Organometallic Reagents For Catalytic Cross-Coupling

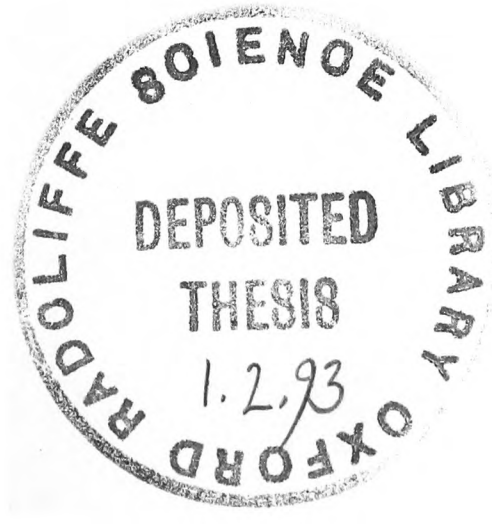
Thesis submitted in partial
fulfilment of the requirements for
the degree of Doctor of Philosophy

by

Mark Pearson

Merton College, Oxford

Michaelmas 1992



To Fiona,

who makes everything worthwhile.

Is this the real life-
Is this just fantasy-
Caught in a land slide-
No escape from reality-
Open your eyes
Look up to the skies and see-
I'm just a poor boy, I need no sympathy-
Because I'm easy come, easy go
A little high, little low,
Anyway the wind blows, doesn't really matter to me,
-to me-,

Freddie Mercury (1946 - 1991)

ASLIB ABSTRACT

Organometallic Reagents for Catalytic Cross-Coupling

M. Pearson Merton College D. Phil. Michaelmas 1992

Phosphine complexes of nickel and palladium provide the best catalysts for the homogeneous catalysed carbon-carbon bond forming reaction between an organometallic nucleophile and an organic electrophile. Use of a homochiral ligand on the catalyst can lead to stereoselectivity in the cross-coupling reaction, with high ee's of coupled product being obtained. The processes of selectivity in the transmetalation step of the catalytic cycle have not been elucidated and the initial aim of the project was to study these processes.

Initial experiments using organotin derivatives as the organometallic nucleophile highlighted the problems of selectivity and the forcing conditions needed in the attempted transfer of a benzyl group from the tin to the palladium catalyst. The compounds [8-(dimethylamino)-1-naphthyl]methyldiphenyltin (**60**) and [2-((dimethylamino)methyl) phenyl]methyldiphenyltin (**70**) were prepared and their reactivity in the palladium catalysed cross-coupling with 2-furoyl chloride, to give 2-benzoylfuran, was investigated. These molecules were found to undergo facilitated transfer of a phenyl group compared to transfer from control molecules. The effect was tested and attributed to the internal nucleophilic attack at the tin atom by the lone pair on the nitrogen atom. The compound [2-((dimethylamino)methyl)-3-trimethylsilylphenyl]methyldiphenyltin (**79**) was prepared to test the effects of steric buttressing within the molecule, but was found to be of the same order of magnitude of reactivity as (**60**) and (**70**). All three molecules showed a reactivity of at least an order of magnitude greater than control compounds. The effect did not prove applicable to the transfer of a benzyl group or in other coupling reactions. The effect of palladium ligation was tested and the ligand triphenyl arsine found to increase the rate of the coupling reaction. The two facilitating processes were found to work in a co-operative fashion, giving a rate enhancement of *ca.* one hundredfold over control reactions.

The nickel catalysed cross-coupling of α-substituted sp^3 hybridised Grignard reagents with allylic esters was attempted, but proved unsuccessful. Stoichiometric reactions with nickel complexes were also found to be unsatisfactory in yielding coupled products.

The synthesis of α-substituted diorganozinc reagents was attempted, but furnished only homocoupled products. The reaction of dibenzylzinc with aldehydes was found to proceed in the absence of catalyst, highlighting the reactivity of a benzylzinc moiety.

ACKNOWLEDGEMENTS

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A debt of gratitude goes to all the staff of the DP for providing a back-up service second to none, in particular Mrs Elizabeth McGuinness and Miss Tina Jackson for all their help with the ^{119}Sn NMR spectroscopy.

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I am forever grateful to my parents who have given me endless support, encouragement and love during my studies.

Finally I would like to express my heartfelt love and thanks to Fiona for all her support, for the long distances she was prepared to travel, for looking after me so well, for helping me through the rough patches and most of all for loving me.

ABBREVIATIONS

Me	Methyl
Et	Ethyl
Pr	Propyl
Bu	Butyl
Ph	Phenyl
Ac	Acetyl
Ar	Aryl
Tf	Triflate
TMEDA	N, N, N', N'-Tetramethylethylenediamine
DAIB	3-*exo*-(Dimethylamino)isoborneol
AIBN	Azobisisobutyronitrile
9-BBN	9-Borabicyclo[3.3.1]nonane
COD	Cyclooctadiene
COT	Cyclooctatetraene
X	Halide
cat	Catalyst
L	Ligand
acac	Acetylacetone
dppe	1, 2-bis(Diphenylphosphino)ethane
dppf	1, 1'-bis(Diphenylphosphino)ferrocene
DIOP	2, 3-Diisopropylidene-2, 3-dihydroxy-1, 4-bis(diphenylphosphino)butane
Chiraphos	2, 3-bis(Diphenylphosphino)butane
dba	Dibenzylideneacetone
BINAP	2, 2'-bis(Diphenylphosphino)-1, 1'-binaphthyl
Cp	Cyclopentadienide
thf	Tetrahydrofuran
DMF	Dimethylformamide
HMPA	Hexamethylphosphoramide
DMSO	Dimethylsulphoxide
RT	Room Temperature
ee	Enantiomeric Excess
*	Chiral Centre
n	normal
sec	secondary

i	iso
t	tertiary
min	Minutes
h	Hour(s)
d	Day(s)
NMR	Nuclear Magnetic Resonance
ppm	parts per million
J	Coupling Constant
GCMS	Gas Chromatography-Mass Spectrum
tlc	Thin Layer Chromatography
equiv.	Equivalent(s)
Temp	Temperature
m.p.	Melting Point

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INTRODUCTION

"I don't want to achieve immortality through my work....I want to achieve it by not dying"

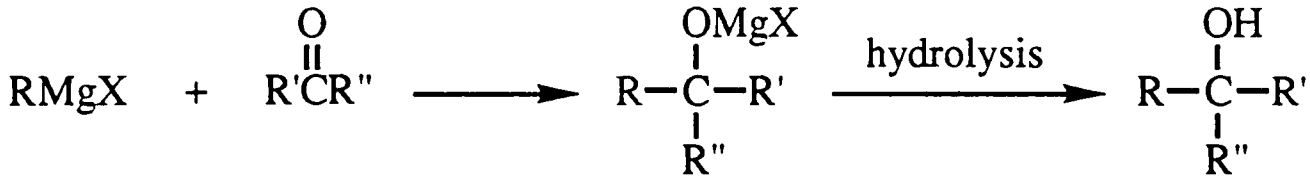
Woody Allen (1935 -)

CHAPTER 1. INTRODUCTION

1.1. Reactivity of Organometallic Reagents

The formation of new carbon-carbon bonds is one of the most critical operations in organic synthesis. The addition of organometallic reagents to organic electrophiles, such as carbonyl compounds, is one of the most important, and oldest, methods of forming such bonds. The reactivity of different organometallic compounds varies with the metal involved, and so the choice of reagent is very important. This will depend on the transformation being performed, as well as other functionalities within the molecule.

One of the earliest examples of this methodology involves the addition of alkyl groups to aldehydes and ketones to give alcohols. This was first attempted using organozinc derivatives,[1] but the method had the disadvantages of low yield and only limited applicability. Barbier improved the procedure by using the more reactive magnesium instead of zinc.[2] Grignard was able to isolate the organomagnesium derivatives, RMgX, and use of these further improved the reaction[3] into a very general method for carbon-carbon bond formation,[4] Scheme 1.



R = alkyl, aryl; R' = alkyl, aryl; R" = H, alkyl, aryl

Scheme 1

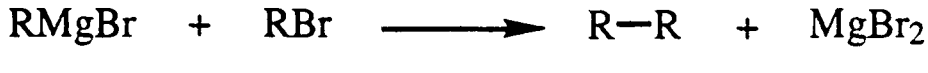
The precise mechanism of the addition is not known, and has been the subject of much speculation over the years.[5] Two extreme proposals have been put forward; a polar heterolytic reaction and a single electron transfer (SET) mechanism. Which one of these

dominates depends on the reagents, solvents, concentrations and other factors which affect the position of the Schlenk equilibrium, Scheme 2.



Scheme 2

The preparation of Grignard reagents from an organic halide and magnesium was found to be accompanied by the formation of Wurtz coupling products, and this was suggested[6] to be due to the side reaction of the Grignard reagent with the halide, Scheme 3.

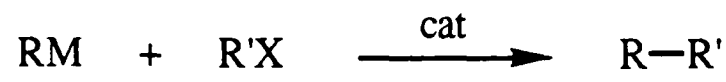


Scheme 3

However, attempts to use this reaction synthetically met with only limited success[4] due to the Grignard reagent being unreactive, only reacting very slowly or undergoing a variety of side reactions, e.g. deprotonation of the halide leading to alkenes or carbenes, metal-halogen exchange leading to a mixture of coupled products or electron transfer processes leading to products derived from radicals. In general, Grignard reagents will only react with active halides (allylic or benzylic), but even these are susceptible to the side reactions mentioned above. Organopotassium and sodium compounds are more reactive than Grignard reagents[7] and couple with less reactive halides in good yields, but present problems in making and keeping them long enough for the halide to be added.

1.2. Catalytic Cross-Coupling Reactions

The coupling of an organometallic reagent (RM) with alkyl or aryl halides (R'X) to give cross-coupled products (R-R') is a very important synthetic reaction. The reaction can be effected in various ways, but one of the best is the use of a transition metal salt or complex catalyst, Scheme 4.

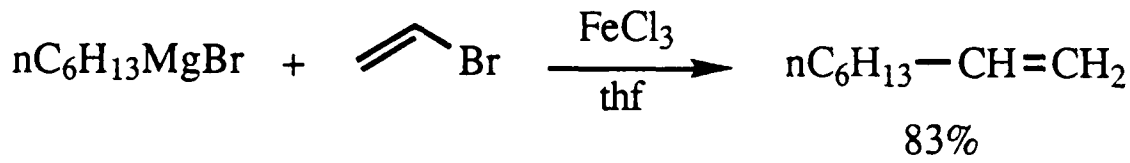


Scheme 4

The catalyst allows a smooth transformation to occur, and so reactions which were not feasible in the absence of catalyst, e.g. the reaction between a Grignard reagent and an unactivated halide, become accessible. Transition metal complexes are able to promote a wide range of coupling reactions for a variety of organometallic reagents, some of which will be discussed below.

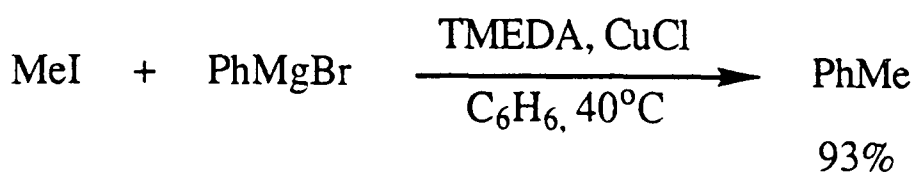
1.2.1. Organomagnesium Derivatives

It has been known for over 50 years that certain transition metal salts (the halides of Fe, Ni, Co) catalyse the cross-coupling between organic halides and Grignard reagents.[8] In 1971 Kochi described the reaction of vinyl bromides with Grignard reagents by use of a soluble, homogeneous iron catalyst[9] to give coupled products in yields of up to 83%, Scheme 5. Since then further reactions catalysed by iron complexes have been reported.[10]



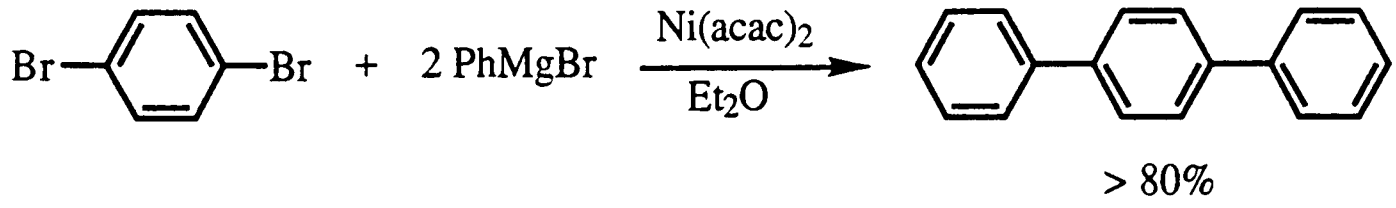
Scheme 5

Copper salts were initially used to catalyse conjugate additions of Grignard reagents[11] but were later developed for cross-coupling with aryl halides,[12] Scheme 6.

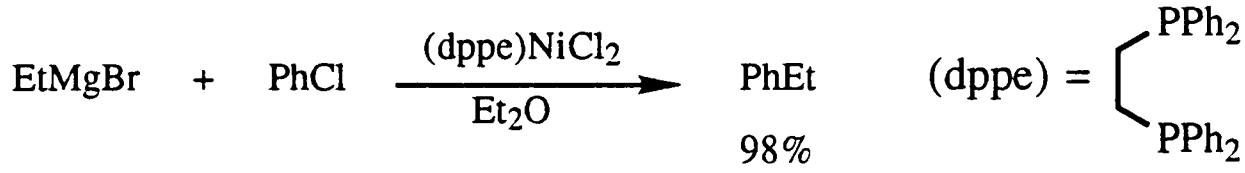


Scheme 6

In 1972 two groups simultaneously reported methods using nickel complexes; Corriu and Masse[13] used $Ni(acac)_2$ to obtain triphenyls, as shown in Scheme 7, and Kumada and co-workers[14] used a range of nickel-phosphine complexes to achieve excellent yields of coupled products, Scheme 8.

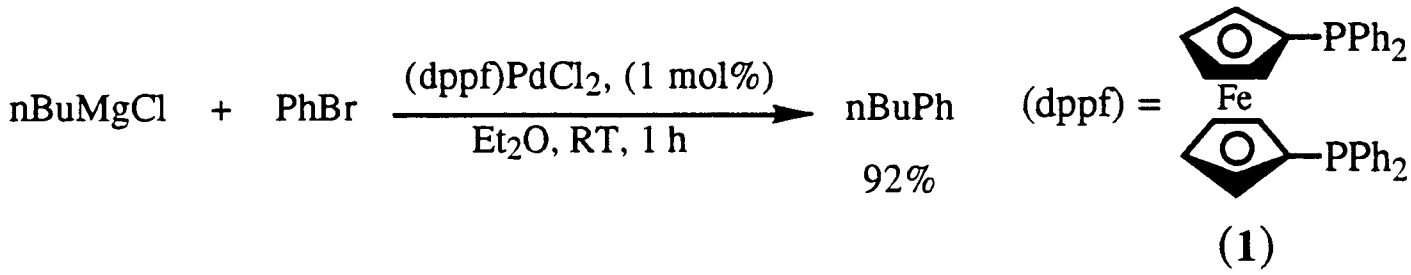


Scheme 7



Scheme 8

Palladium-phosphine catalysts have also been used with great success, especially those with bidentate, chelating phosphines. The (1,1'-diphenylphosphinoferrocene) (dppf) (**1**) ligand of Hayashi,[15] for example, has achieved excellent results, Scheme 9.



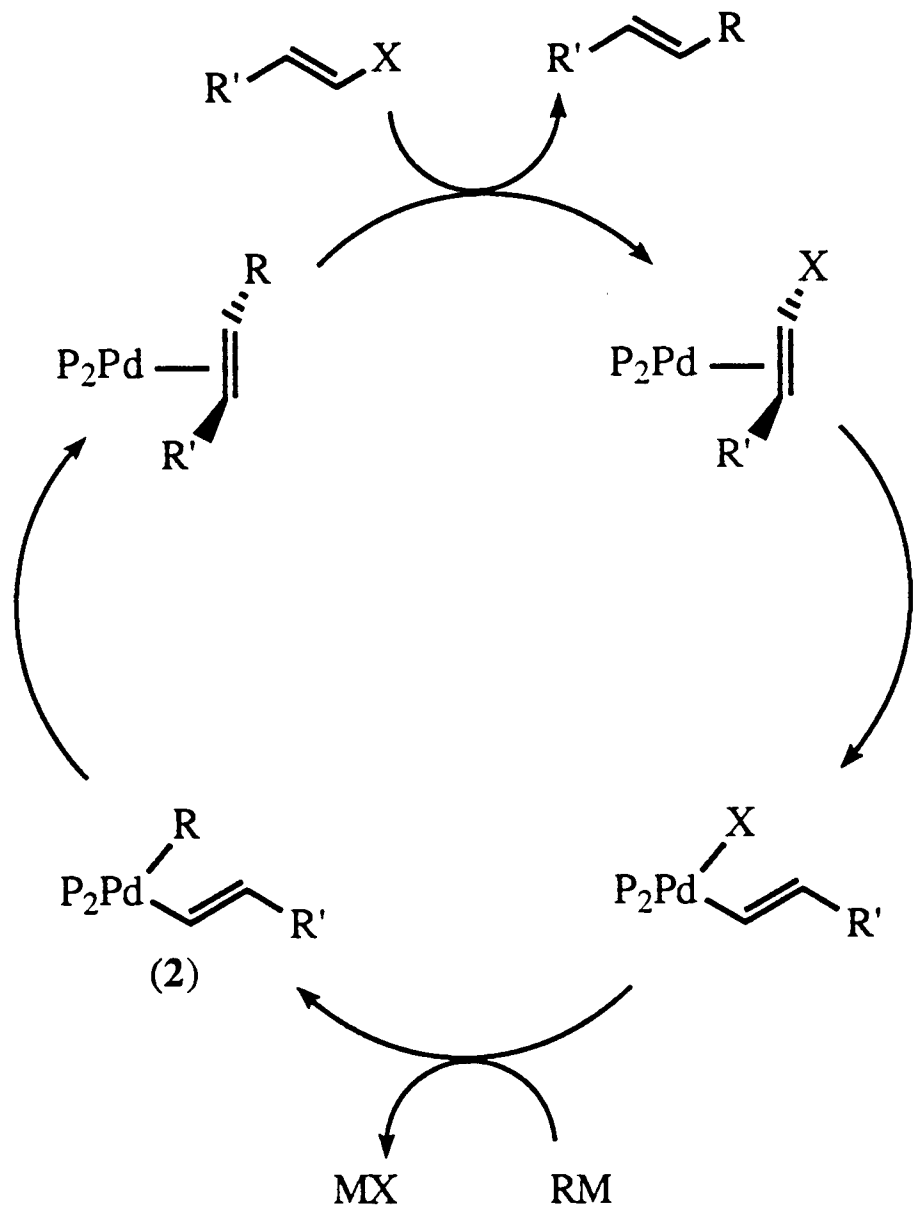
Scheme 9

The differences between Ni and Pd complexes are often small, but sometimes one does have an advantage over the other. Ni complexes are generally cheaper and can have a higher reactivity to organic halides. Pd complexes often give higher yields of coupled products, especially when olefinic or acetylinic substrates are used, as Ni catalysts can lead to di- and oligomerisation. Pd catalysts are generally more compatible with a wide range of organometallic nucleophiles (RM) and also give a better stereoselectivity in many reactions.

The third member of the triad, platinum, is usually not suitable for catalysing coupling reactions, due to the kinetic and thermodynamic stability of Pt (II) species. Catalytic coupling, however, has been reported,[16] with (dppf) (**1**) being the ligand on Pt. *Ab*

initio energy calculations reveal the pronounced difference in thermal lability is due to the change in electronic configuration of the metal during reductive elimination. The change from s^1d^9 to d^{10} is much more favourable for Pd than Pt, thus Pd undergoes reductive elimination much more easily.[17]

The mechanism of the catalysed coupling has been investigated[18] and a proposed catalytic cycle, involving sequential oxidative addition - transmetalation - reductive elimination, is shown in Scheme 10.

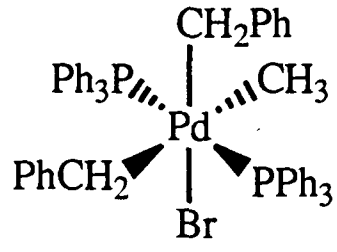


Scheme 10

If the R group in (**2**) has a β-hydrogen atom, then β-elimination is possible. This would lead to a mixture of products, containing reduced halide and isomers of the coupled product. Decomplexation of monodentate ligands (e.g. PPh_3) may promote β-elimination, but bidentate phosphines are known to stabilise the alkyl-metal moiety against this. The

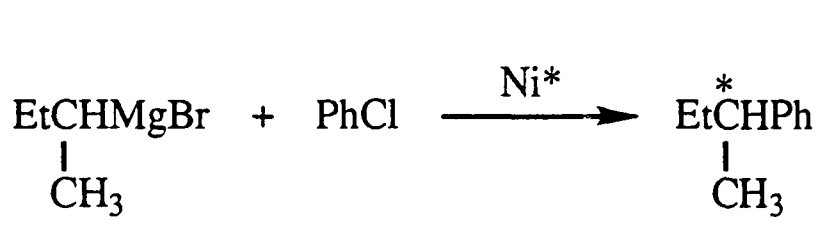
(dppf)$PdCl_2$ complex is thus capable of making the reductive elimination of coupled product much faster than β-elimination, so explaining the high yields observed.

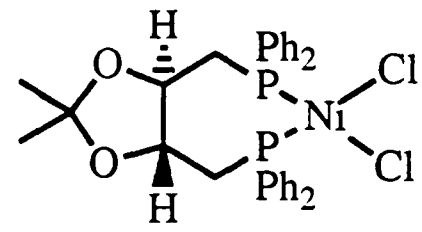
The involvement of higher valencies of Pd in the mechanisms of some coupling reactions has been proposed.[19] Hexacoordinate Pt(IV) species have been isolated and been shown to undergo reductive elimination of coupled products.[20] Analogous Pd(IV) species, such as (**3**), have been postulated to be involved in the catalytic cycle, but not actually observed.



(**3**)

In 1973 Consiglio and Botteghi[21] used the chiral catalyst (-)-(DIOP)$NiCl_2$ (**4**) to achieve the stereoselective coupling of secondary Grignards with unsaturated halides to give products with an enantiomeric excess (ee) of 17%, Scheme 11.





(-) - (DIOP)$NiCl_2$

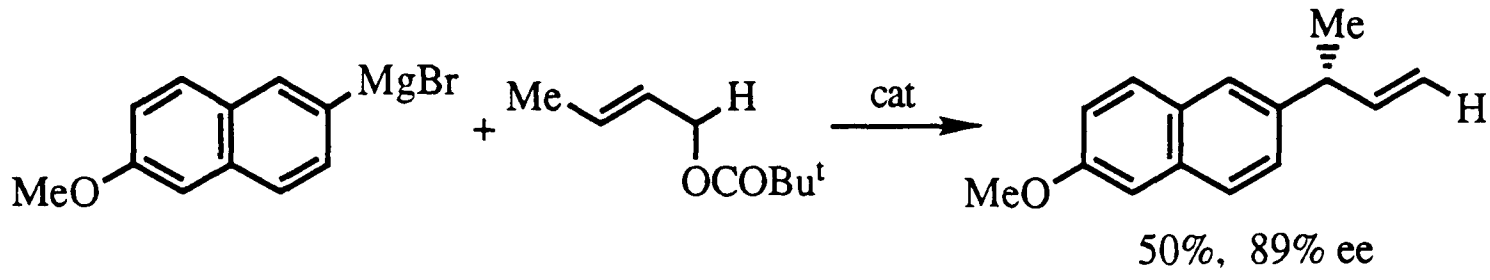
(**4**)

Scheme 11

The chirality in the backbone of the ligand causes the stereoselectivity in the reaction. Asymmetric synthesis using chiral catalysts of both nickel and palladium has since advanced to a stage where ee's of up to 95% are readily achievable.[22]

The catalytic cross-coupling of Grignard reagents with organic halides catalysed by Ni and Pd complexes has received much attention over the past 20 years. It has developed into an extremely useful method for the formation of carbon-carbon bonds,[23] and the methodology is used in the synthesis of natural products and biologically active molecules.[24]

Coupling with other organic electrophiles has also been reported, for example between aryl Grignard reagents and allylic esters,[25] Scheme 12. The chiral catalyst $NiCl_2$ [(-)-(2S, 3S)-2,3-bis(diphenylphosphino)butane] was used to induce ee's in the product 3-aryl-1-butene derivatives (**5**) of up to 89%.

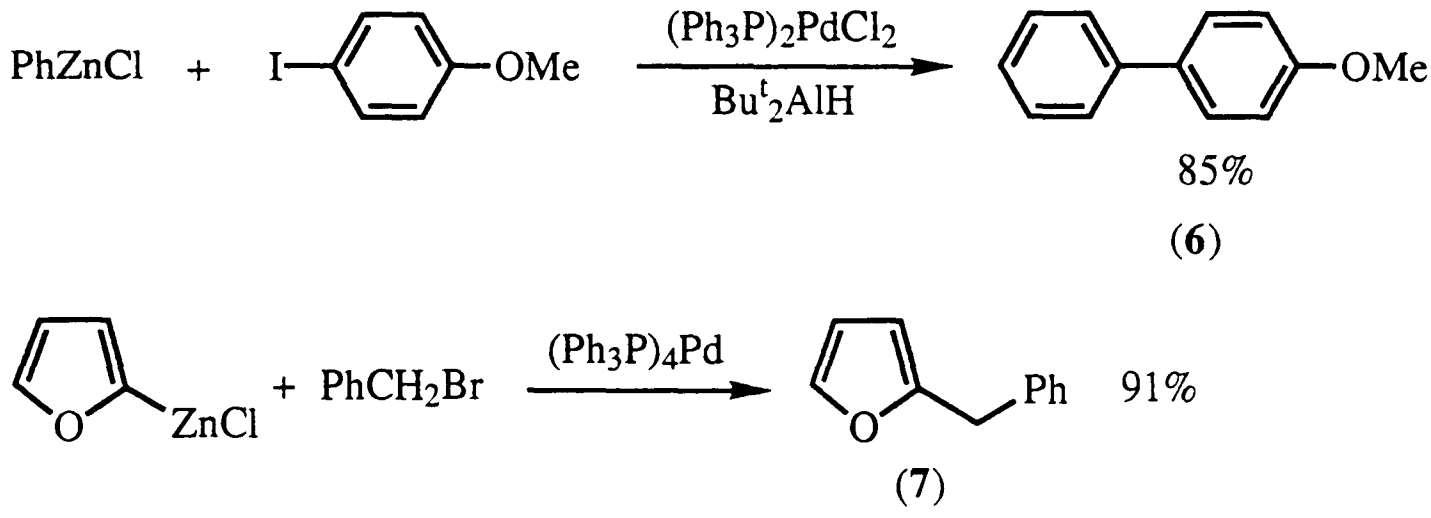


Scheme 12

1.2.2. Organozinc Derivatives

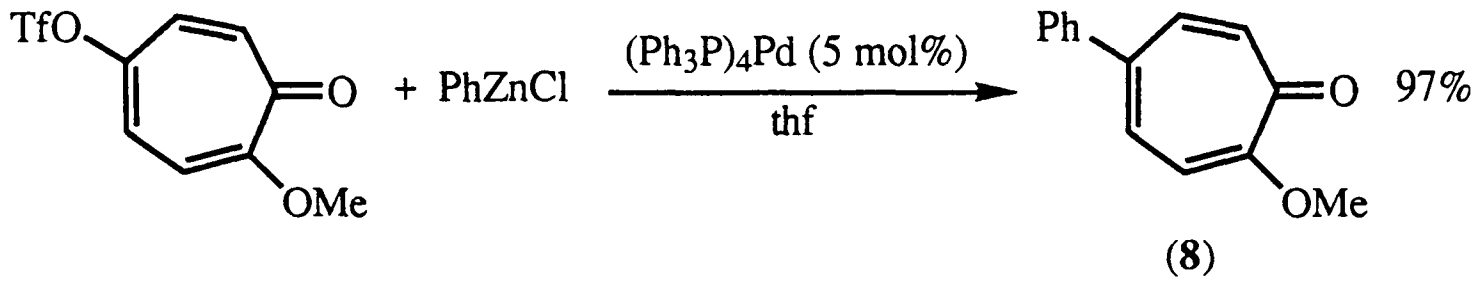
1.2.2.1. Catalytic Cross-Coupling

Organozinc derivatives have been widely used in catalytic cross-coupling reactions.[23a,b] Phenylzinc chloride reacts readily with iodobenzenes in the presence of a Pd(0) catalyst to give unsymmetrical biphenyls such as 4-methoxybiphenyl (**6**)[26] and 2-furylzinc chloride will couple with benzyl bromide to give 2-benzylfuran (**7**),[27] Scheme 13.



Scheme 13

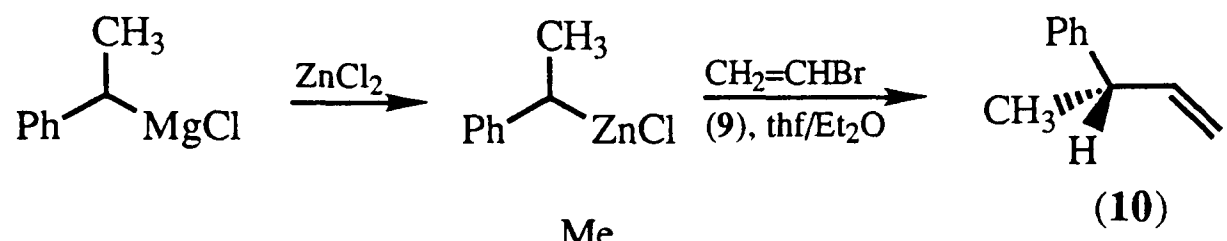
The reaction has been extended[28] and includes the use of electrophiles other than organohalides, such as triflates, as in the synthesis of the biologically active 5-phenyltropone (**8**),[29] Scheme 14.



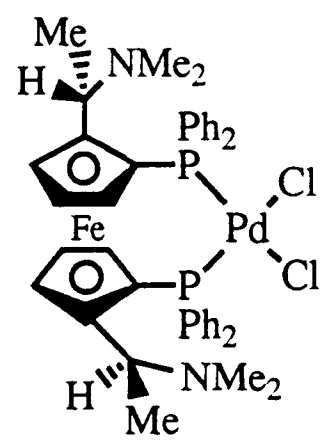
(**8**)

Scheme 14

Asymmetric cross-coupling has been achieved by the use of the chiral Pd complex (**9**), to give 3-phenyl-1-butene (**10**) in 93% ee,[30] Scheme 15.



(**10**)



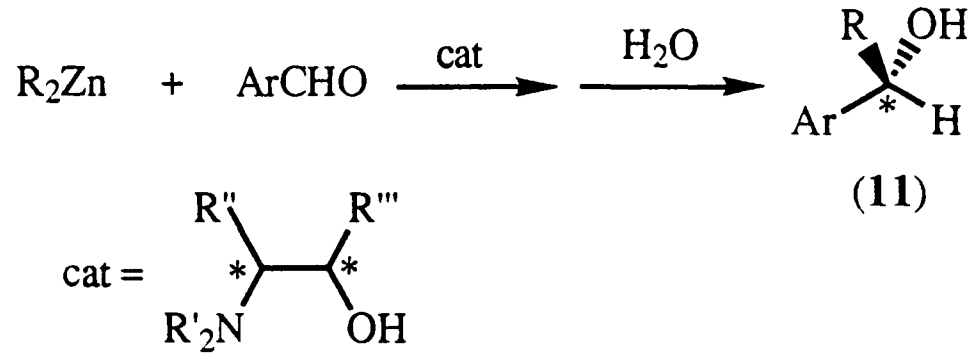
(**9**)

Scheme 15

1.2.2.2. Addition to Aldehydes

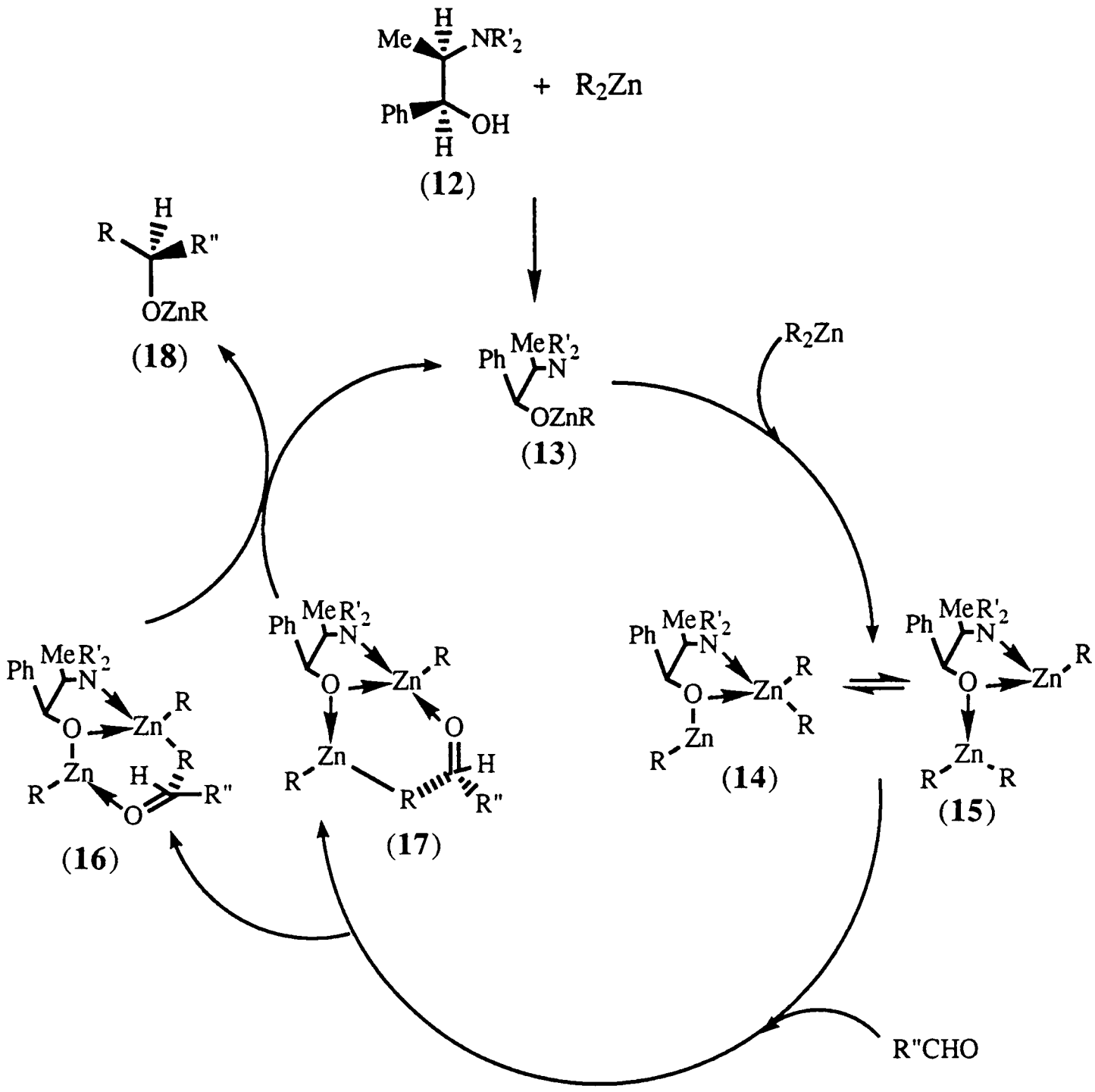
Monomeric dialkylzinc compounds, R_2Zn, have a linear geometry and are inert to simple carbonyl compounds, except at elevated temperatures, because of the nonpolar nature of the alkyl-metal bond. The discovery that the reaction can be accelerated by a catalytic amount of chiral amino alcohol[31] to produce secondary alcohols (**11**), Scheme 16, has since

stimulated much interest,[32,33] with ee's of 100% being achieved. Addition of a stoichiometric quantity of amino alcohol fails to promote the addition reaction.



Scheme 16

Norephedrine derivatives have proved very successful as catalysts and studies into the mechanism have lead to the proposal of a catalytic cycle for the reaction,[34] Scheme 17. The dialkylzinc and norephedrine catalyst (**12**) react to form the alkylzinc monoalkoxide (**13**). This reacts with the dialkylzinc to give a complex which is either (**14**) or (**15**). The nucleophilicity of the alkyl group is increased by coordination of O or N from the catalyst. It is believed that it is the alkyl group of the dialkylzinc and not that of (**13**) which adds to the aldehyde. This is supported by experiments involving polymer bound catalysts.[35] The aldehyde is attacked at the *si* face *via* a six centre transition state (**16**) or (**17**) to afford the chiral alkylzinc alkoxide (**18**) which leads to the product alcohol.

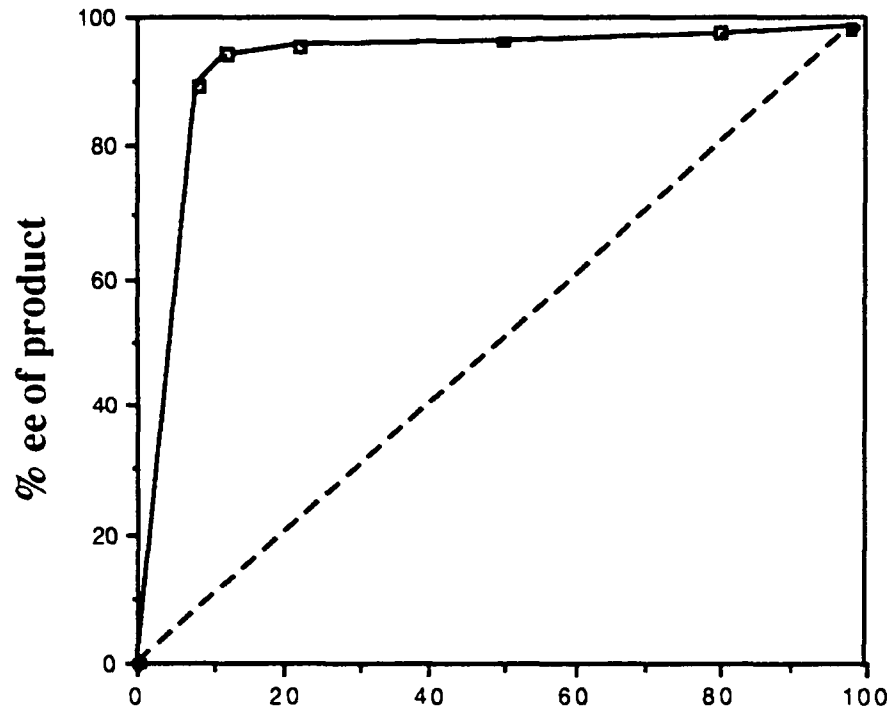


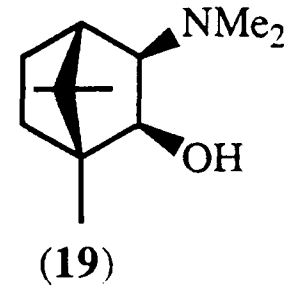
Scheme 17

Noyori has found that use of the catalyst (-)-3-*exo*-(dimethylamino)isoborneol [(-)-DAIB] (**19**) leads to a far from linear relationship between ee values of the chiral auxiliaries and the alcoholic products,[36] Figure 1. The reaction with the amino alcohol in a low ee leads to alkylation products which are very close to those obtained with the enantiomerically pure auxiliary.

This chiral amplification has been explained by the formation of diastereomeric dimers of (**20**), Scheme 18. The homochiral dimers (2S, 2'S) and (2R, 2'R)-(**20**) can be converted to the *meso* heterodimer (2S, 2'R)-(**20**). This *meso* dimer is much more stable than the homochiral dimers and does not lead to alkylation products. The two are

interconverted *via* the monomers (**21**). If an unequal mixture of enantiomers of the chiral auxiliary is used then all of the minor enantiomer goes into forming the stable *meso* dimer, with an equal amount of the major enantiomer. The remainder of the major enantiomer is then free to form a homochiral dimer, (2S, 2'S)-(**20**) or (2R, 2'R)-(**20**), which ultimately leads to product. Hence, even with a small starting ee in the chiral auxiliary pure homochiral dimers are formed which enable high ee's to be achieved in the product.

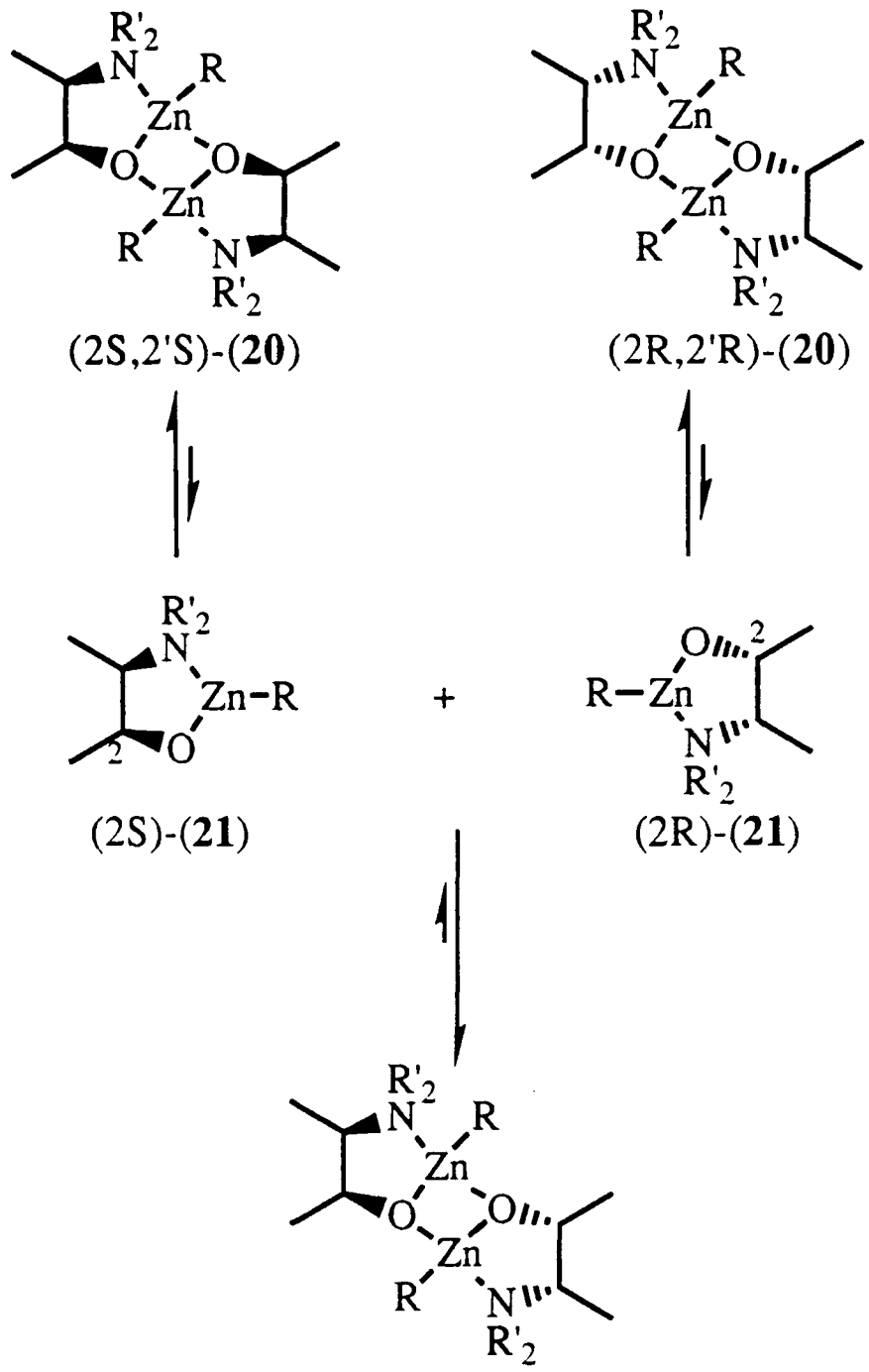




(**19**)

Figure 1: Ee of Adduct as a Function of ee of Chiral Auxiliary

While amino alcohols remain the most widely used chiral auxiliaries for the reaction a number of other systems have been found to be effective, especially complexes of titanium.[37,38,39]



Scheme 18

1.2.3. Organotin Derivatives

1.2.3.1. General Considerations

In general, organotin derivatives are less used as nucleophilic reagents than Grignard reagents due to their lower reactivity. This is easily overcome, however, by transition metal catalysts, especially palladium complexes. Organotin compounds are readily available, stable to air and moisture, thermally stable and compatible with a wide variety of functional groups (e.g. CO_2R, CN, NO_2, OH and CHO), thereby eliminating the need for

protection/deprotection strategies. It is therefore of considerable interest to employ them in organic synthesis.

In the Pd catalysed coupling of organic electrophiles with organotin reagents, known as the Stille reaction, Scheme 19, essentially only one of the groups from the organostannane (**22**) enters into the coupling reaction, a second group being transferred from (**23**) about 100 times slower.[40]

$$RX + \underset{(22)}{R'SnR''_3} \xrightarrow{[PdL_n]} R{-}R' + \underset{(23)}{XSnR''_3}$$

Scheme 19

Thus with a stoichiometric amount of organostannane only one group is transferred. This is not a problem if a relatively simple organic group, e.g. methyl, is to be transferred, since tetramethyltin can be used. If, however, the group is more expensive or difficult to synthesise then the utilisation of only one of four identical groups would be a distinct disadvantage. Fortunately different groups are transferred with different selectivities from tin, the simple alkyl groups having the slowest transfer rate.[41] The order of transfer is given in Figure 2. Thus by using a trimethyl or tributylorganotin reagent the group other than the methyl or butyl groups should transfer exclusively.

$$RC{\equiv}C > RCH{=}CH > Aryl > RCH{=}CH\text{-}CH_2 = ArylCH_2 > alkyl, Me$$

Figure 2: Order of Transfer of Organic Groups from Organostannanes

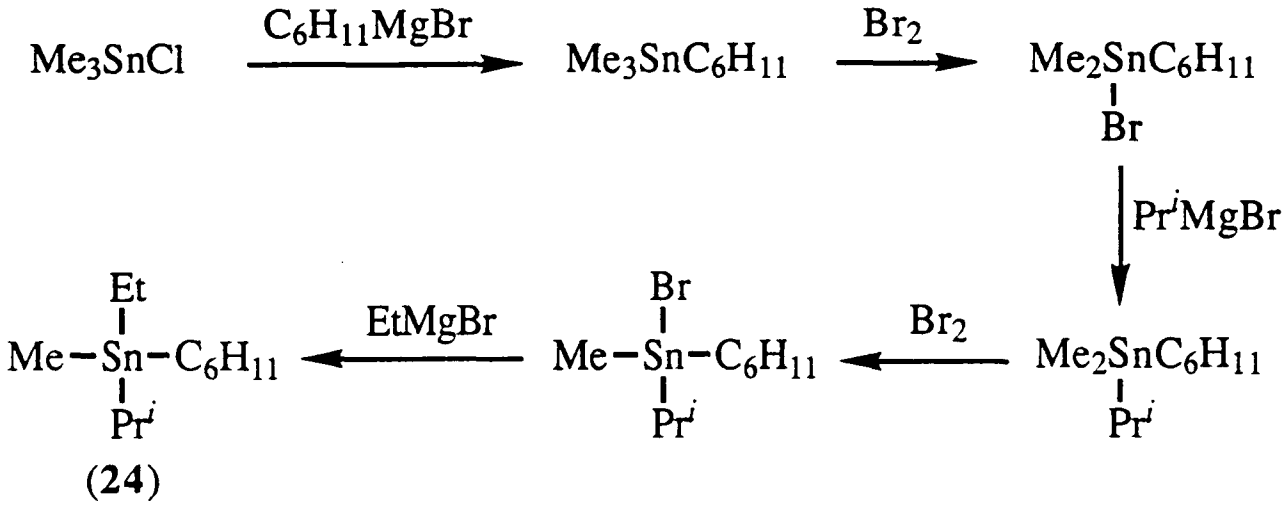
1.2.3.2. Synthesis

One of the best, and most widely used, methods for the synthesis of organostannanes is the reaction of a triorganotin halide with a Grignard reagent, Scheme 20.

$$R_3SnX + R'MgX \longrightarrow R_3SnR' + MgX_2$$

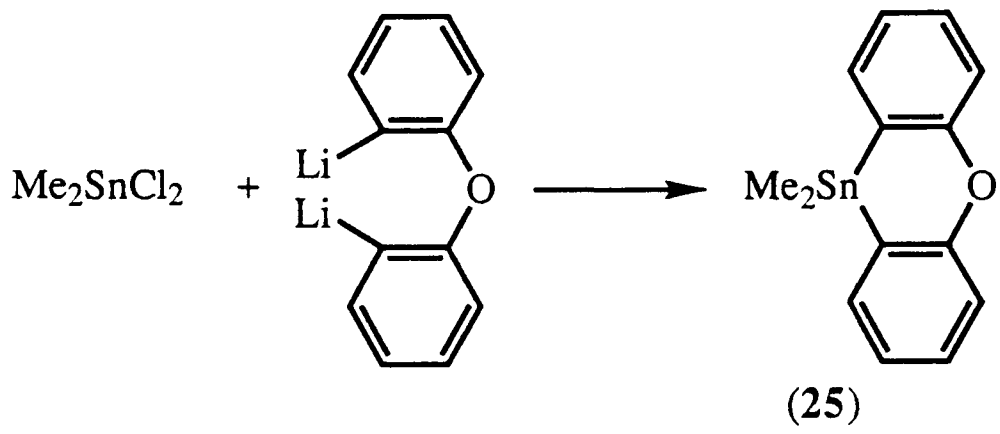
Scheme 20

Mixed tetraalkyltin compounds can be prepared in this way, a striking example being given in Scheme 21 showing the synthesis of the organostannane (**24**), with four different alkyl groups.[42] Aryl-, vinyl- and ethynyltin compounds can be prepared in a similar fashion.[43]



Scheme 21

Organolithium compounds can also be used, particularly when the corresponding Grignard reagents are not readily available, as in the synthesis of 10, 10-dimethylphenoxastannin (**25**),[44] Scheme 22.



Scheme 22

The hydrostannation of alkenes is a particularly useful method for preparing substituted organotin compounds when the substituent would preclude the use of an organolithium or magnesium reagent. The process is a radical chain reaction catalysed by initiators such as azobisisobutyronitrile (AIBN) or UV light, examples are given in Scheme 23.[45,46]

$$Et_3SnH + MeCH{=}CHCO_2Et \xrightarrow{AIBN} Et_3SnCH(Me)CH_2CO_2Et$$

$$Me_3SnH + MeCH{=}CMe_2 \xrightarrow{h\nu} Me_3SnCH(Me)CHMe_2$$

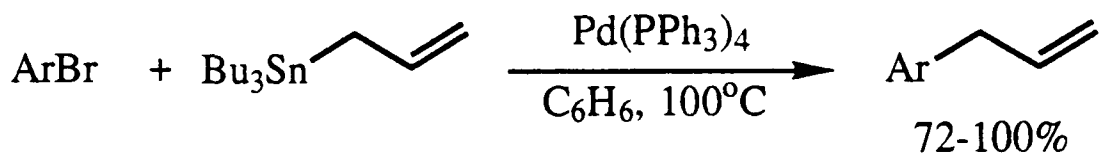
Scheme 23

Other methods include the reaction of stannylmetallic compounds with organic halides and the acidolysis of stannylamines.[43]

1.2.3.3. Direct Coupling Reactions

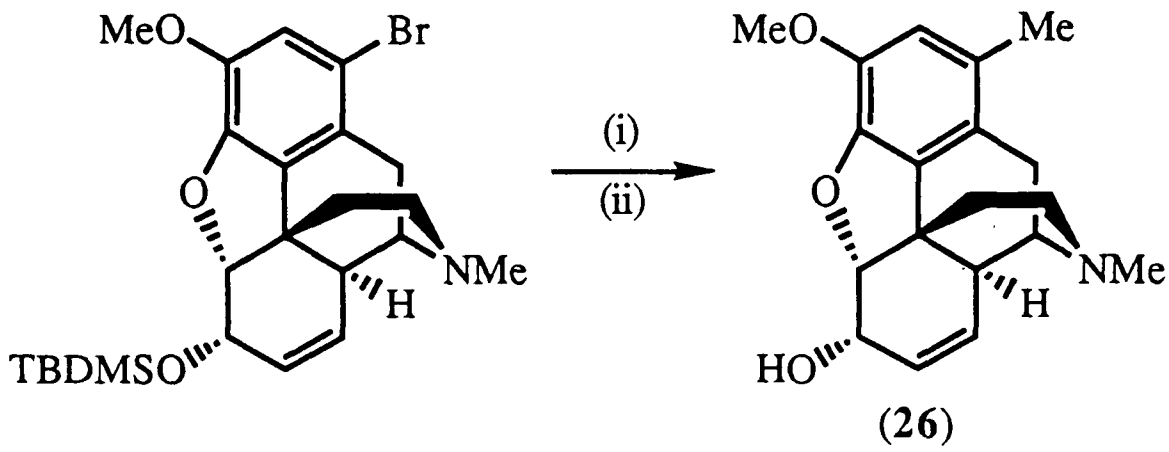
The direct coupling of an organostannane with an organic electrophile, the Stille reaction (Scheme 19), can be applied to a wide variety of electrophiles with a variety of organic moieties being transferred from the tin.[47] A few examples highlighting the synthetic utility of the reaction are given below.

In 1977 the first work on the palladium catalysed coupling of aryl halides with organotin compounds was reported[48] in which an allyltin reagent was used, Scheme 24.



Scheme 24

Since then the methodology has been extended to include the use of vinyltin,[49] aryl and heteroaryltin[50] and alkyl tin reagents, as in the synthesis of the 1-substituted codeine derivative (**26**),[51] Scheme 25.



(26)

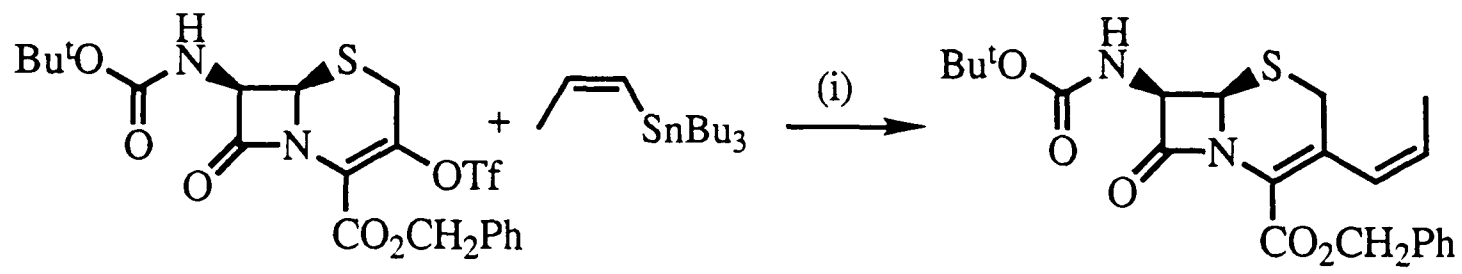
Reagents: (i) Me_4Sn, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, DMF, Et_3N
(ii) *n*-$Bu_4NF.3H_2O$, thf

Scheme 25

When the 'ligandless' catalysts, developed by Beletskaya,[52] (generated from palladium complexes such as $LiPdCl_3$ in donor solvents such as HMPA, DMF or acetone), are used the coupling with aryl iodides occurs at ambient temperature. This is due to the more facile oxidative addition with a coordinatively unsaturated d^{10} 'ligandless' complex.

Aryl triflates, stable compounds and readily available from phenols, have also been used as the electrophilic component.[53,54] This reaction complements the use of aryl halides, but the addition of LiCl is essential for the reaction to proceed.

Substituted vinyl halides[55] and triflates[56] undergo Pd catalysed cross-coupling with alkenyltin reagents to give good yields of conjugated dienes. The methodology has been used by Farina[57] for the synthesis of cephem side-chains in the development of new cephalosporin antibiotics, e.g. (**27**), Scheme 26.

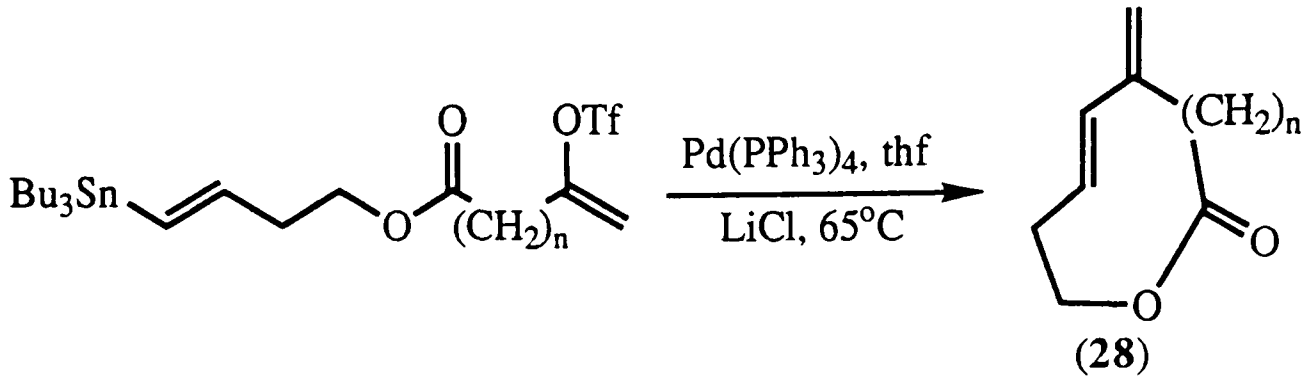


(27)

(i) Pd_2dba_3, P(2-C_4H_3O)$_3$, $ZnCl_2$, N-methylpyrrolidinone, 25°C, 16 h

Scheme 26

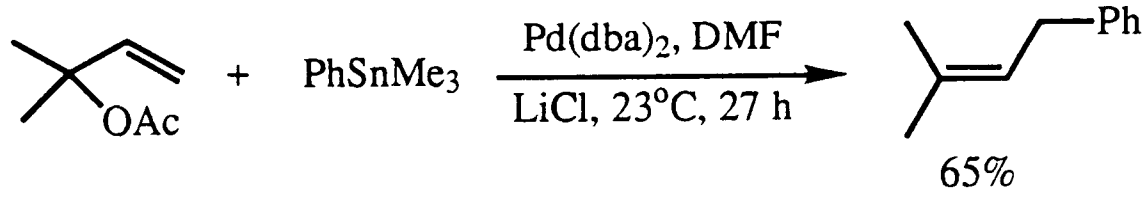
The reaction can be utilised in an intramolecular fashion, for example in the synthesis of biologically active macrocyclic lactones such as (**28**),[58] Scheme 27.



(**28**)

Scheme 27

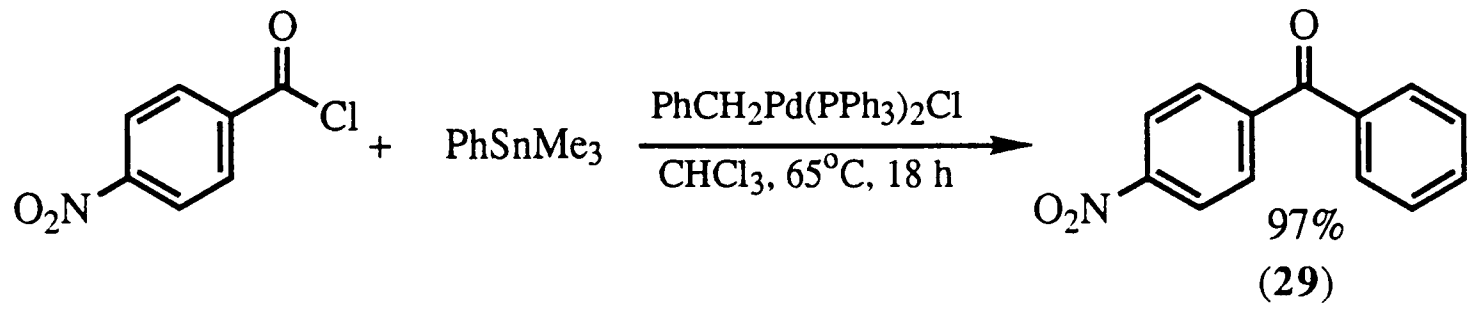
Allylic halides couple efficiently with organostannanes.[59] Allylic acetates, however, are generally less reactive under the standard conditions, but are known to undergo coupling reactions in a few cases,[60] Scheme 28.



65%

Scheme 28

The synthesis of ketones *via* the Pd catalysed reaction of acid chlorides and organotin reagents was first reported by Kosugi *et al* in 1977[61] and has proved to be a very general method with respect to both reaction partners,[40,62,63] and an excellent way of producing functionalised ketones, e.g. (**29**), Scheme 29.

