

Kinetic Protonation

Kinetic protonation, the phenomenology:

Howard E. Zimmerman "Kinetic Protonation Of Enols, Enolates, And Analogues. The Stereochemistry Of Ketonization" *Acc. Chem. Res.* **1987**, *20*, 263-268

Howard E. Zimmerman and Alexey Ignatchenko "Reversal of the Stereochemistry of Kinetic Protonation by Intramolecular Proton Delivery and a Remarkable Dependence of Selectivity on Donor Concentration" *J. Am. Chem. Soc.* **1998**, *120*, 12992-12993

Asymmetric protonation:

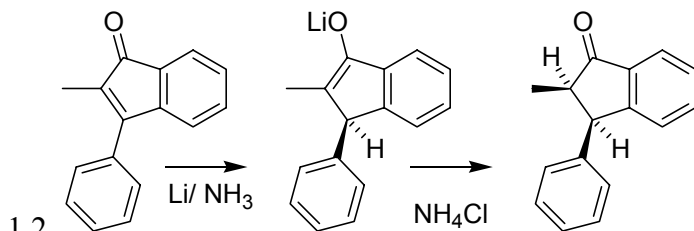
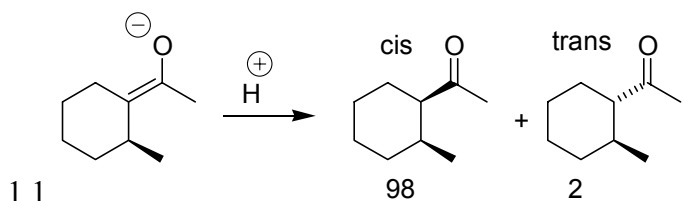
E. Vedejs, A. W. Kruger, N. Lee, S. T. Sakata, M. Stec, and E. Suna "Enantioselective Enolate Protonation with Chiral Anilines: Scope, Structural Requirements, and Mechanistic Implications" *J. Am. Chem. Soc.* **2000**, *122*, 4602-4607

In total synthesis:

Frederick Cohen, Larry E. Overman, and Sylvie K. Ly Sakata "Asymmetric Total Synthesis of Batzelladine D" *Org. Lett.*, **1999**, *1*, 2169-2172.

Andrew Hinman and J. Du Bois "A Stereoselective Synthesis of (-)-Tetrodotoxin" *J. Am. Chem. Soc.* **2003**, *125*, 11510-11511.

1. Envision being able to add a proton to an enolate in a kinetic fashion to arrive at the high-energy ketone. For example:



(Zimmerman, 1987)

- 1.3. Why should Mother Nature choose to add a proton from the side of the prochiral enolate that would result in the higher-energy ketone?

1.3.1. The protonation reaction can be thought of as an S_N2 reaction with an H atom as the reaction center instead of a C atom. The transition states of S_N2 reactions involve a close connection between electrophile and nucleophile.

1.3.2. Another fact that demystifies kinetic protonation is the relatively short bond length of C-H and X-H bonds. C-H ~ 1.1 Å; X-H ~ 1.0 Å; C-C H ~ 1.5 Å.

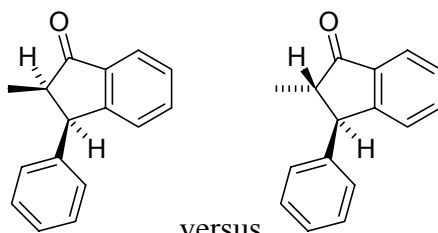
1.3.3. In the S_N2 reaction these bonds are partially formed so in the reaction $R_3C(-) + H-$

$X^* \text{ ----> } R_3CH + X^*(-)$ the t-state: $R_3C\text{--}H\text{---}X^*$ puts the C and X^* atoms in proximity.

1.3.4. This proximity means that groups on $R_3C(-)$ and HX^* interact.

1.3.5. It is not surprising given the above two points that the proton will be delivered from the side opposite of the phenyl group in the example above.

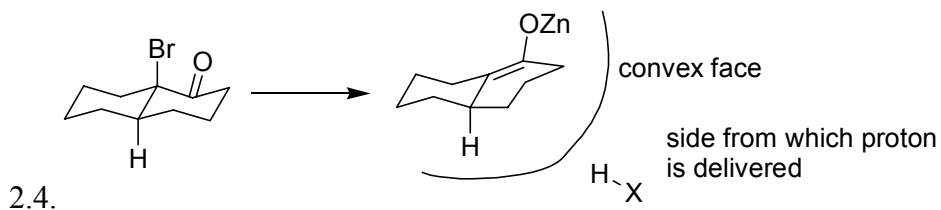
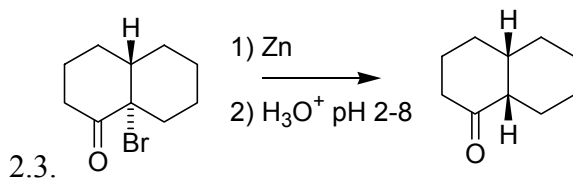
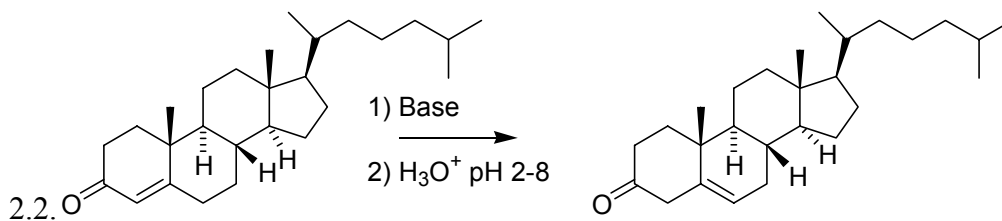
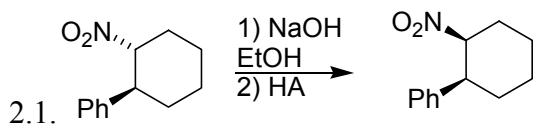
1.3.5.1. This is a kinetic argument. When one switches to thermodynamic considerations, the reason usually cited for the instability of



