REVIEW

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Synthetic approaches to regiospecifically mono- and dilabelled arenes

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A variety of methods for the preparation of selectively mono-, di- or tri-labelled arenes are reviewed. The review concentrates on those for which the application to labelled synthesis has been demonstrated. Further methods, the application of which to labelled synthesis appears viable but which have not been reduced to practise, are included also. The available methods provide a range of substitution patterns.

Keywords: monolabelled arenes; arene synthesis; aromatic substitution

1. Introduction

Recently, there has been a revival of interest in the synthesis of arenes labelled with one or two specifically positioned ^{13}C or ^{14}C atoms. Although earlier syntheses of such molecules were intended to generate substrates for the investigation of reaction mechanisms, more recent work is typically driven by the requirements of metabolism and bioanalytical studies.[1] The ever increasing dominance of mass spectrometry as a preferred technique, both for the identification of metabolites from ADME (absorption, distribution, metabolism and excretion) studies and for the quantification of both parent drug and metabolites in bioanalytical studies, results in a preference for ^{14}C materials with mass spectra that are as simple as possible. Since the benzene used to prepare *U*-^{14}C-labelled aromatic molecules generally originates from the cyclotrimerisation of [$^{14}C_2$]- and unlabelled acetylene, or derivatives thereof, such products typically consist of a mixture of $^{14}C_2$, $^{14}C_4$ and $^{14}C_6$ isotopologues diluted with an excess of unlabelled material, and their mass spectra are correspondingly complex. The spectra of singly or doubly labelled species are simpler, and it is possible to create a simple but distinctive unnatural isotopic pattern by mixing two isotopologues. This can be used to aid the identification of drug-related peaks among those due to endogenous material, and this has therefore led to a resurgence of interest in the techniques involved in the synthesis of point-labelled arenes.

In this review, we attempt to summarise the methods that have been demonstrated as useful for the preparation of point-labelled arenes, noting the apparent advantages and limitations of each. Generally, the methods described are illustrated by the formation of monolabelled arenes, although relevant examples of the synthesis of dilabelled and trilabelled compounds are included. Syntheses where the label introduced is divided between several positions and those with multiple carbon labels are generally excluded. In addition, selected approaches that have been developed in unlabelled form, and which could potentially be applied to labelled syntheses, are described. This field as a whole has not been reviewed critically although the most common methods used are discussed briefly in a recent book.[2] Earlier published work includes a detailed comparison of the methods used for the generation of mono-^{14}C-labelled phenol[3] and two books in which the most common early methods are described in some detail.[2,4]

The present review is organised by synthetic methodology and labelled starting material, starting with the methods that presently appear to be most widely applied. Thus, we commence with the commonly used method involving cyclisation onto labelled ethyl acetate or (less commonly) labelled carbon dioxide. We go on to discuss cyclisations using labelled acetone, malonic acid esters or labelled nitromethane. Less widely used methods, involving cycloaddition, nucleophilic addition to pyranones, intramolecular aldol-type processes and ring-expansion, then follow. The last few sections describe approaches that have not been exploited to their full extent, including ring-closing metathesis, electrocyclisation and acetylene cyclotrimerisation, and then a brief discussion of other methods specific to the preparation of labelled naphthalenes. We conclude with a table designed to guide the reader to appropriate methods for the synthesis of a monolabelled arene with any given substitution pattern.

2. Cyclisation of pentamethylenebis (magnesium) halides with acetate or CO_2

Until the early 1970s, the process used for commercial production of many simple 1-^{14}C-labelled arenes involved the reaction of the Grignard reagent formed from pentamethylene dibromide with ethyl [1-^{14}C]acetate, as outlined in Scheme 1.[5,6] [1-^{14}C]-1-Methylcyclohexanol resulting from the first step is

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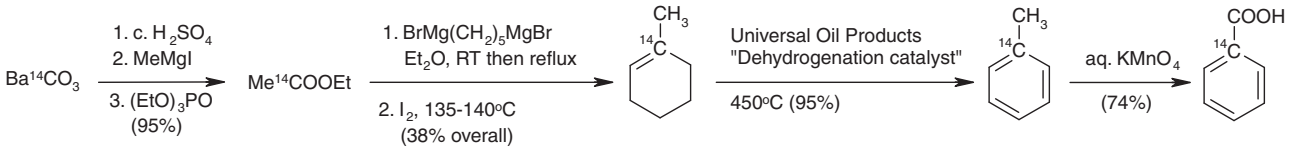


Scheme 1.

dehydrated, using a catalytic amount of iodine, to give [1-^{14}C]-1-methylcyclohexene, and small-scale steam distillation enables isolation of the product using a sealed vacuum system. On a small scale, this is complicated by incomplete distillation of the product, and the need to co-distil the residue with unlabelled 1-methylcyclohexanol, so that much of the intermediate is recovered with a lowered specific activity.[5] Subsequent dehydrogenation to give [1-^{14}C]toluene is carried out in a sealed system at elevated temperature and requires the recycling of mixtures of product and starting material through the catalyst.[7] Dehydrogenation has also been carried out using platinum on alumina[8] or on asbestos.[6] The overall yield of benzoic acid from barium carbonate can be up to 40%,[6] but the safe isolation, purification and handling of the volatile ^{14}C-labelled intermediates is not straightforward and, in addition to the operational complexity of the process, it results in the generation of significant quantities of radioactive waste.[7]

The [1-^{14}C]benzoic acid described above is converted into aniline by means of a Schmidt reaction[7,9,10] or a Hofmann reaction[16] and thence *via* the diazonium salt into a number of 1-substituted [1-^{14}C]benzenes including phenol. The formation and reported further elaboration of these intermediates are outlined in Scheme 2 (references for each procedure are given within the Scheme).

In the absence of concerns over radioactive waste, the cyclisation of 1,5-bis-Grignard reagents with labelled esters remains a viable approach to specifically labelled arenes and, in more recent work, this methodology has been used to prepare [^{13}C]arenes (Table 1).

The dehydrogenation of 1-methylcyclohexene to toluene remains a problematic step, and an alternative method has been developed using palladium on charcoal at 120°C, with maleic acid as a hydrogen acceptor.[25] Even so, this modification is prone to catalyst poisoning by trace impurities in the labelled starting materials and the yield using labelled substrate is very much reduced in comparison with those obtained in unlabelled trials. A further variation in the conditions of this step has been reported in which platinised alumina catalyst is used in an aluminium reaction tube;[26] by this means, the yields are improved somewhat, but at the cost of a degree of isotopic scrambling. By variation of the labelled starting materials, the methodology has also been used to prepare a number of other [1-^{14}C]alkylbenzenes and [1-^{14}C]biphenyl, as summarised in Table 1. In a further extension of this approach (Scheme 3), [3-^{13}C]-1,5-dibromopentane has been prepared from labelled formaldehyde, and the corresponding Grignard reagent coupled with unlabelled ethyl acetate, eventually giving [4-^{13}C]toluene, which has been elaborated further by benzylic bromination and reaction with malonate anion.[27] As with the ^{14}C-labelled intermediates produced above, further elaboration of [^{13}C] toluene has been reported by electrophilic substitution at the toluene stage, direct conversion of [1-^{13}C]benzoic acid to the nitrile, and conversion into labelled aniline, phenol, haloarenes and benzoquinone. These are summarised in Scheme 4 and, again, references for each process are given within the Scheme.

2.1. Reactions of Grignard reagents with CO_2

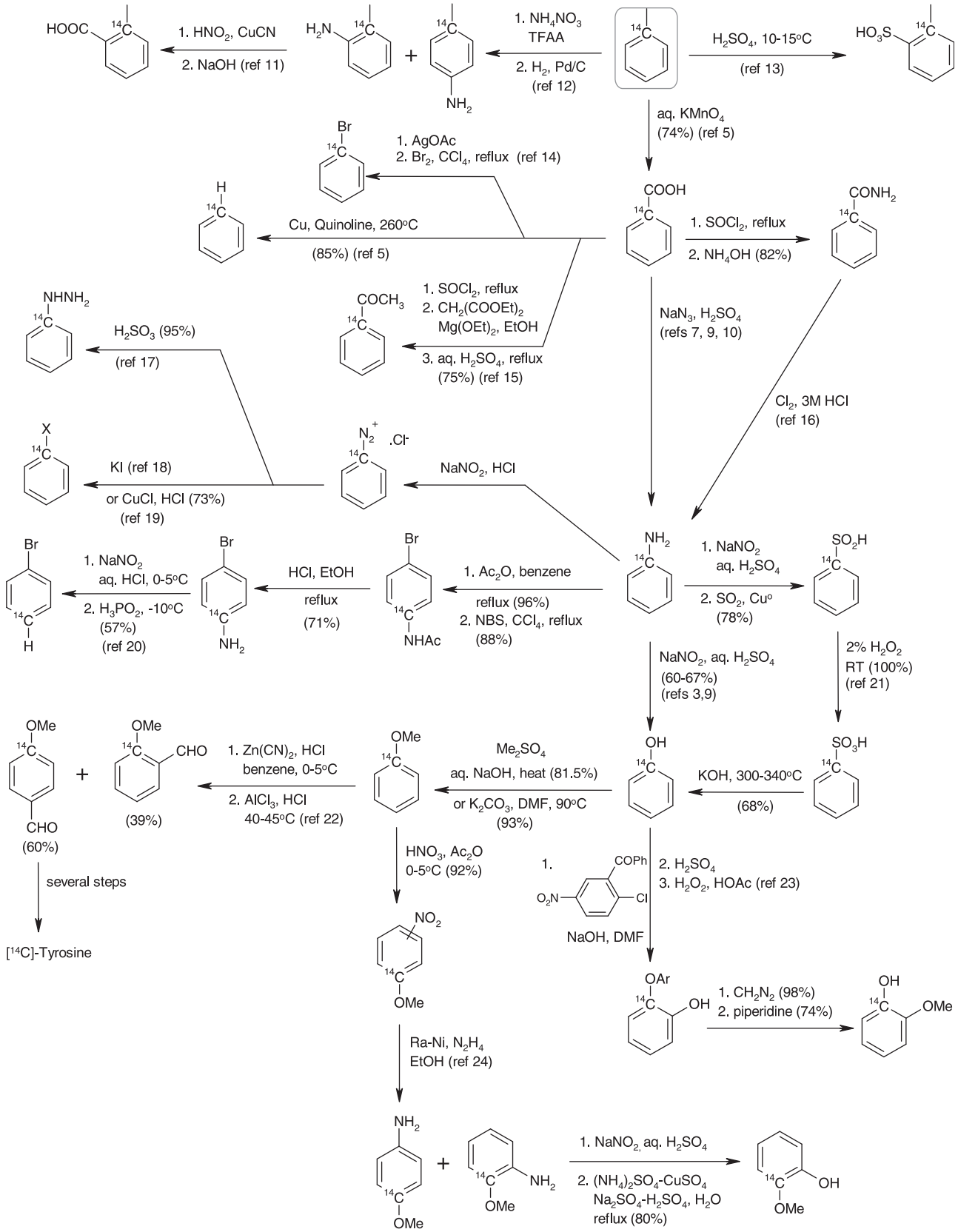
In principle, the direct reaction of a 1,5-bis-Grignard reagent with labelled carbon dioxide provides a direct route to a cyclohexanone, the aromatisation of which would provide a phenol in only two synthetic steps. In the earliest report of this approach (Scheme 5), the key cyclisation required that the ethereal solution be heated under pressure, following which the labelled ketone was isolated by steam distillation followed by vapour phase chromatography, and the product was isolated in only 20% yield. The subsequent aromatisation was carried out at 320°C and gave an overall 7% yield of [1-^{14}C]dimethylphenol, which was further elaborated by nitrosation and reductive alkylation.[38] Later workers were able to carry out the preparation of [^{13}C]cyclohexanone in 24–38% yield using the same approach but without the need to heat the mixture,[39] and a further improvement has been reported, providing [^{14}C]cyclohexanone in 40–60% yield.[40] Further development could enable this to become an economical phenol synthesis.

3. Condensation of acetone with nitromalonaldehyde

One of the more robust methods of incorporating a labelled carbon atom into arenes involves the condensation of labelled acetone with sodium nitromalonaldehyde to give 4-nitrophenol (Scheme 6). This method was originally reported as a means to prepare unlabelled 4-nitrophenol,[41–43] and has been adapted to provide both ^{13}C- and ^{14}C-labelled phenols. The optimum conditions for the process require the use of 4 M aqueous sodium hydroxide as the base at room temperature.[44] Sodium nitromalonaldehyde is a stable solid, which can be prepared in two steps from 2-furaldehyde,[45] although this method does not lend itself readily to the introduction of a carbon label. In contrast, a number of carbon-labelled forms of acetone are commercially available and their preparation has been reviewed recently.[2] Using different labelled forms of acetone, 1-,[44] 2,6-[46] and 1,2,6-labelled 4-nitrophenols[47] have been prepared.

A variety of more complex ketones have been condensed with nitromalonaldehyde to give unlabelled 2-substituted 4-nitrophenols.[48] Fewer condensations with labelled higher ketones have been reported, but these do include the formation of [^{14}C]-2,6-dimethyl-4-nitrophenol from [3-^{14}C]-3-pentanone (Scheme 7).[49] Both [2-^{14}C]- and [3-^{14}C]methoxyacetone are available by Grignard addition to methoxyacetonitrile (Scheme 8), and both have been condensed with sodium nitromalonaldehyde to afford 2-methoxy-4-nitrophenols labelled at C6[50] or C1, respectively (Scheme 8).[51]

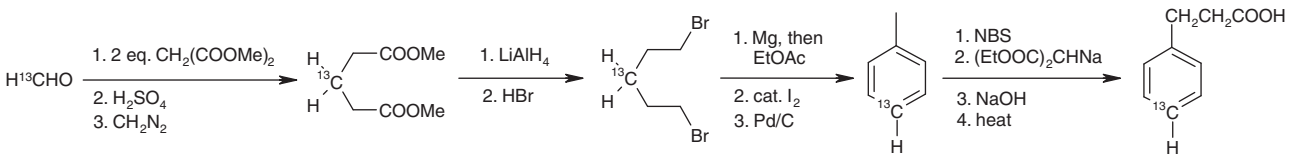
This condensation methodology has also been carried out successfully using 2-, 3- and 4-labelled forms of ethyl acetoacetate, with concomitant ester hydrolysis as illustrated in



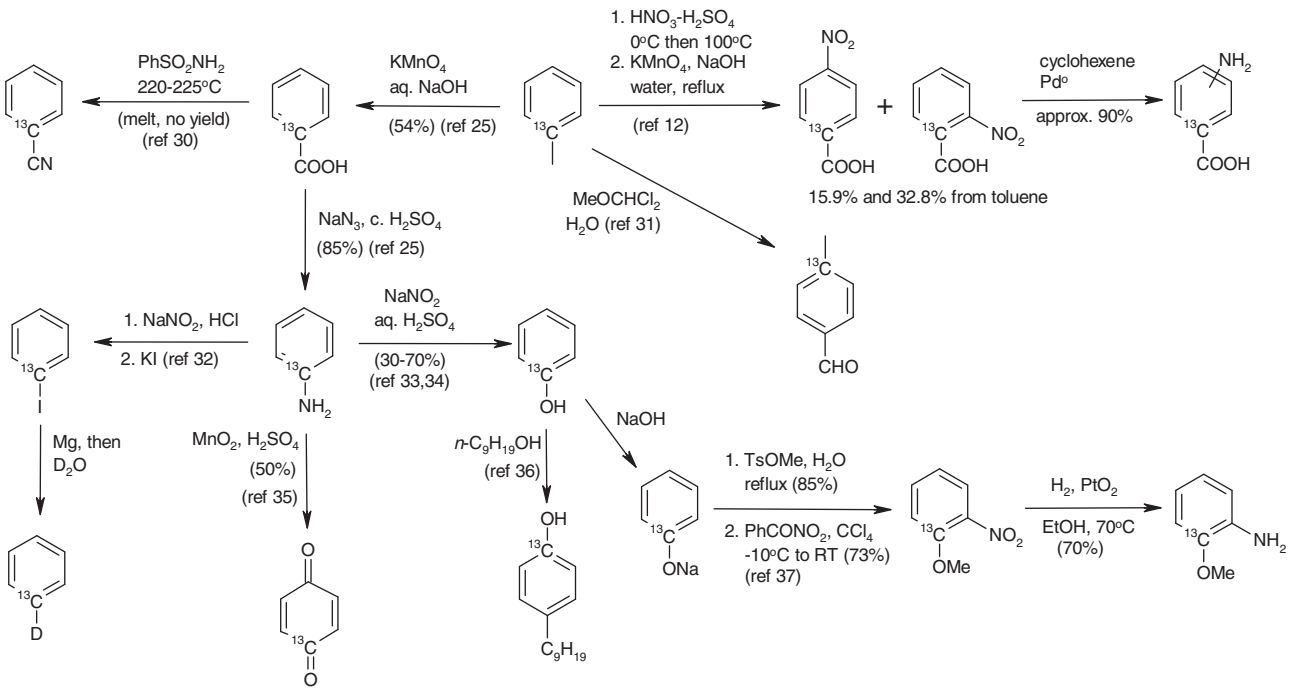
Scheme 2.

Table 1. Direct formation of substituted 13C-benzenes

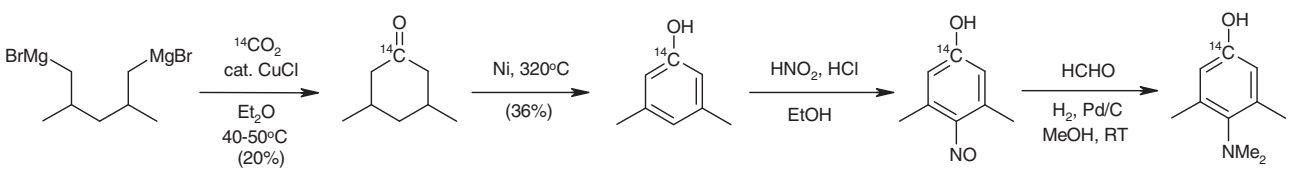
R	*R′*	Dehydration conditions	Dehydrogenation conditions	Reference
H	Me	—	Pt-Al_2O_3, 400°C (62%)	12(a)
H	Me	cat. I_2, 140°C	Pd, maleic acid, 120°C (40%)	25
H	Et	—	Pt-Al_2O_3, 400–450°C (60–70%)	26
H	Pr	—	Pt-Al_2O_3, 400–450°C (60–70%)	26
H	Ph	cat. I_2, 140°C (55% overall)	DDQ, benzene, reflux (64%)	28
3-Me	Me	TsOH, toluene, reflux (92%)	Pd, maleic acid, 130°C (44%)	29
2,4-Me_2	H	TsOH, toluene, reflux (76%)	Pd, maleic acid, 130°C (61%)	29



Scheme 3.

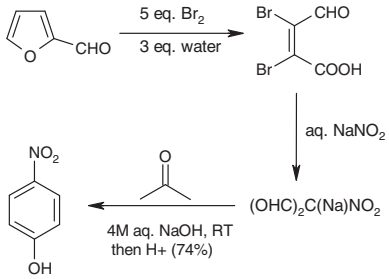


Scheme 4.

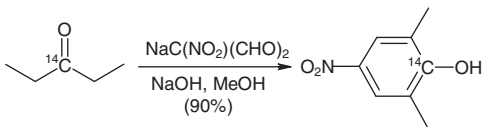


Scheme 5.

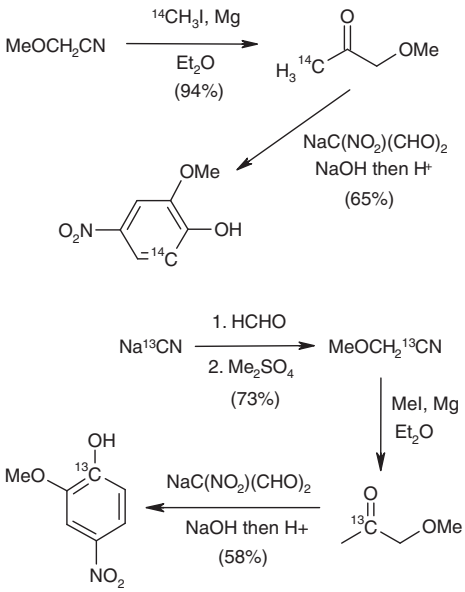
Scheme 9 for the formation of [2-^{14}C]-5-nitrosalicylic acid.[49,52] The [3-^{14}C] form of this intermediate has been elaborated further by simltaneous *O*-methylation and esterification, followed by reduction of the nitro group with subsequent diazotisation of the resulting aniline and reduction to give 2-methoxybenzoic acid. This intermediate, in turn, can be



Scheme 6.



