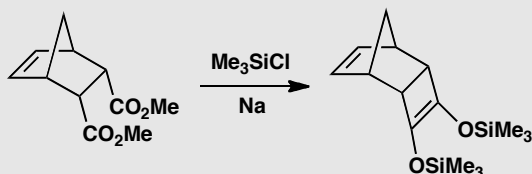


Suggested solutions for Chapter 37

PROBLEM 1

Give a mechanism for the formation of this silylated ene-diol and explain why the Me_3SiCl is necessary.

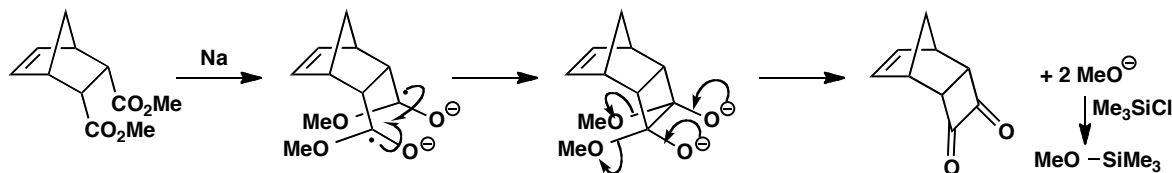


Purpose of the problem

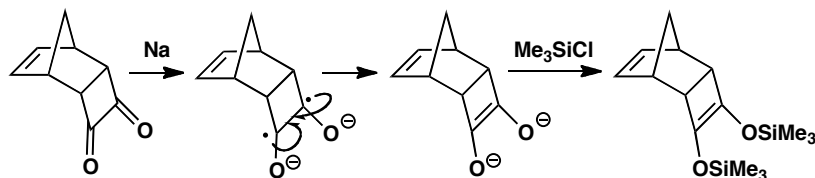
Reminder of an important radical reaction.

Suggested solution

This is an acyloin condensation linking radicals derived from esters by electron donation from a dissolving metal (here sodium). If the esters can form enolates, the addition of Me_3SiCl protects against that problem by removing the MeO^- by-product.



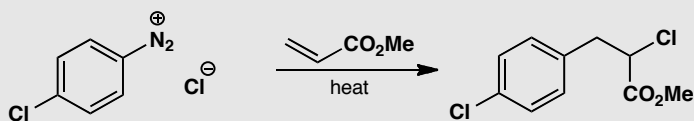
The first product is a very electrophilic 1,2-dione and it accepts electrons from sodium atoms even more readily than do the original esters. The product is an ene diolate that is also silylated under the reaction conditions.



■ Details from B. M. Trost and group, *J. Org. Chem.*, 1978, **43**, 4559.

PROBLEM 2

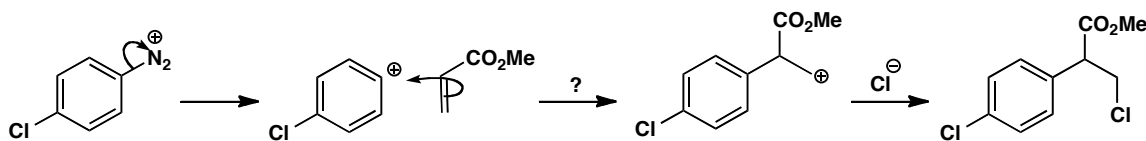
Heating the diazonium salt below in the presence of methyl acrylate gives a reasonable yield of a chloroacid. Why is this unlikely to be nucleophilic aromatic substitution by the S_N1 mechanism (p. 520)? Suggest an alternative mechanism that explains the regioselectivity.

**Purpose of the problem**

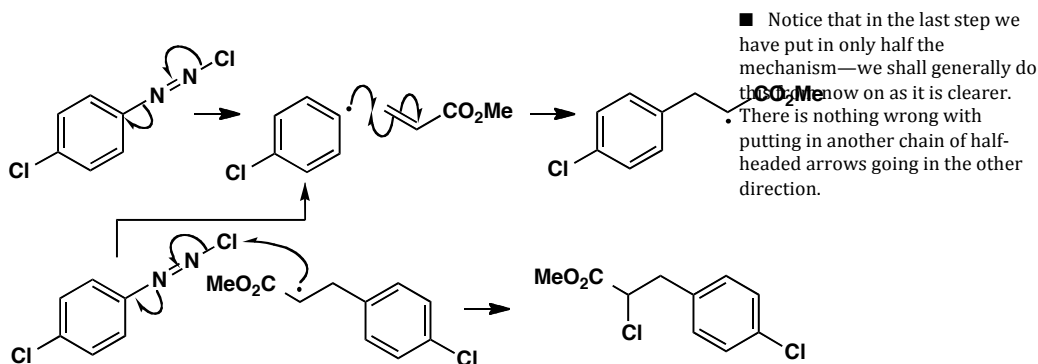
Revision of nucleophilic aromatic substitution with diazonium salts and contrasting cations and radicals.

