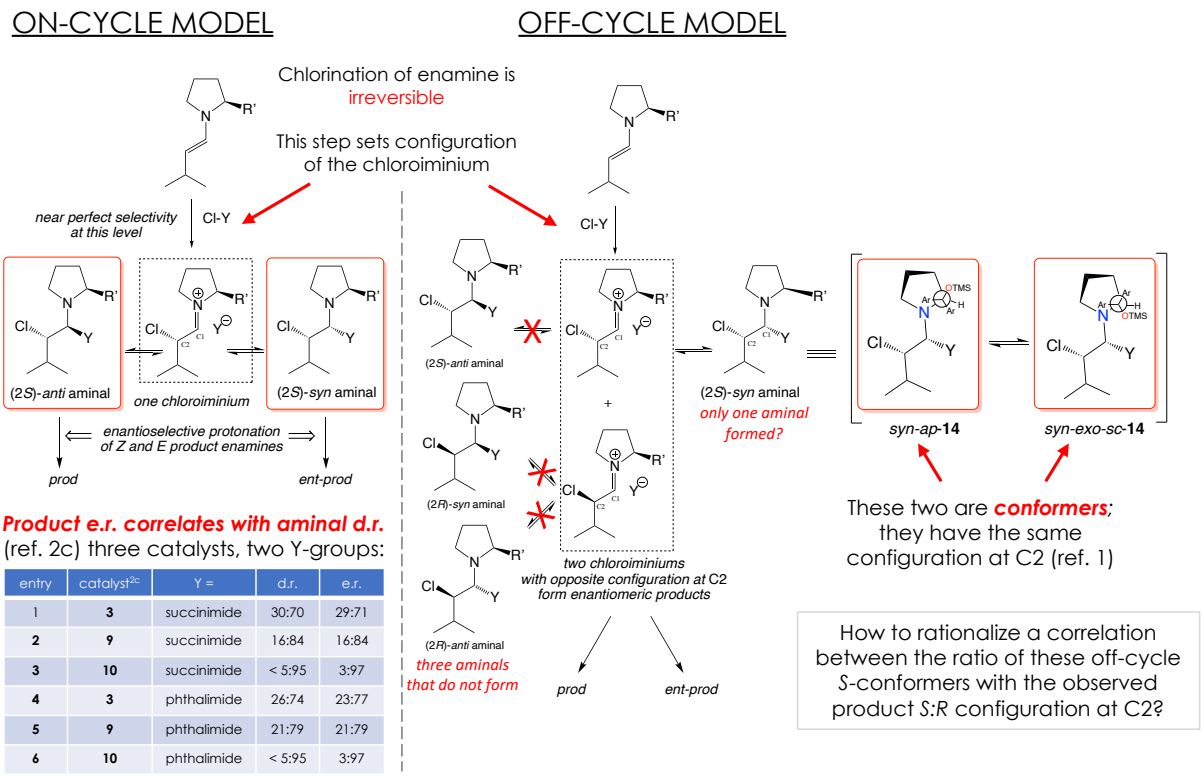
Figure 5. Example of a reaction calorimetry curve with data density of one data point every three seconds. Over 2500 individual data points are shown. The heat flow q is directly proportional to reaction rate according to $q = (\Delta H_{rxn})\cdot(\text{volume})\cdot(\text{reaction rate})$. Integration of the heat flow curve provides fraction conversion. Area under the curve gives the thermodynamic heat of reaction ΔH_{rxn} per mol converted.

Deuterium Incorporation Studies. The lack of significant incorporation of deuterium reported in Ref. 1 for the chlorination reaction using imidazolidinone and diarylprolinol ether catalysts is stated to be inconsistent with the role of a chloroenamine intermediate invoked in the on-cycle model. The conditions of these deuterations are not presented in the text, but study of the Supporting Information reveals that they are markedly different from those of the catalytic reactions in both Ref.1 and Ref. 3 as well as in the work of Burés et al. The *ChemRxiv* contribution of Ref. 1 uses 10 equivalents of added D_2O and 10 equivalents of added TFA-d_1 compared to the catalyst; Burés et al. added no water and 50-fold less acid compared to the catalyst, using the much less acidic acetic acid in place of TFA.[2c] It is also unclear how the reductive workup in ethanol and $NaBH_4$ may have affected the results, especially in reactions that achieve less than one turnover, as in the sole example where conversion is reported in Figure 5 of Ref. 1. The authors concede that these experiments cannot address the intermediacy of chloroenamine species but conclude that "*their presence is not unlikely as chlorination might account for the formation of significant amounts of dichloroaldehyde products*." They neglect to acknowledge both that the mechanistic studies reported by Burés et al. for chlorination were carried out under conditions that avoided significant dichlorination and product racemization,[2c] and that *E* and *Z* product enamines were experimentally observed and found to be the catalyst resting state in the related selenylation reaction, with their hydrolysis rates correlating with product e.r.[2g] The vastly different conditions and the inconclusive results of these deuteration studies lessen their relevance to the central mechanistic question.