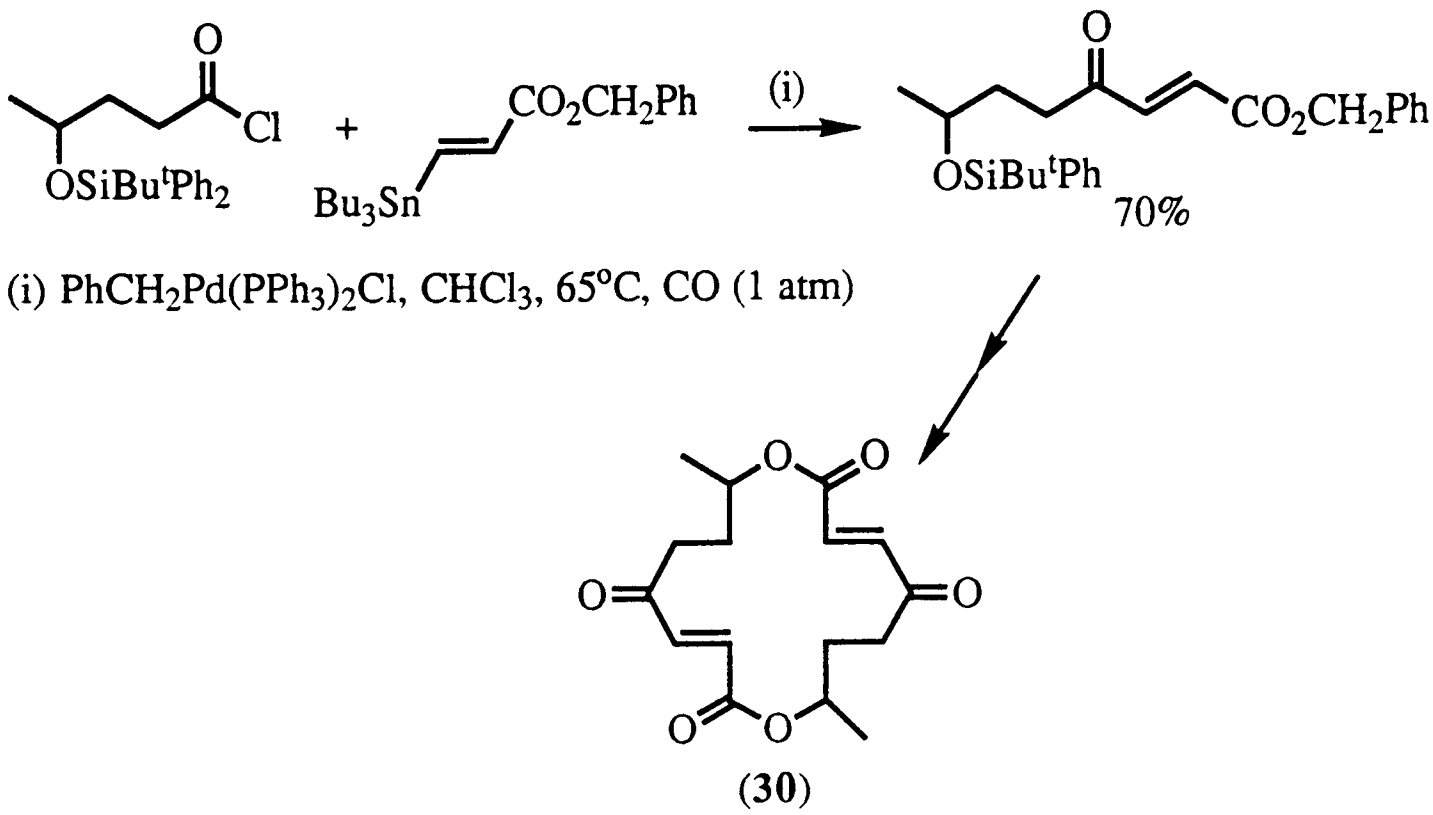


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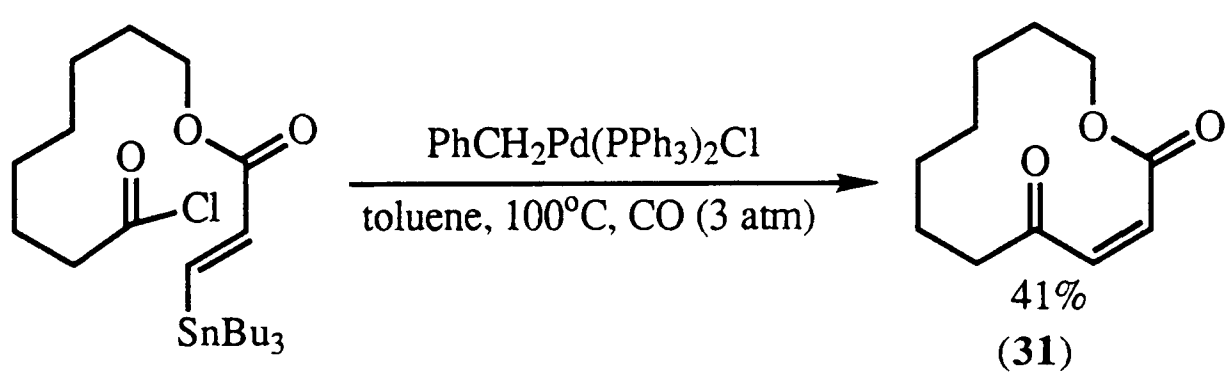
(**29**)

Scheme 29

This route to the formation of ketones is not possible by the use of Grignard reagents, as they will react further with the product ketone (see Section 1.1.), as well as with most functionalities within the molecule. This highlights the synthetic advantages of organotin reagents, and the methodology has been used for the synthesis of a number of natural products, including the macrocyclic antibiotics pyrenophorin (**30**),[64] Scheme 30, and nurpatulolide B (**31**),[65] Scheme 31, in which it is used in an intramolecular fashion.



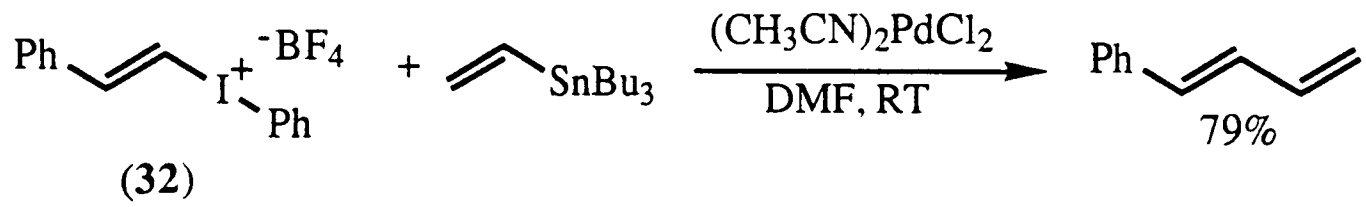
Scheme 30



Scheme 31

The 'ligandless' catalysts of Beletskaya[52] have also been used to good effect, with acetone proving to be the best solvent for the transformations.

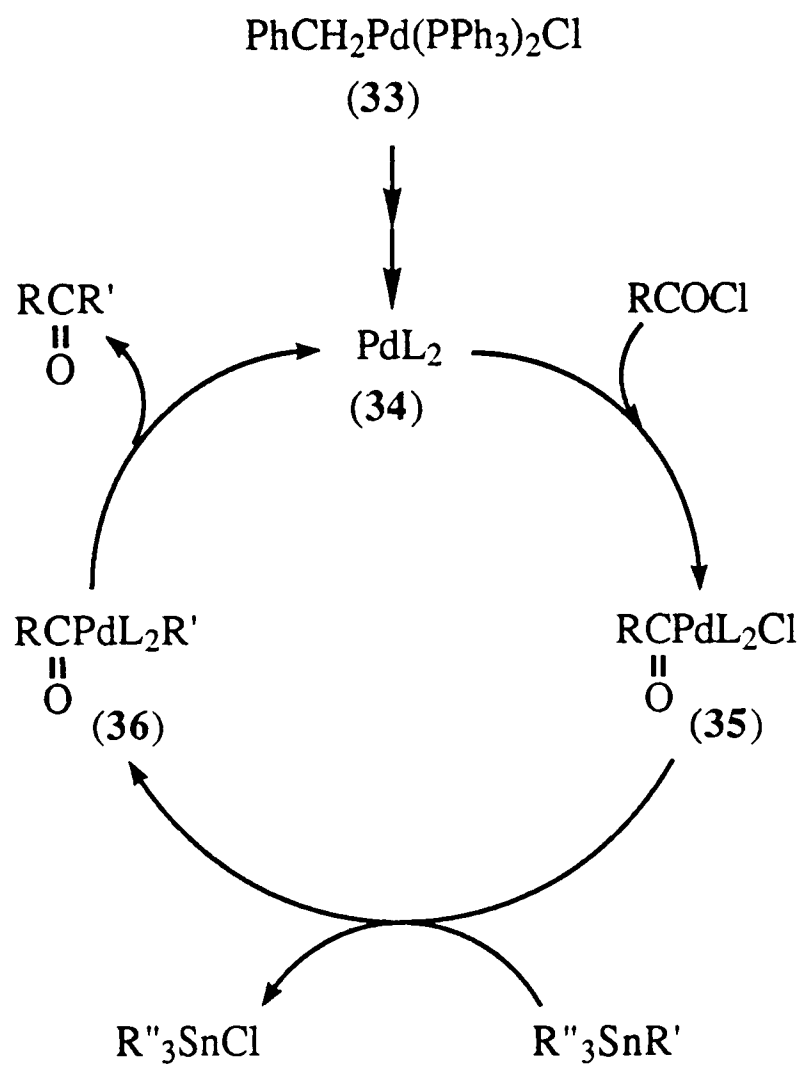
An unusual variant of the Stille reaction has recently been reported[66] in which alkenyliodonium salts (**32**) were used as the coupling partner, Scheme 32.



Scheme 32

A general mechanism for the Stille coupling is shown in Scheme 33.[41] The reaction of an organostannane with an acid chloride is used, but the mechanism applies to all the general reactions given above. The actual mechanisms for each reaction may be different

and this generalised cycle may need to be altered as more information on the processes involved comes to light.



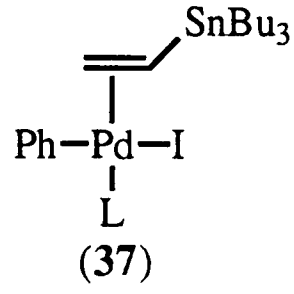
Scheme 33

In the proposed catalytic cycle the active catalyst bis(triphenylphosphine)palladium (0) (**34**) - generated from benzylchlorobis(triphenylphosphine)palladium (II) (**33**) - undergoes oxidative addition of the acid chloride to give the acylchloropalladium(II) complex (**35**). A transmetalation reaction between (**35**) and the organotin yields an acylalkylpalladium(II) species (**36**), which undergoes reductive elimination of the product ketone and regenerates (**34**), which can then take part in further catalytic cycles.

Although the mechanisms of the oxidative addition[67,68] and reductive elimination[19,68,69] are reasonably well understood, much less is known about the transmetalation reaction. It has been proposed to occur by the electrophilic attack of the acylchloropalladium (II) complex (**35**) on the carbon bonded to tin,[62] although there is little direct evidence to support this mechanism. It has been established, however, that the transmetalation of (**35**) by the organotin reagent is the slowest, rate determining step in the

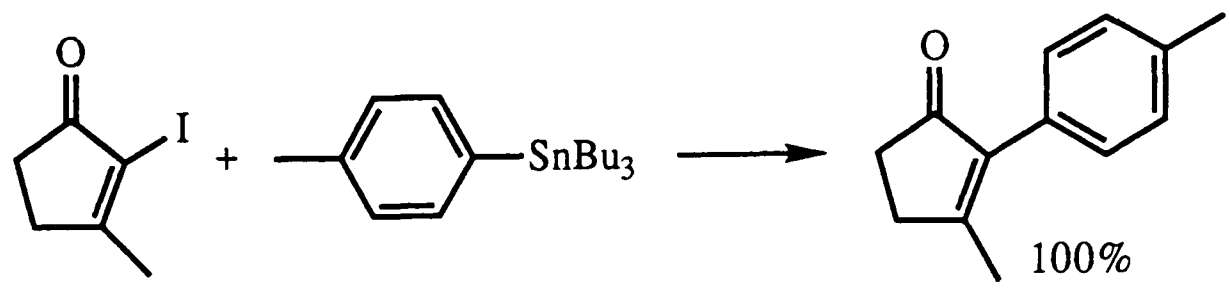
cycle,[41,70] and that it proceeds with a high degree of inversion (>90%) when a substituted benzyl group is transferred.[71] It may also require nucleophilic attack at tin (e.g. by Cl^-) prior to the onset of C-Pd bonding, since reactions involving triflates do not proceed without added LiCl. In fact, it has been shown that analogous reactions with organocopper and mercury reagents are catalysed by iodide ion.[52]

In an important study of the reactivity in Pd catalysed reactions of organostannanes[70] Farina and Krishnan systematically examined the effect of different ligands. They discovered that the electronic properties, rather than the steric properties, of the ligands play a more important role in determining the reactivity of the catalyst. Electron deficient, less basic compounds (such as $AsPh_3$ or $(2\text{-}C_4H_3O)_3P$) were found to promote the reaction of vinyl stannanes over PPh_3. They propose that ligand dissociation is a key step in the transmetalation, with the formation of a monoligated π-complex (**37**) as a key intermediate. This ligand dissociation is rate determining and the ligands which promote the reaction were presumed to dissociate more readily from Pd to allow the formation of (**37**), with the Pd-L bond enthalpy being the most important factor in controlling the rate. Very little acceleration was noted when Me_4Sn was used, which cannot form a π-complex. This supports the role of (**37**) in the accelerated reactions, and the Me_4Sn reaction must proceed through a different pathway, presumably similar to Scheme 33.



(**37**)

Recent work has shown that the addition of silver or copper compounds as co-catalysts can accelerate Stille cross-couplings.[72] The role of the co-catalyst is not known, but it may facilitate the transmetalation step (Sn → Cu → Pd) and thus speed up the cross-coupling. The methodology has been used to produce α-substituted enones,[73] such as 3-methyl-2-*p*-tolyl-2-cyclopentanone (**38**), Scheme 34.



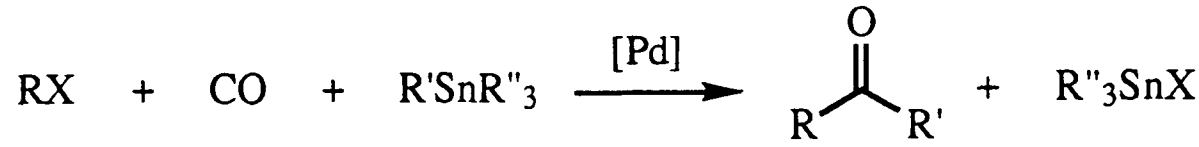
(38)

Reagents: $(PhCN)_2PdCl_2$ (5 mol%), CuI (10 mol%), $AsPh_3$ (10 mol%), N-methylpyrrolidinone, 100°C, 30 min.

Scheme 34

1.2.3.4. Carbonylative Coupling

The Pd catalysed carbonylative coupling of organic electrophiles with organotin compounds in the presence of carbon monoxide, Scheme 35, is a valuable synthetic procedure for a variety of ketones.

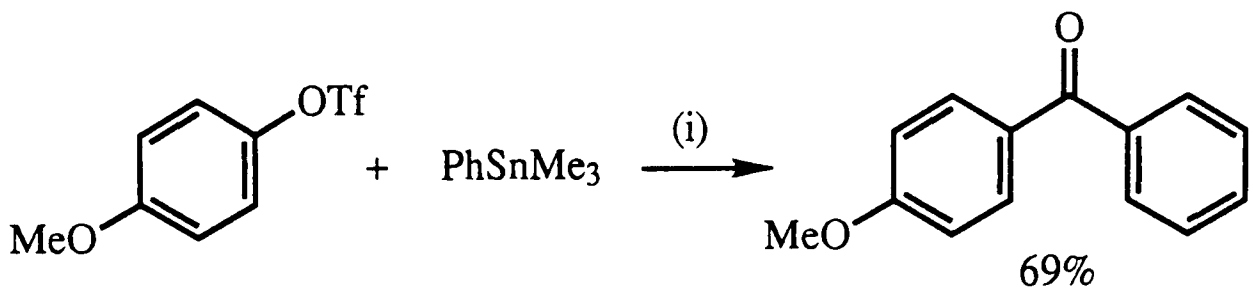


Scheme 35

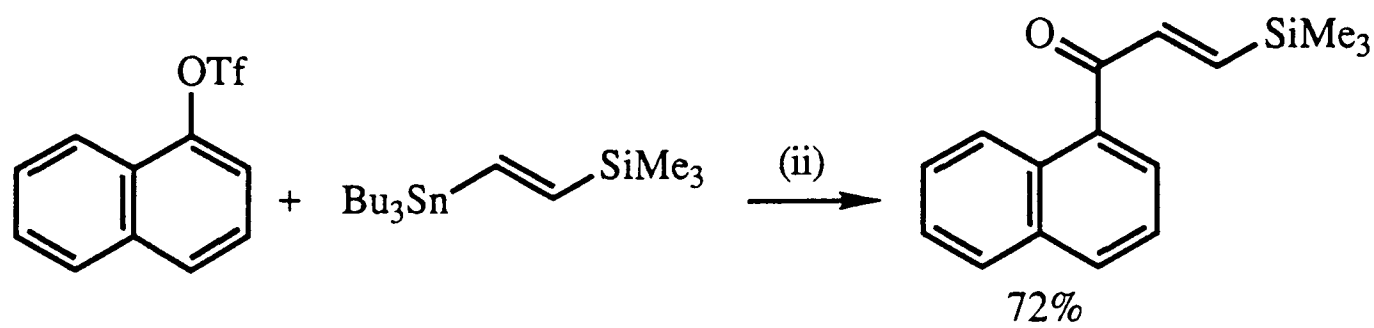
While ketones may be prepared by the direct coupling of organotin reagents with acid chlorides (see section 1.2.3.3.), this route is limited by the availability of the corresponding carboxylic acids. A further advantage of the carbonylation route is that as an acid chloride is not involved then functional groups capable of reacting with an acid chloride (e.g. OH, NH_2 etc) may be present in the substrate.

The first report of such a reaction was by Tanaka[74] in 1979, in which symmetrical tetraalkyltin reagents were carbonylatively coupled with aryl iodides under severe conditions (120°C, HMPA, CO (30 atm), 24 h). Since then the reaction has been developed so that much milder conditions are used and a range of organostannanes and electrophiles can be

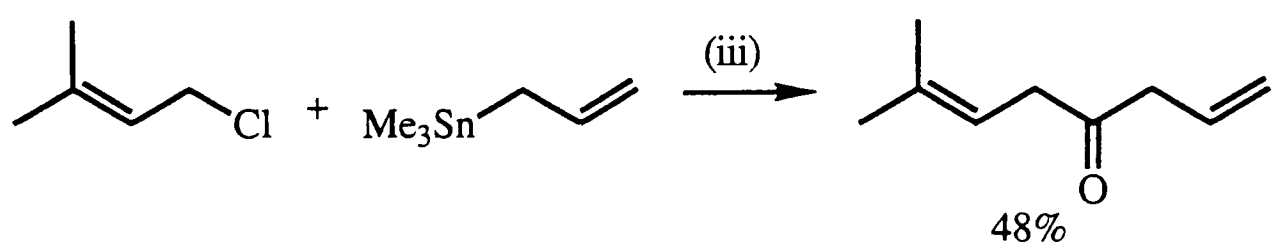
employed, including aryl triflates,[75] allyl halides[76] and vinyl iodides,[77] Scheme 36. The reaction can also be carried out under mild conditions using 'ligandless' catalysts.[52]



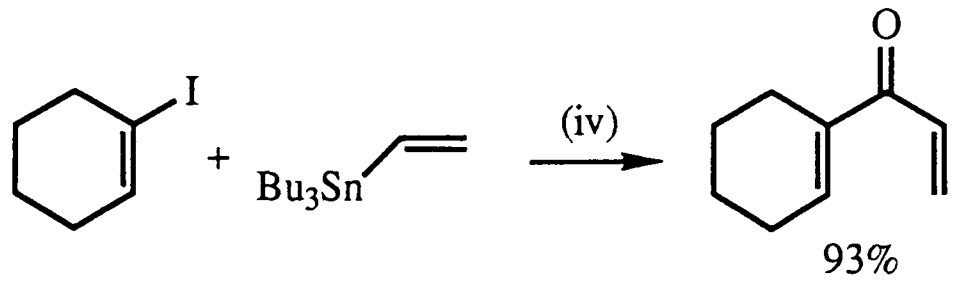
(i) $(dppf)PdCl_2$, DMF, CO (1 atm), LiCl, 100°C, 21 h



(ii) $(dppf)PdCl_2$, DMF, CO (2 atm), LiCl, 70°C, 4 h



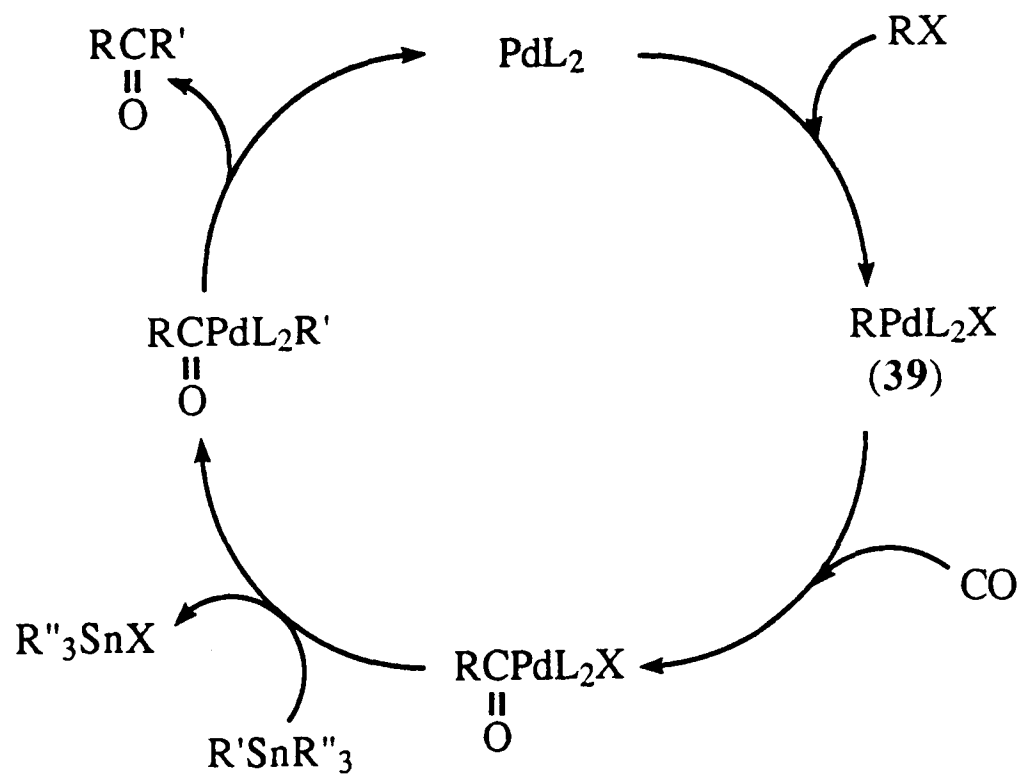
(iii) $(CH_3CN)PdCl_2$, PPh_3, $CHCl_3$, CO (6 atm), 25°C, 48 h



(iv) $(Ph_3P)_2PdCl_2$, thf, CO (50 psi), 50°C, 24 h

Scheme 36

The probable catalytic cycle for this carbonylative coupling reaction, Scheme 37, is analogous to the direct coupling except that CO insertion takes place after the oxidative addition step and prior to the transmetalation step.



Scheme 37

The carbonylation process, however, is in competition with a direct coupling reaction. If transmetalation occurs to complex (**39**) before CO insertion takes place, then a diorganopalladium species will be formed. This should be capable of reductively eliminating the coupled product RR', and regenerating the catalytically active Pd(0) species. The carbonylation reaction may be enhanced by either increasing the concentration of CO by using a higher pressure or by varying the other reaction conditions (temperature, solvent, rate of addition, dilution etc).[78]

1.2.3.5. Disadvantages

The advantages and scope of organotin reagents in synthesis have been highlighted in the previous sections. There are, however, some disadvantages to their use. Forcing conditions (temperatures in excess of 100°C) must sometimes be used to induce coupling, and this may reduce the yields due to thermal instability of substrates, products or catalyst. Hexamethylphosphoramide (HMPA) is often used as a solvent, as it increases the nucleophilicity of organotin compounds, however, its toxicity limits its use as a solvent.

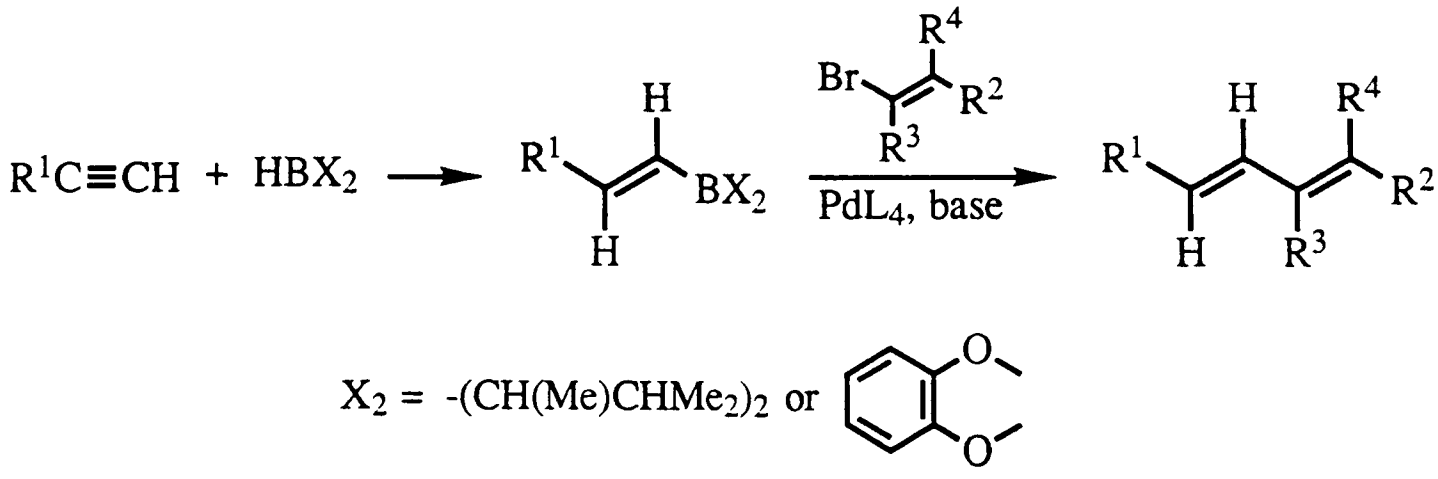
Care must be taken when handling the organotin compounds themselves as R_3SnX and R_4Sn (due to *in vivo* formation of R_3SnX) are both toxic. Maximum toxicity occurs when R = Et or Me, but R = Bu has only very low toxicity and so is the organic group of choice.[43]

1.3. Other Reactions

There are many other coupling reactions which are catalysed by soluble transition metal complexes, especially those of Pd. Although this work does not concern itself with any of them, a couple are worthy of note, i.e. the use of organoboron reagents and the addition-elimination reaction which has come to be known as the Heck reaction.

1.3.1. Organoboron Reagents

In 1979 Suzuki reported the Pd catalysed coupling of 1-alkenylboranes with 1-alkenylhalides to give conjugated dienes.[79] The 1-alkenylboranes are readily available *via* the hydroboration of alkynes, Scheme 38.

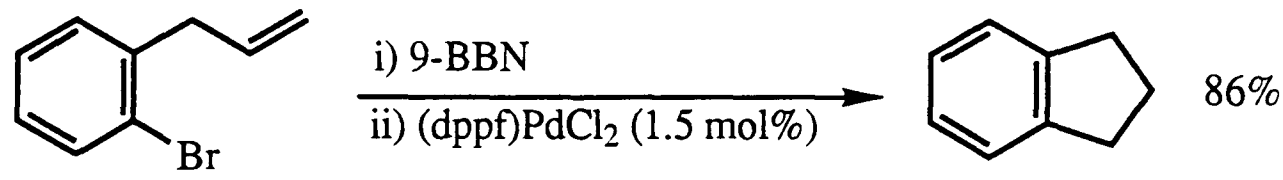


Scheme 38

The coupling reaction was achieved with $(PPh_3)_4Pd$ (1 mol%) as catalyst, and the presence of base (2 equivalents) was essential for the reaction to proceed. Bases which proved successful include NaOMe, NaOEt, NaOAc and NaOH. The reaction with (E)-

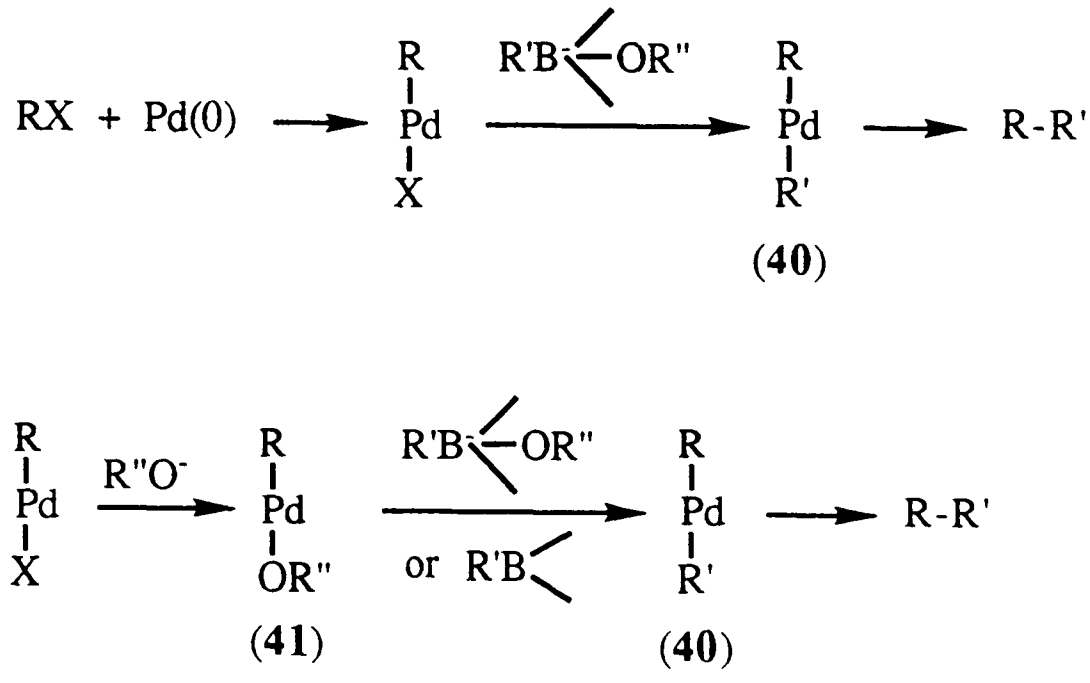
double bonds was found to be stereospecific with retention of configuration, but the use of (Z)-double bonds produced a mixture of isomers.

The advantages of the reaction are the availability of functionalised boranes and their tolerance of other functionalities within the system. The reaction has since been developed to include the use of aryl bromides and a variety of organoboron reagents, with B-alkyl-9-borabicyclo[3.3.1]nonane (9-BBN) derivatives proving especially successful.[80] The reaction can be performed in an intramolecular fashion, giving cyclic products in good yields, Scheme 39. It has also been used in the synthesis of various natural products.[81]



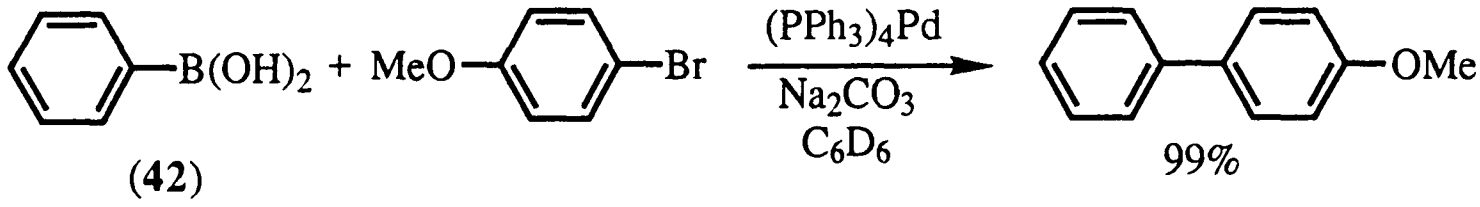
Scheme 39

The mechanism of the reaction is uncertain. The presence of base is essential, and this is believed to accelerate the transmetalation step from B to Pd. Two routes for the reaction are possible, which differ in the role that the base plays, Scheme 40. In the first a borate undergoes the transmetalation with a displacement of halide from the Pd. This gives the diorganopalladium species (**40**) which then reductively eliminates the coupled product. Alternatively the base could displace the halide to give (**41**), and then either a borate or a borane performs the transmetalation to give (**40**).



Scheme 40

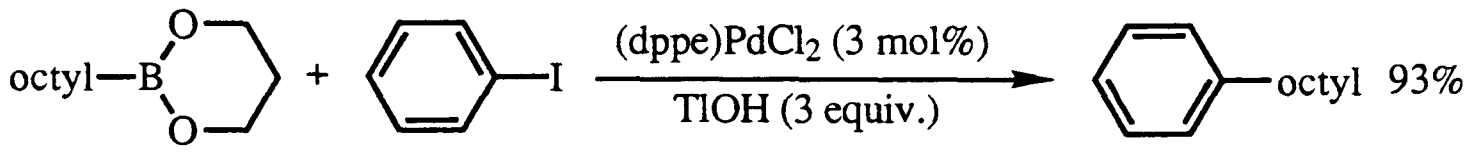
Phenylboronic acid (**42**) will undergo Pd catalysed coupling with halo arenes, in the presence of base,[82] Scheme 41. This reaction has been extended to a range of arylboronic acids, and also to include coupling with triflates.[83]



(**42**)

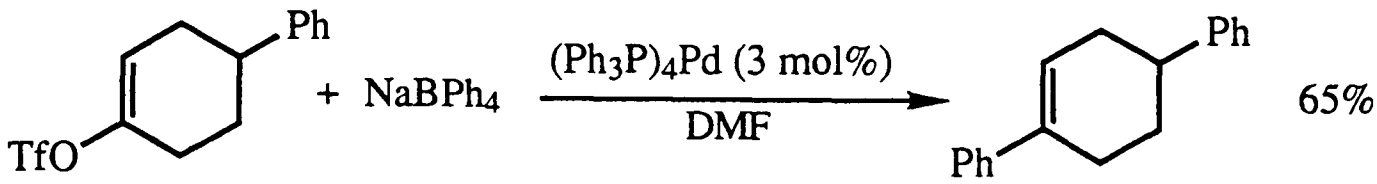
Scheme 41

The reaction with alkylboronic acids is less successful. However, if alkylboronic esters are used then the coupling will take place.[84] In this case the Na salts used as bases previously do not work, but the use of Tl (I) salts has been found to promote the coupling successfully, Scheme 42.



Scheme 42

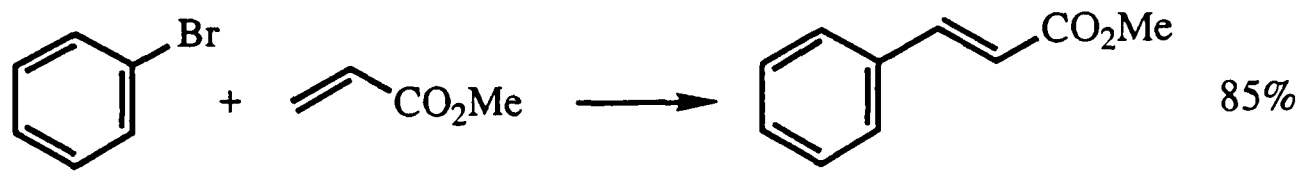
The coupling of vinyl and aryl triflates with sodium tetraarylborates has been reported,[85] and this transformation will proceed in the absence of base, Scheme 43.



Scheme 43

1.3.2. The Heck Reaction

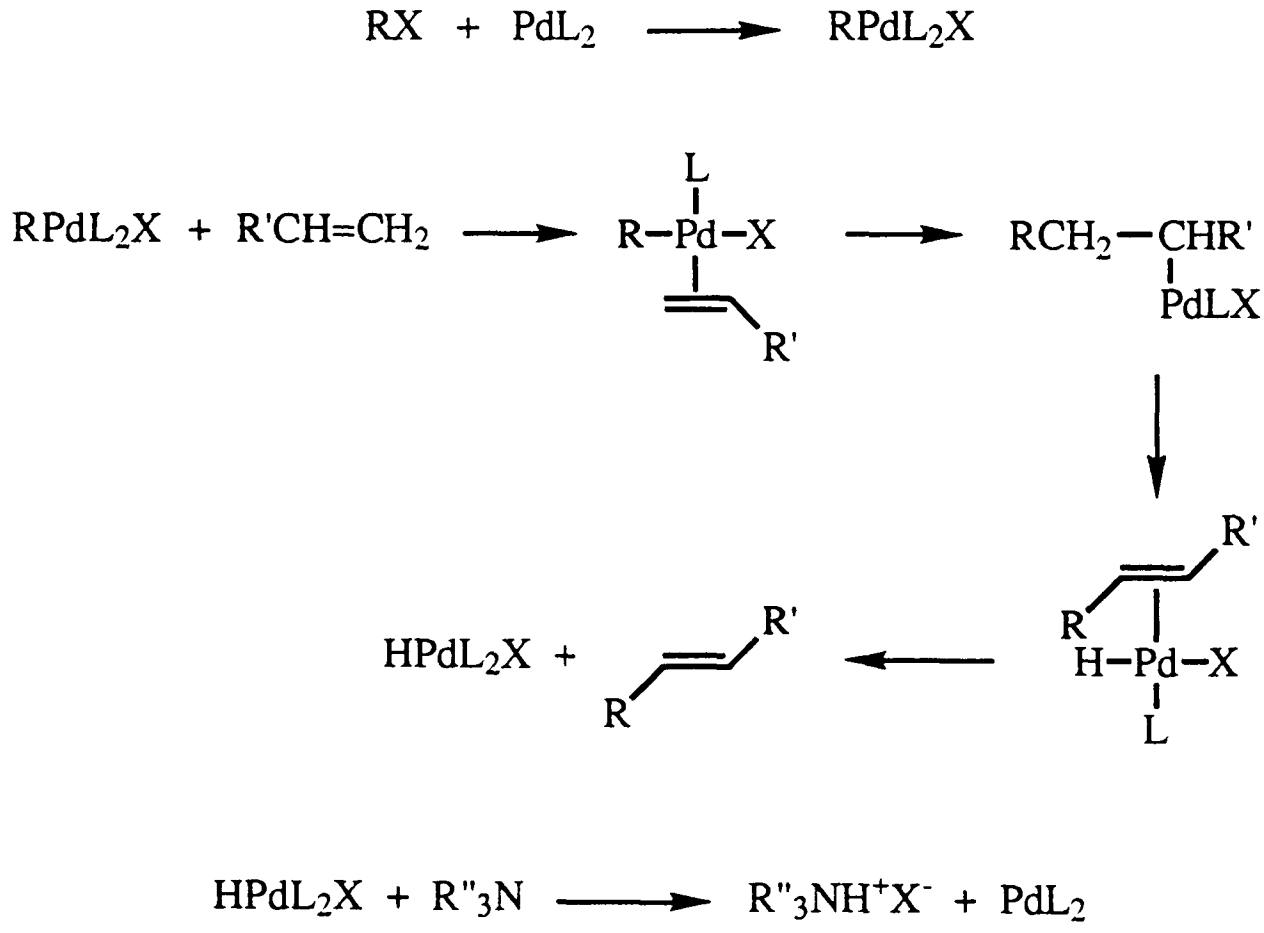
The Heck reaction involves the coupling of an organic halide with an olefinic or acetylinic compound, using a Pd catalyst,[86] Scheme 44.



Reagents: 1-2 mol% $Pd(OAc)_2$:PPh_3 (1:2)
TMEDA, 125°C

Scheme 44

The mechanism of the reaction has been proposed as that shown in Scheme 45. Oxidative addition of the halide to Pd (0) is followed by an insertion of the olefin into the Pd-R bond. β-Elimination then releases the coupled product and produces $HPdL_2X$. The reaction only becomes catalytic in Pd if base is added to the system to remove HX and regenerate the catalytically active PdL_2 species.



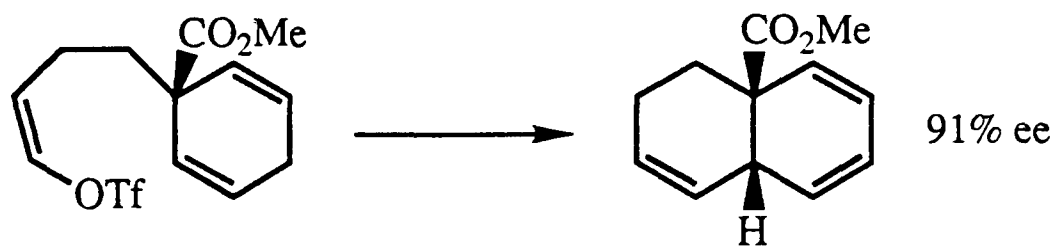
Scheme 45

The reaction is found to tolerate nearly all functional groups, except α,β-unsaturated aldehydes and ketones. A few generalisations can be made about the reaction: (i) The organic group of RX adds to the least substituted carbon of the double bond. If a functional group is attached directly to the double bond, the R group generally adds to the other carbon. (ii) The reaction is stereospecific with 1, 2-disubstituted alkenes, proceeding by a *cis* addition-*cis* elimination sequence. If there is a choice of hydrogens for elimination, the most

stable products are preferred and the most hydridic hydrogen tends to be lost. (iii) The order of reactivity of RX is RI > RBr >> RCl.

The reaction has proved very successful, especially for the synthesis of conjugated olefins[23b,87] and also a range of heterocyclic compounds.[88] Acetylinic compounds have recently been used for the preparation of fulvenes.[89]

The reaction can be performed in an intramolecular fashion with vinyl triflates, and by the addition of a chiral ligand asymmetric decalin derivatives have been prepared,[90] Scheme 46. The stereoselection in other cyclisation reactions can also be controlled by tailoring of the Pd catalyst.[91]



Reagents: $Pd(OAc)_2$ (5 mol%), (R)-BINAP (10 mol%)
K_2CO_3 (2 equiv.), 1-methyl-2-pyrrolidinone, 60°C

Scheme 46

RESULTS AND DISCUSSION

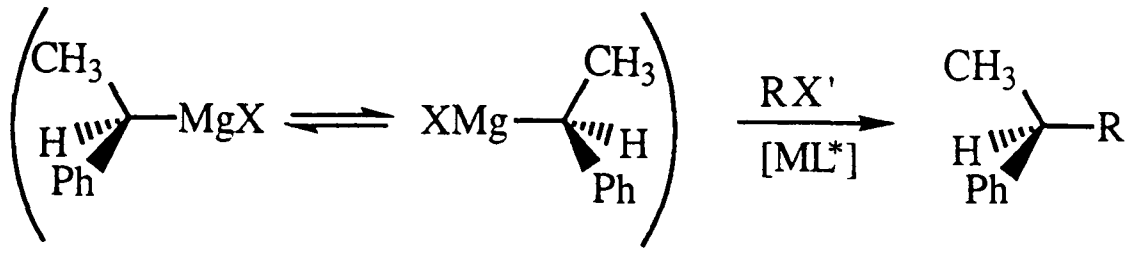
"Everything that happens, happens as it should,
and if you observe carefully, you will find it to be so"
Marcus Aurelius (AD 121 - 180)

CHAPTER 2. RESULTS AND DISCUSSION

2.1. Introduction and Aims

The first reports of asymmetric cross-coupling involving a Grignard reagent appeared in 1973[21] in which ee's of up to 17% were obtained using (-) - DIOP (**4**) as a chiral ligand for the Ni catalysed reaction. Since then asymmetric cross-coupling has been attempted using various kinds of optically active phosphine ligands, with ee's of up to 95% being obtained.[22]

The reaction has been studied most extensively with secondary alkyl Grignard reagents. Use of an optically active ligand for the cross-coupling of a racemic secondary alkyl Grignard reagent induces a kinetic resolution, i.e. the reaction rates of Grignard reagent enantiomers will be different. Racemisation of secondary carbon-magnesium bonds occurs at a moderate rate at ambient temperature.[92] If it is fast on the timescale of catalytic turnover, then one enantiomer of the racemic Grignard reagent may participate in asymmetric cross-coupling preferentially while the other inverts before reaction. The organometallic addition stage defines the overall enantioselectivity provided that the C-C bond forming elimination step is fast. Phenyl stabilised carbanions are usually used, probably to ensure rapid racemisation under catalytic conditions,[93] Scheme 47.



Scheme 47

Little is known about the mechanism of this asymmetric reaction. It is unlikely that the C-C bond forming step produces much stereochemical variation, since the configuration

at the carbon centre is determined in the previous transmetalation step. The reductive elimination step, leading to product, has been shown to proceed with retention of configuration.[19a] The processes of selectivity in the transmetalation at Ni or Pd, however, have not yet been elucidated.

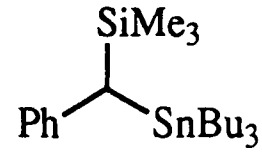
The initial aim of the project was to synthesise chiral organometallic reagents and to use them in the investigation of asymmetric cross-coupling processes. Thus far, little work has been done with chiral organometallic reagents *per se* and it was hoped to use them to probe the transmetalation step of the catalytic cycle.

Preparation will produce a racemic reagent which will interconvert either slowly or rapidly compared to the catalytic coupling reaction. By the use of a homochiral catalyst a rapidly interconverting reagent will lead to enantioselection in the reaction, and a slowly interconverting reagent will lead to a kinetic resolution. This will leave behind an enantiomerically pure reagent. Subsequent transfer of the chiral group to the metal catalyst, followed by reductive elimination of an optically active product will hopefully enable the selectivity of the transmetalation step to be determined.

2.2. Synthesis and Reactions of Benzyltin Compounds

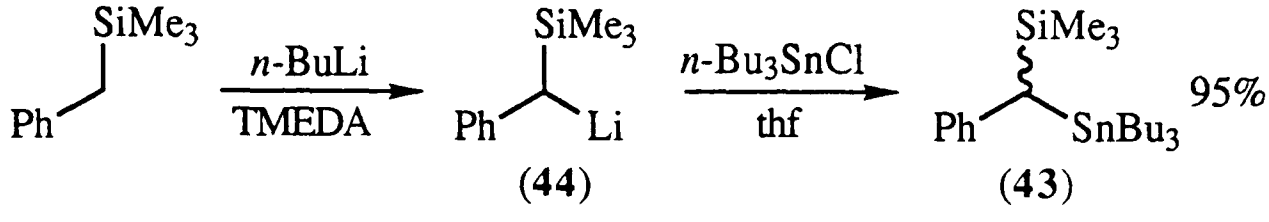
2.2.1. Attempted Cross-Coupling Reactions with a Vinyl Halide

The organometallic compounds which were chosen for the study were α-substituted benzylic compounds, with the metal being tin. It was hoped that these reagents would be slow to interconvert and could then be used in coupling reactions with organic electrophiles using Pd catalysts, i.e. Stille methodology. The initial choice of reagent was (α-trimethylsilyl)benzyltri-*n*-butyltin (**43**), the trimethylsilyl group allowing subsequent functional group interconversion at a later stage if necessary.



(43)

(±)-(**43**) was prepared from benzyltrimethylsilane by deprotonation at the benzylic position with *n*-butyllithium in N, N, N', N' - tetramethylethylenediamine (TMEDA) to give the lithiated species (**44**).[94] This reacted with tri-*n*-butyltin chloride to give, after distillation, the new compound (**43**) in 95% yield, Scheme 48.

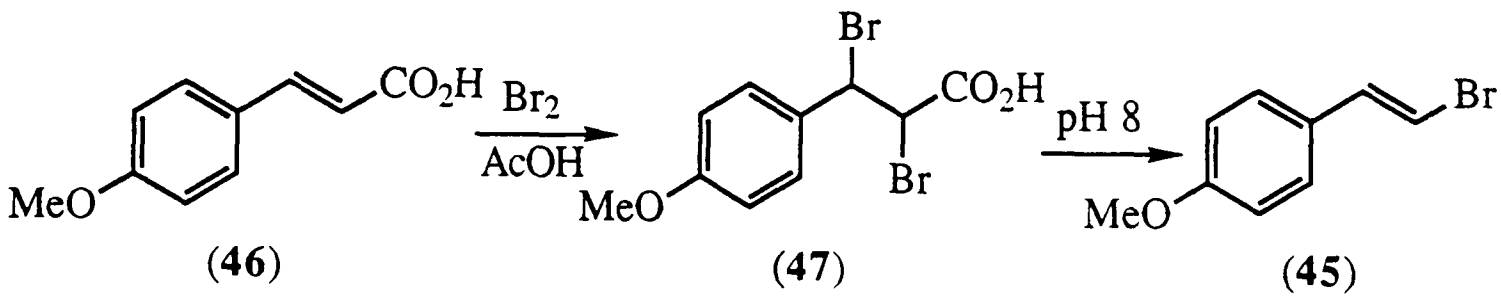


(44) **(43)**

Scheme 48

The proton NMR spectrum showed the benzylic proton as a singlet at 1.87 ppm, but flanked by a double pair of small satellites. These correspond to Sn-H coupling. Three of the naturally occuring isotopes of tin have spin I = 1/2; ^{115}Sn (0.35% abundance), ^{117}Sn (7.6% abundance) and ^{119}Sn (8.6% abundance). The observed satellites are due to ^{117}Sn and ^{119}Sn-H coupling. The low abundance of ^{115}Sn means that ^{115}Sn-H coupling is not seen in the spectrum. The coupling constants for the satellites were 53 and 55 Hz, corresponding to ^{117}Sn and ^{119}Sn respectively.

The electrophilic partner for the coupling was required to be readily available, stereoisomerically pure and efficient in cross-coupling reactions. For these reasons (E)-1'-bromo-2'-(4-methoxyphenyl)ethene (**45**),[95] which can easily be synthesised from the corresponding cinnamic acid (**46**), Scheme 49, was employed.

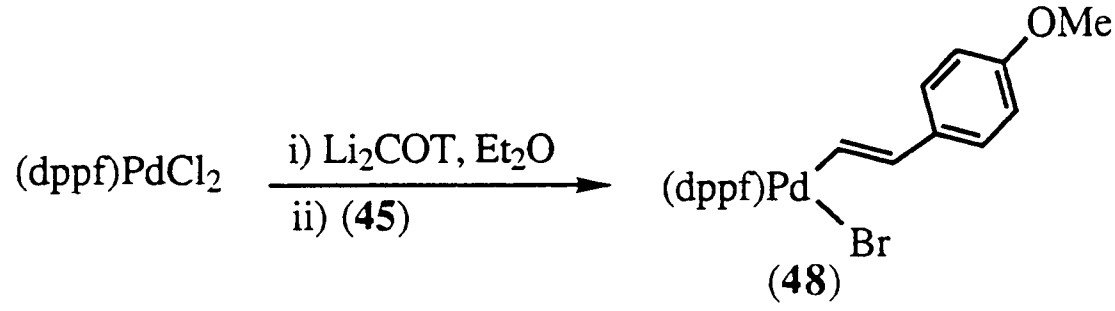


(46) **(47)** **(45)**

Scheme 49

The decarboxylative elimination of (**47**) in aqueous solvent proceeds by an ionic mechanism to give the more stable *trans* double bond in (**45**). The coupling constant of 14 Hz between the olefinic protons in the ^{1}H NMR spectrum of (**45**) confirms the E geometry of the double bond.

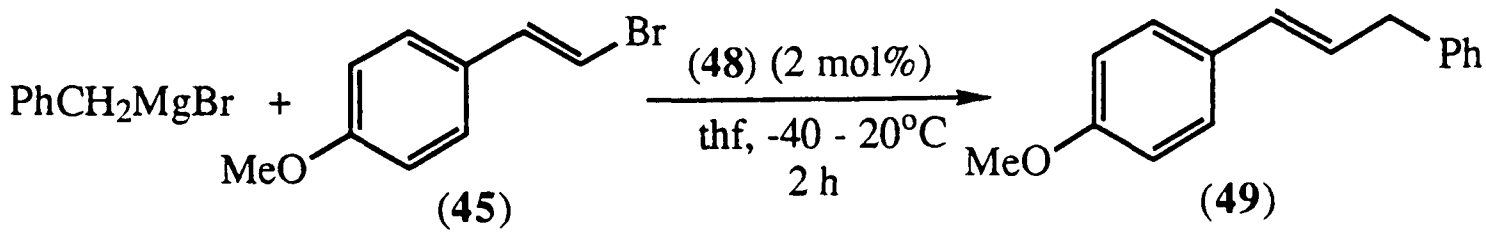
For the initial studies, to test the reaction, an achiral ligand (dppf) (**1**) was chosen for the palladium catalyst. The catalytic cycle involves the oxidative addition of (**45**) to a Pd(0) species to give a Pd(II) intermediate, which, in this system would be bromo[1,1'-bis(diphenylphosphino)ferrocene][(E)-2-(4-methoxyphenyl)ethenyl]palladium(II) (**48**). This is an isolable intermediate,[18b] Scheme 50, and was thus used as the catalyst for the cross-coupling reactions between (**43**) and (**45**).



Scheme 50

(dppf)$PdCl_2$ was prepared by the method of Hayashi,[15] from dichlorobis(acetonitrile)palladium (II) ($(CH_3CN)_2PdCl_2$) and dppf. Reduction of this by dilithium cyclooctatetraenide (Li_2COT)[96] in Et_2O gave a Pd(0) species and addition of (**45**) resulted in an oxidative addition, with (**48**) being isolated by precipitation with pentane.

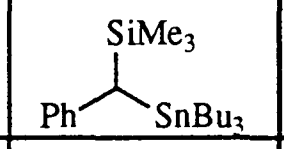
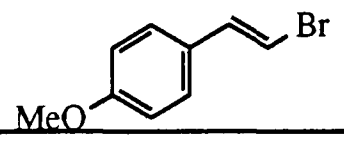
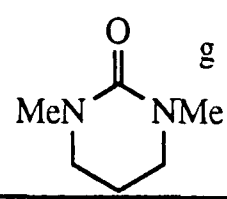
The catalyst (**48**) was tested by using it in a coupling reaction between (**45**) and benzylmagnesium bromide. (**48**) was used in 2 mol% with the reactants being added at -40°C in thf. The reaction was then allowed to warm to ambient temperature and stirred for 2 h. On work-up the coupled product 1-(4-methoxyphenyl)-3-phenylpropene (**49**) was isolated in 73% yield, Scheme 51. The ^{1}H NMR spectrum of (**49**) showed that the coupling constant between the the olefinic protons was 16 Hz, indicating that the double bond had retained its *trans* geometry.



Scheme 51

The coupling of (**45**) and (**43**) using (**48**) as catalyst was then attempted, and the results are given in Table 1.

Table 1: Attempted Pd Catalysed Coupling of Benzyltin Reagents with Organic Electrophiles[a]

Entry	Benzyltin	Electrophile	Solvent	Catalyst	Result[b]
1			thf[c]	(**48**)	No Reaction
2	"	"	thf[d]	(**48**)	No Reaction
3	"	"	DMF[e]	(**48**)	No Reaction
4	"	"	thf[d]	$(Ph_3P)_4Pd$	No Reaction
5	"	"	DMF[e]	$(Ph_3P)_4Pd$	No Reaction
6	"	PhCOCl	toluene[f]	$(Ph_3P)_4Pd$	No Reaction
7		"	DMF[g]	$(Ph_3P)_4Pd$	mixture
8	"	"		$(Ph_3P)_4Pd$	mixture
9	"	"	DMSO[g]	$(Ph_3P)_4Pd$	mixture

[a]Reactions were carried out on a 0.36 mmol (entries 1-6) or 0.092 mmol (entries 7-9) scale in dry, degassed solvents. 2 mol% of catalyst was used in entries 1-5 and 10 mol% in entries 6-9. [b]Determined by ^1H NMR and tlc. [c]-40°C-RT. [d]67°C. [e]100°C. [f]110°C. [g]90°C.

The initial reaction used the protocol employed in the reaction to test the catalyst, i.e. addition of reagents at -40°C and stirring at room temperature. However, after a period of 48 h no reaction had occurred and unreacted starting materials were recovered (entry 1). The reaction was repeated and heated at reflux for 48 h, but again no reaction occurred (entry 2). In an attempt to increase the reactivity of the organotin nucleophile the polar aprotic solvent DMF was used. The reaction was carried out at 100°C, but only unreacted starting materials were recovered (entry 3).

The lack of success prompted a change in catalyst and tetrakis(triphenylphosphine)palladium (0), $(Ph_3P)_4Pd$,[97] was chosen. Reactions were performed in refluxing thf and also in DMF at 100°C, but no coupling product was observed, only unreacted starting materials being recovered (entries 4 and 5).

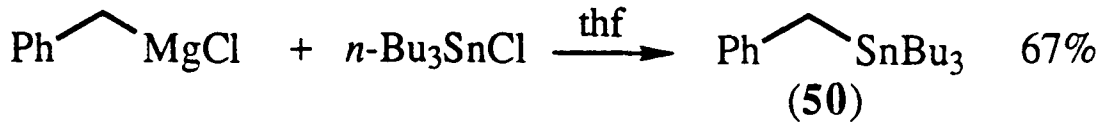
These results indicate that (**43**) is unreactive to vinyl halides in Pd catalysed cross-coupling reactions, which may be due to the relatively low nucleophilic character of the benzyl group bound to tin. This prompted a change of approach.

2.2.2. Attempted Coupling Reactions of Benzyltin Reagents with Acid Chlorides

The cross-coupling of organostannanes with acid chlorides is a well established procedure for the formation of ketones (see Section 1.2.3.3). The cross-coupling of (**43**) with benzoyl chloride was thus attempted using the methodology of Stille.[40] $(Ph_3P)_4Pd$ in 2 mol% was used as the catalyst and the reaction carried out in refluxing toluene for 24 h. Once more, however, (**43**) was found to be unreactive and only starting materials were recovered (Table 1, entry 6).

The lack of reactivity of (**43**) may be due to the low nucleophilicity of the C-Sn bond for the benzyl group and/or an effect, steric or electronic, of the trimethylsilyl group in the α-position. In order to assess the reactivity of the benzyl group the parent molecule

benzyltri-*n*-butyltin (**50**) was prepared by the action of benzylmagnesium chloride on tri-*n*-butyltin chloride, Scheme 52.

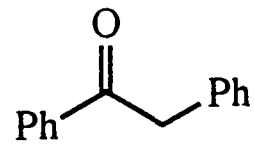


Scheme 52

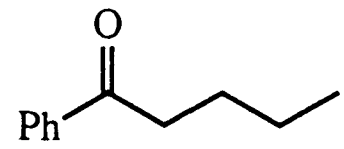
The resonance of the benzylic protons at 2.34 ppm again showed ^{117}Sn and ^{119}Sn-H coupling in the ^{1}H NMR spectrum, the coupling constants being 55 and 57 Hz.

The results of the attempted coupling reactions of (**50**) with benzoyl chloride, which were carried out using forcing conditions of polar aprotic solvents and high temperatures, are given in Table 1.

The successful coupling reaction, with transfer of the benzyl group, would lead to α-phenylacetophenone (**51**) being formed. Any side reaction involving the transfer of a butyl moiety would lead to the formation of valerophenone (**52**).



(**51**)



(**52**)

The proton NMR spectrum of authentic (**51**) contains a characteristic singlet at 4.2 ppm, corresponding to the two benzylic protons. Similarly, there is a characteristic resonance of a triplet centred at 2.92 ppm in the spectrum of an authentic sample of (**52**), corresponding to the CH_2 adjacent to the carbonyl group. The presence of these peaks in the ^{1}H NMR spectrum of crude product should indicate whether a successful reaction has occurred.

The NMR spectrum of the crude product from the reaction performed in DMF (Table 1, entry 7) lacked a signal at 2.34 ppm. This indicated that the benzyl group was no longer bound to tin. (**51**), however, had not been formed in the reaction as the spectrum did not contain a signal at 4.2 ppm. Transfer of a butyl group from (**50**) did not take place, indicated

by the lack of signal at 2.29 ppm. Tlc of the crude product revealed a mixture of at least six species, decomposition presumably accounting for the observed mixture.

The reactions with 1, 3-dimethyl-3, 4, 5, 6-tetrahydro-2(1H)-pyrimidinone (Table 1, entry 8) and DMSO (Table 1, entry 9) as solvent gave similar results, i.e. the disappearance of the signal at 2.34 ppm in the proton NMR spectrum but no identifiable products being formed.

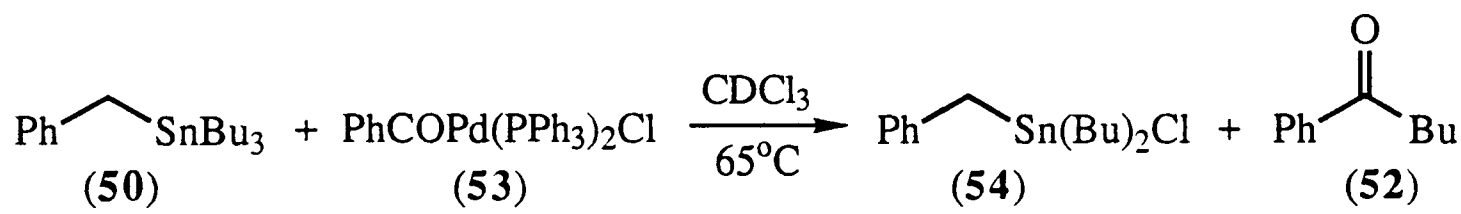
In similar experiments[40] Stille found that the order of transfer of the benzyl and butyl groups depended on the concentration of the catalyst ($PhCH_2Pd(PPh_3)_2Cl$) employed. The reactions were performed with HMPA as solvent and yields of 60-80% of coupled products obtained. The results given above, combined with those of Stille, indicate the significant role played by the solvent in these systems. The choice of solvent is important in determining the nucleophilicity of the organostannane. Certain solvents may lead to forcing conditions being necessary, which can cause decomposition, as described above. This highlights one of the disadvantages of the use of such reagents.