Suggested solution

The cation mechanism is perfectly reasonable as far as the diazonium salt is concerned but it will not do for the alkene. Conjugated esters are electrophilic and not nucleophilic alkenes. Even if it were to attack the aryl cation, we should find the reverse regioselectivity.

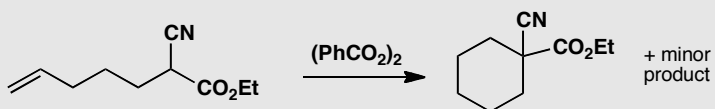


The only way to produce the observed product is to decompose the diazonium salt homolytically. To do this we can draw the salt as a covalent compound or transfer one electron from the chloride ion to the diazonium salt. The other product would be a chlorine radical. Addition to the alkene gives the more stable radical which abstracts chlorine from the diazonium salt and keeps the chain going.



PROBLEM 3

Suggest a mechanism for this reaction and comment on the ring size formed. What is the minor product likely to be?

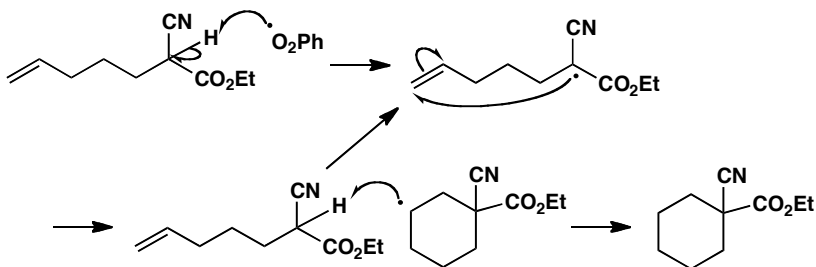


Purpose of the problem

Activated alkenes are not necessary in radical cyclizations.

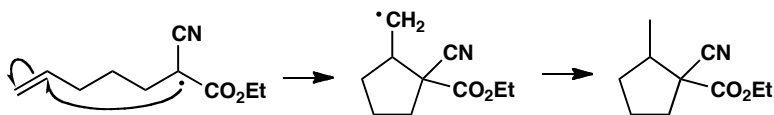
Suggested solution

The peroxide is a source of benzoyloxy radicals ($\text{PhCO}_2\cdot$) and these capture hydrogen atoms to give the most stable radical. The best one here is stabilized by both CN and CO_2Et . Cyclization onto the alkene gives mainly a secondary radical on a six-membered ring and this abstracts a hydrogen from starting material to complete the cycle.



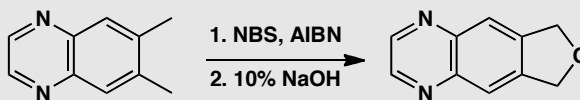
The alternative is to add to the more substituted end of the alkene. This gives a less stable primary radical, but this '5-*exo*' ring closure is

often preferred because the orbital alignment is better. The minor product has a five-membered ring.



PROBLEM 4

Treatment of this aromatic heterocycle with NBS (*N*-bromosuccinimide) and AIBN gives mainly one product but this is difficult to purify from minor impurities containing one or three bromine atoms. Further treatment with 10% aqueous NaOH gives one easily separable product in modest yield (50%). What are the mechanisms for the reactions?

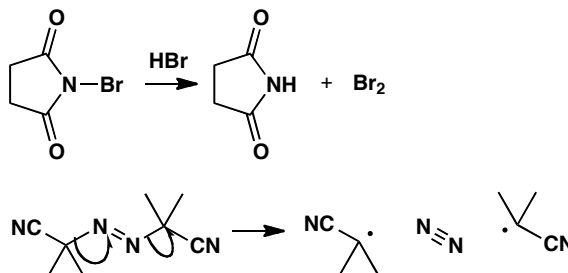


Purpose of the problem

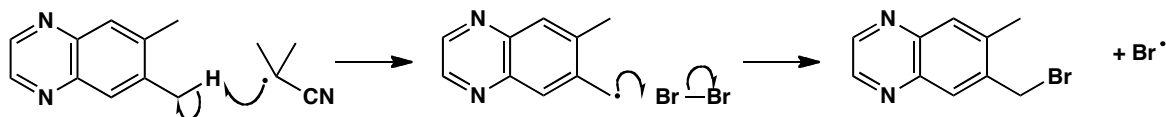
An important radical reaction: bromination at benzylic and allylic positions by NBS, and an application.

