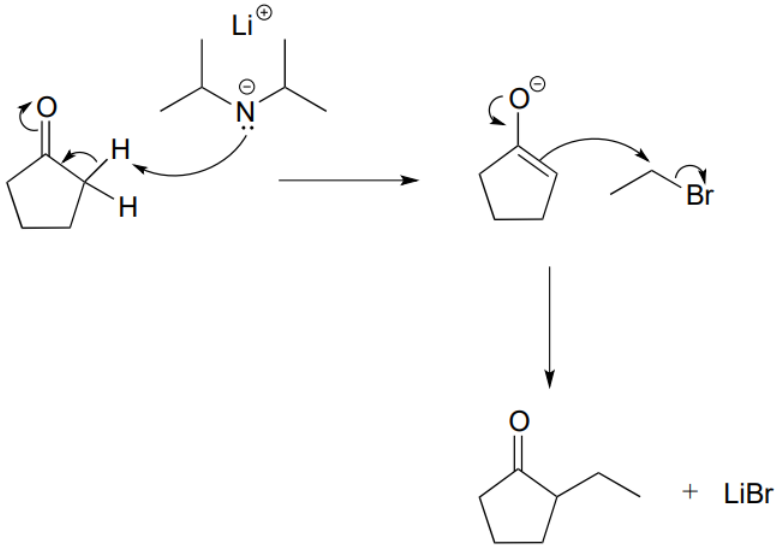
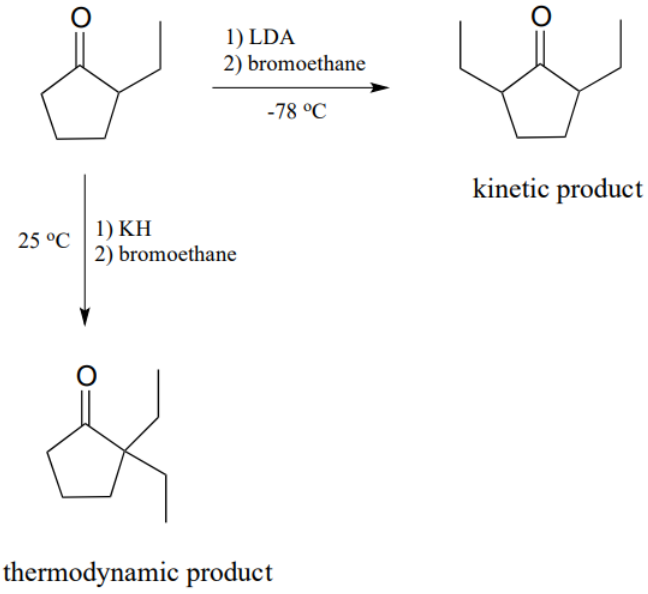
12.5: α-Carbon Reactions in the Synthesis Lab - Kinetic vs. Thermodynamic Alkylation Products

While aldol addition reactions are widespread in biochemical pathways as a way of forming carbon-carbon bonds, synthetic organic chemists working the lab also make use of aldol-like reactions for the same purpose. Consider this reaction:



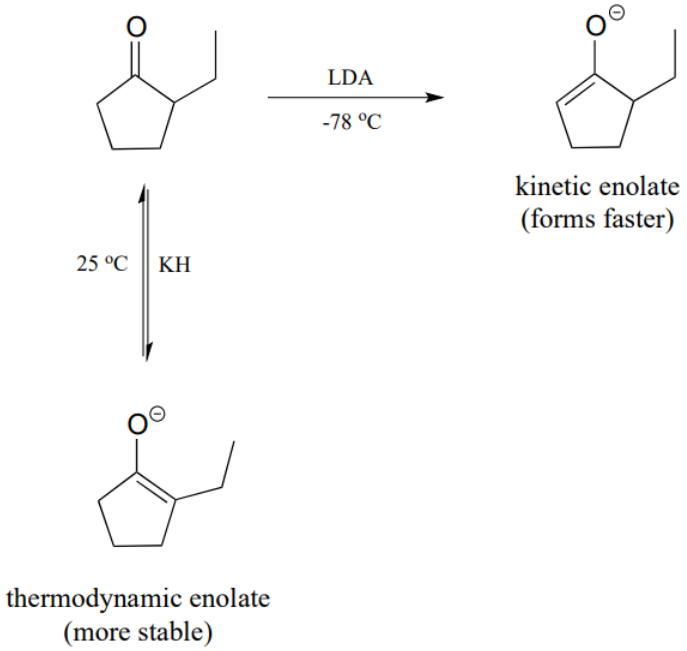
Here, cyclopentanone is deprotonated at an α-carbon by lithium diisopropylamide (LDA), a very strong base commonly used in the synthesis lab. Addition to the reaction mixture of an electrophile in the form of a primary alkyl bromide results in formation of a new carbon-carbon bond. Notice that this is a kind of 'S_N2 variation' on the aldol addition reactions we saw above, because the enolate nucleophile is attacking in S_N2 fashion rather than in a carbonyl addition fashion.

What would happen, though, if we started with 2-ethylcyclopentantone? Because the starting ketone is no longer symmetrical, we could hypothetically obtain two different products:



It turns out that we can control which product we get by selecting the base used in the reaction, and the reaction temperature. If we use LDA and immerse the reaction flask in a dry ice-acetone bath ($-78^{\circ}C$), we get mainly 2,5-diethyl cyclopentanone. If we use potassium hydride (KH) and run the reaction at room temperature, we get mainly 2,2-diethylcyclopentanone.

LDA is a very *hindered* base: the basic nitrogen atom is surrounded by two bulky isopropyl groups, and thus it is more difficult for it to come into contact with an α-proton. The α-protons on the less substituted side of 2-ethylcyclopentanone are less hindered and more accessible to the base. In addition, the cold reaction temperature means that the deprotonation step is irreversible: the system does not have enough energy to overcome the energy barrier for the reverse (reprotonation) reaction. The less substituted enolate forms faster, and once it forms it goes on to attack the bromoethane rather then reversing back to the ketone form. Because it is the rate of enolate formation that determines the major product under these conditions, we say that this reaction is under kinetic control, and the less substituted enolate intermediate is called the kinetic enolate.



If, on the other hand, we use KH as a base, hindrance is no longer an issue because the base is a hydride ion. We run this reaction at room temperature, so the system has enough energy to overcome the energy barrier for re-protonation, and enolate formation is reversible. The enolate in most abundance at equilibrium is therefore not the one that forms fastest, but the one that is more stable. The more substituted enolate is more stable (recall that alkenes are more stable when they are more substituted - the same idea applies here). The more substituted enolate leads to the 2,2-diethyl cyclopentanone product. Because it is the stability of the enolate intermediate that determines the major product under these conditions, we say that this reaction is under thermodynamic control, and the more substituted enolate intermediate is the thermodynamic enolate.
