PALLADIUM CATALYSED HYDROESTERIFICATION AND AMINOCARBONYLATION OF SUBSTITUTED ALKENES AND ALKYNES

Dissertation submitted in fulfilment of the requirements for the degree

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by

Maretha du Plessis

Supervisor: Prof. B.C.B. Bezuidenhoudt

Co-supervisor: Dr. C. Marais

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"The love for organic chemistry lies in the never ending journey to make sense of it."

A section of the work presented in this thesis has already led to the following publication:

Du Plessis, M., Marais, C., Bezuidenhoudt, B.C.B., “Parameters Influencing Reactivity and Regioselectivity in the Methoxycarbonylation of Arylalkenes”, *Synthesis*, **2016**, *48*, 557-565.

The thesis does not contain any reference to this publication.

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LIST OF ABBREVIATIONS

A	acetone
AC	autoclave
AIBN	2,2'-azobis(2-methylpropionitrile)
Ar	aryl
b	branched
BDPPTS	2,4-bis(diphenylphosphino)pentane
BDTBPMB	1,2-bis(di-*tert*-butylphosphinomethyl)benzene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthylene
bn	benzylic
BNPPA	1,1'-binaphthyl-2,2'-diyl hydrogen phosphate
BPPFA	1-[(R)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl dimethyl amine
BPPFOAc	1-[(R)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl acetate
BPPM	1-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine
br.	broad
BSA	borosalicylic acid
calcd	calculated
CC	cyclograph chromatography
CPD	carbon-proton decoupled
δ	chemical shift in parts per million
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBA	*Trans*,*trans*-$(PhCH{=}CH)_2CO$
DBPMB	$1,2\text{-}(CH_2PBut_2)_2C_6H_4$
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanoperoxybenzoic acid
DEAD	diethylazodicarboylate
DEPT	distortionless enhancement by polarization transfer
DHQ-CLB	dihydroquinine *para*-chlorobenzoate
DHQD-CLB	dihydroquinidine *para*-chlorobenzoate
DIBAH(L)	diisobutylaluminium hydride
DIOP	2,2-dimethyl-4,5-bis(diphenyl phosphinomethyl)-1,3-dioxolane
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMF-DMA	dimethylformamide dimethylacetal
DMSO	dimethylsulfoxide
DMTSF	dimethyl(methylthio)sulfonium tetrafluoroborate
DPEphos	bis[2-(diphenylphosphino)ether]
DPPB	1,4-bis(diphenylphosphino)butane
DPPD	1,2-bis(diphenylphosphino)decane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
DPPH	1,2-bis(diphenylphosphino)hexane

DPPP	1,2-bis(diphenylphosphino)propane
DTBPMB	1,2-bis(di-*tert*-butylphosphinomethyl)benzene
ee	enantiomeric excess
EIMS	electron-impact ionization mass spectroscopy
EtOH	ethanol
FCC	flash column chromatography
FID	flame ionization detector
g	gram
GC	gas chromatography
GCMS	gas chromatography-mass spectrometry
h	hour(s)
H	hexane
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation
HTIB	hydroxy(tosyloxy)iodobenzene
Hz	hertz
IBD	iodobenzene
IBX	2-iodoxybenzoic acid
J	coupling constant
l	linear
LDA	lithium diisopropylamide
LICA	lithium isopropylcyclohexylamide
LHMDS	lithium bis(trimethylsilyl)amide
m	milli/multiplet
M^+	parent molecular ion
MCPBA	*meta*-chloroperoxybenzoic acid
MDPP	methyldiphenylphosphine
MeOH	methanol
MEK	methyl ethyl ketone
min	minutes
MOP	2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl
mp	melting point
MsCl	methanesulfonyl chloride
MsOH	methyl sulfonic acid
MTPPB	4-methoxybenzyltriphenylphosphonium bromide
MW	microwave
m/z	mass-to-charge ratio
NBS	*N*-bromosuccinimide
NMDPP	neomenthyldiphenylphosphine
NMMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PAMMAM	polyamidoamine
PCC	$(C_5H_5NH)(CrO_3Cl)$
Ph	phenyl
PIFA	phenyliodine(III)bis(trifluoromethylacetate)/iodobenzenebis(trifluoromethylacetate)
PLC	preparative layer chromatography
PPA	phosphoric acid

ppm	parts per million
PVA	polyvinyl alcohol
PVP	poly(*N*-vinyl-2-pyrrolidone)
Py	pyridine
PYCA	2-pyridinecarboxylic acid
PYPCA	2-piperidinecarboxylic acid
PSIBD	polymer bound iodobenzene I,I-diacetate
PSIBO	polymer-supported iodobenzene
q	quartet
RCM	ring closing metathesis
R.T.	room temperature
R_T	retention time
s	singlet
t	triplet
T	toluene
TBAF	tetrabutyl ammonium fluoride
TBAI	tetrabutyl ammonium iodide
TBATB	tetrabutyl ammonium tribromide
TBDMSCl	*tert*-butyldimethylsilyl chloride
TC	thiophene-2-carboxylate
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
TMSOI/TMSI	trimethylsulfoxonium iodide
TTN	thallium(III) nitrate
TTS	thallium(III) toluene-*para*-sulfonate
TOF	turnover frequency
TolBINAP	2,2'-bis(di-*para*-tolylphosphino)-1,1'-binaphthyl
TsOH	*para*-toluenesulfonic acid
TsCl	*para*-toluenesulfonyl chloride
TPPTS	trisodium tris(*meta*-sulfonatophenyl)phosphine
W	watts

SUMMARY

Since the aim of this study was to investigate the influence of the electronic environment around the double bond of alkenes on the reactivity and regioselectivity of the methoxycarbonylation reaction for developing new methodology towards the synthesis of isoflavonoids, several aryl substituted alkenes were subjected to methoxycarbonylation utilizing the $Pd(OAc)_2/Al(OTf)_3/PPh_3$ catalyst system in MeOH under the optimum conditions of 35 bar of CO pressure and 95 °C. In order to be able to compare current results with literature values, 1-octene, 2-octene and styrene, were the first substrates to be methoxycarbonylated and gave anticipated high conversions (100%, 83% and 91%, respectively) to the expected linear (l) and branched (b) methyl esters, methyl nonanoate and methyl 2-methylnonanoate as well as methyl 3-phenylpropanoate and methyl 2-phenylpropanoate, respectively in a l:b ratio of ca. 3:1. A set of *trans*-β-methylstyrene analogues, i.e. *trans*-β-methylstyrene, *trans*-*p*-methoxy-β-methylstyrene and *trans*-*o*-methoxy-β-methylstyrene as well as a set of allylbenzene analogues, i.e. allylbenzene, *p*-methoxyallylbenzene, *p*-trifluoromethylallylbenzene, *o*-methoxyallylbenzene and *o*-trifluoromethanesulfonyloxyallylbenzene were subjected to the methoxycarbonylation reaction conditions and the products obtained in high conversions (88-96%) except for the alkenes with methoxy substituents in the *para*-position, i.e. *p*-methoxy-β-methylstyrene and *p*-methoxyallylbenzene (49% and 66%, respectively). During these investigations isomerization of the double bond in the β-methylstyrenes to the terminal position, forming allylbenzene analogues proved to be a feasible side-reaction, so the same products, i.e. linear (l), branched (b) and benzylic (bn) carboxylated products were formed from the β-methylstyrenes and corresponding allylbenzenes. During the investigation it was also found that a *p*-methoxy substituent on the β-methylstyrene or allylbenzene resulted in a decrease in reaction rate, while an *o*-methoxy substituent increases the reaction rate substantially in comparison to the *p*-methoxy analogues. *Ortho*-substituents (methoxy or triflate group) also resulted in a drastic increase in the formation of the linear products for both the β-methylstyrene and allylbenzene substrates, i.e. 3:2:1 vs. 10:4:1 and 8:2:1 vs. 15:5:1 vs. 5:1:0, respectively. It was also determined that a more electron-rich aromatic ring has an enhancing effect on the formation of the benzylic products as was determined by the methoxy-carbonylation of 1,3-diphenylpropene, which gave methyl 2,4-diphenylbutanoate in 64%

yield and 95% regioselectivity. Sterically more demanding disubstituted and trisubstituted double bonds, like in α-methylstyrene and 2-methyl-1-phenylprop-1-ene, were also subjected to the methoxycarbonylation reaction and resulted in the formation of methyl 3-phenylbutanoate in 63% and methyl 3-methyl-4-phenylbutanonate in 26% yield, respectively, albeit after extended reaction periods (4-6 h).

Since the availability of CO and thus the CO concentration in solution should have a significant influence on the rate of the reactions unless CO is not involved in the rate limiting step of the process, the effect of mass transfer limitations on the reaction rate of the substrates mentioned above were also studied and it was found that an 8-18% increase in reaction rates were observed for conditions of proper mass transfer for styrene, allylbenzene, and *p*- and *o*-methoxyallylbenzenes where isomerization of the double bond is insignificant.

Since hydroesterification under microwave radiation conditions has not been reported to date, the effect, if any, of microwave radiation vs. thermal heating conditions were also investigated. Owing to the pressure limit (12 bar) of the glass reaction vessel in the microwave reactor all reactions were executed at 12 bar in order to allow direct comparison of the results and a definite increase in reaction rate (99% conversion after only 10 min. vs. 99% after 30 min. at 35 bar) was observed for the microwave hydroesterification reactions of 1-octene and styrene. Although a general increase in reaction rate was not found for the allylbenzene substrate, a ca. 15% increase in yield was observed for *p*-methoxyallylbenzene (20% vs. 37%), *o*-methoxyallylbenzene (73% vs. 89%) and β-methylstyrene (66% vs. 88%) as substrates when the microwave reactions were compared to those performed under conventional heating under the same pressure.

When the nucleophile in the carbonylation reactions was changed from oxygen (methanol) to nitrogen (aniline) and the ligand to BINAP in the same catalyst system, the first aminocarbonylation reaction was observed. Reaction of the *o*- and *p*-methoxy substituted allylbenzenes with aniline, anisidine and 4-chloroaniline resulted in the successful formation of the linear and branched amides (anilides) in 87-97% yield. Extending the methodology to *trans*-β-methylstyrene and α-methylstyrene with aniline, however, gave the amides in only 18% and 16% yield, respectively. When the aminocarbonylation of allylbenzene was investigated with strongly deactivated anilines (2,4-dichloro- and 4-nitroaniline), primary amines (butylamine and benzylamine) and amides (acetamide) no product formation could be detected, so it was suspected that the reaction may be dependent on the pK_a of the amine, with

pK_a-values below 3 being too acidic and pK_a-values above 9 basic enough to be deactivated by complexation to the Lewis acid [$Al(OTf)_3$] in the catalyst system. Although the successful hydroamidation (25% conversion) of 4-chlorobenzylamine (pK_a = 9.17) gave some credence to this hypothesis, this aspect of the investigation still needs more attention in a follow-up investigation.

Subsequently, attention was turned towards the original aim of this project, i.e. methoxycarbonylation of stilbene analogues. Unsubstituted stilbene, 4-methoxystilbene and 2-methoxystilbene, however, gave poor results (conversions = 16-19% and yields = 2-6%), although some selectivity (4:1 for 2-methoxystilbene) towards the formation of the distal isomer, i.e. methyl 3-(2-methoxyphenyl)-2-phenylpropanoate, was observed.

Since the alkoxycarbonylation of alkynes is a well-documented reaction and these substrates could also function as starting material for the synthesis of isoflavonoids, albeit with an additional reduction step, the investigation was changed to the methoxycarbonylation of substituted diphenylacetylenes. In order to evaluate the influence of electron-donating and electron-withdrawing substituents on the rings of the phenylphenylacetylenes on the regioselectivity of the reactions, 4-methoxyphenyl- and (2-methoxyphenyl)phenylacetylene were prepared both in 69% yield by utilizing the Sonogashira coupling under conventional heating conditions (CuI/DABCO/K_2CO_3/DMF). (2,4-Dimethoxyphenyl)phenylacetylene was prepared in 91% yield by utilizing the $Pd(PPh_3)_2Cl_2$/CuI/Et_2NH/DMF reagent system under microwave irradiation (200 W). The electron-deficient diphenylacetylenes, (4-trifluoromethanesulfonyloxyphenyl)phenylacetylene, 4-methoxyphenyl-4'-trifluoromethane-sulfonyloxyphenylacetylene and 4-methoxyphenyl-2',4'-bis(trifluoromethanesulfonyloxy)-phenylacetylene, were prepared in overall 81%, 87% and 19% yields via Sonogashira coupling and formation of the triflate from the free phenolic analogues.

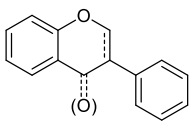
The 2-, 4-methoxy and 4-triflate substituted diphenylacetylenes, with the exception of (2,4-dimethoxyphenyl)phenylacetylene, were excellent substrates for the methoxycarbonylation reaction catalysed by $Pd(OAc)_2$/$Al(OTf)_3$/BINAP and gave good to excellent conversions (>97%) and yields (89%, 89% and 71%). Owing to Lewis acid catalysed methanol addition to the triple bond and subsequent demethylation, (2,4-dimethoxyphenyl)phenylacetylene gave only 35% of the desired product, which was accompanied by 46% of the corresponding deoxybenzoin. While some selectivity towards the proximal isomer of the esters were found for the two monomethoxy substituted diphenylacetylenes (2:1, proximal:distal), the methoxy-

carbonylation of (4-trifluoromethanesulfonyloxyphenyl)phenylacetylene gave the two esters in a ratio of 1:1. Methoxycarbonylation of the 4-methoxyphenyl-4'-trifluoromethane-sulfonyloxyphenylacetylene and 4-methoxyphenyl-2',4'-bis(trifluoromethanesulfonyloxy)-phenylacetylene led to the two ester products in 71 and 72% yields, respectively with the proximal isomer (carboxylate function next to the methoxy carrying ring) obtained in a 3:1 and excellent 18:1 ratio, respectively.

It was thus amply demonstrated that substituted diphenylacetylenes can be methoxy-carbonylated successfully and that high selectivity towards the isomer that would allow cyclization to the 6-membered heterocyclic ring of the isoflavonoid nucleus is possible. Method development for the preparation of diphenylacetylenes with substitution patterns resembling those found in naturally occurring isoflavonoids and the synthesis of those isoflavonoids could therefore be embarked upon with confidence. Complete development of this new methodology towards the synthesis of isoflavonoids and the preparation of these compounds in enantiomerically pure form through stereoselective reduction of the remaining double bond in the methoxycarbonylated diphenylacetylenes, will receive further attention in a follow-up investigation.

INTRODUCTION 1

1.1. Importance of Isoflavonoids

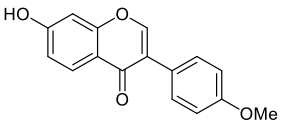


(**1.1**) 3-phenylchroman

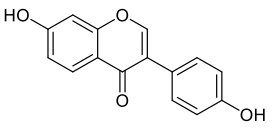
Isoflavonoids can be identified for containing a C_6-C_3-C_6 skeleton based on a 3-phenylchroman structure (**1.1**) with different oxygenation and saturation patterns. Isoflavonoids represent a large class of naturally occurring heterocyclic phenols found almost exclusively in the Leguminosae plant family as secondary metabolites prepared by the chalcone isomerase enzyme.[1,2,3] The first isoflavonoid namely genistein (**1.5**) was identified as a phytoestrogen, i.e. a biologically active secondary plant metabolite that only occur in mammals through dietary intake of especially soy products and some grains, many years ago.[4] The vast potential pharmaceutical use of phytoestrogens were a portent of things to come since isoflavonoids are today one of the most studied compounds in the medicinal field mainly because of its wide variety of biological activities.[2,5]

1.1.1. Anti-cancer properties

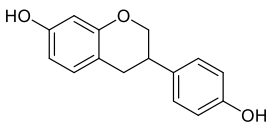
The two most studied isoflavones from a physiological point of view, namely genistein (**1.5**) and daidzein (**1.3**), were evaluated as possible agents for the chemoprevention of hormone-dependant breast, uterus and prostate cancer. Further experimentation showed genistein (**1.5**) and daidzein (**1.3**) to inhibit the growth of human breast cancer, prostate cancer and leukemia cells through anti-proliferation and anti-metastatic action.[3,4,6,7]



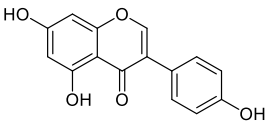
(**1.2**) Formononetin



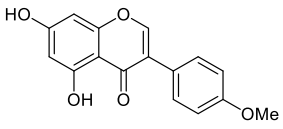
(**1.3**) Daidzein



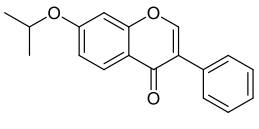
(**1.4**) Equol



(**1.5**) Genistein



(**1.6**) Biochanin A



(**1.7**) Ipriflavone

Equol (**1.4**), a isoflavan, was found to have a beneficial effect on prostate cancer, while biochanin A (**1.6**), a isoflavone, has been identified as an active cancer chemopreventant through apoptosis of breast and prostate cancer as well as chemically induced cancers of the stomach, bladder, lung and blood. Another isoflavone, ipriflavone (**1.7**), has even been developed as an oral treatment for leukemias by increasing bone calcium retention, inhibition of bone breakdown and activating bone-building cells.[8]

1.1.2. Other biological properties

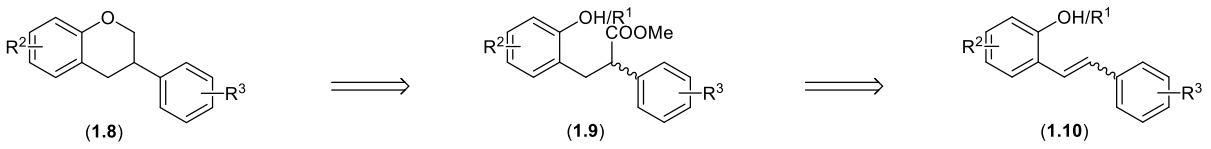
Isoflavonoids, for example equol (**1.4**) and ipriflavone (**1.7**), have been studied for improving menopausal symptoms like preventing osteoporosis and developing hormone replacement therapies.[4,5,8,9,10,11] Research have also shown that phytoestrogens can improve cardiovascular health by reducing cholesterol and risk of atherosclerosis through its anti-angiogenic properties.[5,10,11] The anti-oxidant activity of isoflavonoids gave impetus to its development as treatment for free radical mediated disorders like Alzheimer's and Parkinson's diseases.[5,9,10,11] diseases.[5,9,10,11] Pterocarpans, a subclass of isoflavonoids, are infection-induced phytoalexins and possess fungicidal and bactericidal activities.[4,10]

The above mentioned accumulative literature evidence advocates that isoflavonoids have a variety of benefits and can be used in a preventative manner or as treatment for numerous life-threatening diseases and therefore serves as motivation for developing an alternative synthesis pathway towards isoflavonoids.

1.2. Research project objective

The above mentioned importance of isoflavonoids points to the need to develop new synthetic methodologies consisting of an easily accessible starting materials that could be converted into isoflavonoids by means of catalytic processes and would therefore make an important contribution to this field of natural and biologically important isoflavonoid preparation. It was therefore decided to investigate the application of the relatively recent catalytic process of hydroesterification to the synthesis of isoflavonoids as indicated in Scheme 1-1. In this regard it is envisaged that a suitable olefinic precursor, like stilbene (**1.10**) could be transformed by hydroesterification into a C-3 carboxylate containing moiety (**1.9**) that could be cyclized to produce the heterocyclic C-ring of the isoflavonoid unit (**1.8**). Since most isoflavonoids contain only one chiral centre in the heterocyclic ring, an added advantage of the hydroesterification

protocol could be the establishment of the desired absolute configuration at this chiral centre during the carbonylation process if a chiral alcohol can be used.



$R^1 = R^2 = R^3$ = oxygenated substituents

Scheme 1-1: Possible retrosynthetic pathways towards the synthesis of isoflavonoids.

Although it is known that the steric factors of the alkene or alkyne play a prominent role in regioselective control during hydroesterification reactions, little is known about the influence of the electronic environment around the double or triple bond on the direction of attack of the CO entity. Since regioselective control would constitute a critical element in the process to allow for the successful construction of the heterocyclic C-ring of the isoflavonoid moiety, a variety of arylalkenes, and 1,2-diarylalkenes with electron-withdrawing and electron-donating substituents would be subjected to palladium catalysed hydroesterification to study the electronic effect of substituents on the activity and regioselectivity of the substrate.