Suggested solution

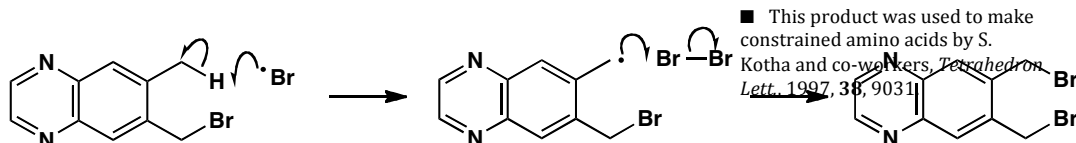
Two preliminary reactions need to take place: NBS is a source of a low concentration of bromine molecules and AIBN initiates the radical chain by forming a nitrile-stabilised tertiary radical.



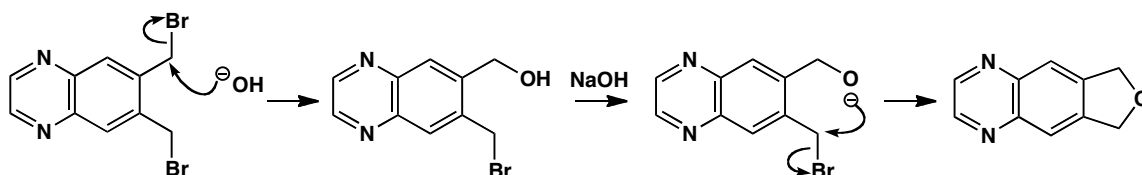
The new radical abstracts hydrogen atoms from the benzylic positions to make stable delocalized radicals. These react with bromine to give the benzylic bromide and release a bromine atom.



All subsequent hydrogen abstractions are carried out by bromine atoms, either of the kind we have just seen or to remove a hydrogen atom from the other methyl group. This reaction provides the HBr that generates more bromine from NBS.

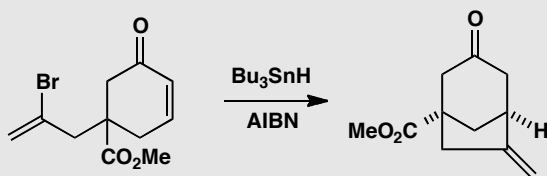


Finally the dibromide reacts with NaOH to give the new heterocycle. Both S_N2 displacements are very easy at a benzylic centre and the second is intramolecular.



PROBLEM 5

Propose a mechanism for this reaction accounting for the selectivity. Include a conformational drawing of the product.

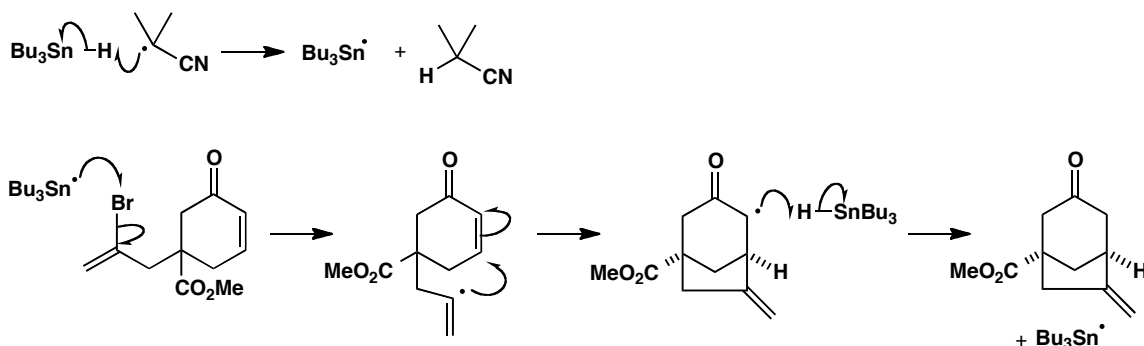


Purpose of the problem

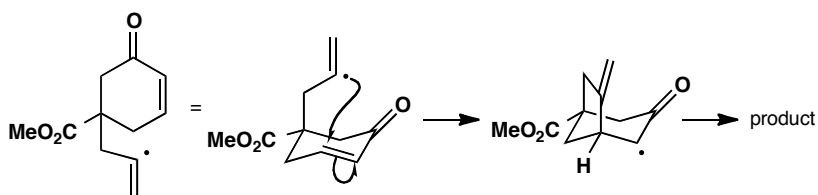
Another important radical reaction: cyclisation of alkyl bromides onto alkenes.