The catalytic cycle for the reaction between an acid chloride and an organostannane (Scheme 33) involves the oxidative addition of the acid chloride to a Pd(0) species, resulting in an acylpalladium chloride species (**35**). The corresponding species for the current system would be benzoylchlorobis(triphenylphosphine)palladium(II), $PhCOPd(PPh_3)_2Cl$ (**53**). Isolation of this intermediate would allow a direct stoichiometric reaction with (**50**). This would enable the feasibility of the use of (**50**), and related compounds, to be tested. A favourable stoichiometric reaction with a known intermediate in the catalytic cycle would give grounds for the possibility of further investigations, hopefully leading to a catalytic system. (**53**) was thus prepared using the method of Suzuki,[98] Scheme 53. The ^{31}P NMR spectrum contained only a singlet at 15.7 ppm, indicating that (**53**) has the *trans* geometry.

$$(Ph_3P)_4Pd + PhCOCl \xrightarrow{\text{toluene}} \underset{(\mathbf{53})}{PhCOPd(PPh_3)_2Cl} \quad 73\%$$

Scheme 53

The stoichiometric reaction between complex (**53**) and compound (**50**) was carried out in $CDCl_3$ at 65°C, according to a similar procedure by Stille,[40] and followed by ^1H NMR. After 6 h a new small singlet appeared in the spectrum at 2.79 ppm. After 22.5 h this had increased considerably in intensity and $^{117,119}Sn$-H coupled satellites could be seen associated with the signal (J = 63, 65 Hz). Also, the benzylic signal from (**50**) was found to be reduced in intensity, and a new triplet appeared at *ca.* 3 ppm. After 46 h a precipitate of palladium was seen in the NMR tube. The spectrum showed a further increase in the intensities of the new signals at 2.79 and 2.98 ppm and a further reduction in the intensity of the resonance at 2.34 ppm. The reaction was filtered and the products separated by preparative tlc. Valerophenone (**52**) was isolated in a yield of 38%, which was responsible for the triplet at 2.98 ppm in the NMR spectrum. The resulting tin complex from transfer of a butyl group, benzyldibutyltin chloride (**54**), was also isolated in a 48% yield; the reaction can thus be represented as shown in Scheme 54. The benzylic protons of (**54**) are responsible for the peak at 2.79 ppm in the NMR spectrum, the downfield shift of *ca.* 0.45 ppm being due to the substitution of Cl for the organic group.



Scheme 54

Starting material (**50**) has δ (^{119}Sn) of -24.2 ppm. The product (**54**) should have a very different chemical shift, and this should allow the reaction to be followed by ^{119}Sn NMR. The reaction was repeated and after 48 h the peak at -24.2 ppm had disappeared and a new one appeared at 107.6 ppm, corresponding to the formation of (**54**).

No α-phenylacetophenone (**51**) was isolated from the reaction mixture, although a small signal was seen at 4.2 ppm in the proton NMR spectrum after 46 h. This indicates that the butyl group is transferred in preference to the benzyl group with the ratio of (**52**):(**51**) being at least 90:10, from integration of the ^1H NMR spectrum.

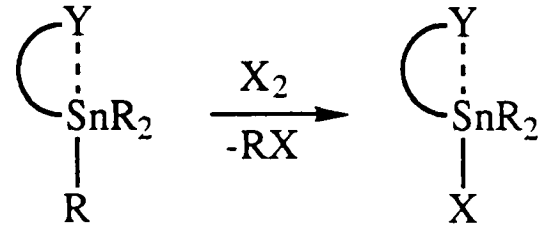
In a similar experiment[40] Stille found that performing the stoichiometric reaction between (**53**) and (**50**) in HMPA produced a (**52**):(**51**) ratio of 2:98. Although he did not report the stoichiometric reaction performed in chloroform, the catalytic reaction between (**50**) and benzoyl chloride, catalysed by (**53**), in $CHCl_3$ is reported. For this the ratio of (**52**):(**51**) was found to be 85:15 (i.e. a reversal in selectivity in going from HMPA to $CHCl_3$), similar to that found in this study. Stille attributes the different transfer order to the formation of different acylpalladium complexes, without proposing what they might be. However different transfer orders of organic groups from tin to platinum (II) complexes have also been observed, depending on the structure of the complex and the solvent used.[99]

These results highlight the complexity of the system and the problems in selective group transfer from tin. It is also evident from the results of these initial cross-coupling reactions that the C-Sn bond, especially to a benzyl group, is strong and only weakly nucleophilic, even in the presence of palladium catalysts. In order to control the reaction and effect efficient transfer a change of approach is required.

2.3. Internally Assisted Transfers

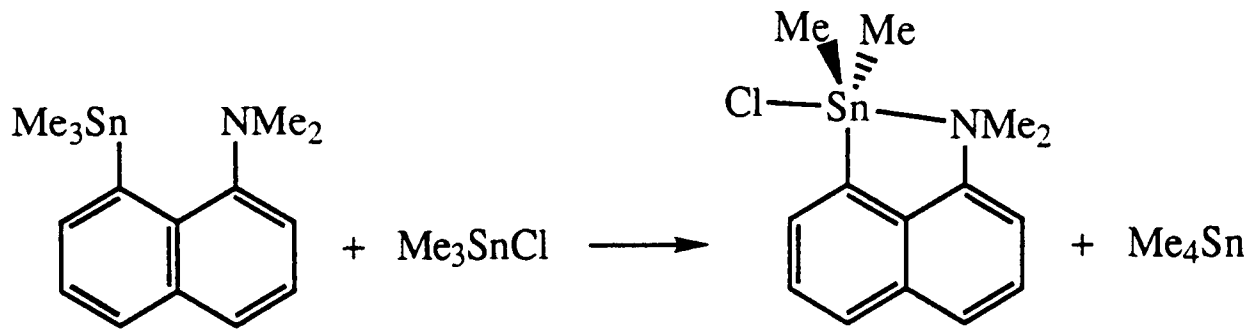
2.3.1. Introduction

Halodemetalations of tetraorganotin compounds have been found to be facilitated by the presence of potential intramolecular coordinating groups, Scheme 55, containing either nitrogen[100] or oxygen.[101] It is thought that intramolecular assistance by these groups facilitates the cleavage of Sn-C bonds *trans* to them.



Scheme 55

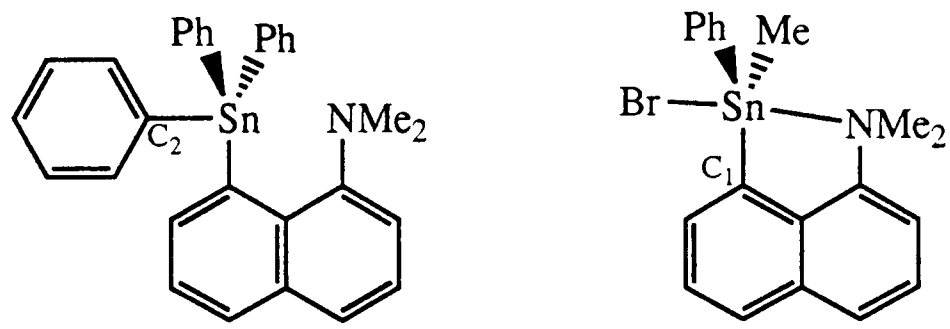
In a similar fashion [8-(dimethylamino)-1-naphthyl]trimethyltin (**55**) shows exceptional reactivity in the redistribution reaction with trimethyltin chloride,[102] Scheme 56.



(**55**) (**56**)

Scheme 56

A study of the structures of the related compounds [8-(dimethylamino)-1-naphthyl]triphenyltin (**57**) and [8-(dimethylamino)-1-naphthyl]methylphenyltin bromide (**58**) gives an insight into the system.[103]

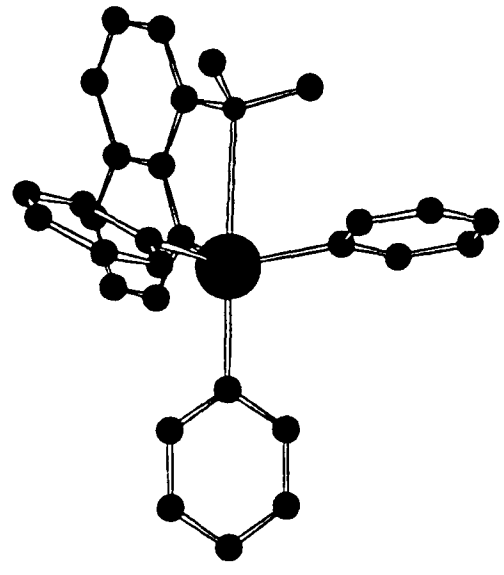


(**57**) (**58**)

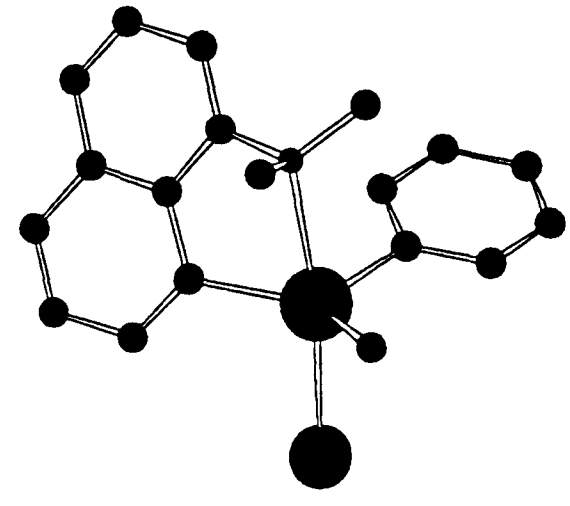
The crystal structure of (**58**), Figure 3, shows that the Sn atom is in a trigonal bipyramidal environment, as a result of Sn-N chelate bonding of the 8-(dimethylamino)-1-naphthyl group. The Sn-C bonds are in the equatorial sites, perpendicular to the naphthyl plane, and the more electronegative N and Br atoms occupy the axial positions. Although the N-Sn-Br angle is almost linear (171.5°), the C_1-Sn-N angle (74.9°) deviates from the ideal trigonal bipyramidal value of 90°. This, however, is to be expected since the angle is determined by the fairly inflexible values of the C-N and Sn-C bond lengths. The length of the Sn-N bond is 2.49 Å.

The crystal structure of (**57**), Figure 3, shows a configuration at tin that is intermediate between a tetrahedron and a trigonal bipyramid. The Sn-C_2 bond distance (2.18 Å) is found to be longer than the other Sn-C_{ipso} bond lengths (2.13-2.14 Å), and the

Sn-N distance is also very long (2.88 Å). This highlights the intermediacy of the geometry, with C_2 and N occupying pseudo-axial positions of a trigonal bipyramid. Further evidence of the weak Sn-N interaction is that the Sn and N atoms at the 1- and 8-positions of the naphthalene rings are in the plane of these rings, while in other 1, 8-disubstituted naphthalenes these substituents are twisted out of plane, due to steric interactions.[104]



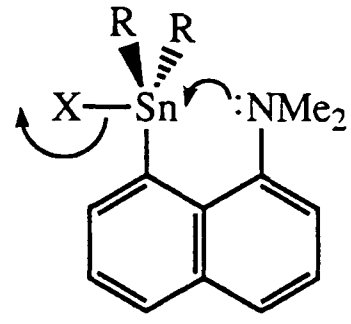
(57)



(58)

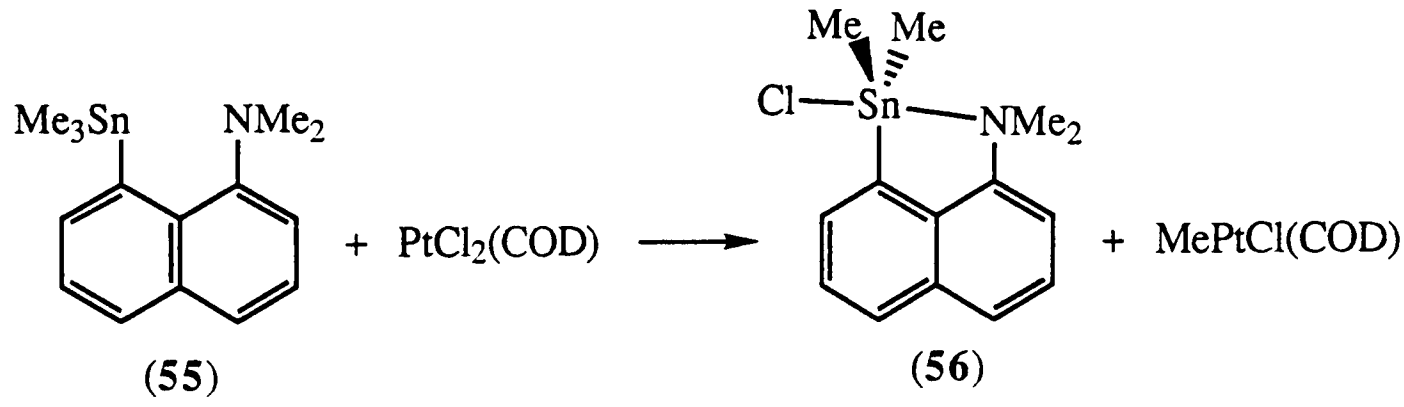
Figure 3: Representations of the crystal structures of (**57**) and (**58**)

The axial arrangement of N and Br in (**58**) and N and C_2 in (**57**) can be seen as being on an S_N2 pathway for substitution with inversion at tetrahedral Sn. The NMe_2 lone pair is the incoming nucleophile with Br and C_2, respectively, being the leaving group, (**59**).



(**59**)

The trimethyl derivative (**55**) has been found to methylate the platinum complex $PtCl_2$(COD) leading to the formation of (**56**) and MePtCl(COD) in quantitative yield,[102] Scheme 57.



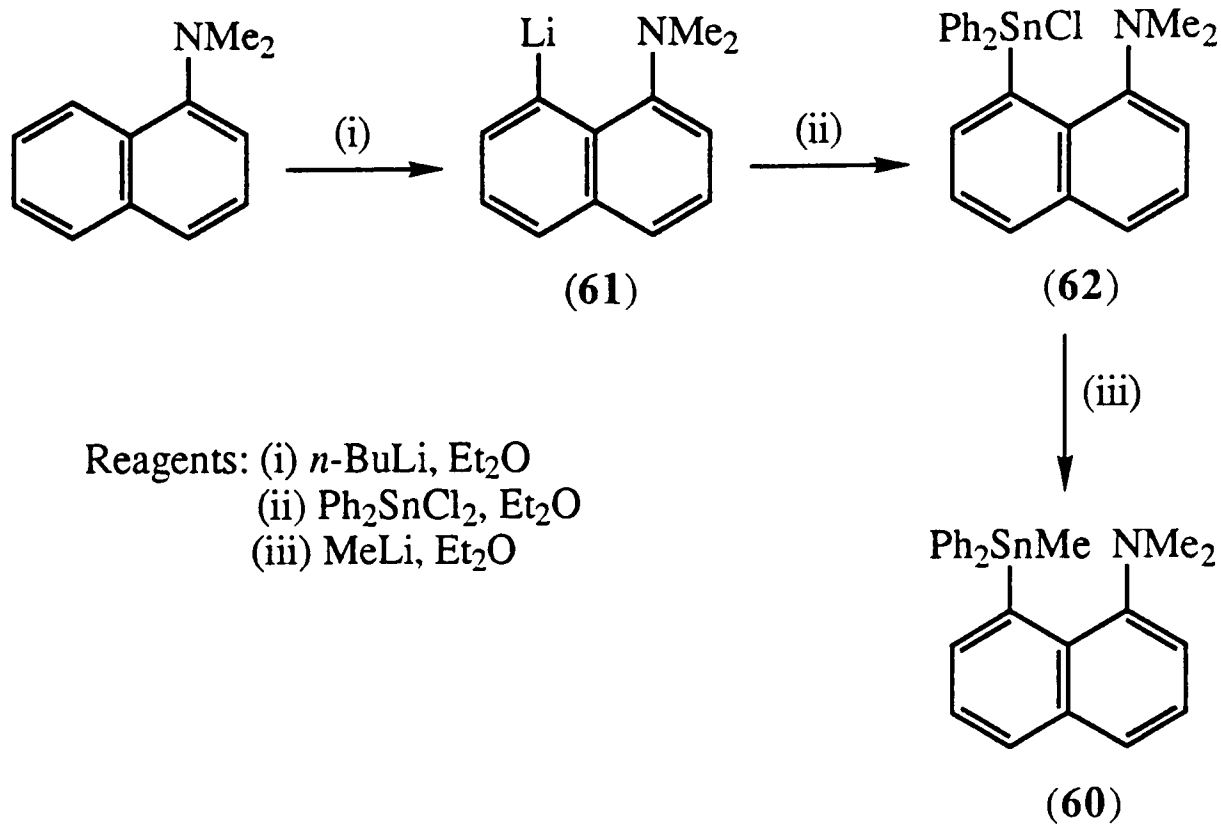
Scheme 57

The transformation has been effected by use of Me_4Sn, but forcing conditions were required and only a 60% yield obtained.[105] This demonstrates that the internal assistance of an NMe_2 group can also facilitate transfer of a group to Pt.

With this in mind it was decided to investigate the use of such compounds for Stille couplings. The rate determining step in the catalytic cycle (Scheme 33) has been established as the transmetalation from Sn to Pd. It was therefore hoped that the internal assistance of the NMe_2 group would facilitate the transfer of organic groups to Pd, so reducing the severity of the conditions needed for coupling.

2.3.2. Coupling Reactions with Internally Assisted Organostannanes

The compounds initially chosen for the investigation were [8-(dimethylamino)-1-naphthyl]triphenyltin[106] (**57**) and [8-(dimethylamino)-1-naphthyl]methyldiphenyltin[106] (**60**), which was synthesised according to the method of van Koten,[102,103] Scheme 58. Organometallic compounds of this type have been used to prepare methyl- and phenylplatinum compounds similar to those described above, showing that transfer from Sn to Pd should be feasible, hopefully with a similar reduction in the severity of the conditions.



Scheme 58

N, N-dimethylnaphthylamine was deprotonated selectively in the 8-position by *n*-butyllithium, giving (**61**). This precipitated out of solution and was collected in a near quantitative yield. This solid was then added to a solution of one equivalent of diphenyltin dichloride to give [8-(dimethylamino)-1-naphthyl]diphenyltin chloride (**62**), in a 35% yield after recrystallisation. The structure of (**62**) should be similar to that of (**58**) and (**56**), with the Sn in a trigonal bipyramid, and the Cl atom in an axial position. This is confirmed by proton NMR by the large downfield shift of H_2 in the naphthyl ring (8.7 ppm) which is in the proximity of the Sn-Cl bond. Reaction of (**62**) with methyllithium furnished (**60**) in 34% yield. The methyl group gave a singlet in the proton NMR spectrum at 0.79 ppm, with Sn-H coupling of 56, 58 Hz.

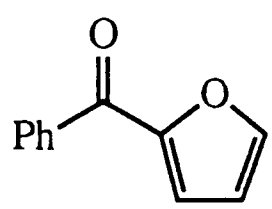
In order to compare the reactivity of these compounds with 'unactivated' molecules an organostannane of similar structure, but without a group capable of acting as an internal nucleophile, was needed as a control. The compound chosen was methyltriphenyltin (**63**). This was prepared simply[107] by the reaction of triphenyltin chloride with a methyl Grignard reagent, Scheme 59. The methyl group appeared at 0.73 ppm (J = 55, 57 Hz) in the ^1H NMR spectrum.

$$Ph_3SnCl + MeMgBr \xrightarrow{Et_2O} Ph_3SnMe \quad 86\%$$
(63)

Scheme 59

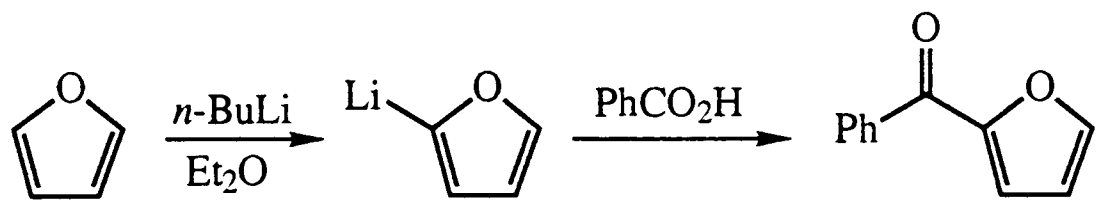
The reaction which was investigated was the Pd catalysed coupling with acid chlorides, and 2-furoyl chloride was chosen as the electrophile. This was because it has been little studied in these types of reaction, and also because the resonances for the furoyl protons appear at a slightly higher field in the NMR spectrum than phenyl and naphthyl protons, thus providing a convenient 'handle' for product analysis.

Transfer of a phenyl group would be expected to occur in preference to a methyl group in both (**60**) and (**63**), and so a successful reaction should yield 2-benzoylfuran (**64**).



(64)

An authentic sample of (**64**) was prepared,[108] Scheme 60, against which the products of the coupling reactions could be compared.

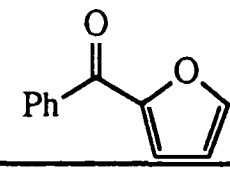
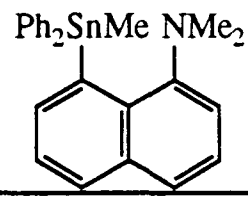
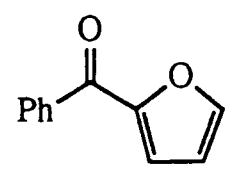
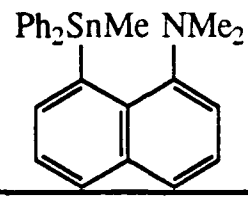
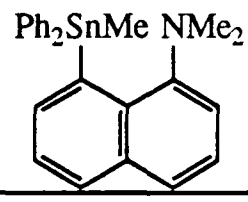
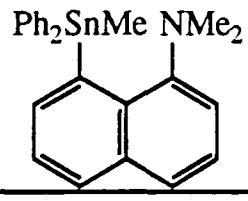
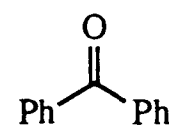
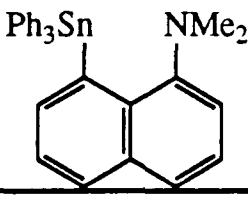


(64)

Scheme 60

The catalyst chosen was (**53**), and this was used at 4 mol% in the reactions. If a phenyl group were transferred to the Pd, then on the first catalytic cycle the acylarylorganopalladium complex would be $PhCOPd(PPh_3)_2Ph$. Reductive elimination from this would lead to benzophenone, which would accompany the formation of (**64**) in 4% of the total yield, if the reaction were quantitative. The reactions were carried out on a 0.1-0.3 mmol scale in dry degassed thf for 22 h, and the results are given in Table 2.

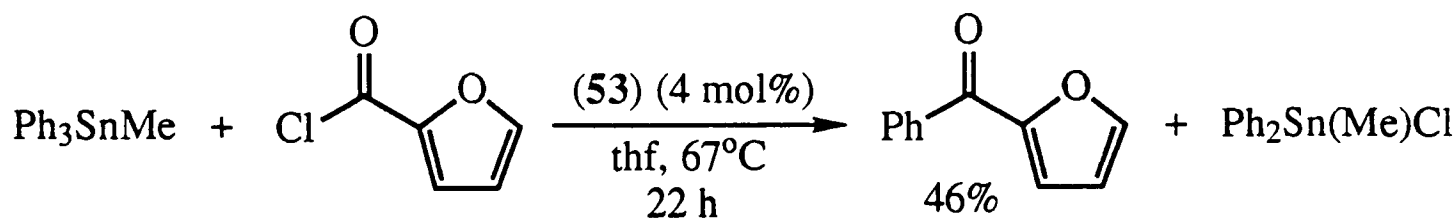
Table 2: Pd Catalysed Coupling of Organostannanes with 2-Furoyl Chloride[a]

Entry	Organotin	Temp (°C)	Product	Yield[b] (%)
1	Ph_3SnMe	67		46
2[c]	Ph_3SnMe	67	No Reaction	
3	Ph_3SnMe	RT	No Reaction	
4		67		37
5[c]		67	No Reaction	
6		RT	No Reaction	
7[d]		67		52
8		67	mixture[e]	

[a]Reactions were carried out on a 0.1-0.3 mmol scale in dry degassed thf with $PhCOPd(PPh_3)_2Cl$ (4 mol%) as catalyst for 22 h. [b]Isolated yield. [c]Reaction carried out in absence of catalyst. [d]PhCOCl used as electrophile. [e]Mixture containing unreacted starting materials and decomposition products.

The control compound (**63**) was found to undergo successful reaction in refluxing thf (67°C), with product (**64**) isolated in 46% yield (entry 1), Scheme 61. As expected this was accompanied by the formation of benzophenone, which was also observed in all subsequent successful reactions involving (**53**) as catalyst. The tin complex methyldiphenyltin chloride

(**65**) was isolated from the reaction and its proton NMR showed a downfield shift of 0.3 ppm for the methyl signal (*cf* proton NMR shift for benzylic protons in (**50**) *vs* (**54**), where $\Delta\delta$ = + 0.45 ppm) relative to the methyl signal from (**63**).

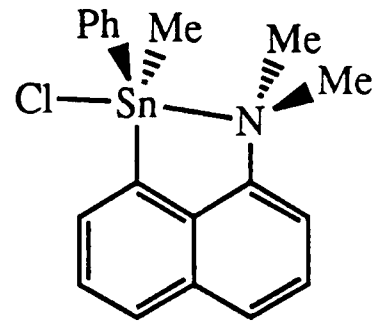


(**63**) (**64**) (**65**)

Scheme 61

Stannane (**63**) was found to be unreactive when the reaction was performed in the absence of catalyst (entry 2) and also when the catalysed reaction was run at room temperature (entry 3). In both instances unreacted starting material was recovered.

The initial reactions of (**60**) proved to be identical to those of the control. (**64**) was isolated in 37% yield from the catalysed reaction at 67°C (entry 4), but only starting material was recovered from the room temperature and uncatalysed reactions (entries 6 and 5). The coupling was also successful when a different electrophile, benzoyl chloride, was used, giving benzophenone as the product (entry 7). From the successful reactions the tin containing product [8-(dimethylamino)-1-naphthyl]methylphenyltin chloride (**66**) was isolated and identified.



(**66**)

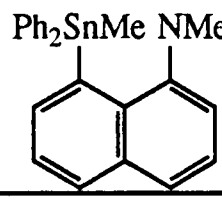
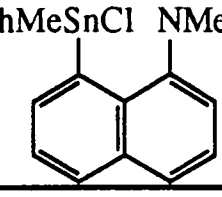
The proton NMR spectrum showed the now expected downfield shift for the methyl group, $\Delta\delta$ = + 0.37 ppm. The signal for H_2 of the naphthyl ring was shifted downfield and observed as a doublet at 8.68 ppm. Two Me resonances were observed for the NMe_2 group at 2.71 and 2.29 ppm. This is due to the group becoming diastereotopic as a result of the Sn-N bonding to the asymmetric Sn centre. This was confirmed in the ^{13}C NMR spectrum

which also showed two resonances for the Me groups at 49.3 and 48.5 ppm. The mass spectrum of (**66**) gave m/z 382 (100%), corresponding to M-Cl.

Reaction of (**57**) was less satisfactory. After 22 h a mixture was obtained, containing mainly unreacted starting materials accompanied by unidentifiable decomposition products (entry 8).

From these experiments the tin by-products (**65**) and (**66**) were isolated, and their ^{119}Sn NMR spectra obtained. The spectra of starting materials (**63**) and (**60**) were also obtained; the chemical shifts are given in Table 3.

Table 3: ^{119}Sn Chemical Shifts of Organotin Compounds[a]

Entry	Organotin	$\delta(^{119}Sn)$
1	Ph_3SnMe	-92.8
2	$Ph_2Sn(Me)Cl$	-38.9
3		-110.8
4		-98.2

[a](93.18 MHz) in thf with values in ppm measured against Me_4Sn as reference ($\delta = 0$).

The ^{119}Sn chemical shift is strongly dependent on the oxidation number of tin, the type of substituents present at tin and especially their electronegativity, the coordination number of tin and the geometrical configuration at the tin centre.[109,110] An increase in the electronegativity of the substituents leads to a decrease in the tin shielding and a downfield shift of the signal. This is observed when an organic group in (**63**) and (**60**) is replaced by

chloride. With these values the reactions could easily be followed by ^{119}Sn NMR, the reactions being performed in an NMR tube. Using this technique the reaction of these two compounds was probed further.

Reaction of the control compound, Ph_3SnMe (**63**), was attempted at 40°C and followed by ^{119}Sn NMR. After 22 h the only peak in the spectrum was that corresponding to starting material, i.e. (**63**) was unreactive at this temperature. The reaction of (**60**) at 40°C was carried out, and after 22 h two peaks were visible in the spectrum, at -110.8 and -98.2 ppm, (**60**) and (**66**) respectively. Assuming that the isotopes of Sn react at the same rate, so that the percentage of ^{119}Sn is the same in both starting material and product, and also that the relaxation time for the ^{119}Sn nucleus is the same in (**60**) and (**66**), then integraion of the peaks gave a value of 45% reaction. After 38 h only the peak at -98.2 was observed, indicating the major tin containing species was (**66**), Figure 4. On work-up (**64**) was isolated in 64% yield.

The results from these experiments indicate that [8-(dimethylamino)-1-naphthyl]methyldiphenyltin (**60**) has an enhanced reactivity compared to methyltriphenyltin (**63**). This effect might be due to the presence of the NMe_2 group which could be capable of acting as an internal nucleophile and attacking the Sn atom. This could facilitate the transfer of a phenyl group to the Pd catalyst. The triphenyl analogue (**57**) shows a reduced reactivity compared to (**63**). The reasons for this reversal in the effect are not known, but may be due to steric interactions hindering the transmetalation step.

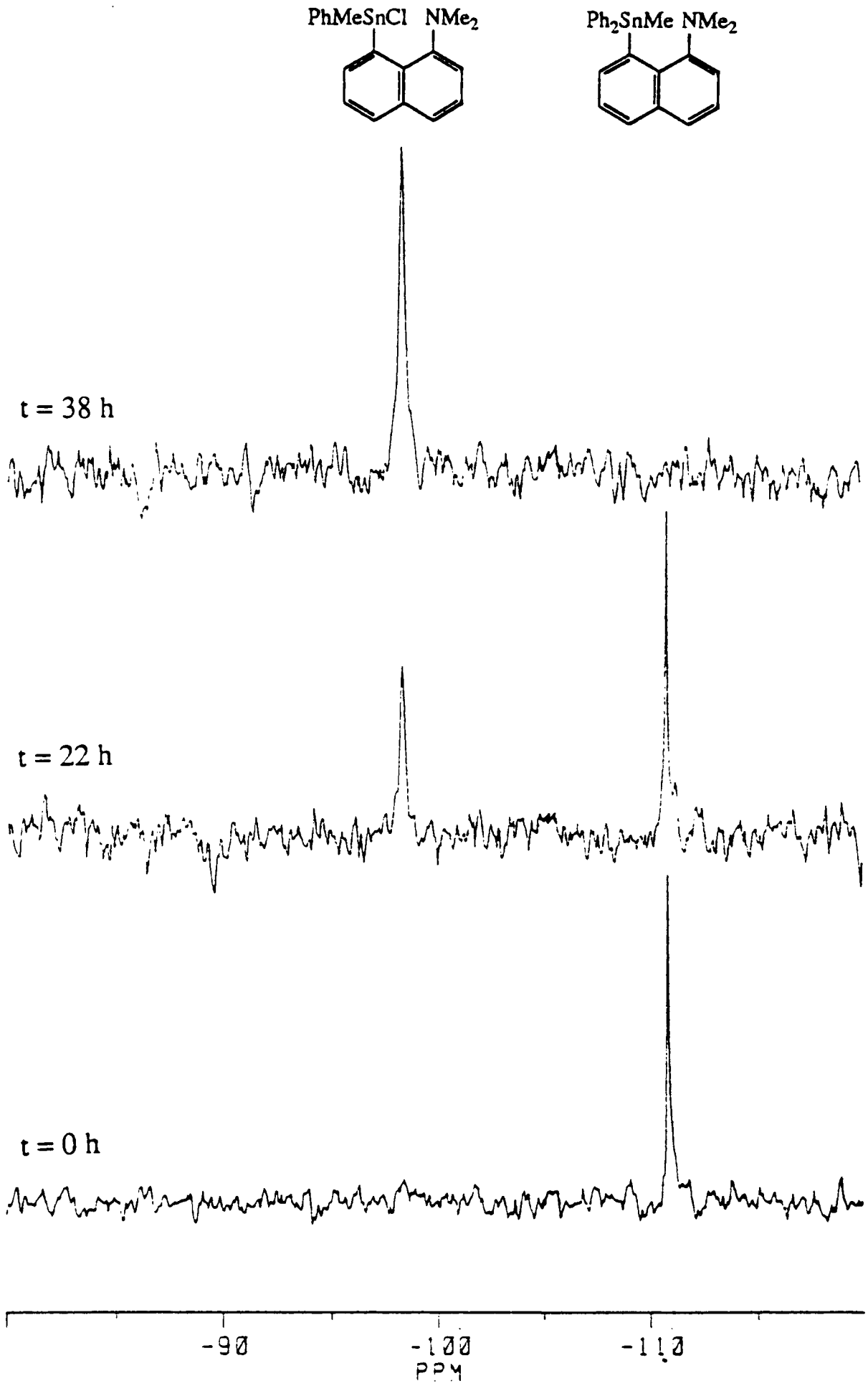
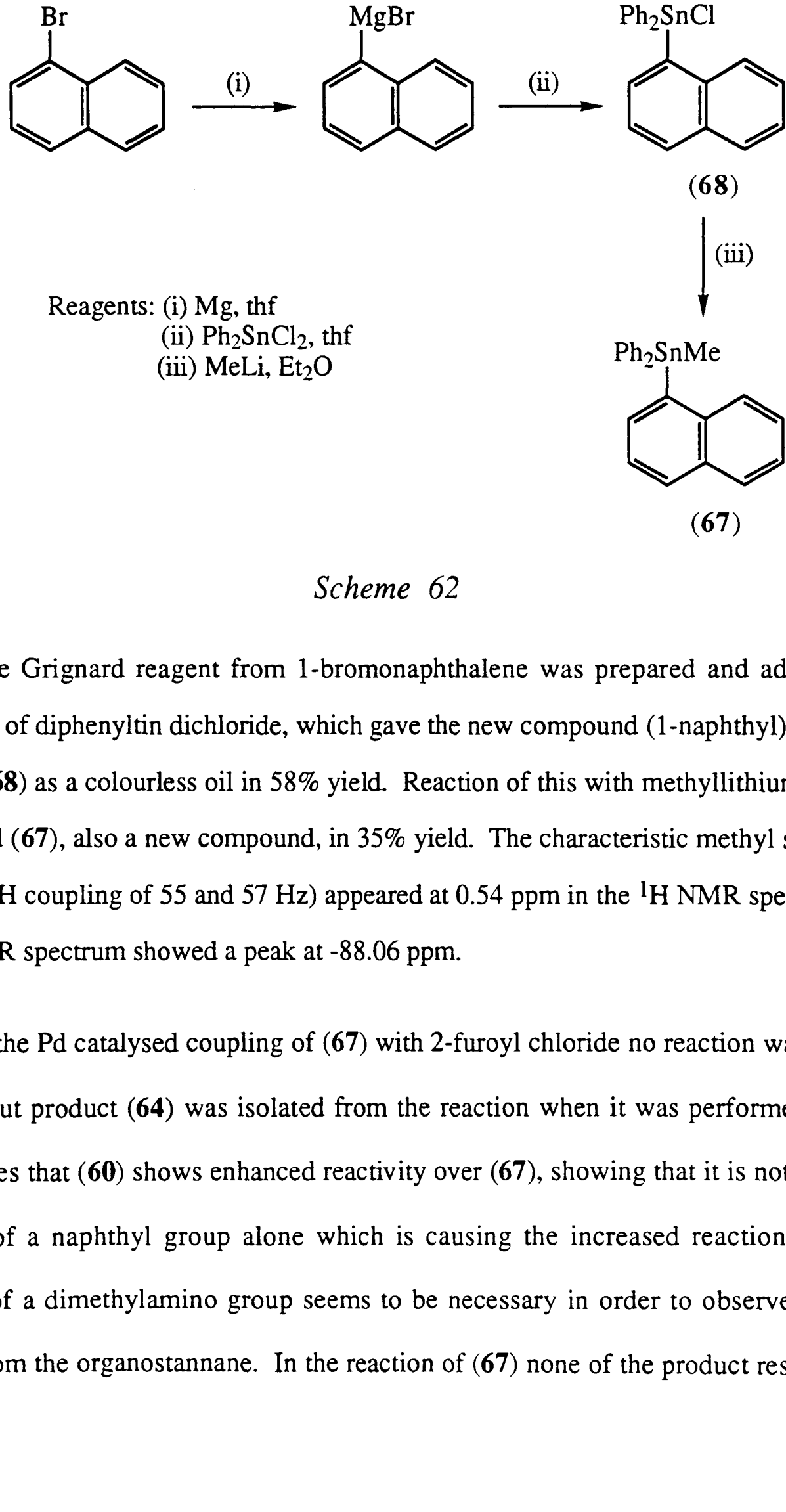


Figure 4: ^{119}Sn NMR spectra of Pd Catalysed Cross-Coupling between [8-(dimethylamino)-1-naphthyl]methyldiphenyltin (**60**) and 2-Furoyl Chloride at 40°C

A closer comparison of reactivity would be between (**60**) and (1-naphthyl) methyldiphenyltin (**67**), as this would enable the effect of a naphthyl group bound to tin to be tested. Compound (**67**), which contains no group capable of acting as an internal nucleophile, was thus prepared according to Scheme 62.



Scheme 62

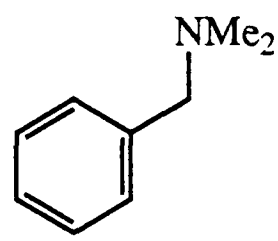
The Grignard reagent from 1-bromonaphthalene was prepared and added to one equivalent of diphenyltin dichloride, which gave the new compound (1-naphthyl)diphenyltin chloride (**68**) as a colourless oil in 58% yield. Reaction of this with methyllithium furnished the desired (**67**), also a new compound, in 35% yield. The characteristic methyl signal (with ^{117,119}Sn-H coupling of 55 and 57 Hz) appeared at 0.54 ppm in the ^{1}H NMR spectrum. The ^{119}Sn NMR spectrum showed a peak at -88.06 ppm.

In the Pd catalysed coupling of (**67**) with 2-furoyl chloride no reaction was observed at 40°C, but product (**64**) was isolated from the reaction when it was performed at 67°C. This implies that (**60**) shows enhanced reactivity over (**67**), showing that it is not merely the presence of a naphthyl group alone which is causing the increased reaction rate. The presence of a dimethylamino group seems to be necessary in order to observe facilitated transfer from the organostannane. In the reaction of (**67**) none of the product resulting from

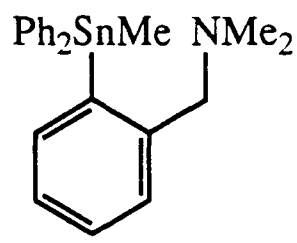
naphthyl group transfer, 2-(1-naphthoyl)furan, was encountered. This indicates that under 'normal' Stille conditions a phenyl group is transferred more readily than a 1-naphthyl group.

2.3.3. Further Amine Assisted Organotin Cross-Couplings

If the facilitated transfer shown by (**60**) is due to the internal nucleophilic attack of the nitrogen lone pair on the tin atom, then by making the lone pair more basic the effect may be further increased. The parent amine, N, N-dimethyl-1-naphthylamine has a pKa value of 4.83.[111] The lone pair will, to some extent, be conjugated into the aromatic system of the naphthalene rings. One way to increase the basicity of the lone pair, therefore, will be to remove the possibility of this type of conjugation. This is achieved in N, N-dimethylbenzylamine (**69**), which has a pKa value of 8.91.[111] It was therefore decided to make the tin analogue of this compound, [2-((dimethylamino)methyl)phenyl] methyldiphenyltin (**70**), and to test its reactivity in the Stille cross-coupling with 2-furoyl chloride.

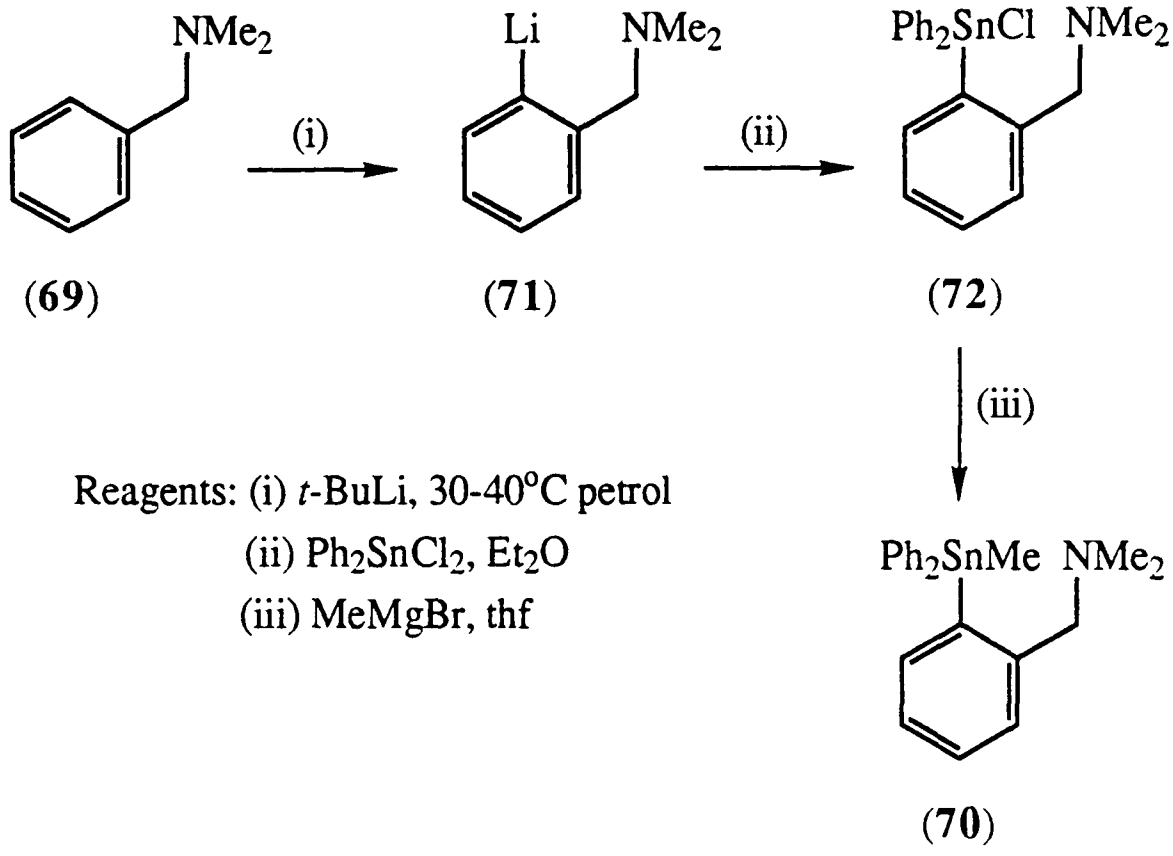


(**69**)



(**70**)

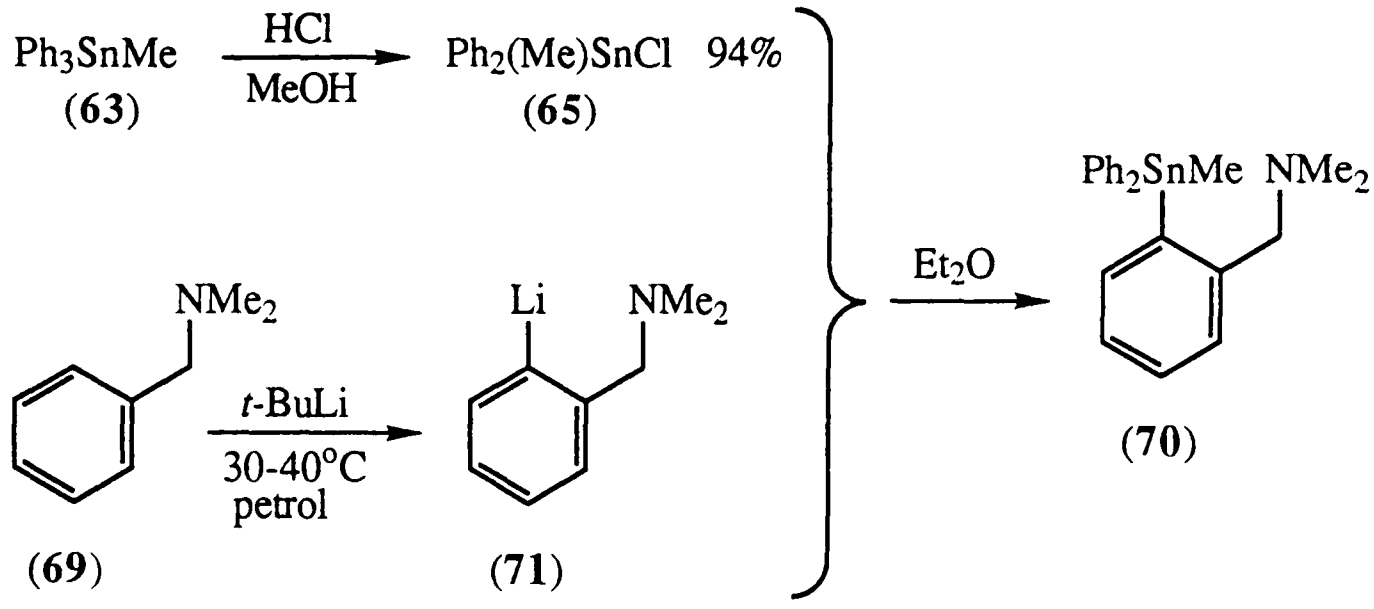
The new compound (**70**) was initially synthesised by an analogous route to that used for the synthesis of (**60**), Scheme 63.



Scheme 63

Deprotonation of (**69**) with *t*-butyllithium resulted in the lithiated species (**71**), which was isolated as a solid in near quantitative yield.[112] The nitrogen atom directs the lithiation to the 2-position. This was added to a solution of Ph_2SnCl_2, and after 20 h [2-((dimethylamino)methyl)phenyl]diphenyltin chloride (**72**) was isolated as a white solid in 36% yield. The proton NMR spectrum showed the doublet for H_6 shifted downfield to 8.5 ppm, due to its proximity to the Sn-Cl bond. This again demonstrates the trigonal bipyramidal structure around the Sn atom due to Sn-N bonding, with the Cl occupying the axial position. Methylation was achieved with methylmagnesium bromide to give (**70**) as a colourless oil. The proton NMR spectrum showed the methyl signal (with J = 58, 60 Hz) at 0.74 ppm. $\delta(^{119}Sn)$ was found to be -115.9 ppm. The yield for the last step of the reaction was 20%, which gave an overall yield of *ca.* 8% from starting amine (**69**).

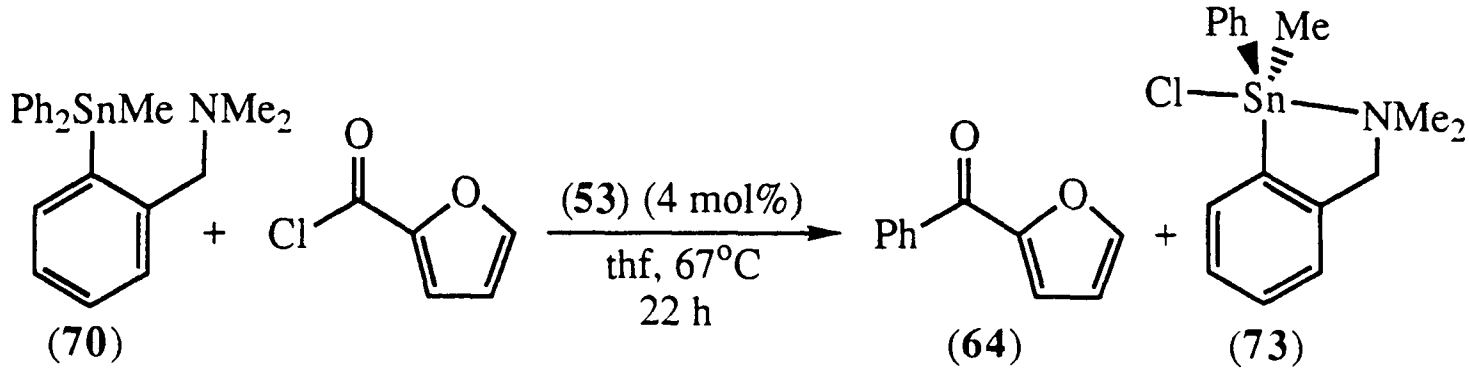
This poor yield prompted a slightly different strategy to be employed, and a much more efficient synthetic route was devised, Scheme 64.



Scheme 64

Methyltriphenyltin (**63**) was prepared as previously described, Scheme 59. One of the phenyl groups was then replaced by Cl by the use of methanolic HCl[113] to give methyldiphenyltin chloride (**65**) in 94% yield. This was then reacted directly with the lithiated species (**71**) to give product (**70**). The overall yield from starting amine by using this route was 38%, a vast improvement on Scheme 63. This route was not optimised but it should be possible to obtain (**70**) in even greater yields by this procedure, and also to apply the approach to the synthesis of the dimethylaminonaphthyl and other organotin compounds.

The cross-coupling reaction of (**70**) and 2-furoyl chloride, with $PhCOPd(PPh_3)_2Cl$ (**53**) (4 mol%) as catalyst, in thf was then investigated. Small scale reaction at 67°C was found to give the desired product (**64**) and the tin by-product (**73**) in moderate isolated yields (*ca.* 40%), Scheme 65, although ^1H NMR of the crude product showed that (**64**) and (**73**) were the major reaction components, present in > 90%.



Scheme 65

(**73**) was characterised and $\delta(^{119}Sn)$ found to be -108.8 ppm. The proton NMR showed the usual downfield shift for the methyl signal ($\Delta\delta$ = + 0.29 ppm). The two NMe_2 methyl groups gave two signals at 2.29 and 1.91 ppm, and the signal for H_6 appeared as a doublet at 8.39 ppm. This evidence again highlights the presence of a chelate structure for (**73**) with internal Sn-N bonding. The mass spectrum gave m/z 346 (25%), corresponding to M-Cl.

The reaction carried out at room temperature failed to give any coupled products and unreacted (**70**) was recovered. The reaction was repeated at 40°C and followed by ^{119}Sn NMR. After 3 h a peak at -108.8 ppm, corresponding to (**73**), was seen in the spectrum. From integration of the peaks the extent of reaction was 8%. Spectra were obtained after 6, 10, 14 and 22 h and the extent of reaction at these times calculated to be 28%, 55%, 80% and 100% respectively, Figure 5.

From these experiments it can be deduced that (**70**) may be slightly more reactive than (**60**), because of the shorter time needed for the complete reaction. However, the relative reactivities are similar, and so the change in basicity in going from a naphthylamine to a benzylamine does not have a marked effect. The critical factor in influencing the increased reactivity (and hence transfer rate) seems largely to be the availability of the lone pair on the nitrogen. One reason why the full effect of the more basic lone pair in (**70**) is not being observed may be due to the internal attack being entropically less favoured than in (**60**), in which the NMe_2 group is held rigidly in place due to the naphthalene ring system. Also the presence of the Sn moiety may have an effect on the basicity of the lone pair which is not present in the parent amine.

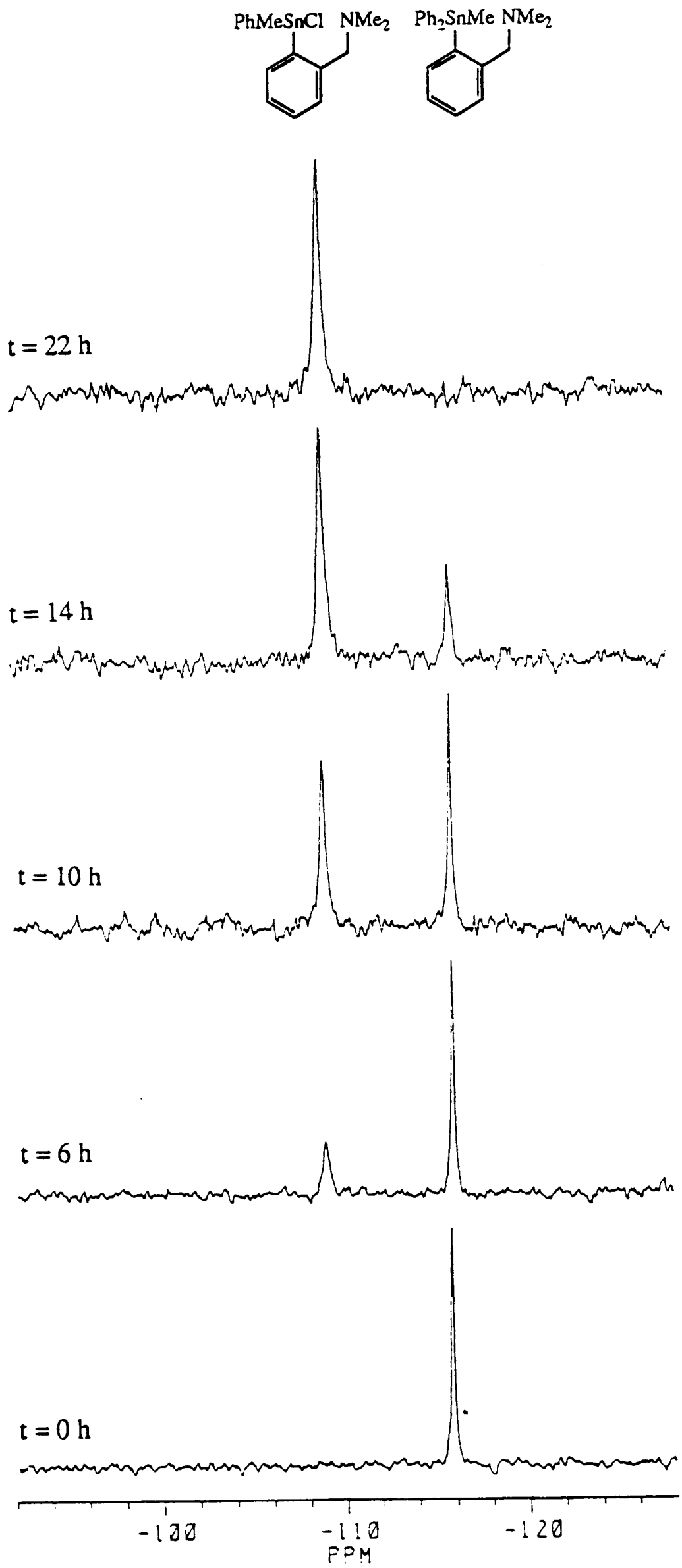


Figure 5: ^{119}Sn NMR Spectra for the Pd Catalysed Coupling of [2-((Dimethylamino) methyl)phenyl]methyldiphenyltin (**70**) with 2-Furoyl Chloride at 40°C

2.3.4. Amine Activation - Inter- or Intramolecular ?

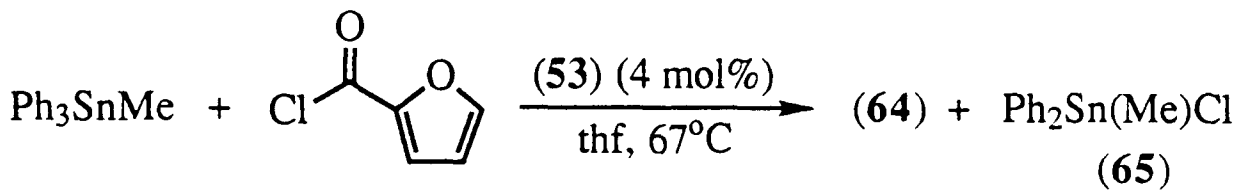
So far it has been demonstrated that molecules which contain an NMe_2 group, (**60**) and (**70**), react at lower temperatures than molecules which do not, (**63**) and (**67**). This has been attributed to the *intra*molecular effect of the lone pair on N acting as an internal nucleophile, (**59**). The possibility exists, however, that the effect could be wholly, or partially, due to *inter*molecular attack by the lone pair on N.

In order to assess the extent of any intermolecular assistance two sets of experiments were performed. The first of these involved reactions of 'unactivated' molecules with an added external amine present in the system, and the second comprised of a set of competitive reactions between the various molecules.

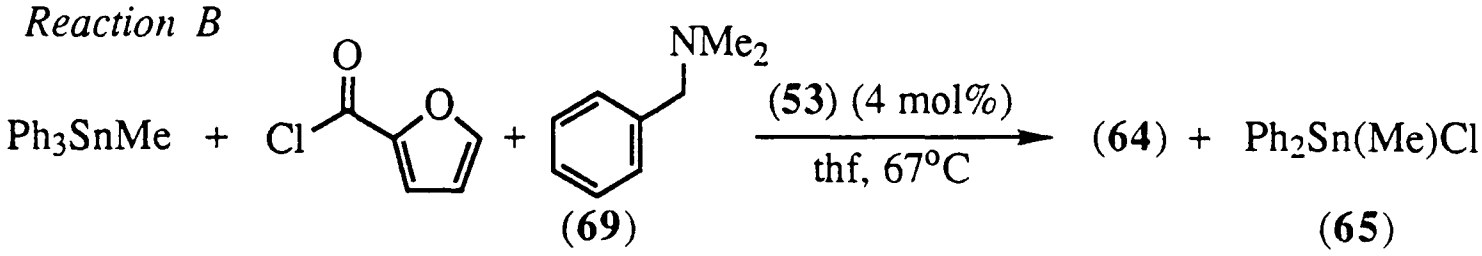
Experiments with added external amine present

The first experiment comprised of two reactions run under identical conditions. The first reaction was the coupling of the control molecule (**63**) with 2-furoyl chloride in refluxing thf with $PhCOPd(PPh_3)_2Cl$ (**53**) (4 mol%) as catalyst (*Reaction A*). The second reaction was identical except that one equivalent of N, N-dimethylbenzylamine (**69**) was added (*Reaction B*), Scheme 66. The reactions were performed in an NMR tube and followed by ^{119}Sn NMR. If the reaction with added (**69**) was found to proceed at a faster rate, then this could be attributed to intermolecular attack at Sn by (**69**).

Reaction A



Reaction B



Scheme 66

After 6 h a new peak had appeared in the spectra of both reactions *A* and *B*, at -39 and -73 ppm respectively. Both peaks correspond to the formation of $Ph_2(Me)SnCl$ (**65**). The different chemical shift in *Reaction B* is due to coordination of the added amine to (**65**). As a result of the increased Lewis acidity of triorganotin halides these compounds tend to be pentacoordinate in the presence of donor molecules,[114] such as (**69**). This was confirmed by the addition of (**69**) to a repeat of *Reaction A*, which caused the peak at -39 ppm to shift to -68 ppm. A similar upfield shift has been reported in triorganotin bromides capable of internal coordination relative to uncoordinated molecules.[110] After 6 h both reactions *A* and *B* were found to be *ca.* 20% complete by integration of the peaks in the spectrum.

Spectra were recorded after 11 and 20 h, during which the peaks at -39 and -73 ppm increased in intensity, with a corresponding decrease in intensity of the signal due to starting material (**63**). After 20 h *Reaction A* was *ca.* 70% complete and *Reaction B ca.* 80% complete. On work-up both yielded coupled product (**64**). Hence the rate of reaction of the 'unactivated' control (**64**) is essentially unaffected by the addition of an external NMe_2 source.

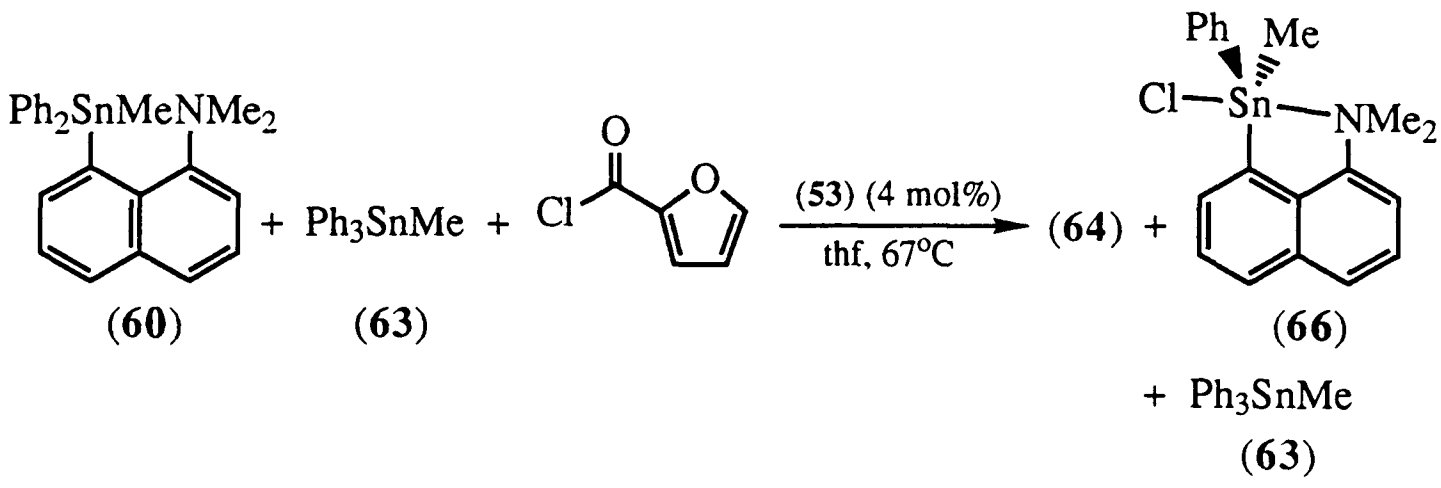
The second experiment involved the reaction of (**63**) and 2-furoyl chloride, with added external amine present, performed at 40°C. Under similar conditions with no external amine (**63**) was unreactive but both (**60**) and (**70**) did react. Thus any successful reaction in the experiment could be ascribed to the intermolecular assistance from the added amine. The reaction was again followed by ^{119}Sn NMR. After 22 h the spectrum showed only one signal, that of unreacted starting material.