1.3. References

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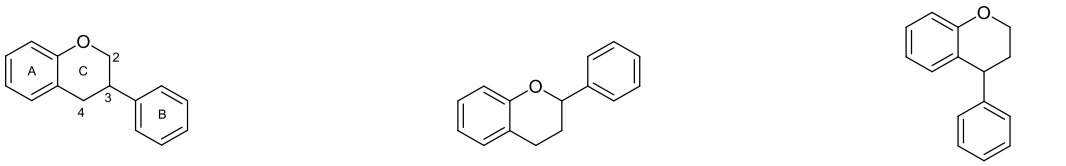
SYNTHESIS OF ISOFLAVONOIDS 2

Isoflavonoids have a diversity of medical applications like the prevention of cancer, osteoporosis, atherosclerosis, Alzheimer's and Parkinson's diseases and may also be used for treatment of these life threatening illnesses. Initially isoflavonoids were isolated from various plant species. Difficulties surrounding the isolation of individual isoflavonoids like low yields, inseparable mixtures, and a desire to study the physiological activities of differently substituted compounds, have stimulated extensive investigations into the synthesis of monomeric isoflavonoids. This served as impetus to develop various synthetic pathways towards isoflavonoids. Currently synthetic methodologies for isoflavonoids can be divided into two main categories, i.e. racemic and stereoselective synthesis of isoflavonoids.

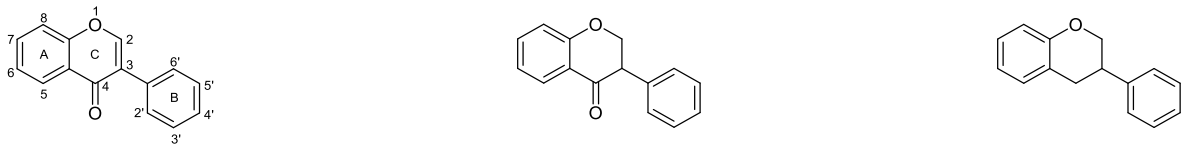
Flavonoids consist of a C_6-C_3-C_6 skeleton, which can be divided into subclasses depending on the arrangement of the B-ring about the heterocyclic C-ring (Figure 2-1). While the phenyl ring is attached to carbon 3 of the heterocyclic ring in the isoflavonoids (**2.1**), the 2-phenylchroman (**2.2**) and 4-phenylchroman (**2.3**) derivatives are labelled as flavonoids and neoflavonoids, respectively.



(**2.1**) Isoflavonoid (**2.2**) Flavonoid (**2.3**) Neoflavonoid

Figure 2-1: Subclasses of flavonoids.

Depending on the oxidation level of the heterocyclic ring, the isoflavonoids can be divided into three subclasses i.e. isoflavones (**2.4**), isoflavanones (**2.5**), isoflavans (**2.1**), (Figure 2-2).



(**2.4**) Isoflavone (**2.5**) Isoflavanone (**2.1**) Isoflavan

Figure 2-2: Subclasses of isoflavonoids.

An additional 5- or 6-membered heterocyclic ring may also be present in the isoflavonoid skeleton which would lead to a pterocarpan (**2.6**) or rotenoid (**2.9**) skeleton, respectively (Figure 2-3). Similarly to the basic isoflavonoids, the pterocarpans family may be subdivided according to the oxidation level of the heterocyclic ring leading to pterocarpans (**2.6**) and 6a-hydroxypterocarpans

(**2.7**), whereas coumestans (**2.8**), the fully oxidized heterocyclic derivative of pterocarpan, represents its own isoflavonoid subclass. Rotenoids (**2.9**), containing an additional carbon and another six-membered heterocyclic ring, consist of 12a-hydroxyrotenoids (**2.10**) and dehydroxyrotenoids (**2.11**), (Figure 2-3).

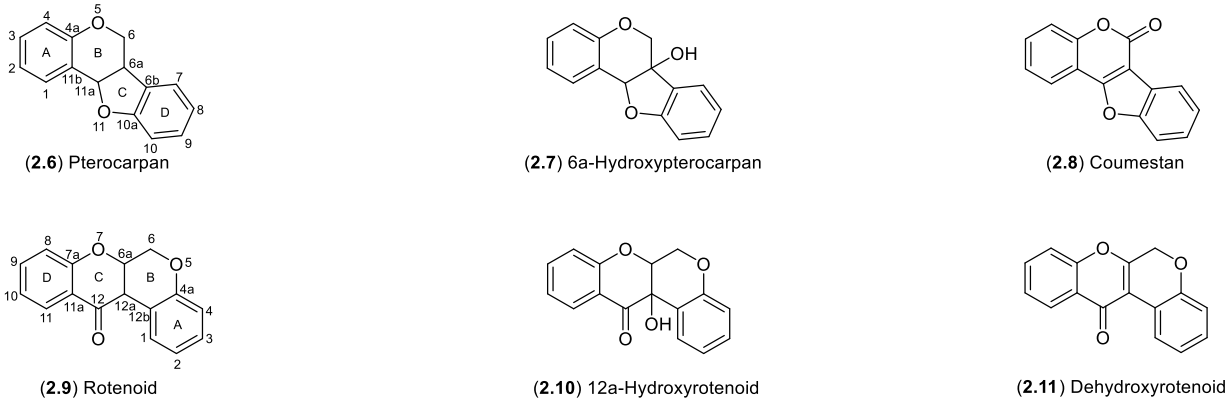


Figure 2-3: Subclasses of pterocarpans and rotenoids.

2.1. Isoflavones and Isoflavanones

Isoflavones are the largest group of isoflavonoids and their synthesis plays a pivotal role in the general preparation of isoflavonoids, since isoflavones (**2.4**) are often key intermediates in the synthesis of isoflavanones (**2.5**), isoflavans (**2.1**) and pterocarpans (**2.6**). Isoflavones (**2.4**) are, therefore, the primary synthetic targets during the synthesis of many isoflavonoids.[1,2,3] Traditional synthetic methods can be divided into three main categories namely the formylation of phenyl benzyl ketones, better known as deoxybenzoins (**2.12**), the oxidative rearrangement of chalcones (**2.13**), and the arylation of a preformed chromanone (**2.14**) ring (Figure 2-4).[3,4,5]

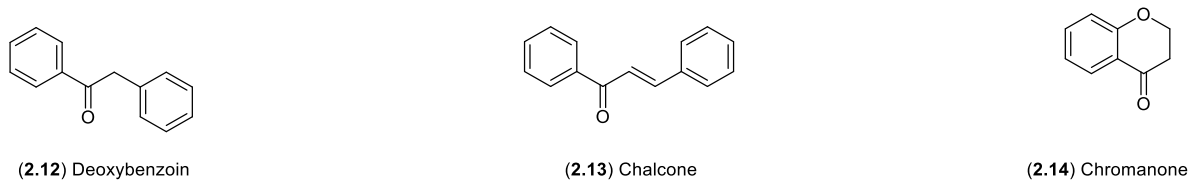
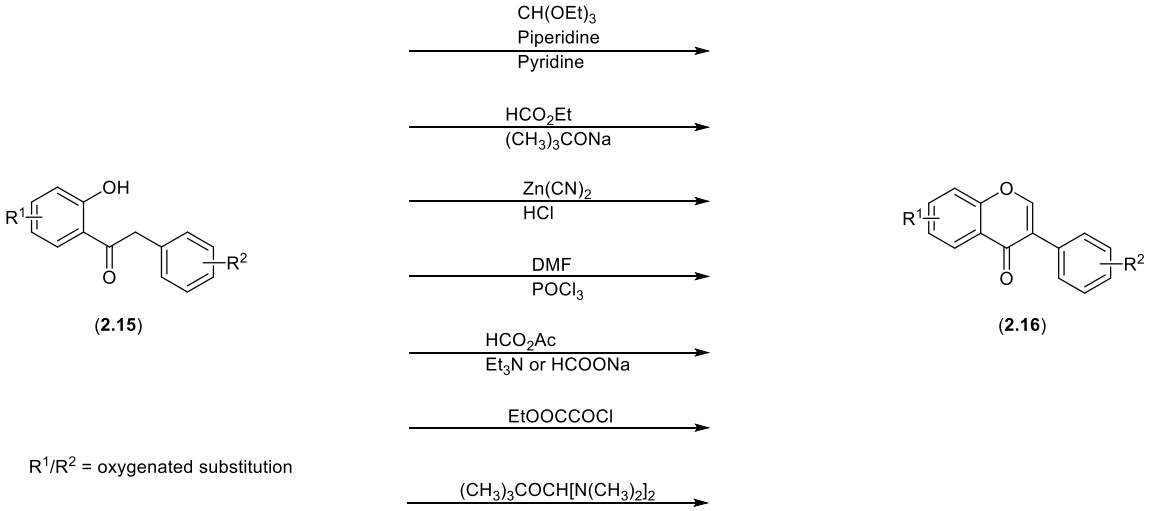


Figure 2-4: General precursors utilized during the preparation isoflavonoids.

2.1.1. Deoxybenzoin route

During the early stages of isoflavonoid research, introduction of a suitable C_1-unit into the α-position of an appropriate 2-hydroxydeoxybenzoin precursor (**2.15**) followed by ring-closure represented the methodology of choice for the preparation of isoflavones.[1,2,4,6] Various formylating agents like triethyl orthoformate, ethyl formate, zinc cyanide, dimethylformamide and acetoformic anhydride have been explored for this purpose (Scheme 2-1). Unfortunately, these reaction conditions usually require the protection of any free hydroxy substituents other than the one in the

2-position and/or have limitations regarding the oxygenation pattern of the isoflavonoid.[1,2,6] The restrictions on the substitution pattern of the isoflavonoid could be circumvented by using ethyl or methyl oxalyl chloride as formylating agent, but this route requires an additional decarboxylation step.[1,2,7] Brederick's reagent [bis(dimethylamino)-*tert*-butoxymethane] also enables formylation of deoxybenzoins under neat/solvent-free conditions with short reaction times.[1,8]

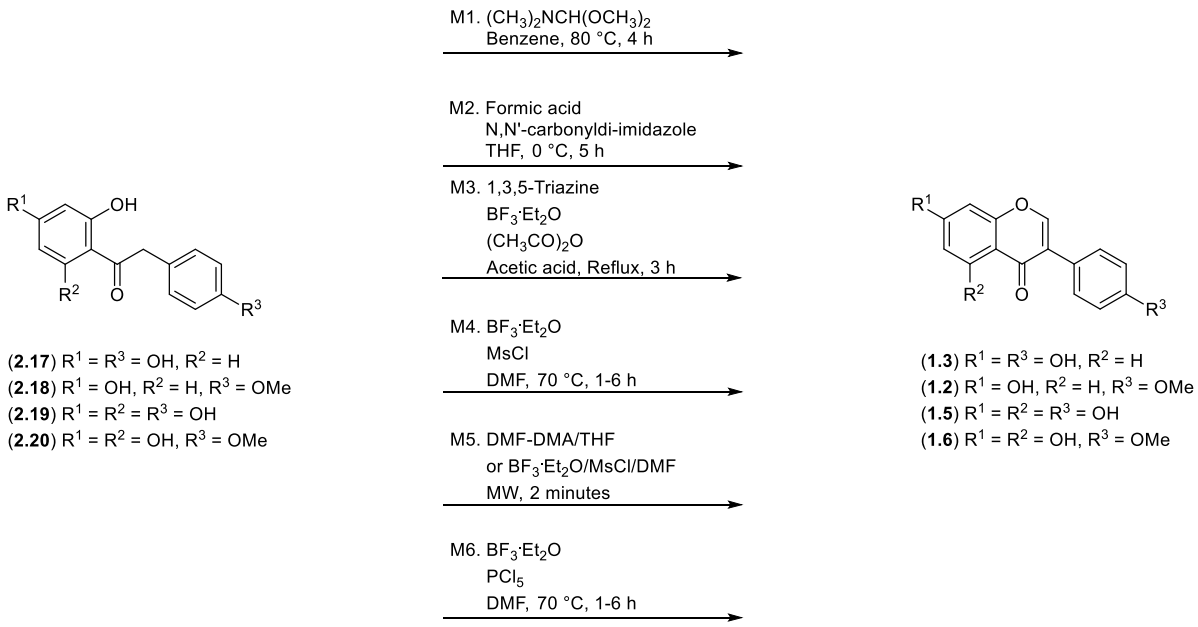


Scheme 2-1: Summary of generally used C_1 formylation reagents.

Numerous methodologies have been developed for the preparation of specific isoflavones like daidzein (**1.3**), fomononetin (**1.2**), genistein (**1.5**) and biochanin A (**1.6**), (Table 2-1, M = Method). Pelter and Foot[9] utilized dimethoxydimethylaminomethane (M1) as formylating agent in the synthesis of numerous isoflavonoids, but when a free OH-substituent is present in the 6-position of the deoxybenzoin e.g. biochanin A (**1.6**), yields of only 15% are found unless this OH-group is protected. Krishnamurty and Prasad[10] developed a novel formylating reagent, *N*-formyl imidazole, which can be prepared in situ from formic acid and *N*,*N*'-carbonyldiimidazole (M2), and used this reagent to effectively synthesize several isoflavonoids with unprotected 5,7-dihydroxy substituents, like biochanin A (**1.6**), in excess of 60% yield. Another methodology, reported by Breitmaier et al.,[11] which does not require the protection of the phenoxy units, utilizes 1,3,5-triazine together with boron trifluoride-diethyl ether (BF_3•Et_2O) as formylating agent (M3). Yields of up to 90% were obtained for a range of isoflavonoids under mild reaction conditions, with the exception of 4'-hydroxyisoflavones, e.g. daidzein (**1.3**) and genistein (**1.5**), which produced slightly lower yields. Wähälä and Hase[12] developed a one-pot BF_3•Et_2O catalysed procedure for the synthesis of polyhydroxyisoflavones from the corresponding phenol and phenylacetic acid precursors (M4). In this instance the intermediate deoxybenzoin is formed first by Friedel-Crafts type coupling after which α-methylation and cyclization is achieved with a solution of MsCl in DMF. A variety of isoflavones were prepared in excellent yield using this protocol, but the presence of a

phloroglucinol A-ring proved to be detrimental to the process yielding only 53% of isoflavone (**1.5**). Nair et al.[13] significantly reduced the reaction times of this protocol to 2 minutes by employing microwave irradiation (M5). In addition, Nair and co-workers[14,15] also managed to increase the efficacy of this methodology by substituting MsCl for PCl_5 (M6). This change in reagents allowed the production of daidzein (**1.3**), formononetin (**1.2**), genistein (**1.5**) and biochanin A (**1.6**) in excellent yield (>90%). Even though these methodologies produce isoflavonoids in high yields, their reliance on a 2-hydroxydeoxybenzoin precursor is a major drawback as the preparation of these analogues are hampered by low yields and a lack of readily available starting material.[4,5]

Table 2-1: Synthesis of daidzein (2.17), formononetin (2.18), genistein (2.19) and biochanin A (2.20).

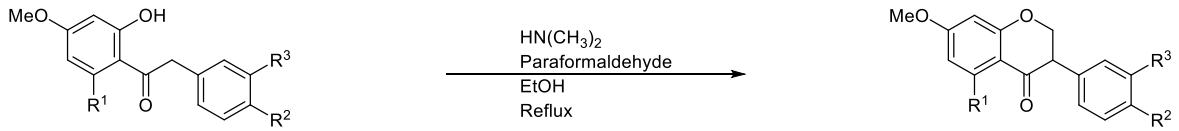


DMF-DMA = Dimethylformamide dimethylacetal

Isoflavonoid	Yield (%)					
	M1[9]	M2[10]	M3[11]	M4[12]	M5[13]	M6[14]
Daidzein (**1.3**)	76	-	72	98	71	92
Formononetin (**1.2**)	85	-	91	96	91	94
Genistein (**1.5**)	-	-	78	53	80	90
Biochanin A (**1.6**)	15	60	81	90	86	92

Isoflavanones (**2.5**), like isoflavones (**2.4**), can be obtained from 2-hydroxydeoxybenzoins (**2.15**) through formylation, but the same disadvantages as discussed for the synthesis of isoflavones, i.e. low yields, protection of free hydroxy substituents and the tedious preparation of the 2-hydroxybenzoin precursor, are still valid.[1,2,5,6] Neelakantan et al.[16] reported a one-step synthesis of isoflavanones (**2.26-2.30**) via the corresponding deoxybenzoins (**2.21-2.25**) by utilizing paraformaldehyde as C-1 unit and were able to obtain the products in yields of 51-67% (Scheme 2-2). This methodology was subsequently improved upon by Aitmambetov et al.[17] who substituted

the dimethylamine and paraformaldehyde for bis(dimethylamino)methane which allowed for the synthesis of **2.30** from **2.25** in comparable yield (66% vs. 65%).

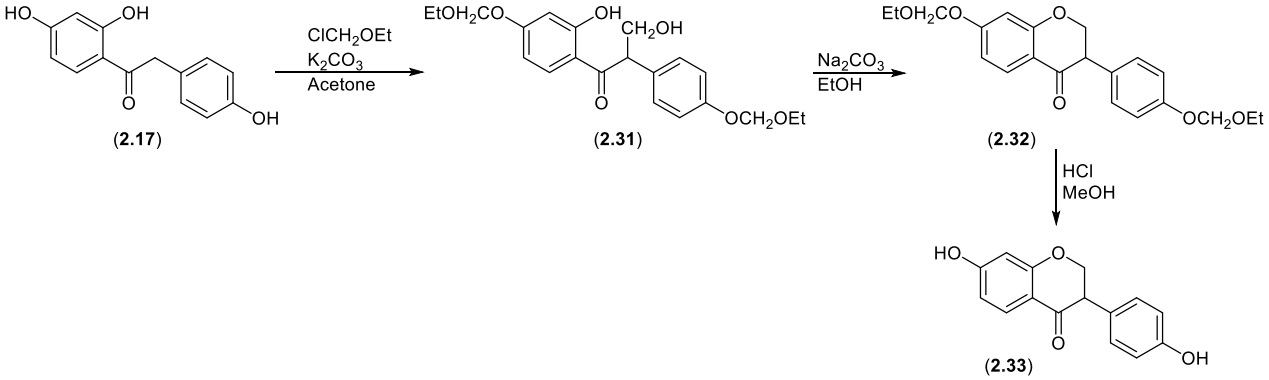


(**2.21**) $R^1 = R^2 = R^3 = H$
(**2.22**) $R^1 = OMe$, $R^2 = R^3 = H$
(**2.23**) $R^1 = R^3 = H$, $R^2 = OMe$
(**2.24**) $R^1 = R^2 = OMe$, $R^3 = H$
(**2.25**) $R^1 = H$, $R^2R^3 = OCH_2O$

(**2.26**) $R^1 = R^2 = R^3 = H$; 61%
(**2.27**) $R^1 = OMe$, $R^2 = R^3 = H$; 51%
(**2.28**) $R^1 = R^3 = H$, $R^2 = OMe$; 67%
(**2.29**) $R^1 = R^2 = OMe$, $R^3 = H$; 54%
(**2.30**) $R^1 = H$, $R^2R^3 = OCH_2O$; 65%

Scheme 2-2: Synthesis of isoflavanones from deoxybenzoins.

Although ethoxymethyl is generally utilized as a protecting group, it was exploited by Jain et al.[18] to introduce the C_1-unit onto the α-carbon of a free phenolic deoxybenzoin (Scheme 2-3). In addition to etherification of the OH groups, the introduction of the α-hydroxymethyl unit allowed for formation of the C-ring under mild conditions. Subsequent acid catalysed deprotection yielded the isoflavanone (**2.33**) in 57% overall yield.

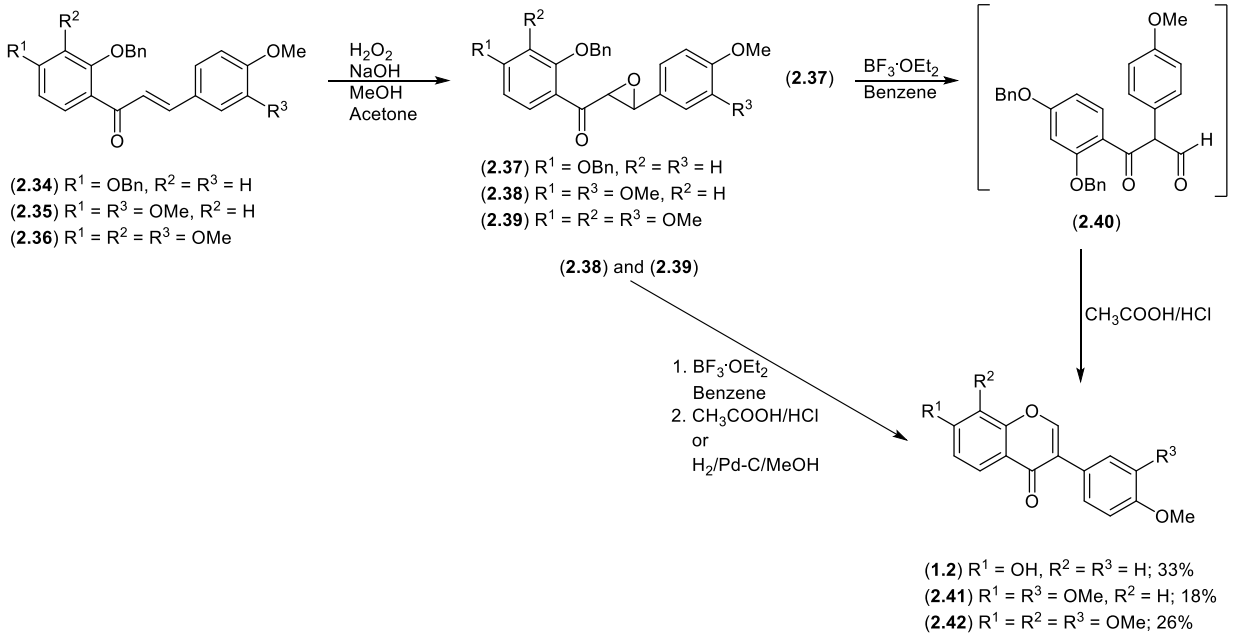


Scheme 2-3 Synthesis of isoflavanones with *in situ* hydroxy group protection.

