

Lecture # 15

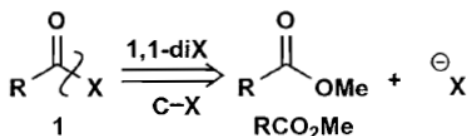
One Group C–C Disconnections II: Carbonyl Compounds

Background Needed for this Chapter

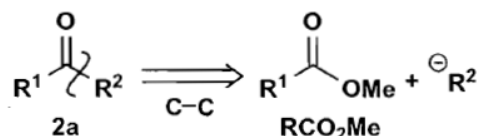
Using Organometallic Reagents to Make C–C Bonds. : Alkylation of Enolates

In chapter 10 we compared C–C disconnections with related two-group C–X disconnections, mainly at the alcohol oxidation level. In this chapter we deal more fully with carbonyl compounds, chiefly aldehydes and ketones, by two related disconnections. We start by comparing the acylation of heteroatoms by acid derivatives such as esters (a 1,1-diX disconnection **1** that can also be described as a one-group C–X disconnection) with the acylation of carbon nucleophiles and move on to compare the 1,2-diX disconnection **3** with the alkylation of enolates **6**. Here we have reversed the polarity. We mention regioselectivity—a theme we shall develop in chapter 14.

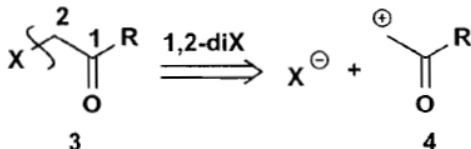
1,1-diX Disconnections:



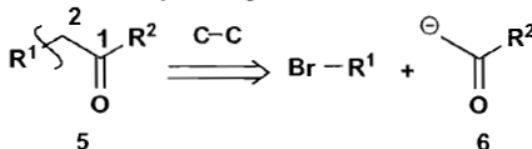
The Corresponding C–C Disconnection:



1,2-diX Disconnections:

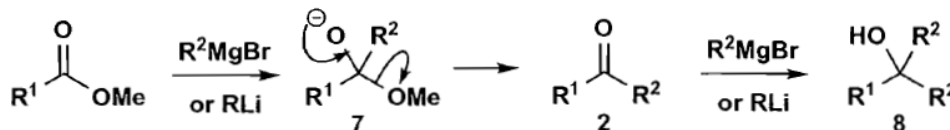


The Corresponding C–C Disconnection:



Synthesis of Aldehydes and Ketones by Acylation at Carbon

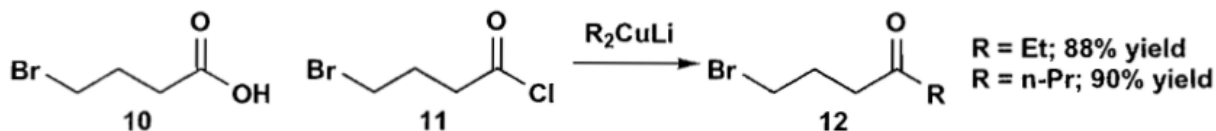
The disconnection **2a** is not useful because, as MeO[−] is the best leaving group from the tetrahedral intermediate **7**, the ketone **2** is formed during the reaction. The ketone is more electrophilic than the ester so it reacts again and the product is the tertiary alcohol **8**.



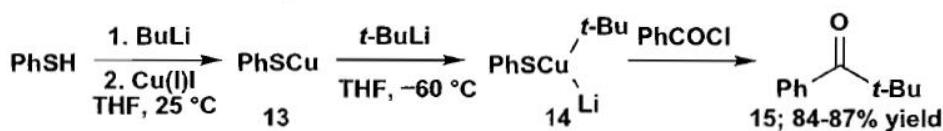
One solution is to use an acid chloride as an acylating agent since that is *more* electrophilic than the ketone. The problem with this approach is that we wish to combine two extremely reactive compounds and an uncontrollable reaction ensues. Successful acylation of the much less reactive, and therefore more selective, organo-copper reagents is known. Treatment of organo-lithium reagents with CuI in dry THF at -78°C gives dialkyl copper lithiums or cuprates¹ R_2CuLi . These react cleanly with acid chlorides, again at low temperature, to give ketones.²