Suggested solution

This time AIBN abstracts the hydrogen from Bu_3SnH and the tin radicals carry the chain along. First they remove the bromine atom from the starting material to make a vinyl radical that cyclises onto the unsaturated ketone to give a radical stabilised by conjugation with the carbonyl group. The chain is completed by abstraction of hydrogen from another molecule of Bu_3SnH , the tin radical formed then allowing the cycle to restart.

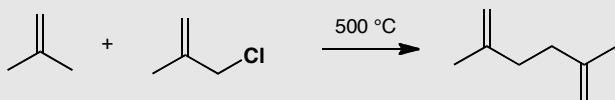


The stereochemistry of the product comes from the requirement of a 1,3-bridge to be diaxial as this is the only way the bridge can reach across the ring. At the moment of cyclisation, the vinyl radical side chain must be in an axial position.



PROBLEM 6

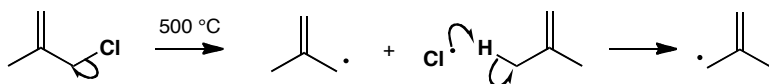
An ICI process for the manufacture of the diene used to make pyrethroid insecticides involved heating these compounds to 500 °C in a flow system. Propose a radical chain mechanism for the reaction.

**Purpose of the problem**

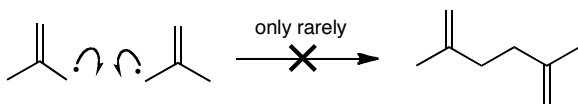
Learning how to avoid a trap in writing radical reactions and to show you that radical reactions can be useful.

Suggested solution

The most likely initiation at 500 °C is the homolytic cleavage of the C–Cl bond to release allyl and chloride radicals. The chloride radicals then attack the alkene and abstract a hydrogen atom to give more of the same allylic radical.

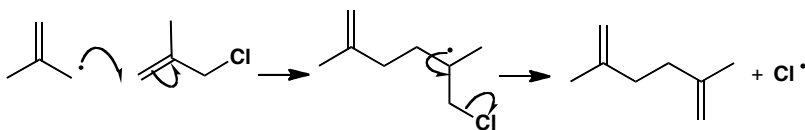


The trap is to form the product by dimerizing the allylic radical. Dimerizing radicals does sometimes occur (in the acyloin reaction for example) but it is a rare process.



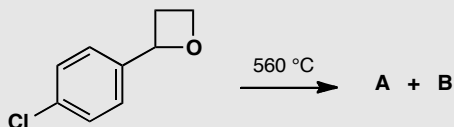
■ The original workers at ICI suggested a different mechanism: D. Holland and D. J. Milner, *Chem. and Ind. (London)*, 1979, 707.

Much more likely is a chain reaction. If we add the allylic radical to the alkene part of the allylic chloride we make a stable tertiary radical that can lose chloride radical and propagate the chain.



PROBLEM 7

Heating this compound to 560 °C gives two products with the spectroscopic data shown below. What are they and how are they formed?



A has IR 1640 cm^{-1} ; m/z 138 (100%) and 140 (33%), δ_{H} (ppm) 7.1 (4H, s), 6.5 (1H, dd, J 17, 11 Hz), 5.5 (1H, dd, J 17, 2 Hz), and 5.1 (1H, dd, J 11, 2 Hz).

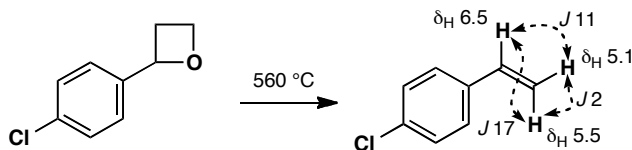
B has IR 1700 cm^{-1} ; m/z 111 (45%), 113 (15%), 139 (60%), 140 (100%), 141 (20%), and 142 (33%), δ_{H} (ppm) 9.9 (1H, s), 7.75 (2H, d, J 9 Hz), and 7.43 (2H, d, J 9 Hz).

Purpose of the problem

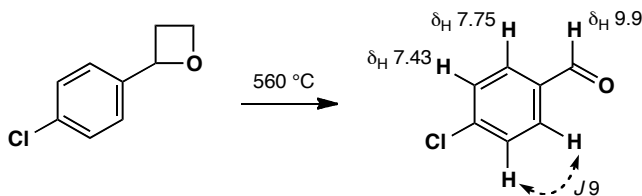
Revision of structure determination and a radical reaction with a difference.

