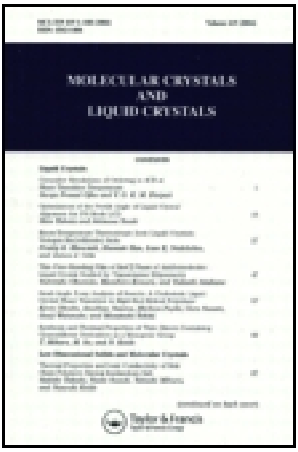

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Cross-Coupling Reactions in the Synthesis of Liquid Crystals†

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The synthesis of structurally complex liquid crystals by traditional linear methods is often difficult, if not impossible. When many functional groups of a specific substitution pattern are required it is very likely that the sequence of reactions will interfere with functional groups already present or the directing effect of such functional groups may lead to the wrong substitution pattern. Syntheses using small, more easily managed units of the correct substitution patterns in high-yielding coupling reactions are a much more viable approach; the possible use of the sub-units in the synthesis of many different final compounds leads to systematic and economic syntheses. Suitable methods of synthesis of liquid crystals by cross-coupling reactions of various types are discussed, examples are provided and issues of selectivity are considered. The methods based on arylboronic acids are particularly useful.

Keywords: cross-coupling, palladium-catalysed, synthesis, selectivity

INTRODUCTION

Probably one of the most desirable synthetic processes in organic chemistry is that for the formation of a carbon-carbon bond. Such a process is valuable because large molecules can then be prepared *via* small, more easily managed units which are subsequently connected together to give the desired product. The long, lath-like molecular structure of most liquid crystalline compounds, and the ever increasing complexity of the more advanced materials demanded by display device engineers, makes cross-coupling reactions[1–5] very important in synthesis. The formation of homocoupled products, which are often difficult to separate from the desired cross-coupled product, needs to be eliminated and selectivity is usually required where two reactive sites exist so that a second cross-coupling reaction can be carried out and the efficient synthesis of unsymmetrical multi-unit compounds (*e.g.* *p*-terphenyls)[2,3] can be achieved.

Since Corriu[6] and Kumada[7] reported in 1972 that the cross-coupling of Grignard reagents with aryl and alkenyl halides could be catalysed by nickel-phosphine

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complexes, a wide variety of coupling reactions has been developed and some are now of great synthetic importance. The synthetic utility of these reactions has been demonstrated by work which shows that organometallics containing zinc,[1-3,8-11] aluminium,[12,13] zirconium,[14,15] tin,[16-18] and boron,[1-5,19-22] for example, can undergo cross-coupling reactions using a palladium catalyst.

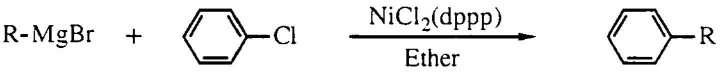
The following account represents a short review of carbon-carbon bond formation methods which we have used for the synthesis of a variety of liquid crystalline compounds and which we believe are invaluable methods for general liquid crystal synthesis.

Fouquet and Schlosser[23] in 1974 reported the coupling of primary tosylates with a variety of Grignard reagents [*e.g.* R′ = alkyl, aryl in **(1)**]. The principal reason given for the

$$\text{R-OH} \longrightarrow \text{R-Tos} \xrightarrow[\substack{\text{Li}_2\text{CuCl}_4 \\ \text{THF}}]{\text{R}'\text{-MgBr}} \text{R-R}' \qquad (1)$$

occurrence of reaction is the chelation of the tosylate with the copper catalyst after the latter's interaction with the Grignard reagent. They also reported that a carbon-carbon bond can be formed by the replacement of allylic and benzylic acetate groups with Grignard reagents, presumably because similar chelate complexes can be formed. Excellent yields are reported for these types of cross-coupling procedure.

A more general cross-coupling method involving the nickel-phosphine complex-catalysed coupling of alkyl, aryl and alkenyl Grignard reagents with aryl and alkenyl halides was reported by Kumada *et al.*[24] [1976, see **(2)**] and several nickel-phosphine complex catalysts were



(2)

reviewed. Generally the best catalyst was found to be dichloro[1,3-*bis*(diphenylphosphine)propane]nickel(II) [NiCl_2(dppp)] and it is reported that fluorides, chlorides, bromides and iodides could all be replaced. With this particular catalyst, the order of reactivity [*i.e.* PhI > PhCl > PhBr > PhF] is unusual but for those cases where there is competition for replacement, and with dichloro[1,2-*bis*(diphenylphosphine)ethane]nickel(II) [NiCl_2(dppe)] in all cases, the usual order of reactivity [PhI > PhBr > PhCl > PhF] is observed. However, dehalogenation occurs during the coupling process in the order PhF < PhCl << PhBr < PhI and when THF is used as the solvent the rate of dehalogenation is much greater than when diethyl ether is used. Therefore, the coupling reactions are best catalysed by NiCl_2(dppp) and should be carried out on aryl chlorides in diethyl ether to give the best compromise of low dehalogenation and high reaction yields. Several examples of quantitative yields are quoted.

It was reported by Negishi, King and Okukado[25] (1977) that aryl bromides or iodides can be cross-coupled with aryl- or benzyl-zinc chlorides in the presence of 5 mol% of $Ni(PPh_3)_4$ or $Pd(PPh_3)_4$ [prepared from $PdCl_2(PPh_3)_2$ and 2 equiv. of di-isobutylaluminium hydride (DIBAL) and triphenylphosphine], [see (**3**)]. The arylzinc chloride is readily prepared by the

$$\text{Ar-ZnCl} \quad + \quad \text{Ar'-Br} \quad \xrightarrow[\text{THF}]{Pd(PPh_3)_4} \quad \text{Ar-Ar'} \tag{3}$$

reaction of the corresponding aryllithium with zinc chloride and good yields of the desired cross-coupled product (with less than 5% homo-coupled product) are reported. This cross-coupling procedure has been used by Zollinger and coworkers[26,27] to synthesise liquid crystalline materials in good yields.

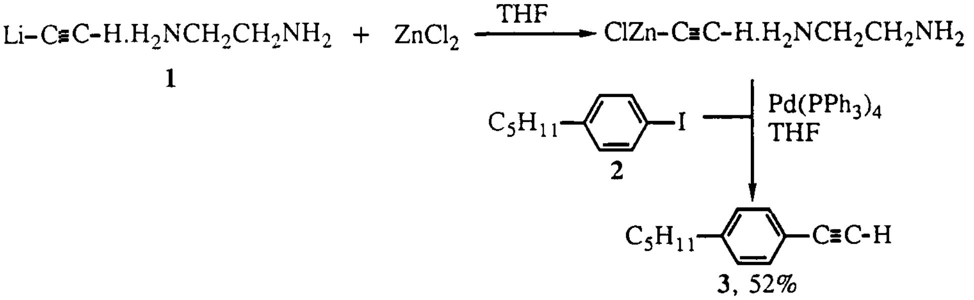
In 1978 Negishi and King[28] reported the very useful tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] catalysed cross-coupling of alkynylzinc chlorides with aryl iodides and activated (*i.e.* by electron-withdrawing substituents, *e.g.* cyano) aryl bromides at room temperature in good yields [see (**4**)]. Our work has shown that non-activated and even deactivated aryl bromides can undergo cross-coupling at elevated temperatures (~67°C, in refluxing THF). This has allowed us to develop a highly successful method of selective

$$\underset{\text{(or Ar)}}{\text{R-C}\equiv\text{C-ZnCl}} \quad + \quad \underset{\text{(or I)}}{\text{Ar'-Br}} \quad \xrightarrow[\text{THF}]{Pd(PPh_3)_4} \quad \underset{\text{(or Ar)}}{\text{R-C}\equiv\text{C-Ar'}} \tag{4}$$