Scheme 7.

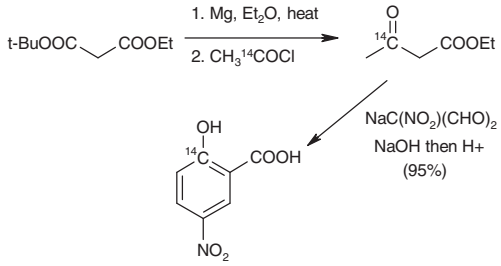


Scheme 8.

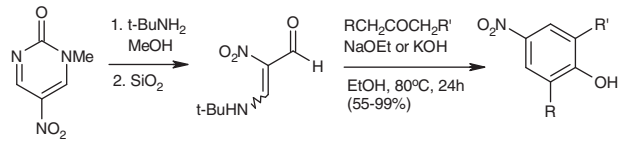
converted into [3-^{14}C]-*o*-anisidine using a Hofmann reaction, and thence into [3-^{14}C]-guaiacol.[24] Further approaches to point-labelled benzenes by reactions with labelled acetoacetates are described in Section 4. However, the corresponding processes using benzoylacetone or acetylacetone were unsuccessful.

A further variation that has been reported recently in unlabelled form involves the condensation of 3-*tert*-butylamino-2-nitro-2-propenal with dialkyl ketones under basic conditions (Scheme 10).[53] This reagent has two advantages over sodium nitromalonaldehyde in being readily soluble in organic solvents and easily prepared by aminolysis of 1-methyl-5-nitro-2-pyrimidone followed by partial hydrolysis on silica gel.[54] The published method uses two equivalents of ketone relative to the enaminone, but such an excess is unlikely to be necessary.

Labelled 4-nitrophenol, prepared as above or by the reaction of labelled nitromethane with 4-pyranone (Sections 4 and 5),[55] has been elaborated into a variety of substituted benzenes. The



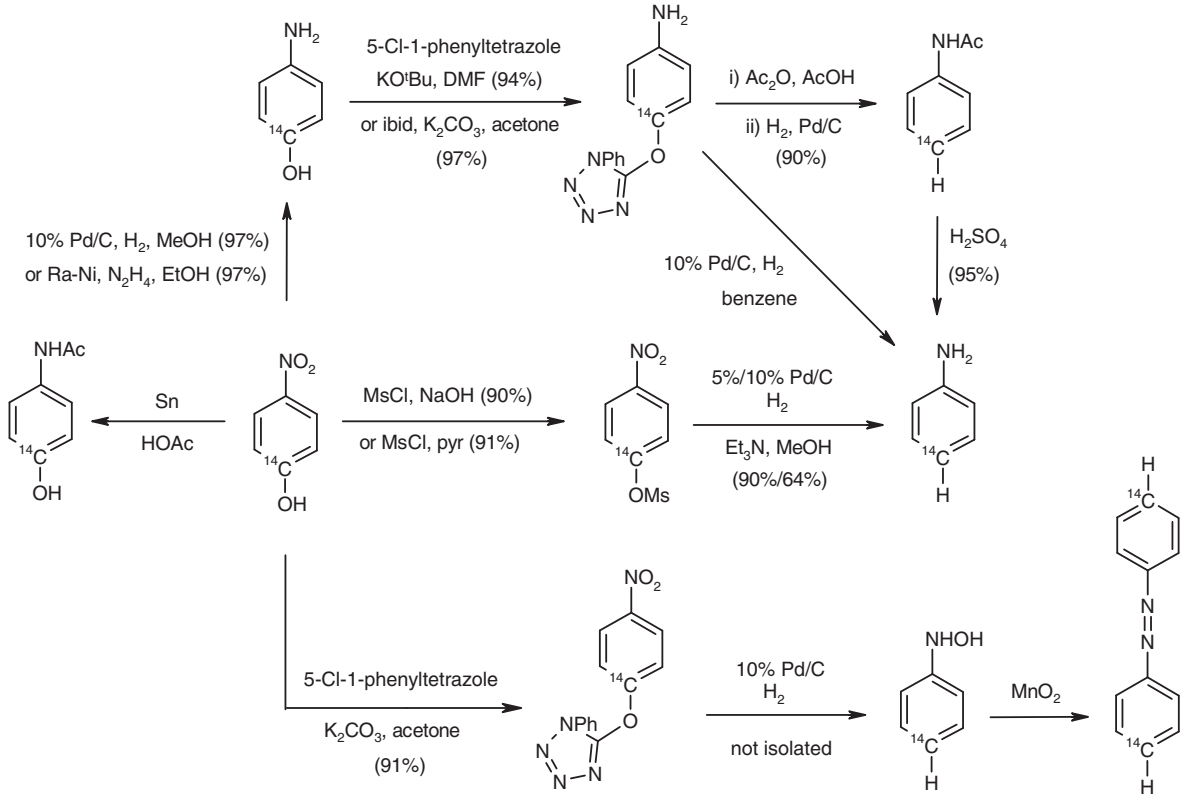
Scheme 9.



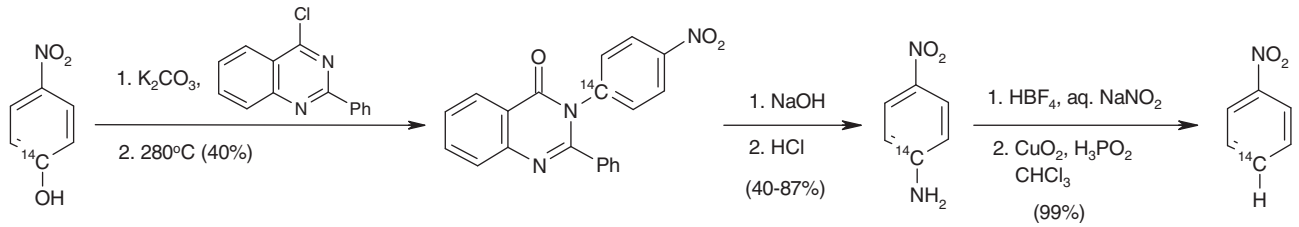
Scheme 10. R^1 = H, Me, Et, *i*-Pr, Ph; R^2 = Me, Pr, *i*-Pr, Ph.

strategies reported commonly involve conversion to monosubstituted benzenes, either by reductive removal of the hydroxyl group to provide nitrobenzene or aniline or by removal of the nitro group. Removal of the hydroxy group from 4-nitrophenol is generally accomplished by derivatisation and reductive displacement of the resulting leaving group with concomitant reduction of the nitro group (Scheme 11); the phenyltetrazole moiety has been employed for this purpose on several occasions.[24,56–59] Similarly, formation of the mesylate followed by hydrogenation results in simultaneous hydrogenolysis of the mesylate and reduction of the nitro group to give aniline directly.[60,61] Other sulphonate esters (and triflate in particular) are expected to be appropriate for this process also, although Rumpel and Limbach reported the relative failure of the brosylate and tosylate in their direct conversion of the nitrobenzene ether to aniline.[60] Deoxygenation of 4-nitrophenol by hydrogenolysis of a dialkylisourea intermediate has also been reported to be inefficient,[60,61] with reduction of the nitro group competing to produce aminophenol as a side product. Partial reduction of the nitro group is also observed during hydrogenolysis of the phenyltetrazolyl ether, with phenylhydroxylamine being formed,[58] manganese oxide oxidation of which afforded labelled azobenzene. The choice of activating group for reduction seems to depend on the oxidation state of the nitrogen. Reduction of the nitro group, prior to hydrogenolysis of the ether, allows for efficient hydrogenolysis with or without protection of the amine.[24] In this case, acetylation of the amine does have the advantage that the resulting acetanilide is less volatile than aniline while, in [^{14}C]-labelled form, it is also more stable towards radiolysis. The direct conversion of [2,6-$^{14}C_2$]-4-nitrophenol to 4-hydroxyacetanilide has also been reported using tin in acetic acid.[62]

An alternative deoxygenation procedure has been described as part of the conversion of labelled 4-nitrophenol into nitrobenzene, wherein *O*-alkylation is carried out to give a 4-(4-nitrophenyl)quinazolinyl ether (Scheme 12). Thermal rearrangement of the ether to give a 3-(4-nitrophenyl)quinazoline is followed by hydrolysis to give 4-nitroaniline, which is diazotised and reduced in turn to provide [4-^{14}C]nitrobenzene.[58] The same process has been used to provide [1-^{13}C]-4-nitroaniline.[42] 4-Labelled aniline synthesised by this method has



Scheme 11.

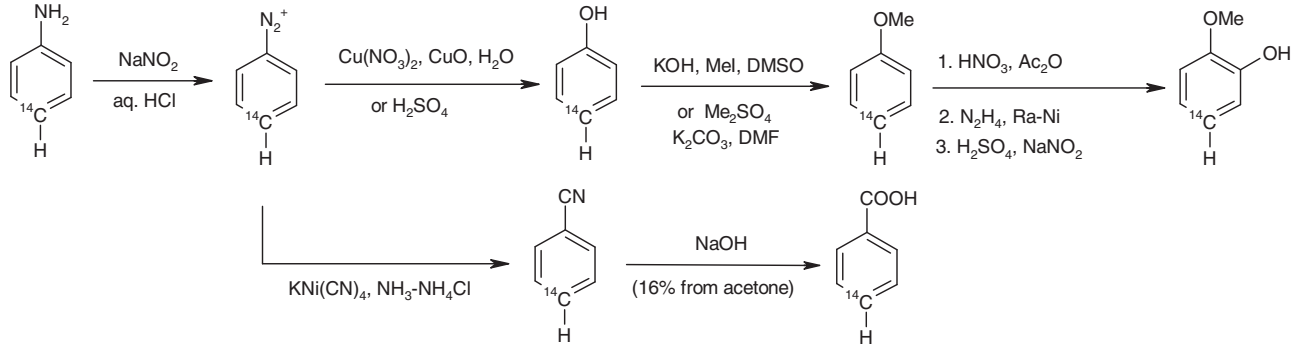


Scheme 12.

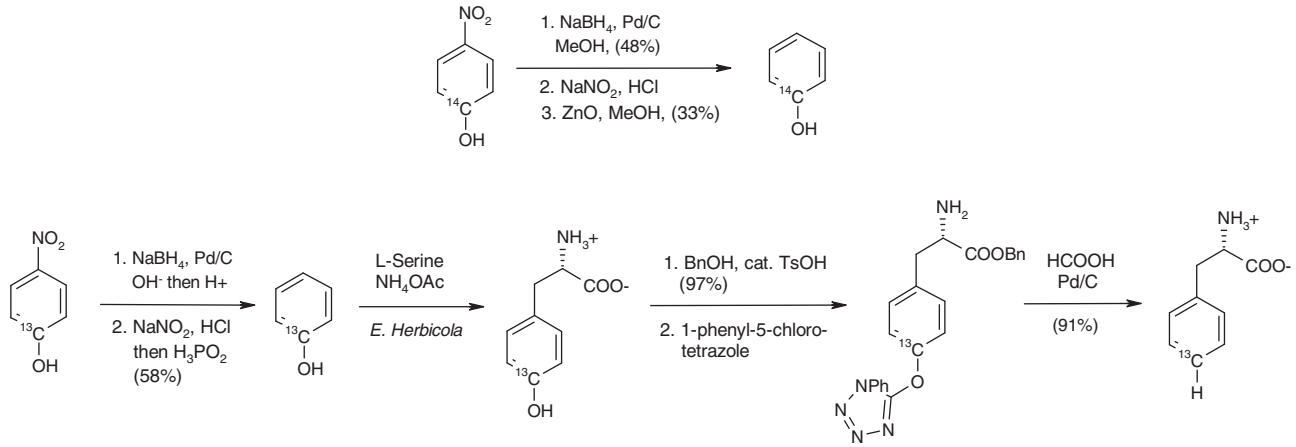
been converted, *via* the diazonium salt, into phenol,[24,59] anisole[61] and to benzoic acid by way of benzonitrile (Scheme 13).[63] The labelled anisole has also been converted into [5-^{14}C]guaiacol[24] by a nitration, reduction, diazotisation and hydrolysis pathway.

Removal of the nitro group from labelled 4-nitrophenol is typically accomplished by reduction to 4-aminophenol, followed by diazotisation and removal of the diazonium substituent, either by reduction with hypophosphorous acid[64] or by decomposition using zinc oxide in methanol (Scheme 14).[3] [1-^{14}C]Anisole has been prepared by essentially the same approach (Scheme 15).[61,65] Labelled phenols prepared by this approach have also been elaborated to provide labelled L-tyrosine, with phenylalanine also produced by deoxygenation.[66]

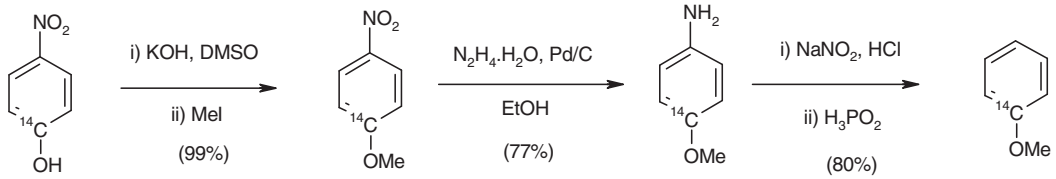
Although a major attraction of labelled 4-nitrophenol as an intermediate for the syntheses of point-labelled arenes lies in the potential to access 1,4-disubstituted systems by maintaining the original substitution pattern, comparatively few examples of this type of approach have been described in practise. A slight variation on the methodology described immediately above, with aminolysis of the methoxy group under high temperature and pressure, has been used for the preparation of [2,6-$^{14}C_2$]-4-aminobenzoic acid (Scheme 16).[46] This sequence provides the labelled acid in a comparatively high 35% yield overall from [1,3-$^{14}C_2$]acetone. A conceptually similar approach has also been used for the preparation of ring-labelled tyrosine. Thus, [2,6-$^{13}C_2$]-4-nitrophenol was converted into the methyl ester of 4-anisic acid in five steps (Scheme 17).[67] Reduction of this intermediate was followed by conversion of the resulting alcohol into 4-hydroxybenzyl bromide in 41% overall yield, the latter being converted into racemic labelled tyrosine in two steps. In a similar sequence to those just described, [2,6-$^{14}C_2$]-4-nitrophenol has also been converted into [3,5-$^{14}C_2$]-4-anisaldehyde (Scheme 18) in an overall 45% yield from [1,3-$^{14}C_2$]acetone. Condensation of this intermediate with the chiral diketopiperazine from L-valine and glycine followed by



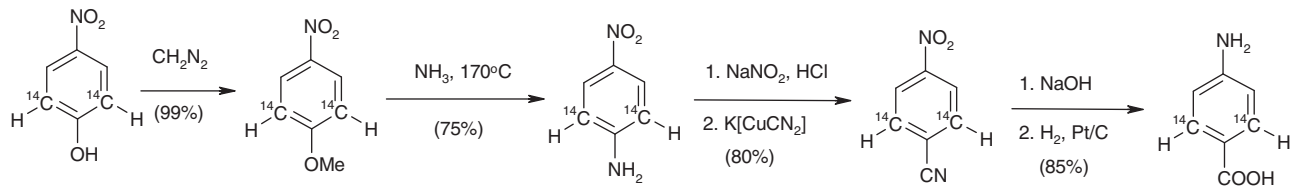
Scheme 13.



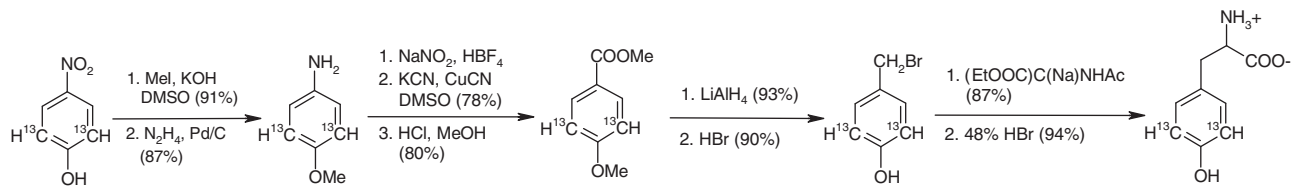
Scheme 14. Also from [1,3-$^{13}C_2$]acetone to give (S)-[3′,5′-$^{13}C_2$]tyrosine and (S)-[3′5′-$^{13}C_2$]phenylalanine.



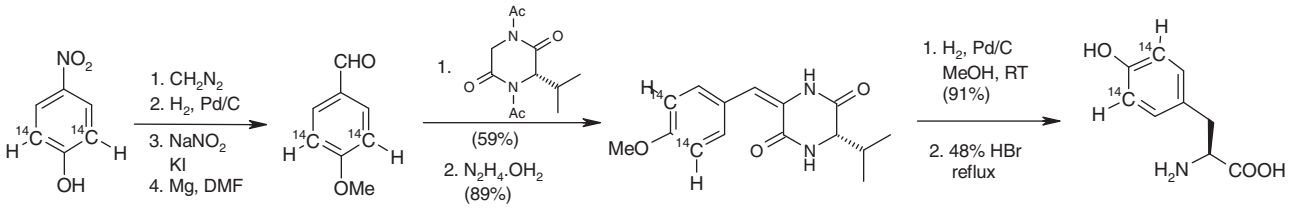
Scheme 15.



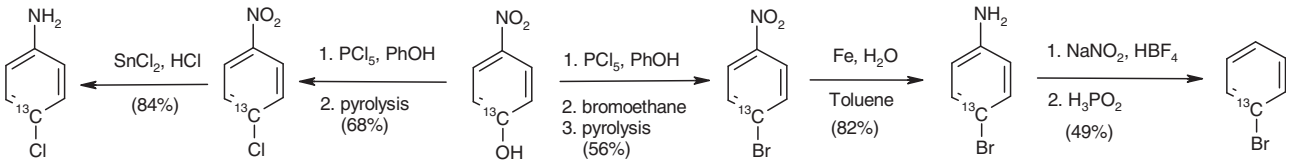
Scheme 16.



Scheme 17.



Scheme 18.



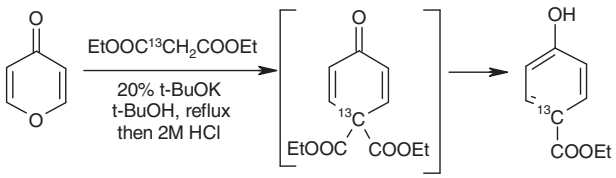
Scheme 19.

hydrogenation and global deprotection with hydrobromic acid gave [*hydroxyphenyl*-3,5-$^{14}C_2$](S)-tyrosine.[68]

Potentially, a more general approach to labelled 1,4-disubstituted arenes might proceed *via* 4-halonitrobenzenes, which are activated towards nucleophilic displacement of the halogen. Pyrolysis of the mixed tetraaryloxyphosphonium chloride obtained from 4-nitrophenol, phosphorus pentachloride and phenol provides 4-chloronitrobenzene,[63] while exposure of the same intermediate to bromoethane prior to pyrolysis provides 4-bromonitrobenzene (Scheme 19).[69] Subsequent elaboration by nucleophilic aromatic substitution has not been reported although these processes are well known for unlabelled substrates.[70] Both halonitrobenzenes have been reduced to the corresponding aniline, with subsequent diazotisation and reduction of the bromoaniline to provide [1-^{13}C]bromobenzene (Scheme 19). A slight variation on this approach is provided by conversion of 4-nitrophenol to the triflate, which can undergo palladium-catalysed coupling reactions,[71] although in the absence of the metal catalyst, hydrolysis of the triflate occurs in preference to displacement.[72]

4. Condensation of malonate with 4-pyranone and related systems

A comparatively recent approach to monolabelled arenes, which has found favour in the preparation of ^{13}C-arenes, involves the double Michael addition of diethyl [2-^{13}C]malonate to 4-pyranone with concomitant loss of one ester from an intermediate dienone to give ethyl [1-^{13}C]-4-hydroxybenzoate (Scheme 20).[55,73] Like the condensation of acetone with nitromalonaldehyde, this process provides an initial 4-substituted [4-^{13}C]phenol, amenable to elaboration to provide a variety of substitution patterns. Subsequent workers have used this method for the preparation of [1,4-$^{13}C_2$]- and [1,3,5-$^{13}C_3$]-4-hydroxybenzoates[74,75] with or without the introduction of additional deuterium labels. In these latter cases, additional labels are introduced, *via* labelled 4-pyranones, from either [2-^{13}C]- or [1,3-$^{13}C_2$]acetone by condensation either with diethyl oxalate,[75] or with triethyl orthoformate,[74,76] as exemplified in Scheme 21. We have also established that the condensation of 4-pyranone with diethyl [^{14}C]malonate provides ethyl [1-^{14}C]-4-hydroxybenzoate in good radiochemical yield and with better than 95% recovery of activity.[77]

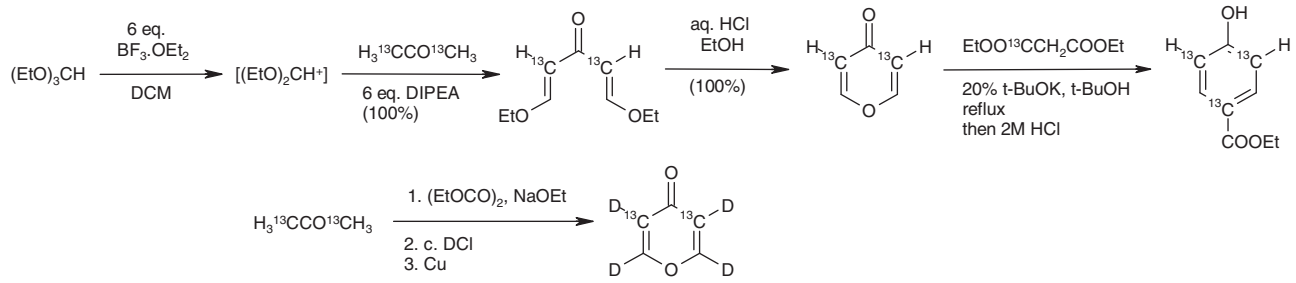


Scheme 20.