The results from these experiments, i.e. addition of external amine neither increases the rate of reaction nor promotes the reaction of an 'unactivated' molecule, indicate that intermolecular effects do not play a large part in the enhancement of the reaction. This

supports the theory that the acceleration of transfer is due to an intramolecular attack by nitrogen at tin.

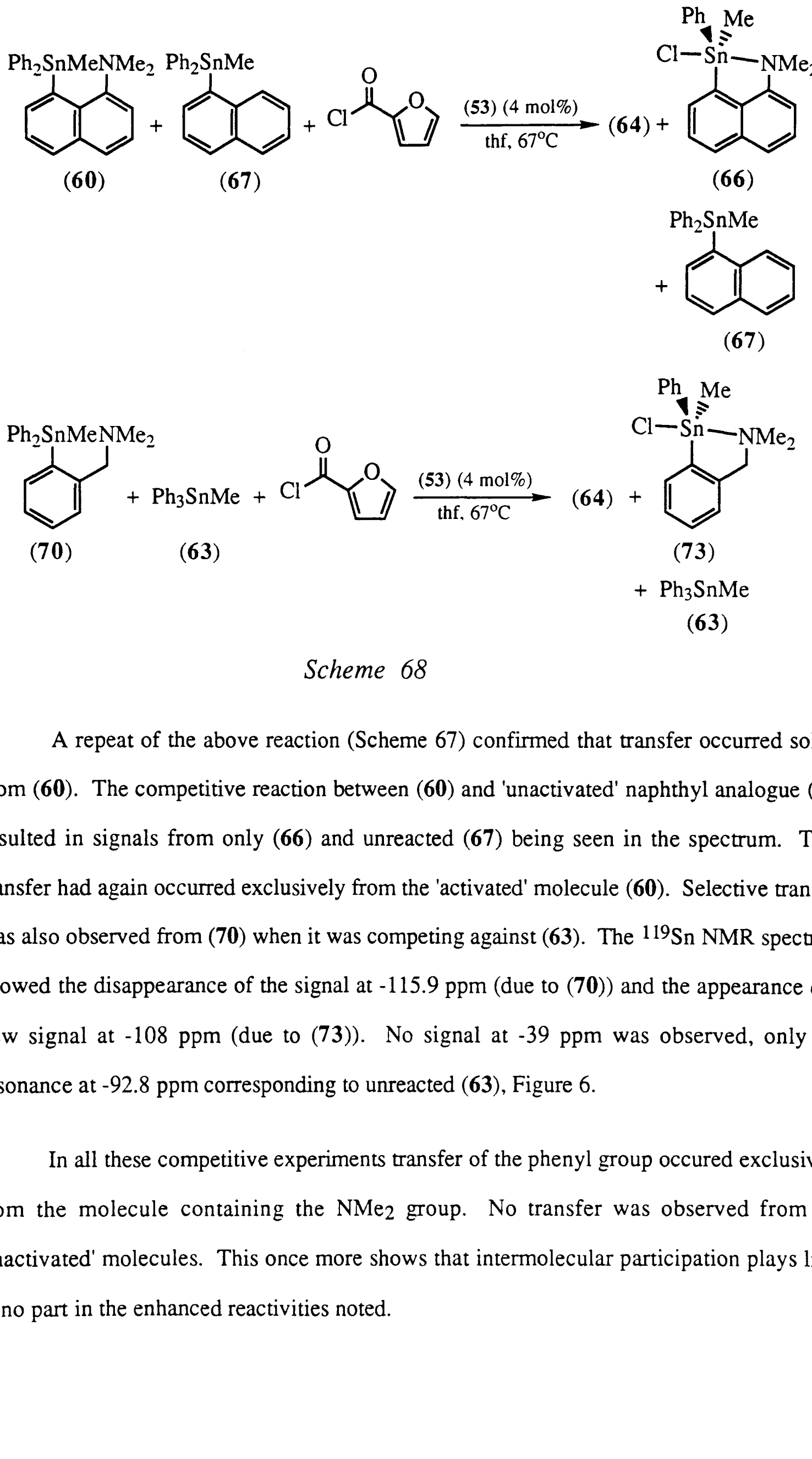
Intermolecular Competitive Reactions Between Different Organotin Reagents

A series of competitive reactions between 'activated' and 'unactivated' molecules was performed under conditions in which both were known to react. One equivalent of 'unactivated' compound, one equivalent of 'activated' compound and one equivalent of 2-furoyl chloride were reacted with (**53**) (4 mol%) as catalyst in refluxing thf. The first reaction involved competition between (**60**) and (**63**) and was analysed by product isolation. Transfer of a phenyl group from either molecule would result in coupled product (**64**) being formed. Different tin by-products would be formed, however, and it was the presence of (**65**) and/or (**66**) which was looked for. The reaction was carried out and on work-up the only by-product isolated was [8-(dimethylamino)-1-naphthyl]methylphenyltin chloride (**66**). No methyldiphenyltin chloride (**65**) was observed. This indicates that transfer occurred exclusively from the 'activated' molecule (**60**), Scheme 67.



Scheme 67

The next set of reactions, using the method described above, were followed by ^{119}Sn NMR. This would enable the identity of the tin containing species to be directly identified during the reaction. The results are given in Scheme 68.



Scheme 68

A repeat of the above reaction (Scheme 67) confirmed that transfer occurred solely from (**60**). The competitive reaction between (**60**) and 'unactivated' naphthyl analogue (**67**) resulted in signals from only (**66**) and unreacted (**67**) being seen in the spectrum. Thus transfer had again occurred exclusively from the 'activated' molecule (**60**). Selective transfer was also observed from (**70**) when it was competing against (**63**). The ^{119}Sn NMR spectrum showed the disappearance of the signal at -115.9 ppm (due to (**70**)) and the appearance of a new signal at -108 ppm (due to (**73**)). No signal at -39 ppm was observed, only the resonance at -92.8 ppm corresponding to unreacted (**63**), Figure 6.

In all these competitive experiments transfer of the phenyl group occured exclusively from the molecule containing the NMe_2 group. No transfer was observed from the 'unactivated' molecules. This once more shows that intermolecular participation plays little or no part in the enhanced reactivities noted.

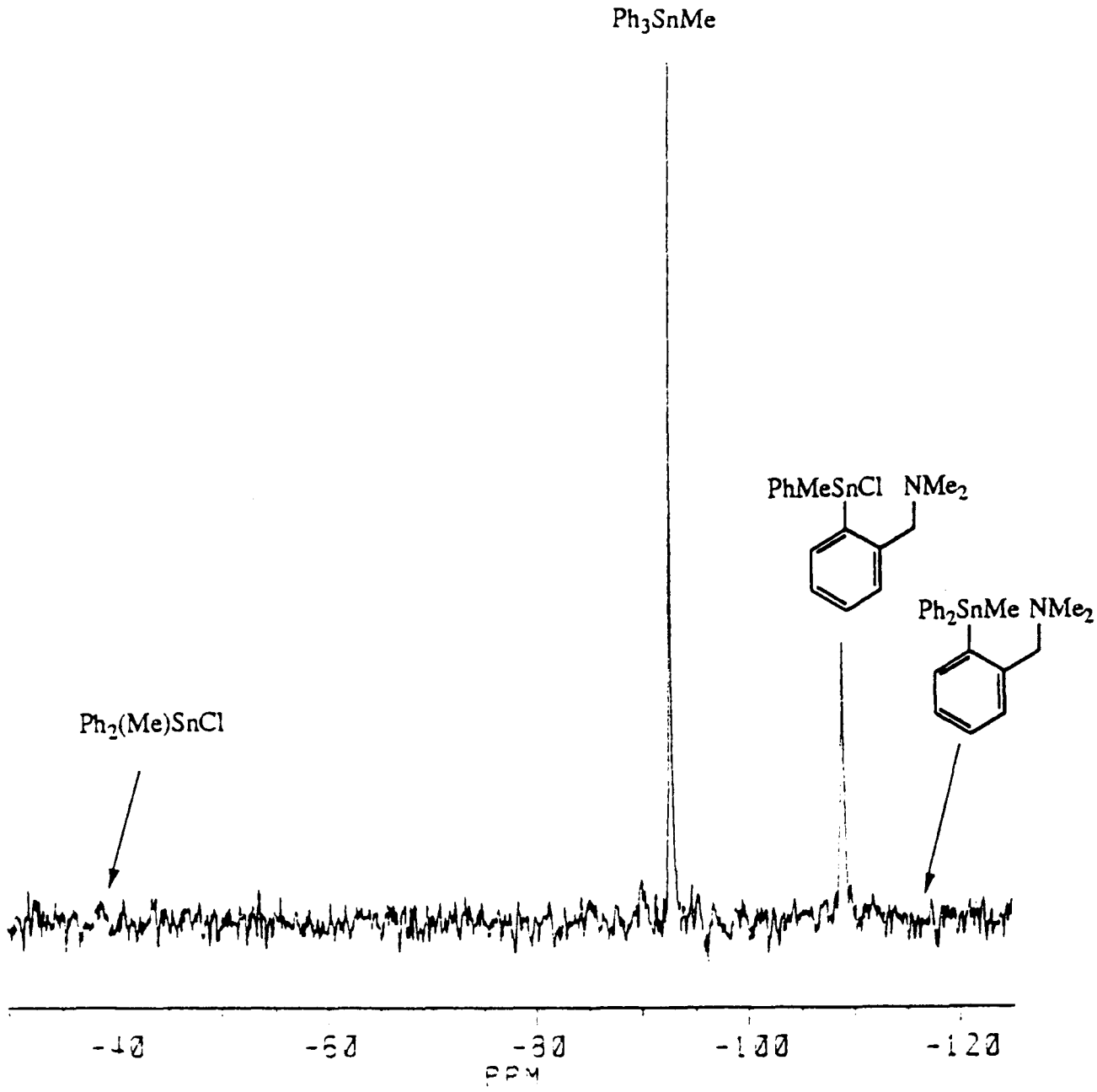
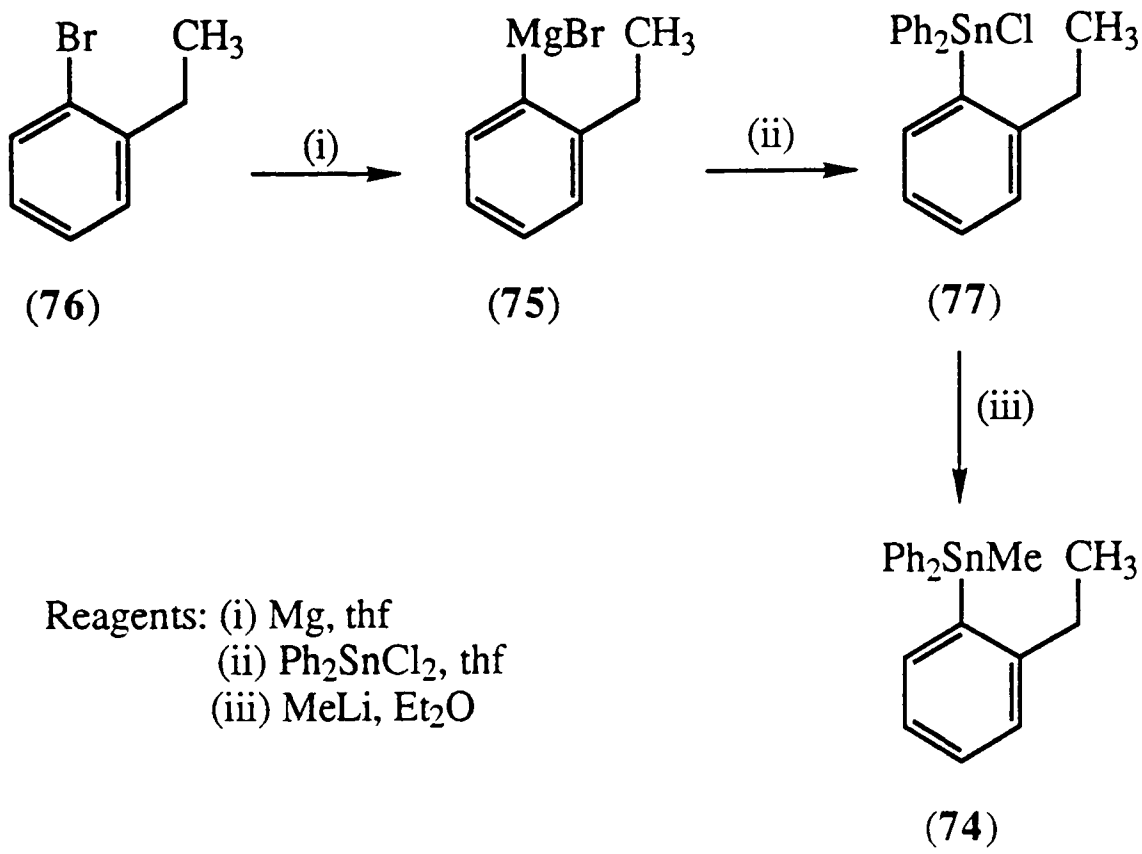


Figure 6: ^{119}Sn NMR Spectrum from the Competitive Coupling Reaction Between Methyl triphenytin (**63**) and [2-((Dimethylamino)methyl)phenyl] methyldiphenyltin (**70**) at 67°C

The conclusions which can be drawn from these experiments is that the facilitated transfer of a phenyl group from (**60**) and (**70**) occurs due to the presence of the NMe_2 moiety within those molecules, and that the effect is an *intra*molecular phenomenon.

So far this facilitation of transfer has been ascribed to an electronic effect, i.e. the internal attack of the lone pair of electrons on N at the Sn centre. No consideration has been given to the steric effects that an *ortho*-substituent on a phenyl ring bound to tin might cause. In order to gauge any steric effects an analogue of the 'activated' compounds was needed that could not act as an internal nucleophile. The simplest analogue would be one

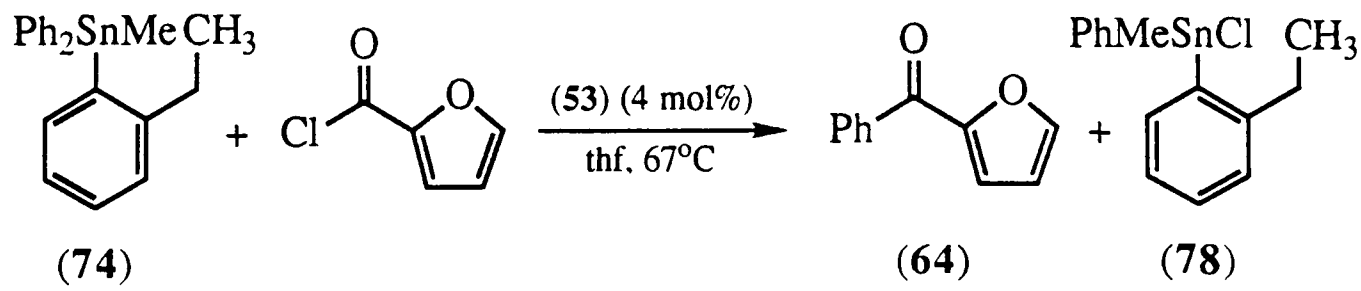
with an alkyl chain in the *ortho*-position, and so [(2-ethyl)phenyl]methyldiphenyltin (**74**) was prepared, Scheme 69.



Scheme 69

The Grignard reagent (**75**) from 1-bromo-2-ethylbenzene (**76**) was prepared and reacted with diphenyltin dichloride to give [(2-ethyl)phenyl]diphenyltin chloride (**77**) as a colourless oil in 82% yield. Methylation with methyllithium gave (**74**) in 51% (overall yield of 42% from starting (**76**)). The proton NMR of this new compound had the Sn-Me signal at 0.79 ppm (J = 53, 55 Hz) and the ^{119}Sn NMR spectrum had a resonance at -91.5 ppm.

The coupling of (**74**) with 2-furoyl chloride was then attempted, using the standard procedure, in refluxing thf, Scheme 70.



Scheme 70

The reaction was followed by ^{119}Sn NMR, and after 22 h only the peak corresponding to (**74**) was seen. After 50 h this was still the only discernible peak in the spectrum. The reaction was then stopped and worked up. The main component isolated

from the reaction mixture was indeed unreacted (**74**), but some (**64**) (< 10%) was also identified. The presence of the tin by-product (**78**) was not seen in the ^{119}Sn spectrum because of its low concentration but its presence in the reaction mixture must be assumed, by analogy with the other successful coupling reactions.

This result indicates that the steric effect of a substituent in the *ortho*-position slows down the reaction. If this is also the case in the molecules which have an NMe_2 group present then the facilitation of transfer must be wholly due to electronic effects.

The conclusions which can be drawn from these control experiments are:

(i) Molecules which contain an NMe_2 group in a suitable position undergo facilitated transfer of a phenyl group to a Pd catalyst.

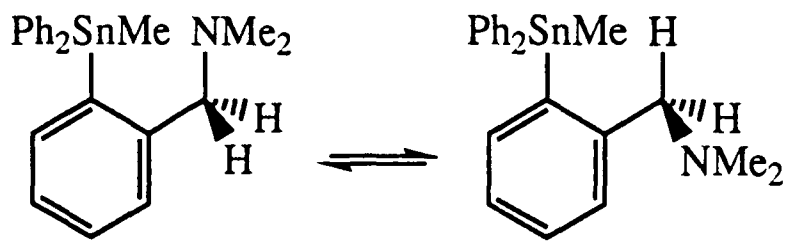
(ii) The effect is an electronic one, the lone pair on the nitrogen atom attacking the tin atom in an S_N2 type reaction. Steric interactions probably play no part in the rate enhancement.

(iii) The effect is an intramolecular phenomenon, with intermolecular interactions playing little or no role in causing the observed increase in rate of reaction.

2.3.5. Effect of Steric Buttressing in the Organotin Reagent

Reagent (**60**), in which the Sn and N substituents are in the 1- and 8-positions respectively, is a sterically rigid molecule. The geometry of the molecule and the steric crowding between these substituents (forcing the methyl groups on N away from Sn) ensures that the lone pair on N is in the correct position for attack at Sn. (**70**), however, is much less rigid and the steric interactions between the two substituents will force the NMe_2 group away from the Sn centre, thus reducing the extent of attack of the lone pair. The NMe_2 group is also able to rotate away from the Sn centre, Scheme 71. This rotation would remove the lone pair from the area in which it could exert an influence on the transfer of an

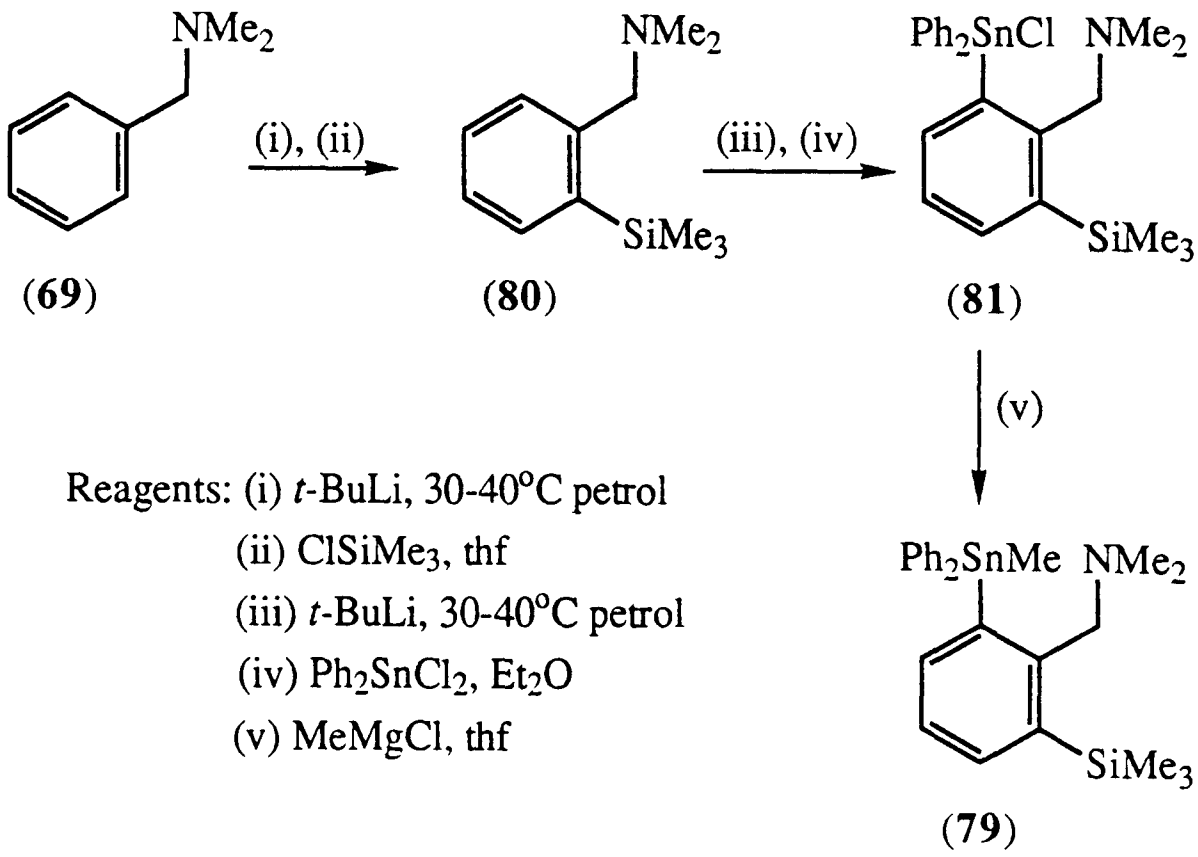
organic group. This would reduce the level of possible enhancement of the more basic lone pair in (**70**), thereby not utilising its full potential.



Scheme 71

In order to counteract these possible effects it would be necessary to have a bulky substituent at the 3-position. This would then serve two purposes. Firstly, it would prevent, or at least reduce, rotation away from the Sn centre and secondly, if the group was large enough it might force the N atom closer to the Sn atom. The combined effects of the increased basicity of the benzylamine lone pair and the steric buttressing within the molecule[115] were hoped to increase the reactivity of the system further.

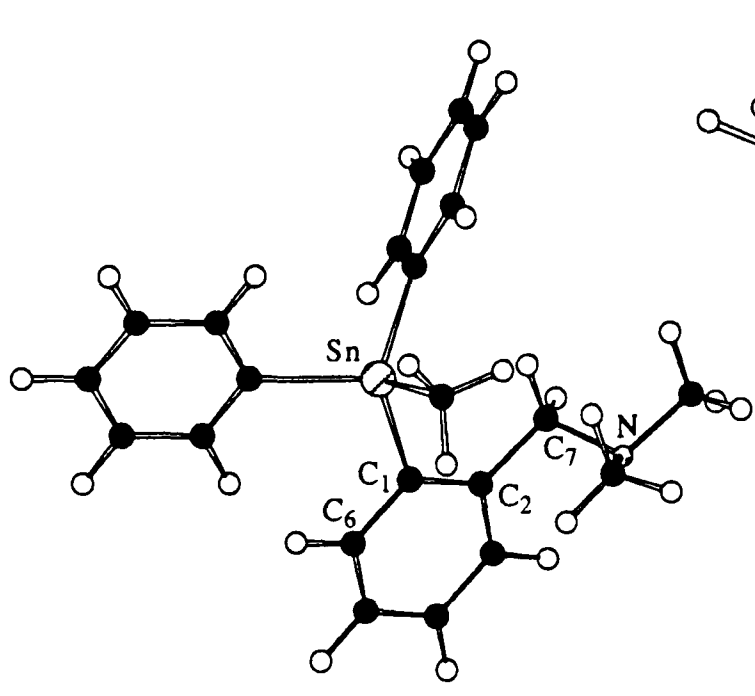
A trimethylsilyl group was chosen as the bulky group for the 3-position, and the novel compound [(2-((dimethylamino)methyl)-3-trimethylsilyl)phenyl]methyldiphenyltin (**79**) was prepared, Scheme 72.



Scheme 72

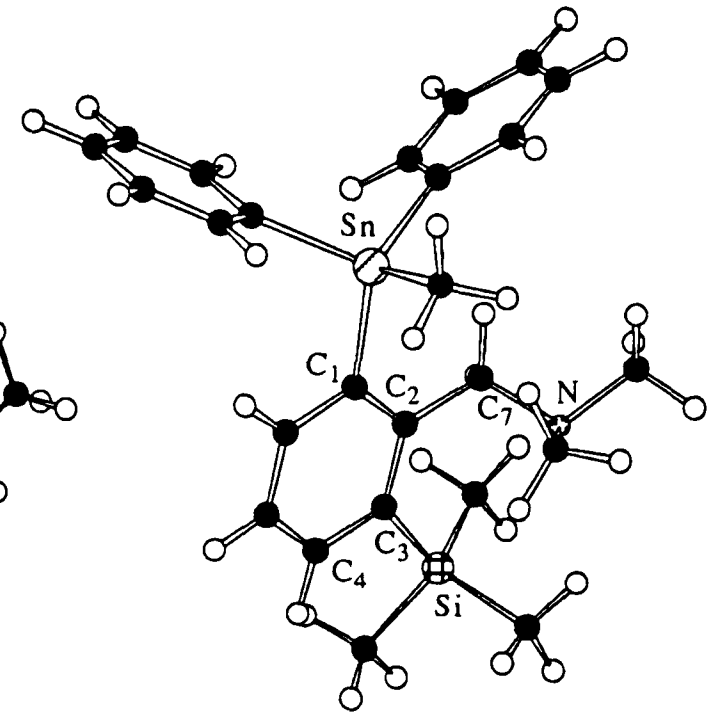
Directed lithiation of (**69**) with *t*-butyllithium gave (**71**),[112] which was reacted with chlorotrimethylsilane to give 2-(trimethylsilyl)-N, N-dimethylbenzylamine (**80**), in 63% yield. A second directed lithiation gave the species with the lithium at the other *ortho*-position relative to the amine moiety. Reaction of this with diphenyltin dichloride furnished [(2-((dimethylamino)methyl)-3-trimethylsilyl)phenyl]diphenyltin chloride (**81**). Purification by recrystallisation from hot Et_2O gave white crystals. The ^1H NMR spectrum of these crystals showed peaks corresponding to the protons in Et_2O, even after prolonged drying *in vacuo*, indicating that some Et_2O molecules were incorporated in the crystal. From integration of the peaks the amount of Et_2O was calculated as *ca.* 0.4 molecules per molecule of (**81**), and this was supported by elemental analysis. Methylation with methylmagnesium chloride, which proved more successful than with methyllithium, gave (**79**) as a white solid. The proton NMR spectrum showed the methyl group bound to tin at 0.70 ppm (J = 70, 72 Hz) and the ^{119}Sn NMR spectrum had a peak at -123.5 ppm.

Initial molecular modelling studies were carried out on the molecules (**70**) and (**79**) using PCMODEL on an Apple Macintosh II, and the structures are shown in Figure 7, with bond angles given below the molecules. A comparison of the bond angles shows that the $SiMe_3$ group pushes the CH_2NMe_2 substituent towards the Sn substituent in (**79**), although the increased steric crowding within the molecule causes the Sn atom to be bent slightly further away from the CH_2NMe_2 group. Care should be taken, however, in using these models for accurate predictions. The modelling program uses generalised parameters for heavy atoms and so the accuracy of the structures cannot be guaranteed. The models do, however, give a preliminary representation of the molecules and demonstrate that the side chains in (**79**) are forced closer together than in (**70**), but that the effect is only slight. For buttressing to be effective an additional substituent at C_6 in (**79**) would be required to prevent the Sn substituent from bending away fron the CH_2NMe_2 group.



(70)

C_6 - C_1 - Sn	115.8°
C_2 - C_1 - Sn	125°
C_1 - C_2 - C_7	125°
C_3 - C_2 - C_7	116°



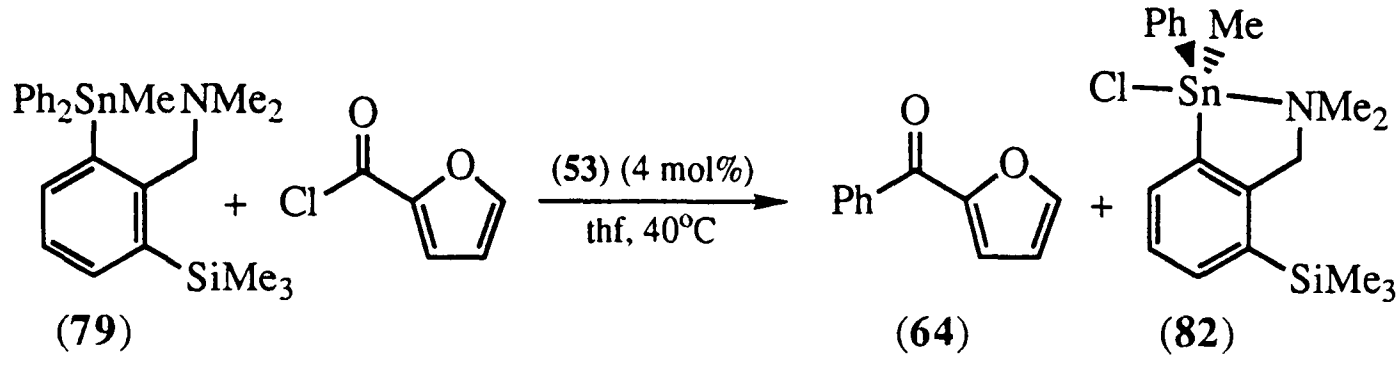
(79)

C_6 - C_1 - Sn	112.5°
C_2 - C_1 - Sn	127.5°
C_1 - C_2 - C_7	121.5°
C_3 - C_2 - C_7	119.3°
C_2 - C_3 - Si	127.5°
C_4 - C_3 - Si	113.1°

Figure 7: PCMODEL representations of (**70**) and (**79**)

The reaction of (**79**) with 2-furoyl chloride was then attempted using the standard procedure and followed by ^{119}Sn NMR. After 17 h at ambient temperature the only signal in the spectrum was that of the unreacted starting material.

The reaction was heated at 40°C and after 6 h a new peak appeared at - 119.3 ppm due to the formation of the tin by-product [(2-((dimethylamino)methyl)-3-trimethylsilyl)phenyl]methylphenyltin chloride (**82**). Integration of the two peaks showed a 33% reaction. After 22 h the same two peaks were present, however this time the peak at -119.3 ppm had the greater intensity, integration revealing 84% reaction. After 28 h the only peak present was the one at -119.3 ppm, indicating 100% reaction, Scheme 73.



Scheme 73

On work-up (**82**) was isolated and characterised. The proton NMR spectrum showed the usual downfield shift for the Sn-Me group ($\Delta\delta$ = + 0.30 ppm) and H_6 (signal at 8.45 ppm) and also two peaks at 2.30 and 1.91 ppm for the diastereotopic methyl groups of the NMe_2. The mass spectrum gave m/z 418 (10%), corresponding to M-Cl.

The observed reactivity of (**79**) is therefore similar to that of (**70**), so all the 'activated' molecules appear to have approximately the same reactivity. Direct comparisons were made by two different methods, described below.

The first direct comparison of the reactivity of (**60**), (**70**) and (**79**) can be made by comparing the extent of reaction in the Pd catalysed cross-coupling with 2-furoyl chloride at 40°C, as determined by integration of the peaks in the ^{119}Sn NMR spectra. The results are shown in Figure 8, in which Ph_3SnMe (**63**) has also been included as the control.

Reagent (**63**) showed no reaction at 40°C, but all the 'activated' molecules showed complete conversion between 22-38 h, with (**60**) being marginally the slowest to react and (**70**) the fastest. This suggests that the increased basicity of the lone pair in (**70**) is increasing the rate of reaction further, albeit only slightly.

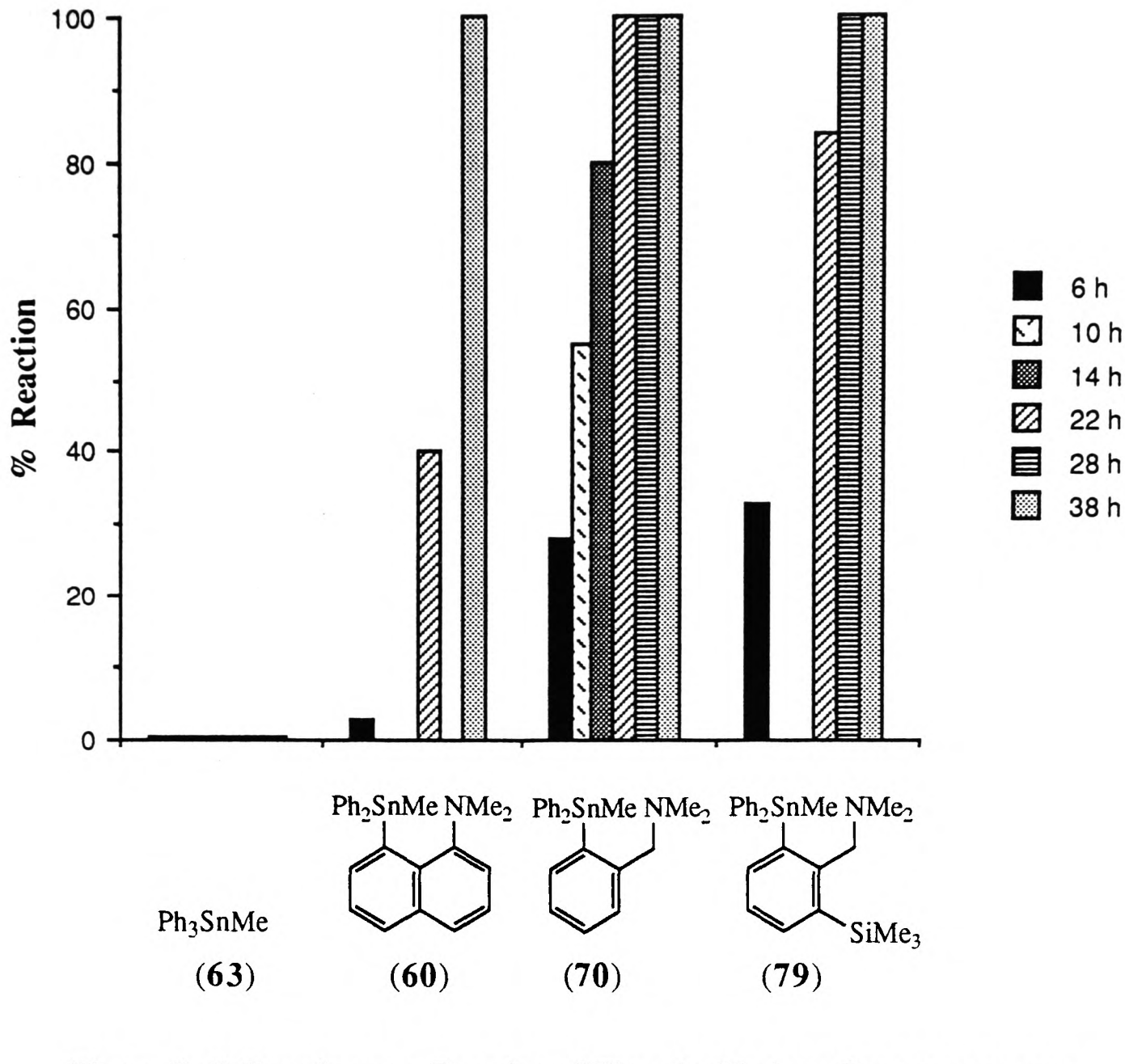


Figure 8: % Reaction as a Function of Time for Various Organostannanes

The second method of direct comparison was a set of competitive reactions between two organotin compounds. One equivalent of each organostannane was reacted with one equivalent of 2-furoyl chloride and the reaction followed by ^{119}Sn NMR. If selective transfer from only one reagent were to occur, this could be easily detected. The results are given in Table 4.

The reactions were performed at 40°C and ^{119}Sn NMR spectra taken after 22 h. In all the reactions signals from both unreacted starting materials as well as both possible tin by-products were observed. The spectrum from entry 2 is shown in Figure 9. This means that transfer occurred from both molecules, and there was no dominent preference for any one compound.

Table 4: Competitive Experiments between Organostannanes in the Pd Catalysed Cross-Coupling with 2-Furoyl Chloride at 40°C[a]

Entry	Starting Materials	Tin Containing Species at End of Reaction[b]
1	(**60**) and (**70**)	(**60**), (**66**), (**70**) and (**73**)
2	(**70**) and (**79**)	(**70**), (**73**), (**79**) and (**82**)
3	(**60**) and (**79**)	(**60**), (**66**), (**79**) and (**82**)

[a]Reactions were carried out on a 0.1-0.18 mmol scale with $PhCOPd(PPh_3)_2Cl$ (4 mol%) as catalyst in thf at 40°C. [b]Determined by ^{119}Sn NMR.

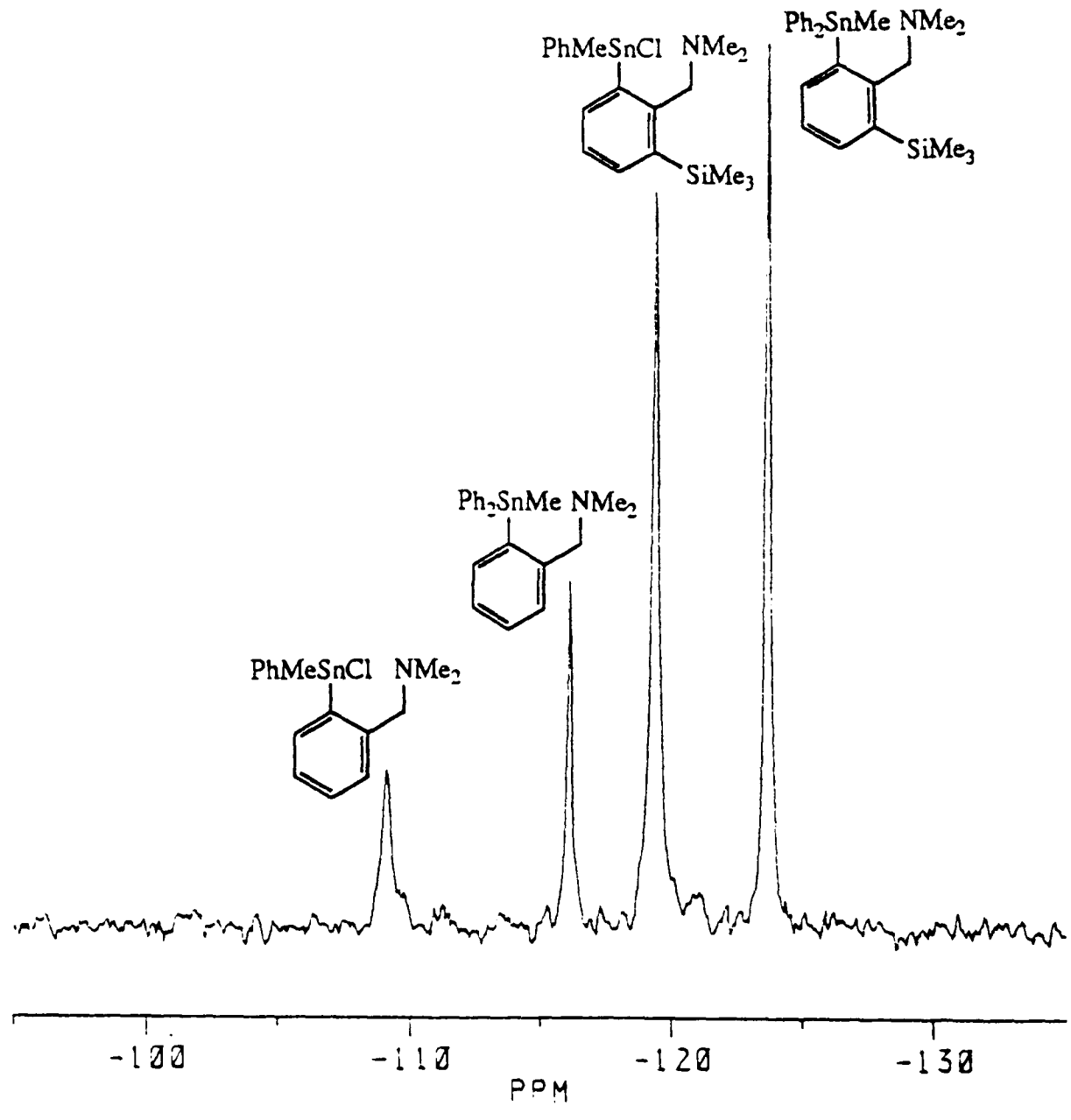


Figure 9: ^{119}Sn NMR Spectrum from the Competitive Coupling Reaction Between Organostannanes (**70**) and (**79**)

The results from both these comparative exercises show that while (**70**) may show slightly greater reactivity than the other 'activated' molecules, they are all approximately the same reactivity (within a factor of *ca.* 2), but all are at least an order of magnitude more reactive than 'unactivated' molecules.

A further conclusion can therefore be added to those given above, i.e. the enhancement of reactivity is brought about by the presence of a lone pair on the nitrogen but the relative basicity of this lone pair has only a small effect on the rate enhancement.

2.3.6. Effects of Palladium Ligation

All the reactions described above were performed with $PhCOPd(PPh_3)_2Cl$ (**53**) as the catalyst. Changing the ligands on the metal can alter the reaction markedly. Farina has found that the rate of Stille reactions can be drastically increased by the choice of ligand, especially in the transfer of a vinyl group.[70] The use of alternative ligands was therefore investigated. If an accelerated transfer could be achieved then it was hoped that the combined effects of this acceleration with use of an 'activated' molecule would bring about transmetalation under even milder conditions.

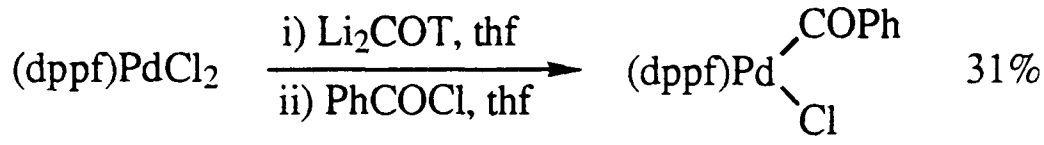
Initial experiments were performed using Ph_3SnMe (**63**) as the organostannane, and the results are given in Table 5.

Table 5: Coupling of Methyltriphenyltin (**63**) with 2-Furoyl Chloride Using Different Catalysts[a]

Entry	Catalyst	Temp (°C)	Time (h)	^{119}Sn NMR Yield (%)[b]	Isolated Yield (%)[c]
1	(dppf)PdCOPh(Cl)	67	22		30
2	(dppf)PdCOPh(Cl)	RT	22	No Reaction[d]	
3	"$(Ph_2PC_6F_5)_4Pd$"[e]	40	22	No Reaction[d]	
4	"$(Ph_2PC_6F_5)_4Pd$"[e]	67	19	90	
5	"$(Ph_3As)_4Pd$"[e]	40	6	53	
6	"$(Ph_3As)_4Pd$"[e]	40	17	100	83
7	"$(Ph_3As)_4Pd$"[e]	RT	22	No Reaction[d]	

[a]Reactions were carried out on a 0.2-0.3 mmol scale with 4 mol% of catalyst in thf. [b]From integration of peaks. [c]Isolated yield of 2-benzoylfuran. [d]Determined by ^{119}Sn NMR. [e]Catalyst prepared *in situ*.

The chelating biphosphine (dppf) (**1**) has been found to be a very effective ligand for catalytic cross-coupling reactions. The analogous complex to (**53**), (dppf)PdCOPh(Cl) (**83**) was thus prepared, Scheme 74, for use as a catalyst.

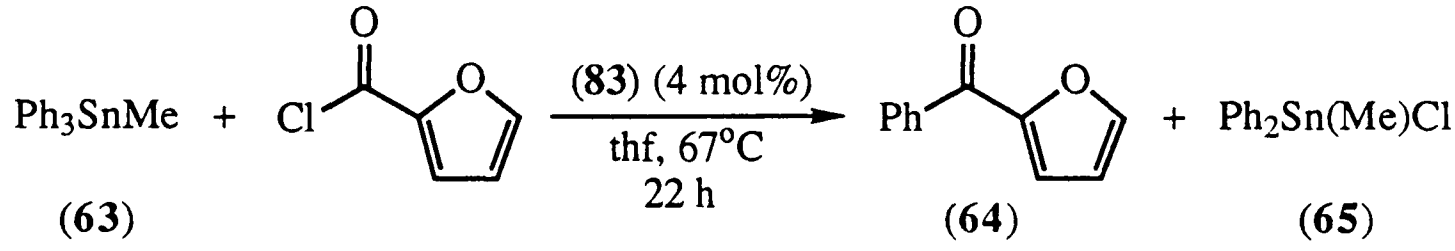


(**83**)

Scheme 74

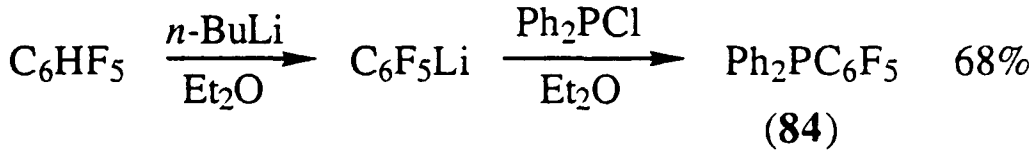
$(dppf)PdCl_2$ was reduced with Li_2COT and benzoyl chloride added. This oxidatively added to the Pd(0) species to give the new complex (**83**) in 31% isolated yield. The ^{31}P NMR spectrum showed two doublets at 21.9 and 2.54 ppm ($J_{P\text{-}P}$ = 56 and 54.6 Hz respectively). This shows the two phosphorus atoms are *cis* to each other, rather than having the *trans* geometry of (**53**).

(**83**) was used as the catalyst (4 mol%) in the coupling of (**63**) with 2-furoyl chloride in thf at 67°C, and coupled product (**64**) was isolated in 30% yield (entry 1), Scheme 75. The reaction was repeated at 40°C and followed by ^{119}Sn NMR. After 22 h the spectrum showed only unreacted starting material (entry 2).



Scheme 75

Farina found that when the ligands pentafluorophenyldiphenylphosphine (**84**) and triphenyl arsine were used, they greatly enhanced the rate of Stille couplings. It was therefore decided to use these ligands for the current system, and (**84**) was prepared by the method of Kemmitt,[116] Scheme 76.



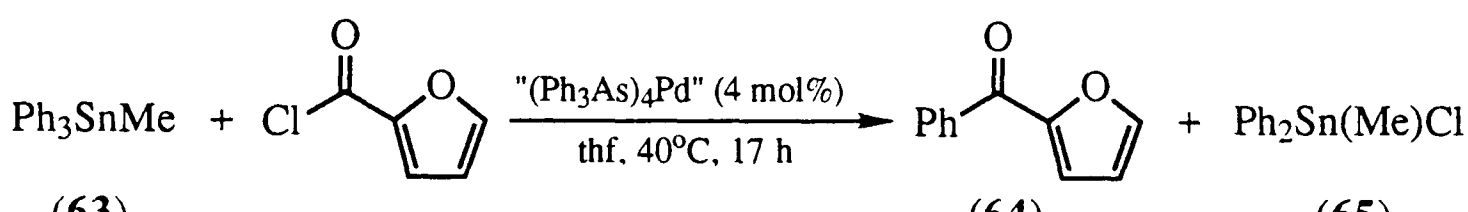
Scheme 76

Deprotonation of pentafluorobenzene with *n*-butyllithium and subsequent reaction with chlorodiphenylphosphine gave (**84**) as white crystals in 68% yield. The ^{31}P NMR spectrum showed a triplet at -23.06 ppm, due to P-F coupling.

The catalysts were prepared *in situ* by adding four equivalents of ligand to one equivalent of bis(dibenzylideneacetone)palladium (0), $Pd(dba)_2$, (prepared according to the method of Ishii[117]) in thf. The initial deep purple solution changed to yellow over a period of 2 min, forming the catalyst which can be represented as "L_4Pd". The reagents were then added to this solution.

The reaction using "$(Ph_2PC_6F_5)_4Pd$" as catalyst was carried out at 40°C and followed by ^{119}Sn NMR. After 22 h no reaction had occurred (entry 3), and so the mixture was heated at reflux. After 19 h the peak at -92.8 ppm had virtually disappeared and a new one appeared at -40 ppm, corresponding to 90% reaction (entry 4).

The reaction with "$(Ph_3As)_4Pd$" as catalyst was also carried out at 40°C and followed by ^{119}Sn NMR. After 6 h the peak due to (**65**) was seen in the spectrum, integration showing 53% reaction (entry 5). Another spectrum obtained after 17 h showed only the presence of by-product (**65**). Coupled product (**64**) was isolated in 83% yield (entry 6), Scheme 77. The reaction was repeated at room temperature, but no reaction occurred (entry 7).



(**63**) (**64**) (**65**)

Scheme 77

These results show that, while the ligands (dppf) (**1**) and (**84**) give no assistance to the coupling, Ph_3As as a ligand greatly accelerates the reaction. This is in agreement with the findings of Farina, thus ligand dissociation and the formation of a π-complex can be assumed.

It has, therefore, been possible to facilitate the transfer of a phenyl group from tin by two separate methods: (i) the incorporation of an NMe_2 group on the organostannane and (ii) modification of the catalyst by use of Ph_3As as ligand. To see whether these two effects would work together cooperatively the coupling reaction was attempted using 'activated' molecule (**70**) with "$(Ph_3As)_4Pd$" as catalyst. The results are given in Table 6.

Table 6: Coupling of [2-((Dimethylamino)methyl)phenyl]methyldiphenyltin (**70**) with 2-Furoyl Chloride using "$(Ph_3As)_4Pd$" as Catalyst[a]

Entry	Temp (°C)	Time (h)	^{119}Sn NMR Yield (%)[b]
1	40	6	100
2	RT	6	52
3	RT	17	82
4	RT	29	93

[a]Reactions were carried out on a 0.18 mmol scale with "$(Ph_3As)_4Pd$" (4 mol%) as catalyst (prepared *in situ*) in thf. [b]From integration of peaks

The reaction was performed at 40°C and after 6 h the ^{119}Sn NMR spectrum showed that complete conversion of (**70**) to by-product (**73**) had occurred (entry 1). The reaction was repeated at room temperature and after 6 h was found to be 52% complete (entry 2). Spectra recorded after 17 and 29 h showed the reaction to be 82% and 93% complete respectively (entries 3 and 4).

These results conclusively show that there is a cooperative effect between the two facilitating processes. A phenyl group can be transferred using conditions under which transfer was previously not possible.

Isolation of the catalytic intermediate $PhCOPd(AsPh_3)_2Cl$ (**85**) was achieved according to Scheme 78. $Pd(dba)_2$ was reacted with two equivalents of Ph_3As, the solution once more turning yellow. Oxidative addition of benzoyl chloride and precipitation with 30-40°C petroleum ether gave (**85**).

$$Pd(dba)_2 \xrightarrow[\text{ii) PhCOCl}]{\text{i) } Ph_3As \text{ (2 equiv.), thf}} PhCOPd(AsPh_3)_2Cl \quad 36\%$$

(**85**)

Scheme 78

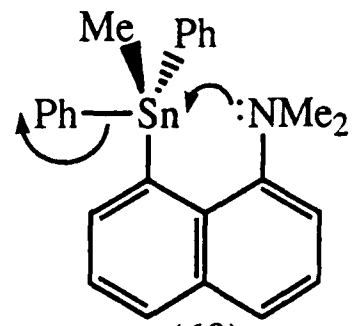
The catalytic activity of (**85**) was tested in a reaction between control (**63**) and 2-furoyl chloride at 40°C. After 22 h coupled product (**64**) was isolated in 82% yield, and PhCOPh was also observed, which would be expected from the first catalytic cycle.

One further competitive reaction was performed between (**70**) and (**79**), using (**85**) as catalyst. This was to determine if the steric buttressing within (**79**) would show any effect with the new catalyst. However, both (**70**) and (**79**) were found to react at approximately the same rate, showing 41% and 49% reaction respectively after 22 h, by integration of the peaks in the ^{119}Sn NMR spectrum.

The results from these reactions using Ph_3As as a ligand for the catalyst and the 'activated' molecule (**70**) together conclusively show that there is a cooperative effect between the two facilitating processes. The combined effect of these two processes produces a rate enhancement of *ca.* 100 over the transfer from an 'unactivated' molecule with phosphine ligands on the catalyst. This rate enhancement reduces the severity of the conditions needed for transfer of a phenyl group and thus overcomes one of the disadvantages in the use of organostannanes in organic synthesis.

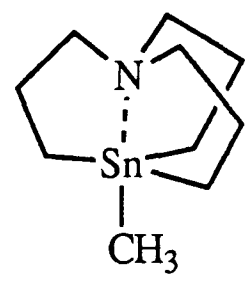
2.3.7. Conclusions

The chemistry of the organotin reagents described above leads to the following conclusions. The presence of a suitably placed NMe_2 group in a tin reagent can facilitate the transfer of a phenyl group from the tin in the Pd catalysed cross-coupling with 2-furoyl chloride. This effect is due to the lone pair on the nitrogen atom acting as an internal nucleophile which attacks the tin atom in an S_N2 type fashion, shown for (**60**) below. This produces a rate enhancement of approximately twenty times that of 'unactivated' reagents. The effect is an intramolecular phenomenon with steric factors playing little or no part. The size of the effect is little affected by the basicity of the lone pair or steric buttressing within the molecule.



(60)

In a paper published during the preparation of this thesis Vedejs reports a similar activation of Sn-C bonds in molecules such as 1-aza-5-stannabicyclo[3.3.3]undecane (**86**).[118] Crystallographic data show the Sn-CH_3 bond is longer than the Sn-CH_2 bonds.[119] Metal-alkyl exchange occurs at this exocyclic bond leading to selective transfer of a single primary group. (**86**) was found to be more reactive than simple R_4Sn compounds in the Pd catalysed Stille coupling with both aryl halides and benzoyl chloride with reaction occurring between room temperature and 105°C.



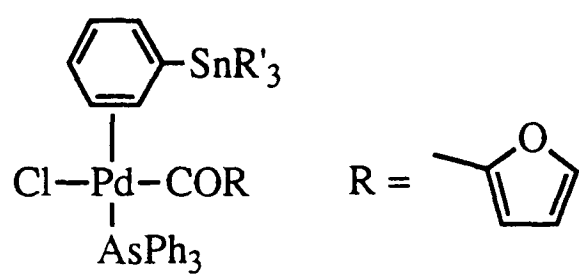
(86)

Vedejs ascribes this increased reactivity to Sn-N coordination in the transition state. This internal coordination is assumed to accelerate the formation of the diorganopalladium species prior to reductive elimination of the coupled product. As the ring C-Sn bonds are constrained to occupy pseudoequatorial sites in the trigonal bipyramid around Sn, only the axial alkyl group is activated by internal coordination, thus assuring selective transfer.

These results show a similar effect to that described above, i.e. the activation of Sn-C bonds resulting in accelerated transfer in Stille coupling reactions. They also support the theory that the cause of the acceleration is due to the internal attack of the Sn atom by the lone pair on N. The 'levelling-off' of the effect observed with the more basic lone pairs of (**70**) and (**79**) may be due either to a lack of discrimination within these molecules or to a change in the rate determining step of the mechanism.

A rate enhancement is also observed when the phosphine ligands on the metal catalyst are exchanged for arsine ligands. These two effects can work cooperatively and further facilitation of the reaction is observed, with a rate enhancement of approximately one hundredfold being seen over control reactions.

This is in accord with the findings of Farina[70] and thus a similar mechanism in which ligand dissociation is rate determining in the transmetalation step can be assumed to be operating, the key intermediate being the mono-ligated π-complex (**87**).



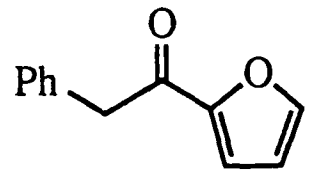
(**87**)

2.3.8. Transfer of a Benzyl Group

2.3.8.1. Synthesis and Coupling of Benzyltin Reagents

The transfer of a benzyl group from tin requires more forcing conditions than the transfer of a phenyl group. It was hoped that by the design of a suitable 'activated' molecule this transfer could be facilitated. Use of Ph_3As as a ligand for the catalyst might also cause the transmetalation to be effected under mild conditions.

The same reaction was investigated, i.e. coupling with 2-furoyl chloride. Successful coupling should give 2-furylbenzylketone (**88**) as the product, and so an authentic sample of this was prepared. The method chosen was analogous to that used for the preparation of 2-benzoylfuran (Scheme 60), i.e. deprotonation of furan followed by reaction with phenyl acetic acid. This afforded (**88**) as a colourless liquid. The proton NMR spectrum showed a characteristic singlet at 4.13 ppm for the benzylic CH_2 next to the carbonyl group, which was used to determine the presence of (**88**) in crude reaction mixtures.



(**88**)

In order to determine which groups should accompany a benzyl group on the Sn atom of an 'activated' molecule various organostannanes were prepared and their coupling reaction investigated. This also served to establish the control conditions for the transfer from an 'unactivated' molecule.

Benzylmethyldiphenyltin (**89**) was prepared by the action of benzylmagnesium chloride on methyldiphenyltin chloride (**65**), Scheme 79. The proton NMR spectrum of this colourless oil showed the benzylic protons' resonance as a singlet at 2.85 ppm with ^{117,119}Sn-H coupling of 65, 67 Hz, and the methyl singlet at 0.50 ppm (J = 54, 56 Hz). Benzyltriphenyltin (**90**) and benzyltrimethyltin (**91**) were prepared in a similar fashion by reaction of benzylmagnesium chloride with triphenyltin chloride and trimethyltin chloride respectively, Scheme 79. The ^{1}H NMR spectrum of (**90**) showed a singlet at 3.01 ppm (J = 66, 68 Hz) for the benzylic protons, and for (**91**) the signal appeared at 2.34 ppm (J = 60, 62 Hz) with the methyl proton signal at 0.07 ppm (J = 53, 55 Hz). $\delta(^{119}Sn)$ for (**91**) was found to be 3.69 ppm.

$Ph_2(Me)SnCl + PhCH_2MgCl \longrightarrow Ph_2(Me)SnCH_2Ph$ 54%

(**89**)

$Ph_3SnCl + PhCH_2MgCl \longrightarrow Ph_3SnCH_2Ph$ 72%

(**90**)

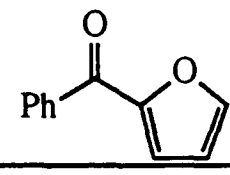
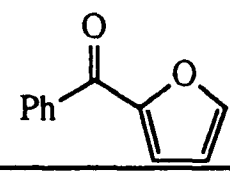
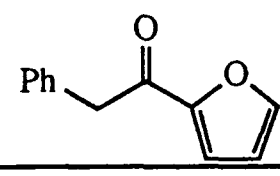
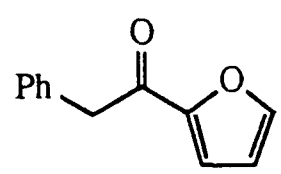
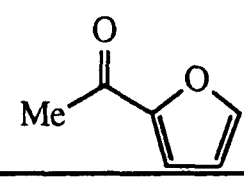
$Me_3SnCl + PhCH_2MgCl \longrightarrow Me_3SnCH_2Ph$ 52%

(**91**)

Scheme 79

The coupling of these benzyltin reagents with 2-furoyl chloride was then attempted, using $PhCOPd(PPh_3)_2Cl$ (**53**) (4 mol%) as catalyst and the results are given in Table 7.

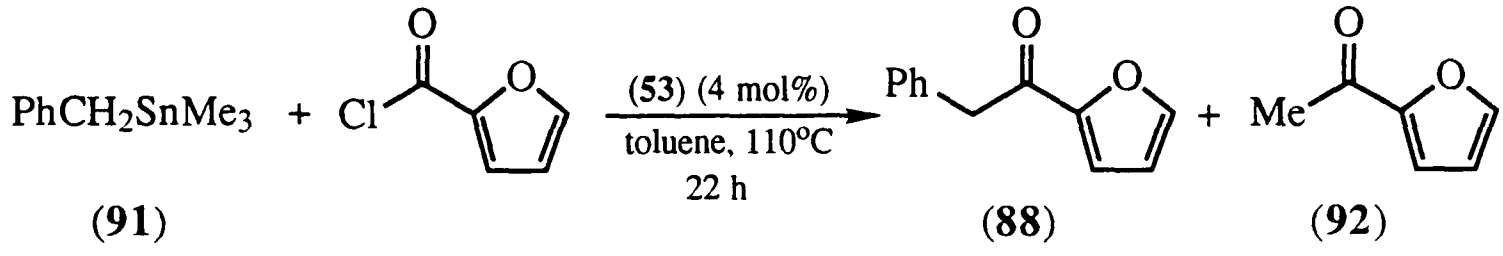
Table 7: Pd Catalysed Coupling of Benzyltin Compounds with 2-Furoyl Chloride[a]

Entry	Tin Compound	Solvent	Temp (°C)	Product	Yield (%)[b]
1	$Ph_2(Me)SnCH_2Ph$	thf	67		80
2	Ph_3SnCH_2Ph	thf	67		28
3	Me_3SnCH_2Ph	thf	67		trace[c]
4	Me_3SnCH_2Ph	toluene	110		10
					trace

[a]Reactions were carried out on a 0.2-0.3 mmol scale in dry, degassed solvents using $PhCOPd(PPh_3)_2Cl$ (4 mol%) as catalyst for 22 h. [b]Isolated yield. [c]Detected by ^1H NMR.

