Enamine and Iminium Organocatalysis

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Scope of Lecture

SOMO and photoredox catalysis
proline aldol reactions
detection of enamines
cascade organocatalysis
enantioselective Diels-Alder reactions
enantioselective reduction of iminium ions
List-Houk model and alternatives
1+rate law analysis

enamine and iminium organocatalysis

Key Questions

1. Proline vs. Mannich Reactions

\[
\text{MeO} + \text{Me} + \text{MeCOH}\rightarrow \text{Me} + \text{Me} + \overset{\text{why a turnover?}}{\text{OH}}
\]

2. Organocascade Reactions

\[
\text{Me} + \text{HCO} + \overset{\text{PMP}}{\text{Me}} + \overset{\text{CO}_{2}E}{\text{Et}}\rightarrow \overset{\text{NHPMP}}{\text{Me}} + \overset{\text{iPr}}{\text{Me}}
\]

86% yield
14:1 dr, 99% ee

3. Organo-SOMO/Photoredox Catalysis

\[
\text{HCO} + \overset{\text{Br}}{\text{CO}_{2}Et} + \overset{\text{CO}_{2}Et}{\text{Br}} \rightarrow \overset{\text{visible light}}{\text{fluorescent bulb}} \rightarrow \overset{\text{organocatalyst (20 mol%)}}{\text{Ru(bpy)}_{3}Cl_{2} (0.5 mol%)}} \rightarrow \text{Me} + \overset{\text{(2,6-lutidine, DMF, 23 °C)}}{\text{83% yield, 95% ee}}
\]

Helpful References


I thank Dr. Rob Knowles and Dr. Jaclyn Henderson for some helpful discussions and material for the preparation of this lecture.
As Macmillan points out, mentions of the word "organocatalysis" have truly exploded in the literature (ISI Web of Knowledge, ref 1):

Macmillan writes (ref 1):

"Why was organocatalysis so long overlooked as an area of research?...One perspective worth considering is that it is impossible to overlook a field that does not exist yet...researchers cannot work on a problem that has not been identified."

This may be a bit harsh, but there is a ring of truth to it. In Seebach's defense, hardly any of the reactivity that will be discussed in the first part of this lecture (proline aldol and Mannich reactions, reductions of $\alpha,\beta$-unsaturated iminium ions, enantioselective Diels-Alder reactions) are actually new. Rather, they are "simply" enantioselective variants of old reactions. However, in the second part of the lecture, I will show you some genuinely new reactivity in the context of SOMO catalysis.

The seminal work in this area came simultaneously from Hajos and Parrish (JOC 1974 39 1615) at Hoffmann-La Roche, and Eder, Sauer, and Weichert at Schering AG (ACIEE 1971 10 496). They reported that proline catalyzed this cyclization:

(Eder and co-workers used harsher conditions involving perchloric acid at elevated temperatures, but accomplished the same transformation.) Other amino acids, methylated proline, and piperocolic acid are either ineffective catalysts or give low enantioselectivity.

As usual, these intramolecular reactions preceded the intermolecular versions by quite a bit. In 2000, List and Barbas showed that intermolecular proline-catalyzed reactions can work (JACS 2000 122 2395):

The mechanism of these reactions is proposed to be analogous to how type I aldolases work (Bachrach, Section 5.3):
Kinetics of Intermolecular Proline Aldol Reactions


Despite some recent controversy (see below), there is now little doubt that enamines are the nucleophilic species in these reactions and that C-C bond formation is rate-limiting. Gschwind and co-workers have looked at the self-aldolization of propionaldehyde under synthetically relevant conditions (20 mol% L-proline in $d_5$-DMSO at 300 K) with real-time NMR:

\[
\begin{align*}
\text{Me} &+ \text{Me} \rightarrow \text{MeCH(OH)CH(OH)} + \text{MeCH(OH)CH} = \text{CH} \\text{CHO} \\
\end{align*}
\]

In agreement with previous studies, two diastereomeric aldol addition products are formed, along with some condensation product. Over the course of the reaction:

1. The enamine is E-configured and s-trans, regardless of [enamine]. Incidentally, this is the same conformation that Houk predicts is reactive (see discussion below).

\[
\begin{align*}
\text{E} &\rightarrow \text{Me} \\
\end{align*}
\]