Suggested solution

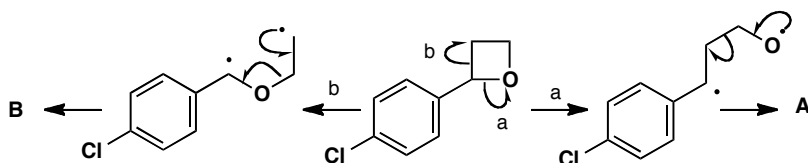
Compound **A** contains chlorine (m/z 138/140, 3:1) and that fits $\text{C}_8\text{H}_7\text{Cl}$. It still has the 1,4-disubstituted benzene ring (four aromatic Hs) and it is an alkene (IR 1640) with three hydrogens on it with characteristic coupling. We can write the structure immediately as there is no choice. The four aromatic hydrogens evidently have the same chemical shift.



Compound **B** has m/z 140/142, 3:1 and a carbonyl group (at 1700 cm^{-1}) which fits $\text{C}_7\text{H}_5\text{ClO}$ and looks like an aldehyde (δ_{H} 9.9). It still has the disubstituted benzene. The structure is even easier this time!

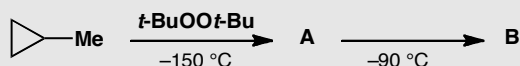


So how are these products formed? At such high temperatures, σ -bonds break and the weakest bonds in the molecule are the C–C and C–O bonds in the four-membered ring next to the benzene ring. Breaking these bonds releases strain and allows one of the radical products to be secondary and delocalised.

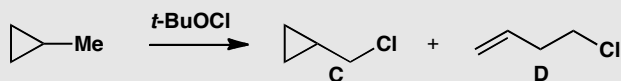


PROBLEM 8

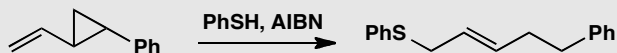
Treatment of methylcyclopropane with peroxides at very low temperature (-150°C) gives an unstable species whose ESR spectrum consists of a triplet with coupling of 20.7 gauss and fine splitting showing dtt coupling of 2.0, 2.6, and 3.0 gauss. Warming to a mere -90°C gives a new species whose ESR spectrum consists of a triplet of triplets with coupling 22.2 and 28.5 gauss and fine splitting showing small ddd coupling of less than 1 gauss.



If methylcyclopropane is treated with $t\text{-BuOCl}$, various products are obtained but the two major products are **C** and **D**. At lower temperatures more of **C** is formed and at higher temperatures more of **D**.



Treatment of the more substituted cyclopropane below with PhSH and AIBN gives a single product in quantitative yield. Account for all these reactions, identifying **A** and **B** and explaining the differences between the various experiments.

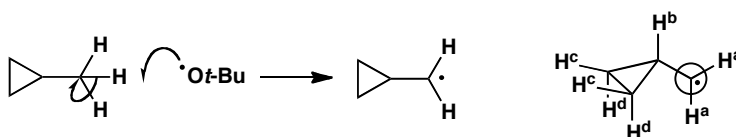


Purpose of the problem

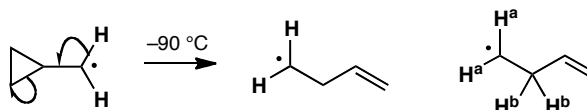
Working out the consequences of an important substituent effect on radical reactions: the cyclopropyl group.

Suggested solution

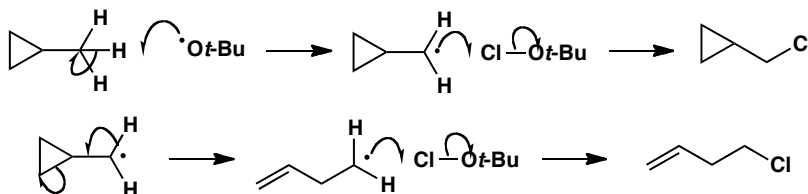
The peroxide is a source of $t\text{-BuO}\cdot$ radicals and these abstract a hydrogen from the methyl group of the hydrocarbon. The first spectrum is that of the cyclopropylmethyl radical. The odd electron is in a p orbital represented by a circle and the planar $\text{CH}_2\cdot$ group is orthogonal to the plane of the ring but the two H^{a} s are the same because of rapid rotation. The odd electron has a large coupling to the two hydrogens (H^{a}) on the same carbon, a smaller doublet coupling to H^{b} , and small couplings to the two H^{c} s and two H^{d} s. The coupling to H^{b} is small because the p orbital containing the odd electron is orthogonal to the $\text{C}-\text{H}^{\text{b}}$ bond.



Warming to $-90\text{ }^{\circ}\text{C}$ causes decomposition to an open-chain radical. The odd electron is coupled to the two hydrogens on its own carbon (H^{a}) and those on the next carbon (H^{b}) each giving a triplet (22.2 and 28.5). Coupling to the more remote hydrogens is small.