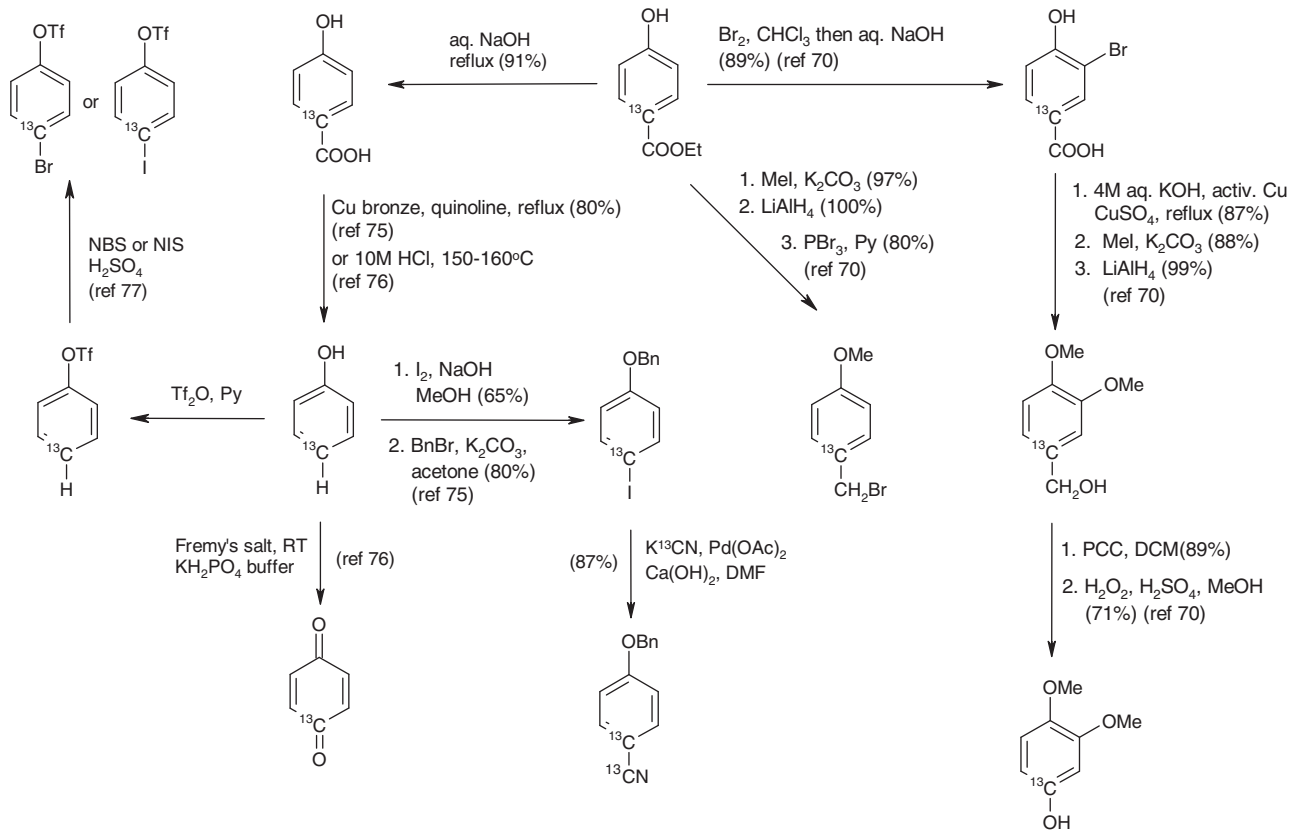
A significant attraction of this methodology is that the initially formed hydroxybenzoate is readily elaborated, by a combination of electrophilic substitution, carboxyl reduction, and decarboxylation steps to provide a variety of mono-, di- and tri-substituted arene scaffolds (Scheme 22). Most of these intermediates can be reached in two or three steps from the initially formed arene. In terms of the range of products that are readily accessed, this is therefore one of the most versatile of the methods presently available. Simple *O*-methylation, reduction of the carboxyl function and nucleophilic bromination of the primary intermediate gives [1-^{13}C]-4-methoxybenzyl bromide, which has been elaborated into labelled L-tyrosine.[55] A similar sequence has also been carried out using ethyl [1,3,5-$^{13}C_3$,$^{2}H_4$]-4-hydroxybenzoate.[75] 3,5-Dibromination of ethyl 4-hydroxybenzoate has also been reported, with subsequent copper-catalysed displacement of bromine giving ethyl 3,4,5-trihydroxybenzoate.[74] Other targets of interest are available from ethyl 4-hydroxybenzoate by saponification, followed by decarboxylation of the resulting acid. This process has been carried out using the classical copper-promoted method[78] but is more conveniently carried out under milder conditions in concentrated hydrochloric acid.[79] The labelled phenol obtained has been *para*-iodinated in good yield[78] and has also been oxidised to [1-^{13}C]benzoquinone.[79]

Regioselective 4-halogenation can also be carried out *via* the triflate derived from the phenol, and selective displacement of either triflate or halide from the product can be carried out.[71] Carbon-labelled ethyl benzoate can also be prepared from the 4-hydroxy derivative by its derivatisation as the 5-tetrazolyl ether, followed by catalytic hydrogenolysis (Scheme 23).[75]

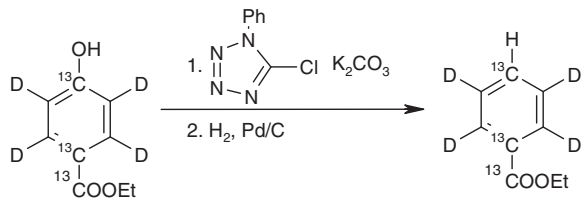
The generation of a specifically labelled benzene derivative by coupling of ethyl [2-^{13}C]cyanoacetate with a pyrylium salt, as shown in Scheme 24, was first described in the 1970s.[80] This methodology was unavoidably limited by the need to prepare



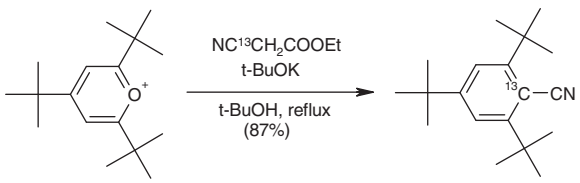
Scheme 21.



Scheme 22.



Scheme 23.

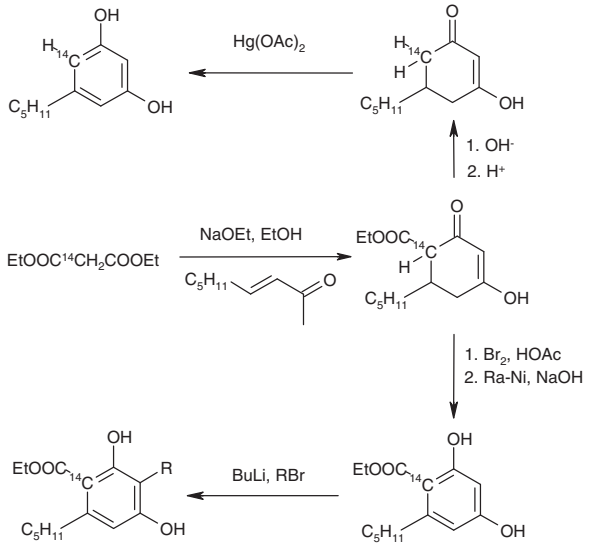


Scheme 24.

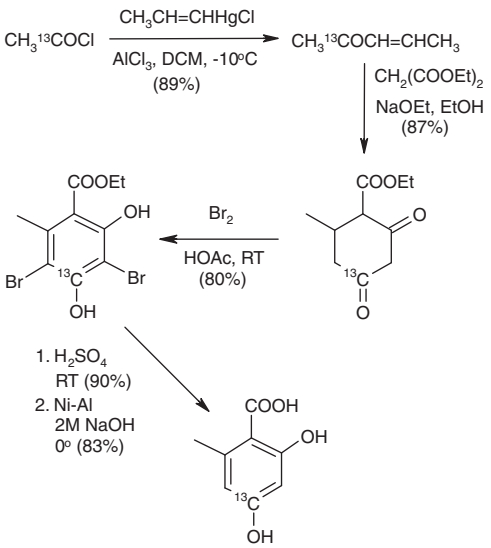
the pyrylium salt, and also by ring-opening reactions that compete in the absence of bulky 2- and 6-substituents.[81]

4.1. Reactions of malonate or malononitrile with other electrophiles

In addition to its coupling with 4-pyranone, nucleophilic attack of malonate or malononitrile on a variety of α,β-unsaturated carbon electrophiles, in particular, provides a further means for the construction of various substituted arene systems. A representative example is given in Scheme 25, where Michael addition of the anion of diethyl [2-^{14}C]malonate to an enone is followed by an intramolecular ester aldol condensation of the primary adduct. The resulting regioselectively ^{14}C-labelled diketoester is hydrolysed, decarboxylated and finally oxidised to give [4-^{14}C]-5-amylresorcinol, of interest for the preparation



Scheme 25.

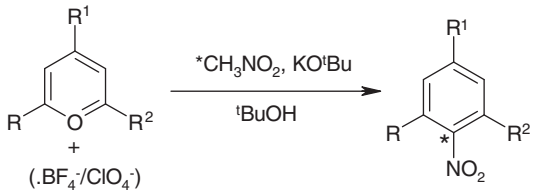


Scheme 26.

of radiolabelled cannabinoids.[82] An alternative elaboration scheme involves aromatisation of the cyclocondensation product followed by alkylation at the site between the phenolic hydroxy groups.[2] Similar sequences have been carried out using 1-labelled malonates,[83,84] but these lead unavoidably to distribution of the label between the ring and the carboxylate group, making their use less generally attractive. In contrast, use of a carbonyl-labelled enone component results in regioselective labelling at the 4-position of 2,4-dihydroxy-6-alkylbenzoic acids, as exemplified in Scheme 26.[85,86]

5. Addition of nitromethane anion to pyrylium salts and related species

In recent years, nitroalkanes have been proposed as suitable precursors for the synthesis of benzene derivatives.[87] As with the preceding approaches, a major advantage of these methods is the avoidance of regiochemical issues. At present, the



Scheme 27. *R*, R^2 = H, Me, R^1 = Me, OMe; * = ^{11}C or ^{13}C.

synthesis of arenes *via* addition of the nitromethane anion to pyrylium salts and other related species (Scheme 27) has only been used for unlabelled and $^{11/13}C$-labelling. Early examples of the treatment of 2,4,6-trisubstituted pyrylium salts with either unlabelled[88,89] or [^{13}C]nitromethane[90] in the presence of an alkoxide (Scheme 27) gave the corresponding 2,4,6-polysubstituted nitrobenzene derivatives in good yields (45–90%).

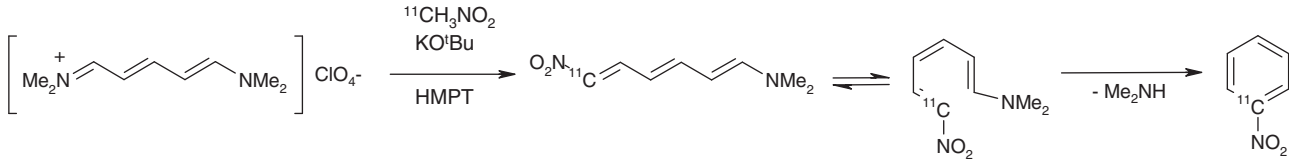
In more recent years, Mäding *et al.* have expanded this methodology and adapted it for the generation of ^{11}C-labelled radiotracers for the monitoring of biological processes by positron emission tomography. They found that the methodology could also be applied to the synthesis of *para*-substituted nitrobenzenes with the successful preparation of [4-^{11}C]-4-nitroanisole.[91]

Mäding and Steinbach have also described the synthesis of [1-^{11}C]nitrobenzenes[92] by the synchronous disrotatory six-electron cyclisation of captodative hexatrienes into arenes. The synthesis of these [^{11}C]hexatrienes (c.f. Section 11) requires the generation of a suitable precursor such as 5-dimethylaminopenta-2,4-dienylidenedimethylammonium perchlorate. These precursors are readily prepared from pyridinium salts such as *N*-(2,4-dinitrophenyl)pyridinium chloride which are very unstable under basic conditions, and undergo ring opening with dimethylamine to produce the 5-dimethylaminopenta-2,4-dienal. Further reaction with dimethylamine perchlorate affords the pentamethinium salt in reasonable yields. Under basic conditions, nitromethane readily reacts with the 5-dimethylaminopenta-2,4-dienylidenedimethylammonium perchlorate salt to form the hexatriene and dimethylamine. Subsequent cyclisation and aromatisation at elevated temperature gave rise to the nitrobenzene derivatives (Scheme 28). This methodology can also be applied to the synthesis of [^{11}C]anisole,[93] [3-^{11}C]-3-nitrotoluene, [^{11}C]-4-nitrotoluene and their corresponding toluidines (Scheme 29).[94] A further option that has been reported recently in unlabelled form involves the direct reaction of nitromethane with a 4-pyranone to give a 4-nitrophenol.[95]

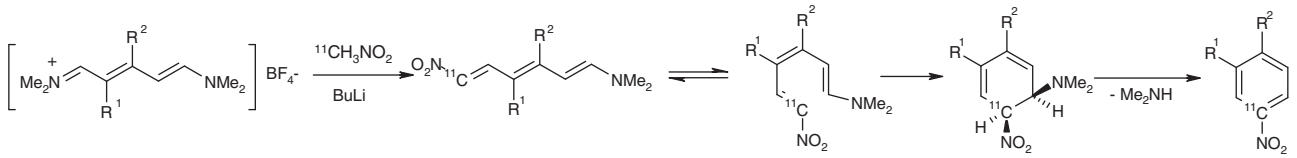
The nitro group is also able to undergo functional group transformations as illustrated by the subsequent conversion of [1-^{11}C]nitrobenzene to [1-^{11}C]aniline and [1-^{11}C]phenol (Scheme 30).[96]

A further example of the use of nitromethane in arene synthesis is the synthesis of substituted phenols by a [5+1]-annulation approach. Dong *et al.* describe a one-pot procedure, where under mildly basic conditions α-alkenoylketenedithioacetals undergo the [5+1]-annulation reaction with nitromethane.[97] 1,8-Diazabicyclo[5.4.0]undec-7-ene and dimethylformamide (DMF) were found to be the best conditions to effect the transformation in moderate-to-good yields (52–82%) (Scheme 31).

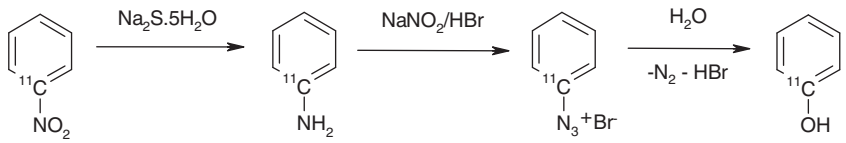
Although ^{14}C-labelled nitromethane is not routinely available, there is literature precedent for its use and its relatively simple



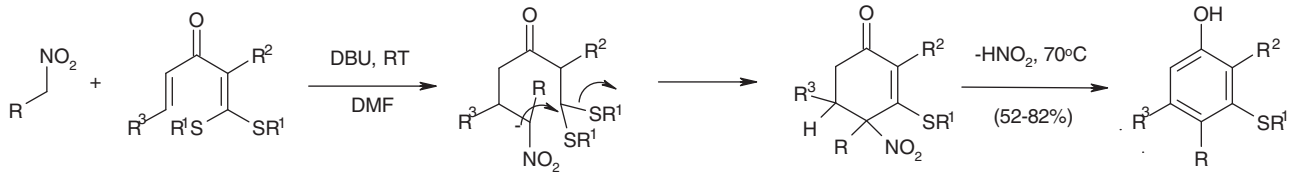
Scheme 28.



Scheme 29. R^1 = OMe, R^2 = *H* for anisole derivatives; R^1 = Me, R^2 = H or R^1 = *H*, R^2 = Me for toluene derivatives.



Scheme 30.



Scheme 31. Where *R* = Alkyl, CO_2, Et; R^1 = Alkyl, R^2 = PhCHO or 4-ClC_6H_4NHCO; R^3 = Aryl, Thienyl or Furyl.

preparation from [^{14}C]methyl iodide and silver nitrite.[49,98,99] However, there are concerns with this approach, primarily with the volatility of nitromethane (unlabelled b.p. 101°C),[100] the adequate trapping of this substrate and volatile by-products such as methyl nitrite (b.p. 12°C) and the formation of methyl nitrate, which is potentially explosive.[2] Nevertheless, the addition of nitromethane to pyrylium salts and related species appears quite attractive as the process has the potential to minimise the number of labelled steps if the desired unlabelled precursor can be prepared. Another advantage of this methodology is that it allows the preparation of mono, *meta* and *para* di-substituted and polysubstituted labelling patterns.

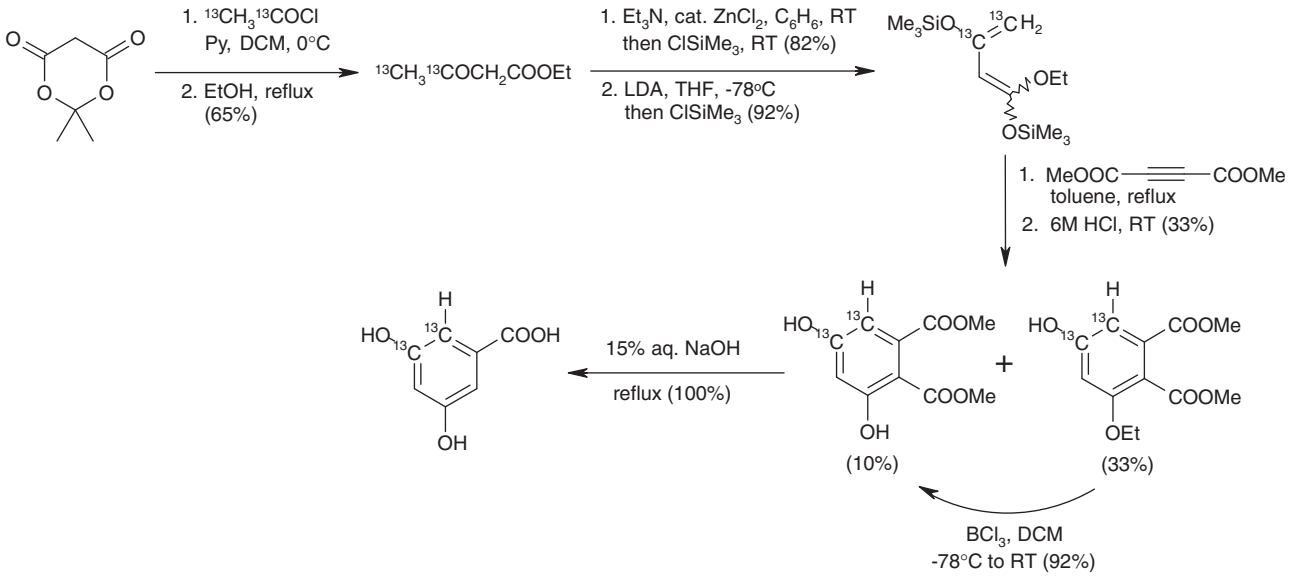
6. Cycloaddition

Given that the formation of arenes by dehydrogenation of cyclohexenes is a well-established process, an obvious route to regioselectively labelled arenes therefore presents itself *via* cyclohexenes, which are themselves prepared by [4+2] cycloaddition. The key to this approach is therefore the efficient preparation of either the diene or dienophile cycloaddition component in labelled form. In principle, aromatic systems can also be prepared by the dehydro-Diels-Alder reaction of enynes;[101] this approach is generally restricted to the preparation of condensed systems but other variants, using alkyne dienophiles in particular, provide the same overall transformation.