2. NMR exchange spectroscopy ("EXSY") is a technique that allows the rate of interconversion between equilibrating species to be measured, so long as the exchange rate is suitable (for a more precise definition, you will have to wait until Chem 117 next semester). If two peaks have a "crosspeak" then there is exchange. The volume of the crosspeak is related to the rate of exchange.
Here is a schematic for the exchange equilibria:

Regardless of how enamine is formed, this is the proposed kinetic scheme for intermolecular proline aldol reactions (to maintain consistency with previous lectures, we're using a new set of letters to denote the various chemical species now):

Q: Does this fit the observed kinetic data?

To answer this question, we need to draw a 1+rate law for this. This is more complicated than the 1+rate laws we have considered. For example, step 1 produces water as well as C·K and it reasonable to think that additional water would shift this equilibrium left towards starting materials. Assuming product release is irreversible,

\[
v = \frac{K_1 K_2 k_3 [H_2O][K][A][C]}{[H_2O] \left(1 + \frac{K_1 [K]}{[H_2O]} + \frac{K_2 [K]}{[H_2O]} + \frac{K_3 [K]}{[H_2O]} \right)}
\]

Assuming that we can ignore any catalysis (perhaps by water) of oxazolidinone formation, one can see that \( K_1 \) and \( K_1' \) will be merged into some smaller apparent equilibrium constant \( K_1' \).
Absorbing $K_1$ and $K_i$ gives this expression:

$$v = \frac{K_1 K_2 k_3 [H_2O][K][A][C]_T}{[H_2O] + K'_i[K] + K'_i K_2[A]}$$

Experimentally, it has been determined that the rate can be fitted to an approximate power law expression:

$$v = k [H_2O]^{-0.7} [K]^{0.6} [A]^{0.9} [C]_T$$

Note that for a multi-step reaction, the exponents do not imply the molecularity of any particular step. Suppose the enamine formation is rate-limiting. In that case, the reaction becomes elementary and the rate law is (the pre-equilibrium assumption for step 1 is no longer valid since it’s now the “last” step):

$$k_i [K][C]_T$$

If enamine formation is rate-limiting, the rate law is:

$$v = k_i [K][C]_T$$

Since the reaction is about first order in aldehyde, this can be discarded. (Neither water nor aldehyde take the reaction forwards to product, so they don’t appear in the numerator.) What if aldol addition is rate-limiting?

$$\frac{[K][A][C]_T}{[H_2O] + K'_i[K]} = \alpha \frac{1}{x+c}$$

Similarly, $[H_2O]$ no longer appears in the numerator, since water will not speed up the reaction if aldol addition is rate-limiting. Additionally, the $K_2$ term is small, so it does not appear in the denominator. (1) does correspond to the power law above. To see this for $[H_2O]$, hold other concentrations constant ($x=\text{[H}_2\text{O]}$).

This is a bit less than negative first order in water, depending on how big $c$ is. Finally, let $y = [K]$, and we get:

$$\frac{[K][A][C]_T}{[H_2O] + K'_i[K]} \alpha \frac{1}{d+y}$$

before the rate-determining step, slowing down the reaction. Increasing the amount of ketone increases the amount of this intermediate. However, because both water and ketone are incorporated before $C \cdot K$ goes to product in a multi-step process, their kinetic orders have magnitudes less than one.

Further Evidence

Until a few years ago, the idea that these reactions go through imine intermediates was itself controversial. Even the stoichiometry of the transition state was unclear. Here were some of the leading proposals for the Hajo-Parrish reaction:

**Hajos model**

**Swaminathan model**

**Agami model**

**Houk model**

The Hajos and Houk models have the same stoichiometry, so we cannot distinguish between them with kinetics. These reactions work in completely homogeneous media, so the Swaminathan model is unlikely.

Q: How can the number of prolines in the TS be determined?
Further Evidence
The classic experiment is to examine the relationship between catalyst enantiopurity and the product enantiopurity. This is called a **nonlinear effects experiment**. Despite some initial reports by Agami that these were involved in the Hajos-Parrish reaction, very careful studies showed that there is no such effect (Houk/List JACS 2003 125 16):

![Graph showing ee vs. Proline with two linear regressions with R^2 values of 0.997 and 0.998.]