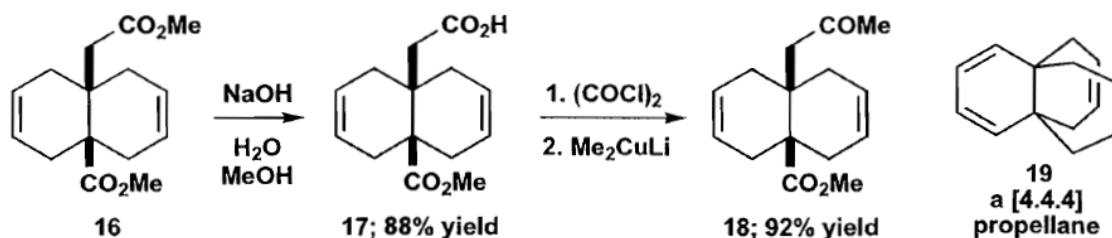
A simple example that also shows some chemoselectivity is the preparation of the ketones **12**; R = Et or Pr by reaction of the bromoacid chloride **11** with the appropriate dialkyl copper lithium. The bromoacid **10** is available and can be converted into a range of bromoketones by this method.³



Only one alkyl group is transferred from R_2CuLi and to avoid wasting the other R group, complexing agents can be added. Posner⁴ uses a PhS group to stabilise the organo-copper reagent **14** with one *t*-Bu group that is cleanly transferred to the acid chloride. Friedel-Crafts reactions of *t*-BuCOCl are plagued with loss of CO so this is a better method.



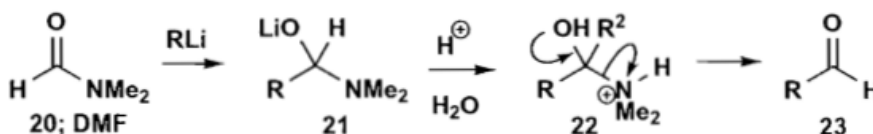
In his synthesis of the [4.4.4]‘propellane’ **19**, Paquette made the diester **16** easily but wanted the *mono* methyl ketone **18**. Rather than add MeLi directly, he first hydrolysed one ester to the free acid **17** and then made the acid chloride with oxalyl chloride. Reaction with Me₂CuLi gave the ketone in excellent yield.⁵



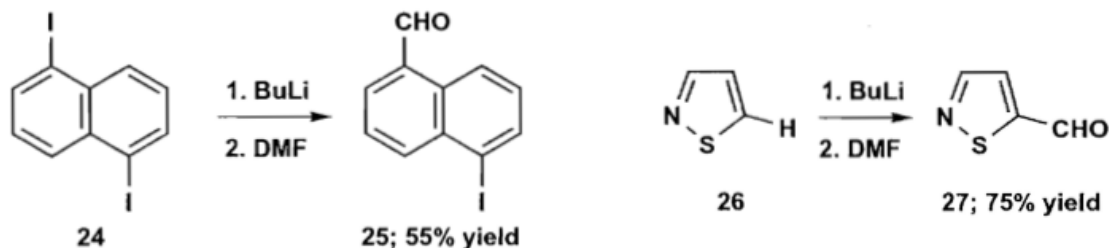
Direct Formylation of Organo-Lithiums with DMF

Another method is to use a much *less* electrophilic acylating agent than an ester. This sounds crazy but DMF **20** reacts directly with organo-lithium compounds to give good yields of aldehydes

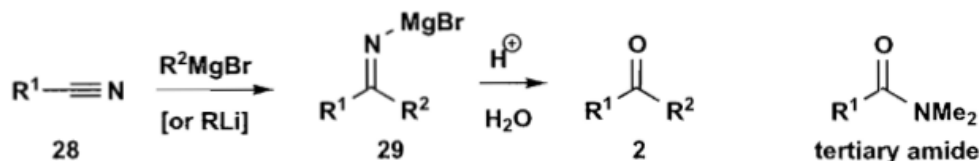
23. Now the tetrahedral intermediate **21** is stable under the reaction conditions as Me₂N[−] is such a bad leaving group. The aldehyde **23** is formed only during work-up in aqueous acid **22**.



