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Homologation of ketones into carboxylic acids

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Contents

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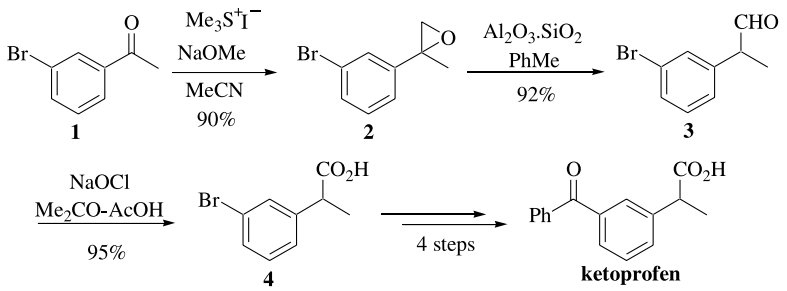


Scheme 1.

1. Introduction

Efficient functional group transformations have been the goal of organic chemists for many years. Reports have appeared on atom economy[1] and towards the ideal synthesis[2] highlighting these goals. The addition of a one carbon unit to a ketone to homologate it to a carboxylic acid is an important transformation that chemists have tackled from many different angles in the hope of achieving this goal. Strategies have used intermediates such as epoxides, vinyl heteroatoms and halides, nitriles or alkenes to give the homologated acids. Generally, only those reactions which do not alter the carbon skeleton next to the ketone will be discussed. The purpose of this article is to provide a general overview of the important synthetic reactions which have been designed to effect this transformation. A wide variety of approaches have been published especially on the preparation of the NSAIDs (e.g. ibuprofen, naproxen, and pranoprofen). A comprehensive discussion of the entire subject is difficult, but a number of excellent reviews have appeared,[3] and references to them will be made wherever possible to allow for a wider scope of synthetic methods. An attempt has been made to survey the relevant literature through June 2003.

2. Via epoxides

Substituted and unsubstituted epoxides have proven to be a popular platform in which to introduce the one carbon unit. Some methods involve epoxide rearrangement to the homologated aldehyde which is then oxidized by a variety of methods to give the corresponding carboxylic acid. Other epoxide rearrangement methods achieve the transformation to the homologated carboxylic acid directly. Representative aldehyde oxidation methods include $KMnO_4$,[4] $K_2Cr_2O_7$,[5] Ag_2O,[6] NaOCl,[7] $NaClO_2$,[8] and Oxone.[9]

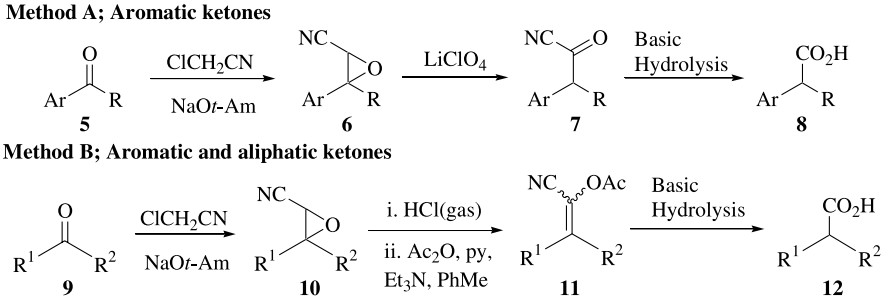
2.1. Unsubstituted epoxides

Corey et al. in 1962 introduced the one carbon unit by using epoxides formed from the reaction of dimethylsulfoxonium methylide and ketones.[10] These epoxides in turn were rearranged under Lewis acid conditions ($BF_3{\cdot}Et_2O$)[11] to give the homologated aldehydes. Other reagents which have been used to rearrange epoxides to aldehydes are, $ZnCl_2$,[12] $InCl_3$,[13] $(t\text{-}Bu_2BrC_6H_2O)_2AlMe$,[14] $MgBr_2{\cdot}Et_2O$[15] and TsOH.[16] Ohta Pharmaceuticals used this type of strategy to prepare ketoprofen,[17] Scheme 1. After rearrangement of epoxide **2** with $Al_2O_3{\cdot}SiO_2$, the aldehyde was oxidized with NaOCl to give the homologated carboxylic acid **4** in 95%. The homologated acid **4** was produced in 3 steps from ketone **1** in 79% yield. Four additional steps from acid **4** gave ketoprofen in 57% from **1**.

2.2. α-Cyano epoxides

White et al. developed methods whereby aromatic or aliphatic ketones could be transformed into α-cyano epoxides by the Darzens reaction[18] and these could be rearranged followed by hydrolysis to give the homologated carboxylic acids,[19] Scheme 2. Method A was found to be only amenable to aromatic ketones and did not work on aliphatic ketones. Aromatic ketones **5** were transformed into glycidic esters **6**, which in turn were converted to acylnitriles **7** by a catalytic amount (4%) of $KHSO_4$, $Li(OOCCF_3)$ or $LiClO_4$ in toluene or xylene at reflux. The acylnitrile was then directly hydrolyzed in aqueous base to give the corresponding homologated acid **8**.

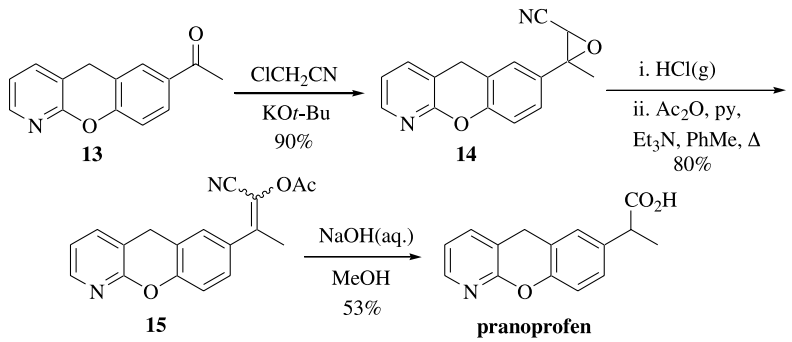
Method B was found to work with both aromatic and aliphatic ketones, although this was a less direct route. Dry HCl converts glycidonitrile **10** into an intermediate α-hydroxy-β-chloronitrile which is acetylated and dehydrohalogenated to give the α-acetoxyacrylonitrile **11**.[20] Basic hydrolysis and acidification gave the desired carboxylic



Scheme 2.

Table 1. Range of substrates transformed using White's methods

Ketone	Homologated acid	Method A yield (%)	Method B yield (%)
p-Isobutylacetophenone	2-(*p*-Isobutylphenyl)propionic acid	72	73
α-Tetralone	1,2,3,4-Tetrahydro-1-naphthoic acid	47	68
Cyclohexanone	Cyclohexane carboxylic acid		57
Cyclopentanone	Cyclopentane carboxylic acid		51
2-Pentanone	2-Methylpentanoic acid		57



Scheme 3.

acids **12**. The range of substrates investigated and yields is shown in Table 1.

Toyo Stauffer Chemical Co., Ltd, Japan used White's method B to prepare pranoprofen,[21] Scheme 3 in 38% overall yield from ketone **13**.

The α-cyano epoxide **14** was prepared in 90% yield from ketone **13** under standard Darzens conditions. Treatment of **13** with HCl(g) converted **14** to an intermediate α-hydroxy-β-chloronitrile, which was then acetylated and dehydrohalogenated to give the α-acetoxyacrylonitrile **15** in 80% yield as a mixture of isomers. Hydrolysis of **15** under basic conditions then gave pranoprofen in 53% yield. An alternative method to hydrolysis is treatment of the α-acetoxyacrylonitriles with piperidine and the corresponding amide is formed,[22] which can be hydrolyzed under the usual conditions to the homologated acid. α,α-Dicyano-epoxides have also been used to effect the homologation of ketones to carboxylic acids.[23]

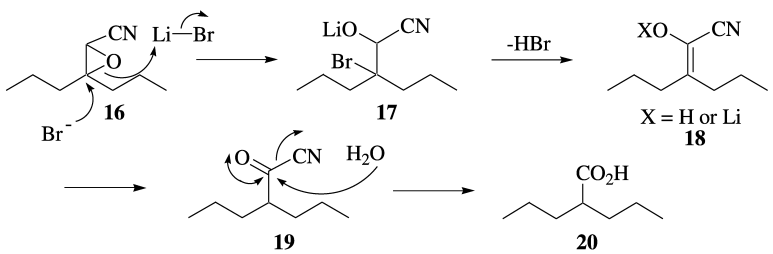
Badham et al.[24] reported an expanded scope of method A developed by White. In the rearrangement, lithium perchlorate in xylene was replaced with safer LiBr, DMF, CH_3CN and water which allowed the rearrangement to work with both aromatic and aliphatic ketones. The intermediate acylnitrile formed during the rearrangement was also hydrolyzed in situ to give the homologated acid directly. One drawback to these methods was that cyanide was liberated during the rearrangement and hydrolysis, and appropriate safety precautions had to be taken when running this chemistry. The rearrangement using LiBr was found not to work if the ketone contained α,α-dialkyl substitution. If the ketone was α,β-unsaturated the rearrangement was found to give an α,β,γ,δ-unsaturated aldehyde instead of the expected acid. In the preparation of SB-207499,[25] this methodology was amenable to multikilo scale.[26] Two mechanisms of the rearrangement of the α-cyano epoxide have been proposed depending on the substrate.[26] The proposed mechanism for the alkylalkyl ketone[27] is shown in Scheme 4.

In the proposed mechanism, bromide attacks the epoxide at the quaternary position either in a S_N1 or S_N2 fashion to give intermediate **17**, which then undergo loss of the elements of HBr to give the enol or enolate **18**. This enol or enolate may be protonated to give **19**, which underwent hydrolysis in situ to give the desired carboxylic acid **20**. The range of substrates investigated is shown in Table 2.

α-Cyano epoxides can also be hydrolyzed to the α-ester epoxide by treatment with K_2CO_3 in MeOH.[28] These α-ester epoxides under alkaline hydrolysis give the homologated acid (see Section 2.3).

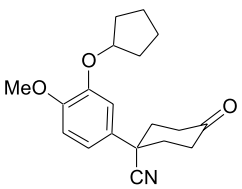
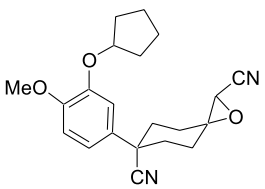
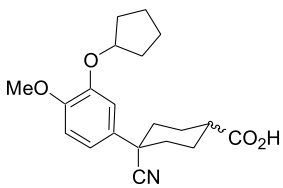
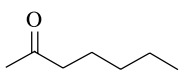
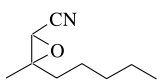
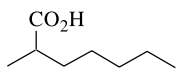
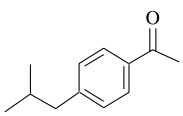
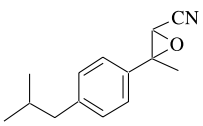
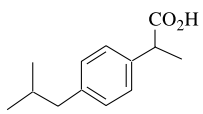
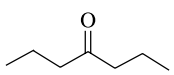
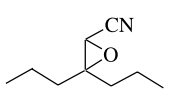
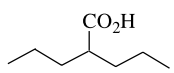
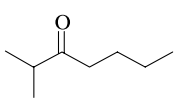
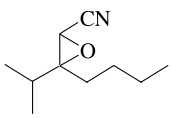
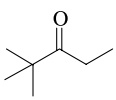
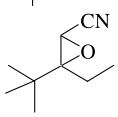
2.3. α-Ester epoxides

The Darzens condensation is a well-established method for



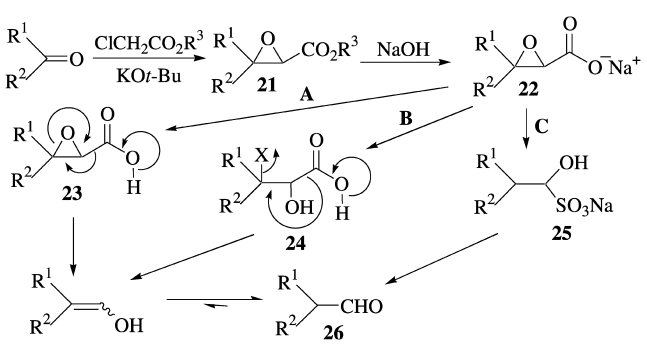
Scheme 4.

Table 2. Range of ketones investigated for the rearrangement of α-cyano epoxides using lithium bromide

Ketone	α-Cyano epoxide	Yield (%)	Homologated acid	Yield (%)
		73		75
		68		63
		73		54
		61		49
		61	No reaction	
		46	No reaction	

the synthesis of α-ester epoxides (glycidic esters).[29] These compounds in turn can be transformed to give the corresponding homologated aldehydes.[30] The first synthesis of a glycidic ester was shown by Erlenmeyer,[31] but Darzens developed and generalized the reaction.[32] The mechanisms of rearrangement of glycidic esters are shown in Scheme 5.

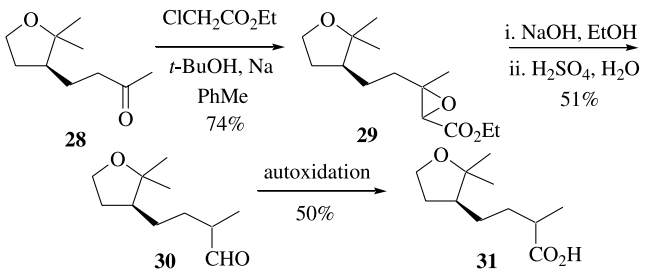
The first step in each of these methods is aqueous hydrolysis of ester **21** to glycidate salt **22**. Path **A** represents the most common sequence for effecting decarboxylation. Compound **22** is transformed into compound **23** which is pyrolyzed to give the homologated aldehyde **26**. Path **B** is the addition of HCl or HBr to the glycidic acid to give **24**, which when treated with alkali decarboxylation occurs with concomitant loss of hydrogen halide to give aldehyde **26**.[33,34] Path **C** occurs when the glycidate **22** is heated with a saturated solution of sodium bisulfite to give the bisulfite adduct of the aldehyde which in turn can give aldehyde **26**.[33] Gora et al. used path **A** to prepare new homoterpenoidal tetrahydrofuran derivatives,[35] Scheme 6.



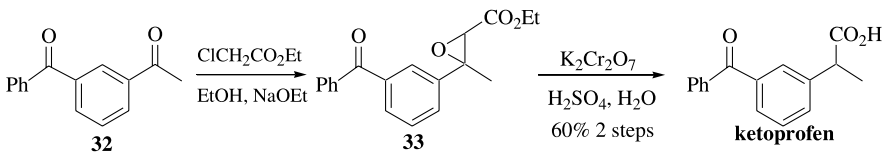
Scheme 5.