2.1.2. Chalcone route

A more popular route for the formation of isoflavones, especially when complex substitution patterns are required, entails the oxidative rearrangement of chalcones, which are readily available by condensation of acetophenones and benzaldehydes.[1,3,5,6] The first attempts at converting chalcones into isoflavones, came from Seshadri and co-workers,[19] who transformed the chalcone (**2.34**) into the epoxide (**2.37**) by treatment with alkaline H_2O_2 (Scheme 2-4). Subsequent Lewis acid (BF_3•Et_2O) assisted rearrangement of the epoxide gave the α-formyldeoxybenzoin (**2-40**), which was then subjected to either hydrogenolysis or acid catalysed hydrolysis of the benzyl unit(s) leading to spontaneous cyclization to the isoflavone (**1.2**) in 33% overall yield.[19,20] Bhrara et al.[20] managed to convert the epoxide (**2.37**) directly into the isoflavone (**1.2**) through acidification of the BF_3•OEt_2 reaction mixture and obtained a yield of 13% in this way. By applying this method these

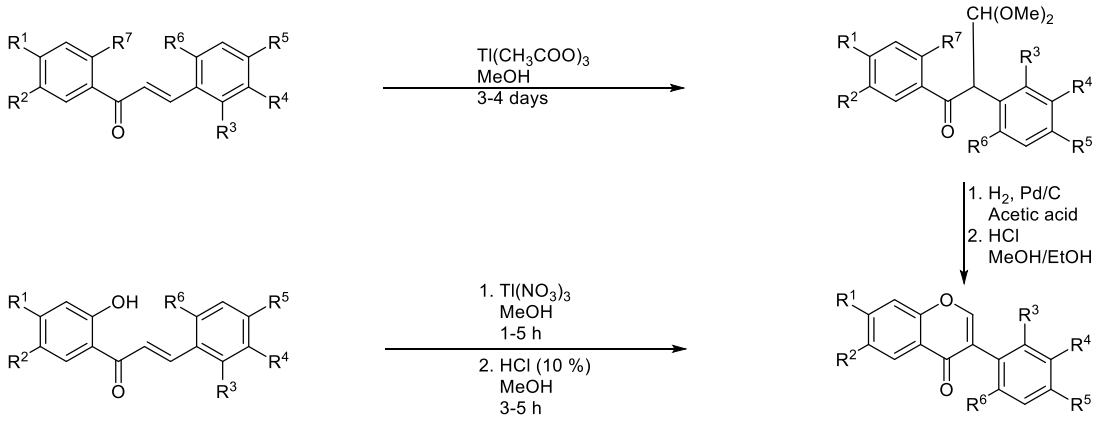
researchers were able to also synthesize isoflavones (**2.41**) and (**2.42**) in yields of 18% and 26%, respectively.



Scheme 2-4: Synthesis of isoflavones utilizing BF_3•OEt_2.

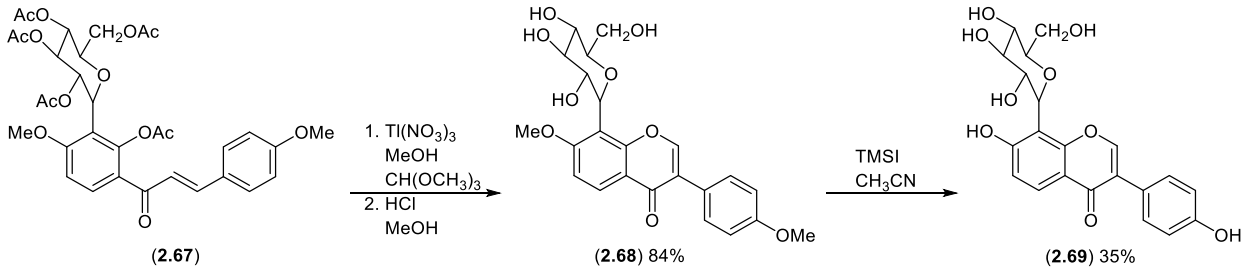
Currently most isoflavones are prepared directly from the chalcone analogue by thallium(III) assisted oxidative 1,2-aryl shift rearrangement.[2,4,6] This methodology was first reported by Ollis et al.[21] who employed thallium(III) acetate to synthesize isoflavones **2.59**-**2.62** in moderate yields (Table 2-2, entries 1-4). Similar to the BF_3•OEt_2 protocol, the thallium(III) salt would induce an oxidative 1,2-aryl migration of the chalcone A-ring to yield the acetal (**2.51**-**2.54**), which was then converted to the isoflavone by acid catalysed cyclisation. As a consequence the methodology requires protection of the *ortho*-hydroxy function on the chalcone's B-ring in order to achieve decent isoflavone yields. McKillop et al.[22] and Farkas et al.[23] improved this methodology by substituting the thallium(III) acetate with thallium(III) nitrate, which led to improved yields of the isoflavones of up to 77% and performing the reaction in one step without isolating the intermediate acetal (Table 2-2, entries 5-8). It was also established that, although yields are generally higher, this protocol does not necessitate the protection of the 2'-hydroxy group (B-ring) of the chalcone.

Table 2-2: Synthesis of isoflavones with thallium(III) salts.



Entry	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Chalcone	Acetal	Isoflavone	Tl-salt	Yield % (overall)
1	OMe	H	H	H	OMe	H	OBn	(**2.43**)	(**2.51**)	(**2.59**)	$Tl(OAc)_3$	74 (16)
2	OEt	H	OMe	OEt	OMe	H	OBn	(**2.44**)	(**2.52**)	(**2.60**)	$Tl(OAc)_3$	42 (8)
3	OMe	OMe	H	OCH_2O		H	OBn	(**2.45**)	(**2.53**)	(**2.61**)	$Tl(OAc)_3$	31 (23)
4	OMe	OMe	H	OCH_2O		OMe	OBn	(**2.46**)	(**2.54**)	(**2.62**)	$Tl(OAc)_3$	59 (4)
5	OMe	H	H	OCH_2O		OMe	H	(**2.47**)	(**2.55**)	(**2.63**)	$Tl(NO_3)_3$	47
6	OBn	H	H	H	OMe	OBn	H	(**2.48**)	(**2.56**)	(**2.64**)	$Tl(NO_3)_3$	70
7	OBn	H	OMe	OBn	OMe	H	H	(**2.49**)	(**2.57**)	(**2.65**)	$Tl(NO_3)_3$	77
8	OBn	H	OMe	OMe	OBn	OMe	H	(**2.50**)	(**2.58**)	(**2.66**)	$Tl(NO_3)_3$	73

This methodology was successfully applied to the preparation of the precursor **2.68** during the synthesis of the C-glycosidyl isoflavone, puerarin (**2.69**), found in Chinese herbal medicine (Scheme 2-5).[24]

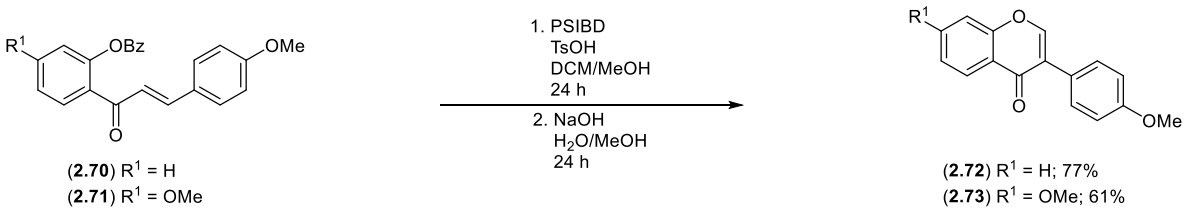


(**2.67**) (**2.68**) 84% (**2.69**) 35%

Scheme 2-5: Synthesis of puerarin (2.69).

Although numerous chalcone analogues can be prepared in excellent yield, the aforementioned chalcone route towards isoflavones still has some disadvantages: (i) the chalcone must be at least partially soluble in methanol otherwise low yields are observed, (ii) thallium salts can also react with chromene double bonds so these should be protected or, alternatively the chromene entity should be introduced at the end of the process, e.g. by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), (iii) the presence of electron-withdrawing aryl substituents like NO_2, decreases the migratory aptitude of the aryl ring and thus leads to poor yields, and (iv) the methodology is based on stoichiometric quantities of highly poisonous thallium reagents.[1,6,23,25]

As an alternative to the thallium salts, hypervalent iodine reagents, i.e. iodosylbenzene and hydroxy(tosyloxy)iodobenzene (HTIB, also known as Kosher's reagent), were reported for inducing the oxidative 1,2-aryl migration in chalcones leading to the acetal intermediates.[26,27,28] Acid catalysed cyclization of the acetal again render the corresponding isoflavone. In a one-pot process based on this methodology Kawamura et al.[25] were able to prepare isoflavones from chalcones utilizing HTIB. Although HTIB is not as poisonous as $Tl(NO_3)_3$, this reagent is unstable and requires anaerobic conditions for storage and handling. In order to address this issue and generate a much safer reagent, polymer bound iodobenzene I,I-diacetate (PSIBD) was used in conjunction with *para*-toluenesulfonic acid (TsOH) to synthesize isoflavones **2.72** and **2.73** in a one-pot transformation from the corresponding chalcones (**2.70** and **2.71**) in moderate to good yields (60-75%), (Scheme 2-6).[25]



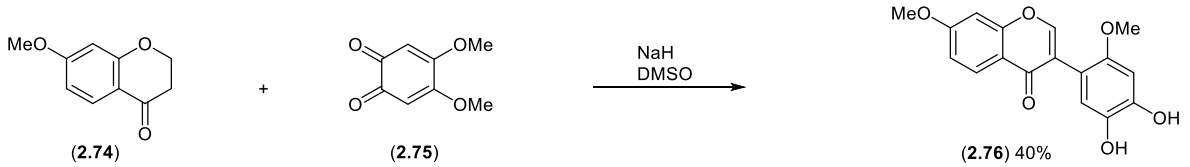
(**2.70**) R^1 = H
(**2.71**) R^1 = OMe

(**2.72**) R^1 = H; 77%
(**2.73**) R^1 = OMe; 61%

Scheme 2-6: Environmentally friendly synthesis of isoflavones, utilizing hypervalent iodine(III).

2.1.3. Arylation route

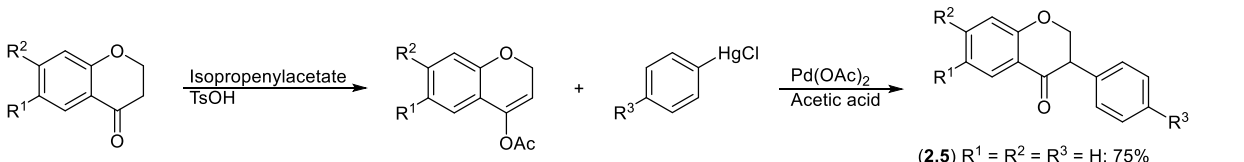
Direct arylation of the chromanone skeleton provided an alternative route towards the preparation of isoflavonoids.[1] In this regard it has been shown that treatment of chromanones, like **2.74**, with a substituted *ortho*-benzoquinone, like **2.75**, and sodium hydride in dimethyl sulphoxide (DMSO) lead to the formation of isoflavones, like **2.76**, albeit in low yields like 40% (Scheme 2-7).[29]



(**2.74**) (**2.75**) (**2.76**) 40%

Scheme 2-7: Sodium hydride synthesis of isoflavanones (2.76).

Since the discovery of the Heck[30] and Suzuki[31] type reactions this methodology has also been applied to the direct synthesis of isoflavanones from chromanones. One of the first reports for the construction of an isoflavanone skeleton by direct arylation of a chromanone precursor came from Kasahara et al.[32] (Scheme 2-8). The enol esters (**2.79-2.81**) of the chromanones were coupled to an arylmercuric halide (**2.82-2.84**) in the presence of palladium acetate to yield a variety of substituted isoflavanones (**2.5**, **2.85-2.90**) in good yields (60-75%).



(**2.77**) $R^1 = R^2 = H$
(**2.78**) $R^1 = OMe$, $R^2 = H$
(**2.74**) $R^1 = H$, $R^2 = OMe$

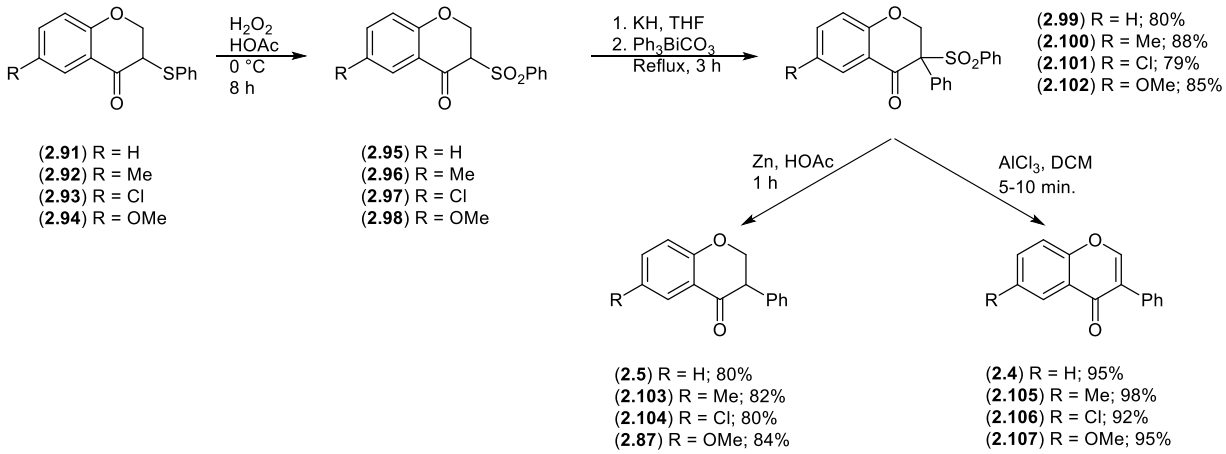
(**2.79**) $R^1 = R^2 = H$
(**2.80**) $R^1 = OMe$, $R^2 = H$
(**2.81**) $R^1 = H$, $R^2 = OMe$

(**2.82**) $R^3 = H$
(**2.83**) $R^3 = OMe$
(**2.84**) $R^3 = Cl$

(**2.5**) $R^1 = R^2 = R^3 = H$; 75%
(**2.85**) $R^1 = R^2 = H$, $R^3 = OMe$; 75%
(**2.86**) $R^1 = R^2 = H$, $R^3 = Cl$; 60%
(**2.87**) $R^1 = OMe$, $R^2 = R^3 = H$; 68%
(**2.88**) $R^1 = R^3 = OMe$, $R^2 = H$; 70%
(**2.89**) $R^1 = OMe$, $R^2 = H$, $R^3 = Cl$; 68%
(**2.26**) $R^1 = R^3 = H$, $R^2 = OMe$; 60%
(**2.28**) $R^1 = H$, $R^2 = R^3 = OMe$; 70%
(**2.90**) $R^1 = H$, $R^2 = OMe$, $R^3 = Cl$; 70%

Scheme 2-8: Synthesis of isoflavanones utilizing an organomercury compound.

Arylation of chromanones in the absence of palladium catalysts have also been accomplished by either arylbismuth(V)[33] or aryllead(IV)[34,35] compounds (Scheme 2-9). When triphenylbismuth(III) carbonate is utilized as aryl source, the aryl unit is introduced in a cross-coupling fashion onto a 3-sulfonylchromanone precursor (**2.95-2.98**). The 3-phenyl-3-sulfonylchromanone (**2.99-2.102**) could then be transformed to either the isoflavanone (**2.5**, **2.87**, **2.103** and **2.104**) or the isoflavone (**2.4**, **2.105-2.107**) in excellent yields by employing reductive or Lewis acid assisted elimination conditions, respectively. Arylbismuth(V) or aryllead(IV) compounds are, however, not readily available in all the substitution patterns displayed by natural products and the synthesis of these reactants may be cumbersome.



(**2.91**) R = H
(**2.92**) R = Me
(**2.93**) R = Cl
(**2.94**) R = OMe

(**2.95**) R = H
(**2.96**) R = Me
(**2.97**) R = Cl
(**2.98**) R = OMe

(**2.99**) R = H; 80%
(**2.100**) R = Me; 88%
(**2.101**) R = Cl; 79%
(**2.102**) R = OMe; 85%

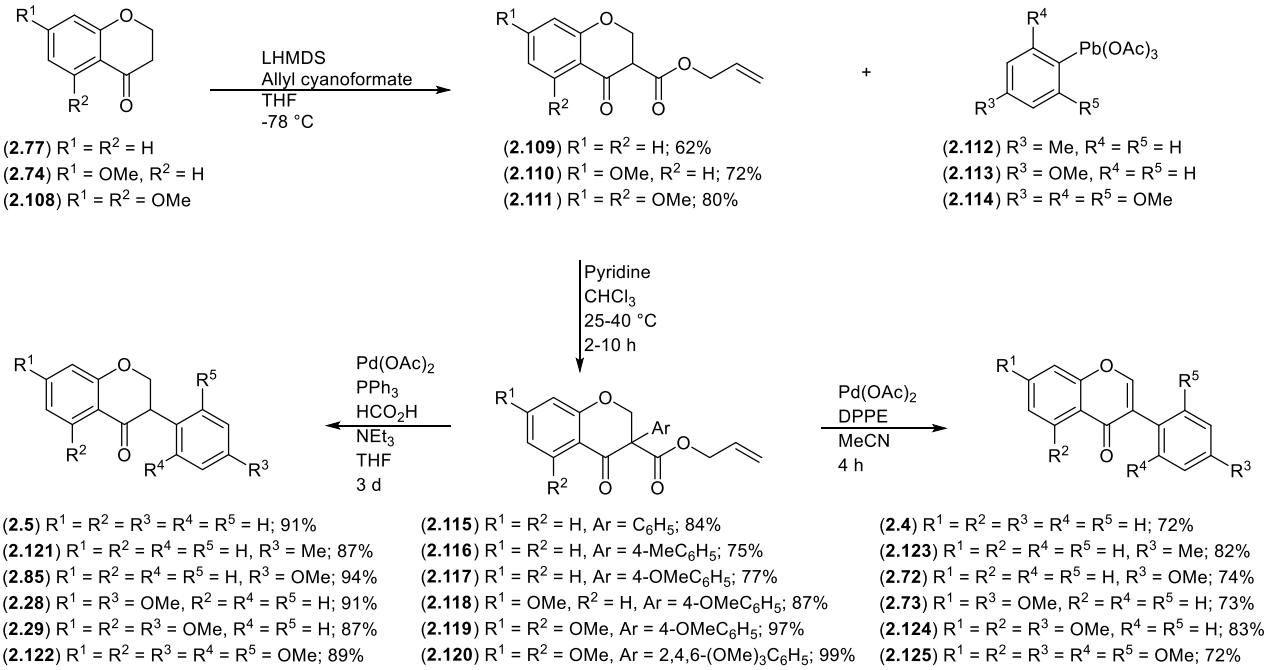
(**2.5**) R = H; 80%
(**2.103**) R = Me; 82%
(**2.104**) R = Cl; 80%
(**2.87**) R = OMe; 84%

(**2.4**) R = H; 95%
(**2.105**) R = Me; 98%
(**2.106**) R = Cl; 92%
(**2.107**) R = OMe; 95%

Scheme 2-9: Arylation with Ph_3BiCO_3.

Alternatively, a 3-phenyl unit is introduced onto a 3-allylformatechromanone precursor (**2.109-2.111**), prepared from the corresponding chromanone. Aryllead(III) acetate (**2.112-2.114**) is then employed as aryl source followed by palladium catalysed deallyloxycarbonylation and deallyloxycarbonylation-dehydrogenation, to yield isoflavanones (**2.5**, **2.28**, **2.29**, **2.85**, **2.121** and **2.122**) and isoflavones (**2.4**, **2.72**, **2.73**, **2.123-2.125**), respectively (Scheme 2-10). Donelly and co-workers[35] developed this methodology even further by utilizing methoxymethyl (MOM)-protected

hydroxyphenyllead triacetates, which yields isoflavones that can easily be deprotected to synthesize 2'-hydroxyisoflavones, as plausible pterocarpan precursors, in 90-98% yields.