In the reaction of (**89**) in refluxing thf the proton NMR spectrum of the crude product lacked a signal at 4.13 ppm, indicating that no (**88**) had been formed. Coupled product (**64**), from phenyl transfer, was isolated in 80% yield (entry 1). The tin by-product $PhCH_2(Me)SnPh(Cl)$ was also isolated, and the signals for the benzylic CH_2 and Me were both shifted downfield relative to (**89**) due to the presence of the Cl ($\Delta\delta$ = + 0.13 and + 0.22 ppm respectively). This shows that the phenyl group is transferred in preference to both the methyl and benzyl groups. This is confirmed by the reaction of (**90**), in which no (**88**) was observed in the proton NMR spectrum, but (**64**) was again isolated in 28% yield (entry 2). The tin by-product $PhCH_2SnPh_2(Cl)$ showed a downfield shift for the benzylic protons of + 0.18 ppm in the ^1H NMR spectrum relative to (**90**). Reaction of (**91**) in refluxing thf showed that a trace of the desired (**88**) had been formed, due to a small signal at 4.13 ppm in the crude NMR spectrum (entry 3). The major component of the reaction mixture, however,

was unreacted starting material. The reaction was repeated at a higher temperature (110°C) in refluxing toluene. This time a larger peak was seen at 4.13 ppm in the spectrum of the reaction mixture. Isolation by preparative tlc gave a fraction which, by proton NMR, appeared to contain a mixture of the desired product (**88**) as well as the other possible coupled product 2-acetylfuran (**92**), the resonance due to the methyl group occurring at 2.49 ppm, Scheme 80. This was confirmed by GCMS analysis, the GC trace giving the ratio of (**88**):(**92**) as 9:1 (corresponding to yields of *ca.* 10% and trace amounts respectively) (entry 4). The mass spectrum showed peaks corresponding to M+1 (100%) for both molecules.



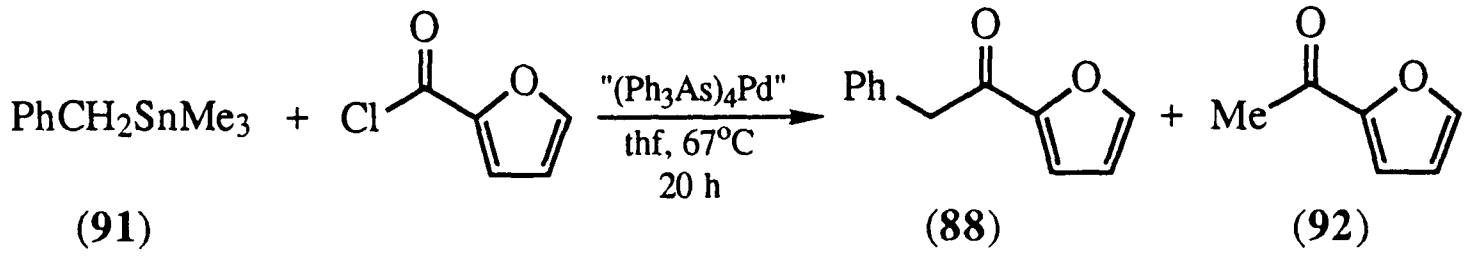
(**91**) (**88**) (**92**)

Scheme 80

The results from these experiments give the transfer order of the groups from tin as Ph > $PhCH_2$ > Me. This is in accord with the transfer order quoted by Stille.[41] The organic group of choice to accompany the benzyl residue on Sn in an 'activated' molecule, therefore, is a methyl group. The findings also highlight the severity of the conditions needed for the transfer to occur.

In an attempt to moderate the conditions, and also to test the effect of the arsine ligand, the reaction of (**91**) with 2-furoyl chloride was attempted with the catalyst "$(Ph_3As)_4Pd$". This was made *in situ* as described above. The reaction was performed in thf at 67°C, conditions in which very little reaction occurred previously (Table 7, entry 3). After 20 h the peak at 3.69 ppm in the ^{119}Sn NMR spectrum had disappeared, indicating that no starting material was present. However, there were six major peaks in the spectrum, indicating that the use of Ph_3As as a ligand for the metal catalyst had instigated a variety of reactions and resulted in a number of tin containing species. Work-up and isolation by preparative tlc gave a fraction which contained a mixture of the desired product (**88**) as well

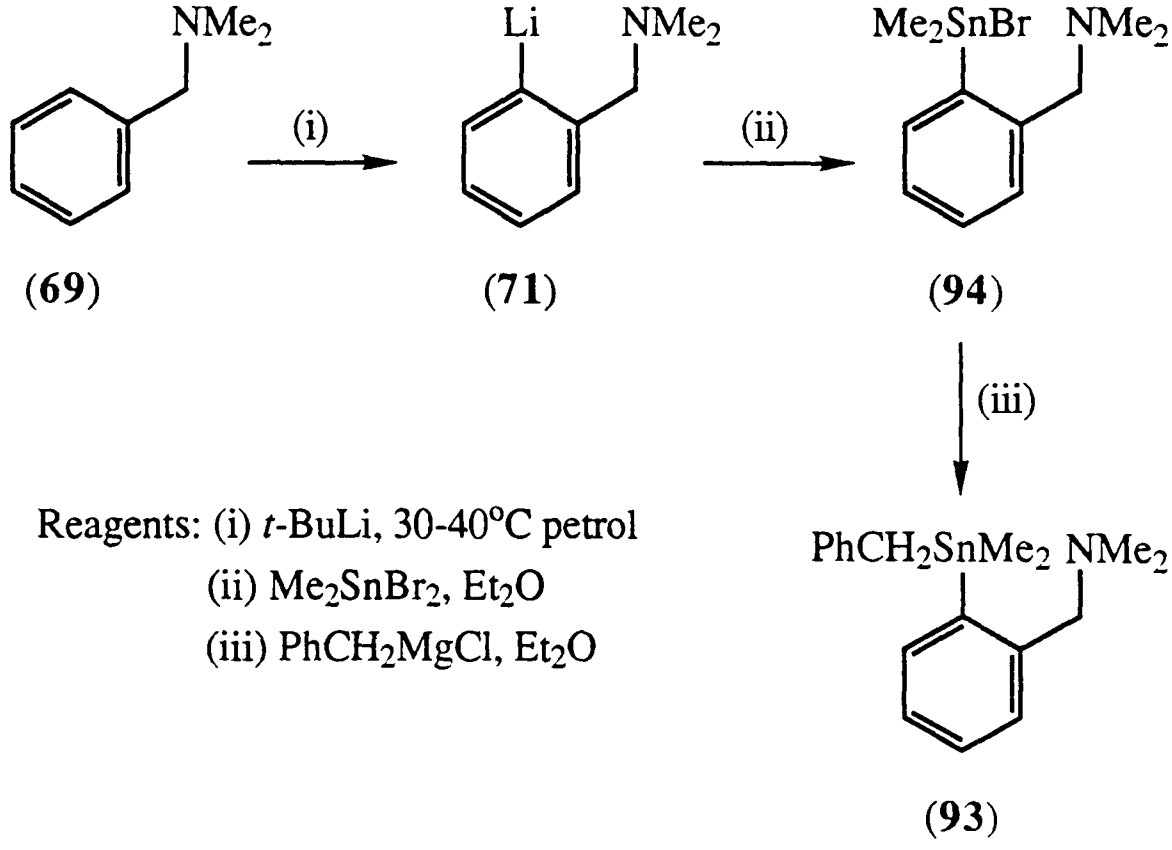
as 2-acetylfuran (**92**), Scheme 81. This was confirmed by GCMS analysis, the GC trace giving the ratio of (**88**):(**92**) as 9:1 (corresponding to 26% and 3% yields respectively).



(**91**) (**88**) (**92**)

Scheme 81

Although the severity of the conditions has been reduced they are still quite forcing. It was therefore hoped that by use of an 'activated' molecule the conditions could be moderated further, leading to the selective transfer of a benzyl group. [2-((Dimethylamino)methyl)phenyl]benzyldimethyltin (**93**), which has methyls accompanying the benzyl groups, was therefore prepared in a procedure analogous to that employed for the other 'activated' molecules, Scheme 82.



(**69**) (**71**) (**94**) (**93**)

Reagents: (i) *t*-BuLi, 30-40°C petrol
(ii) Me_2SnBr_2, Et_2O
(iii) $PhCH_2MgCl$, Et_2O

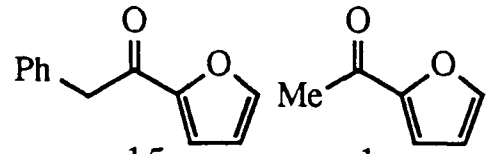
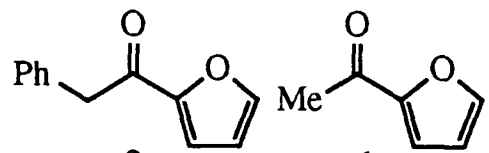
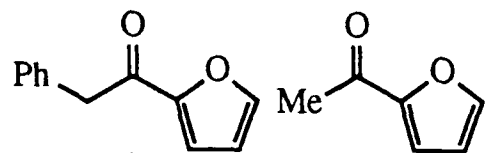
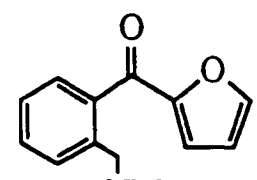
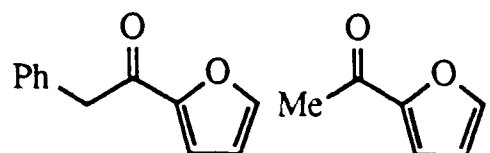
Scheme 82

The lithiated species (**71**) was reacted with dimethyltin dibromide to give [2-((dimethylamino)methyl)phenyl]dimethyltin bromide (**94**) as a white solid in 49% yield. Once more this showed the characteristic H_6 doublet at 8.27 ppm in its proton NMR spectrum, and the $SnMe_2$ resonance occurred at 0.98 ppm (J = 62, 64 Hz). Reaction of (**94**)

with a benzyl Grignard reagent furnished the new (**93**) in 52% yield; overall yield from (**69**) being 25%. The proton NMR spectrum showed an upfield shift for H_6 relative to (**94**) due to the replacement of the halide by the organic group (i.e. the reverse of that which occurs in the coupling reaction of the other 'activated' molecules), the signal appearing at 7.60 ppm. The same was true for the $SnMe_2$ signal, the singlet occurring at 0.14 ppm ($\Delta\delta$ = -0.84). The ^{119}Sn NMR showed a peak at -59.51 ppm.

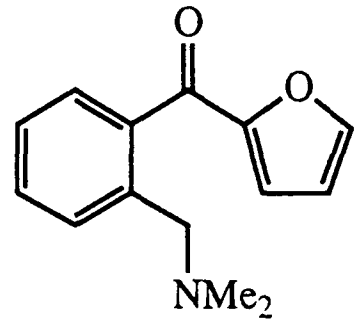
Stannane (**93**) was then used in the coupling reaction with 2-furoyl chloride. The results are given in Table 8.

Table 8: Pd Catalysed Coupling of [2-((Dimethylamino)methyl)phenyl]benzyldimethyltin (**93**) with 2-Furoyl Chloride[a]

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Products[c]
1	(**53**)	thf	40	96	 15 1
2	"$(Ph_3As)_4Pd$"[b]	thf	40	22	 3 1
3	"$(Ph_3As)_4Pd$"[b]	thf	67	22	 8 1 
4	"$(Ph_3As)_4Pd$"[b]	toluene	110	5	 15 1

[a]Reactions were carried out on a 0.22 mmol scale in dry, degassed solvents with 4 mol% catalyst. [b]Catalyst made *in situ*. [c]Isolated products with relative ratios as determined by GC.

The first reaction was performed in thf at 40°C with (**53**) as catalyst. After 22 h two new peaks had appeared in the ^{119}Sn NMR spectrum, but a considerable quantity of (**93**) still remained. The reaction was left for 4 d, after which time six peaks were seen in the spectrum, none of which corresponded to (**93**). On work-up and isolation both coupled products (**88**) and (**92**) were detected (^{1}H NMR and GCMS) in a ratio of *ca.* 15:1 and a yield of *ca.* 11% and trace amounts respectively (entry 1). The reaction was repeated using "$(Ph_3As)_4Pd$" as catalyst. After 22 h at 40°C no less than seven different tin containing species were seen in the ^{119}Sn NMR spectrum, but no starting material (**93**) remained. On work-up both (**88**) and (**92**) were again observed in a ratio of *ca.* 3:1 in yields of *ca.* 6% and 2% (entry 2). The reaction was then performed in refluxing thf and again both (**88**) and (**92**) were seen in a ratio of *ca.* 8:1 (respective yields *ca.* 12% and 1.5%). In this reaction the aqueous washings were basified and re-extracted. From this a sample of 2-[2'-((dimethylamino)methyl)]benzoylfuran (**95**) was identified and isolated in 3% (entry 3). The proton NMR spectrum showed the CH_2NMe_2 resonance at 3.53 ppm and the NMe_2 resonance at 2.03 ppm. The mass spectrum gave m/z 230 (100%), corresponding to M+1. Finally the temperature of the reaction was increased by using refluxing toluene as the solvent, but this also led to both coupled products being formed in a ratio of *ca.* 15:1, with yields of *ca.* 15% and trace amounts respectively (entry 4).



(**95**)

In all the above reactions the ^{119}Sn NMR spectra show a complicated mixture of species (presumably containing both tin by-products from coupling reactions and decomposition products), and a range of coupling products in differing amounts was observed. Entry 3 shows the coupling product from all three different groups on the tin

atom. This highlights the lack of selectivity in the reaction for this molecule. Yields are also poor, even under forcing conditions.

2.3.8.2. Conclusions

The lack of selectivity and the poor yields obtained in the coupling of benzyltin compounds show that, as yet, a benzyl group cannot be selectively transferred in a satisfactory fashion. The internal assistance of a nitrogen lone pair did not prove applicable to the transfer of such sp^3 centres and fairly forcing conditions were still needed. The Ph_3As ligand had little effect on the reaction, which may be due to either the reaction proceeding *via* a different pathway to that proposed by Farina or a change in the rate determining step of the mechanism.

However, by further modification of reagent, catalyst and conditions it is hoped that this process will become feasible. The work of Vedejs suggests that the internal assistance by a nitrogen lone pair is a general effect and the use of molecules such as (**86**), in which the exocyclic moiety is a benzyl group, may overcome the problems encountered in this study with the transfer of this group. If the parent benzylic compound can be transferred then an α-substituted moiety should also be able to be transferred. This will then allow chiral organotin compounds to be used and the process and stereochemistry of the transmetalation step to be investigated.

2.3.9. Other Stille Coupling Reactions

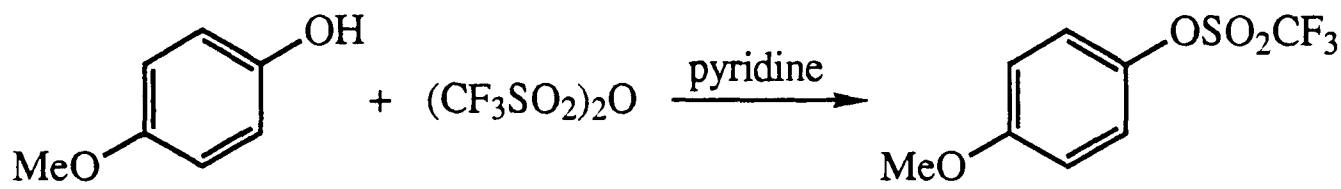
The success achieved using molecules (**60**), (**70**) and (**79**) in the Pd catalysed coupling with 2-furoyl chloride prompted an investigation into their use in other Stille type coupling reactions. This would serve the dual purpose of testing their general applicability

for such reactions, and seeing if there was again any facilitation in the transfer of the phenyl group. Experiments were performed using [2-((dimethylamino)methyl)phenyl] methyldiphenyltin (**70**) as the 'activated' compound and its reaction (i) with aryl triflates and (ii) in carbonylative coupling reactions was studied.

2.3.9.1. Attempted Facilitation of Aryl Triflate Cross-Coupling

The Pd catalysed coupling of organostannanes with aryl triflates has been found to be an excellent method for C-C bond formation.[53,54] The presence of LiCl is essential for the reaction to proceed. The purpose of the following reactions was to use the Stille methodology for the coupling but to use (**70**) as the nucleophile to see if any improvement could be obtained.

The aryl triflate chosen for the electrophile was 4-methoxyphenyl triflate (**96**). This was prepared in 84% yield from 4-methoxyphenol by reaction with triflic anhydride in pyridine,[120] Scheme 83.

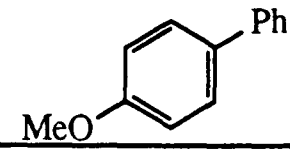
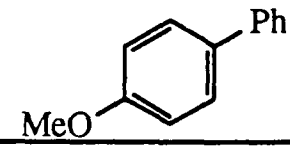
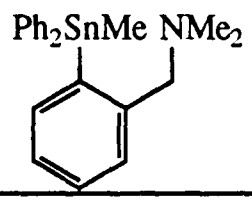
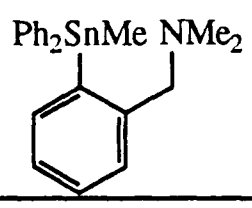


(96)

Scheme 83

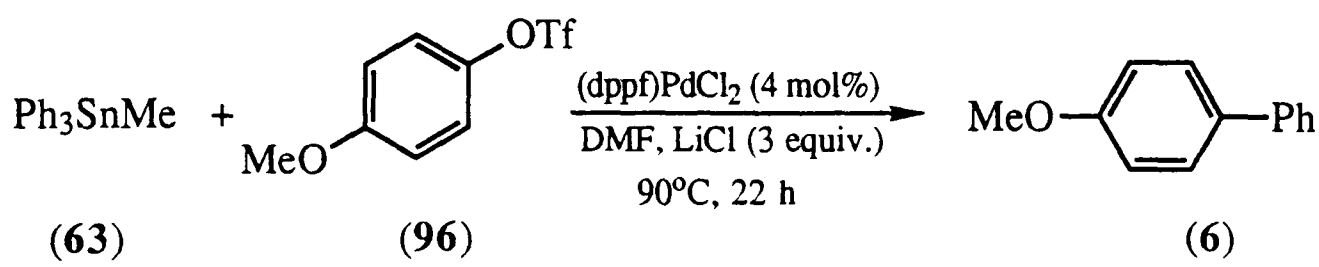
Coupling reactions were carried out with both Ph_3SnMe (**63**), as a control, and (**70**) in DMF at 90°C for 22 h with added LiCl (3 equivalents). Stille used $(dppf)PdCl_2$ as the catalyst for the couplings, so this was employed as well as $PhCOPd(PPh_3)_2Cl$ (**53**), for comparison. The results are given in Table 9.

Table 9: Pd Catalysed Coupling Between Organostannanes and 4-Methoxyphenyl triflate (**96**)[a]

Entry	Tin Compound	Catalyst	Product	Yield (%)[b]
1	Ph_3SnMe	$(dppf)PdCl_2$		73
2	Ph_3SnMe	$PhCOPd(PPh_3)_2Cl$		20[c]
3		$(dppf)PdCl_2$	No Reaction	
4		$PhCOPd(PPh_3)_2Cl$		15[c]

[a]Reactions were carried out on a 0.17 mmol scale with 4 mol% catalyst in dry DMF at 90°C for 22 h. [b]Isolated yield. [c]Unreacted starting material also recovered.

The reaction of (**63**) with (**96**) gave the desired coupled product, 4-methoxybiphenyl (**6**) in a yield of 73% (entry 1), Scheme 84. The proton NMR spectrum showed the methoxy resonance at 3.87 ppm and the mass spectrum gave m/z 171 (100%), corresponding to M+1. The sample was found to be identical to a commercial sample of 4-methoxybiphenyl.



(**63**) (**96**) (**6**)

Scheme 84

The reaction was repeated with (**53**) as catalyst, but proved to be less successful with (**6**) being isolated in only 20% yield. Unreacted (**63**) was also recovered from the reaction (entry 2). The reaction of (**70**) with (**96**) using $(dppf)PdCl_2$ as catalyst also proved unsuccessful. ^{119}Sn NMR and tlc showed no reaction and only unreacted starting materials

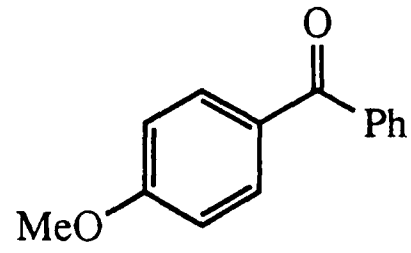
were recovered (entry 3). When (**53**) was used as catalyst the ^{119}Sn NMR spectrum showed a new peak -112.9 ppm, corresponding to (**73**). Integration showed that the reaction had gone to 20% completion, corresponding to 5 turnovers of catalyst. On work-up the coupled product (**6**) was isolated in 15% yield, along with (**73**) (12%) and unreacted starting materials (entry 4).

These results show that the control compound (**63**) proved to be the best reagent for the coupling reaction (entry 1). With (**70**), (**53**) proved to be the better catalyst and no reaction was observed with (dppf)$PdCl_2$.

The conclusion that can be drawn from this is that while (**70**) will undergo Pd catalysed coupling with aryl triflates, its reactivity appears to be less than that of (**63**), only a few turnovers of catalyst occurring. There appears to be no advantage, therefore, in the use of compounds such as (**70**) in this type of coupling reaction. The reason for this reversal in reactivity, and also the different reactivity with different catalysts, is as yet unknown, but suggests a different mechanism is in operation.

2.3.9.2. Carbonylative Coupling

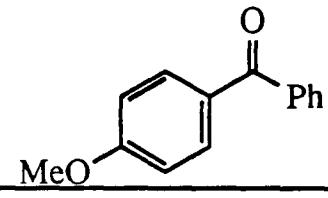
The Pd catalysed carbonylative coupling of organostannanes with electrophiles, in the presence of carbon monoxide, is a useful method for the preparation of ketones (see Section 1.2.3.4.), catalysts being used in 1-4 mol%. Once more the reaction of (**70**) was compared with that of (**63**) to see if it offered any advantages in the carbonylative coupling with aryl triflates. 4-Methoxyphenyl triflate (**96**) was again used as the electrophile, and the method of Stille used for the reactions.[75] The product obtained from the transfer of a phenyl group would be 4-methoxybenzophenone (**97**). Stille obtained (**97**) in a 69% yield using $PhSnMe_3$ in the reaction.



(**97**)

Reactions were performed in a Fischer-Porter bottle in DMF under a carbon monoxide atmosphere at a pressure of 2 atm. After 22 h the pressure was released, the ^{119}Sn NMR spectrum of the mixture obtained and the reaction worked-up, if necessary. Initial experiments were done with compound (**63**), and the results are given in Table 10. Stille found that the best catalyst for the reaction was (dppf)$PdCl_2$, and so this was used, with added LiCl (3 equivalents).

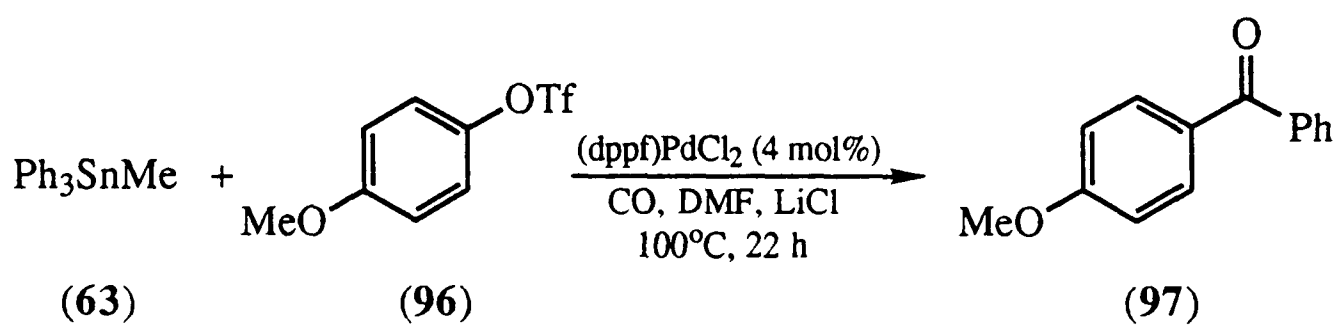
Table 10: Pd Catalysed Carbonylative Coupling Between Methyltriphenyltin (**63**) and 4-Methoxyphenyltriflate (**96**)[a]

Entry	Solvent	Temp (°C)	Product	Yield (%)[b]
1	thf	75	No Reaction[c]	
2	DMF	100		13
3	DMF	60	No Reaction[c]	

[a]Reactions were carried out on a 0.27 mmol scale in dry solvents with (dppf)$PdCl_2$ (4 mol%) as catalyst and LiCl (3 equiv.) under CO (2 atm) for 22 h. [b]Isolated yield. [c]Determined by ^{119}Sn NMR and tlc.

(**63**) was found to be unreactive when the carbonylative coupling reaction was performed in thf at 75°C. ^{119}Sn NMR and tlc indicated that no reaction had occurred (entry 1). The reaction was repeated in DMF at 100°C. After 22 h the ^{119}Sn NMR spectrum showed that nearly all the starting reagent (**63**) had gone and a new peak at -193.2 ppm appeared as the major peak in the spectrum. On work-up the proton NMR of the crude

reaction mixture showed a resonance for a methyl group bound to tin at 1.03 ppm, corresponding to $Ph_2(Me)SnCl$. Isolation of the reaction components by preparative tlc gave unreacted (**96**), $Ph_2(Me)SnCl$ and the desired (**97**) in 13% yield (entry 2), Scheme 85. This had the methoxy resonance at $\delta = 3.91$ in the proton NMR spectrum. The reaction was repeated at 60°C, but no reaction occurred (entry 3).



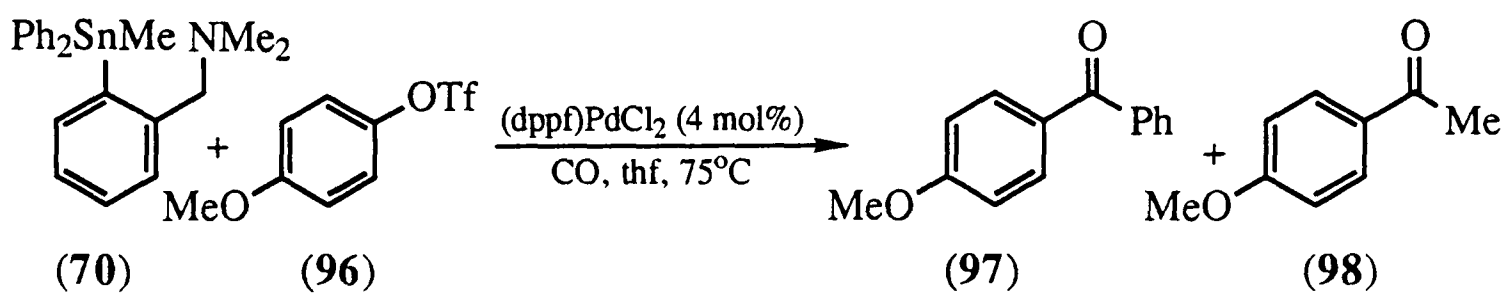
Scheme 85

Compound (**63**), therefore, will perform the carbonylative coupling reaction, but not as successfully as the $PhSnMe_3$ employed by Stille (*cf* 13% *vs* 69% yield). The ^{119}Sn NMR spectrum for the successful reaction showed a peak at -193.2 ppm for an unknown tin containing species. Isolation of this species from the reaction mixture was not possible and its identity is uncertain. Tabulated values of ^{119}Sn NMR chemical shifts[109] unfortunately do not include any triflate compounds, and so the effect of the triflate anion in the system is difficult to gauge. The value of -193 ppm, however, is in the region for tin compounds containing Sn-O bonds. Great care should be taken, however, in giving too much credence to this value as the chemical shift is greatly dependent on a number of factors (see p. 46) and coordination can cause large changes in δ values.

(**70**) was then used as the organotin reagent for the coupling in order to assess whether it had any advantages over (**63**). The procedure for the reaction was the same as outlined above. Initial experiments, however, were carried out in the absence of LiCl to see whether the NMe_2 group could act as an internal nucleophile to facilitate the reaction.

The reaction of (**70**) in thf at 75°C with $(dppf)PdCl_2$ as catalyst was found to give a mixture of at least six different tin containing species (by ^{119}Sn NMR) after 22 h, the major species being unreacted (**70**). On work-up and isolation by preparative tlc (**97**) was isolated

in a yield of 4%. The product obtained from the transfer of a methyl group, 4-methoxy acetophenone (**98**), was also isolated in 3% and identified by comparison with a commercial sample, Scheme 86. The proton NMR showed a resonance at 3.87 ppm for the methoxy group and the aromatic protons appeared as two doublets at 7.94 and 6.93 ppm. The mass spectrum gave m/z 151 (100%), corresponding to (M+1) for (**98**).



(**70**) (**96**) (**97**) (**98**)

Scheme 86

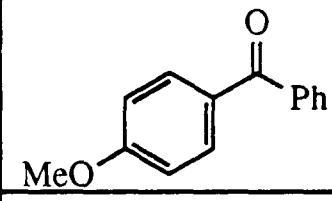
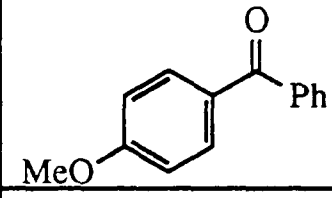
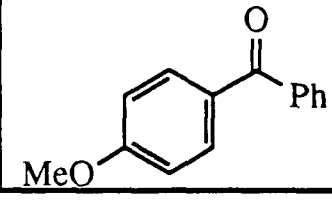
The reaction was repeated using DMF as the solvent at 100°C. ^{119}Sn NMR revealed at least 12 tin containing species. Again both (**97**) and (**98**) were isolated in yields of 3% and 7% respectively. Reactions using (**53**) as the catalyst proved unsuccessful in both thf and DMF, ^{119}Sn NMR and tlc showing only unreacted starting materials to be present.

These results show that the reaction is a complex one. Transfer of both phenyl and methyl groups occured, but the yields of these coupled products were very low, corresponding to a few turnovers of catalyst. The multitude of tin containing species present in the reaction mixture is indicative of either many other side reactions occurring or decomposition of reagents taking place. The lack of success of these carbonylative coupling reactions may have been due to the absence of LiCl from the system.[75] The reactions were therefore repeated with LiCl present and the results are given in Table 11.

The reaction in DMF at 100°C with $(dppf)PdCl_2$ as catalyst showed two peaks in the ^{119}Sn NMR spectrum, at -112.3 and -193.3 ppm. The peak at -112.3 ppm corresponds to (**73**), which was isolated from the reaction mixture. The species with δ = -193.3 was not isolated and again its identity is unclear. Coupled product (**97**) was isolated in a 13% yield and no (**98**), resulting from methyl transfer, was seen (entry 1). The reaction was repeated at

60°C, conditions under which Ph_3SnMe did not react. ^{119}Sn NMR showed peaks at -118.8 (unreacted (**70**)) and -193.7 ppm. Coupled product (**97**) was again isolated, in 9% yield (entry 2). Reaction using (**53**) as catalyst in thf at 75°C gave no coupling reaction (entry 3). The reaction was repeated in DMF at 100°C and the ^{119}Sn NMR spectrum showed mainly starting material and a small quantity of (**73**) (δ = -112.4). Preparative tlc gave a trace of coupled product (**97**) (corresponding to about one turnover of catalyst), which was identified by GCMS (entry 4).

Table 11: Pd Catalysed Carbonylative Coupling Between [2-((Dimethylamino)methyl) phenyl]methyldiphenyltin (**70**) and 4-Methoxyphenyltriflate (**96**) with LiCl Present[a]

Entry	Catalyst	Solvent	Temp (°C)	Product	Yield (%)[b]
1	$(dppf)PdCl_2$	DMF	100		13[d]
2	$(dppf)PdCl_2$	DMF	60		9[d]
3	$PhCOPd(PPh_3)_2Cl$	thf	75	No Reaction[c]	
4	$PhCOPd(PPh_3)_2Cl$	DMF	100		3[d]

[a]Reactions were carried out on a 0.15 mmol scale in dry solvents with 4 mol% of catalyst and LiCl (3 equiv.) under CO (2 atm) for 22 h. [b]Isolated yield. [c]Determined by ^{119}Sn NMR and tlc. [d]Unreacted starting material and decomposition products were also recovered.

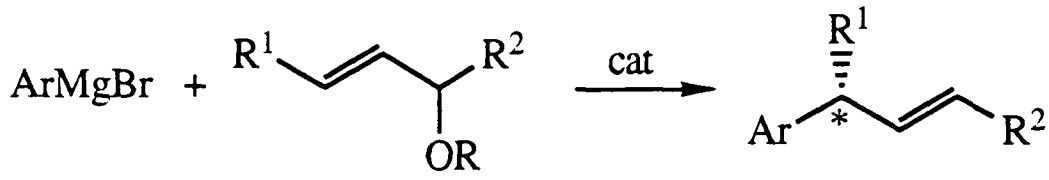
These results show that even with added LiCl the system is not well suited for a carbonylative coupling reaction, in contrast to the earlier results obtained for the direct coupling with acid chlorides. The best result obtained with (**70**) (Table 11, entry 1) gave the desired (**97**) in the same yield as the control (**63**), which was much less than that obtained by

Stille. The catalysts perform only a very few turnovers before the reaction stops. This may be due to decomposition of the catalyst, as the solutions turn black after a few minutes heating. The tin species which has $\delta = -193$ was again observed, but its identity was unable to be determined. Its formation may be due to the presence of the LiCl and/or triflate anion in the system causing decomposition or coordinating to the tin.

2.4. Ni Catalysed Reactions of Grignard Reagents

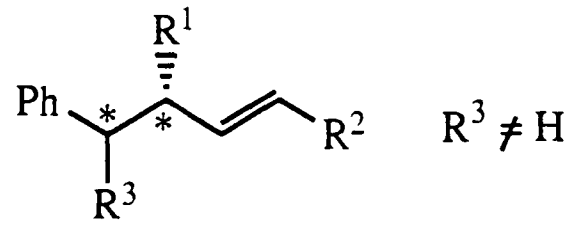
2.4.1. Introduction

In 1985 Hiyama described the catalytic asymmetric cross-coupling of aryl Grignard reagents with allylic esters,[25] Scheme 87. The catalyst used was $NiCl_2$[(S, S)-Chiraphos] and ee's of up to 89% were obtained.



Scheme 87

All of Hiyama's examples involved the coupling of aryl Grignard reagents. If this reaction could be extended to incorporate sp^3 hybridised Grignard reagents, and α-substituted benzylic reagents in particular, then the scope of the reaction would be greatly increased. The use of α-substituted benzylic Grignard reagents would produce two asymmetric centres within the new molecule (**99**). This would allow for diastereo- and enantioselectivity in the reaction to be investigated, and hopefully controlled, by the use of appropriate chiral ligands.

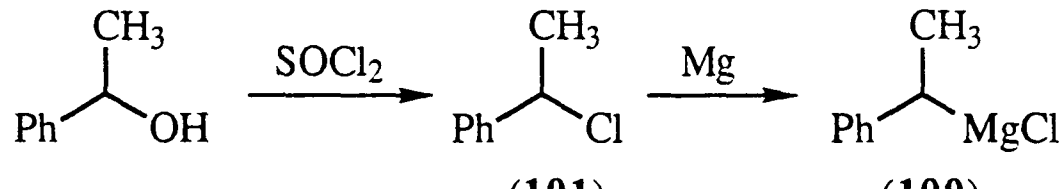


(**99**)

An investigation into the use of α-substituted Grignard reagents was thus undertaken, following the methodology of Hiyama, and the results are presented below.

2.4.2. Synthesis of Reagents

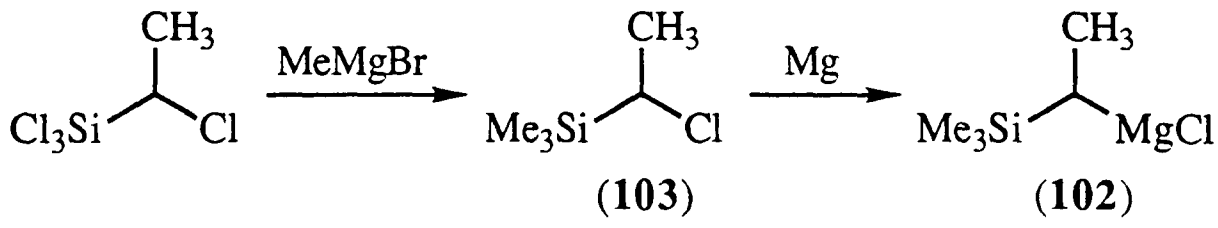
A range of α-substituted Grignard reagents was prepared for the study. α-Methylbenzylmagnesium chloride (**100**) was prepared according to Scheme 88. *sec*-Phenethyl alcohol was converted to 1-chloro-1-phenylethane (**101**), by the action of thionyl chloride, which was converted to (**100**) by reaction with activated magnesium. The Mg was activated by dry stirring under an inert atmosphere for 1 d. During this time the magnesium turned black and an Mg mirror was seen on the inside of the vessel.[121]



(**101**) (**100**)

Scheme 88

1-Trimethylsilylethylmagnesium chloride (**102**) was prepared as shown in Scheme 89. 1-Chloroethyltrichlorosilane was methylated with methylmagnesium bromide to give (1-chloroethyl)trimethylsilane (**103**)[122] in 68% yield. This was converted to the Grignard reagent (**102**) by reaction with magnesium activated with 1, 2-dibromoethane.

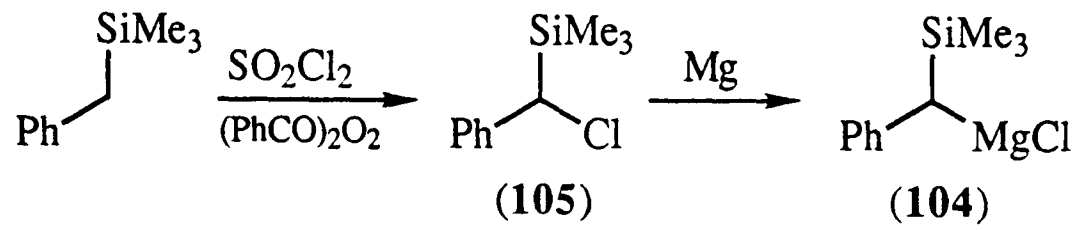


(**103**) (**102**)

Scheme 89

Finally, (α-trimethylsilyl)benzylmagnesium chloride (**104**) was prepared according to Scheme 90. Benzyltrimethylsilane was chlorinated at the α-position by reaction with sulphuryl chloride and a catalytic amount of benzoyl peroxide.[123] This afforded (α-chloro)benzyltrimethylsilane (**105**) as a colourless oil in 36% yield. The proton NMR

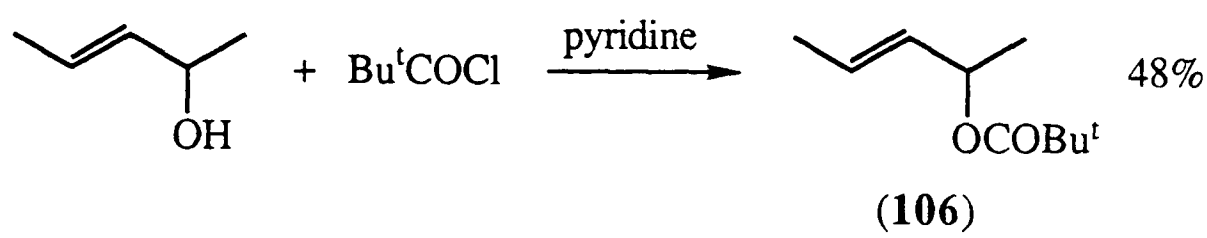
spectrum showed a downfield shift from 2.12 to 4.36 ppm for the benzylic proton, as well as a halved integral. This was converted to (**104**) by reaction with magnesium which had been activated by the 'dry stir' method.



(**105**) (**104**)

Scheme 90

Hiyama achieved the best results using the allylic ester 3-penten-2-yl pivaloate (**106**), and so this ester was prepared by reaction of the allylic alcohol with pivaloyl chloride in pyridine, Scheme 91. The ^{1}H NMR spectrum of (**106**) gave the ^{3}J coupling constant for the olefinic protons as 15 Hz, showing that the double bond was *trans*. The resonances for the two methyl groups appeared as doublets at 1.69 and 1.26 ppm.



(**106**)

Scheme 91

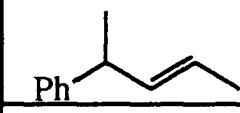
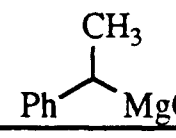
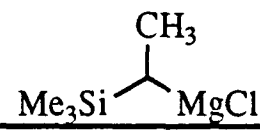
In order to test the feasibility of the reaction initial experiments were performed using an achiral Ni catalyst, (dppe)$NiCl_2$ (**107**), which was prepared from $NiCl_2.6H_2O$ and dppe.[124] The ^{31}P NMR spectrum of (**107**) contained a singlet at 53.9 ppm.

2.4.3. Attempted Catalytic Reactions

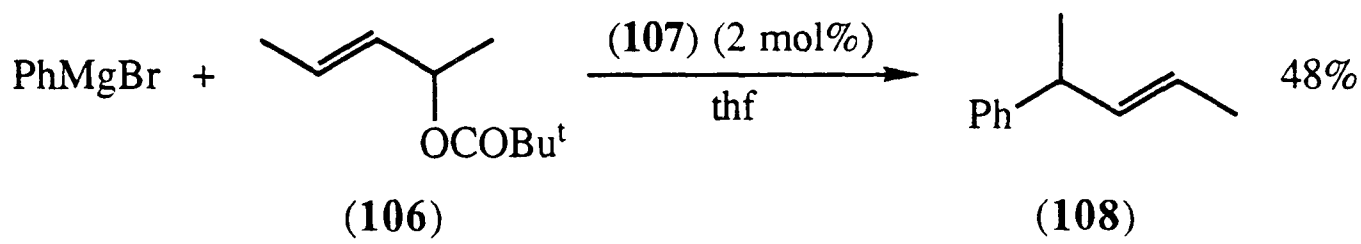
The coupling of Grignard reagents with (**106**) was then attempted. (**107**) was used as catalyst (2 mol%) and the reactions performed in thf at ambient temperature. The results are given in Table 12.

The reaction was tested by using an aryl Grignard reagent, phenylmagnesium bromide. This gave the expected product 4-phenylpent-2-ene (**108**) in 48% yield (entry 1), Scheme 92. The proton NMR gave the resonances for the methyl groups as doublets at 1.72 and 1.39 ppm and the H_4 signal was a multiplet centred at 3.47 ppm. Interestingly, when Hiyama attempted this reaction using $NiCl_2$[(S, S)-Chiraphos] as catalyst he reports that no trace of (**108**) was observed.

Table 12: Attempted Ni Catalysed Coupling of 3-Penten-2-yl Pivaloate (**106**) with Grignard Reagents[a]

Entry	Grignard Reagent	Time (h)	Products	Yield (%)[b]
1	PhMgBr	20		48
2		28	mixture[c]	
3		28	mixture[c]	
4		21	mixture[c]	

[a]Reactions were carried out on a 0.6 mmol scale in dry, degassed thf with (dppe)$NiCl_2$ (2 mol%) as catalyst. [b]Isolated yield. [c]Unidentifiable mixture of products containing recovered 3-penten-2-yl pivaloate.



(**106**) (**108**)

Scheme 92

Reaction of both (**100**) and (**102**) furnished mixtures of products (entries 2 and 3). Unreacted starting ester (**106**) was recovered but the other components of the mixture

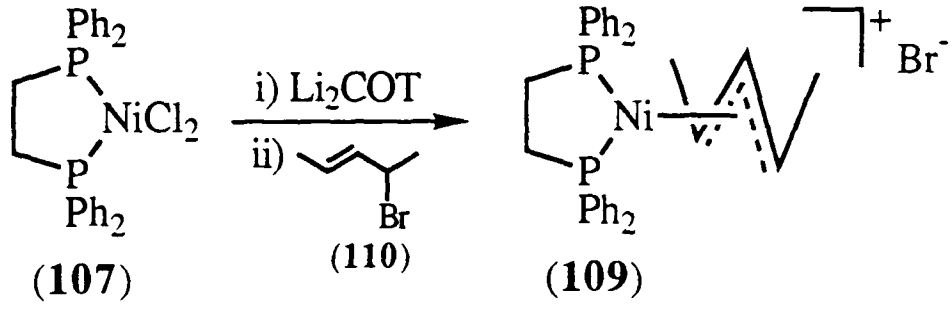
proved unidentifiable. No coupling product, however, was observed in either case. The lack of success with α-substituted magnesium reagents prompted the use of the parent benzylmagnesium chloride. Reaction with (**106**) unfortunately afforded another unidentifiable mixture, again containing unreacted (**106**) (entry 4).

The catalytic coupling using these Grignard reagents was not, therefore, successful. In order to determine whether the reaction was at all feasible it was decided to isolate an intermediate in the catalytic cycle and use it for stoichiometric reactions with the Grignard reagents.

2.4.4. Attempted Stoichiometric Reactions

In the catalytic cycle the oxidative addition of (**106**) to the Ni catalyst would presumably lead to a Ni-allyl complex. These complexes can be readily prepared from allyl bromides. It was therefore decided to perform the stoichiometric reactions with such a complex, 1, 2-bis(diphenylphosphino)ethanenickel (η^3-(1, 3-dimethyl)allyl)bromide (**109**), in this case.

The allyl bromide 2-bromopent-3-ene (**110**) was prepared from the corresponding alcohol by the action of phosphorus tribromide, in 68% isolated yield. (dppe)$NiCl_2$ was reduced with Li_2COT *in situ* and (**110**) added to this Ni(0) species, to give a red solution. Precipitation with pentane caused a brown solid to form. This was washed repeatedly with water to give (**109**) as a deep red solid, Scheme 93.

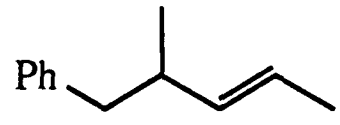


(**107**) (**110**) (**109**)

Scheme 93

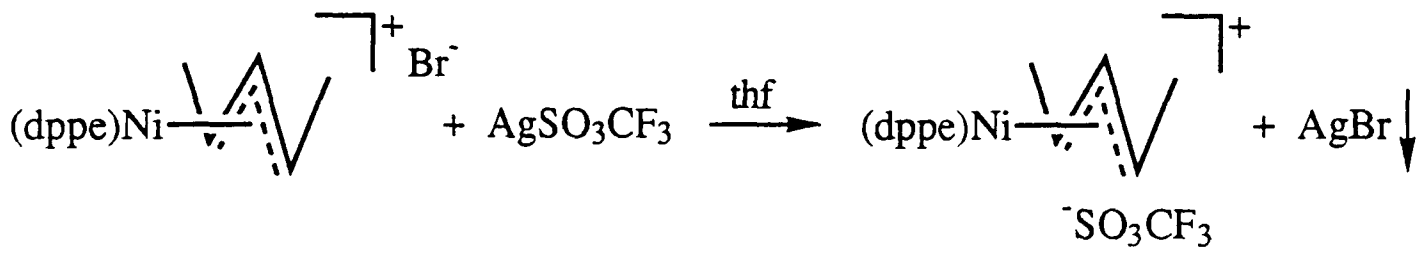
The actual structure of (**109**) is uncertain. The ^{31}P NMR spectrum showed a singlet at 42.3 ppm, which suggests that in solution the molecule is symmetric or fluxional.

The stoichiometric reaction between (**109**) and benzylmagnesium chloride was attempted. The reaction was run for 24 h at room temperature, but on work-up an unidentifiable mixture was obtained. This mixture, however, did not contain any of the desired coupling product (**111**).



(**111**)

In order to ensure that the Ni complex used was the symmetric η^3-allyl complex, with no halide bound to Ni, (**109**) was reacted with silver triflate, Scheme 94. The solution changed from deep red to yellow and a grey precipitate of AgBr was formed. The yellow solution contained the complex (**112**) in which the triflate anion should not be coordinated to the Ni, and so should have the desired symmetric structure. The ^{31}P NMR spectrum showed a singlet in the spectrum at 49.2 ppm.

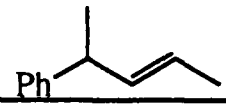


(**109**) (**112**)

Scheme 94

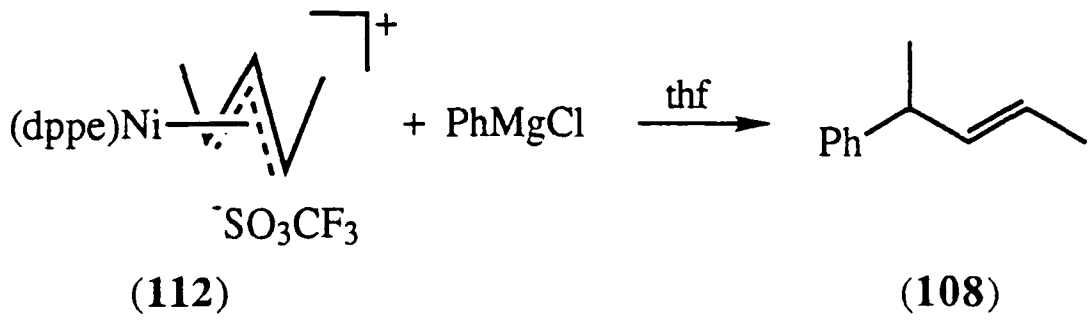
Stoichiometric reactions of complex (**112**), prepared *in situ* as described above, were then attempted and the results are given in Table 13. Once (**112**) had been formed the solution was cooled and the Grignard reagent added. The reaction was then stirred at room temperature for 20 h.

Table 13: Stoichiometric Reactions Between Ni Complex (**112**) and Grignard Reagents[a]

Entry	Grignard Reagent	Temp (°C)[b]	Products	Yield (%)[c]
1	PhMgBr	-65		37
2		-10	mixture[d]	
3		-70	mixture[d]	

[a]Reactions were carried out on a 0.12 mmol scale in dry, degassed thf and stirred at room temperature for 20 h. [b]Temperature of addition of Grignard reagent. [c]Isolated yield. [d]Unidentifiable mixture.

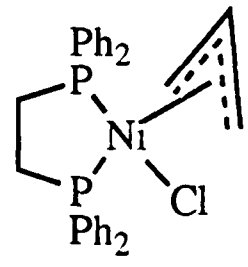
In the reaction between (**112**) and phenylmagnesium chloride the Grignard reagent was added at -65°C, causing the yellow solution immediately to turn deep red. On warming to room temperature this colour intensified. After 20 h coupled product (**108**) was obtained from the reaction mixture in 37% isolated yield (entry 1), Scheme 95. The stoichiometric reaction with benzylmagnesium chloride was attempted, with addition being performed at -10° and -70°C. In both cases a colour change from yellow to red was seen on addition, but an unidentifiable mixture was obtained from these reactions (entries 2 and 3). Neither of the mixtures was found to contain any of the desired coupled product (**111**).



(**112**) (**108**)

Scheme 95

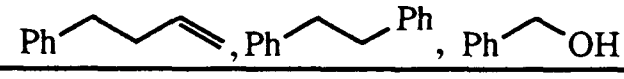
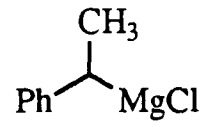
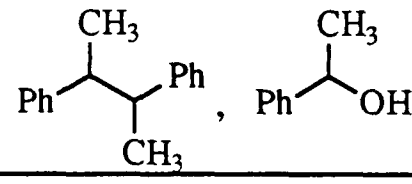
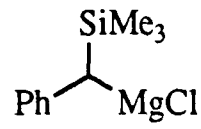
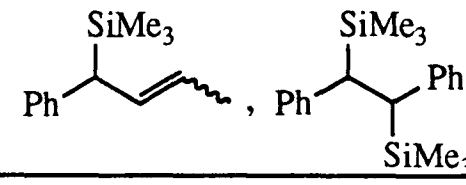
These results seem to indicate that the coupling reaction is applicable only to aryl Grignard reagents. In a final attempt to achieve coupling with benzylic Grignard reagents the stoichiometric reaction was attempted with the simple η^3-allyl complex 1, 2-bis(diphenylphosphino)ethanenickel (η^3-allyl)chloride (**113**),[125] and the results are given in Table 14.



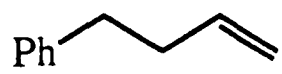
(**113**)

Reaction with benzylmagnesium chloride produced a mixture of products. The desired coupled product, 4-phenylbut-1-ene (**114**), was observed in trace amounts and identified by the GCMS spectrum. Also isolated were bibenzyl and benzyl alcohol (entry 1). A sample of the Grignard reagent alone was quenched in a similar fashion to the reaction and bibenzyl and benzyl alcohol were observed. The amounts from the Grignard reagent alone, however, were about half those observed in the attempted coupling reaction.

Table 14: Stoichiometric Reactions Between Ni Complex (**113**) and Grignard Reagents[a]

Entry	Grignard Reagent	Isolated Products
1		
2		
3		

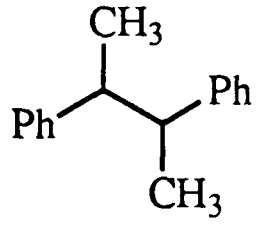
[a]Reactions were carried out on a 0.2 mmol scale in dry, degassed thf and stirred at room temperature for 20 h.



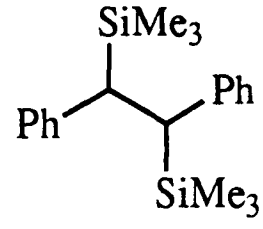
(**114**)

Reaction of (**100**) also gave a mixture of products. No coupled product was observed, but bi(α-methyl)benzyl (**115**) and *sec*-phenethyl alcohol were isolated (entry 2). These were also found in a sample of the Grignard reagent, but again not in the same

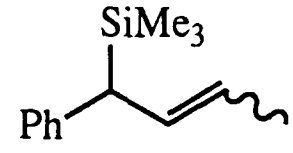
quantities as isolated from the reaction. Reaction with (**104**) again gave a mixture of products. Isolation by preparative tlc gave a fraction which contained two species, bi(α-trimethylsilyl)benzyl (**116**) and 4-phenyl-4-trimethylsilylbut-2-ene (**117**) (entry 3).



(**115**)



(**116**)



(**117**)

The proton NMR spectrum for (**116**) showed signals for the benzylic protons at 2.70 and 2.60 ppm. The proton NMR spectrum of (**117**) showed that both the *cis* and *trans* isomers were present. The resonances for the olefinic protons appeared as multiplets at 5.82 ppm (H_3) and 5.48 ppm (H_2). H_4 gave two resonances corresponding to *cis* and *trans* isomers, which were doublets (J = 10 Hz) at 3.30 and 2.89 ppm. The resonances for the methyl groups appeared as a multiplet at 1.69 ppm. The presence of both (**116**) and (**117**) was supported by the GCMS spectrum, which showed peaks for both M+1 ions. The GC trace showed two peaks for (**117**) for the two isomers and two peaks were also seen for (**116**). Both species were formed in *ca.* 15% yield. A sample of the Grignard reagent was quenched but neither (**116**) nor (**117**) was found to be present in the sample.

These results indicate that while some coupling occurred (entries 1 and 3) the extent of the reaction was not large. (**114**) was found in only trace amounts and (**117**) (the isomerised expected coupled product 4-phenyl-4-trimethylsilylbut-1-ene) isolated in only 15%. All these reactions were accompanied by the formation of homocoupled Grignard reagents. These are presumably formed by the Grignard reagent displacing both the chloride and allyl groups from the Ni, or by an electron transfer from RMg to Ni. Reductive elimination from the resulting diorganonickel species leading to formation of the homocoupled product. None of the reactions were clean, a mixture being formed in each case.

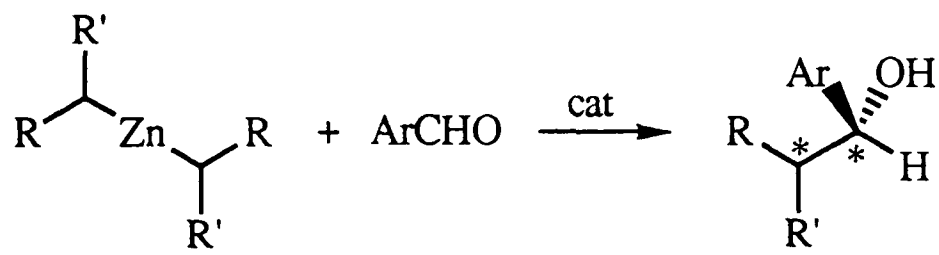
It is therefore evident that the allylnickel coupling of sp^3 hybridised Grignard reagents is much more problematic than that of sp^2 hybridised ones. Although the reactions

described above did not prove successful enough to extend the study to the use of a chiral ligand on the metal centre it is hoped that future investigations may reveal conditions under which the stoichiometric reactions will be more successful. This would then allow the catalytic reaction to be developed. The use of α-substituted Grignard reagents could then be used to probe the selectivity of the coupling reaction.

2.5. Addition of Diorganozinc Reagents to Aldehydes

2.5.1. Introduction

The catalysed addition of diorganozinc compounds to aldehydes is a very efficient method for the production of secondary alcohols. The most widely used catalysts are secondary amino alcohols. If chiral amino alcohols are used then enantioselective addition can occur, with ee's of 100% being readily available (see Section 1.2.2.2.). Thus far the reaction has been limited mainly to alkylzinc, especially Et_2Zn and Me_2Zn, and vinylzinc compounds. The use of dibenzylzinc compounds, and especially α-substituted benzyl compounds, has not been studied and so their use in this reaction was investigated. The successful addition of an α-substituted diorganozinc compound would produce a secondary alcohol with two asymmetric centres, Scheme 96. Use of a chiral catalyst would allow the diastereo- and enantioselectivity of the reaction to be investigated, and hopefully controlled.



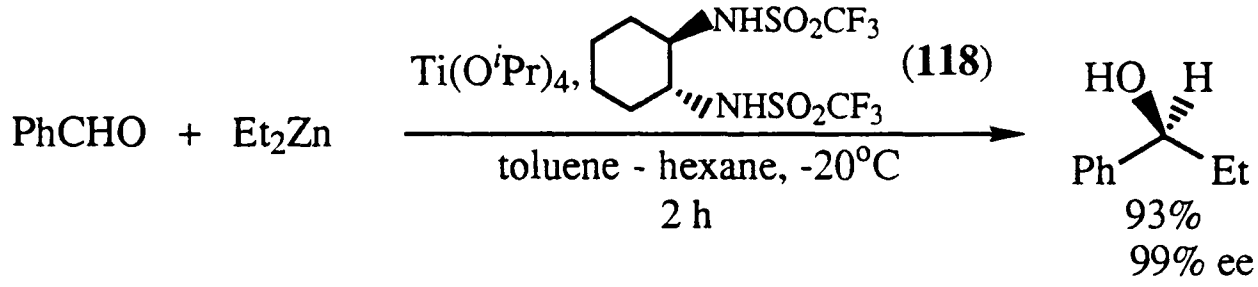
Scheme 96

Most of the addition reactions so far have been performed in non-ethereal solutions, using toluene or hydrocarbons as solvents.[33] One of the most general methods of preparing diorganozinc compounds is the transmetalation of organomagnesium reagents with zinc salts.[126,127] In most cases the Grignard reagents are used in ethereal solvents, leading to an

ethereal solution of the diorganozinc reagent. The difference in solvents for the preparation and reaction of the zinc compounds may lead to problems in the use of such systems. Seebach has recently reported addition reactions catalysed by titanium complexes[38] carried out in ethereal solutions and it was therefore hoped to extend the reaction of benzylic compounds to also be done in ethereal solutions.

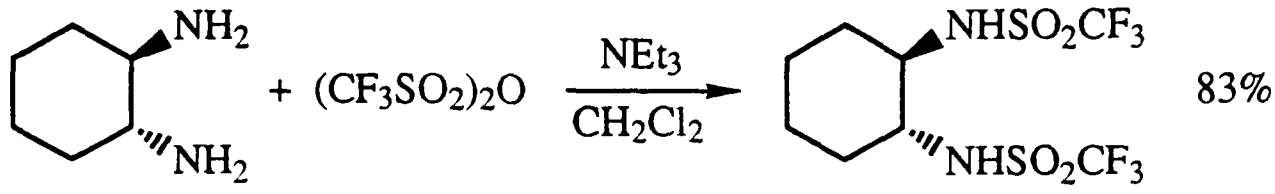
2.5.2. Attempted Catalytic Reactions

Yoshioka has described the alkylation of aldehydes catalysed by a chiral disulphonamide-titanium tetra-*iso*-propoxide-dialkyl zinc system[37] in which excellent yields and ee's were obtained, Scheme 97. The catalyst system used was 2 mol% of $Ti(O^iPr)_4$ with 0.5 mol% of the chiral disulphonamide auxiliary *trans*-1, 2-bis (trifluoromethanesulphonamide)cyclohexane (**118**).