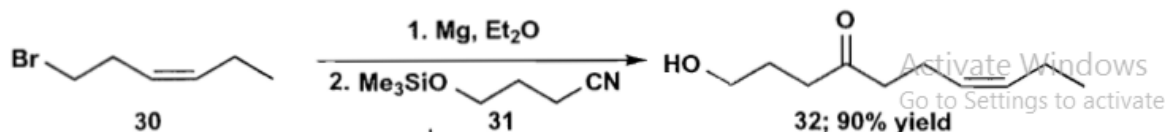
The organo-lithium reagent can be made by exchange of Li for a halide or by deprotonation. With di-iodide **24**, one iodine may be exchanged with one equivalent of BuLi and the aldehyde **25** is the product.⁶ The aromatic heterocycle isothiazole **26** has its most acidic hydrogen (marked) next to sulfur and it gives one aldehyde **27** in good yield.⁷



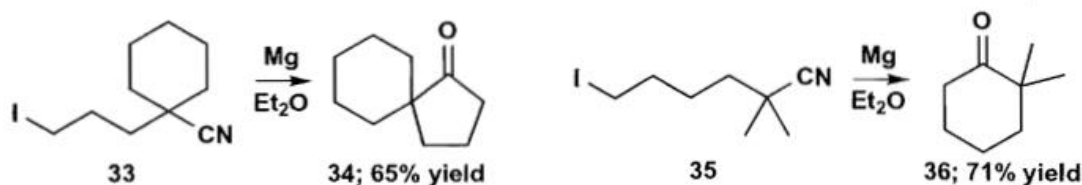
A more reactive equivalent for ketone synthesis is a nitrile **28**. Addition of a Grignard reagent gives an intermediate **29**, stable under the reaction conditions, rather like **21**. Hydrolysis in acid solution releases the ketone **2**. The exactly analogous reagent to DMF would be a tertiary amide but these are often so unreactive as to be useless.⁸



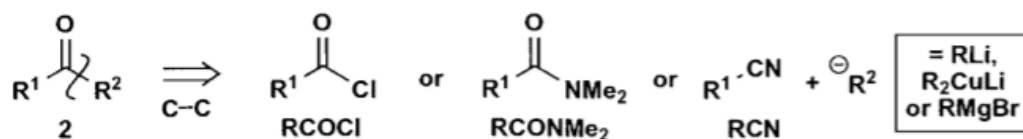
Grignard reagents are usually better than organo-lithiums in these reactions⁹ and may be even better with a catalytic amount of copper (I). A good example is the coupling of the Grignard reagent derived from **30** with the protected nitrile **31** giving an excellent yield of the ketone **32**. As a bonus, the protecting group drops off in the work-up.¹⁰



These reactions may be intramolecular giving five- or six-membered cyclic ketones such as the spiro (two rings with one common atom) compound **34** and the hindered cyclohexanone **36**.¹¹

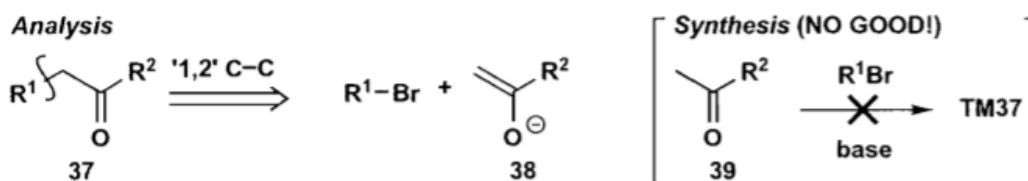


Please note that this whole section—indeed all of the chapter so far—relates to the C–C disconnection between the carbonyl group and whatever is joined to it **2**. The nucleophilic reagent is an organometallic derivative of Li, Cu or Mg and the electrophile is an acid chloride, a tertiary amide or a nitrile. In the next section we disconnect the C–C bond one further from the carbonyl.

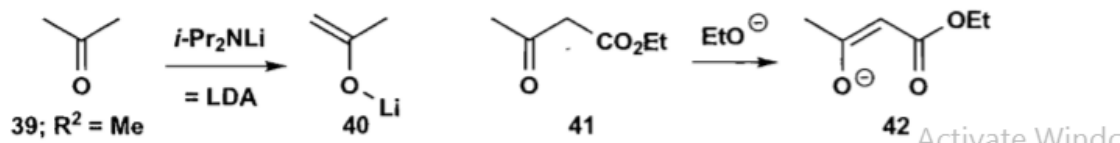


Carbonyl Compounds by Alkylation of Enols

Disconnection **37** again uses the natural polarity of the carbonyl group but at the next bond **37** since we hope to use some enolate derivative **38** in an alkylation reaction. But—and it is a big but—do not think for a moment that you can make **37** just by mixing the ketone **39** with an alkyl halide and some base. The problem is that the ketone is itself electrophilic and the self-condensation by the aldol reaction (chapter 19) is generally preferred to alkylation.