(**2.77**) $R^1 = R^2 = H$
(**2.74**) R^1 = OMe, R^2 = H
(**2.108**) $R^1 = R^2$ = OMe

(**2.109**) $R^1 = R^2 = H$; 62%
(**2.110**) R^1 = OMe, R^2 = H; 72%
(**2.111**) $R^1 = R^2$ = OMe; 80%

(**2.112**) R^3 = Me, $R^4 = R^5 = H$
(**2.113**) R^3 = OMe, $R^4 = R^5 = H$
(**2.114**) $R^3 = R^4 = R^5$ = OMe

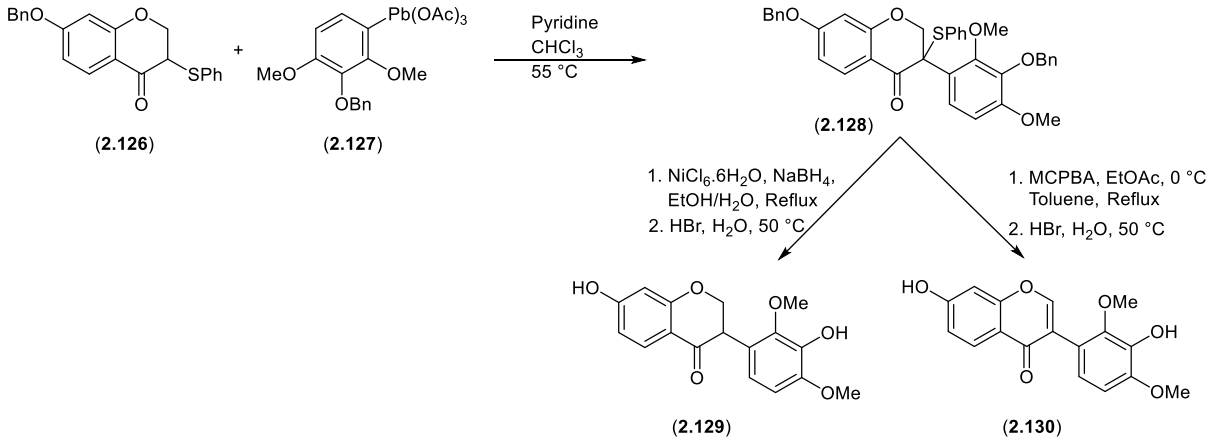
(**2.5**) $R^1 = R^2 = R^3 = R^4 = R^5 = H$; 91%
(**2.121**) $R^1 = R^2 = R^4 = R^5 = H$, R^3 = Me; 87%
(**2.85**) $R^1 = R^2 = R^4 = R^5 = H$, R^3 = OMe; 94%
(**2.28**) $R^1 = R^3$ = OMe, $R^2 = R^4 = R^5 = H$; 91%
(**2.29**) $R^1 = R^2 = R^3$ = OMe, $R^4 = R^5 = H$; 87%
(**2.122**) $R^1 = R^2 = R^3 = R^4 = R^5$ = OMe; 89%

(**2.115**) $R^1 = R^2 = H$, Ar = C_6H_5; 84%
(**2.116**) $R^1 = R^2 = H$, Ar = 4-MeC_6H_5; 75%
(**2.117**) $R^1 = R^2 = H$, Ar = 4-OMeC_6H_5; 77%
(**2.118**) R^1 = OMe, $R^2 = H$, Ar = 4-OMeC_6H_5; 87%
(**2.119**) $R^1 = R^2$ = OMe, Ar = 4-OMeC_6H_5; 97%
(**2.120**) $R^1 = R^2$ = OMe, Ar = 2,4,6-$(OMe)_3C_6H_5$; 99%

(**2.4**) $R^1 = R^2 = R^3 = R^4 = R^5 = H$; 72%
(**2.123**) $R^1 = R^2 = R^4 = R^5 = H$, R^3 = Me; 82%
(**2.72**) $R^1 = R^2 = R^4 = R^5 = H$, R^3 = OMe; 74%
(**2.73**) $R^1 = R^3$ = OMe, $R^2 = R^4 = R^5 = H$; 73%
(**2.124**) $R^1 = R^2 = R^3$ = OMe, $R^4 = R^5 = H$; 83%
(**2.125**) $R^1 = R^2 = R^3 = R^4 = R^5$ = OMe; 72%

Scheme 2-10: Arylation with $ArPb(OAc)_3$.

Combes et al.[36] followed with a combinatorial approach in which 3-mercaptochromanone (**2.126**) were coupled to an aryllead(III) complex (**2.127**) to yield a 3,3-disubstituted precursor (**2.128**), (Scheme 2-11). Nickel boride (in situ) reductive elimination or *meta*-chloroperoxybenzoic acid (MCPBA) oxidation to the corresponding sulfone, followed by thermal elimination, yielded the isoflavanone (**2.129**) or isoflavone (**2.130**), respectively.[36]

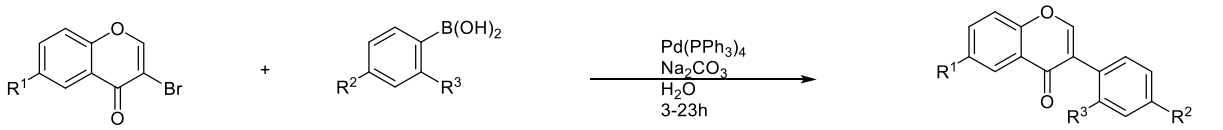


(**2.126**) (**2.127**) (**2.128**) (**2.129**) (**2.130**)

Scheme 2-11: Synthesis of isoflavonoid natural products, 2.129 and 2.130, via arylation.

One of the first reports to employ conventional Suzuki coupling, i.e. organohalide and boronic acid cross-coupling, for the synthesis of isoflavones originated from the Suzuki research group.[37] Palladium catalysed coupling between 3-bromochromones (**2.131-2.133**) and phenylboronic acids

(**2.134-2.138**) in an aqueous medium rendered a variety of isoflavones (**2.72**, **2.106**, **2.107**, **2.123**, **2.139** and **2.140**) in high yields (Scheme 2-12).



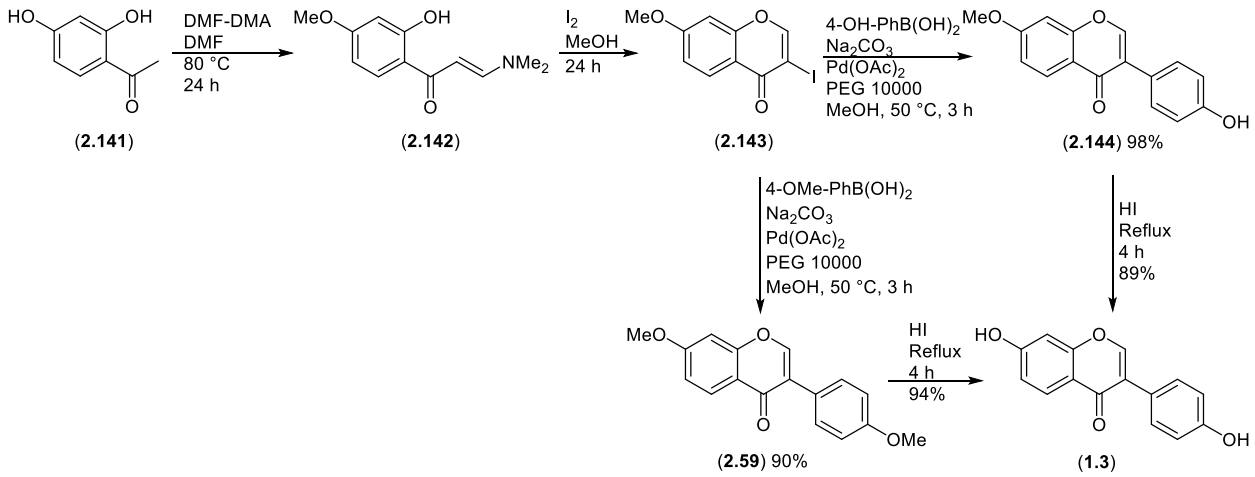
(**2.131**) R^1 = H
(**2.132**) R^1 = Cl
(**2.133**) R^1 = OMe

(**2.134**) R^2 = Me, R^3 = H
(**2.135**) R^2 = OMe, R^3 = H
(**2.136**) R^2 = H, R^3 = Me
(**2.137**) R^2 = H, R^3 = H
(**2.138**) R^2 = F, R^3 = H

(**2.123**) R^1 = R^3 = H, R^2 = Me; 84%
(**2.72**) R^1 = R^3 = H, R^2 = OMe; 94%
(**2.139**) R^1 = R^2 = H, R^3 = Me; 94%
(**2.106**) R^1 = Cl, R^2 = R^3 = H; 71%
(**2.107**) R^1 = OMe, R^2 = R^3 = H; 87%
(**2.140**) R^1 = R^3 = H, R^2 = F; 80%

Scheme 2-12: Arylation with phenylboronic acids.

This synthetic protocol was later modified by Priefer et al.[38] who utilized PEG 10000 instead of water which allowed the omission of excess phosphine ligand generally required for this transformation. The synthesis of daidzein (**1.3**), from dimethyldaidzein (**2.59**) and isoformononetin (**2.144**), was demonstrated as a model reaction toward various isoflavones commonly found in soybeans (Scheme 2-13). The Suzuki-coupling proved very efficient producing dimethyldaidzein (**2.59**) and isoformononetin (**2.144**) in 90% and 98% yield, respectively.



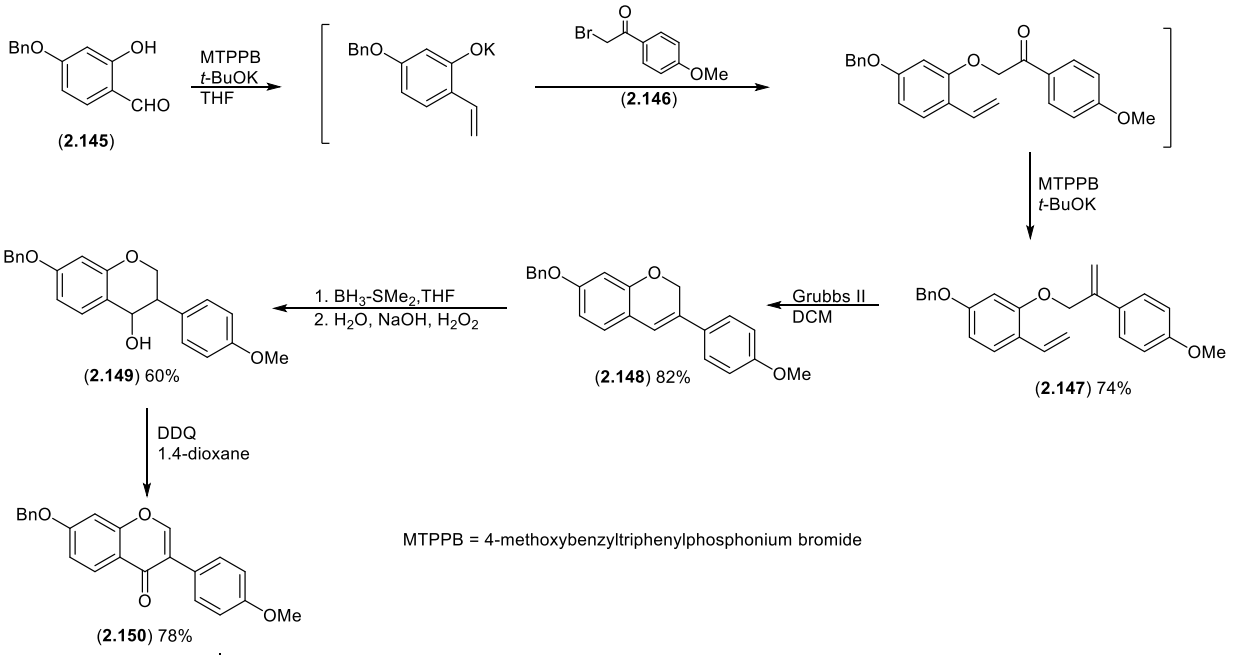
(**2.141**) (**2.142**) (**2.143**) (**2.144**) 98%
(**2.59**) 90% (**1.3**)

Scheme 2-13: Synthesis of daidzein (1.3) utilizing PEG 10000.

2.1.4. Alternative transition metal catalysed routes

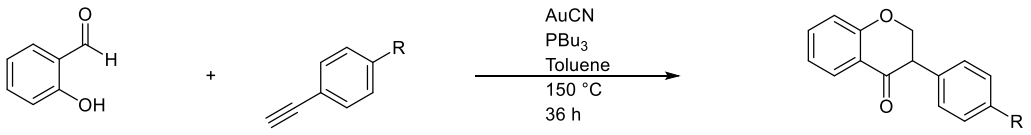
Although the chalcone and deoxybenzoin routes represent biomimetric approaches toward the isoflavonoid skeleton, alternative transition metal methodologies, with the exception of arylation of chromanones (vide supra), have also been developed for construction of the C-ring of isoflavonoids. In this regard, ring-closing metathesis (RCM), exploiting the ruthenium based Grubbs II catalyst, was used for the construction of the C-ring of an isoflavene (**2.148**) as key intermediate in the synthesis of isoflavonoids (Scheme 2-14).[39] Hydroboration of the isoflavene (**2.148**) and subsequent DDQ oxidation renders the corresponding isoflavone (**2.150**). Although the RCM gave

the isoflavene in high yield (82%), the multistep approach proved detrimental to the overall yield (28%) of this methodology.



Scheme 2-14: Synthesis of isoflavone (2.150) utilizing Wittig and RCM methodologies.

Lewis acid assisted annulation also proved successful by Skouta and Li[40] (Scheme 2-15). Gold(I) was found sufficiently active to induce cyclisation between 2-hydroxybenzaldehyde (**2.151**) and phenylacetylene (**2.152-2.154**) constructing the C-ring in one step (75%). Although some degree of derivatisation was reported for these transition metal routes, the scope of these reactions is still poorly explored.



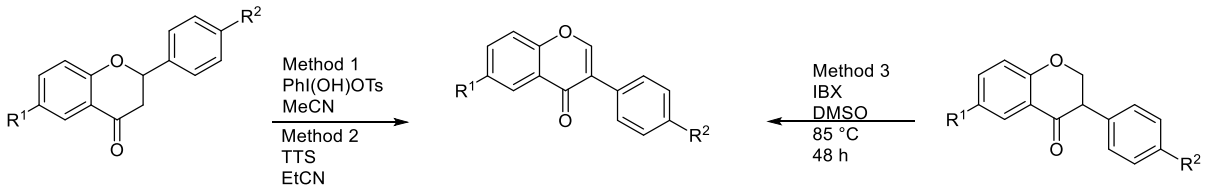
Scheme 2-15: Synthesis of isoflavanones via gold catalysed annulation.

2.1.5. Interconversions

Since many types of flavonoids differ with regards to the unsaturation, oxygenation level of the heterocyclic ring or position of the phenyl ring, these compounds can easily be transformed into one another. Isoflavones, for example, can be obtained from the corresponding flavanone using either a hypervalent iodine reagent[41] or thallium(III) toluene-*para*-sulfonate (TTS),[42] (Table 2-3, entries 1-6). A 1,2-aryl migration rearrangement is realised in a similar fashion to that observed for chalcones (cf. paragraph 2.1.2.) to yield the corresponding isoflavone, however, higher yields were

obtained with the use of TTS instead of PhI(OH)OTs. Alternatively, isoflavones (**2.4**, **2.72**, **2.106**, **2.123**, **2.161-2.163**) can also be prepared from the appropriate isoflavanones (**2.5**, **2.85** and **2.121**), obtained via gold annulation (vide supra), utilizing 2-iodoxybenzoic acid (IBX) as oxidizing agent,[40] or DDQ oxidation[43] (Table 2-3, entries 7-9).

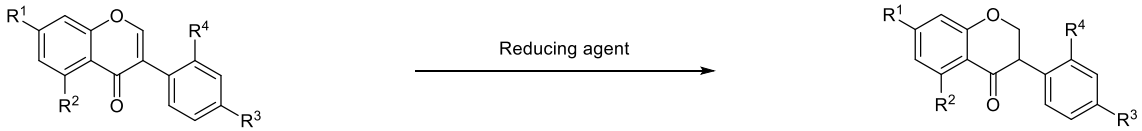
Table 2-3: Preparation of isoflavones from flavanones and isoflavanones.



Entry	R^1	R^2	Flavanone	R^1	R^2	Isoflavanone	Isoflavone	M1[41] Yield (%)	M2[42] Yield (%)	M3[40] Yield (%)
1	H	H	(**2.155**)	-	-	-	(**2.4**)	75	94	-
2	H	OMe	(**2.156**)	-	-	-	(**2.72**)	76	96	-
3	Cl	H	(**2.157**)	-	-	-	(**2.106**)	72	96	-
4	Cl	OMe	(**2.158**)	-	-	-	(**2.161**)	80	94	-
5	Cl	Me	(**2.159**)	-	-	-	(**2.162**)	78	94	-
6	Me	Cl	(**2.160**)	-	-	-	(**2.163**)	75	85	-
7	-	-	-	H	H	(**2.5**)	(**2.4**)	-	-	45
8	-	-	-	H	Me	(**2.121**)	(**2.123**)	-	-	54
9	-	-	-	H	OMe	(**2.85**)	(**2.72**)	-	-	63

The reduction of isoflavones to the corresponding isoflavanones through palladium catalysed hydrogenation date back to the 1960's (Table 2-4).[2,44] A major disadvantage of this approach is secondary reduction toward the corresponding isoflavan which is often observed unless diisobutylaluminium hydride (DIBAL), K- or L-Selectride® or NaHTe is used as reducing agent which increases isoflavanone yields to >90%.[1,5,6,45] Although K- or L-Selectride® gave the highest yield for unsubstituted isoflavanones (entry 3 vs. 4), low tolerance for highly oxygenated phenyl rings were observed (entry 10 vs. 11). The use of DIBAL proved superior for substrates with free hydroxy units and highly oxygenated phenyl rings.

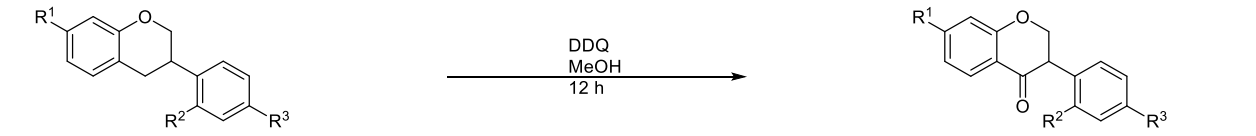
Table 2-4: Reduction of isoflavones to isoflavanones.



Entry	R^1	R^2	R^3	R^4	Isoflavone	Isoflavanone	Reducing agent	Yield (%)
1	OMe	H	H	H	(**2.164**)	(**2.26**)	H_2/Pd-C	40
2	OMe	H	H	H	(**2.164**)	(**2.26**)	H_2/Pd-C	80
3	H	H	H	H	(**2.4**)	(**2.5**)	DIBAL	72
4	H	H	H	H	(**2.4**)	(**2.5**)	K- or L-Selectride®	96
5	OMe	H	OMe	H	(**2.73**)	(**2.28**)	K- or L-Selectride®	82
6	OMe	H	OMe	H	(**2.73**)	(**2.28**)	NaHTe	61
7	OMe	H	OMe	H	(**2.73**)	(**2.28**)	DIBAL	87
8	OH	H	OH	H	(**1.3**)	(**2.33**)	DIBAL	70
9[a]	OMOM	H	OMOM	H	(**2.165**)	(**2.167**)	DIBAL	93
10[a]	OMOM	H	OMOM	OMOM	(**2.166**)	(**2.168**)	DIBAL	87
11[a]	OMOM	H	OMOM	OMOM	(**2.166**)	(**2.168**)	K- or L-Selectride®	40

[a]OMOM = OCH_2OCH_3

Isoflavanones (**2.72**, **2.172** and **2.173**) can also be prepared via DDQ oxidation of the corresponding isoflavans (**2.169**-**2.171**), (Scheme 2-16).[46] The mechanism is hypothesized to exploit the reactive nature of an intermediary quinone methide which allows attack by methanol on the benzylic carbon to introduce the oxygen in position 4 followed by subsequent oxidation to the carbonyl.



(**2.169**) $R^1 = R^3 = OMe$, $R^2 = OCH_2OCH_3$
(**2.170**) $R^1 = OMe$, $R^2 = OCH_2OCH_3$, $R^3 = H$
(**2.171**) $R^1 = R^2 = H$, $R^3 = OMe$

(**2.172**) $R^1 = R^3 = OMe$, $R^2 = OCH_2OCH_3$; 86%
(**2.173**) $R^1 = OMe$, $R^2 = OCH_2OCH_3$, $R^3 = H$; 91%
(**2.72**) $R^1 = R^2 = H$, $R^3 = OMe$; 61%

Scheme 2-16: Oxidation of isoflavans to isoflavanones.

