UNIVERSITY OF SOUTHAMPTON

INVENTION OF NOVEL PALLADIUM-CATALYSED THREE-COMPONENT COUPLINGS

By Carl-Gustaf Pierre Saluste

A thesis submitted for the fulfilment of the requirements for the degree of Doctor of Philosophy

FACULTY OF SCIENCE

DEPARTMENT OF CHEMISTRY

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This manuscript describes the original work done wholly by the author while registered as a postgraduate student at the University of Southampton. Examples and procedures which are used from the literature have been clearly cited

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ABSTRACT

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A three component synthesis of *N-tert*-butyl substituted amidines from aryl halides, *tert*-butyl isonitrile and a tin amide component was developed. The optimum catalyst was tris-(dibenzylideneacetone)dipalladium(0) chloroform with 2 equivalents of 1,1'-bis (diphenylphosphino)ferrocene as ligand. An improvement to this method, allowing for the use of free amines in the presence of caesium carbonate as base, thus avoiding tin compounds, was subsequently established. The optimum catalyst was palladium dichloride or palladium diacetate with 2 equivalents of 1,1'-*bis* (diphenylphosphino)ferrocene as ligand. A wide range of *N*-tert-butyl substituted amidines were synthesised from electron rich, electron poor, electronically neutral, and heterocyclic aryl bromides or triflates and primary or secondary, cyclic or acyclic, aliphatic or aromatic amines. The stereochemistry of the amidines so formed was established by NMR and molecular modelling (including DFT calculations) and found to be the thermodynamically less stable (*Z*)-imine stereoisomer. Removal of the *tert*-butyl group with strong sulphuric acid was found to be viable to give secondary amidines. Intramolecular insertions to afford cyclic amidines were accomplished. The tin-free methodology was then applied to the synthesis of imidates and thioimidates from aryl bromides, isonitriles and the sodium salts of alcohols, phenols and thiols in high yields. It was found that a wide range of isonitriles were compatible with this reaction (primary, secondary, and tertiary). Phenoxyimidates formed in the above way reacted with amines with weak acid catalysis to afford amidines variously substituted on the nitrogen derived from an isonitrile thus avoiding the limitation to tertiary alkyl isonitriles found in the direct amidine synthesis. A 1-pot procedure was developed which gave good overall yields. The controlled double insertion of isonitriles into the aryl bromide / ethoxide /palladium catalyst system to give α-iminoimidates was also investigated and a reaction system was established to accomplish this novel chemistry selectively. Crystal structures of some α-iminoimidates were obtained, which allowed predictions about the order of the isonitrile insertion to be made.

Abbreviations Listed in Alphabetical Order

APCI	Atmospheric Pressure Chemical Ionisation
app	Apparent
atm	Atmosphere(s)
BINAP	Binaphtyl
b.p.	Boiling Point
bpy	Bipyridyl
brm	Broad Multiplet
brs	Broad Singlet
CIR-FTIR	Cylindrical Internal Reflectance-Fourier Transform Infrared spectroscopy
C_{13}	*n*-Tridecane
DEPT	Distortionless Enhancement by Polarisation Transfer
DBA	Dibenzylidene Acetone
DCM	Dichloromethane
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
dppb	1,1'-*bis*-(diphenylphosphino)butane
dppe	1,1'-*bis*-(diphenylphosphino)ethane
dppf	1,1'-*bis*-(diphenylphosphino)ferrocene
E^+	Electrophile
ES^+	Positive Electrospray Mass Spectroscopy
Ether	Diethyl ether
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectroscopy
GOESY	Gradient NOE Enhancement Spectroscopy
GPC	Gel Permeation Chromatography
HPLC-MS	High-Performance Liquid Chromatography-Mass Spectroscopy
IR	Infrared Spectroscopy
LRMS	Low Resolution Mass Spectroscopy
m.p.	Melting Point

N/A	Not Applicable
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Nu^-	Nucleophile
$Pd_2DBA_3 \cdot CHCl_3$	tris-(dibenzylideneacetone)dipalladium(0) Chloroform
R.T.	Room Temperature
soln	Solution
THF	Tetrahydrofuran
UV/Vis	Ultraviolet/Visible Spectroscopy

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Mamma, Tante Saima e Monica, siete le persone piu' importanti della mia vita. A voi e papa' dedico questi tre anni cosi' speciali di studio, lavoro, sacrificio e tantissima gioia e felicita'.

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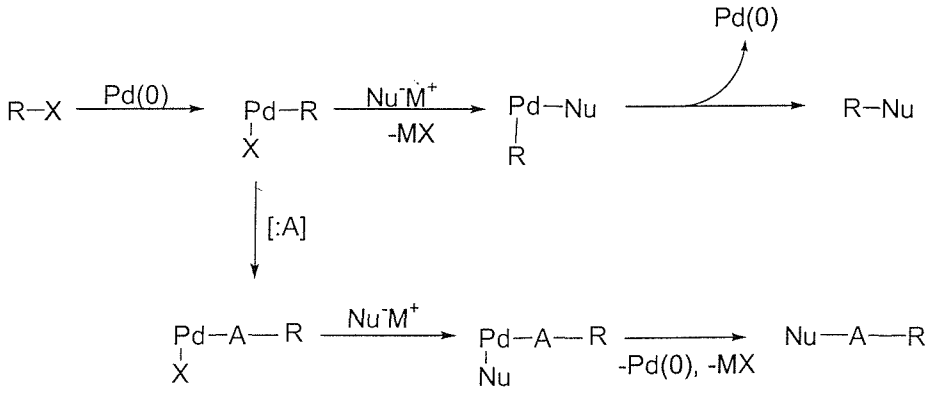
1. Palladium-Catalysed Carbonylation

1.1 General

The palladium-catalysed coupling of halides and triflates lacking β-hydrogens with Main Group organometallics *via* oxidative addition-transmetallation-reductive elimination sequences has been broadly developed. This whole sequence is often referred to as *cross-coupling*. In the transmetallation process, the organometallic species transfers its organic group to palladium in exchange for a halide (X)-group. Organometallic derivatives of tin, zinc and boron are the most widely used. In catalytic cycles, the transmetallation step is often rate limiting. This can be of great advantage in the development of three-component couplings as it allows for the trapping of the oxidative addition intermediate by a carbenoid or, for example, an alkene or alkyne. In order for the trapping to occur, it is fundamental that the trapping step is much faster than the transmetallation, as outlined in Scheme 1.



Scheme 1

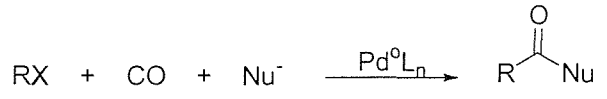
In this thesis, novel methodologies for palladium-catalysed three-component couplings with isonitriles have been developed. The emphasis of this review will lie on the much more widely studied palladium-catalysed carbonylation, which is the closest analogy to isonitrile insertion. The latter will also be discussed according to available relevant literature. Alkene-and alkyne insertion will not be discussed.

1.2. Palladium-Catalysed Carbonylation

The cornerstone of modern synthetic organic chemistry is based on carbon-carbon bond forming reactions and the carbonyl group is one of the most versatile functionalities for this purpose. Apart from being susceptible to nucleophilic attack at carbon and electrophilic attack at oxygen, it also has a polarising effect on neighbouring atoms and functional groups. Therefore clean and high-yielding methodologies for direct incorporation of the (C=O) fragment are highly desirable and successful methods are based on transition metal catalysis. For the purpose of this thesis, only palladium-mediated reactions will be briefly discussed. One very important aspect of carbonylation chemistry is the possibility to bias the reaction towards either single or double insertion of carbon monoxide (CO). In the following brief outline of the utility of carbon monoxide in synthesis, only single insertion will be considered. A more detailed picture of the mechanistic aspects determining single *vs* double insertion of CO will be given in the second part of this chapter.

1.2.1 Utility of Single Carbonylation Reactions in Synthesis

The three-component coupling between aromatic halides, triflates, or diazonium salts, CO and a nucleophile is the best-established carbonylation reaction, as shown in Scheme 2.



X=I, Br, Cl, OTf, N_2^+

Nu^-=OH^-, RO^-, $RCOO^-$, F^-, HNRR', R'M or H^-

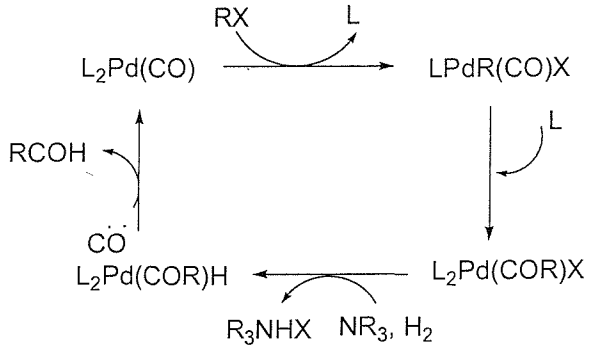
Scheme 2

Alkenes, alkynes and diazonium salts can also be successfully used as substrates in palladium-catalysed carbonylation chemistry.

Most work has been carried out with aryl halides, giving a valuable route to aromatic aldehydes, ketones, carboxylic acids, esters, anhydrides, acid fluorides and amides. These features will be discussed in sections 1.2.2 to 1.2.7.

1.2.2 Formation of Aldehydes and Ketones

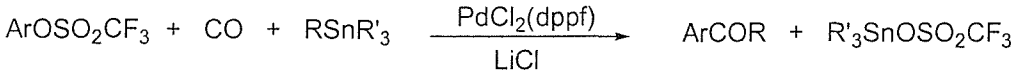
The Lewis-acid catalysed Gattermann-Koch synthesis[1] of aromatic aldehydes was the first example of use of CO in this context. The favoured substrates for aldehyde and ketone synthesis are halocarbons. In the classical palladium-catalysed aldehyde synthesis, aryl, heteroaryl and vinylic halides or triflates are coupled with CO and a hydride. More recent developments allow for the conversion of the substrates in presence of bulky, chelating phosphine ligands, also possible by low-pressure carbonylation of chloroarenes.[2] Synthesis of β,γ-unsaturated aldehydes from the corresponding allylic halide is possible too[3] and the mechanism for the carbonylation reaction giving aldehydes is outlined in Scheme 3.



Scheme 3

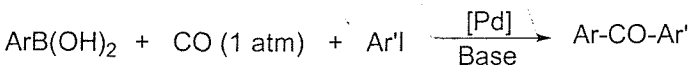
Ketones are obtained by the coupling of suitable organic halides[4] or triflates[5] with an organometallic species, for example stannane or borane, in the presence of CO. The most limiting side reaction when using halides is the formation of biaryls,[6] especially when using electron-poor substrates. This side reaction is normally suppressed by increasing the CO-pressure and can also be very conveniently overcome by using triflates. This methodology benefits from mild reaction conditions and a wide functional group tolerance. Most organic groups (alkyl, aryl, vinyl and alkynyl) can

be successfully transferred from the organostannane and a CO-pressure of 1 bar is sufficient for the reaction to take place, as shown in Scheme 4.



Scheme 4

Ishiyama *et al.*[7] described a protocol for ketone synthesis using boronates, given in Scheme 5.



Scheme 5

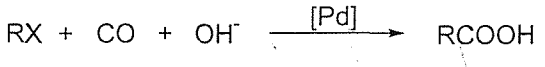
The outcome of the reaction was found to be solvent-and base dependent and a suspension of potassium carbonate in anisole gave the best selectivity for ketone over biaryl formation. A series of unsymmetrical biaryl ketones were synthesised in yields ranging from 60-90%.

1.2.3 Synthesis of Carboxylic Acids and Their Derivatives

In the context of carbonylation chemistry, carboxylic acids and their derivatives can be regarded as an electrophilic fragment [E^+] joined to a nucleophilic unit [Nu^-] through the CO-group. The [E^+]-fragment is a suitable carbon-based functional group and the [$Nu]^-$ is represented by one of the species [$OH]^-$, [$RO]^-$, [$R_2N]^-$, [$RCOO]^-$, or [$X]^-$. This reactivity pattern, by which CO links an electrophilic with a nucleophilic fragment, constitutes one of the most useful features of carbonylation chemistry.

1.2.4 Synthesis of Carboxylic Acids

Again, the substrates of choice are aryl, benzyl and vinyl halides. Because of the necessity to introduce an $[OH]^-$ -functionality, it is common to use biphasic reaction systems.[8] This approach was particularly useful with di-or polyhalogenated substrates in order to bias the reaction towards carbonylation of only one of the C-X groups. After the formation of the first carboxylate group, the product was trapped as the corresponding alkali salt in the aqueous medium, thus not in contact with the catalyst any longer. The carboxylic acid formation is outlined in Scheme 6.

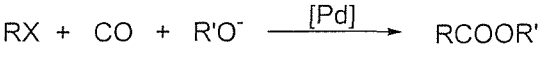


Scheme 6

1.2.5 Synthesis of Carboxylic Esters

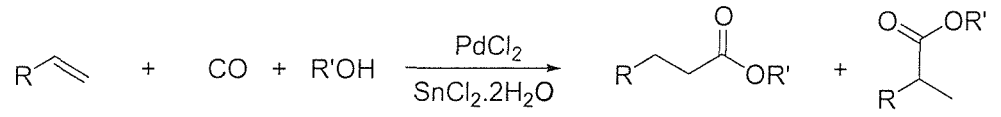
The synthesis of this category of compounds has been the most widely investigated in carbonylation chemistry. Important reasons are the possibility of using the alcohol component as solvent as well as reactant in many cases and carboxylic esters are important intermediates in many organic reactions.

The most convenient route to esters from aryl-, heteroaryl- and vinyl halides was developed by Heck *et al.*[9] and the reaction conditions were generally mild. The reaction is outlined Scheme 7.



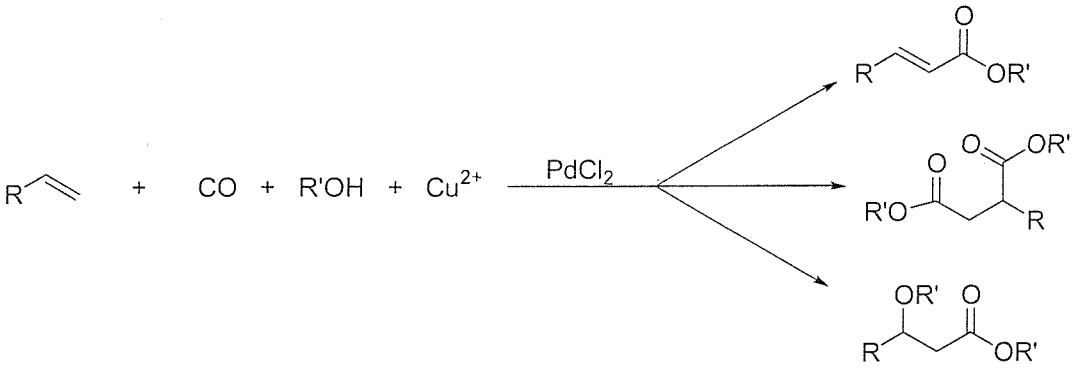
Scheme 7

Ester synthesis from alkenes is sometimes referred to as hydroesterification. Two isomeric products can form; one linear and one branched and addition of tin(II) chloride can strongly enhance selectivity for linear products.[10] The reaction in its most general form is described in Scheme 8.



Scheme 8

Under oxidative conditions, for example in the presence of copper(II) salts which can re-oxidise palladium(0) to palladium(II), several outcomes are possible.[11] Under neutral conditions, linear 1-alkenes gave principally β-alkoxy esters, whereas under basic conditions, formation of 1,2-diesters predominated. These reactions are summarised in Scheme 9.

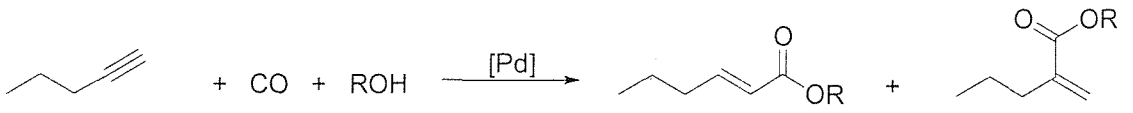


Scheme 9

Another important application is the route to β,γ-unsaturated esters by carbonylation of π-allyl palladium complexes.[12] In this case too the mild reaction conditions constituted an attractive feature. The reaction is outlined in Scheme 10.

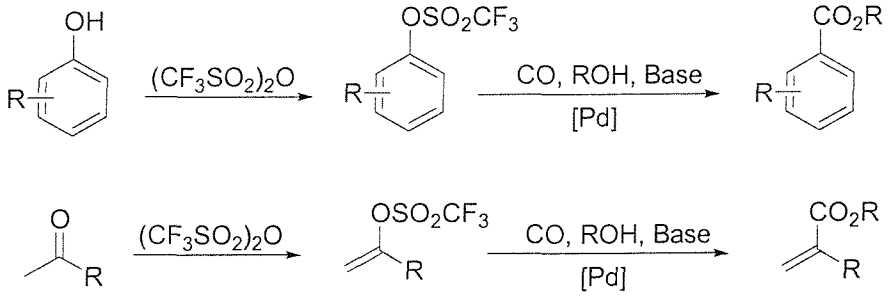
Scheme 10

Ester synthesis is also possible from alkynes. Again, formation of linear and branched products took place and tin(II) chloride was added to the reactions in order to increase selectivity for the linear compounds.[10] In this case, the products were α,β-unsaturated esters as illustrated in Scheme 11.



Scheme 11

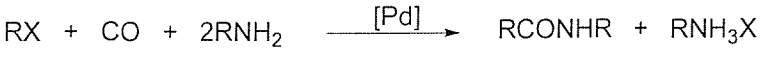
Classically, ester synthesis has been carried out from halides. Use of triflates has vastly increased the range of available substrates, even though side reactions with $[OH]^-$ and $[RO]^-$ have to be suppressed. This feature was particularly useful for derivatives of phenols and enols to give esters of aromatic and α,β-unsaturated carboxylic acids.[13] Use of chelating phosphine ligands like 1,1'-bis-diphenylphosphinoferrocene (dppf) and 1,2-bis-diphenylphosphinopropane (dppp) led to superiour results compared to triphenylphosphine (PPh_3).[13] This chemistry is outlined in Scheme 12



Scheme 12

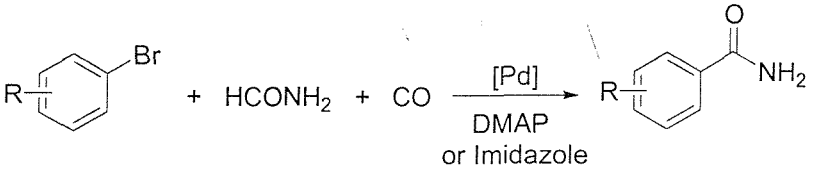
1.2.6 Synthesis of Amides

The amidation chemistry can conveniently be viewed in close analogy with the ester synthesis where the alcohol component has been replaced with an amine. The standard halides therefore react with primary and secondary amines to give the corresponding amides, as in Scheme 13.



Scheme 13

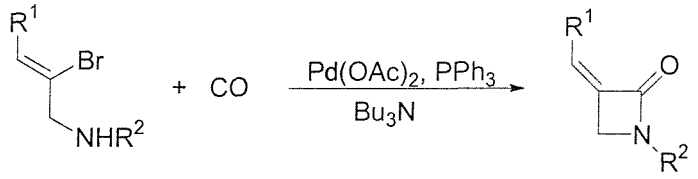
If the reacting amine is very weakly basic (e.g. primary aromatic) or valuable, a tertiary amine is added to neutralise the acid by-product HX. If not, an excess of the reacting amine is normally used. Amidation reactions generally proceed faster than esterifications due to the better nucleophilicity of amines compared to alcohols.[14] In analogy with the esterification reactions, triflates are generally excellent substrates also for amidation and the reaction conditions are mild.[15] The synthesis of primary aromatic amides has been subject to investigation[16] and a very recent addition to this chemistry was made by Schnyder *et al.*[17] by devising a method using formamide as a synthon for ammonia. This chemistry is described in Scheme 14.



Scheme 14

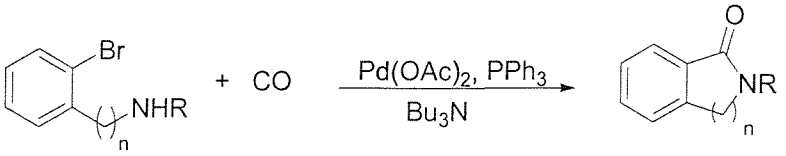
The methodology allowed for the conversion of a variety of aromatic and heteroaromatic substrates and the reported yields were good to excellent.

The formation of lactams is a very important *intramolecular* application of the amidation reaction. In this case too, palladium-based catalysts have been used alongside other metals. The formation of α-methylene-β-lactams[18] is outlined in Scheme 15.



Scheme 15

The synthesis of five-membered rings required more forcing conditions (CO-pressure and use of other metal catalysts). Aryl-condensed lactams could be conveniently obtained from the appropriate substrates[19] as in Scheme 16.

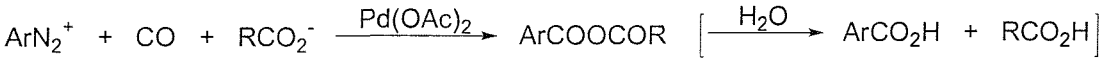


n=1,2,3

Scheme 16

1.2.7 Synthesis of Anhydrides

The main routes to palladium-catalysed anhydride synthesis are from arenediazonium ions and aryl halides. The former has been reported as a route to aromatic carboxylic acids[20] which are formed as hydrolysis products from the corresponding anhydride intermediates. This has later been confirmed and a range of mixed anhydrides could be synthesised by this route[21] given in Scheme 17.

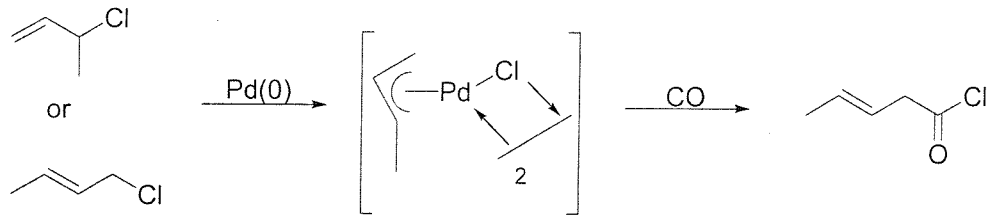


Scheme 17

Disproportionation is a common side reaction in the anhydride synthesis and the high reactivity of arenediazonium salts allowed for the carbonylation reaction to take place at room temperature. Iodoarenes also underwent the same reaction, but the higher temperatures required led to disproportionation.[22]

1.2.8 Synthesis of Acyl Halides

Few carbonylation-based routes to acyl halides are reported. One drawback is that any nucleophile present in the system may react with the acyl halide product. In the absence of a nucleophile, allylic chlorides were converted to 3-alkenoyl chlorides under vigorous conditions[23] as in Scheme 18.



Scheme 18

Aryl iodides could be converted to aroyl fluorides in the following reaction[24] where the caesium fluoride acted as the fluoride source, shown in Scheme 19.

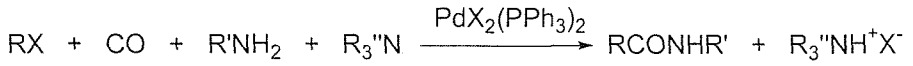
Scheme 19

1.3 The Mechanism of Palladium-Catalysed Carbonylation

In the previous paragraphs, a brief overview of the utility of CO in organic synthesis was given. The underlying mechanisms were not discussed in great detail and the aim of this section is to give an overview of the mechanistic studies of palladium-catalysed amide and ester formation. Firstly, the single carbonylation mechanisms will be discussed. Then, double carbonylation will be treated and further mechanistic data will be given, as the study of double carbonylation has helped investigating the selectivity between the two processes. The key feature is the CO-pressure, with atmospheric CO-pressure favouring single carbonylation and higher pressure leading to more or less extensive double carbonylation.

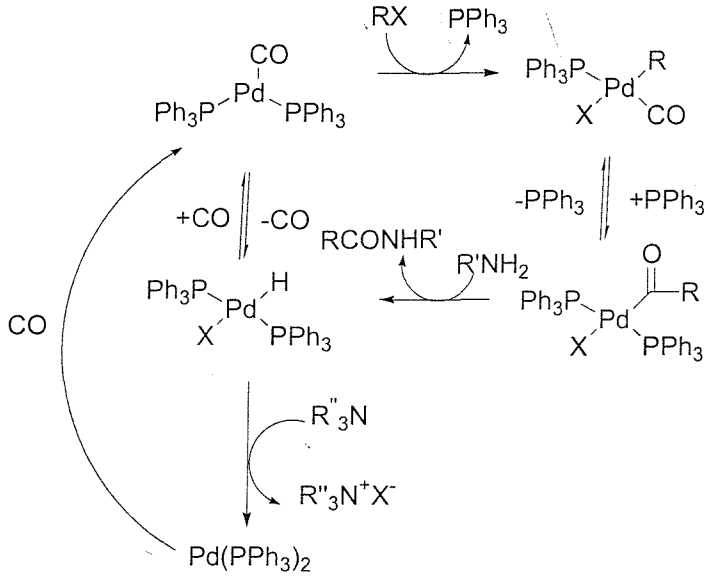
1.3.1 Palladium-Catalysed Amide Synthesis

Heck and Schoenberg[14] first described the palladium-catalysed amide formation. In the investigated reaction system, use of aryl, vinyl and heterocyclic halides was successful and the reaction is described in Scheme 20.



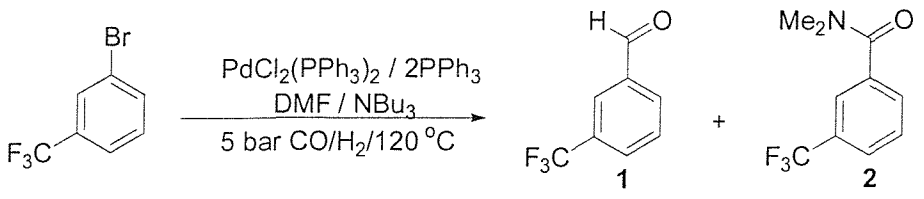
Scheme 20

A tertiary amine was generally added to neutralise the hydrogen halide formed and found to be necessary for the reaction to proceed when using aniline. More basic amines could be used in excess as an alternative to addition of the tertiary amine. The reaction worked for primary and secondary amines and was suggested to proceed *via* the mechanism given in Scheme 21.



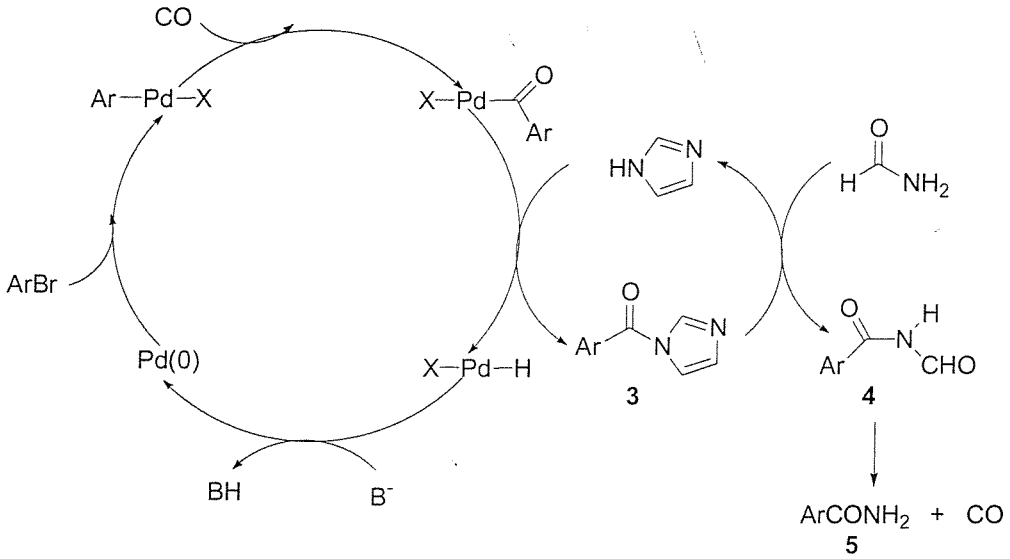
Scheme 21

The given catalytic cycle did not account for the formation of primary aromatic amides from ammonia, described by Schnyder *et al.*[17] almost three decades later. The starting point for this investigation was the observation of a side product in the reductive carbonylation reaction described in Scheme 22.



Scheme 22

3-Trifluoromethylbenzaldehyde **1** and *N,N*-dimethyl-3-trifluoromethylbenzamide **2** were isolated in yields of 17% and 0.2% respectively. The amide side product was ascribed to reaction with the solvent and trials with formamide in presence of a variety of bases were undertaken. Dimethylaminopyridine (DMAP), 4-pyrrolidinopyridine (PPY) and imidazole gave the best results. This observation indicated that these compounds might have an additional role besides scavenging the formed acid, as they are powerful Lewis bases. GC-monitoring of the reaction when performed with imidazole as the base, showed the presence of the imidazolide **3**, which led to the suggestion of the catalytic cycle given in Scheme 23.



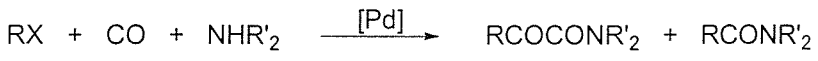
Scheme 23

The first steps are analogous to the classical mechanisms for palladium-catalysed carbonylation of aryl halides, where the nucleophiles react directly with the aroyl moiety. Formamide is a very weak nucleophile and an acylating catalyst is therefore necessary for the reaction to take place. The intermediate **4** decomposes to give the product **5** and CO.

1.3.2 Palladium-Catalysed α-Ketoamide Synthesis

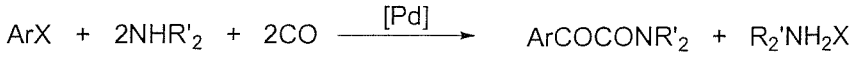
In 1982, Tanaka and co-workers[25] reported the formation of α-ketoamides as the first example of double carbonylation. As seen in the previous section, many examples of

single carbonylation were already known and the key difference was the CO-pressure. In order to achieve double carbonylation, a CO-pressure of 20-40 atm was necessary. The reaction invariably led to a mixture of single and double carbonylation products as shown in Scheme 24.



Scheme 24

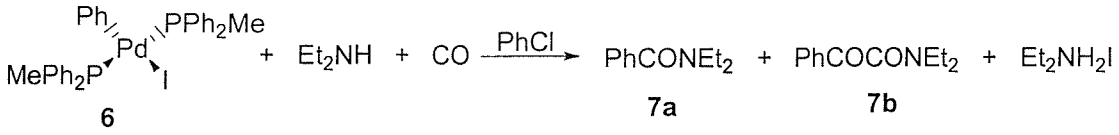
As for the catalyst, systems with bidentate phosphine ligands were found to exhibit the greatest selectivity for double carbonylation. The length of the carbon bridge between the phosphine groups had a crucial effect; a longer carbon chain gave better selectivity for double carbonylation and the best catalyst was 1,2-bis(diphenylphosphino)butane palladium(II) chloride, [$PdCl_2$(dppb)]. This catalyst was superior to the corresponding propane and ethane analogues. Aliphatic amines of "medium" bulk, for example diethylamine, gave the best results. More compact as well as bulkier amines favoured single carbonylation, whereas primary amines gave mainly the Schiff base of the α-ketoamide, together with small quantities of the benzamide. Some years later, a very systematic and detailed study of the factors biasing the reaction towards double CO-insertion appeared,[26] with the investigation of the reaction given in Scheme 25.



Scheme 25

The first parameter to be investigated was the catalyst. The nature of the phosphine ligand was found to be very important; monodentate as well as chelating ligands were effective. Strongly basic, coordinating phosphines with limited bulkiness gave the lowest selectivity for double carbonylation. Alongside $PdCl_2$(dppb), palladium(II) chloride methyldiphenyl phosphine [$PdCl_2(PMePh_2)_2$] was also found to work well. Ligandless systems and catalysts based on other transition metals gave only very limited conversion of the starting materials. In order to gain more information about

the catalytic cycle, the oxidative addition product **6** from PhI was synthesised and subsequently reacted with CO and diethylamine as shown in Scheme 26.



Scheme 26

A very unexpected observation was the formation of benzamide **7a** in only very low concentration during the initial period of the reaction. The α-ketoamide **7b** was found to form in a zero-order process. These findings prompted an investigation of the influence of the aryl source. For PhI, the reaction was accelerated by higher temperature, but became less selective for double carbonylation. Increased CO-pressure enhanced the selectivity for double carbonylation and did also accelerate the reaction. For bromobenzene (PhBr), the reaction was retarded with increasing CO-pressure. It suggested that the rate-determining step was different for PhBr and PhI. The oxidative addition is therefore most likely to be the rate-determining step in the case of PhBr, whereas for PhI it is probably at a later stage. The influence of the electronic nature of the aryl substrates was investigated next and the results are given in Table 1.

Table 1: Carbonylation of *para*-Substituted Aryl Bromides

Substituent	Amide (%)	α-Ketoamide (%)	Total Yield (%)
CN	65	35	98
CF_3	37	63	89
Ac	33	67	100
Cl	31	69	91
H	10	90	80
OPh	9	91	89
Me	16	84	84
OMe	8	92	22
NMe_2	14	86	26

Conditions: ArBr / Et_2N / $PdCl_2(PMePh_2)_2$ = 1 / 3 / 0.01. p(CO) = 10 atm, T=100 °C.

Electron-poor substrates were found to lower the selectivity for α-ketoamide formation, favouring amide formation. Moderately electron-rich aryl halides favoured double CO-insertion, leading to good overall conversions. Substrates with very strong electron-donating groups did favour double insertion, but with poor global yields. Steric hindrance around the halogen substituent had a retarding effect on the reaction. One *ortho*-alkyl group halved the reaction rate, but did not affect the ratio between the single and double carbonylation product. Two *ortho*-substituents, on the other hand, did not allow for any reaction to take place. Attention was then turned to the influence of the amine. An investigation of the influence of steric factors and basicity showed that sterically more demanding secondary amines favoured double CO-insertion. Small, nucleophilic amines gave preference for amide formation instead. Very interestingly, aniline afforded exclusively the amide product in a yield of 73%. These interesting results are summarised in Table 2.

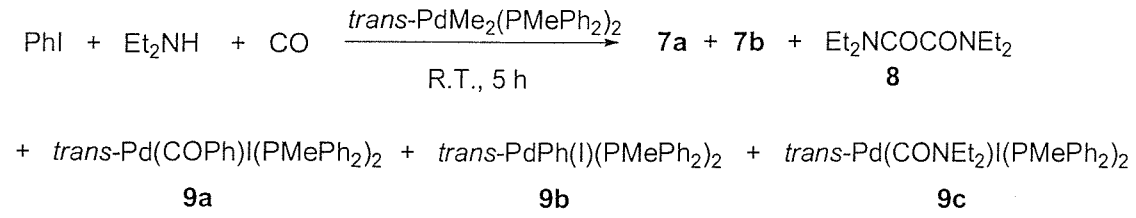
Table 2: Influence of the Amine Component in the Carbonylation Reaction

Amine	Amide (%)	α-Ketoamide (%)	Total Yield (%)
Me_2NH	93	7	73
Et_2NH	25	75	78
Pr_2NH	9	91	33
$^iPr_2NH$	100	0	4
$^tBu_2NH$	0	0	0
Pyrrolidine	100	0	95
Piperidine	79	79	83
Hexamethyleneimine	76	76	71
$PhCH_2(Me)NH$	23	23	39
$PhCH_2(Me)NH$[a]	32	32	79
Ph(Me)NH	0	0	0
Ph(Me)NH[b]	100	0	8
$(PhCH_2)_2NH$	0	0	0
diallylamine	0	0	0

Conditions: PhBr / Amine / $PdCl_2(PMePh_2)_2$= 1 / 5 / 0.02, p(CO) =10 atm., T=100 °C.

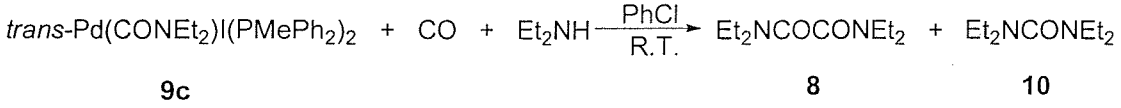
a. For 72 h, Et_3N was added. b. For 48 h, Et_3N was added.

In order to gain a deeper understanding of the mechanism of the amide and α-ketoamide formation, characterisation of the reaction intermediates in the catalytic system had to be attempted. The reaction in Scheme 27 was therefore studied.



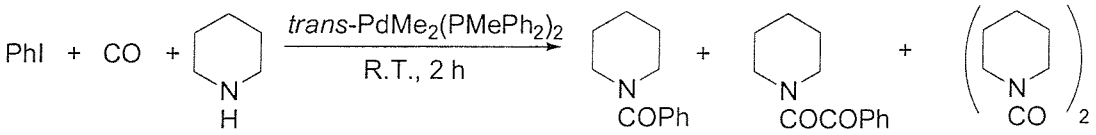
Scheme 27

Benzamide **7a** and α-ketoamide **7b** were formed together with *N,N,N',N'*-tetraethyloxalamide **8** and the presence of the palladium complexes **9a** and **9b** was deduced by NMR. The complex **9c** was isolated from the reaction mixture and treated with PhI in the presence of CO (20 atm) and triethylamine at room temperature. No transformation took place, but reaction was observed with CO (20 atm) in the presence of diethylamine as in Scheme 28.



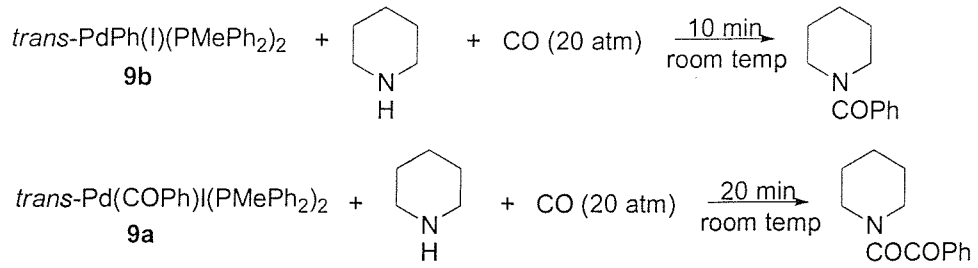
Scheme 28

A mixture of **8** and tetraethylurea **10** was formed. Finally, reaction of **9c** with **9a** did not give any conversion. A system affording predominantly the monocarbonylation product was also examined, as shown in Scheme 29.



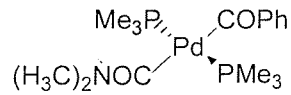
Scheme 29

In this case, NMR-studies indicated that the benzoyl species **9a** was absent, which suggested that this species must be an intermediate in the case of α-ketoamide formation, but for the amide formation, it is not. An investigation of the following reactions between isolated palladium-complexes **9a** and **9b** and piperidine under CO-pressure as in Scheme 30 supported this assumption further.



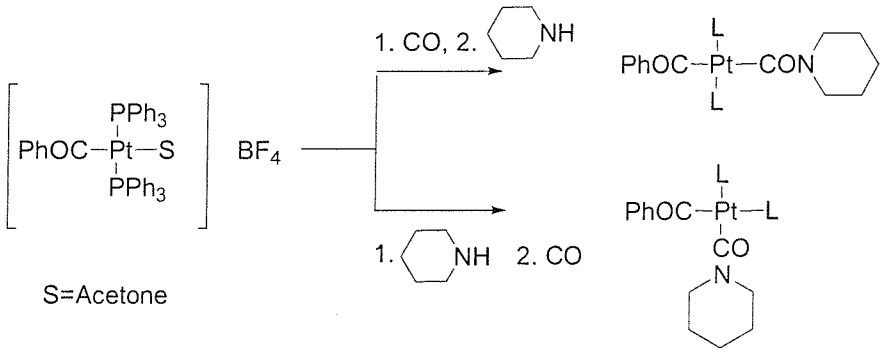
Scheme 30

The formation of single and double carbonylation products was found to be selective, which strongly supported the above assumption. Further insight into the mechanism of double carbonylation was gained by studying the fate of the analogue **11** that undergoes reductive elimination.[27] This part of the catalytic cycle, consisting of attack by the amine on **11** followed by reductive elimination, takes place after the rate-determining step. It is therefore very rapid and identification of this intermediate is not possible. Bulky phosphine ligands favour the dissociation of ligand and reductive elimination, so trimethylphosphine and dimethylamine were used to minimise steric interactions in the preparation of complex **11**, found to be stable in acetone solution.



11

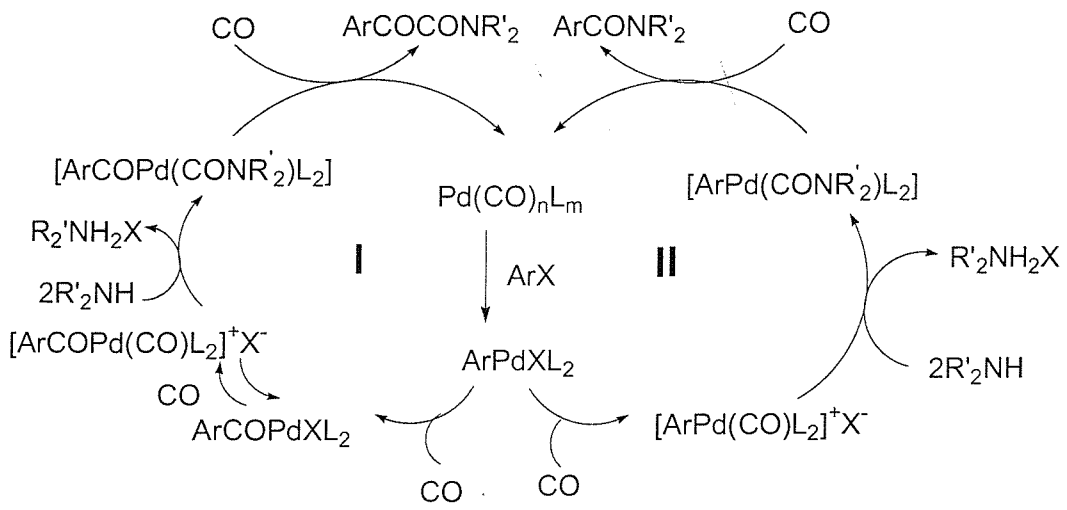
In order for reductive elimination to take place, *cis*-configuration is necessary. Although this study did not give any information about the conversion of **11** to the corresponding *cis*-isomer, a study of the platinum analogues of these complexes showed some very interesting results, as detailed in Scheme 31.



Scheme 31

It was clearly seen that the order of addition influenced the stereochemistry of the complexes. How this feature translates to the mechanism of carbonylation is not yet known.

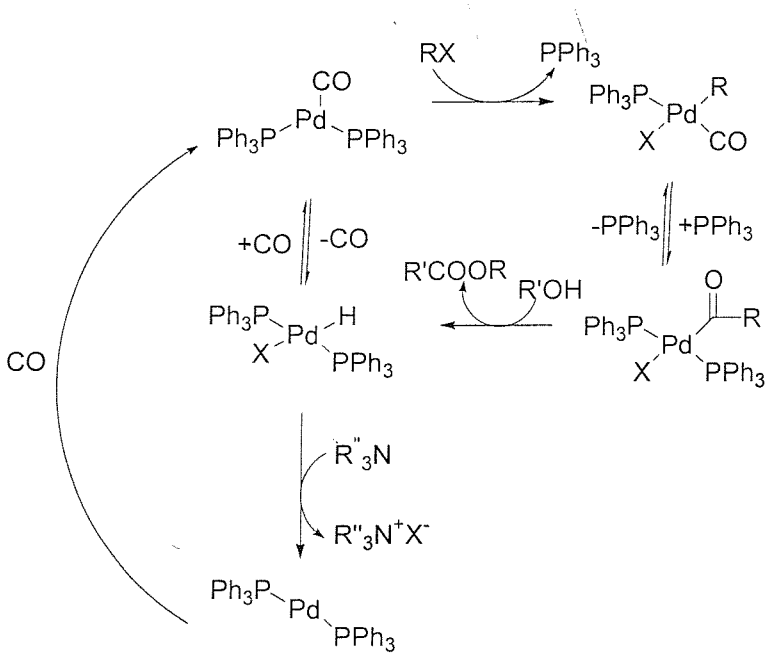
As shown in this brief account on factors governing the outcome of the carbonylation reaction, the mechanisms for the single and double insertion of CO are strictly related. The following catalytic cycle has been proposed on the basis of experimental results[26] and the break point between these two closely related reactions comes with the fate of the oxidative addition product as in Scheme 32.



Scheme 32

1.3.3 Palladium-Catalysed Ester Synthesis

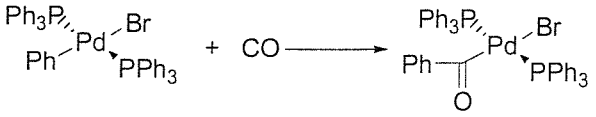
Palladium-catalysed ester synthesis was first described by Heck *et al.*[9] and the reactivity of aryl and vinylic substrates was investigated. Palladium(II) acetate [$Pd(OAc)_2$] was used as the catalyst in a ligandless system and the iodides were found to be the most viable substrates. Electron-poor bromides also reacted and the addition of PPh_3 was necessary in order to use non-activated bromides. In general, electron-poor substrates gave faster reaction than electron-rich iodides or bromides. The mechanism given in Scheme 33 was suggested as the most likely for ester formation in case of both aromatic and vinylic substrates.



Scheme 33

The catalytically active species was thought to arise from the very facile CO-insertion into palladium compounds.[9] A more systematic study of the mechanism has been carried out by Moser *et al.*[29] by Cylindrical Internal Reflectance–Fourier Transform Infrared spectroscopy, (CIR-FTIR), which allowed for the acquisition of *in situ* infrared spectra. In order to obtain a picture of the underlying catalytic cycle, the steps of the mechanism suggested by Heck[9] were repeated on a stoichiometric basis. To make this study feasible, it was assumed that CO is not co-ordinated to the palladium catalyst prior to the oxidative addition step. Firstly, the oxidative addition

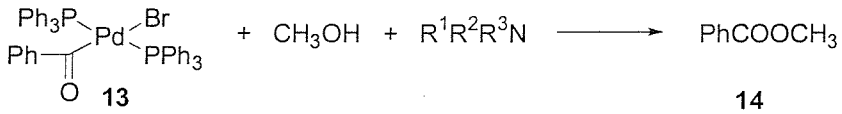
intermediate **12** was synthesised[28] and NMR-data indicated *trans*-configuration of **12**, which was subsequently carbonylated to give the benzoyl complex **13** as in Scheme 34.



12 **13**

Scheme 34

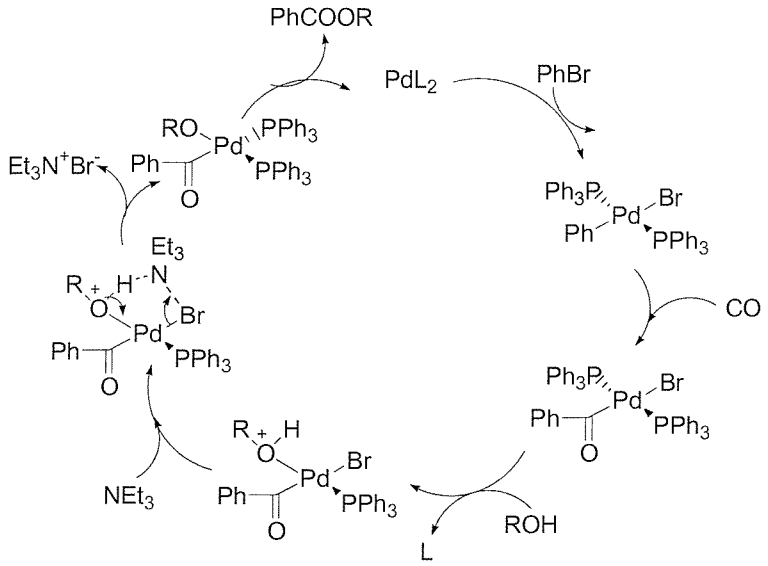
IR-measurements showed a clear signal for the carbonyl group, which did not disappear upon removal of CO and heating under nitrogen for two hours. This result showed that the formation of **13**, also confirmed by NMR-spectroscopy, was irreversible. The fate of **13** was then investigated by reaction with methanol and a range of tertiary amines to give methyl benzoate **14** as shown in Scheme 35.