Darzens condensation of keto-ether **28** with ethyl chloroacetate in the presence of sodium in toluene gave a diastereomeric mixture of α-ester epoxide **29** in 74% yield. Alkaline hydrolysis of **29** followed by decarboxylation gave aldehyde **30** in 51% yield. On storage at room temperature for 2 months the aldehyde autoxidized to give the homologated acid **31** in 50% yield. Lu et al. also synthesized ketoprofen by use of glycidic esters[36] in 2 steps from ketone **32** in 60% yield, Scheme 7.

The Darzens methodology differentiated the two ketones with subsequent rearrangement of **33** and oxidation of the resultant aldehyde occurring in 1 step. Ketone **32** was prepared in 3 steps from benzoic acid by bromination, a Friedel–Crafts reaction and a Grignard reaction to obtain 3-acetylbenzophenone. The overall yield of ketoprofen from benzoic acid was 32%. Lithium bis(trimethylsilyl)amide can also be used as a base for the Darzens synthesis of



Scheme 6.

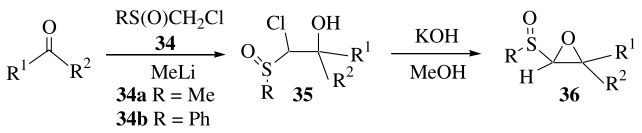


Scheme 7.

glycidic esters.[37] A variety of patents[38–40] and publications[41] has appeared using this methodology especially for the manufacture of NSAIDs and their derivatives.

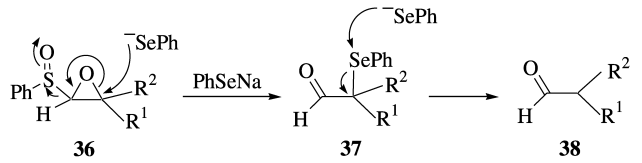
2.4. α-Arylsulfinyl epoxides

α-Arylsulfinyl epoxides were initially reported by Durst in 1969.[42] They were easily prepared from 1-chloroalkyl phenyl sulfoxides[43] and carbonyl compounds via chlorohydrins, Scheme 8.



Scheme 8.

Yamakawa et al.[44] found that the β-carbon of α-arylsulfinyl epoxides was reactive towards PhSeNa to give either dialkyl ketones or aldehydes. The mechanism by which compound **36** was transformed into aldehyde **38** is shown in Scheme 9.



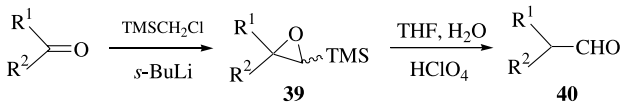
Scheme 9.

The α-arylsulfinyl epoxides were treated with multiple equivalents of sodium benzeneselenoate in ethanol to give the aldehyde. The unreacted sodium benzeneselenoate was recovered as diphenyl diselenide in near quantitative yield, however, the health risks associated with the use of selenium are well known and care should be taken in performing the reactions. A selection of substrates which were investigated is shown in Table 3.

If compound **36** is pyrolyzed the corresponding α,β-unsaturated aldehyde is isolated.[45]

2.5. α-Trimethylsilyl epoxides

α-Trimethylsilyl epoxides were introduced by Stork et al.[46] who showed that epoxidation of a vinylsilane gave an α-trimethylsilyl epoxide. Magnus et al.[48] introduced the formation of α-trimethylsilyl epoxides by chemistry that was closely analogous to the classical Darzens reaction. The mechanism of how α-trimethylsilyl epoxides are transformed into homologated aldehydes has been elucidated by Hudrlik et al.[47] Magnus showed epoxides **39** were rearranged under mild acidic conditions (20% aqueous THF/5–10% $HClO_4$) to give the homologated aldehyde **40**, Scheme 10.



Scheme 10.

Where α-trimethylsilyl epoxides were formed as epimers, the carbon bearing the TMS group the predominant epimer was the one that resulted from having the TMS group in the least sterically encumbered environment. Sterically unhindered aldehydes and ketones posed no problems for formation of the epoxides. Sterically hindered ketones especially nopinone and camphor gave lower yields of the α-trimethylsilyl epoxide. A selection of substrates investigated is shown in Table 4.

When the α-trimethylsilyl epoxide **41**, was rearranged to give homologated aldehyde **42**, a mixture of double bond isomers was obtained in 78% yield. Yamaguchi et al. has used a TES group instead of a TMS group to effect the same rearrangement,[49] Scheme 11. After hydrolysis of **43** with methane sulfonic acid to the aldehyde, the aldehyde was then oxidized with $NaClO_2$ to the corresponding carboxylic acid. No yield was given in the paper, however, for the transformation.

Table 3. Preparation of homologated aldehydes from ketones via α-arylsulfinyl epoxides

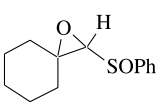
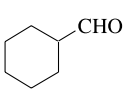
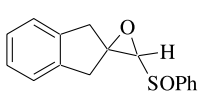
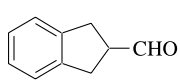
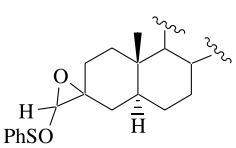
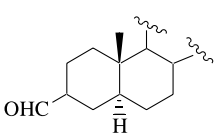
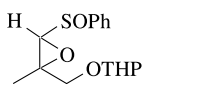
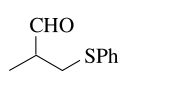
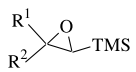
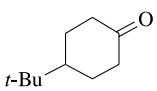
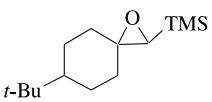
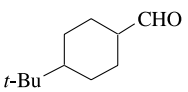
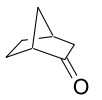
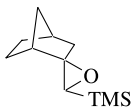
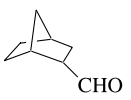
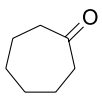
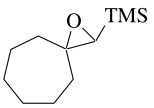
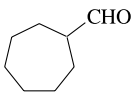
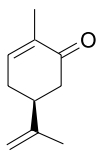
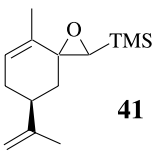
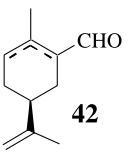
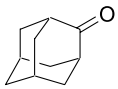
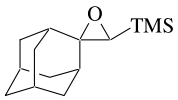
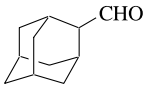
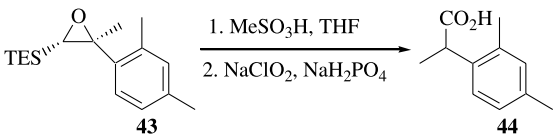
α-Arylsulfinyl epoxide	Homologated aldehyde	Yield (%)	α-Arylsulfinyl epoxide	Homologated aldehyde	Yield (%)
		80			90
		96			75

Table 4. Preparation of homologated aldehydes via α-trimethylsilyl epoxides

Ketone		Yield (%)	Homologated aldehyde	Yield (%)
		88		72
		76		73
		58		98
	 **41**	76	 **42**	78
		95		71

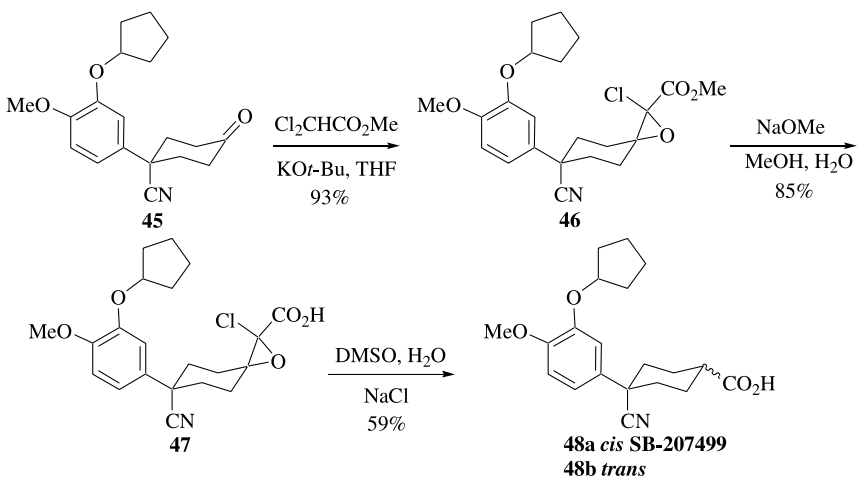


Scheme 11.

2.6. α-Chloro α-ester epoxides

An extension of the methodology in Section 2.3 uses methyldichloroacetate in the Darzens reaction. This was used to prepare SB-207499,[26,50] Scheme 12. Rearrangement of **47** gave the acid directly without the need for further oxidation.

Treatment of ketone **45** with methyl dichloroacetate and potassium *t*-butoxide gave compound **46** as an approximate 3.5:1 ratio of isomers in 93% yield.[51] Hydrolysis of ester **46** then gave the epoxy acid **47** in 85% yield. Treatment of acid **47** under the Krapcho decarboxylation conditions[52] at 150°C in a pressure vessel gave acids **48** (**48a/48b** 1:1) in a crude yield of 59%. A drawback to this method was the use of high temperature and high pressure to effect the transformation. This methodology has also been used to prepare ibuprofen.[53] A variation of this is the rearrangement of the α-cyano α-ester epoxide which can prepared in 2 steps by first forming the α-ester acrylonitrile and then epoxidation.[54]



Scheme 12.

Table 5. Preparation of nitriles from ketones using TosMIC

Ketone	Homologated nitrile	Yield (%)
Adamantanone	2-Cyanoadamantane	93
(+)-Camphor	2-Cyanocamphane	80
t-Butyl methyl ketone	2-Cyano-2,4-dimethyl pentane	70
Estrone 3-methyl ester	17β-Cyano-1,3,5(10)-estratriene-3-ol methyl ester	69
Andostra-1,4-diene-3,17-dione	17-Cyanoandostra-1,4-dien-3-one	47
Di-isopropyl ketone	3-Cyano-2,4-dimethylpentane	65

3. Via nitriles

A variety of methodologies have been developed which are able to transform a ketone into a nitrile thus adding the one carbon. Most methods either use cyanide salts or liquid HCN so care must be taken when performing the chemistry. These nitriles in turn can be hydrolyzed to give the homologated carboxylic acid. There are various methods for the hydrolysis of nitriles to the corresponding carboxylic acid; such methodologies include aqueous HCl,[55] aqueous H_2SO_4,[56] aqueous NaOH,[57] and aqueous $Ba(OH)_2$.[58]

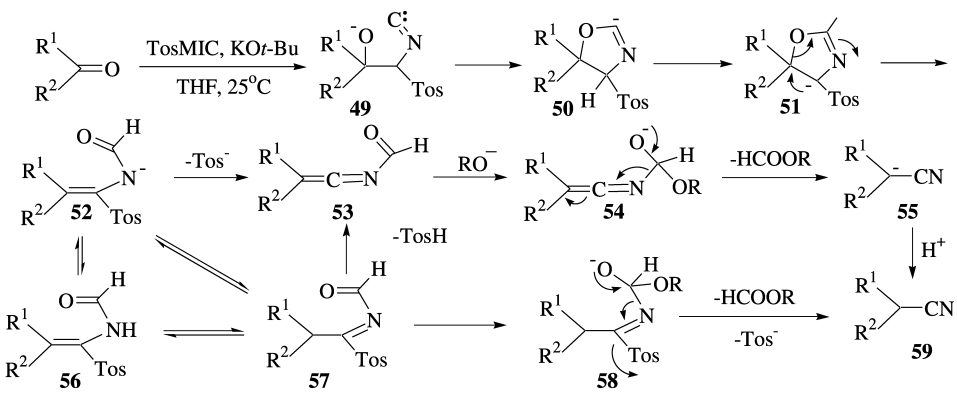
3.1. Unsubstituted nitriles

van Leusen et al. developed a technique of using tosylmethylisocyanide (TosMIC) for the transformation of ketones into nitriles[59] and a selection of substrates is shown in Table 5. The substrates investigated range from simple aliphatic, aromatic and steroidal ketones to sterically hindered ones. The severely hindered carbonyl of di-*t*-butyl ketone did not react, whereas *t*-butyl methyl ketone and di-isopropyl ketone were converted.[60]

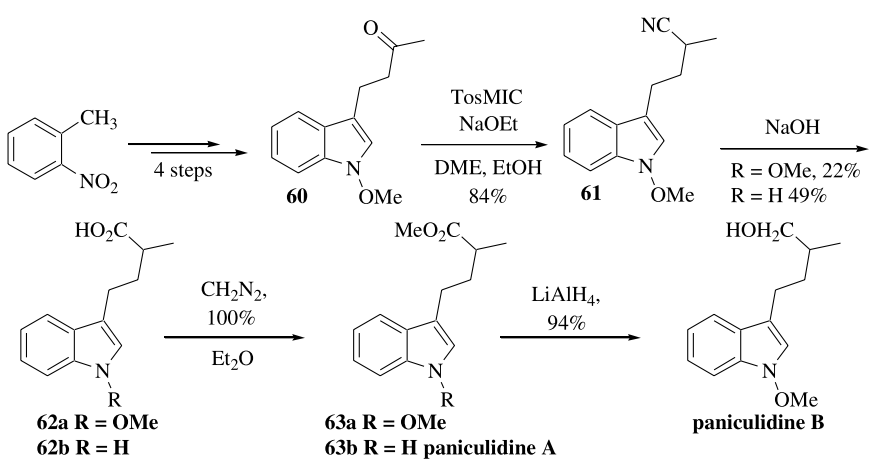
The proposed mechanism of formation of a nitrile from a ketone using TosMIC is shown in Scheme 13.

Somei et al. reported syntheses of paniculidine A and B using TosMIC,[61] Scheme 14. Reaction of **60** gave nitrile **61** in 84% yield. Alkaline hydrolysis of nitrile **61** gave **62a** in 22% yield along with **62b** in 49% yield. Both carboxylic acids (**62a**, **62b**) were methylated quantitatively to yield **63a** and **63b**, paniculidine A. Reduction of ester **63a** yielded paniculidine B in 94%.

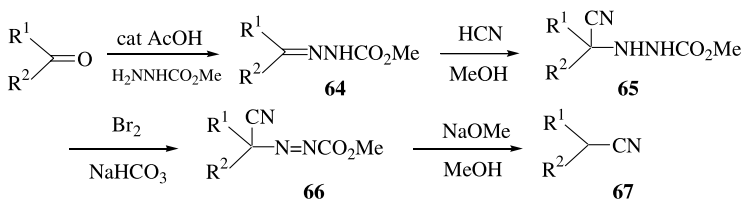
Other publications which have appeared using TosMIC are in the preparation of a spin labeled probe,[62] ketoprofen[63]



Scheme 13.