If the homochiral catalyst-catalyst complexes are less reactive than heterochiral (meso) complexes, then the line would be curved upwards (asymmetric amplification). Similarly, ee is unchanged with dilution (more dilute = aggregation less likely):

![Graph showing ee vs. Triketone 1 concentrations with two constant lines at 80% ee for both 1a and 1b.]

From microscopic reversibility arguments, the fact that the retro-aldol reaction is first-order in proline means that the forward aldol reaction is also first-order. This also has the advantage of definitively being related to the C-C bond forming step:

![Graph showing initial rate vs. Proline with a linear regression line with k = 0.10 s^{-1} M^{-1} and R^2 = 0.998.]

Finally, performing the reaction in ^18_O-labeled water gives incorporation of the label at the ketone. This is required by the mechanism, which generates an iminium ion which must be hydrolyzed by solvent (List PNAS 2004 101 5839):

![Chemical reaction diagram showing the hydrolysis of a triketone under Ar four days, resulting in 40%, 50%, and 10% incorporation rates.]

This excludes the Hajos model, which does not proceed via an iminium ion. (Initial reports were to the contrary, but careful experiments give incorporation.)
The Houk-List Model for Stereoselectivity

All of this evidence points to a one-proline enamine mechanism. Houk considered a variety of intermolecular reactions, both selective and unselective, and List measured their enantioselectivities (JACS 2003 125 2475). One considered reaction:

\[
\begin{align*}
\text{Me} & \quad \text{Me} + \quad \text{Me} \quad \text{H} & \quad \xrightarrow{\text{proline}} & \quad \text{Me} \quad \text{OH} \quad \text{Me}
\end{align*}
\]

A variety of parameters were looked at:

\[
\begin{align*}
\text{HO}_2\text{C}^- & \quad \text{N} & \quad \text{CO}_2\text{H} \\
\text{syn or anti enamine} & \quad \text{Re or Si face of aldehyde}
\end{align*}
\]

enamine-aldehyde rotamers

As it turns out, unless the carboxylic acid and the aldehyde are engaged in hydrogen bonding, the incipient alkoxide is not effectively stabilized, and therefore the TS is very high in energy.

The computations (B3LYP/6-31G*) led to this "metal-free" Zimmerman-Traxler model:

favored

disfavored (+1.0 kcal)

Thus, anti-enamines are preferred, as is an equatorial aldehyde. Here are two equivalent renderings of the favored TS:

attraction between negatively charged oxygen and positively charged N-C-H hydrogen atom

This is the lowest energy TS leading to the minor product:

Selectivity is predicted to be lower with cyclohexanone, since this makes both the equatorial and axial aldehyde conformers equally bad:
Of course, the computations are useless if they don't agree with reality. In general, the correlation is good, although the predicted selectivities are a bit too high:

$$y = 1.7x$$
$$R = 0.93$$

The Hajos-Parrish reaction seems to work along similar lines (Houk *ACIE* 2004 43 5766). The favored transition state is:

Houk also examined the uncatalyzed and Hajas pathways:

uncatalyzed TS (+10.2 kcal)  carbinolamine intermediate (+12.4)

Since the hemiaminal leading up to the Hajas TS is already higher in energy than the uncatalyzed TS, Houk concludes the Hajas model is incorrect.

If you don't believe any of this, the results for the closely related proline-catalyzed Mannich reactions are very compelling. Let's apply the same model to this reaction (Houk *OL* 2003 5 1249):

E imines are more stable than Z imines, so this gives this TS:

Indeed, this gives the correct facial selectivity and explains why the sense of induction is turned over from the aldol reaction. Note that for donor aldehydes, this favors syn-Mannich products:

So how can one obtain *anti*-Mannich products?
**Mannich Reactions**

A different catalyst turns out to be highly anti-selective:

\[
\begin{align*}
\text{Me} \quad \text{HN} \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} \quad \text{HN} \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

70%, 94:6 anti:syn >99% ee

This catalyst was designed by computations, which predicted this transition state (Houk/Barbas *JACS* 2006 128 1040):

Deletion of the methyl group reduces selectivity by about 1 kcal.

