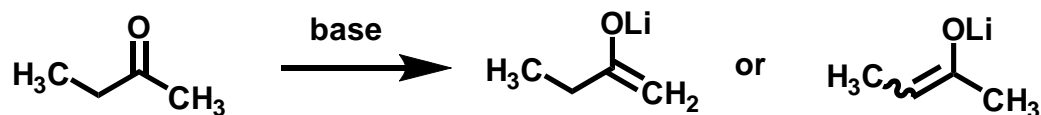


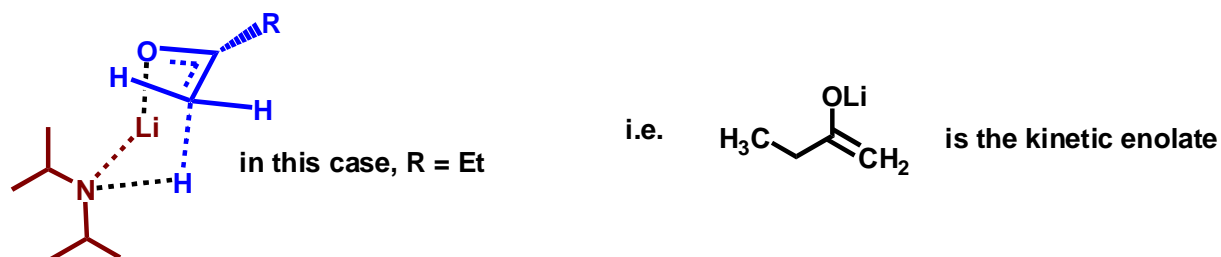
Regioselectivity in Kinetics Aldols/'Kinetic' Enolate Generation

In ketones, there is often the issue that there is more than one potential site for deprotonation. The question then becomes one addressing which site is deprotonated. We'll start by considering a very simple example, like 2-butanone (methyl ethyl ketone).

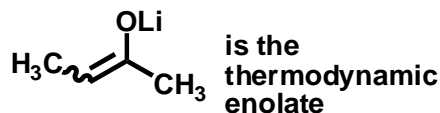


It often, in fact *usually*, turns out that one of the sites is more rapidly deprotonated, and deprotonation at the other site gives the more stable anionic species. These are called the **kinetic** (faster) and **thermodynamic** (more stable) enolates, respectively.

With a base like LDA, and low temperatures, one gets rapid deprotonation, and practically not an equilibrating system. These types of bases such as LDA have been made to be sterically bulky for many reasons. As a result, the site at which deprotonation occurs fastest is the least sterically hindered site, which in simple cases means deprotonation from the least sterically hindered side.

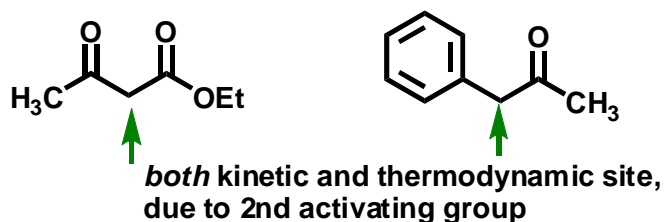


If you can equilibrate the enolates, like we have previously with a weak base and unlowered temperatures, then one gets the most thermodynamically stable enolate. In simple cases, such as 2-butanone or ones like it, an enolate is like a double bond; the more highly substituted alkene is the thermodynamically most stable (this is due to hyperconjugation). So in simple cases, the **thermodynamic** enolate is opposite to the kinetic one.



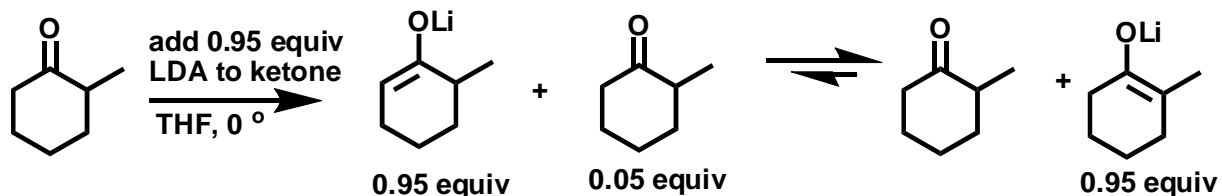
To summarize, in most cases, the kinetic enolate is the less substituted one, while the thermodynamic enolate is the more substituted one.

There is a caveat though, that these rules are for cases where there isn't an additional activating (acidifying) group. An ester (or other carbonyl), or even a phenyl group, are sufficiently acidifying that both the kinetic and thermodynamic site of deprotonation are the same, i.e....

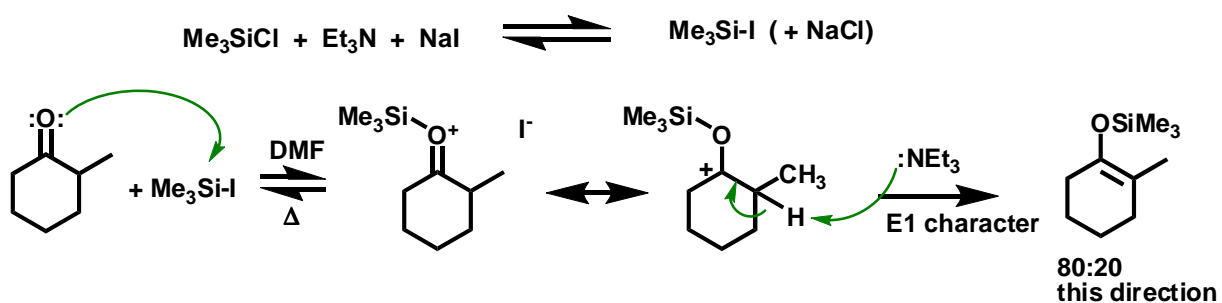


So how does one get a stoichiometrically generated 'thermodynamic enolate'? The above does bring up the question as to how one gets the thermodynamic enolate under conditions that are otherwise kinetic in nature (full equivalent of enolate or close at any one time). There are two common approaches that I'll list here.

- a) Adding just *under* 1 equiv of LDA to the ketone is sometimes effective. This is normally done by adding the base to the ketone, rather than the other way around. This tends to work because there will be some unde protonated ketone and enolate (deprotonated) present at the same time, and *these two species* will equilibrate. I've chosen a higher temperature than -78°C , arbitrarily 0°C to show this.



- b) Make a silyl enol ether (also called an enol silane) under weak base conditions. These conditions generate the more substituted silyl enol ether mostly. These can often be used in aldol type reactions, or the lithium enolate itself can be generated using *n*-BuLi in a non-deprotonating process.



and then....