Ion Mobility Mass Spectroscopic Studies. Ref. 1 contains a small stand-alone section on mass spectroscopic studies aimed at identification of the relative stability of chloroiminium ions. The *E*-chloroiminium from either the *syn* or *anti* aminal **25** is the more stable isomer formed with the *syn*-Bn-substituted catalyst **3b**. Yet the mechanism presented in Scheme 5 and the calculated DFT structures in Figures 3 and 4 in Ref. 1 show the *Z*-chloroiminium of catalyst **3c**. The *E* and *Z* chloroiminiums **Int4** and **Int4a** from **3c** are very similar in energy, which is not surprising, given that **3c** is *trans* and "C2-like." By contrast, catalyst **3b** has the two ring substituents *cis*, making a direct comparison of chloroiminiums difficult. It is thus unclear how these mass spectroscopic results relate to the rest of the study, as they do not seem to be consistent with other structures presented, and no conclusions concerning the mechanistic proposals are drawn from them.

Diarylprolinol Ether System

Figure 6 compares the chlorination mechanisms of Ref. 2c and Ref. 1, with structures of aminal species that have been proposed as either on-cycle or off-cycle intermediate species shown in red boxes. Burés et al. presented data showing that the d.r. of the aminals correlated with the e.r. of the reaction products. We proposed that these species arise from a single chloroiminium species with fixed configuration at C2[12] and that these aminals lead directly to the enantiomeric products (Figure 6 below, left) via one of the elimination mechanisms proposed in Figure 3.[2g,7] The thesis of Ref. 1 is that these aminal species are off-cycle and that two chloroiminium species with opposite configuration at C2 lead to the reaction products (Figure 6, right). They proposed that the two species suggested in our work to be one *syn* and one *anti* aminal intermediate are instead two conformers of a unique *syn*-stereoisomer, as shown in Figure 6, below right, redrawn from Scheme 8 in Ref. 1. The inference is that it is simply an uncanny coincidence that the ratio of two parasitic, off-cycle ***conformers*** of a single molecule with fixed *S* configuration at C2 closely matches the enantiomeric product *S*:*R* configuration at C2 in all six examples probed.



entry	catalyst[2c]	Y =	d.r.	e.r.
1	**3**	succinimide	30:70	29:71
2	**9**	succinimide	16:84	16:84
3	**10**	succinimide	< 5:95	3:97
4	**3**	phthalimide	26:74	23:77
5	**9**	phthalimide	21:79	21:79
6	**10**	phthalimide	< 5:95	3:97

Figure 6. Comparison of the Burés et al. on-cycle model (left)[2c] and the Christmann and coworkers off-cycle model (right)[1]. Proposed structures of observed aminals are shown in the red boxes for each model.

In the model shown in Figure 6, right, only *one* of these two chloroiminium ions participates in *syn*-aminal formation, and neither of the *anti* aminal species is formed. The authors do not offer an explanation of why the other three aminals are forbidden, although this would appear to be a selectivity issue worthy of consideration. They propose that the presence of the single *syn* aminal is simply an off-cycle nuisance that drains active catalyst but cannot influence product enantioselectivity. However, it must be noted that the siphoning off of only one of the two chloroiminium isomers into aminal species **14** in itself represents a *downstream* selection process, the very conclusion that the authors have rejected from the beginning. Selectively sequestering a substantial fraction of the catalyst in this manner will initially skew product enantiomeric excess towards the *opposite* enantiomer; ultimately, the overall outcome dictated by the shielding model will not be observed until the full aminal concentration eventually finds its way back into the cycle in the final turnovers. A key takeaway is that the process will manifest a temporally changing enantiomeric excess, which would be especially observable at high mol% catalyst in cases where the aminal concentration represents a significant fraction of the total catalyst.