Scheme 97

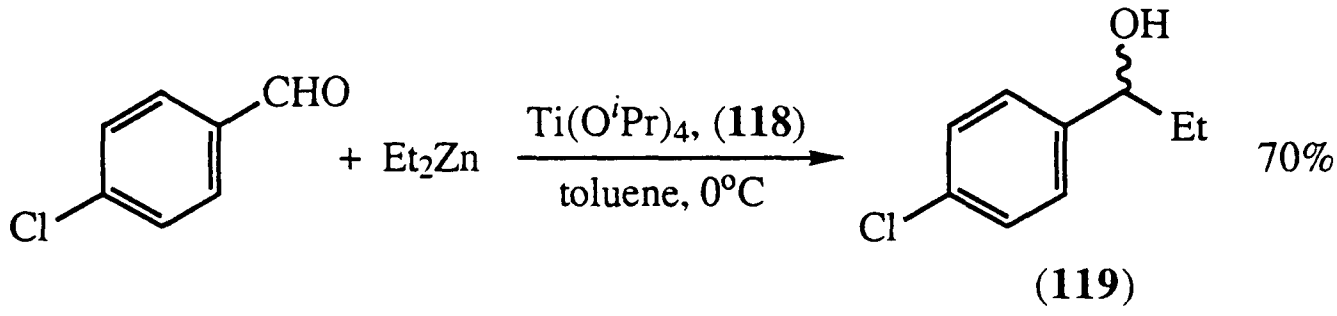
The success of this excellent catalytic system, with only a small amount of chiral auxiliary needed, prompted its use for the current study. Initial experiments were performed using the racemic (±)-(**118**), prepared from the *trans* diamine by reaction with triflic anhydride and triethylamine in CH_2Cl_2,[128] Scheme 98. The ^{13}C NMR spectrum of (**118**) showed the signal from CF_3 at 121.5 ppm as a quartet, due to C-F coupling, with J = 320 Hz.



(118)

Scheme 98

The catalytic system was tested by using it for the addition of diethylzinc to *p*-chlorobenzaldehyde. $Ti(O^iPr)_4$ (10 mol%) and (±)-(**118**) (2.5 mol%) were initially reacted together at 40°C for 20 min in toluene. The solution was cooled to -70°C, the other reagents added and the reaction stirred at 0°C for 2 h. The addition product 1-(*p*-chlorophenyl)propan-1-ol (**119**) was isolated in 70%, Scheme 99. The reaction was repeated in the absence of catalyst but no reaction occurred, unreacted aldehyde being recovered.

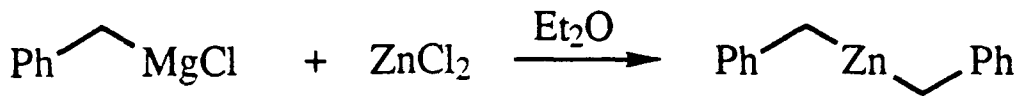


(119)

Scheme 99

These results show that the system is acting as an efficient catalyst for the reaction. The synthesis of dibenzylzinc compounds was then attempted, with the intention of using the $Ti(O^iPr)_4$-(**118**) system to catalyse their addition to aldehydes.

The parent dibenzylzinc (**120**) was prepared by the reaction between benzylmagnesium chloride and ethereal zinc chloride solution,[127] Scheme 100.



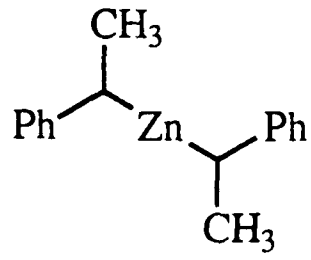
(120)

Scheme 100

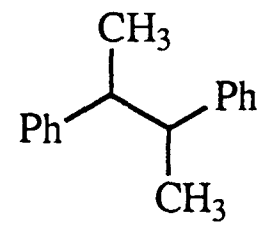
The proton NMR spectrum of (**120**) showed a singlet at 1.48 ppm corresponding to the benzylic protons. The ^1H NMR spectrum of the starting Grignard reagent showed its

benzylic protons as a singlet at 1.72 ppm. No peak at 1.72 ppm was seen in the spectrum of (**120**), indicating that no unreacted Grignard reagent was present in the sample.

The synthesis of di[(α-methyl)benzyl]zinc (**121**) was then attempted using a similar procedure. (α-Methyl)benzylmagnesium chloride (**100**) was prepared as described previously and the ^{13}C NMR spectrum of the solution showed only peaks corresponding to the Grignard reagent. (**100**) was added to ethereal zinc chloride and during the course of the reaction a grey precipitate formed. The reaction product was isolated as a white solid, but unfortunately was found to be the homocoupled bi(α-methyl)benzyl (**115**) rather than the desired (**121**). Repeated attempts at the synthesis of (**121**) also proved unsuccessful, furnishing only (**115**).



(**121**)



(**115**)

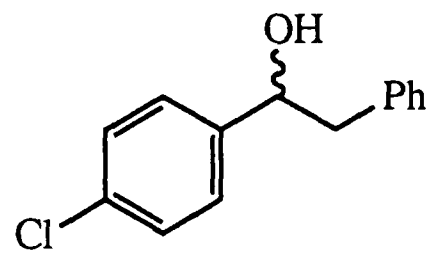
The proton NMR of (**115**) showed two multiplets at 2.76 and 2.68 ppm for the benzylic protons. Similarly the methyl groups gave rise to two doublets in the spectrum, at 1.10 and 0.91 ppm, for the *meso* and *dl* isomers.

The mechanism for the formation of the homocoupled product is unclear. The grey precipitate formed during the reaction may be a mixture of metallic zinc and inorganic salts.

The problems encountered in the synthesis of the α-substituted zinc reagent meant that it was not suitable to use for the addition to aldehydes. However it was decided to pursue the investigation with the parent dibenzylzinc (**120**), and its reaction with *p*-chlorobenzaldehyde was studied. If the reaction proved successful in toluene it was hoped to develop it to work in ethereal solutions.

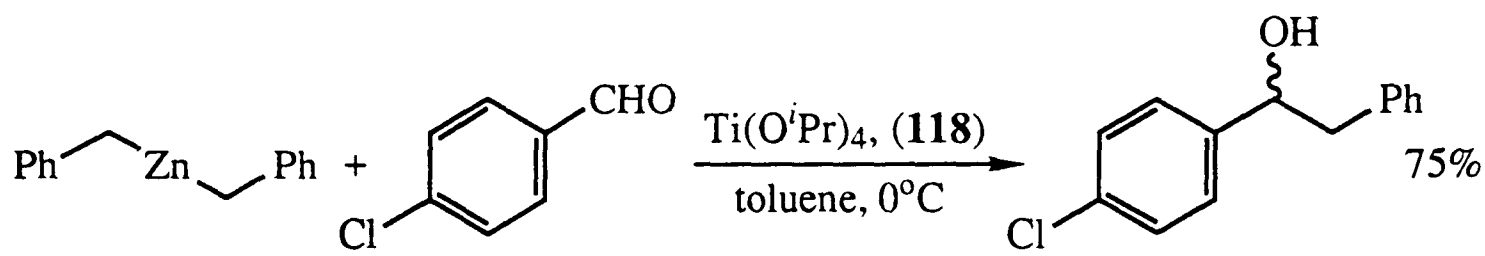
Successful addition of (**120**) to the aldehyde would produce the adduct 1-(4-chlorophenyl)-2-phenylethanol (**122**). An authentic sample of (**122**) was thus prepared by

reaction of benzylmagnesium chloride with *p*-chlorobenzaldehyde. The proton NMR spectrum showed the CH proton as a multiplet signal at 4.87 ppm, the diastereotopic CH_2 protons as a multiplet at 3.00 ppm and the OH proton as a doublet at 2.16 ppm.



(122)

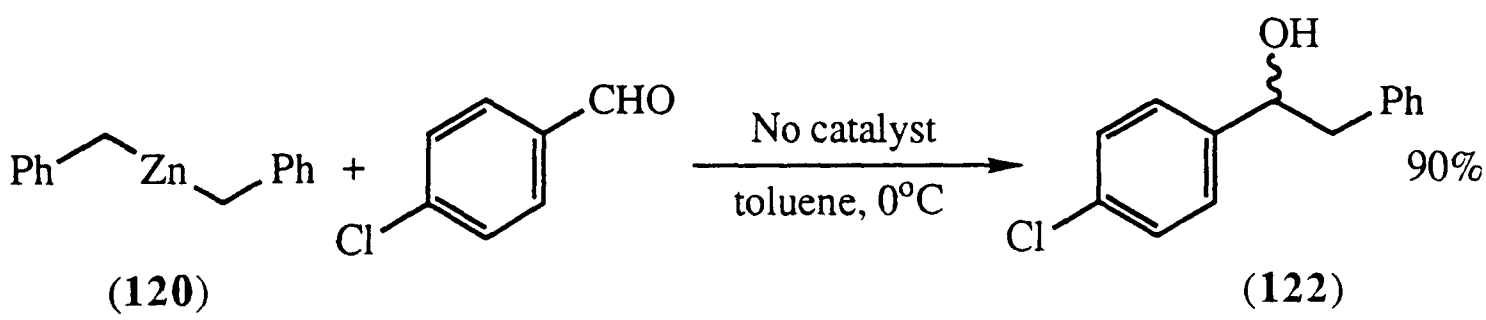
The reaction of (**120**) with *p*-chlorobenzaldehyde was then performed with the $Ti(O^iPr)_4$-(±)-(**118**) catalyst system, in a fashion identical to that used in the reaction of Et_2Zn. The addition product (**122**) was isolated from the reaction in a 75% yield, Scheme 101.



(120) **(122)**

Scheme 101

As a control reaction (**120**) was added to the aldehyde alone, in the absence of catalyst. Under these conditions Et_2Zn failed to react. However, with (**120**), the adduct (**122**) was isolated in 90% yield, Scheme 102. The reaction was repeated, and a similar result obtained.



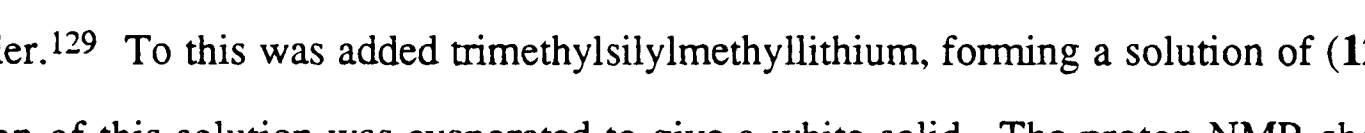
(120) **(122)**

Scheme 102

This surprising result shows that the dibenzylzinc reagent will add to the aldehyde without catalyst present. A possible explanation for this could be the presence of either

some Grignard reagent or a magnesium containing species, capable of forming a Grignard type species from (**120**), which then adds to the aldehyde.

The ^{1}H NMR data for (**120**) suggests that the Grignard reagent itself is not present, but does not discount the presence of some other Mg containing species. A route to a benzylic compound which does not involve Mg was therefore needed in order that the reactivity of the benzyl group on the Zn could be tested. The benzylic compound chosen was benzyl(trimethylsilylmethyl)zinc (**123**). If this molecule did not transfer its benzyl group in the uncatalysed reaction then the reaction of (**120**) may be due to the presence of an impurity. (**123**) was prepared as shown in Scheme 103.



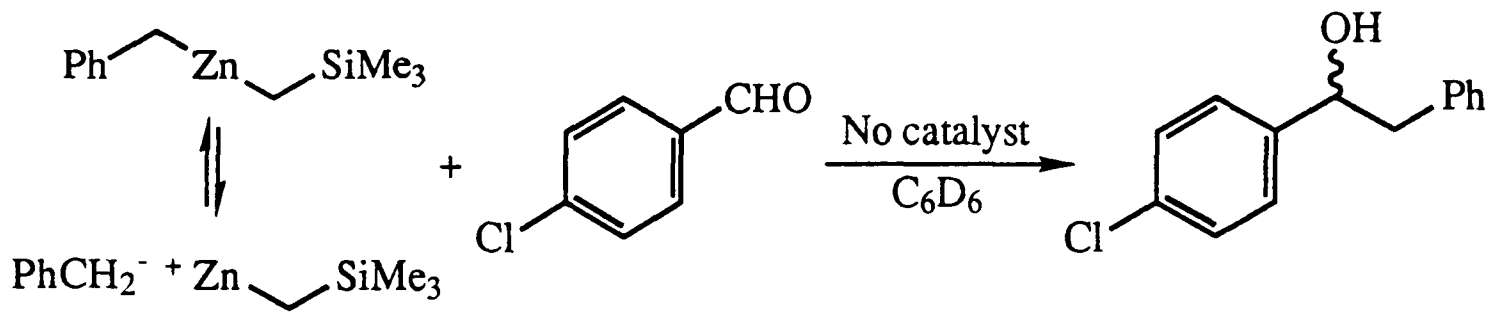
(**124**) (**123**)

Scheme 103

A solution of benzylzinc bromide (**124**) was prepared from benzyl bromide and zinc powder.[129] To this was added trimethylsilylmethyllithium, forming a solution of (**123**). A portion of this solution was evaporated to give a white solid. The proton NMR showed a peak at 2.0 ppm corresponding to the benzylic protons and a peak at -0.65 ppm for the CH_2SiMe_3 protons.

The reaction between (**123**) and *p*-chlorobenzaldehyde was performed in the presence of the catalyst system Ti(O^{i}Pr)$_4$-(±)-(**118**), and the reaction stirred at ambient temperature for 3 h. The ^{1}H NMR spectrum of the reaction mixture showed no aldehyde proton resonance, indicating that reaction had occurred. On work-up the ^{1}H NMR spectrum of the crude product contained the peaks at 4.87, 3.00 and 2.16 ppm from adduct (**122**).

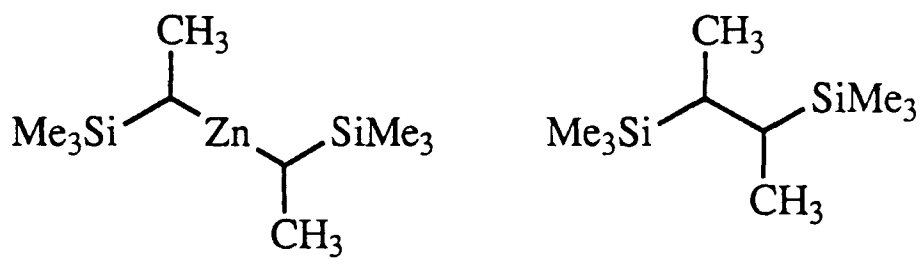
The reaction was then repeated in the absence of the catalyst and once more stirred at room temperature for 3 h. On work-up the proton NMR spectrum of the crude reaction product was found to contain the same peaks corresponding to (**122**), Scheme 104. The presence of (**122**) was also supported by tlc analysis.



(123) **(122)**

Scheme 104

These results support the earlier findings that a benzyl group on Zn will add to an aldehyde in the absence of catalyst. This means that the reaction, and any subsequent stereoselectivity, cannot be controlled. This lack of control means that benzylzinc compounds are not the ideal reagents with which to investigate any asymmetric processes. The use of other α-substituted zinc compounds could, however, be used and the synthesis of di[(1-trimethylsilyl)ethyl]zinc (**125**) was therefore attempted.

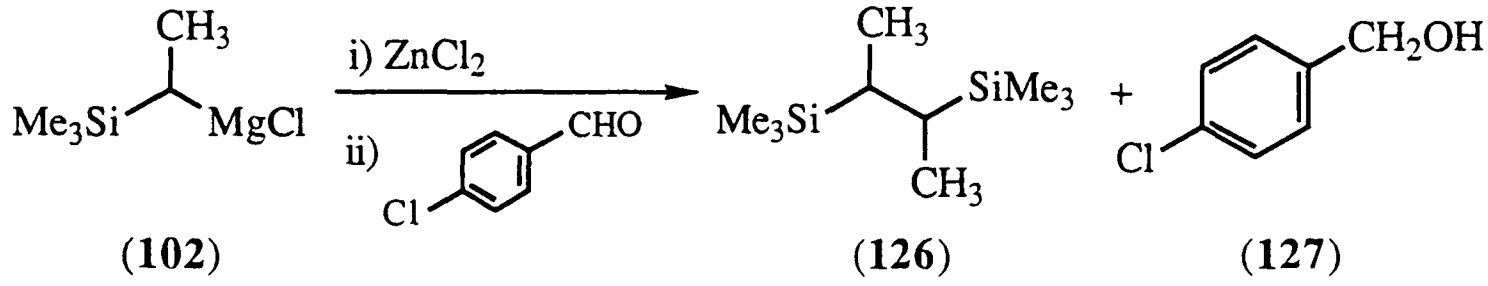


(125) **(126)**

The Grignard reagent 1-trimethylsilylethylmagnesium chloride (**102**) was prepared and reacted with ethereal $ZnCl_2$. After 4 d[130] a grey precipitate had formed. The reaction was filtered and evaporated to give a white solid which was found to be the homocoupled product 2, 3-di(trimethylsilyl)butane (**126**). The proton NMR spectrum showed two overlapping doublets at 0.93 ppm for the CH_3 groups, a multiplet at 0.71 ppm for the two CH protons and peaks at 0.01 and -0.02 for the $SiMe_3$ groups of the two isomers of (**126**).

Hence, attempts to make two different α-substituted diorganozinc compounds both failed, with homocoupled product being isolated in both instances. This highlights the problematical nature of compounds of this type and may be the result of steric interactions involving the α-substituents.

The attempted preparation of (**125**) was repeated but this time isolation was not attempted. The resulting ethereal solution was changed to a toluene solution, by repeated addition of toluene and evaporation, and was added to *p*-chlorobenzaldehyde both in the presence and the absence of catalyst system $Ti(O^iPr)_4$-(±)-(**118**). In both reactions homocoupled product (**126**) was observed along with some unreacted aldehyde. The reduction product *p*-chlorobenzylalcohol (**127**) was also isolated from both reactions, Scheme 105.



(**102**) (**126**) (**127**)

Scheme 105

Addition of Grignard reagent (**102**) alone to *p*-chlorobenzaldehyde also furnished (**127**). This implies that the zinc reagent (**125**) is not formed in the reaction, or has a reactivity similar to the Grignard reagent. Homocoupling of the Grignard reagent and reduction of the aldehyde, presumably by the sterically hindered Grignard reagent, occurs.

2.5.3. Conclusions

The surprising findings that a benzylzinc reagent will add to an aldehyde without a catalyst highlights the reactivity of these compounds. This increased nucleophilic character of the Zn-C bond may be due to the greater polarity of the Zn-benzyl bond compared to the Zn-ethyl bond in Et_2Zn. The non-catalysed addition will not be selective, both enantiomers of the secondary alcohol being formed in equal amounts.

The lack of success in preparing samples of α-substituted zinc reagents, by the standard procedure using Grignard reagents, indicates that this is not the ideal system with which to work. If their synthesis could be achieved by other routes,[131] developed since this part of the project was completed, then the addition reaction to aldehydes could be investigated. This would allow the use of chiral catalysts and the process of selectivity to be studied, and hopefully controlled.

EXPERIMENTAL

"Happy the man who could
understand the causes of things"
Virgil (70 - 19 BC)

CHAPTER 3. EXPERIMENTAL

3.1. General Experimental Techniques

3.1.1. Instrumental

Elemental microanalyses were carried out by Mrs V. Lamburn in the Dyson Perrins Laboratory, using a Carlo Erba 1106 elemental analyser.

NMR spectra: ^{1}H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) or a Bruker WH 300 (300 MHz) spectrometer and are referenced to the residual solvent peak ($CHCl_3$: $\delta = 7.27$). ^{13}C NMR spectra were recorded on a Varian Gemini 200 (50.31 MHz), a Bruker AM 250 (62.89 MHz) or a Bruker AM 500 (125.8 MHz) spectrometer and are referenced to the residual solvent peaks ($CDCl_3$; $\delta = 77.0$). ^{31}P NMR spectra were recorded on a Bruker AM 250 (101.2 MHz) and are referenced to 85% aqueous phosphoric acid (H_3PO_4). ^{119}Sn NMR spectra were recorded on a Bruker AM 250 (93.18 MHz) and are referenced to tetramethyltin ($SnMe_4$; $\delta = 0$). Abbreviations used in the description of spectra are: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dq = doublet of quartets, ddq = doublet of doublet of quartets, m = multiplet, br = broad, J = coupling constant in Hz.

Infra red spectra were recorded on a Perkin Elmer 297 or a Perkin Elmer 1750 Fourier Transform spectrometer. Samples were prepared on NaCl plates as Nujol mulls, in KBr discs, in solution or as thin films as indicated. Abbreviations used in the description of spectra are: w = weak, m = medium, s = strong, br = broad.

Mass spectra were recorded by Dr R. T. Aplin or Mr R. Procter on a Varian MAT CH7, V. G. Micromass 16F or ZAB-1F/16F spectrometers or on a Trio-1 GCMS spectrometer. Values are followed, in parentheses, by the intensity as a percentage of the base peak.

Melting points were recorded on a Reichert-Koffler block, and are uncorrected.

3.1.2. Experimental Procedures

All manipulations of air sensitive reagents were carried out under argon atmospheres using standard vacuum line techniques.[132]

Solvents were purchased from Rhône-Poulenc, Fisons or the Aldrich Chemical Companies and were dried by distillation from standard drying agents according to the procedures described by Perrin *et al.*[133] Solvents were deoxygenated by repeated freeze-thaw cycles, in which the solvent was frozen in liquid nitrogen, allowed to warm *in vacuo* and flushed with argon.

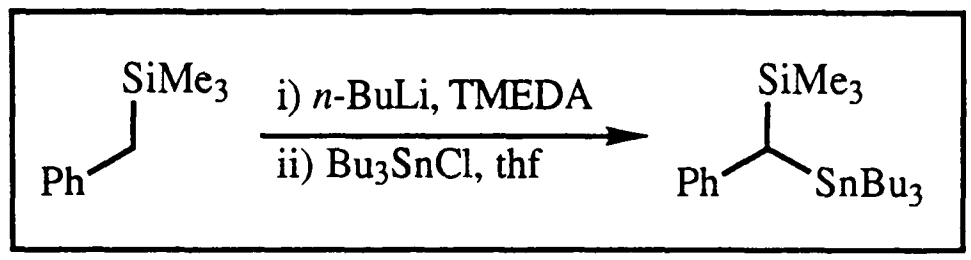
Chromatography was performed on Merck silica gel 60H, 230-300 mesh using the flash chromatographic method of Still.[134] Preparative tlc was performed on glass plates coated with silica gel HF.254.

All reagents were purchased from the Aldrich Chemical Co. apart from benzyltrimethylsilane (Fluka); benzoyl chloride, thionyl chloride, sulphuryl chloride, benzoyl peroxide and nickel dichloride hexahydrate (BDH); bromine and phosphorus tribromide (Fisons); 1-chloroethyltrichlorosilane (Lancaster); carbon monoxide (Argo International Ltd) and palladium dichloride (Johnson Matthey).

n-Butyllithium (1.6 M in hexanes and 2 M in pentane), *t*-butyllithium (1.7 M in pentane), methyllithium (1.4 M in Et_2O), trimethylsilylmethyllithium (1 M in pentane), methylmagnesium bromide (3 M in Et_2O), methylmagnesium chloride (3 M in thf), phenylmagnesium bromide (3 M in Et_2O) benzylmagnesium chloride (1 M in Et_2O and 2 M in thf), diethylzinc (1 M in hexanes) and zinc chloride (1 M in Et_2O) were obtained from the Aldrich Chemical Co..

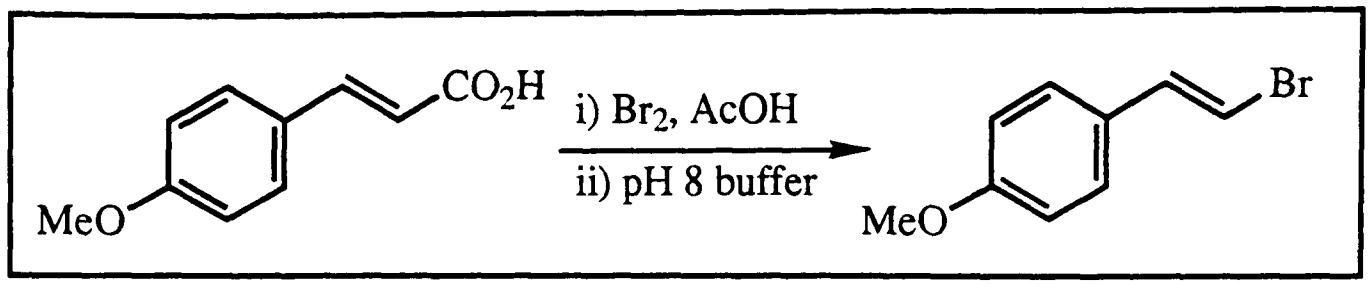
3.2. Experimental for Section 2.2.

(α-Trimethylsilyl)benzyltri-*n*-butyltin (**43**)



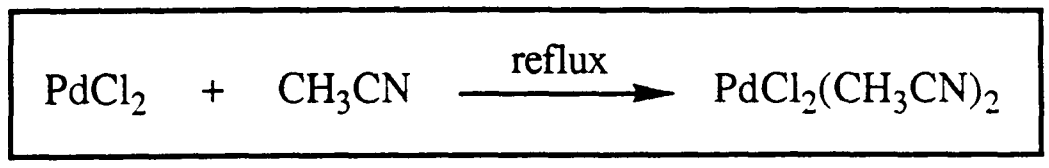
To a mixture of benzyltrimethylsilane (3.00 g, 18 mmol) and N, N, N', N'-tetramethylethylenediamine (2.61 g, 22.5 mmol) at 0°C was added *n*-butyllithium (14.1 ml, 1.6 M, 22.5 mmol), causing the solution to turn yellow.[94] The reaction mixture was stirred for 4 h and then tri-*n*-butyltin chloride (5.85 g, 18 mmol) in dry thf (15 ml) was added, causing the solution to turn colourless. The reaction was stirred overnight and then quenched with water. The aqueous layer was extracted with Et_2O (2 x 30 ml), the combined organic layers washed with dilute aqueous HCl (50 ml), dried over $MgSO_4$ and evaporated to give a yellow oil (7.78 g). Impurities were removed by distillation at 90°C/0.1 mmHg, (α-trimethylsilyl)benzyltri-*n*-butyltin being left as a non-distillable, colourless oil (7.71 g, 95%). Found: C, 58.3; H, 9.12. $C_{22}H_{42}SiSn$ requires C, 58.3; H, 9.28 %. ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.20-6.91 (5H, m, Ph), 1.87 (1H, s, ^2J (^{117,119}Sn-H) 53, 55 Hz, Ph-C*H*-Sn), 1.48-1.22 (12H, m, Sn-CH_2-CH_2), 0.91-0.82 (15H, m, -CH_2CH_3) and 0.05 (9H, s, $SiMe_3$); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 145.4 (*ipso*-Ph), 128.3, 128.0, 122.6 (aromatic carbons), 28.9, 27.3, 13.4 (CH_2), 24.2 (CH), 10.4 (CH_2CH_3) and -0.12 ($SiMe_3$); ν_{max} (thin film) 2950 (s), 2920 (s), 2848 (m), 1591 (m), 1486 (m), 1460 (m), 1245 (s) and 1203 (m) cm^{-1}; m/z (DEI) 397 (14%, M-Bu), 163 (15, M-$SnBu_3$) and 73 (61, $SiMe_3$).

(E)-1'-Bromo-2'-(4-methoxyphenyl)ethene (**45**)



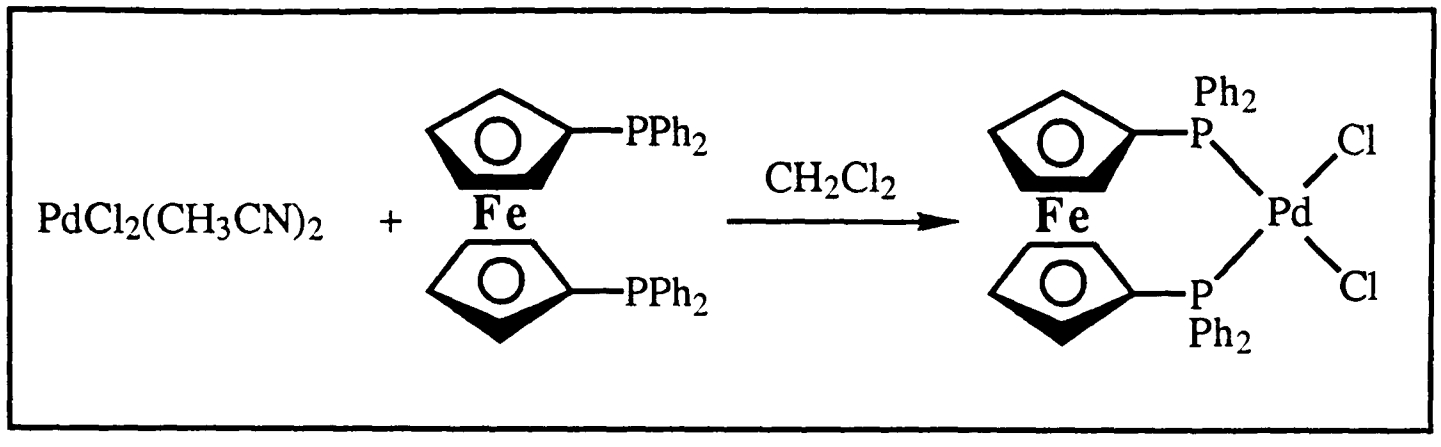
To a suspension of (E)-4-methoxycinnamic acid (10.65 g, 60 mmol) in glacial acetic acid (35 ml) was added bromine (9.60 g, 60 mmol) in glacial acetic acid (25 ml) over a period of 90 min. The reaction was stirred overnight, filtered and washed with glacial acetic acid. The resulting white solid was recrystallised from Et_2O/hexane to give white crystals (12.24 g). These were added to a buffer solution of pH 8 (1.5 l with K_2HPO_4 (20 g) and KH_2PO_4 (0.5 g)) and stirred for 3 h. The buffer solution was extracted with CH_2Cl_2 (3 x 250 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a yellow solid. Recrystallisation from hot hexane gave (E)-1'-bromo-2'-(4-methoxyphenyl)ethene (5.41 g, 43%) as white needles, m.p. 53-55°C (lit.[95] 55-55.5°C); ^1H NMR[135] (200 MHz): δ ($CDCl_3$) 7.26 (2H, d, J = 10 Hz, H_3, H_5), 7.07 (1H, d, J = 14 Hz, C*H*=CHBr), 6.88 (2H, d, J = 10 Hz, H_2, H_4), 6.61 (1H, d, J = 14 Hz, CH=C*H*Br) and 3.83 (3H, s, OCH_3); ν_{max} (nujol) 3065 (m), 1884 (w), 1792 (m), 1607 (s), 1570 (m), 1525 (s), 1252 (s), 1229 (m), 1190 (s) and 1110 (m) cm^{-1}.

Bis(acetonitrile)palladium Dichloride



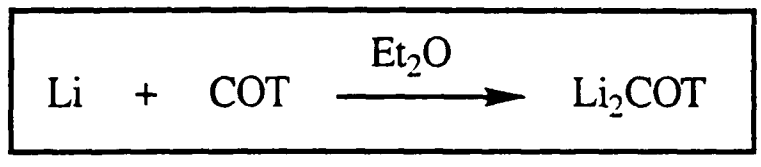
Palladium dichloride (1.00 g, 5.65 mmol) was added to acetonitrile (55 ml) and the reaction heated at reflux overnight, forming a red solution. On cooling an orange precipitate formed. Hexane (100 ml) was added and the solid collected to give bis(acetonitrile)palladium dichloride (1.23 g, 85%) as an orange solid, m.p. >260°C (lit.[136] 450°C (decomp.)); ν_{max} (nujol) 2346 (m) (CN) cm^{-1}.

1,1'-Bis(diphenylphosphino)ferrocenylpalladium Dichloride



To a solution of bis(acetonitrile)palladium dichloride (400 mg, 1.54 mmol) in CH_2Cl_2 (10 ml) was added 1,1'-bis(diphenylphosphino)ferrocene (**1**) (855 mg, 1.54 mmol) and the solution stirred for 1 h. Et_2O (30 ml) was then added causing light brown crystals to precipitate, which were filtered and dried to give 1,1'-bis(diphenylphosphino)ferrocenyl palladium dichloride as a brown solid, m.p. 250°C (decomp.) (lit.[15] 256°C (decomp.)); ^1H NMR[15] (200 MHz): δ ($CDCl_3$) 7.95-7.40 (20H, m, Ph), 4.42 (4H, s, Cp) and 4.20 (4H, s, Cp); ^{13}C NMR (53.31 MHz): δ ($CDCl_3$) 152.4-128.1 (aromatic carbons); ^{31}P NMR (101.2 MHz): δ ($CDCl_3$) 30.9; ν_{max} (nujol) 1301 (m), 1272 (m), 1166 (m), 1098 (m), 1032 (m), 749 (s), 722 (s) and 690 (s) cm^{-1}.

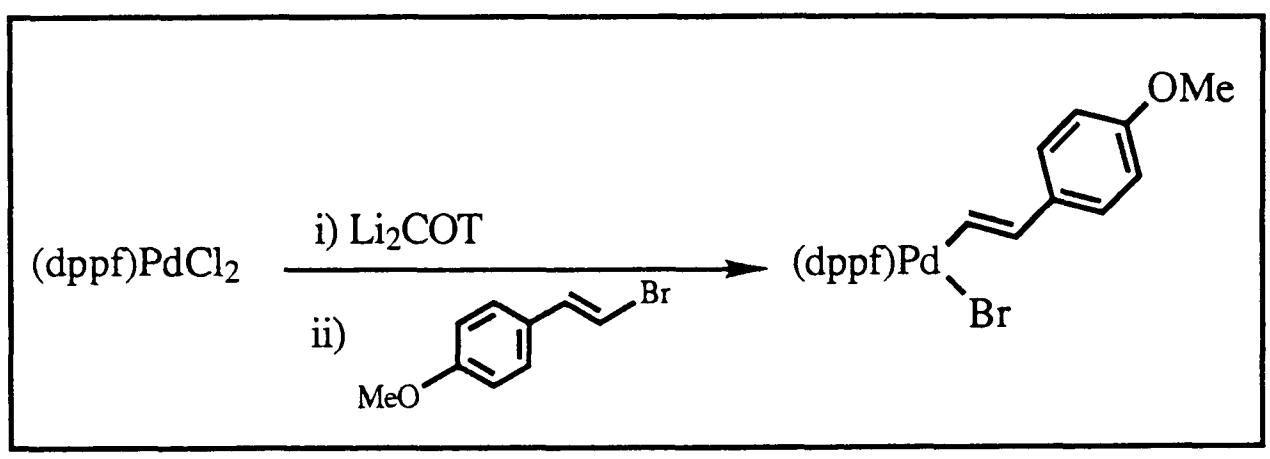
Dilithium Cyclooctatetraenide[96]



Lithium (*ca.* 1.20 g, 35% dispersion in oil, 60 mmol) was washed with dry hexane (2 x 30 ml), dried *in vacuo* and suspended in dry, degassed Et_2O (40 ml) at 0°C. To this was added cyclooctatetraene (1.35 ml, 12 mmol) and the solution stirred overnight. The resulting brown solution was filtered *via* cannula and the remaining solid washed with dry, degassed Et_2O (20 ml), which was filtered. A portion (1 ml) of the ethereal solution of

dilithium cyclooctatetraenide was hydrolysed and titrated against 0.1 M HCl to determine its concentration.

Bromo[1, 1'-bis(diphenylphosphino)ferrocene][(E)-2-(4-methoxyphenyl)ethenyl]palladium (48)



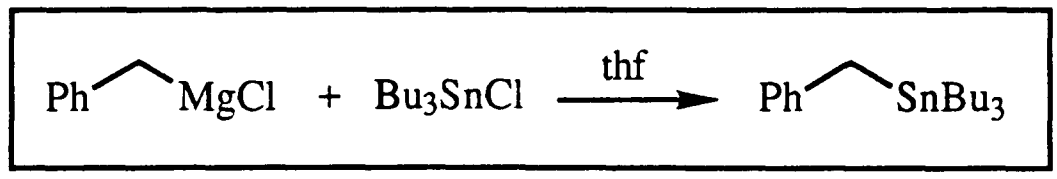
To a suspension of 1, 1'-bis(diphenylphosphino)ferrocenepalladium dichloride (0.35 g, 0.51 mmol) in dry degassed thf (25 ml) at -60°C was added ethereal Li_2COT (4.25 ml, 0.12 M, 0.51 mmol), causing the solution to turn deep red. The reaction was allowed to warm to -20°C over a period of 30 min and then (E)-1'-bromo-2'-(4-methoxyphenyl)ethene (**45**) (1.00 g, 4.7 mmol) in dry, degassed thf (10 ml) was added and the reaction stirred for 1 h. It was then warmed to room temperature and pentane (200 ml) added, causing a yellow precipitate to form. This was filtered, washed repeatedly with pentane, water then pentane again and dried *in vacuo* to give bromo[1, 1'-bis(diphenylphosphino)ferrocene][(E)-2-(4-methoxyphenyl)ethenyl]palladium (0.395 g, 94%) as a yellow powder, m.p. 155°C (decomp.) (lit.[18b] 156-157°C (decomp.)); ^1H NMR[18b] (200 MHz): δ (CD_2Cl_2) 8.01-7.23 (24H, m, aromatic protons), 6.58 (1H, m, CH=C*H*Ar), 6.12 (1H, m, C*H*-Pd), 4.52-4.21 (8H, m, Cp) and 3.78 (3H, s, OCH_3); ν_{max} (KBr) 3018 (m), 2415 (m), 1620 (m), 1518 (s), 1450 (s), 1220 (s), 1200 (s), 1025 (s) and 852 (m) cm^{-1}.

Attempted Pd Catalysed Coupling of (α-Trimethylsilyl)benzyltri-*n*-butyltin (**43**) with (E)-1'-Bromo-2'-(4-methoxyphenyl)ethene (**45**): General Procedure (Table 1, entry 2)

To a solution of bromo[1, 1'-bis(diphenylphosphino)ferrocene][(E)-2-(4-methoxyphenyl)ethenyl]palladium (**48**) (6 mg, 2 mol%) in dry, degassed thf (1 ml) under argon was added (E)-1'-bromo-2'-(4-methoxyphenyl)ethene (**45**) (77 mg, 0.36 mmol) and (α-trimethylsilyl)benzyltri-*n*-butyltin (**43**) (163 mg, 0.36 mmol) in dry degassed thf (2 ml) and the reaction heated at 67°C for 2 d. The solvent was evaporated and the resulting orange solid triturated with hexane (2 x 10 ml). This was filtered through a short silica gel plug and evaporated to give a colourless liquid. ^{1}H NMR and tlc, with hexane as eluent, indicated only unreacted starting materials.

When DMF was used as solvent the reaction was diluted with Et_2O on completion. This was washed several times with water and evaporated to give an orange solid, which was then triturated as above.

Benzyltri-*n*-butyltin (**50**)



To a solution of tri-*n*-butyltin chloride (2.00 g, 6.2 mmol) in dry thf (15 ml) at 0°C was added benzylmagnesium chloride (3.7 ml, 2 M, 7.4 mmol). The reaction was stirred at ambient temperature for 6 h and then quenched with water. The aqueous layer was extracted with Et_2O (2 x 20 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a colourless oil (1.8 g). Purification by column chromatography on silica gel with hexane gave benzyltri-*n*-butyltin as a colourless liquid (1.59 g, 67%). ^{1}H NMR[137] (200 MHz): δ ($CDCl_3$) 7.2-7.02 (5H, m, Ph), 2.34 (2H, s, ^{2}J (^{117,119}Sn-H) 55, 57 Hz, SnCH_2), 1.2-1.6 (12H, m, Sn-CH_2CH_2) and 0.95-0.80 (15H, m, -CH_2CH_3); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 143.8 (*ipso*-Ph), 128.4, 127.1, 122.9 (aromatic carbons), 28.9, 27.2, 18.0, 13.5,

(CH_2) and 9.1 (CH_3); ^{119}Sn NMR (93.18 MHz): δ (thf) -24.26; ν_{max} (thin film) 2950 (m), 2920 (m), 2844 (m), 1598 (m), 1489 (s), 1450 (m), 1373 (m) and 1207 (s) cm^{-1}.

Attempted Pd Catalysed Coupling of Benzyltin Compounds with Benzoyl Chloride: General Procedure (Table 1, entry 7)

To a solution of benzyltri-*n*-butyltin (**50**) (35 mg, 0.092 mmol) and tetrakis(triphenylphosphine)palladium (0) (10 mg, 10 mol%) in dry degassed DMF (1 ml) under argon was added benzoyl chloride (13 mg, 0.092 mmol) in dry degassed DMF (2 ml) and the reaction heated at 90°C for 24 h. The solution was diluted with Et_2O (10 ml) and washed with water (3 x 20 ml), aqueous KF solution (10 ml) and brine (10 ml). The organic layer was concentrated, dissolved in EtOAc, filtered and evaporated to give a yellow oil.

When toluene was used as the solvent, after 24 h the reaction was simply evaporated to give a yellow liquid.

trans-Benzoylchlorobis(triphenylphosphine)palladium (II) (**53**)

$$Pd(PPh_3)_4 + PhCOCl \xrightarrow{\text{toluene}} PhCOPd(PPh_3)_2Cl$$

To a solution of tetrakis(triphenylphosphine)palladium (0) (400 mg, 0.34 mmol) in dry, degassed toluene (40 ml) was added benzoyl chloride (240 mg, 1.7 mmol) in dry, degassed toluene (20 ml) and the reaction stirred for 19 h. The volume was then reduced to approximately 2 ml and dry Et_2O (80 ml) added, causing a yellow precipitate to form. This was filtered, washed with Et_2O and dried to give benzoylchlorobis(triphenylphosphine) palladium (II) (128 mg, 49%)[98] as a yellow powder, m.p. 150°C (decomp.). Found: C, 66.3; H, 4.79. $C_{43}H_{35}ClOP_2Pd$ requires C, 66.9; H, 4.54 %; ^1H NMR[98] (200 MHz): δ

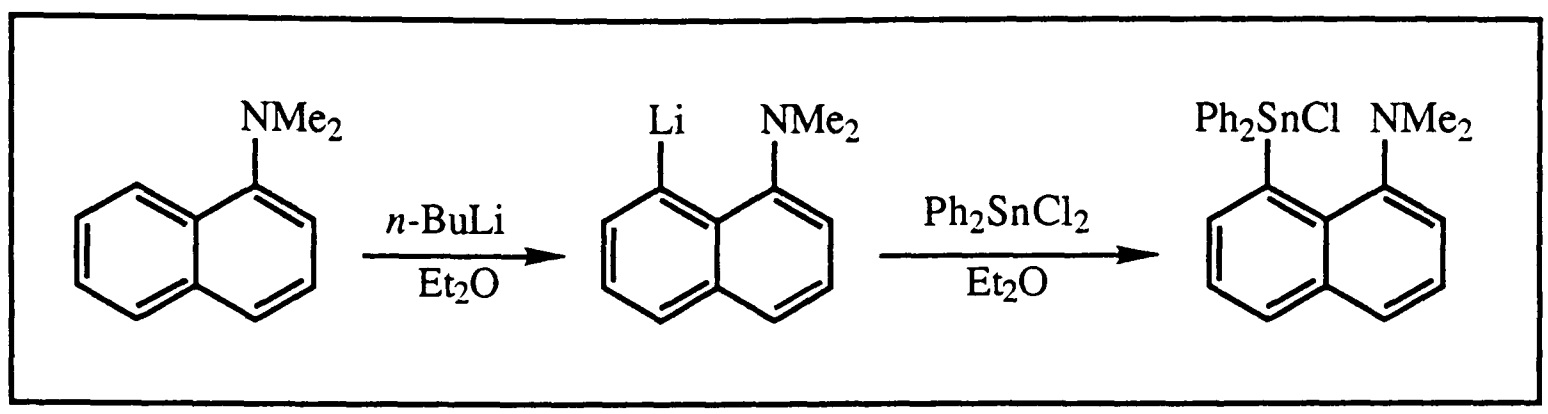
($CDCl_3$) 7.76-6.89 (m, aromatic protons); ^{31}P NMR (101.2 MHz): δ ($CDCl_3$) 15.7; ν_{max} (KBr) 1637 (s) (C=O), 1435 (m), 1150 (m), 1096 (m), 870 (s), 743 (s) and 692 (s) cm^{-1}.

Stoichiometric Coupling Between Benzyltri-*n*-butyltin (**50**) and Benzoylchlorobis(triphenylphosphine)palladium (II) (**53**)

To benzoylchlorobis(triphenylphosphine)palladium (II) (**53**) (30 mg, 0.039 mmol) in a 5 mm NMR tube was added benzyltri-*n*-butyltin (**50**) (30 mg, 0.078 mmol) in dry, degassed $CDCl_3$ (0.6 ml). The reaction was heated at 65°C and followed by ^1H NMR. After 47 h a black precipitate had formed in the NMR tube. The reaction was filtered through Celite and evaporated. Isolation of the reaction products was achieved by preparative tlc with hexane:Et_2O (2:1) as eluent to give valerophenone: ^1H NMR: δ ($CDCl_3$) 7.97-7.04 (5H, m, Ph), 2.97 (2H, t, J = 8 Hz, $COCH_2$) and 1.80-0.80 (7H, m, $CH_2CH_2CH_3$), in addition to benzyldi-*n*-butyltin chloride: ^1H NMR: δ ($CDCl_3$) 7.92-7.51 (5H, m, Ph), 2.79 (2H, s, ^2J ($^{117,119}Sn$-H) 64, 66 Hz, $PhCH_2Sn$) and 1.62-0.81 (18H, m, Bu_2).

3.3. Experimental for section 2.3.

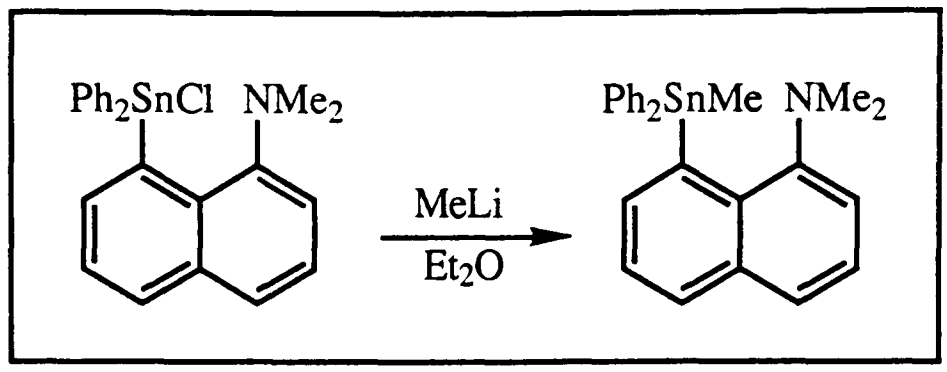
[8-(Dimethylamino)-1-naphthyl]diphenyltin Chloride (62)



To a solution of N, N-dimethyl-1-naphthylamine (4.00 g, 23.4 mmol) in dry Et_2O (40 ml) was added *n*-butyllithium (11.7 ml, 2 M, 23.4 mmol), causing the solution to turn yellow. The reaction was stirred for 24 h during which time a yellow precipitate formed. This was allowed to settle and the mother liquor removed by syringe. The remaining solid was washed with 30-40°C petroleum ether (3 x 15 ml) and dried *in vacuo* to give 2.855 g of yellow solid.[102]

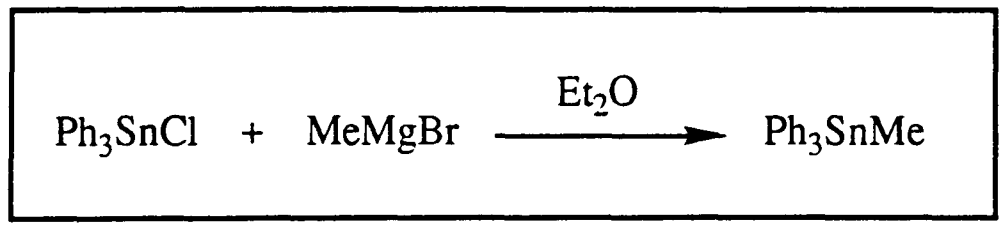
Diphenyltin dichloride (3.83 g, 11.1 mmol) was dissolved in dry Et_2O (30 ml) and the yellow solid slowly added to it, causing a white precipitate to form. The reaction was stirred for 2 h then the solvent removed *in vacuo* to give a white solid. This was triturated with hot toluene, which was filtered through Celite and evaporated to give a white oily solid. This was washed with 30-40°C petroleum ether (3 x 10 ml) and recrystallised from toluene/30-40°C petroleum ether to give [8-(dimethylamino)-1-naphthyl]diphenyltin chloride (1.90 g, 35%) as a white solid, m.p. 177-179°C. Found: C, 61.1; H, 5.00. $C_{24}H_{22}ClNSn$ requires C, 60.2; H, 4.64 %; ^1H NMR (200 MHz): δ ($CDCl_3$) 8.77 (1H, d, J = 7 Hz, H_2) 8.08-7.36 (15H, m, aromatic protons) and 2.33 (6H, s, NMe_2); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 149.7-116.9 (aromatic carbons) and 49.1 (NMe_2); ν_{max} (KBr) 3063 (m), 3000 (m), 1563 (m), 1470 (s), 1455 (s), 1429 (s), 1367 (m), 1076 (m), 1021 (m), 826 (s) and 787 (s) cm^{-1}; m/z (EI) 479 (2%, M^+), 444 (24, M-Cl), 402 (30, M-Ph), 127 (50, $C_{10}H_7$) and 77 (50, Ph).

[8-(Dimethylamino)-1-naphthyl]methyldiphenyltin (**60**)



To a suspension of [8-(dimethylamino)-1-naphthyl]diphenyltin chloride (**62**) (700 mg, 1.5 mmol) in Et_2O (15 ml) at -20°C was added methyllithium (1.1 ml, 1.4 M, 1.5 mmol). The reaction was heated at reflux for 3 h then stirred at room temperature for 22 h, filtered and evaporated to give a white solid. Recrystallisation from hot hexane yielded [8-(dimethylamino)-1-naphthyl]methyldiphenyltin (236 mg, 35%) as a white solid, m.p. 140-142°C (lit.[102] 147°C); ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.91-7.09 (16H, m, aromatic protons), 2.32 (6H, s, NMe_2) and 0.79 (3H, s, ^2J (^{117,119}Sn-H) 56, 58 Hz, SnMe); ^{119}Sn NMR (93.18 MHz): δ (thf) -110.8; ν_{max} (KBr) 3043 (w), 2953 (w), 2861 (w), 1561 (m), 1456 (s), 1428 (s), 1363 (s), 1075 (m), 1021 (m), 825 (s), 780 (s), 730 (s) and 700 (s) cm^{-1}.

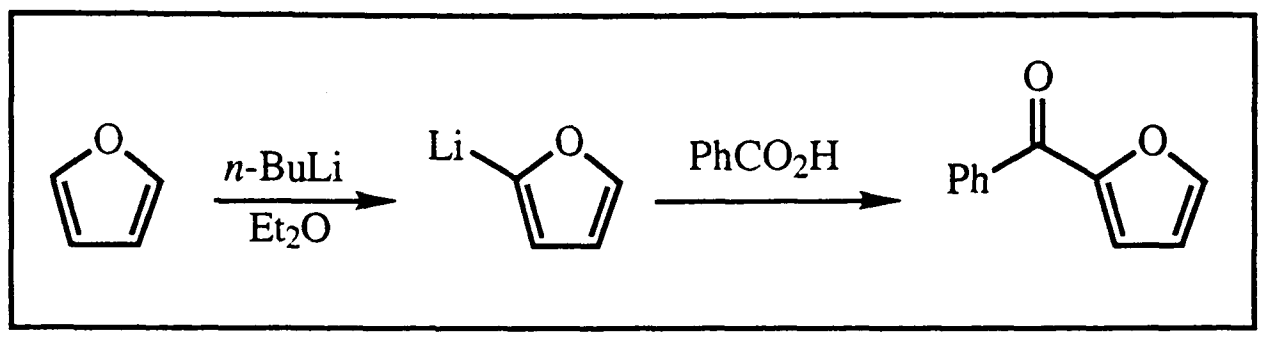
Methyltriphenyltin (**63**)



To a suspension of triphenyltin chloride (3.85 g, 10 mmol) in dry Et_2O (40 ml) was slowly added methylmagnesium bromide (3.66 ml, 3 M, 11 mmol). The reaction was stirred for 15 h and then quenched with water. The aqueous layer was extracted with Et_2O (2 x 30 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give methyltriphenyltin (3.14 g, 86%) as a white solid, m.p. 61-63°C (lit.[107] 61°C); ^{1}H NMR[107] (200 MHz): δ ($CDCl_3$) 7.58 (6H, m, *o*-Ph), 7.37 (9H, m, *m*- + *p*-Ph) and 0.73 (3H, s, ^2J

(^{117,119}Sn-H) 55, 57 Hz, SnMe); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 139.4 (*ipso*-C), 137.0 (*p*-Ph), 129.1 (*m*-Ph), 128.6 (*o*-Ph) and -10.7 (SnMe); ^{119}Sn NMR[138] (93.18 MHz): δ (thf) -92.8; ν_{max} (nujol) 3041 (m), 3022 (m), 1418 (s), 1320 (m), 1289 (m) and 1065 (s) cm^{-1}.

2-Benzoylfuran (**64**)



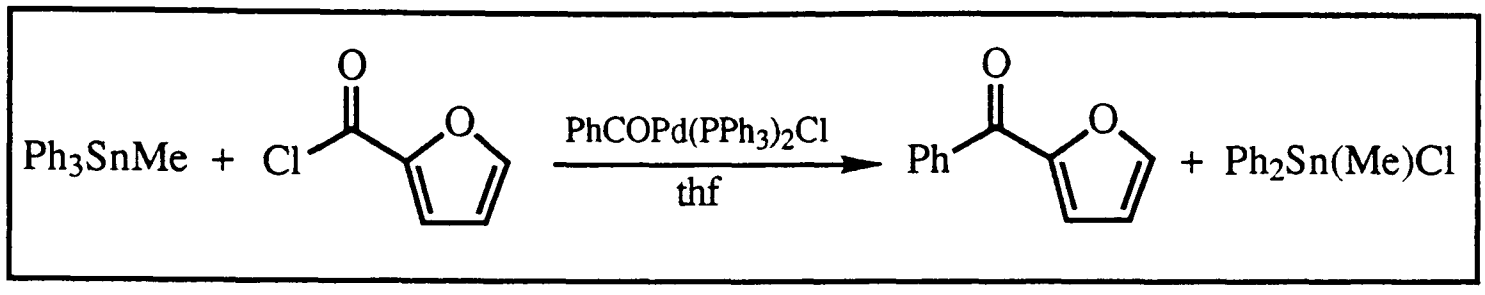
To a solution of furan (408 mg, 6 mmol) in dry Et_2O (10 ml) was added *n*-butyllithium (2.4 ml, 2 M, 4.8 mmol) and the resulting suspension stirred for 20 min. A solution of benzoic acid (293 mg, 2.4 mmol) in dry Et_2O (4 ml) was added over a period of 1 h and then the reaction quenched with water. The aqueous layer was extracted with Et_2O (2 x 10 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a yellow liquid. Distillation by Kugelröhr with an oven temperature of 150°C/0.3mmHg (lit.[108] 135-140°C/0.3mmHg) gave 2-benzoylfuran as a colourless liquid (180 mg, 44%). ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.99 (2H, d, J = 6.5 Hz, *o*-Ph), 7.71 (1H, s, H_5), 7.56 (3H, m, *m*- + *p*-Ph), 7.25 (1H, dd, J = 3.5, 1.8 Hz, H_4) and 6.61 (1H, d, J = 3.5 Hz, H_3); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 182.8 (C=O), 152.4 (C_2), 147.3 (C_5), 137.4 (*ipso*-Ph), 132.7, 129.4, 128.5 (Ph), 120.5 and 112.3 (C_4, C_3); ν_{max} ($CDCl_3$) 3680 (w), 2960 (w), 1652 (s) (C=O), 1599 (s), 1560 (s), 1318 (s), 1292 (s), 1260 (m), 1178 (m) and 1083 (m) cm^{-1}. m/z (DCI(NH_3)) 173 (100%, M+1).

Catalytic Cross-Coupling Reactions

The catalytic cross-coupling reactions described here, and also later, were carried out in either a Schlenk tube (fitted with a reflux condenser when necessary) or an 8 mm

diameter NMR tube in dry, degassed solvents under an argon atmosphere on a 0.1-0.3 mmol scale. ^{119}Sn NMR spectra were recorded in 8 mm tubes surrounded with a 10 mm jacket tube with d_6-acetone as the lock solvent.

Pd Catalysed Coupling of Organostannanes with Acid Chlorides: General procedure (Table 2, entry 1). **2-Benzoylfuran (64)**



To a solution of methyltriphenyltin (**63**) (100 mg, 0.27 mmol) and $PhCOPd(PPh_3)_2Cl$ (**53**) (8.3 mg, 4 mol%) in dry, degassed thf (5 ml) under argon was added 2-furoyl chloride (80 mg, 0.6 mmol) and the reaction heated at 67°C for 22 h. The reaction mixture was diluted with Et_2O (10 ml), which was washed with water (3 x 10 ml). The aqueous layer was extracted with Et_2O (1 x 20 ml) and the combined organic layers washed with 5% aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated to give an oil. Isolation of the reaction products was achieved by preparative tlc with 30-40°C petroleum ether:Et_2O (2:1) as eluent to give 2-benzoylfuran. ^1H NMR (200 MHz): δ ($CDCl_3$) 7.99 (2H, d, J = 6.5 Hz, *o*-Ph), 7.71 (1H, s, H_5), 7.56 (3H, m, *m*- + *p*-Ph), 7.25 (1H, dd, J = 3.5, 1.8 Hz, H_4) and 6.61 (1H, d, J = 3.5 Hz, H_3); m/z (DCI(NH_3)) 173 (100%, M+1).

Benzophenone. White solid, m.p. 45-47°C (lit.[139] 47-48°C); ^1H NMR (200 MHz): δ ($CDCl_3$) 7.82 (4H, m, *o*-Ph) and 7.64-7.45 (6H, m, *m*- +*p*-Ph); m/z (DCI(NH_3)) 183 (100%, M+1).

2-Furylbenzylketone (**88**). ^1H NMR (200 MHz): δ ($CDCl_3$) 7.61 (1H, br, s, H_5), 7.48-7.12 (6H, m, Ph + H_4), 6.53 (1H, dd, J = 3.5, 1.6 Hz, H_3) and 4.13 (2H, s, CH_2); m/z (DCI(NH_3)) 187 (100%, M+1).

2-Acetylfuran (92). Yellow oil; ^{1}H NMR[140] (200 MHz): δ ($CDCl_3$) 7.58 (1H, m, H_5), 7.21 (1H, m, H_4), 7.54 (1H, m, H_3) and 2.50 (3H, s, CH_3); m/z (DCI(NH_3)) 128 (100%, M+18), 111 (90, M+1) and 95 (8, M-Me).

2-[2'-(Dimethylamino)methyl]benzoylfuran (95). Yellow oil; ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.63 (1H, s, H_5), 7.43-7.24 (5H, m, Ph), 6.86 (1H, d, J = 3 Hz, H_4), 6.52 (1H, m, H_3), 3.53 (2H, s, CH_2) and 2.03 (6H, s, NMe_2); m/z (DCI(NH_3)) 230 (100%, M+1).

Methyldiphenyltin Chloride (65). Yellow oil; for spectroscopic data see later.

[8-(Dimethylamino)-1-naphthyl]methylphenyltin chloride (66). Yellow oil; ^{1}H NMR (200 MHz): δ ($CDCl_3$) 8.68 (1H, d, J = 5.3 Hz, H_6), 7.98-7.20 (10H, m, aromatic protons), 2.71 (3H, s, NMe), 2.29 (3H, s, NMe) and 1.16 (3H, s, ^{2}J (^{117,119}Sn-H) 65, 67 Hz, SnMe); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 149-117 (aromatic carbons), 49.3, 48,5 (NMe_2) and -0.5 (SnMe); ^{119}Sn NMR (93.18 MHz): δ (thf) -98.2; ν_{max} ($CDCl_3$) 3056 (m), 3005 (m), 1749 (m), 1565 (m), 1466 (s), 1381 (m), 1266 (m) and 1096 (m) cm^{-1}; m/z (CI(NH_3)) 382 (100%, M-Cl).

Methyl(1-naphthyl)phenyltin Chloride. Yellow oil; ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.98-7.44 (12H, m, aromatic protons) and 1.18 (3H, s, ^{2}J (^{117,119}Sn-H) 56, 58 Hz, SnMe).