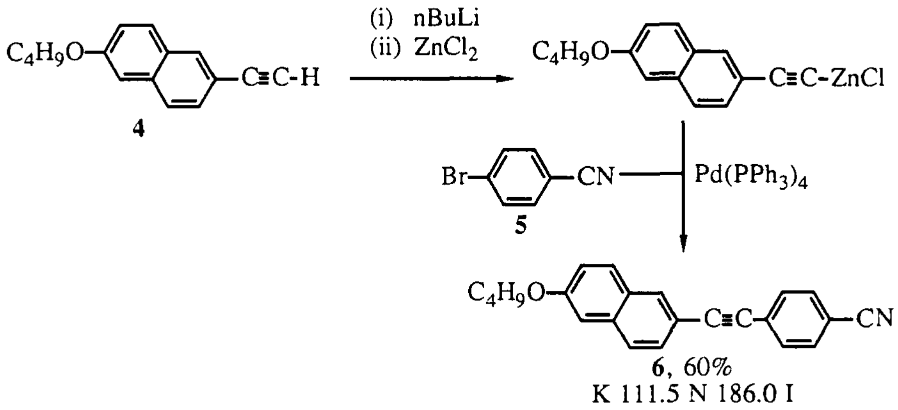
cross-coupling to 1-bromo-4-iodobenzene derivatives by the use of an initial cross-coupling to the iodo-substituent at room temperature followed by another cross-coupling at elevated temperature (see Selectivity in Cross-coupling). It has also been found by Chen and He[29] (1987) and by ourselves[3] (1988) that phenolic triflate derivatives (*e.g.* compound **8**; see Triflates in Cross-coupling) couple to alkynylzinc reagents under similar conditions to those required for aryl bromides. The cross-coupling reaction of triflates is particularly important because it enables a carbon-carbon bond to be formed at a phenolic site, which is useful when halogen-containing starting materials are unavailable, and it can be used with vinyl triflates obtained from carbonyl compounds.

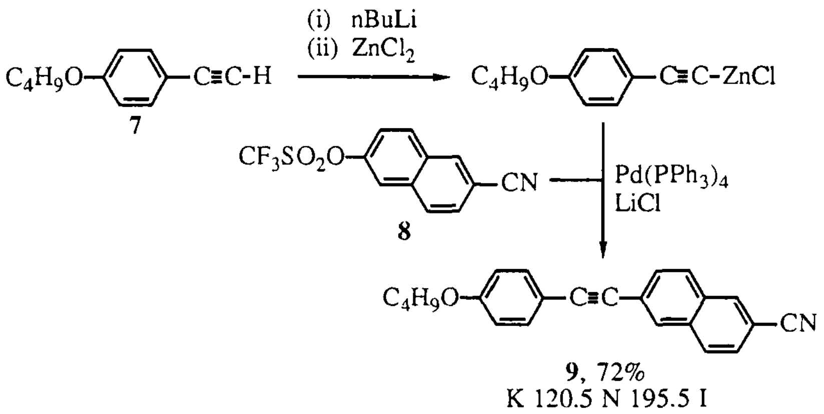
The alkynylzinc chloride coupling method involves lithiation at the acidic proton site of the terminal alkyne, followed by treatment with zinc chloride. Subsequent addition of the aryl chloride, bromide, iodide or triflate and the catalyst enables coupling to occur. Those reactions involving aryl iodides or activated aryl bromides proceed at room temperature but others require elevated temperatures and only activated aryl chlorides can be successfully used.

This method also enables terminal alkynes to be directly prepared from aryl iodides by incorporating the use of lithium acetylide ethylenediamine complex (compound **1**) at room



temperature. Subsequently the terminal alkyne so prepared can be used in a further coupling process to give tolanes such as **6** and **9** and the method is therefore useful for preparing both intermediates and final products (all yields quoted here are after purification of crude products by column chromatography followed by recrystallisation).



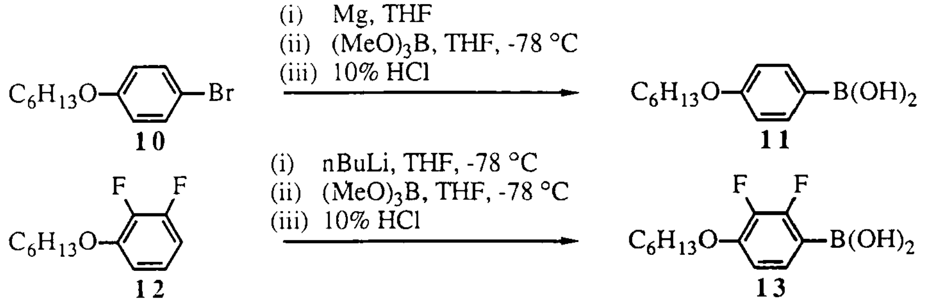


The method developed by Negishi and King[28] is similar in its end result to the earlier cross-coupling method of Sonogashira *et al.*[30,31] (1975) which involves the direct coupling of a terminal alkyne to an aryl iodide or an aryl bromide catalysed by either $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ and copper(I) iodide. The latter procedure may appear to be better than the equivalent zinc coupling method in that there is no need to make the alkynylzinc chloride, but the crude products are usually much more difficult to purify than those from the zinc coupling procedure.

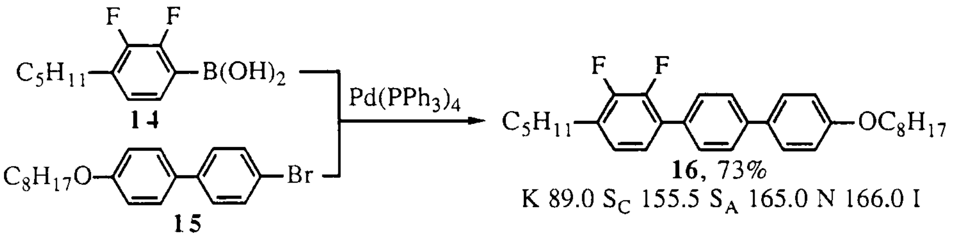
The most recent and by far the best overall method of preparing unsymmetrical biaryl or multi-aryl systems [see (**5**)] was developed by Suzuki *et al.*[21] (1981) and later this method provided excellent results for Miller and Dugar[22] (1984) and ourselves[1-3] (1986). The procedure

$$\mathrm{Ar{-}B(OH)_2} \quad + \quad \underset{\text{(or I)}}{\mathrm{Ar'{-}Br}} \xrightarrow[\mathrm{Pd(PPh_3)_4}]{\substack{\text{1,2-Dimethoxyethane} \\ \text{2M-Na}_2\text{CO}_3}} \mathrm{Ar{-}Ar'} \qquad (5)$$