**Oxazolidinone Intermediates?**

Despite the success of the List-Houk mechanistic framework, Seebach and Eschenmoser have proposed an alternate pathway that involves oxazolidinones (*Helv Chim Acta* 2007 90 425). Here is the List-Houk mechanism:

(1) The enamine carboxylate might arise from an E2 elimination as depicted, or perhaps by deprotonation of the iminium ion formed from proline and acetone.

(2) The carboxylate is proposed to assist the nucleophilicity of the enamine (similar to halolactonization):

(3) From various X-ray structures and calculations, it's been suggested that the concave/convex shape of these structures might give rise to high stereoselectivity.
(4) It's been suggested that the 9-membered hydrogen bonds required by the List-Houk model are implausible. However, the usual proscription against such rings is based on the transannular interactions in medium-sized cycloalkanes. Gellmann has shown that these H-bonds are, in fact, quite plausible (JACS 1990, 112, 8630; CSD: PAGTIA):

![Chem 106 Enamine and Iminium Organocatalysis](image)

Sunoj has looked at the relative energetics of both mechanisms computationally using a variety of methods (ACIE 2010 49 6373).

**List-Houk (correct enantio- and diastereoselectivity)**

<table>
<thead>
<tr>
<th></th>
<th>B3LYP/6-31+G**</th>
<th>MP2/6-31+G**</th>
<th>M05-2X/6-31+G**</th>
</tr>
</thead>
<tbody>
<tr>
<td>predicted ee</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>98.5</td>
</tr>
<tr>
<td>predicted dr</td>
<td>5.4:1</td>
<td>1.2:1</td>
<td>1:1.7</td>
</tr>
</tbody>
</table>

**Seebach-Eschenmoser (correct ee, incorrect dr)**

<table>
<thead>
<tr>
<th></th>
<th>B3LYP/6-31+G**</th>
<th>MP2/6-31+G**</th>
<th>M05-2X/6-31+G**</th>
</tr>
</thead>
<tbody>
<tr>
<td>predicted ee</td>
<td>95</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>predicted dr</td>
<td>1:3.9</td>
<td>1:4.6</td>
<td>1:2</td>
</tr>
</tbody>
</table>

实验 ee: 99%; dr: 4:1 anti: syn

So both models get the enantioface right, but the predictions of diastereoselectivity are better with the List-Houk enamine model. More compelling are the substantially higher barriers for the Seebach oxazolidinone pathway (by about 11 kcal/mol):

(5) However, in DMSO, a lot of these hydrogen bonds do get disrupted (DMSO is a very good H-bond acceptor). However, it seems plausible that in a transition state, H-bonding to an internal donor might be feasible due to entropic effects. Noncovalent interactions are also generally stronger in transition states, since they're more polarized.

(6) The Seebach-Eschenmoser proposal does not take advantage of intramolecular general acid catalysis, and so an alkoxide is formed. Although DMSO is very polar, it is not a hydrogen bond donor, so the alkoxide is expected to be quite unstable. From the ground state side, the enamine carboxylate is not expected to be very well stabilized either.
**Enamine vs. Iminium Activation Modes**

Q: Why is proline a catalyst for aldol reactions? i.e., Why does it lower the activation barrier?

- (1) general acid catalysis: COOH stabilizes forming alkoxide
- (2) *enamine activation*

- most isolated carbonyl groups in ketones and aldehydes have very low enol content; the catalyst increases the amount of "enol" available

- actually, it's an enamine, not an enol; on the Mayr scale, enamines are much more reactive

\[
\begin{align*}
\text{Me} & \quad \text{N} \\
\text{O} & \quad \text{C} \\
\text{H} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{OEt} \\
\text{Me} & \quad \text{OTMS} \\
\text{Me} & \quad \text{OEt}
\end{align*}
\]

- enols are not available on the scale, but this shows that you need approximately two oxygens to equal one nitrogen!