[2-((Dimethylamino)methyl)phenyl]methylphenyltin Chloride (73). Yellow oil; ^{1}H NMR (200 MHz): δ ($CDCl_3$) 8.39 (1H, d, J = 7.4 Hz, H_6), 7.78-7.14 (8H, m, aromatic protons), 3.54 (2H, s, CH_2NMe_2), 2.29 (3H, s, NMe), 1.91 (3H, s, NMe) and 1.01 (3H, s, ^{2}J (^{117,119}Sn-H) 64, 66 Hz, SnMe); ^{119}Sn NMR: δ (thf) -108.8; ν_{max} (thin film) 3060 (m), 2884 (m), 1588 (m), 1462 (s), 1441 (s), 1010 (s), 733 (s) and 701 (s) cm^{-1}; m/z (DCI(NH_3)) 346 (25%, M-Cl) and 136 (100, $PhCH_2NMe_2$).

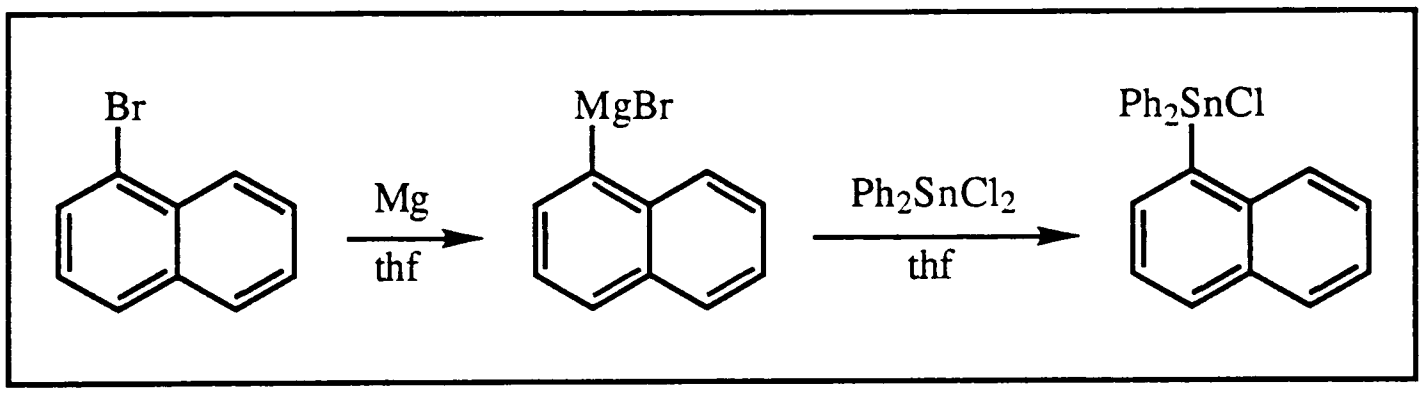
[(2-Dimethylamino)methyl-3-trimethylsilyl)phenyl]methylphenyltin Chloride (82). Colourless oil; ^{1}H NMR (200 MHz): δ ($CDCl_3$) 8.45 (1H, d, J = 7.4 Hz, H_6), 8.00-

7.30 (7H, m, aromatic protons), 3.66 (2H, s, CH_2NMe_2), 2.30 (3H, s, NMe), 1.91 (3H, s, NMe), 1.00 (3H, s, ^2J (^{117,119}Sn-H) 68, 70 Hz, SnMe) and 0.33 (9H, s, $SiMe_3$); ^{119}Sn NMR (93.18 MHz): δ (thf) -119.3; ν_{max} (thin film) 2862 (m), 1650 (s), 1468 (s), 1252 (s), 854 (s) and 734 (s) cm^{-1}; m/z (DCI(NH_3)) 418 (10%, M-Cl) and 208 (100, M-SnMePhCl).

Benzylmethylphenyltin Chloride. Yellow oil; ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.80-7.02 (10H, m, aromatic protons), 3.98 (2H, s, ^2J (^{117,119}Sn-H) 62, 64 Hz, $SnCH_2$) and 0.72 (3H, s, ^2J (^{117,119}Sn-H) 65, 67 Hz, SnMe).

Benzyldiphenyltin Chloride. Yellow oil; ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.65-7.09 (15H, m, aromatic protons) and 3.19 (2H, s, ^2J (^{117,119}Sn-H) 70, 72 Hz, $SnCH_2$).

(1-Naphthyl)diphenyltin Chloride (**68**)

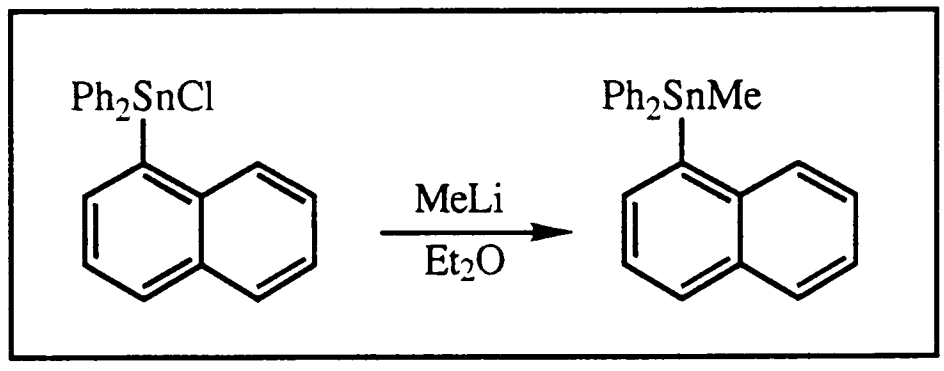


Magnesium (137 mg, 5.1 mmol) was covered with dry thf (4 ml) and a crystal of I_2 added, causing the solution to turn brown. 1-Bromonaphthalene (1.025 g, 5 mmol) was dissolved in dry thf (6 ml) and 2 ml of this solution added to the magnesium, which was stirred until the colour disappeared. The remainder of the 1-bromonaphthalene solution was added and the reaction stirred for 30 min, during which time the magnesium disappeared and the solution turned yellow.

Diphenyltin dichloride (1.72 g, 5 mmol) was dissolved in dry thf (6 ml) and the solution of Grignard reagent added to this *via* cannula, and stirred for 24 h. The thf was removed *in vacuo* to give a white solid. This was triturated with hot toluene, which was filtered through Celite and evaporated to give a milky liquid (2.52 g). Recrystallisation from

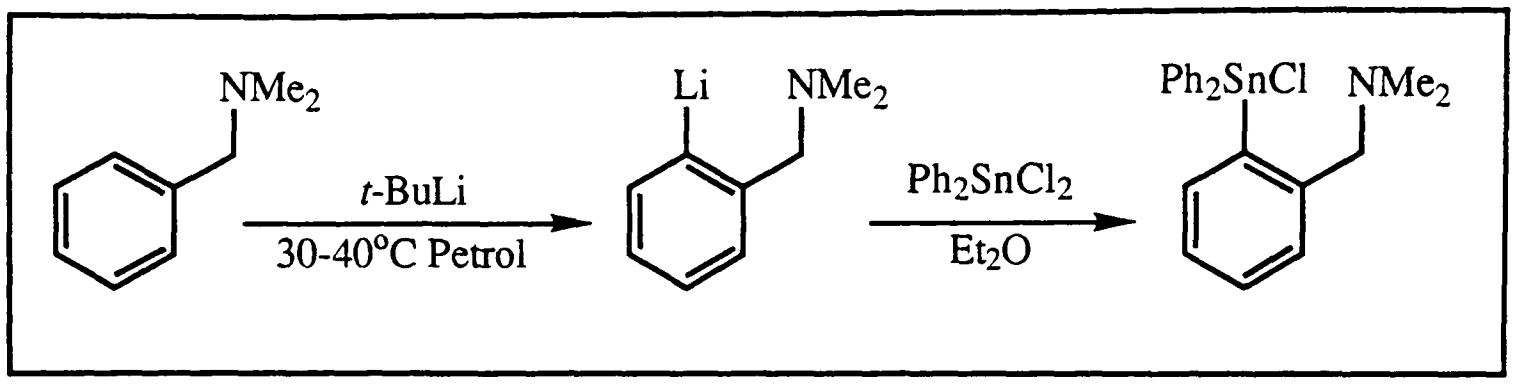
hot hexane gave (1-naphthyl)diphenyltin chloride (1.27 g, 58%) as a white powder, m.p. 105-107°C. Found: C, 60.5; H, 3.93. $C_{22}H_{17}ClSn$ requires C, 60.6; H, 3.91 %; ^1H NMR (200 MHz): δ ($CDCl_3$) 8.1-7.1 (m, aromatic protons); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 149.2-126.0 (aromatic carbons); ν_{max} (KBr) 3046 (w), 1501 (m), 1428 (s), 1073 (m), 996 (m), 799 (s), 776 (s), 731 (s) and 696 (s) cm^{-1}; m/z (EI) 410 (20%, M-Cl), 127 (72, $C_{10}H_7$) and 77 (54, Ph).

(1-Naphthyl)methyldiphenyltin (**67**)



To a solution of (1-naphthyl)diphenyltin chloride (**68**) (1.00 g, 2.3 mmol) in dry Et_2O (10 ml) at -20°C was added methyllithium (1.7 ml, 1.4 M, 2.3 mmol). The reaction was heated at reflux for 3 h and then stirred at room temperature for 21 h. It was quenched with water, the aqueous layer extracted with Et_2O (2 x 10 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a viscous oil (696 mg). Purification by column chromatography on silica gel with hexane:Et_2O (2:1) gave (1-naphthyl)methyldiphenyltin as a colourless liquid (326 mg, 35%). Found: C, 66.7; H, 5.07. $C_{23}H_{20}Sn$ requires C, 66.5; H, 4.86 %; ^1H NMR (200 MHz): δ ($CDCl_3$) 8.97-7.18 (17H, m, aromatic protons) and 0.54 (3H, s, ^2J ($^{117,119}Sn$-H) 55, 57 Hz, SnMe); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 139.8-125.8 (aromatic carbons) and -9.1 (Me); ^{119}Sn NMR (93.18 MHz): δ (thf) -88.06; ν_{max} (thin film) 3062 (s), 3013 (s), 2921 (s), 1952 (m), 1878 (m), 1820 (m), 1502 (s), 1429 (s), 1330 (m), 1255 (m), 1075 (s), 794 (s), 775 (s), 727 (s) and 699 (s) cm^{-1}; m/z (EI) 416 (8%, M^+), 401 (20, M-Me), 339 (51, M-Ph), 289 (100, M-$C_{10}H_7$), 247 (15% $C_{10}H_7Sn$) and 77 (34, Ph).

[2-((Dimethylamino)methyl)phenyl]diphenyltin Chloride (72)

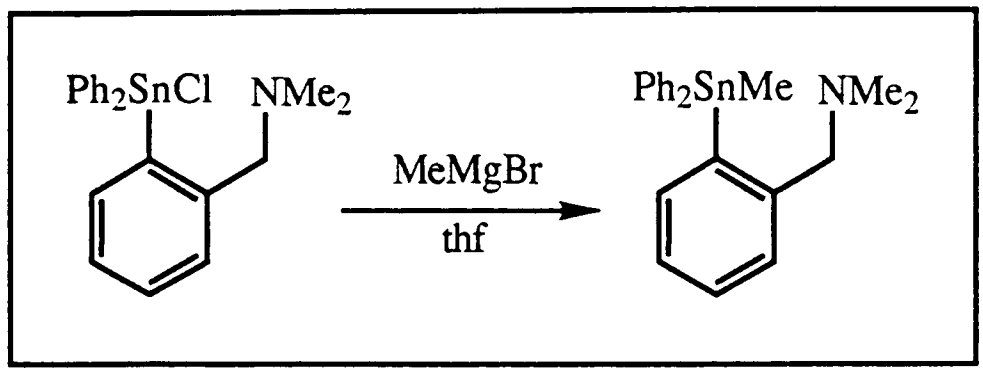


To a solution of N, N-dimethylbenzylamine (532 mg, 4 mmol) in dry degassed 30-40°C petroleum ether (10 ml) was added *t*-butyllithium (2.35 ml, 1.7 M, 4 mmol), causing the solution to turn yellow and a white precipitate to form. The reaction was stirred for 20 min, then allowed to settle and the orange mother liquor removed by syringe. The white solid was washed with 30-40°C petroleum ether (3 x 10 ml) and dried *in vacuo* to give 2-lithio-N, N-dimethylbenzylamine (**71**) as a white solid (432 mg).[112]

Diphenyltin dichloride (1.05 g, 3 mmol) was dissolved in dry Et_2O (10 ml) and the 2-lithio-N, N-dimethylbenzylamine (**71**) added as a solid, causing a fine white precipitate to form. The reaction was stirred for 20 h and then the solvent removed *in vacuo*. The resulting white solid was triturated with hot toluene (2 x 10 ml), which was filtered through Celite and evaporated to give [2-((dimethylamino)methyl)phenyl]diphenyltin chloride (597 mg, 33%) as a white solid, m.p. 172-174°C. Found: C, 56.5; H, 4.75; N, 2.62. $C_{21}H_{22}ClNSn$ requires C, 56.9; H, 4.9; N, 3.2 %; ^1H NMR (300 MHz): δ ($CDCl_3$) 8.52 (1H, d, J = 7 Hz, H_6), 7.76-7.2 (13H, m, aromatic protons), 3.58 (2H, s, CH_2) and 1.92 (6H, s, NMe_2); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 141.5-127 (aromatic carbons), 64.8 (CH_2) and 45.7 (NMe_2); ν_{max} (KBr) 3063 (m), 2989 (m), 1479 (m), 1458 (m), 1430 (s), 1077 (m), 998 (m), 842 (m), 759 (s), 729 (s) and 698 (s) cm^{-1}; m/z (EI) 442 (8%, M^+), 408 (13, M-Cl) and 366 (100, M-Ph).

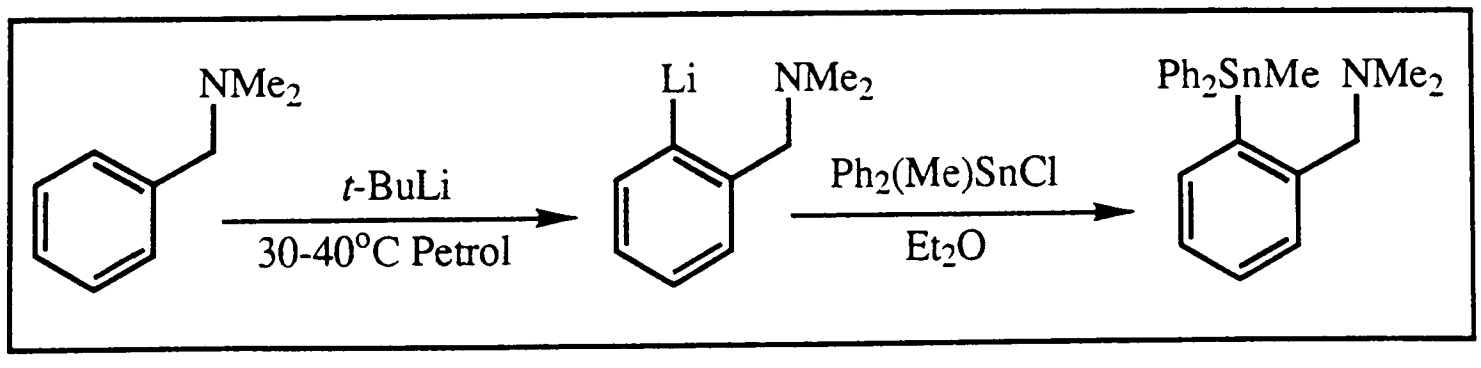
[2-((Dimethylamino)methyl)phenyl]methyldiphenyltin (70)

Method A:



To a solution of [2-((dimethylamino)methyl)phenyl]diphenyltin chloride (**72**) (440 mg, 1 mmol) in dry thf (10 ml) was added methylmagnesium bromide (0.33 ml, 3 M, 1 mmol), causing the solution to turn yellow. The reaction was stirred for 16 h and then quenched with water. The aqueous layer was extracted with Et_2O (2 x 10 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give an oily solid (364 mg). Purification by column chromatography on silica gel with hexane:Et_2O (4:1) gave [2-((dimethylamino)methyl)phenyl]methyldiphenyltin as a colourless oil (84 mg, 20%). Found: C, 62.4; H, 6.10; N, 3.10. $C_{22}H_{25}NSn$ requires C, 62.6; H, 5.93; N, 3.32 %; ^1H NMR (200 MHz): δ ($CDCl_3$) 7.70-7.15 (14H, m, aromatic protons), 3.37 (2H, s, CH_2), 1.84 (6H, s, NMe_2) and 0.74 (3H, s, ^2J ($^{117,119}Sn$-H) 58, 60 Hz, SnMe); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 146-127 (aromatic carbons), 65.4 (CH_2), 44.9 (NMe_2) and -9.2 (SnMe); ^{119}Sn NMR (93.18 MHz): δ (thf) -115.9; ν_{max} (thin film) 3061 (m), 2984 (m), 2950 (m), 2923 (m), 2857 (m), 2820 (m), 1458 (m), 1414 (s), 1034 (m), 1010 (m), 727 (s), 711 (s) and 700 (s) cm^{-1}. m/z (Probe CI) 408 (10%, M-Me) and 346 (100, M-Ph).

Method B:

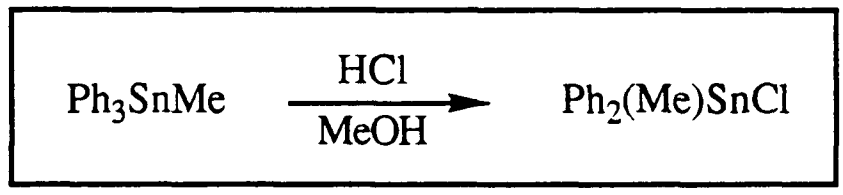


To a solution of N, N-dimethylbenzylamine (2.025 g, 15 mmol) in dry, degassed 30-40°C petroleum ether (25 ml) was added *t*-butyllithium (8.8 ml, 1.7 M, 15 mmol), causing

the solution to turn yellow and a white precipitate to form. The reaction was stirred for 40 min, allowed to settle and the orange mother liquor removed by syringe. The white solid was washed with 30-40°C petroleum ether (2 x 10 ml) and dried *in vacuo* to give 2-lithio-N, N-dimethylbenzylamine (**71**) as a white solid (2.17 g).[112]

Methyldiphenyltin chloride (**65**) (4.8 g, 15 mmol) was dissolved in dry Et_2O (20 ml) and the 2-lithio-N, N-dimethylbenzylamine (**71**) added to it as a solid, causing a white precipitate to form. The reaction was stirred for 17 h and then the solvent removed *in vacuo* to give a brown solid. This was triturated with hot toluene (2 x 30 ml), which was filtered through Celite and evaporated to give a brown liquid (5.797 g). Purification by column chromatography on silica gel with 30-40°C petroleum ether:Et_2O (2:1) gave [2-((dimethylamino)methyl)phenyl]methyldiphenyltin as a colourless oil (2.403 g, 38%).

Methyldiphenyltin Chloride (**65**)

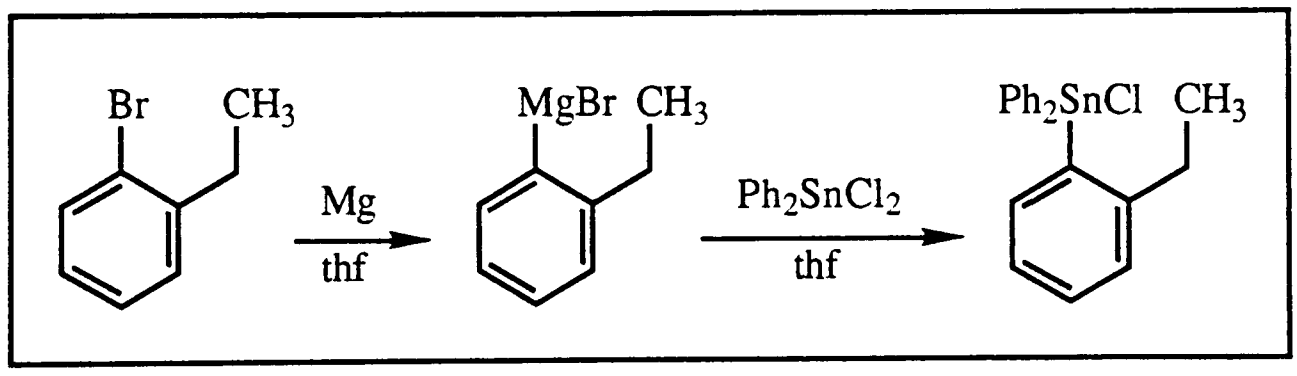


To a solution of methyltriphenyltin (**63**) (200 mg, 0.55 mmol) in methanol (10 ml) was added methanolic HCl (0.6 ml of 1.37 M solution, 0.8 mmol) and the reaction stirred overnight. It was then evaporated and the resulting oil dissolved in Et_2O (20 ml), dried over $MgSO_4$ and evaporated to give methyldiphenyltin chloride as a yellow oil (160 mg, 90%).[113] ^1H NMR (200 MHz): δ ($CDCl_3$) 7.62 (4H, m, *o*-Ph), 7.45 (6H, m, *m*- + *p*-Ph) and 1.04 (3H, s, ^2J ($^{117,119}Sn$-H) 57, 59 Hz, SnMe); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 139.0 (*ipso*-C), 136.0 (*o*-Ph), 130.4 (*p*-Ph), 129.1 (*m*-Ph) and -3.6 (SnMe); ^{119}Sn NMR (93.18 MHz): δ (thf) -38.9; ν_{max} (thin film) 3050 (m), 1482 (m), 1431 (s), 1334 (m), 1302 (w), 1072 (m), 998 (m), 728 (s) and 696 (s) cm^{-1}.

Competitive Pd Catalysed Coupling of Organostannanes with 2-Furoyl Chloride: General Procedure

To a solution of [8-(dimethylamino)-1-naphthyl]methyldiphenyltin (**60**) (75 mg, 0.16 mmol), methyltriphenyltin (**63**) (56 mg, 0.16 mmol) and $PhCOPd(PPh_3)_2Cl$ (**53**) (5 mg, 4 mol%) in dry, degassed thf (3 ml) in an 8 mm NMR tube under argon was added 2-furoyl chloride (21 mg, 0.16 mmol). The ^{119}Sn NMR spectrum was taken and then the reaction heated at 67°C for 22 h, when another ^{119}Sn NMR spectrum was obtained. The reaction mixture was diluted with Et_2O (10 ml), which was washed with water (3 x 10 ml). The aqueous layer was extracted with Et_2O (1 x 20 ml) and the combined organic layers washed with 5% aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated to give an oil. Isolation of the reaction products was achieved by preparative tlc with 30-40°C petroleum ether:Et_2O (2:1) as eluent.

[(2-Ethyl)phenyl]diphenyltin Chloride (77)

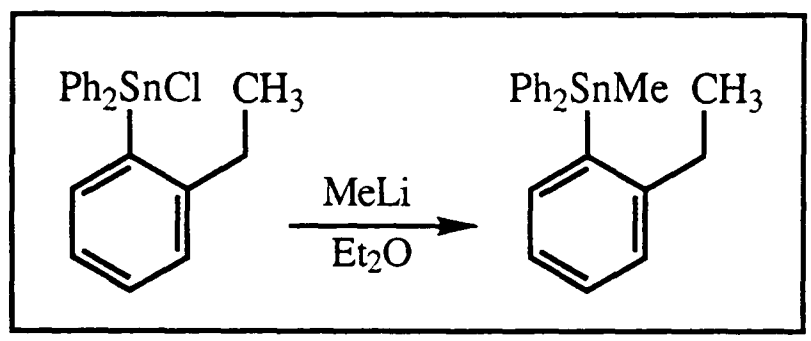


Magnesium (285 mg, 10.9 mmol) was covered with dry thf (3 ml) and a crystal of I_2 added, causing the solution to turn brown. 1-Bromo-2-ethylbenzene (2 g, 10.8 mmol) was dissolved in dry thf (20 ml) and 2 ml of this solution added to the magnesium, which was stirred until the colour disappeared. The remainder of the 1-bromo-2-ethylbenzene solution was added over 15 min and the reaction stirred for 90 min, during which time the magnesium disappeared and the solution turned yellow.

Diphenyltin dichloride (3.7 g, 10.8 mmol) was dissolved in dry thf (20 ml) and the solution of Grignard reagent (**75**) added to it *via* cannula. The reaction was stirred at room

temperature for 19 h then evaporated *in vacuo* to give a viscous oil. This was triturated with hot toluene, which was filtered through Celite and evaporated to give a colourless oil. Purification by column chromatography on silica gel with hexane:EtOAc (1:1) yielded [(2-ethyl)phenyl]diphenyltin chloride (3.67 g, 82%) as a white solid, m.p. 48-50°C; ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.88-7.20 (14H, m, aromatic protons), 2.73 (2H, q, J = 7.5 Hz, CH_2) and 1.10 (3H, t, J = 7.5 Hz, CH_3); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 150.9-126.7 (aromatic carbons), 32.7 (CH_2) and 16.0 (CH_3); ν_{max} (thin film) 3066 (s), 3051 (s), 2967 (s), 1481 (m), 1469 (m), 1431 (s), 1074 (s), 998 (m), 757 (s), 730 (s) and 697 (s) cm^{-1}; m/z (EI) 379 (22%, M-Cl), 299 (10, M-Ph-Cl), 181 (100) and 77 (52, Ph).

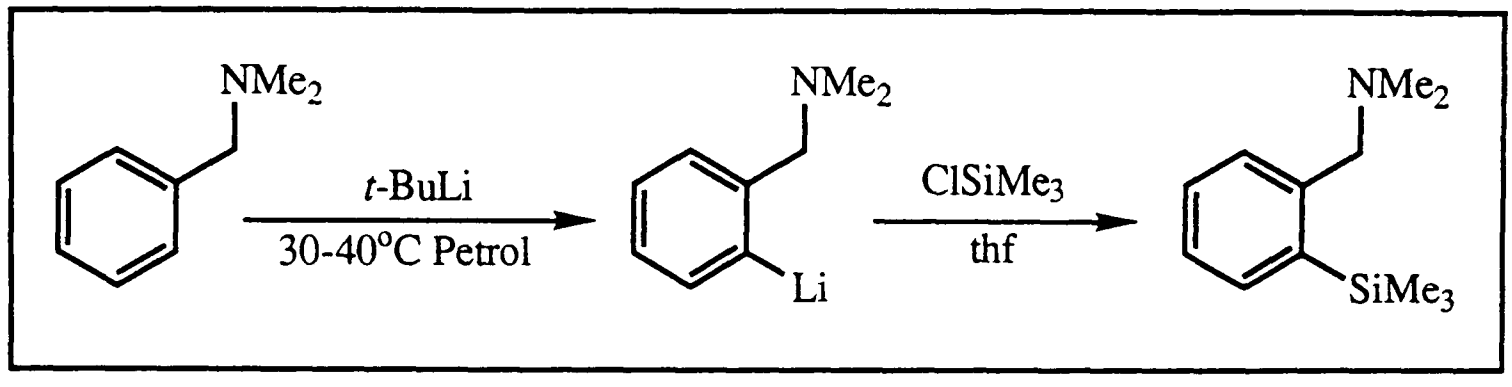
[(2-Ethyl)phenyl]methyldiphenyltin (**74**)



To a solution of [(2-ethyl)phenyl]diphenyltin chloride (**77**) (2.00 g, 4.8 mmol) in dry Et_2O (25 ml) at -30°C was added methyllithium (3.6 ml, 1.4 M, 5 mmol). The reaction was stirred at -30°C for 30 min and then at ambient temperature for 28 h. It was quenched with water, the aqueous layer extracted with Et_2O (2 x 20 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a colourless oil (1.29 g). Purification by column chromatography on silica gel with 30-40°C petroleum ether:Et_2O (1:1) gave [(2-ethyl)phenyl]methyldiphenyltin as a colourless oil (964 mg, 52%). Found C, 64.4; H, 5.87. $C_{21}H_{22}Sn$ requires C, 64.2; H, 5.61 %. ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.72-7.14 (14H, m, aromatic protons), 2.68 (2H, q, J = 7.5 Hz, CH_2), 1.11 (3H, t, J = 7.5 Hz, $CH_2C\mathit{H}_3$) and 0.79 (3H, s, ^{2}J (^{117,119}Sn-H) 53, 55 Hz, $SnC\mathit{H}_3$); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 151.6, 140.3, 138.9 (*ipso*-carbons), 137.7-125.7 (aromatic carbons), 32.5 (CH_2), 16.2 (CH_2CH_3) and -8.9 ($SnCH_3$); ^{119}Sn NMR (93.18 MHz): δ (thf) -91.5; ν_{max} (thin film) 3060 (s), 2965

(s), 1954 (w), 1877 (w), 1817 (w), 1581 (m), 1481 (m), 1464 (s), 1075 (s), 726 (s) and 700 (s) cm^{-1}; m/z (Probe EI) 377 (80%, M-Me), 316 (19, M-Ph), 197 (64, SnPh) and 77 (41, Ph).

2-(Trimethylsilyl)-N, N-dimethylbenzylamine (**80**)

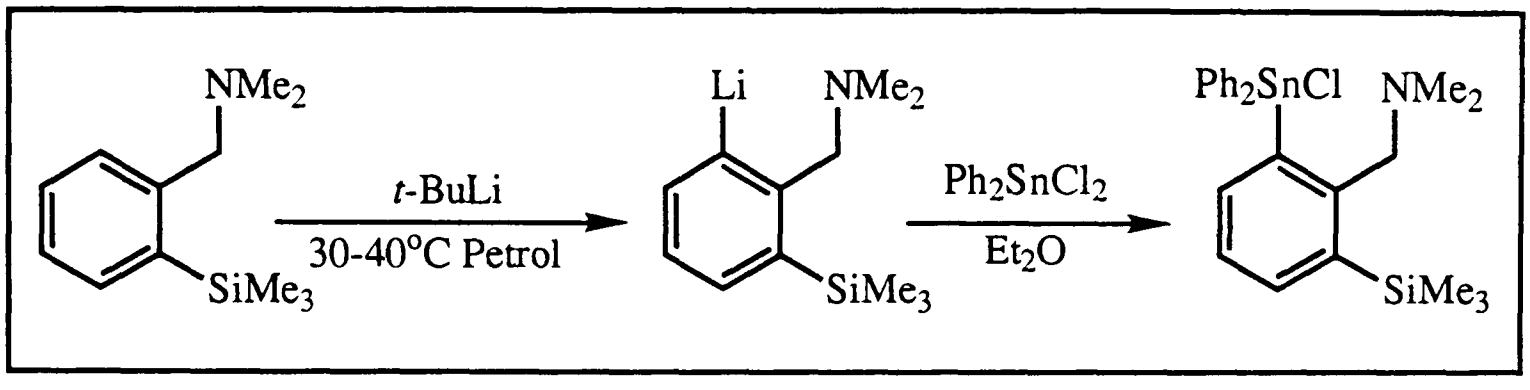


To a solution of N, N-dimethylbenzylamine (2.13 g, 16 mmol) in dry, degassed 30-40°C petroleum ether (20 ml) was added *t*-butyllithium (9.4 ml, 1.7 M, 16 mmol) causing the solution to turn yellow and a white precipitate to form. The reaction was stirred for 40 min, then allowed to settle and the orange mother liquor removed by syringe. The white solid was washed with 30-40°C petroleum ether (3 x 10 ml) and dried *in vacuo* to give 2-lithio-N, N-dimethylbenzylamine (**71**) as a white solid (2.25 g).[112]

Chlorotrimethylsilane (1.73 g, 16 mmol) was dissolved in dry, degassed thf (10 ml) and the 2-lithio-N, N-dimethylbenzylamine (**71**) added as a solid, followed by a further 10 ml of thf. The resulting yellow solution was stirred for 24 h and then quenched with 1 M aqueous NaOH. The aqueous layer was extracted with Et_2O (2 x 20 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a brown liquid. Purification by column chromatography on silica gel with 30-40°C petroleum ether:Et_2O (1:1) gave 2-(trimethylsilyl)-N, N-dimethylbenzylamine as a colourless liquid (2.24 g, 63%). Found: C, 69.2; H, 10.35; N, 7.18. $C_{12}H_{21}NSi$ requires C, 69.5; H, 10.15; N, 6.76 %. ^1H NMR[141] (200 MHz): δ ($CDCl_3$) 7.58-7.19 (4H, m, aromatic protons), 3.51 (2H, s, CH_2), 2.21 (6H, s, NMe_2) and 0.32 (9H, s, $SiMe_3$); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 145.6, 138.9 (*ipso*-carbons), 135.0, 129.2, 128.9, 126.4 (CH), 64.6 (CH_2), 45.3 (NMe_2) and 0.37 ($SiMe_3$); ν_{max} (thin film) 2948 (m), 2816 (m), 2769 (m), 1460 (m), 1249 (m), 1123 (m), 1031 (m), 838 (s)

and 746 (s) cm^{-1}; m/z (DCI(NH_3)) 208 (100%, M+1), 192 (42, M-Me), 149 (8, M-CH_2NMe_2), 134 (13, M-$SiMe_3$), 73 (12, $SiMe_3$) and 58 (97, CH_2NMe_2).

[(2-((Dimethylamino)methyl)-3-trimethylsilyl)phenyl]diphenyltin Chloride (**81**)

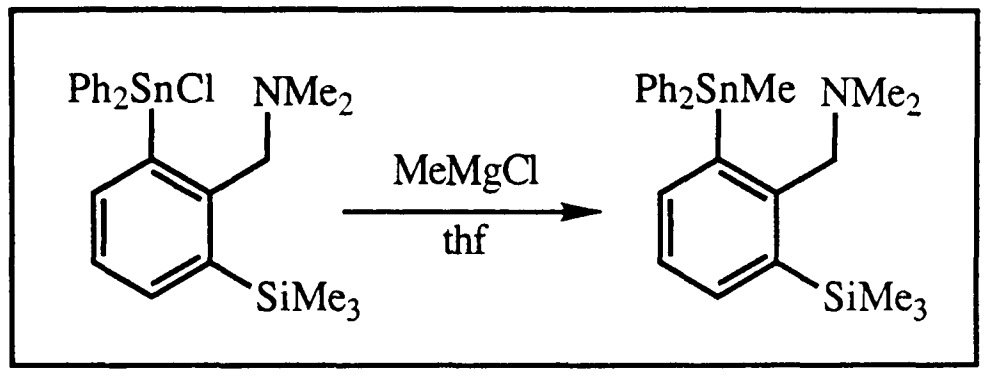


To a solution of (2-trimethylsilyl)-N, N-dimethylbenzylamine (**80**) (2.05 g, 10 mmol) in dry, degassed 30-40°C petroleum ether (20 ml) was added *t*-butyllithium (5.9 ml, 1.7 M, 10 mmol) causing the solution to turn red and a white precipitate to form. The reaction was stirred for 17 h, then allowed to settle and the orange mother liquor removed by syringe. The white solid was washed with 30-40°C petroleum ether (3 x 10 ml) and dried *in vacuo* to give 2-lithio-6-trimethylsilyl-N, N-dimethylbenzylamine as a white solid (2.08 g).

Diphenyltin dichloride (3.36 g, 9.78 mmol) was dissolved in dry Et_2O (20 ml) and the 2-lithio-6-trimethylsilyl-N, N-dimethylbenzylamine added as a solid. The reaction was stirred for 22 h and then the solvent removed *in vacuo* to give a white solid. This was triturated with hot toluene, which was filtered through Celite and evaporated to give a brown solid. Purification by column chromatography on silica gel with 30-40°C petroleum ether:Et_2O (1:1) followed by recrystallisation from hot Et_2O gave [(2-((dimethylamino)methyl)-3-trimethylsilyl)phenyl]diphenyltin chloride (1.66 g, 33%) as white plates, m.p. 140-141°C. Found: C, 56.0; H, 6.49; N, 2.34. $C_{24}H_{30}ClNSiSn.(0.4Et_2O)$ requires C, 56.4; H, 6.36; N, 2.57 %. ^1H NMR (200 MHz): δ ($CDCl_3$) 8.59 (1H, d, J = 7 Hz, H_6), 7.86-7.37 (12H, m, aromatic protons), 3.70 (2H, s, CH_2), 1.96 (6H, s, NMe_2) and 0.34 (9H, s, $SiMe_3$); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 141.9-127.6 (aromatic carbons), 64.8 (CH_2), 45.8 (NMe_2) and 0.23 ($SiMe_3$); ν_{max} (KBr) 3044 (m), 2967 (m), 1949 (w), 1873

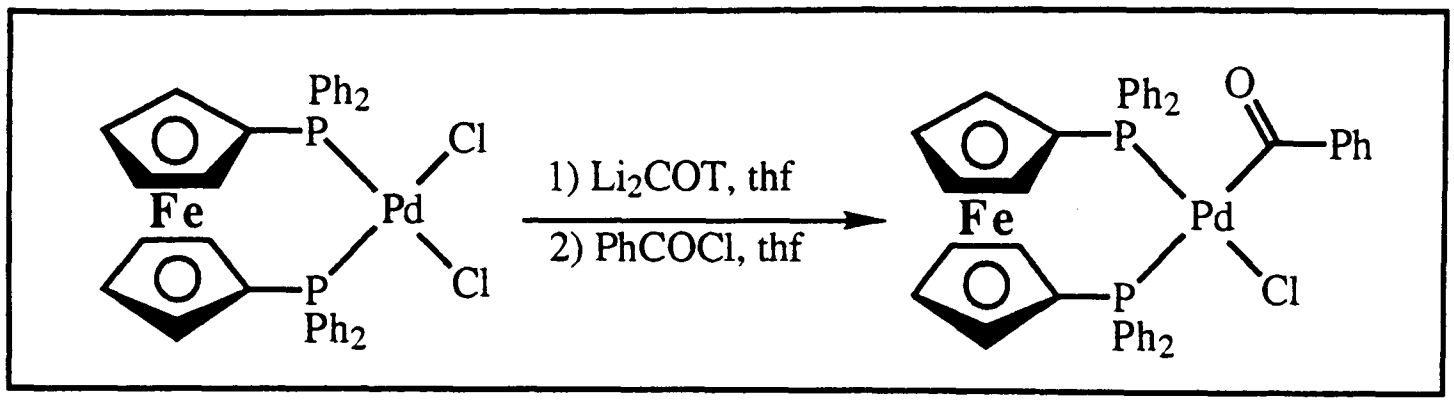
(w), 1566 (w), 1466 (m), 1429 (s), 1395 (s), 1354 (m), 1252 (s), 1000 (s), 849 (s), 754 (s), 726 (s) and 697 (s) cm^{-1}; m/z (EI) 480 (13%, M-Cl), 438 (58, M-Ph), 309 (10, Ph_2SnCl), 206 (20, M-(Ph_2SnCl)), 77 (51, Ph) and 73 (97, $SiMe_3$).

[(2-((Dimethylamino)methyl)-3-trimethylsilyl)phenyl]methyldiphenyltin (**79**)



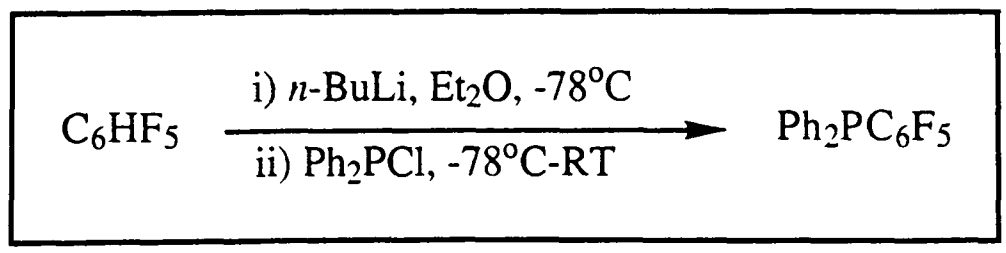
To a solution of [(2-((dimethylamino)methyl)-3-trimethylsilyl)phenyl]diphenyltin chloride (**81**) (1.3 g, 2.5 mmol) in dry thf (15 ml) was added methylmagnesium chloride (0.85 ml, 3 M, 2.5 mmol) and the reaction stirred for 16 h. It was quenched with water, the aqueous layer extracted with Et_2O (2 x 20 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a colourless oil (973 mg). Purification by column chromatography on silica gel with 30-40°C petroleum ether:Et_2O (3:1) gave [(2-((dimethylamino)methyl)-3-trimethylsilyl)phenyl]methyldiphenyltin (315 mg, 25%) as a white solid, m.p. 108-110°C. Found: C, 60.6; H, 6.57; N, 2.59. $C_{25}H_{33}NSiSn$ requires C, 60.7; H, 6.68; N, 2.83 %; ^1H NMR (200 MHz): δ ($CDCl_3$) 7.59-7.26 (13H, m, aromatic protons), 3.53 (2H, s, CH_2), 1.82 (6H, s, NMe_2), 0.70 (3H, s, ^2J ($^{117,119}Sn$-H) 70, 72 Hz, SnMe) and 0.31 (9H, s, $SiMe_3$); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 151.3-126.2 (aromatic carbons), 64.4 (CH_2), 44.8 (NMe_2), 0.63 ($SiMe_3$), -9.1 (SnMe); ^{119}Sn NMR (93.18 MHz): δ (thf) -123.5; ν_{max} (KBr) 3043 (m), 2950 (m), 2822 (m), 2359 (m), 1955 (w), 1888 (w), 1704 (w), 1427 (s), 1391 (m), 1356 (m), 1248 (s), 1087 (m), 1023 (m), 852 (s), 756 (s), 728 (s) and 700 (s) cm^{-1}; m/z (Probe EI) 480 (5%, M-Me), 418 (12, M-Ph), 289 (100, Ph_2SnMe), 197 (51, SnPh), 77 (79, Ph) and 73 (28, $SiMe_3$).

1,1'-Bis(diphenylphosphino)ferrocenylpalladium Benzoyl Chloride (**83**)



To a suspension of 1,1'-bis(diphenylphosphino)ferrocenylpalladium dichloride (91.3 mg, 0.125 mmol) in dry, degassed thf (5 ml) at -70°C was added ethereal Li_2COT (0.56 ml, 0.265 M, 0.15 mmol) causing the solution to turn brown. At -50°C a solution of benzoyl chloride (70 mg, 0.5 mmol) in dry, degassed thf (1 ml) was added and the reaction allowed to reach ambient temperature. The solvent was then removed *in vacuo* and the resulting solid dissolved in dry degassed toluene (15 ml), which was filtered and concentrated to a volume of approximately 2 ml. Dry Et_2O (40 ml) was added to precipitate 1,1'-bis(diphenylphosphino)ferrocenylpalladium benzoyl chloride (30.5 mg, 31%) as a yellow powder, m.p. 180°C (decomp.). Found: C, 61.6; H, 3.87. $C_{41}H_{33}ClFeOP_2Pd$ requires C, 61.4; H, 4.12 %; ^1H NMR (200 MHz): δ ($CDCl_3$) 8.26-6.90 (25H, m, Ph), 4.88 (1H, br, s, Cp), 4.73 (1H, br, s, Cp), 4.58 (1H, br, s, Cp), 4.49 (1H, br, s, Cp), 4.10 (2H, br, s, Cp), 3.48 (1H, br, s, Cp) and 3.46 (1H, br, s, Cp); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 172 (C=O) and 143-127 (aromatic carbons); ^{31}P NMR (101.2 MHz): δ (toluene) 21.90 (d, J_{P-P} 56 Hz) and 2.54 (d, J_{P-P} 54.6 Hz); ν_{max} (KBr) 1651 (s) (C=O), 1435 (m), 1158 (m), 1099 (m), 871 (m) and 695 (s) cm^{-1}; m/z (FAB) 659 (100%, M-PhCO) and 105 (80, PhCO).

Pentafluorophenyldiphenylphosphine (**84**)



To a solution of *n*-butyllithium (6.25 ml, 1.6 M, 10 mmol) at -78°C was added pentafluorobenzene (1.68 g, 10 mmol) in dry Et_2O (5 ml) dropwise over 15 min. The

reaction was stirred at -78°C for 2 h then a solution of chlorodiphenylphosphine (2.2 g, 10 mmol) in dry Et_2O (6 ml) was added and the reaction allowed to warm to room temperature. The resulting solution was filtered and evaporated to give a yellow solid (3.44 g). Recrystallisation from hot ethanol gave pentafluorophenyldiphenylphosphine (2.38 g, 68%) as a white powder, m.p. 68-70°C (lit.[116] 68-70°C); ^1H NMR (200 MHz): δ ($CDCl_3$) 7.47-7.38 (m, aromatic protons); ^{31}P NMR[142] (101.2 MHz): δ -23.06 (t, J_{P-F} 39 Hz); ν_{max} (KBr) 3071 (s), 3052 (s), 2353 (m), 1897 (m), 1640 (s), 1586 (s), 1470 (br s), 1289 (s), 1090 (s), 972 (s) and 795 (s) cm^{-1}; m/z (DCI(NH_3)) 353 (100%, M+1).

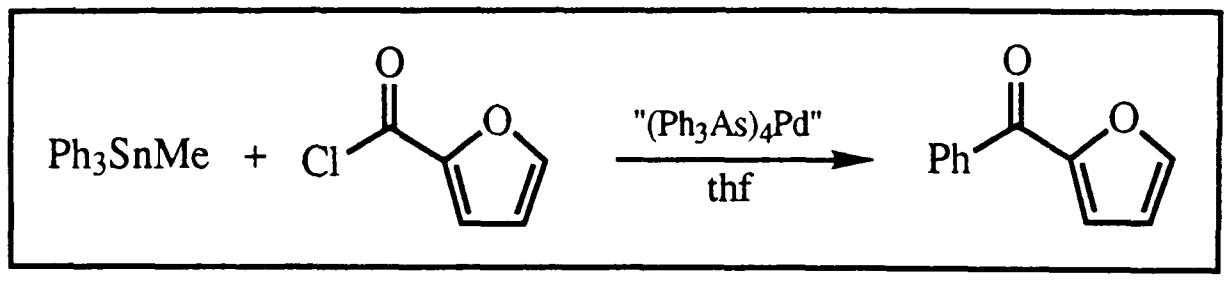
Bis(dibenzylideneacetone)palladium

$$PdCl_2 + dba \xrightarrow[MeOH]{NaOAc} Pd(dba)_2$$

To a solution of sodium acetate (2.05 g, 25 mmol) and dibenzylideneacetone (2.34 g, 10 mmol) in hot methanol (40 ml) was added palladium dichloride (532 mg, 3 mmol) and the reaction stirred for 4 h, during which time a purple precipitate was formed. This was filtered, washed with water and acetone and dried *in vacuo* to give bis(dibenzylideneacetone)palladium (2.08 g) as a purple solid, m.p. 139-142°C (lit.[117] 135°C); ^1H NMR[117] (200 MHz): δ ($CDCl_3$) 7.48-5.81 (br, m, bound & unbound dba); ν_{max} (KBr) 3053 (w), 1645 (s) (C=O), 1589 (s), 1445 (m), 1343 (m), 1284 (s), 979 (m), 762 (s) and 700 (s) cm^{-1}.

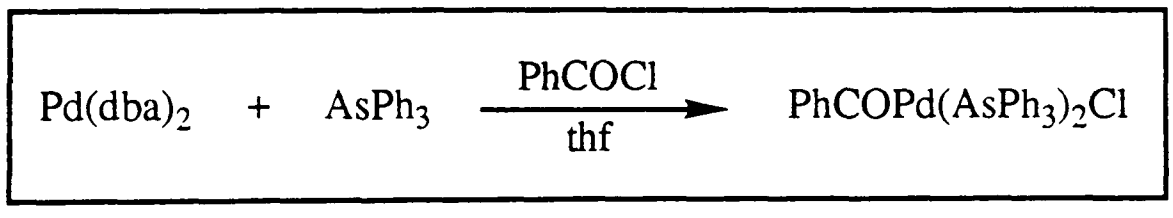
Coupling of Organostannanes with 2-Furoyl Chloride using Catalysts Prepared *in situ*:

General Procedure (Table 5, entry 6)



Triphenylarsine (13.5 mg, 0.04 mmol) and palladium bis(dibenzylideneacetone) (6.2 mg, 0.01 mmol) were dissolved in dry, degassed thf (1 ml) in an 8 mm NMR tube, the solution rapidly changing from a deep purple to yellow colour. To this was added trimethylphenyltin (**63**) (100 mg, 0.27 mmol) and 2-furoyl chloride (70 mg, 0.52 mmol) in dry degassed thf (2 ml) and the reaction heated at 40°C for 22 h, after which the ^{119}Sn NMR spectrum was obtained. The reaction mixture was diluted with Et_2O (10 ml), which was washed with water (3 x 10 ml). The aqueous layer was extracted with Et_2O (1 x 20 ml) and the combined organic layers washed with 5% aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated to give an oil. Isolation of the reaction products was achieved by preparative tlc with 30-40°C petroleum ether:Et_2O (2:1) as eluent.

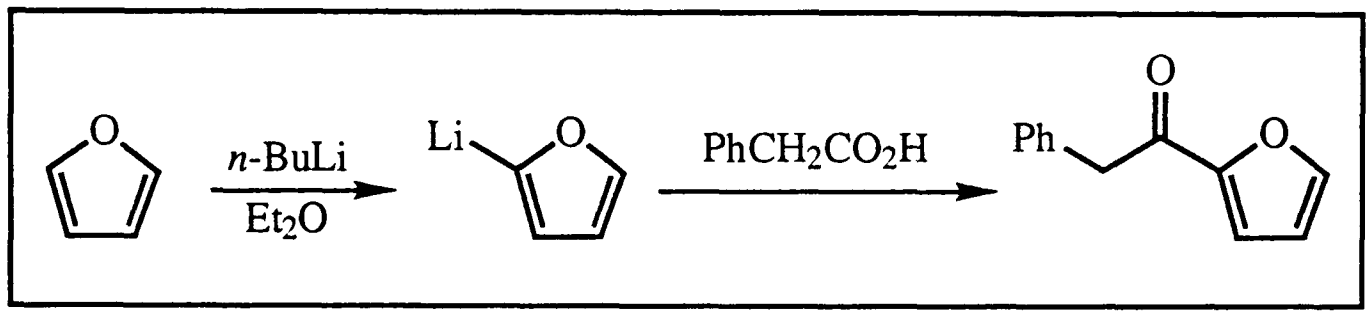
trans-Benzoylchlorobis(triphenylarsine)palladium (II) (**83**)



Triphenylarsine (147 mg, 0.48 mmol) and bis(dibenzylideneacetone)palladium (67 mg, 0.12 mmol) were dissolved in dry, degassed thf (4 ml), the solution turning from purple to yellow. To this was added benzoyl chloride (85 mg, 0.6 mmol) and the reaction stirred for 28 h. The resulting green solution was concentrated and 30-40°C petroleum ether (30 ml) added, causing a yellow precipitate to form. This was filtered, washed with 30-40°C petroleum ether and dried *in vacuo* to give *trans*-benzoylchlorobis(triphenylarsine)palladium

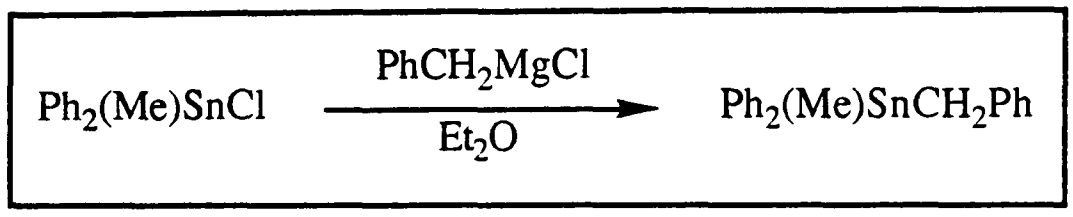
(II) (37.4 mg, 36%) as a yellow powder, m.p. 111-114°C (decomp.). Found: C, 57.6; H, 3.82. $C_{43}H_{35}As_2ClOPd$ requires C, 60.1; H, 4.07 %. ^1H NMR (200 MHz): δ ($CDCl_3$) 7.83-6.90 (m, aromatic protons); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 169.6 (CO), 143.6-135.6 (aromatic carbons); ν_{max} (KBr) 3049 (m), 1649 (s) (C=O), 1590 (m), 1576 (m), 1483 (m), 1435 (m), 1152 (m), 867 (m), 737 (m) and 671 (m) cm^{-1}.

2-Furylbenzylketone (**88**)



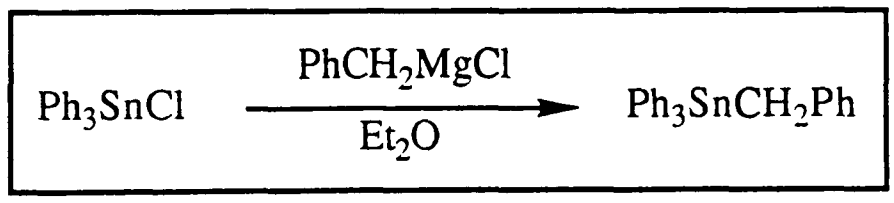
To a solution of furan (816 mg, 12 mmol) in dry Et_2O (4 ml) was added *n*-butyllithium (4.8 ml, 2 M, 9.6 mmol) and the resulting suspension stirred for 30 min. A solution of phenylacetic acid (653 mg, 4.8 mmol) in dry Et_2O (8 ml) was added over a period of 1 h and the reaction quenched with water.[108] The aqueous layer was extracted with Et_2O (2 x 10 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a yellow oil. Distillation by Kugelröhr with an oven temperature of 94°C/0.3mmHg (lit.[143] 104°C/0.6mmHg) gave 2-furylbenzylketone as a colourless liquid (551 mg, 62%). ^1H NMR[144] (200 MHz): δ ($CDCl_3$) 7.61 (1H, br, s, H_5), 7.48-7.12 (6H, m, Ph + H_4), 6.53 (1H, dd, J = 3.5, 1.6 Hz, H_3) and 4.13 (2H, s, CH_2); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 186.9 (C=O), 152.6 (C_2), 146.8-112.5 (aromatic carbons), 134.2 (*ipso*-Ph) and 45.3 (CH_2); ν_{max} (thin film) 3133 (m), 3031 (m), 1685 (s) (C=O), 1603 (m), 1568 (s), 1496 (s), 1466 (s), 1392 (s), 1302 (s), 1260 (s), 1160 (s), 1085 (s), 1039 (s), 914 (s) and 884 (s) cm^{-1}; m/z (DCI(NH_3)) 187 (100%, M+1).

Benzylmethyldiphenyltin (**89**)



To a solution of methyldiphenyltin chloride (**65**) (150 mg, 0.46 mmol) in dry Et_2O (3 ml) was added benzylmagnesium chloride (0.25 ml, 2 M, 0.5 mmol) and the reaction stirred for 20 h. It was quenched with water, the aqueous layer extracted with Et_2O (2 x 10 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a yellow oil (129 mg). Purification by column chromatography on silica gel with hexane:Et_2O (4:1) gave benzylmethyldiphenyltin as a colourless oil (94 mg, 54%). ^1H NMR[145] (200 MHz): δ ($CDCl_3$) 7.6-7.0 (15H, m, aromatic protons), 2.85 (2H, s, ^2J ($^{117,119}Sn$-H) 65, 67 Hz, $SnCH_2$) and 0.50 (3H, s, ^2J ($^{117,119}Sn$-H) 54, 56 Hz, SnMe); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 141.7, 140.0 (*ipso*-carbons), 136.7-123.8 (aromatic carbons), 19.9 ($SnCH_2$) and -11.4 (SnMe); ν_{max} (thin film) 3063 (m), 3019 (m), 1599 (m), 1492 (m), 1452 (m), 1428 (m), 1208 (m), 1075 (m), 755 (m), 728 (s) and 697 (s) cm^{-1}.

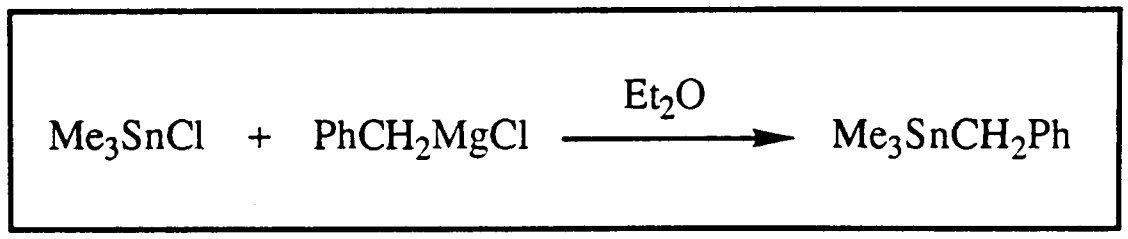
Benzyltriphenyltin (**90**)



To a suspension of triphenyltin chloride (355 mg, 0.92 mmol) in dry Et_2O (10 ml) was added benzylmagnesium chloride (0.5 ml, 2 M, 1.01 mmol) and the reaction stirred for 16 h. It was quenched with water, the aqueous layer extracted with Et_2O (2 x 10 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a white solid. Recrystallisation from hot ethanol gave benzyltriphenyltin (294 mg, 72%) as white plates; m.p. 88-89°C (lit.[146] 90-91°C); ^1H NMR (200 MHz): δ ($CDCl_3$) 7.6-6.9 (20H, m, aromatic protons) and 3.01 (2H, s, ^2J ($^{117,119}Sn$-H) 66, 68 Hz, $SnCH_2$); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 141.6, 138.4 (*ipso*-carbons), 130.0-124.1 (aromatic carbons) and 19.9 ($SnCH_2$);

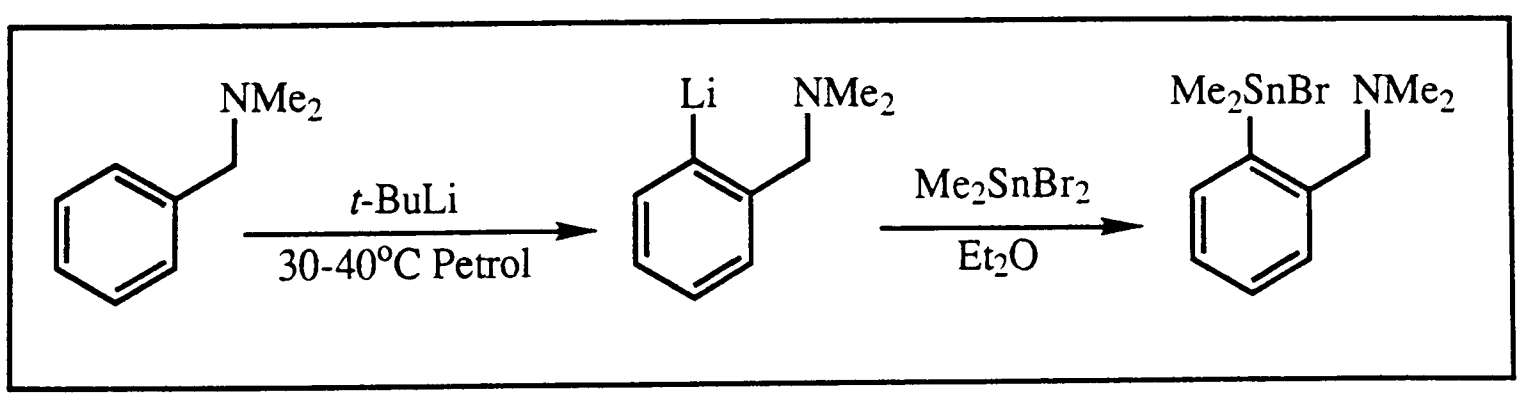
ν_{max} (nujol) 1585 (m), 1470 (s), 1322 (m), 1290 (m), 1062 (m), 1010 (m), 986 (m), 741 (m) and 686 (s) cm^{-1}.

Benzyltrimethyltin (**91**)



To a solution of trimethyltin chloride (398 mg, 2 mmol) in dry Et_2O (10 ml) was added benzylmagnesium chloride (1.1 ml, 2 M, 2.2 mmol). The reaction was stirred for 17 h and then quenched with water. The aqueous layer was extracted with Et_2O (2 x 10 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a colourless oil. Purification by column chromatography on silica gel with hexane:Et_2O (6:1) gave benzyltrimethyltin as a colourless oil (266 mg, 52%). ^1H NMR[147] (200 MHz): δ ($CDCl_3$) 7.25-7.00 (5H, m, Ph), 2.34 (2H, s, ^2J ($^{119,117}Sn$-H) 60, 62 Hz, CH_2) and 0.07 (9H, s, ^2J ($^{119,117}Sn$-H) 53, 55 Hz, SnMe); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 143.4 (*ipso*-C), 128.5 (*m*-Ph), 126.9 (*o*-Ph), 123.2 (*p*-Ph), 20.0 (CH_2) and -10.3 (Me); ^{119}Sn NMR (93.18 MHz): δ (thf) 3.69; ν_{max} (thin film) 3024 (m), 2913 (m), 1600 (m), 1491 (s), 1451 (m), 1209 (m), 754 (s) and 697 (s) cm^{-1}.