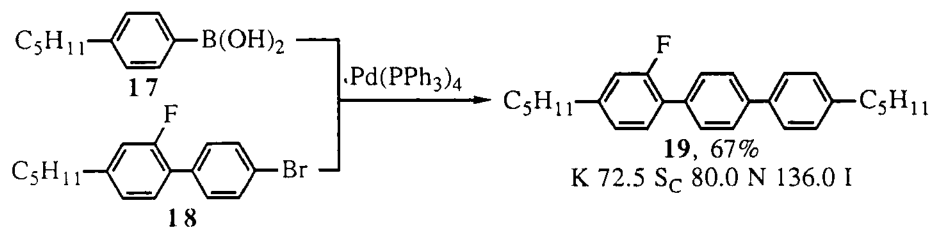
involves the cross-coupling of an arylboronic acid with an aryl bromide, aryl iodide or an activated aryl chloride. The boronic acid (*e.g.*, compounds **11**, **13**, **14** and **17**) can be easily prepared in excellent yield from an aryllithium or an aryl Grignard reagent by treatment with tri-isopropyl borate or trimethyl borate in dry THF at −78°C under dry nitrogen, followed by the hydrolysis of the borate ester (*in situ*) with 10% hydrochloric acid.[2,3,32] The arylboronic acids



are stable in air and not sensitive to moisture; they can be prepared in large quantities, stored and used when required. The spectra of the 'boronic acids' frequently give no confirmation of a boronic acid structure and the products often appear to be mixtures of anhydrides and boronic acid; the purity of the products is further complicated by their tendency to coordinate with THF and often this accounts for their soft waxy nature and their poorly resolved nmr spectra. However, addition of aqueous 10% potassium hydroxide to the product, removal of any impurity by an ether wash (*e.g.* any material produced by moisture reacting with the intermediate lithium or Grignard reagent or coordinated THF), followed by acidification and extraction into ether gives a crystalline solid with a well resolved nmr spectrum (although the —OH protons are still often not revealed); any anhydride originally present is converted into the boronic acid by this treatment. Such a purification procedure is useful to characterise the boronic acid but is usually unnecessary since the anhydride will be hydrolysed in the reaction conditions and any THF does not interfere.[3] The coupling reaction is carried out in a two-phase medium of benzene/ethanol[1-5,21] or 1,2-dimethoxyethane[33,34] and aqueous 2M-sodium carbonate. The boronic acid is added in 10–20% excess and the reaction is catalysed by 3 mol% of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$]. A nitrogen atmosphere is used to protect the catalyst and the stirred mixture is heated under reflux until glc analysis reveals a complete reaction (usually ~3–4 hours, but often overnight for convenience).

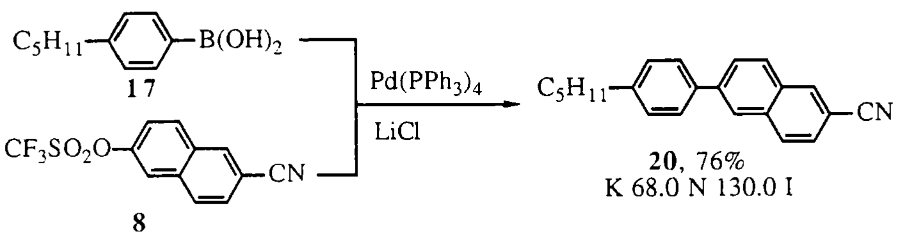


16, 73%
K 89.0 S_C 155.5 S_A 165.0 N 166.0 I



19, 67%
K 72.5 S_C 80.0 N 136.0 I

We have recently found that aryl triflates (*e.g.*, compound **8**; see Triflates in Cross-coupling) can be coupled with arylboronic acids in the same manner as aryl iodides and aryl bromides (this procedure was subsequently reported in the literature).[35,36]

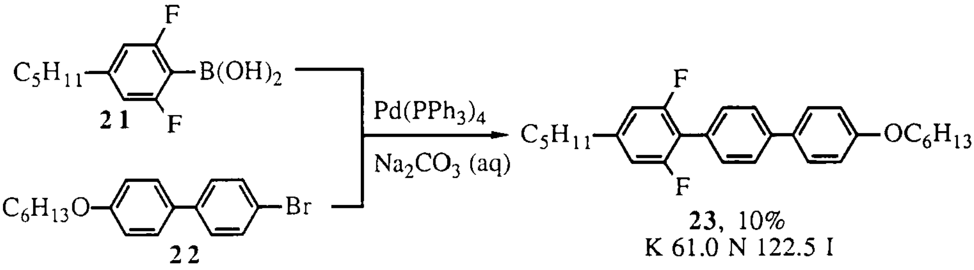


20, 76%
K 68.0 N 130.0 I

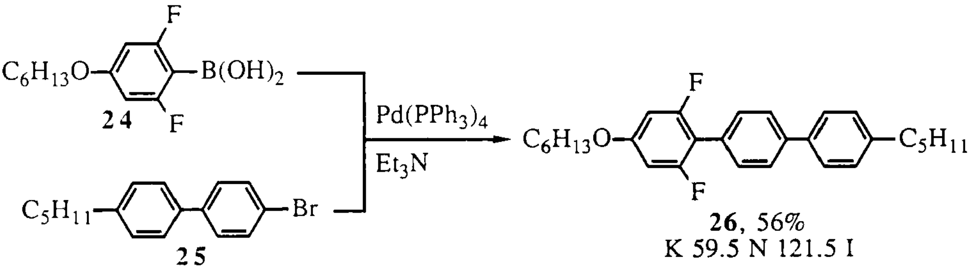
Aryl iodides react much faster than aryl bromides and the latter are similar in reactivity to phenolic triflates; those compounds with electron-withdrawing groups (*e.g.* cyano-substituents) tend to react faster than others and overall yields are always high. By using combinations of iodo, bromo or triflate functional groups, selective couplings can be achieved which enables a separate subsequent coupling reaction to be carried out (see Selectivity in Cross-coupling).

The boronic acid coupling reaction offers the advantages of high yields, clean products with no homocoupling, no necessity for anhydrous conditions (in most cases) and the boronic acid can be pre-prepared, stored and used when convenient. Additionally, because arylboronic acids can be formed at low temperatures, *i.e.* −78°C (unlike arylzinc chlorides), they are essential when *ortho* halogeno-substituted arylmetals are being used because, at the higher temperatures required to form Grignard reagents or arylzinc chlorides, benzyne formation occurs.[2,3]

When using certain boronic acids, especially those which contain electron-withdrawing substituents (*e.g.* fluoro-substituents) the aqueous basic conditions of the coupling process causes hydrodeboronation of the boronic acid.[3,37,38] If there is no steric hindrance and a large enough excess of boronic acid is used then the efficiency of the coupling process will not be affected and high yields will result (*e.g.* in 2,3-difluoro-substituted phenylboronic acids such as **14**).[2,3] However, if either component is sterically hindered then the rate of coupling is reduced and the rate of hydrodeboronation becomes significant and will lead to low product yields (*e.g.* in 2,6-difluoro-substituted phenylboronic acids such as **21**). The use of triethylamine as base in anhydrous conditions,[32] whilst not providing as good yields as when aqueous sodium carbonate is used for normal systems, prevents hydrodeboronation and leads to acceptable product yields (compare the yields of compounds **23** and **26**).



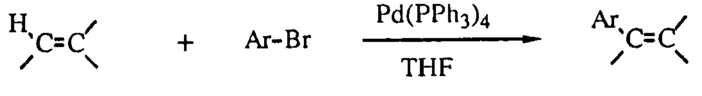
23, 10%
K 61.0 N 122.5 I



26, 56%
K 59.5 N 121.5 I

More recently, Suzuki[37,39] has developed an anhydrous cross-coupling procedure which utilises the esters of boronic acids with thallium(I) carbonate as base and provides excellent yields of cross-coupled products. Both Suzuki[40] and Snieckus[38] have also achieved excellent results using potassium phosphate (K_3PO_4) as the base in anhydrous conditions.

A useful palladium-catalysed cross-coupling reaction is the vinylation of organic halides[41] [commonly referred to as the 'Heck Reaction,' see (**6**)]. This is a convenient method for forming carbon-carbon bonds at unsubstituted vinylic positions as shown in the equation below. The organic halide employed is restricted to aryl, heterocyclic, benzylic or vinylic types



(6)

with a bromo- or an iodo-substituent (although it seems probable that aryl or vinyl triflates as used in other coupling processes would also couple).