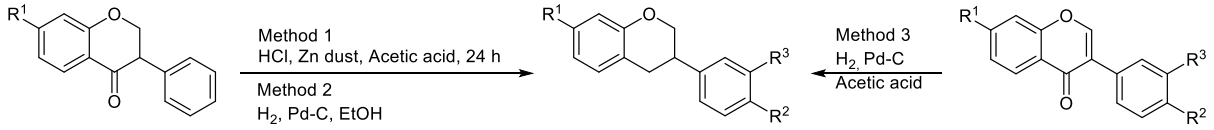
Although these interconversions are often moderate to high yielding and is performed in a single step, the precursor still requires preparation. Many of the preparative procedures described earlier thus have to be combined with the interconversion should any of these protocols be considered.

2.2. Isoflavans

Up to the 1970's isoflavans were almost exclusively prepared by the reduction of isoflavones or isoflavanones (Table 2-5).[2,3,4,5,6] Inoue[47] utilized two methodologies, i.e. a) modified Clemmensen reduction (Method 1) and b) catalytic hydrogenation over palladium on carbon (Method 2) for the reductive preparation of isoflavans from isoflavones and/or isoflavanones. Although these methods gave comparable, acceptable yields (78% and 80%), the presence of a 7-methoxy substituent leads to a drop in yields for both methods of ca. 20% (Table 2-5, entry 1 vs. 2), while the Clemmensen reduction also requires prolonged reaction times. The problem with compounds with a 7-methoxy

substituent was, however, addressed by reducing the isoflavone instead of the isoflavanone and performing the hydrogenation in acetic acid (Method 3), a process which also tolerates free hydroxy functions of the aromatic rings (entries 3-5).[23,48]

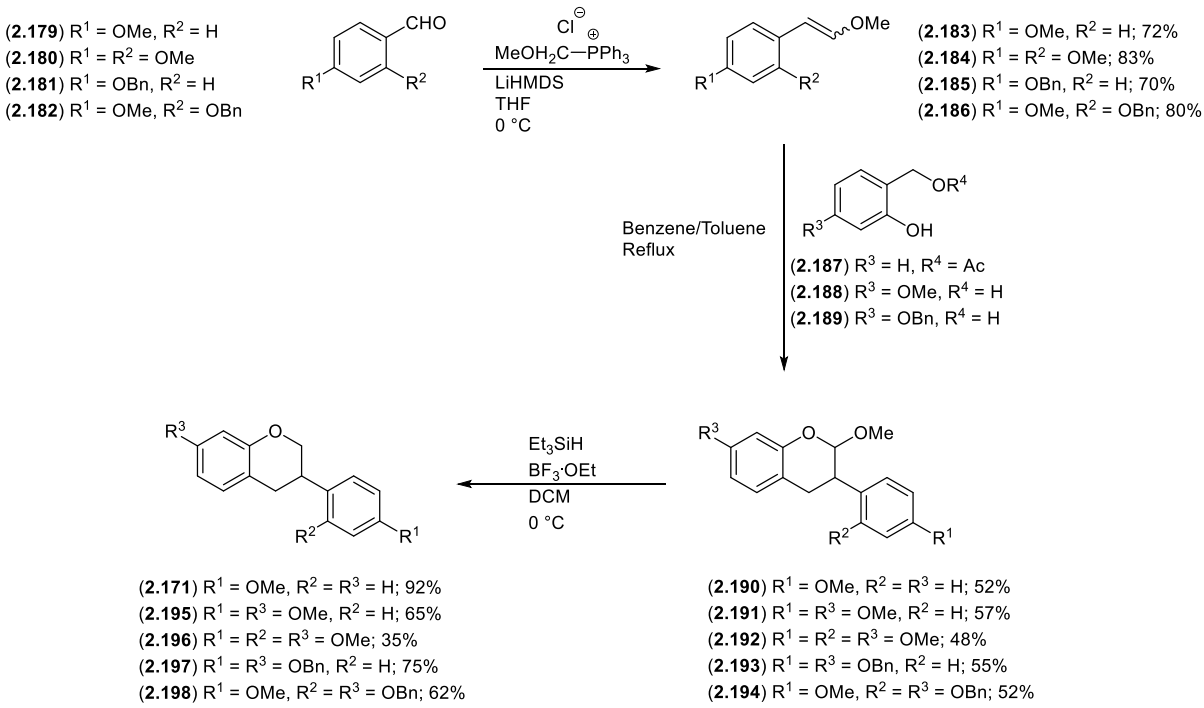
Table 2-5: Interconversions towards isoflavans.



Entry	R^1	Isoflavanone	R^1	R^2	R^3	Isoflavone	Isoflavan[a]	M1[47] Yield (%)	M2[47] Yield (%)	M3[23,48] Yield (%)
1	H	(**2.5**)	-	-	-	-	(**2.1**)	78	80	-
2	OMe	(**2.26**)	-	-	-	-	(**2.175**)	63	53	-
3	-	-	OH	H	OH	(**2.174**)	(**2.176**)	-	-	86
4	-	-	OH	OMe	H	(**1.2**)	(**2.177**)	-	-	92
5	-	-	OMe	OH	H	(**2.144**)	(**2.178**)	-	-	87

[a]Undefined R-groups = H

In 2008 Gharpure et al.[49] reported a general multistep synthesis of a variety of isoflavan analogues through heteronuclear Diels-Alder cycloaddition of a quinone methide to a benzylic enol ether (Scheme 2-17). Wittig methodology was utilized to prepare the aryl substituted enol ethers (**2.183-2.186**), which was reacted with the 2-hydroxybenzyl alcohol derivatives (**2.187-2.189**) transformed in situ into the quinone methide dienophiles. Low regioselectivity for the cycloaddition resulted in only moderate yields (46-58%), but the final reduction of the 2-methoxyisoflavan precursors (**2.190-2.194**) toward the isoflavans (**2.171**, **2.195-2.198**) proceeded smoothly (92% yield). The presence of a 7-methoxy substituent (**2.195**), however, resulted in the isoflavans to be formed in only 65% whereas the presence of an additional 2'-methoxy substituent (**2.196**) on the B-ring reduced the yield even further to only 35%. By opting for benzyl instead of methyl protection of the 7- and 2'-hydroxy functions, the yields for (**2.197**) and (**2.198**) could be improved to 75% and 62%, respectively.

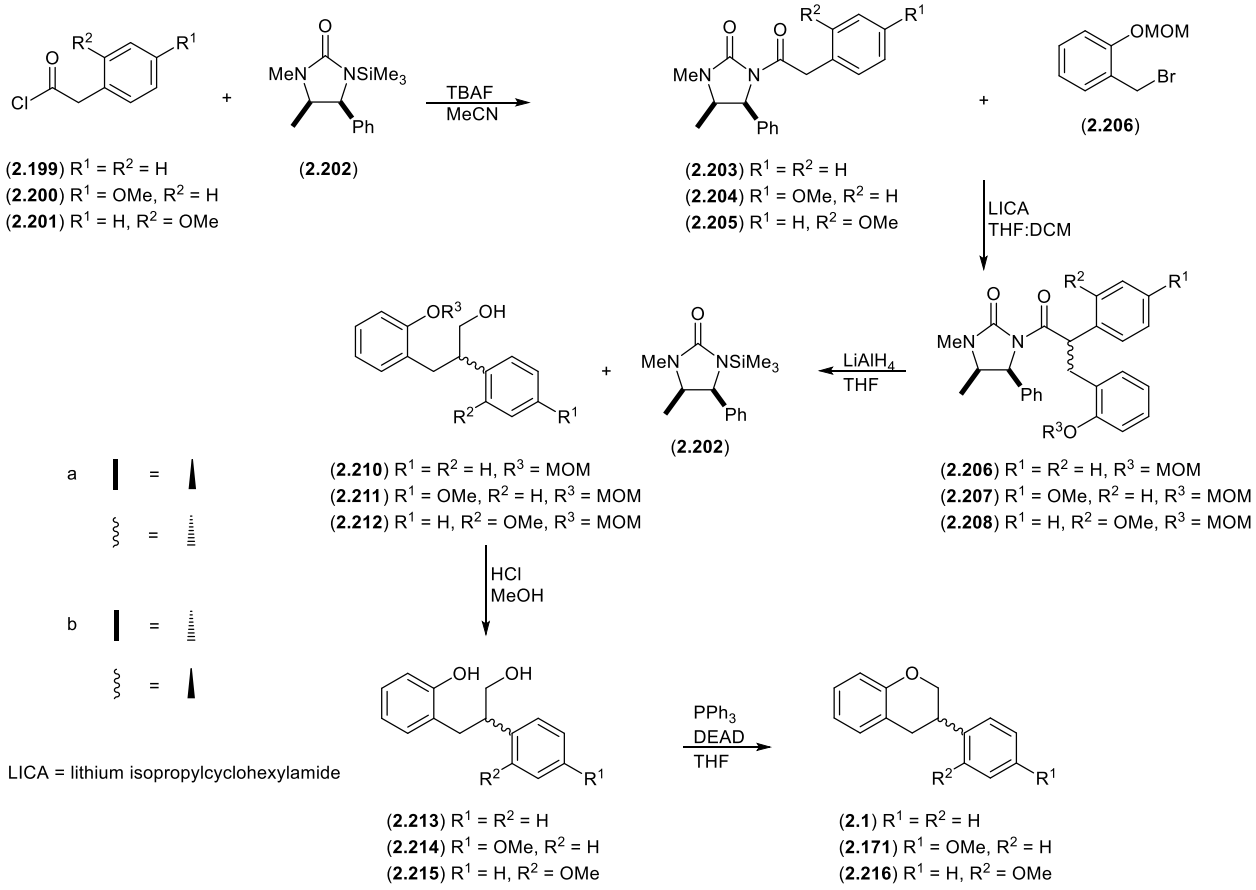


Scheme 2-17: Direct synthesis to isoflavans from benzaldehydes utilizing Wittig and cycloaddition methodologies.

2.2.1. Stereoselective synthesis of Isoflavans

Even though numerous protocols could be followed toward the synthesis of isoflavans none of these established routes incorporated any stereoselectivity. In 1993 Ferreira and coworkers[50,51,52] were the first to report an enantioselective synthesis of isoflavans (Table 2-6). Based on the α-benzylation of phenylacetates bearing imidazolidinone chiral auxiliaries, both enantiomers of isoflavans **2.1**, **2.171** and **2.216** could be prepared in moderate overall yield (48-67%) and high ee (enantiomeric excess; 94-99%) over five steps.

Table 2-6: Enantioselective synthesis of isoflavans.



(**2.199**) $R^1 = R^2 = H$
(**2.200**) R^1 = OMe, $R^2 = H$
(**2.201**) $R^1 = H$, R^2 = OMe

(**2.202**)

(**2.203**) $R^1 = R^2 = H$
(**2.204**) R^1 = OMe, $R^2 = H$
(**2.205**) $R^1 = H$, R^2 = OMe

(**2.206**)

(**2.206**) $R^1 = R^2 = H$, R^3 = MOM
(**2.207**) R^1 = OMe, $R^2 = H$, R^3 = MOM
(**2.208**) $R^1 = H$, R^2 = OMe, R^3 = MOM

(**2.202**)

(**2.210**) $R^1 = R^2 = H$, R^3 = MOM
(**2.211**) R^1 = OMe, $R^2 = H$, R^3 = MOM
(**2.212**) $R^1 = H$, R^2 = OMe, R^3 = MOM

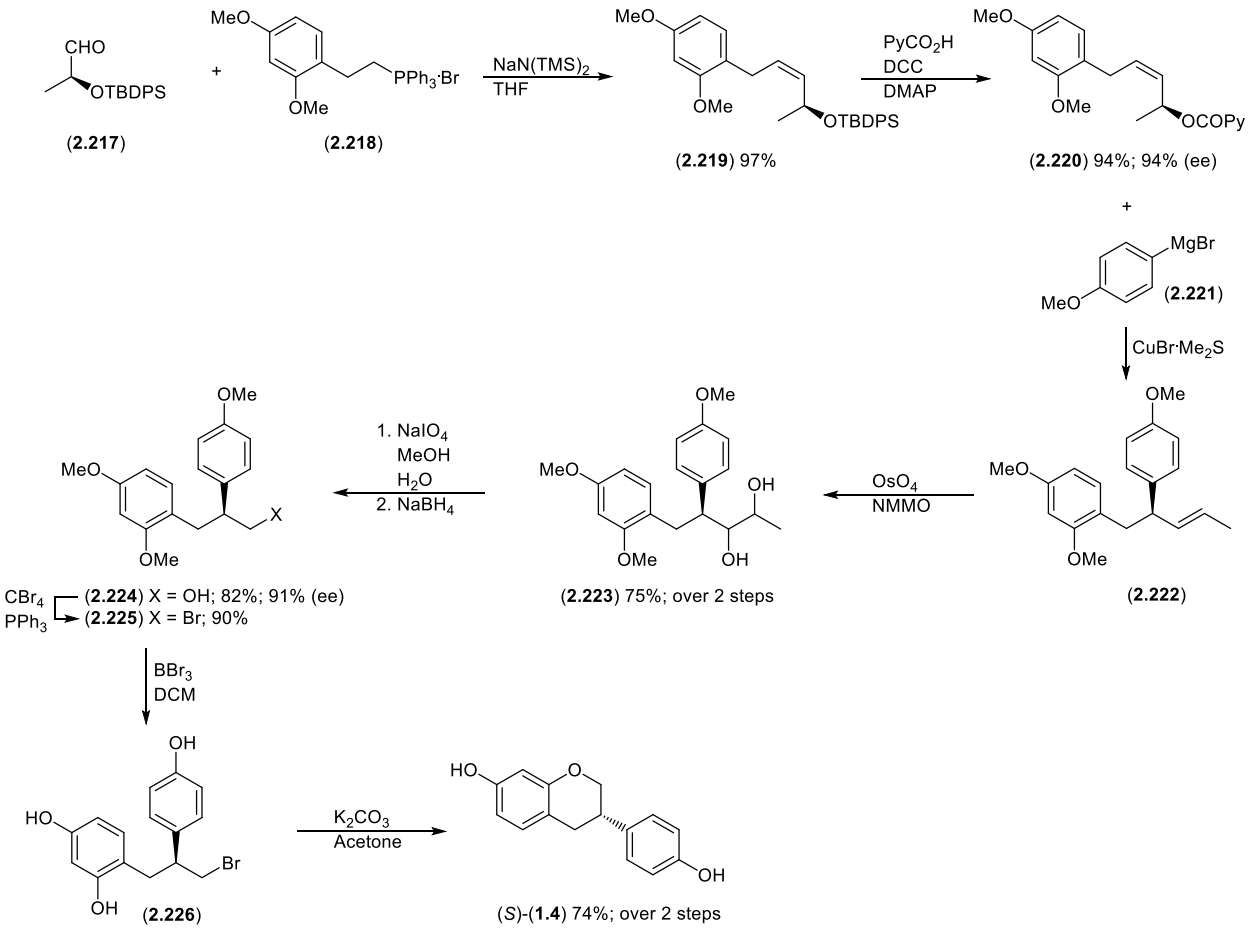
a = ; = ;
b = ; =

(**2.213**) $R^1 = R^2 = H$
(**2.214**) R^1 = OMe, $R^2 = H$
(**2.215**) $R^1 = H$, R^2 = OMe

(**2.1**) $R^1 = R^2 = H$
(**2.171**) R^1 = OMe, $R^2 = H$
(**2.216**) $R^1 = H$, R^2 = OMe

N-acyl-imidazolidinone (%)	Alkylation product (%)	Propanol (%)	Hydrolysis product (%)	Isoflavan (%)	ee (%)	*R/S*
(**2.203a**) 91	(**2.207a**) 90	(**2.210a**) 84	(**2.213a**) 97	(**2.1a**) 92	96	*S*
(**2.203b**) 90	(**2.207b**) 86	(**2.210b**) 77	(**2.213b**) 98	(**2.1b**) 87	94	*R*
(**2.204a**) 75	(**2.208a**) 84	(**2.211a**) 89	(**2.214a**) 94	(**2.171a**) 85	99	*S*
(**2.204b**) 80	(**2.208b**) 92	(**2.211b**) 85	(**2.214b**) 85	(**2.171b**) 80	99	*R*
(**2.205a**) 72	(**2.209a**) 88	(**2.212a**) 90	(**2.215a**) 85	(**2.216a**) 73	98	*S*
(**2.205b**) 73	(**2.209b**) 90	(**2.212b**) 76	(**2.215b**) 95	(**2.216b**) 75	99	*R*

The most recent stereoselective synthesis of isoflavans was published by Takashima and Kobayashi[53] for the preparation of (*S*)-equol (**1.4a**), (Scheme 2-18). Naturally occurring L-lactate was transformed into aldehyde (**2.217**) which was incorporated into the picolinate derivative (**2.220**). Stereoselectivity was consequently induced during the cuprate arylation establishing the absolute configuration of what would ultimately become carbon-3 of the isoflavan. The 9-step methodology renders the isoflavan (**1.4a**) in excellent ee (>90%), albeit in only 36% overall yield.

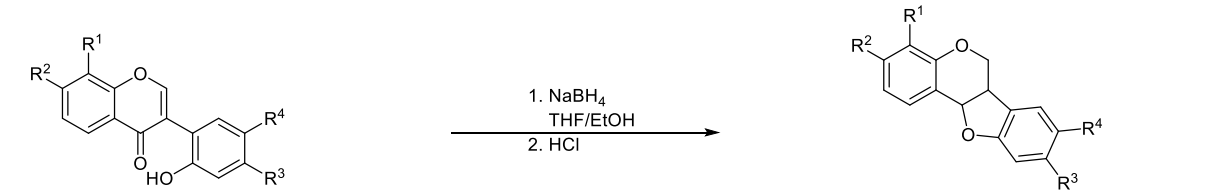


Scheme 2-18: Enantioselective synthesis of (*S*)-equol (1.4).

2.3. Pterocarpans

2.3.1. Pterocarpans

Isoflavones, isoflavanones and isoflavans are often utilized as precursors for single step transformations to produce pterocarpans. In the 1960's pterocarpans were synthesized from preformed isoflavones through either catalytic hydrogenation[54,55] or reduction with reagents like $LiAlH_4$[54] or $NaBH_4$,[54,56,57,58] followed by acid catalysed dehydrative cyclization (Scheme 2-19). The mild $NaBH_4$ conditions are still the method of choice for this purpose ca. fifty years later.[59,60]



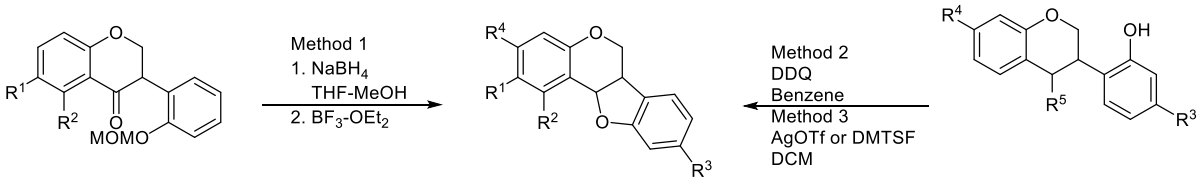
(**2.227**) $R^1 = R^3 = R^4 = H$, $R^2 = OH$
(**2.228**) $R^1 = R^4 = H$, $R^2 = OH$, $R^3 = OMe$
(**2.229**) $R^1 = R^3 = OMe$, $R^2 = OH$, $R^4 = H$
(**2.230**) $R^1 = R^2 = OMe$, $R^3 = R^4 = H$
(**2.231**) $R^1 = R^2 = R^3 = OMe$, $R^4 = H$
(**2.232**) $R^1 = H$, $R^2 = OCH_2Ph$, $R^3 = R^4 = OMe$

(**2.233**) $R^1 = R^3 = R^4 = H$, $R^2 = OH$; 57 %
(**2.234**) $R^1 = R^4 = H$, $R^2 = OH$, $R^3 = OMe$; 55 %
(**2.235**) $R^1 = R^3 = OMe$, $R^2 = OH$, $R^4 = H$; 30 %
(**2.236**) $R^1 = R^2 = OMe$, $R^3 = R^4 = H$; 70 %
(**2.237**) $R^1 = R^2 = R^3 = OMe$, $R^4 = H$; 89 %
(**2.238**) $R^1 = H$, $R^2 = OCH_2Ph$, $R^3 = R^4 = OMe$; 73 %

Scheme 2-19: Preparation of pterocarpans from preformed isoflavones.