If enamines are more nucleophilic, it's reasonable to expect that iminium ions are more electrophilic. This is similar to how Lewis acids or hydrogen bond donors activate carbonyl groups:

These are all LUMO-lowering strategies. While organocatalytic activation may not be as powerful in increasing reactivity as Lewis acid catalysis, it can be an advantage in getting catalyst turnover. Iminium ions are so easily hydrolyzed by water, they are generally considered to be in equilibrium with their carbonyl counterparts. MacMillan has taken advantage of this for Diels-Alder reactions (*JACS* 2000 122 4243):

\[
\begin{align*}
\text{Me} & \quad \text{OAc} \\
\text{H} & \quad \text{CHO}
\end{align*}
\]

11:1 endo:exo 72%, 85% ee

This also works with α,β-unsaturated ketones (*JACS* 2002 124 2458), but requires a different catalyst:

\[
\begin{align*}
\text{Me} & \quad \text{COEt}
\end{align*}
\]

11:1 endo:exo 72%, 85% ee

Note that, in contrast to proline aldol reactions, these occur in protic media, where there may be some hydrophobic acceleration. Exactly how selectivity is obtained here is still up for debate (Houk *Acc Chem Res* 2004 37 558). Instead, I will discuss what's known about models for organocatalytic transfer hydrogenation (reviews: MacMillan *Acc Chem Res* 2007 40 1327; Adolfsson *ACIE* 2005 44 3340).

These reactions were developed as a synthetic analog to natural hydride reductions which occur with NADH or FADH₂. β,β-Disubstituted aldehydes can be reduced effectively (MacMillan *JACS* 2005 127 32, List *ACIE* 2005 44 108) with Hantzsch esters as the hydride source:

Hantzsch ester
Organocatalytic Hydride Reductions

An initial result:

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Ph} & \quad \text{H} \\
\end{align*}
\]

\[\overset{20 \text{ mol\% cat}}{\text{Hantzsch ester, PhMe, \(-30^\circ C\)}}\]

\[\overset{\text{96\% conv., 75\% ee}}{\text{Me}}\]

Under slightly different conditions, the reaction improves:

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Ph} & \quad \text{H} \\
\end{align*}
\]

\[\overset{20 \text{ mol\% cat}}{\text{Hantzsch ester, dioxane, 13^\circ C}}\]

\[\overset{\text{77\%, 90\% ee}}{\text{Me}}\]

An anomalous case (see below) is this tert-butyl catalyst:

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{Ph} & \quad \text{H} \\
\end{align*}
\]

\[\overset{20 \text{ mol\% cat}}{\text{Hantzsch ester, CHCl₃, \(-30^\circ C\)}}\]

\[\overset{\text{91\%, 93\% ee}}{\text{Me}}\]

**Advantages:** bench-stable reagent; a good alternative to hydrogenation (usually needs optimization) or copper-based hydrides (unreliable); E and Z isomers converge to the same product

**Disadvantages:** the Hantzsch pyridine is a stoichiometric byproduct, which must be removed by chromatography (acid-base extraction doesn't work); the Hantzsch pyridine is quite a large reagent for delivering just one hydrogen

\[\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et} \quad \text{byproduct} \quad \text{Hantzsch pyridine}\]

The convergence of E and Z starting materials to the same products suggests a Curtin-Hammett scenario where a dienamine intermediate can rotate to isomerize the olefins:

**Stereochemical Model**

What controls the stereoselectivity? Having established the favored iminium ion geometry, we must now consider two iminium ion rotamers:

\[\pi-\pi \text{ orcation-}\pi \text{ interaction?}\]

\[\text{better than}\]

\[\text{preferred attack}\]

1. In the left-hand rotamer, the bulky tert-butyl group ensures that the benzyl group rotates over the β-face of the electrophile, making the hydride reagent come from the bottom.

2. Both the attractive π-π/cation-π interactions and repulsive steric interactions (as the carbons pyramidalize) are expected to become more important in the transition state.
The ground state conformational preferences of these systems have been studied (Tomkinson et al. OL 2009 11 133). The X-ray structures shown below are similar to the solution phase structures, as shown by NMR studies. Here is an X-ray structure of a free imidazolidinone catalyst (CSD: POPRES):

This is the X-ray structure of the corresponding iminium ion (CSD: DOSKIG01). Note the rotation in the benzyl group:

Calculations show the penalty for rotating the benzyl group in the ground state of the iminium ion is about 1 kcal/mol—very small. I doubt these ground state pictures tell us much about the transition state; the fact that the benzyl group doesn't seem to be covering the β-face very effectively in the X-ray structure is meaningless.