Much work on the palladium-catalysed cross-coupling of organo-tin reagents with vinyl and aryl triflates has recently been reported by Stille.[17,18] This type of cross-coupling appears to be very versatile as alkyl, vinyl, alkynyl and aryl tin reagents are all reported to couple in the presence of lithium chloride (3 equiv.) and 2 mol% $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ in high yields under mild conditions. Both catalysts are reported to give good results and although shorter reaction times and/or milder conditions apply to the latter, the former enabled selectivity to be achieved where two different reactive sites existed. The presence of lithium chloride is essential for the formation of the arylpalladium chloride and this applies to all the other cross-coupling procedures involving triflates.

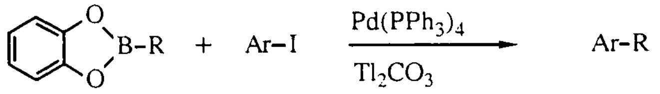
Although organometallic reagents of methyl, aryl, alkenyl, benzyl or alkynyl moieties have frequently been successfully used for cross-coupling, those involving alkyl groups containing β-hydrogen atom(s) have not always given satisfactory results due to β-elimination. The cross-coupling of secondary or tertiary alkyl reagents has also been found to be especially difficult because it is accompanied by isomerization of the alkyl group and/or the reduction of the halides. However, Hayashi *et al.*[42] (1984) reported the development of a catalyst capable of facilitating the cross-coupling of secondary and primary alkyl Grignard reagents and alkylzinc reagents with aryl or alkenyl halides. The catalyst for the process is dichloro[1,1′-*bis*(diphenylphosphino)ferrocene]palladium(II) [$PdCl_2$(dppf)] and is reported to produce the desired cross-coupled product in exceedingly high yield [see **(7)**]. The catalyst is thought to perform the reductive elimination process much faster than β-elimination because of a large P-Pd-P angle and a small Cl-Pd-Cl angle.

$$\text{R-MgBr} \quad + \quad \text{Ar-Br} \quad \xrightarrow[\text{THF}]{\text{PdCl}_2\text{(dppf)}} \quad \text{R-Ar} \qquad (7)$$

More recently Castle and Widdowson[43] have reported the cross-coupling of alkyl Grignard reagents with alkyl iodides [see **(8)**]. Good yields are made possible by pre-reducing the $PdCl_2$(dppf) catalyst using di-isobutylaluminium hydride (DIBAL) which enables a faster oxidative addition process (normally very slow for alkyl halides) and good yields are reported.

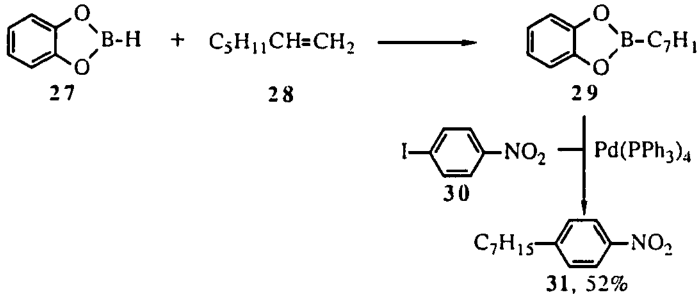
$$\text{R-MgBr} \quad + \quad \text{R}'\text{-I} \quad \xrightarrow[\text{THF}]{\substack{\text{PdCl}_2\text{(dppf)} \\ \text{DIBAL}}} \quad \text{R-R}' \qquad (8)$$

A recent method of coupling an alkyl chain to an aryl system is provided by the use of a 2-alkyl-1,3,2-benzodioxaborole[39,40] and a palladium catalyst [see **(9)**]. Although we have never found the need to use a direct alkyl to aryl coupling in our synthetic work (see below for our alternatives), we have investigated the possibility of using the recent 2-alkyl-1,3,2-benzodioxaborole coupling in the synthesis of liquid crystals. The preparation of

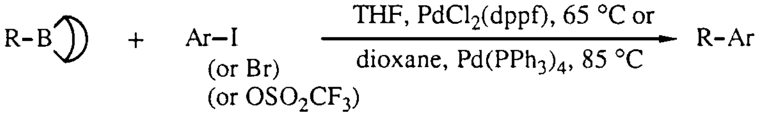


(9)

the alkyl-substituted boron compound (see **29**) involves the reaction of 1,3,2-benzodioxaborole (catechol borane) with an appropriate alkene either in a sealed tube at 100°C[44] or at room temperature in the presence of a rhodium catalyst.[45] The coupling procedure involves the use of an aryl iodide with thallium(I) carbonate under anhydrous conditions; the use of aryl bromides is possible but reactions are unreliable.

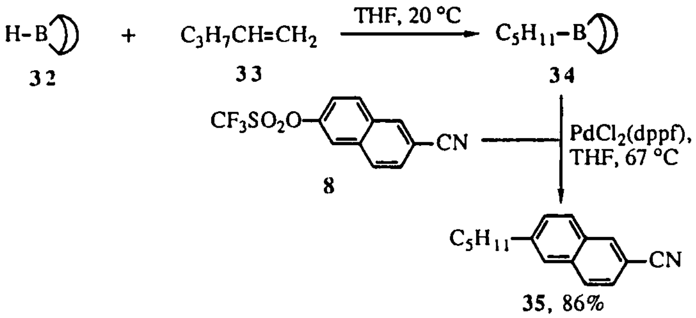


Another method of coupling alkyl chains to aryl iodides, bromides and triflates [see (**10**)] involves the use of 9-borabicyclo[3.3.1]nonane (9-BBN).[40] This method appears very promising, with near-quantitative yields quoted and where two leaving groups are present, an excellent degree of selectivity is reported. The alkyl boron species is easily prepared, *in situ*, at



(10)

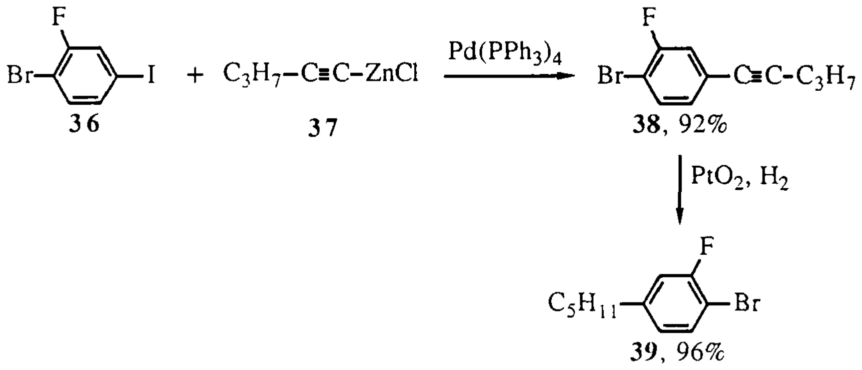
room temperature from 9-BBN and an appropriate terminal alkene in THF. Subsequently, the appropriate aryl iodide, bromide or triflate and catalyst is added and the mixture is heated at the appropriate temperature. In view of these interesting results, the method was used to prepare some compounds in excellent yield (*e.g.*, compound **35**) in one of our areas of work.