It is important to note that the assignment in Ref. 1 of species **14** shown in Figure 6 above rests on ***calculated*** NMR shifts; Ref. 1 mentions several times that not only did the experimental data fail to make the assignment of the minor aminal species or confirm that the two are conformers, but that even the calculated assignments are uncertain:

> *"still no safe assignment of the minor species was possible." "NOE data was not entirely conclusive on the nature of the minor species and the process of the two interconverting aminal species…" "further analysis… may be needed to confirm the NMR shift assignments*"[1]

Only the calculated *syn*, and not the *anti*, assignments for species **11** and **14** (Y = succinimide and phthalimide, respectively) are given in the Ref. 1 manuscript itself. Turning to the S.I., we find that *anti* assignments are reported only for **11**. It is concerning that the authors do not report calculated *anti* assignments for aminal **14**, the species presented in their model reproduced here in Figure 6, right**.** They have arbitrarily chosen the two proposed *syn* conformers of **14** without presenting the comparative evidence – either for or against – the *anti* configuration.

It is also concerning that the description of the calculations reported in the Supporting Information states that rather than using the conventional protocol of a Boltzmann weighting based on calculated energies, "*The NMR chemical shifts were calculated by averaging the conformer chemical shifts with weights, or percentages, for each conformer determined by minimizing the deviation between the experimental and theoretical shifts using the excel solver function*". This is clearly not appropriate, as, ironically, was discussed in detail by one of the corresponding authors of Ref. 1 in a review on computational prediction of NMR chemical shifts.[13]

A further issue of concern in the calculations related to these aminal species arises in the conformational searches for the *syn*-**14** species. In calculating energies for conformers as a function of dihedral angle, the authors of Ref. 1 report (S.I., p. 164) an energy difference of nearly 12 kcal/mol between conformers at –180° and 180°, which clearly must describe the same molecule.

In summary, the authors' conclusion that they "*reevaluate the incorrect assignment made in the literature*" is neither internally consistent nor supported by experimental data and calculations. It is an evaluation based on NMR assignments that admittedly are not confirmed or are missing altogether. It is an evaluation that neglects a body of compelling evidence and ignores the fact that we demonstrated how our model can account for either *syn* or *anti* as the major aminal species. And it is an evaluation that *supports* rather than *refutes* the proposal of the influence of intermediates

that appear subsequent to enamine attack on Cl–Y, downstream from the step considered key to determining stereoselectivity in the shielding model.

A Note About the Downstream Paradigm

This discussion highlights, as we previously demonstrated,[2h] that in catalyst systems where downstream intermediates play a role, selectivity may be determined in a hierarchical fashion, as shown in Figure 7. The first level in these organocatalytic systems is described by the generally accepted shielding model with attack of the enamine on an electrophile. Selectivity achieved at this level may be altered, for example, in some cases where stable species are able to form on the catalytic cycle downstream from this elementary step.

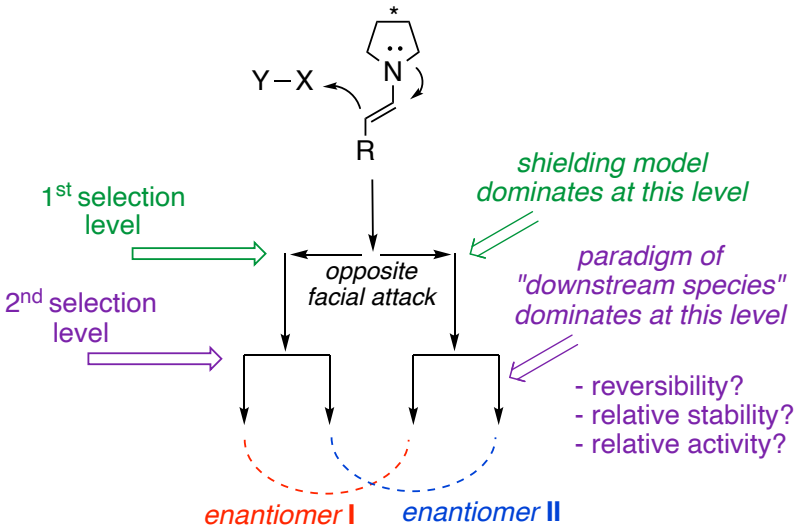


Figure 7. Hierarchy of selection in enamine catalysis. Redrawn from Ref. 2h.