Isoflavanones like **2.39-2.41** may also be transformed into the corresponding pterocarpans (**2.6**, **2.246** and **2.247**) if the reduction with $NaBH_4$ is performed in the presence of BF_3•Et_2O (Table 2-7 entries 1-3, Method 1).[40] Under oxidative reaction conditions (Method 2) the isoflavan skeleton, i.e. 2'-hydroxyisoflavan (**2.242**), can be transformed to the corresponding pterocarpan (**2.234**), albeit in low yield (30%).[61] Formation of the furan ring is significantly enhanced (up to 82% for **2.6**) by the addition of Lewis acids like AgOTf or dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF), if a 4-benzylmercaptyl unit is attached to the isoflavan skeleton (Method 3).[60,62]

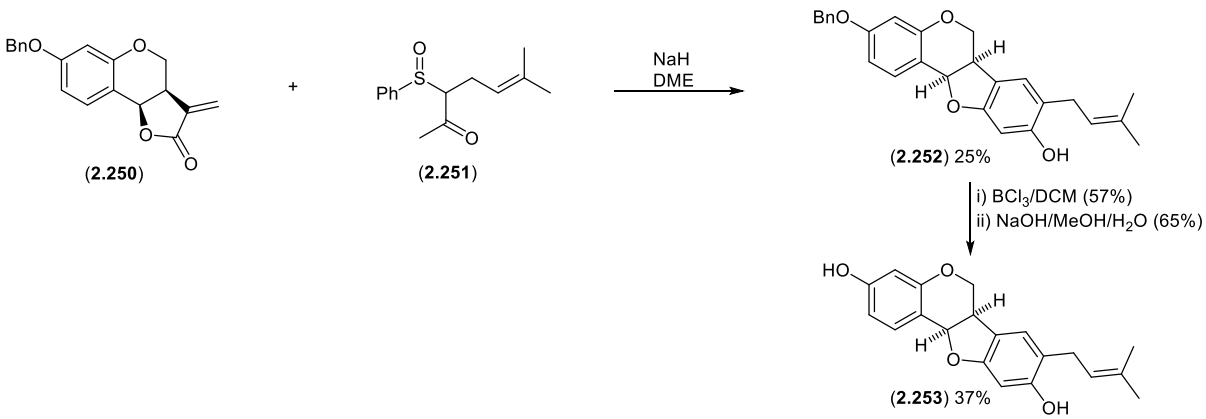
Table 2-7: Interconversion of isoflavanones and isoflavans to pterocarpans.



Entry	R^1	R^2	Isoflavanone	R^3	R^4	R^5	Isoflavan	Pterocarpan[a]	M1[40] Yield (%)	M2[61] Yield (%)	M3[60,62] Yield (%)
1	H	H	(**2.239**)	-	-	-	-	(**2.6**)	91	-	-
2	Cl	H	(**2.240**)	-	-	-	-	(**2.246**)	53	-	-
3	-(CH)$_4$-		(**2.241**)	-	-	-	-	(**2.247**)	75	-	-
4	-	-	-	OMe	OH	H	(**2.242**)	(**2.234**)	-	30	-
5	-	-	-	H	H	SCH_2Ph	(**2.243**)	(**2.6**)	-	-	82
6	-	-	-	H	OMe	SCH_2Ph	(**2.244**)	(**2.248**)	-	-	52
7	-	-	-	OMe	OMe	SCH_2Ph	(**2.245**)	(**2.249**)	-	-	50

[a]Undefined R-groups = H

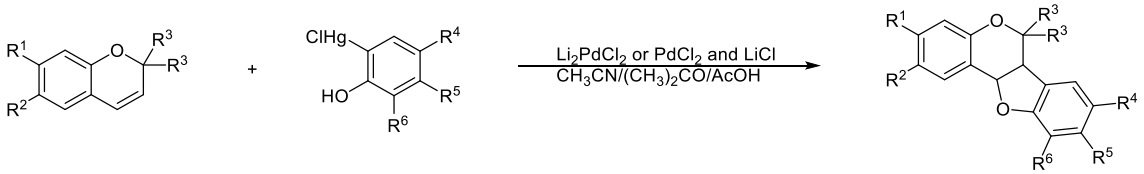
In an unconventional approach 1,3-Michael-Claisen condensation was exploited to construct the aromatic D-ring of the pterocarpan skeleton in a multistep protocol to prepare the natural product sophorapterocarpan A (**2.253**) in 9% yield (Scheme 2-20). Although the starting materials, **2.250** and **2.251**, were prepared in 7 and 2 steps, respectively, this approach allowed for diasteriomeric control to yield the *cis*-pterocarpan (**2.252**). Subsequent manipulation of **2.252** yielded (±)-*cis*-sophorapterocarpan A (**2.253**) as the final product.[63]



Scheme 2-20: Synthesis of (±)-*cis*-sophorapterocarpan A (2.253) utilizing 1,3-Michael-Claisen condensation.

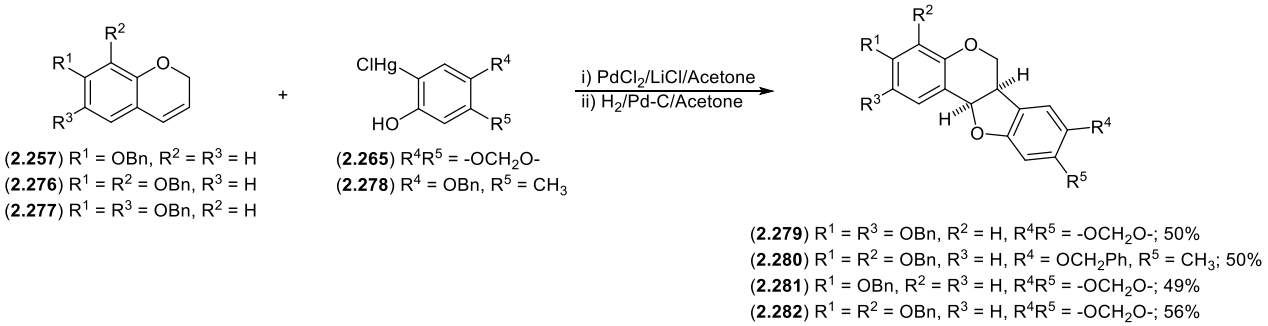
A widely reported synthesis route towards the preparation of pterocarpans involves the palladium catalysed cross-coupling between 2-hydroxyarylmercury compounds (**2.261-2.266**) and *2H*-chromenes (**2.254-2.260**), (Table 2-8).[59,64,65,66,67,68] The stability of organomercury compounds[69] and presumed accessibility to a variety of substitution patterns on the arylmercury units makes this a very versatile approach, although the procedure and yields for the preparation of the mercury derivatives are not reported in any of these publications. It must also be noted that only low to moderate yields (11-58%) were obtained for oxygenated substrates.

Table 2-8: Synthesis of pterocarpans utilizing organomercury compounds.



Entry	R^1	R^2	R^3	Chromene	R^4	R^5	R^6	2-Hydroxyarylmercury	Pterocarpan	Yield (%)
1	H	H	H	(**2.254**)	H	H	H	(**2.261**)	(**2.6**)	85
2	OMe	H	H	(**2.255**)	H	H	H	(**2.261**)	(**2.248**)	54
3	OMe	OBn	H	(**2.256**)	OBn	OMe	H	(**2.262**)	(**2.267**)	50
4	OBn	H	H	(**2.257**)	OBn	OBn	H	(**2.263**)	(**2.268**)	57
5	OBn	H	H	(**2.257**)	OMe	OBn	H	(**2.264**)	(**2.269**)	54
6	H	H	H	(**2.254**)	OCH_2O		H	(**2.265**)	(**2.270**)	36
7	OMe	H	H	(**2.255**)	OCH_2O		H	(**2.265**)	(**2.271**)	58
8	OCH_2O		Me	(**2.258**)	OCH_2O		H	(**2.265**)	(**2.272**)	43
9	OCH_2O		Me	(**2.258**)	CHO	H	OMe	(**2.266**)	(**2.273**)	11
10	H	OMe	Me	(**2.259**)	CHO	H	OMe	(**2.266**)	(**2.274**)	21
11	OMe	H	Me	(**2.260**)	CHO	H	OMe	(**2.266**)	(**2.275**)	20

This methodology was nevertheless used by Netto and co-workers[70,71] for the synthesis of various biologically significant pterocarpans with free hydroxy instead of benzyloxy substituents (**2.279-2.282**) in moderate yields (49-56%), (Scheme 2-21).[71]



(**2.257**) R^1 = OBn, R^2 = R^3 = H
(**2.276**) R^1 = R^2 = OBn, R^3 = H
(**2.277**) R^1 = R^3 = OBn, R^2 = H

(**2.265**) R^4R^5 = -OCH_2O-
(**2.278**) R^4 = OBn, R^5 = CH_3

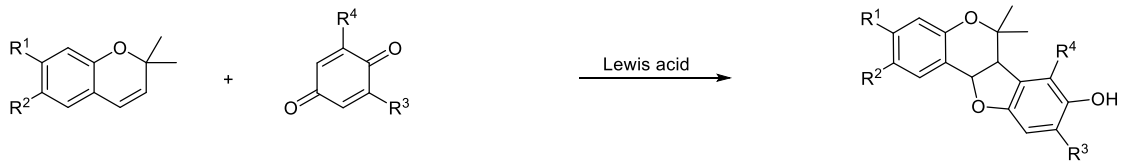
(**2.279**) R^1 = R^3 = OBn, R^2 = H, R^4R^5 = -OCH_2O-; 50%
(**2.280**) R^1 = R^2 = OBn, R^3 = H, R^4 = OCH_2Ph, R^5 = CH_3; 50%
(**2.281**) R^1 = OBn, R^2 = R^3 = H, R^4R^5 = -OCH_2O-; 49%
(**2.282**) R^1 = R^2 = OBn, R^3 = H, R^4R^5 = -OCH_2O-; 56%

Scheme 2-21: Synthesis of naturally occurring pterocarpan analogues.

It has also been established that the C-ring of pterocarpans can be formed from chromene (**2.258**, **2.260**, **2.283** and **2.284**) and 1,4-benzoquinone (**2.285-2.287**) derivatives via a formal [3+2]

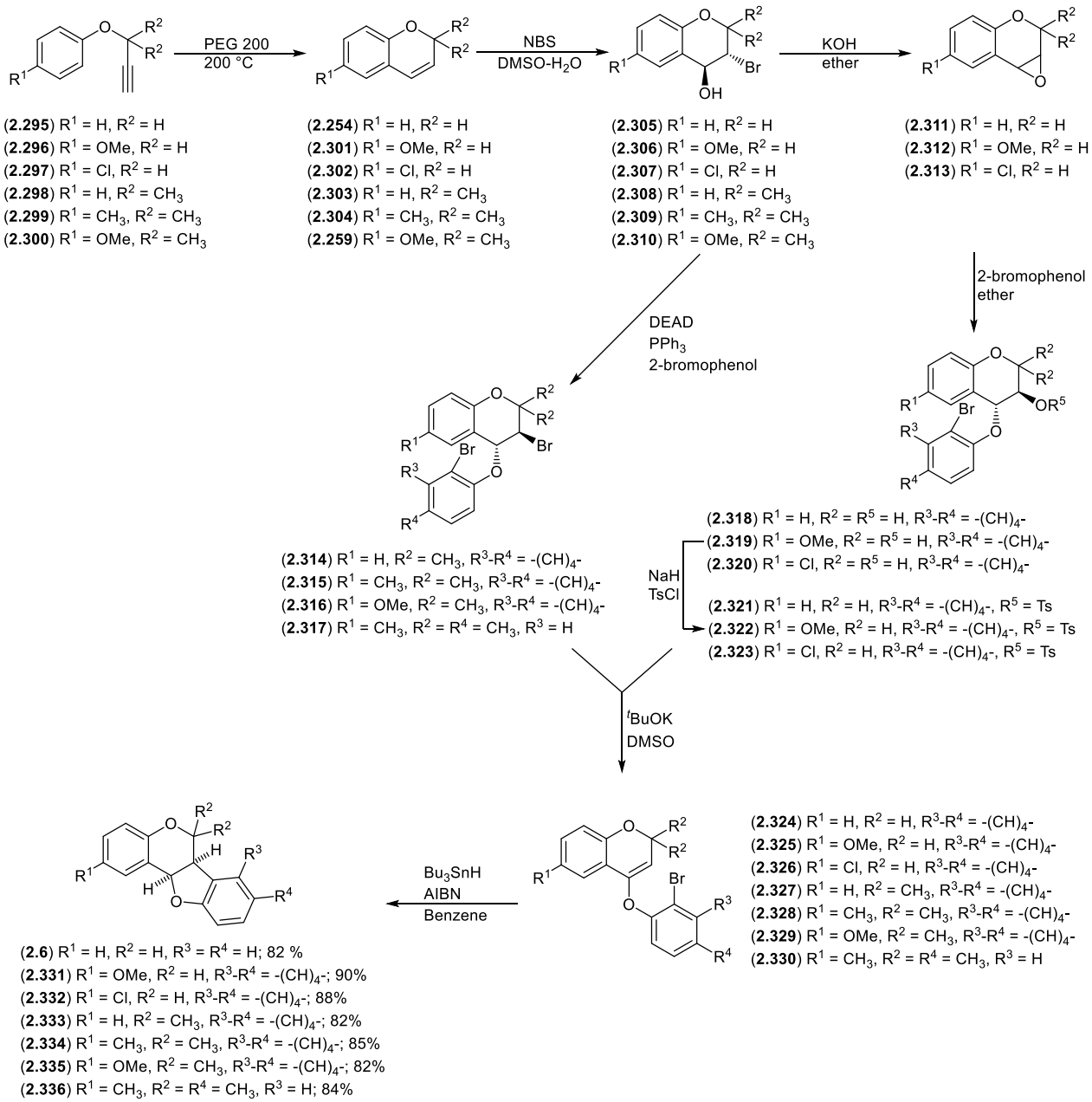
cycloaddition sequence in the presence of a Lewis acid (Table 2-9). Lewis acids utilized in this protocol include BF_3•OEt_2,[72,73,74] $TiCl_4$[72,73] and $SnCl_4$[72] for *N*-substituted pterocarpans, however $TiCl_4$/$Ti(OiPr)_4$[75] and $ZnCl_2$[76] were also used for the synthesis of oxygenated pterocarpans (**2.288-2.294**) in moderate yields (38-62%).

Table 2-9: Formal [3+2] cycloaddition route towards pterocarpans.



Entry	R^1	R^2	Chromene	R^3	R^4	Benzoquinone	Product	Lewis acid	Yield (%)
1	OMe	H	(**2.260**)	OMe	H	(**2.285**)	(**2.288**)	$TiCl_4$/$Ti(OiPr)_4$	62
2	OMe	H	(**2.260**)	OMe	OMe	(**2.286**)	(**2.289**)	$TiCl_4$/$Ti(OiPr)_4$	56
3	OBn	H	(**2.283**)	OMe	H	(**2.285**)	(**2.290**)	$TiCl_4$/$Ti(OiPr)_4$	51
4	OBn	H	(**2.283**)	OMe	OMe	(**2.286**)	(**2.291**)	$TiCl_4$/$Ti(OiPr)_4$	45
5	OBn	H	(**2.283**)	OBn	H	(**2.287**)	(**2.292**)	$TiCl_4$/$Ti(OiPr)_4$	48
6	OBn	OMe	(**2.284**)	OMe	H	(**2.285**)	(**2.293**)	$ZnCl_2$	50
7	OCH_2O		(**2.258**)	OMe	H	(**2.285**)	(**2.294**)	$ZnCl_2$	38

Gopalsamy and Balasubramanian[77] developed a more general synthesis toward pterocarpans by exploiting intramolecular radical cyclization for the formation of the C-ring in the final step (Scheme 2-22). The substrate scope of this reaction was expanded over 13 years to include the synthesis of **2.6** and **2.331-2.336**.[78] In spite of this being a 7-step methodology, the yields throughout the synthesis was above 80%.



(**2.295**) R^1 = H, R^2 = H
(**2.296**) R^1 = OMe, R^2 = H
(**2.297**) R^1 = Cl, R^2 = H
(**2.298**) R^1 = H, R^2 = CH_3
(**2.299**) R^1 = CH_3, R^2 = CH_3
(**2.300**) R^1 = OMe, R^2 = CH_3

(**2.254**) R^1 = H, R^2 = H
(**2.301**) R^1 = OMe, R^2 = H
(**2.302**) R^1 = Cl, R^2 = H
(**2.303**) R^1 = H, R^2 = CH_3
(**2.304**) R^1 = CH_3, R^2 = CH_3
(**2.259**) R^1 = OMe, R^2 = CH_3

(**2.305**) R^1 = H, R^2 = H
(**2.306**) R^1 = OMe, R^2 = H
(**2.307**) R^1 = Cl, R^2 = H
(**2.308**) R^1 = H, R^2 = CH_3
(**2.309**) R^1 = CH_3, R^2 = CH_3
(**2.310**) R^1 = OMe, R^2 = CH_3

(**2.311**) R^1 = H, R^2 = H
(**2.312**) R^1 = OMe, R^2 = H
(**2.313**) R^1 = Cl, R^2 = H

(**2.314**) R^1 = H, R^2 = CH_3, R^3-R^4 = -$(CH)_4$-
(**2.315**) R^1 = CH_3, R^2 = CH_3, R^3-R^4 = -$(CH)_4$-
(**2.316**) R^1 = OMe, R^2 = CH_3, R^3-R^4 = -$(CH)_4$-
(**2.317**) R^1 = CH_3, R^2 = R^4 = CH_3, R^3 = H

(**2.318**) R^1 = H, R^2 = R^5 = H, R^3-R^4 = -$(CH)_4$-
(**2.319**) R^1 = OMe, R^2 = R^5 = H, R^3-R^4 = -$(CH)_4$-
(**2.320**) R^1 = Cl, R^2 = R^5 = H, R^3-R^4 = -$(CH)_4$-

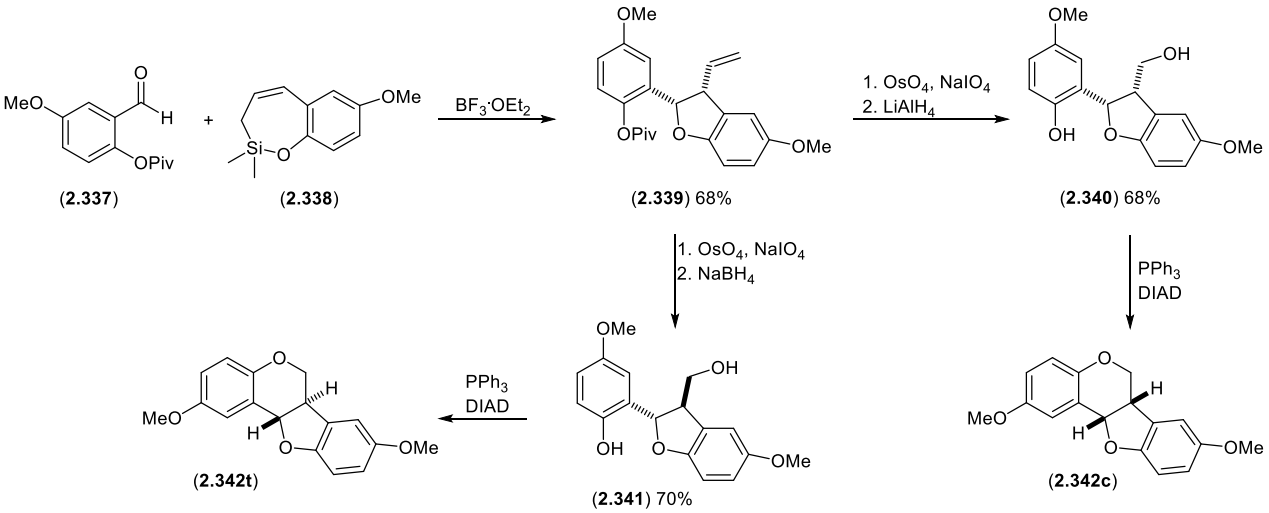
(**2.321**) R^1 = H, R^2 = H, R^3-R^4 = -$(CH)_4$-, R^5 = Ts
(**2.322**) R^1 = OMe, R^2 = H, R^3-R^4 = -$(CH)_4$-, R^5 = Ts
(**2.323**) R^1 = Cl, R^2 = H, R^3-R^4 = -$(CH)_4$-, R^5 = Ts

(**2.324**) R^1 = H, R^2 = H, R^3-R^4 = -$(CH)_4$-
(**2.325**) R^1 = OMe, R^2 = H, R^3-R^4 = -$(CH)_4$-
(**2.326**) R^1 = Cl, R^2 = H, R^3-R^4 = -$(CH)_4$-
(**2.327**) R^1 = H, R^2 = CH_3, R^3-R^4 = -$(CH)_4$-
(**2.328**) R^1 = CH_3, R^2 = CH_3, R^3-R^4 = -$(CH)_4$-
(**2.329**) R^1 = OMe, R^2 = CH_3, R^3-R^4 = -$(CH)_4$-
(**2.330**) R^1 = CH_3, R^2 = R^4 = CH_3, R^3 = H

(**2.6**) R^1 = H, R^2 = H, R^3 = R^4 = H; 82 %
(**2.331**) R^1 = OMe, R^2 = H, R^3-R^4 = -$(CH)_4$-; 90%
(**2.332**) R^1 = Cl, R^2 = H, R^3-R^4 = -$(CH)_4$-; 88%
(**2.333**) R^1 = H, R^2 = CH_3, R^3-R^4 = -$(CH)_4$-; 82%
(**2.334**) R^1 = CH_3, R^2 = CH_3, R^3-R^4 = -$(CH)_4$-; 85%
(**2.335**) R^1 = OMe, R^2 = CH_3, R^3-R^4 = -$(CH)_4$-; 82%
(**2.336**) R^1 = CH_3, R^2 = R^4 = CH_3, R^3 = H; 84%

Scheme 2-22: Synthesis of pterocarpans through a radical cyclization process.