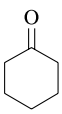
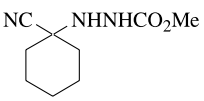
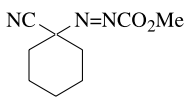
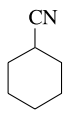
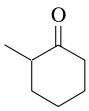
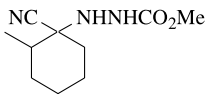
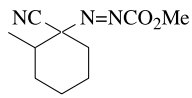
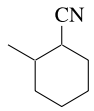
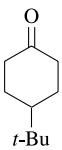
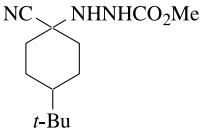
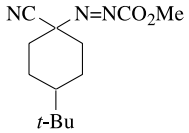
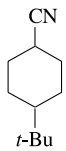
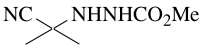


Scheme 14.



Scheme 15.

Table 6. Homologation of ketones to nitriles via methyldialkylcyanodiazene carboxylates

Ketone	Hydrazine	Yield (%)	Diazine	Yield (%)	Homologated nitrile	Yield (%)
		97		95		94
		90		96		n/a
		90		96		96
		98				

and cannabinoid derivatives.[64] A reaction of TosMIC with aldehydes and ketones leading in 2 steps via *N*-(1-tosyl-1-alkenyl)formamides to carboxylic acids has been reported by Schöllkopf et al.[65] (see Section 12) with this reaction later shown to proceed through nitriles.[66] Ziegler et al. describe a method of using methyldialkylcyanodiazene carboxylates as intermediates for transforming aliphatic ketones into nitriles, Scheme 15.[67]

The ketones were first converted to methoxycarbonyl hydrazones **64**, which when reacted with liquid HCN in methanol gave **65**. Bromination and susbequent treatment with catalytic NaOMe gave the corresponding nitriles **67**. Only acetone, cyclo-hexanone and two substituted cyclo-hexanones were reported for this transformation, so it is unknown how general this transformation is Table 6. Chiba et al. expanded on this work showing when acylhydrazones where subjected to electrolytic oxidation in methanol containing NaCN the corresponding nitriles were formed in 1 step.[68] Cacchi et al. reported a procedure using *p*-toluenesulfonyl hydrazone to give compounds similar to **64**.[69] Reese et al. reported the formation of 2,4,6-tri-isopropylbenzenesulfonyl hydrazones of aliphatic and alicyclic ketones.[70] These hydrazones reacted readily with KCN to give the corresponding nitriles. In another method, Kurihara et al. reported the use of diethyl

Table 7. Homologation of ketones via cyanophosphates intermediates

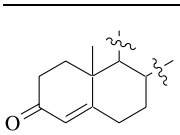
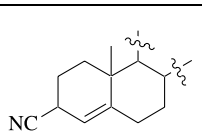
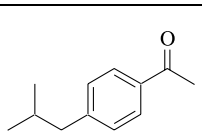
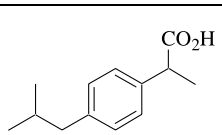
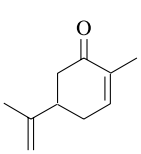
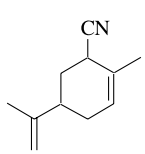
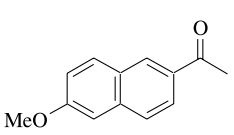
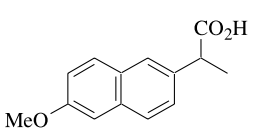
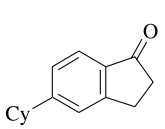
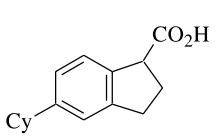
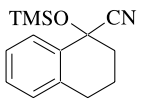
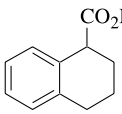
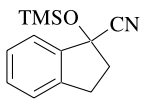
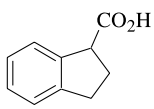
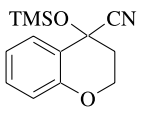
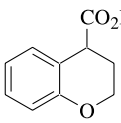
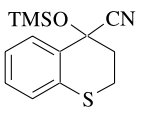
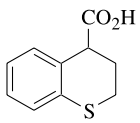
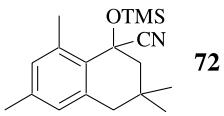
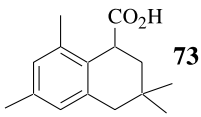
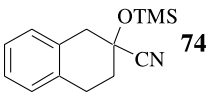
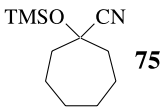
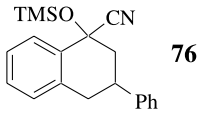
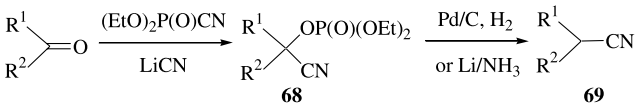
Ketone	Homologated nitrile	Yield (%)	Ketone	Homologated acid	Yield (%)
	 **70**	91			81
	 **71**	89			81
		89			71

Table 8. Preparation of homologated acids from TMS-cyanohydrins

TMS-cyanohydrin	Homologated acid	Yield (%)	TMS-cyanohydrin	Homologated acid	Yield (%)
		68			74
		77			71
 **72**	 **73**	10	 **74**	Complex mixture	
 **75**	Complex mixture		 **76**	Water soluble product	

phosphorocyanidate and LiCN for the transformation of aromatic and α,β-unsaturated carbonyl compounds into nitriles via cyano phosphate intermediates **68**, Scheme 16.[71]



Scheme 16.

Cyano phosphate **68** could be hydrogenated or treated with lithium and ammonia[72] to give nitrile **69**. These nitriles were then hydrolyzed to give the corresponding homologated carboxylic acid, Table 7.

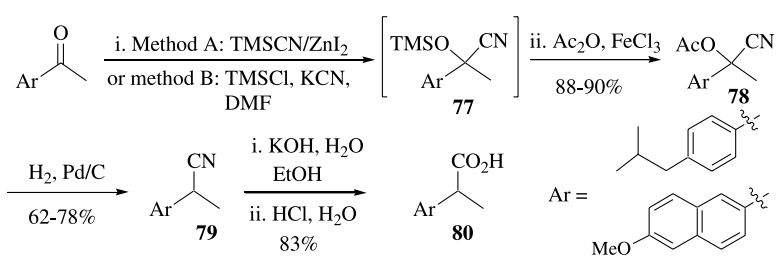
When cyclic enones are used the corresponding unsaturated nitrile **70** and **71** are formed in excellent yield with no isomerization or reduction of the alkene in the Li/NH_3 reduction step. This method however has not been used for aliphatic ketones.

3.2. Via cyanohydrins

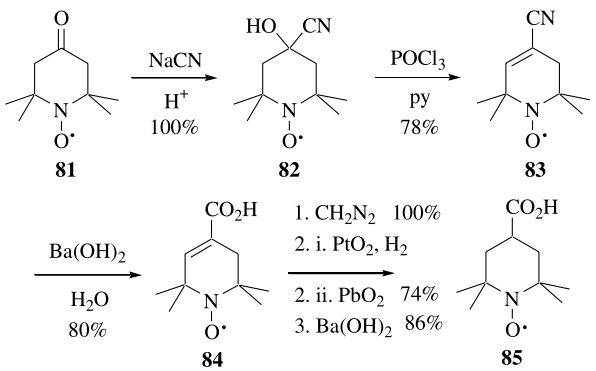
3.2.1. Trimethylsilyl cyanohydrins. TMS-cyanohydrins are easily prepared by treating ketones with TMSCN[73] or TMSCl, KCN[74] to introduce the one carbon unit. The cyanohydrins can then be treated with $SnCl_2$/acid to effect two transformations, reduction of the benzylic oxygen and hydrolysis of the nitrile group to give the desired homologated acid. A variety of substrates investigated are shown in Table 8.[75]

The order of addition of reagents was found to be critical for reducing side product formation (e.g. hydroxy acids)[76] and that the cyanosilyl ether should be treated at room temperature with $SnCl_2$, then acetic acid and finally concentrated HCl followed by vigorous stirring and the rapid application of sufficient heat to bring the heterogeneous mixture to reflux. There were limitations to the method, acid **73** was isolated in only 10% yield from **72** indicating that the reductive hydrolysis was sensitive to steric hindrance. Both cyanohydrins **74** and **75** gave a complex mixture of the corresponding α-hydroxy-acids and unsaturated by-products presumably due to a lack of benzylic stabilization during reduction. A water soluble product from compound **76** resulted in the apparent hydrolysis of the phenyl substituted ether linkage. Hiyama et al. used a similar approach for the preparation of 2-arylpropanoic acids,[77] Scheme 17.

The TMS-cyanohydrins **77** were formed by reaction of a methyl aryl ketone with TMSCN in benzene with ZnI_2 or with TMSCl and KCN in DMF, followed by O-acetylation with Ac_2O in the presence of $FeCl_3$ as catalyst[78] giving the cyanohydrin acetate **78**. Catalytic hydrogenation of **78** gave the corresponding 2-arylpropanenitriles **79** and alkaline



Scheme 17.



Scheme 18.

hydrolysis gave the 2-arylpropanonic acids **80**. Cyanohydrins **77** were converted into their *O*-acetyl derivatives because the cyanohydrins as well as their TMS ethers[75] did not undergo reductive C–O cleavage whereas the acetoxy group did. An alternative method to give **79** was treatment of a TMS-cyanohydrin **77** with TMSCl, NaI in acetonitrile.[79] Other publications using this methodology include preparation of sterically driven anhydrides[80] and methylene bridged benzopyrenes.[81]

3.2.2. Unsubstituted cyanohydrins. Addition of the one carbon unit via cyanohydrins is one of the classical methods for introduction of the one carbon unit. Addition of cyanide to the ketone can occur using sodium[82]/potassium[83] cyanide or diethylaluminum cyanide.[84] Hsai et al. used this methodology to prepare a spin labeled probe,[82] Scheme 18.

Sodium cyanide was added to **81** to give the cyanohydrin **82** in quantitative yield. Dehydration of **82** using $POCl_3$ gives the olefin **83** in 78%. Hydrolysis of the nitrile was achieved using aqueous $Ba(OH)_2$ to give the homologated carboxylic acid **84**. The ester was then formed of the acid, and hydrogenation of the double bond also resulted in the oxygen being hydrogenated to the hydroxyl. Re-oxidation to the radical was achieved with PbO_2 and finally hydrolysis of the ester gave the desired spin probe **85** in 68%. Tabushi et al. has used this strategy to functionalize a bicyclo[3.3.0]-octane,[85] Scheme 19.

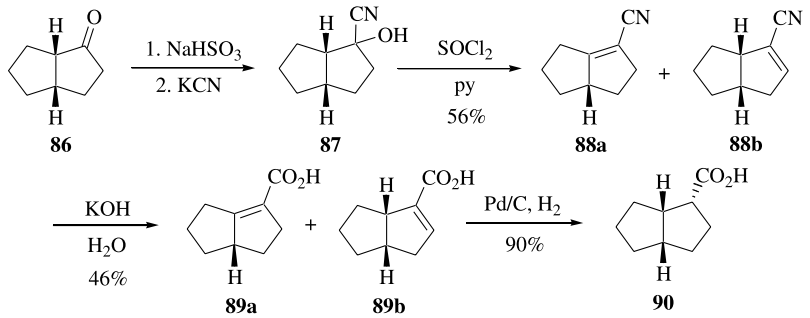
Cyanohydrin **87** was prepared from the sodium bisulfite adduct of **86** with potassium cyanide by Cope's procedure.[83] Dehydration of cyanohydrin **87**[86] produced two products **88a** and **88b** in a 45:55 ratio as determined by NMR or vapor phase chromatography. This mixture was then carried forward to give isomeric carboxylic acids **89a/89b** 44:56, which were both hydrogenated to give quantitatively **90** as a single saturated compound. This approach has also been used in the synthesis of SB-207499[26,87] and for steroids.[88]

4. Via vinyl heteroatoms or halides

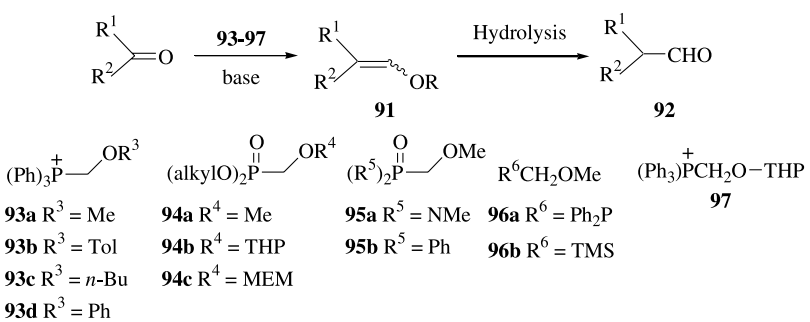
Vinyl heteroatoms or halides are useful moieties in which to introduce the one carbon unit. Hydrolysis or oxidation of these moieties gives the homologated aldehyde or the acid directly.

4.1. Enol ethers

Several reagents have been developed for the transformation of ketones into enol ethers, Scheme 20. Examples include **93a**[89,90] **93b**,[90] **93c**,[91] **93d**,[90,92] **94a**,[93] **94b**,[94] **94c**,[94] **95a**,[93] **95b**,[95] **96a**,[96] **96b**[97] and **97**.[98] Formation of the enol ethers and hydrolysis of them usually occurs in good yield, although there can be some problems. The by-product triphenylphosphine oxide is sometimes difficult to remove,

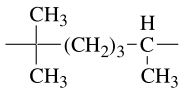
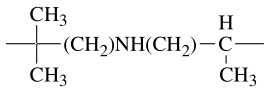


Scheme 19.



Scheme 20.

Table 9. Preparation of homologated aldehydes from ketones via enol ether intermediates

R^1	R^2	OR	Reagent	Enol ether (%)	Homologated aldehyde (%)
Ph	Me	OMEM	**94c**	85	72
	$-(CH_2)_5-$	OTHP	**94b**	88	92
		OMe	**96a**	Not isolated	91
		OMe	**93a**	84	79
	$-(CH_2)_5-$	OMe	**96b**	85	90
Et	Et	OTol	**93b**	72	79

lower yields with hindered ketones and side reactions can occur with enolizable aldehydes and ketones. Hydrolysis of the OR group of the enol ether can also prove difficult in the presence of other sensitive functional groups. To address some of these issues reagents **94b**, **94c** and **97** were introduced to allow for mild hydrolysis of the enol ether. Reagent **96a**[96] and an in situ preparation of **94a**[99] were shown to react with hindered enolizable ketones to give the enol ethers in good yield.