The key point for this hierarchical downstream paradigm is that opposite product enantiomers can ultimately arise from the same selection at the first level, as can be seen from Figure 7. In fact, our results for both chlorination and selenylation with Y = succinimide or phthalimide implied *near perfect selection* at the enamine level of the shielding model, even though the observed outcomes ranged from 99 %*ee* (*S*) to 44 %*ee* (*R*), all in reactions employing the (*S*) configuration of the catalyst. We considered this point to be broadly supportive of our proposed on-cycle model, since it meant that we did not need to search for a separate rationalization for why enamine attack on succinimide and phthalimide electrophiles gives results so widely different from similar reactions following the shielding model. High selectivity in the attack of the enamine on electrophiles is in fact what is observed in the majority of reactions catalyzed by both imidazolidinone and diarylprolinol ether catalysts,[14] including aminoxylation, fluorination, bromination, Michael addition to nitrostyrenes, Michael addition to vinylketones, amination, Mannich reactions, and even chlorination reactions employing a chlorinating agent that does not generate a coordinating counterion.[15] Prior to our work, chlorination and selenylation reactions using succinimide or phthalimide reagents thus presented a perplexing outlier for the shielding model: Why would these reagents alone among all of the above examples exhibit such diminished selectivity at the enamine attack? And, in the case of selenylation, how can the shielding model explain the reversal of product stereochemistry observed in switching solvent from toluene to CD_2Cl_2?[2g,6] Our downstream paradigm conforms to the shielding model at the first selection level; we simply demonstrated that in the cases we studied, the outcome at the first level may be altered by subsequent selection processes downstream, which are not significant in similar enamine reactions with other electrophiles.[16]

Figure 7 implies that simple perusal of the structures at the first level may not provide full insight into the stereochemical outcome in all cases. This possibility has been proposed before in other asymmetric catalytic systems and has been called an "enantioselective refinement,"[17] which may lead to either an erosion or an enhancement of enantioselectivity achieved in the first level. The importance of understanding this hierarchy of selectivity is hardly an academic question; since parameters that affect selectivity at the first and second hierarchical levels may be different, design and optimization of asymmetric catalytic processes clearly should consider the nature and role of species at each level.

A Note About Curtin-Hammett

The authors of Ref. 1 emphasize the fact that the Curtin-Hammett principle was originally proposed for conformers, not diastereomeric species. This is of little significance, however, since the principle has been masterfully applied to a wide range of types of interconverting intermediate species, most notably in the landmark Landis and Halpern treatment of enantioselective hydrogenation[18]. The IUPAC definition of the Curtin Hammett principle[19] states that the ratio of products formed from two rapidly interconverting conformational isomers "*is controlled only by the difference in standard free energies (⊥⊥$G^{\ddagger}$) of the respective* ***transition states***". This has often been taken, erroneously,[20] to mean that the relative stability of the interconverting species is not relevant. However, as can be seen in Figure 8 below, the value of $\Delta\Delta G^{\ddagger}$ (given by the encircled (1)) is influenced *both* by the relative stabilities ([A"]/[A'] encircled (4)) *and* the relative reactivities (k" and k' encircled (2) and (3)). The product ratio [Y]/[X] may be written in three different ways: in terms of $\Delta\Delta G^{\ddagger}$; or K_{eq} and k"/k'; or [A"]/[A'] and k"/k'. Indeed, the IUPAC definition goes on to state: "*It is also true that the product composition is formally related to the relative concentrations of A' and A" (i.e., the conformational equilibrium constant) and the respective rate constants of their reactions.*"

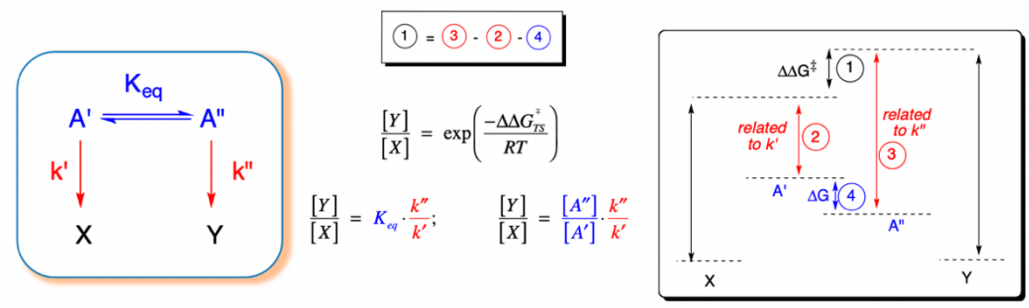


Figure 8. The Curtin Hammett principle as described in the IUPAC Gold Book.[19]