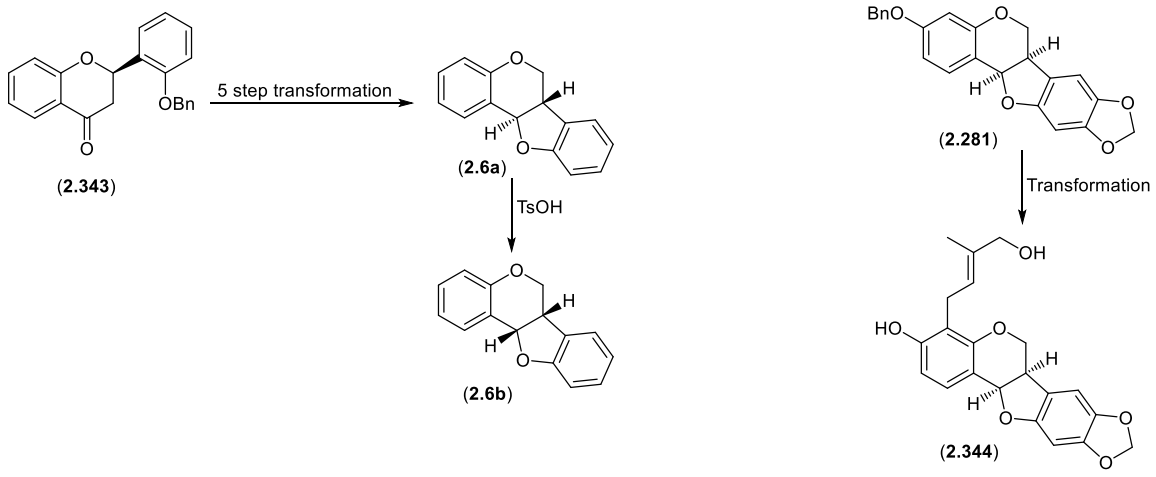
While most direct pterocarpan synthesis methodologies start with a dihydrobenzopyran entity (i.e. chromene or chrmanone) to which the C- and D-rings are attached, Rodriguez-Garcia et al.[79] reported an alternative approach wherein the B-ring (pyran) is established in the final step (Scheme 2-23). Following allylation, Claisen rearrangement and RCM, the dihydrobenzofuran system (**2.339**) is formed diasterioselectively (*cis*) by means of a modified intramolecular Hosomi-Sakurai reaction. This key intermediate (**2.339**) is then subjected to subsequent oxidative degradation and reduction after which the pterocarpan skeleton is established via intramolecular Mitsunobu condensation. The diasterioselectivity of the pterocarpan is determined by the preceding reducing agent and separation process as $LiAlH_4$ and $NaBH_4$ render *cis*- (**2.342c**) and *trans*- pterocarpans (**2.342t**), respectively.



Scheme 2-23: Diasterioselective synthesis of pterocarpans.

2.3.2. Stereoselective synthesis of Pterocarpans

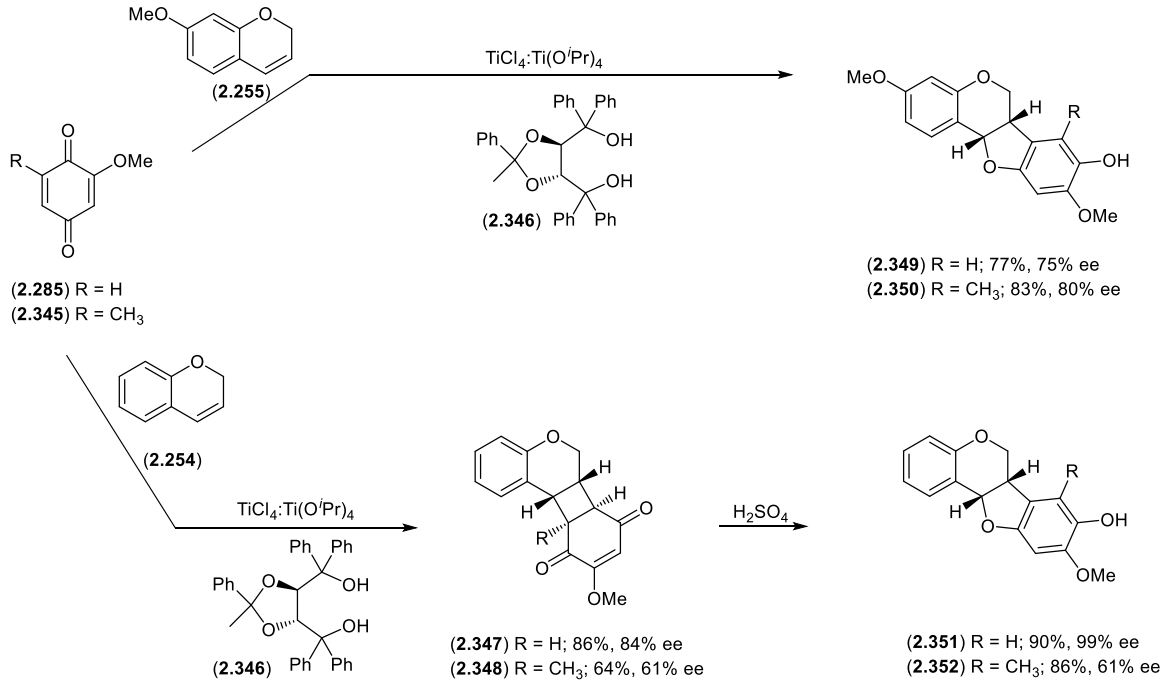
Methodology for the stereoselective synthesis of pterocarpans is rather limited. One approach centred around the resolution of racemic precursors as demonstrated by Antus and co-workers.[80,81] Enantiomerically enriched 2'-benzyloxyflavanone (**2.343**), obtained by means of fractional crystallization, is transformed into *trans*-(6a*S*,11a*R*)-pterocarpan (**2.6a**) via a 5 step process utilizing i) $Tl(NO_3)_3$, ii) $LiAlH_4$, iii) TsCl/py, iv) Pd-C/H_2 and v) NaOMe for respectively ring contraction, reduction, protection, deprotection and ring closure.[80] Subsequent acid catalysed epimerization of the latter then yielded the *cis*-(6a*S*,11a*S*)-pterocarpan (**2.6b**). A similar protocol was employed for the synthesis of (-)-cabenegrin A-I (**2.344**) from the racemic pterocarpan (**2.281**), (Scheme 2-24).[81]



Scheme 2-24: Preparation of pterocarpans through resolution of racemic precursors.

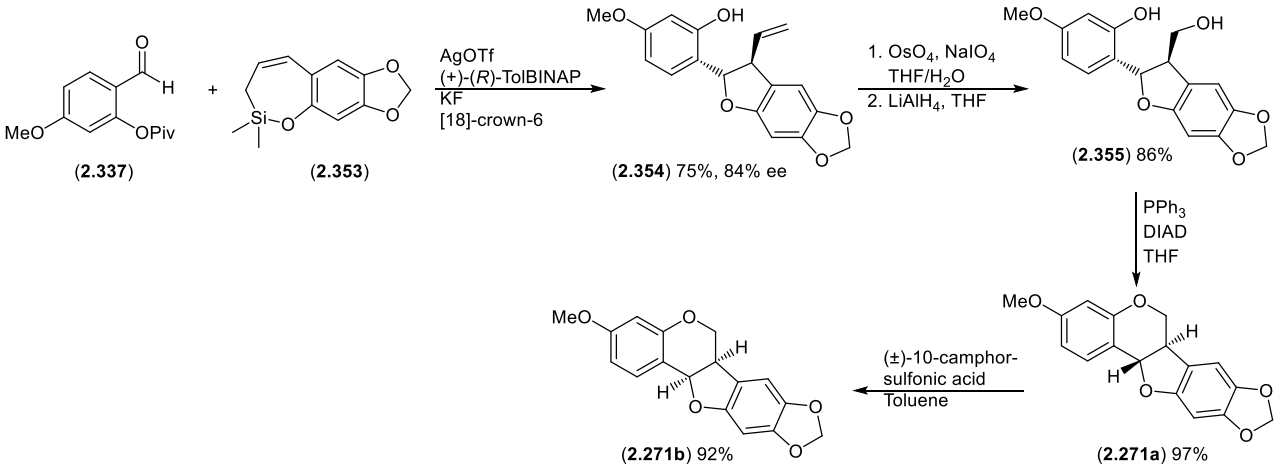
Engler et al.[82] modified their established titanium mediated [3+2] cycloaddition reaction (cf. paragraph 2.4.1.) to include the TADDOL derivative, 2-methyl-α,α,α',α',2-pentaphenyl-1,3-dioxolane-4,5-dimethanol (**2.346**), as chiral titanium ligand, which prompted enantioselective annulation of the chromene (Scheme 2-25). Both unsubstituted chromene (**2.285**) and 7-

methoxychromene (**2.345**) substrates were employed as starting materials but while the 7-methoxychromene (**2.255**) yielded the corresponding pterocarpans directly, the unsubstituted chromene formed the cyclobutane intermediates (**2.347** and **2.348**), which could be rearranged to the pterocarpans (**2.351** and **2.352**) via acid catalysis. With the exception of (**2.352**), (86% yield, 61% ee), the pterocarpans were obtained in high yield (77-90%) and ee (75-99%) via this protocol.



Scheme 2-25: Sterioselective synthesis of pterocarpans utilizing Ti-TADDOLate reagent.

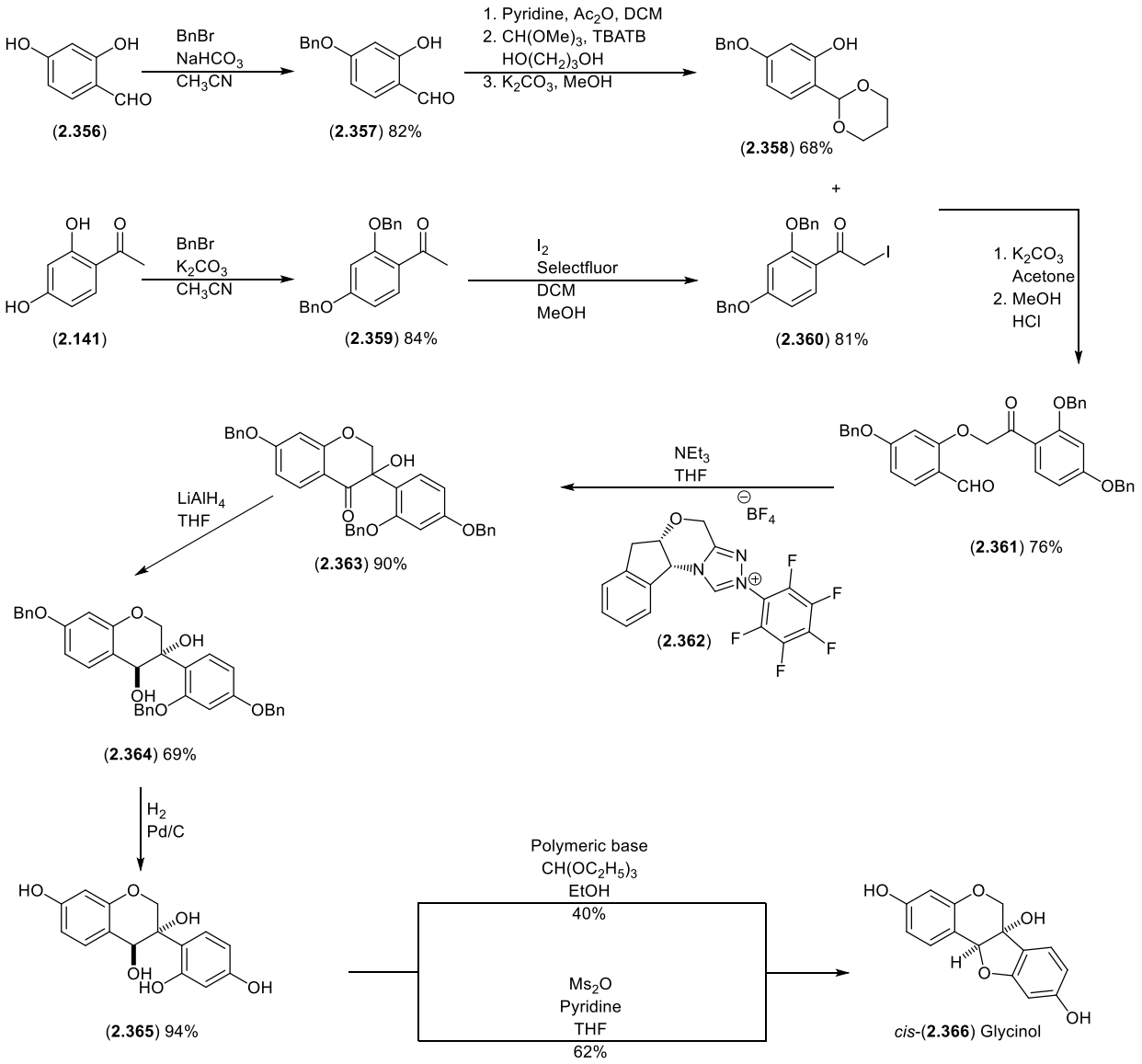
Rodriguez-Garcia and co-workers[79,83] also adapted their methodology (cf. paragraph 2.4.1.)[79] by utilizing a BINAP ligand together with AgOTf as Lewis acid during the Hosomi-Sakurai transformation (Scheme 2-26).[83] When (+)-(*R*)-TolBINAP was utilized the (*S*)-absolute configuration was established at both carbons 2 and 3 (**2.354**) in 84% ee (75% yield). Subsequent $OsO_4/NaIO_4$ oxidation, $LiAlH_4$ reduction and Mitsunobu condensation yielded the *trans*-(6a*R*,11a*S*)-pterocarpan (**2.271a**) in 83% yield over 3 steps, which was epimerised to the *cis*-(6a*S*,11a*S*)-isomer (**2.271b**) by means of acid catalysis (92% yield).



Scheme 2-26: Silver catalyzed chiral synthesis of pterocarpan (2.271b).

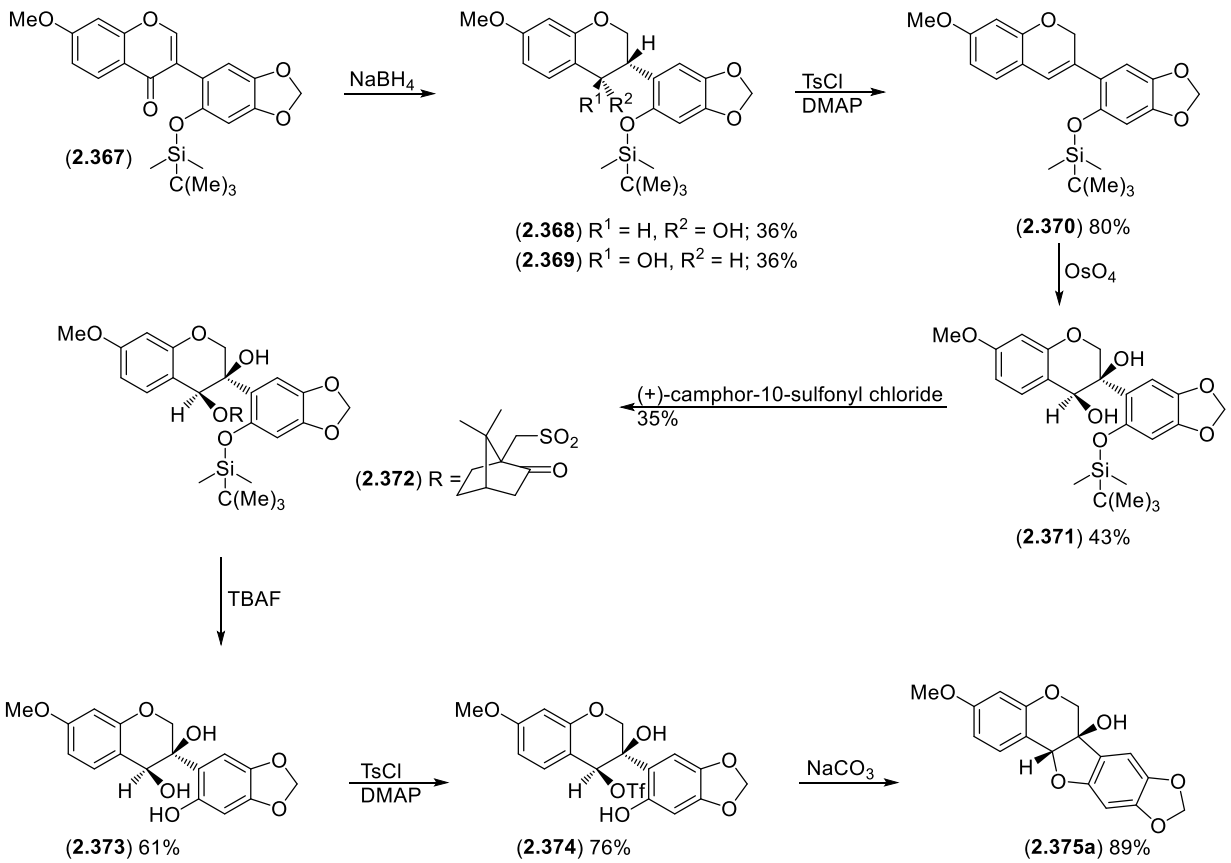
2.4. 6a-Hydroxypterocarpans

Malik and Erhardt[84] reported methodology for the racemic synthesis of the 6a-hydroxypterocarpan, (±)-glycinol (**2.366**), in which a benzoin condensation was used to generate the 3-hydroxyisoflavanone (**2.363**) as key intermediate in the synthesis of (±)-glycinol (Scheme 2-27). Although the triazole catalyst (**2.362**) utilized during the benzoin condensation was enantiomerically pure, no asymmetric induction was observed for this step of the synthetic protocol. Lithium chelation during the reduction of **2.363** with $LiAlH_4$ yields, diastereoselectively, the corresponding *trans*-isoflavan-3,4-diol (**2.364**). Although this approach lacked any enantioselectivity, the 20% overall yield (10 steps) represented an improvement over many previous methodologies.



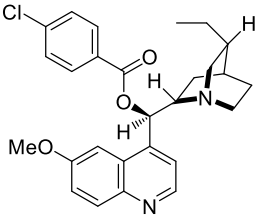
Scheme 2-27: Synthesis of (±)-Glycinol (2.366).

Initial interest in the enantioselective synthesis of 6a-hydroxypterocarpans was inspired by the antifungal properties of the phytoalexin, (+)-pisatin (**2.375a**). The first reported synthesis of pisatin (**2.375a**) was based on the interconversion of the appropriate isoflavone (**2.367**), which was reduced to the isoflavan-4-ol (**2.368**) and subsequently dehydrated to the corresponding isoflavene [3-phenyl-2*H*-chromene, (**2.370**)], (Scheme 2-28).[85] Osmium tetraoxide dihydroxylation produced a racemic mixture of the corresponding isoflavan-3,4-diol (**2.371**) which, upon esterification with (+)-camphor-10-sulfonyl chloride, was chromatographically resolved to (+)-pisatin (**2.375a**) in 4% overall yield after 8 steps.