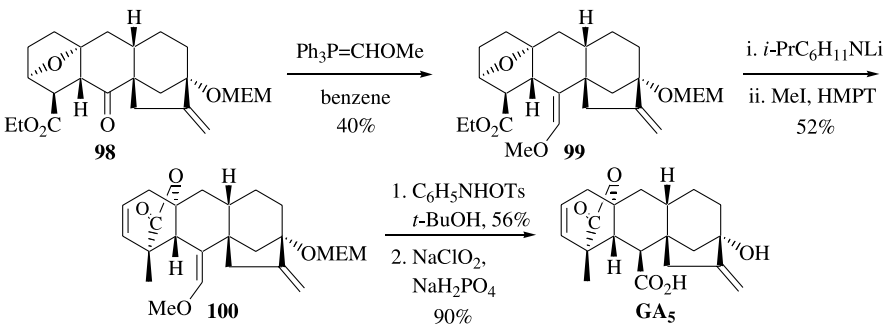
Representative hydrolysis methods of the enol ether **91** to the homologated aldehyde **92** include aqueous $HClO_4$[90,100] *p*TsOH,[101] aqueous HCOOH,[102] TMSI,[103] and aqueous HCl.[104] A selection of substrates investigated is shown in Table 9.

De Clercq et al. used reagent **93a** in the total synthesis of GA_5,[105] Scheme 21. Conversion of **98** to **99** by reaction with $Ph_3P{=}CHOMe$ (**93a**) gave the enol ether **99** in a 90:10 *E*/*Z* ratio in 40% yield along with 50% of a cyclopentanone derivative arising from base induced oxygen bridge opening. Treatment of **99** with lithium isopropylcyclohexylamide followed by addition of methyl iodide resulted in lactone **100** in 52% yield. Acid hydrolysis of **100** to the hydroxyaldehyde (56% yield) followed by sodium chlorite oxidation[8a] (90% yield) gave GA_5.

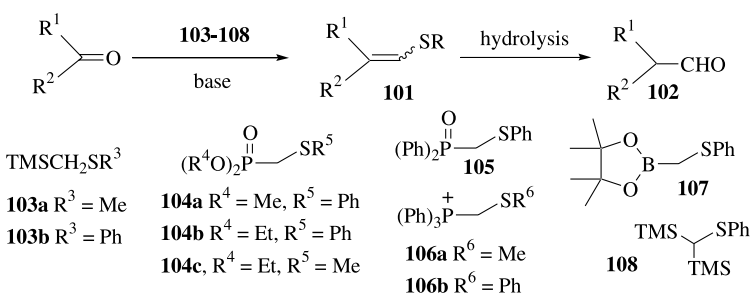
Other strategies where the enol ether has been used as the homologation tool is in preparation of the taxane A and B ring;[106] scaffold for the preparation of pyrethrins;[107] preparation of cyclopropyl precursors;[108] and acetic acid derivatives.[109]

4.2. Thio enol ethers

Thio enol ethers can easily be prepared from the anion of **103a** or **103b**[110,111] **104a**,[112] **104b**,[113] **104c**,[114] **105**,[115] **106a**,[116] **106b**,[117] **107**,[118] and **108**[119] followed by addition of a ketone (or aldehyde) to give the thio enol ether **101**, Scheme 22.

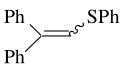
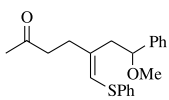
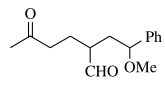
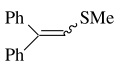
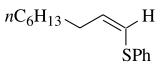
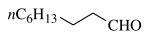
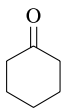
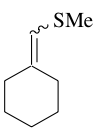
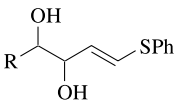
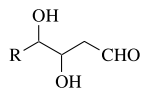


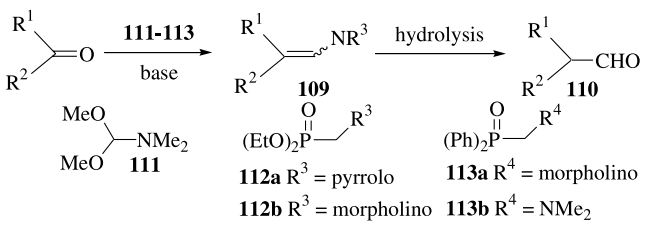
Scheme 21.



Scheme 22.

Table 10. Preparation of homologated aldehydes from thio enol ethers

Ketone	Thio enol ether	Yield (%)	Thio enol ether	Homologated aldehyde	Yield (%)
		83			100
		84			60
		43			50



Scheme 23.

Enolizable ketones can prove problematic with the corresponding vinyl sulfides being isolated in low yield.[120] A number of methods exist for the hydrolysis of **101** with mercury salts,[114b,121] although the hydrolysis can prove problematic and be substrate dependant,[122] Table 10.

Other hydrolysis methods include *p*-TsOH,[123] strong acid,[124] $TiCl_4$[125] and addition of RSH across the double bond to form the *S*,*S*-acetal then hydrolysis.[126]

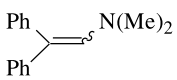
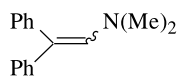
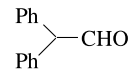
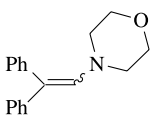
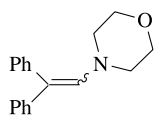
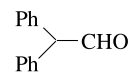
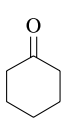
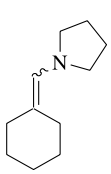
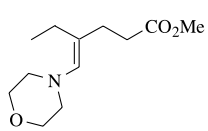
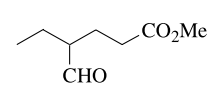
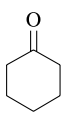
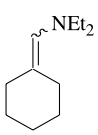
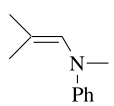
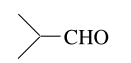
4.3. Enamines

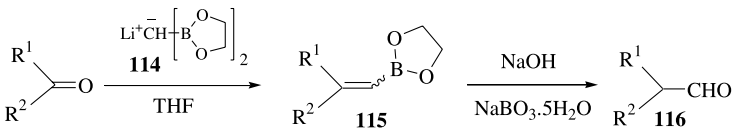
A wide variety of reagents exist for the transformation of carbonyl compounds to enamines in generally good to excellent yield, and the hydrolysis of these enamines is frequently quantitative. Similar problems associated with the formation and hydrolysis of enol ethers may occur with the use of reagents **111**-**113**. Some reagents are limited to aldehydes,[127] but reagents **111**,[128] **112a**,[129] **112b**,[130] **113a**[131] and **113b**[132] react with ketones, Scheme 23. An in situ preparation of reagent **112** with dimethyl(diazomethyl)-phosphonate in the presence of amines (e.g. pyrrole, Et_2NH, *i*-Pr_2NH) also gave good yields of the enamines **109**.[99]

Representative hydrolysis methods of enamine **109** to homologated aldehyde **110** include, aqueous HCl,[133] aqueous AcOH,[134] and aqueous oxalic acid.[135] A selection of substrates that are transformed is shown in Table 11.

Reagents **112a**, **112b** and **113b** have only been used for aromatic ketones, and it is unknown whether they may work

Table 11. Preparation of homologated aldehydes from enamine intermediates

Ketone	Enamine	Yield (%)	Enamine	Homologated aldehyde	Yield (%)
					44, 2 steps
		90			100
		66			45
		70			78



Scheme 24.

Table 12. Homologated of ketones to aldehydes via vinyl boronic acids

Ketone	Homologated aldehyde	Yield (%)
Et_2CO	Et_2CHCHO	74
PhCOMe	PhCH(Me)CHO	80
$Me_2C{=}CHCOMe$	$Me_2C{=}CH(Me)CHO$	81
$EtO_2C(CH_2)_2COMe$	$EtO_2C(CH_2)_2(Me)CHO$	65

for aliphatic ketones. The in situ preparation of **112b** was shown to work with sterically hindered ketones and aliphatic ketones.[99]

4.4. Vinyl boronic esters

Vinyl boronic esters can be prepared from the reaction of lithium bis(ethylenedioxyboryl)methide **114** with ketones or aldehydes.[136] These vinyl boronic esters can then be oxidized to the homologated aldehyde, Scheme 24.[137]

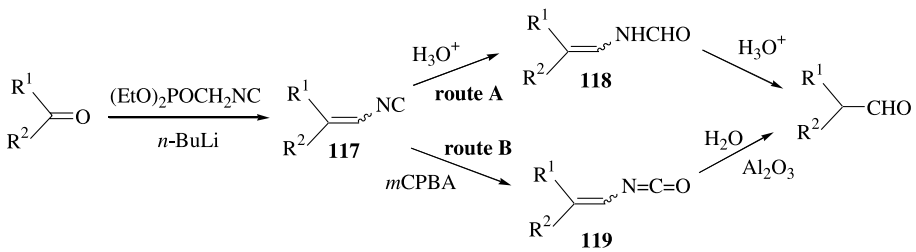
Sodium perborate or buffered hydrogen peroxide were investigated as oxidizing agents for **115** to **116**. Sodium perborate was chosen as the use of hydrogen peroxide may have resulted in aldehyde peroxide by-products which were considered hazardous. A selection of substrates investigated is shown in Table 12.

4.5. Vinyl isocyanides

Schöllkopf et al.[138] showed that ketones and aldehydes reacted via a Wittig–Horner–Emmons reaction using diethyl (isocyanomethyl)phosphonate to give α,β-unsaturated isocyanides **117**. van Leusen et al.[139] showed these can then either hydrolyzed under acidic conditions (route A) or hydrolyzed after oxidation to α,β-unsaturated isocyanate (route B) to give the homologated aldehyde, Scheme 25.

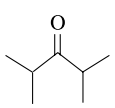
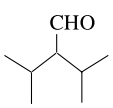
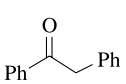
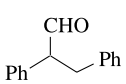
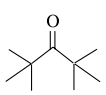
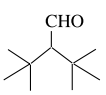
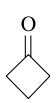
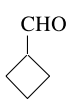
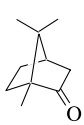
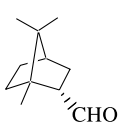
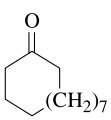
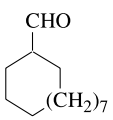
van Leusen's paper describes 20 examples with the yields being good to excellent. A selection of substrates which van Leusen investigated is shown in Table 13.

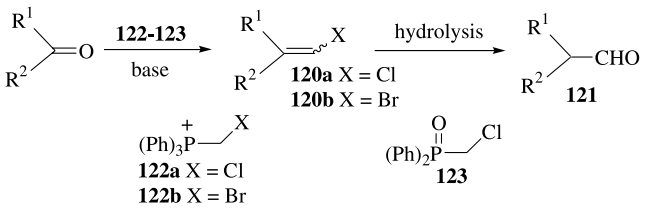
The reactions were found to be clean and intermediates **117**, **118** and **119** need not be isolated. The method has a wide scope and was shown to work on sterically hindered ketones, a strained ketone, large-ring ketone, enolizable ketone an aliphatic aldehyde and an unsaturated aldehyde. Acid-sensitive substrates have also been used and in those cases, route B was the method of choice, since the hydrolysis was essentially achieved under neutral conditions. The hydrolysis in route B was achieved when the entire reaction mixture was passed slowly through a short column of alumina. Care was to be taken with the column to



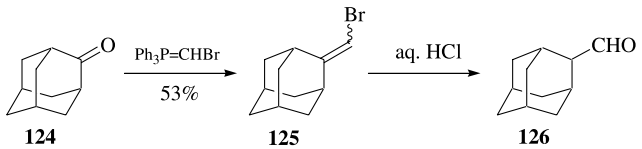
Scheme 25.

Table 13. Homologated aldehydes via Wittig–Horner–Emmons olefination of ketones

Ketone	Homologated aldehyde	Route A yield (%)	Route B yield (%)	Ketone	Homologated aldehyde	Route A yield (%)	Route B yield (%)
		89	90			81	
		54	48			91	
		97	86			98	89



Scheme 26.



Scheme 27.

stop it from cracking due to the gas evolved during hydrolysis.

4.6. Vinyl halides

Ketones and aldehydes may be transformed into vinyl halides by the use of base and reagents **122a**,[116a,140] **122b**,[141,142] and **123**.[116b] These vinyl halides can then be transformed into homologated aldehydes by hydrolysis, Scheme 26.

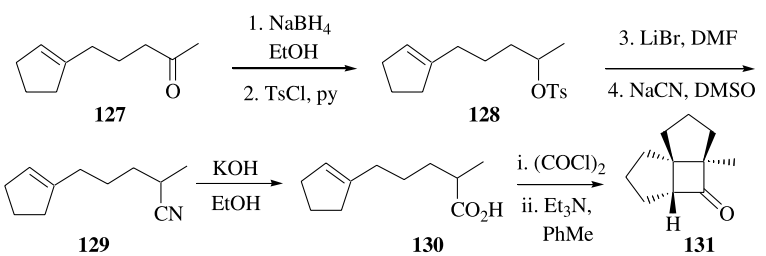
There are limited methods for the hydrolysis of vinyl halides,[143] with most being harsh and not general, leaving this method with limited scope. Sasaki et al. prepared adamantane-2-carbaldehyde **126** from ketone **124** with reagent **122b**, Scheme 27.[142] However, no yield was given for the hydrolysis in the paper.

5. Via alcohols

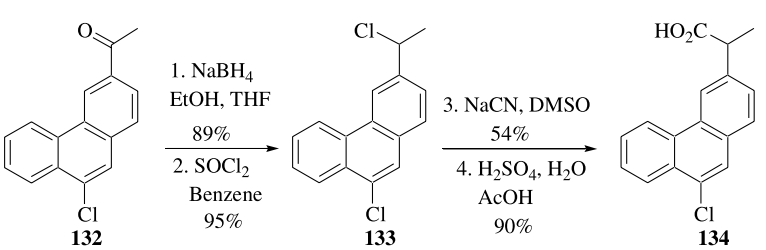
There are several methods by which the initial alcohol is formed such as by reduction or hydrogenation of the ketone. This alcohol in turn can be transformed into a variety of groups for further reaction to introduce the one carbon unit. Yadav et al. tosylated the alcohol and displaced it with cyanide to introduce the one carbon in the preparation of angularly fused triquinane systems,[144] Scheme 28.

Ketone **127** was reduced to the alcohol, and activated as the tosylate **128**. Displacement of the tosylate with LiBr gave the bromide which was displaced by sodium cyanide to give nitrile **129**. Basic hydrolysis of the nitrile gave the desired homologated acid **130**. The overall yield of **130** from **127** was 44%. The acid chloride was obtained from **130** and oxalyl chloride and was immediately reacted with Et_3N in toluene at reflux to give 1-methyl tricyclo[5.3.0.$0^{3,7}$]decan-2-one **131** in 45% yield. Fernandez et al. also used this strategy to synthesis phenanthrylalkanoic acid **134**,[145] Scheme 29. The ketone was reduced to alcohol **133**, transformation to the chloride **133** in 85% over 2 steps and subsequent displacement with sodium cyanide in DMSO gave the nitrile, which was hydrolyzed to give the homologated acid **134** in 49% over 2 steps.