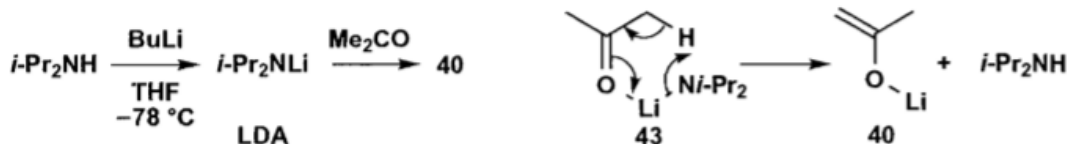


We need first of all to convert the ketone **39** *completely* into some enolate derivative so that there is no ketone left for self-condensation. In this chapter we shall restrict ourselves to lithium enolates **40** and anions **42** of 1,3-dicarbonyl compounds **41**. Each of these reagents acts as the enolate anion of acetone **38**; $\text{R}^2 = \text{Me}$.

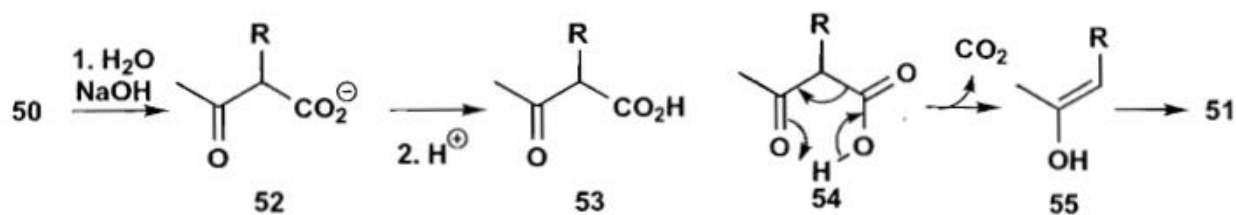


Lithium Enolates of Simple Carbonyl Compounds

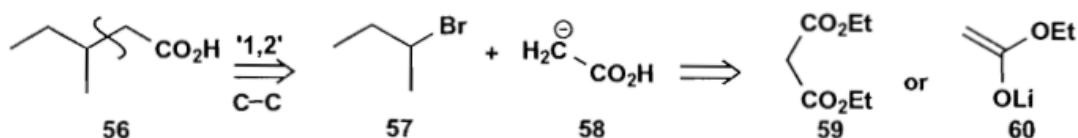
Lithium enolates **40** are usually made with LDA (Lithium Di-isopropylAmide). We need a strong base—one strong enough to convert the ketone immediately into the lithium enolate. Butyl lithium would be strong enough but it attacks the carbonyl group as a nucleophile instead. We therefore use the BuLi to make LDA—a strong but very hindered base that usually does not attack the carbonyl group. The reagent LDA is prepared in dry THF at low temperature¹² and the ketone added by syringe also at low temperature. The lithium atom bonds to the oxygen and the amide is then in perfect position to remove the proton **43**.



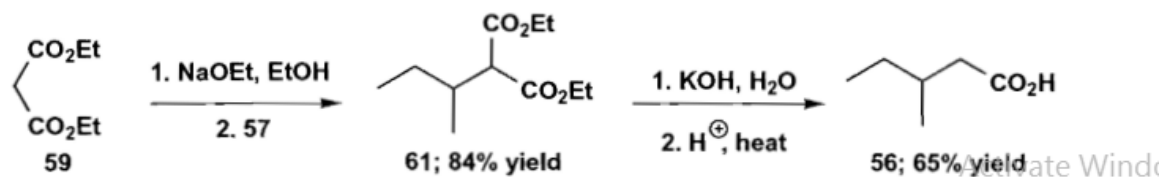
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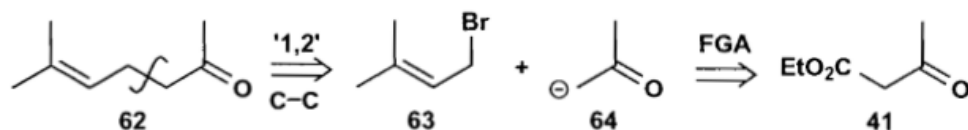
The extra ester group is not normally added to the preformed ketone as ethyl acetoacetate **41** is available and the diester is available diethyl malonate **59**. If it is necessary to make the 1,3-dicarbonyl compound, this can be done by methods described in chapters 19 and 20. The carboxylic acid **56** can be disconnected at the branchpoint to an alkyl halide and the synthon **58** that could be realised as the anion of diethyl malonate **59** or the lithium enolate of ethyl acetate.