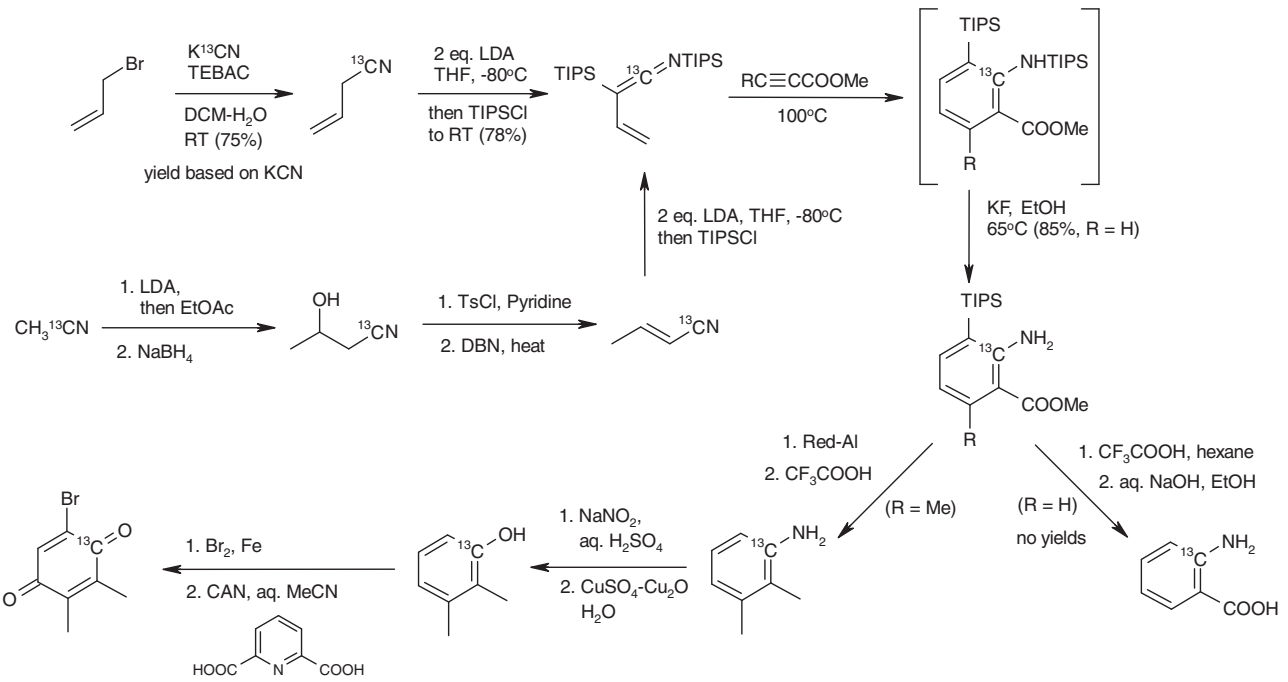
6.1. Arenes by Diels-Alder cycloaddition with a labelled diene

Five methods have been reported for the preparation of labelled dienes for further use in arene synthesis. These are: the generation of a dienolate system from labelled acetoacetate, the formation of a dienimine from crotononitrile or allyl cyanide, allylmetallic addition to an aldehyde with subsequent elimination, the formation of a diene by Wittig olefination and the formation of a reactive furan derivative from labelled succinate. In the first of these,[102] dilabelled ethyl acetoacetate is converted into an active diene, which undergoes cycloaddition with dimethyl acetylenedicarboxylate and subsequent acid-promoted elimination of the elements of trimethylsilanol to give a phthalate derivative directly. Usefully, this intermediate undergoes selective mono-decarboxylation on base-hydrolysis, generating a 1,2-dilabelled 1,3,5-trisubstituted arene (Scheme 32). This sequence has also been carried out using ethyl [2-^{13}C]acetoacetate.

The generation of a diene system from either allyl cyanide[103] or crotononitrile[104] relies on deprotonation of the substrate with LDA, and trapping of the resulting anion as di-*TIPS*-protected dienimine (Scheme 33). Subsequent cycloaddition with methyl propiolate or methyl 2-butynoate generates a substituted methyl anthranilate, which can be elaborated by conventional means to give 1,2-disubstituted, 1,2,3-trisubstituted or 1,2,3,4-tetrasubstituted arenes. In principle, direct desilylative coupling of the *C*-silylated intermediate with a carbon electrophile is also

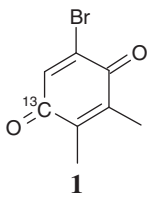


Scheme 32.



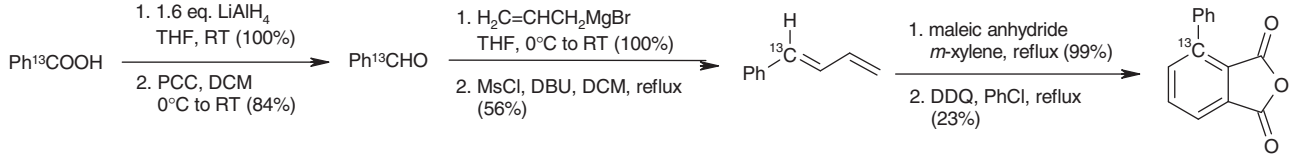
Scheme 33.

possible, but has not been reported. The authors do, however, also report the preparation of [4-^{13}C]crotononitrile from ethyl [2-^{13}C]acetate[103] and its elaboration by the same means to give the alternative labelled product **1**.[104]

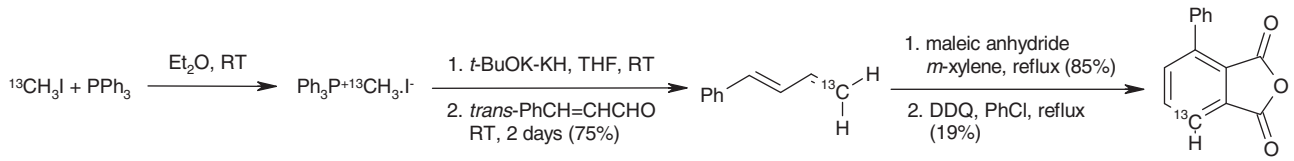


1

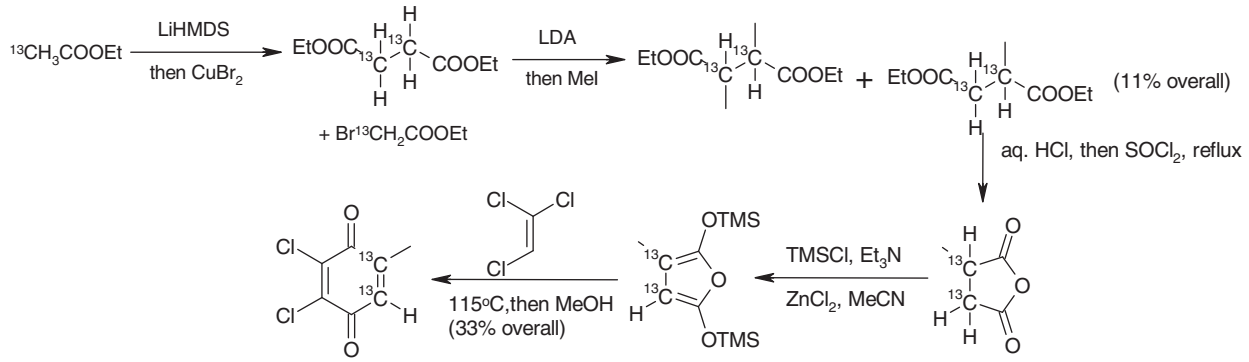
Two approaches have been used to prepare differentially ^{13}C-labelled 3-phenylphthalic anhydrides.[105] In the first of these, allylmagnesium bromide addition to labelled benzaldehyde gives a homoallylic alcohol, whose dehydration gives the desired diene (Scheme 34). Subsequent cycloaddition with maleic anhydride and dehydrogenation with DDQ gives [3-^{13}C]-3-phenylphthalic anhydride. Realistically, this approach is limited to cases where the aldehyde precursor lacks an α-hydrogen, so that the Grignard addition step is not complicated by side-reactions. The isotopomer of 3-phenylphthalic anhydride is prepared by Wittig olefination of cinnamaldehyde with labelled methylenetriphenylphosphorane to give [4-^{13}C]-1-phenyl-1,3-butadiene (Scheme 35), which is subjected to the same cycloaddition and oxidation sequence as above. In both cases, the weakest step in the sequence is the final dehydrogenation, which could, in principle, be improved using different reagents.



Scheme 34.



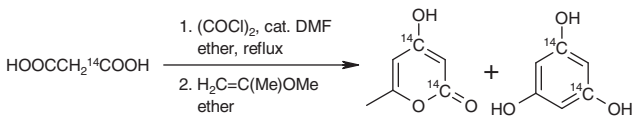
Scheme 35.



Scheme 36.

Finally, the direct introduction of two adjacent labels into a benzoquinone has been reported using a sequence involving the oxidative homocoupling of ethyl [2-^{13}C]acetate to give diethyl [2,3-$^{13}C_2$]succinate (Scheme 36). Subsequent methylation is nonselective, so that the overall yield of the monomethylated intermediate is modest. Acid hydrolysis of the diester followed by anhydride formation and silylation gives a [3,4-$^{13}C_2$]furan, whose cycloaddition gives the labelled benzoquinone directly.[106]

2-Pyranones have not been reported as used for the preparation of labelled arenes, but this class of dienes has considerable potential for the direct generation of a range of arene substitution patterns by inverse electron-demand cycloaddition.[107] Again, the key requirement is the availability of the desired diene in labelled form; one example of the preparation of a ^{14}C-labelled 2-pyranone with the label distributed between positions 2 and 4 has been described (Scheme 37)[108] but, since in this case half of the label is lost during the Diels-Alder/aromatisation sequence, the process is of limited value. However, two recent reports describe methods that could readily be adapted to provide labelled 2-pyranones from dimethyl acetonedicarboxylate (Scheme 38)[109] or from β-ketoesters (Scheme 39).[110] Moreover, other recent publications describe the generation of 2-pyranones by methods that are also amenable to the incorporation of carbon labels; among the most applicable are the halolactonisation of enynes, generated from a (potentially labelled) alkyne by Sonogashira coupling,[111] and the sequential dehydrogenation of δ-lactones.[112]

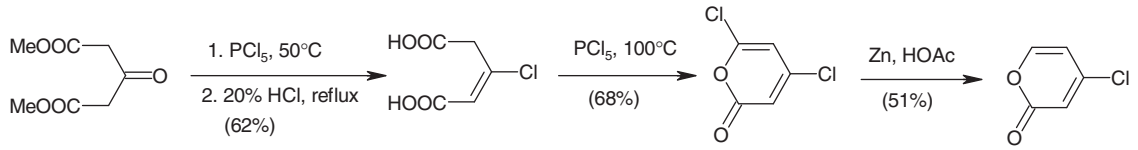


Scheme 37. (label is distributed equally between the sites indicated).

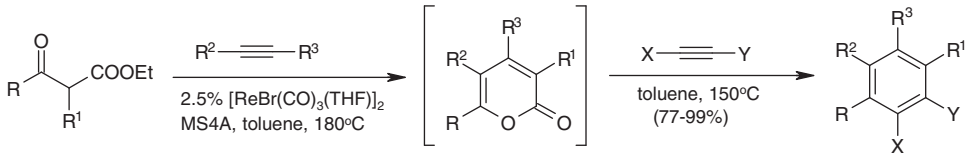
6.2. Arenes by Diels-Alder cycloaddition with a labelled dienophile

The incorporation of a label into a dienophile should be simpler than incorporation into a diene. [2,3-$^{13}C_2$]Maleic anhydride is commercially available and can also be prepared from [2,3-$^{13}C_2$]succinic acid. The latter is dehydrogenated by bromination followed by dehydrobromination to give [2,3-$^{13}C_2$]fumaric acid, which undergoes isomerisation and dehydration on heating with phosphorus pentoxide.[113] The cycloaddition of [2,3-$^{13}C_2$]maleic anhydride with perdeuterated butadiene[114] and with 2,3-dimethylbutadiene to give [1,2-$^{13}C_2$]phthalic anhydrides has been described.[115]

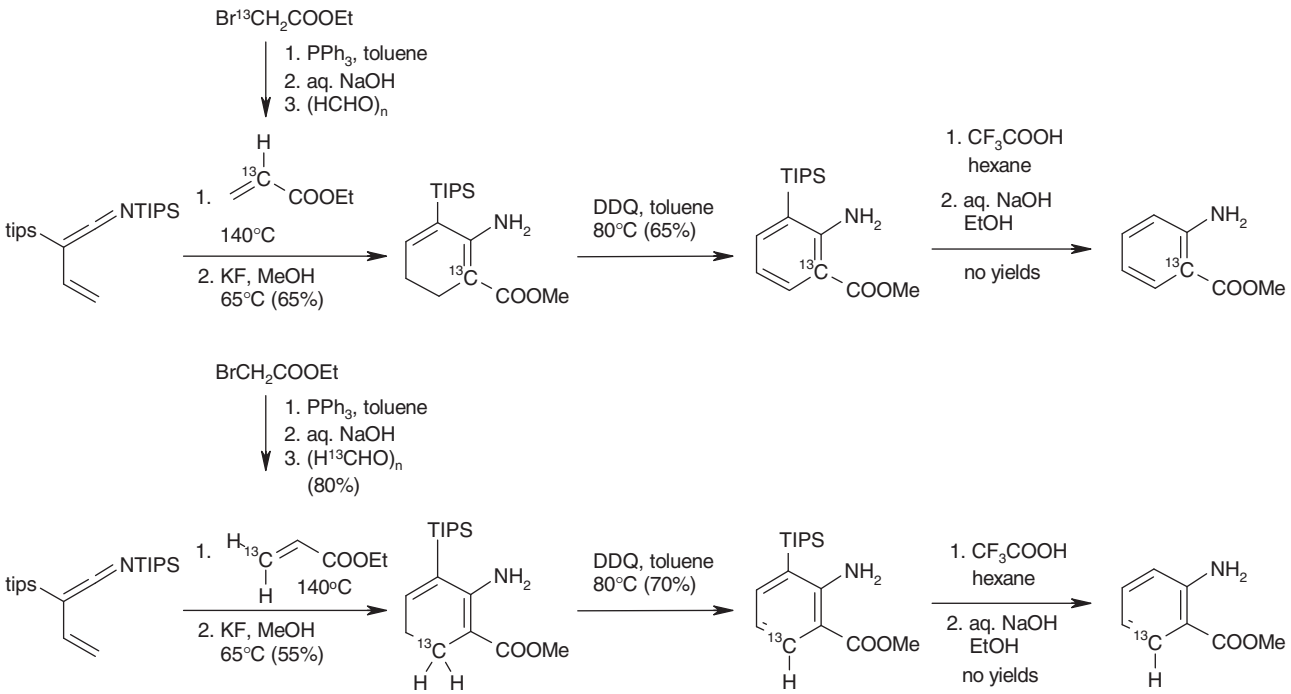
Acrylonitrile, the 3-^{13}C-form of which is commercially available, and acrylates are also reactive dienophiles, and are more versatile than maleic anhydride for the generation of specific labelling and substitution patterns. Ethyl [2-^{13}C]- and [3-^{13}C]acrylates have both been prepared by a Wittig reaction of (ethoxycarbonylmethylene)triphenylphosphorane with paraformaldehyde;[106] both undergo cycloaddition with TIPS-protected dienimines to give [1-^{13}C]- and [6-^{13}C]anthranilates (Scheme 40).



Scheme 38.



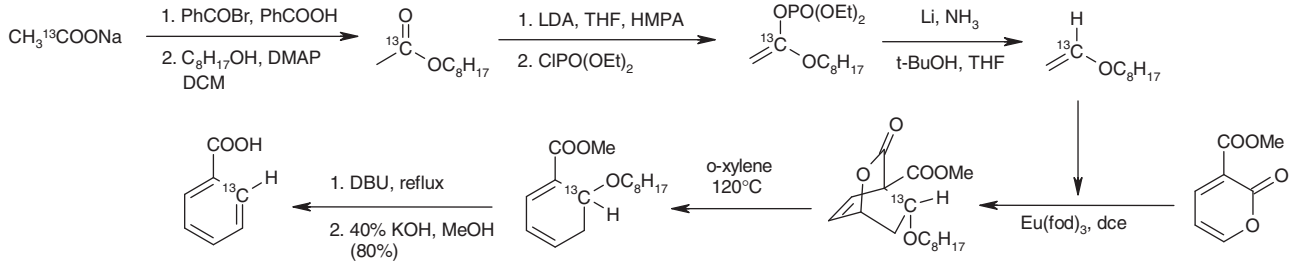
Scheme 39. R = Me, Am, Ph; R^1 = *H*, Me, Am; R^2 = *H*, Ph, $^nC_6H_{13}$; R_3 = Ph, $^nC_6H_{13}$; X = COOEt; Y = *H*, COOEt.



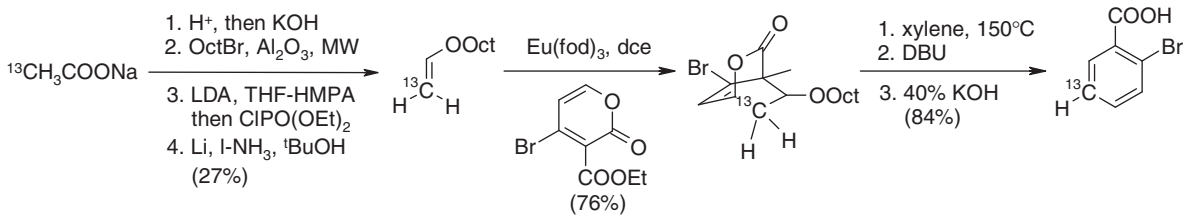
Scheme 40.

Wittig and Horner-Wadsworth-Emmons processes are the most widely described methods for the preparation of carbon-labelled acrylates and related intermediates[2,116] but, in particular, methyl [3-^{13}C]acrylate can also be prepared conveniently by methylation of methyl 2-(phenylsulfinyl)acrylate with [^{13}C]methyl iodide; on subsequent thermolytic cycloelimination of benzenesulfinic acid,[117] the labelled acrylate distils directly from the reaction mixture. The very reactive dienophile, ethyl 2-(benzenesulfonyl)acrylate, has also been prepared in 2-^{13}C-labelled form.[118] Nitroalkenes are also reactive dienes where elimination from the [4+2] cycloadduct can lead to an arene;[119] this approach has not been reported using labelled nitroalkenes, but these are available by a Henry reaction using either a [1-^{14}C]aldehyde[120] or [^{14}C]nitromethane (c.f. Section 5).[121] The generation of a nitroalkene dienophile and its cycloaddition *in situ* with aromatisation of the product has also been described in unlabelled form;[88] such a process, if carried out in one pot, would be attractive for the preparation of ^{14}C-arenes in particular.