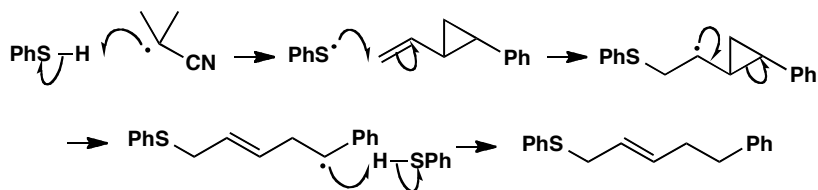


Decomposition of the same hydrocarbon with $t\text{-BuOCl}$ produces the same sequence of radicals but they can now be intercepted by the chlorine atom of the reagent, releasing more $t\text{-BuO}\cdot$ radicals and a radical chain is started. At lower temperatures the ring opening is slower so more of the cyclopropane is captured.



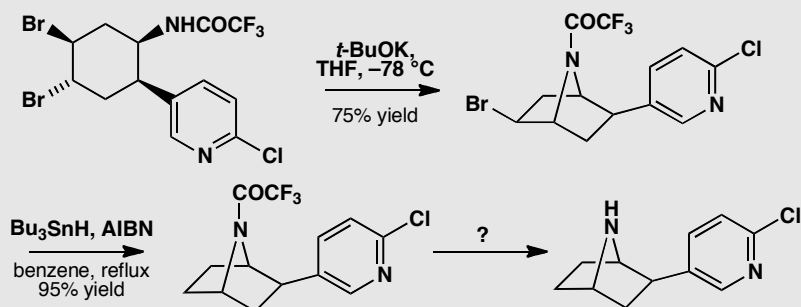
The last example also produces a radical next to a cyclopropane ring but this time it can decompose very easily to give a stable secondary benzylic radical. This captures a hydrogen atom from PhSH releasing

$\text{PhS}\cdot$ and maintaining an efficient radical chain. Ring opening of cyclopropanes is now a standard way of detecting radicals.



PROBLEM 9

The last few stages of Corey's epibatidine synthesis are shown here. Give mechanisms for the first two reactions and suggest a reagent for the last step.

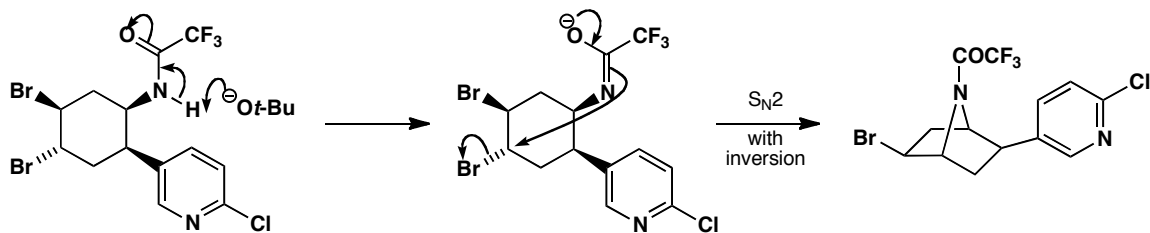


Purpose of the problem

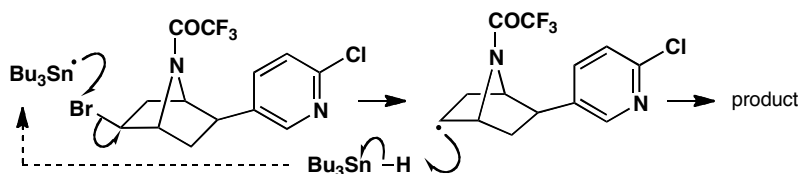
Application of radical reactions in an important sequence plus revision of conformation and stereochemistry.

Suggested solution

The first step involves deprotonation of the rather acidic amide (the CF_3 group helps) and the displacement of the only possible bromide – the one on the opposite face of the six-membered ring as the $\text{S}_{\text{N}}2$ reaction must take place with inversion.



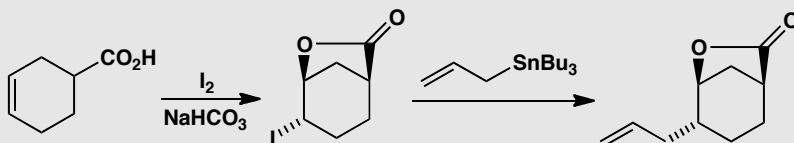
The second step is a standard dehalogenation by Bu_3SnH . AIBN generates $\text{Bu}_3\text{Sn}^\bullet$ by hydrogen abstraction from the reagent and this removes the bromine. Make sure you complete the chain and do not use H^\bullet at any point.