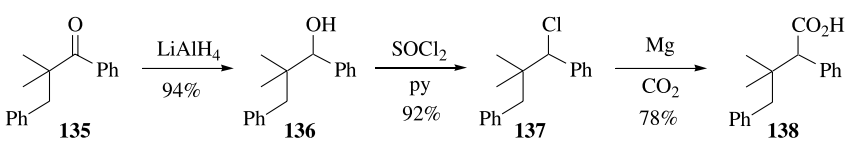
Attempted transformation of ketone **132** into the nitrile directly using TosMIC resulted in only 3% nitrile and 50% of the starting material was recovered in pure form. This methodology has also been used in the preparation of 2-[4-(2-thiazolyloxy)phenyl]propionitrile and analogs,[146] 4-(α-alkyl-α-cyanomethyl)-2,6-disubstituted phenols[147] and NSAIDs.[148] A variation of this methodology involves after the halide is formed, formation of the Grignard and



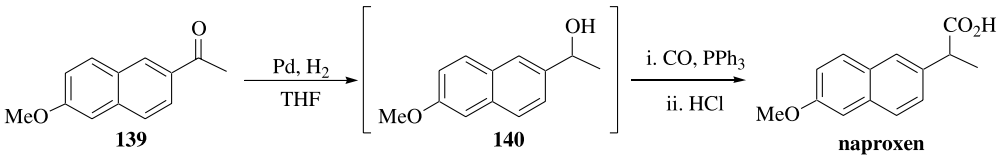
Scheme 28.



Scheme 29.



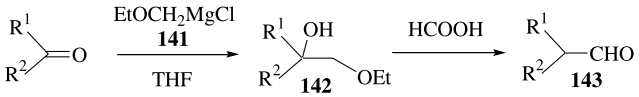
Scheme 30.



Scheme 31.

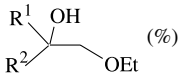
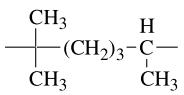
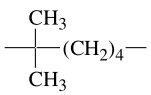
then reaction with CO_2 to introduce the carboxylic acid,[149] Scheme 30.

Reduction of the hindered ketone **135** with $LiAlH_4$ gave alcohol **136** in 94% yield. The alcohol was turned into chloride **137**, which was activated as a Grignard and quenched with CO_2 to give the homologated acid **138** in 78% yield. Maryanoff et al. also reported a similar sequence in the preparation of intermediates in the synthesis of hexahydropyrrolo[2,1-*a*]iso- quinolines.[150] Hiyama et al. reported a sequence where the alcohol was acetylated and then reacted with TosMIC to give the nitrile.[151] The homologated carboxylic acid can also be prepared in 1 step from the ketone by the use of palladium, with a 2 step transformation, one pot sequence. Xie et al. used this to prepare naproxen in 1 step from ketone **139**,[152] Scheme 31.



Scheme 32.

Table 14. Synthesis of homologated aldehydes via α-metallated ethers

R^1	R^2	 (%)	Homologated aldehyde (%)
Me	Me	70	75
Ph	Me	55	88
	$-(CH_2)_4-$	77	76
	$-(CH_2)_5-$	76	75
	$-(CH_2)_6-$	92	77
	$-(CH_2)_7-$	75	81
	$-(CH_2)_{11}-$	94	85
		65	85
		65	75

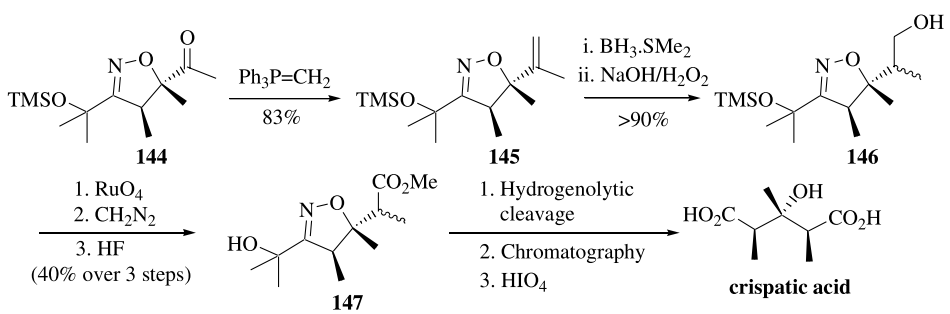
Initially the alcohol was formed by hydrogenation which was then carbonylated to give the homologated acid.

Ketone **139** was reduced with H_2 in the presence of 5–10% Pd/C in THF at 50°C to give in situ alcohol **140**. Triphenylphosphine was then added and addition of CO in THF/HCl at 100–150°C and a CO pressure of 6–10 MPa initially gave the acyl palladium species, which was hydrolyzed by HCl in situ to give naproxen in one step and 90% yield. Seayad et al. used a catalyst system of $PdCl_2(PPh_3)_2$/TsOH/HCl to effect the same transformation in the preparation of ibuprofen.[153] Reaction rates with TOF up to 1200 h^{-1} and ibuprofen selectivity of 95% were achieved at 388 K under a CO partial pressure of 5.4 MPa. An alternative general procedure to homologate ketones into carboxylic acids uses α-metalated ethers, Scheme 32.[154,155]

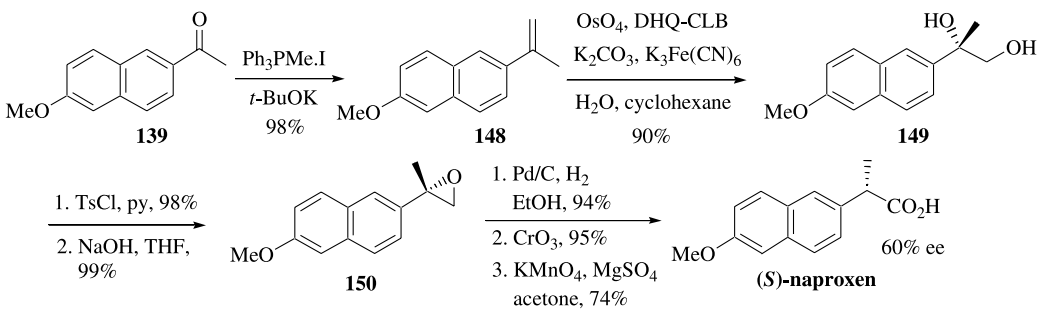
The sequence involves the reaction of Grignard **141** with aldehydes or ketones to give 2-ethoxy alcohols **142**. These alcohols **142** in turn were transformed into the homologated aldehydes **143** by heating with formic acid. A selection of substrates investigated by this method are shown in Table 14.

6. Via olefins

There are several general strategies for formation of the olefin from the ketone, with a variety of strategies then existing to transform the double bond into the homologated carboxylic acid. Such reagents to form the double bond include Wittig reagents;[156] Horner reagents;[157] Wadsworth–Emmons reagents[158] and Peterson reagents.[110] For example the double bond can be hydroborated and the alcohol oxidized to give the homologated acid. There are various methods for the transformation of a primary alcohol into a carboxylic acid, such methods include CrO_3/acid,[159] $KMnO_4$,[160] NaOCl,[161] and RuO_4 or its equivalents.[162] Curran et al. added the one carbon unit using a Wittig/hydroboration/oxidation sequence in the preparation of



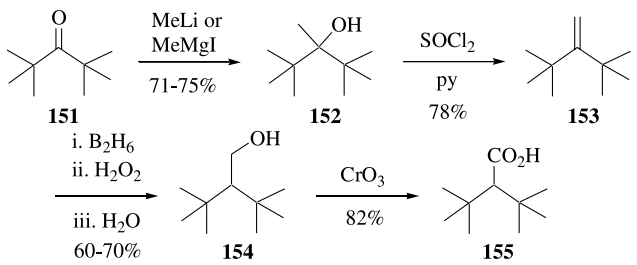
Scheme 33.



Scheme 34.

an intermediate in the synthesis of crispatic acid,[163] Scheme 33.

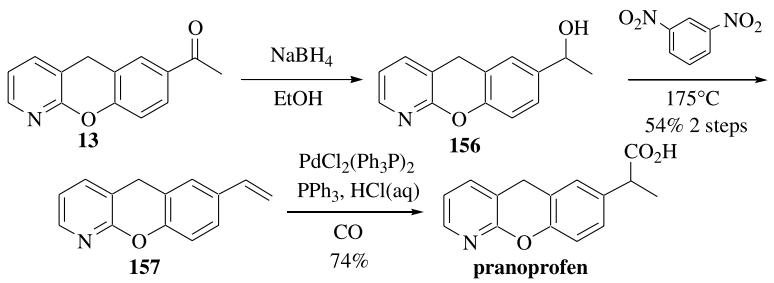
Using a standard Wittig reaction, **145** was produced in 83% yield. Hydroboration of **145** with $BH_3{\cdot}SMe_2$[164] gave a 1:1 mixture of diasterioisomers in >90% yield. Oxidation of alcohol **146** using RuO_4, subsequent ester formation and silyl removal gave **147** in 40% over 3 steps. In three additional steps crispatic acid was produced. Zhao et al.



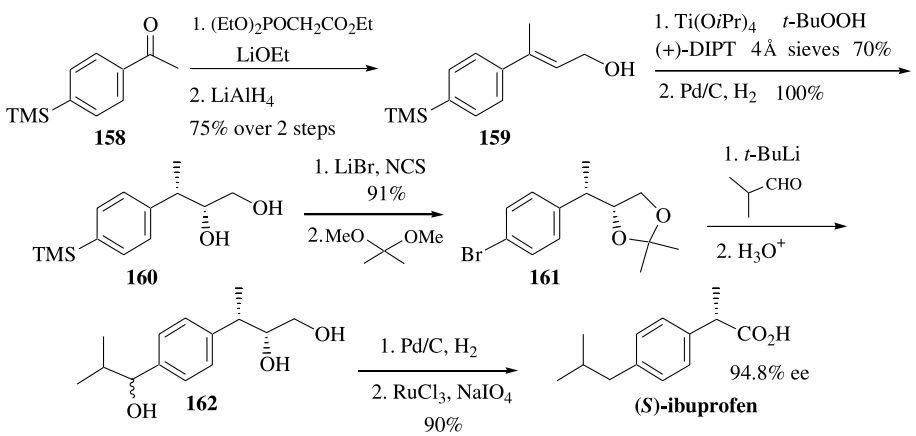
Scheme 35.

published an asymmetric method for the preparation of (*S*)-ibuprofen and (*S*)-naproxen[165] where the stereochemistry was established by a combination of Sharpless asymmetric dihydroxylation[166,167] and catalytic hydrogenation of the chiral terminal epoxide,[168] Scheme 34. Wittig reaction on ketone **139** gave isoprene **148** in 98% yield, which was dihydroxylated[169] to diol **149** in 78% ee as measured by Mosher's monoester.[170] Activation of the primary hydroxyl as a tosylate and then closure to the epoxide gave **150** in 97% over 2 steps. Hydrogenation of the epoxide with 10% Pd/C resulted in inversion of the stereochemistry at the benzylic position, with partial racemization. Subsequent oxidation gave the aldehyde in 95% yield and further oxidation with $KMnO_4$ gave (*S*)-naproxen in 60% ee. (*S*)-Ibuprofen was also synthesized in 60% ee by this method.

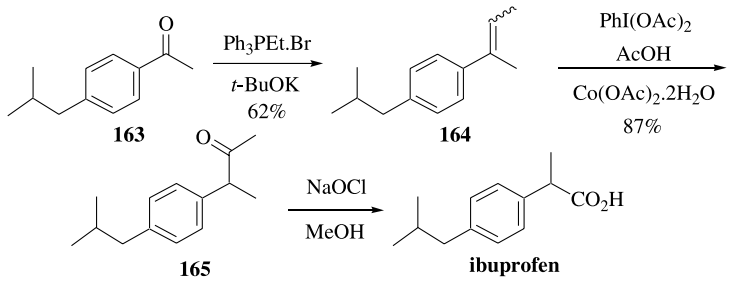
Other publications using the olefination/hydroboration strategy are in the preparation of α,β-disubstituted β-amino acids[171] And Fridamycin E.[172] Newman et al.[173] and others[174] have reported addition of MeLi to ketones



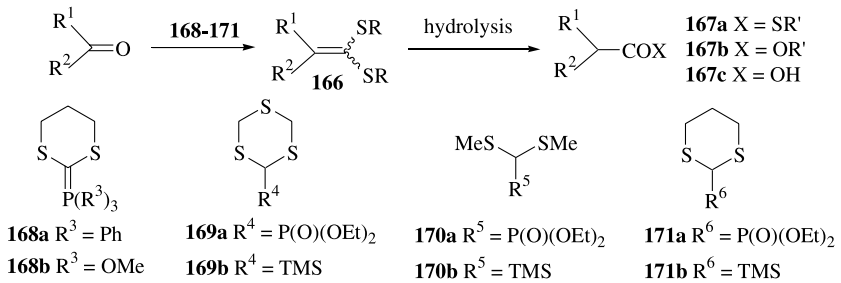
Scheme 36.



Scheme 37.



Scheme 38.



Scheme 39.

then elimination to give the double bond, Scheme 35. Methyl lithium of Grignard was added to ketone **151** to give **152** in 71–75% yield. Alcohol **152** was then dehydrated to give olefin **154** in 78% yield. Hydroboration and oxidation gave the homologated carboxylic acid **155**.

Schaumann et al. extended this to include cyclic hindered ketones for homologation to the carboxylic acid.[175] Mitsubishi Petrochemicals[176] used a similar sequence for the olefin preparation to prepare pranoprofen in 2 steps from ketone **13**, Scheme 36.

Ketone **13** was reduced with $NaBH_4$ and the alcohol eliminated to give styrene **157** in 54% yield over 2 steps. Palladium carbonylation of the styrene[177] gave pranoprofen in 74% yield. Alper et al. have performed an asymmetric carbonylation on a substituted styrene in their preparation of ibuprofen and naproxen.[178]

Hamon et al.[179] prepared (*S*)-ibuprofen and (*S*)-ketoprofen by initially doing a Wittig reaction, to give an α,β-unsaturated ester, Scheme 37.