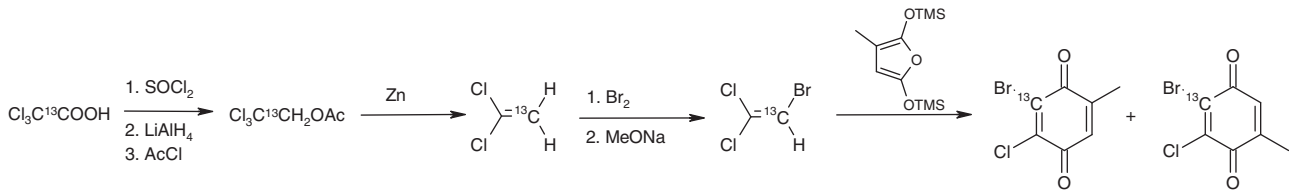
Labelled arenes have also been prepared by [4+2] cycloaddition of labelled haloalkenes or alkyl vinyl ethers, with subsequent hydrogen halide or alcohol elimination from the adduct facilitating aromatisation. Elaboration of a suitable acetic acid derivative is a particularly attractive option for the preparation of suitable dienophiles, and Kajiwara *et al.* have reported a method by which [1-^{13}C]acetate is converted, in the first instance, into an ester enol phosphate.[122] Dissolving metal reduction of this intermediate gives an alkyl [1-^{13}C]vinyl ether, which undergoes inverse electron demand [4+2] cycloaddition with 3-methoxycarbonyl-2-pyranone. [4+2] Cycloelimination of CO_2 from the adduct, followed by base-promoted aromatisation and hydrolysis, provides [2-^{13}C]benzoic acid (Scheme 41). The same procedure, using [2-^{13}C]acetate,[122,123] provides an alkyl [2-^{13}C]vinyl ether and thence a [3-^{13}C]benzoic acid (Scheme 42), and a similar unlabelled process has been described for the generation of substituted acetanilides from 3-acetamide-2-pyranones and alkyl vinyl ethers.[124] An



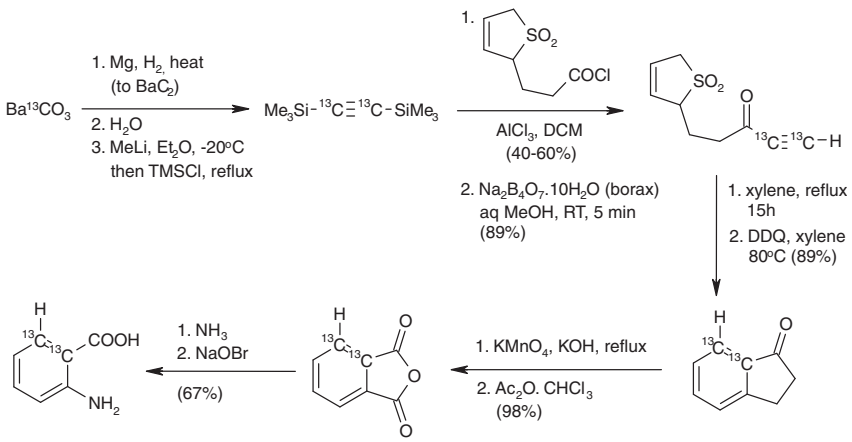
Scheme 41.



Scheme 42.



Scheme 43.

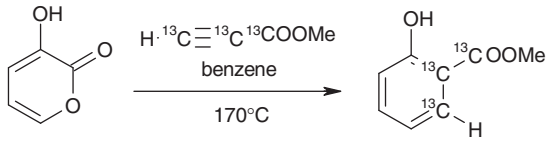


Scheme 44.

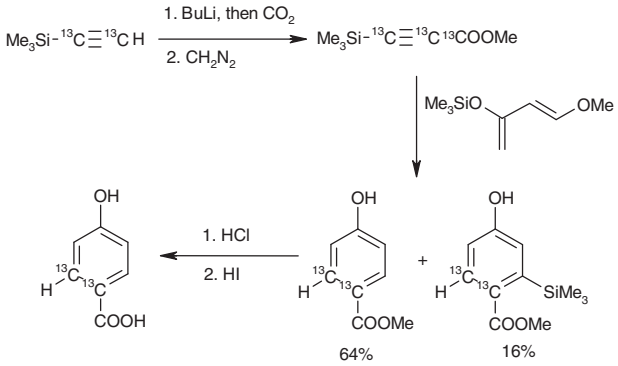
alternative approach uses [1-^{13}C]trichloroethanol, obtained by the reduction of [1-^{13}C]trichloroacetic acid, as the starting material;[125] the alcohol is converted into the corresponding acetate, which suffers reductive elimination of halogen and the acetate group on treatment with zinc. Subsequent bromination gives a dienophile, whose cycloaddition with a 2,5-bis(silyloxy)furan gives a halogenated benzoquinone (Scheme 43).

In all these cases, the arene synthesis requires aromatisation of the initial cycloadduct. Cycloaddition of a diene with an acetylene, or an acetylene synthon, provides a more direct preparation of labelled arenes as exemplified in Scheme 44.[126] Although this approach has not been widely used for the preparation of labelled arenes, many unlabelled examples have been reported, along with two further examples where the dienophile is labelled as methyl propiolate. Cycloaddition in these cases requires elevated temperatures when 3-hydroxy-2-pyranone is used as the dienophile (Scheme 45),[127] but the normal demand cycloaddition with Danishefsky's diene proceeds efficiently under very much milder conditions

(Scheme 46).[128] Propiolic acid is commercially available in both ^{13}C and ^{14}C labelled forms, providing a comparatively simple access into specifically substituted point-labelled arenes. The process tolerates a variety of substituents on the acetylene including aryl,[129] boronate,[130] hydroxyalkyl,[131] phosphonium,[132] silyloxy[133] and trihalomethyl groups.[134] Dienes used include Danishefsky's diene,[126] pyranones including those bearing acylamino[135] and arylthio substituents,[136] diene-substituted α-amino acids[137] and carbohydrate-derived homochiral dienes.[138] Again, several methods are available for the introduction of a carbon label into an alkyne. A label can be introduced at either acetylenic carbon by the Corey-Fuchs reaction sequence, using either a labelled aldehyde[139] or a labelled carbon tetrabromide, although the latter precursor is particularly expensive. [2-^{13}C]Phenylacetylene has been prepared by addition of [^{13}C]methylmagnesium iodide to benzaldehyde, followed by oxidation, and dehydration of the resulting acetophenone *via* either the *gem*-dichloride[140] or the enol phosphate.[141] The same product can also be obtained by nucleophilic bromination of [1-^{13}C]phenylacetaldehyde followed by elimination, although in this case the product is a mixture of isotopomers in consequence of a small amount of 1,2-aryl migration during the bromination step.[142]



Scheme 45.

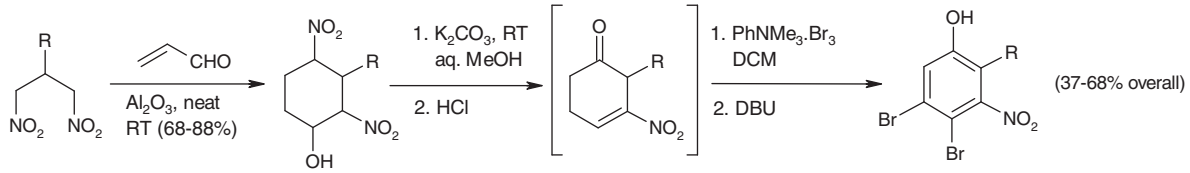


Scheme 46.

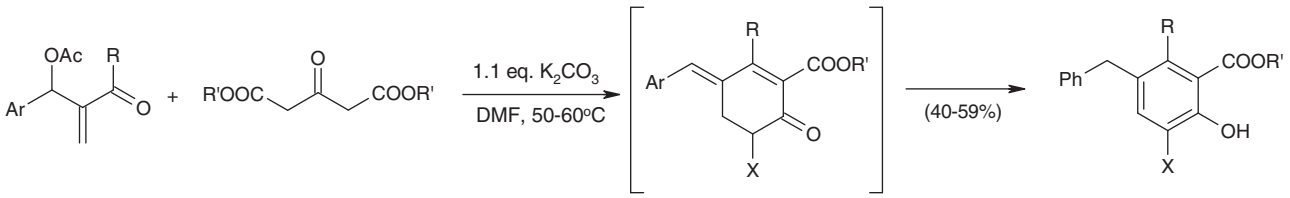
6.3. Arenes by formal [3+3]-cycloaddition

Arenes may be formed directly by cycloaddition of a 1,3-dielectrophile with a 1,3-dinucleophile. The former is commonly an enone or related system. These are available in labelled forms by a number of approaches, including Wittig and related olefinations and the formylation of vinylic precursors. This approach can therefore be adapted for the preparation of carbon-labelled arenes, although no such syntheses have been published to date. The anions derived from 1,3-dinitroalkanes are convenient nucleophiles for this type of cyclisation, as exemplified in Scheme 47,[143] although their preparation in labelled form is not entirely straightforward. 2-Phenyl-1,3-dinitropropane has also been reported to provide arenes on reaction with enone products from the Baylis-Hillman reaction.[144] Products from the Baylis-Hillman reaction also undergo formal [3+3] condensation with acetonedicarboxylates by means of a S_N'/aldol reaction sequence related to those described in Sections 4 and 8, with subsequent aromatisation (Scheme 48).[145]

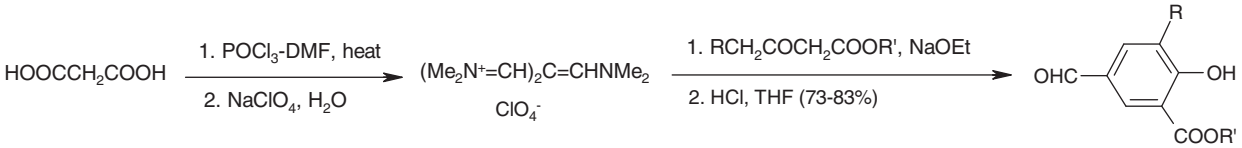
β-Ketoesters have been used more generally as nucleophiles, as exemplified in Scheme 49.[146] In the case illustrated, the



Scheme 47.



Scheme 48. Ar = Ph, *p*-C_6H_4Cl, *p*-Tol.



Scheme 49.

electrophilic vinamidinium salt component is prepared from malonic acid, which is available in a variety of ^{13}C and ^{14}C-labelled forms, making this a potentially convenient entry into tetrasubstituted labelled arenes, with the label potentially derived from either of the precursors. A further formal [3+3] cycloaddition method,[147] which is more amenable to being used for the preparation of labelled arenes involves allylsilane addition to a propargylaldehyde in the presence of a gold(I) catalyst, followed by 6-endo-dig cyclisation (Scheme 50); the metal carbene intermediate rearranges to regenerate the catalyst and liberate the 1,3-disubstituted arene product. In this case, preparation of the propargylaldehyde with a label at C-1 should be relatively straightforward and would lead to a product with a label at C-5 (*meta* to both substituents).

7. Addition of nucleophiles to 2-pyranone

In addition to its potential as a diene in Diels-Alder processes, 2-pyranone undergoes addition by nucleophiles. Where the attacking species is an anion derived from a ketone, ester or nitrile, the initial adduct can cyclise to give a bicyclic species from which carbon dioxide is lost to form an aromatic system. This process, as exemplified by the reaction of 2-pyranones with malononitrile, is outlined in Scheme 51.[148] The immediate attraction in this particular form of the process lies in the commercial availability of labelled malononitrile, but it is somewhat limited by the requirement for a cyano or other electron withdrawing group at C-3 of the pyranone precursor, so that the product is necessarily a 2,6-dicyanoaniline. A slightly different range of products is available by reaction of the pyranone precursor with ketones in the presence of base (Scheme 52), although in most cases the products remain more highly substituted than is usually desirable for the synthesis of labelled compounds. Nevertheless, the ketone precursor could be prepared in labelled form in many cases, as could the pyranone: a typical preparation is illustrated in Scheme 53,[149] in which either precursor is potentially available in carbon-labelled form. A final option in this context is the reaction of 2-pyranones with acetyltrimethylsilane, as illustrated in Scheme 54.[157] In this case, the products prepared are comparatively simple with a 1,2,4-trisubstitution pattern, and with the label available either from the pyranone component as above or (in principle) from acetyltrimethylsilane.

8. Cyclisation of enolates

8.1. Aldol condensation

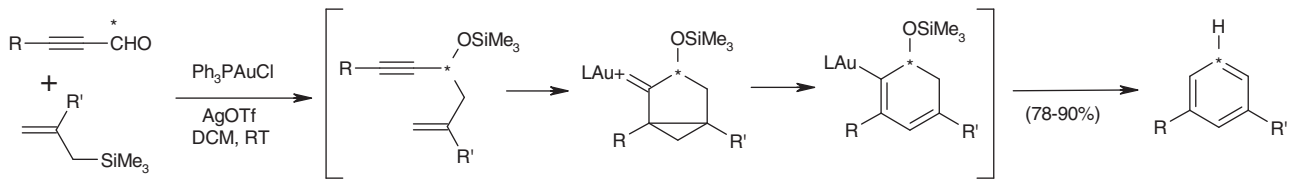
The one-pot conjugate addition of malonates to enones, with intramolecular ester aldol condensation of the adduct, is described in Section 4. The same approach can be used to generate arenes from a number of other nucleophilic precursors. As described for the process with malonate, the reaction of ethyl acetoacetate with α,β-unsaturated esters can be carried out with a carbon label in either the acetoacetate (Scheme 55)[158] or the unsaturated ester component (Scheme 56).[159] In a conceptually similar approach (Scheme 57), the reaction of a diketone with an enaminoketone generates a dialkylaniline product.[160]

Lewis acid promoted aldol-based annulation reactions using 1,3-dicarbonyl precursors have also been described by the group of Langer. The most thoroughly developed form of their approach involves titanium(IV)-mediated addition of the bis(silyl enol ethers) derived from 1,3-diketones or β-ketoesters with 1,3-dielectrophiles accessed from 1,3-malondialdehyde, 1,3-diketones, 2-acyl-1,3-diketone or β-ketoesters, as generalised in Scheme 58. The product formed is typically a highly substituted benzoate or aryl ketone, although simpler products can be produced by replacing the enone with malonaldehyde *bis*(dimethyl acetal).[161]

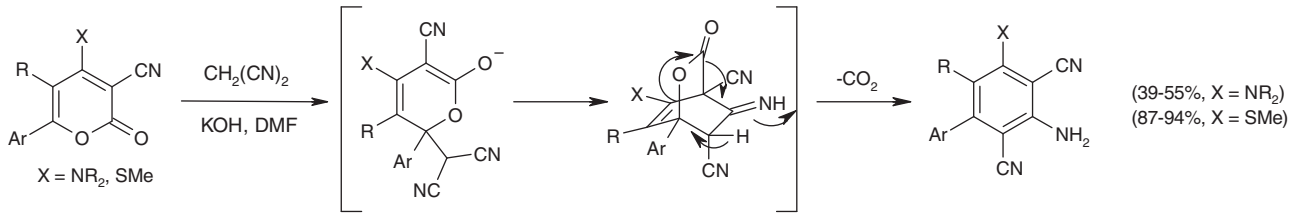
2-Labelled malonates and pyruvates undergo self-condensation to give 1,3,5-trilabelled aromatic systems. Such a trimerisation has been used to prepare [$^{14}C_3$]phloroglucinol from diethyl [2-^{14}C]malonate (Scheme 59).[162] The corresponding reaction of pyruvate is more versatile, as illustrated for the cyclotrimerisation of both 2- and 3-labelled forms of sodium pyruvate in Scheme 60.[163,164] Conveniently, the starting material is available from the cyanation of labelled acetate,[163] and the sequence has also been described using ^{14}C-labelled pyruvate.[165]

8.2. Dieckmann and related processes

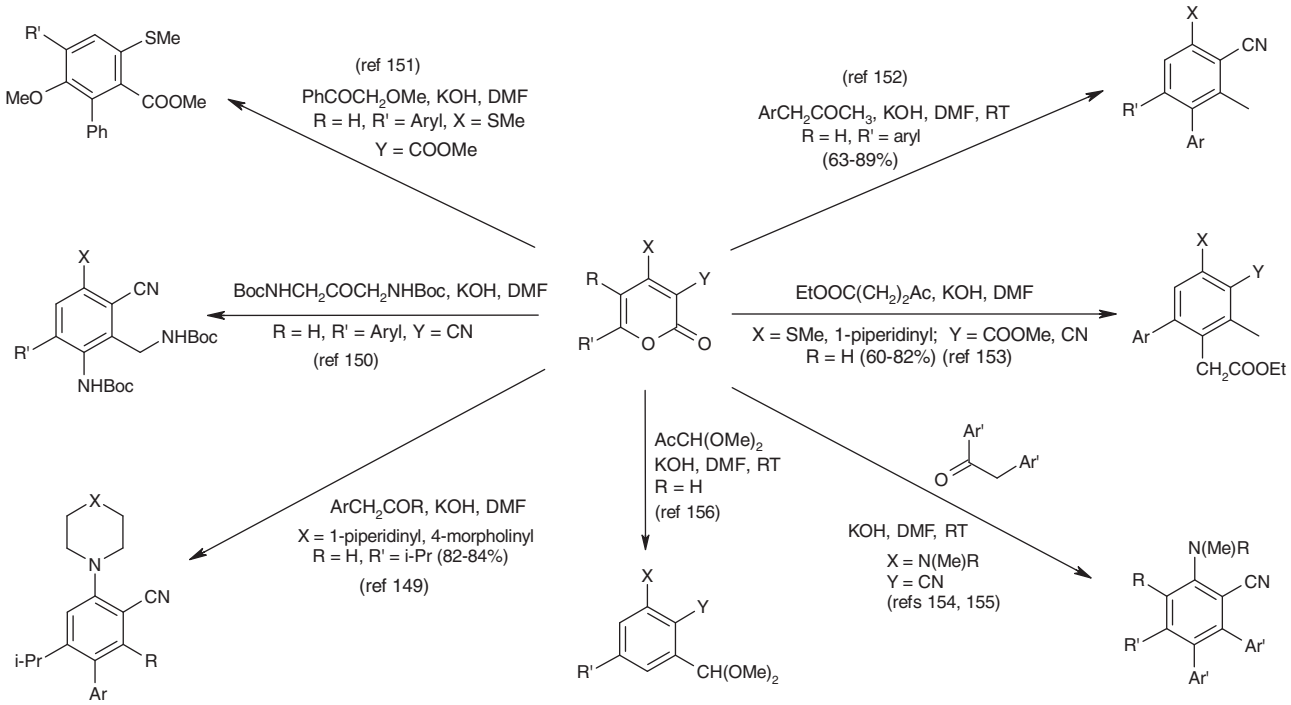
A method that has been used on a number of occasions for the preparation of phenols in relatively few steps involves the pyrolytic cyclocondensation of 1,7-dilabelled pimelic acid (Schemes 61 and 62).[166] This cyclisation achieves the same type of conversion as a Dieckmann cyclisation with subsequent



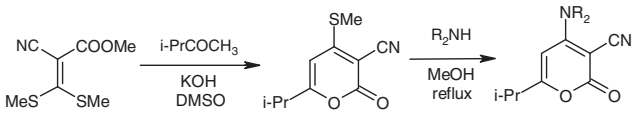
Scheme 50. (* = proposed labelling position, *L* = ligand, *R* = aryl or *n*-C_6H_{13}, *R* = *H*, Me, Ph).



Scheme 51.

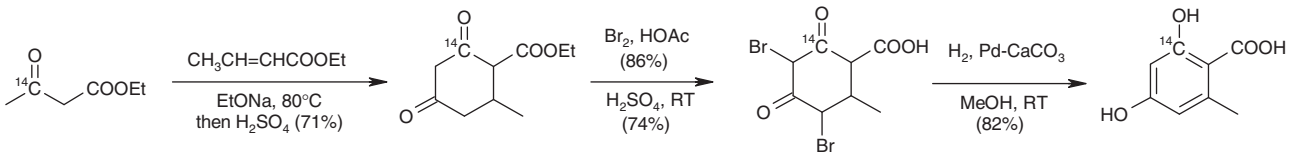


Scheme 52.