Finally we need to hydrolyse the amide. This normally requires strong acid or alkali but the CF_3 group makes this amide significantly more electrophilic than most and milder conditions can be used. Corey actually used NaOMe in methanol at 13°C for two hours and got a yield of 96%. Any reasonable conditions you may have chosen would be fine too.

PROBLEM 10

How would you make the starting material for this sequence of reactions? Give a mechanism for the first reaction that explains its regio- and stereoselectivity. Your answer should include a conformational drawing of the product. What is the mechanism of the last step? Attempts to carry out this last step by iodine/lithium exchange and reaction with allyl bromide failed. Why? Why is the alternative shown here successful?

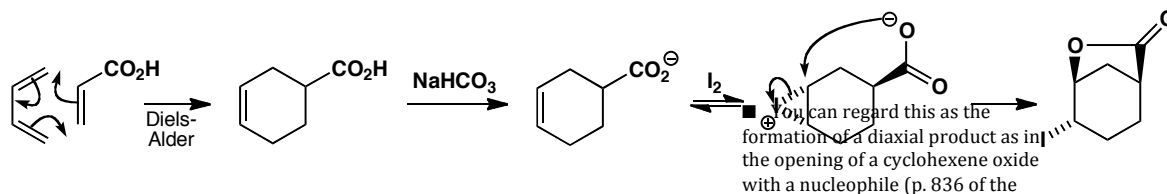


Purpose of the problem

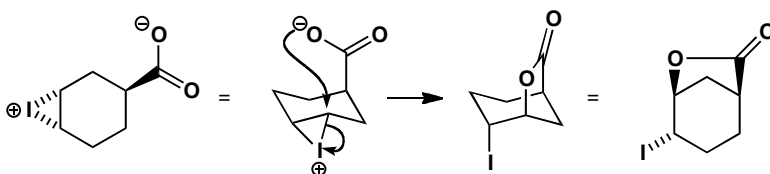
Application of radical reactions when the alternative ionic reactions fail.

Suggested solution

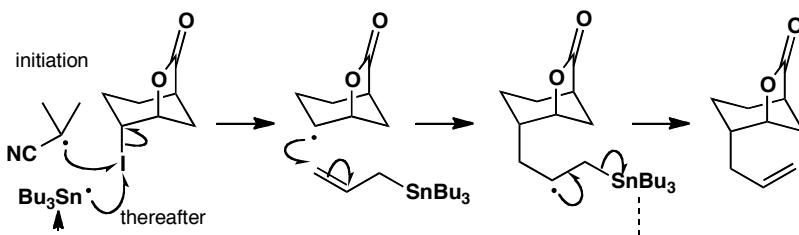
The starting material is an obvious Diels-Alder product as it is a cyclohexene with a carbonyl group outside the ring on the opposite side. The first step is iodolactonization. Iodine attacks the alkene reversibly on both sides but, when it attacks opposite the carboxylate anion, the lactone ring snaps shut.



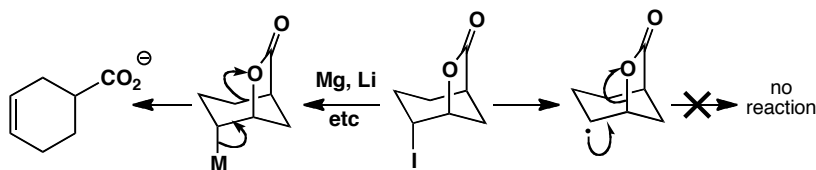
The problem asks for a conformational drawing of the product and indeed that is necessary. The 1,3-lactone bridge must be diaxial as that is the only way for the carboxylate to reach across and therefore it must attack from an axial direction too.



The last step is initiated by AIBN which removes the iodine atom from the compound to make a secondary radical. This attacks the allyl stannane and the intermediate loses $\text{Bu}_3\text{Sn}^\bullet$ and that takes over the job of removing iodine atoms to keep the chain going. The radical intermediate has no stereochemistry at the planar radical carbon and attack occurs from the bottom face to avoid the blocking lactone bridge.

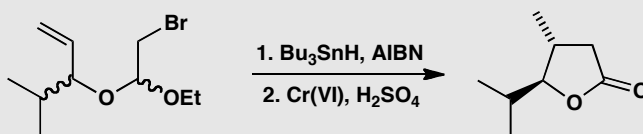


Anionic reactions cannot be used for this allylation. If the iodine were metallated, the organometallic compound would immediately expel the lactone bridge as carboxylate ion is a good leaving group. The radical is stable because the C-O bond is strong and not easily cleaved in radical reactions.