13 **14**

Scheme 35

The reaction rate was found to increase with the basicity of the amine. Control reactions carried out without addition of amine were very slow compared to the cases where tertiary amine had been added. These results conclusively confirmed the intervention of the amine in the catalytic process and the catalytic cycle shown in Scheme 36 can be envisaged.[28]



Scheme 36

1.3.4 Palladium-Catalysed Synthesis of α-Ketoesters

The α-ketoester synthesis is an important reaction in its own right, but it is also of great interest for the synthesis of α-ketoacids. Whereas hydrolysis of α-ketoamides to the corresponding acid requires harsh conditions, the esters can be easily hydrolysed, providing thus a convenient route to α-ketoacids. The mechanism was studied in depth by Ozawa and co-workers[29] and found to be different from the mechanism of the α-ketoamide/amide formation. Again, the reaction, often leading to a mixture of ester and α-ketoester, can be summarised as in Scheme 37.

$$ArI + 2CO + ROH + Et_3N \xrightarrow{[Pd]} ArCOCOOR + ArCOOR + Et_3NHI$$

Scheme 37

The most important part of this work was done with aryl iodides. The bromides gave much slower reaction and vinyl substrates were found to be completely inert. An investigation of the ligand influence, in which only monodentate phosphine ligands were considered, clearly showed that the selectivity for double carbonylation increased with the bulkiness of the ligand. A ligand : palladium stoichiometry of (2 :

1) gave the greatest selectivity for double carbonylation. Higher phosphine concentrations were found to retard the reaction overall. Temperatures of 60-80 °C were necessary for the reaction to take place at a reasonable rate and high temperature was found to increase the selectivity for single carbonylation. The effect of CO-pressure was also subject to investigation and the outcome given in Table 3.

Table 3 Effect of CO-Pressure on the formation of Esters and α-Ketoesters

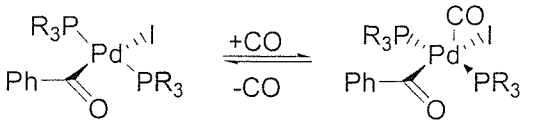
CO (atm)	Ester (%)	α-Ketoester (%)	Total Yield (%)
20	44	14	58
40	36	21	57
60	30	28	58
80	26	31	57

Conditions: PhI (5 mmol), *sec*-BuOH (11 mmol), Et_2N (7.6 mmol), $PdCl_2(PPh_3)_2$ (0.05 mmol), $CHCl_2$ (2 mL) at 70 °C for 48 h.

Although the selectivity was not very pronounced, an increase in CO-pressure did clearly favour double carbonylation.

The effect of the alcohol component was investigated with palladium(II) chloride-*bis*-tricyclohexyl phosphine [$PdCl_2(PCy_3)_2$] as the catalyst precursor. Primary alcohols and metal alkoxides gave mainly single carbonylation whereas secondary substrates of moderate bulkiness gave rise to α-ketoesters predominantly. The solvent was also found to have a marked effect on the outcome; less polar solvents such as dichloromethane (DCM) or benzene afforded mainly α-ketoesters. Polar solvents, for example DMF or acetone, favoured single CO-insertion.

Attention was then turned to the mechanism. Complexes with the general structure **15a**, identified as the main species in the catalytic cycle, were used for this study. Firstly, they were subject to CO pressure and the coordination of CO was found to be reversible by IR-spectroscopy. NMR-studies confirmed that the phosphine ligands remain attached to palladium during the coordination step and that there is a rapid equilibrium between the complexes **15a** and **15b** as shown in Scheme 38.



15a **15b**

Scheme 38

In the mechanistic study of double carbonylation leading to α-ketoamide formation,[26] it could be established that CO-coordinated aroylpalladium complexes undergo nucleophilic attack of secondary amines to give α-ketoamides, whereas amides are formed through attack on arylpalladium complexes. In the ester case, reaction between the complex *trans*-Pd-(COPh)I(PPh_3)$_2$ **16a**, *sec*-BuOH and triethylamine at variable CO-pressure, gave a mixture of the α-ketoester and ester. The relative yield of the double carbonylation product increased linearly with increasing CO-pressure. To gain further understanding of this process, benzoyl-and phenylpalladium iodides were compared for reactivity towards *sec*-BuOH in the presence of triethylamine under CO-pressure. The results are summarised in Table 4.

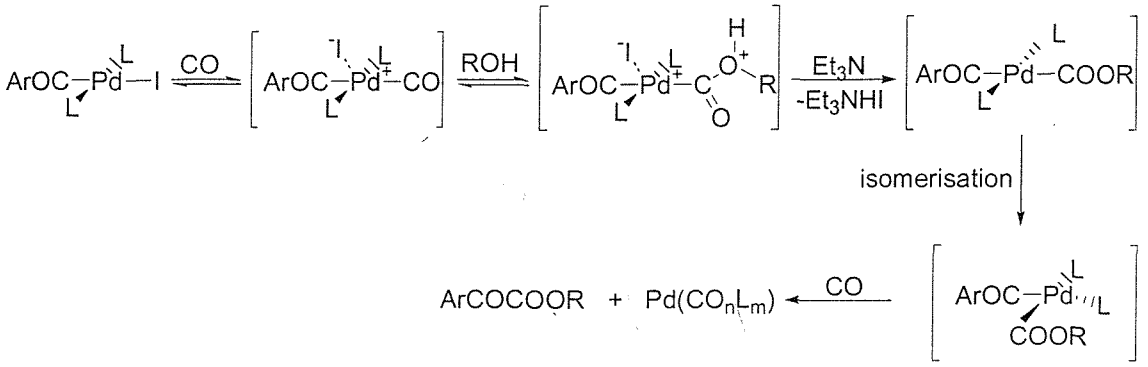
Table 4 Comparison of Reactivities of Benzoyl-and Phenylpalladium Complexes

Complex	CO (atm)	Ester (%)	α-Ketoester (%)	Total Yield (%)
16a	20	10	32	42
16b	20	8	31	39
16a	60	4	54	58
16b	60	4	54	58
16c	20	8	20	28
16d	20	5	17	22
16c	60	2	30	32
16d	60	1	32	33

Conditions: Complex (0.025 mmol), *sec*-BuOH (0.5 mL), Et_3N (0.5 mL), solvent: [CH_2Cl_2 (1.0 mL)+PhCl (0.28 mL)] $PdCl_2(PPh_3)_2$ (0.05 mmol), T=70 °C for 1-2 h.
16a; *trans*-PdPh(I)(PPh_3)$_2$, **16b**; *trans*-Pd(COPh)I(PPh_3)$_2$, **16c**; *trans*-PdPh(I)(PCy_3)$_2$, **16d**; *trans*-Pd(COPh)I(PCy_3)$_2$.

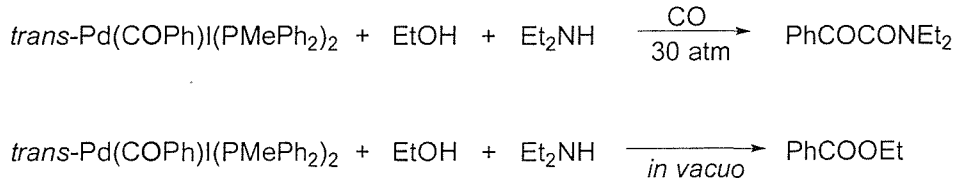
The results shown in Table 4 indicated that the phenyl- and benzoylpalladium complexes had essentially the same reactivity towards *sec*-BuOH in the presence of CO and triethylamine. This observation suggested that the benzoylpalladium intermediate generated by CO-insertion into the phenylpalladium complex was

responsible for the ester as well as α-ketoester formation. It also indicated that CO insertion must be faster than the subsequent reactions to give the reaction products. For α-ketoester formation the following processes illustrated in Scheme 39, can be envisaged.



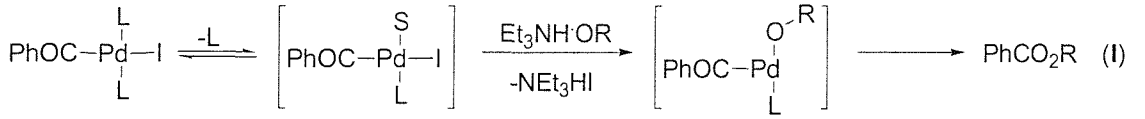
Scheme 39

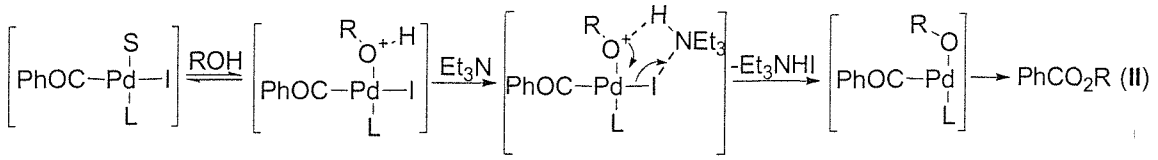
Regarding the ester formation, reaction of the acylpalladium intermediate with alcohols and tertiary amine had so far been assumed to proceed by attack of the alcohol on the acylcarbonyl group. This study showed that more acidic alcohols favour ester formation. An investigation of the competitive reactions, using equimolar amounts of ethanol and diethylamine also gave valuable information, as summarised in Scheme 40.



Scheme 40

The exclusive formation of the ester in absence of CO, in sharp contrast with the result obtained in presence of CO, excluded the possibility of direct nucleophilic attack by the alcohol on the acyl group. Two plausible pathways could account for the ester formation. This is illustrated in Scheme 41.

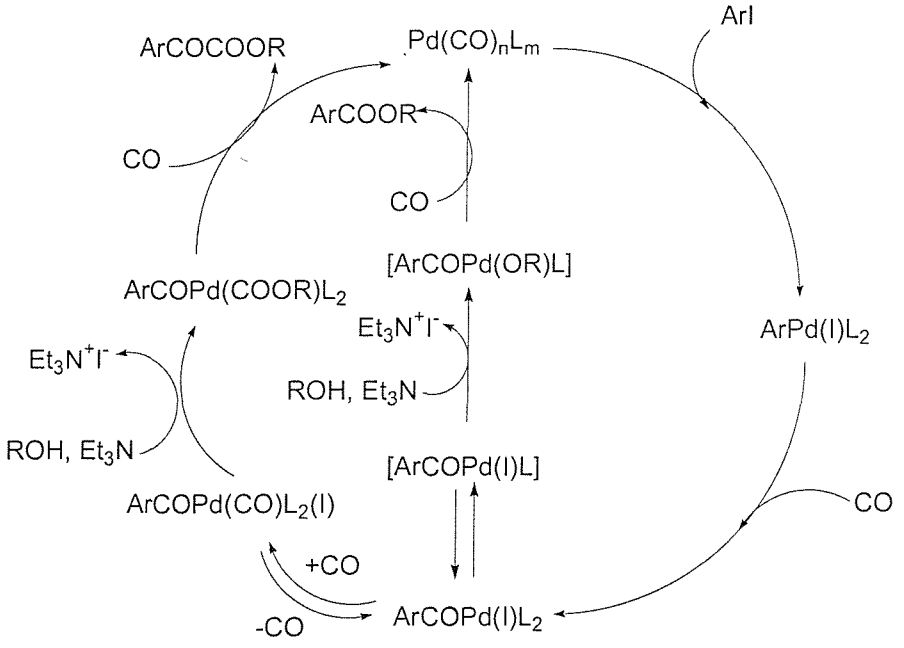




S=Solvent

Scheme 41

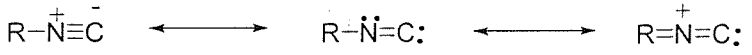
It was, at this stage, not possible to establish unambiguously which of the pathways was responsible for the ester formation. Evidence for the pre-formation of an alkoxide species had been given by Moser *et al.*[28] who investigated the mechanism of ester formation by CIR-FTIR-spectroscopy, previously described in detail. With these results in hand, the intervention of the following catalytic cycle for the formation of esters and α-ketoesters was suggested[29] as in Scheme 42.



Scheme 42

1.4 Insertion of Isonitriles into Palladium-Carbon Bonds

As seen in the previous chapter, CO is a very important one-carbon source, allowing for the palladium-catalysed synthesis of a variety of carbonyl compounds. Isonitriles are electronically equivalent to the carbon monoxide molecule and are stronger σ-donors and weaker π-acceptors than CO. They can be formulated as a hybrid of the following two resonance structures, shown in Scheme 43.

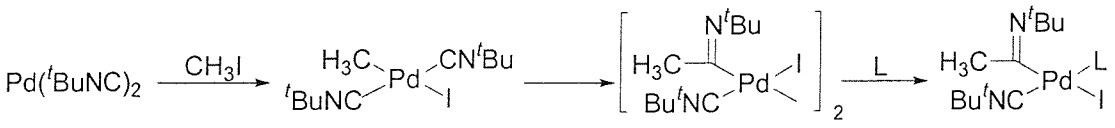


Scheme 43

Isonitriles usually react with organopalladium complexes to give imidoyl compounds and such insertions have been observed with alkyl-, alkynyl-, and other organopalladium complexes. Moreover, double, triple and polyinsertions of isonitriles are known from the literature.[30] These processes can lead to formation of other organopalladium complexes or, by depalladation, to organic compounds.[30] Isonitrile insertion has by no means been as extensively investigated as CO-insertion and there is much less information available. The aim of this chapter is to summarise the most salient mechanistic results and preparative work.

1.4.1 Mechanistic Details of Isonitrile Insertion into the Palladium-Carbon Bond

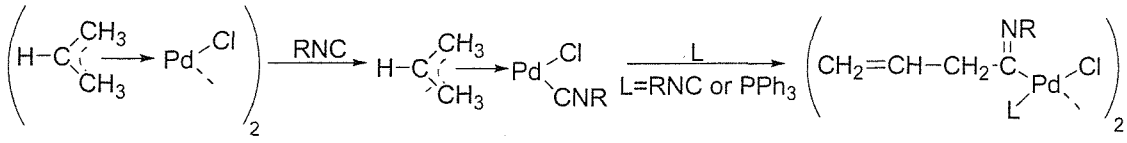
Isonitrile insertion into the palladium-carbon bond was first reported in 1969[31] and investigation of the following reaction established *trans*-alignment of the iodo and σ-iminoacyl groups for the complex **17** as outlined in Scheme 44.



17

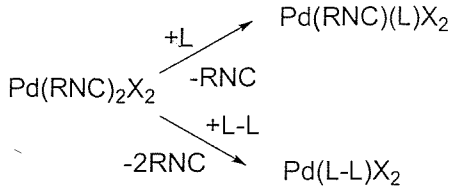
Scheme 44

A more detailed investigation of the influence of the electronic nature of the isonitrile on the insertion into the palladium-carbon bond was performed on the allylic system,[32] where a comparison between *p*-nitrophenyl isonitrile, cyclohexyl isonitrile (CyNC) and phenyl isonitrile (PhNC) was made. The reaction sequence is shown in Scheme 45.



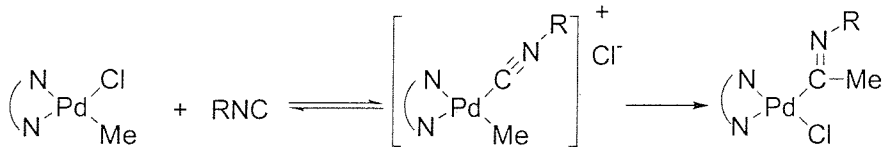
Scheme 45

The insertion reaction was favoured by increasing electron-donating ability of the isonitrile component, giving only marginal insertion for the *p*-nitrophenyl isonitrile. Isonitriles are themselves known to be good ligands to palladium, which was confirmed in a study where $Pd(RNC)_2X_2$-complexes were reacted with neutral monodentate and bidentate phosphines, arsines and pyridine ligands as in Scheme 46.[33]



Scheme 46

Use of the arsines required harsher conditions than the phosphines and very interestingly, only the bidentate ligands were able to displace both isonitrile ligands. Even use of an excess of the monodentate ligands allowed for displacement of only one isonitrile unit, whereas pyridine and bipyridine ligands did not give any isonitrile displacement. In one interesting study, isonitrile insertion was performed into palladium-carbon bonds of complexes containing bidentate nitrogen ligands,[34] as shown in Scheme 47.

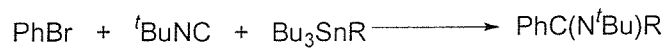


Scheme 47

Only single insertion of the isonitrile was observed and the formation of a cationic intermediate was supported by conductivity measurements of the reaction mixtures. The rate of migration of the methyl group was found to be faster for more electrophilic isonitriles.

1.4.2 Palladium-Catalysed Three-Component Couplings with Isonitriles

As seen in the first part of the carbonylation chapter, several compound classes are accessible through three-component couplings with CO as the carbenoid fragment. Not many cases of the corresponding reactions employing isonitriles are known, though potentially very valuable. One of the main reasons is the tendency of isonitriles to cause multiple insertions to transition metal complexes,[35] which leads to isonitrile polymers. Isonitriles have been found to insert stepwise into metal-carbon bonds and sterics of the R-group in the RNC-structure often plays an important role in determining the multiplicity of the insertion. The first example of successful three-component couplings with *tert*-butyl isonitrile (^{t}BuNC) was reported in a communication by Kosugi *et al.*[36] and can be summarised as in Scheme 48.



Scheme 48

Tributyltin derivatives of the nucleophiles R were used, and the results are shown in Table 5.

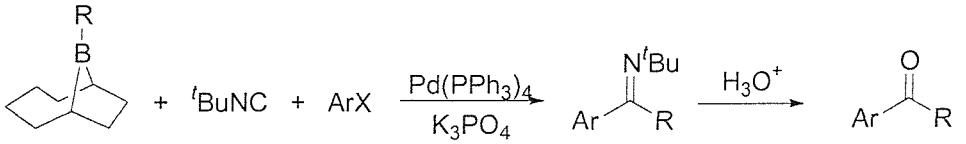
Table 5 Palladium-Catalysed Reaction of Bromobenzene with Organotin Compounds and ^{t}BuNC

Bu_3Sn-R	Product	Yield GC(%)
-OMe	PhC(=N^{t}Bu)OMe	63
-OEt	PhC(=N^{t}Bu)OEt	48[a]
-NEt_2	PhC(=N^{t}Bu)NEt_2	22
-SPh	PhC(=N^{t}Bu)SPh	10
-$CH_2CH{=}CH_2$	PhC(=N^{t}Bu)$CH_2CH{=}CH_2$	trace
-$CH{=}CH_2$	PhC(=N^{t}Bu)$CH{=}CH_2$	trace
-$C(OEt){=}CH_2$	PhC(=N^{t}Bu)$C(OEt){=}CH_2$	30
-C≡CPh	PhC(=N^{t}Bu)C≡CPh	52, 40[a]
-CN	PhC(=N^{t}Bu)CN	61[b]
-Ph	$Ph_2C{=}N^tBu$	0
-H	PhCH=N^{t}Bu	0

Conditions: PhBr (1.0 mmol), Bu_3SnR (1.2 mmol), ^{t}BuNC (1.5 mmol), $[Pd(PPh_3)_3]_4$ (0.1 mmol), heating in sealed tubes at 120 °C for 20 h.

a. Isolated yield, b. PhI instead of PhBr.

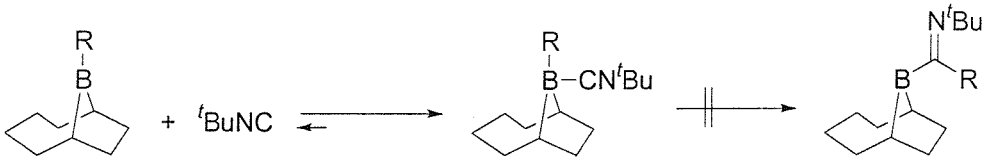
As seen, a wide variety of nucleophiles were screened and the tin compounds with the more polarised Sn-R bonds gave the best results. Use of tin compounds is inconvenient because of their toxicity and hydrolysis sensitivity, but these results were nevertheless very important in this context. More recently, a three-component coupling of haloarenes, ^{t}BuNC and 9-alkyl-9-BBN derivatives has been described[37] as in Scheme 49.



Scheme 49

Interestingly, the isonitrile was used as a synthon for CO and the alkyl-9-BBN compounds were generated *in situ* by hydroboration of the corresponding alkenes. Palladium(II) catalyst precursors were not effective and the isonitrile stoichiometry was found to be of fundamental importance. Equimolar amounts of ^{t}BuNC and BBN-complex gave the best results, whereas excess of isonitrile prevented the reaction from taking place. It is not known why excess isonitrile inhibits the reaction, but treatment of 9-octyl-9-BBN with ^{t}BuNC, followed by IR-spectroscopy, gave a boron-

isonitrile complex that may work as a buffer stock to reduce the concentration of free isonitrile to a minimum as illustrated in Scheme 50.



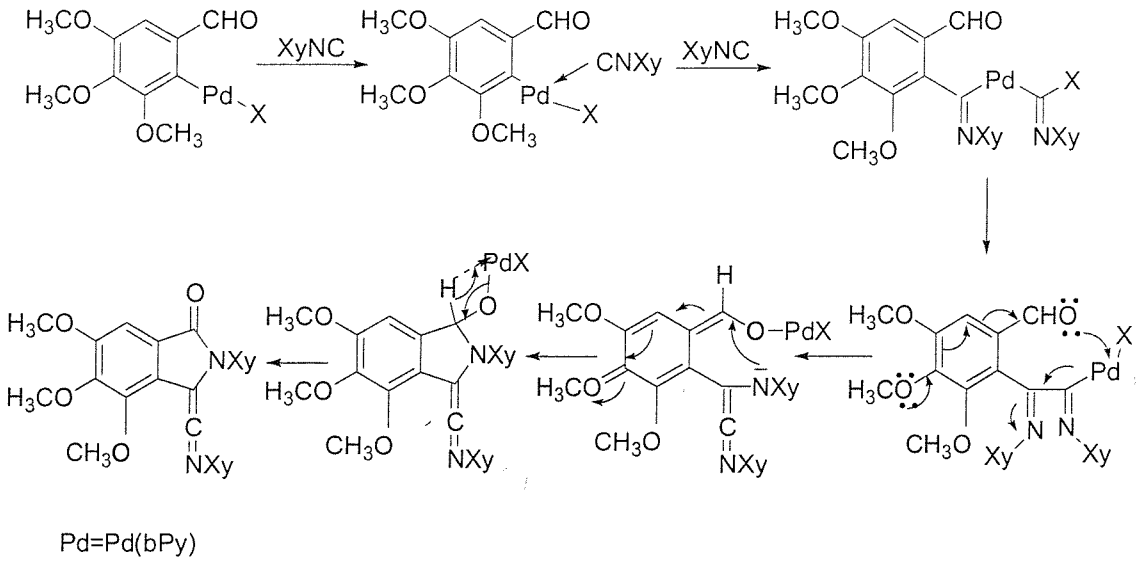
Scheme 50

Iodoarenes were found to be the best substrates and yields were in the range of 48-97%.

In the current piece of work, the synthesis of amidines,[38, 39] imidates,[39] thioimidates[39] and α-iminoimidates has been investigated in more depth with the results of Kosugi[36] as background. For amidine synthesis, the conditions using tin amides first had to be optimised to give quantitative GC-yields, then a methodology based on Hartwig's and Buchwald's chemistry,[40] avoiding the use of tin synthons, was developed. These results will be discussed in more detail in the *Results and Discussion* section.

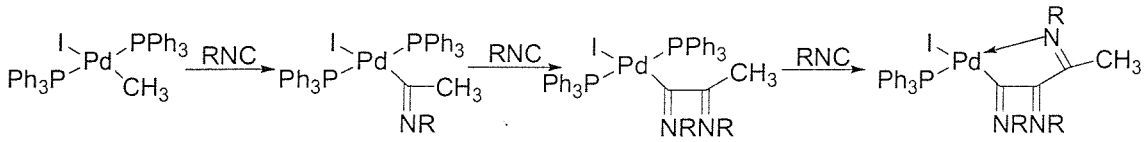
1.4.3 Multiple Insertion of Isonitriles into the Palladium-Carbon Bond

The facile insertion of isonitriles into the palladium-carbon bond easily allows for the insertion of more than one isonitrile unit. This section will give examples of double, triple and multiple isonitrile insertion. Double insertion of isonitriles followed by depalladation to give organic compounds has, to our knowledge, so far been described only for the synthesis of ketenimines[41] as summarised in Scheme 51.



Scheme 51

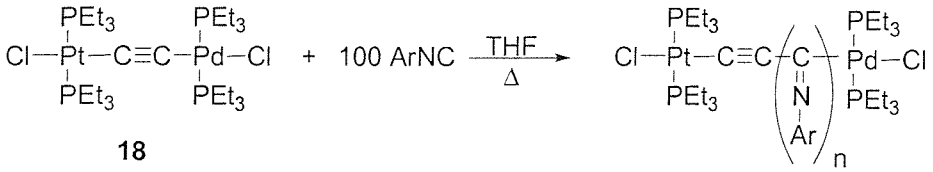
Controlled triple insertion of isonitriles is known from the literature[42] from a study in which the reactivity of *ortho*-substituted phenyl isonitrile to alkyl and phenyl palladium complexes was examined. The reaction is given in Scheme 52.



Scheme 52

No further isonitrile insertion took place, possibly because of the formation of the stable five-membered chelate complex.

The main interest for polyisonitriles lies in their unique properties due to their rigid helical structure.[43] The heterodinuclear μ-ethynediyl complex **18** was found to catalyse the polymerisation of aryl isonitriles[43] described in Scheme 53.



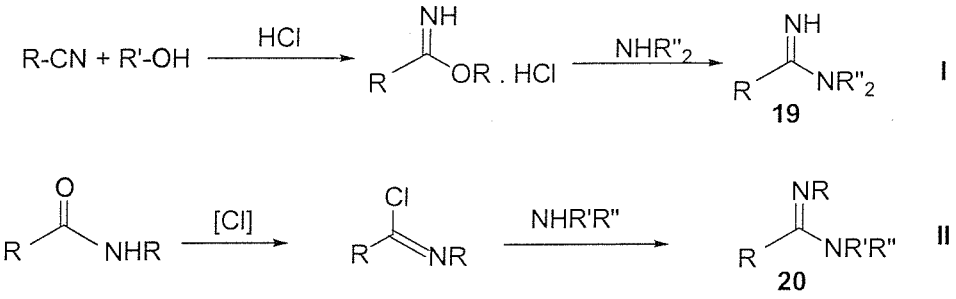
Scheme 53

The reaction worked well for phenyl, *p*-nitrophenyl and *p*-tolylisonitrile. 2,6-xylyl isonitrile gave only double insertion due to steric hindrance. Characterisation of the polymeric materials was made difficult by their insolubility in organic solvents, which was improved by the introducing alkyl chains on the phenyl ring of the isonitriles. Characterisation by spectroscopic techniques and Gel Permeation Chromatography (GPC) showed that the obtained polymers had a very narrow distribution of molecular weights.

2. Palladium-Catalysed Amidine Formation from Tin Amides, Aryl Halides and Isonitriles

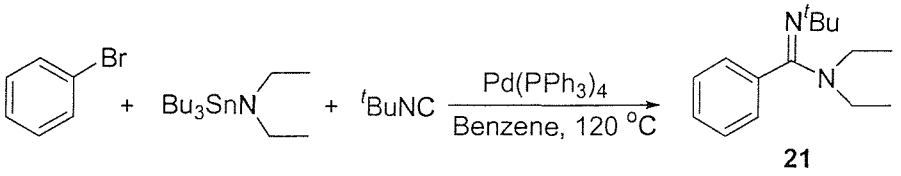
2.1 Introduction

The synthesis of amidines with general structure **19** and **20** has classically been accomplished by routes involving moisture-sensitive imidoyl esters **I** or imidoyl chlorides[44] **II** and these methodologies require more than one step. The second route is known as the Pinner synthesis[45] when ammonia is used as the amine. This chemistry is summarised in Scheme 54.



Scheme 54

A one-pot procedure for the synthesis of amidines with the general structure **19** and **20** would therefore be of great interest. In this piece of work, we have focused our efforts on the development of a one-pot procedure for the synthesis of tertiary amidines **20**. The only example in the literature of this type of reaction was described by Kosugi *et al.*,[36] where the amidine **21** was formed in 22% yield (by GC). The reaction is shown in Scheme 55.

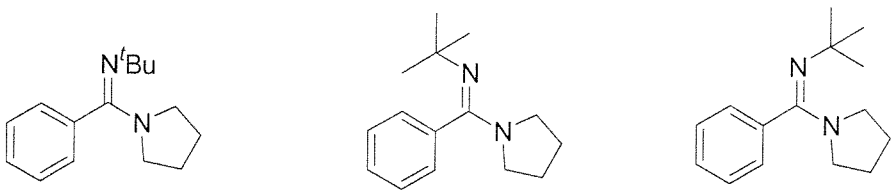


Scheme 55

This chapter will account for the optimisation of the original reaction and a mechanism for the catalytic cycle will also be proposed.

2.2 Optimisation of the Catalytic Cycle for Amidine Formation

In order to improve the yield of the palladium-catalysed reaction in Scheme 55, some modifications were implemented. To start with, two fixed parameters were changed; the more reactive 1-(1,1,1-tributylstannyl)pyrrolidine **22** was synthesised[46] and used instead of the diethylamine analogue. In the original paper,[36] $Pd(PPh_3)_4$, was used as catalyst and the second modification was to generate the catalytically active $Pd(0)L_2$-species *in situ* from tris-(dibenzylideneacetone)dipalladium(0) chloroform, ($Pd_2DBA_3.CHCl_3$) by adding it to the reaction mixture together with the appropriate phosphine ligand. This modification allowed for the easy screening of different phosphine ligands. The amidine found to correspond to the *E*-isomer **23a** was synthesised according to the literature[47] to be used as GC-standard. Later studies of the tin-free system for amidine synthesis showed that the stereochemical outcome was different when synthesis of the same compound was performed by a palladium chemistry, which gave the same amidine in *Z*-conformation, **23b**. These results based on NMR-observations and theoretical calculations are discussed in detail in paragraph 3.6. The amidine **23** was not isolated when investigating the tin system, so no information about the stereochemistry of the *tert*-butyl group is available in this case. Different steric requirements of the tin amide compared to the free amine used in the tin-free system could influence the stereochemical outcome, so throughout this chapter reference is made to the general structure **23** with undefined stereochemistry of the *tert*-butyl group. The different configurations are given in Figure 1.

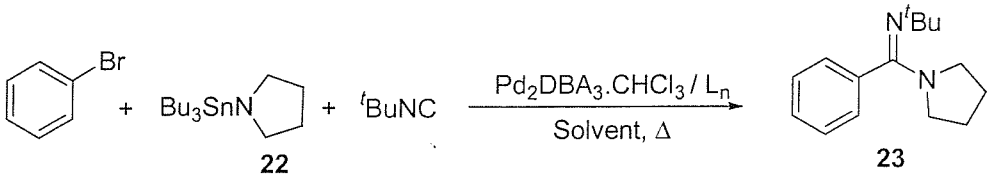


23 23a 23b

Figure 1

One very interesting observation was the possibility of quantitatively and irreversibly isomerise **23a** to **23b** in presence of aqueous acid.

N-Phenylpyrrolidine, which would be the arylamine resulting from the two-component coupling between PhBr and pyrrolidine was also synthesised according to the literature[48] to be used as GC-reference but it did not form in the investigated reactions. The investigated variable parameters were the influence of ligands, solvents, tin amide and temperature. The model system subject to optimisation is shown in Scheme 56.



22 23

Scheme 56

2.2.1 Influence of the Phosphine Ligand

Phosphine ligands can be either monodentate or bidentate. The former consist of single PR_n units and require a ligand : palladium-ratio of 2 : 1 to form the catalytically active PdL_2-species and the decay of the bulky, unstable intermediates **24** is a factor which promotes the reductive elimination step. In the latter case the ligand molecule consists of two phosphine groups, separated by a spacer. Therefore the ligand : Pd-ratio 1 : 1 gives the active intermediate **25**. Two important factors have to be considered in this case; the angle between the phosphine groups (*bite angle*) and the angle between the Pd and the phosphine (*cone angle*). These two factors determine the optimum angle of attack on the intermediates of the catalytic

cycle and when carrying out optimisation work, it is important to try ligands with a range of bite angles. Figure 2 shows general forms of the PdL_2-intermediates.

24 **25**

Figure 2

The use of bidentate, chelating ligands has in many ways revolutionised palladium chemistry in terms of scope and limitation. An important example thereof is given in the development of Hartwig and Buchwald's palladium-catalysed synthesis of arylamines.[40] For this reason it is important to use a selection of monodentate and bidentate ligands for the optimisation. PPh_3, *tris*(*o*-tolyl)phosphine [P(*o*-Tol)$_3$], dppf, 1,1'-*bis*(diphenylphosphino)ethane (dppe) and dppp were chosen for this purpose. Firstly, the ligand : palladium ratio was briefly for investigated for [P(*o*-Tol)$_3$] and dppf by trying reactions with ratios of (1 : 1) and (2 : 1). With [P(*o*-Tol)$_3$] the GC-yields were of 6% and 9% respectively, whereas use of dppf gave GC-yields of 23% and 34%, indicating that better results were obtained with a (2 : 1)-ratio. The full range of ligands was then tried and the results are given in Table 6.

Table 6: Effect of Phosphine Ligands in the Formation of 23

Ligand	Res. PhBr, (%)			23, (GC, %)		
	2 h	8 h	24 h	2 h	8 h	24 h
P(*o*-Tol)$_3$	84.6	48.3	24.0	7.4	27.2	24.0
"	80.9	51.4	35.3	11.2	20.1	26.8
PPh_3	91.3	46.8	15.1	2.6	33.8	32.4
"	88.0	39.6	29.2	7.0	30.2	37.9
dppe	89.7	70.1	22.2	2.0	61.3	22.2
"	86.0	81.3	16.9	6.2	20.4	48.3
dppf	83.6	38.1	0	6.1	60.9	92.3
"	80.1	33.3	3.4	9.4	50.3	86.1
dppp	93.3	80.0	17.6	1.7	22.2	57.6
"	96.1	78.3	20.0	0	31.1	64.0

Conditions: PhBr (0.2 mmol), **22** (0.24 mmol), ^{t}BuNC (0.3 mmol), Ligand (10 mol%), $Pd_2DBA_3.CHCl_3$ (2.5 mol%), Toluene (2 mL). T=109 °C. Reactions carried out in duplicate.

From the results given in Table 6 it could be shown that the bidentate ligands gave the best results. The monodentate ligands P(*o*-Tol)$_3$ and PPh_3 gave very similar results, though less satisfactory than the bidentate ligands. The ligands dppe and dppp are air-sensitive and therefore more difficult to handle than dppf, which is, on the other hand the most expensive of these three bidentate ligands. The better result when using dppf and its greater stability made it the ligand of choice, in spite of cost. The next step in the optimisation procedure was to investigate the effect of the solvent.

2.2.2 Influence of the Solvent

The choice of solvent plays a fundamental role in palladium chemistry. Apart from the effects of different boiling points and solubility of the reactants, the electronic co-ordinating effect of solvent molecules like THF, dioxane and DMF with the catalyst can often lead to changes in reactivity.[49] Toluene, benzene, dioxane, DMF and THF were all investigated and the results are given in Table 7.

Table 7: Influence of the Solvent on the Formation of 23

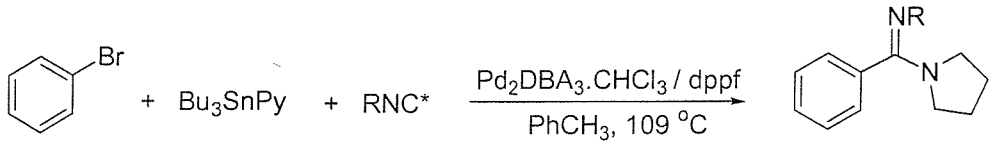
Solvent	Ligand	Res. PhBr, (%)			23, (GC, %)		
		1 h	8 h	24 h	1 h	8 h	24 h
Toluene	PPh_3	91.8	65.2	40.2	1.8	27.2	25.1
"	"	88.3	64.8	48.6	4.3	23.7	26.0
Toluene	dppf	94.6	47.0	0	1.6	40.0	82.1
"	"	92.3	39.8	0	4.2	42.4	86.4
Benzene	PPh_3	90.4	69.8	9.6	3.3	69.8	9.6
"	"	95.2	81.0	17.8	0.8	10.0	53.7
Benzene	dppf	86.9	38.4	0	7.9	59.3	100
"	"	94.2	32.7	0	2.4	60.0	93.1
Dioxane	PPh_3	97.8	80.1	32.9	0	12.2	30.9
"	"	91.6	77.9	41.0	0	13.3	28.7
Dioxane	dppf	94.4	58.3	5.0	2.4	29.1	60.8
"	"	89.2	69.4	11.2	5.3	22.1	58.4
DMF	PPh_3	98.1	21.7	15.4	0	12.4	32.3
"	"	96.3	75.8	10.3	0	12.6	27.8
DMF	dppf	94.2	57.6	8.4	2.2	22.4	69.1
"	"	89.0	68.8	10.2	5.0	17.8	75.8
THF*	PPh_3	-	-	86.4	-	-	0
"	"	-	-	92.0	-	-	0
THF*	dppf	-	-	0	-	-	100
"	"	-	-	0	-	-	100

Conditions: PhBr (0.2 mmol), **22** (0.24 mmol), ^{t}BuNC (0.3 mmol), Ligand (10 mol%), $Pd_2DBA_3.CHCl_3$ (2.5 mol%), Solvent (2 mL). T=109 °C. (*) Reactions carried out in sealed tubes from which permanent gasses had been removed. All reactions performed in duplicate.

As described in section 2.2.1, the ligand : palladium-ratio (2 : 1) gave rise to better results and was therefore taken as standard conditions at this stage of the optimisation. Due to the completely different nature of the bidentate dppf and monodentate ligands such as PPh_3, it was of interest to try both with the full range of solvents. As seen in Table 7, dppf gave the best results with all solvents, of which benzene and THF gave the most satisfactory results. It was desirable to avoid benzene because of its toxicity and THF, which gave quantitative conversion when employing dppf, had the disadvantage of requiring the use of sealed tubes. The reaction with THF was also attempted at 65 °C, but GC-analysis indicates that no conversion was taking place. Therefore it was decided to take toluene as the standard solvent.

2.2.3 Use of other Isonitriles

Once established the optimum conditions for the reaction with ^{t}BuNC, it was desirable to extend the scope of the methodology to include the use of other isonitriles for the amidine synthesis. *n*-Butyl isonitrile (*n*-BuNC), benzyl isonitrile (BnNC), CyNC and PhNC were tried. Again, the corresponding amidines were synthesised[44] and used as GC-standards for calibrations against C_{13}. Repeated attempts to perform these syntheses as one-pot reactions failed, giving conversions below 5%. GC-analysis of the reactions showed that the isonitriles disappeared with time, whereas the ratio between the internal standard and PhBr changed very little. It was believed that the successful insertion of ^{t}BuNC compared to the other isonitriles was due to its greater bulk, making it more stable towards polymerisation. Another hypothesis was that the isonitriles could deactivate the palladium catalyst by complexation. In the cases of BnNC and PhNC, the lack of success could also have been due to their thermal instability. In order to improve these results, slow addition of the isonitriles with a syringe pump was performed to keep the isonitrile concentration low, but to a limited success. The reactions were carried out as in Scheme 57.

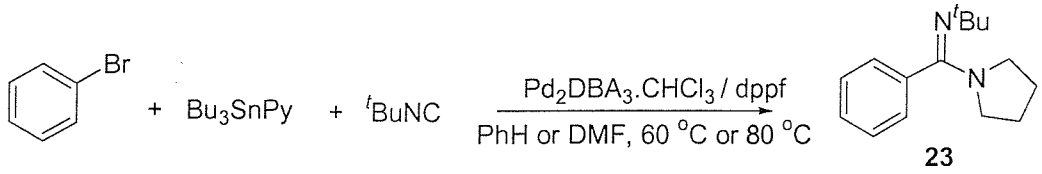


26: R=Cy
27: R=Bn

*RNC added over 13 h

Scheme 57

CyNC and BnNC gave rise to the expected products **26** and **27** in GC-yields of 42% and 36% respectively. No product formation or conversion of PhBr was observed when using *n*-BuNC and PhNC and the isonitriles disappeared with time. Believing that the problems were due to polymerisation of the isonitriles, the possibility of performing the reactions at lower temperature was considered. Benzene and DMF were tried and initial experiments to optimise the new conditions were performed with ^{t}BuNC as in Scheme 58.



Scheme 58

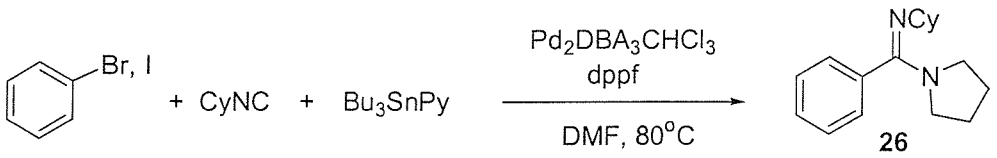
At 60 °C, no conversion of starting materials took place even after 24 h. The reaction was then investigated at 80 °C and the results are summarised in Table 8.

Table 8: Influence of the Solvent on the Formation of 23 at Lower Temperature

Solvent	Time (h)	Res. PhBr (%)	23, (GC, %)
DMF	19	31.2	65.3
	46	0	100
Benzene	24	93.8	0
	47	80.4	7.4
	61	71.9	7.3
	84	60.4	7.6
	174	46.3	6.8

Conditions: PhBr (0.2 mmol), **22** (0.24 mmol), ^{t}BuNC (0.3 mmol), dppf (10 mol%), $Pd_2DBA_3.CHCl_3$ (2.5 mol%), DMF or PhH (2 mL). T=80 °C.

DMF proved to be the best solvent at 80 °C and when 1 eq of dppf was used instead of 2 eq, the conversion stopped at 60%. The optimum conditions were then applied for the synthesis of the *N*-cyclohexylamidine **26** from PhBr as well as PhI by mixing all the components and slow isonitrile addition was also tried. Scheme 59 summarises this chemistry.



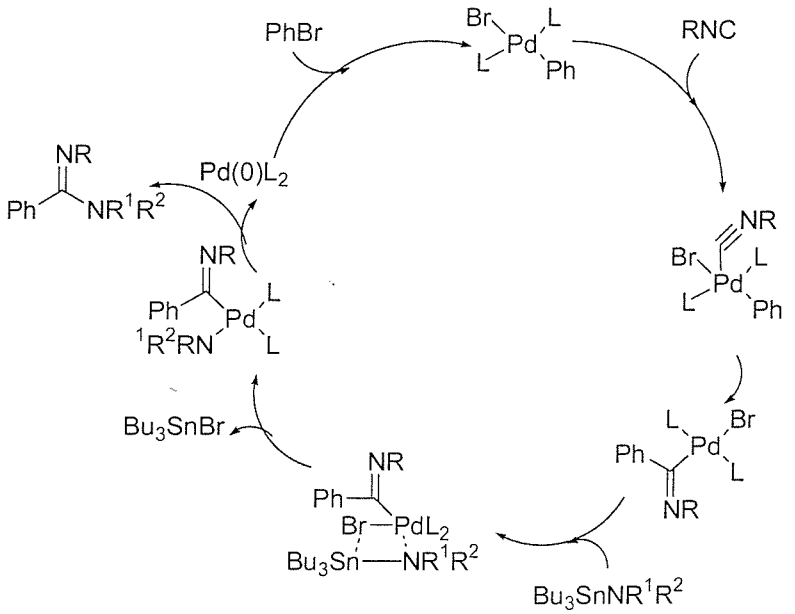
Scheme 59

No reaction was observed, but the possibility of successfully carrying out the synthesis of **23** at a lower temperature than 109 °C is valuable. In conclusion CyNC and BnNC still had to be added by a syringe pump at 109 °C in toluene in order to

get insertion. The fate of the isonitrile has not been established and detailed investigations as described in the introduction would need to be performed.

2.3 Mechanistic Studies

The palladium-catalysed amidine synthesis can be viewed as a Stille coupling[4] in which the oxidative addition product is trapped with a carbenoid (isonitrile) before the reductive elimination step, as schematically outlined in the introduction. The mechanism for palladium-catalysed amidine formation has not yet been described in the literature. Considering the Stille coupling together with the palladium-catalysed carbonylation and isonitrile insertion mechanisms previously described, a plausible mechanism can be outlined as in Scheme 60.



Scheme 60

The steps are as follows:

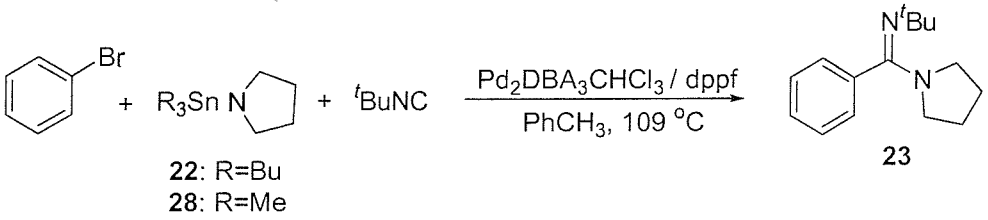
1. Oxidative addition of PhX to the $14e^-$ $Pd(0)L_2$-species gives a $16e^-$ palladium(II)-intermediate

2. Isonitrile insertion gives an unstable $18e^-$ palladium(II)-intermediate, which undergoes migratory insertion into the Pd-Ph bond to give a stable $16e^-$ palladium(II)-intermediate.

3. Transmetallation from tin to palladium in a concerted fashion, with formation of tributyltin bromide as a by-product.

4. Reductive elimination to give the amidine and re-generation of the $Pd(0)L_2$-catalyst

Although it has not been possible to carry out a complete mechanistic study, some preliminary conclusions can be drawn from the experimental work. Firstly, it was of interest to establish whether the transmetallation step is rate determining, which was done by comparing the effect **22** and its trimethyl analogue 1-(1,1,1-trimethylstannyl) pyrrolidine **28**.[46] The reaction is shown in Scheme 61.



Scheme 61

The latter is expected to give faster reaction if the transmetallation step is rate determining. By monitoring the reactions by GC with C_{13} as internal standard, the results shown in Table 9 were obtained.

Table 9: Effect of the Tin Amide on the Reaction Time in the Formation of 23

Time (h)	Res. PhBr, (%)		23, (GC, %)	
	28	**22**	**28**	**22**
0.5	97.9	98.4	4.1	0
1	85.4	96.3	12.8	0
1.5	75.3	95.4	23.3	0
2	52.4	92.8	50.4	4.7
2.5	19.8	89.3	77.6	7.1
3	4.2	84.2	97.9	10.4
3.5	1.5	78.7	100	16.2
8	-	33.1	-	57.4
12	-	9.3	-	79.8
24	-	0	-	84.1

Conditions: PhBr (0.2 mmol), **22** or **28** (0.24 mmol), ^{t}BuNC (0.3 mmol), dppf (10 mol%), $Pd_2DBA_3.CHCl_3$ (2.5 mol%), Toluene (2 mL). T=109 °C.