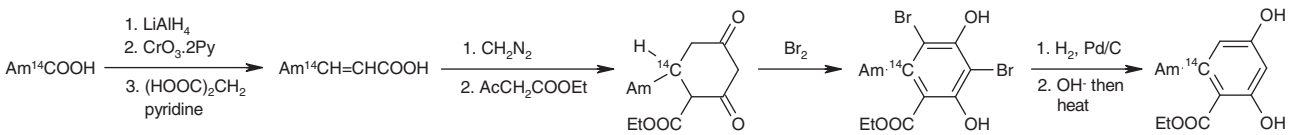


Scheme 53.

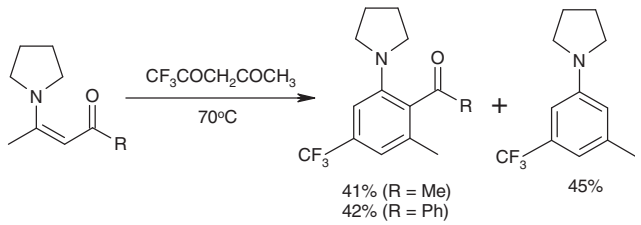
Scheme 54.



Scheme 55.

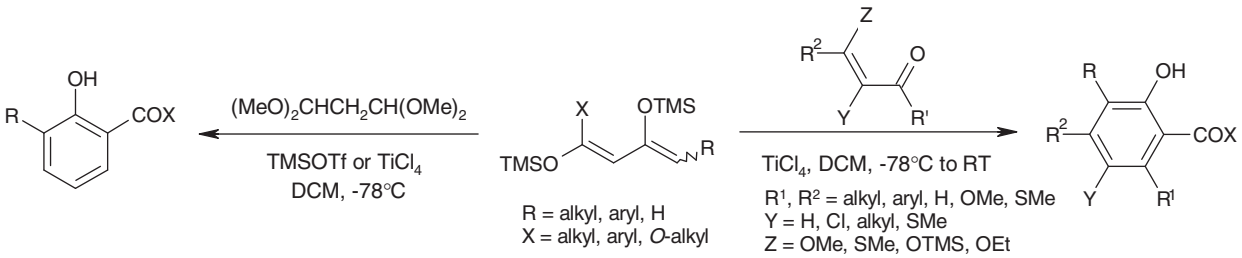


Scheme 56.

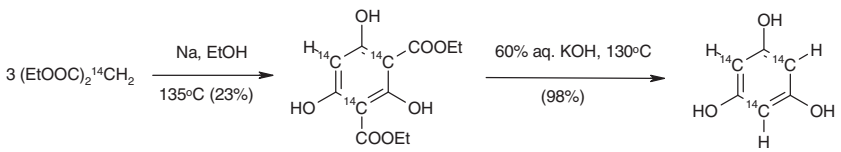


Scheme 57.

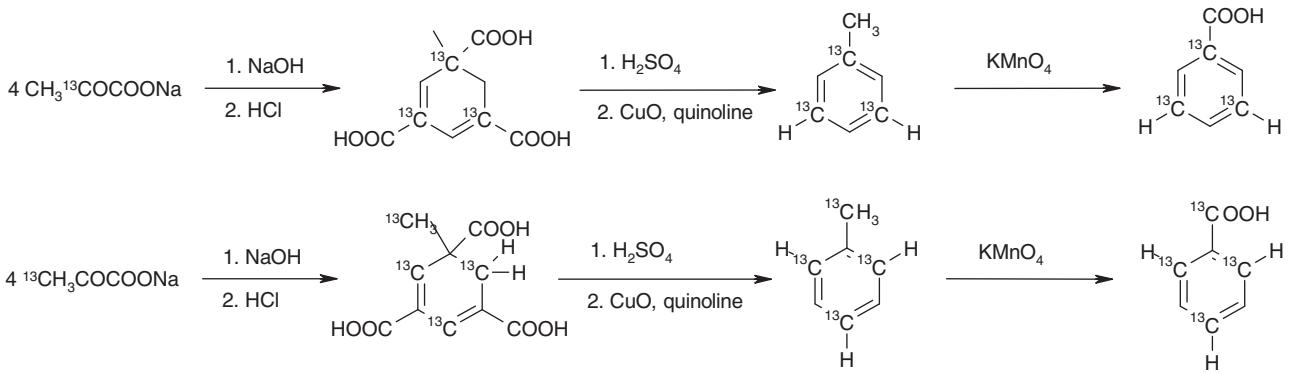
hydrolysis and decarboxylation, but has been postulated as a concerted process proceeding *via* a four-membered transition state.[167] The label is introduced by addition of an excess of labelled cyanide to pentamethylene dibromide; this is necessarily somewhat inefficient in terms of the introduced label, although the excess can often be recovered,[4] and an improvement in yield is reported when the reaction is carried out in acetonitrile in the presence of 18-crown-6.[168] Hydrolysis of the dinitrile gives the diacid, which is then heated strongly with



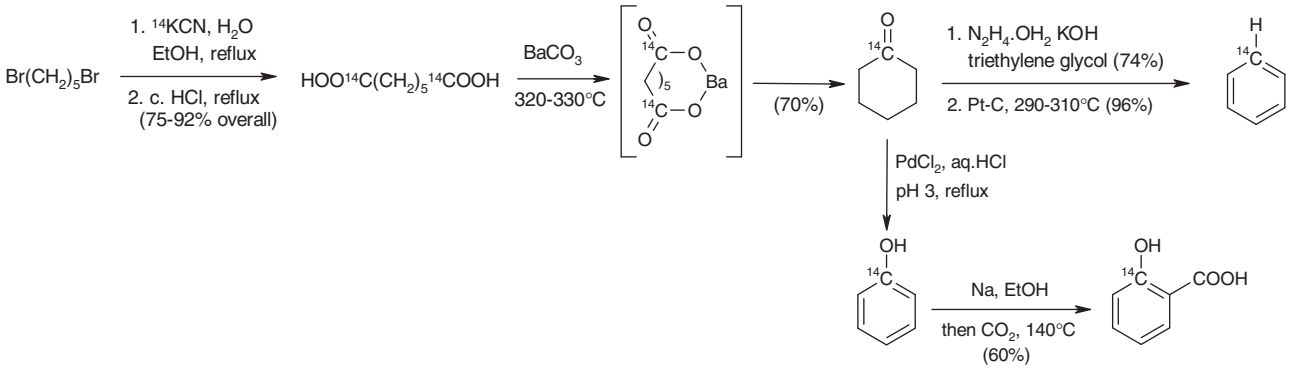
Scheme 58.



Scheme 59.



Scheme 60.



Scheme 61.

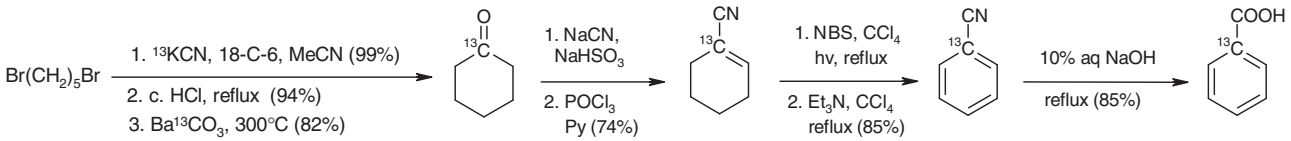
barium carbonate, initially forming the barium dicarboxylate, which undergoes the cyclisation described above. The major weakness of this sequence is therefore the unavoidable loss during this step of half of the introduced label: the 70% chemical yield corresponds only to a 35% radiochemical yield. Furthermore, in the preparation of [^{13}C]arenes by this method, [^{13}C]barium carbonate was used in order to ensure that no isotopic dilution occurred.[168] The cyclohexanone produced is either converted into benzene by hydrazone formation followed by pyrolysis over platinum on carbon or, more usefully, into monolabelled phenol by dehydrogenation with palladium(II) chloride.[169] In addition to the further transformations described earlier, phenol produced in this way has been converted by a Kolbe-Schmitt reaction into [2-^{14}C]salicylic acid.[169] Alternative routes of elaboration from [1-^{13}C]cyclohexanone include cyanohydrin formation, followed by dehydration and aromatisation to give benzonitrile. Subsequent hydrolysis provides [1-^{13}C]benzoic acid (Scheme 62).[170]

A variation on the approach above is to convert the open-chain dinitrile into the diethyl ester by means of a Pinner reaction followed by hydrolysis of the bis-imidate;[171] the diester then undergoes Dieckmann cyclisation under basic conditions but, again, the following decarboxylation step involves loss of half of the label used. Methylation adjacent to the ketone is followed by addition of phenyllithium and aromatisation with DDQ to give the monolabelled biphenyl (Scheme 63).

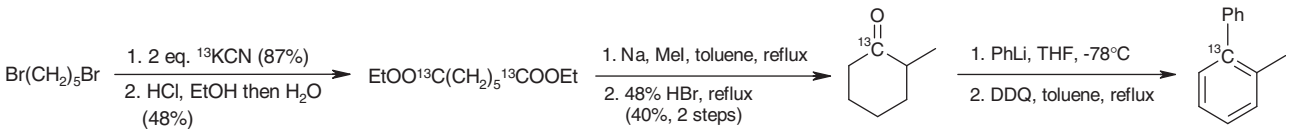
8.3. Fujimoto-Belleau annulation

A more efficient utilisation of introduced isotope is achieved by Fujimoto-Belleau annulation. A number of earlier references use this methodology for the construction of labelled steroids,[172,173] following the partial oxidative degradation of the A-ring of 3-keto-Δ^4-steroids and the introduction of a labelled methyl group by Grignard addition to the resulting lactone (Scheme 64). Subsequent acid- or base-induced acyclisation gives the 4-labelled 3-keto-Δ^4-steroid, the A-ring of which undergoes aromatisation under oxidative conditions. In one published variation on this approach, a 1,2-double bond is introduced into the cyclisation product by dehydrogenation (Scheme 65); acid catalysed rearrangement of the dienone in the presence of acetic anhydride gives a ring A aromatic [10-^{14}C]steroid.[172] A further variation (Scheme 66) involves the α-acylation of the lactone precursor with dilabelled acetyl chloride, and decarboxylative ring closure of the resulting diketoacid to give [3,4-$^{12}C_2$]estradiol benzoate.[174]

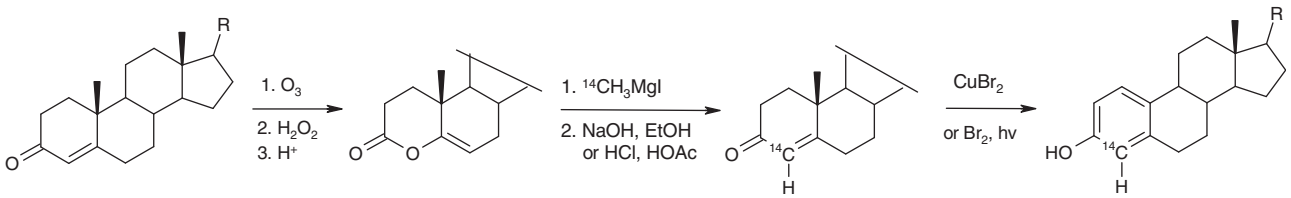
The Fujimoto-Belleau reaction has also been used in a few syntheses of simpler molecules: the labelled benzazepine synthesis outlined in Scheme 67 is exactly analogous to the basic sequence used for the syntheses of labelled steroids.[175] Two syntheses of 1,3-dihydroxyarene derivatives, using the related cyclisation of a methylketone enolate onto an ester, have been reported (Schemes 68 and 69): in these cases, the label is introduced by reaction of an acyl chloride with labelled



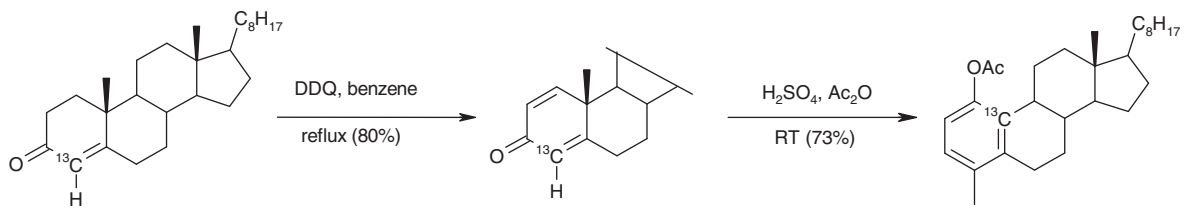
Scheme 62.



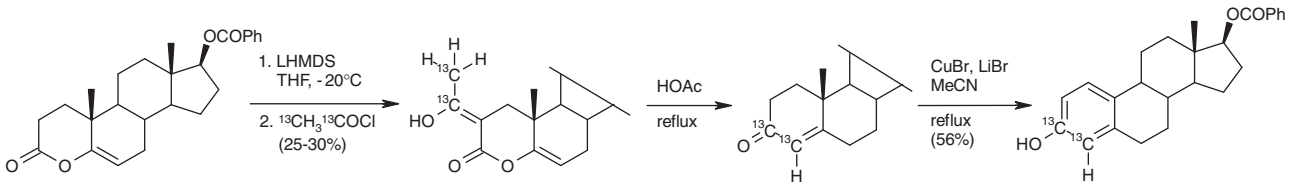
Scheme 63.



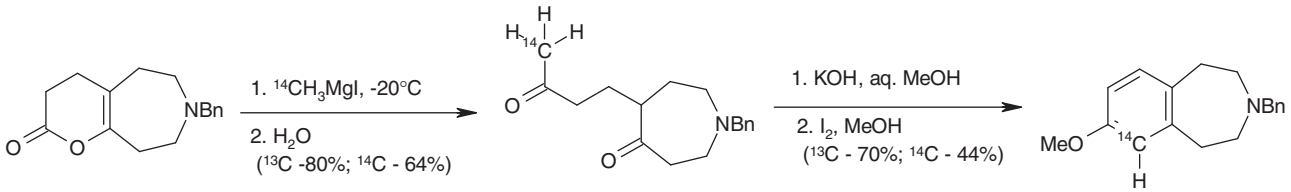
Scheme 64.



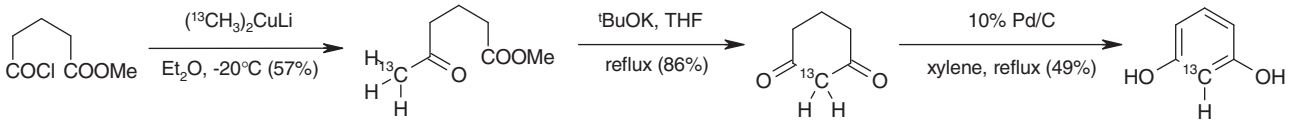
Scheme 65.



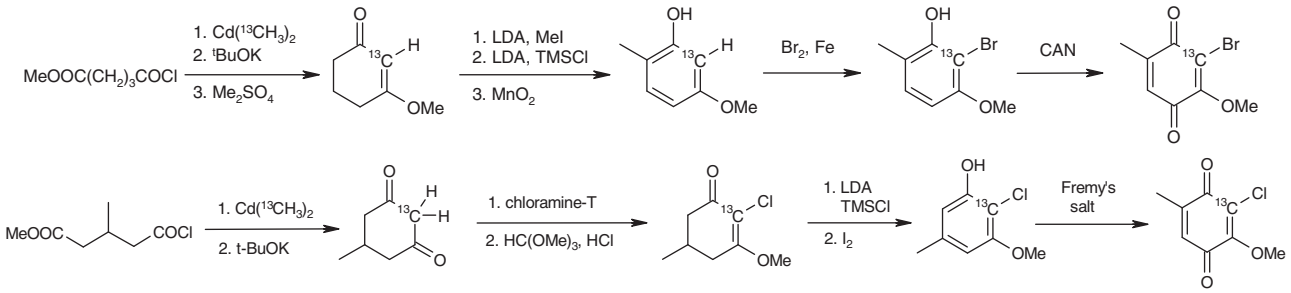
Scheme 66.



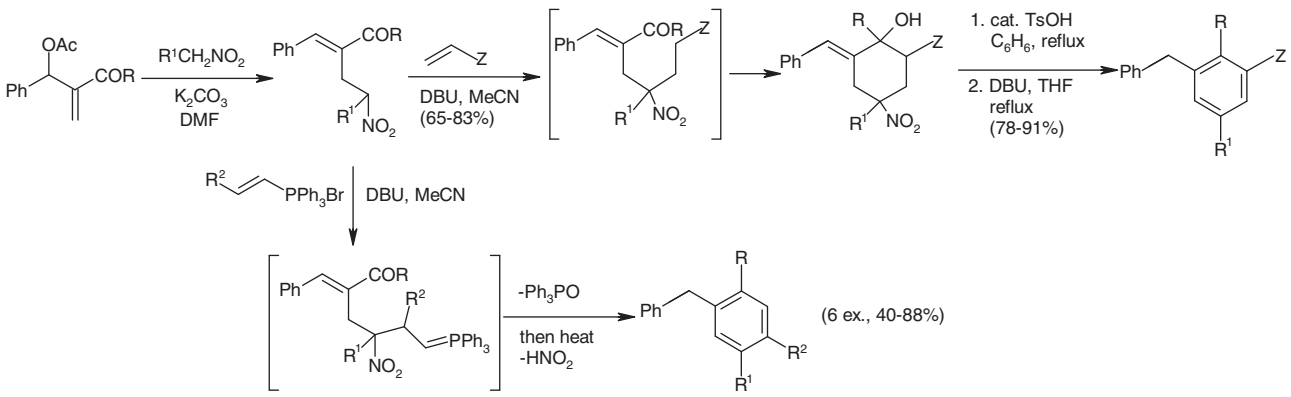
Scheme 67.



Scheme 68.



Scheme 69.



Scheme 70. Z = Ac, COEt, COOMe, CN, SO_2Ph; R^1,R^2 = alkyl.

lithium dimethylcuprate[176] or with dimethylcadmium.[177] This type of process is necessarily inefficient, with half of the label being lost in either case. In principle, a more efficient introduction of the label could be achieved by the palladium-catalysed coupling of an acyl chloride with a labelled methylzinc halide or mixed cuprate reagent. This approach is of particular interest in that, where required, it can directly deliver an arene bearing a carbon label at an unfunctionalised centre.

A number of other methods involving cyclisation onto an ester or ketone have been reported for the preparation of unlabelled arenes, and could be extended to the preparation of labelled systems. As shown in Scheme 70, S_N' addition of a

nitroalkane anion to a Baylis-Hillman enone product, followed by addition either to a second enone molecule or to a vinylphosphonium salt, gives an intermediate that can undergo base-promoted or Wittig-type cyclisation and subsequent aromatisation.[178] This and a number of related arene-forming processes starting from nitroalkanes have been reviewed recently.[88] As discussed in Sections 5 and 6, nitroalkanes, Baylis-Hillman reaction precursors and acrylates are all amenable to labelling by a variety of means. Metal-catalysed intramolecular ketone allylation offers a mechanistically different but conceptually similar approach, illustrated in Scheme 71.[179] The precursor for this reaction could be assembled quickly in labelled form with a label at the carbonyl carbon or at either of the olefinic centres.

9. Ring expansion

The preparation of [^{13}C]bromobenzene has been described by Seebach *et al.*[180] *via* a ring expansion reaction starting from cyclopentene and [^{13}C]bromoform (Scheme 72). This is an interesting and high yielding route into labelled aromatic derivatives and its application to [^{14}C]bromobenzene is feasible. The ^{14}C label could be introduced *via* bromoform, from [1,3-^{14}C]acetone,[181] or from [^{14}C]cyclopentene,[182] all of which have been reported.

Further examples of this approach can be seen in the preparation of selectively labelled chloronaphthalenes. As shown in Scheme 73, where addition of a dichlorocarbene species derived from either [^{14}C] or [^{13}C]chloroform under basic[183] or phase transfer conditions[184] to an indene followed by ring expansion gives naphthalene derivatives labelled at the β-position in reasonable yields.