Reaction of ketone **161** with triethylphosphonoacetate gave mainly the thermodynamically more stable (*E*)-isomer (*E*/*Z* 17:1). Reduction of the mixture of esters with $LiAlH_4$ yielded allylic alcohols **159** which were subjected to the Sharpless epoxidation, giving the epoxide in 70% yield and >98% optical purity after one crystallization. Hydrogenolysis of the epoxy alcohol with 10% Pd/C at −60°C went quantitatively with inversion of configuration to yield diol **160**. Electrophilic substitution of the TMS group and protection of the diol as the acetonide gave **161**. Lithium exchange of the bromide with *t*-BuLi and reaction with 2-methylpropanal, then removal of the protecting group under acidic conditions gave triol **162**. Hydrogenolysis gave the diol, which was cleaved with ruthenium trichloride and sodium periodate to give (*S*)-ibuprofen in 90% yield. Analysis of the derived amide (thionyl chloride, (*S*)-phenylethylamine) by HPLC, compared with diastereomers as standards showed the synthetic ibuprofen to have an optical purity of 96.4%. Shimizu et al. used a different methodology after the Wittig reaction to introduce the carboxylic acid, Scheme 38.[180]

A Wittig reaction with $Ph_3PEt{\cdot}Br$ and *t*-BuOK with ketone **163** gave olefin **164** in 62% yield as a mixture of geometric isomers. Addition of $PhI(OAc)_2$ and $Co(OAc)_2{\cdot}2H_2O$ in AcOH gave ketone **165** in 87% yield at 99% conversion. Oxidation of **165** with aqueous NaOCl transformed the ketone to ibuprofen.

7. Via acetals/ketals

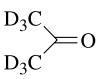
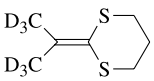
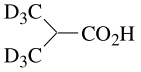
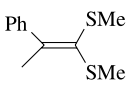
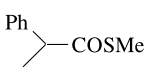
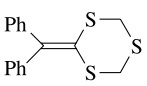
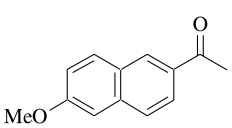
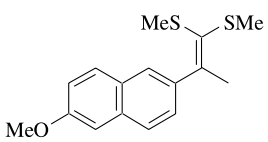
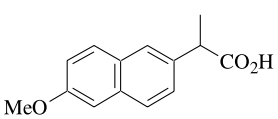
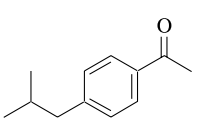
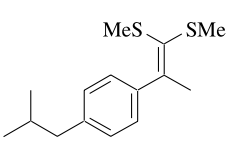
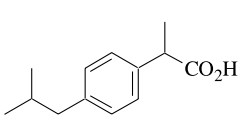
A variety of acetals/ketals have been used to introduce the one carbon unit containing either oxygen, nitrogen or sulfur or a mixture of both. These are versatile intermediates which may be transformed by reduction/hydrolysis to aldehydes, or derivatives of carboxylic acids.

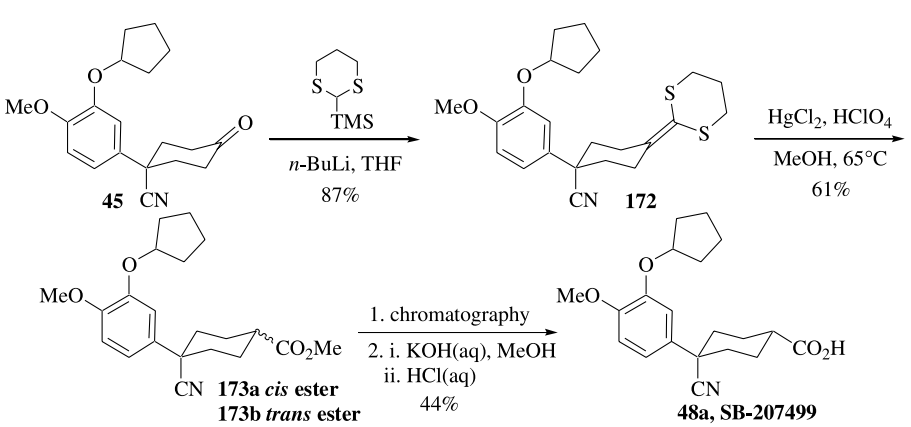
7.1. Ketene *S*,*S*-acetals

The most widely employed methods for the synthesis of ketene *S*,*S*-acetals involve Wittig, or Wittig–Horner reactions of the phosphorus reagents **168a**,[181] **168b**,[182] **169a**,[181,183] **170a**,[183] **171a**[181,183] with carbonyl compounds, Scheme 39.

Alternatively the use of **169b**,[184] **170b**[184,185] and **171b**[186] produces the ketene *S*,*S*-acetals by a variant of the Peterson olefination. Although the reaction of **168a** and **168b** appears to be limited to aldehydes, the more nucleophilic metallated reagent **169a**, **169b**, **170b** and **171** reacted with both aldehydes and ketones giving good to excellent yields of the ketene *S*,*S*-acetal **166**. Similar problems associated with the formation and hydrolysis of enol ethers may occur with the use of reagents **168**-**171**. Depending on the

Table 15. Homologation of ketones using ketene *S*,*S*-acetals as intermediates

Ketone	Ketene *S*,*S*-acetal	Yield (%)	Homologated product	Yield (%)
		88		44
				88
		72		
		78		70
		80		74

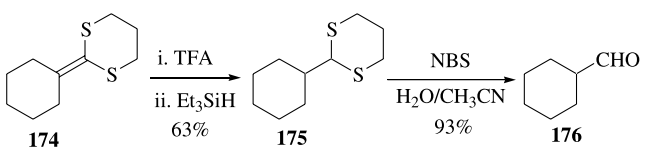


Scheme 40.

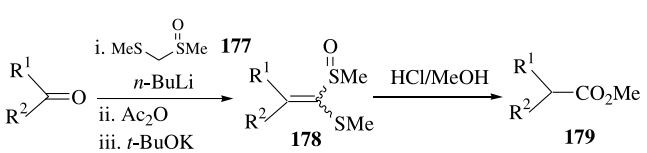
hydrolysis conditions used either the thioester,[185,187] ester[188] or carboxylic acid[189] can be isolated, Table 15.

Christensen et al. used reagent **171b** in the synthesis of SB-207499,[26,190] Scheme 40. Ketone **45** was reacted with the lithium anion of **171b** to give ketene *S*,*S*-acetal **172** in 87% yield. Mercury (II) chloride mediated methanolysis of **172** provided an approximately 11:1 mixture of *cis* and *trans* esters **173** which were separated by flash chromatography. Saponification of ester **173a** with potassium hydroxide gave acid **48a**, SB-207499 in 44% yield.

Alternative hydrolysis methods have been introduced to eliminate the toxicity of mercury salts and risk of using perchloric acid.[191] Copper (II) salts and silica gel or copper (II) sulfate in methanol[192] have been used to give the corresponding homologated esters. Strong acids (glacial AcOH, HCl) have been used to hydrolyze ketene *S*,*S*-acetals to the acids directly,[189b] as well as TFA followed by CaOCl (or hydrogen peroxide) treatment in the preparation of SB-207499.[193] Ketene *S*,*S*-acetals can also be transformed into aldehydes in a 2 step sequence, as shown in the example of the ketene *S*,*S*-acetal of cyclohexanone, Scheme 41.[185a]

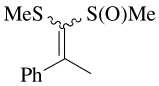
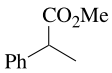
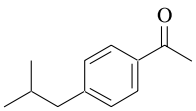
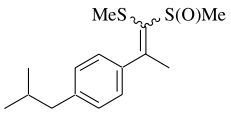
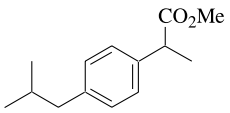
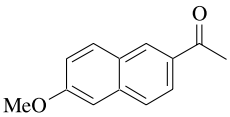
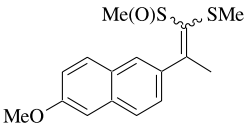
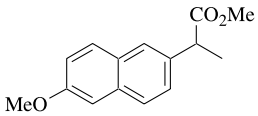
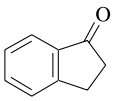
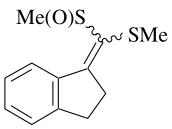
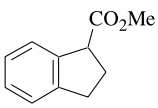
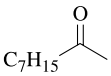
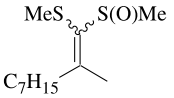
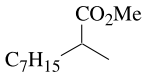


Scheme 41.



Scheme 42.

Table 16. Homologation of ketones using ketene *S*,*S*-acetal mono-oxides

Ketone	Ketene *S*,*S*-acetal mono-oxide	Yield (%)	Homologated ester	Yield (%)
		69		69
		73		92
		67		56
		59		43
		59		44

The double bond was first reduced by a combination of TFA and Et_3SiH. Bromination and hydrolysis then gave homologated aldehyde **176** in 93% yield.

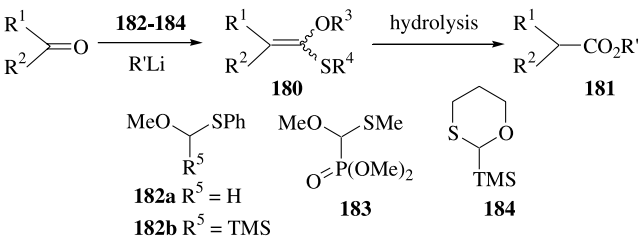
7.2. Ketene *S*,*S*-acetal mono-oxides

Ogura et al. showed ketene *S*,*S*-acetal mono-oxides intermediates could effect the one carbon transformation,[194] Scheme 42. The ketene *S*,*S*-acetal mono-oxides had to be formed as a 3 step sequence.

Using the original process on ketones which worked for aldehydes in the presence of Triton B, product **178** was not obtained.[195] This was thought to be due to enolization and/or fast self-condensation of the starting material in the presence of Triton B. A solution to this problem was after addition of the anion of **177** to the ketone, the resulting tertiary hydroxyl was acylated and then eliminated in the presence of *t*-BuOK to give **178**. Compound **178** can also be prepared from the ketene *S*,*S* acetal by oxidation[196] The ketene *S*,*S* mono-oxides can be hydrolyzed to **179** using methanolic aqueous HCl. A variety of substrates were investigated, and this sequence was shown to work with both aliphatic and aromatic ketones, Table 16.

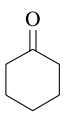
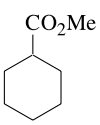
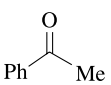
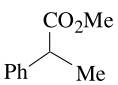
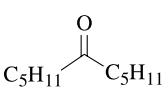
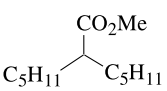
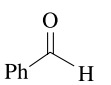
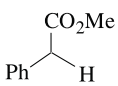
7.3. Ketene *O*,*S*-acetals

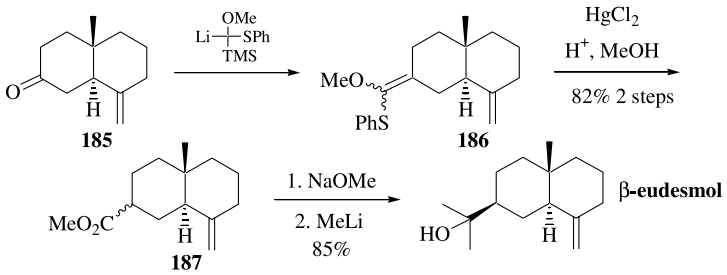
There are various methods for the conversion of carbonyl compounds into ketene *O*,*S*-acetals **180**. These can then be hydrolyzed to the homologated esters,[197] Scheme 43. Reagents **182a**,[198] **182b**,[197,199] **183**[183b] and **184**[200] have been used to effect the transformation of a ketone or aldehyde to a ketene *O*,*S*-acetal.



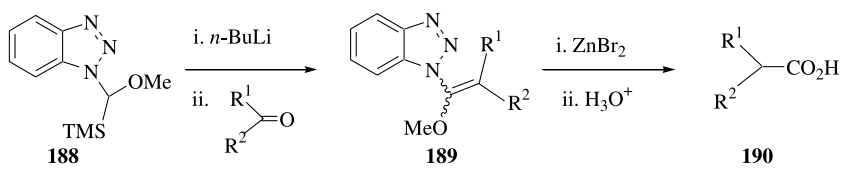
Scheme 43.

Table 17. Preparation of homologated esters from ketones and aldehydes

Ketone	Homologated ester	Yield (%)	Ketone/aldehyde	Homologated ester	Yield (%)
		88			91
		92			89

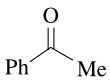
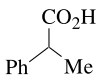
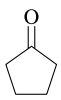
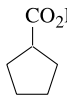
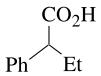
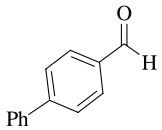
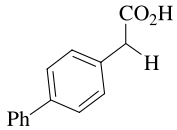
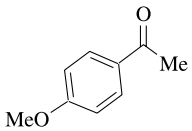
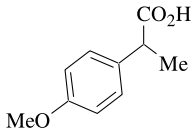
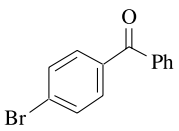
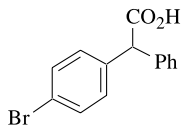


Scheme 44.



Scheme 45.

Table 18. Homologation of ketones to carboxylic acids using ketene *N*,*O*-acetals intermediates

Ketone	Homologated acid	Yield (%)	Ketone/aldehyde	Homologated acid	Yield (%)
		28			55
		55			45
		53			43

Hydrolysis of the ketene *O*,*S*-acetals occurs with the use of $HgCl_2$ and conc. HCl in MeOH,[197] to give the homologated methyl ester. The mechanism of hydrolysis of the ketene *O*,*S*-acetal has been investigated by Schmir et al. using aqueous HCl and aqueous $HClO_4$.[201] A selection of substrates investigated by this procedure using **182b** is shown in Table 17.

de Groot et al. has used this methodology to prepare β-eudesmol, Scheme 44.[197a] Lithiated reagent **182b** was added to ketone **185** to give ketene *O*,*S*-acetals **186**, which was immediately hydrolyzed to give the homologated ester **187** in 82% yield over 2 steps. Methanolysis at reflux of **187** caused isomerization of the exo-methylene double bond into the ring. Equilibration of the esters **187** with NaOMe, followed by addition of MeLi gave β-eudesmol in 85% yield.