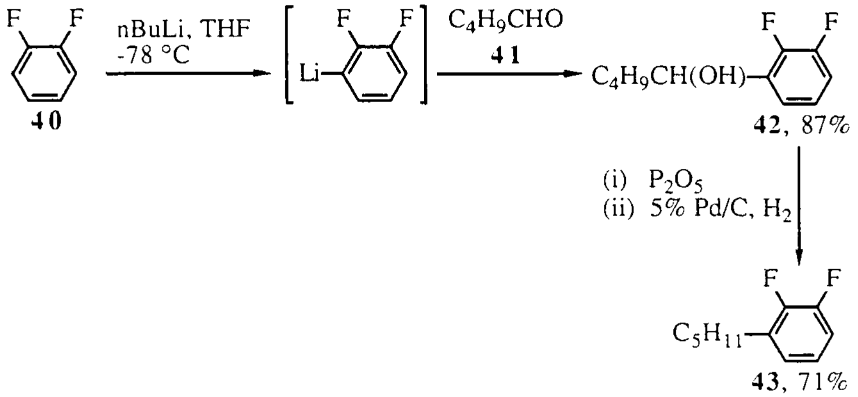
The 9-BBN method[40] of alkyl coupling to aryl systems has the advantage in that it can also be carried out on aryl bromides and triflates, whereas the catechol borane method[39] is, in our experience, effectively restricted to aryl iodides.

All of the above methods for the direct coupling of an alkyl chain to an aryl system proceed more easily or even exclusively with $PdCl_2(dppf)$ as the catalyst which is, however, less available and more expensive than $Pd(PPh_3)_4$ and those methods developed by Hayashi *et al.*[42] which involve simple alkyl Grignard reagents or alkylzinc reagents offer the advantage of great simplicity and are inexpensive. However, as mentioned previously, these methods have, as yet, not been necessary in our work on the preparation of liquid crystal compounds for the reasons given below.

We have successfully used two methods for introducing an alkyl-moiety into an aryl-system and they are relatively simple procedures, which are inexpensive and provide excellent yields. Firstly, where a leaving group is present, we use the alkynylzinc chloride coupling technique developed by King *et al.*[28] (see earlier, and **38**) followed by catalytic hydrogenation of the triple-bond moiety.[1,3]



Secondly, where a leaving group is not present but a lithium derivative can be formed, we treat the lithium derivative with the appropriate aldehyde (*e.g.*, **41**). Subsequent dehydration/catalytic hydrogenation provides the desired alkyl-substituted compound.



Both of these methods provide very high overall isolated yields and we find them to be preferable to the direct alkyl chain coupling procedures discussed above.

Our second method involves a dehydration step and both methods involve a hydrogenation stage. Therefore, if functional groups are present which are sensitive to dehydration or hydrogenation then neither of these methods would be suitable and in such cases, perhaps one of the direct alkyl coupling methods could be used advantageously.

TRIFLATES IN CROSS-COUPLING

The use of triflate derivatives in palladium-catalysed cross-coupling reactions is important in organic synthesis because they provide a means of forming a carbon-carbon bond at a phenolic or enolic site. In some areas of synthetic organic chemistry (*e.g.*, in the synthesis of natural products) appropriate halides may not be readily available but phenols and perhaps more importantly carbonyl compounds are often abundant.

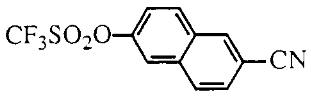
We have successfully prepared and used both aryl and vinyl triflate derivatives. Aryl triflates can be prepared by two methods and both produce high product yields. Both methods

$$\text{(a)}\quad \text{Ar-OH} + (CF_3SO_2)_2O \xrightarrow[0\text{ to }20\ ^\circ C]{\text{Pyridine}} \underset{90\%}{\text{Ar-OSO}_2CF_3}$$

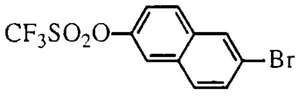
$$\text{(b)}\quad \text{Ar-OH} + (CF_3SO_2)_2NPh \xrightarrow[-78\text{ to }20\ ^\circ C]{CH_2Cl_2,\ Et_3N} \underset{90\%}{\text{Ar-OSO}_2CF_3}$$

are similar in ease of operation although method (**b**)[46] is preferable because *N*-phenyltriflamide is a crystalline solid and more easily handled than the triflic anhydride used in method (**a**).[17,18] However, method (**a**) has been most used by us for reasons of economy since triflic anhydride is much cheaper than *N*-phenyltriflamide.

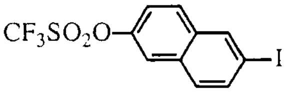
One aspect of our work on the synthesis of liquid crystal materials in which triflate couplings have been most useful involves 2,6-disubstituted naphthalene compounds.[3] The only readily available starting material with this substitution pattern is 6-bromo-2-naphthol. To use both sites to full effect, a triflate derivative is prepared to enable the synthesis of liquid crystal compounds by means of two (selective) palladium-catalysed cross-coupling procedures. Compounds **8, 44** and **45** were prepared in high yields by using method (**b**) and were easily purified by column chromatography. They were then used in palladium-catalysed cross-coupling



8, 98%
mp 93-94 °C



44, 98%
mp 52-53 °C



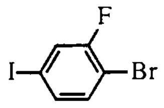
45, 99%
mp 65-66 °C

procedures in the same manner as aryl halides except that a three-fold excess of lithium chloride is added to the reaction mixture. In the case of compounds **44** and **45**, selective couplings were then possible (see Selectivity in Cross-coupling).

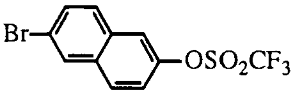
The synthesis of vinyl triflates is best carried out by treating the enolate anion (prepared by the action of LDA on the appropriate carbonyl compound) with *N*-phenyltriflamide in THF at −78°C.[47]

SELECTIVITY IN CROSS-COUPLING

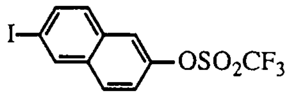
In the synthesis of long, lath-like molecules of general structure, it is essential to be able to perform cross-coupling reactions selectively at one site in a system and subsequently to be able to carry out a second (different) cross-coupling. This is most often accomplished by using aryl systems with two leaving groups chosen from iodo, bromo, chloro or trifluoromethanesulphonate (triflate). Some examples of the systems we have frequently used are shown below (compounds **36** and **44**–**52**).