versus is the fact that the electron clouds in the larger groups, Ph and Me, are interacting in the cis product and not in the trans product: steric interactions.

1.3.5.2. These facts lead us to believe that the 'kinetic product' should differ from the thermodynamic product and there are only two choices; there are only two prochiral faces.

2. Without the above facts the following reactions might seem rather like magic.



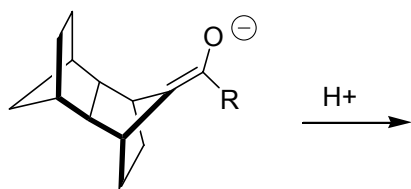
3. While the seven reactions above do not appear to be that structurally related, they do have something interesting in common.

3.1. The proton accesses the less sterically hindered face of the enolate.

3.1.1. The proton needs to access the pi-cloud of the enolate.

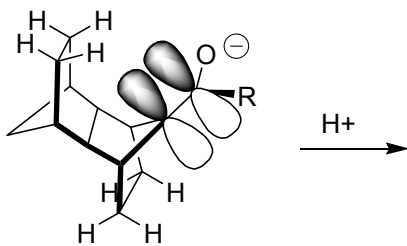
3.1.2. Make a model to convince yourself that these electrons are more accessible from the convex face.

3.1.3. Applying this principle to



3.1.4.

Can you predict the product?

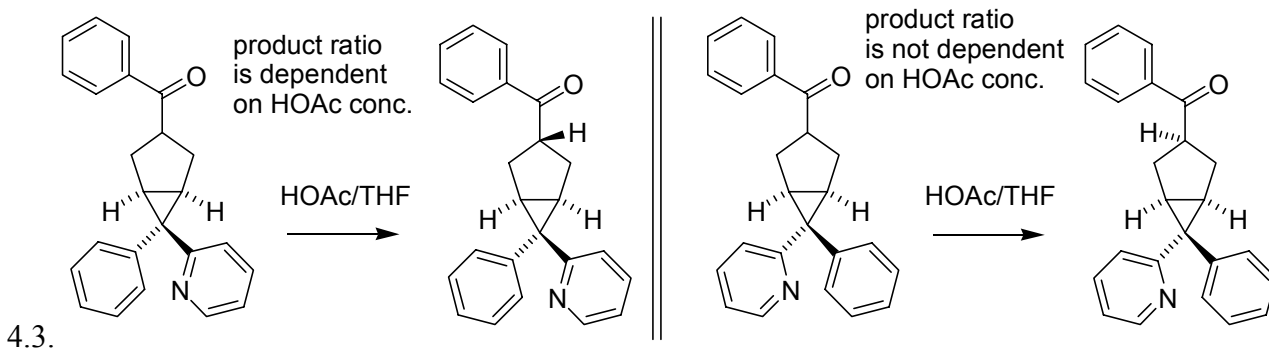


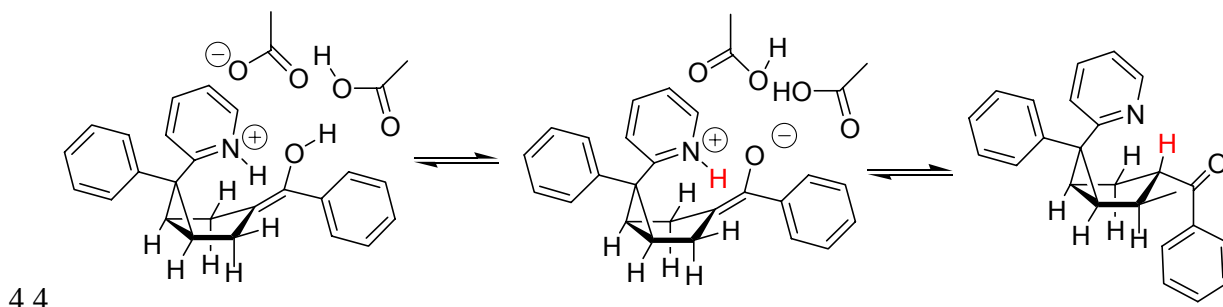
3.1.5. Does this help?