The reaction profiles with the tin amides **22** and **28** are shown in Figure 3.

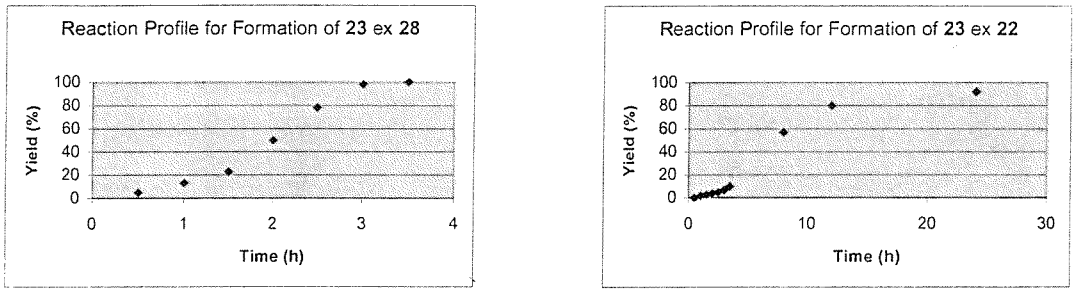
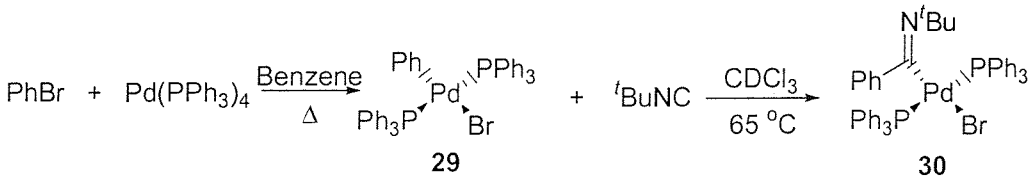


Figure 3

It is clearly seen that use of the trimethyl analogue gives a higher reaction rate, proving that the transmetallation is the rate-limiting step of the catalytic cycle. One common feature is an apparent induction period of the reactions; in both cases the profile was sigmoid, indicating that the reaction is very slow at the start. This may mean that the slow formation of a catalytically active species is necessary for the reaction to take place. Some more insight into the mechanism was gained by generating the oxidative addition intermediate **29** according to the literature[28] and reacting it with ^{t}BuNC to give **30** as in Scheme 62.



Scheme 62

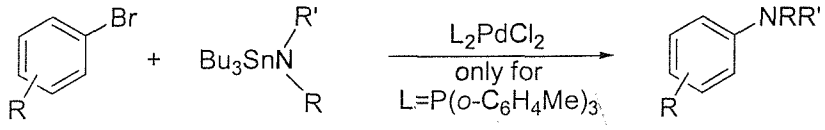
The experiment was carried out in an NMR-tube and analysed after 0.5, 1.5, 2.5 and 3.5 hours. It was observed that the isonitrile had already inserted after 0.5 h, which indicated that the isonitrile insertion step is fast. The synthesis of **29**, which required 20 h in refluxing benzene, could indicate that the oxidative addition step is slow. This data cannot be used for definite conclusions, as it does not mimic the chosen reaction system for the catalyst and palladium source. Another factor that may govern the kinetics of the catalytic cycle is the use of $Pd_2DBA_3.CHCl_3$ as the palladium(0)-source. It has generally been assumed that the dibenzylideneacetone (DBA) units of the complex are spectator ligands once replaced by the phosphines. Recent investigations of the Heck reaction[50] show that these BA-units do indeed compete with the phosphine ligands for the vacant sites of palladium, which may slow down the reaction. The conclusions to be drawn from this brief investigation of the mechanism are:

- The isonitrile insertion is fast
- The transmetallation step is rate-determining

3 Development of a Tin-Free System for Amidine Synthesis

3.1 Introduction

In 1983, Kosugi *et al.*[51] described a palladium-catalysed two-component coupling reaction for the synthesis of arylamines by reacting PhBr and a tin amide as shown in Scheme 63.



Scheme 63

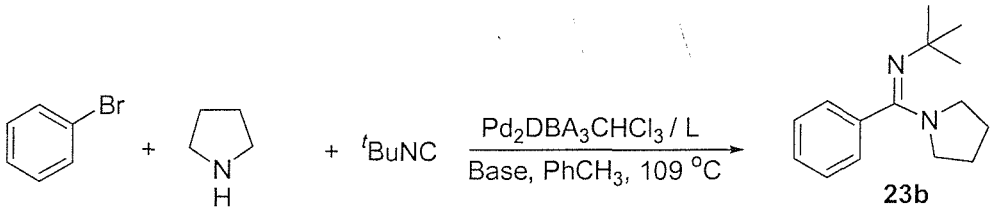
The main limitation of this methodology was the use of tin amides as synthons for the amines. In the mid-nineties, Hartwig and Buchwald[40] developed a method using the free amine and a base instead of the tin amide, avoiding the use of tin and extending the scope of the arylamine synthesis. With the tin-based methodology for amidine synthesis established, the next objective was to develop a tin-free methodology.

3.2 Optimisation of the Catalytic Cycle for Amidine Formation

The establishment of the tin-free system was acquired through investigation of the effect of the base, ligands, palladium source and solvents. Firstly, it was necessary to optimise the reaction with respect to the base, which was the new parameter in this system. Due to the novelty of this reaction, once the optimum conditions for any one parameter had been established, reinvestigation of other aspects of the methodology often became necessary.

3.2.1 Influence of the Base

The logical approach was to translate the tin system as closely as possible to a tin-free version. In the development of a palladium-catalysed tin-free system for the synthesis of arylamines, caesium carbonate (Cs_2CO_3) and sodium *tert*-butoxide, (NaO^tBu) gave rise to the best results.[40] The first step was to investigate the effect of two different bases as well as excess of pyrrolidine. The effect of two inherently very different ligands dppf and PPh_3 was also investigated in the synthesis of **23b**. The chemistry is summarised in Scheme 64 and the results are given in Table 10.



Scheme 64

Table 10: Ligand and Base Optimisation for the Synthesis of 23b

Ligand	Base	Res. PhBr, (%)		**23b**, (GC, %)	
		6 h	18 h	6 h	18 h
dppf	Cs_2CO_3	69.6	32.5	5.9	48.1
"	"	88.7	38.5	8.0	43.2
PPh_3	Cs_2CO_3	86.4	33.6	5.0	38.4
"	"	79.8	36.3	11.4	44.9
dppf	NaO^tBu	69.9	51.4	18.9	32.7
"	"	75.9	49.0	10.8	27.6
PPh_3	NaO^tBu	76.6	38.1	12.2	38.6
"	"	70.4	51.2	14.4	29.8
dppf	Pyrrolidine (2 eq)	95.2	89.1	0	0
"	"	100	88.0	0	0
PPh_3	Pyrrolidine (2 eq)	94.3	80.4	0	0
		92.0	87.1	0	0

Conditions: PhBr (0.2 mmol), Pyrrolidine (0.24 mmol=1 eq) or (0.48 mmol=2 eq), base (0.24 mmol), ^{t}BuNC (0.3 mmol), ligand (10 mol%), $Pd_2DBA_3.CHCl_3$ (2.5 mol%), Toluene (2 mL). T=109 °C. The reactions were performed in duplicate.

The best results were obtained by use of Cs_2CO_3 in combination with dppf, as depicted in Table 10. It is interesting, though somewhat unexpected, that the excess of

amine did not lead to any of the desired reaction. It has to be emphasised that the results were often variable, which could be traced back to the quality of the Cs_2CO_3, whose dryness was of fundamental importance for the reaction to proceed with good yield.

3.2.2 Influence of the Palladium Source

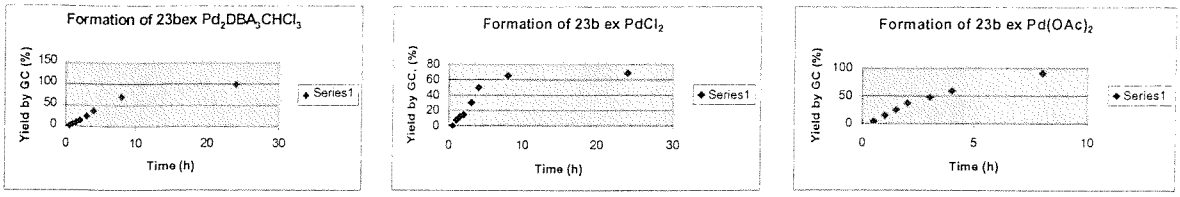
So far, only the palladium(0) source $Pd_2DBA_3.CHCl_3$ had been considered. In theory, it should allow for the facile formation of the catalytically active $Pd(0)L_2$-species in presence of an appropriate phosphine ligand L. It is well-known that palladium(II) sources can be reduced to palladium(0) *in situ*[52] and be used as catalyst precursors. It was therefore of interest to investigate the influence of palladium(II) sources. The palladium(II)-salts palladium dichloride ($PdCl_2$) and palladium acetate [$Pd(OAc)_2$] were tried as well as the palladium(II) catalyst precursor 1,1'-*bis*[(diphenylphosphino)ferrocene]dichloropalladium ($PdCl_2$dppf). Whilst examining the various palladium sources, the influence of the stoichiometry of the amine component was also investigated. The results are summarised in Table 11.

Table 11: Effect of Palladium Source on the Tin-Free System

Pd-Source	Ligand	Eq. Pyrrolidine	Res. PhBr (%)			**23b** (GC, %)		
			2 h	6 h	24 h	2 h	6 h	24 h
$Pd_2DBA_3{\cdot}CHCl_3$	dppf	5	6.9	0	-	91.0	100	-
$Pd_2DBA_3{\cdot}CHCl_3$	dppf	1.5	38.3	9.6	0	60.2	88.8	100
$PdCl_2$	dppf	5	0	-	-	100	-	-
$PdCl_2$	dppf	1.5	36.1	0	-	67.3	100	-
$PdCl_2$	dppf	1.1	54.4	0	-	49.2	100	-
$PdCl_2$	dppf	0.9	68.6	22.2	8.9	18.1	51.0	63.1
$Pd(OAc)_2$	dppf	5	0	-	-	100	-	-
$Pd(OAc)_2$	dppf	1.5	0	-	-	100	-	-
$PdCl_2dppf$[a]	dppf	5	20.2	0	-	69.8	87.9	-
$PdCl_2dppf$		5	56.4	21.6	10.4	35.3	59.8	66.9

Conditions: PhBr (0.2 mmol), pyrrolidine: as specified, ^{t}BuNC (0.3 mmol), dppf (10 mol%), $Pd_2DBA_3.CHCl_3$ (2.5 mol%), $PdCl_2$, $Pd(OAc)_2$ and $PdCl_2dppf$ (5 mol%). a. $PdCl_2dppf$ (5 mol%)+ dppf (5 mol%). Toluene (2 mL). T=109 °C.

These results clearly showed that the palladium(II)-sources allowed for shorter reaction times. With $PdCl_2$, the reactions were faster with excess pyrrolidine, whereas in the case of $Pd(OAc)_2$, it did not seem to influence the outcome. For the palladium(II)-salts, the chloride is cheaper than the acetate. Therefore they can be considered complementary to each other; if the cost of the amine is high, the acetate is the palladium source of choice, whereas with cheap amines, $PdCl_2$ may be more convenient to use. The poorer result with $PdCl_2dppf$ is somewhat surprising and not fully understood, as this complex is an expected intermediate in the pre-activation step of the catalytic cycle. The fact that addition of an extra equivalent of dppf improved the outcome of the reaction, may indicate that the extra phosphine is necessary to reduce the palladium(II) complex to (0) state, which is well-known from the literature.[51] The reaction profiles for the preparations of **23b** by $Pd_2DBA_3.CHCl_3$, $PdCl_2$ and $Pd(OAc)_2$ were constructed and are given in Figure 4.



Conditions: PhBr (0.2 mmol), Cs_2CO_3, (0.24 mmol), pyrrolidine (1.0 mmol), ^{t}BuNC (0.3 mmol), dppf (10 mol%), toluene (2 mL). T=109 °C. $Pd_2DBA_3.CHCl_3$ (2.5 mol%), $Pd(OAc)_2$ (5 mol%), $PdCl_2$ (2.5 mol%).

Figure 4

As seen, the reaction profiles of the tin-free system are linear. In the tin system, sigmoid reaction profiles were observed with $Pd_2DBA_3.CHCl_3$ and the reactions had a distinct initiation period, as described in paragraph 2.3. In this case, there does not seem to be any initiation period for the same reaction. The palladium(II) catalyst precursors give rise to results very similar to the palladium(0)-system.

3.2.3 Optimisation of the Ligand and its Stoichiometry

Although good results had been obtained with $PdCl_2$ and $Pd(OAc)_2$ together with dppf, a further range of ligands and the influence of the ligand : palladium ratio were examined. Ligand-free systems were also studied. Presence of the ligand may improve the stability of the catalyst, preventing it from undergoing deactivating side reactions. On the other hand, it may limit the scope of the reactions by preventing bulky substrates reacting. A set of new ligands taking into account steric and electronic effects was chosen and investigation of the influence of the electron-rich ligands *tris*(2-furyl)phosphine, *tris*(2-methoxyphenyl)phosphine and the bulky, electron-rich 2-(di-*tert*-butylphosphino)biphenyl was performed along with the electron-poor bis(pentafluorophenyl)phenylphosphine. The bidentate ligands dppe, dppp and *rac*-BINAP were also tried and at this stage of the optimisation, only palladium(II) sources were considered. The results are shown in Table 12.

Table 12: Effect of Ligands on the Tin-Free System

Pd-Source	Ligand	L:Pd-Ratio	Eq. Pyrrolidine	Res. PhBr			**23b** (GC, %)		
				2 h	6 h	20 h	2 h	6 h	20 h
$PdCl_2$	*rac*-BINAP	2	5	100	18.4	9.6	0	76.8	81.4
$PdCl_2$	dppf	1	5	24.1	0	-	78.1	100	-
$PdCl_2$	dppf	2	5	0	-	-	100	-	-
$PdCl_2$	dppf	4	5	72.3	39.1	0	22.2	57.1	100
$PdCl_2$	dppf	1	1.5	46.3	19.6	9.1	40.6	71.1	83.4
$PdCl_2$	no ligand	0	5	95.1	70.2	37.2	0	20.1	53.7
$PdCl_2$	PPh_3	4	5	89.6	65.0	47.9	4.2	21.7	28.2
$PdCl_2$	$(2\text{-furyl})_3P$	4	5	87.0	54.6	44.8	6.8	32.3	35.8
$PdCl_2$	$(C_6F_5)_2PhPPh$	4	5	94.2	91.4	81.0	0	0	0
$PdCl_2$	$Ph\text{-}C_6H_4(o\text{-}^tBu)_2P$	4	5	100	93.6	74.2	0	0	11.2
$PdCl_2$	$P(o\text{-}MeO\text{-}C_6H_5)_3$	4	5	93.7	89.1	83.6	0	0	0
$PdCl_2$	dppe	2	5	46.4	15.6	0	48.7	83.3	100
$PdCl_2$	dppp	2	5	0	-	-	100		
$Pd(OAc)_2$	dppf	1	5	0	-	-	100		
$Pd(OAc)_2$	dppf	1	1.5	0	-	-	100		
$Pd(OAc)_2$	no ligand	0	5	85.2	45.7	24.3	7.7	35.4	56.1

Conditions: PhBr (0.2 mmol), Cs_2CO_3 (0.24 mmol), pyrrolidine: as specified, ^{t}BuNC (0.3 mmol), ligand: as specified (1:1 ratio=5 mol%), Pd(II)-source (5 mol%), toluene (2 mL). T=109 °C.

As expected, a large excess of dppf had a retarding effect on the reaction. Excess ligand can influence the oxidative addition step by competing for vacant co-ordination sites of the catalyst. The ligand : palladium ratio of 1 : 1 gave the best results for $PdCl_2$ and $Pd(OAc)_2$ alike, but for $PdCl_2$ a longer reaction time was required when using only 1 eq dppf. The ligand-free systems displayed satisfactory results too and conversion stopped at the indicated yields, probably because of deactivation of the catalyst by decomposition to palladium metal. The bidentate ligands *rac*-BINAP, dppp and dppe also gave excellent results. The BINAP-ligand is very expensive and dppp and dppe are air sensitive, so it was decided to keep using dppf. The other monodentate ligands were inferior and the excellent results obtained with the bidentate ligands did therefore not prompt any further optimisation.

3.2.4 Optimisation of the Solvent

Another parameter of interest was the solvent effect. Toluene, DMF, dioxane and THF were tried, the latter at 65 °C. No conversion was observed for THF. Benzene was excluded because of its toxicity and use of THF at high temperatures was avoided because of the inconvenience of using sealed tubes. The results are given in Table 13.

Table 13: The Effect of Different Solvents

Solvent	Res. PhBr, (%)			**23h**, (GC, %)		
	2 h	6 h	24 h	2 h	6 h	24 h
Toluene	100	5.2	0	0	92.1	100
DMF	61.7	54.4	21.3	29.0	37.2	64.4
Dioxane	87.1	81.4	55.8	0	0	23.1
THF	100	94.2	87.4	0	0	0

Conditions: PhBr (0.2 mmol), pyrrolidine (0.24 mmol), ^{t}BuNC (0.3 mmol), dppf (10 mol%), Cs_2CO_3 (0.24 mmol), $PdCl_2$ (5 mol%), solvent (2 mL). T=109 °C.

Toluene proved to be the best solvent in terms of reaction time and yield. It was therefore taken as solvent of choice for the future preparative amidine synthesis. As seen in Table 13, there is an initiation time for toluene, which is in contrast with the findings described in section 3.2.2. This deviation cannot be explained at present.

3.2.5 Influence of the Aryl Source

The last step of the optimisation was to try the conditions established for PhBr on the other phenyl sources PhI, chlorobenzene (PhCl) and phenyl triflate (PhOTf). It is anticipated that the order of reactivity should be PhI>PhOTf≥PhBr>>PhCl. The conclusions are based on the yield of **23b** and the results summarised in Table 14.

Table 14: Influence of the Phenyl source on the Formation of 23b

PhX	**23b**, (GC, %)			
	1 h	2 h	5 h	24 h
PhBr	22.2	87.8	100	-
"	18.4	77.1	100	-
PhCl	0	0	0	0
"	0	0	0	0
PhI	4.3	11.4	76.7	84.1
"	8.2	15.3	71.1	79.6
PhOTf	59.0	100	-	-
"	80.9	100	-	-

Conditions: PhX (0.2 mmol), Pyrrolidine (0.24 mmol), ^{t}BuNC (0.3 mmol), dppf (10 mol%), Cs_2CO_3 (0.24 mmol), $Pd_2DBA_3.CHCl_3$ (2.5 mol%), toluene (2 mL). T=109 °C. Reactions performed in duplicate

As seen from Table 14, PhOTf gave the fastest reaction, but it is still comparable with PhBr. This observation is very useful as it increases the potential of this methodology by allowing substrates originating from phenols to be prepared and used as amidine precursors. PhI is consistently worse than PhBr and PhOTf. The failure of PhCl to react under these reaction conditions is not surprising. Conditions allowing the use of PhCl in palladium-catalysed arylamine synthesis are available,[53] but were not considered in this investigation.

3.3 Establishment of Work-up Conditions

Tertiary amidines such as **23b** are strongly basic compounds with pKa-values of the conjugate acids ranging from 10 to 12 for their conjugate acids.[54] This feature leads to difficulties in the purification, which was attempted on silica and basic alumina. Various eluent systems were tired and addition of methanolic ammonia to the eluents did not solve the problem. A recent publication on the synthesis of primary amidines[55] describes the successful use of an acetate resin for the purification of the products. Use of the same resin did not lead to any success in this case. This was probably due to the stronger basicity of tertiary amidines compared to the primary ones, hence making them bind more strongly to the solid phase. A different approach takes the

pronounced basicity of these tertiary amidines into consideration; they should be easily protonated, forming salts with weak acids. These salts should be soluble in the aqueous layer, which could then be washed with an appropriate organic solvent to remove organic impurities. Basification and extraction of the aqueous layer would then provide the amidines of good purity.

Validation of this method was performed by extraction of **23b** with acetic acid (2.5% by volume in water) followed by basification with potassium hydroxide pellets. Firstly, determination of the repartition coefficient K_r, ($K_r = K_{org} / K_{AcOH}$) of **23b** between diethyl ether and acetic acid was attempted. This failed as GC-analysis indicated that **23b** went completely into the acetic acid layer after the first extraction. The stability of **23b** in an acidic medium was determined by preparing four vials with known concentrations of **23b** and C_{13} as the internal standard. Potassium hydroxide pellets and a volume of diethyl ether were then added to each vial at different times and the ethereal layer was analysed by GC. The results are given in Table 15.

Table 15: Monitoring of Stability of 23b *vs* Time

Time (h)	Area Ratio (C_{13} : **23b**)
0.25	0.552
0.5	0.566
1.5	0.566
8	0.564

This important result showed that **23b** was stable to the acidic conditions. In order to investigate the effect of work-up on the yield, the recovery was determined by dissolving 2 mmol of **23b** in diethyl ether and carrying out the extraction with dilute acetic acid. Basification followed by extraction with diethyl ether then allowed recovery of the amidine **23b** in a yield of 91%. Considering the simplicity of the method, this recovery is very satisfactory and indicates the suitability of this work-up method for the preparative work to be described in section 3.7.

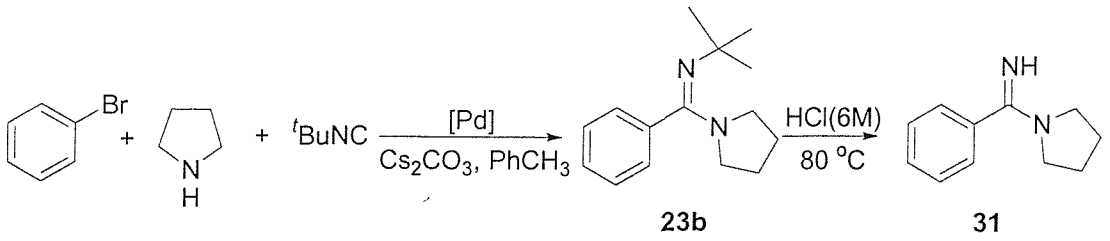
3.4 Determination of Scope

Before undertaking the preparative work to obtain *N-tert*-butyl substituted arylamidines, a screening was performed in order to establish the substrates to be used. Primary, secondary (cyclic and acyclic) and aromatic amines were tested together with electron neutral, electron poor, electron rich and heteroaromatic aryl bromides. The outcome of the reactions was estimated by observing loss of starting materials and appearance of possible product peaks. Calibrations were not obtained, but the outcome showed that substrates of the above categories were viable. An exception was 2-bromotoluene and 2,6-dibromotoluene. In the first case, very limited product formation was observed. For the more hindered substrate, no reaction took place. This observation was also made in the investigation of the α-ketoamide formation,[26] where the reaction rate was halved by the presence of one *ortho*-substituent and impeded with two *ortho*-substituents.

3.5 Deprotection of *N-tert*-Butyl-substituted Amidines

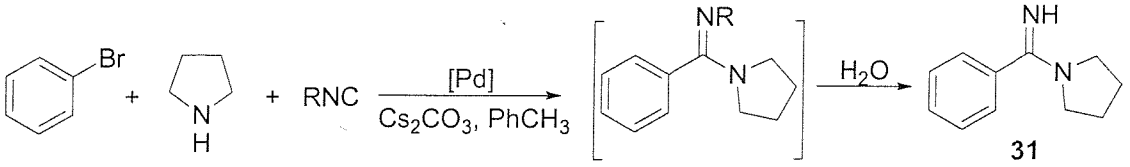
In order to extend the scope of the described methodology, it was desirable to be able to remove the *tert*-butyl group of the tertiary amidines to generate the corresponding secondary amidines. Treatment of compound **23b** with TFA at room temperature or reflux was unsuccessful. Harsh conditions consisting of heating in hydrochloric acid (6 M) were required to remove the *tert*-butyl group. This sequence could be conveniently carried out as a one-pot procedure by synthesising **23b** in toluene, evaporating the solvent, adding the hydrochloric acid and heating at 80 °C, which yielded the secondary amidine **31**.

This *tert*-butyl deprotection is known from the literature[56] for heterocyclic compounds incorporating amidine fragments and could be successfully applied in this case. The chemistry is shown in Scheme 65.



Scheme 65

The secondary amidine was isolated in a yield of 60% over two steps. As this does not constitute a viable route in the case of more unstable molecules, other routes to secondary amidines have also been investigated. Attempts to insert trimethylsilyl isonitrile and *tert*-butyl-dimethylsilyl isonitrile have been performed. These silyl amidines should be prone to hydrolysis and by facile silyl group removal, giving rise to the corresponding secondary amidine **31**, as shown in Scheme 66.



R=$SiMe_3$ or Si^tBuMe_2

Scheme 66

Unfortunately use of the silyl isonitriles failed and the reason was probably an unfavourable equilibrium, which is shifted towards the cyanide form as in Scheme 67.

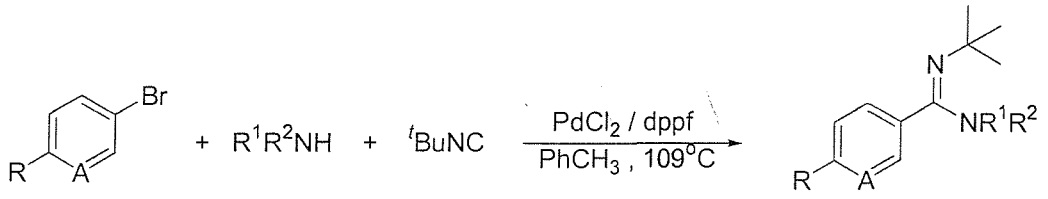
Scheme 67

In conclusion, the *tert*-butyl removal has so far been successful only by boiling in hydrochloric acid.[56] This method worked well in this case, but due to its harshness it

cannot be considered as a general route for generation of secondary amidines from *N*-*tert*-butyl substituted tertiary amidines.

3.6 Preparative *N*-*tert*-Butyl Arylamidine Synthesis

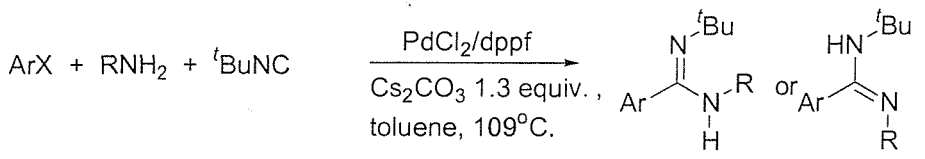
With the optimised conditions in hand, a range of amidines were prepared by the reaction described in Scheme 68.



21, 23, 32a-k

Scheme 68

Arylamidines derived from primary amines can exist in the two tautomeric forms **33a** and **33b**, as shown in Scheme 69.



33a **33b**

Scheme 69

^{13}C-NMR shifts of the *tert*-butyl groups indicate that the amidines derived from primary amines exist in the tautomeric form **33b**, as the quartet of the *tert*-butyl group has a distinctive upfield shift compared to the other cases. This feature was investigated by DFT-calculations which showed that the energetically most favourable conformation by 7.8 kcal/mol was the *E*-isomer shown in Figure 5. This result is clearly consistent with the NMR-data.

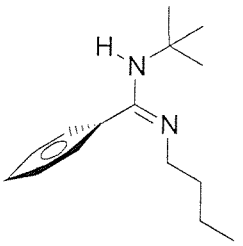


Figure 5

As mentioned in paragraph 2.2, a very interesting observation was made for amidine of the general structure **23**; when it was prepared as a GC-standard by the literature procedure[47], distinctly different NMR-characteristics were observed to when it was synthesised by palladium catalysis. The complete interpretations of the NMR-data are given for each case in the *Experimental Section* but the very important differences are highlighted and the structures of the two isomers are given below in Figure 6.

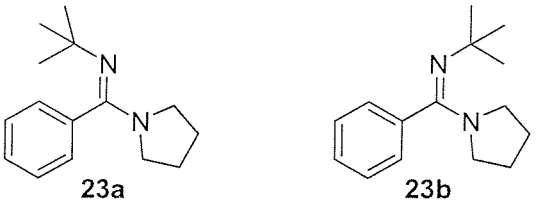
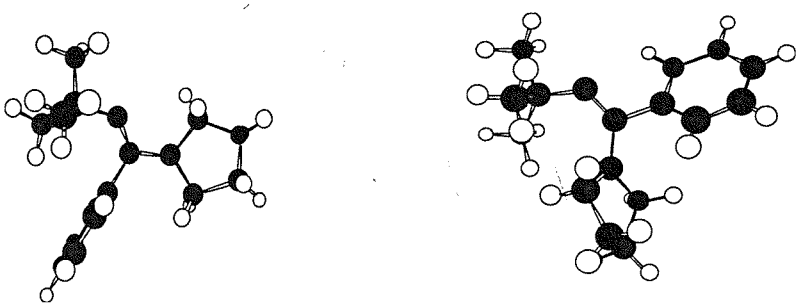


Figure 6

MOPAC-calculations show that for the *E*-isomer **23a**, there is very good overlap between the pyrrolidine nitrogen lone pair and the imine double bond. There should therefore be a substantial barrier to rotation about the (C-N)-bond due to partial double bond character, whereas for the *Z*-isomer **23b**, the pyrrolidine nitrogen lone pair and the imine double bond should be at approximately right angle to each other. This feature gives a stronger single-bond character to the (C-N)-bond. In terms of NMR-results, the pyrrolidine carbons should all be different for **23a**, whereas for **23b** there should be only two sets of pyrrolidine carbons. This prediction could be verified and it could be stated that the literature procedure[47] led to formation of **23a**, whereas the three-component coupling gave formation of **23b**. This outcome is remarkable as DFT-calculations clearly show that the *E*-isomer is more stable by 7.8 kcal/mol. In the case of **23a**, the chemical shift of the *tert*-butyl protons was in the range of 1.3 ppm. For **23b** the chemical shift was in the range of 1.0 ppm and the other amidines **21** and **32a-k** showed very similar chemical shifts for the *tert*-butyl protons. This observation

led to the conclusion that the amidines **21**, **32a**, **32c-g** and **32j-k** formed exclusively as *Z*-isomers. In the case of **32f** a mixture of the *Z* and *E*-isomers was obtained, with the *Z*-isomer as the main product. This deviation from the above result cannot be explained at present. The amidines **32b** and **32h** had the *E*-configuration showed in Figure 5. The Chem3D pictures of the *E*-isomer **23a** and *Z*-isomer **23b** are shown in Figure 7.



23a **23b**

Figure 7

The synthesised amidines were isolated as described in section 3.3 and analytical purity was achieved by distillation under reduced pressure. The isolated yields were overall good. The results of the preparative work and the ^{13}C-NMR correlations of the *tert*-butyl carbons are shown in Table 16.

Table 16: Synthesised *N-tert*-Butyl Substituted Arylamidines

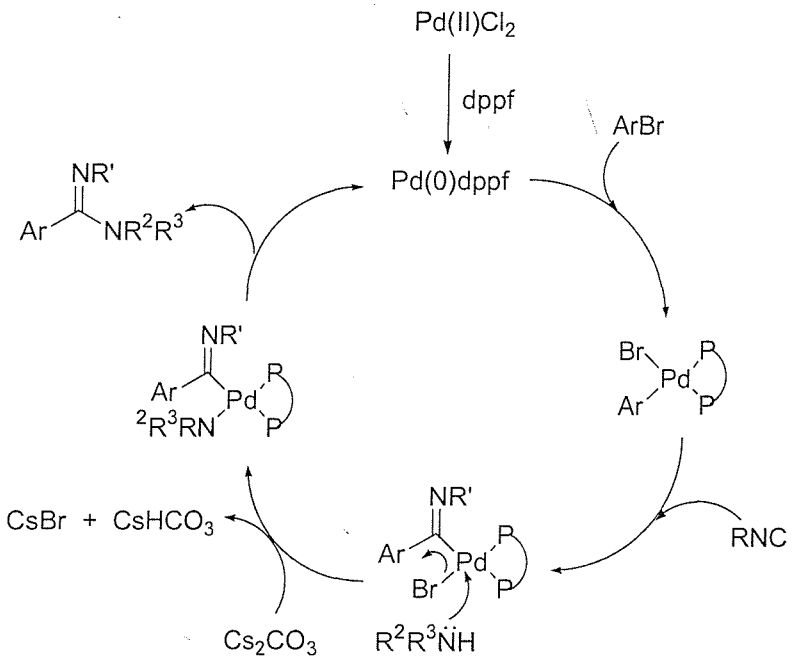
ArX	Amine (R^1; R^2)	Compound	Yield (GC, %)[a]	^{13}C-Shift (ppm)	
				$C(CH_3)_3$	CH_3
C_6H_5Br	$-(CH_2)_4-$	**23b**	78 / 58[b]	52.79	33.01
C_6H_5Br	Bu, H	**32a**	55 / 29[b]	51.44	29.44
C_6H_5Br	Ph, H	**32b**	45 / 40[c]	52.17	29.08
C_6H_5Br	Et, Et	**21**	61	52.71	32.85
p-$Me_2NC_6H_4Br$	$-(CH_2)_4-$	**32c**	74	52.87	33.14
p-$Me_2NC_6H_4Br$	$-(CH_2)_2O(CH_2)_2-$	**32d**	76	53.21	32.69
p-$MeOC_6H_4Br$	$-(CH_2)_4-$	**32e**	83 / 79[c]	52.82	33.09
p-$MeOC_6H_4Br$	$-(CH_2)_2O(CH_2)_2-$	**32f**	76[d]	53.14	32.59 (maj)
p-$MeOC_6H_4Br$	$-(CH_2)_2O(CH_2)_2-$	**32f-1**	N/A	55.14	29.50 (min)
p-$MeCOC_6H_4Br$	$-(CH_2)_4-$	**32g**	61	52.87	33.11
p-$MeCOC_6H_4Br$	Bu, H	**32h**	49	51.66	29.37
p-$MeCOC_6H_4Br$	$-(CH_2)_2O(CH_2)_2-$	**32i**	62	53.21	32.67
3-Bromopyridine	$-(CH_2)_4-$	**32j**	71	52.97	33.21
3-Bromopyridine	$-(CH_2)_2O(CH_2)_2-$	**32k**	57	53.38	32.80
C_6H_5Br	$-(CH_2)_4-$	**31**	60[e]	N/A	N/A

a. Conditions: 5 equiv. amine, 1.5 equiv. ^{t}BuNC, 1.3 equiv. Cs_2CO_3, 5 mol.% $PdCl_2$, 10 mol.% dppf, toluene, 109 °C, 3 – 24 h. b. Conditions: as (a) but 1 equiv. amine, 5 mol.% $Pd(OAc)_2$, 5 mol% dppf. c. Conditions: as (b) but 1.5 equiv. amine. d. Isolated as a mixture of two isomers in a ratio of 4 : 1. e. Conditions as (a), followed by treatment of crude material with HCl (6 M).

As expected, the yields were highest when using pyrrolidine. Diethylamine is sterically more encumbered and not equally reactive. *n*-Butylamine is a primary amine and can undergo β-hydride elimination to give the corresponding imine as a side product. This could account for the moderate yields. Aniline is a primary amine without β-hydrogens, but a comparatively poor nucleophile. As a comparison to the standard conditions (Table 16 footnote **a**), some preparative reactions were carried out with $Pd(OAc)_2$ and a lower amine stoichiometry, (footnotes **b** and **c**).

3.7 Mechanism of the Catalytic Cycle for Amidine Formation

The closest analogy to the investigated tin free three-component coupling to give amidines is the palladium-catalysed synthesis of arylamines.[40] The mechanism suggested for the amidine synthesis takes into account the mechanism for arylamine formation[40] and the isonitrile insertion is believed to occur analogously to the tin system previously described. The suggested mechanism for the catalytic cycle is shown in Scheme 70.



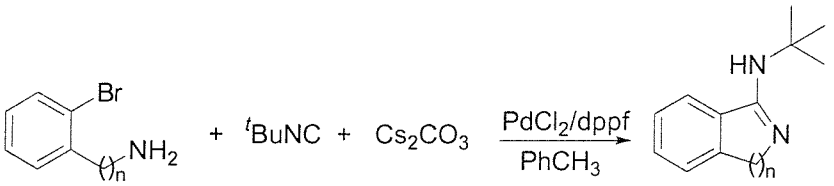
Scheme 70

The steps of the catalytic cycle are analogous to the cycle discussed for the tin system apart from the transmetallation. This is now taking place by direct attack of the amine, and the role of the base is to neutralise the hydrobromic acid formed as a by-product from the attack. Due to the electron-withdrawing effect of the palladium, it cannot be excluded that the attack occurs on the imino group. The early mechanistic assumptions for palladium-catalysed ester[9] and amide[14] formation takes this possibility into account, the base would then neutralise the acid formed from the decomposition of the putative hydride intermediate to regenerate the catalytically active species with concomitant HBr-formation. It is emphasised that acid catalysis is

normally necessary in order to achieve attack on imino functionalities in classical organic synthesis. More mechanistic details will follow in chapter 4 of this section.

3.8 *Intramolecular* Amidine Formation

As seen in section 1.2.5 of the introduction, it is possible to successfully synthesise aryl-condensed lactams by reaction between aniline substrates and CO.[19] The same reaction should be possible with isonitriles as the carbenoid species. The substrates **34a** and **34b** were reacted with ^{t}BuNC to give the cyclic amidines **35a** and **35b** in yields of 64% and 67% respectively. The preparative reactions are shown in Scheme 71.



n=1 **34a**
n=2 **34b**

n=1 **35a**
n=2 **35b**

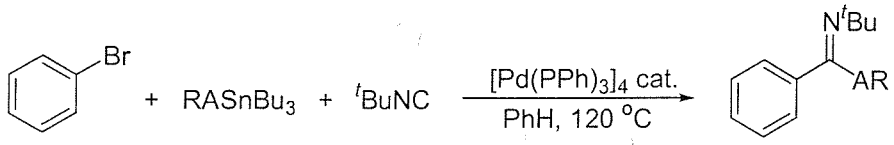
Scheme 71

The NMR-results clearly indicate the given configuration for compounds **35a** and **35b**. The reaction failed to work when attempted with other isonitriles and GC-monitoring of the reactions indicated the presence of unreacted starting material. The mechanism should be analogous to that suggested for the *intermolecular* amidine formation in section 3.7. Lack of time and establishment of different priorities did not allow this part of the project to be thoroughly pursued. It is nevertheless very interesting to see that the tin-free methodology developed for *intermolecular* amidine formation can also be applied to *intramolecular* reactions.

4 Synthesis of Imidates and Thioimidates

4.1 Introduction

In the publication by Kosugi *et al.*[36] from 1986, which was the background to the tin system for amidine synthesis, the coupling of tin derivatives of methanol (MeOH) and benzene thiol (PhSH) with PhBr and ^{t}BuNC was also reported as in Scheme 72.



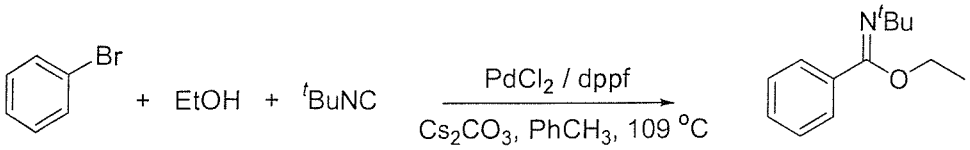
36 AR=OCH_3
37 AR=SPh

Scheme 72

The imidate **36** was reported to form in a GC-yield of 63%, whereas the thioimidate **37** was formed in a GC-yield of 10%. No follow-up to this work has been found in the literature and it was therefore of great interest to extend the scope of the tin-free methodology developed for amidine synthesis to include imidates and thioimidate formation with alcohols and thiols.

4.2 Development of Conditions for Imidate Synthesis

Given the close resemblance between amidine and imidate synthesis, it was logical to first try to translate the conditions established in the amidine case, to the synthesis of imidates. Firstly, ^{t}BuNC was tried and the reaction is shown in Scheme 73.



38a

Scheme 73

The reaction was over in 19 h and GC-analysis indicated complete conversion. The long reaction time suggested the advantage of trying a more active ethoxide source

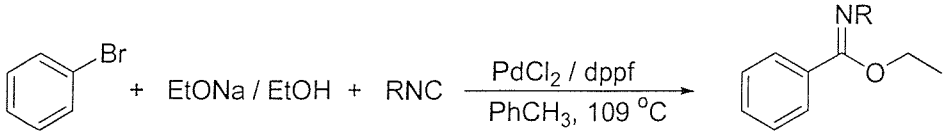
than EtOH itself, as alcohols are weaker nucleophiles than amines. Reactions with PhBr, ^{t}BuNC and EtOH in presence of Cs_2CO_3 and the much cheaper K_2CO_3 were compared with use of sodium ethoxide as a 2 M-solution in ethanol (NaOEt/EtOH), which is a more powerful nucleophile than EtOH itself, in the formation of **38a**. The results are given in Table 17.

Table 17: Effect of EtOH/base *vs* EtONa/EtOH on the Formation of 38a

Base	EtOH (mmol)	NaOEt (mmol)	Res. PhBr, (%)			**38a**, (GC, %)		
			2 h	4 h	16 h	2 h	4 h	16 h
Cs_2CO_3	2.0	-	77.6	50.8	18.1	12.1	37.2	57.1
"	"	-	65.1	40.0	6.9	6.0	42.7	67.3
K_2CO_3	2.0	-	90.7	75.1	15.4	2.2	6.7	45.2
EtONa*	-	2.0	25.1	0	-	72.1	100	-
"	-	"	0	-	-	100	-	-

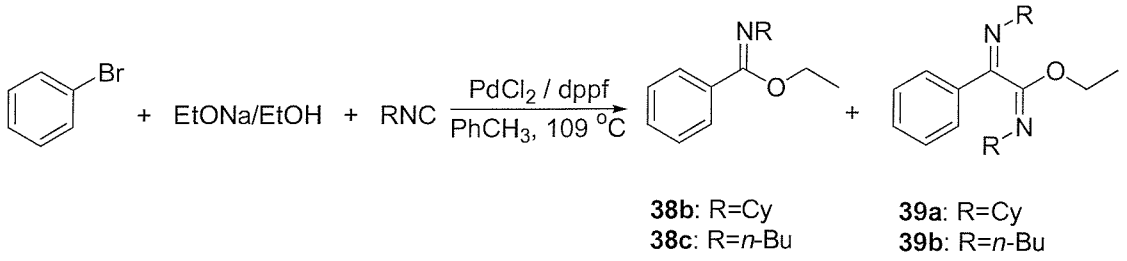
Conditions: PhBr (0.4 mmol), carbonate base (0.48 mmol), ^{t}BuNC (0.6 mmol), dppf (10 mol%), $PdCl_2$ (5 mol%), Toluene (4 mL). (*) EtONa as a 2M-solution in EtOH (1 mL), toluene (3 mL). T=98 °C. Reactions performed in duplicate and one reaction failed when using K_2CO_3

It was clearly seen that use of a NaOEt/EtOH-solution greatly improved conversions as well as reaction time compared to the system with EtOH and carbonate bases. Use of NaOEt/EtOH-solution was therefore taken as standard conditions for subsequent work. Whereas tertiary arylamidines are very strong bases,[54] imidates are not and it should therefore be possible to purify them on silica. Because of the hydrolysis sensitivity of imidates in acidic medium, it might be necessary to carry out the purification with triethylamine in the eluent. Trial reactions with CyNC and *n*-BuNC very unexpectedly showed that both isonitriles would insert to give the imidates 1-ethyl-*N*1-cyclohexyl-1-benzenecarboximidate 38b and 1-ethyl-*N*1-butyl-1-benzenecarboximidate 38c in isolated yields of 30% and 39% respectively. The standard method for the syntheses successively described is shown in Scheme 74.



Scheme 74

As seen, the yields of **38b** and **38c** were noticeably lower than the yield of the *N-tert*-butyl imidate **38a**. Repetition of the reactions showed the same trend and an answer to this puzzling question was given by monitoring the reactions by HPLC-MS. It was noticed that double insertion of the isonitrile was competing with the desired single insertion, thus giving rise to mixtures of products as outlined in Scheme 75.



38b: R=Cy
38c: R=*n*-Bu

39a: R=Cy
39b: R=*n*-Bu

Scheme 75

The stereochemical outcome of the double insertion products **39a** and **39b** was suggested by crystallographic studies, as described in section 5.5. The ratio between the single-and double insertion products could not be established at this point, but later work with reactions followed by GC in presence of an internal standard allowed for predictions of quantitative results. This very interesting feature was further investigated by establishing conditions favouring the double insertion of the isonitriles. It turned out that sodium salts of aliphatic alcohols gave rise to double insertion, whereas sodium phenoxide only gave single insertion when using CyNC and *n*-BuNC. The reason is not yet understood, but it is noteworthy that sodium phenoxide and sodium ethoxide are comparable in terms of nucleophilicity, but the phenol is much more acidic than ethanol. This result suggested that the single *vs* double isonitrile insertion may be pH-dependent. Electron-neutral and electron-rich aryl bromides tended to give double insertion, whereas electron-poor substrates showed preference for single insertion. This trend was in accordance with the palladium-catalysed carbonylation to give amides and α-ketoamides,[26] where the electronic nature of the aromatic halides had the same influence as described here. It is also noteworthy that use of aniline gave rise to amide formation exclusively.[26] At this stage it was of interest to investigate the effects of $Pd_2DBA_3.CHCl_3$ *vs* $PdCl_2$ and toluene *vs* dioxane. As previously mentioned, the DBA-ligands have proven to interact with the active $Pd(0)L_2$-catalyst[50] and dioxane is a co-ordinating solvent whereas toluene is not. As for the palladium catalyst, differences biasing the reaction

towards single or double insertion of the isonitrile might be inherent in either system. The solvents could also interact differently with the catalyst and influence the nucleophile too; toluene, being less polar than dioxane, would give a tighter [Na^{+-}OEt]-ion pair, hence a less active nucleophile. These features may therefore influence the outcome of the single or double isonitrile insertion. A set of reactions was investigated to clarify these hypotheses and the results are accounted for in Table 18.

Table 18: Effect of Dioxane *vs* Toluene and $PdCl_2$ *vs* $Pd_2DBA_3.CHCl_3$ on the Formation of 38b and 39a

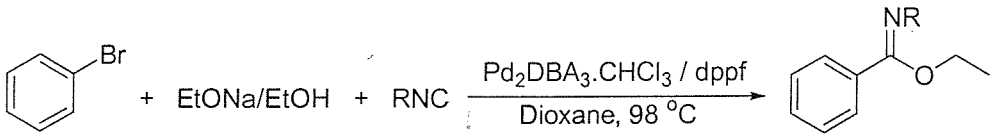
Pd-Source	Solvent	Res. PhBr, (%)			**38b**, (GC, %)			**39a** (GC, %)			**38b/39a**		
		1 h	2 h	4 h	1 h	2 h	4 h	1 h	2 h	4 h	1 h	2 h	4 h
$PdCl_2$	Toluene	25.1	-	-	31.2	-	-	46.1	-	-	0.67	-	-
"	"	46.3	9.9	-	18.6	42.1	-	36.8	49.4	-	0.51	0.85	-
$PdCl_2$	Dioxane	17.1	1.2	-	21.6	34.0	-	32.1	39.7	-	0.69	0.85	-
"	"	2.0	-	-	23.2	-	-	31.0	-	-	0.75	-	-
$Pd_2DBA_3.CHCl_3$	Toluene	53.4	45.1	12 1	12.6	25.3	32.2	27.1	42.0	42.8	0.48	0.60	0.73
"	"	66.1	11.6	-	9.6	22.2	-	17.2	45.9	-	0.56	0.48	-
$Pd_2DBA_3.CHCl_3$	Dioxane	4.2	-	-	34.4	-	-	39.1	-	-	0.85	-	-
"	"	10.3	-	-	29.6	-	-	43.2	-	-	0.70	-	-

Conditions: PhBr (0.4 mmol), CyNC (0.6 mmol), EtONa (1 mL, 2M in EtOH), dppf (10 mol%), $PdCl_2$ (5 mol%), $Pd_2DBA_3.CHCl_3$ (2.5 mol%), toluene (3 mL). T=98 °C. Reactons performed in duplicate.