Livinghouse et al. has reported procedures for the hydrolysis of ketene *O*,*S*-acetals to the homologated thio ester. These are either using TMSCl, NaI in dry acetonitrile,[199a] and subsequent filtration of the reaction mixture through alumina,[202] or addition of MeSLi to give the thio ester.[203] Representative thio ester hydrolysis methods include aqueous KOH[204] aqueous NaOH,[205] and $LiOH/H_2O_2$.[206]

7.4. Ketene *N*,*O*-acetals

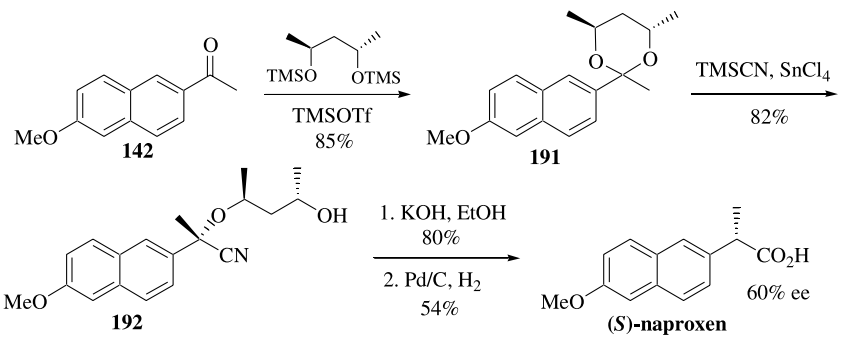
Katritzky et al. reported a method which used trimethylsilyl(methoxy)benzotriazol-1-ylmethane[207] as the Peterson type precursor to give ketene *N*,*O*-acetals, **189**, Scheme 45.[208] These were then hydrolyzed to give the homologated acid **190**.

Lithiation of **188**[207] gave a deep blue solution of the anion which underwent a Peterson olefination with aldehydes and ketones to give **189**. The crude product was then treated with $ZnBr_2$ in the presence of HCl(aq) to provide the corresponding one-carbon homologated acid **190**. The range of substrates varies from aliphatic to aromatic and is shown in Table 18.

7.5. *O*,*O*-Ketals

Sugai et al. reported the formation of aldehyde *O*,*O*-acetals and their conversion into homologated esters.[209] Hiyama et al. used this idea, with the use of a chiral *O*,*O*-ketal to introduce chirality into the homologation sequence,[210] Scheme 46.

Ketone **142**[211] was converted into the chiral *O*,*O*-ketal **191**



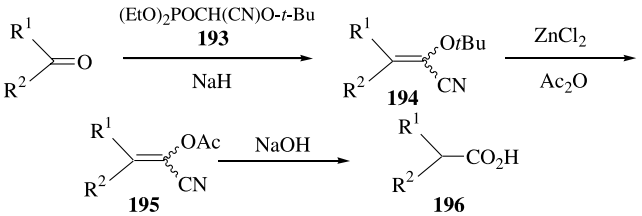
Scheme 46.

by the reaction of (*S*,*S*)-2,4-bis(trimethylsiloxy)pentane in the presence of TMSOTf[212] (84–85% ee diol). TMSCN was then added in the presence of $SnCl_4$ to give a 74% de mixture of nitrile **192** in 89% yield. Alkaline hydrolysis and subsequent hydrogenation gave (*S*)-naproxen in 43% over the 2 steps. The optical purity of the acid was estimated at 60% ee, with the hydrogenation proceeding in inversion of stereochemistry.[213]

8. Via acrylonitriles

8.1. α-*tert*-Butoxyacrylonitriles

Phosphonate **193**[214,215] has been employed as an operational equivalent of a carboxyl anion in a Horner–Emmons modification of the Wittig reaction[216] After formation of **194**, transformation into α-acetoxyacrylonitriles **195** and subsequent hydrolysis affords the homologated carboxylic acid. This method appears to be fairly general, however, acid labile groups, such as acetals do not survive to conditions for the transformation of **195** into **196**, Scheme 47.



Scheme 47.

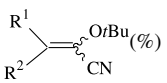
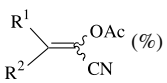
The hydrolysis of the *tert*-butoxy group in **194** proved difficult under a variety of acid conditions. On transforming **194** into **195** by reaction with $ZnCl_2$ in acetic anhydride, the α-acetoxy group was found to be more easily hydrolyzed to give the homologated acid. The steric bulk of diethyl *tert*-butoxy(cyano)methylphosphonate limited the reaction to those ketones which possessed three or more α-hydrogen's. A variety of substrates were found to be transformed in good yield, Table 19. In some cases the α-acetoxyacrylonitrile need not be isolated but taken directly into the hydrolysis stage. Care again must be taken as cyanide is liberated during the hydrolysis. Not only can the phosphonate **193** be used to prepare carboxylic acids, but treatment of the intermediate α-acetoxyacryonitrile **195** with alkoxides or amines, gave esters or amides respectively.[217]

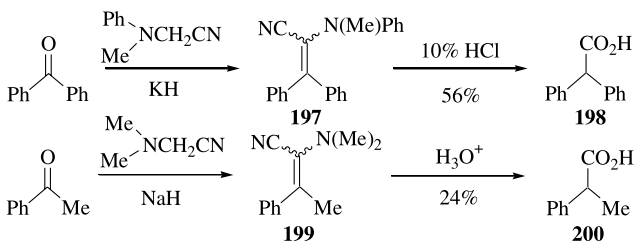
8.2. α-Aminoacrylonitriles

A method for the homologation of aldehydes,[218] acetophenone[218c] and benzophenone[218a] uses α-aminoacrylonitriles[219] to achieve the one carbon transformation. The α-cyano enamine synthon is known to be synthetically equivalent to an acyl cyanide in which the carbonyl group is masked as an enamine.[220] The transformation for each ketone is shown in Scheme 48.

Benzophenone and acetophenone were reacted with the α-aminonitriles to give the α-aminoacrylonitriles **197** and **199**, respectively. Hydrolysis of these gave the homologated carboxylic acids **198** and **200** in 56 and 24%, respectively. No other ketones have been reported for this transformation and it is unknown how general this strategy would be for other substrates.

Table 19. Homologation of ketones to carboxylic acids via α-*tert*-butoxyacrylonitriles

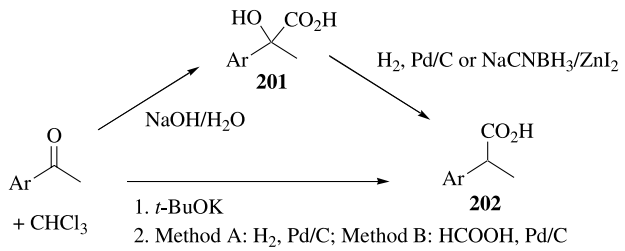
Ketone				Homologated acid (%)
R^1	R^2			
CH_2CH_2Ph	CH_2CH_2Ph	84	90	99
CH_3	Ph	93	94	96
Ph	Ph	86	95	100
$-(CH_2)_5-$		88	88	95
2-Methylcyclohexanone		78	90	92
Cholest-4-en-3-one		86	80	79
Methyl levulinate		74	89	84
5α-Androstane-3,17-dione		92	Not isolated	55



Scheme 48.

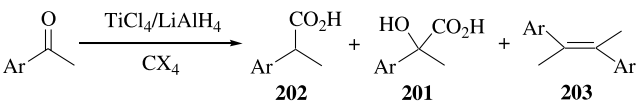
9. Via α-hydroxy acids

This methodology has been developed for aryl methyl ketones and involves two main strategies. The first is addition of dihalocarbenes generated by a base,[221] or low valent titanium.[222] The second is electrolysis of the ketone in the presence of carbon dioxide. Sinisterra et al. developed[221] the addition of dihalocarbenes to aryl ketones using base, Scheme 49.



Scheme 49.

The dihalocarbene was prepared by the addition of base to $CHCl_3$ which when added to the ketone gave hydroxy acid **201** The hydroxy acid was reduced with sodium cyanoborohydride/zinc iodide for a 2 step process or directly by a one pot method by addition of Pd/C using hydrogen or an hydrogen donor such as formic acid to give the acid **202** directly. A selection of substrates investigated is shown in Table 20.



Scheme 50.

The yields are moderate, 35–60% for the one pot procedure. For the low valent titanium procedure,[223] the ratio of $TiCl_4$ to $LiAlH_4$ was found to be critical. Depending on the molar ratio between the two reagents, various products could be formed, Scheme 50.

An excess of $LiAlH_4$ favored the synthesis of the carboxylic acid **202** directly. The optimum conditions were 1/2.5 to 1/3 for $TiCl_4/LiAlH_4$. This was explained that an excess of $LiAlH_4$ decreased the generation of the titanium complex that favored the reductive coupling of the ketone to give **203**, and the hydrogenolysis of the intermediate 2-hydroxy acid **201**. The yields for this procedure are higher 60–78% than the base generated carbene procedure. Another method in which to give the hydroxy acid is by electrochemistry. The ketone is subject to electrolytic reduction and then addition of CO_2 gives the hydroxy acid. Palladium hydrogenation gave the desired homologated carboxylic acid.[224,225] Wang et al. has used this to prepare naproxen in 2 steps from ketone **139** in 85% yield, Scheme 51.[224] Ibuprofen has also been prepared this way.[225]

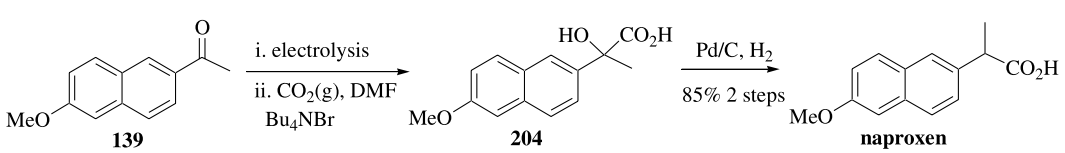
10. Via homologation/alkylation

There are various methods for the homologation of alkyl aryl ketones to introduce the one carbon unit. One strategy consists of treatment of the substrate with $AgNO_3$, $CH(OMe)_3$ and I_2,[226] then alkylation. De Brabander et al. asymmetrically prepared (*S*)-ibuprofen by the $AgNO_3$ method, Scheme 52.[227] Ketone **163** was oxidatively rearranged (I_2, $AgNO_3$, $CH(OMe)_3$) to give the methyl ester **205** in 98% yield. Acylation of (1*S*)-2,10-bornanesultam with ester **205** using Weinreb conditions[228] gave **206** in 79% yield. Deprotonation of **206** resulted in selective formation of the *Z*-(*O*)-lithium enolate which was alkylated at −60°C with MeI. Product **207** was obtained in 83% yield and >95% de. Finally H_2O_2 cleavage gave (*S*)-ibuprofen in 89% yield and 95% ee with recovery of the bornanesultam auxiliary in 95% yield.

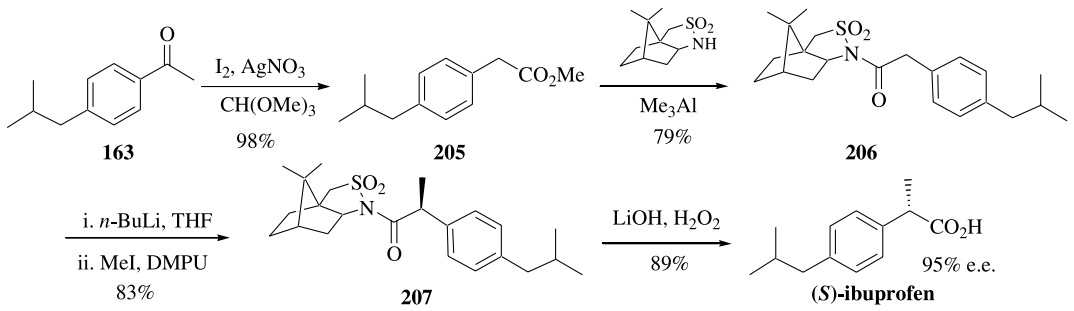
Another variation is the use of $Tl(NO_3)_3$ absorbed onto Montmorillonite K-10 clay[229] to give the homologated ester, which can then be alkylated. Hagmann et al. used this to prepare 11*H*-dibenzo[*b*,*e*][1,4]dioxepinacetic acids,[230] Scheme 53.

Table 20. Preparation of aryl carboxylic acids from aryl ketones via in situ α-hydroxy acids

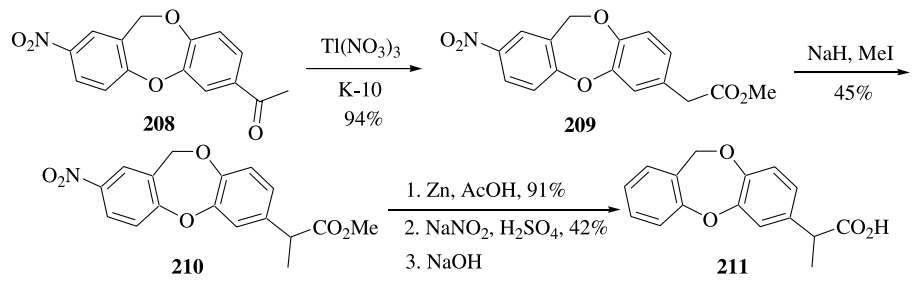
Ar	Method A yield (%)	Method B yield (%)	Ar	Method A yield (%)	Method B yield (%)
C_6H_5	55	60	*p*-$MeOC_6H_4$	45	50
p-Me–C_6H_4	40	45	*p*-ClC_6H_4	35	45
p-*iso*-$C_3H_7C_6H_4$	40	45	6-MeO-2-napthyl	40	45
p-*iso*-$C_4H_9C_6H_4$	40	40	α-Thienyl	35	45



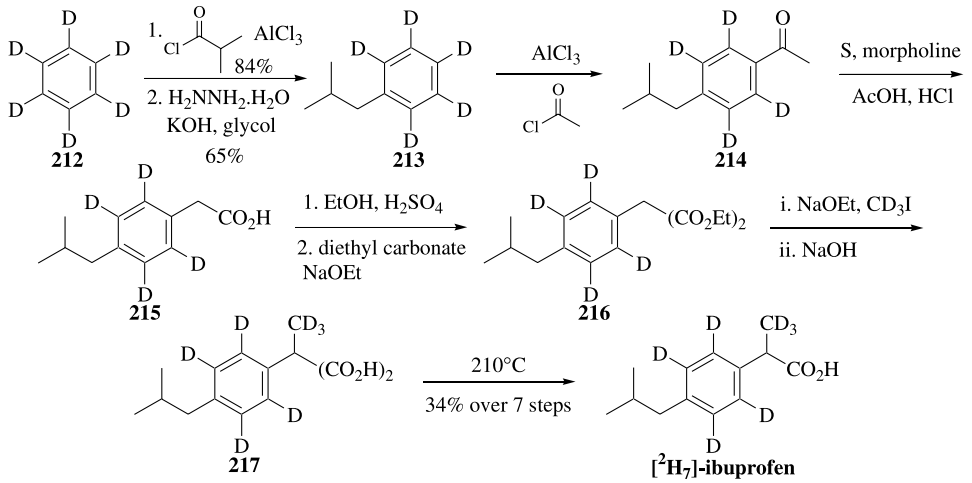
Scheme 51.



Scheme 52.



Scheme 53.