Glass *et al.* have utilised similar methodology in the synthesis of substituted naphthalenes. Their catalytic ring expansion method involves the treatment of indenone with trimethylsilyldiazomethane in the presence of a palladium catalyst to afford the silylcyclopropanated intermediate. Reaction with an organometallic nucleophile affords the cyclopropylcarbinol which, under Lewis acidic conditions, undergoes ring expansion to regioselectively substituted naphthalenes.[185] A carbon label would be most conveniently introduced *via* the indenone from either [^{14}C]acetic acid or [^{14}C]benzaldehyde rather than from trimethylsilyldiazomethane (Scheme 74).[186]

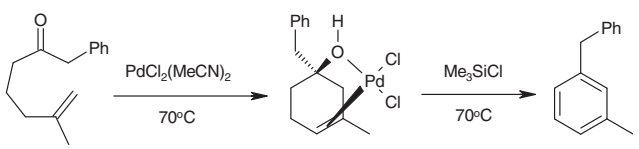
A general synthesis for 2-fluoro-1-naphthols from 1-indanones has also been reported. Initially, the 1-indanones are converted to difluoromethyl 2-fluoro-1-naphthyl ethers by reaction with a difluorocarbene source such as trimethylsilyl 2-fluorosulfonyl-2,2-difluoroacetate. These ethers are then converted to the respective naphthols by heating with a mixture of acetic acid and 48% HBr in good yields (Scheme 75). As with the previous method, the source of the label is most likely to arise from the starting indanone rather than the carbene source.[187]

A further approach, which has been used for annulations of a labelled benzene ring onto a pre-existing cycloheptatriene nucleus, involves the reaction of the anion of methyl phenyl sulphone with an anhydride; subsequent addition of a second (unlabelled) methyl phenyl sulphone anion and base promoted ring expansion gives the labelled arene product (Scheme 76).[188]

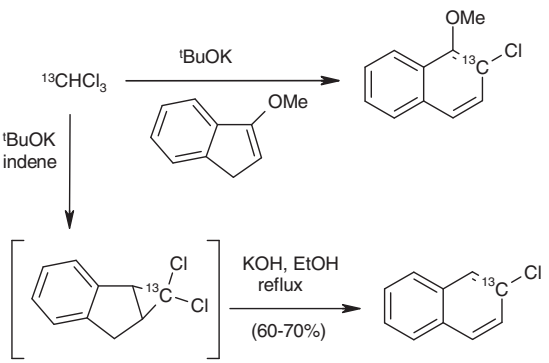
10. Ring-closing metathesis

Ring-closing olefin metathesis (RCM) has become an important reaction for the construction of cyclic compounds due to its simplicity, functional group tolerance and the range of ring sizes that can be constructed. Although RCM has generally been used for the synthesis of alicyclic compounds, more recent reports have expanded this methodology and utilised it for the construction of aromatic compounds.[189] Recently, Yoshida *et al.* have reported the preparation of a range of phenols utilising the ruthenium-catalyzed RCM/tautomerisation of 1,4,7-trien-3-ones *via* cyclohexa-2,5-dienones (Scheme 77).[190] The process is reported to provide phenols in good yields in a regioselective manner.

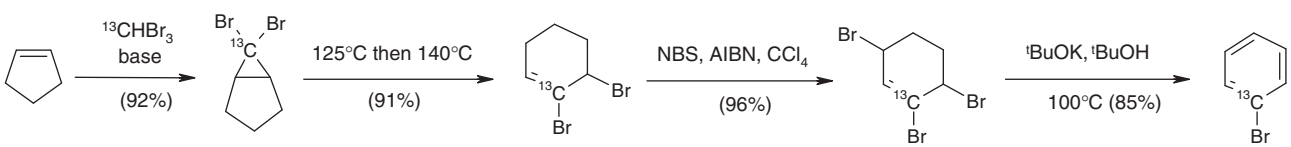
In addition to the synthesis of phenols, the methodology has been extended to the preparation of benzene and aniline derivatives by sequential RCM and acid-catalysed dehydration (Scheme 78) and RCM/oxidation (Scheme 79) sequences, respectively. In the preparation of benzene derivatives, 1,4,7-trien-3-ols were subjected to RCM with catalyst **2** or **3** (7.5 mol%) in dichloromethane. The dehydration process was accelerated by the addition of a catalytic amount of *p*-TsOH, affording a number of substrates in excellent yields (80–99%) (Scheme 78).[191] Application of RCM to 1,4,7-trien-3-amines followed by subsequent oxidation with MnO_2 afforded the



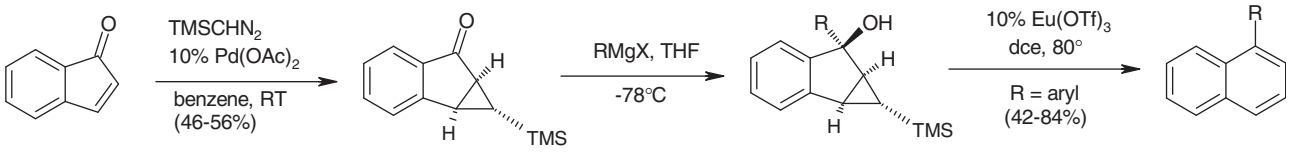
Scheme 71.



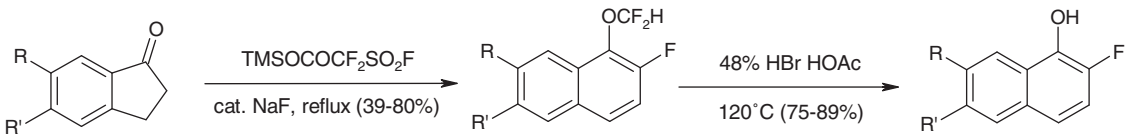
Scheme 73.



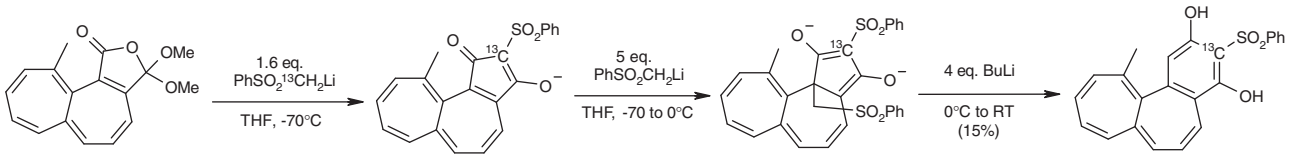
Scheme 72.



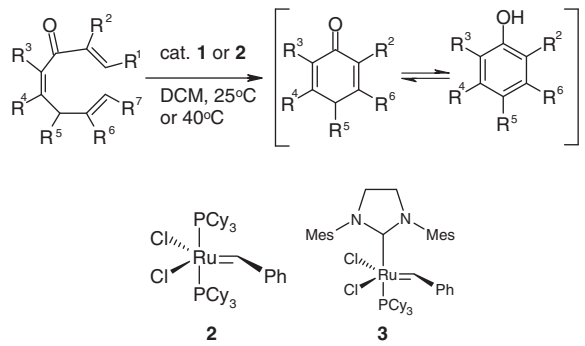
Scheme 74.



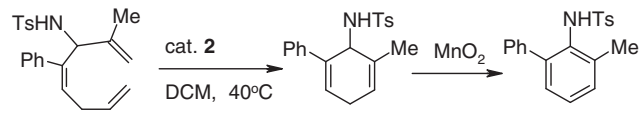
Scheme 75. R/R′ = H/H, Me/H, H/Cl, H/Ome.



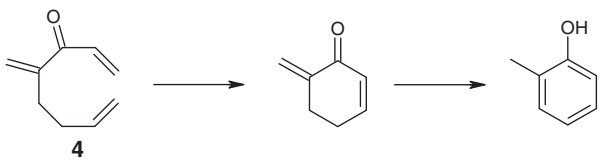
Scheme 76.



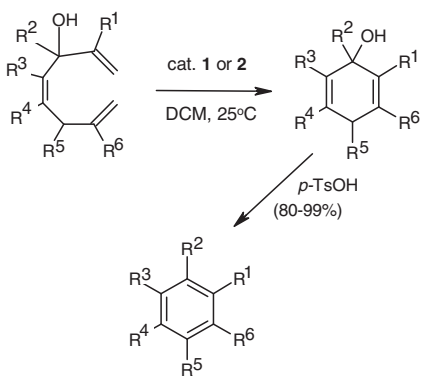
Scheme 77. $R^1 = H$, Me; $R^2 = H$, Alkyl, CH_2OH, CH_2OAc; $R^3 = H$, *n*-Pr, Ph, $SiMe_3$; R^4 = *n*-Pr, H, D; $R^5 = H$ (fails for $R^5 = OSi\text{-}t\text{-}BuMe_2$).



Scheme 79.



Scheme 80.

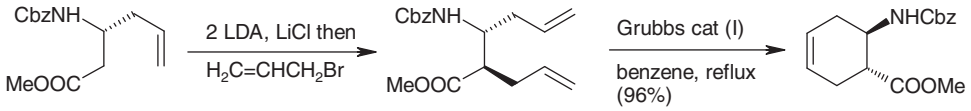


Scheme 78. $R^1 = H$, Alkyl; Cl, $(CH_2)_2OR$, R^2 = H, Me, R^3 = Alkyl, SiR_3, Ph; R^4 = n-Pr, H, D, Ph; R^5/R^6 = H, Me.

corresponding aniline derivative, again in a good yield (77%) (Scheme 79).

This approach for the synthesis of labelled arenes is limited by the difficulty of preparing the triene and, in particular, the construction of the internal *cis* double bond. The use of 4-methylene-1,7-octadien-3-ones (Scheme 80, **4**), containing an external carbon–carbon double bond, provides a partial solution to this problem by, with RCM being followed by isomerisation of the *exo* carbon-carbon double bond to an *endo* position accompanied by tautomerisation (Scheme 80).[192] In general the reactions were performed with Grubbs' second generation catalyst (1.5 mol%). However, by employing the Hoveyda-Grubbs' catalyst,[193] the yields of more electron-deficient systems could be improved.

The combination of RCM and dehydration/oxidation/tautomerisation or isoaromatisation has the potential to produce a wide variety of arene derivatives. Its functional group tolerance and regiospecific nature makes it a valuable route into the construction of both simple and complex aromatic rings.[194] A number of approaches to **4** (Scheme 80) or an equivalent precursor can be envisaged: **4** could arise from the oxidation of 4-methylene-1,7-octadien-3-ols, with the alcohol prepared either by vinylation of 2-methylene-5-hexenals, which could be obtained by the Mannich/Hofmann degradation, or by



Scheme 81.

aldol/dehydration of 5-hexenals. An alternative route would involve the coupling of α,β-unsaturated aldehydes with 2-halo-1,5-hexadienes, obtained by the allylation of 2,3-dihalopropenes. Difficulties associated with the construction of this type of precursor might also be avoided by employing the corresponding 1,3-diols as starting materials.[190] These are potentially accessible in labelled form by allylation of the corresponding 3-hydroxycarbonyl compound with an appropriate labelled allylmetallic reagent.

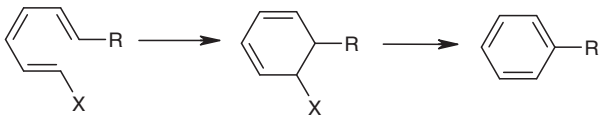
Simpler examples are known, which give rise to cyclohexenes rather than arenes as the initial product. One such example from Gardiner *et al.*[195] is shown in Scheme 81. In this case, it may be possible to construct the starting material shown from bromoacetic acid and cyanide, with either component being the labelled source.

11. Electrocyclisation

A potentially useful entry into arene systems involves thermally allowed electrocylisation of an acyclic triene, followed by elimination of a nucleofugic substituent to form the aromatic system (Scheme 82). Raap *et al.*[196] have used this approach for the introduction of a ^{13}C label into benzonitrile by means of a Wittig reaction of cyanomethylphosphonate anion with a captodative dienal (Scheme 83); the resulting triene undergoes thermal cyclisation and elimination of dimethylamine to give [1-^{13}C]benzonitrile. DIBALH reduction of the latter gives [1-^{13}C]benzaldehyde, which is elaborated to labelled phenylalanine. The same authors have developed a route to related diene systems (Scheme 84) with a view to permitting the introduction of a label at any position of an arene system.

A similar approach has been described by Brown *et al.*,[197] in which the Horner-Wadsworth-Emmons reaction of an aldehyde with a deprotonated dimethyl (5-chloro-2,4-pentadienyl)phosphonate bearing chlorine as a suitable terminal leaving group gives a triene. Cyclisation and aromatisation occurs on heating in pyridine, with the former aldehyde carbon becoming C-1 of the arene product. Ideally in this case, the triene possesses an *E,Z,E*-configuration, because disrotatory thermal cyclisation is far faster than with the *Z,Z,E*- or *Z,Z,Z*-stereoisomers (Scheme 85). From the standpoint of labelled synthesis, this approach has the attraction that a label can be introduced easily into the aldehyde precursor, either by reaction of an anion with labelled DMF or an equivalent, or by reduction of a nitrile. The approach has been demonstrated only for aromatic aldehydes, but there is no reason to suppose that it would not be applicable to aliphatic precursors also. More recently, the gold-catalysed electrocyclisation of dienyne precursors has been reported (Scheme 86)[198]; in this case, aromatisation occurs without the need for loss of a substituent.

A number of variations on the principle of electrocyclisation have been reported as means to prepare labelled arenes. The ruthenium-catalysed reaction illustrated in Scheme 87[199] is an elegant entry into 1,2,3-trisubstituted systems, although the synthesis of the precursor in labelled form would be lengthy.



Scheme 82.

Scheme 88, by comparison, outlines a process with the potential for direct preparation of labelled arenes from [2-^{13}C]- or [2-^{14}C]acetic acid *via* labelled thioglycolic acid; in this case, electrocyclisation is followed by cheletropic cycloelimination of sulphur to generate the arene product.[200]

Finally, the process illustrated in Scheme 89[201] is not strictly an electrocyclisation, but the overall transformation is similar; cyclisation occurs on treatment of a carboxyl-substituted enyne with acetic anhydride, forming a 4-substituted 3,5-diacetyloxybenzoic acid. As above, adaptation of this method for the synthesis of a labelled arene would require only the preparation of the propargaldehyde precursor with a carbon label at C-1, leading ultimately to a label at C-2 in the product.

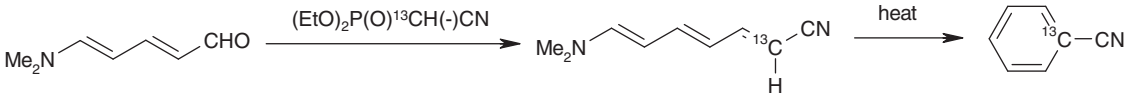
12. Cyclotrimerisation of acetylenes

The trimerisation of acetylene is widely used for the preparation of *U*-^{14}C-labelled aromatics,[202] but has not been applied to regioselective introduction of one or two labels. This approach may be viable where the process involves two electronically dissimilar acetylenes, in which case a label could be introduced *via* a propiolate, for example (Scheme 90; c.f. Section 6).[203] Better regiochemical control has been reported using a stepwise ruthenium-mediated trimerisation process (Scheme 91),[204] although the efficiency required for labelled arene synthesis remains to be demonstrated.

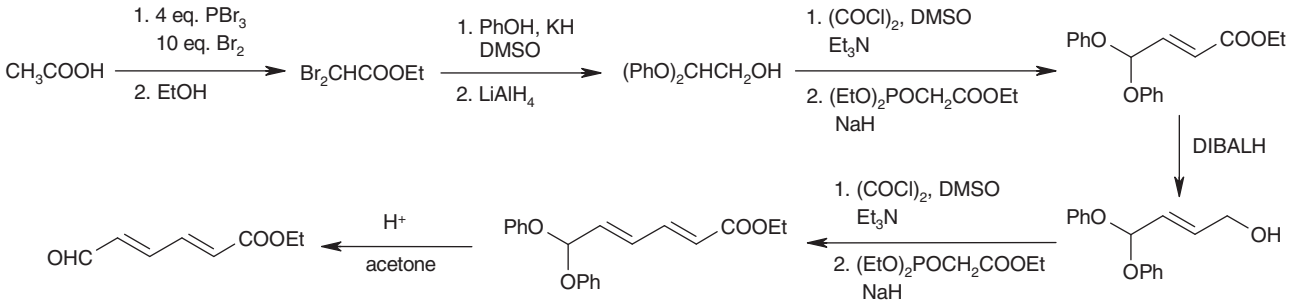
A more promising approach, which has been reported recently, involves the reaction of two molecules of an acetylenedicarboxylate with an acetylene equivalent, as summarised in Scheme 92.[205] Assuming that mono- or *bis*-decarboxylation of the adducts from this process could be achieved, this would allow the introduction of a carbon label from the enol acetate precursor. A further departure from the basic trimerisation approach involves the reaction of two molecules of acetylene with a ketone under organocatalytic[206] or, as illustrated in Scheme 93, manganese-catalysed conditions.[207] In these cases, however, any label would be most conveniently introduced *via* the ketone precursor.

13. Other methods

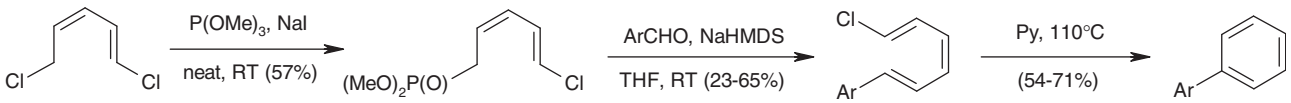
One method for the preparation of labelled arenes by pinacol coupling has been described (Scheme 94): this involves the preparation of diethyl adipate, with cyanide as the source of the label.[208] With the incorporation of a functional group in the precursor or by modification of the route to provide a phenol, it has considerable potential for application to the synthesis of 1,2-dilabelled arenes.



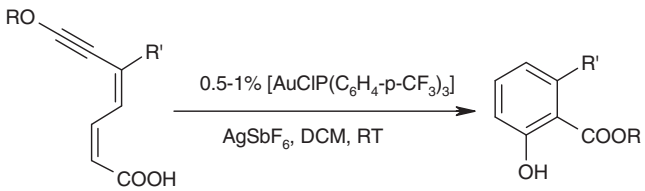
Scheme 83.



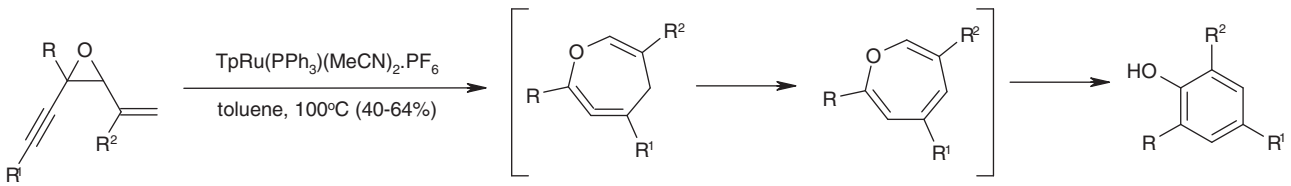
Scheme 84.



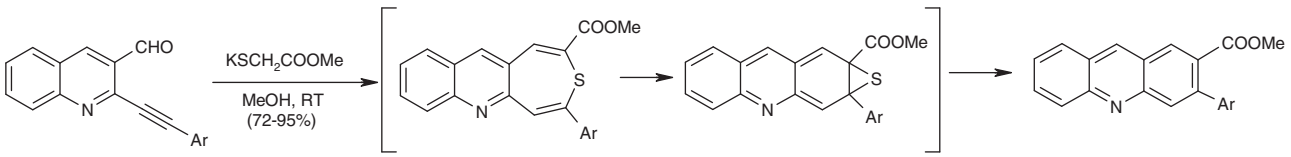
Scheme 85.



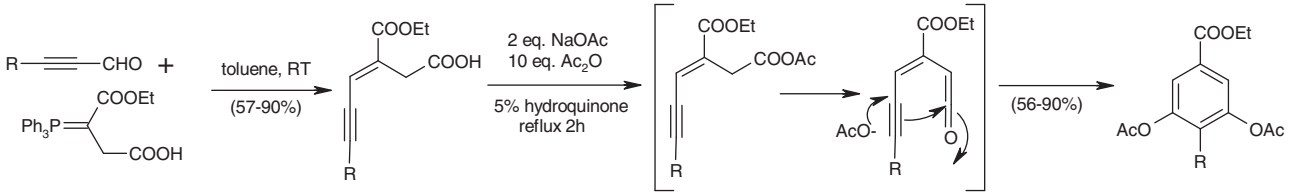
Scheme 86. *R* = Me, Et; *R*′ = aryl, CH = CHPh, *C*≡CPh, Bu, *t*-Bu, $SiMe_3$.



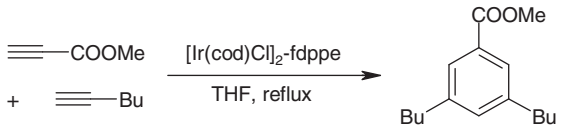
Scheme 87.