It could be observed that the overall conversion was better with toluene, whereas dioxane improved the ratio of **38b** to **39a** and seemed to allow for a faster reaction. The palladium source did not seem to have any noticeable effect on the result. When using toluene, the yields of **38b** and **39a** added up with the residual PhBr. With dioxane, there was a proportion of PhBr whose fate could not be accounted for by GC-analysis. For all these entries, the CyNC had been consumed when the reactions were considered to be complete. Calibrations inevitably lead to errors and use of three different calibrations to assess the outcome may multiply this error. The difference between toluene and dioxane was nevertheless clear by the above results. In the case of dioxane, triple insertion of CyNC may have taken place, giving rise to a compound too heavy to be detected by GC-analysis of the reaction mixture. This hypothesis cannot be concluded with certainty, but if it were the case, slow addition of the isonitrile should suppress multiple insertions. When adding the isonitriles CyNC, *n*-

BuNC and BnNC to the reaction mixtures with a syringe pump over 2 h GC-analysis indicated the very clean formation of the expected single insertion products.

Very interestingly, it was necessary to resort to $Pd_2DBA_3.CHCl_3$ as $PdCl_2$ did not give rise to any reaction and this feature is not yet understood. This reaction is outlined in Scheme 76.

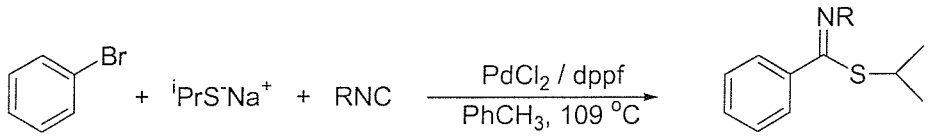


Scheme 76

With these results in hand, preparative work could be carried out.

4.3 Development of Conditions for Thioimidate Synthesis

As anticipated from Kosugi's work,[36] use of the phenyl tributyltin sulfide gave the corresponding thioimidate in a GC-yield of 10%. Firstly, the sodium salt of isopropyl thiol was generated and reacted in the three-component couplings PhBr, and the isonitriles ^{t}BuNC, CyNC, *n*-BuNC and BnNC as in Scheme 77.



40a R=^{t}Bu **40c** R=*n*-Bu
40b R=Cy **40d** R=Bn

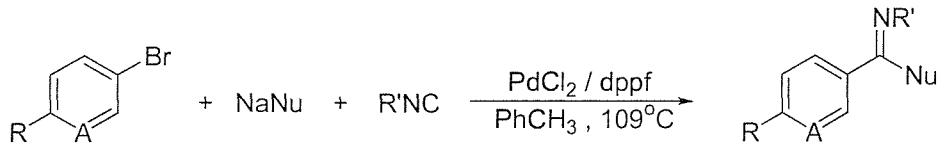
Scheme 77

GC-analysis indicated that reaction was taking place, hence allowing for use of the methodology developed for imidate synthesis. No double insertion of the isonitriles was observed. Attempts to react the sodium salt of benzene thiol in the above reaction failed. This result was not too surprising, considering the low yield reported by Kosugi.[36]

The drastic difference when comparing the effect of the sodium salts of aromatic and aliphatic thiols is very interesting. Again, an influence of the pH could be invoked in order to rationalise the outcome. Aliphatic thiols have a pKa-value similar to phenol, whereas benzene thiol is about 10^3 times more acidic than phenol.

4.4 Preparative Imidate and Thioimidate Synthesis

The various experiments described so far led to the establishment of conditions for the synthesis of these compounds. More effort was put into the optimisation of imidate synthesis than thioimidate synthesis for reasons of time. A range of imidates **38a-k** and thioimidates **40a-d** were synthesised as in Scheme 78.



Scheme 78

The isolated imidates and thioimidates are given in Table 19.

Table 19: Isolated Imidates and Thioimidates

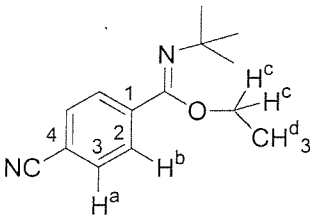
ArX	NaNu	R'NC	Product	Yield, (%)
C_6H_5Br	EtONa	^{t}BuNC	**38a**	92
C_6H_5Br	EtONa	CyNC	**38b**	39 / 84*
C_6H_5Br	EtONa	*n*-BuNC	**38c**	30 / 70*
C_6H_5Br	EtONa	BnNC	**38d**	52*
p-CN-C_6H_4Br	EtONa	^{t}BuNC	**38e**	89
p-CN-C_6H_4Br	EtONa	CyNC	**38f**	72
p-CN-C_6H_4Br	PhONa	CyNC	**38g**	83
3-Bromopyridine	EtONa	^{t}BuNC	**38h**	70
3-Bromopyridine	EtONa	CyNC	**38i**	69
p-$MeOC_6H_4Br$	EtONa	^{t}BuNC	**38j**	82
C_6H_5Br	PhONa	^{t}BuNC	**38k**	86
C_6H_5Br	PhONa	CyNC	**38l**	69
C_6H_5Br	PhONa	*n*-BuNC	**38m**	68
C_6H_5Br	^{i}PrSNa	^{t}BuNC	**40a**	74
C_6H_5Br	^{i}PrSNa	CyNC	**40b**	64
C_6H_5Br	^{i}PrSNa	*n*-BuNC	**40c**	62
C_6H_5Br	^{i}PrSNa	BnNC	**40d**	40

* Isonitrile added over 2 h.

The synthesis of these compounds is described in the *Experimental Section* and yields overall were good. Slow addition of the isonitrile was, as discussed previously, necessary in some cases in order to favour single insertion. Electron-poor aromatic substrates favour the formation of single insertion products, whereas electron-neutral and electron rich substrates seemed to give preferential double isonitrile insertion. In general, use of BnNC gave rise to consistently worse yields, which could be due to the thermal instability of the isonitrile.

4.5 Isomerism in the Imidate and Thiomidate Synthesis

In almost all the imidate forming reactions, a single isomer was formed. In the case of the four examples derived from *tert*-butyl isonitrile and ethoxide **38a**, **38e**, **38h** and **38j** the room temperature signals in the ^{1}H-NMR spectra were very broad. In the case of *p*-cyano substituted example **38e** cooling to –20 °C gave well resolved spectra of a 2.7 : 1 mixture of isomers (see below). In the case of phenyl- and 3-pyridyl substituted imidates **38a** and **38h** ^{1}H-NMR spectra taken at 80 °C in DMSO showed a single well-resolved compound. In the case of the *p*-methoxy substituted imidate **38j** the broad room temperature spectra sharpened to give two isomers (4.4 : 1) at 80 °C and this is probably the only case where a mixture of (*E*)- and (*Z*)-imine functions was obtained. It is very likely based on the stereochemistry of the amidines as described in paragraph 3.6 and of the double insertion products as in paragraph 5.5, that the imidates have the (*Z*) stereochemistry of the imine group, but it has not been proven. The two conformers of imidate **38e** were examined by low temperature NMR including NOE-experiments by the GOESY-technique. Substantial differences in chemical shifts were noted between the two conformers as in Figure 8.



38e

Figure 8

The GOESY-experiments gave the results summarised in Table 20.

Table 20: Results of GOESY-Experiments on Imidate 38e

^{1}H-NMR Shifts (ppm)			^{13}C-NMR Shifts (ppm)					
Proton(s)	Major	Minor	C-Atom	Major	Minor	C-Atom	Major	Minor
H^a	7.70	7.70	C=N	156.27 (s)	154.59 (s)	C4	113.22 (s)	112.60 (s)
H^b	7.64	7.41	C1	139.76 (s)	142.02 (s)	OCH_2	66.48 (t)	61.63 (t)
H^c	3.79	4.10	C2	132.89 (2d)	139.76 (2d)	CMe_3	55.13 (s)	53.21 (s)
H^d	1.32	1.28	C3	129.52 (2d)	129.01 (2d)	CMe_3	30.56 (q)	32.51 (s)
tert-Butyl	1.30	1.04	C≡N	119.26 (s)	119.17 (s)	CH_2Me	15.98 (q)	14.85 (q)

- Clear NOE was observed between H^b and H^c and *tert*-butyl protons of the two conformers
- Irradiation of H^b (major) gave 1% enhancement of H^c (major).
- Irradiating H^b (minor) gave no enhancement of H^c (minor), but small enhancement of *tert*-butyl (minor).
- Irradiating H^c (minor) had no effects whereas H^c (major) gave enhancement of H^b (major).

Molecular Modelling showed the existence of two conformers of similar energy (2 - 4 : 1 ratio) of the imidates **38a**, **38h** and **38j**, presumably the result of restricted rotation about the imine - oxygen bond, which provides information on the imine stereochemistry. The two conformers (A) and (B) of the (*Z*)-imidate might be expected to be of similar energy, whereas in the (*E*)-imidate (C) should be strongly favoured over (D). Extensive theoretical modelling of these systems using molecular mechanics (Merck MMFF94 parameters) and Density Functional Theory (B3LYP method with 6-31G* basis set) was carried out.[57] This result showed that C was 8 kCal/mol more stable than D, and it also showed that neither A nor B was an energy minimum. Two minima consistent with the two conformers observed in the –20 °C spectra of **38e** could not be found. In the minima, it was found that the geminal OCH_2 protons were in different environments, again inconsistent with the NMR studies. More studies are needed, as, at this point, the imine stereochemistry in the imidates has not been proven. The conformers are shown in Figure 9.

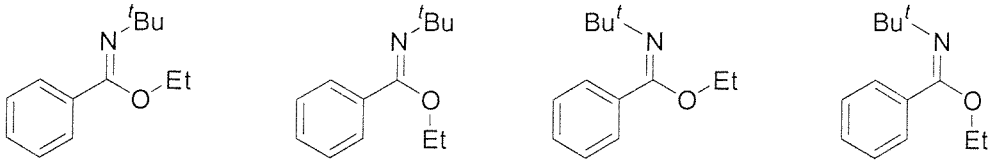


Figure 9

The thioimidates were all isolated as mixtures of isomers and none showed line broadening in the NMR. Faster rotation about the NC-S single bond than the NC-O bond due to poorer overlap between sulphur lone pairs and C=N π^* orbitals would be expected. Reduced steric barriers due to the longer C-S bond would also be expected, so it is likely that the observed isomers are due to the (*E*/*Z*) configuration of the imine double bond. Although there are consistent and substantial differences in the NMR of the major and minor isomers we have not yet been able to assign which is which.

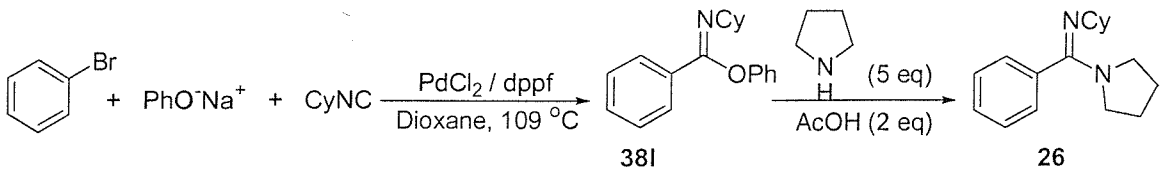
4.6 Conversion of Imidates to Amidines

4.6.1 Introduction

The imidate synthesis allowed for the use of a much wider range of isonitriles than seen in the amidine case, where only ^{t}BuNC worked successfully. The conversion of the phenoxy imidate **38l** to amidine by reaction with an amine was investigated. For the synthesis of primary amidines, the reaction is known as the Pinner synthesis,[45] described in section 2.1. It was thought to use phenoxyimidates as substrates because of the better leaving group ability of the phenoxide anion PhO^- compared to the ethoxide anion EtO^- and they could be synthesised in excellent yields. Two main aspects were of importance in the optimisation of this reaction. Firstly, favourable conditions for the displacement of the PhO^--group had to be established. Secondly, it would be convenient to develop a one-pot method from the aryl bromide through to the amidine.

4.6.2 Optimisation of the Conversion of Imidates to Amidines

In a first attempt, the imidate **38l** was stirred at R.T. with pyrrolidine (5 eq) in THF and no reaction took place. Reflux for 15 h did not lead to any reaction either and more forcing conditions like microwave irradiation of the reaction mixture in diphenyl ether was not successful. The key to success was the use of an acid catalyst. The imino group (C=N) is less reactive than the carbonyl group (C=O) towards nucleophilic attack but can be activated by protonation. Reaction of **38l** with pyrrolidine (5 eq) and hydrochoric acid (2 eq) in dioxane at reflux for 24 h gave the amidine **26** in a yield of 52%. The same conversion were also tried with the weaker acid catalysts AcOH and TFA, which allowed the reaction to be completed in 2 h. As no difference in efficiency was noticed between these acids, the much cheaper and less harmful AcOH was used as the acid catalyst. Next, the possibility of a one-pot procedure was investigated. The imidate **38l** was synthesised in toluene and at completion pyrrolidine (5 eq) and AcOH (2 eq) were added and heating continued. Only partial conversion was achieved over 24 h and prolonged heating did not increase conversions. The same reaction was then tried in dioxane, which has a boiling point of 100 °C and is an aprotic, polar solvent, thus favouring S_N2-reactions. This is described in Scheme 79.



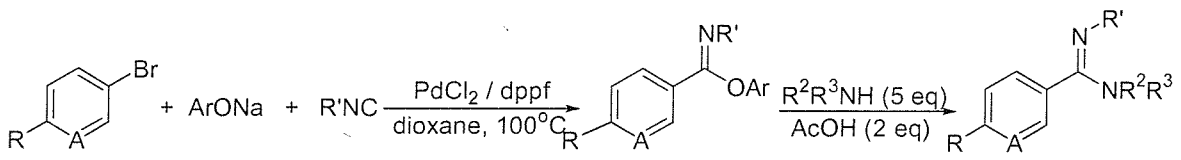
Scheme 79

The reaction was followed by HPLC-MS and the first step of the reaction carried out overnight in order to ensure complete conversion of the PhBr. It was not possible to successfully monitor the formation of **38l** *vs* consumption of the starting materials by this technique. The second step was complete in 3 h, with an overall yield of 60%.

4.6.3 Synthesis of Amidines from Phenoxyimidates

With the conditions developed so far, the synthesis of a range of tertiary amidines *via* phenoxyimidates could be undertaken and the scope of this reaction proved to be very wide. The full range of amines could be used with success. In order to achieve activation of the nucleophilic substitution step, synthesis of imidates with the sodium salts of *p*-nitrophenol and pentafluorophenol was attempted. These deactivated nucleophiles did not insert. *p*-Fluorophenol did insert but no reaction was observed in the second step. The stereochemistry cannot be assigned with certainty, as no amidines have been synthesised from *N-tert*-butyl substituted imidates. In analogy with the case of the *N*-tert butyl amidines, the stereochemistry of the amidines obtained *via* this route is assumed to correspond to the *Z*-configuration. The quantitative isomerisation of **23a** to **23b** when treating the former with aqueous acid suggests that the *Z*-isomer should form also in this case. It is emphasised that further studies will need to be performed in order to gain more evidence for the stereochemical assignment.

The preparative amidine synthesis was carried out as in Scheme 80.



Scheme 80

The results are given in Table 21.

Table 21: Synthesis of Amidines *via* Imidates

ArX	Amine R_2, R_3	R'NC	Product	Yield, (%)
C_6H_5Br	$-(CH_2)_4-$	CyNC	**26**	60
p-MeCO-C_6H_4Br	Ph, H	CyNC	**41a**	84
C_6H_5Br	$-(CH_2)_2O(CH_2)_2-$	BuNC	**41b**	56
C_6H_5Br	$-(CH_2)_2O(CH_2)_2-$	CyNC	**41c**	64
3-Bromopyridine	$-(CH_2)_4-$	CyNC	**41d**	83
C_6H_5Br	$PhCH_2$, H	BuNC	**41e**	49
C_6H_5Br	Bu, Bu	BuNC	**41f**	62

As seen, the global yields were overall very good. The amidines were isolated by extraction with aqueous hydrochloric acid by the same method as described in paragraph 2.3 and further purified by Kugelrohr-distillation. The volatility of the amine may influence the success of the second step; attempts to use diethylamine as the nucleophile for the phenoxide displacement, was not successful. The higher-boiling dibutylamine worked well and the difference could only be explained by a higher concentration of the amine present in the reaction mixture. There are no chemical differences between these two secondary amines to justify such a difference in terms of reactivity.

5 Double insertion of Isonitriles

5.1 Introduction

The interest to consider double isonitrile insertion has risen throughout the work related to the imidate synthesis. When using NaOEt as the nucleophile in the three-component imidate synthesis, mixtures of products originating from single and double insertion of the isonitriles were obtained, as described in section 3.2. In this context an important analogy to consider was the single *vs* double CO-insertion in the palladium-catalysed carbonylation reaction. A detailed discussion of the various aspects of this reaction is given in the introduction. This chapter will be describing two main areas; firstly, a series of experiments carried out in order to establish factors biasing the reaction towards single or double isonitrile insertion will be accounted for. Then, the development of conditions leading to selective double insertion will be described.

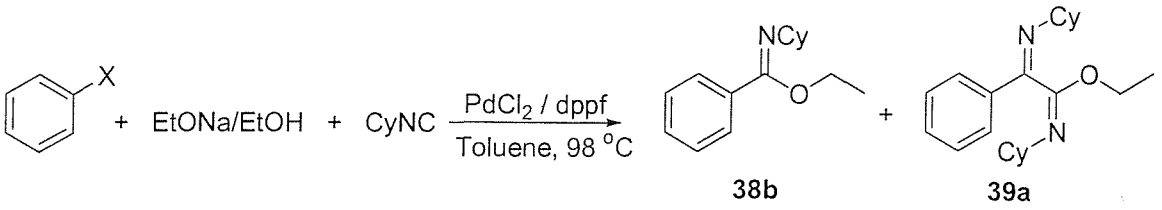
5.2 Investigation of Ways of Biasing to Single or Double Isonitrile Insertion

The influence of ArX (X=Br, I, OTf), crown ether, ligands, isonitrile stoichiometry, palladium source and solvent were investigated and will be described throughout this section. CyNC was used for this investigation and the ethoxide source was the (NaOEt/EtOH)-solution described in section 3.2.

5.2.1 Influence of the Aryl Source

The reactivity of aryl compounds ArX in palladium chemistry depends on the X-group and is normally in the order I > OTf ≥ Br >> Cl. As discussed in section 2.2.2 of the introduction, the rate-determining step of the catalytic cycle may depend on the X-group. It is therefore of interest to investigate the influence of the X-group on the overall reactivity of the system. The ratio of single *vs* double insertion product may be

greatly influenced by the X-group on the aromatic substrate, depending on the operating mechanism. The investigated reaction is described in Scheme 81.



38b **39a**

Scheme 81

The results are shown in Table 22.

Table 22: Influence of ArX on the Single *vs* Double Insertion of CyNC to give 38b and 39a

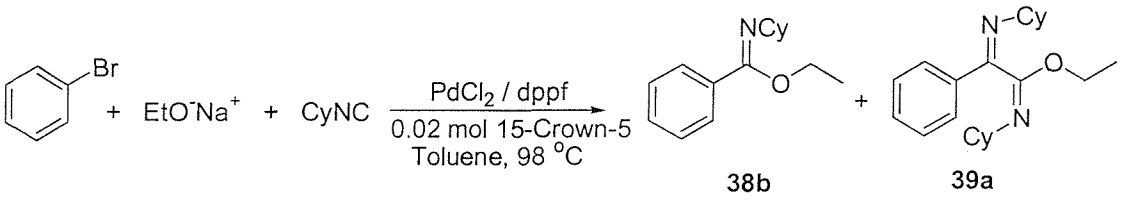
PhX	Res. PhX, (%)	**38b**, (GC, %)	**39a** (GC, %)	**38b/39a**
	2 h	2 h	2 h	2 h
PhBr	0	27.2	41.6	0.65
PhI	0	9.4	15.4	0.61
"	0	8.8	13.1	0.67
PhOTf	0	0	0	-
"	0	0	0	-

Conditions: PhX (0.2 mmol), CyNC (0.3 mmol), EtONa (1.0 mmol, 0.5 mL, 2M in EtOH), dppf (10 mol%), $PdCl_2$ (5 mol%), toluene (1.5 mL). T=98 °C. Control experiment with PhBr. Other reactions performed in duplicate.

These results were remarkable for the use of ArI because of the poor observed results. The disappearance of a very large proportion of the starting material could not be accounted for in terms of formation of **38b** and **39a**. Triple insertion of CyNC may have taken place and the product would not be detectable by GC-analysis of the reaction mixture due to its molecular weight. In the case of PhOTf, GC-analysis indicated that CyNC was left unreacted, whereas the triflate disappeared. In conclusion, there was no reason to change from PhBr to another phenyl source.

5.2.2 Influence of the Presence of Crown Ether

It was of great interest to study the influence of 15-crown-5 in the three-component coupling. This particular crown ether complexes the Na^+, hence making the ethoxide anion (EtO^-) more reactive as a nucleophile. As for the NaOEt/EtOH-system, two factors can lead to deactivation. Hydrogen bonding between EtO^- and EtOH will reduce the nucleophilicity of the EtO^- anion and the tightness of the $[Na^+{}^-OEt]$ ion pair will also have the same effect. Therefore, addition of suitable crown ether to complex the Na^+ cation should lead to favoured single insertion of CyNC. Equimolar amounts of 15-crown-5 and NaOEt were used and the reaction is described in Scheme 82.



Scheme 82

Table 23 summarises the outcome of this study.

Table 23: Influence of 15-Crown-5 on the Formation of 38b and 39a

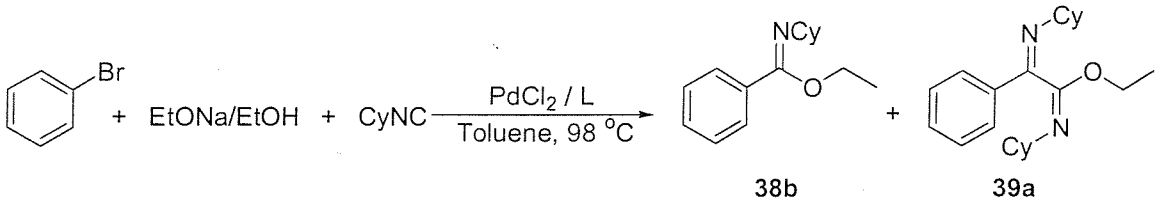
15-Crown-5	Res. PhBr, (%)			**38b**, (GC, %)			**39a**, (GC, %)			**38b/39a**		
	1 h	2 h	5 h	1 h	2 h	5 h	1 h	2 h	5 h	1 h	2 h	5 h
0.02 mol	78.1	13.4	0	20.4	38.8	45.0	20.9	32.8	35.7	0.98	1.18	1.26
"	62.8	12.6	10.7	14.6	45.2	44.7	13.2	35.6	33.1	1.10	1.27	1.35
0	87.8	19.3	8.6	1.2	8.8	10.2	8.9	55.1	53.0	0.13	0.16	0.19
"	76.0	22.4	12.9	6.3	9.0	11.8	20.7	47.8	49.4	0.30	0.19	0.24

Conditions: PhBr (0.4 mmol), CyNC (0.6 mmol), EtONa (1 mL, 2M in EtOH), 15-Crown-5: as specified, dppf (10 mol%), $PdCl_2$ (5 mol%), toluene (3 mL). T=98 °C. Reactions performed in duplicate.

It was observed that the yields were modest and 15-crown-5 alone did not completely reverse the selectivity in favour of single insertion of CyNC, but the results were nevertheless very interesting as they showed that the presence of crown ether had a marked influence on the **38b** : **39a** ratio, favouring the formation of the single insertion product **38b**.

5.2.3 Effect of the Phosphine Ligand

The choice of ligand is a critical parameters to consider when studying and optimising palladium-catalysed reactions. Difference in bulk, electronic nature, basicity and chelating capacities of the ligand determines the reactivity of a given catalytic system. The influence of the phosphine ligand in the case of α-ketoamide synthesis is described in section 2.2.2 of the introduction. Less hindered monodentate phosphine ligands were found to favour double carbonylation, with trimethylphosphine giving the best selectivity. In the case of bidentate ligands, increasing the length of the bridging alkyl chain led to the same result, with dppb as the ligand of chioce.[25] For the α-ketoester synthesis, only monodentate phosphine ligands were considered and bulky, electron-rich ligands found to favour double carbonylation.[27] For the purpose of this study, a wide range of phosphine ligands was considered. The aim was to cover the influence of steric and electronic factors, and both mono- and bidentate ligands were used. Also a ligand-free system was examined. This chemistry is outlined in Scheme 83.



38b 39a

Scheme 83

The effect of varying the ligand is shown in Table 24.

Table 24: Effect of the Ligand on the Single *vs* Double Insertion of CyNC

Ligand	Res. PhBr, (%)			**38b**, (GC, %)			**39a** (GC, %)			**38b/39a**		
	2 h	6 h	24 h	2 h	6 h	24 h	2 h	6 h	24 h	2 h	6 h	24 h
dppf	63.1	22.7	-	1.9	17.1	-	27.1	38.0	-	0.07	0.45	-
"	57.4	9.1	-	6.2	21.6	-	34.7	40.2	-	0.18	0.54	-
dppp	93.0	82.1	16.8	2.4	3.1	6.0	2.1	4.4	16.1	1.14	0.91	0.37
"	82.7	62.1	10.4	1.9	2.8	6.8	1.1	4.0	12.8	1.72	0.70	0.53
dppe	96.1	88.6	16.6	1.4	1.1	3.2	1.3	3.1	5.8	1.07	0.33	0.55
"	95.0	85.3	22.0	0.7	2.4	5.4	2.4	4.4	7.9	0.29	0.55	0.68
P(*o*-Tol)$_3$	12.1	-	-	23.1	-	-	27.1	-	-	0.85		
"	2.4	-	-	29.4	-	-	32.3	-	-	0.91		
PPh_3	86.8	74.2	45.3	3.2	5.1	10.6	7.6	12.2	30.6	0.44	0.42	0.35
"	94.2	63.1	29.8	3.4	6.4	12.4	5.9	11.9	33.8	0.58	0.54	0.37
PPh_2Me	45.1	18.0	-	16.0	27.4	-	36.1	43.2	-	0.44	0.63	-
"	29.8	24.4	-	19.2	21.6	-	42.7	41.9	-	0.45	0.52	-
P(Furyl)$_3$	89.6	78.1	32.3	3.4	8.2	12.0	4.1	13.0	21.7	0.83	0.63	0.55
"	90.2	82.7	35.9	2.8	5.7	12.4	4.9	6.0	11.9	0.57	0.95	1.04
P(Cy)$_3$	83.2	16.2	10.7	3.1	8.1	9.1	9.6	14.2	16.3	0.32	0.57	0.56
"	88.7	13.9	10.1	3.2	7.4	7.6	8.4	10.0	12.4	0.38	0.74	0.61
P(^{t}Bu)$_3$	84.5	62.4	10.2	2.6	12.1	12.6	10.0	23.0	31.3	0.26	0.53	0.40
"	69.3	35.8	14.6	3.1	10.0	15.0	16.2	22.4	33.6	0.19	0.45	0.45
No Ligand	76.4	54.2	46.0	6.4	14.2	13.8	12.3	22.8	27.9	0.52	0.62	0.65

Conditions: PhBr (0.4 mmol), CyNC (0.6 mmol), EtONa (1 mL, 2M in EtOH), ligand as specified (10 mol%), $PdCl_2$ (5 mol%), toluene (3 mL). T=98 °C. Reactions performed in duplicate. Second ligandless reaction failed.

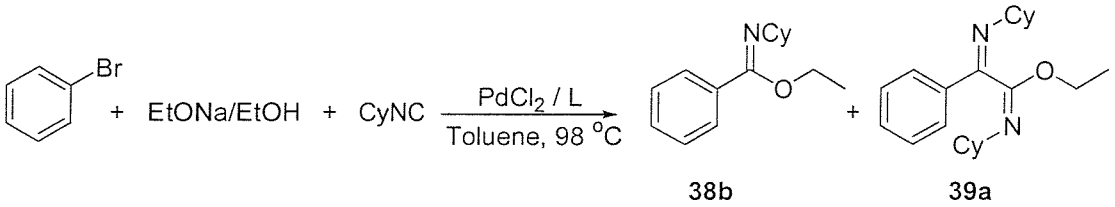
The results shown in Table 24 are sometimes inconsistent, but nevertheless useful for establishing trends. In the case of very low GC-yields, errors also arise by inaccurate integration of the peaks.

The bidentate ligands with a small bite angle (dppe and dppp) gave much worse overall conversion than dppf with a large bite angle. The comparison between P(*o*-Tol)$_3$, PPh_3 and PPh_2Me showed that the bulkier P(*o*-Tol)$_3$ gave a higher **38b** : **39a** ratio and also a much higher activity than the less bulky PPh_3 and PPh_2Me. The surprisingly good activity of PPh_2Me compared to PPh_3 might be due to steric and electronic effects cancelling out, as PPh_3 is bulkier and more electron-poor than PPh_2Me. The ligands tricyclohexylphosphine PCy_3 and *tris-tert*-butylphosphine P^{t}Bu$_3$ are bulkier and more electron-rich than the phenylphosphines. For PCy_3 the yield of **38b** and **39a** were overall poor, so it is deceptive to draw any conclusion about its

influence on the relative ratio. P^tBu_3 was comparable to PPh_3 and PPh_2Me and the ligand-free system appeared to work surprisingly well, though not of any use in this context.

5.2.4 Influence of the Isonitrile Stoichiometry

The effect of the CyNC-stoichiometry was investigated with the rationale that a low concentration of CyNC should favour the formation of the single insertion compound **38b** and the proportion of **39a** should increase with increasing CyNC-concentration. The reaction is given in Scheme 84.



Scheme 84

Reactions covering both extremes of CyNC-concentration (given in equivalents relative to PhBr) were examined. The results are shown in Table 25.

Table 25: Effect of [CyNC] on Formation of 38b and 39a

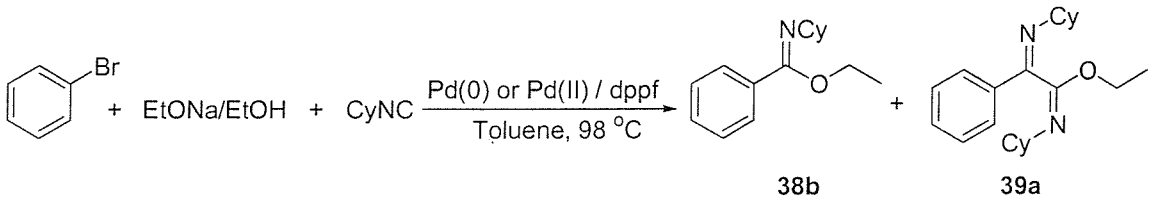
CyNC (eq)	Res. PhBr, (%)			38b, (GC, %)			39a (GC, %)			38b/39a		
	1 h	2 h	6 h	1 h	2 h	6 h	1 h	2 h	6 h	1 h	2 h	6 h
0.25	83.1	80.9	-	11.1	10.0	-	0	5.2	-	n/a	1.92	-
0.5	62.9	54.6	-	21.2	15.3	-	12.2	10.1	-	1.73	1.51	-
1	69.1	27.0	21.9	9.7	21.8	20.1	24.1	26.7	24.8	0.40	0.82	0.81
2	85.1	44.5	39.5	1.8	7.0	4.4	12.8	33.1	32.0	0.14	0.21	0.14
5	90	71	0	0.9	5.2	15.3	19.6	60.8	69.1	0.05	0.09	0.22

Conditions: PhBr (0.4 mmol), CyNC (0.25-5 mmol), EtONa (1 mL, 2M in EtOH), dppf (10 mol%), $PdCl_2$ (5 mol%), toluene (3 mL). T=98 °C.

It is interesting to see that even very low CyNC-concentration gave rise to formation of the double insertion product **39a** and the conversion increased with the concentration of CyNC. The reaction time also increased with increasing [CyNC]. This trend could be expected in the cases of low [CyNC], but the data in Table 25 indicates that high [CyNC] has a retarding effect on the reaction. Isonitriles are good ligands for palladium and the retarding effect is probably due to partial deactivation of the catalyst by the isonitrile to give complexes that are not catalytically active.

5.2.5 Effect of the Palladium Source

It was of interest to systematically compare palladium(0) and palladium(II)-sources in the context of this reaction. Also palladium on charcoal (Pd/C) as heterogeneous catalyst was considered. The investigated reactions are summarised as in Scheme 85 and the outcome is shown in Table 26.



38b **39a**

Scheme 85

Table 26: Effect of Palladium Source on Formation of 38b and 39a

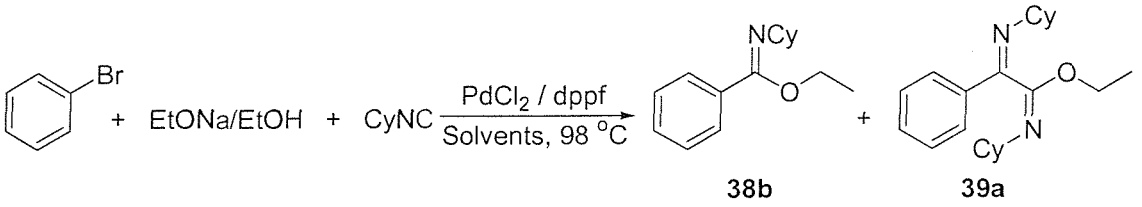
Pd-Source	Res. PhBr, (%)			**38b**, (GC, %)			**39a**, (GC, %)			**38b/39a**		
	1 h	2 h	16 h	1 h	2 h	16 h	1 h	2 h	16 h	1 h	2 h	16 h
$Pd_2DBA_3.CHCl_3$	55.1	0	-	8.1	32.4	-	25.7	40.0	-	0.32	0.81	-
"	0	-	-	23.8	-	-	35.1	-	-	0.68	-	-
Pd/C	96.2	81.7	0	2.0	3.1	8.8	3.7	6.2	10.1	0.54	0.50	0.87
$Pd(OAc)_2$	26.4	-	-	21.3	-	-	32.7	-	-	0.65	-	-
"	8.9	-	-	22.0	-	-	35.4	-	-	0.62	-	-
$PdCl_2$	29.4	9.3	-	7.9	31.8	-	31.3	44.3	-	0.25	0.72	-
"	36.7	14.1	-	3.8	28.9	-	26.9	43.2	-	0.14	0.67	-

Conditions: PhBr (0.4 mmol), CyNC (0.6 mmol), EtONa (1 mL, 2M in EtOH), dppf (10 mol%), $Pd_2DBA_3.CHCl_3$ (2.5 mol%), other Pd-sources (5 mol%), toluene (3 mL). T=98 °C. Duplicate reaction with Pd/C failed.

The effect of the palladium source did not seem very pronounced. In the case of palladium on charcoal, the yields were very poor. GC-analysis showed a very messy trace and complete disappearance of the starting materials, which indicated that the reaction did not proceed cleanly. In conclusion, there was no reason to switch from $PdCl_2$ to any other palladium source.

5.2.6 Effect of the Solvent

As seen in previous sections, the choice of solvent can greatly influence the outcome of palladium catalysed reactions. Therefore, a selection of co-ordinating and non co-ordinating solvents was examined as in Scheme 86.



38b **39a**

Scheme 86

All reactions apart from the cases of dioxane and toluene were carried out in sealed tubes and the results are shown in Table 27.

Table 27: Effect of the Solvent on Formation of 38b and 39a

Solvent	Res. PhBr, (%)		38b, (GC, %)		39a, (GC, %)		38b/39a	
	4 h	8 h	4 h	8 h	4 h	8 h	4 h	8 h
DME	-	0	-	21.2	-	63.4	-	0.33
"	-	0	-	24.4	-	58.7	-	0.41
Benzene	-	0	-	26.1	-	49.0	-	0.53
"	-	46.4	-	6.8	-	44.1	-	0.15
THF	-	5.1	-	17.3	-	70.4	-	0.25
"	-	0	-	19.8	-	65.0	-	0.30
Dioxane	6.7	-	33.2	-	44.7	-	0.74	-
"	4.0	-	35.3	-	48.6	-	0.73	-
Toluene	1.7	-	35.8	-	48.9	-	0.73	-

Conditions: PhBr (0.4 mmol), CyNC (0.6 mmol), EtONa (1 mL, 2M in EtOH), dppf (10 mol%), $PdCl_2$ (5 mol%), solvent (3 mL). T=98 °C. Reactions performed in duplicate. Control reaction with toluene.

It was noticed that THF and DME seemed to favour double insertion of CyNC. This was a very interesting result that required more investigation, as the reaction temperature was bound to be lower than 98 °C, considering the boiling points of THF and DME. The results relative to toluene and dioxane indicated that there was no difference in their capacity of biasing the reaction towards the formation of either **38b** or **39a**, which was in contrast with the findings accounted for in section 3.2. Although dioxane gave an overall yield of **38b** and **39a** lower than with toluene, it gave a higher **38b** : **39a** ratio. The temperature factor may explain why dioxane is so different from THF and DMF. As the internal pressure of the sealed tubes is not known, the actual internal temperature cannot be known with certainty, but this result prompted an investigation of the effect of the temperature on the reaction. $PdCl_2$ and $Pd_2DBA_3.CHCl_3$ were compared in this study because of the different electronic nature of the palladium and also because of the scarce solubility of the dichloride in toluene which, at lower temperatures, might prevent it from reacting. The palladium(0) precursor is soluble in toluene at room temperature. The results are given in Table 28.

Table 28: Effect of the Temperature on formation of 38b and 39a

T (°C)	Pd-Source	Res. PhBr, (%)				38b, (GC, %)				40a, (GC, %)				38b/39a			
		10 h	20 h	40 h	60 h	10 h	20 h	40 h	60 h	10 h	20 h	40 h	60 h	10 h	20 h	40 h	60 h
50	$Pd_2DBA_3.CHCl_3$	97.2	84.1	83.4	77.6	0	2.9	3.2	2.0	0	12.5	12.0	10.3	0	0.23	0.27	0.19
50	$PdCl_2$	98.3	96.1	94.4	85.7	0	0	0	0.7	0	1.8	2.9	4.0	0	0	0	0.18
70	$Pd_2DBA_3.CHCl_3$	76.2	63.8	47.6	33.1	0.5	1.0	2.5	7.8	17.2	28.5	40.1	45.3	0.03	0.04	0.06	0.17
70	$PdCl_2$	85.8	70.0	52.7	41.1	0.3	1.0	2.0	6.6	9.0	22.1	30.7	38.0	0.03	0.05	0.07	0.17
		1 h	4 h	8 h	12 h	1 h	4 h	8 h	12 h	1 h	4 h	8 h	12 h	1 h	4 h	8 h	12 h
90	$Pd_2DBA_3.CHCl_3$	70.3	38.6	28.2	20.7	3.6	13.4	21.9	20.6	21.2	33.0	39.1	39.9	0.17	0.41	0.54	0.52
90	$PdCl_2$	72.5	35.9	29.2	26.1	4.8	12.1	22.6	20.0	19.7	34.6	38.9	40.3	0.24	0.35	0.59	0.49
		0.5 h	1 h	2 h	4 h	0.5 h	1 h	2 h	4 h	0.5 h	1 h	2 h	4 h	0.5 h	1 h	2 h	4 h
110	$Pd_2DBA_3.CHCl_3$	71.6	41.3	19.7	17.8	4.5	15.2	32.6	31.7	22.3	32.4	40.6	38.6	0.20	0.47	0.80	0.82
110	$PdCl_2$	78.4	46.0	22.9	13.6	3.4	12.4	30.3	25.7	17.4	26.8	37.3	26.8	0.19	0.46	0.82	0.96

Conditions: PhBr (0.4 mmol), CyNC (0.6 mmol), EtONa (1 mL, 2M in EtOH), dppf (10 mol%), $PdCl_2$ (5 mol%), $Pd_2DBA_3.CHCl_3$ (2.5 mol%), toluene (3 mL). T as specified.

The **38b** : **39a** ratio was found to increase with increasing temperature. At 50 °C, the $PdCl_2$ reaction had a long induction time, but the final result was very similar to $Pd_2DBA_3.CHCl_3$. In the other cases, the final outcomes were all similar to each other and no induction period, possibly due to the low solubility of the dichloride in toluene at low temperature, was observed. As found in the investigation of palladium-catalysed amide and α-ketoamide formation, increasing the temperature also led to a larger proportion of single carbonylation product.[26] Although isonitriles and CO are electronically very similar, there are great physical differences. Whereas isonitriles are generally liquids or solids at room temperature, CO is a gas. It can therefore not be stated with certainty that the same factors influence the similar outcome in either case. Gibb's Free Energy (ΔG) of a reaction is given by the equation $\Delta G=\Delta H-T\Delta S$. As the entropy term ΔS is more negative for double carbenoid insertion than for the single insertion, ΔG becomes less negative at higher temperature, which diminishes the importance of the TΔS factor.

5.2.7 Conclusions

This study has not led to the establishment of clear-cut conditions for the synthesis of **38b** and **39a**. Mixtures of both these compounds are obtained, but some clear trends can nevertheless be seen.

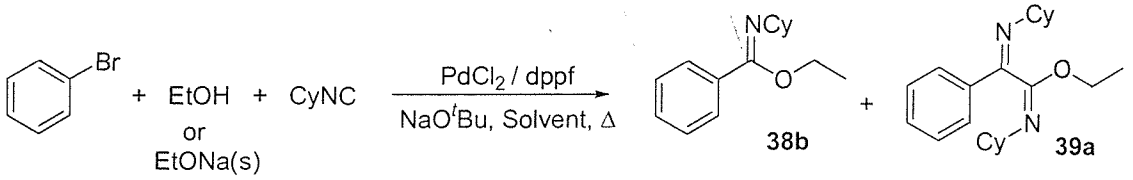
- The best ArX-source seems to be PhBr. PhOTf ethanolised before reaction.
- Use of 15-crown-5 favoured single insertion of CyNC.
- Examination of the ligands indicated that the bulkier P(*o*-Tol)$_3$ favoured single insertion of CyNC and the less bulky PPh_2Me double insertion, but there was no necessity to switch from dppf to other ligands.
- Increased CyNC-concentration favoured double insertion of the isonitrile.
- Varying the palladium source did not have any clear effect on the reaction.
- Use of THF in sealed tubes favoured double insertion of CyNC, possibly due to lower temperature
- The ratio of single to double insertion product increased with increasing temperature.

5.3 Examination of a Different Reaction System

Throughout the investigation accounted for in section 4.2, the ethoxide source has been a solution of sodium ethoxide in ethanol (NaOEt/EtOH). It is anticipated that the reactivity of the EtO^- depends on the tightness of the $[Na^+OEt]$ ion pair as well as hydrogen-bonding interactions between EtOH and EtO^-. It was therefore of interest to examine a system in which EtOH was not a major component. Another feature of interest was to find an easy way to change the counterion of EtO^- in order to determine the effect of the ion pair discussed above. One important difference to point out as for the set-up is that a new set of glassware was used for this part of the work. Glass vials with fitted, individual reflux condensers were used and the reactions carried out at the actual boiling point of the solvent, at atmospheric pressure.

5.3.1 Trials with Sodium *tert*-butoxide and Ethanol

An initial system taking into account the indicated requirements was the use of NaO^{t}Bu together with EtOH. In this case, EtOH was no longer a co-solvent as in the study described in section 4.2. The solvent optimisation (paragraph 4.2.6) showed that THF seemed to favour double insertion of CyNC. Use of dioxane and toluene led to very similar results, giving an improved **38b** : **39a** ratio. Therefore, THF, toluene and dioxane were compared together with the effect of solid NaOEt as in Scheme 87. The results are summarised in Table 29.



Scheme 87

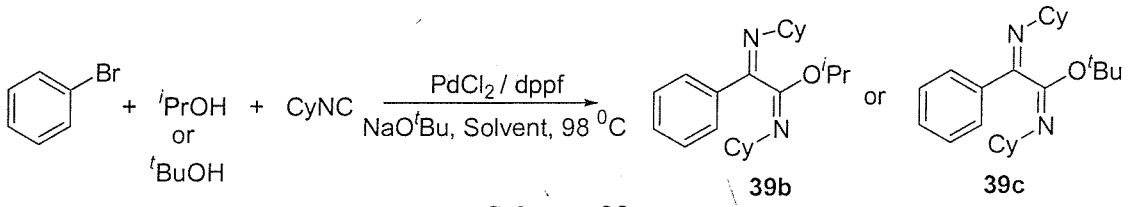
Table 29: Effect of Solvents and NaOEt(s) *vs* NaO^{t}Bu/EtOH on Formation of 38b and 39a

Solvent	Ethoxide Source	Res. PhBr, (%)		**38b**, (GC, %)		**39a** (GC, %)		**38b/39a**	
		15 h	65 h	15 h	65 h	15 h	65 h	15 h	65 h
Toluene	NaOEt	31.3	-	11.1	-	51.4	-	0.22	-
"	"	0	-	29.7	-	66.7	-	0.45	-
"	EtOH/NaO^{t}Bu	0	-	20.4	-	29.6	-	0.69	-
"	"	46.6	-	5.3	-	32.1	-	0.17	-
THF[a]	NaOEt	100	100	0	0	0	0	0	0
"	"	100	100	0	0	0	-	0	0
"	EtOH/NaO^{t}Bu	-	61.1	-	1.4	-	6.1	-	0.23
"	"	-	46.0	-	4.8	-	33.0	-	0.15
Dioxane	NaOEt	0	-	19.2	-	65.2	-	0.29	-
"	"	0	-	21.6	-	59.7	-	0.36	-
"	EtOH/NaO^{t}Bu	19.1	-	2.4	-	74.0	-	0.03	-
"	"	0	-	5.3	-	92.3	-	0.06	-

Conditions: PhBr (0.2 mmol), CyNC (0.6 mmol), NaO^{t}Bu (0.24 mmol), EtOH (1.0 mmol), dppf (10 mol%), $PdCl_2$ (5 mol%), solvent (2 mL). T=98 °C. a. T=65 °C. Duplicate reactions were performed.

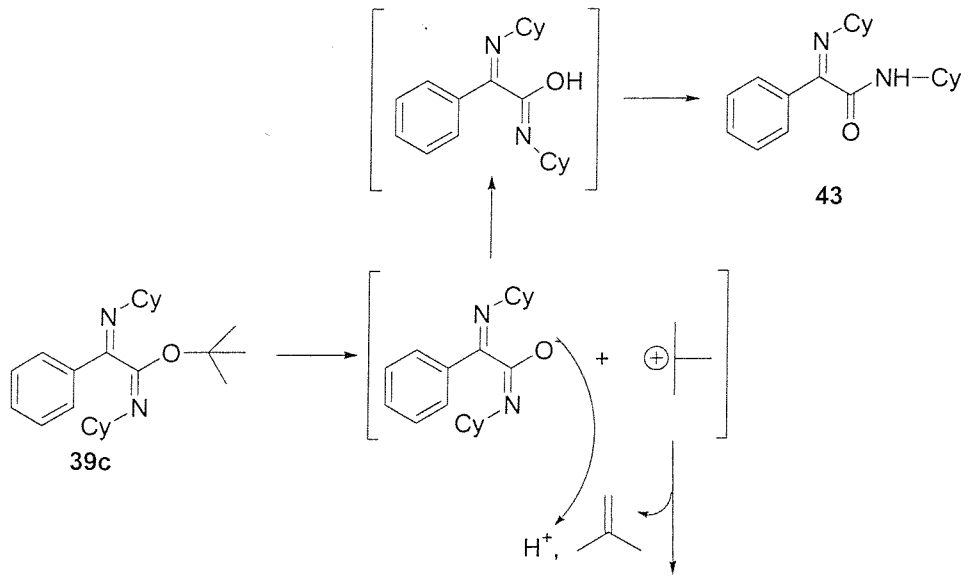
As seen, THF gave poor results, probably due to its low boiling point. Dioxane was better in the cases of NaOEt(s), possibly because of improved solubility of the sodium salt. In the case of NaO^{t}Bu/EtOH, use of dioxane led to very clean formation of the

double insertion product **39a** and this very good result was found to be reproducible, but unexplained. At this point, two important questions were raised; firstly, would it be possible to insert other alcohols and secondly, what effect would potassium *tert*-butoxide (KO^{t}Bu), with a weaker ion pair, have on the system? Investigation of reactions with isopropanol and *tert*-butanol indicated that the double insertion products **39b** and **39c** seemed to form very cleanly, as summarised in Scheme 88.