The anomaly is that the catalyst which only has a tert-butyl group is still very selective:

I don't have a good explanation for this. Enones also work in this chemistry, but with a slightly different system (MacMillan JACS 2006 128 12662; Houk OL 2009 11 4298):

The product can be explained by this model, but it might not be right (see the Houk paper):

preferred attack
Organocatalytic Cascades

Taxol is a potent anticancer agent used in the treatment of lung, ovarian, breast, neck, and other cancers, with sales of $1.6 billion US in 2000. Until 1993, taxol had to be extracted from the bark of the pacific yew tree and prepared via semi-synthesis. Now, BMS uses cultured Taxus cells in a fermentation process. Taxol is extracted and purified directly from the broth.

Q: Why can't we make taxol in ten steps?

Analysts estimate that the world will need 1 040 kg of taxol/year by 2012. Despite our best efforts, total synthesis is clearly not up to the job:

Each of these groups used cutting-edge chemical methodology and very clever synthetic logic, but none of their routes is even remotely amenable to a large-scale process route. This problem is certainly not unique to taxol.

Here's what I think the biggest problem is: the complexity of molecules scales exponentially with size, but the complexity introduced by a synthetic sequence scales even less than linearly with its length.

MacMillan points out that the yield of a synthetic sequence also drops exponentially with its length. A somewhat unsatisfactory, literal explanation is that the total yield is just the product of the yields of every step. But why don't reactions give 100% yield?

(1) The reactions are intrinsically "dirty" and give side products which account for the remainder of the mass balance.

(2) Purification is "lossy."

Just how lossy is purification? Hudlicky has recently done some simple experiments (Synlett 2010 18 2701) which show that, in general, one cannot expect more than a ca. 94% yield for any given reaction which involves workup and chromatography.

<table>
<thead>
<tr>
<th>Step</th>
<th>Mass Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filtration</td>
<td>1001.7 mg</td>
</tr>
<tr>
<td>Aqueous Extraction</td>
<td>978.6 mg</td>
</tr>
<tr>
<td>Fraction Collection</td>
<td>985.0 mg</td>
</tr>
<tr>
<td>Separation</td>
<td>980.1 mg</td>
</tr>
</tbody>
</table>

This is bad news if you want to use a sequence of 37 steps. The top synthesis, Wender's, already has an average yield of 85%, suggesting that there is nothing wrong with the reactions themselves; they're simply not generating enough complexity per step.
Enamine and Iminium Organocatalysis

MacMillan proposes that we circumvent the defects of "stop-and-go" synthesis by combining several steps into one step. For example, consider this sequence (JACS 2005 127 15053):  

Without catalyst, one is at the mercy of the complex energy landscape that is intrinsic to the reaction; there is no guarantee that the desired reaction lies on the minimum energy path. Nor is it guaranteed that there is only one minimum energy path, such that the reaction will be "clean" and have no other side products. So using a tunable catalyst is a real advantage in that sense.

(3) One complaint about this chemistry is that it makes strings of stereocenters efficiently, but is relatively ineffective at building structural complexity. Is this true? You decide.

This area has been reviewed recently: "Organocatalytic Cascade Reactions..." Enders, D. et al. Nature Chemistry 2010, 2, 167-178. Here is another example from the Hayashi group for the synthesis of oseltamivir (ACIE 2009 48 1304):

This represents the merging of two catalytic cycles. First, the catalyst forms an iminium ion with the aldehyde (A), which undergoes a Friedel-Crafts alklylation. Then, the product tautomerizes into a nucleophilic enamine (B), which is chlorinated.

(1) This reduces the number of purifications required, which is good. However, simply performing reactions in a cascade, rather than stop-and-go sense does not by itself improve the intrinsic yield of a reaction.

(2) Cascade reactions are not new. In fact, we've already seen quite a few such reactions in the course already. However, most of them are diastereoselective in nature. For example, this cascade reaction was discussed in Lecture 10 on page 14:

Unfortunately, the second step delivers the incorrect stereocenter at the nitro group. (All of this occurs in one pot.)
Fortunately, a hetero-conjugate addition/epimerization strategy, followed by some other manipulations delivers Tamiflu in 57% overall yield from the nitroalkene, which is pretty good. Overall, there are nine reactions, three separate one-pot operations, and one column chromatography purification.