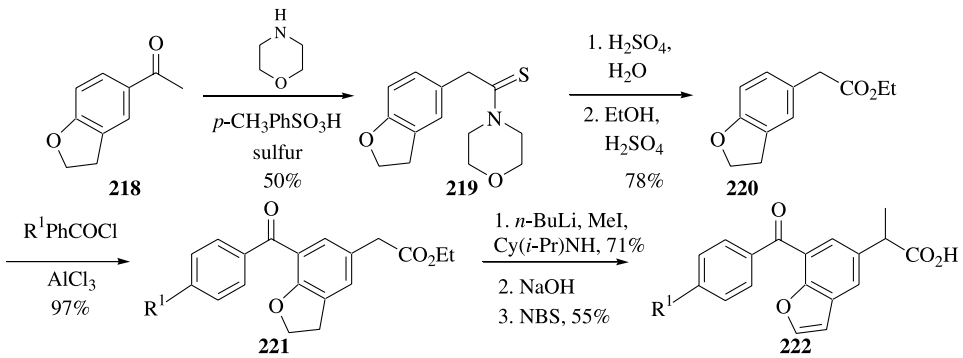


Scheme 54.

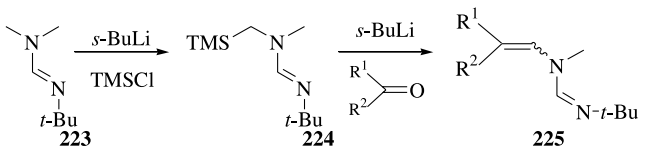
Treatment of ketone **208** with $Tl(NO_3)_3$ on K-10 clay gave ester **209** in 94% yield. Alkylation of **209** with MeI gave **210** in 45% yield. Removal of the nitro group and ester hydrolysis gave the α-methyl acetic acid **211**. This methodology has also been used to prepare (isobutylphenyl)-acetic and propionic acid.[231] Another method is the Willgerodt–Kindler reaction[232] where the ketone is treated with sulfur and a dry primary or secondary amine to give a thioamide which can be hydrolyzed to the acid. Halstead et al. described the preparation of $[^2H_4]$-ibuprofen and $[^2H_7]$-ibuprofen[233] by this method, Scheme 54.

[Ar-$^2H_5$]-isobutyrophenone **213** was prepared by Friedel–Crafts acylation of benzene-d_6 **212** in 84% yield. Reduction of **213** via the Huang–Minlon modification[234] of the Wolff–Kishner reduction yielded [Ar-$^2H_5$]-isobutylbenzene **213** in 65% yield. Friedel–Crafts acylation of **213** gave acetophenone **214** which was converted to the phenyl acetic acid **215** via the Willgerodt–Kindler reaction and hydrolysis of the resulting thiomorpholide. Compound **215** was esterified and on heating with diethyl carbonate and NaOEt gave malonic ester **216**. Deprotonation of **216** and alkylation with either $[^2H_3]$–CH_3I or CH_3I followed by hydrolysis gave **217** or its $[^2H_4]$-analog. Decarboxylation of **217** at 210°C gave $[^2H_7]$-ibuprofen in about 20% overall yield. Dunn et al.[235] used the Willgerodt–Kindler reaction to introduce the one carbon unit in the preparation of analgesic and anti-inflammatory 7-aroylbenzofuran-5-yl-acetic acids **222**, Scheme 55.

For the Willgerodt–Kindler reaction, morpholine was used as the amine to give the thioamide **219** in 50% yield. Subsequent hydrolysis and esterification gave the ethyl ester **220** in 78% yield, which underwent a Friedel–Crafts



Scheme 55.



Scheme 56.

acylation to give **221** in 97% yield. Alkylation of ester **221**, hydrolysis and oxidation with NBS gave the benzofurans **222**. This methodology has also been used to prepare 2-(4-alkylphenyl)propionic acids,[236] and 4-cyclohexylphenyl acetic acids.[237]

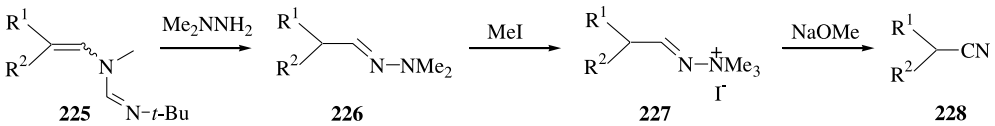
11. Via enamidines

Meyers et al. developed chemistry on the use of enamidines in synthesis.[238] Enamidines were found to react to give either homologated nitriles or aldehydes depending on the reaction conditions used. The general scheme for the preparation of enamidines is shown in Scheme 56.

Enamidines were prepared by metalation/silylation of **223**[239] to give **224**,[240] which are metalated again and treated with various ketones (or aldehydes) to give enamidines **225** as a mixture of geometric isomers. It was found that addition of 2.0 equiv. HMPA prior to addition of enolizable carbonyl compounds to the anion of **224** gave good yields of the Peterson product **225**. In one study, enamidines **225** were shown to give homologated nitriles, Scheme 57.[241]

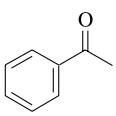
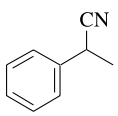
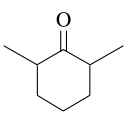
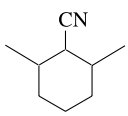
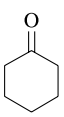
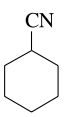
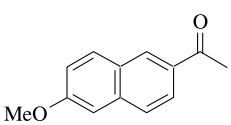
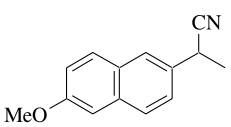
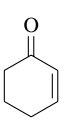
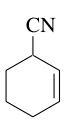
For the preparation of nitriles, enamidines **225** were exchanged to the hydrazone **226** with by *N*,*N*-dimethylhydrazine. These hydrazones **226** were treated with MeI to give the salt **227** and subjected to NaOMe elimination to give nitriles **228** in good yield. A variety of ketones, from aromatic to aliphatic to enones were examined, Table 21.

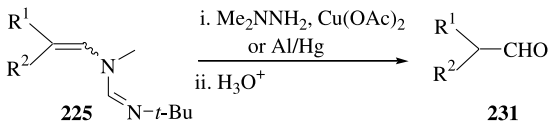
Compound **229** gave nitrile **230** in 66% yield. If TosMIC was used for the same transformation, the corresponding pyrrole was formed.[60] By altering the reaction conditions of compound **225**, homologated aldehydes could be isolated. Enamidine **225** when treated with *N*,*N*-dimethylhydrazine and $Cu(OAc)_2$[242,243] or aluminum amalgam reduction[244] then aqueous acid hydrolysis gave the corresponding aldehydes **231**, Scheme 58.



Scheme 57.

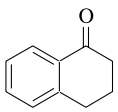
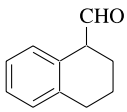
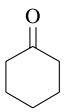
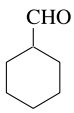
Table 21. Homologation of ketones to nitriles via enamidines

Ketone	Homologated nitrile	Yield (%)	Ketone	Homologated nitrile	Yield (%)
		82			85
		89			65
 **229**	 **230**	66			



Scheme 58.

Table 22. Homologation of ketones to aldehydes via enamidines

Ketone	Homologated aldehyde	Yield (%)
		60[a]
		84[b]
		62[a]

[a] Precursor enamidine **225** was cleaved by hydrazinolysis with 1,1-dimethylhydrazine followed by acid hydrolysis of methiodides obtained from the intermediate hydrazones.
[b] Enamidine was cleaved to diphenylacetaldehyde by using aluminum amalgam in moist ether, giving the corresponding *N*-methyl enamine, which was cleaved with aqueous acid.

Table 22 shows several examples of this method which was shown to work on ketones.

12. Via 1-formylamino-1-arylsulfonyl alkenes

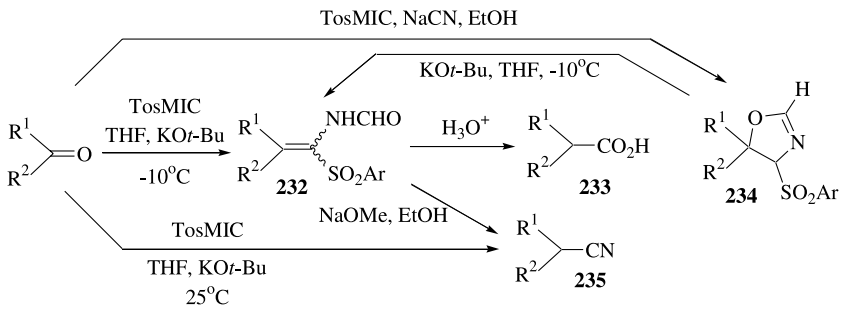
Schöllkopf showed that 1-formylamino-1-arylsulfonyl alkenes were formed when α-metalated isocyanomethylaryl sulfones (e.g. TosMIC) were allowed to react with ketones or aldehydes at −10°C,[65,245] Scheme 59. This is in contrast to van Leusen's results where when the temperature of the reaction was ambient, the homologated nitrile **235** was formed. The 1-formylamino-1-arylsulfonyl alkenes **232** were then converted into carboxylic acids on heating with dilute acid.

Heating the ketone in ethanol with TosMIC in the presence of NaCN as the basic catalyst, 4-arylsulfonyl-2-oxazolines **234** were isolated.[246] Treatment of these compounds with potassium *tert*-butoxide at −10°C gave the 1-formylamino-1-aryl-sulfonyl alkenes **232**. This 2 step approach to compound **232** was sometimes superior to the one step direct method.[245] Heating **232** with NaOMe in ethanol gave the corresponding homologated nitrile **235**.[66] The range of substrates which Schöllkopf reported is shown in Table 23.

13. Miscellaneous

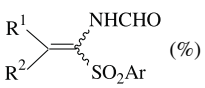
Liebeskind et al. used acetylene to introduce the one carbon unit for homologation of a ketone into a carboxylic acid,[247] Scheme 60, with the reaction sequence being amenable to the sensitive β-lactam ring.

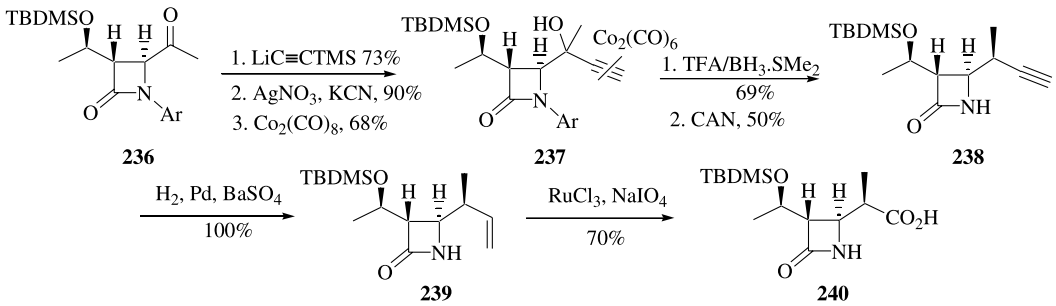
Addition of TMSC≡CLi to **236** gave a 1:1 mixture of alcohols in 73% yield. Desilylation was accomplished with $AgNO_3$/KCN[248] in 90% yield and complexation with $Co_2(CO)_8$ gave **237** in 68% yield. Reduction of the complexed propargyl alcohol was achieved using the Maryanoff modification (BH_3·SMe_2/TFA)[249] of the Nicholas reaction.[250] Simultaneous deprotection of the β-lactam nitrogen and decomplexation of the alkyne using ceric ammonium nitrate gave **238** in 50% yield. Lindlar reduction of the alkyne gave **239** in quantitative yield and oxidative cleavage gave the homologated acid **240** in 70% yield.



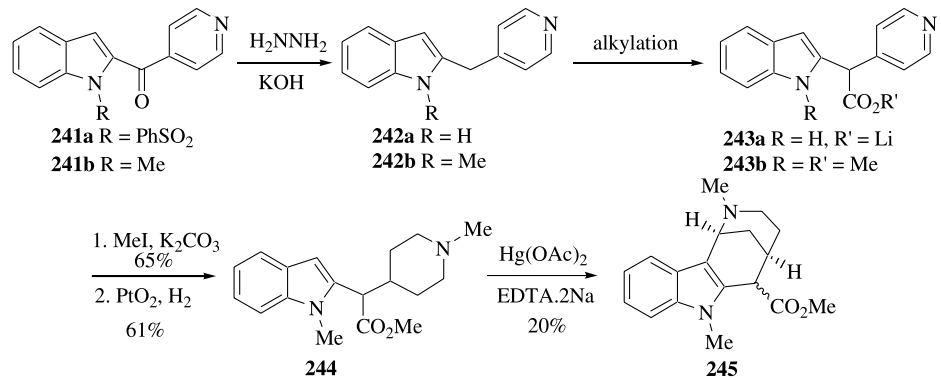
Scheme 59.

Table 23. Homologated acid from ketones/aldehydes via 1-formylamino-1-arylsulfonyl alkenes

R^1	R^2	Ar	 (%)	Homologated acid (%)
C_6H_5	H	C_6H_5	72	65
C_6H_5	CH_3	*p*-CH_3–C_6H_4	42	
α-Napthyl	CH_3	*p*-CH_3–C_6H_4	50	
–$(CH_2)_5$–		*p*-CH_3–C_6H_4	61	85
CH_3	CH_3	*p*-CH_3–C_6H_4	83	62
C_6H_5–CH=CH	H	*p*-CH_3–C_6H_4	73	67



Scheme 60.



Scheme 61.

Hiyama et al. has also used an acetylene to introduce the one carbon unit in the preparation of naproxen.[251] Bosch et al.[252] prepared intermediates in the preparation of the *Strychnos* ring system using a Wolff–Kishner reduction of a ketone and then alkylation, Scheme 61.

Wolff–Kishner reduction of **241a** gave **242a**, with concomitant loss of the $PhSO_2$ group in 64% yield. Compound **242a** was then alkylated using *n*-BuLi and CO_2 to give **243a** in 49% yield. However, without a protecting group on nitrogen it proved difficult to further functionalize. By using the methyl protecting group on nitrogen, compound **242b** was alkylated using KH and dimethyl carbonate to give methyl ester **243b** in 40% yield. With a further 3 steps, **243b** was transformed into the Strychnos ring system **245** in 7.5% yield over the 3 steps.

14. Conclusion

A wide variety of methodologies have been developed to homologate a ketone (or aldehyde) into a carboxylic acid, and which constitute a valuable class of synthetic reactions. These methodologies involve intermediates such as aldehydes, epoxides, nitriles and vinyl heteroatoms, with the synthetic sequences ranging from a single step to multiple transformations. A wide variety of substrates have been transformed both aliphatic, alkenyl and aromatic ketones some of them asymmetrically to give the desired products. Although there are multiple methods and reagents available for this transformation, chemists will still aspire to develop more efficient, practical and broader solutions to overcome some of the limitations with current methodologies.

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