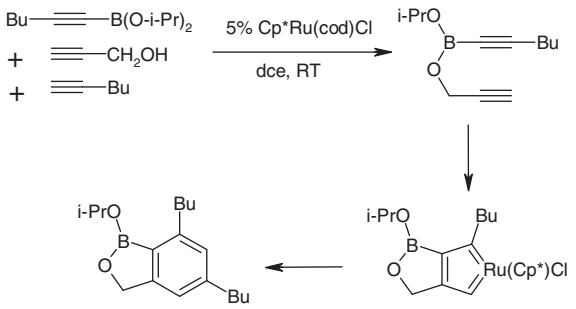
Scheme 88.



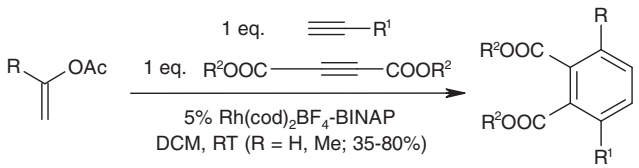
Scheme 89. *R* = H, Am, aryl, CH = CHPh, 3-thienyl



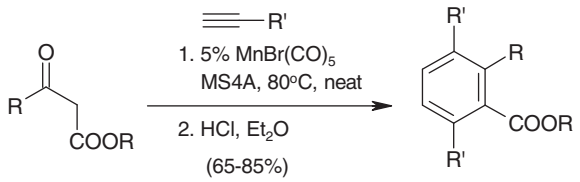
Scheme 90.



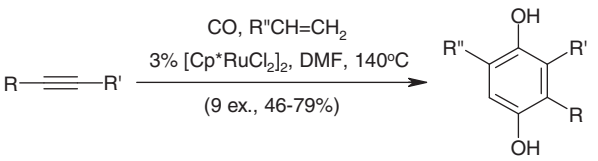
Scheme 91.



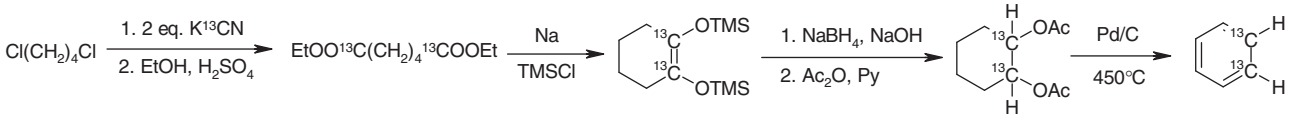
Scheme 92. $R^1 = {}^nC_6H_{13}$, ${}^nC_{10}H_{21}$, Bn, Cy, Ph, $SiMe_3$.



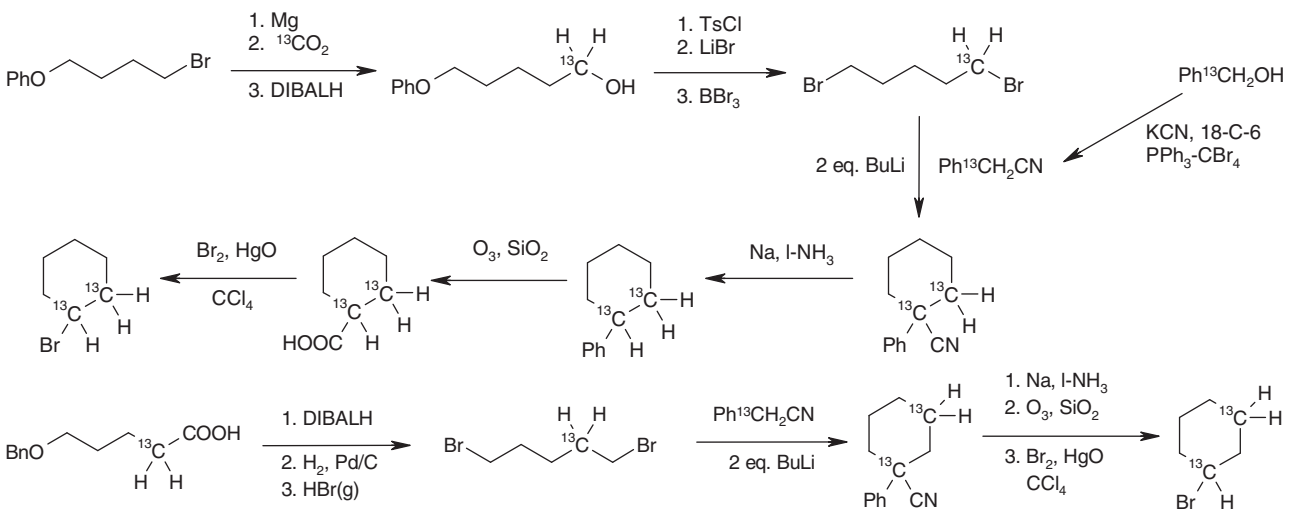
Scheme 93. $R = Me$, Ph; $R^1 = Me$, Et; $R^2 = Ar$.



Scheme 96.



Scheme 94.



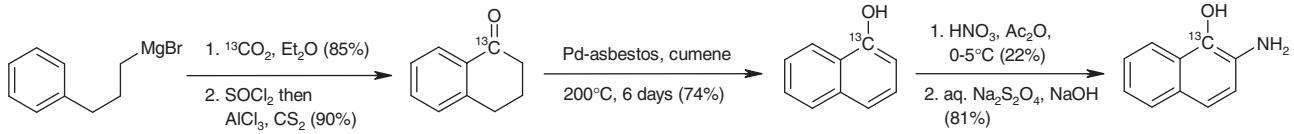
Scheme 95.

An additional process with potential for the preparation of specifically dilabelled products is illustrated in Scheme 95,[209] in which labelled phenylacetonitrile is cycloalkylated at the benzylic centre to give a 1,1-disubstituted cyclohexane, which is elaborated further. Aromatisation of the cyclohexanes produced in this case can be envisaged. A further method with potential for the preparation of 1,4-dilabelled products involves the formal four-component coupling of an alkene, an acetylene, and two moles of carbon monoxide (Scheme 96).[210] Again, either the acetylene or olefin component could be labelled rather than the carbon monoxide, giving rise to other labelling patterns.

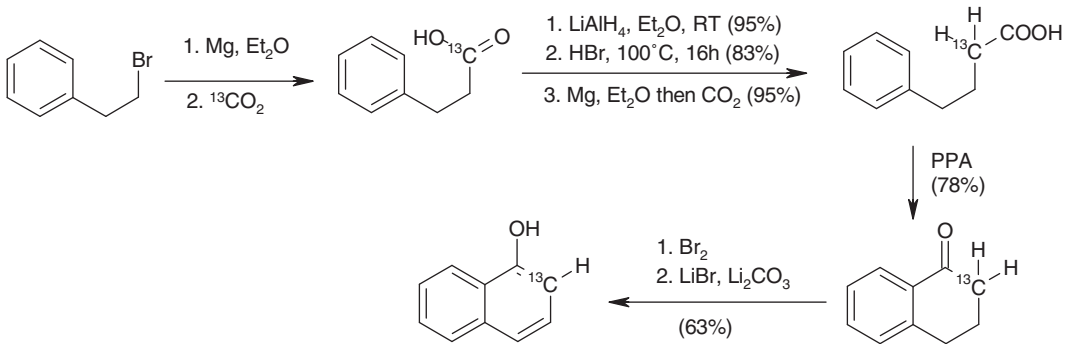
14. Additional approaches to labelled naphthalenes

In principle, many of the labelling methods described elsewhere in this review are applicable to the synthesis of regioselectively labelled condensed aromatics. A number of additional methods are available for the preparation of labelled naphthalenes and, by implication, other polycyclic systems; this includes the addition of dichlorocarbene to indene, followed by ring-expansion, as described in Section 9.

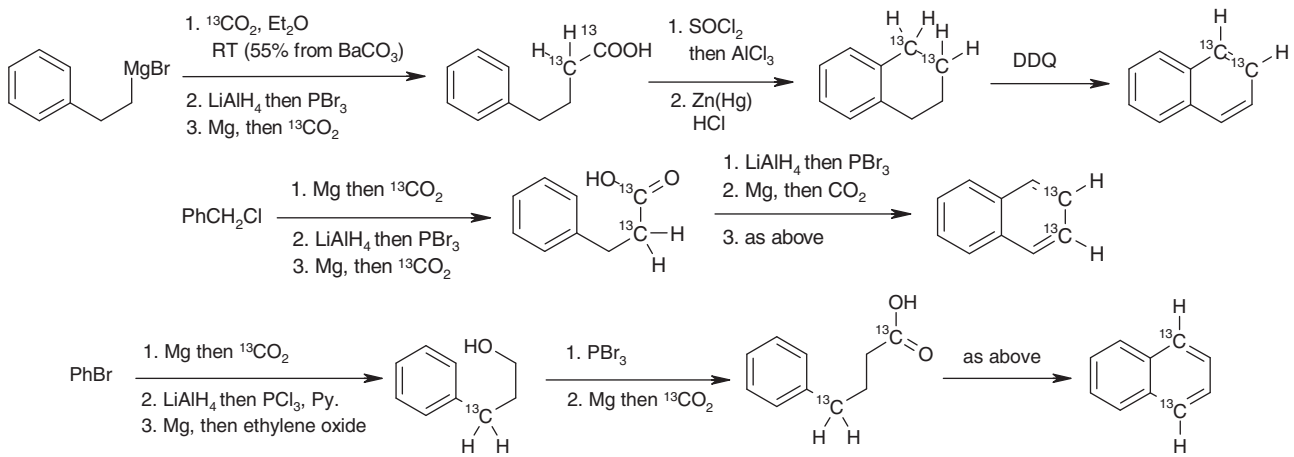
By far the most commonly reported and flexible means for the selective introduction of one or two labels into the naphthalene core involves iterative construction of the second ring, enabling the label to be located at the chosen position. This is illustrated for the assembly of a [1-^{13}C]naphthalene in Scheme 97[211] and for



Scheme 97.



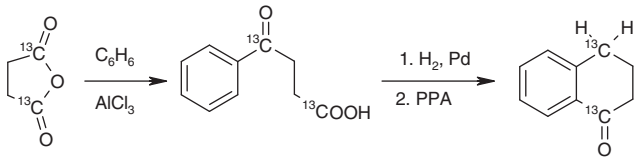
Scheme 98.



Scheme 99.

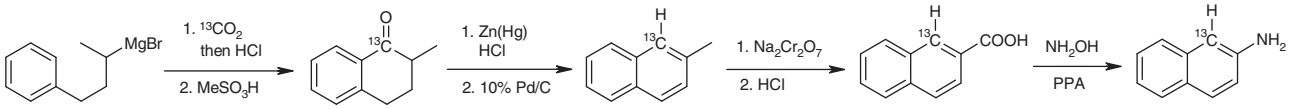
a [2-^{13}C]naphthalene in Scheme 98,[212] and some representative examples of the preparation of dilabelled naphthalenes are shown in Scheme 99.[213] The approach is open to a number of variations: the labelled carbon is conveniently introduced by carboxylation as in Schemes 97,98 and 99, but can as easily be introduced using labelled cyanide,[214] while 1,4-dilabelling has also been carried out by sequential Friedel-Crafts reactions of benzene with [1,4-$^{13}C_2$]succinic anhydride (Scheme 100).[215] Elaboration of the arene product by oxidation of a benzylic methyl group and subsequent Lossen rearrangement, along the lines of the processes described in Section 2, has also been described (Scheme 101).[216]

A number of methods have been developed for unlabelled naphthalene syntheses, and suitable labelled precursors are readily available to permit several of these to be used for the preparation of labelled naphthalenes. Among those with potential for labelled synthesis are [4+2] cycloaddition (Scheme 102; Section 6),[217] ring-expansion (Section 9), ring-closing metathesis (c.f. Section 10),[218] electrocyclisation (Section 11) and the condensation of an *ortho*-dihalobenzene with two equivalents of an acetylene (c.f. Section 12).[219]

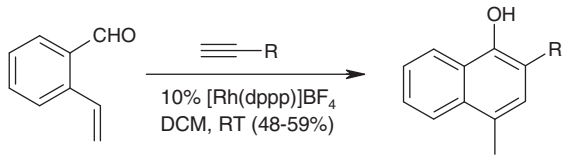


Scheme 100.

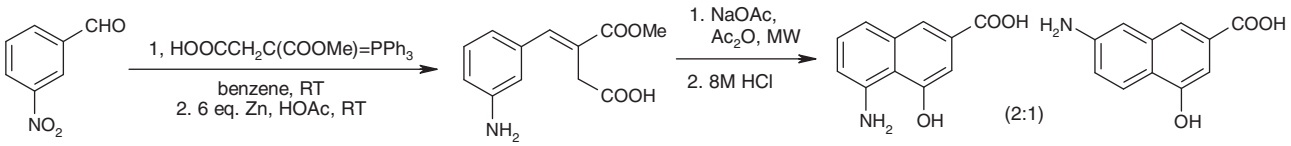
The Wittig reaction, where either component is potentially available in labelled form, has been used to prepare intermediates whose cyclisation under Friedel-Crafts conditions gives a naphthalene, as exemplified in Scheme 103.[220] Precursors for the intramolecular Friedel-Crafts reaction are also available by reaction of 2-nitrotoluene with acrylonitrile or an acrylate (Scheme 104),[221] while a Wittig reaction has also been used to introduce a β-bromo-β-deuterovinyl group; Sonogashira coupling of the intermediate with a terminal acetylene gives an enyne, which in turn gives a deuterated naphthalene product on treatment with base (Scheme 105).[222] Alternative approaches *via* acetylenic intermediates are illustrated in Schemes 106 and 107; in the former sequence, cyclisation of a



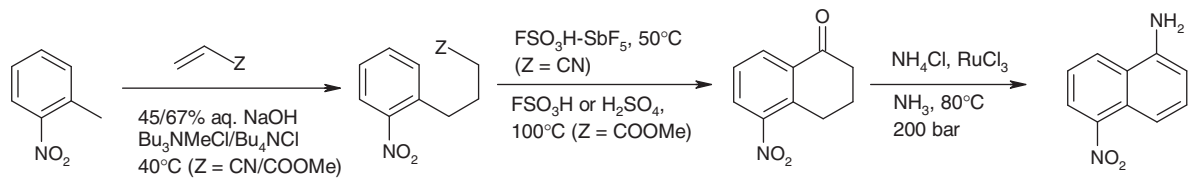
Scheme 101.



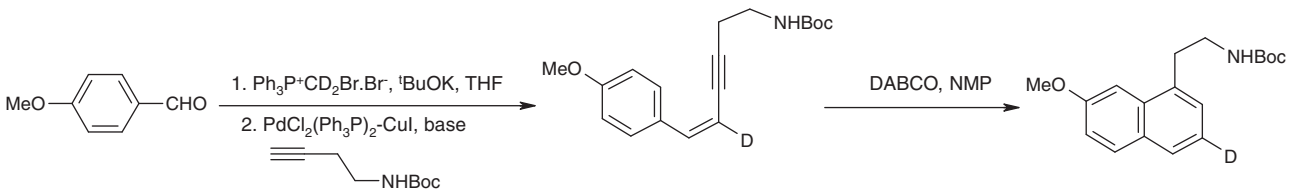
Scheme 102.



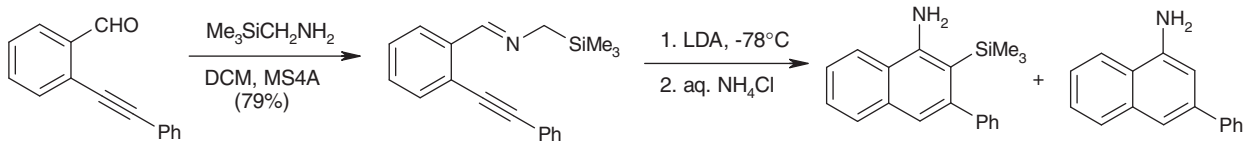
Scheme 103.



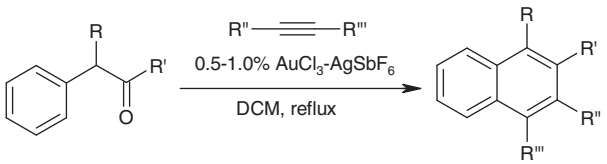
Scheme 104.



Scheme 105.



Scheme 106.



Scheme 107. R = H, Bu, Ph; R^1 = H, Me, OEt (or R^1–R^2 = -$(CH_2)_4$-), R^3 = H, Me, Ph, Br; R^4 = Ph, CH_2OBn.

silyl-stabilised anion onto the acetylene forms an azepine, whose rearrangement by a ring-opening/ring-closing process provides a 1-naphthylamine product.[223] In the latter, gold-catalysed addition of an alkyne to a benzyl ketone is followed by an intramolecular Friedel-Crafts reaction to give the naphthalene product.[224]

15. Conclusion

A wide variety of methods are now available for the preparation of selectively mono-, di- or tri-carbon labelled arenes. Many of these have already been demonstrated to provide the desired products in good yields and, where the substrates are radiolabelled, with good recovery of radioactivity. Moreover, the available methods also provide a range of substitution patterns; the Table below provides a summary and an index to the methods applied for the preparation of arenes with differing substitution patterns.

Substitution position	C-1 function	Other key groups	Section (Scheme)
1-	COOH		2(1,4), 8(62)
	COOEt		4(22)
	CN		8(62), 11(83)
	$COCH_3$		2(2)
	CH_3		2(1)
	NO_2		5(28)
	NH_2		2(2,4), 5(30)
	OH, OR		2(2,4), 3(14,15), 5(30), 7(59)
	Br		2(2), 3(19), 9(72)
	Cl		2(2)
	I		2(2,4)
	SO_3H		2(2)
2-	H	2-COOH	6(41)
4-	H	4-Br	2(2)
	H	4-CN/COOH	3(13)
	H	4-NH_2/NHAc	3(11)
	H	4-NO_2	3(12)
	H	4-OH/OR	3(12), 4(22)
	H	4-OTf	4(22)
	H	4-CH_2CH_2COOH	2(3)
1,2-	CH_3	2-SO_3H	2(2)
	CH_3	2-COOH	2(2)
	Ph	2-CH_3	8(63)
	-OR	2-OH	2(2)
	-OH	2-COOH	8(61)
	OMe	2-NO_2/NH_2	2(2)
	-NH_2	2-COOH	6(33)
	COOH	2-NO_2	2(4)
	COOR	2-NH_2	6(40,44)
1,4-	CH_3	CHO	2(4)
	NH_2, NHAc	4-Br	2(2)
	OMe	4-CHO	2(2)
	OMe	4-NO_2/NH_2	3(15)
	OH	4-alkyl	2(4), 3(14)
	OH	4-NH_2	3(11)
	OH	4-NO_2	3(6,11)
	COOEt	4-OH	4(20)
	COOH	4-OH/OR	4(22)
	Br/Cl	4-NH_2/NO_2	3(19)
	I	4-OBn	4(22)
	Br/I	4-OTf	4(22)
2,3-	H	2-COOMe; 3-NH_2	6(40)
2,6-	H	2,4-$(OH)_2$	8(68)
3,4-	H	3-COOH; 4-Br	6(42)
1,2,3-	NH_2	2,3-Me_2	6(33)
	OH	2,3-Me_2	6(33)
	Ph	2,3-COOCO	6(34)
1,2,4-	OH	2-COOH, 4-NO_2	3(9)
	OH	2-OMe, 4-NO_2	3(8)
1,3,4-	COOEt, COOH	4-OH/OR, 3-Br	4(22)
	OH	3,4-$(OMe)_2$	4(22)
1,3,5-	OH	3-COOH, 5-OH	6(32)
	OH	3,5-$(OH)_2$	6(37)
2,3,4-	H	2,3-OCOCO; 4-Ph	6(35)
2,4,6-	H	2,4-$(OH)_2$, 6-alkyl	4(25)
1,2,3,5-	OH	2-COOH, 3-CH_3, 5-OH	8(55)
1,2,3,5-	alkyl	2-COOEt, 3.5-$(OH)_2$	8(56)
1,3,4,5-	OH	3,5-Me_2, 4-NO	2(5)
	OH	3-OH, 4-COOH, 5-CH_3	4(26)
1,2,4,6-	NO_2	2,4,6-$alkyl_3$	5(27)
	OH	2,6-$alkyl_2$, 4-NO_2	3(10)

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