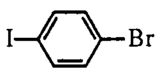
36



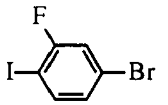
44



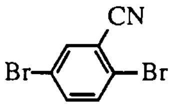
45



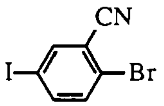
46



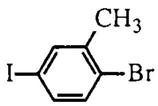
47



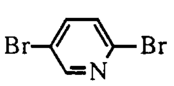
48



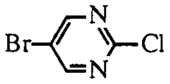
49



50



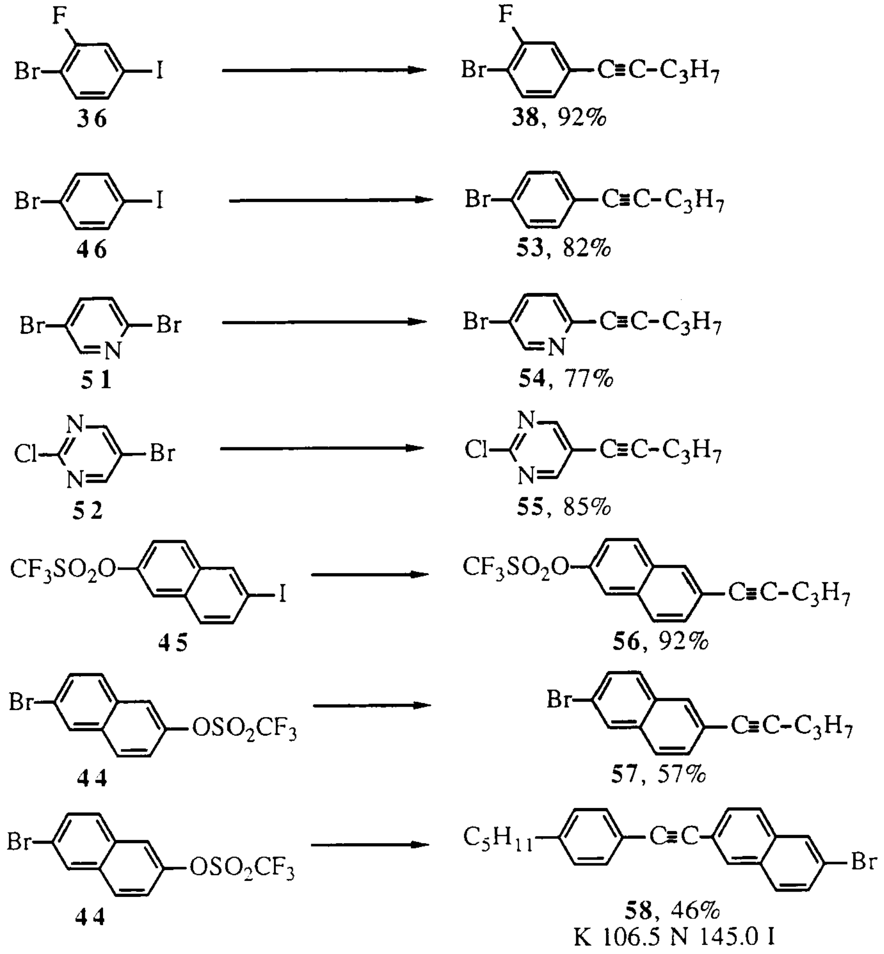
51



52

Selectivity in alkynylzinc chloride couplings is, in most cases, 100%. Such couplings occur at aryl iodide and activated aryl bromide sites at room temperature, whereas others (*e.g.* bromo-, and activated chloro-substituted aryls) require elevated temperatures. This means that selective alkynylzinc chloride couplings are very useful in the synthesis of valuable intermediates (*e.g.*, compounds **38** and **53**–**57**).

The site of reaction in the coupling procedure involving compound **45** was entirely as expected since the reaction was carried out at room temperature in the absence of lithium chloride (except, of course, for the lithium chloride formed in the reaction). However, the coupling procedure involving compound **44** had to be carried out at an elevated temperature and the use of glc analysis revealed the presence of starting material and two products (gc/ms reveals 75% reaction at the triflate site and 25% reaction at the bromo site) with no evidence for double coupled material. The two products were easily separated by column chromatography with compound **57** being isolated in 57% yield. The fact that the triflate site is preferred is surprising because when in different compounds aryl bromide systems seem to react more quickly than aryl triflate derivatives. Perhaps the bromo-substituent activates the triflate site or the triflate group deactivates the bromo site, or a combination of both effects, when the two substituents are present in the same molecule. The preparation of compound **58**, which is similar to the formation of compound **57**, involves the reaction of the zinc reagent of compound **3** with compound **44** and illustrates the use of a selective coupling to produce an easily isolated liquid crystal in 46% yield.



36 → **38**, 92%

46 → **53**, 82%

51 → **54**, 77%

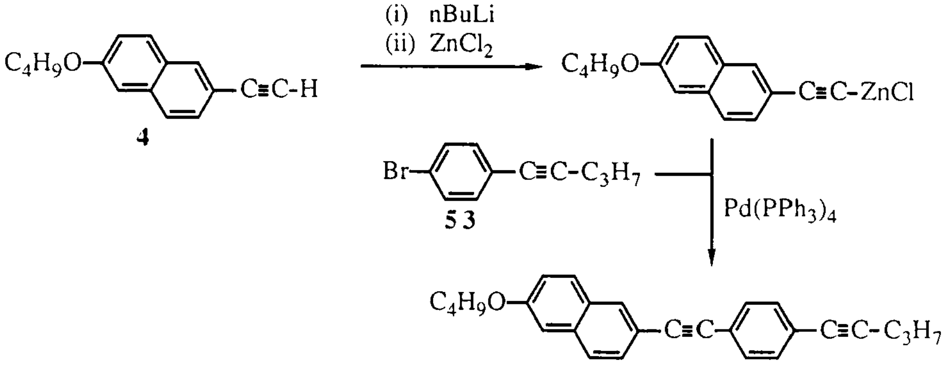
52 → **55**, 85%

45 → **56**, 92%

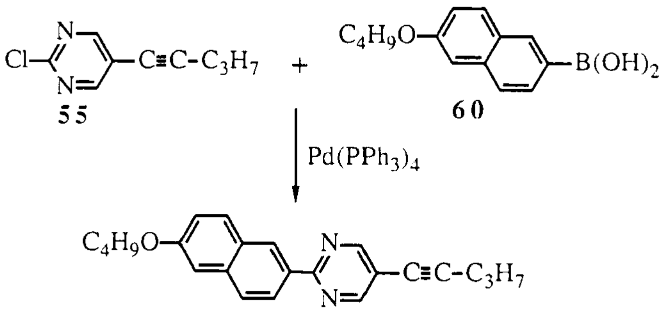
44 → **57**, 57%

44 → **58**, 46%
K 106.5 N 145.0 I

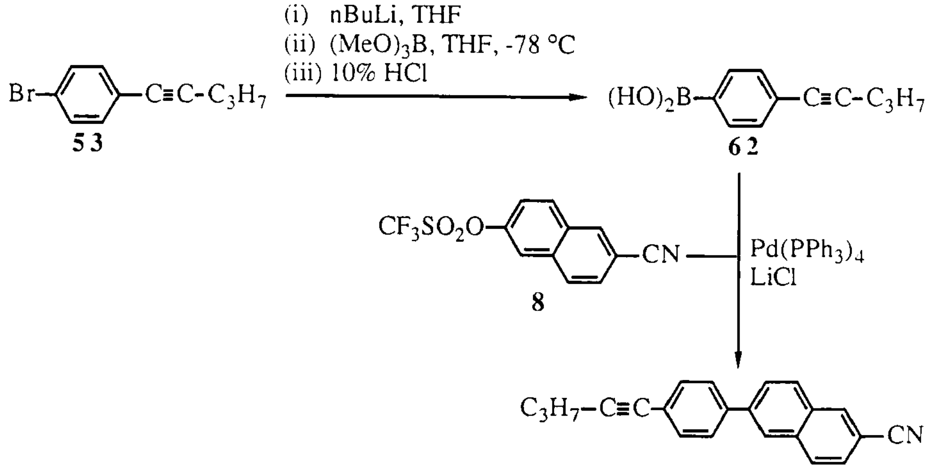
All the compounds shown above can undergo a further coupling with another alkyl- or aryl-substituted zinc chloride (*e.g.*, as in the synthesis of compound **59** from compound **53**) or with an arylboronic acid (*e.g.*, as in the synthesis of compound **61** from compound **55**). Some of the intermediates can, if desired, be converted into arylboronic acids and subsequently coupled to an aryl-substituted iodide, bromide, triflate or activated chloride (*e.g.*, as in the synthesis of compound **63** from compound **53**).