The authors of Ref. 1 seem to have misunderstood the "Curtin-Hammett scenario" developed by Burés et al.[2] and its implications. In two places in Ref. 1, they suggest that the C-H model implies that only thermodynamics need to be considered. Thus, they write *"**augmenting** the relative stabilities of intermediates **rather than** the relative energies of transition states"* (our emphases in bold). To properly represent the Curtin-Hammett paradigm, this sentence should be constructed as: "***considering*** the relative stabilities of intermediates ***as well as*** *the relative energies of transition states"*. The authors of Ref. 1 also state: *"the on-cycle model proposes the stereochemical outcome to be thermodynamically controlled, i.e. the formation of the major enantiomer must proceed through the most stable aminal"*. In fact, the key point in the body of work by Burés et al. is that ***both*** thermodynamics ***and*** the relative reactivity of the intermediates must be considered in any reaction system. In our chlorination studies,[2c] the *experimentally observed* correlation between aminal ratio and product e.r. was used to suggest that the diastereomers have similar reaction rates *in that case*. However, the

related selenylation reaction we studied[2g] gives a clear example where product ratios are determined by the *experimentally observed* difference in reaction rates of two *experimentally observed* intermediates of equal concentrations. Taken together, these correlations provide a consistent rationale that cannot be extracted from the shielding model alone. The interplay between kinetics and thermodynamics in these systems was discussed by us in Ref. 2f, which is not cited by the authors of Ref. 1. Extensive examples of both thermodynamic and kinetic control were treated in that work.

The authors of Ref. 1 deride the observed experimental relationships between product selectivity and relative reactivities and concentrations of downstream intermediates as misplaced "cause" and "effect." They suggest that these compelling correlations are simply coincidental ("*apparent correlation*"), but they neglect to consider the wealth of evidence, including spectroscopic and kinetic data from three different reactions, as summarized in our *Acc. Chem. Res.* of Ref. 2h, which speaks to the generality of the mechanism in cases where the shielding model alone offers inadequate insight. In a comparative evaluation of the shielding model and the on-cycle downstream paradigm for the cases we studied, we venture that William of Ockham would favor the on-cycle model of Burés et al.[2] as uniquely capable of rationalizing the totality of the observations.

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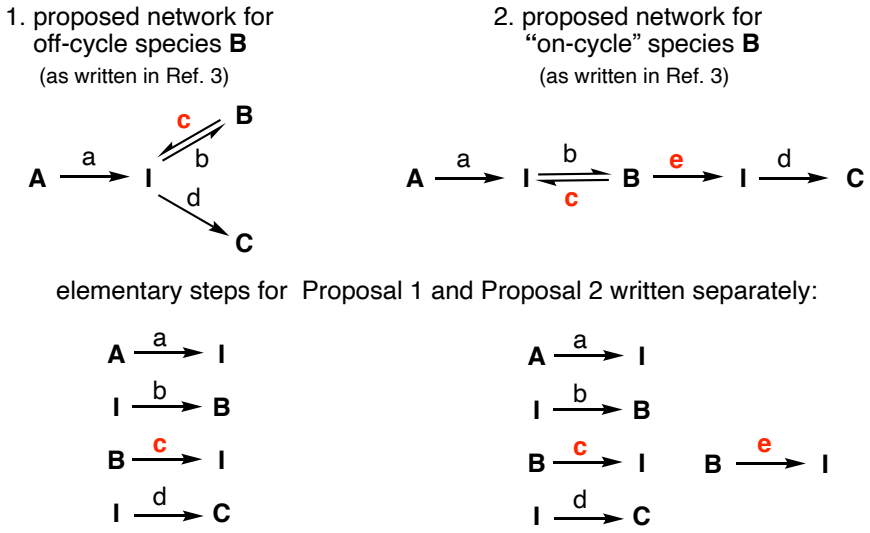
4 Ref. 3 made an erroneous comparison of off-cycle and on-cycle networks as shown below, redrawn from Figure 8, Ref. 3. By writing out the elementary steps separately in each case, we see that the "on-cycle" network on the right side has two separate steps through which intermediate **B** reacts to produce intermediate **I**: the step with rate constant "**c**," which occurs in both the off-cycle and the on-cycle case, and an extra step with rate constant "**e**". A reaction network cannot contain two distinct elementary steps leading from one intermediate to a second intermediate because this is a violation of the principle of microscopic reversibility. Therefore, rate constant "**c**" must equal rate constant "**e**". If that is the case, however, the step containing rate constant "**e**" is redundant, and it becomes clear that the two networks shown are, in fact, identical. Rather than representing an off-cycle and an on-cycle network, both networks contain intermediate **B** as an off-cycle species.