Scheme 88

The double insertion product **39b** formed as major product in a GC-yield of 92%. In the case of **39c**, the preparative reaction was attempted but the product isolated as *N*-cyclohexyl-2-cyclohexylimino-2-phenylacetimide **43**, which is probably formed in an E1-type reaction as shown in Scheme 89.

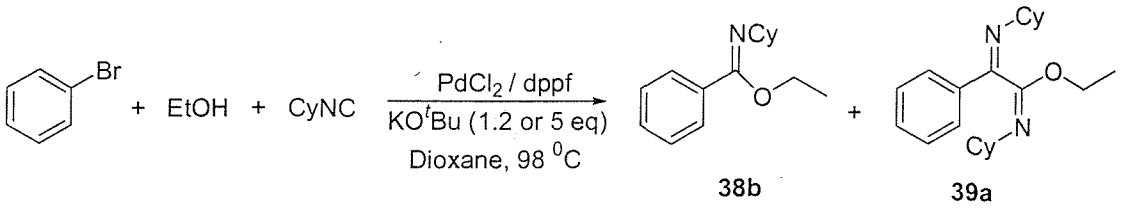


Scheme 89

Formation of **43** was conclusive; loss of the *tert*-butyl group was clearly indicated by NMR as well as Positive Electrospray Mass Spectroscopy (ES$^+$), which showed (M-

^{t}Bu) as the strongest ionisation peak. The same decomposition could take place for the single insertion product **43**, but this reaction has not been investigated.

Use of KO^{t}Bu is anticipated to favour single insertion of CyNC and the reactions in Scheme 90 investigated.



Scheme 90

In order to favour single insertion of CyNC, 1.5 eq rather than 3 eq of CyNC were used and **38b** and **39a** formed in a ratio of 7 : 3 when using 1.2 eq of KO^{t}Bu. These results required a more detailed investigation of the counterion effect. Lithium *tert*-butoxide LiO^{t}Bu, NaO^{t}Bu, KO^{t}Bu and caesium *tert*-butoxide CsO^{t}Bu were used for this purpose. LiO^{t}Bu gave limited conversions and overall non-conclusive GC-results. The results are summarised in Table 30.

Table 30: Effect of M^+-Counterion on Formation of 38b and 39a

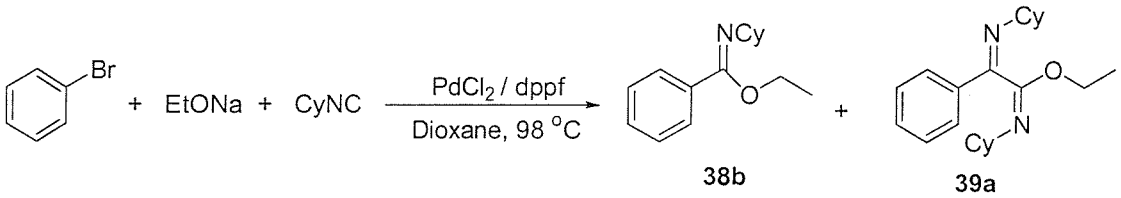
tert-Butoxide	Res. PhBr, (%)			38b, (GC, %)			39a, (GC, %)			38b/39a		
	1 h	2 h	4 h	1 h	2 h	4 h	1 h	2 h	4 h	1 h	2 h	4 h
NaO^{t}Bu	82.4	60.6	40.9	2.0	3.9	4.2	10.4	32.1	46.5	0.19	0.12	0.09
"	95.6	68.9	33.4	0	5.1	6.3	2.2	19.0	55.4	0	0.27	0.11
KO^{t}Bu	87.2	60.6	4.8	4.5	22.3	59.8	6.2	12.4	25.9	0.73	1.96	2.31
"	79.8	57.4	10.8	7.0	24.4	54.1	7.7	13.6	24.7	0.91	1.79	2.19
CsO^{t}Bu	89.0	31.3	14.2	2.3	45.7	64.1	3.4	8.4	10.2	0.67	5.44	6.28
"	81.6	24.4	17.9	7.4	52.0	66.4	4.1	10.3	11.4	1.80	5.05	5.82

Conditions: PhBr (0.4 mmol), CyNC (0.6 mmol), MO^{t}Bu (0.48 mmol), EtOH (2 mmol), dppf (10 mol%), $PdCl_2$ (5 mol%), dioxane (3 mL). T=98 °C. Reactions performed in duplicate.

It could be clearly established that the counterion had a marked effect on the outcome, with the sodium salt strongly favouring double isonitrile insertion and the caesium salt single insertion, though not as selectively as NaO^{t}Bu favoured double insertion.

5.3.2 Mechanistic Investigations

The very clean formation of double insertion products using the EtOH/NaO^{t}Bu-system is interesting but difficult to understand. How does the much lower concentration of EtOH of this system influence the outcome? The following experiment was carried out as shown in Scheme 1



Scheme 91

The volume of EtOH was kept constant and different amounts of NaOEt/EtOH-solution added. The results are given in Table 31.

Table 31: Effect of NaOEt-Concentration on the Formation of 38b and 39a

NaOEt (µL)	EtOH (µL)	Res. PhBr, (%)	38b, (GC, %)	39a, (GC, %)	38b/39a
60	440	18.2	2.3	34.4	0.066
"	"	41.8	1.7	21.2	0.080
120	380	24.3	3.4	41.3	0.082
"	"	16.8	2.3	40.7	0.057
240	260	19.4	5.2	43.1	0.13
"	"	0	7.0	53.8	0.13
500	0	0	10.8	48.7	0.22
"	"	0	15.9	50.1	0.32

Conditions: PhBr (0.4 mmol), CyNC (0.6 mmol), NaOEt (2 M in EtOH)/EtOH as specified, dppf (10 mol%), $PdCl_2$ (5 mol%), toluene (3 mL). T=98 °C. Samples taken after 15 h. Reactions performed in duplicate.

It was seen that low base concentration favoured double insertion of CyNC. This could now be concluded with certainty, as the EtOH-concentration was constant in all the experiments. Another important question was whether the presence of *tert*-butanol (^{t}BuOH), which is anticipated to insert much slower than EtOH had any effect? This feature was investigated by keeping the concentration of NaO^{t}Bu/^{t}BuOH constant (0.24 mmol NaO^{t}Bu in 0.24 mL ^{t}BuOH) and varying the amount of EtOH. The results are illustrated in Table 32.

Table 32: Effect of *tert*-Butanol on the Formation of 38b and 39a

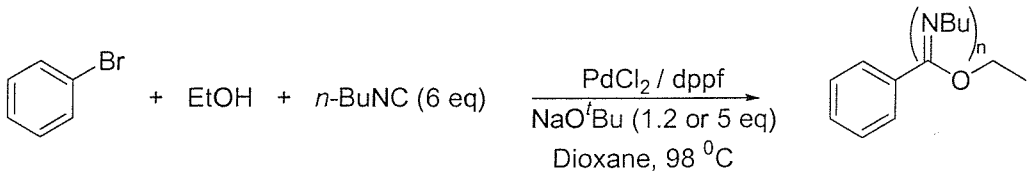
EtOH (mmol)	Res. PhBr, (%)	38b, (GC, %)	39a, (GC, %)	38b/39a
10	5.0	11.1	44.3	0.25
"	8.3	10.6	43.4	0.24
1	0.8	9.0	57.1	0.16
"	10.7	6.8	49.5	0.14
0.5	0	1.5	63.1	0.02
"	0	2.0	60.8	0.03
0.25	0	0.6	54.5	0.01
"	0	0.8	58.3	0.01

Conditions: PhBr (0.4 mmol), CyNC (0.6 mmol), EtOH as specified, NaO^{t}Bu (0.24 mmol in 0.24 mL BuOH), dppf (10 mol%), $PdCl_2$ (5 mol%), toluene (3 mL). T=98 °C. Samples taken after 15 h. GC-yields are reported. Reactions performed in duplicate.

Apart from the expected products **38b** and **39a**, the amide **43** and possibly **42** did also form. They could arise either from pathways as described in Scheme 92, or by ethene or EtOH-elimination from the products **38b** and **39a**. Even though it was not possible investigate the imidate formation from ^{t}BuOH in depth, the established formation of the decomposition product **43** accounted for the starting material and products not adding up in Table 32. As for **38b** and **39a**, increasing the quantity of EtOH seemed to disfavour their formation and an optimum EtOH-stoichiometry was found to be between 2.5-5 eq to PhBr. This result could not be explained in light of this investigation. In conclusion, this reaction was found to be very specific for the double isonitrile insertion and only its merits for preparative work can be described at this stage.

5.4 Preparative α-Iminoimidate Synthesis

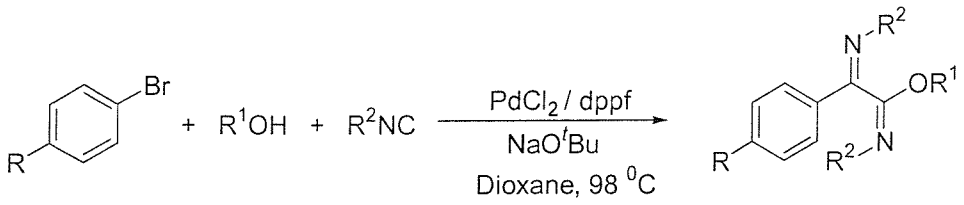
Use of the alcohol and NaO^{t}Bu allowed for the highly selective synthesis of α-iminoimidates, product of from double insertion of the isonitriles. It was therefore desirable to synthesise a range of α-iminoimidates from various aryl bromides and alcohols. Because of the limitation of the GC-analysis method due to the high molecular weights of possible products originating from triple or poly-insertion of the isonitriles, their formation could not be excluded. The following reaction was investigated in order to validate the proposed methodology for synthesis of α-iminoimidates and the chemistry is described in Scheme 92.



Scheme 92

The selectivity for double insertion of the isonitrile was investigated by carrying out the reaction with a large excess of *n*-BuNC. ^{13}C-NMR-spectroscopy clearly showed two (C=N) signals and ^{1}H-NMR was also indicated selective formation of the double insertion product **39b**. No signals for single and triple insertion products were observed. On the other hand, mass spectroscopy (ES^+) and GC-MS analysis contrasted these observations by indicating masses due to single (n=1) and triple (n=3) insertion of *n*-BuNC too. The selectivity for double isonitrile insertion therefore seems to be very high, but not complete.

The scope of the reaction was investigated by trying different combinations of aryl bromides, isonitriles and alcohols. Only aliphatic alcohols gave rise to double isonitrile insertion. Phenol gave single insertion exclusively. BnNC did not work in any of the cases and ^{t}BuNC gave rise to some double insertion only with electron-poor aryl bromides. The reactions to form double insertion products did not proceed cleanly and were therefore not viable for preparative purposes. CyNC and *n*-BuNC could be used in combination with any aryl bromide. With these results in hand it was possible to successfully undertake preparative work as outlined in Scheme 93.



Scheme 93

The α-iminoimidates **39a-39h** were isolated in good to excellent yields and the results given in Table 33. The synthetic procedure is described in the *Experimental Section.*

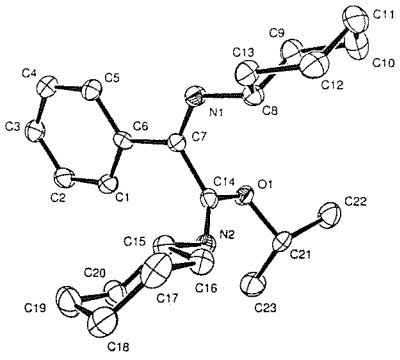
Table 33: Isolated α-Iminoimidates

ArX	R^1OH	R^2NC	Product	Yield, (%)
C_6H_5Br	EtOH	CyNC	**39a**	79
C_6H_5Br	EtOH	*n*-BuNC	**39b**	70[a]
C_6H_5Br	^{i}PrOH	CyNC	**39d**	88
p-$MeOC_6H_4Br$	EtOH	CyNC	**39e**	72
p-$MeOC_6H_4Br$	EtOH	*n*-BuNC	**39f**	74
p-$MeOC_6H_4Br$	^{i}PrOH	CyNC	**39g**	71
p-CN-C_6H_4Br	EtOH	CyNC	**39h**	73

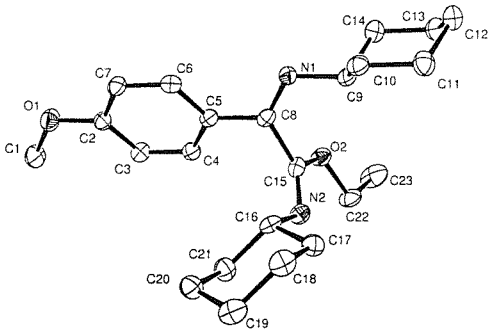
a. 40b isolated as a mixture of two isomers in a ratio of 92 : 8 by ^{1}H-NMR.

5.5 Structure Determination by X-Ray Crystallography

Crystals suitable for X-ray analysis were obtained by recrystallisation of the solid α-iminoimidates **39d** and **39e** from hexane. ORTEP-pictures of **39d** and **39e** are given below and (*Z,Z*)-configuration is observed. Only one of the components of the unit cells is depicted in Figure 6. For complete data, please see Appendix 1 and 2.



39d



39e

Figure 10

The most relevant bond lengths and bond angles are listed in Tables 34a and 34b.

Table 34a

Selected Bond Lengths and Angles for (39d)

C7-N1	1.275(3)
C7-C14	1.516(3)
C14-N2	1.266(3)
C14-O1	1.359(3)
N1-C7-C6	119.9(2)
N1-C7-C14	123.4(2)
N2-O1-C14	122.3(2)
N2-C14-C7	128.7(2)

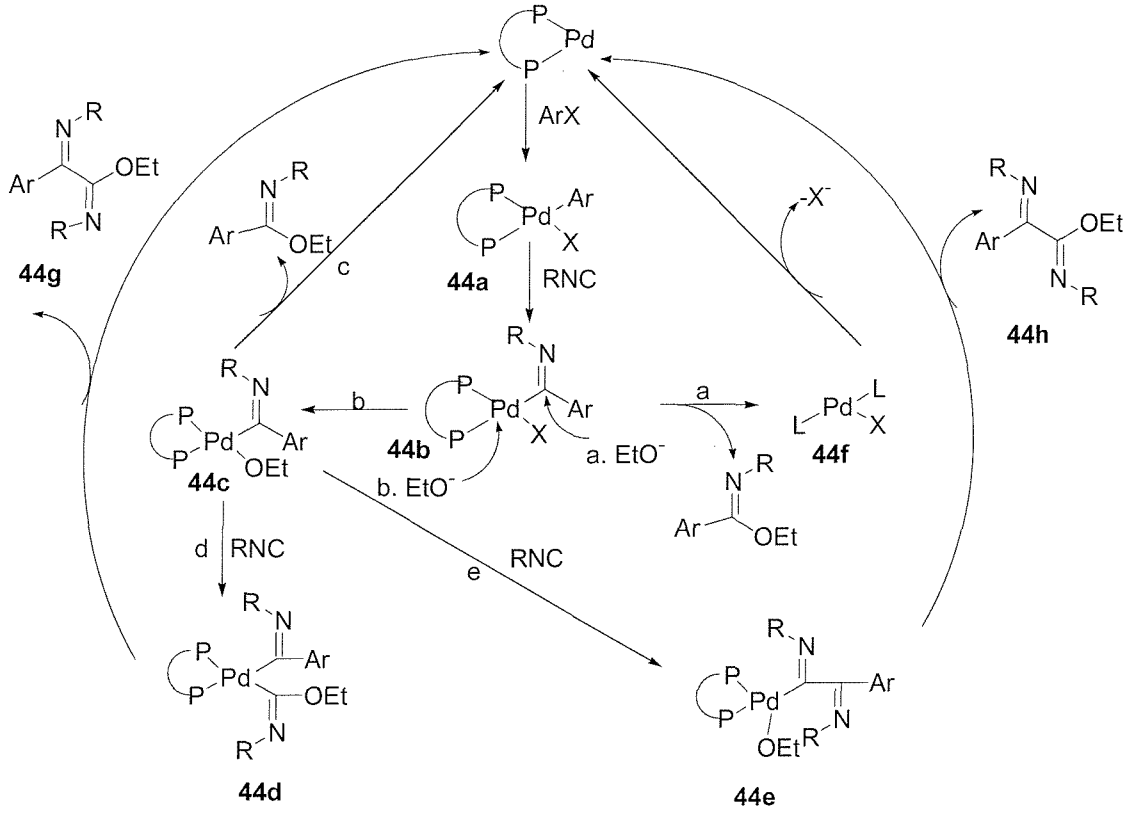
Table 34b

Selected Bond Lengths and Angles for (39e)

C8-N1	1.282(3)
C8-C15	1.505(4)
C15-N2	1.260(3)
C15-O2	1.359(3)
N1-C8-C5	120.8(3)
N1-C8-C15	123.3(2)
N2-O2-C15	122.2(3)
N2-C15-C8	128.0(2)

5.6 Mechanism

With the results described herein, it was not possible to draw any precise conclusions about the mechanism for single and double isonitrile insertion. Possible mechanisms could account for the formation of single and double insertion products are summarised in Scheme 94.



Scheme 94

The common steps for all these mechanisms are the oxidative addition and the first isonitrile insertion to form the intermediate **44b**, which can then undergo the following reactions:

a. Attack of the ethoxide anion EtO^- to the imino functionality, followed by reductive elimination to give the single isonitrile insertion product and the unstable anionic palladium(0)-species **44f**, which would lose the halide anion X^- to regenerate the active Pd(0)-catalyst under the concomitant formation of the salt metal halide salt MX, with M^+ being the counterion of EtO^-.

b. EtO^--attack onto the palladium centre, displacing the halide anion X^-. The species **44c** could either undergo reductive elimination *via* pathway **c** to yield the single insertion product or, if the second isonitrile insertion was faster than the reductive elimination, insert the second isonitrile molecule either into the palladium-oxygen bond (pathway **d**) or the palladium-carbon bond (pathway **e**). The intermediates

44d and **44e** could then, by reductive elimination, give rise to the products **44g** and **44h** respectively and regenerate the palladium catalyst.

Among the parameters discussed in this chapter, the following could be concluded:

- Strength of the ethoxide source: should influence pathway **a**. this was clearly seen, as the preference for formation of single insertion product **38b** was strongly depending on the alkali metal counterion M^+. For the formation of **38b** over **39a**, CsOEt>KOEt>NaOEt, *i.e.* the stronger ethoxide source clearly favoured single insertion of the isonitrile. This was also evident when investigating the influence of the crown ether 15-crown-5; addition of crown ether, giving a more powerful nucleophile, favoured single isonitrile insertion. The experiments with variable [EtO^-] also pointed in this direction; it would be difficult to rationalise how increased [EtO^-] could affect the **38b** : **39a** ratio if partition between single and double isonitrile insertion was from the common intermediate **44c**. Other features to be taken into account are that ethoxide attack on the palladium *vs* attack on the imide carbon may make different demands on EtO^- nucleophilicity and it would also be possible for **44c** to be attacked by a second EtO^-. The results obtained in this brief study were not sufficient to make predictions in these directions.

- Ligand effect: Bulky ligands will give a more hindered palladium centre, overall favouring single isonitrile insertion. Pathway **b** should be disfavoured over **a** and the reductive elimination step should, in general, be favoured. With the current results, it was not possible to make any predictions about the influence of the electronic nature of the ligands.

- Isonitrile concentration: A low isonitrile concentration favoured single insertion, whereas a higher concentration favoured the formation of the double insertion product **39a**. This observation is in strong support of pathway **d**.

- The relative configurations of the cyclohexyl groups of **39d** and **39e** obtained by X-ray crystallography can arise only from reductive elimination of **44d**. This is the strongest piece of evidence presented so far.

In conclusion, for the moment most evidence seems to point towards attack by the EtO^- on palladium to give the intermediate **44c**, from which partition then occurs. This observation would be consistent with partition between single (pathway **c**) and double isonitrile insertion (pathway **d**) as shown in the left-hand part of Scheme 95.

It must however be emphasised that more detailed and systematic mechanistic investigations would need to be performed in order to make more precise statements about the mechanism.

6 Experimental

6.1 General Notes

Reactions requiring inert atmosphere were carried out in oven-dried glassware using Standard Schlenk techniques. De-gassed reactions refer to freeze and thaw cycles of the reaction mixture prior to heating *in vacuo*. Toluene and THF were distilled over sodium and collected under argon. Oxygen-free dioxane was obtained by passing a stream of argon through dry solvent immediately prior to use. TLC-analysis was carried out using foil-backed sheets coated with silica gel (0.25 mm) and containing the fluorescent indicator UV_{254}. Column chromatography on silica used Kieselgel 60 230-400 mesh (Merck 9385) silica gel, columns being packed under light pressure.

6.2 Instrumentation

Proton NMR-spectra were obtained at 300 MHz on a Bruker AC 300 spectrometer or on a Bruker DPX 400 spectrometer at 400 MHz. Carbon NMR spectra were recorded at 75 MHz or 100 MHz on the above spectrometers. Signal multiplicities were determined using the Distortionless Enhancement by Polarisation Transfer (DEPT) spectral editing technique. Coupling constants (*J*) are given in Hz. Chemical shifts are reported in ppm on the δ-scale relatively to the signal of the solvent used.

Infra-red spectra were recorded on a Nicolet impact 400 spectrometer.

Gas Chromatography was performed on a Hewlett Packard HP6890 series, equipped with 7683 autoinjector and Hewlett Packard HP5 column (crosslinked with 5% PhMe silicone, 30m x 0.32mm x 0.25 nm). Liquid Chromatography-Mass Spectroscopy (LC-MS) was performed with an Agilent 1100 LCMSD instrument in positive electrospray mode.

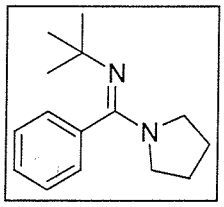
Melting points were determined in open capillary tubes using a Gallenkamp Electrothermal melting point apparatus and are uncorrected.

Kugelrohr-distillation was carried out with a Buchi 420851 oven.
UV-spectra were recorded on a Hewlett-Packard 8452A Diode Array Spectrometer using two-way quartz cells.

All low-resolution mass spectra were recorded on a Micromass Platform Quadrupole Mass Analyser in positive electrospray mode (ES^+), using acetonitrile as solvent. High resolution mass spectra were recorded on a Micromass LCT instrument in positive APCI-mode.

6.3 Preparative

Synthesis of (*E*)-*N*-(*tert*-Butyl)-*N* [1-phenyl-1-tetrahydro-1*H*-1-pyrrolylmethylidene]amine 23a[47]

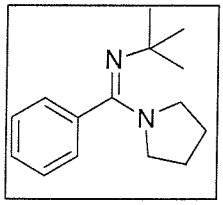


Iron(III) chloride (6.00 g, 0.037 mol) was covered with dry CCl_4 (30 mL) in a 100mL Schlenk flask fitted with a reflux condenser. Benzonitrile (5.00 g, 0.049 mol) was added by means of a syringe to the above slurry under vigorous stirring and a deep-red solution was obtained. After 10 min, *tert*-butyl chloride (4.23 g, 0.046 mol) was added, the solution turned yellow and under moderate heat evolution, a crystalline precipitate of the same colour began to appear. After 3 h stirring, a dense yellow slurry had formed, which was subsequently subject to aminolysis by addition of pyrrolidine (3.45 g, 0.048 mol) as a solution in dry DCM (20 mL) over 1 h at –10 °C. During the addition, the slurry turned brownish and after complete addition, the organic solvents were evaporated. The so-obtained brownish residue was taken up in water (15 mL) and NaOH-solution (25 mL, 8 M) was added dropwise over 10 min at 0 °C. Finally, extraction of the crude product was carried out by swirling with ether (8x30 mL) directly in the reaction flask, followed by isolation of the ethereal layers. The ethereal solution was dried over $NaSO_4$, evaporated and a brown oil (3.53 g) recovered. Excess benzonitrile was removed by gentle Kugelrohr-distillation and part of the residue (2.83 g) was left in the freezer for 12 days and another part used for purification attempts. The formation of a solid was observed and it was purified by precipitation from ether and pentane. The title product was obtained as a brown, crystalline solid (1.19 g, 14%), m.p. 50-51 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ= 7.563–7.578 (3H, m, Ph), 7.377-7.399 (2H, m, Ph), 4.289-4.311 (2H, m, CH_2), 3.052-3.095 (2H, m, CH_2), 2.103-2.146 (2H, m, CH_2), 1.872 (2H, app. brs, CH_2), 1.304 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$):

δ=161.83 (s, C=N), 131.92 (d, *CPh*), 130.19 (s, *CPh*), 129.54 (d, 2x*CPh*), 127.93 (d, 2x*CPh*), 58.01 (s, $C(CH_3)_3$), 52.37 (t, NCH_2), 51.26 (t, NCH_2), 31.32 (q, $3xCH_3$), 25.31 (t, CH_2), 25.10 (t, CH_2) ppm. **IR** (cm^{-1}, DCM-solution): 3685(m), 1612(s), 1453(m), 1193(m). **LRMS** (ES, m/z, %). Found: 231 (100, MH^+), 232 (18). **Elemental analysis** (%) calcd for $C_{15}H_{22}N_2$: C 78.21, H 9.63, N 12.16; found: C 78.37, H 10.06, N 12.31. **UV/Vis** (λ_{max}, nm): 210 (ε=6300), 228 (ε=8000), 322 (ε=370).

Synthesis of (*Z*)- *N*-(*tert*-Butyl)-*N* [1-phenyl-1-tetrahydro-1*H*-1-pyrrolylmethylidene]amine 23b

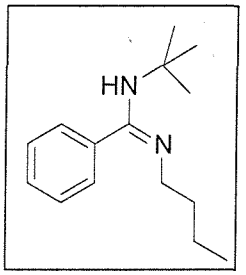


This preparation is given as a general procedure for the one-pot amidine synthesis.

Dry Cs_2CO_3 (0.85 g, 2.6 mmol), dppf (0.11 g, 0.20 mmol), PhBr (0.33 g, 2.0 mmol) and pyrrolidine (0.71 g, 10 mmol) were added to a 30 mL Schlenk tube under argon. Dry, de-gassed toluene (10 mL) was added, followed by ^{t}BuNC (0.34 mL, 3.0 mmol) and finally $PdCl_2$ (17.7 mg, 0.10 mmol) was added against a flow of argon. Another aliquote of toluene (10 mL) was added and the tube fitted with a stopper. The mixture was heated with stirring at 109 °C for 4 h. After cooling to room temperature, the reaction mixture was added to ether (20 mL) and the resulting slurry filtered to give a dark-brown solution which was extracted with dilute acetic acid (2.5% in water, 6x5 mL). The combined aqueous extractions were washed with ether (2x10 mL), then treated with a concentrated KOH-solution (30 mL) in presence of ether (20 mL). The ethereal layer was collected and the aqueous layer extracted with ether (3x30 mL). The combined ether phases were dried over $MgSO_4$ before evaporation. Kugelrohr distillation (oven temp 100–110 °C / 1 mmHg) gave the title compound as a pale yellow oil which crystallised to a white solid (0.36 g, 78%). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ=7.329–7.346 (3H, m, Ph), 7.201-7.226 (2H, m, Ph), 3.110 (4H, app. brs,

2xNCH$_2$), 1.786 (4H, app. brs, 2xCH$_2$), 1.001 (9H, s, 3xCH$_3$) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=156.55 (s, C=N), 139.34 (s, *CPh*), 128.53 (d, 2x*CPh*), 127.99 (d, 2x*CPh*), 127.88 (d, *CPh*), 52.80 (s, C(CH$_3$)$_3$), 47.60 (t, 2xNCH$_2$), 33.11 (q, 3xCH$_3$), 25.46 (t, 2xCH$_2$) ppm. **Elemental analysis** (%) calcd for $C_{15}H_{22}N_2$: C 78.21, H 9.63, N 12.16; found: C 78.06, H 9.83, N 11.99. **UV/Vis** (λ_{max}, nm): 210 (ε=6300), 228 (ε=8000), 322 (ε=370).

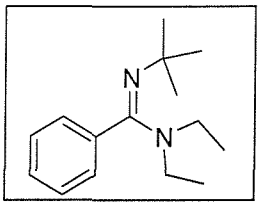
Synthesis of (*E*)-*N*1-Butyl-*N*'1-(*tert*-butyl)-1-benzenecarboximidamide 32a



The title product was synthesised from PhBr (0.32 g, 2.0 mmol), *n*-butylamine (0.72 g, 0.010 mol), Cs_2CO_3 (0.832 g, 2.6 mmol), dppf (0.12 g, 0.21 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (18.9 mg, 0.11 mmol) in dry toluene (20 mL). The mixture was heated under argon for 10 h and work-up gave the crude product as a brown oil. Further purification was achieved by Kugelrohr-distillation (oven temp 90-95 °C / 1 mmHg) which gave the title product as a pale-yellow oil (0.23 g, 50%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.348-7.385 (2H, m, Ph), 7.217-7.247 (3H, m, Ph), 3.003 (2H, t, J=7.0 Hz, CH$_2$), 1.420 (11H, brs, CH$_2$+3xCH$_3$), 1.295 (2H, sextet, J=7.4 Hz, CH$_2$), 0.844 (3H, t, J=7.4 Hz, CH$_3$) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ=157.30 (s, C=N), 137.32 (s, *CPh*), 128.39 (d, 2x*CPh*), 127.75 (d, 2x*CPh*), 127.44 (d, *CPh*), 51.42 (s, C(CH$_3$)$_3$), 50.83 (t, CH$_2$), 35.03 (t, CH$_2$), 29.44 (q, 3xCH$_3$), 20.70 (t, CH$_2$), 14.26 (q, CH$_3$) ppm. **LRMS** (ES, m/z, %). Found: 233 (100, MH$^+$). **HRMS** (APCI, MH$^+$). $C_{15}H_{25}N_2$ calculated: 233.2018, found: 233.2024. **IR** (cm^{-1}, neat): 2957 (s), 2926 (m), 2870 (m), 1640 (s), 1492 (m), 1377 (s), 1358 (s), 1220 (s). **UV/Vis** (λ_{max}, nm): 210 (ε=1300), 222 (ε=10400), 264 (ε=4400).

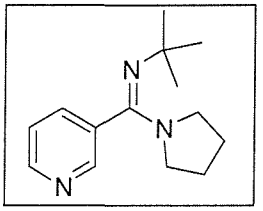
Synthesis of (*Z*)-*N*'1-(*tert*-Butyl)-*N*1, *N*1-diethyl-1-benzenecarboximidamide 21



Amidine **21** was synthesised from PhBr (0.32 g, 2.0 mmol), diethylamine (0.70 g, 9.6 mmol), Cs_2CO_3 (0.85 g, 2.6 mmol), dppf (0.11 g, 0.20 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (19.9 mg, 0.11 mmol). The mixture was heated at 109 °C for 6 h. Work-up followed by Kugelrohr-distillation (oven temp 80-90 °C / 1 mmHg) gave the title compound as a transparent oil, (0.14 g, 61%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.320-7.340 (3H, m, Ph), 7.199-7.208 (2H, m, Ph), 3.131 (4H, q, J=6.8 Hz, 2xCH_2), 1.017 (6H, t, J=6.8 Hz, 2xCH_3), 0.967 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=155.88 (s, C=N), 138.08 (s, *CPh*), 128.84 (d, 2x*CPh*), 127.73 (d, *CPh*), 127.56 (d, 2x*CPh*), 52.56 (s, $C(CH_3)_3$), 41.17 (t, 2xNCH_2), 32.70 (q, 3xCH_3), 13.60 (q, 2xCH_3) ppm. **HRMS** (APCI, MH^+). $C_{15}H_{25}N_2$ calculated: 233.2018, found: 233.2024. **IR** (cm^{-1}, neat): 2965 (m), 2356 (w), 1614 (s), 1596 (s), 1279 (m), 1200 (m), 1091 (m). **UV/Vis** (λ_{max}, nm): 210 (ε=10402), 228 (ε=10562), 260 (ε=4105).

Synthesis of (*Z*)-*N*-(*tert*-Butyl)-*N*-[1-(3-pyridyl)-1-tetrahydro-1*H*-1-pyrrolylmethylidene]amine 32i

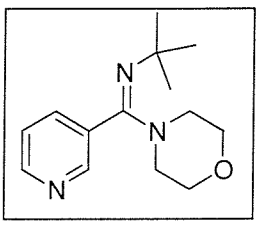


The synthesis was carried out from 3-bromopyridine (0.32 g, 2.0 mmol), pyrrolidine (0.73 g, 0.011 mol), Cs_2CO_3 (0.84 g, 2.6 mmol), dppf (0.11 g, 0.20 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (19.6 mg, 0.11 mmol) in dry toluene (20 mL). The

mixture was heated at 109 °C for 5 h. Work-up followed by Kugelrohr-distillation (oven temp 105-110 °C / 1 mmHg) gave the title compound as a transparent oil which crystallised in the freezer to give a white solid, (0.33 g, 71%), m.p. 28-30 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ=8.585 (1H, dd, J_1=5.2, J_2=1.9 Hz, Py), 8.482 (1H, d+fs, J=2.0 Hz, Py), 7.544 (1H, dt, J_1=7.7, J_2=1.9 Hz, Py), 7.298 (1H, dd, J_1=5.2, J_2=7.8 Hz, Py), 3.109 (4H, brs, 2xNCH_2), 1.803 (4H, brs, 2xCH_2), 0.994 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=152.78 (s, C=N), 149.02 (d, *CPy*), 148.92 (d, *CPy*), 135.68 (d, *CPy*), 134.84 (s, *CPy*), 122.94 (d, *CPy*), 52.82 (s, $C(CH_3)_3$), 47.59 (t, 2xNCH_2), 33.05 (q, 3xCH_3), 25.26 (t, 2xCH_2) ppm. **LRMS** (ES, m/z, %). Found: 232 (100, MH^+). **IR** (cm^{-1}, neat): 2962 (s), 2886 (m), 1606 (s), 1538 (s), 1473 (m), 1377 (s), 1356 (s), 1220 (m), 1186 (m), 1025 (m). **Elemental analysis** (%) calcd for $C_{14}H_{21}N_3$: C 72.69, H 9.15, N 18.16; found: C 72.72, H 9.22, N 18.47. **UV/Vis** (λ_{max}, nm): 212 (ε=10800), 224 (ε=11300), 260 (ε=5400).

Synthesis of (*Z*)-*N*-(*tert*-butyl)-*N*-[1-morpholino-1-(3-pyridyl)-methylidene]amine 32j.

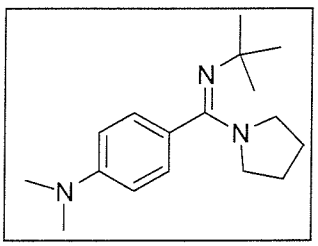


Compound **32j** was obtained from 3-bromopyridine (0.33 g, 2.1 mmol), morpholine (0.88 g, 0.010 mol), Cs_2CO_3 (0.83 g, 2.6 mmol), dppf (0.11 g, 0.20 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (20.2 mg, 0.11 mmol). The mixture was heated at 109 °C for 6 h. Work-up followed by Kugelrohr-distillation (oven temp 110-115 °C / 1 mmHg) gave the title compound as a pale-green, transparent oil, (0.28 g, 57%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ=8.590 (1H, dd, J_1=5.0, J_2=1.7 Hz, Py), 8.429-8.435 (1H, m, Py), 7.502 (1H, dt, J_1=7.5, J_2=1.7 Hz, Py), 7.296 (1H, dd, J_1=7.5, J_2=5.0 Hz, Py), 3.593 (4H, t, J=4.8 Hz, 2xCH_2), 3.082-3.097 (4H, m, 2xCH_2), 0.960 (9H, s,

3xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=153.92 (s, C=N), 149.50 (d, *CPy*), 149.27 (d, *CPy*), 136.18 (d, *CPy*), 132.89 (s, *CPy*), 122.96 (d, *CPy*), 66.88 (t, 2xOCH_2) 53.22 (s, $C(CH_3)_3$), 46.27 (t, 2xNCH_2), 32.64 (q, 3xCH_3) ppm. **LRMS** (ES, m/z, %). 248 (100, MH^+). **IR** (cm^{-1}, neat): 2963 (s), 2900 (m), 1622 (s), 1451 (m), 1409 (m), 1300 (m), 1146 (s). **Elemental analysis** (%) calcd for $C_{14}H_{21}N_3O$: C 67.98, H 8.56, N 16.99; found: C 67.96, H 8.28, N 16.61. **UV/Vis** (λ_{max}, nm): 210 (ε=10500), 258 (ε=4500).

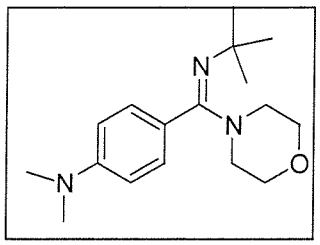
Synthesis of (*Z*)-*N*1, *N*1-dimethyl-4-[(*tert*-butylimino)-(tetrahydro-1*H*-1-pyrrolyl)methyl] aniline 32c



The amidine **32c** was synthesised from *N,N*-dimethyl-4-bromobenzene (0.40 g, 2.2 mmol), pyrrolidine (0.71 g, 0.010 mol), Cs_2CO_3 (0.81 g, 2.5 mmol), dppf (0.11 g, 0.20 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (21.6 mg, 0.12 mmol). The mixture was heated at 109 °C for 3 h. Work-up followed by Kugelrohr-distillation (oven temp 120-125 °C / 1 mmHg) gave the title compound as a white, crystalline material, (0.40 g, 74%), m.p. 91-92 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.050 (2H, d, J=8.5 Hz, Ar), 6.683 (2H, d, J=8.5 Hz, Ar), 3.161 (4H, app. brs, 2xCH_2), 2.984 (6H, s, 2xCH_3), 1.790 (4H, app. brs, 2xCH_2), 1.054 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$): δ=157.75 (s, C=N), 149.98 (s, *CAr*), 129.35 (d, 2x*CAr*), 128.83 (d, *CAr*), 111.53 (d, 2x*CAr*), 52.87 (s, $C(CH_3)_3$), 47.66 (t, 2xNCH_2), 40.53 (q, $N(CH_3)_2$), 33.14 (q, 3xCH_3) 25.50 (t, 2xCH_2) ppm. **LRMS** (ES, m/z, %).274 (100, MH^+). **IR** (cm^{-1}, neat): 2952 (s), 2855 (m), 2805 (m), 1597 (s), 1519 (s), 1378 (s), 1350 (s), 1221 (s), 1189 (m), 1165 (m). **Elemental analysis** (%) calcd for $C_{17}H_{27}N_3$: C 74.68, H 9.95, N 15.37; found: C 74.59, H 10.32, N 15.64. **UV/Vis** (λ_{max}, nm): 210 (ε=11900), 230 (ε=14300), 282 (ε=3200).

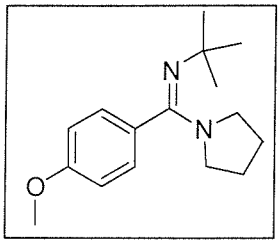
Synthesis of (*Z*)-*N*1, *N*1-dimethyl-4-[(*tert*-butylimino)-(morpholino)methyl]aniline 32d.



The amidine **32d** was synthesised according to the standard procedure from *N,N*-dimethyl-4-bromobenzene (0.40 g, 2.2 mmol) and morpholine (0.89 g, 0.011 mol), Cs_2CO_3 (0.86 g, 2.7 mmol), dppf (0.11 g, 0.11 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (20.4 mg, 0.11 mmol). The mixture was heated at 109 °C for 4 h. Work-up followed by Kugelrohr-distillation (oven temp 130-135 °C / 1 mmHg) gave **32d** as a yellow, crystalline material, (0.44 g, 76%), m.p. 125-127 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.014 (2H, d, J=8.4 Hz, Ar), 6.660 (2H, d, J=8.4 Hz, Ar), 3.595 (4H, t, J=4.3 Hz, 2xCH_2), 3.116 (4H, t, J=4.3 Hz, 2xCH_2), 2.976 (6H, s, 2xCH_3), 1.014 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=158.94 (s, C=N), 150.35 (s, C*Ar*), 129.89 (d, 2xC*Ar*), 124.42 (s, C*Ar*), 111.47 (d, 2xC*Ar*), 67.35 (t, 2xOCH_2), 53.21 (s, $C(CH_3)_3$), 46.58 (t, 2xNCH_2), 40.45 (q, 2xCH_3), 32.69 (q, 3xCH_3) ppm. **LRMS** (ES, m/z, %). Found 290 (100, MH^+). **IR** (cm^{-1}, neat): 2963 (m), 2891 (m), 1611 (s), 1522 (m), 1350 (s), 1250 (s), 1169 (s). **Elemental analysis** (%) calcd for $C_{17}H_{27}N_3O$: C 70.55, H 9.40, N 14.52; found: C 70.73, H 9.46, N 14.72. **UV/Vis** (λ_{max}, nm): 208 (ε=11900), 264 (ε=8900), 328 (ε=9100).

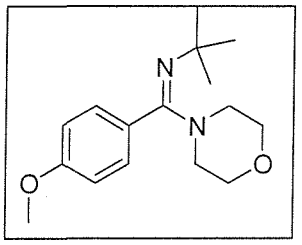
Synthesis of (*Z*)-*N*-(*tert*-butyl)-*N*-[1-(4-methoxyphenyl)-1-tetrahydro-1*H*-pyrrolylmethylidene]amine 32e



The amidine **32e** was synthesised from 4-bromoanisole (0.38 g, 2.0 mmol), pyrrolidine (0.71 g, 0.010 mol), Cs_2CO_3 (0.85 g, 2.6 mmol), dppf (0.12 g, 0.20 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (17.7 mg, 0.10 mmol) in dry toluene (20 mL). The mixture was heated at 109 °C for 2 h. Work-up followed by Kugelrohr-distillation (oven temp 100-110 °C / 1 mmHg) gave the title product as a pale-yellow oil that immediately crystallised to a white solid, (0.43 g, 83%), m.p. 56-57 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.123 (2H, d, J=8.8 Hz, Ar), 6.881 (2H, d, J=8.8 Hz, Ar), 3.834 (3H, s, OCH_3), 3.110 (4H, brm, 2x$\underline{C}H_2$), 1.762-1.806 (4H, m, 2x$\underline{C}H_2$), 1.015 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$): δ=159.24 (s, $\underline{C}Ar$), 156.63 (s, $\underline{C}$=N), 129.71 (d, 2x$\underline{C}Ar$), 129.11 (d, $\underline{C}Ar$), 113.40 (d, 2x$\underline{C}Ar$), 55.35 (q, O$\underline{C}H_3$) 52.83 (s, $\underline{C}(CH_3)_3$), 47.61 (t, 2xN$\underline{C}H_2$), 33.14 (q, 3x$\underline{C}H_3$), 25.48 (t, 2x$\underline{C}H_2$) ppm. **LRMS** (ES, m/z, %). Found: 261 (100, MH^+). **IR** (cm^{-1}, neat): 2958 (s), 2921 (m), 1597 (s), 1509 (m), 1375 (s), 1354 (s), 1245 (s), 1186 (m), 1221 (s), 1025 (m). **Elemental analysis** (%) calcd for $C_{16}H_{24}N_2O$: C 73.81, H 9.29, N 10.76; found: C 73.83, H 9.50, N 10.95 **UV/Vis** (λ_{max}, nm): 210 (ε=10700), 230 (ε=13500).

Synthesis of (*Z*)-*N*-(*tert*-butyl)-*N*-[1-(4-methoxyphenyl)-1-morpholinomethylidene]amine 32f.

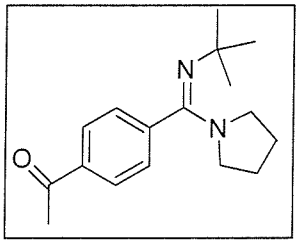


The amidine **32f** was obtained from 4-bromoanisole (0.38 g, 2.0 mmol), morpholine (0.87 g, 0.010 mol), Cs_2CO_3 (0.79 g, 2.4 mmol), dppf (0.12 g, 0.21 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (20.0 mg, 0.11 mmol) in dry toluene (20 mL). Work-up followed by Kugelrohr-distillation yielded a greyish solid, (0.42 g, 76%), m.p. 79-80 °C. ^{1}H-NMR indicated that two isomers of the title compound had formed in a ratio of 4 :1.

Major Isomer ^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.099 (2H, d, J=8.5 Hz, Ar), 6.879 (2H, d, J=8.5 Hz, Ar), 3.836 (3H, s, OCH_3), 3.603 (4H, t, J=4.8 Hz, 2xNCH_2), 3.292 3.103 (4H, t, J=4.8 Hz, 2xOCH_2), 0.998 (9H, s, CH_3) ppm. **Minor Isomer ^{1}H-NMR**[a] (300 MHz, $CDCl_3$): δ=3.671 (4H, t, J=5.2 Hz, 2xN$\underline{C}H_2$), 3.292 (4H, t, J=5.2 Hz, 2xO$\underline{C}H_2$), 1.361 (9H, s, 3x$\underline{C}H_3$) ppm. **Major Isomer ^{13}C-NMR** (75 MHz, $CDCl_3$): δ=159.57 (s, $\underline{C}$=N), 157.73 (s, $\underline{C}Ar$), 130.13 (d, 2x$\underline{C}Ar$), 129.13 (s, $\underline{C}Ar$), 113.40 (d, 2x$\underline{C}Ar$), 67.20 (t, 2x$O\underline{C}H_2$), 55.30 (q, $O\underline{C}H_3$), 53.14 (s, $\underline{C}(CH_3)_3$), 46.41 (t, 2xN$\underline{C}H_2$), 32.59 (q, 3x$\underline{C}H_3$) ppm. **Minor Isomer ^{13}C-NMR**[b] (75 MHz, $CDCl_3$): δ=66.62 (t, 2x$O\underline{C}H_2$), 55.14 (q, $O\underline{C}H_3$), 44.08 (t, 2xN$\underline{C}H_2$), 29.50 (q, 3x$\underline{C}H_3$) ppm. **LRMS** (ES, m/z, %). Found: 277 (100, MH^+). **IR** (cm^{-1}, neat): 3352 (m), 2965 (m), 2899 (m), 2843 (m), 1616 (s), 1506 (m), 1457 (m), 1360 (s), 1242 (s), 1243 (s). **Elemental analysis** (%) calcd for $C_{16}H_{24}N_2O_2$: C 69.53, H 8.75, N 10.14; found: C 69.35, H 8.84, N 10.53. **UV/Vis** (λ_{max}, nm): 206 (ε=10900), 230 (ε=10300), 244 (ε=8400).

a. The aromatic signals are not distinguishable in the ^{1}H-NMR-spectrum. b. The aromatic signals are not distinguishable in the ^{13}C-NMR-spectrum.