![Chem 106 Diagram](image)

1. The second one-pot procedure sequentially cleaves the tert-butyl ester, converts the liberated carboxylic acid into the acyl chloride, and displaces the chloride with azide.

2. The third one-pot procedure first converts the acyl azide into the amine via a Curtius rearrangement. The advantage of these conditions is that the reaction occurs at ambient temperatures. The amine is trapped by acetic anhydride. Zinc then reduces the nitro group. Finally, ammonia is added to chelate the zinc, and potassium carbonate initiates a retro-conjugate addition to generate the olefin.

Obviously, this is a very nice synthesis, but the fact that the conjugate addition is not catalyst controlled means that its $dr$ is at the mercy of the various stereocenters present:

A more sophisticated "cycle-specific" strategy is to use more than one catalyst at the same time (MacMillan *ACIE* 2009 48 4349). This requires the catalysts be orthogonal:

- Three sequential one-pot operations

$$
\text{ketone aldol (proline)}
$$

- Selective for enamine catalysis

- Selective for iminium catalysis

- Friedel-Crafts alkylation (imidazolidinone)
**Steroselectivity in Cascades**

A common feature in these cascade reactions is that they give very high overall enantioselectivities, even if the component reactions are not very enantioselective. How is this possible?

Consider a two-step cascade in which the first step produces an $x:1-x$ enantiomeric ratio of products, where $x$ is the mole fraction of R configuration produced at stereocenter 1. Similarly, step 2 has a selectivity of $y$:

\[
\text{starting material} \xrightarrow{\text{step 1}} xR_1 \rightarrow x(1-y)R_1-S_2 \quad \text{step 2} \rightarrow xyR_1-R_2
\]

(1-x)S_1

(1-x)yS_1-R_2

(1-x)(1-y)S_1-S_2

If this seems a bit abstract, maybe revisiting this example will help:

![Chemical structures](image)

The Friedel-Crafts alkylation is step 1, and has some intrinsic enantioselectivity $x$. The chlorination is step 2, and has another intrinsic selectivity $y$.

(1) Without a loss in generality, suppose that the $R_1-R_2$ product is the desired one. How much of it is formed? A mole fraction of $xy$.

(2) Where does the enantiomer of the desired product, $S_1-S_2$, come from? It comes from an incorrect first step, followed by an incorrect second step. Hence, a mole fraction of $(1-x)(1-y)$ is formed. Since $1-x$ and $1-y$ are small fractions (i.e., less than 1), multiplying them together gives an even smaller number.

(3) The enantiomeric ratio of the product is therefore $xy$ divided by $(1-x)(1-y)$. Division by a very small number between 0 and 1 increases the size of $xy$ by a lot. This is why the enantiomeric ratio of the product is very large.

(4) The enantiomeric ratio of the product can be big, even if the enantioselectivity of the component steps is not that great. For example, suppose steps 1 and 2 have ee's of 80%. That would be considered good, but great. In our language, this would mean $x = y = 0.9$. This gives an enantiomeric ratio of 81:1, or an ee of 97.6% (which, for one step, would be considered excellent).

Thus, it is relatively easy to get almost enantiopure product:
Enamine and Iminium Organocatalysis

Enantioselective Catalysis Using SOMO Activation.

MacMillan's clever idea is that enamines are very electron rich, and therefore more easily oxidized than amines or iminiums:

![Chemical structures showing SOMO activation](image)

(The ionization potentials are shown in bold; the lower the number, the easier it is to oxidize.) Oxidation of the enamine produces a radical cation, which is an ambident electrophile:

![Chemical structures showing radical cation formation](image)

In the jargon of organocatalysis, this is "SOMO activation"---the generation of a singly occupied molecular orbital which can undergo many subsequent reactions. One of the first examples was an aldehyde allylation, which is very useful synthetically:

![Chemical structures showing allylation](image)

Q: What's in between an enamine and an iminium?