The two proposed networks cannot give different kinetic profiles, as the work in Ref. 3 erroneously showed. The conclusions drawn in Ref. 3 about on- and off-cycle intermediates are thus invalid because they are based on this faulty kinetic analysis. Note also that this kinetic analysis in Ref. 3 depicts a stoichiometric and not a catalytic reaction network.

5 An excellent discussion of these points is given in this *Perspective* article: Harvey, J.M.; Himo, F.; Maseras, F.; Perrin, L. Scope and Challenge of Computational Methods for Studying Mechanism and Reactivity in Homogeneous Catalysis. *ACS Catalysis* **2019**, *9*, 6803-6813.

6 The relationship between product enamines and product e.r. was determined in the selenylation reactions monitored by NMR spectrsocopy in Ref. 2g. Reactions carried out in toluene exhibited only the *E*-enamine and gave an e.r. of 96.5:3.5 to the major *S* product. Reactions in CD_2Cl_2 showed equal concentrations of two product enamines that reacted at relative rates that correlated with the 30.5:69.5 product e.r., in a solvent-induced reversal

leading to the *R*-product as major. These studies revealed that the species identified as the *E*-enamine reacts slower than the *Z*-enamine in CD_2Cl_2, thus providing a rationalization for the solvent effect on the stereochemical outcome of the reaction, a feature difficult to explain by the shielding model alone.

7 Page 27 of the Supporting Information of Ref. 2g presents both of the scenarios discussed here: Mechanism **B**: major product arising from *anti*-elimination from a major *anti*-aminal; and Mechanism **C**: major product arising from *syn*-elimination from a major *syn* aminal.

8 See p. S11 of the Supporting Information of Ref. 2c.

9 The catalytic cycle shown in Table 1 is drawn as a simplified network in order to highlight the process for mathematical determination of relationships between rates of intermediate and product formation. The on-cycle simulation in Figure 4, right, represents the full catalytic network studied by Burés et al. in Ref. 2, as shown in Figure 1, right.

10 It is important to clarify that the condition for steady-state operation in a catalytic reaction is ***not*** that the concentration of an intermediate species is approximately constant, as is often assumed, but that the rate of production of **I** is much greater than its rate of change in concentration ($r_{formation,\mathbf{I}} >> d[\mathbf{I}]/dt$).

11 Ref. 1 states: "*To identify these subtleties, it is essential to follow individual concentrations over time (NMR spectroscopy) rather than observing a single value for the whole system, for example, the amount of energy released (reaction calorimetry)*." While we agree that obtaining information about individual concentrations is indeed valuable, the task of uncovering any subtleties to be found in the relative rates of intermediates and products requires significantly greater data density than the collection of one data point for every ca. 20% conversion. Moreover, modeling based on data-dense, global kinetic profiles can provide exquisite insight into reaction mechanisms; see, for example, Blackmond, D.G. Kinetic Profiling of Catalytic Organic Reactions as a Mechanistic Tool. *J. Am. Chem. Soc.* **2015**, *137*, 10852-10866.

12 Because we observed *two* (suggested to be one *syn*, one *anti*) and not *four* (two *syn*, two *anti*) intermediates with the connectivity of the aminal, and because these intermediates were shown to be in rapid equilibrium, we proposed that a single configuration exists at the C2 position, which was set in the enamine attack on *N*-chlorosuccinimide. The observed rapid equilibrium is proposed to involve the interconversion between a *syn* and an *anti* aminal via this single chloroiminium ion and its succinimide counterion.

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16 In these cases, we may think of the downstream paradigm as "shielding model ***plus***".

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18 Landis, C. R.; Halpern, J. Asymmetric Hydrogenation of Methyl-(2)-α-acetamidocinnamate Catalyzed by {1,2-Bis((phenyl-*o*-anisoyl)phosphino)ethane)rhodium(I): Kinetics, Mechanism, and Origin of Enantioselectivity. *J. Am. Chem. Soc.* **1987**, *109*, 1746.

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20 Indeed, the original definition of the C-H principle helped to propagate this misunderstanding. See: Seeman, J.I. The Curtin-Hammett Principle and the Winstein-Holness Equation: New Definition and Recent Extensions to Classical Concepts. *J. Chem. Ed.* **1986**, *63*, 42-48.