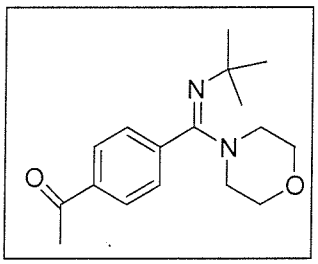
Synthesis of (*Z*)-1-{4-[(*tert*-butylimino)(tetrahydro-1*H*-1-pyrrolyl)methyl]phenyl}-1-ethanone 32g



The title compound was synthesised from 4-bromoacetophenone (0.40 g, 2.0 mmol), pyrrolidine (0.73 g, 0.010 mol), Cs_2CO_3 (0.83 g, 2.6 mmol), dppf (0.12 g, 0.20 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (19.5 mg, 0.11 mmol) in dry toluene (20 mL). The mixture was heated at 109 °C for 4 h. Work-up followed by Kugelrohr-distillation (oven temp 110-120 °C / 1 mmHg) gave **32g** as pale-yellow crystals, (0.33 g, 61%), m.p. 79-80 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.952 (2H, d, J=8.1 Hz, Ar), 7.336 (2H, d, J=8.1 Hz, Ar), 3.093 (4H, brs, 2xCH_2), 2.631 (3H, s, CH_3), 1.770-1.812 (4H, m, 2xCH_2), 0.995 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=197.81 (s, C=O), 155.03 (s, C=N), 144.46 (s, C*Ar*), 136.55 (s, C*Ar*), 128.86 (d, 2xC*Ar*), 128.10 (d, 2xC*Ar*), 52.87 (s, $C(CH_3)_3$), 47.59 (t, 2xNCH_2), 33.11 (q, 3xCH_3), 26.79 (q, CH_3), 25.41 (t, 2xCH_2) ppm. **LRMS** (ES, m/z, %). 273 (100, MH^+). **IR** (cm^{-1}, neat): 2963 (m), 2866 (m), 1679 (s), 1614 (s), 1598 (s), 1380 (s), 1356 (s), 1268 (m), 1220 (m). **Elemental analysis** (%) calcd for $C_{17}H_{24}N_2O$: C 74.96, H 8.88, N 10.28; found: C 74.62, H 8.93, N 10.28. **UV/Vis** (λ_{max}, nm): 210 (ε=13300), 240 (ε=17800), 278 (ε=2800).

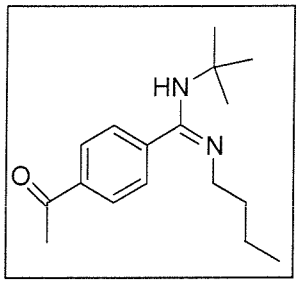
Synthesis of (*Z*)-1-{4-[(*tert*-butylimino)(tetrahydro-1*H*-1-morpholino)methyl]phenyl}-1-ethanone 32i



The title compound **32i** was synthesised from 4-bromoacetophenone (0.40 g, 2.0 mmol), morpholine (0.73 g, 0.010 mol), Cs_2CO_3 (0.81 g, 2.5 mmol), dppf (0.11 g, 0.20 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (19.8 mg, 0.11 mmol) in dry toluene (20 mL). The mixture was heated at 109 °C for 5 h. Work-up followed by Kugelrohr-distillation gave **32i** as yellow crystals, (0.35 g, 62%), m.p. 102-104 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.956 (2H, d, J=8.1 Hz, Ar), 7.322 (2H, d, J=8.1 Hz, Ar), 3.607 (4H, t, J=4.8 Hz, 2xCH_2), 3.090 (4H, t, J=4.8 Hz, 2xCH_2), 2.636 (3H, s, CH_3), 0.98 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=197.69 (s, C=O), 156.02 (s, C=N), 142.52 (s, C*Ar*), 136.67 (s, C*Ar*), 129.36 (d, 2xC*Ar*), 128.06 (d, 2xC*Ar*), 67.12 (t, 2xOCH_2), 53.23 (s, $C(CH_3)_3$), 46.26 (t, 2xNCH_2), 32.69 (q, 3xCH_3), 26.80 (q, CH_3) ppm. **Elemental analysis** (%) calcd for $C_{17}H_{24}N_2O_2$: C 70.80, H 8.39, N 9.71; found: C 70.69, H 8.24, N 9.64. **UV/Vis** (λ_{max}, nm): 210 (ε=14200), 238 (ε=16700), 274 (ε=5000).

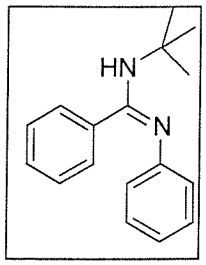
Synthesis of (*E*)-*N*'1-(*tert*-butyl)-*N*1-butyl-1-benzenecarboximidamine 32h



The title compound was synthesised from 4-bromoacetophenone (0.40 g, 2.0 mmol), *n*-butylamine (0.74 g, 0.010 mol), Cs_2CO_3 (0.82 g, 2.5 mmol), dppf (0.11 g, 0.20 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (18.9 mg, 0.11 mmol) in dry toluene (20 mL). The mixture was heated at 109 °C for 8 h. Work-up followed by Kugelrohr-distillation (oven temp 120-125 °C / 1 mmHg) gave an orange solid, (0.27 g, 49%), m.p. 74-76 °C, corresponding to **32h**.

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.969 (2H, d, J=8.1 Hz, Ar), 7.322 (2H, d, J=8.1 Hz, Ar), 2.947 (2H, t, J=7.0 Hz, CH_2), 2.624 (3H, s, CH_3), 1.41 (11H, brs, CH_2, 3xCH_3), 1.258 (2H, sextet, J=7.0 Hz, CH_2), 0.824 (3H, t, J=7.0 Hz, CH_3) ppm. **^{13}C-NMR** (75MHz, $CDCl_3$): δ=197.73 (s, C=O), 155.99 (s, C=N), 141.70 (s, *CAr*), 136.92 (s, *CAr*), 128.53 (d, 2x*CAr*), 128.07 (d, 2x*CAr*), 51.69 (s, $C(CH_3)_3$), 50.58 (t, NCH_2), 34.72 (t, CH_2), 29.38 (q, 3xCH_3), 26.69 (q, CH_3), 20.48 (t, CH_2), 14.04 (q, CH_3) ppm. **HRMS** (APCI, MH^+). $C_{17}H_{27}N_2O$ calculated: 275.2121, found: 289.2109. **IR** (cm^{-1}, neat): 3375 (m), 2958 (s), 2926 (s), 2866 (s), 2840 (s), 2495 (m), 1672 (s), 1633 (s), 1603 (m), 1520 (m), 1457 (s), 1385 (s), 1220 (s). **Elemental analysis** (%) calcd for $C_{17}H_{26}N_2O$: C 74.41, H 9.55, N 10.21; found: C 74.14, H 9.37, N 10.19. **UV/Vis** (λ_{max}, nm): 208 (ε=14900), 246 (ε=13200), 270 (ε=5300).

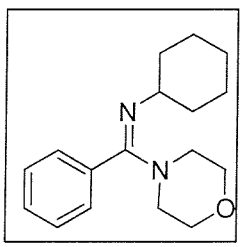
Synthesis of (*E*)-*N*-tert-Butyl-*N'*-phenyl-benzamidine 32b



The title compound was synthesised from PhBr (0.34 g, 2.1 mmol), aniline (0.93 g, 0.010 mol), Cs_2CO_3 (0.80 g, 2.4 mmol), dppf (0.12 g, 0.20 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol) and $PdCl_2$ (18.2 mg, 0.10 mmol) in dry toluene (20 mL). The mixture was heated at 109 °C for 20 h. Work-up followed by Kugelrohr-distillation (oven temp 140-150 °C / 1 mmHg) gave **32b** as yellow crystals, (0.24 g, 45%), m.p. 115-117 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.232 (5H, app. brs, Ph), 7.059 (2H, t, J=7.7 Hz, Ph), 6.782 (1H, t, J=7.4 Hz, Ph), 6.623 (2H, d, J=7.7 Hz, Ph), 4.372 (1H, s, NH), 1.56 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ=155.90 (s, C=N) 151.58 (s, *CPh*), 136.63 (s, *CPh*), 128.83 (d, *CPh*), 128.73 (d, 2x*CPh*), 128.37 (d, 2x*CPh*), 128.22 (d, 2x*CPh*), 122.96 (d, 2x*CPh*) 120.77 (d, *CPh*), 52.15 (s, $C(CH_3)_3$), 29.04 (q, 3xCH_3) ppm. **LRMS** (ES, m/z, %). 253 (100, MH^+). **IR** (cm^{-1}, neat): 2959 (w), 2893 (w), 1611 (s), 1598 (s), 1507 (s), 1483 (m), 1261 (m), 1209 (m). **Elemental analysis** (%) calcd for $C_{17}H_{20}N_2$: C 80.91, H 7.99, N 11.10; found: C 81.00, H 8.18, N 11.07. **UV/Vis** (λ_{max}, nm): 212 (ε=14400), 242 (ε=11100), 278 (ε=5000).

Synthesis of Cyclohexyl-(morpholin-4-yl-phenyl-methylene)amine 41c

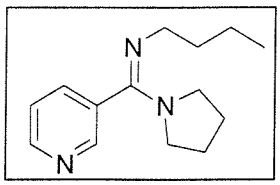


This preparation is characteristic for amidines obtained *via* imidates.

To a 50 mL Schlenk flask with a reflux condenser under argon at room temperature was added dppf (0.12 g, 0.22 mmol), sodium phenoxide (6 mL of a 1.7 M soln. in THF), PhBr (0.32 g, 2.1 mmol) in dry, deoxygenated dioxane (2 mL) and CyNC (0.38 mL, 3.0 mmol). $PdCl_2$ was then added against a counterflow of argon. Finally, dioxane (13 mL) was used to wash all solids from the sides of the flask and the flask was then heated at 98 °C (oil bath temp, the internal temp was 92 °C). After 3 h GC indicated complete loss of PhBr and the reaction mixture was allowed to cool to room temperature before morpholine (0.88 g, 0.010 mol) and glacial acetic acid (0.24 g, 4.0 mmol) in dioxane (2x1 mL) were added. After heating for 8 h at 98 °C, GC indicated complete loss of the intermediate imidate. After cooling to room temperature diethyl ether (20 mL) was added and the resulting slurry extracted with aqueous hydrochloric acid (6x10 mL, 0.2 M). The combined aqueous layers were washed with ether (6x15 mL) then made strongly basic by addition of KOH-pellets. The aqueous layer was then extracted with diethyl ether (6x30 mL), the ethereal layer dried over $MgSO_4$, filtered and evaporated to give brown-greyish crystals which were Kugelrohr-distilled (oven temp 120-130 °C / 1 mmHg) to give the title compound **41c** as white crystals, (0.35 g, 64%), m.p. 74-76 °C.

^{1}H-NMR (400 MHz, $CDCl_3$): δ=7.354-7.422 (3H, m, Ph), 7.149 (2H, dd, J=7.8, 2.0 Hz, Ph), 3.683 (4H, t, J=4.8 Hz, 2xOCH_2), 3.190 (4H, t, J=4.8 Hz, 2xNCH_2), 2.795 (1H, tt, J=10.2, 4.1 Hz, NCH), 1.683 (2H, d pentet, J=13, 3.7 Hz, 2xCH), 1.520-1.552 (3H, m), 1.386 (2H, qd, J=11.7, 3.3 Hz, CH_2), 1.189 (2H, qt, J=12.0, 3.5 Hz, CH_2), 1.080 (1H, qt, J=12.2, 3.4 Hz, CH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ=160.41 (s, C=N), 135.07 (s, *CPh*), 128.91 (d, 2x*CPh*), 128.76 (d, *CPh*), 128.15 (d, 2x*CPh*), 67.33 (t, 2xOCH_2), 58.71 (d, NCH), 46.87 (t, 2xNCH_2), 35.76 (t, 2xCH_2), 26.15 (t, CH_2), 25.23 (t, 2xCH_2) ppm. **LRMS** (ES^+, m/z, %): 273.1 (MH^+, 100%). **IR** (cm^{-1}, neat): 2955 (m), 2930 (m), 2879 (m), 1608 (s), 1586 (m), 1407 (m), 1337 (m), 719 (m). **Elemental analysis** (%) calcd for $C_{17}H_{24}N_2O$: C 74.96, H 8.88, N 10.28; found: C 74.89, H 8.96, N 10.11. **UV/Vis** (λ_{max}, nm): 210 (ε=10400).

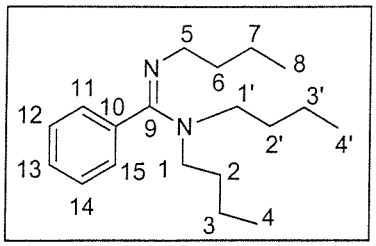
Synthesis of Butyl-(pyridin-3-yl-pyrrolidin-1-yl-methylene)amine 41d



The intermediate imidate was obtained from 3-bromopyridine (0.33 g, 2.1 mmol), dppf (0.12 g, 0.20 mmol), sodium phenoxide (6 mL of a 1.7 M soln. in THF), *n*-BuNC (0.32 mL, 3.0 mmol) and $PdCl_2$ (18.0 mg, 0.10 mmol) in dioxane (15 mL). After heating at 98 °C for 4 h the reaction mixture was allowed to cool to room temperature. Pyrrolidine (0.71 g, 0.010 mol) and glacial acetic acid (0.24 g, 4.0 mmol) were added and the resulting mixture heated under argon at 98 °C for further 3 h. Work-up and Kugelrohr-distillation (oven temp 130–135 °C / 1 mmHg) gave the amidine **41d** as a transparent oil (0.40 g, 83%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ=8.618 (1H, dd, J_1=4.8, J_2=1.5 Hz, Py), 8.453 (1H, s+fs, Py), 7.497-7.521 (1H, m, Py), 7.356 (1H, dd, J_1=5.0, J_2=2.2 Hz, Py), 3.206 (4H, app. brs, 2xCH_2), 2.944 (2H, t, J=7.4 Hz, CH_2), 1.831-1.863 (4H, m, 2xCH_2), 1.399 (2H, pentet, J=7.7 Hz, CH_2), 1.223 (2H, sextet, J=7.4 Hz, CH_2), 0.797 (3H, t, J=7.4 Hz, CH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ=156.80 (s, C=N) 149.60 (d, *CPy*), 148.54 (d, *CPy*), 135.24 (d, *CPy*), 131.98 (s, *CPy*), 123.60 (d, *CPy*), 50.80 (t, NCH_2), 47.76 (t, 2xNCH_2) 35.16 (t, CH_2), 25.38 (t, 2xCH_2), 20.62 (t, CH_2), 14.16 (q, CH_3) ppm. **LRMS** (ES^+, m/z, %): 232.1 (MH^+, 100). **HRMS** (APCI, MH^+). $C_{14}H_{22}N_3$ calculated: 232.1814, found: 232.1815. **IR** (cm^{-1}, neat): 2976 (m), 2920 (s), 2848 (w), 1621 (s), 1593 (m), 1454 (m), 1252 (m). **UV/Vis** (λ_{max}, nm): 212 (ε=10800), 252 (ε=5100).

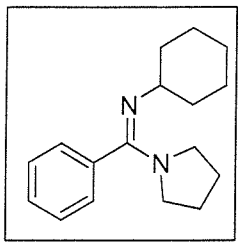
Synthesis of *N*, *N*, *N'*-Tributyl-benzamidine 41f



The intermediate imidate was obtained from PhBr (0.32 g, 2.1 mmol), dppf (0.12 g, 0.21 mmol), sodium phenoxide (6 mL of a 1.7 M soln. in THF), *n*-BuNC (0.32 mL, 3.0 mmol) and $PdCl_2$ (20.0 mg, 0.11 mmol) in dioxane (15 mL). After heating at 98 °C for 4 h the reaction mixture was allowed to cool to room temperature. Dibutylamine (1.31 g, 0.010 mol) and glacial acetic acid (0.24 g, 4.0 mmol) were added and the resulting mixture heated under argon at 98 °C for further 72 h. Work-up and Kugelrohr-distillation (oven temp 160–165 °C / 1 mmHg) gave **41f** as a transparent oil (0.37 g, 62%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.316-7.355 (3H, m, 12-14), 7.097 (2H, dd, J_1=5.7, J_2=1.4 Hz, Ph), 3.113 (4H, brs, 1, 1'), 2.868 (2H, t, J=7.4 Hz, 5), 1.464 (4H, pentet, J=7.7 Hz, 2, 2'), 1.373 (2H, pentet, J=7.4 Hz, 6), 1.123-1.244 (2H, m, 7), 1.147-1.257 (4H, m, 3, 3'), 0.828 (6H, t, J=7.4 Hz, 4, 4'), 0.774 (3H, t, J=7.4 Hz, 8) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ=161.20 (s, 9) 135.70 (s, 10), 128.37 (d, 11, 15 *or* 12, 14), 128.20 (d, 13), 127.97 (d, 11, 15 *or* 12, 14), 50.61 (t, 5), 46.97 (t, 1, 1'), 34.96 (t, 6), 30.40 (t, 2, 2'), 20.57 (t, 7), 20.24 (t, 3, 3'), 14.17 (q, 8), 14.08 (q, 4, 4') ppm. **LRMS** (ES^+, m/z, %): 289.3 (MH^+, 100). **HRMS** (APCI, MH^+). $C_{19}H_{33}N_2$ calculated: 289.2644, found: 289.2630. **IR** (cm^{-1}, neat): 2964 (m), 2931 (m), 2855 (w), 1616 (s), 1593 (m), 1464 (m), 1304 (m). **UV/Vis** (λ_{max}, nm): 210 (ε=9800), 222 (ε=9300), 262 (ε=2900).

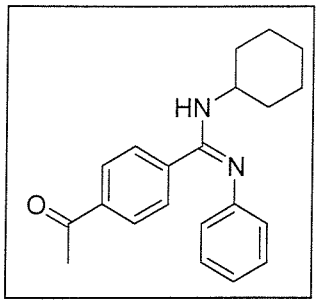
Synthesis of *N*-Cyclohexyl-*N*-[1-phenyl-1-tetrahydro-1*H*-1-pyrrolylmethylidene]amine 26



The intermediate imidate was obtained from PhBr (0.32 g, 2.0 mmol), dppf (0.12 g, 0.22 mmol), sodium phenoxide (6 mL of a 1.7 M soln. in THF), CyNC (0.38 mL, 3.0 mmol) and $PdCl_2$ (19.2 mg, 0.11 mmol) in dioxane (15 mL). After heating at 98 °C for 3 h the reaction mixture was allowed to cool to room temperature. Pyrrolidine (0.68 g, 9.6 mmol) and glacial acetic acid (0.25 g, 4.1 mmol) were added and the resulting mixture heated under argon at 98 °C for further 2 h. Work-up and Kugelrohr-distillation (oven temp 170-185 °C / 1 mmHg) gave the title compound as a white solid, (0.31 g, 60%), m.p. 55-56°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.393-7.418 (3H, m, Ph), 7.151-7.171 (2H, m, Ph), 3.194 (4H, brs, 2xCH_2), 2.691 (1H, tt, J_1=4.3, J_2=10.0 Hz, CH), 1.827 (4H, brs, 2xCH_2), 1.634 (2H, d pentet, J_1=10.2, J_2=3.4 Hz, CH_2), 1.453-1.539 (4H, m, 2xCH_2), 0.998-1.144 (4H, m, 2xCH_2) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=158.57 (s, C=N), 136.74 (s, *CPh*), 128.58 (d, 2x*CPh*) 128.07 (d, *CPh*), 127.23 (d, 2x*CPh*), 58.56 (d, NCH) 47.73 (t, 2xNCH_2), 35.83, (t, 2xCH_2), 25.80 (t, 2xCH_2), 25.37 (t, 3xCH_2) ppm. **LRMS** (ES, m/z, %). Found: 257 (100, MH^+). **IR** (cm^{-1}, DCM-solution): 3034(m), 2928(s), 2853(s), 2357(w), 1591(s), 1416(m), 1360(m), 1070(m). **Elemental analysis** (%) calcd for $C_{17}H_{24}N_2$: C 79.64, H 9.44, N 10.92; found: C 79.33, H 9.31, N 10.48. **UV/Vis** (λ_{max}, nm): 212 (ε=14400), 226 (ε=14500), 258 (ε=4900).

Synthesis of 4-Acetyl-*N*-cyclohexyl-*N'*-phenyl-benzamidine 41a

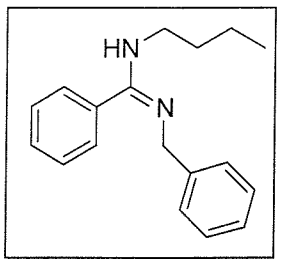


The intermediate imidate was obtained from 4-bromoacetophenone (0.41 g, 2.0 mmol), dppf (0.12 g, 0.21 mmol), sodium phenoxide (6 mL of a 1.7 M soln. in THF, 0.010 mol), CyNC (0.38 mL, 3.0 mmol) and $PdCl_2$ (19.2 mg, 0.11 mmol) in dioxane (15 mL). After heating at 98 °C for 3 h the reaction mixture was allowed to cool to room temperature. Aniline (0.95 g, 0.010 mol) and glacial acetic acid (0.24 g, 4.0 mmol) were added and the resulting mixture heated under argon at 98 °C for further 74 h. Work-up and Kugelrohr-distillation (oven temp 170-185 °C / 1 mmHg) gave the title compound **41a** as a yellow solid, (0.54 g, 84%), m.p. 143-145 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.803 (2H, d, J=8.1 Hz, Ph), 7.299 (2H, d, J=8.1 Hz, Ph), 7.035 (2H, t, J=7.4 Hz, Ph), 6.787 (1H, t, J=7.4 Hz, Ph), 6.603 (2H, d, J=7.4 Hz, Ph), 4.421 (1H, s, NH), 4.048 (1H, app. brs, CH), 2.541 (3H, s, CH_3), 2.186 (2H, app. brs, CH_2), 1.641-1.779 (4H, brm, 2xCH_2), 1.446-1.484 (2H, brm, CH_2), 1.229-1.298 (4H, brm, 2xCH_2) ppm. **^{13}C-NMR**[a] (75 MHz, $CDCl_3$) δ=197.45 (s, C=O), 150.78 (s, *CPh*), 137.01 (s, *CPh*), 128.84 (d, 2x*CPh*), 128.40 (d, 2x*CPh*), 128.16 (d, 2x*CPh*), 122.94 (d, 2x*CPh*), 121.32 (d, *CPh*), 49.62 (d, NCH), 33.05 (t, CH_2), 26.66 (q, CH_3), 25.85 (t, CH_2), 24.87 (t, 3xCH_2) ppm. **LRMS** (ES, m/z, %). 321 (100, MH^+). **IR** (cm^{-1}, neat): 2927 (s), 2858 (m), 1670 (s), 1624 (m), 1448 (m), 1286 (m), 1203 (s). **Elemental analysis** (%) calcd for $C_{21}H_{24}N_2O$: C 78.71, H 7.55, N 8.74; found: C 78.46, H 7.69, N 8.66. **UV/Vis** (λ_{max}, nm): 208 (ε=14200), 250 (ε=14700).

a. (s, *CPh*) missing in the ^{13}C-NMR spectrum.

Synthesis of *N*-Benzyl-*N'*-butyl-benzamidine 41e

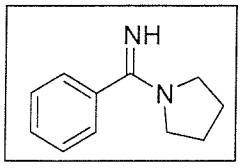


The intermediate imidate was obtained from PhBr (0.33 g, 2.1 mmol), dppf (0.12 g, 0.21 mmol), sodium phenoxide (6 mL of a 1.7 M soln. in THF, 0.010 mol), *n*-BuNC (0.28 mL, 3.0 mmol) and $PdCl_2$ (18.4 mg, 0.10 mmol) in dioxane (15 mL). After heating at 98 °C for 4 h the reaction mixture was allowed to cool to room temperature. Benzylamine (1.05 g, 0.010 mol) and glacial acetic acid (0.24 g, 4.0 mmol) were added and the resulting mixture heated under argon at 98 °C for further 18 h. Work-up and Kugelrohr-distillation (oven temp 140-150 °C / 1 mmHg) gave the title compound as a yellow oil, (0.23 g, 45%).

^{1}H-NMR (400 MHz, DMSO-d_6, 373 K) δ=7.368-7.441 (2H, m, Ph), 7.228-7.286 (7H, m, Ph), 7.143-7.119 (1H, m, Ph), 4.308 (2H, s, CH_2), 3.196 (2H, app. brs, NCH_2), 1.509 (2H, pentet, J=7.3 Hz, CH_2), 1.334 (2H, sextet, J=7.3 Hz CH_2), 0.877 (3H, t, J=7.3 Hz) ppm. **^{13}C-NMR**[a] (100 MHz, DMSO-d_6, 373 K) δ=159.48 (s, C=N), 143.41 (s, *CPh*), 137.06 (d, s, *CPh*), 128.99 (d, 2x*CPh*), 128.66 (d, 2x*CPh*), 128.34 (d, 2x*CPh*), 127.96 (d, 2x*CPh*), 126.70 (d, *CPh*), 20.57 (t, CH_2), 14.33 (q, CH_3) ppm. **LRMS** (ES, m/z, %). 267.1 (100, MH^+). **HRMS** (APCI, MH^+). $C_{18}H_{23}N_2$ calculated: 267.1861, found: 267.1858. **IR** (cm^{-1}, neat): 2966 (m), 2925 (m), 2858 (m), 1634 (s), 1491 (s), 1286 (m). **UV/Vis** (λ_{max}, nm): 2128 (ε=13500), 260 (ε=3500).

a. Missing signals: NCH_2, $NHCH_2$. One of the butyl methylene group's CH_2 is very ill-defined.

Synthesis of Phenyl (tetrahydro-1*H*-1-pyrrolyl) methanimine 31



A. According to the Literature Procedure[58]

Pyrrolidine (1.0 g, 0.014 mol) was introduced into a 100 mL Schlenk flask fitted with a reflux condenser together with dry ether (5 mL). Methylmagnesium bromide (3.0 M in ether, 4.7 mL, 0.014 mol) was added with a dry syringe and the resulting solution refluxed for 30 min. A white slurry formed. Benzonitrile (0.70 g, 6.8 mmol) in dry ether (7 mL) was added dropwise to the slurry, and the mixture refluxed for 2h. After cooling, an ether : conc. HCl-solution (4 : 1), (15 mL) was added. Finally, a concentrated KOH-solution was added and a white precipitate was formed. The reaction mixture was filtered, the solid residue washed with $CHCl_3$ (10 mL) and the aqueous layer extracted with $CHCl_3$ (3x25 mL). The combined organic solutions were dried over $MgSO_4$ and the solvent then evaporated under reduced pressure. A yellow oil (1.06 g) was obtained and the crude product was purified by Kugelrohr-distillation, (oven temp 85-95 °C / 1 mmHg). The title compound in its pure form was isolated as a yellow oil, (0.81 g, 68%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.358 (5H, s, Ph), 5.524 (1H, brs, NH), 3.348 (4H, brs, 2xCH_2), 1.900 (4H, brs, CH_2) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=167.47 (s, C=N), 139.71 (s, *CPh*), 128.93 (d, *CPh*), 128.56 (d, 2x*CPh*), 126.61 (d, 2x*CPh*), 48.20 (t, 2xNCH_2), 25.81 (t, 2x CH_2) ppm. **LRMS** (ES, m/z, %). Found: 175.0 (100, MH^+). **HRMS** (APCI, MH^+). $C_{11}H_{15}N_2$ calculated: 175.1235, found: 175.1232. **IR** (cm^{-1}, neat): 4048 (m), 3312 (s), 3056 (s), 2966 (s), 2867 (s), 1586 (s), 1450 (s), 1345 (s), 1217 (s), 1180 (s), 1027 (s). **UV/Vis** (λ_{max}, nm): 210 (ε=11800), 226 (ε=12700), 264 (ε=6200).

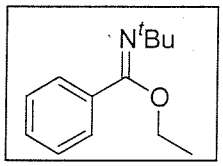
B. By *tert*-butyl deprotection of 23b[56]

The amidine **23b** was synthesised on a 2 mmol scale in toluene as described in this section and the crude material isolated by evaporation of the solvent as a dark-brown oil (0.63 g). Hydrochloric acid (20 mL, 6 M) was added and the mixture heated in a Schlenk tube at 80 °C for 18 h. The reaction mixture was allowed to cool to room temperature before adding it to ether (30 mL). The aqueous layer was separated and was further washed with ether (3x10 mL) before basification with KOH-pellets. The

alkaline aqueous solution was extracted with ether (4x15 mL), the ethereal layer dried over $MgSO_4$ and evaporated to give a brown oil (0.23 g), which was found to correspond to the title product of 85% purity. Further purification was achieved by Kugelrohr-distillation and a pale-yellow oil (0.21 g, 60%) corresponding to **31** was isolated. The characterisation data is in agreement with the above.

Synthesis of 1-Ethyl-*N*1-(*tert*-butyl)-1-benzenecarboximidate 38a

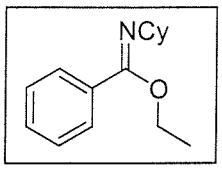
This preparation is characteristic for imidates



To a 30 mL Schlenk vial under argon at room temperature was added dppf (0.11 g, 0.20 mmol), sodium ethoxide (5 mL of a 2.0 M soln. in EtOH), PhBr (0.33 g, 2.1 mmol) and ^{t}BuNC (0.34 mL, 3.0 mmol). $PdCl_2$ (19.8 mg, 0.11 mmol) was then added against a counterflow of argon. Finally, toluene (12 mL) was used to wash all solids from the sides of the vial, which was then heated at 109 °C in a Stem block. After 2 h GC indicated complete loss of PhBr and the reaction mixture was allowed to cool to room temperature before water (20 mL) was added. The organic layer was separated and the aqueous solution extracted with ether (4x15 mL). The combined organics were dried over $MgSO_4$, filtered and evaporated to give a yellow oil, which was further purified on silica with petrol:ether (4:1 + 5% NEt_3) to give **38a** as a pale-yellow oil (0.38 g, 92%).

^{1}H-NMR (400MHz, DMSO, T=353 K) δ=7.487-7.503 (3H, m, Ph), 7.440-7.462 (2H, m, Ph), 4.056 (2H, q, J=7.0 Hz, OCH_2), 1.322 (3H, t, J=7.0 Hz, CH_3), 1.264 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (100 MHz, DMSO, T=353 K) 156.63 (s, C=N), 136.88 (s, *CPh*), 129.74 (d, *CPh*), 128.86 (d, 2x*CPh*), 128.73 (d, 2x*CPh*), 63.22 (t, OCH_2), 53.69 (s, $C(CH_3)_3$), 32.14 (q, 3xCH_3), 15.55 (q, CH_3) ppm. **LRMS** (ES^+, m/z, %): 206.0 (MH^+, 100). **HRMS** (APCI, MH^+). $C_{13}H_{20}NO$ calculated: 206.1545, found: 206.1547. **IR** (cm^{-1}, neat): 2968 (m), 1716 (m), 1634 (s), 1352 (m), 1260 (s), 1107 (s). **UV/Vis** (λ_{max}, nm): 208 (ε=9100), 226 (ε=6800), 262 (ε=1700).

Synthesis of *N*-Cyclohexyl-benzimidic acid ethyl ester 38b



A. By direct addition of CyNC

The title compound **38b** was synthesised from PhBr (0.16 g, 1.0 mmol), dppf (58.8 mg, 0.11 mmol), CyNC (0.20 mL, 1.5 mmol), sodium ethoxide (2.5 mL of a 2.0 M soln. in EtOH) and $PdCl_2$ (9.6 mg, 0.053 mmol) in dry toluene (7 mL). The mixture was heated at 109 °C for 6 h. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave the title compound as a red oil, (0.068 g, 29%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.401-7.422 (3H, m, Ph), 7.296-7.328 (2H, m, Ph), 4.221 (2H, q, J=7,0 Hz, OCH_2), 3.142 (1H, tt, J_1=9.9 J_2=5.0 Hz, NCH), 1.328 (3H, t, J=7.0 Hz, CH_3), 1.180-1.740 (10H, m, 5xCH_2) ppm. **^{13}C-NMR** (300 MHz, $CDCl_3$) 158.99 (s, C=N), 133.37 (s, *CPh*), 128.99 (d, *CPh*), 128.28 (d, 2x*CPh*), 127.57 (d, 2x*CPh*), 60.95 (t, OCH_2), 57.59 (d, NCH), 35.50 (t, 2xCH_2), 25.70 (t, CH_2), 24.56 (t, 2xCH_2), 14.49 (q, CH_3) ppm. **LRMS** (ES^+, m/z, %): 232.3 (MH^+, 100). **HRMS** (APCI, MH^+). $C_{15}H_{22}NO$ calculated: 232.1701, found: 232.1700. **IR** (cm^{-1}, neat): 2957 (m), 2930 (m), 2868 (w), 1672 (s), 1628 (m), 1448 (m), 1205 (s). **UV/Vis** (λ_{max}, nm): 208 (ε=7300), 220 (ε=5000).

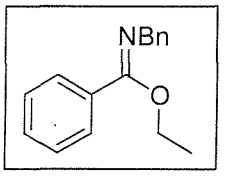
B. By slow addition of CyNC

This preparation is characteristic for the syntheses requiring slow addition of the isonitrile.

To a 30 mL Schlenk vial under argon at room temperature was added dppf (0.059 g, 0.11 mmol), sodium ethoxide (2.5 mL of a 2.0 M soln. in EtOH), PhBr (0.16 g, 1.0 mmol) and $Pd_2DBA_3{\cdot}CHCl_3$ (26.1 mg, 0.025 mmol). Dry, oxygen-free dioxane (8 mL)

was then added to the vial to wash all solids from the sides of the vial. The vial was then sealed with a Schlenk arm fitted with a rubber seal on the top. A solution of CyNC (0.20 mL) in dry dioxane (1 mL) was prepared and transferred to a syringe. The needle was introduced into the vial through the rubber seal and the syringe fitted to a syringe pump. The vial was heated at 98 °C for 2 h, during which time the CyNC-solution was added to the reaction mixture. The reaction was immediately analysed by GC, which indicated complete loss of PhBr and the reaction mixture was allowed to cool to room temperature before water (10 mL) was added. The organic layer was separated and the aqueous extracted with ether (2x25 mL). The combined organics were dried over $MgSO_4$, filtered and evaporated to give a brown oil, which was further purified on silica with petrol:ether (4:1 + 5% NEt_3) to give **38b** as a pale-yellow oil (0.19 g, 83%). The characterisation data are in agreement with the above.

Synthesis of *N*-Benzyl-benzimidic acid ethyl ester 38d



A. By direct addition of BnNC

The imidate **38d** was synthesised from PhBr (0.21 g, 1.3 mmol), dppf (68.1 mg, 0.12 mmol), BnNC (0.25 mL, 2.0 mmol), sodium ethoxide (3 mL of a 2.0 M soln. in EtOH) and $PdCl_2$ (13.0 mg, 0.073 mmol) in dry toluene (7 mL). The mixture was heated at 109 °C for 15 h. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave the title compound as a yellow oil, (0.093 g, 31%).

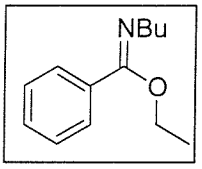
^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.293-7.539 (10H, m, Ph), 4.574 (2H, s, CH_2), 4.405 (2H, d, J=7.0 Hz, OCH_2), 1.422 (3H, t, J=7.0 Hz, CH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ=161.92 (s, C=N), 141.55 (s, *CPh*), 132.52 (s, *CPh*), 129.66 (d, *CPh*), 128.54 (d, 2x*CPh*), 128.44 (d, 2x*CPh*), 128.01 (d, 2x*CPh*) 127.13 (d, *CPh*), 126.53 (d, *CPh*), 61.64 (t, OCH_2), 53.65 (t, NCH_2), 14.63 (q, CH_3) ppm. **LRMS** (ES, m/z, %).

240 (100, MH^+). **IR** (cm^{-1}, neat): 3206 (w), 2976 (m), 2896 (w), 2356 (m), 1712 (m), 1667 (s), 1594 (m), 1492 (m), 1444 (m), 1271 (s). **UV/Vis** (λ_{max}, nm): 210 (ε=11400), 258 (ε=1800). **HRMS** (APCI, MH^+). $C_{16}H_{18}NO$ calculated: 240.1388, found: 240.1380.

B. By slow addition of BnNC

The title compound **38d** was synthesised from PhBr (0.16 g, 1.0 mmol), dppf (55.9 mg, 0.10 mmol), sodium ethoxide (2.5 mL of a 2.0 M soln. in EtOH) and $Pd_2DBA_3{\cdot}CHCl_3$ (25.6 mg, 0.025 mmol) in dry dioxane (7 mL). BnNC (0.20 mL, 1.5 mmol) in dry dioxane (1 mL) was added to the reaction mixture at 98 °C over 2 h by means of a syringe pump. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave the expected product as a yellow oil, (0.13 g, 52%). The characterisation data in agreement with the above.

Synthesis of *N*-Butyl-benzimidic acid ethyl ester 38c



A. By direct addition of *n*-BuNC

The title compound was synthesised from PhBr (0.16 g, 1.0 mmol), dppf (60.0 mg, 0.11 mmol), *n*-BuNC (0.16 mL, 1.5 mmol), sodium ethoxide (2.5 mL of a 2.0 M soln. in EtOH) and $PdCl_2$ (10.2 mg, 0.057 mmol) in dry toluene (8 mL). The mixture was heated at 109 °C for 15 h. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave **38c** as a yellow oil, (0.072 g, 35%).

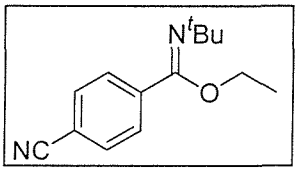
^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.403-7.420 (3H, m, Ph), 7.324-7.356 (2H, m, Ph), 4.326 (2H, q, J=7.0 Hz, OCH_2), 3.254 (2H, t, J=7.0 Hz, NCH_2), 1.522 (2H, pentet, J=7.3 Hz, CH_2), 1.343 (3H, t, J=7.0 Hz, CH_3) 1.223-1.289 (2H, m, CH_2), 0.864 (3H, t, J=7.3 Hz, CH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) 160.44 (s, C=N), 132.86 (s, *CPh*),

129.13 (d, <u>C</u>*Ph*), 128.22 (d, 2x<u>C</u>*Ph*), 127.87 (d, 2x<u>C</u>*Ph*), 61.01 (t, O<u>C</u>H$_2$), 49.75 (t, N<u>C</u>H$_2$), 34.18 (t, <u>C</u>H$_2$), 20.36 (t, <u>C</u>H$_2$), 14.43 (q, <u>C</u>H$_3$), 13.93 (q, <u>C</u>H$_3$) ppm. **LRMS** (ES$^+$, m/z, %): 206.2 (MH$^+$, 100). **HRMS** (APCI, MH$^+$). $C_{13}H_{20}NO$ calculated: 206.1545, found: 206.1537. **IR** (cm^{-1}, neat): 2975 (m), 2930 (m), 2853 (w), 1615 (s), 1576 (m), 1435 (m), 1337 (m). **UV/Vis** (λ_{max}, nm): 210 (ε=8000), 218 (ε=6300), 262 (ε=1100).

B. By slow addition of *n*-BuNC

The title compound was synthesised from PhBr (0.17 g, 1.1 mmol), dppf (59.0 mg, 0.11 mmol), sodium ethoxide (2.5 mL of a 2.0 M soln. in EtOH) and $Pd_2DBA_3{\cdot}CHCl_3$ (24.9 mg, 0.025 mmol) in dry dioxane (8 mL). *n*-BuNC (0.20 mL, 1.5 mmol) in dry dioxane (1 mL) was added to the reaction mixture at 98 °C over 2 h by means of a syringe pump. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave the **38c** as a red oil, which required further purification. Kugelrohr-distillation (oven temp 85-90 °C / 1 mmHg) gave the title compound as a pale-yellow oil, (0.13 g, 52%). The characterisation data in agreement with the above.

Synthesis of *N-tert*-Butyl-4-cyanobenzimidic acid ethyl ester 38e

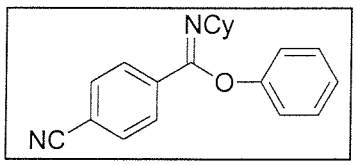


The title compound was synthesised from 4-cyanobromobenzene (0.37 g, 2.0 mmol), dppf (0.11 g, 0.20 mmol), ^{t}BuNC (0.34 mL, 3.0 mmol), sodium ethoxide (5 mL of a 2.0 M soln. in EtOH, 0.010 mol) and $PdCl_2$ (20.7 mg, 0.11 mmol) in dry toluene (14 mL). The mixture was heated at 109 °C for 1.5 h. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave **38e** as a dense, yellow oil, (0.41 g, 89%), consisting of two different isomers in a ratio of 1 : 2.7. As a comparison, ^{1}H-NMR data at room temperature, 100 °C and -20 °C is given.

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.672 (2H, d, J=8.2 Hz, Ar), 7.554 (2H, brs, Ar), 3.907 (2H, brs, OCH_2), 1.279-1.320 (12H, brm, 4xCH_3) ppm. **^{1}H-NMR** (400 MHz, DMSO-d_6, 353 K) δ=7.714 (2H, d, J=8.3 Hz, Ar), 7.443 (2H, d, J=8.3 Hz, Ar), 3.843 (2H, q, J=7.0 Hz, OCH_2), 1.120 (3H, t, J=7.0 Hz, CH_3), 1.068 (9H, s, 3x CH_3) ppm. **Major Isomer ^{1}H-NMR** (400 MHz, $CDCl_3$, 253 K) δ=7.692 (2H, d, J=8.0 Hz, Ar), 7.443 (2H, d, J=8.0 Hz, Ar), 3.779 (2H, q, J=7.0 Hz, OCH_2), 1.349 (9H, s, 3xCH_3), 1.303 (3H, t, J=7.0 Hz, CH_3) ppm. **Minor Isomer ^{1}H-NMR**[a] (400 MHz, $CDCl_3$, 253 K) δ=7.398 (2H, d, J=8.0 Hz, Ar), 4.088 (2H, q, J=7.0 Hz, OCH_2), 1.261 (3H, t, J=7.0 Hz, CH_3), 1.021 (9H, s, 3xCH_3) ppm. **Major Isomer ^{13}C-NMR** (100 MHz, $CDCl_3$, 253 K) δ=155.85 (s, C=N), 139.34 (s, *CAr*), 132.47 (d,2x*CAr*), 129.09 (d, 2x*CAr*), 118.84 (s, C≡N), 112.80 (s, *CAr*), 66.06 (t, OCH_2), 54.71 (s, $C(CH_3)_3$), 32.09 (q, 3xCH_3), 15.61 (q, CH_3) ppm. **Minor Isomer ^{13}C-NMR** (100 MHz, $CDCl_3$, 253 K) δ=154.16 (s, C=N), 141.59 (s, *CAr*), 132.06 (d,2x*CAr*), 128.59 (d, 2x*CAr*), 118.75 (s, C≡N), 112.17 (s, *CAr*), 61.21 (t, OCH_2), 52.78 (s, $C(CH_3)_3$), 31.14 (q, 3xCH_3), 14.43 (q, CH_3) ppm. **LRMS** (ES, m/z, %). 231 (100, MH^+). **HRMS** (APCI, MH^+). $C_{14}H_{19}N_2O$ calculated: 305.1654, found: 305.1653. **IR** (cm^{-1}, neat): 2970 (s), 2351 (m), 1680 (s), 1266 (s). **UV/Vis** (λ_{max}, nm): 210 (ε=9400), 244 (ε=12100).

a. One of the aromatic signals overlap with the major isomer.

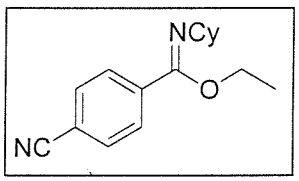
Synthesis of 4-Cyano-*N*-cyclohexyl-benzimidic acid phenyl ester 38g



The imidate **38g** was synthesised from 4-cyanobromobenzene (0.37 g, 2.0 mmol), dppf (0.11 g, 0.20 mmol), CyNC (0.38 mL, 3.0 mmol), sodium phenoxide (6 mL of a 1.7 M soln. in THF) and $PdCl_2$ (20.0 mg, 0.11 mmol) in dry toluene (14 mL). The mixture was heated at 109 °C for 1.5 h. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave the title compound as a dense, yellow oil, (0.50 g, 83%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.889 (2H, d, J=8.4 Hz, Ar), 7.597 (2H, d, J=8.4 Hz, Ar), 7.277 (2H, t, J=7.7 Hz, Ar), 7.034 (1H, t, J=7.7 Hz, Ar), 6.872 (2H, d+fs, J=8.4 Hz, Ar), 3.844 (1H, tt, J_1=10.3, J_2=3.9 Hz, CH), 1.226-1.340 (3H, m, CH_2+CH), 1.376-1.648 (3H, m, CH_2+CH), 1.732-1.814 (4H, m, 5xCH_2) ppm. **^{13}C-NMR** (75MHz, $CDCl_3$): δ=155.45 (s, C=N), 149.90 (s, C*Ar*), 137.75 (s, C*Ar*), 132.28 (d, 2xC*Ar*), 130.16 (d, 2xC*Ar*), 129.40 (d, 2xC*Ar*), 123.10 (d, C*Ar*), 118.59 (s, C≡N), 116.37 (d, 2xC*Ar*), 113.86 (s, C*Ar*), 56.63 (d, NCH), 33.69 (t, 2xCH_2), 25.80 (t, CH_2), 24.62 (t, 2xCH_2) ppm. **LRMS** (ES^+, m/z, %). 305.1 (100, MH^+). **HRMS** (APCI, MH^+). $C_{20}H_{21}N_2O$ calculated: 305.1654, found: 305.1653. **IR** (cm^{-1}, neat): 2928 (s), 2855 (m), 2232 (m), 1671 (s), 1447 (m), 1283 (s). **UV/Vis** (λ_{max}, nm): 212 (ε=15600), 254 (ε=19400).

Synthesis of 4-Cyano-*N*-cyclohexyl-benzimidic acid ethyl ester 38f



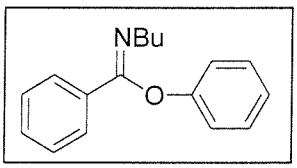
The imidate **38f** was synthesised from 4-cyanobromobenzene (0.37 g, 2.0 mmol), dppf (0.12 g, 0.21 mmol), CyNC (0.38 mL, 3.0 mmol), sodium ethoxide (5 mL of a 2.0 M soln. in EtOH) and $PdCl_2$ (19.6 mg, 0.11 mmol) in dry toluene (14 mL). The mixture was heated at 109 °C for 1.5 h. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave the desired compound as a yellow oil, (0.37 g, 72%), consisting of a mixture of three isomers in a ratio of 90: 9:1.