59, 77%
K 126.5 N 171.0 I

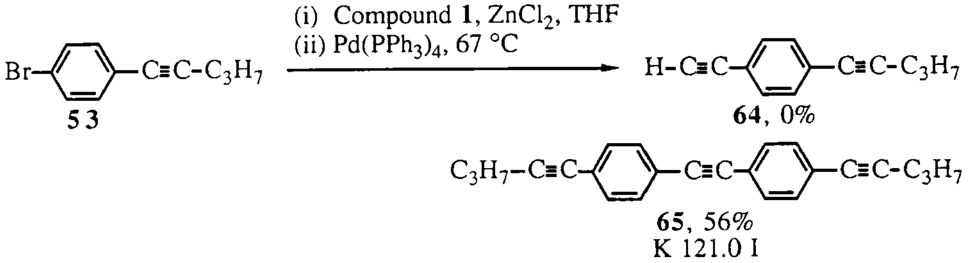


61, 74%
K 136.5 N 146.5 I



63, 74%
K 113.0 N 193.0 I

In an attempt to obtain compound **64** by using the lithium acetylide ethylenediamine complex (compound **1**) and the aryl bromide unit (compound **53**, which was prepared by a selective coupling reaction), the reaction mixture was heated under reflux. Compound **64** was not produced, but a good yield of compound **65** was obtained. This is because the terminal alkyne initially produced (compound **64**) is metallated by the zinc derivative of compound **1** and couples with the starting bromo-substituted system (compound **53**). The process must be very fast because no starting material or intermediate compound **64** is detected by glc analysis.

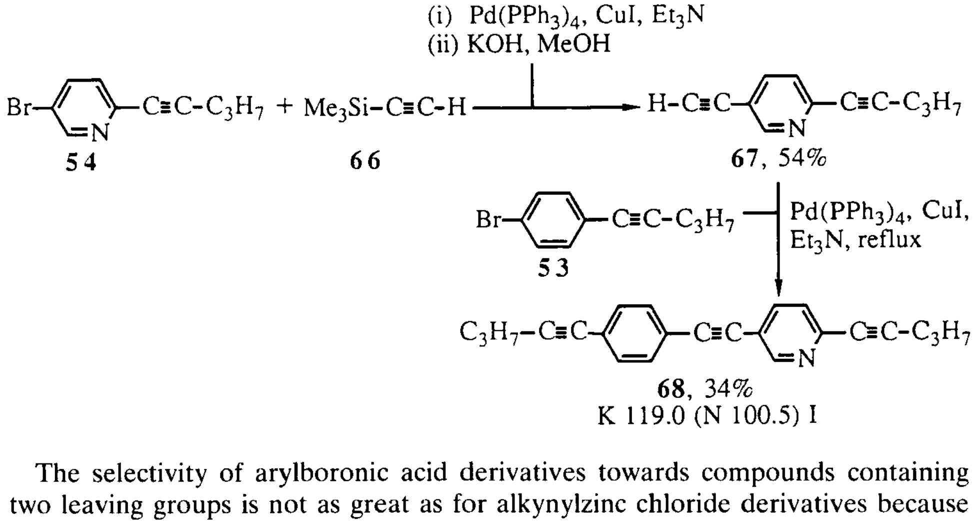


53

64, 0%

65, 56%
K 121.0 I

When compound **67**, of similar structure to compound **64**, was required a different approach was used starting with compound **54**. The use of trimethylsilylacetylene under the conditions of Sonogashira[30,32] led to compound **67** in good yield. Compound **67** has thus been obtained by two selective coupling procedures, and this compound is then coupled in a third procedure to compound **53**, itself being the product of a selective coupling, to give compound **68**.



54

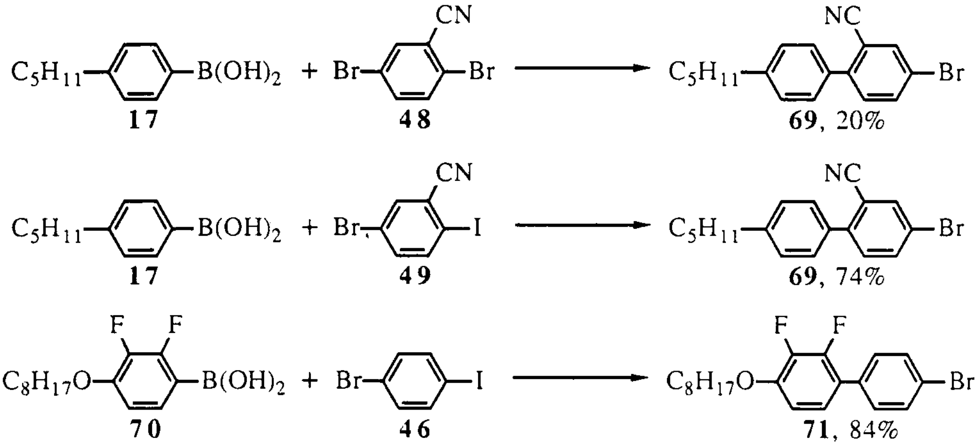
66

67, 54%

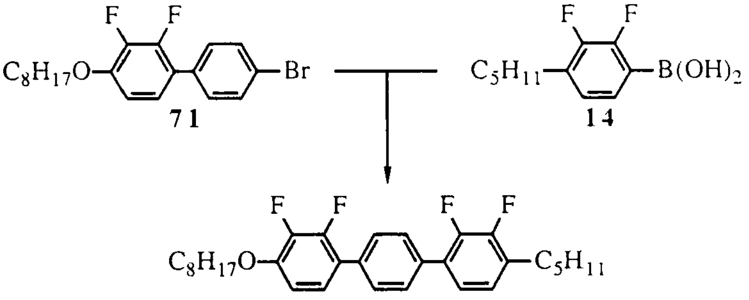
53

68, 34%
K 119.0 (N 100.5) I

The selectivity of arylboronic acid derivatives towards compounds containing two leaving groups is not as great as for alkynylzinc chloride derivatives because elevated temperatures are required for all leaving groups. However, by careful monitoring of the reaction by glc analysis, selectivity can be obtained with excellent isolated yields of the desired compounds. Compound **69** was first obtained from the known compound **48**[48] but here selectivity was not good. Three products, (both possible isomeric mono-coupled products and the terphenyl produced by double coupling) and the starting dibromo-substituted compound were present in the crude mixture. Careful purification by column chromatography was required to isolate compound **69** (the other components could not be isolated) and a low yield was obtained. The synthesis of compound **69**



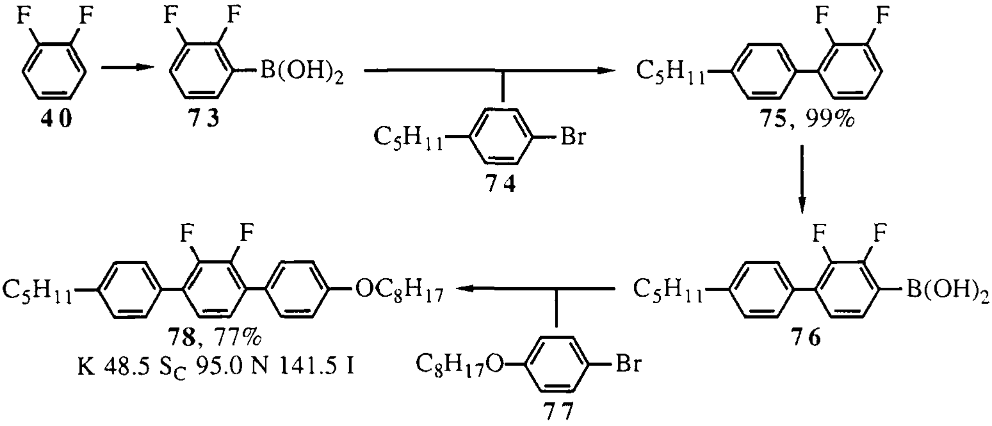
by a selective coupling on the bromo-iodo-substituted compound (**49**) enabled a high isolated yield to be obtained. A similar, high yield of compound **71** was obtained by a selective coupling of a difluoro-substituted phenylboronic acid with 1-bromo-4-iodobenzene (compound **46**).



72, 51%
K 111.5 N 120.5 I

The remaining leaving group of these compounds can be involved in another cross-coupling procedure (usually to another arylboronic acid since any coupling to an alkynylzinc chloride derivative would normally have been carried out first because of the better selectivity) to give an unsymmetrical product (*e.g.*, compound **72**).