4. There are interactions with other functionality that cause some complications.

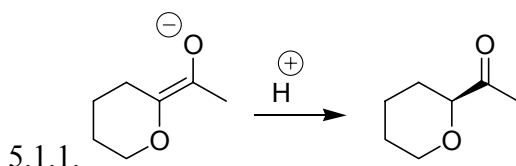
4.1. Steric considerations are not everything.

4.2. Consider the following example (Zimmerman 1998)





5. What would be the requirements to accomplish this in an enantiospecific reaction?



5.1.2. Here the prochiral sp^2 C atom α to the ring O atom is protonated in a facially selective manner.

5.1.3. Obviously we will not be able to accomplish the above reaction without an optically pure proton donor.

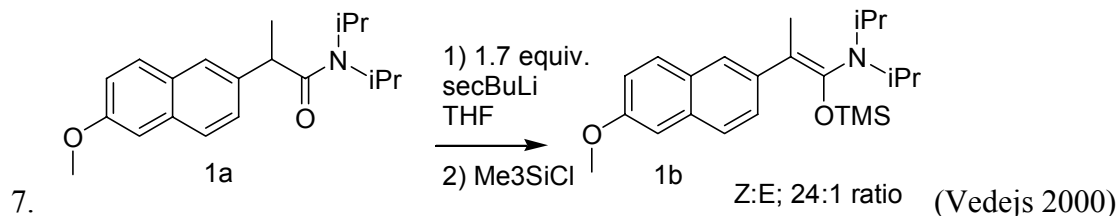
5.1.4. The above reaction is only possible because the (S) molecule shown above and the chiral proton donor are diastereomeric to the pair consisting of the (R) molecule and the chiral proton donor.

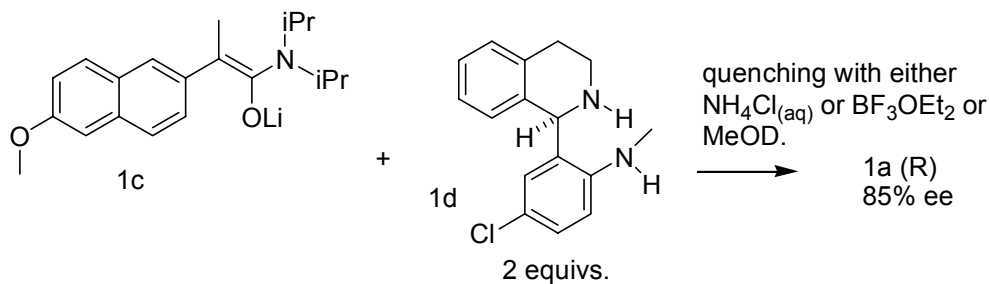
5.1.5. Since the evolutions of the (S) and the (R) product in this case have different rates of protonation by a chiral source, one might expect to be able to perform this reaction.

5.1.6. In the first example a chiral proton source is not necessary because the cis and the trans 1-acyl-2-methylcyclohexane molecules are diastereomers.

5.1.6.1. As such the rates of protonation leading to these two products are different.

6. From a synthetic point of view, chiral induction by adding a proton is advantageous because the proton is so small and ubiquitous in organic molecules—the method should be generally applicable.





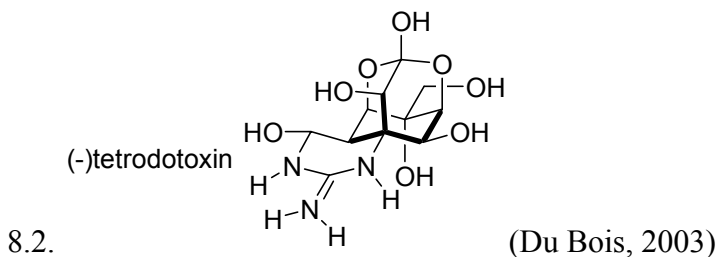
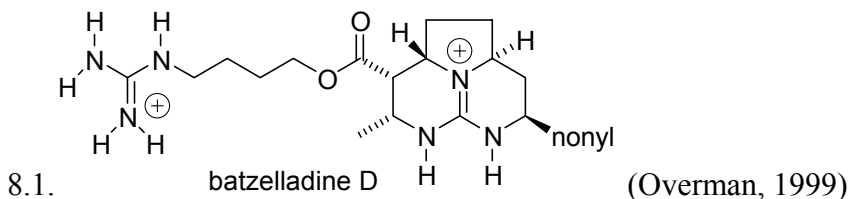
7.1.

7.2. With 5 mol % of 1d and excess *sec*-butyllithium and an achiral proton source, (PhCH₂CO₂Et), resulted in (*R*)-1a with >90% ee.

7.2.1. This result makes this procedure highly attractive, if conditions can be worked out.

However the results depend quite a bit on the nature of the amide substrate.

8. Kinetic protonation in total synthesis has been done many times. I offer two examples below.



8.3. Hopefully you can immediately see where kinetic protonation might be applicable in the first example.