Major Isomer ^{1}H-NMR (400 MHz, $CDCl_3$): δ=7.715 (2H, d, J=8.6 Hz, Ar), 7.409 (2H, d, J=8.6 Hz, Ar), 4.222 (2H, q, J=7.0 Hz, OCH_2), 3.022 (1H, tt, J_1=10.1, J_2=4.1 Hz, NCH), 1.814-1.717 (2H, m, CH_2), 1.504-1.601 (3H, m, CH_2+CH), 1.388-1.480 (2H, m, CH_2), 1.315 (3H, t, J=7.0 Hz, CH_3), 1.101-1.215 (3H, m, CH_2+CH) ppm. **Minor Isomer 1 ^{1}H-NMR**[a] (400 MHz, $CDCl_3$): δ=7.859 (2H, d, J=8.6 Hz, Ar), 7.755 (2H, d, J=8.6 Hz, Ar), 4.036 (2H, q, J=7.0 Hz, OCH_2), 3.280 (1H, tt, J_1=10.1, J_2=4.1 Hz, NCH) ppm. **Minor Isomer 2 ^{1}H-NMR**[a] (400 MHz, $CDCl_3$): δ=7.922 (2H, d,

J=8.6 Hz, Ar), 7.615 (2H, d, J=8.6 Hz, Ar), 3.487 (2H, q, J=7.0 Hz, OCH_2), 2.854 (1H, tt, J_1=10.1, J_2=4.1 Hz, NCH) ppm. **Major Isomer ^{13}C-NMR** (100 MHz, $CDCl_3$): δ=156.90 (s, C=N), 137.79 (s, *CAr*), 132.39 (d, 2x*CAr*), 128.62 (d, 2x*CAr*), 118.51 (s, C≡N), 113.13 (s, *CAr*), 61.54 (t, OCH_2), 57.80 (d, NCH), 35.09 (t, 2xCH_2), 25.78 (t, CH_2), 24.55 (t, 2xCH_2), 14.43 (q, CH_3) ppm. **LRMS** (ES^+, m/z, %). 257.1 (100, MH^+). **HRMS** (APCI, MH^+). $C_{16}H_{21}N_2O$ calculated: 257.1654, found: 257.1656. **IR** (cm^{-1}, neat): 2930 (s), 2853 (m), 2225 (m), 1659 (s), 1591 (m), 1489 (m), 1205 (s). **UV/Vis** (λ_{max}, nm): 212 (ε=15400), 226 (ε=14500), 232 (ε=22700).

a. The other signals overlap with the major isomer. ^{13}C-NMR: the signals of the minor isomer are not sufficiently above noise level.

Synthesis of *N*-Butyl-benzimidic acid phenyl ester 38m

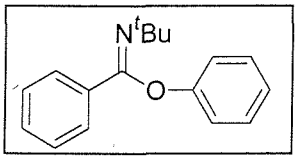


The imidate **38m** was synthesised from PhBr (0.20 g, 1.3 mmol), dppf (67.7 mg, 0.12 mmol), *n*-BuNC (0.20 mL, 2.0 mmol), sodium phenoxide (3.5 mL of a 1.7 M soln. in THF) and $PdCl_2$ (11.9 mg, 0.068 mmol) in dry toluene (7 mL). The mixture was heated at 109 °C for 5 h. Work-up and purification on silica with petrol : ether (4:1 + 5% NEt_3) gave the title compound as a pale-yellow oil, (0.21 g, 68%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.834 (2H, d, J_1=7.0 Hz, Ph), 7.256-7.398 (5H, m, Ph), 7.012 (1H, t, J=7.3 Hz, Ph), 6.914 (2H, d, J=8.1 Hz, Ph), 3.532 (2H, t, J=7.0 Hz, CH_2), 1.684 (2H, pentet, J=7.0 Hz, CH_2) 1.451 (2H, sextet, J=7.3 Hz, CH_2), 0.956 (3H, t, J=7.3 Hz, CH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) 155.74 (s, C=N), 152.99 (s, *CPh*), 133.26 (s, *CPh*), 130.65 (d, *CPh*), 129.97 (d, 2x*CPh*), 129.28 (d, 2x*CPh*), 128.49 (d, 2x*CPh*), 122.48 (d, *CPh*), 116.22 (d, 2x*CPh*), 48.05 (t, NCH), 32.93 (t, CH_2) 20.86 (t, CH_2), 14.10 (q, CH_3) ppm. **LRMS** (ES^+, m/z, %): 254.1 (MH^+, 100). **HRMS** (APCI, MH^+) $C_{17}H_{20}NO$ calculated: 254.1545, found: 254.1537. **IR** (cm^{-1},

neat): 2955 (m), 2924 (m), 2858 (m), 1660 (s), 1588 (m), 1489 (s), 1208 (s). **UV/Vis** (λ_{max}, nm): 210 (ε=13200), 240 (ε=13600), 270 (ε=3800).

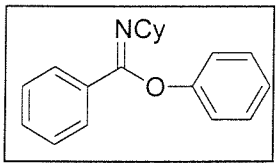
Synthesis of *N-tert*-Butyl-benzimidic acid phenyl ester 38k



The imidate **38k** was synthesised from PhBr (0.20 g, 1.3 mmol), dppf (70.1 mg, 0.13 mmol), ^{t}BuNC (0.22 mL, 2.0 mmol), sodium phenoxide (3.5 mL of a 1.7 M soln. in THF) and $PdCl_2$ (12.1 mg, 0.068 mmol) in dry toluene (7 mL). The mixture was heated at 109 °C for 5 h. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave the title compound as a white solid, (0.27 g, 86%), m.p. 62-63 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.680 (2H, dd, J_1=7.6, J_2=1.8 Hz, Ph), 7.196-7.330 (5H, m, Ph), 6,963 (1H, t, J=7.4 Hz, Ph), 6.852 (2H, d, J=8.1 Hz, Ph),1.439 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ=156.61 (s, C=N), 150.85 (s, *CPh*), 134.34 (s, *CPh*), 129.99 (d, *CPh*), 129.68 (d, 2x*CPh*), 129.08 (d, 2x*CPh*), 128.33 (d, 2x*CPh*), 122.45 (d, *CPh*), 117.67 (d, 2x*CPh*), 55.13 (s, $C(CH_3)_3$), 30.52 (q, 3xCH_3) ppm. **LRMS** (ES^+, m/z, %): 254.1 (MH^+, 100). **Elemental analysis** (%) calcd for $C_{17}H_{19}NO$: C 80.60, H 7.56, N 5.53; found: C 80.56, H 7.71, N 5.59. **IR** (cm^{-1}, neat): 2960 (m), 2919 (m), 2848 (m), 1737 (m), 1670 (m), 1594 (m), 1492 (m), 1206 (s). **UV/Vis** (λ_{max}, nm): 210 (ε=13800), 236 (ε=12700), 260 (ε=3300).

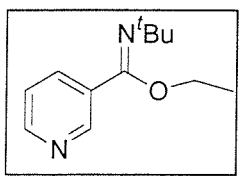
Synthesis of *N*-Cyclohexylbenzimidic acid methyl ester 38l



The title compound **38l** was synthesised from PhBr (0.20 g, 1.3 mmol), dppf (68.8 mg, 0.13 mmol), CyNC (0.25 mL, 2.0 mmol), sodium phenoxide (3.5 mL of a 1.7 M soln. in THF) and $PdCl_2$ (11.9 mg, 0.068 mmol) in dry toluene (7 mL). The mixture was heated at 109 °C for 5 h. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave the expected imidate as an orange solid, (0.24 g, 69%), m.p. 81-83 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.771 (2H, dd, J_1=8.1, J_2=2.3 Hz, Ph), 7-201-7.348 (5H, m, Ph), 6.984 (1H, t, J=7.4 Hz, Ph), 6.893 (2H, dd, J_1=8.9, J_2=1.2 Hz, Ph), 3.819 (1H, tt, J_1=9.8, J_2=3.7 Hz, NCH), 1.266-1.793 (10H, m, 5xCH_2) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=155.89 (s, C=N), 151.38 (s, *CPh*), 133.24 (s, *CPh*), 130.29 (d, *CPh*), 129.74 (d, 2x*CPh*), 128.72 (d, 2x*CPh*), 128.29 (d, 2x*CPh*), 122.33 (d, *CPh*), 116.38 (d, 2x*CPh*), 56.13 (d, NCH), 33.73 (t, 2xCH_2), 25.76 (t, CH_2), 24.66 (t, 2xCH_2) ppm. **LRMS** (ES^+, m/z, %). 280.3 (100, MH^+). **HRMS** (APCI, MH^+). $C_{19}H_{22}NO$ calculated: 280.1701, found: 280.1693. **Elemental analysis** (%) calcd for $C_{19}H_{21}NO$: C 81.63, H 7.58, N 5.01; found: C 81.20, H 7.78, N 5.33. **IR** (cm^{-1}, neat): 2930 (s), 2853 (m), 1649 (s), 1486 (m), 1208 (s). **UV/Vis** (λ_{max}, nm): 210 (ε=12600), 240 (ε=11000).

Synthesis of *N*-tert-Butyl-nicotinimidic acid ethyl ester 38h



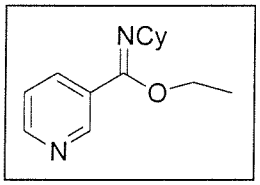
3-Bromopyridine (0.20 g, 1.3 mmol), dppf (70.2 mg, 0.13 mmol), ^{t}BuNC (0.21 mL, 2.0 mmol), sodium ethoxide (3.0 mL of a 2.0 M soln. in EtOH, 6.0 mmol) and $PdCl_2$

(12.3 mg, 0.069 mmol) and dry toluene (7 mL) were heated at 109 °C overnight. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave the title compound as an pale-yellow oil, (0.18 g, 70%).

^{1}H-NMR (400 MHz, DMSO-d_6, 353 K) δ=8.842 (1H, dd, J_1=4.8, J_2=2.4 Hz, Py), 8.578 (1H, d, J=2.4 Hz, Py), 8.001 (1H, dt, J_1=7.5, J_2=2.0 Hz, Py), 7.662 (1H, dd, J_1=7.1, J_2=4.7 Hz, Py), 4.239 (2H, q, J=7.0 Hz, OCH_2), 1.491 (3H, t, J=7.0 Hz, CH_3), 1.328 (9H, s, 3xCH_3) ppm. **^{13}C-NMR**[a] (75 MHz, $CDCl_3$): δ=173.20 (d, C*Py*), 150.14 (d, C*Py*), 149.14 (d, C*Py*), 135.71 (s, C*Py*), 123.20 (d, C*Py*) ppm. **LRMS** (ES^+, m/z, %): 207.1 (MH^+, 100). **HRMS** (APCI, MH^+) $C_{12}H_{19}N_2O$ calculated: 207.1497, found: 207.1489. **IR** (cm^{-1}, neat): 2930 (m), 2848 (m), 1668 (s), 1455 (m), 1279 (s). **UV/Vis** (λ_{max}, nm): 210 (ε=5900), 264 (ε=4500).

a. Missing signals: (s, C=N), (s, $C(CH_3)_3$). The signals due to (OCH_2), (3xCH_3) and (CH_3) appear as very broad and ill-defined.

Synthesis of *N*-Cyclohexyl nicotinimidic acid ethyl ester 38i

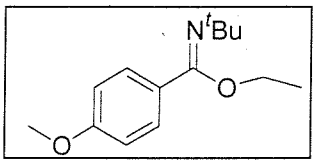


3-Bromopyridine (0.20 g, 1.3 mmol), dppf (65.0 mg, 0.12 mmol), CyNC (0.25 mL, 2.0 mmol), sodium ethoxide (3.0 mL of a 2.0 M soln. in EtOH) and $PdCl_2$ (11.8 mg, 0.068 mmol) and dry toluene (7 mL) were heated at 109 °C for 15 h. Work-up and purification on silica with petrol:ether (4:1 + 5% NEt_3) gave the title compound **38i** as an pale-yellow oil, (0.20 g, 69%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ=8.637 (1H, dd, J_1=5.0, J_2=1.9 Hz, Py), 8.578 (1H, m, Py), 7.631 (1H, dt, J_1=7.5, J_2=1.5 Hz, Py), 7.350 (1H, dd, J_1=7.5, J_2=5.0 Hz, Py), 4.216 (2H, q, J=7.2 Hz, OCH_2), 3.086 (1H, tt, J_1=10.3, J_2=4.1 Hz, NCH), 1.646-1.733 (2H, m, CH_2), 1.566-1.592 (3H, m, CH_2+CH), 1.394-1.463 (2H, m, CH_2), 1.313 (3H, t, J=7.2 Hz, CH_3), 1.172-1.216 (3H, m, CH_2+CH) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$):

δ=156.20 (s, C=N), 150.27 (d, *CPy*), 148.72 (d, *CPy*), 135.43 (d, *CPy*), 129.22 (s, *CPy*), 123.43 (d, *CPy*), 61.41 (t, OCH_2), 57.89 (d, NCH), 35.16 (t, 2xCH_2), 25.76 (t, CH_2), 24.57 (t, 2xCH_2), 14.42 (q, CH_3) ppm. **LRMS** (ES^+, m/z, %): 233.2 (MH^+, 100). **HRMS** (APCI, MH^+) $C_{14}H_{21}N_2O$ calculated: 233.1654, found: 233.1644. **IR** (cm^{-1}, neat): 2930 (m), 2848 (m), 1668 (s), 1455 (m), 1279 (s). **UV/Vis** (λ_{max}, nm): 210 (ε=5900), 264 (ε=4500).

Synthesis of *N-tert*-Butyl-4-methoxybenzimidic acid ethyl ester 38j

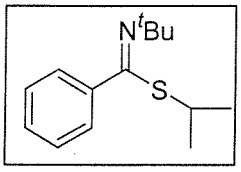


4-Bromoanisole (0.24 g, 1.3 mmol), dppf (68.0 mg, 0.12 mmol), ^{t}BuNC (0.21 mL, 2.0 mmol), sodium ethoxide (3.0 mL of a 2.0 M soln. in EtOH, 6.0 mmol) and $PdCl_2$ (12.1 mg, 0.069 mmol) and dry toluene (7 mL) were heated at 109 °C overnight. Work-up and purification on silica with petrol:ether (5:1 + 5% NEt_3) gave **38j** as yellow, impure oil. Further purification was achieved by Kugelrohr-distillation (oven temp. 120-125 °C / 1 mmHg) to give the title compound as a colourless oil, (0.24 g, 82%), found to consist of two isomers in a ratio of 4.4 : 1.

Major Isomer ^{1}H-NMR (400 MHz, DMSO-d_6, 353 K): δ=7.294 (2H, d, J=8.7 Hz, Ar), 6.937 (2H, d, J=8.7 Hz, Ar), 3.936 (2H, q, J=6.9 Hz, OCH_2), 3.800 (3H, s, OCH_3), 1.224 (3H, t, J=6.9 Hz, CH_3), 1.181 (9H, s, 3xCH_3) ppm. **Minor Isomer ^{1}H-NMR**[a] (400 MHz, DMSO-d_6, 353 K): δ=7.916 (2H, d, J=8.6 Hz, Ar), 7.032 (2H, d, J=8.6 Hz, Ar), 4.303 (2H, q, J=6.9 Hz, OCH_2), 3.852 (3H, s, OCH_3), 1.323 (3H, t, J=6.9 Hz, CH_3) ppm. **Major Isomer ^{13}C-NMR**[b] (100 MHz, $CDCl_3$): δ=131.71 (d, *CAr*), 129.68 (d, *CAr*), 113.66 (d, 2x*CAr*) ppm. **LRMS** (ES^+, m/z, %). 236.1 (100, MH^+). **HRMS** (APCI, MH^+). $C_{14}H_{22}NO_2$ calculated: 236.1651, found: 236.1645. **IR** (cm^{-1}, neat): 2970 (s), 2902 (m), 1676 (s), 1588 (m), 1474 (m), 1266 (s). **UV/Vis** (λ_{max}, nm): 208 (ε=8800), 248 (ε=6200).

a. (t, 3x$\underline{C}H_3$) missing. Does probably overlap with the same signal of the major isomer. b. Signals due to quaternary carbons are missing and alkyl signals very broad and ill-defined.

Synthesis of 1-Isopropyl-*N*1-(*tert*-butyl)-1-benzenecarboximido thioate 40a



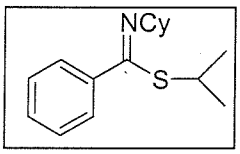
This preparation is given as a general procedure for the synthesis of the thioimidates. To a 30 mL Schlenk vial under argon at room temperature was added dppf (66.2 mg, 0.12 mmol), sodium propane-2-thiolate (0.51 g, 5.0 mmol), PhBr (0.20 g, 1.3 mmol) and ^{t}BuNC (0.22 mL, 2.0 mmol). $PdCl_2$ (12.2 mg, 0.069 mmol) was then added against a counterflow of argon. Finally, toluene (13 mL) was used to wash all solids from the sides of the vial, which was then heated at 109 °C in a Stem block. After 6 h GC indicated complete loss PhBr and the reaction mixture was allowed to cool to room temperature before ether (10 mL) and concentrated aqueous potassium hydroxide solution (5 mL) were added. The aqueous layer was extracted with ether (3x15 mL). The combined organics were dried over $MgSO_4$, filtered and evaporated to give a brown oil with a pungent smell. Further purification was achieved by elution on silica with petrol:ether (2:1) to give **40a** as a yellow oil (0.22 g, 74%), found to consist of two isomers by NMR.

Major Isomer ^{1}H-NMR (300MHz, $CDCl_3$): δ=7.568-7.600 (2H, m, Ph), 7.322-7.377 (3H, m, Ph), 2.977 (1H, septet, J=6.7 Hz, CH), 1.496 (9H, s, 3xCH_3), 1.147 (6H, d, J=6.7 Hz, 2xCH_3) ppm. **Minor Isomer ^{1}H-NMR** (300MHz, $CDCl_3$): δ=7.323 (2H, app. brs, Ph), 7.258 (3H, app. brs, Ph), 3.717 (1H, septet, J=6.7 Hz, CH), 1.342 (6H, d, J=6.7 Hz, 2xCH_3), 1.110 (9H, s, 3xCH_3) ppm. **Major Isomer ^{13}C-NMR**[a] (75MHz, $CDCl_3$): δ=140.02 (s, $\underline{C}Ph$), 129.02 (d, $\underline{C}Ph$), 128.27 (d, 2x$\underline{C}Ph$), 128.22 (d, 2x$\underline{C}Ph$), 57.37 (s, $\underline{C}(CH_3)_3$), 31.72 (d, $\underline{C}H$), 29.51 (q, 3x$\underline{C}H_3$), 23.85 (q, 2x$\underline{C}H_3$) ppm. **Minor Isomer ^{13}C-NMR**[b] (75MHz, $CDCl_3$): δ=127.74 (d, 2x$\underline{C}Ph$), 127.42 (d, 2x$\underline{C}Ph$), 50.66 (s, $\underline{C}(CH_3)_3$), 38.82 (q, 3x$\underline{C}H_3$), 35.42 (d, $\underline{C}H$), 22.45 (q, 2x$\underline{C}H_3$) ppm. **LRMS** (ES, m/z, %). Found: 236 (100, MH^+). **HRMS** (APCI, MH^+). $C_{14}H_{22}NS$ calculated:

236.1473, found: 236.1477. **IR** (cm^{-1}, neat): 2960 (m), 2924 (m), 1639 (m), 1602 (s), 1439 (m), 1362 (m), 1286 (m), 1235 (s), 1202 (s). **UV/Vis** (λ_{max}, nm): 212 (ε=9900), 234 (ε=7700), 266 (ε=3800).

a. Singlet due to (C=N) is missing. b. Singlets due to (C=N) and quaternary aromatic carbons are missing.

Synthesis of 1-Isopropyl-*N*1-cyclohexyl-1-benzenecarboximido thioate 40b

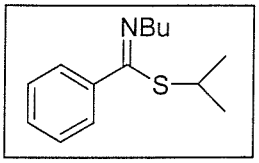


The thioimidate **40b** was synthesised from PhBr (0.20 g, 1.3 mmol), dppf (67.0 mg, 0.13 mmol), CyNC (0.25 mL, 2.0 mmol), sodium propane-2-thiolate (0.50 g, 5.0 mmol) and $PdCl_2$ (12.7 mg, 0.072 mmol) in dry toluene (13 mL). The mixture was heated at 109 °C for 5 h. Work-up and purification on silica with petrol : ether (2 :1) gave the title compound as a pale-yellow oil, (0.21 g, 64%), found to consist of two isomers in a ratio of 3.1 : 1 by NMR.

Major Isomer ^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.610-7.641 (2H, m, Ph), 7.376-7.397 (3H, m, Ph), 3.868 (1H, tt, J_1=10.3, J_2=4.2 Hz, CH), 3.071 (1H, septet, J=6.3 Hz, CH), 1.236-1.845 (10H, m, 5xCH_2, 1.152 (6H, t, J=6.3 Hz, 2xCH_3) ppm. **Minor Isomer ^{1}H-NMR**[a] (300 MHz, $CDCl_3$) δ=7.225-7.251 (3H, m, Ph), 3.273 (1H, tt, J_1=10.3, J_2=4.2 Hz, CH), 1.362 (6H, t, J=6.3 Hz, 2xCH_3), 1.236-1.845 (10H, m, 5xCH_2) ppm. **Major Isomer ^{13}C-NMR** (300 MHz, $CDCl_3$) δ=161.19 (s, C=N), 139.63 (s, *CPh*), 129.43 (d, *CPh*), 128.51 (d, 4x*CPh*), 62.86 (d, CH), 37.71 (d, CH), 33.28 (t, 2xCH_2), 25.92 (t, CH_2) 25.00 (t, 2xCH_2), 24.16 (q, 2xCH_3,) ppm. **Minor Isomer ^{13}C-NMR**[b] (300 MHz, $CDCl_3$) δ=128.83 (d, *CPh*), 127.22 (d, 4x*CPh*), 60.79 (d, CH), 34.90 (d, CH), 34.41 (t, 2xCH_2), 24.38 (t, 2xCH_2), 22.75 (q, 2xCH_3) ppm. **LRMS** (ES^+, m/z, %): 262.1 (MH^+, 100). **HRMS** (APCI, MH^+). $C_{16}H_{24}NS$ calculated: 262.1629, found: 262.1644. **IR** (cm^{-1}, neat): 2927 (s), 2852 (m), 1618 (m), 1598 (m), 1450 (m), 1367 (m), 1209 (m). **UV/Vis** (λ_{max}, nm): 208 (ε=10900), 236 (ε=8100).

a. Multiplet for (2H, Ph) overlaps with major isomer, septet for (1H, CH) overlaps with NCH-signal of major isomer. b. Missing singnals: (s, C=N) and (s, *CPh*).

1-Isopropyl-*N*1-butyl-1-benzenecarboximido thioate 40c

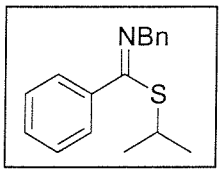


The thioimidate **40c** was synthesised from PhBr (0.20 g, 1.3 mmol), dppf (66.8 mg, 0.13 mmol), *n*-BuNC (0.20 mL, 2.0 mmol), sodium propane-2-thiolate (0.50 g, 5.0 mmol) and $PdCl_2$ (12.5 mg, 0.072 mmol) in dry toluene (13 mL). The mixture was heated at 109 °C for 5 h. Work-up and purification on silica with petrol:ether (2:1) gave the title compound as a pale-yellow oil, (0.19 g, 62%), found to consist of two isomers in a ratio of 3.7 : 1 by NMR.

Major Isomer ^{1}H-NMR (400 MHz, $CDCl_3$): δ=7.606-7.637 (2H, m, Ph), 7.387-7.408 (3H, m, Ph), 3.686 (3H, t, J=7.0 Hz, NCH_2), 3.111 (1H, septet, J=7.0 Hz, CH), 1.745 (2H, pentet, J=7.0 Hz, CH_2), 1.460 (2H, sextet, J=7.0 Hz, CH_2), 1.147 (6H, d, J=7.0 Hz, 2xCH_3), 0.980 (3H, t, J=7.0 Hz, CH_3) ppm. **Minor Isomer ^{1}H-NMR** (400 MHz, $CDCl_3$): δ=7.354-7.381 (2H, m, Ph), 7.239-7.265 (3H, m, Ph), 3.839 (1H, septet, J=7.0 Hz, CH), 3.307 (2H, t, J=7.0 Hz, NCH_2), 1.561 (2H, pentet, J=7.0 Hz, CH_2), 1.371 (6H, d, J=7.0 Hz, 2xCH_3), 1.321 (2H, sextet, J=7.0 Hz, CH_2), 0.886 (3H, t, J=7.0 Hz, CH_3) ppm. **Major Isomer ^{13}C-NMR** (100 MHz, $CDCl_3$): δ=162.95 (s, C=N), 139.60 (s, *CPh*), 129.47 (d, *CPh*), 128.48 (d, 2x*CPh*), 128.36 (d, 2x*CPh*), 54.49 (t, NCH_2), 37.87 (d, CH), 32.92 (t, CH_2), 24.21 (q, 2xCH_3), 20.87 (t, CH_2), 14.16 (q, CH_3) ppm. **Minor Isomer ^{13}C-NMR**[a] (100 MHz, $CDCl_3$): δ=128.96 (d, *CPh*), 127.36 (d, 2x*CPh*), 53.26 (t, NCH_2), 34.81 (d, CH), 33.76 (t, CH_2), 22.93 (q, 2xCH_3), 20.62 (t, CH_2) ppm. **LRMS** (ES, m/z, %). Found: 236 (100, MH^+). **HRMS** (APCI, MH^+). $C_{14}H_{22}NS$ calculated: 236.1473, found: 236.1474. **IR** (cm^{-1}, neat): 2957 (m), 2930 (m), 1619 (s), 1445 (m), 1199 (m). **UV/Vis** (λ_{max}, nm): 210 (ε=9700), 236 (ε=8800).

a. Missing signals: (s, C=N), (d, *CPh*) and (d, 2x*CPh*).

Synthesis of *N*-Benzyl-thiobenzimidic acid isopropyl ester 40d

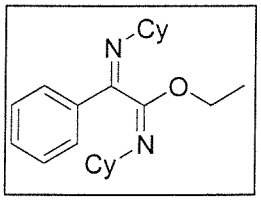


The thioimidate **40d** was synthesised from PhBr (0.21 g, 1.3 mmol), dppf (68.1 mg, 0.13 mmol), BnNC (0.22 mL, 2.0 mmol), sodium propane-2-thiolate (0.51 g, 5.0 mmol) and $PdCl_2$ (12.8 mg, 0.072 mmol) in dry toluene (7 mL). The mixture was heated overnight under argon at 109 °C. Work-up and purification on silica with petrol:ether (4:1) gave the title compound as a pale-yellow oil, (0.13 g, 40%), found to consist of two isomers by NMR in a ratio of 1 : 2.

Major Isomer ^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.740-7.715 (2H, m, Ph), 7.298-7.421 (8H, m, Ph), 4.943 (2H, s, CH_2), 3.213 (1H, septet, J=7.0 Hz, CH), 1.194 (6H, d, J=7.0 Hz, 2xCH_3) ppm. **Minor Isomer ^{1}H-NMR**[a] (300 MHz, $CDCl_3$): δ=4.577 (2H, s, CH_2), 3.990 (1H, septet, J=7.0 Hz, CH), 1.421 (6H, d, J=7.0 Hz, 2xCH_3) ppm.. **Major Isomer ^{13}C-NMR**[b] (75 MHz, $CDCl_3$): δ=140.17 (s, *CPh*), 139.41 (s, *CPh*), 129.62 (d, *CPh*), 128.38 (d, 4x*CPh*), 127.93 (d, 2x*CPh*), 127.27 (d, *CPh*), 127.14 (d, *CPh*), 126.67 (d, *CPh*), 58.35 (t, CH_2), 38.36 (d, CH), 24.23 (q, 2xCH_3) ppm. **Minor Isomer ^{13}C-NMR**[c] (75 MHz, $CDCl_3$): δ=140.98 (s, *CPh*), 129.17 (d, *CPh*), 128.47 (d, 2x*CPh*), 128.43 (d, 4x*CPh*), 128.28 (d, 2x*CPh*), 126.45 (d, *CPh*), 56.94 (t, CH_2), 35.07 (d, CH), 23.02 (q, 2xCH_3) ppm. **LRMS** (ES^+, m/z, %): 270.1 (MH^+, 100). **HRMS** (APCI, MH^+). $C_{17}H_{20}NS$ calculated: 270.1316, found: 270.1302. **IR** (cm^{-1}, neat): 2960 (m), 1613 (s), 1596 (s), 1495 (m), 1452 (m). **UV/Vis** (λ_{max}, nm): 210 (ε=9700), 236 (ε=8800).

a. The aromatic signals overlap with the major isomer's. b. (s, C=N) missing . c. Missing singnals: (s, C=N) and (s, *CPh*).

Synthesis of (*Z,E*)-*N*-Cyclohexyl-2-cyclohexylimino-2-phenylacetimidic acid ethyl ester_39a

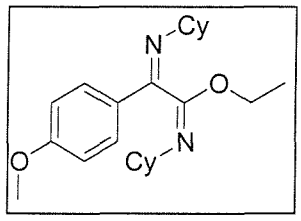


This preparation is given as a general procedure for the synthesis of the α-iminoimidates.

Dry NaO^{t}Bu (0.24 g, 2.5 mmol), dppf (0.11 g, 0.20 mmol), PhBr (0.32 g, 2.0 mmol) and ethanol (0.46 g, 10 mmol) was added to a 50 mL Schlenk tube fitted with a reflux condenser under argon. Dry, oxygen-free dioxane (20 mL) was added, followed by CyNC (0.75 mL, 6.0 mmol) and finally $PdCl_2$ (18.6 mg, 0.11 mmol) was added against a flow of argon. A Schlenk arm was fitted to the top of the reflux condenser and the apparatus connected to the Schlenk line. The reaction mixture was heated under vigorous stirring at 98 °C for 3 h. After cooling to room temperature, the reaction mixture was filtered and evaporated to give a brown oil, which was purified on silica with petrol:ether (4:1+5% NEt_3). A very dense, pale-yellow oil, found to correspond to the title product, was obtained (0.56 g, 83%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.738-7,770 (2H, m, Ph), 7.334-7.396 (3H, m, Ph), 4.330 (1H, dq, J_1=11.2, J_2=7.2 Hz, OCH_2), 4.229 (1H, dq, J_1=11.2, J_2=7.2 Hz, OCH_2), 3.251 (1H, tt, J_1=10.1, J_2=4.4 Hz, NCH), 2.932 (1H, tt, J_1=10.1, J_2=4.4 Hz, NCH), 1.318 (3H, t, J=7.2 Hz, CH_3) 1.176-1.826 (20H, m, 10xCH_2) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=158.94 (s, C=N), 154.90 (s, C=N), 136.13 (s, *CPh*), 130.54 (d, *CPh*), 128.56 (d, 2x*CPh*), 127.54 (d, 2x*CPh*), 64.20 (d, NCH), 60.99 (t, OCH_2), 58.14 (d, NCH), 35.15 (t, CH_2), 34.34 (t, CH_2), 34.01 (t, CH_2), 33.68 (t, CH_2), 25.85 (t, CH_2), 25.79 (t, CH_2), 24.74 (t, CH_2), 24.56 (t, 2xCH_2), 24.40 (t, CH_2), 14.56 (q, CH_3) ppm. **LRMS** (ES^+, m/z, %). 341.3 (100, MH^+). **HRMS** (APCI, MH^+). $C_{22}H_{33}N_2O$ calculated: 341.2593, found: 341.2587. **IR** (cm^{-1}, neat): 2927 (s), 2853 (m), 1670 (s), 1624 (m), 1447 (m), 1287 (m) 1206 (s). **UV/Vis** (λ_{max}, nm): 208 (ε=18600), 252 (ε=17400).

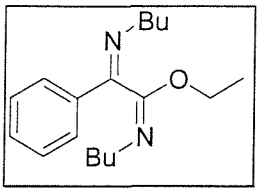
Synthesis of (*Z,E*)-*N*-Cyclohexyl-2-cyclohexylimino-2-(4-methoxyphenyl)-acetimidic acid ethyl ester 39e



The compound **39e** was synthesised from 4-bromoanisole (0.38 g, 2.1 mmol), dppf (0.11 g, 0.20 mmol), CyNC (0.750 mL, 6.0 mmol), NaO^{t}Bu (0.240 g, 2.5 mmol), ethanol (0.46 g, 0.010 mol) and $PdCl_2$ (20.9 mg, 0.12 mmol) in dry dioxane (13 mL). The mixture was heated at 109 °C under argon for 15 h. Work-up and purification on silica with petrol:ether (4:1+5% NEt_3) gave the title compound as a very dense pale-yellow oil, which crystallised after 6 days under high vacuum to give the title product as a white solid, (0.66 g, 85%), m.p. 132-134 °C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ=7.694 (2H, d, J=8.8 Hz, Ar), 6.887 (2H, d, J=8.2 Hz, Ar), 4.336 (1H, dq, J_1=10.6, J_2=7.2 Hz, OCH_2), 4.192 (1H, dq, J_1=10.6, J_2=7.2 Hz, OCH_2), 3.834 (3H, s, OCH_3), 3.199 (1H, tt, J_1=9.8, J_2=4.5 Hz, NCH), 2.925 (1H, tt, J_1=9.8, J_2=4.5 Hz, NCH), 1.309 (3H, t, J=7.4 Hz, CH_3), 1.173-1.828 (20H, m, 10xCH_2) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=161.56 (s, C*Ar*), 158.27 (s, C=N), 155.15 (s, C=N), 129.16 (d, 2xC*Ar*), 128.92 (s, C*Ar*), 113.89 (d, 2xC*Ar*), 64.05 (d, NCH), 60.92 (t, OCH_2), 58.16 (d, NCH), 55.50 (q, OCH_3), 35.16 (t, CH_2), 34.38 (t, CH_2), 34.14 (t, CH_2), 33.80 (t, CH_2), 25.88 (t, CH_2), 25.81 (t, CH_2), 24.82 (t, CH_2), 24.60 (t, 2xCH_2), 24.49 (t, CH_2), 14.58 (q, CH_3) ppm. **LRMS** (ES^+, m/z, %). 371.0 (100, MH^+). **Elemental analysis** (%) calcd for $C_{23}H_{34}N_2O_2$: C 74.55, H 9.25, N 7.56; found: C 74.25, H 9.31, N 7.36. **IR** (cm^{-1}, neat): 2926 (s), 2853 (m), 1666 (s), 1605 (m), 1510 (m), 1292 (m), 1250 (s). **UV/Vis** (λ_{max}, nm): 210 (ε=15000), 270 (ε=19400).

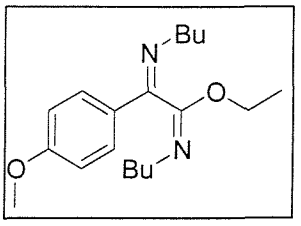
Synthesis of (*Z,E*)-*N*-Butyl-2-butylimino-2-phenylacetimidic acid ethyl ester 39b



The title compound **39b** was synthesised from PhBr (0.32 g, 2.1 mmol), dppf (0.11 g, 0.20 mmol), *n*-BuNC (0.66 mL, 6.0 mmol), NaO^{t}Bu (0.24 g, 2.5 mmol), ethanol (0.48 g, 0.010 mol) and $PdCl_2$ (20.0 mg, 0.11 mmol) in dry dioxane (20 mL). The mixture was heated at 98 °C under argon for 4 h. Work-up and purification on silica with petrol:ether (4:1+5% NEt_3) gave **39b** as a yellow oil, (0.42 g, 69%), consisting of two isomers in a ratio of 92 : 8.

Major Isomer ^{1}H-NMR (400 MHz, $CDCl_3$): δ=7.710-7.743 (2H, m, Ph), 7.379-7.422 (3H, m, Ph), 4.279 (2H, m, OCH_2), 3.448 (2H, t, J=7.2 Hz, NCH_2), 3.033 (2H, t, J=7.2 Hz, NCH_2), 1.718 (2H, sextet, J=7.2 Hz, CH_2), 1.453 (4H, pentet, J=7.2 Hz, 2xCH_2), 1.333 (3H, t, J=7.2 Hz CH_3), 1.280 (2H, sextet, J=7.2 Hz, CH_2), 0.964 (3H, t, J=7.2 Hz, CH_3) 0.839 (3H, t, J=7.2 Hz, CH_3) ppm. **Minor Isomer 1 ^{1}H-NMR** (400 MHz, $CDCl_3$): δ=7.859 (2H, d, J=8.6 Hz, Ph), 7.755 (2H, d, J=8.6 Hz, Ph), 4.162 (2H, q, J=7.2 Hz, OCH_2), 3.251 (2H, t, J=7.2 Hz, NCH_2), 3.132 (2H, t, J=7.2 Hz, NCH_2) ppm. The other signals overlap with the major isomer. **Major Isomer ^{13}C-NMR** (75 MHz, $CDCl_3$): δ=161.07 (s, C=N), 156.47 (s, C=N), 135.48 (s, C*Ph*), 130.70 (d, C*Ph*), 128.71 (d, 2xC*Ph*), 127.28 (d, 2xC*Ph*), 61.11 (t, OCH_2), 54.95 (d, NCH), 49.17 (d, NCH), 33.74 (t, CH_2), 33.02 (t, CH_2), 20.87 (t, CH_2), 20.62 (t, CH_2), 14.54 (q, CH_3), 14.13 (q, CH_3), 14.06 (q, CH_3) ppm. **LRMS** (ES^+, m/z, %): 289.0 (MH^+, 100). **HRMS** (APCI, MH^+). $C_{18}H_{29}N_2O$ calculated: 289.2280, found: 289.2295. **IR** (cm^{-1}, neat): 2955 (m), 2932 (m), 2870 (m), 1672 (s), 1626 (m), 1448 (m), 1284 (m), 1205 (s). **UV/Vis** (λ_{max}, nm): 208 (ε=13700), 250 (ε=13100).

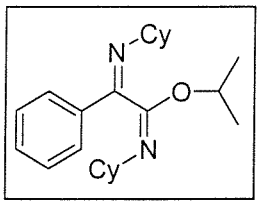
Synthesis of (*Z,E*)-*N*-Butyl-2-butylimino-2-(4-methoxyphenyl)-acetimidic acid ethyl ester 39f



The title compound **39f** was synthesised from 4-bromoanisole (0.39 g, 2.1 mmol), dppf (0.11 g, 0.20 mmol), *n*-BuNC (0.66 mL, 6.0 mmol), NaO^{t}Bu (0.25 g, 2.5 mmol), ethanol (0.46 g, 0.010 mol) and $PdCl_2$ (18.8 mg, 0.11 mmol) in dry dioxane (20 mL). The mixture was heated at 98 °C under argon for 4 h. Work-up and purification on silica with petrol:ether (4:1+5% NEt_3) gave the title compound as a yellow oil, (0.52 g, 78%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ=7.668 (2H, d, J=8.8 Hz, Ar), 6.908 (2H, d, J=8.8 Hz, Ar), 4.244-4.308 (2H, m, OCH_2), 3.844 (3H, s, OCH_3), 3.408 (2H, t+fs, J_1=7.0 Hz, NCH_2), 3.026 (2H, t, J=7.2 Hz, NCH_2), 1.700 (2H, sextet, J=7.2 Hz, CH_2), 1.406-1.509 (4H, m, 2xCH_2), 1.328 (3H, t, J=7.2 Hz CH_3), 1.285 (2H, sextet, J=7.2 Hz, CH_2), 0.958 (3H, t, J=7.2 Hz, CH_3), 0.846 (3H, t, J=7.2 Hz, CH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=161.71 (s, C*Ar*), 160.39 (s, C=N), 156.47 (s, C=N), 128.92 (d, 2xC*Ar*), 128.31(d, C*Ar*), 114.07 (d, 2xC*Ar*), 61.06 (t, OCH_2), 55.51 (q, OCH_3), 54.79 (t, NCH_3), 49.22 (t, NCH_2), 33.79 (t, CH_2), 33.15 (t, CH_2), 20.89 (t, CH_2), 20.66 (t, CH_2), 14.57 (q, CH_3), 14.16 (q, CH_3), 14.11 (q, CH_3) ppm. **LRMS** (ES^+, m/z, %): 319.1 (MH^+, 100). **Elemental analysis** (%) calcd for $C_{19}H_{30}N_2O_2$: C 71.66, H 9.49, N 8.79; found: C 71.27, H 9.55, N 8.59. **IR** (cm^{-1}, neat): 2957 (m), 2930 (m), 2900 (m), 1672 (s), 1604 (s), 1511 (m), 1465 (m), 1255 (s). **UV/Vis** (λ_{max}, nm): 212 (ε=12900), 272 (ε=18100).

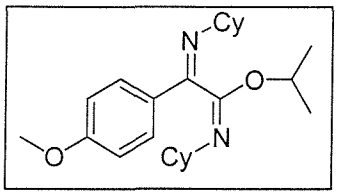
Synthesis of (*Z,E*)-*N*-Cyclohexyl-2-cyclohexylimino-2-phenylacetimidic acid isopropyl ester 39d



The title compound was synthesised from PhBr (0.32 g, 2.0 mmol), dppf (0.11 g, 0.20 mmol), CyNC (0.80 mL, 6.0 mmol), NaO^{t}Bu (0.24 g, 2.5 mmol), isopropanol (0.61 g, 0.010 mol) and $PdCl_2$ (21.8 mg, 0.12 mmol) in dry dioxane (20 mL). The mixture was heated at 98 °C under argon for 6 h. Work-up and purification on silica with petrol:ether (4:1+5% NEt_3) gave the title compound as a yellow oil, which was further purified by Kugelrohr-distillation (oven temp 130-135 °C / 1 mmHg) to give **39d** as a transparent, very dense oil (0.62 g, 88%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.747-7.784 (3H, m, Ph), 7.370-7.394 (2H, m, Ph), 5.289 (1H, septet, 5.7 Hz, CH), 3.300 (1H, tt, J_1=9.2, J_2=5.0 Hz, NCH), 2.930 (1H, tt, J_1=9.2, J_2=5.0 Hz, NCH), 1.828 (2H, app. brs, CH_2), 1.596-1.681 (6H, m, 3xCH_2), 1.487-1.501 (2H, m, CH_2), 1.192-1.381 (20H, m, 10xCH_2, 6H, t, J=5.7 Hz, 2xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ=159.12 (s, C=N), 154.05 (s, C=N), 136.22 (s, *CPh*), 130.49 (d, *CPh*), 128.71 (d, 2x*CPh*), 127.53 (d, 2x*CPh*), 67.45 (d, CH), 64.00 (d, NCH), 58.03 (d, NCH), 35.13 (t, CH_2), 34.29 (t, CH_2), 34.02 (t, CH_2), 33.57 (t, CH_2), 25.85 (t, 2xCH_2), 24.77 (t, CH_2), 24.52 (t, CH_2), 24.48 (t, 2xCH_2), 22.05 (q, CH_3), 21.97 (q, CH_3) ppm. **LRMS** (ES, m/z, %). 355 (100, MH^+). **HRMS** (APCI, MH^+) $C_{23}H_{35}N_2O$ calculated: 355.2749, found: 355.2763. **IR** (cm^{-1}, neat): 2928 (s), 2856 (m), 1662 (s), 1617 (s), 1446 (m), 1287 (s), 1209 (s). **UV/Vis** (λ_{max}, nm): 208 (ε=14000), 252 (ε=14500).

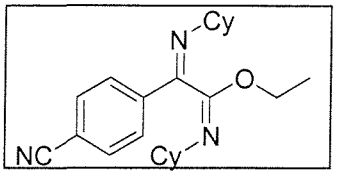
Synthesis of (*Z,E*)-*N*-Cyclohexyl-2-cyclohexylimino-2-(4-methoxyphenyl)-acetimidic acid isopropyl ester 39g



Compound **39g** was synthesised from 4-bromoanisole (0.37 g, 2.0 mmol), dppf (0.11 g, 0.20 mmol), CyNC (0.80 mL, 6.0 mmol), NaO^{t}Bu (0.24 g, 2.5 mmol), isopropanol (0.63 g, 0.011 mol) and $PdCl_2$ (20.8 mg, 0.11 mmol) in dry dioxane (20 mL). The mixture was heated at 98 °C under argon for 7 h. Work-up and purification on silica with petrol:ether (4:1+5% NEt_3) gave the title compound as a yellow oil, which was further purified by Kugelrohr-distillation (oven temp 140-150 °C / 1 mmHg) to give the title compound as a transparent, very dense oil (0.55 g, 71%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.701 (2H, d, J=8.8 Hz, Ar), 6.882 (2H, d, J=8.8 Hz, Ar), 5.275 (1H, septet, 5.6 Hz, CH), 3.835 (3H, s, OCH_3), 3.246 (1H, tt, J_1=10.3, J_2=4.7 Hz, NCH), 2.921 (1H, tt, J_1=10.3, J_2=4.7 Hz, NCH), 1.772-1.811 (2H, m, CH_2), 1.507-1.686 (6H, m, 3xCH_2), 1.407-1.476 (2H, m, CH_2), 1.329-1.387 (2H, m, CH_2), 1.303 (3H, d, J=5.6 Hz, CH_3), 1.239 (3H, d, J=5.6 Hz, CH_3), 1.110-1.309 (4H, brm, CH_2), 1.039-1.218 (4H, m, 2xCH_2) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ=161.50 (s, C=N), 158.43 (s, C=N), 154.27 (s, C*Ar*), 129.14 (d, 2xC*Ar*), 129.00 (s, C*Ar*), 113.86 (d, 2xC*Ar*), 67.34 (d, CH), 63.82 (d, NCH), 58.04 (d, NCH), 55.49 (q, OCH_3), 35.13 (t, CH_2), 34.33 (t, CH_2), 34.15 (t, CH_2), 33.68 (t, CH_2), 25.87 (t, 2xCH_2), 25.12 (t, CH_2), 24.83 (t, CH_2), 24.54 (t, 2xCH_2), 22.06 (q, CH_3), 21.97 (q, CH_3) ppm. **LRMS** (ES, m/z, %). 385 (100, MH^+). **HRMS** (APCI, MH^+). $C_{24}H_{37}N_2O_2$ calculated: 385.2855, found: 385.2841. **IR** (cm^{-1}, neat): 2925 (s), 2853 (m), 1667 (s), 1604 (s), 1511 (s), 1444 (m), 1270 (s). **UV/Vis** (λ_{max}, nm): 206 (ε=10900), 272 (ε=13600).

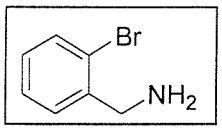
Synthesis of (*Z,E*)-2-(4-Cyano-phenyl)-*N*-cyclohexyl-2-cyclohexylimino acetimidic acid ethyl ester 39h



The title compound **39h** was synthesised from 4-cyano-bromobenzene (0.37 g, 2.1 mmol), dppf (0.11 g, 0.20 mmol), CyNC (0.80 mL, 6.0 mmol), NaO^{t}Bu (0.23 g, 2.5 mmol), ethanol (0.46 g, 0.010 mol) and $PdCl_2$ (20.4 mg, 0.11 mmol) in dry dioxane (20 mL). The mixture was heated overnight at 98 °C under argon. Work-up and purification on silica with petrol:ether (4:1+5% NEt_3) gave the title compound as a brownish, dense oil which was further purified by Kugelrohr-distillation (oven temp 135-140 °C / 1 mmHg) to give an orange, very dense oil (0.55 g, 75%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.861 (2H, d, J=8.2 Hz, Ph), 7.680 (2H, d, J=8.2 Hz, Ph), 4.346 (1H, dq, J_1=12.0, J_2=6.0 Hz OCH_2), 4.220 (1H, dq, J_1=12.0, J_2=6.0 Hz OCH_2), 3.277 (1H, tt, J_1=10.5, J_2=4.5 Hz, CH), 2.745-2.898 (1H, m, CH), 1.316 (3H, t, J=7.2 Hz, CH_3), 1.181-1.833 (20H, m, 5xCH_2) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ=157.33 (s, C=N), 153.66 (s, C=N), 140.09 (s, *CPh*), 132.37 (d, 2x*CPh*), 128.04 (d, 2x*CPh*), 118.69 (s, C≡N), 113.86 (s, *CPh*), 64.48 (d, NCH), 61.23 (t, OCH_2), 58.17 (d, NCH), 35.30 (t, CH_2), 35.06 (t, CH_2), 34.39 (t, CH_2), 33.76 (t, CH_2), 33.52 (t, CH_2), 25.74 (t, CH_2), 25.67 (t, CH_2), 24.38 (t, 2xCH_2), 24.13 (t, CH_2), 14.45 (q, CH_3) ppm. **LRMS** (ES^+, m/z, %): 366.1 (MH^+, 100). **HRMS** (APCI, MH^+). $C_{23}H_{32}N_3O$ calculated: 366.2545, found: 366.2542. **IR** (cm^{-1}, neat): 2930 (s), 2852 (m), 2227 (m), 1670 (s), 1450 (m), 1287 (m), 1204 (s). **UV/Vis** (λ_{max}, nm): 208 (ε=16300), 264 (ε=25800).