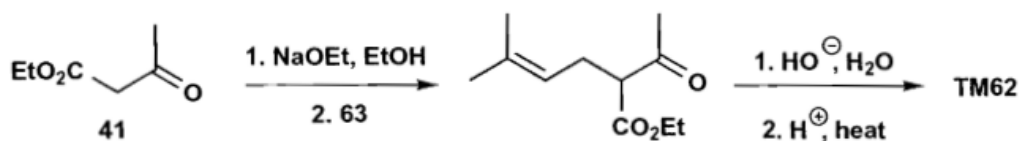
One published synthesis uses the malonate route.¹⁴ Ethoxide is used as the base so that it doesn't matter if it attacks the esters as a nucleophile.



A good example of a ketone made by this strategy is used in the synthesis of terpenes. After the usual '1,2' C-C disconnection, adding the ester group to the enolate **64** gives ethyl acetoacetate **41**.



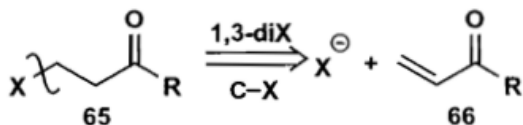
The alkylation goes well as **63** is the reactive allylic halide 'prenyl bromide' and hydrolysis and decarboxylation occur as usual.¹⁵



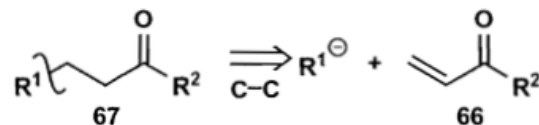
Carbonyl Compounds by Conjugate Addition

The remaining style of C–C disconnection takes us straight to conjugate addition and we are still using the natural polarity of the carbonyl group. Conjugate addition of a heteroatom to the enone **66** gives the 1,3-relationship in **65** and the same process with a carbon nucleophile gives **67**.

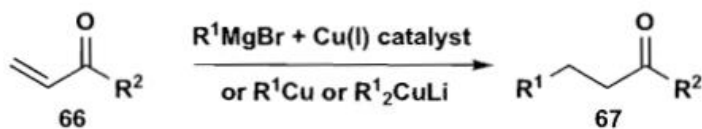
1,3-diX Disconnections:



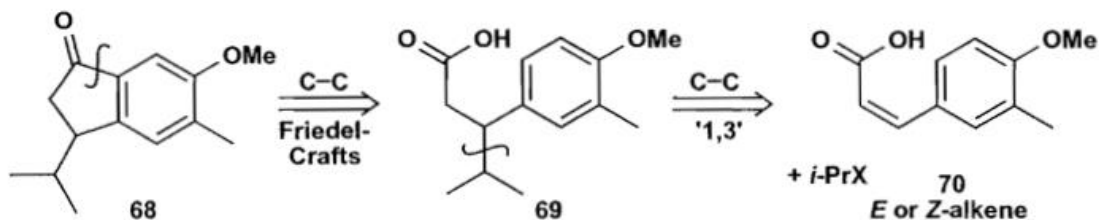
The Corresponding C–C Disconnection:



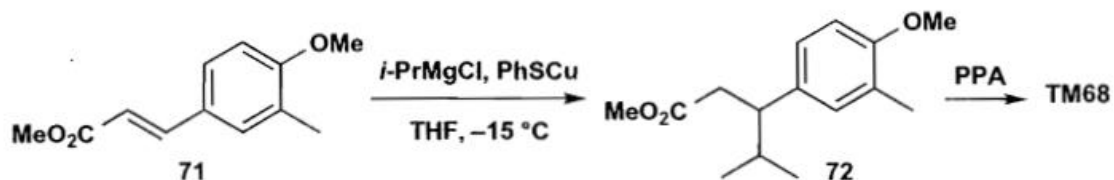
We can use either organo-lithiums or Grignard reagents as the carbon nucleophiles but we need copper (I) to ensure conjugate addition. Without Cu(I) both nucleophiles are inclined to add directly to the carbonyl group. We can use the same reagents that we used to make ketones in this chapter.