An alternative to the use of selectivity in cross-coupling is shown by the preparation of compound **78**.[2] Compound **40** has two acidic protons (*ortho* to the fluoro-substituents) and they are both equivalent. This enables the boronic acid **73** to be prepared which was coupled to compound **74**, an aryl bromide (an aryl iodide, triflate or activated chloride could also have been used) to give compound **75**. The boronic acid of this compound was prepared and coupled to a different aryl bromide (compound **77**) to give an unsymmetrical product (compound **78**). This synthesis leading to compound **78** does not involve a selectivity issue since the position of coupling is unambiguous, but two coupling procedures have been used to provide an unsymmetrical product.



CONCLUSION

The use of palladium-catalysed cross-coupling reactions in the synthesis of liquid crystal materials has enabled compounds with more complex substitution patterns to be prepared which otherwise would not be obtainable. Even for compounds where an alternative synthetic route is available, synthesis by the use of a cross-coupling method can simplify the procedure and usually increases the product yields.

The use of selective couplings to synthesise liquid crystals is essential to obtain complete generality of the structure. Such selective couplings usually require the synthesis of an appropriate bromo-iodo-substituted, bromo-substituted triflate or iodo-substituted triflate derivatives.

The structure of liquid crystal materials has, traditionally, been quite simple and their synthesis, although not always straightforward, has been executed by a linear synthesis. There are very many, as yet unsynthesised, liquid crystal materials which, because of the development of metal-catalysed cross-coupling procedures, can now be produced. The future synthesis of liquid crystal materials can be much improved by incorporating the use of cross-coupling methods. Such compounds may well provide advanced materials with a whole range of exciting physical properties and perhaps lead to the development of new applications for liquid crystal materials.

Although this paper deals exclusively with low molar mass, calamitic liquid crystal compounds, the techniques can equally be used in the preparation of interesting discotic and polymeric liquid crystal materials.

The mechanisms of these cross-coupling reactions have not been discussed here but an excellent review by Poetsch[49] deals with mechanisms and gives further examples of liquid crystal synthesis.

Acknowledgments

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References

1. G. W. Gray, M. Hird, D. Lacey and K. J. Toyne, *Mol. Cryst. Liq. Cryst.*, **172**, 165 (1989).
2. G. W. Gray, M. Hird, D. Lacey and K. J. Toyne, *J. Chem. Soc., Perkin Trans. 2*, 2041 (1989).
3. M. Hird, Ph.D. Thesis, University of Hull, 1990.
4. G. W. Gray, M. Hird and K. J. Toyne, *Mol. Cryst. Liq. Cryst.*, in the press.
5. G. W. Gray, M. Hird and K. J. Toyne, *Mol. Cryst. Liq. Cryst.*, in the press.
6. R. J. P. Corriu and J. P. Masse, *J. Chem. Soc. Chem. Commun.*, 144 (1972).
7. K. Tamao, K. Sumitani and M. Kumada, *J. Am. Chem. Soc.*, **94**, 4374 (1972).
8. E. Negishi, A. O. King and N. Okukado, *J. Org. Chem.*, **42**, 1821 (1977).
9. A. O. King, N. Okukado and E. Negishi, *J. Chem. Soc., Chem. Commun.*, 683 (1977).
10. A. O. King and E. Negishi, *J. Org. Chem.*, **43**, 358 (1978).
11. E. Negishi, *Acc. Chem. Res.*, **15**, 340 (1982).
12. E. Negishi and S. Baba, *J. Chem. Soc., Chem. Commun.*, 596 (1976).
13. S. Baba and E. Negishi, *J. Am. Chem. Soc.*, **98**, 6729 (1976).
14. E. Negishi and D. E. Van Horn, *J. Am. Chem. Soc.*, **99**, 3168 (1977).
15. N. Okukado, D. E. Van Horn, W. L. Klima and E. Negishi, *Tetrahedron Lett.*, 1027 (1978).
16. M. Kosugi, K. Sasazawa, Y. Shimizu and T. Migala, *Chem. Lett.*, 301 (1977).
17. W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, **108**, 3033 (1986).
18. A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, **109**, 5478 (1987).
19. N. Miyaura, K. Yanmada and A. Suzuki, *Tetrahedron Lett.*, 3437 (1979).
20. N. Miyaura and A. Suzuki, *J. Chem. Soc., Chem. Commun.*, 866 (1979).
21. N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Commun.*, **11**, 513 (1981).
22. R. B. Miller and S. Dugar, *Organometallics*, **3**, 1261 (1984).
23. G. Fouquet and M. Schlosser, *Angew. Chem. Int. Ed. Engl.*, **13**, 82 (1974).
24. K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato and M. Kumada, *Bull. Chem. Soc. Jpn.*, **49**, 1958 (1976).
25. E. Negishi, A. O. King and N. Okukado, *J. Org. Chem.*, **42**, 1821 (1977).
26. U. Lauk, P. Skrabal and H. Zollinger, *Helv. Chim. Acta*, **64**, 1847 (1981).
27. U. Lauk, P. Skrabal and H. Zollinger, *Helv. Chim. Acta*, **66**, 1574 (1983).
28. A. O. King and E. Negishi, *J. Org. Chem.*, **43**, 358 (1978).
29. Q. Chen and Y. He, *Tetrahedron Lett.*, **28**, 2387 (1987).
30. K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, **50**, 4467 (1975).
31. J. W. Tilley and S. Zawoiski, *J. Org. Chem.*, **53**, 386 (1988).
32. W. J. Thompson and J. Gaudino, *J. Org. Chem.*, **49**, 5237 (1984).
33. J.-m. Fu, M. J. Sharp and V. Snieckus, *Tetrahedron Lett.*, **29**, 5459 (1988).
34. S. Gronowitz, A. B. Hornfeldt and Y. H. Yang, *Chemica Scripta*, **26**, 311 (1986).
35. A. Huth, I. Beetz and I. Schumann, *Tetrahedron*, **45**, 6679 (1989).
36. J.-m. Fu and V. Snieckus, *Tetrahedron Lett.*, **31**, 1665 (1990).
37. Y. Hoshino, N. Miyaura and A. Suzuki, *J. Chem. Soc. Jpn.*, **61**, 3008 (1988).
38. V. Snieckus, personal communication. We are very grateful to Professor Snieckus for helpful comments.
39. M. Sato, N. Miyaura and A. Suzuki, *Chem. Lett.*, 1405 (1989).
40. T. Oh-e, N. Miyaura and A. Suzuki, *Synlett*, 221 (1990).
41. R. F. Heck, *Org. React.*, **27**, 345 (1982).
42. T. Hayashi, M. Konishi, Y. Kobori, M. Kumada, T. Higuchi and K. Hirotsu, *J. Am. Chem. Soc.*, **106**, 158 (1984).
43. P. L. Castle and D. A. Widdowson, *Tetrahedron Lett.*, **27**, 6013 (1986).
44. H. C. Brown and S. K. Gupta, *J. Am. Chem. Soc.*, **93**, 1816 (1971).
45. D. Mannig and H. Noth, *Angew. Chem. Int. Ed. Engl.*, **24**, 878 (1985).
46. J. B. Hendrickson and R. Bergeron, *Tetrahedron Lett.*, **46**, 4607 (1973).
47. J. E. McMurray and W. J. Scott, *Tetrahedron Lett.*, **24**, 979 (1983).
48. D. E. Pearson, W. E. Stamper and B. R. Suthers, *J. Org. Chem.*, **28**, 3147 (1963).
49. E. Poetsch, *Kontakte* (Darmstadt), **2**, 15 (1988).