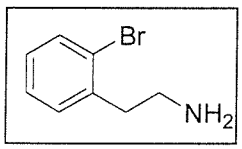
Synthesis of 2-Bromobenzylamine 34a[59]



2-Bromobenzaldehyde (5.0 g, 0.027 mol) was refluxed together with hydroxylamine hydrochloride (5.0 g, 0.072 mol) and pyridine (5 mL) in ethanol (50 mL) for 1 h. All solvent was evaporated and the yellow oily residue treated with water at 0 °C. The crude material (6.1 g) was obtained as a white solid. Recrystallisation from hot ethanol : water (1 : 1) gave the intermediate 2-bromobenzaldehyde oxime as white needles (4.92 g, 90%), m.p. 127-128 °C, lit.[59] 125-126 °C.
The NMR-data is in agreement with the literature.[59]

The intermediate 2-bromobenzaldehyde oxime (4.5 g, 0.023 mol) was added to a 250 mL roundbottomed flask together with ethanol (25 mL), water (17 mL) and concentrated HCl (17 mL). Zinc dust (4.5 g, 0.063 mol) was added portionwise to keep the temperature above 40 °C Further HCl (10 mL) was added and the mixture heated at 60 °C for 10 min. The mixture was then allowed to cool to room temperature, water (20 mL) added and the residual zinc filtered off. Evaporation of the ethanol gave an aqueous residue that was basified with NaOH-pellets to give a dense, white slurry. This was transferred to a Buchner funnel, washed with ether (3x100 mL) and the ethereal layer dried over $MgSO_4$. Evaporation gave a yellow oil (3.01 g, 70%) found to correspond to the title product 2-Bromobenzylamine.
The NMR-data is in agreement with the literature.[59]

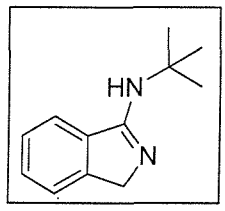
Synthesis of 2-(2Bromophenyl)-1-ethylamine 34b[60]



A dry 100 mL Schlenk flask was charged with $AlCl_3$ (1.36 g, 0.010 mol) and cooled to 0 °C. Dry ether (25 mL) was added, followed by a suspension of $LiAlH_4$ (0.57 g, 0015 mol) in dry ether (20 mL). To the resulting suspension, 2-

bromophenylacetonitrile (2.0 g, 0.010 mol) was added as a solution in dry ether (10 mL) by means of a syringe at 0 °C. This mixture was stirred at room temperature for 22 h before cooling to 0 °C again. The reaction was quenched by pouring the content of the flask onto a mixture of ice and water, whereby a whitish solid appeared. This was dissolved by addition of H_2SO_4 (15 mL, 2 M) and this solution transferred to a separating funnel. The organic layer was discarded and the aqueous washed with ether (20 mL) before treatment with aqueous NaOH (10 mL, 1 M) in the presence of ether (20 mL). The ethereal layer was collected and the aqueous extracted with ether (3x50 mL) and the combined ethereal layers dried over $MgSO_4$ before evaporation to yield the title product as a yellow oil, (1.70 g, 85%).
The NMR-data is in agreement with the literature.[60]

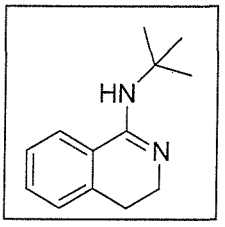
Synthesis of *tert*-Butyl-(2,3-dihydro-isoindol-1-ylidene)-amine 35a



2-Bromobenzylamine (0.19 g, 1.0 mmol) was added to a Schlenk vial together with dry Cs_2CO_3 (0.40 g, 1.2 mmol), dppf (28.2 mg, $5.0x10^{-5}$ mol), ^{t}BuNC (0.17 mL, 1.5 mmol) and dry toluene (7 mL). Finally, palladium(II) chloride (9.2 mg, $5x10^{-5}$ mol) was added, the walls of the vial washed with dry toluene (3 mL) and the vial flushed with argon for 2 minutes. The reaction mixture was heated for 1 h, until GC-analysis indicated complete conversion of the starting materials. After cooling, ether (10 mL) was added, and the resulting mixture filtered. Work-up was achieved by extraction of the organic layer with acetic acid (5x8 mL, 2.5% by volume in water). The acetic acid solution was then washed with ether (2x5 mL), basified with KOH-pellets and extracted with ether (6x15 mL). Drying over $MgSO_4$ and evaporation gave a brown oil (0.29 g), which was Kugelrohr-distilled (oven temp 95-100 °C / 1 mmHg) to give the title compound as a white solid (0.12 g, 64%), m.p. 88-90 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.541-7.522 (1H, m, Ph), 7.349-7.410 (3H, m, Ph), 4.690 (2H, s, CH_2), 1.541 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ=161.42 (s, C=N), 149.53 (s, *CPh*), 135.69 (s, *CPh*), 128.08 (d, *CPh*), 126.35 (d, *CPh*), 122.36 (d, *CPh*), 118.06 (d, *CPh*), 60.53 (t, CH_2), 51.40 (s, $C(CH_3)_3$), 29.07 (q, 3xCH_3) ppm. **LRMS** (ES, m/z, %). 188.9 (100, MH^+). **IR** (cm^{-1}, neat): 2970 (s), 2351 (m), 1680 (s), 1266 (s). **UV/Vis** (λ_{max}, nm): 208(ε=9400), 228 (10200), 264 (ε=3400), 280 (2200). **Elemental analysis** (%) calcd for $C_{12}H_{16}N_2$: C 76.55, H 8.57, N 14.88; found: C 76.46, H 8.69, N 14.73.

Synthesis of *tert*-Butyl-(2,3-dihydro-2-isoquinolin-1-ylidene)-amine 35b



2-(2-Bromophenyl)-ethylamine (0.20 g, 1.0 mmol) was added to a Schlenk vial together with dry Cs_2CO_3 (0.42 g, 1.3 mmol), dppf (28.6 mg, $5.0x10^{-5}$ mol), ^{t}BuNC (0.17 mL, 1.5 mmol) and dry toluene (7 mL). Finally, palladium(II) chloride (9.0 mg, $5x10^{-5}$ mol) was added, the walls of the vial washed with dry toluene (3 mL) and the vial flushed with argon for 2 minutes. The reaction mixture was heated for 1 h, until GC-analysis indicated complete conversion of the starting materials. After cooling, ether (10 mL) was added, and the resulting mixture filtered. Work-up was achieved by extraction of the organic layer with acetic acid (5x8 mL, 2.5% by volume in water). The acetic acid solution was then washed with ether (2x5 mL), basified with KOH-pellets and extracted with ether (6x15 mL). Drying over $MgSO_4$ and evaporation gave a brown oil (0.26 g), which was Kugelrohr-distilled (oven temp 110-115 °C / 1 mmHg) to give the title compound as a white solid (0.12 g, 64%), m.p. 110-113 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ=7.216-7.442 (5H, m, Ph), 3.532 (2H, t, J=6.7 Hz, CH_2), 2.718 (2H, t, J=6.7 Hz, CH_2), 1.490 (9H, s, 3xCH_3) ppm. **^{13}C-NMR** (75 MHz, $CDCl_3$) δ=140.01 (s, *CPh*), 130.73 (d, *CPh*), 128.88 (s, *CPh*), 128.11 (d, *CPh*), 126.92 (d, *CPh*), 123.32 (d, *CPh*), 51.95 (s, $C(CH_3)_3$), 43.83 (t, NCH_2), 29.17 (q, 3xCH_3),

27.92 (t, $\underline{C}H_2$) ppm. **LRMS** (ES, m/z, %). 203.0 (100, MH^+). **HRMS** (APCI, MH^+). $C_{13}H_{19}N_2$ calculated: 203.1548, found: 203.1541. **IR** (cm^{-1}, neat): 2952 (s), 2359 (s), 1686 (s), 1360 (s), 1273 (s). **UV/Vis** (λ_{max}, nm): 208(ε=9400), 228 (10200), 264 (ε=3400), 280 (2200).

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Appendix A X-Ray Crystallographic data for (*Z,E*)-*N*-Cyclohexyl-2-cyclohexylimino-2-phenylacetacetimidic acid isopropyl ester 39d

Table 1. Crystal data and structure refinement.

Chemical Name	(*Z,E*)-*N*-Cyclohexyl-2-cyclohexylimino-2-phenylacetimidic acid isopropyl ester **39d**
Empirical formula	$C_{23}H_{34}N_2O$
Formula weight	354.52
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 9.1902(5) Å b = 14.4440(7) Å β = 94.398(2)° c = 15.8727(10) Å
Volume	2100.8(2) Å^3
Z	4 (2 molecules)
Density (calculated)	1.121 Mg / m^3
Absorption coefficient	0.068 mm^{-1}
F(000)	776
Crystal	Colourless Block
Crystal size	0.50 x 0.30 x 0.13 mm^3
θ range for data collection	2.94 – 25.03°
Index ranges	$-10 \le h \le 10, -17 \le k \le 17, -18 \le l \le 18$
Reflections collected	10645
Independent reflections	6538 [R_{int} = 0.0447]
Completeness to θ = 25.03°	98.3 %
Max. and min. transmission	0.9915 and 0.9668
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6538 / 1 / 474
Goodness-of-fit on F^2	1.013
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0471, $wR2$ = 0.0913
R indices (all data)	$R1$ = 0.0753, $wR2$ = 0.1018
Absolute structure parameter	Not reliably determined
Extinction coefficient	0.0080(10)
Largest diff. peak and hole	0.176 and −0.208 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	6127(3)	7015(2)	−1238(2)	27(1)	1
C2	7110(3)	6813(2)	−1835(2)	31(1)	1
C3	8556(3)	7064(2)	−1693(2)	30(1)	1
C4	9027(3)	7525(2)	−958(2)	30(1)	1
C5	8050(3)	7728(2)	−362(2)	24(1)	1
C6	6589(3)	7466(2)	−499(2)	21(1)	1
C7	5576(3)	7616(2)	181(2)	19(1)	1
C8	5117(3)	8048(2)	1585(2)	25(1)	1
C9	5658(3)	7406(2)	2298(2)	33(1)	1
C10	4808(4)	7533(2)	3083(2)	43(1)	1
C11	4834(3)	8540(2)	3370(2)	40(1)	1
C12	4284(3)	9179(2)	2653(2)	33(1)	1
C13	5167(3)	9049(2)	1885(2)	28(1)	1
C14	4002(3)	7323(2)	−14(2)	21(1)	1
C15	3195(3)	8769(2)	−566(2)	24(1)	1
C16	2143(3)	9365(2)	−103(2)	29(1)	1
C17	2268(3)	10382(2)	−353(2)	40(1)	1
C18	2016(3)	10505(2)	−1303(2)	41(1)	1
C19	3062(3)	9913(2)	−1758(2)	39(1)	1
C20	2946(3)	8895(2)	−1513(2)	30(1)	1
C21	2375(3)	6032(2)	178(2)	25(1)	1
C22	2411(3)	5300(2)	855(2)	40(1)	1
C23	1996(3)	5659(2)	−694(2)	41(1)	1
N1	6064(2)	7944(1)	894(1)	24(1)	1
N2	2945(2)	7792(1)	−346(1)	22(1)	1
O1	3847(2)	6431(1)	236(1)	24(1)	1
C24	10138(3)	7327(2)	3115(2)	35(1)	1
C25	10494(3)	7371(2)	2277(2)	42(1)	1
C26	10414(3)	8200(3)	1854(2)	43(1)	1
C27	9986(3)	8988(2)	2257(2)	45(1)	1
C28	9625(3)	8953(2)	3088(2)	37(1)	1
C29	9698(3)	8118(2)	3522(2)	24(1)	1
C30	9271(3)	8070(2)	4409(2)	25(1)	1
C31	8300(3)	8739(2)	5616(2)	25(1)	1
C32	6627(3)	8742(2)	5559(2)	29(1)	1
C33	6076(3)	8746(2)	6441(2)	35(1)	1
C34	6688(3)	9549(2)	6967(2)	42(1)	1
C35	8355(3)	9559(2)	7010(2)	37(1)	1
C36	8906(3)	9557(2)	6132(2)	30(1)	1
C37	9420(3)	7132(2)	4847(2)	23(1)	1
C38	11782(3)	7393(2)	5495(2)	26(1)	1
C39	11866(3)	7670(2)	6421(2)	29(1)	1
C40	12063(3)	6836(2)	7013(2)	29(1)	1
C41	13413(3)	6284(2)	6825(2)	33(1)	1
C42	13316(3)	5980(2)	5900(2)	30(1)	1
C43	13123(3)	6812(2)	5315(2)	31(1)	1
C44	8084(3)	5738(2)	5081(2)	25(1)	1
C45	7698(3)	5881(2)	5978(2)	31(1)	1
C46	6933(3)	5209(2)	4554(2)	38(1)	1
N3	8782(2)	8791(2)	4758(1)	28(1)	1
N4	10475(2)	6820(2)	5312(1)	26(1)	1
O2	8166(2)	6642(1)	4667(1)	25(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C6	1.380(4)
C1–C2	1.390(3)
C2–C3	1.379(4)
C3–C4	1.384(4)
C4–C5	1.384(4)
C5–C6	1.396(3)
C6–C7	1.495(3)
C7–N1	1.275(3)
C7–C14	1.516(3)
C8–N1	1.461(3)
C8–C9	1.518(4)
C8–C13	1.521(3)
C9–C10	1.532(4)
C10–C11	1.523(4)
C11–C12	1.522(4)
C12–C13	1.527(4)
C14–N2	1.266(3)
C14–O1	1.359(3)
C15–N2	1.476(3)
C15–C20	1.515(3)
C15–C16	1.524(4)
C16–C17	1.529(4)
C17–C18	1.519(4)
C18–C19	1.512(4)
C19–C20	1.527(4)
C21–O1	1.467(3)
C21–C23	1.500(4)
C21–C22	1.506(4)
C24–C29	1.388(4)
C24–C25	1.396(4)
C25–C26	1.372(4)
C26–C27	1.377(4)
C27–C28	1.386(4)
C28–C29	1.389(4)
C29–C30	1.493(4)
C30–N3	1.276(3)
C30–C37	1.524(4)
C31–N3	1.467(3)
C31–C36	1.519(4)
C31–C32	1.533(4)
C32–C33	1.524(4)
C33–C34	1.513(4)
C34–C35	1.528(4)
C35–C36	1.519(4)
C37–N4	1.257(3)
C37–O2	1.364(3)
C38–N4	1.469(3)
C38–C39	1.520(3)
C38–C43	1.536(4)
C39–C40	1.529(4)
C40–C41	1.524(4)
C41–C42	1.529(4)
C42–C43	1.520(4)
C44–O2	1.466(3)
C44–C46	1.506(4)
C44–C45	1.508(4)
C6–C1–C2	120.3(3)
C3–C2–C1	120.1(3)
C2–C3–C4	120.0(3)

C3–C4–C5	120.0(3)
C4–C5–C6	120.2(2)
C1–C6–C5	119.4(2)
C1–C6–C7	120.9(2)
C5–C6–C7	119.5(2)
N1–C7–C6	119.9(2)
N1–C7–C14	123.4(2)
C6–C7–C14	116.7(2)
N1–C8–C9	108.5(2)
N1–C8–C13	109.1(2)
C9–C8–C13	110.4(2)
C8–C9–C10	112.0(2)
C11–C10–C9	111.2(2)
C12–C11–C10	111.0(2)
C11–C12–C13	110.9(2)
C8–C13–C12	111.1(2)
N2–C14–O1	122.3(2)
N2–C14–C7	128.7(2)
O1–C14–C7	109.0(2)
N2–C15–C20	109.5(2)
N2–C15–C16	108.0(2)
C20–C15–C16	111.0(2)
C15–C16–C17	110.8(2)
C18–C17–C16	111.1(2)
C19–C18–C17	110.8(2)
C18–C19–C20	111.3(2)
C15–C20–C19	111.1(2)
O1–C21–C23	110.3(2)
O1–C21–C22	105.1(2)
C23–C21–C22	113.4(2)
C7–N1–C8	121.0(2)
C14–N2–C15	118.8(2)
C14–O1–C21	118.11(19)
C29–C24–C25	120.2(3)
C26–C25–C24	119.9(3)
C25–C26–C27	120.0(3)
C26–C27–C28	120.7(3)
C27–C28–C29	119.8(3)
C24–C29–C28	119.3(2)
C24–C29–C30	120.5(2)
C28–C29–C30	120.1(3)
N3–C30–C29	119.9(2)
N3–C30–C37	123.4(2)
C29–C30–C37	116.8(2)
N3–C31–C36	109.7(2)
N3–C31–C32	108.5(2)
C36–C31–C32	110.7(2)
C33–C32–C31	110.4(2)
C34–C33–C32	111.9(2)
C33–C34–C35	111.1(2)
C36–C35–C34	111.3(2)
C31–C36–C35	111.2(2)
N4–C37–O2	122.5(2)
N4–C37–C30	128.7(2)
O2–C37–C30	108.8(2)
N4–C38–C39	108.6(2)
N4–C38–C43	108.1(2)
C39–C38–C43	109.9(2)
C38–C39–C40	112.4(2)
C41–C40–C39	110.6(2)
C40–C41–C42	110.5(2)
C43–C42–C41	110.8(2)
C42–C43–C38	112.1(2)

O2–C44–C46	105.1(2)
O2–C44–C45	109.0(2)
C46–C44–C45	112.8(2)
C30–N3–C31	120.2(2)
C37–N4–C38	119.8(2)
C37–O2–C44	116.13(19)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	20(1)	36(2)	26(2)	0(1)	2(1)	1(1)
C2	27(2)	44(2)	21(2)	−4(1)	3(1)	3(1)
C3	26(2)	38(2)	27(2)	0(1)	8(1)	3(1)
C4	24(2)	33(2)	32(2)	1(1)	4(1)	−3(1)
C5	26(2)	19(1)	28(2)	−2(1)	2(1)	−5(1)
C6	23(2)	20(1)	19(1)	1(1)	−2(1)	3(1)
C7	20(1)	17(1)	21(2)	4(1)	0(1)	2(1)
C8	25(2)	31(2)	20(2)	−9(1)	2(1)	−2(1)
C9	36(2)	32(2)	31(2)	−3(1)	7(1)	5(1)
C10	49(2)	48(2)	33(2)	9(2)	13(2)	11(2)
C11	36(2)	61(2)	24(2)	−11(2)	7(1)	3(2)
C12	31(2)	32(2)	35(2)	−13(1)	3(1)	−1(1)
C13	26(2)	29(2)	31(2)	−7(1)	5(1)	0(1)
C14	26(2)	22(2)	16(1)	−2(1)	4(1)	−4(1)
C15	23(2)	20(1)	27(2)	2(1)	−1(1)	−2(1)
C16	31(2)	28(2)	29(2)	−2(1)	3(1)	−1(1)
C17	37(2)	25(2)	57(2)	−5(2)	11(2)	−1(2)
C18	32(2)	26(2)	64(2)	17(2)	0(2)	0(2)
C19	44(2)	39(2)	36(2)	12(1)	6(2)	4(2)
C20	36(2)	26(2)	29(2)	2(1)	2(1)	−3(1)
C21	19(2)	26(2)	30(2)	1(1)	4(1)	−5(1)
C22	35(2)	37(2)	49(2)	13(2)	7(2)	−2(2)
C23	39(2)	45(2)	39(2)	−11(2)	2(2)	−9(2)
N1	22(1)	27(1)	24(1)	−3(1)	2(1)	0(1)
N2	23(1)	22(1)	23(1)	1(1)	2(1)	−1(1)
O1	19(1)	23(1)	29(1)	4(1)	2(1)	−3(1)
C24	40(2)	40(2)	26(2)	2(1)	6(1)	−8(2)
C25	46(2)	55(2)	26(2)	−5(2)	9(1)	−16(2)
C26	36(2)	73(3)	18(2)	−1(2)	2(1)	−11(2)
C27	39(2)	62(2)	34(2)	27(2)	1(2)	0(2)
C28	35(2)	45(2)	31(2)	12(1)	2(1)	2(2)
C29	19(1)	34(2)	20(2)	4(1)	−3(1)	−1(1)
C30	23(2)	29(2)	22(2)	3(1)	−1(1)	−3(1)
C31	28(2)	26(1)	21(2)	6(1)	4(1)	2(1)
C32	26(2)	32(2)	29(2)	4(1)	−2(1)	−3(1)
C33	28(2)	42(2)	34(2)	1(2)	3(1)	1(2)
C34	35(2)	59(2)	35(2)	−13(2)	12(1)	2(2)
C35	40(2)	45(2)	26(2)	−5(1)	3(1)	−5(2)
C36	26(2)	32(2)	32(2)	2(1)	4(1)	1(1)
C37	24(2)	26(2)	17(2)	−3(1)	3(1)	−3(1)
C38	22(2)	26(2)	30(2)	5(1)	−3(1)	−9(1)
C39	27(2)	27(2)	33(2)	−3(1)	−6(1)	0(1)
C40	28(2)	33(2)	27(2)	−2(1)	4(1)	0(1)
C41	31(2)	34(2)	32(2)	0(1)	−1(1)	2(1)
C42	21(2)	32(2)	36(2)	−6(1)	4(1)	4(1)
C43	26(2)	41(2)	27(2)	−4(1)	3(1)	−12(1)
C44	26(2)	24(2)	27(2)	2(1)	5(1)	−1(1)
C45	31(2)	35(2)	27(2)	2(1)	6(1)	−5(1)
C46	42(2)	35(2)	37(2)	−5(1)	6(2)	−10(2)
N3	29(1)	31(1)	23(1)	4(1)	2(1)	2(1)

N4	27(1)	28(1)	23(1)	1(1)	1(1)	−3(1)
O2	23(1)	29(1)	24(1)	1(1)	0(1)	−5(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	5132	6841	−1339	33	1
H2	6786	6501	−2343	37	1
H3	9228	6921	−2100	36	1
H4	10022	7702	−862	35	1
H5	8375	8046	141	29	1
H8	4093	7880	1385	30	1
H9A	6706	7527	2449	39	1
H9B	5560	6756	2103	39	1
H10A	3784	7334	2954	52	1
H10B	5242	7138	3546	52	1
H11A	4213	8612	3849	48	1
H11B	5843	8715	3569	48	1
H12A	4362	9830	2845	39	1
H12B	3243	9045	2492	39	1
H13A	4769	9456	1421	34	1
H13B	6193	9231	2033	34	1
H15	4222	8944	−378	28	1
H16A	2365	9300	514	35	1
H16B	1132	9148	−242	35	1
H17A	1540	10751	−69	47	1
H17B	3251	10616	−161	47	1
H18A	1000	10329	−1488	49	1
H18B	2153	11163	−1450	49	1
H19A	4073	10131	−1617	47	1
H19B	2844	9978	−2376	47	1
H20A	1967	8658	−1708	36	1
H20B	3679	8530	−1797	36	1
H21	1655	6522	305	30	1
H22A	3146	4833	745	60	1
H22B	1450	5005	854	60	1
H22C	2659	5587	1407	60	1
H23A	2074	6156	−1108	61	1
H23B	996	5420	−731	61	1
H23C	2672	5159	−810	61	1
H24	10196	6753	3408	42	1
H25	10793	6828	2000	50	1
H26	10653	8231	1283	51	1
H27	9938	9561	1962	54	1
H28	9328	9500	3361	44	1
H31	8666	8151	5889	30	1
H32A	6259	9297	5245	35	1
H32B	6254	8187	5247	35	1
H33A	4997	8783	6391	41	1
H33B	6357	8158	6730	41	1
H34A	6362	9501	7546	51	1
H34B	6307	10138	6717	51	1
H35A	8721	10118	7319	44	1
H35B	8738	9009	7326	44	1
H36A	8612	10140	5838	35	1
H36B	9986	9528	6180	35	1
H38	11729	7958	5130	32	1
H39A	10961	8001	6539	35	1
H39B	12695	8101	6538	35	1
H40A	12162	7051	7606	35	1
H40B	11190	6433	6939	35	1
H41A	13500	5732	7195	39	1
H41B	14295	6669	6946	39	1

H42A	14216	5643	5782	36	1
H42B	12480	5553	5791	36	1
H43A	13018	6595	4722	37	1
H43B	14007	7205	5385	37	1
H44	9044	5412	5078	31	1
H45A	8457	6252	6285	46	1
H45B	7624	5278	6256	46	1
H45C	6760	6204	5977	46	1
H46A	6003	5541	4546	56	1
H46B	6821	4591	4797	56	1
H46C	7226	5149	3975	56	1

Appendix B X-Ray Crystallographic data for (*Z,E*)-*N*-Cyclohexyl-2-cyclohexylimino-2-(4-methoxyphenyl)-acetimidic acid ethyl ester 39e

Table 1. Crystal data and structure refinement.

Chemical name	(*Z,E*)-*N*-Cyclohexyl-2-cyclohexylimino-2-(4-methoxyphenyl)-acetimidic acid ethyl ester **39e**	
Empirical formula	$C_{23}H_{34}N_2O_2$	
Formula weight	370.52	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 8.1962(3) Å	α = 90°
	b = 16.6508(7) Å	β = 91.117(2)°
	c = 31.3636(16) Å	γ = 90°
Volume	4279.5(3) Å^3	
Z	8	
Density (calculated)	1.150 Mg / m^3	
Absorption coefficient	0.073 mm^{-1}	
F(000)	1616	
Crystal	Block; colourless	
Crystal size	0.20 × 0.20 × 0.20 mm^3	
θ range for data collection	3.13 – 25.38°	
Index ranges	$-9 \le h \le 9$, $-16 \le k \le 19$, $-37 \le l \le 31$	
Reflections collected	17160	
Independent reflections	6998 [R_{int} = 0.0675]	
Completeness to θ = 25.38°	89.2 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9856 and 0.9856	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6998 / 0 / 492	
Goodness-of-fit on F^2	0.921	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0564, $wR2$ = 0.1074	
R indices (all data)	$R1$ = 0.1513, $wR2$ = 0.1421	
Extinction coefficient	0.0025(4)	
Largest diff. peak and hole	0.220 and –0.232 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick
(1997), University of Göttingen, Germany).
Further information: http://www.soton.ac.uk/~xservice/strat.htm

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	599(4)	10823(2)	496(1)	37(1)	1
C1'	4667(4)	10989(2)	−2045(1)	36(1)	1
C2'	5577(4)	9738(2)	−1748(1)	25(1)	1
C2	−644(4)	9665(2)	811(1)	24(1)	1
C3	352(4)	9709(2)	1170(1)	26(1)	1
C3'	6701(3)	9108(2)	−1755(1)	28(1)	1
C4	259(3)	9115(2)	1476(1)	25(1)	1
C4'	6718(3)	8543(2)	−1434(1)	27(1)	1
C5	−841(3)	8480(2)	1437(1)	22(1)	1
C5'	5587(3)	8571(2)	−1105(1)	22(1)	1
C6'	4445(3)	9186(2)	−1117(1)	26(1)	1
C6	−1862(3)	8460(2)	1076(1)	24(1)	1
C7'	4436(3)	9772(2)	−1433(1)	26(1)	1
C7	−1756(3)	9039(2)	764(1)	26(1)	1
C8	−920(4)	7847(2)	1768(1)	22(1)	1
C8'	5646(3)	7988(2)	−748(1)	23(1)	1
C9'	6892(3)	6976(2)	−323(1)	26(1)	1
C9	−2215(3)	6775(2)	2130(1)	26(1)	1
C10	−2576(4)	5965(2)	1924(1)	28(1)	1
C10'	7256(4)	6126(2)	−474(1)	30(1)	1
C11	−2684(4)	5316(2)	2264(1)	32(1)	1
C11'	7454(4)	5549(2)	−100(1)	33(1)	1
C12'	8777(4)	5835(2)	210(1)	33(1)	1
C12	−3954(4)	5516(2)	2595(1)	34(1)	1
C13	−3641(4)	6338(2)	2792(1)	33(1)	1
C13'	8396(4)	6678(2)	369(1)	32(1)	1
C14'	8199(4)	7259(2)	−4(1)	29(1)	1
C14	−3530(4)	6987(2)	2448(1)	29(1)	1
C15	575(4)	7757(2)	2050(1)	24(1)	1
C15'	4175(4)	7999(2)	−464(1)	23(1)	1
C16'	2656(4)	7116(2)	−895(1)	27(1)	1
C16	1977(3)	6956(2)	1562(1)	25(1)	1
C17'	1201(4)	7393(2)	−1166(1)	31(1)	1
C17	2348(4)	6075(2)	1645(1)	30(1)	1
C18'	956(4)	6849(2)	−1551(1)	34(1)	1
C18	2597(4)	5612(2)	1230(1)	34(1)	1
C19	3933(4)	5997(2)	965(1)	34(1)	1
C19'	755(4)	5974(2)	−1420(1)	35(1)	1
C20'	2197(4)	5698(2)	−1142(1)	35(1)	1
C20	3553(4)	6877(2)	882(1)	34(1)	1
C21'	2444(4)	6245(2)	−756(1)	30(1)	1
C21	3318(4)	7333(2)	1298(1)	31(1)	1
C22'	3158(3)	8635(2)	162(1)	29(1)	1
C22	1691(4)	8128(2)	2730(1)	34(1)	1
C23'	3860(4)	9102(2)	532(1)	36(1)	1
C23	1131(4)	8539(2)	3126(1)	47(1)	1
N1'	6864(3)	7521(1)	−691(1)	26(1)	1
N1	−2185(3)	7399(1)	1798(1)	24(1)	1
N2	1872(3)	7382(1)	1973(1)	26(1)	1
N2'	2838(3)	7633(1)	−516(1)	26(1)	1
O1	−626(2)	10205(1)	481(1)	33(1)	1
O1'	5718(2)	10297(1)	−2067(1)	33(1)	1
O2	362(2)	8161(1)	2422(1)	28(1)	1
O2'	4491(2)	8490(1)	−125(1)	27(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O1	1.438(3)
C1–H1A	0.9800
C1–H1B	0.9800
C1–H1C	0.9800
C1'–O1'	1.440(3)
C1'–H1'1	0.9800
C1'–H1'2	0.9800
C1'–H1'3	0.9800
C2'–O1'	1.372(3)
C2'–C7'	1.376(4)
C2'–C3'	1.396(4)
C2–O1	1.371(3)
C2–C3	1.381(4)
C2–C7	1.391(4)
C3–C4	1.381(4)
C3–H3	0.9500
C3'–C4'	1.378(4)
C3'–H3'	0.9500
C4–C5	1.393(4)
C4–H4	0.9500
C4'–C5'	1.401(4)
C4'–H4'	0.9500
C5–C6	1.396(4)
C5–C8	1.481(4)
C5'–C6'	1.388(4)
C5'–C8'	1.484(4)
C6'–C7'	1.391(4)
C6'–H6'	0.9500
C6–C7	1.379(4)
C6–H6	0.9500
C7'–H7'	0.9500
C7–H7	0.9500
C8–N1	1.282(3)
C8–C15	1.505(4)
C8'–N1'	1.274(3)
C8'–C15'	1.512(4)
C9'–N1'	1.467(3)
C9'–C10'	1.523(4)
C9'–C14'	1.528(4)
C9'–H9'	1.0000
C9–N1	1.471(3)
C9–C10	1.522(4)
C9–C14	1.526(4)
C9–H9	1.0000
C10–C11	1.523(4)
C10–H10A	0.9900
C10–H10B	0.9900
C10'–C11'	1.524(4)
C10'–H10C	0.9900
C10'–H10D	0.9900
C11–C12	1.523(4)
C11–H11A	0.9900
C11–H11B	0.9900
C11'–C12'	1.518(4)
C11'–H11C	0.9900
C11'–H11D	0.9900
C12'–C13'	1.523(4)
C12'–H12A	0.9900
C12'–H12B	0.9900
C12–C13	1.520(4)
C12–H12C	0.9900

C12–H12D	0.9900
C13–C14	1.531(4)
C13–H13A	0.9900
C13–H13B	0.9900
C13'–C14'	1.524(4)
C13'–H13C	0.9900
C13'–H13D	0.9900
C14'–H14A	0.9900
C14'–H14B	0.9900
C14–H14C	0.9900
C14–H14D	0.9900
C15–N2	1.260(3)
C15–O2	1.359(3)
C15'–N2'	1.261(3)
C15'–O2'	1.364(3)
C16'–N2'	1.472(3)
C16'–C21'	1.524(4)
C16'–C17'	1.523(4)
C16'–H16'	1.0000
C16–N2	1.477(3)
C16–C17	1.520(4)
C16–C21	1.524(4)
C16–H16	1.0000
C17'–C18'	1.519(4)
C17'–H17A	0.9900
C17'–H17B	0.9900
C17–C18	1.530(4)
C17–H17C	0.9900
C17–H17D	0.9900
C18'–C19'	1.525(4)
C18'–H18A	0.9900
C18'–H18B	0.9900
C18–C19	1.528(4)
C18–H18C	0.9900
C18–H18D	0.9900
C19–C20	1.519(4)
C19–H19A	0.9900
C19–H19B	0.9900
C19'–C20'	1.525(4)
C19'–H19C	0.9900
C19'–H19D	0.9900
C20'–C21'	1.525(4)
C20'–H20A	0.9900
C20'–H20B	0.9900
C20–C21	1.526(4)
C20–H20C	0.9900
C20–H20D	0.9900
C21'–H21A	0.9900
C21'–H21B	0.9900
C21–H21C	0.9900
C21–H21D	0.9900
C22'–O2'	1.450(3)
C22'–C23'	1.503(4)
C22'–H22A	0.9900
C22'–H22B	0.9900
C22–O2	1.443(3)
C22–C23	1.498(4)
C22–H22C	0.9900
C22–H22D	0.9900
C23'–H23A	0.9800
C23'–H23B	0.9800
C23'–H23C	0.9800
C23–H23D	0.9800

C23–H23E	0.9800
C23–H23F	0.9800

O1–C1–H1A	109.5
O1–C1–H1B	109.5
H1A–C1–H1B	109.5
O1–C1–H1C	109.5
H1A–C1–H1C	109.5
H1B–C1–H1C	109.5
O1'–C1'–H1'1	109.5
O1'–C1'–H1'2	109.5
H1'1–C1'–H1'2	109.5
O1'–C1'–H1'3	109.5
H1'1–C1'–H1'3	109.5
H1'2–C1'–H1'3	109.5
O1'–C2'–C7'	124.2(3)
O1'–C2'–C3'	115.7(2)
C7'–C2'–C3'	120.1(3)
O1–C2–C3	124.5(2)
O1–C2–C7	115.3(3)
C3–C2–C7	120.2(2)
C2–C3–C4	119.3(3)
C2–C3–H3	120.4
C4–C3–H3	120.4
C4'–C3'–C2'	119.9(3)
C4'–C3'–H3'	120.0
C2'–C3'–H3'	120.0
C3–C4–C5	121.9(3)
C3–C4–H4	119.1
C5–C4–H4	119.1
C3'–C4'–C5'	121.2(3)
C3'–C4'–H4'	119.4
C5'–C4'–H4'	119.4
C6–C5–C4	117.8(2)
C6–C5–C8	121.2(2)
C4–C5–C8	121.1(3)
C6'–C5'–C4'	117.5(2)
C6'–C5'–C8'	121.0(2)
C4'–C5'–C8'	121.5(3)
C7'–C6'–C5'	122.1(3)
C7'–C6'–H6'	119.0
C5'–C6'–H6'	119.0
C7–C6–C5	121.0(3)
C7–C6–H6	119.5
C5–C6–H6	119.5
C2'–C7'–C6'	119.3(3)
C2'–C7'–H7'	120.4
C6'–C7'–H7'	120.4
C6–C7–C2	119.9(3)
C6–C7–H7	120.0
C2–C7–H7	120.0
N1–C8–C5	120.8(3)
N1–C8–C15	123.3(2)
C5–C8–C15	115.9(2)
N1'–C8'–C5'	121.2(2)
N1'–C8'–C15'	123.8(2)
C5'–C8'–C15'	114.9(2)
N1'–C9'–C10'	109.3(2)
N1'–C9'–C14'	108.9(2)
C10'–C9'–C14'	110.6(2)
N1'–C9'–H9'	109.3
C10'–C9'–H9'	109.3
C14'–C9'–H9'	109.3

N1–C9–C10	109.4(2)
N1–C9–C14	108.7(2)
C10–C9–C14	110.4(2)
N1–C9–H9	109.4
C10–C9–H9	109.4
C14–C9–H9	109.4
C11–C10–C9	110.2(2)
C11–C10–H10A	109.6
C9–C10–H10A	109.6
C11–C10–H10B	109.6
C9–C10–H10B	109.6
H10A–C10–H10B	108.1
C9'–C10'–C11'	111.4(2)
C9'–C10'–H10C	109.4
C11'–C10'–H10C	109.4
C9'–C10'–H10D	109.4
C11'–C10'–H10D	109.4
H10C–C10'–H10D	108.0
C12–C11–C10	111.8(2)
C12–C11–H11A	109.3
C10–C11–H11A	109.3
C12–C11–H11B	109.3
C10–C11–H11B	109.3
H11A–C11–H11B	107.9
C12'–C11'–C10'	111.1(2)
C12'–C11'–H11C	109.4
C10'–C11'–H11C	109.4
C12'–C11'–H11D	109.4
C10'–C11'–H11D	109.4
H11C–C11'–H11D	108.0
C11'–C12'–C13'	110.5(2)
C11'–C12'–H12A	109.6
C13'–C12'–H12A	109.6
C11'–C12'–H12B	109.6
C13'–C12'–H12B	109.6
H12A–C12'–H12B	108.1
C13–C12–C11	111.2(2)
C13–C12–H12C	109.4
C11–C12–H12C	109.4
C13–C12–H12D	109.4
C11–C12–H12D	109.4
H12C–C12–H12D	108.0
C12–C13–C14	111.2(2)
C12–C13–H13A	109.4
C14–C13–H13A	109.4
C12–C13–H13B	109.4
C14–C13–H13B	109.4
H13A–C13–H13B	108.0
C12'–C13'–C14'	110.7(2)
C12'–C13'–H13C	109.5
C14'–C13'–H13C	109.5
C12'–C13'–H13D	109.5
C14'–C13'–H13D	109.5
H13C–C13'–H13D	108.1
C13'–C14'–C9'	111.6(2)
C13'–C14'–H14A	109.3
C9'–C14'–H14A	109.3
C13'–C14'–H14B	109.3
C9'–C14'–H14B	109.3
H14A–C14'–H14B	108.0
C13–C14–C9	110.5(2)
C13–C14–H14C	109.6
C9–C14–H14C	109.6

C13–C14–H14D	109.6
C9–C14–H14D	109.6
H14C–C14–H14D	108.1
N2–C15–O2	122.2(3)
N2–C15–C8	128.0(2)
O2–C15–C8	109.8(2)
N2'–C15'–O2'	122.8(2)
N2'–C15'–C8'	128.2(2)
O2'–C15'–C8'	108.9(2)
N2'–C16'–C21'	109.7(2)
N2'–C16'–C17'	109.9(2)
C21'–C16'–C17'	110.8(2)
N2'–C16'–H16'	108.8
C21'–C16'–H16'	108.8
C17'–C16'–H16'	108.8
N2–C16–C17	109.1(2)
N2–C16–C21	109.4(2)
C17–C16–C21	110.3(2)
N2–C16–H16	109.3
C17–C16–H16	109.3
C21–C16–H16	109.3
C18'–C17'–C16'	110.7(2)
C18'–C17'–H17A	109.5
C16'–C17'–H17A	109.5
C18'–C17'–H17B	109.5
C16'–C17'–H17B	109.5
H17A–C17'–H17B	108.1
C16–C17–C18	111.7(2)
C16–C17–H17C	109.3
C18–C17–H17C	109.3
C16–C17–H17D	109.3
C18–C17–H17D	109.3
H17C–C17–H17D	107.9
C17'–C18'–C19'	111.6(2)
C17'–C18'–H18A	109.3
C19'–C18'–H18A	109.3
C17'–C18'–H18B	109.3
C19'–C18'–H18B	109.3
H18A–C18'–H18B	108.0
C17–C18–C19	111.1(2)
C17–C18–H18C	109.4
C19–C18–H18C	109.4
C17–C18–H18D	109.4
C19–C18–H18D	109.4
H18C–C18–H18D	108.0
C20–C19–C18	110.6(2)
C20–C19–H19A	109.5
C18–C19–H19A	109.5
C20–C19–H19B	109.5
C18–C19–H19B	109.5
H19A–C19–H19B	108.1
C18'–C19'–C20'	110.8(2)
C18'–C19'–H19C	109.5
C20'–C19'–H19C	109.5
C18'–C19'–H19D	109.5
C20'–C19'–H19D	109.5
H19C–C19'–H19D	108.1
C19'–C20'–C21'	111.3(2)
C19'–C20'–H20A	109.4
C21'–C20'–H20A	109.4
C19'–C20'–H20B	109.4
C21'–C20'–H20B	109.4
H20A–C20'–H20B	108.0

C19–C20–C21	111.2(2)
C19–C20–H20C	109.4
C21–C20–H20C	109.4
C19–C20–H20D	109.4
C21–C20–H20D	109.4
H20C–C20–H20D	108.0
C16'–C21'–C20'	110.8(2)
C16'–C21'–H21A	109.5
C20'–C21'–H21A	109.5
C16'–C21'–H21B	109.5
C20'–C21'–H21B	109.5
H21A–C21'–H21B	108.1
C16–C21–C20	111.3(2)
C16–C21–H21C	109.4
C20–C21–H21C	109.4
C16–C21–H21D	109.4
C20–C21–H21D	109.4
H21C–C21–H21D	108.0
O2'–C22'–C23'	106.5(2)
O2'–C22'–H22A	110.4
C23'–C22'–H22A	110.4
O2'–C22'–H22B	110.4
C23'–C22'–H22B	110.4
H22A–C22'–H22B	108.6
O2–C22–C23	107.4(2)
O2–C22–H22C	110.2
C23–C22–H22C	110.2
O2–C22–H22D	110.2
C23–C22–H22D	110.2
H22C–C22–H22D	108.5
C22'–C23'–H23A	109.5
C22'–C23'–H23B	109.5
H23A–C23'–H23B	109.5
C22'–C23'–H23C	109.5
H23A–C23'–H23C	109.5
H23B–C23'–H23C	109.5
C22–C23–H23D	109.5
C22–C23–H23E	109.5
H23D–C23–H23E	109.5
C22–C23–H23F	109.5
H23D–C23–H23F	109.5
H23E–C23–H23F	109.5
C8'–N1'–C9'	119.2(2)
C8–N1–C9	119.2(2)
C15–N2–C16	118.0(2)
C15'–N2'–C16'	117.4(2)
C2–O1–C1	117.5(2)
C2'–O1'–C1'	116.8(2)
C15–O2–C22	116.6(2)
C15'–O2'–C22'	116.7(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	35(2)	32(2)	44(2)	11(2)	−1(2)	−9(2)
C1'	40(2)	29(2)	39(2)	9(1)	−1(2)	7(2)
C2'	27(2)	23(2)	24(2)	1(1)	−4(2)	−5(1)
C2	25(2)	23(2)	25(2)	3(1)	1(1)	4(1)
C3	28(2)	22(2)	29(2)	−2(1)	−2(2)	−1(1)

C3'	28(2)	33(2)	24(2)	−1(2)	4(1)	1(2)
C4	25(2)	28(2)	23(2)	−2(1)	0(1)	2(1)
C4'	26(2)	26(2)	30(2)	−1(1)	−5(2)	4(1)
C5	24(2)	22(2)	19(2)	−1(1)	0(1)	1(1)
C5'	22(2)	26(2)	18(2)	−2(1)	−4(1)	−3(1)
C6'	26(2)	30(2)	23(2)	−4(1)	2(1)	2(1)
C6	22(2)	24(2)	26(2)	−3(1)	2(1)	0(1)
C7'	27(2)	26(2)	26(2)	−3(1)	−1(2)	2(1)
C7	26(2)	30(2)	22(2)	0(1)	−2(1)	0(1)
C8	22(2)	24(2)	21(2)	−3(1)	1(1)	5(1)
C8'	23(2)	23(2)	22(2)	−4(1)	−2(1)	−2(1)
C9'	22(2)	26(2)	28(2)	4(1)	0(1)	2(1)
C9	22(2)	30(2)	25(2)	3(1)	−4(1)	0(1)
C10	26(2)	31(2)	26(2)	−2(1)	−1(1)	−1(1)
C10'	30(2)	31(2)	30(2)	1(1)	1(1)	2(1)
C11	35(2)	29(2)	31(2)	4(1)	−1(2)	−4(1)
C11'	35(2)	26(2)	38(2)	1(1)	3(2)	2(1)
C12'	38(2)	32(2)	29(2)	6(2)	0(2)	5(2)
C12	36(2)	38(2)	29(2)	8(2)	1(2)	−3(2)
C13	34(2)	39(2)	26(2)	3(2)	0(2)	0(2)
C13'	31(2)	38(2)	28(2)	3(1)	−3(2)	1(1)
C14'	34(2)	26(2)	27(2)	−2(1)	−1(2)	2(1)
C14	33(2)	26(2)	27(2)	1(1)	−1(2)	0(1)
C15	28(2)	23(2)	21(2)	0(1)	−3(2)	−4(1)
C15'	26(2)	21(2)	21(2)	2(1)	−2(1)	1(1)
C16'	28(2)	31(2)	22(2)	−3(1)	2(1)	−3(1)
C16	18(2)	30(2)	26(2)	0(1)	−5(1)	2(1)
C17'	33(2)	33(2)	28(2)	1(1)	−2(2)	−1(2)
C17	27(2)	31(2)	31(2)	2(1)	0(1)	−2(1)
C18'	30(2)	40(2)	31(2)	2(2)	−2(2)	−4(2)
C18	37(2)	27(2)	39(2)	−4(2)	−1(2)	2(2)
C19	36(2)	36(2)	31(2)	−12(2)	−3(2)	6(2)
C19'	36(2)	38(2)	31(2)	−11(2)	6(2)	−11(2)
C20'	41(2)	29(2)	34(2)	−2(2)	4(2)	−3(2)
C20	31(2)	39(2)	30(2)	−2(2)	2(2)	2(2)
C21'	31(2)	33(2)	27(2)	1(1)	2(1)	−1(1)
C21	34(2)	27(2)	32(2)	−1(1)	2(2)	3(1)
C22'	30(2)	35(2)	20(2)	1(1)	2(2)	6(1)
C22	27(2)	50(2)	25(2)	−5(2)	−8(2)	3(2)
C23'	38(2)	42(2)	29(2)	−8(2)	2(2)	6(2)
C23	46(2)	59(2)	35(2)	−16(2)	−9(2)	13(2)
N1'	29(2)	25(1)	25(1)	1(1)	1(1)	0(1)
N1	25(2)	27(1)	22(1)	4(1)	0(1)	3(1)
N2	27(2)	28(1)	24(1)	−1(1)	−3(1)	2(1)
N2'	26(2)	29(1)	23(1)	−1(1)	1(1)	1(1)
O1	34(1)	33(1)	31(1)	9(1)	−6(1)	−7(1)
O1'	34(1)	33(1)	33(1)	10(1)	3(1)	3(1)
O2	25(1)	35(1)	22(1)	−4(1)	−4(1)	4(1)
O2'	26(1)	33(1)	22(1)	−5(1)	0(1)	−1(1)