PROBLEM 11

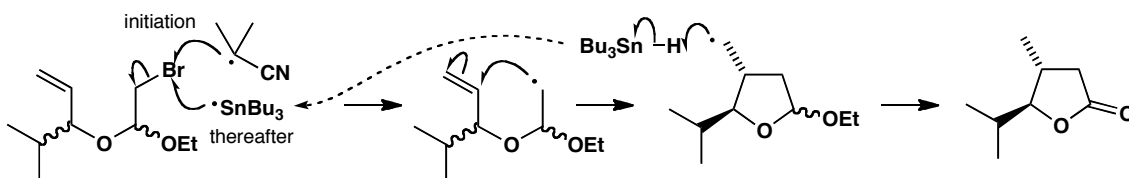
Suggest a mechanism for this reaction explaining why a mixture of diastereoisomers of the starting material gives a single diastereoisomer of the product. Is there any other form of selectivity?

**Purpose of the problem**

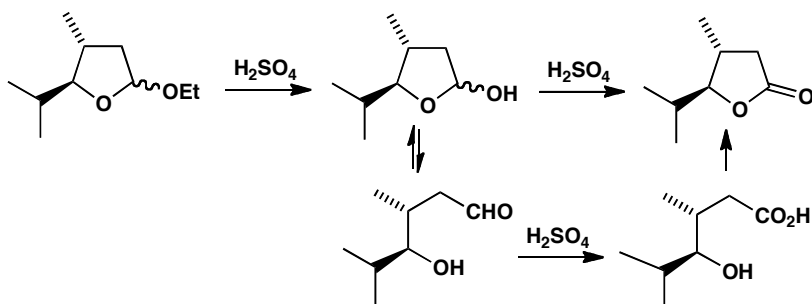
A radical ring-closing reaction with a curious stereochemical outcome.

Suggested solution

The abstraction of bromine, at first by AIBN and thereafter by $\text{Bu}_3\text{Sn}\cdot$ produces a radical that again does not eliminate but adds to an alkene. A five-membered ring is formed (this is usually the more favourable closure) by attack on the alkene on the opposite side from that occupied by the *i*-Pr group. The product is a mixture of diastereoisomers as no change occurs at the acetal centre.

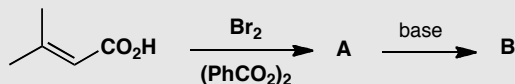


Acid-catalysed oxidation first hydrolyses the acetal and then oxidizes either the hemiacetal or the aldehyde to the lactone. Now the molecule is one diastereoisomer as the ambiguous centre is planar. The other form of selectivity is the ring size (see the textbook, p. 1000ff).



PROBLEM 12

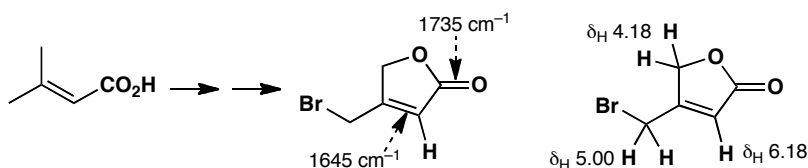
Reaction of this carboxylic acid ($C_5H_8O_2$) with bromine in the presence of dibenzoyl peroxide gives an unstable compound **A** ($C_5H_6Br_2O_2$) that gives a stable compound **B** ($C_5H_5BrO_2$) on treatment with base. Compound **B** has IR 1735 and 1645 cm^{-1} and NMR δ_H 6.18 (1H, s), 5.00 (2H, s) and 4.18 (2H, s). What is the structure of the stable product **B**? Deduce the structure of the unstable compound **A** and mechanisms for the reactions.

**Purpose of the problem**

Revision of structural analysis in combination with an important radical functionalization.

Suggested solution

The starting material is $C_5H_8O_2$ so the stable compound **B** has gained a bromine and lost three hydrogens. There must be an extra double bond equivalent (DBE) somewhere in **B**. The IR spectrum shows that the OH has gone and suggests a carbonyl group, possibly an ester because of the high frequency, and an alkene. The NMR shows that both methyl groups have gone and have been replaced by CH_2 groups. The bromine must be on one of them and the ester oxygen on the other. The extra DBE is a ring.



Since both methyl groups are functionalized, unstable **A** must have one Br on each methyl group. The peroxide produces benzoyl radicals that abstract protons from both allylic positions to give stabilised radicals that attack bromine molecules to give bromide radicals to continue the chain reaction. In base the carboxylate cyclises onto the *cis* CH_2Br group.