CAN is ceric ammonium nitrate (NH₄)Ce(NO₃)₆, which is a strong oxidant (even stronger than Cl₂!) which reacts to generate a chiral enamine radical cation.
SOMO Activation
If the nucleophile is allyltrimethylsilane, then this produces:

\[
\begin{align*}
\text{R}^+ & \text{Si(CH}_3\text{)}_3 \text{H} \\
\text{R}^- & \text{Si(CH}_3\text{)}_3 \text{H} \\
\text{R} & \text{Si(CH}_3\text{)}_3 \text{H} \\
\end{align*}
\]

\[\text{H}_{2}\text{O} \rightarrow \text{H}_2\text{O} + \text{R}^- \text{Si(CH}_3\text{)}_3 \text{H}
\]

(catalyst substituents omitted)

The regioselectivity can be explained by a radical version of the \(\beta\)-silicon effect; donation of the Si-C bonds into the radical is good. (However, the \(\beta\)-silicon effect for radicals is much less than for carbocations.) The radical gets oxidized to the carbocation (which is why two equivalents of CAN are required), and then base comes in and does a Peterson olefination.

**stereochemical model**

cation–\(\pi\) interaction between benzyl group and allyl radical cation?

(Historical Note: This use of stoichiometric CAN for similar reactions was previously reported by Narasaka (Chem Lett 1992 2099.)

Aldehydes can be coupled with enolate equivalents, which produces *umpolung* 1,4-dioxygenated relationships (MacMillan JACS 2007 1297004): (DTBP = 2,6-di-tert-butylpyridine)

\[
\begin{align*}
\text{HCOMe} + \text{OTMS} & \rightarrow \text{HCOMe} \text{Ph} \\
\text{HCOMe} + \text{OTMS} & \rightarrow \text{HCOMe} \text{Ph} \\
\end{align*}
\]

A dramatic demonstration of the power of this activation mode to produce complex architectures as well as stereodefined arrays is this cascade polyene cyclization (MacMillan JACS 2010 132 5027):

\[
\begin{align*}
\text{Cu(OTf)}_2 \text{NaTFA/TFA} & \text{1PrCN/DME} \text{23 °C} \\
& \rightarrow \text{56%, 92% ee} \\
\end{align*}
\]

\[
\begin{align*}
\text{HCOMe} & \rightarrow \text{HCOMe} \\
\text{HCOMe} & \rightarrow \text{HCOMe} \\
\end{align*}
\]

(CAN is ineffective here due to an inner-sphere nitrate transfer. It is interesting that both the yield and ee go up when the aryl group on the catalyst changes from phenyl to naphthyl. To me, this strongly suggests an enhanced cation–\(\pi\) interaction with a larger aromatic surface.)
If the nucleophile is allylttrimethylsilane, then this produces:

\[
\begin{align*}
\text{Nucleophile:} & \quad \text{Silicon-stabilized radical.} \\
\text{Reaction:} & \quad \text{Reduction to an enamine.} \\
\text{Catalyst:} & \quad \text{Peterson olefination.}
\end{align*}
\]

The regioselectivity can be explained by a radical version of the \( \beta \)-silicon effect; donation of the \( \text{Si-C} \) bonds into the radical is good. (However, the \( \beta \)-silicon effect for radicals is much less than for carbocations.) The radical gets oxidized to the carbocation (which is why two equivalents of CAN are required), and then base comes in and does a Peterson olefination.

**Stereochemical model**

- Cation-\( \pi \) interaction between benzyl group and allyl radical cation?

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\[
\text{Aldehyde} + \text{Enolate} \rightarrow \text{Cyclization}
\]

A dramatic demonstration of the power of this activation mode to produce complex architectures as well as stereodefined arrays is this cascade polyene cyclization (MacMillan JACS 2010 132 5027):

- CAN (2 equiv.), H\( \text{O} \), DTBP, acetone, 24h, \(-20\ ^\circ\text{C}\)
- 74% yield, 93% ee

\[
\begin{align*}
\text{(Catalyst substituents omitted)}
\end{align*}
\]

\[
\begin{align*}
\text{Aldehyde} + \text{Allyl Vinyl Ether} \rightarrow \text{Cyclization}
\end{align*}
\]

- Cu(OTf)\( _2 \), NaTFA/TFA, iPrCN/DME, 23\ ^\circ\text{C}
- 56%, 92% ee

CAN is ineffective here due to an inner-sphere nitrate transfer. It is interesting that both the yield and ee go up when the aryl group on the catalyst changes from phenyl to naphthyl. To me, this strongly suggests an enhanced cation-\( \pi \) interaction with a larger aromatic surface.