[2-((Dimethylamino)methyl)phenyl]dimethyltin Bromide (**94**)

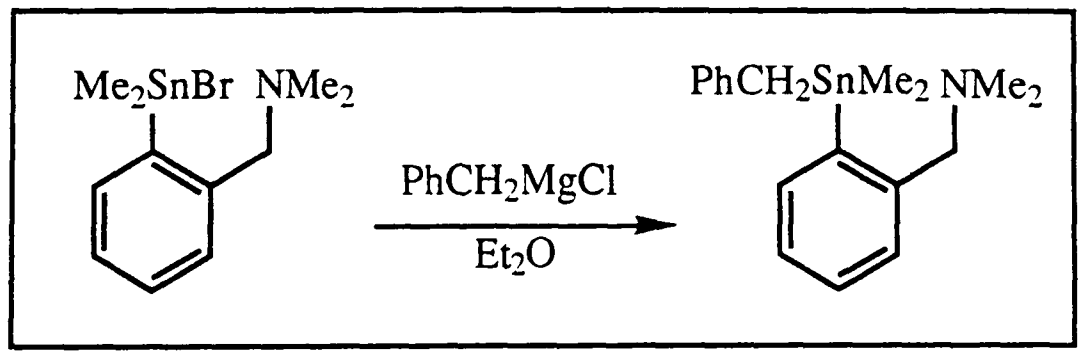


To a solution of N, N-dimethylbenzylamine (1.47 g, 11 mmol) in dry degassed 30-40°C petroleum ether (30 ml) was added *t*-butyllithium (6.5 ml, 1.7 M, 11 mmol) causing the solution to turn yellow and a white precipitate to form. The reaction was stirred for 30

min, then allowed to settle and the orange mother liquor removed by syringe. The white solid was washed with 30-40°C petroleum ether (3 x 10 ml) and dried *in vacuo* to give 2-lithio-N, N-dimethylbenzylamine (**71**) as a white solid (1.27 g).[112]

Dimethyltin dibromide (2.78 g, 9 mmol) was dissolved in dry Et_2O (25 ml) and the 2-lithio-N, N-dimethylbenzylamine (**71**) added as a solid, causing a fine white precipitate to form. The reaction was stirred for 22 h and then the solvent removed *in vacuo*. The resulting brown solid was triturated with hot toluene (2 x 20 ml) which was filtered through celite and evaporated to give a light brown solid. Recrystallisation from hot toluene and washing with 30-40°C petroleum ether gave [2-((dimethylamino)methyl)phenyl]dimethyltin bromide (1.97 g, 49%) as a white solid, m.p. 140-141°C. Found: C, 36.4; H, 4.88; N, 3.71. $C_{11}H_{18}BrNSn$ requires C, 36.4; H, 4.96; N, 3.86 %. ^1H NMR (200 MHz): δ ($CDCl_3$) 8.27 (1H, d, J = 6.2 Hz, H_6), 7.40-7.12 (3H, m, aromatic protons), 3.65 (2H, s, CH_2), 2.34 (6H, s, NMe_2) and 0.98 (6H, s, ^2J ($^{117,119}Sn$-H) 62, 64 Hz, $SnMe_2$); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 141.9 (*ipso*-C), 138.7, 129.8, 128.3, 126.8 (aromatic carbons), 65.0 (CH_2), 45.3 (NMe_2) and 0.95 ($SnMe_2$); ν_{max} (KBr) 2887 (m), 2848 (m), 1973 (w), 1860 (w), 1700 (w), 1586 (w), 1568 (w), 1460 (s), 1357 (m), 1172 (m), 1008 (s), 841 (s) and 774 (s) cm^{-1}; m/z (EI) 348 (17%, M-Me), 284 (20, M-Br), 134 (42, $PhCH_2NMe_2$), 91 (100, CH_2Ph) and 58 (98, CH_2NMe_2).

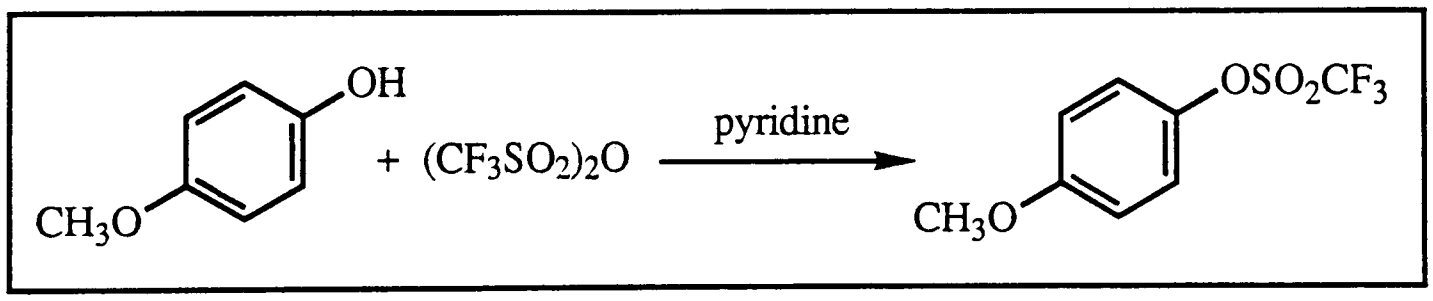
[2-((Dimethylamino)methyl)phenyl]benzyldimethyltin (**93**)



To a solution of [2-((dimethylamino)methyl)phenyl]dimethyltin bromide (**94**) (1.1 g, 3.03 mmol) in dry thf (40 ml) was added benzylmagnesium chloride (7.6 ml, 2 M, 15.2 mmol) and the reaction heated at reflux for 15 h. It was quenched with saturated aqueous

NH_4Cl solution (20ml), the aqueous layer extracted with Et_2O (2 x 20 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a light brown oil. Purification by column chromatography on silica gel with 30-40°C petroleum ether:Et_2O (10:1) gave [2-((dimethylamino)methyl)phenyl]benzyldimethyltin as a colourless liquid (587 mg, 52%). Found: C, 57.8; H, 6.87. $C_{18}H_{25}NSn$ requires C, 57.8; H, 6.69 %. ^1H NMR (200 MHz): δ ($CDCl_3$) 7.60 (1H, m, H_6), 7.32-6.97 (8H, m, aromatic protons), 3.45 (2H, s, CH_2NMe_2), 2.50 (2H, s, ^2J ($^{117,119}Sn$-H) 62, 64 Hz, CH_2Sn), 2.18 (6H, s, NMe_2) and 0.14 (6H, s, ^2J ($^{117,119}Sn$-H) 52, 54 Hz, $SnMe_2$); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 145.7, 144.1, 142.3 (*ipso*-carbons), 137.3-123.0 (aromatic carbons), 66.0 (CH_2NMe_2), 45.2 (NMe_2), 21.9 (CH_2Sn) and -9.24 ($SnMe_2$); ^{119}Sn NMR (93.18 MHz): δ (thf) -59.51; ν_{max} (thin film) 2981 (m), 2950 (m), 2822 (s), 2783 (s), 1935 (w), 1856 (w), 1798 (w), 1599 (s), 1490 (s), 1458 (s), 1363 (m), 1208 (s), 1026 (s), 748 (s) and 698 (s) cm^{-1}; m/z (EI) 360 (4%, M-Me), 284 (58, M-CH_2Ph), 91 (100, CH_2Ph) and 58 (21, CH_2NMe_2).

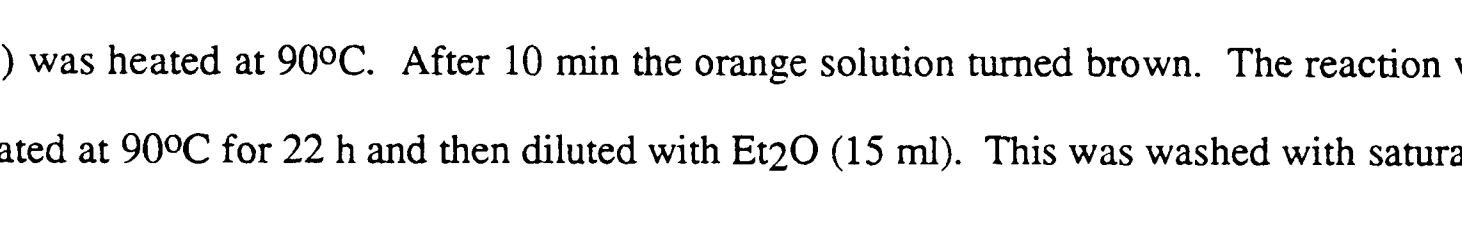
4-Methoxyphenyl triflate (**96**)



To a solution of 4-methoxyphenol (1.24 g, 10 mmol) in dry pyridine (0.79 g, 10 mmol, 0.8 ml) at 0°C was added trifluoromethanesulphonic anhydride (2.82 g, 10 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The mixture was dissolved in Et_2O (20 ml) and filtered to remove the resulting white precipitate. The ethereal solution was washed several times with water, dried over $MgSO_4$ and evaporated to give a brown liquid.[120] Purification by column chromatography on silca gel with 30-40°C petroleum ether:Et_2O (4:1) gave 4-methoxyphenyl triflate as a colourless liquid (2.15 g, 84%). ^1H NMR (200 MHz): δ ($CDCl_3$) 7.22 (2H, d, J = 9.2 Hz, H_2, H_6), 6.94 (2H, d, J =

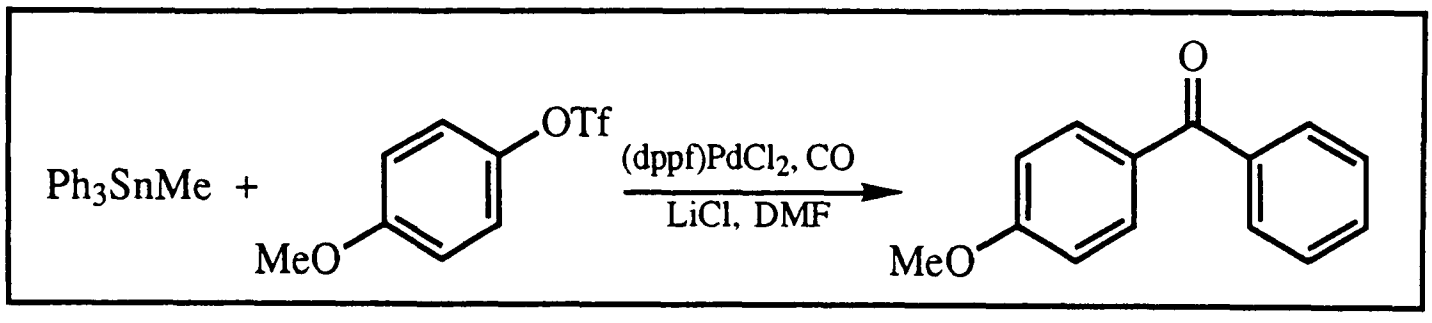
9.2 Hz, H_3, H_5) and 3.84 (3H, s, OCH_3); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 159.4 (MeO-*C*), 143.3 (TfO-*C*), 122.5 (C_2, C_6), 115.2 (C_3, C_5) and 55.6 (OCH_3); ν_{max} (thin film) 2953 (w), 2843 (w), 1504 (m), 1421 (m), 1211 (m), 1170 (m) and 889 (m) cm^{-1}; m/z (DCI(NH_3)) 256 (10%, M^+) and 123 (100, CH_3OPhO).

Pd Catalysed Coupling of Organostannanes with 4-Methoxyphenyl triflate (**96**): General Procedure (Table 9, entry 1). **4-Methoxybiphenyl (6)**



A solution of methyltriphenyltin (**U**) (62 mg, 0.17 mmol), 4-methoxyphenyltriflate (**96**), lithium chloride (22 mg, 0.5 mmol) and (dppf)$PdCl_2$ (5 mg, 4 mol%) in dry DMF (2 ml) was heated at 90°C. After 10 min the orange solution turned brown. The reaction was heated at 90°C for 22 h and then diluted with Et_2O (15 ml). This was washed with saturated aqueous NH_4Cl solution (10 ml), water (2 x 10 ml) and brine (10 ml), dried over $MgSO_4$ and evaporated to give a brown solid (58 mg). Purification by preparative tlc with 30-40°C petroleum ether:Et_2O (3:1) as eluent gave 4-methoxybiphenyl as a white solid, m.p. 87-88°C (lit.[148] 89°C); ^1H NMR[149] (200 MHz): δ ($CDCl_3$) 7.60-7.31 (7H, m, aromatic protons), 7.02 (2H, d, J = 8.8 Hz, H_3, H_5) and 3.88 (3H, s, OCH_3); ν_{max} (KBr) 2960 (m), 1608 (m), 1522 (m), 1490 (s), 1290 (m), 1271 (m), 1252 (s), 1201 (s), 1187 (s), 1038 (s), 836 (s) and 760 (s) cm^{-1}; m/z (DCI(NH_3)) 185 (12%, M+1), 184 (100, M^+).

Pd Catalysed Carbonylative Coupling Between Organostannanes and 4-Methoxyphenyl triflate (**96**): General Procedure (Table 10, entry 2). **4-Methoxybenzophenone (97).**

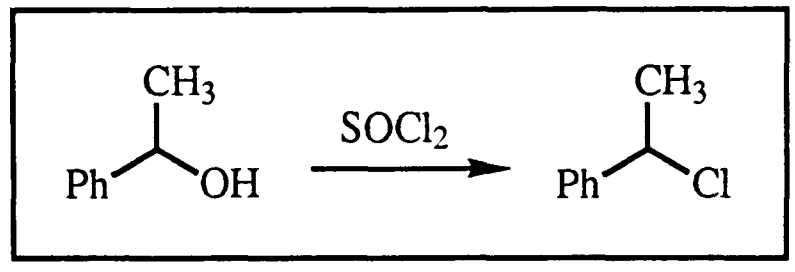


To a solution of methyltriphenyltin (**63**) (100 mg, 0.27 mmol), (dppf)$PdCl_2$ (8 mg, 4 mol%) and lithium chloride (35.6 mg, 0.84 mmol) in dry DMF (2 ml) under argon in a Fischer-Porter bottle was added 4-methoxyphenyl triflate (104 mg, 0.4 mmol) in dry DMF (1 ml). The solution was cooled to -70°C, evacuated and then filled with carbon monoxide gas to a pressure of 8 psi. This was repeated two more times and then the reaction was slowly heated to 100°C, developing a pressure of *ca.* 10 psi. The reaction was stirred at this temperature and pressure for 22 h. The reaction was cooled, vented and diluted with Et_2O (15 ml), which was washed with water (3 x 10 ml) and brine (10 ml), dried over $MgSO_4$ and evaporated to give a brown oil (110 mg). Purification by preparative tlc with 30-40°C petroleum ether:Et_2O (2:1) as eluent gave 4-methoxybenzophenone as a colourless oil (7.5 mg, 13%). ^1H NMR (200 MHz): δ ($CDCl_3$) 7.87–7.44 (7H, m, aromatic protons), 6.98 (2H, d, J = 8.8 Hz, H_3, H_5) and 3.90 (3H, s, OCH_3); ν_{max} (thin film) 2934 (w), 2840 (w), 1652 (m), 1599 (s) (C=O), 1280 (m), 1259 (s), 1170 (m) and 1148 (m) cm^{-1}; m/z (DCI(NH_3)) 213 (90%, M+1), 212 (92, M^+) and 135 (100, M-Ph).

4-Methoxyacetophenone (**BC**). Colourless oil. ^1H NMR[150] (200 MHz): δ ($CDCl_3$) 7.96 (2H, d, J = 10.5 Hz, H_2, H_6), 6.94 (2H, d, J = 10.5 Hz, H_3, H_5), 3.89 (3H, s, OCH_3) and 2.58 (3H, s, $COCH_3$); ν_{max} (thin film) 2340 (w), 1670 (s) (C=O), 1604 (m), 1359 (m), 1260 (m), 1021 (m) and 833 (m) cm^{-1}; m/z (DCI(NH_3)) 151 (100%, M+1) and 135 (46, M-Me).

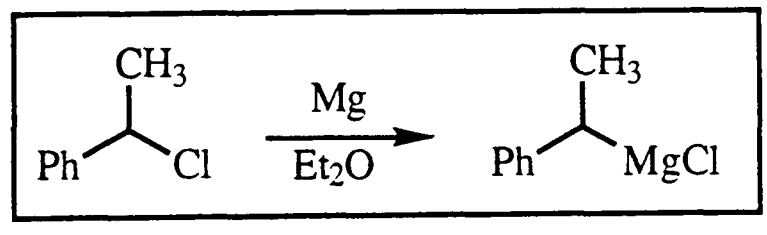
3.4. Experimental for section 2.4.

1-Chloro-1-phenylethane (**101**)



To thionyl chloride (11.4 g, 96 mmol) was added *sec*-phenethyl alcohol (9.76 g, 80 mmol), causing an exothermic reaction to occur. The reaction was stirred for 45 min and then the excess thionyl chloride removed under reduced pressure. Distilation in a Kugelröhr with an oven temperature of 78°C/16 mmHg (lit.[151] 85°C/20 mmHg) gave 1-chloro-1-phenylethane as a colourless liquid (10.9 g, 97.5%). ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.42 (5H, m, Ph), 5.15 (1H, q, J = 6.8 Hz, PhC*H*) and 1.87 (3H, d, J = 6.8 Hz, CH_3); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 143.1 (*ipso*-Ph), 128.8 (*m*-Ph), 128.4 (*p*-Ph), 126.7 (*o*-Ph), 58.8 (CH) and 26.5 (CH_3); ν_{max} (thin film) 3032 (m), 2990 (s), 2926 (m), 1492 (s), 1451 (s), 1231 (m), 1049 (m) and 1028 (m) cm^{-1}; m/z (DCI(NH_3)) 105 (100%, M-Cl).

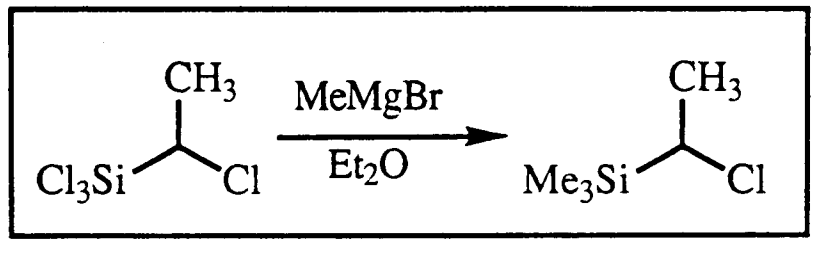
(α-Methyl)benzylmagnesium Chloride (**100**)[121]



Magnesium turnings (16 g) were activated by dry stirring in a Schlenk tube under an inert atmosphere of argon for 1 day, during which time they turned black and a magnesium mirror formed on the inside of the vessel. It was then covered in dry Et_2O and cooled to 0°C. 1-Chloro-1-phenylethane (**101**) (14.0 g, 0.1 mol) was dissolved in dry Et_2O (160 ml) and added to the vigorously stirred magnesium over a period of 3.5 h. The reaction was then stirred for a further 2 h before being filtered *via* cannula into a Schlenk tube. The

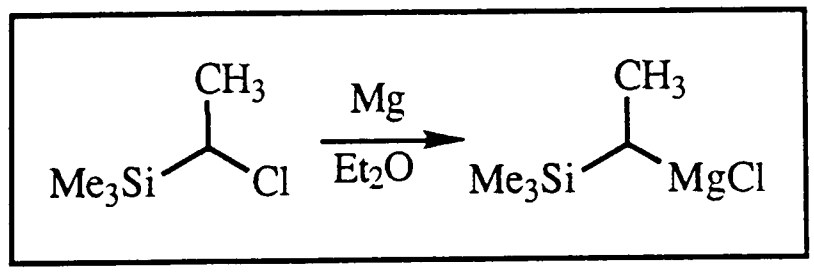
magnesium turnings were washed with dry Et_2O (40 ml), which was filtered into the Schlenk. The solution of Grignard reagent could be kept for several weeks at 0°C and was titrated against 0.1 M HCl before use. ^{13}C NMR[121] (62.89 MHz): δ (Et_2O) 159.2 (*ipso*-Ph), 127.9, 122.4, 116.9 (aromatic carbons), 28.5 (CH) and 17.0 (CH_3).

(1-Chloroethyl)trimethylsilane (**103**)[122]



To a solution of 1-chloroethyltrichlorosilane (6 g, 30 mmol) in dry Et_2O (20 ml) at 0°C was added methylmagnesium bromide (35 ml, 3 M, 105 mmol) over a period of 3 h, causing a white precipitate to be formed. The reaction was stirred at room temperature overnight and then quenched with dilute aqueous HCl. The aqueous layer was extracted with Et_2O (2 x 20 ml) and the combined organic layers dried over $MgSO_4$ and evaporated to give (1-chloroethyl)trimethylsilane as a colourless liquid (2.77 g, 68%). ^1H NMR (200 MHz): δ ($CDCl_3$) 3.36 (1H, q, J = 7.5 Hz, CH), 1.50 (3H, d, J = 7.5 Hz, CH-CH_3) and 0.11 (9H, s, $SiMe_3$); ν_{max} (thin film) 2961 (m), 2926 (w), 1441 (w), 1253 (s), 1012 (m) and 841 (s) cm^{-1}.

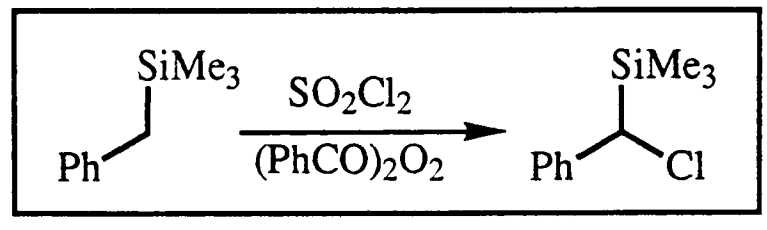
1-Trimethylsilylethylmagnesium Chloride (**102**)



To magnesium turnings (475 mg, 19 mmol) suspended in dry Et_2O (10 ml) was added 1 ml of a solution of (1-chloroethyl)trimethylsilane (**103**) (2.45 g, 18 mmol) in dry Et_2O (6 ml) and a small amount of 1, 2-dibromoethane (50 µl). The reaction was heated

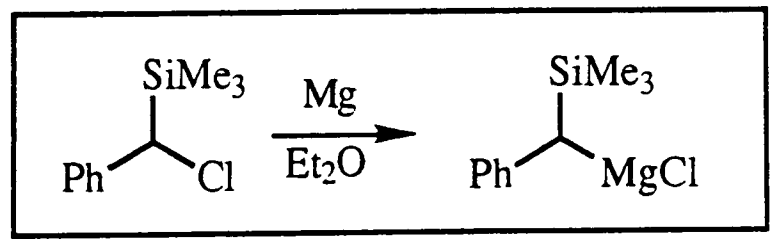
briefly until refluxing and then the remainder of the (1-chloroethyl)trimethylsilane solution was added at such a rate as to maintain reflux. The reaction was stirred at room temperature overnight then filtered *via* cannula into a Schlenk tube. The solution of Grignard reagent could be kept at 0°C for several weeks, and was titrated against 0.1 M HCl before use.

(α-Chloro)benzyltrimethylsilane (**105**)[123]



Benzyltrimethylsilane (4.00 g, 24 mmol), sulphuryl chloride (2.62 g, 20 mmol) and a small amount of benzoyl peroxide were heated at reflux for 5 h, giving a brown oil (4.56 g). Distilation by Kugelröhr with an oven temperature of 120°C/25 mmHg gave (α-chloro)benzyltrimethylsilane as a colourless liquid (1.41 g, 36%). ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.25 (5H, m, Ph), 4.36 (1H, s, CH) and 0.11 (9H, s, $SiMe_3$); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 140.4 (*ipso*-Ph), 128.4, 127.1, 126.7 (aromatic carbons), 52.9 (CH) and -3.7 ($SiMe_3$); ν_{max} (thin film) 2955 (m), 1598 (m), 1493 (m), 1450 (m), 1249 (s), 1120 (m), 1072 (m) and 841 (s) cm^{-1}; m/z (DCI(NH_3)) 216 (8%, M+18), 199 (5, M+1), 164 (24, M-Cl), 91 (100) and 77 (48, Ph).

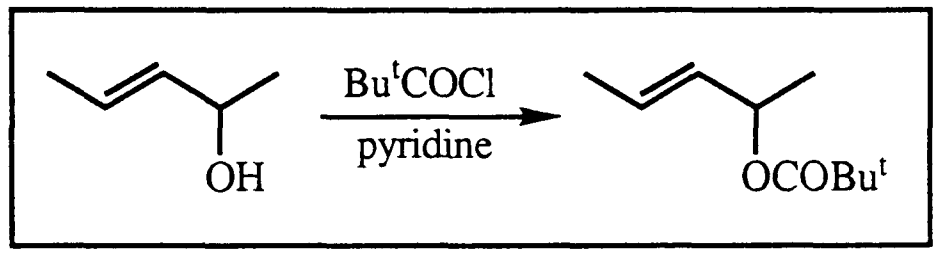
(α-Trimethylsilyl)benzylmagnesium Chloride (**104**)[121]



Magnesium turnings (700 mg, 28 mmol) were activated by dry stirring in a Schlenk tube under an inert atmosphere of argon for 1 day, during which time they turned black and a magnesium mirror was formed on the inside of the vessel. It was then covered in dry Et_2O

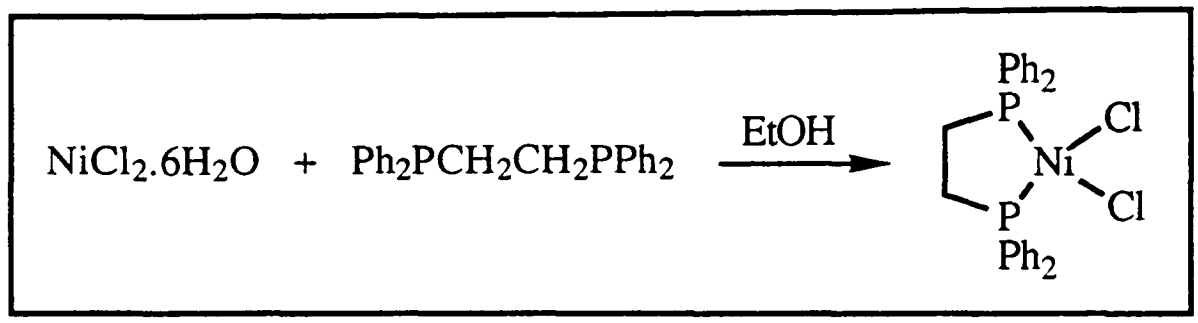
and cooled to 0°C. (α-Chloro)benzyltrimethylsilane (**105**) (913 mg, 4.6 mol) was dissolved in dry Et_2O (8 ml) and added to the vigorously stirred magnesium over a period of 2 h. The reaction was then stirred for a further 2 h before being filtered *via* cannula into a Schlenk tube. The magnesium turnings were washed with dry Et_2O (10 ml), which was filtered into the Schlenk. The solution of Grignard reagent could be kept for several weeks at 0°C and was titrated against 0.1 M HCl before use.

3-Penten-2-yl Pivaloate (**106**)



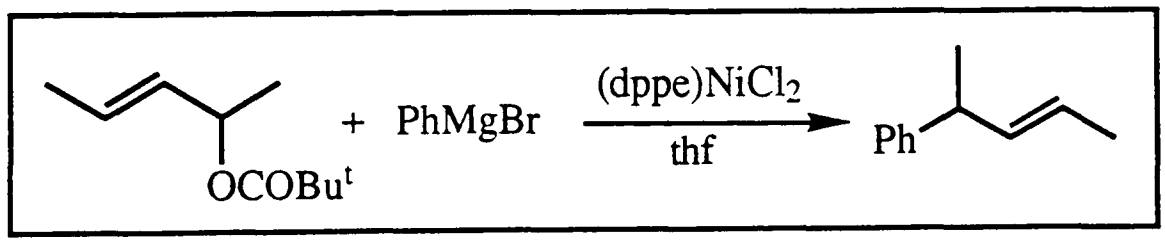
To a solution of 3-penten-2-ol (1.18 g, 13.7 mmol) in dry pyridine (15 ml) was added trimethylacetylchloride (2.48 g, 20.55 mmol), causing a white precipitate to form. The reaction was stirred at room temperature overnight and then quenched with water. The aqueous layer was extracted with Et_2O (3 x 20 ml) and the combined organic layers washed successively with dilute aqueous HCl (2 x 10 ml), water (15 ml), 10% aqueous Na_2CO_3 (2 x 10 ml) and water (15 ml). The Et_2O was dried over $MgSO_4$ and evaporated to give a colourless oil (2.27 g). Distilation by Kugelröhr with an oven temperature of 70°C/20 mmHg yielded 3-penten-2-yl pivaloate as a colourless liquid (1.12 g, 48%). ^1H NMR (200 MHz): δ ($CDCl_3$) 5.70 (1H, dq, J = 15, 6 Hz, CH_3CH=C), 5.47 (1H, ddq, J = 15, 6.8 1.8 Hz, C=C*H*CHCH_3), 5.28 (1H, m, C*H*(OR)CH_3), 1.69 (3H, d, J = 6 Hz, CH_3CH=C), 1.26 (3H, d, J = 6.5 Hz,CH(OR)CH_3) and 1.19 (9H, s, Bu^t); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 178.0 (CO), 131.0, 127.4 (*C*H=*C*H), 70.5 (*C*H(OR)), 38.5 (*C*(CH_3)$_3$), 26.9 (C(*C*H_3)$_3$), 20.0 (CH(OR)-*C*H_3) and 17.5 (=CH-*C*H_3); ν_{max} (thin film) 2975 (br, m), 1812 (m), 1728 (s) (C=O), 1481 (m), 1283 (m), 1162 (s) and 1041 (m) cm^{-1} m/z (DCI(NH_3)) 188 (22%, M+18), 171 (8, M+1) and 86 (100, M - COBu^t).

[1, 2-Bis(diphenylphosphino)ethane]nickel (II) Dichloride (**107**)[124]



To a solution of nickel dichloride hexahydrate (642 mg, 2.7 mmol) in hot ethanol (8 ml) was added 1, 2-bis(diphenylphosphino)ethane (1.07 g, 2.7 mmol) in hot ethanol (100 ml), causing an orange precipitate to be formed. This was filtered and dried *in vacuo* to give [1, 2-bis(diphenylphosphino)ethane]nickel (II) dichloride (1.11 g, 78%) as an orange powder, m.p. >230°C. Found: C, 58.6; H, 4.27. $C_{26}H_{24}Cl_2NiP_2$ requires C, 59.1; H, 4.58%. ^{1}H NMR (200 MHz): δ ($CDCl_3$) 8.02 (8H, m, *o*-Ph), 7.51 (12H, m, *m*- + *p*-Ph) and 2.16 (4H, d, J_{P-H} = 17.8 Hz, CH_2); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 133.7, 131.9, 129.1 (aromatic carbons) and 27.4 (CH_2); ^{31}P NMR (101.2 MHz): δ ($CDCl_3$) 53.9; ν_{max} (KBr) 3054 (m), 1482 (m), 1435 (s), 1427 (m), 1410 (m), 1098 (s) and 818 (s) cm^{-1}.

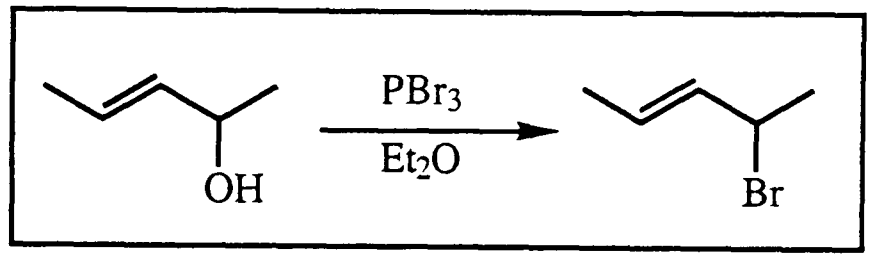
Attempted Ni Catalysed Coupling of 3-Penten-2-yl Pivaloate (**106**) with Grignard Reagents: General Procedure (Table 12, entry 1). **4-Phenylpent-2-ene (108)**



To a solution of 3-penten-2-yl pivaloate (**106**) (102 mg, 0.6 mmol) and (dppe)$NiCl_2$ (**107**) (6.3 mg, 2 mol%) in dry thf (1 ml) at 0°C was added phenylmagnesium bromide (0.166 ml of 3 M solution, 0.5 mmol) over a period of 30 min. The reaction was stirred at ambient temperature for 20 h and then quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with thf (3 x 20 ml) and the combined organic layers dried over $MgSO_4$ and evaporated to give a yellow oil (69 mg). Purification by preparative tlc

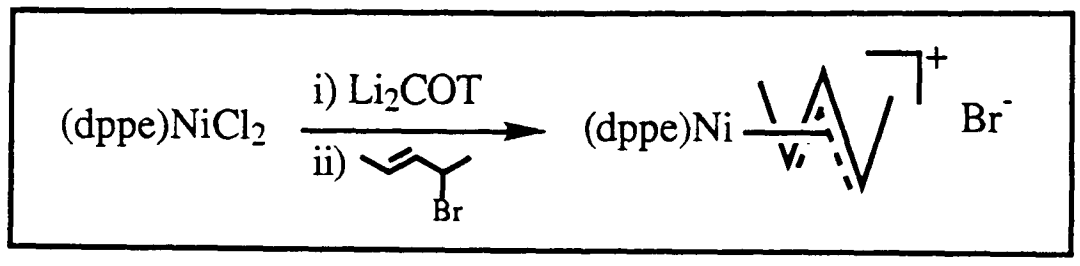
with hexane:EtOAc (10:1) as eluent gave 4-phenylpent-2-ene as a colourless oil (35 mg, 48%). ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.50-7.12 (5H, m, Ph), 5.78-5.42 (2H, m, C*H*=C*H*), 3.47 (1H, m, Ph-C*H*), 1.72 (3H, d, J = 6 Hz, C=CHCH_3) and 1.39 (3H, d, J = 7 Hz, CHCH_3); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 146.7 (*ipso*-Ph), 136.4 (*C*H=CHCH$_3$), 128.5, 127.3, 126.1 (aromatic carbons), 123.8 (C=*C*HCH$_3$), 42.3 (Ph-*C*H), 21.3 (Ph-CH-*C*H$_3$) and 17.8 (C=CH-*C*H$_3$); ν_{max} (thin film) 3026 (m), 2965 (s), 1602 (w), 1492 (m), 1451 (s), 1377 (m), 1015 (m) and 964 (m) cm^{-1}; m/z (DCI(NH_3)) 147 (12%, M+1), 146 (50, M$^+$) and 131 (100, M-Me).

2-Bromopent-3-ene (**110**)



To a solution of 3-penten-2-ol (1.88 g, 21.8 mmol) in dry Et_2O (15 ml) was added phosphorus tribromide (2.36 g, 8.72 mmol) over a period of 20 min. The reaction was stirred in the absence of light for 27 h. It was then poured onto ice, the aqueous layer extracted with Et_2O (2 x 20 ml), the combined organic layers washed with brine (20 ml), dried over $MgSO_4$ and evaporated to give 2-bromopent-3-ene as a colourless liquid (2.2 g, 68%). ^{1}H NMR (200 MHz): δ ($CDCl_3$) 5.73 (2H, m, C*H*=C*H*), 4.70 (1H, m, C*H*Br), 1.77 (3H, d, J = 6.7 Hz, CH_3-CH=) and 1.71 (3H, d, J = 5.5 Hz, CH_3-CHBr); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 134.4, 127.3 (*C*H=*C*H), 50.3 (CHBr), 26.0 (CHBr-*C*H$_3$) and 17.2 (*C*H$_3$-CH=C); ν_{max} (thin film) 2989 (m), 2919 (m), 1666 (w) (C=C), 1448 (m), 1378 (w), 1182 (m), 1011 (m) and 962 (m) cm^{-1}; m/z (DCI(NH_3)) 68 (100%, M-Br).

[1, 2-Bis(diphenylphosphino)ethane]nickel (η^3-(1, 3-dimethyl)allyl)bromide (**109**)



To a suspension of [1, 2-bis(diphenylphosphino)ethane]nickel (II) dichloride (**107**) (1.06 g, 2 mmol) in dry, degassed thf (15 ml) at -78°C was added ethereal $Li_2(COT)$ (8.3 ml, 0.26 M, 2.2 mmol). The reaction was stirred for 15 min at this temperature then allowed to warm to room temperature. 2-Bromopent-3-ene (**110**) (372 mg, 2.5 mmol) in dry, degassed thf (5 ml) was then added, causing the solution to turn a deep red colour. The reaction was stirred at ambient temperature for 10 min then filtered *via* cannula into dry, degassed pentane (80 ml), causing a brown precipitate to be formed. The precipitate was allowed to settle and the pentane removed with a syringe. The brown solid was washed with pentane (2 x 30 ml) and dried *in vacuo* to give a brown solid.

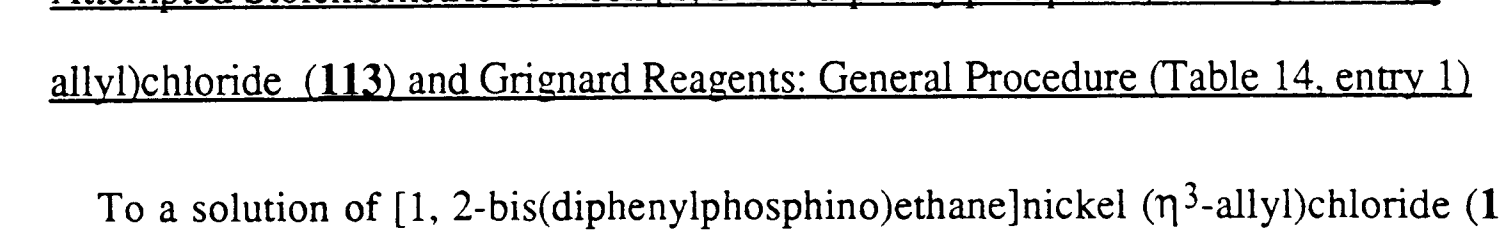
The brown solid was dissolved in degassed CH_2Cl_2 (20 ml) and washed repeatedly with degassed water, which was removed with a syringe. The CH_2Cl_2 was removed *in vacuo* to give [1, 2-bis(diphenylphosphino)ethane]nickel (η^3-(1, 3-dimethyl)allyl)bromide (856 mg, 71%) as a red solid, m.p. 154-156°C. Found: C, 60.8; H, 5.62. $C_{31}H_{33}BrNiP_2$ requires C, 61.4; H, 5.45 %; ^{31}P NMR (101.2 MHz): δ ($CDCl_3$) 42.3; ν_{max} (KBr) 1483 (m), 1435 (s), 1098 (m), 745 (m) and 684 (s) cm^{-1}.

Attempted Stoichiometric Reaction of [1, 2-Bis(diphenylphosphino)ethane]nickel (η^3-(1, 3-dimethyl)allyl)bromide (**109**) with Benzylmagnesium Chloride

To a solution of [1, 2-bis(diphenylphosphino)ethane]nickel (η^3-(1, 3-dimethyl)allyl)bromide (**109**) (100 mg, 0.16 mmol) in dry degassed thf (2 ml) at 0°C under argon was added benzylmagnesium chloride (80 µl, 2 M, 0.16 mmol). The reaction was stirred at room temperature for 23 h and then quenched with saturated aqueous NH_4Cl

solution. The aqueous layer was extracted with CH_2Cl_2 (2 x 15 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give an orange solid (48 mg), which proved to be an intractable mixture.

Attempted Stoichiometric Reaction Between Ni Complex (**112**) and Grignard Reagents: General Procedure (Table 13, entry 1). **4-Phenylpent-2-ene (108)**



To a solution of [1, 2-bis(diphenylphosphino)ethane]nickel (η^3-(1, 3-dimethyl)allyl)bromide (**109**) (75 mg, 0.12 mmol) in dry, degassed thf (4 ml) was added silver triflate (32 mg, 0.12 mmol), causing the solution to go from a deep red colour to yellow and a grey precipitate to form. The reaction was stirred for 15 min then filtered *via* cannula into a Schlenk tube and cooled to -65°C. Phenylmagnesium chloride (66 µl, 2 M, 0.132 mmol) was added, causing the solution to turn deep red. The reaction was allowed to warm to room temperature, during which time the colour became more intense, and was stirred for 20 h. It was quenched with saturated aqueous NH_4Cl solution, the aqueous layer extracted with Et_2O (2 x 15 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a yellow oil (15 mg). Purification by preparative tlc with hexane:Et_2O as eluent gave 4-phenylpent-2-ene as a colourless oil (6.5 mg, 37%).

Attempted Stoichiometric between [1, 2-Bis(diphenylphosphino)ethane]nickel (η^3-allyl)chloride (**113**) and Grignard Reagents: General Procedure (Table 14, entry 1)

To a solution of [1, 2-bis(diphenylphosphino)ethane]nickel (η^3-allyl)chloride (**113**) (107 mg, 0.2 mmol) in dry, degassed thf (5 ml) at 0°C under argon was added benzylmagnesium chloride (0.1 ml, 2 M, 0.2 mmol), causing the solution to turn deep

purple. The reaction was stirred at room temperature for 20 h and then quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O (2 x 10 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give an orange solid. This was triturated with Et_2O (2 x 20 ml) which was filtered and evaporated to give an orange oil (41 mg). Isolation of the reaction products was achieved by preparative tlc, with hexane:Et_2O (2:1) as eluent.

4-Phenylbut-1-ene (114). Colourless oil; ^1H NMR (200 MHz): δ ($CDCl_3$) 7.4-7.1 (5H, m, Ph), 5.98-5.79 (3H, m, C*H*=C*H*$_2$), 2.75 (2H, m, C*H*$_2$-CH=CH$_2$) and 2.40 (2H, m, PhC*H*$_2$); m/z (DCI(NH_3)) 132 (20%, M^+) and 91 (100, $PhCH_2$).

Bibenzyl. Colourless oil; ^1H NMR (200 MHz): δ ($CDCl_3$) 7.4-7.15 (10H, m, Ph) and 2.97 (4H, s, CH_2); m/z (DCI(NH_3)) 200 (32%, M+18) and 91 (100, $PhCH_2$).

Benzyl Alcohol. Colourless oil; ^1H NMR (200 MHz): δ ($CDCl_3$) 7.45-7.23 (5H, m, Ph), 4.70 (2H, s, CH_2) and 1.77 (1H, br s, OH); m/z (DCI(NH_3)) 108 (100%, M^+).

Bi(α-methyl)benzyl (115). Colourless oil; ^1H NMR (200 MHz): δ ($CDCl_3$) 7.46-7.01 (20H, m, Ph), 2.94 (2H, m, CH), 2.80 (2H, m, CH), 1.30 (6H, m, CH_3) and 1.06 (6H, m, CH_3).

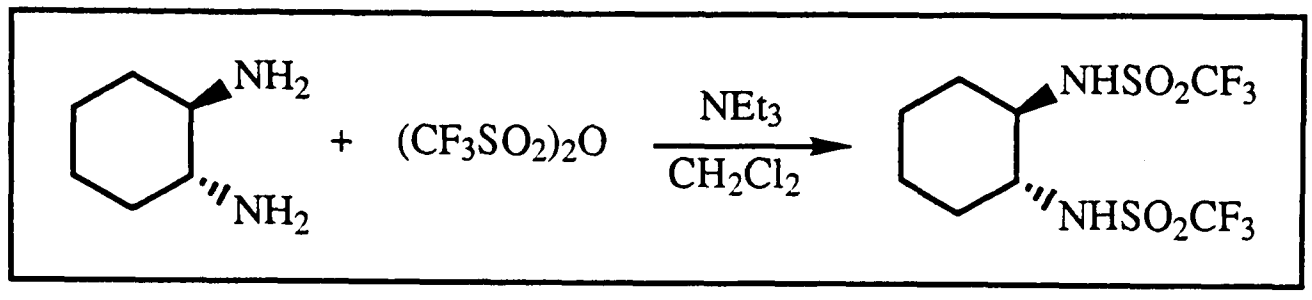
***sec*-Phenethyl Alcohol.** Yellow oil; ^1H NMR (200 MHz): δ ($CDCl_3$) 7.43-7.21 (5H, m, Ph), 4.93 (1H, q, J = 6.5 Hz, CH), 1.81 (1H, br s, OH) and 1.52 (3H, d, J = 6.5 Hz, CH_3).

Bi(α-trimethylsilyl)benzyl (116). Colourless oil; ^1H NMR (200 MHz): δ ($CDCl_3$) 7.30-6.98 (10H, m, Ph), 2.70 (1H, s, CH), 2.60 (1H, s, CH), 0.03 (9H, s, $SiMe_3$) and 0.01 (9H, s, $SiMe_3$); m/z (DCI(NH_3)) 344 (8%, M+18), 90 (60, PhCH) and 73 (100, $SiMe_3$).

***cis* and *trans*-4-Phenyl-4-trimethylsilylbut-2-ene (117).** Colourless oil; ^1H NMR (200 MHz): δ ($CDCl_3$) 7.29-6.82 (10H, m, Ph), 5.82 (2H, m, H_3), 5.48 (2H, m, H_2), 3.30 (1H, d, J = 10 Hz, H_4), 2.89 (1H, d, J = 10 Hz, H_4) and 1.69 (6H, m, CH_3); m/z (DCI(NH_3)) 205 (22%, M+1), 90 (90, PhCh) and 73 (100, $SiMe_3$).

3.5. Experimental for Section 2.5.

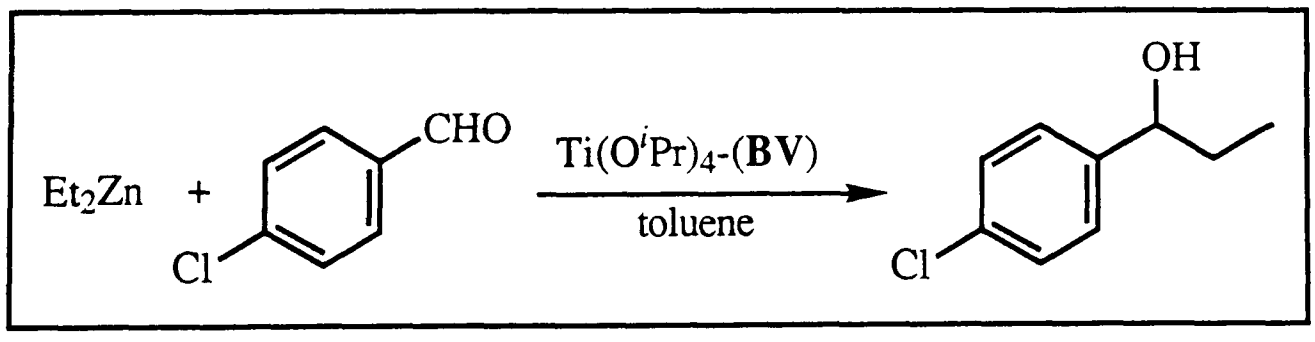
(±)-*trans*-1, 2-Bis(trifluoromethanesulphonamide)cyclohexane (**118**)



To a solution of (±)-*trans*-1, 2-diaminocyclohexane (228 mg, 2 mmol) in dry CH_2Cl_2 at -78°C was added triethylamine (0.52 ml, 4 mmol) and trifluoromethanesulphonic anhydride (0.67 ml, 4 mmol) and the reaction stirred for 45 min.[128] The resulting white solid was filtered, washed with CH_2Cl_2 and dried *in vacuo* to give (±)-*trans*-1, 2-bis(trifluoromethanesulphonamide)cyclohexane (624 mg, 83%) as a white powder, m.p. 237-238°C. Found: C, 25.3; H, 3.16; N, 7.29. $C_8H_{12}F_6N_2O_4S_2$ requires C, 25.4; H, 3.17; N, 7.40 %. ^{1}H NMR (300 MHz): δ (d_6-DMSO) 9.15 (2H, s, NH), 2.74 (2H, br s, CH) and 2.55-1.80 (8H, m, CH_2); ^{13}C NMR (125.8 MHz): δ (d_6-acetone) 121.5 (q, J = 320 Hz, CF_3), 60.4 (CH), 34.8 and 25.9 (CH_2); ν_{max} (KBr) 3291 (br s) (NH), 2964 (s), 2934 (s), 2872 (s), 1462 (m), 1374 (w), 1181 (m) and 908 (m) cm^{-1}; m/z (DCI(NH_3)) 396 (100%, M+18) and 245 (35, M-SO_2CF_3).

Catalytic Addition of Organozinc Reagents to *p*-Chlorobenzaldehyde: General Procedure.

1-(*p*-Chlorophenyl)propan-1-ol (119)



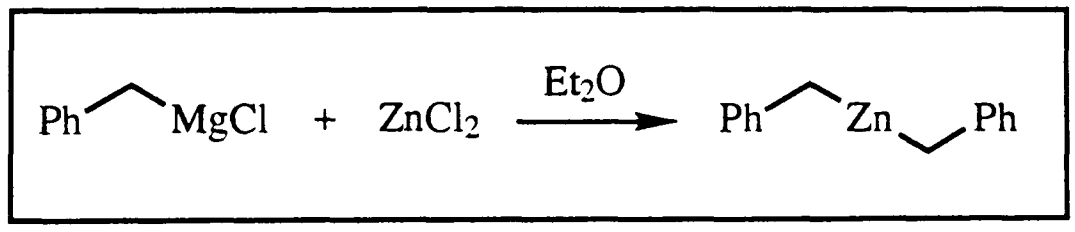
(±)-*trans*-1, 2-Bis(trifluoromethanesulphonamide)cyclohexane (**118**) (22.7 mg, 0.06 mmol) and titanium tetra-*iso*-propoxide (0.071 ml, 0.24 mmol) were dissolved in dry,

degassed toluene (2 ml) under argon and stirred at 40°C for 20 min. The solution was cooled to -78°C and diethylzinc (3 ml, 1 M, 3 mmol) was added, causing the solution to turn orange. *p*-Chlorobenzaldehyde (351 mg, 2.5 mmol) in dry, degassed toluene (1 ml) was added and the reaction stirred at 0°C for 2 h. The reaction was quenched with 2 M aqueous HCl solution, the aqueous layer extracted with toluene (2 x 10 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give 1-(*p*-chlorophenyl)propan-1-ol as a colourless oil (297 mg, 70%). ^1H NMR: δ ($CDCl_3$) 7.28 (4H, m, aromatic protons), 4.58 (1H, t, J = 7.5 Hz, CH), 1.98 (1H, d, J = 3 Hz, OH), 1.74 (2H, m, CH_2) and 0.91 (3H, t, J = 7.5 Hz, CH_3); ν_{max} (thin film) 3352 (br s), 2967 (s), 2934 (s), 2877 (s), 1598 (s), 1492 (m), 1410 (m), 1092 (s), 1014 (s) and 825 (s) cm^{-1}.

1-(4-chlorophenyl)-2-phenylethanol (**122**) (spectroscopic data given below) was isolated when both dibenzylzinc (**120**) and benzyl(trimethylsilyl)methylzinc (**123**) were used in the addition reaction.

***p*-Chlorobenzylalcohol** (**127**). White solid, m.p. 72-73°C (lit.[152] 71-72.5°C); ^1H NMR (200 MHz): δ ($CDCl_3$) 7.36-7.26 (4H, m, aromatic protons), 4.64 (2H, s, CH_2), 2.06 (1H, br s, OH); ν_{max} (nujol) 2900 (br s), 1085 (m), 1015 (m), 822 (w), 793 (w) cm^{-1}.

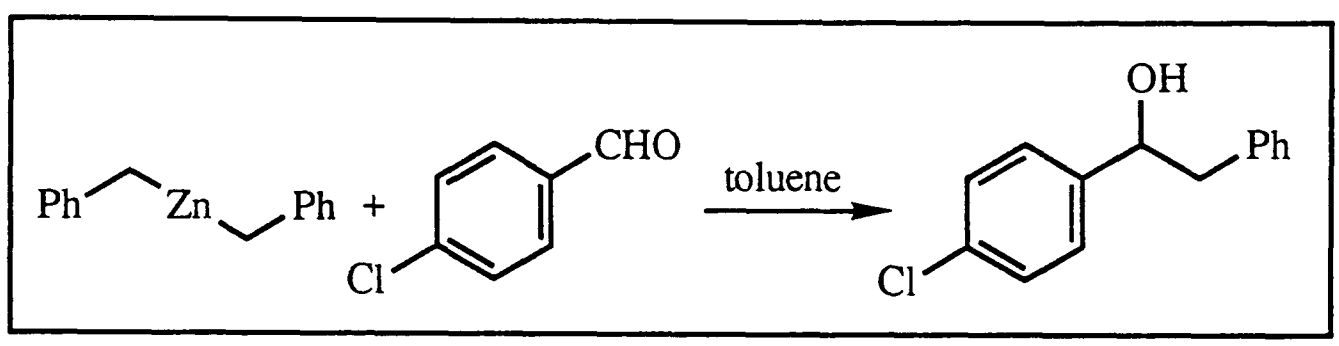
Dibenzylzinc (**120**)[127]



To a solution of benzylmagnesium chloride (20 ml, 1 M, 20 mmol) in a centrifuge vessel under argon was added an ethereal solution of zinc chloride (10 ml 1 M, 10 mmol), causing a fine white precipitate to form. The reaction was stirred at ambient temperature overnight and then centrifuged. The ethereal layer was transferred to a Schlenk tube *via* cannula and the remaining white solid washed with dry, degassed Et_2O (15 ml), which was centrifuged and transferred to the Schlenk. The Et_2O was removed *in vacuo* and dry,

degassed toluene (20 ml) added. This solution was filtered into another Schlenk tube, where the toluene was removed *in vacuo* to give a brown oil. This was washed with dry, degassed 30-40°C petroleum ether (3 x 20 ml) and dried *in vacuo* to give dibenzylzinc as a yellow oil (1.06 g, 43%). ^{1}H NMR (200 MHz): δ (C_6D_6) 6.95 (10H, m, aromatic protons) and 1.44 (4H, s, CH_2).

Addition of Organozinc Reagents to *p*-Chlorobenzaldehyde in the Absence of Catalyst: General Procedure. **1-(4-Chlorophenyl)-2-phenylethanol (122)**



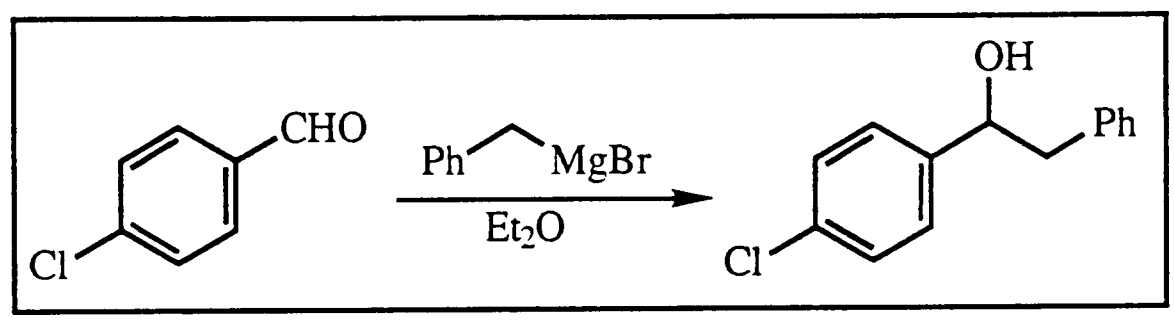
To a solution of dibenzylzinc (**120**) (100 mg, 0.4 mmol) in dry, degassed toluene (1 ml) at -78°C was added *p*-chlorobenzaldehyde (47 mg, 0.33 mmol) in dry, degassed toluene (1 ml), causing the solution to turn red. The reaction was stirred at room temperature for 3 h and then quenched with 2 M aqueous HCl solution. The aqueous layer was extracted with toluene (2 x 10 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give 1-(4-chlorophenyl)-2-phenylethanol as a colourless oil (72.5 mg, 90%).

Attempted Synthesis of Di[(α-methyl)benzyl]zinc

Anhydrous zinc chloride (800 mg, 5.9 mmol) was placed in a centrifuge vessel under argon and suspended in dry, degassed Et_2O (10 ml). To this was added an ethereal solution of α-methylbenzylmagnesium chloride (**100**) (22.5 ml, 0.32 M, 7.2 mmol) and the reaction stirred for 2.5 h. The solution was then centrifuged and the Et_2O transferred *via* cannula into a Schlenk tube. The remaining grey solid was washed with dry, degassed Et_2O (20 ml),

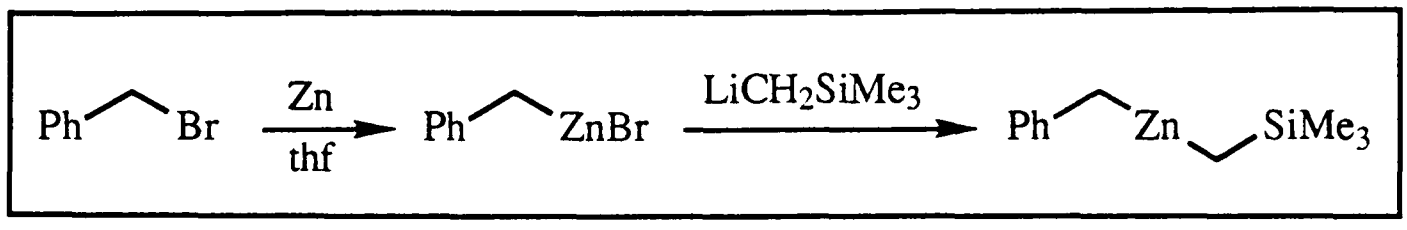
which was centrifuged and transferred to the Schlenk. The solvent was removed *in vacuo* to give a white solid which was recrystallised from hot, dry, degassed hexane to give a white solid (400 mg). On examination, this proved to be the homocoupled product bi-(α-methyl)benzyl (**115**), m.p. 122-124°C (lit.[153] 125°C); ^{1}H NMR[154] (200 MHz): δ (C_6D_6) 7.05 (20H, m, aromatic protons), 2.76 (2H, m, CH), 2.68 (2H, m, CH), 1.10 (6H, d, J = 7 Hz, CH_3) and 0.91 (6H, d, J = 7 Hz, CH_3); ^{13}C NMR (53.31 MHz): δ(C_6D_6) 148.4 (*ipso*-Ph), 128.1, 126.1, 125.8 (aromatic carbons), 47.1, 46.3 (CH), 20.7 and 17.9 (CH_3); ν_{max} (KBr) 3205 (m), 3165 (m), 2954 (m), 2932 (m), 1427 (m), 1176 (m) and 1096 (m) cm^{-1}.

1-(4-Chlorophenyl)-2-phenylethanol (**122**)



To a solution of *p*-chlorobenzaldehyde (1.4 g, 10 mmol) in dry Et_2O at 0°C was added benzylmagnesium chloride (10 ml, 1 M, 10 mmol), causing the solution to turn red. The reaction was stirred for 15 min, during which time the red colour disappeared, and then quenched with water. The aqueous layer was extracted with Et_2O (2 x 20 ml), the combined organic layers dried over $MgSO_4$ and evaporated to give a colouorless oil (1.82 g). Purification by column chromatography on silica gel with hexane:EtOAc (4:1) gave 1-(4-chlorophenyl)-2-phenylethanol as a colourless oil. ^{1}H NMR (200 MHz): δ ($CDCl_3$) 7.22 (9H, m, aromatic protons), 4.87 (1H, m, CH), 3.00 (2H, m, CH_2) and 2.16 (1H, d, J = 2.7 Hz, OH); ^{13}C NMR (50.31 MHz): δ ($CDCl_3$) 142.5, 137.8, 133.4 (*ipso*-carbons), 129.8-127 (aromatic CH carbons), 74.7 (CH) and 46.0 (CH_2); ν_{max} (thin film) 3380 (br, s) (OH), 2918 (s), 1598 (m), 1490 (m), 1451 (m), 1410 (m), 1088 (m), 1045 (m) and 1011 (m) cm^{-1}; m/z (DCI(NH_3)) 233 (5%, M+1), 214 (100, M-H_2O), 179 (50, M-H_2O-Cl) and 89 (9, $PhCH_2$).

Benzyl(trimethylsilylmethyl)zinc (**123**)



To a suspension of zinc powder (670 mg, 10.5 mmol) in dry, degassed thf (1 ml) at 0°C was added a solution of benzyl bromide (1.20 g, 7 mmol) in dry, degassed thf (5 ml) over a period of 1 h. The reaction was stirred at 5°C for 4 h and then filtered *via* cannula into a Schlenk tube to give a solution of benzylzinc bromide.[129]

This solution was cooled to 0°C and trimethylsilyllithium (7 ml, 1 M, 7 mmol) added over a period of 1 h. The reaction was stirred for 16 h, during which time a white precipitate formed. The solution was filtered *via* cannula into a Schlenk tube, where it was kept as a solution. A portion was removed and the solvent evaporated to give a white solid, the NMR spectrum of which was taken. ^{1}H NMR (200 MHz): δ (C_6D_6) 7.3-6.7 (5H, m, Ph), 2.0 (2H, s, PhCH_2), 0.09 (9H, s, $SiMe_3$) and -0.65 (2H, s, CH_2SiMe_3).

Attempted Synthesis of Di[(1-trimethylsilyl)ethyl]zinc

To magnesium turnings (40 mg, 1.65 mmol) suspended in dry degassed Et_2O (2 ml) was added 0.5 ml of a solution of (1-chloroethyl)trimethylsilane (200 mg, 1.5 mmol) in dry degassed Et_2O (4 ml) and a small amount of 1, 2-dibromoethane (20 µl). The reaction was heated briefly until refluxing and then the remainder of the (1-chloroethyl)trimethylsilane solution was added. The reaction was stirred overnight, cooled to 0°C and ethereal zinc chloride (0.75 ml, 1 M, 0.75 mmol) added. The resulting solution was stirred at room temperature for 4 d,[130] during which time a grey precipitate formed. The solution was filtered and evaporated to give a white solid. On examination, this crude reaction product was found to be 2, 3-di(trimethylsilyl)butane (**126**). ^{1}H NMR (200 MHz): δ(C_6D_6) 0.92 (12H, m, CH_3), 0.71 (4H, m, CH), 0.01 (18H, s, $SiMe_3$) and -0.02 (18H, s, $SiMe_3$); m/z (DCI(NH_3)) 220 (23%, M+18), 90 (100) and 73 (55. $SiMe_3$).

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"In science, read by preference the newest works; in literature, the oldest"

Edward Bulwer-Lytton (1803 - 1873)

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"For this relief much thanks"

William Shakespeare (1564 - 1616)

[Hamlet]