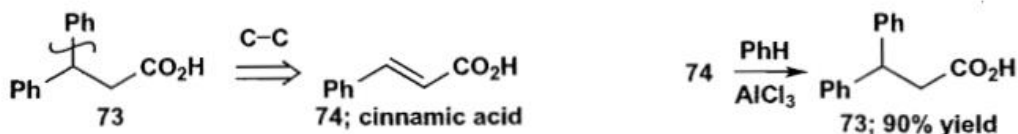
In Corey's synthesis¹⁶ of a marine allomone, he wanted the cyclic ketone **68**. The Friedel-Crafts disconnection gives some derivative of the carboxylic acid **69** and disconnection between the branchpoints gives the unsaturated acid **70** (it doesn't matter whether this is the *E*- or *Z*- isomer as the alkene disappears).



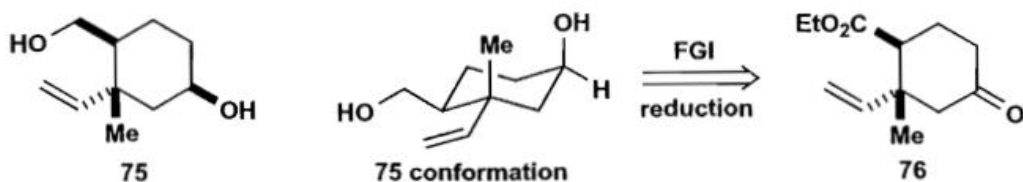
In practice he used the *E*-unsaturated ester **71**, as that was easier to make, and added isopropyl Grignard with a CuSPh catalyst (see compound **13** above) to avoid wasting one equivalent of the Grignard. The ester product **72** cyclised to the target with polyphosphoric acid without a specific ester hydrolysis step. No doubt this works so well because it is an intramolecular reaction giving a five-membered ring.



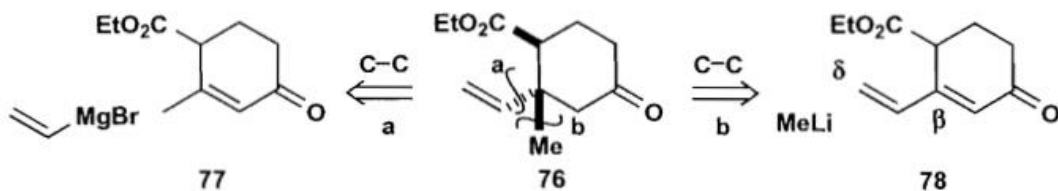
Aromatic compounds are good enough nucleophiles to add in conjugate fashion under Friedel-Crafts conditions so that no organo-metallic reagent is needed. Benzene adds to cinnamic acid **74** with AlCl_3 as catalyst to give **73** in one step.¹⁷



In the synthesis of the diol **75** stereochemistry is important. The diol could be made from the keto-ester by stereoselective reduction using a suitable reducing agent (chapter 12) as the alcohol on the six-membered ring is axial.¹⁸



Disconnection of the ketone **76** with conjugate addition in mind could remove the vinyl group **76a** or the methyl group **76b**. There are two reasons why we prefer **a**. The addition is likely to occur from the opposite face of the molecule to the CO_2Et group and that is where we want the vinyl group. Conjugate addition to **78** might occur at the β -position but it could equally well occur at the very exposed δ -position. The starting material **77** is also the available Hagemann's ester **77**.



The vinyl Grignard reagent was used with Cu(I) catalysis and the reduction of both ester and ketone was achieved with LiAlH_4 . The stereoselectivity was excellent and **75** could easily be separated from the minor equatorial alcohol. In the next chapter we shall revisit both the use of copper in getting regioselectivity and the stereoselectivity of such reactions.