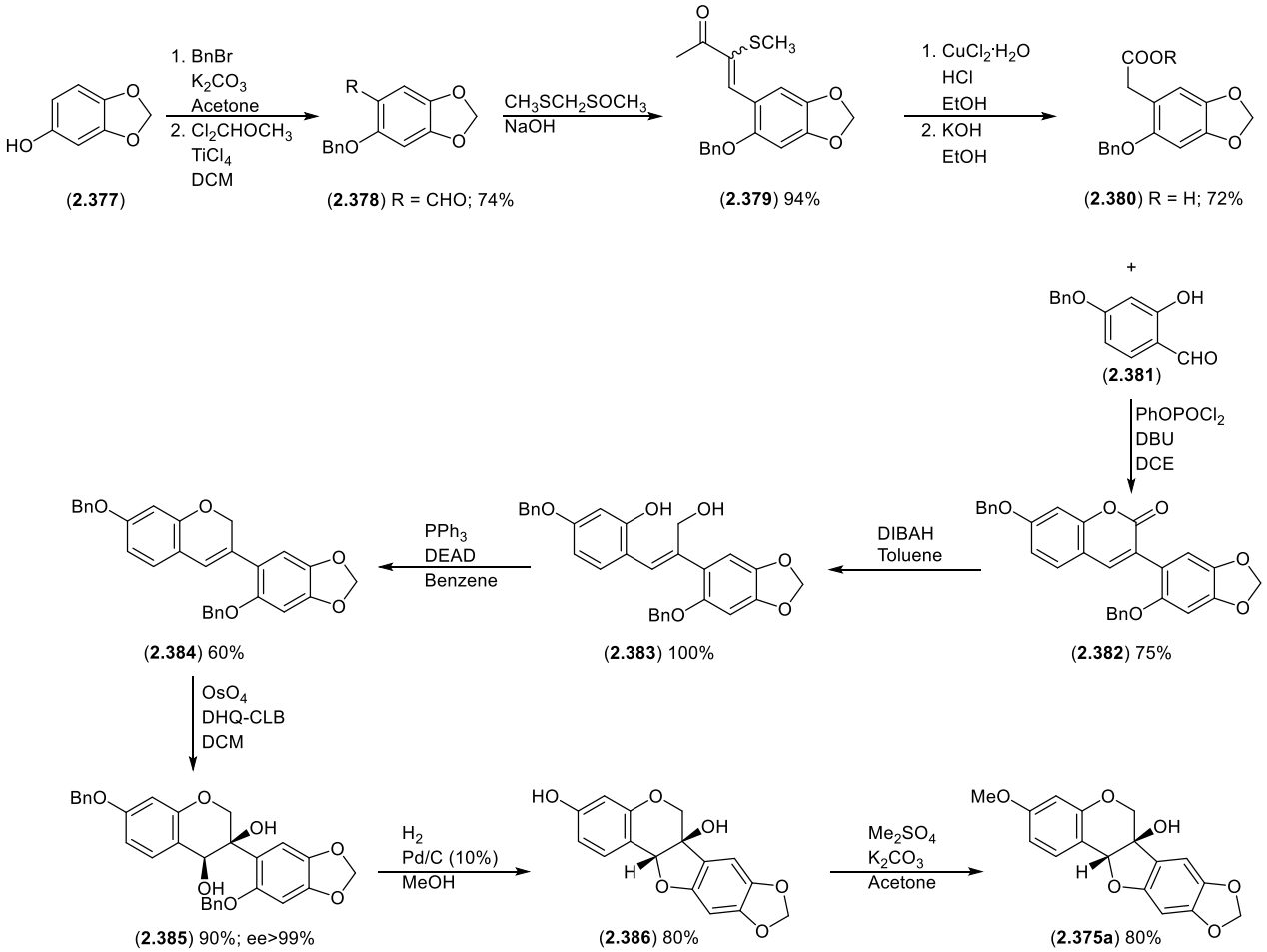


Scheme 2-28: Synthesis of (+)-pisatin (2.375a).

Pinard et al.[86] published the first total enantioselective synthesis of (+)-pisatin (**2.375a**), (Scheme 2-29). Similar to the protocol reported by Mori and Kisida[85] (vide supra), the isoflavan-3,4-diol (**2.371**) was the key intermediate. Pinard et al.,[86] however, did not rely on chromatographic resolution but incorporated dihydroquinine *para*-chlorobenzoate (DHQ-CLB), (**2.376**) as chiral catalyst (Sharpless asymmetric dihydroxylation) to obtain the (3*R*,4*S*)-isoflavan-3,4-diol (**2.385**) in 94% ee. Annulation established the (6a*R*,11a*R*)-pterocarpan (**2.386**), which was methylated to give (+)-pisatin (**2.375a**). Although this approach consisted of 11 steps the overall yield of 13% was much better than what was obtained by Mori and Kisida.

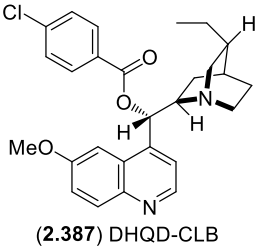


(**2.376**) DHQ-CLB

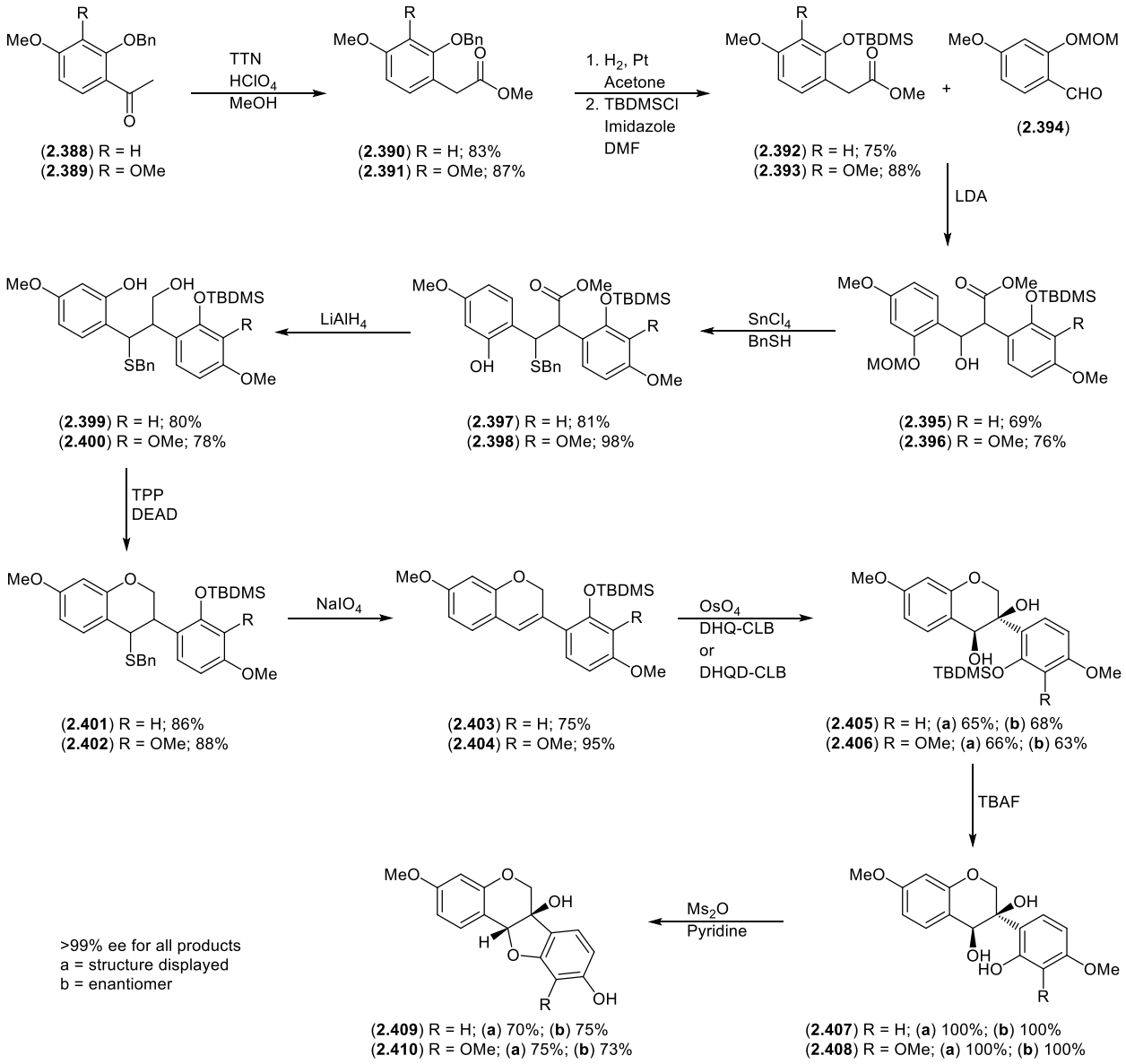


Scheme 2-29: Complete enantioselective synthesis of (+)-pisatin (2.375a).

Ferreira et al.[87] developed methodology based on the aldol reaction between substituted phenylacetates (**2.392** and **2.393**) and benzaldehyde (**2.394**) to, not only allow the synthesis of both enantiomers of the *cis*-6a-hydroxypterocarpan (**2.409a**), but also the less stable[39,87] *trans*-6a-hydroxypterocarpan enantiomers (Scheme 2-30). As with the Pinard methodology chiral induction was achieved by Sharpless asymmetric dihydroxylation of the isoflavene intermediates (**2.403** and **2.404**), (Scheme 2-28). In addition to DHQ-CLB (**2.376**), which gave the (3*R*,4*S*)-isoflavan-3,4-diols (**2.405a** and **2.406a**), dihydroquinidine *para*-chlorobenzoate (DHQD-CLB), (**2.387**), led to the formation of the enantiomeric (3*S*,4*R*)-isoflavan-3,4-diols (**2.405b** and **2.406b**), all in moderate yields (63-68%), but excellent ee values of >99%. Subsequent deprotection and cyclisation established the respective *cis*-6a-hydroxypterocarpan enantiomers **2.409** and **2.410**, which was accompanied by small quantities (ca. 10%) of the *trans*-enantiomers formed as a result of epimerisation at C-4 during the formation of the furan ring.[87]



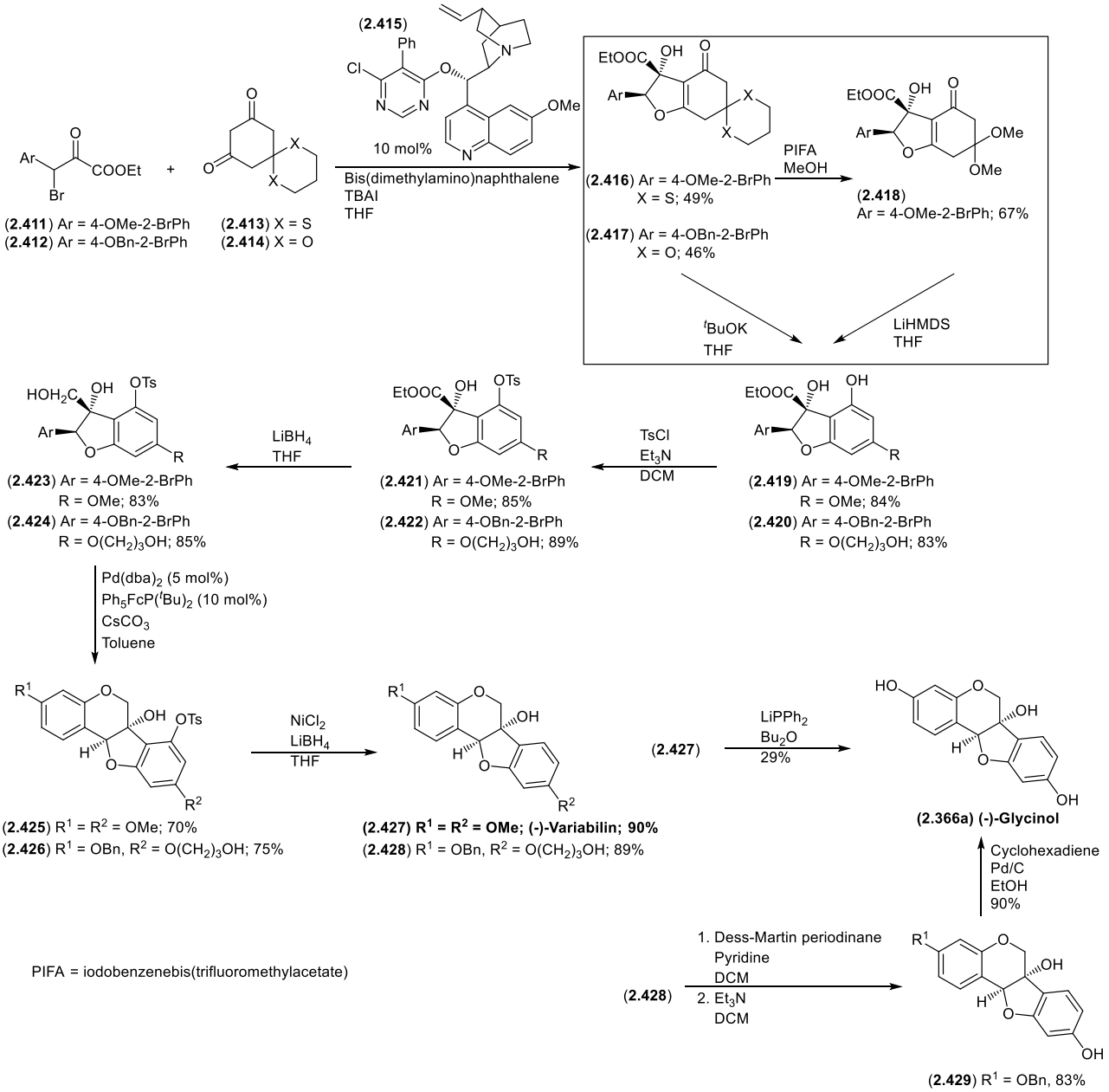
(**2.387**) DHQD-CLB



Scheme 2-30: Synthesis of enantiopure *cis*-6a-hydroxypterocarpans.

Similar to the methodology used for the enantioselective synthesis of pterocarpans (cf. Scheme 2.26), Calter and Li[88] developed a total synthesis for two phytoalexin 6a-hydroxypterocarpan analogues, i.e. (-)-variabilin (**2.427**) and (-)-glycinol (**2.430**), by the initial stereoselective formation of the furanoid unit, which was eventually transformed into the corresponding 6a-hydroxypterocarpan by formation of the six-membered B-ring (Scheme 2-31). The key transformation in this methodology entailed a stereoselective interrupted Feist-Benary reaction between the β-bromo-α-ketoester (**2.411** or **2.412**) and the cyclic thioacetal (**2.413**) or acetal (**2.414**) leading to the substituted dihydrofuranes (**2.416** and **2.417**). While the acetal precursor (**2.417**) is employed for the synthesis of only (-)-glycinol (**2.366a**), the thioacetal (**2.416**) is transformed to (-)-variabilin (**2.427**) but can also yield (-)-glycinol (**2.366a**) following demethylation. Formation of the pterocarpan was achieved via modified Buchwald-Hartwig cross-coupling to yield the (6a*S*,11a*S*)-*cis*-6a-hydroxypterocarpan intermediates (**2.425** and **2.426**). Removal of the 8-tosyloxy

moiety is realised with nickel(II) catalysed $LiBH_4$ reduction gave (-)-variabilin (**2.427**). Ether hydrolysis and debenzylation converted **2.428** into (-)-glycinol (**2.366a**) in 75% yield over the two steps. Alternatively, (-)-glycinol (**2.366a**), could be obtained by demethylation of (-)-variabilin (**2.427**), albeit in low yield (29%). This methodology thus allowed for the synthesis of (-)-variabillin (**2.427**) and (-)-glycinol (**2.366a**) in overall yields of 12% and 14%.



Scheme 2-31: Synthesis of (-)-variabilin (2.427) and (-)-glycinol (2.366a).

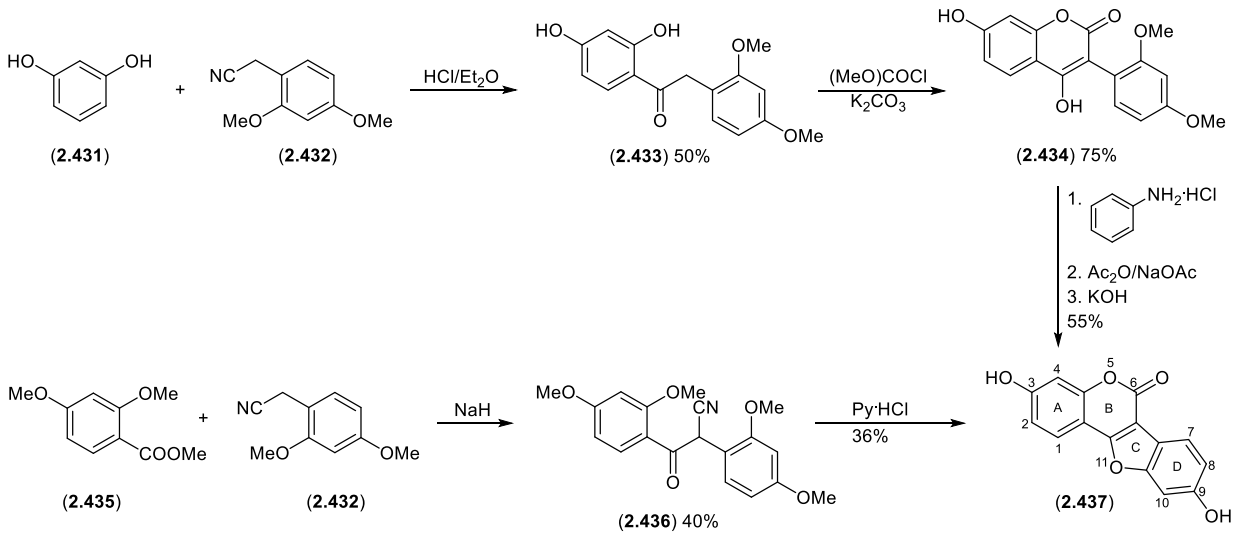
2.5. Coumestans

Even though coumestans may be considered as fully oxidised pterocarpans, the syntheses of these two classes of compounds differ considerably. Whereas pterocarpans are most commonly prepared from isoflavones, isoflavanones, isoflavans or 2*H*-chromene derivatives (cf. paragraph 2.4.1.),

construction of the coumestan skeleton is often established via deoxybenzoin or coumarin intermediates. In addition to these methodologies a number of alternative approaches have also been developed.

2.5.1. Deoxybenzoin and coumarin methodologies

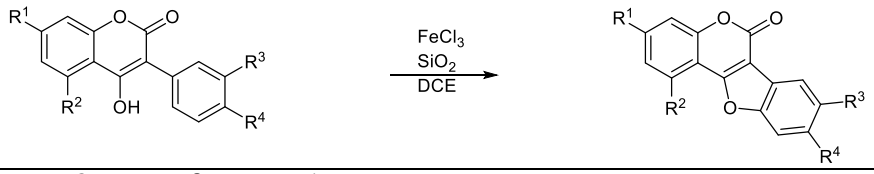
One of the first syntheses of naturally occurring coumestrol (**2.437**), a phytochemical with estrogenic properties,[89] by Emerson and Bickoff[90] proceeded through the deoxybenzoin intermediate (**2.433**) which was treated with dimethylcarbonate (or ethylchloroformate)[91] to afford 3-aryl-4-hydroxycoumarin (**2.434**) in 75% yield (Scheme 2-32).[92] Although demethylation and ring closure toward the coumestan skeleton could be achieved with hydriodic acid,[91] aniline hydrochloride was found to be more effective.[90] Acetylation of the 4-hydroxy function followed by treatment of the intermediate coumestryl acetate with base, yielded coumestrol (**2.437**) in 55% from the coumarin precursor (**2.434**), resulting in an overall yield of 21%.[92,93] Kawase[94] prepared the cyanodeoxybenzoin (**2.436**) instead and was able to convert it (**2.436**) into coumestrol (**2.437**) in a single step with pyridinium hydrochloride in an overall yield of 14% (Scheme 2-32).[92]



Scheme 2-32: The first synthesis of coumestrol (2.437).

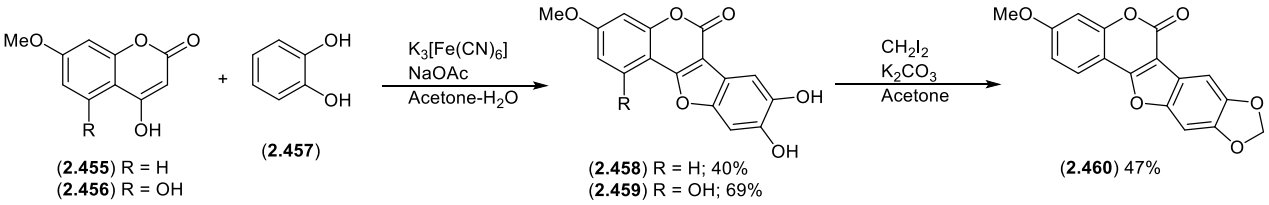
Zhao et al.[95] developed a general set of reaction conditions for constructing the coumestan skeleton from 3-aryl-4-hydroxycoumarin derivatives (Table 2-10). The ferric chloride-silicon oxide system does not require an *ortho* oxygen on the aryl substituent to allow formation of the furan ring. A postulated radical mechanism affords ring closure for a range of oxygenated analogues in moderate to high yields (50-89%), with the exception of 1-methoxy derivatives **2.453** (32%) and **2.454** (33%) in which case the yields decreased significantly.

Table 2-10: Convertion of 3-aryl-4-hydroxycoumarins into coumestans.



Entry	R^1	R^2	R^3	R^4	2*H*-Chromen-2-one	Coumestans	Yield (%)
1	H	H	H	H	(**2.438**)	(**2.8**)	60
2	H	H	H	OMe	(**2.439**)	(**2.447**)	89
3	H	H	H	Cl	(**2.440**)	(**2.448**)	87
4	H	H	OMe	OMe	(**2.441**)	(**2.449**)	86
5	H	OMe	H	H	(**2.442**)	(**2.450**)	64
6	OMe	H	H	OMe	(**2.443**)	(**2.451**)	70
7	OMe	H	OMe	OMe	(**2.444**)	(**2.452**)	50
8	OMe	OMe	H	OMe	(**2.445**)	(**2.453**)	32
9	OMe	OMe	OMe	OMe	(**2.446**)	(**2.454**)	33

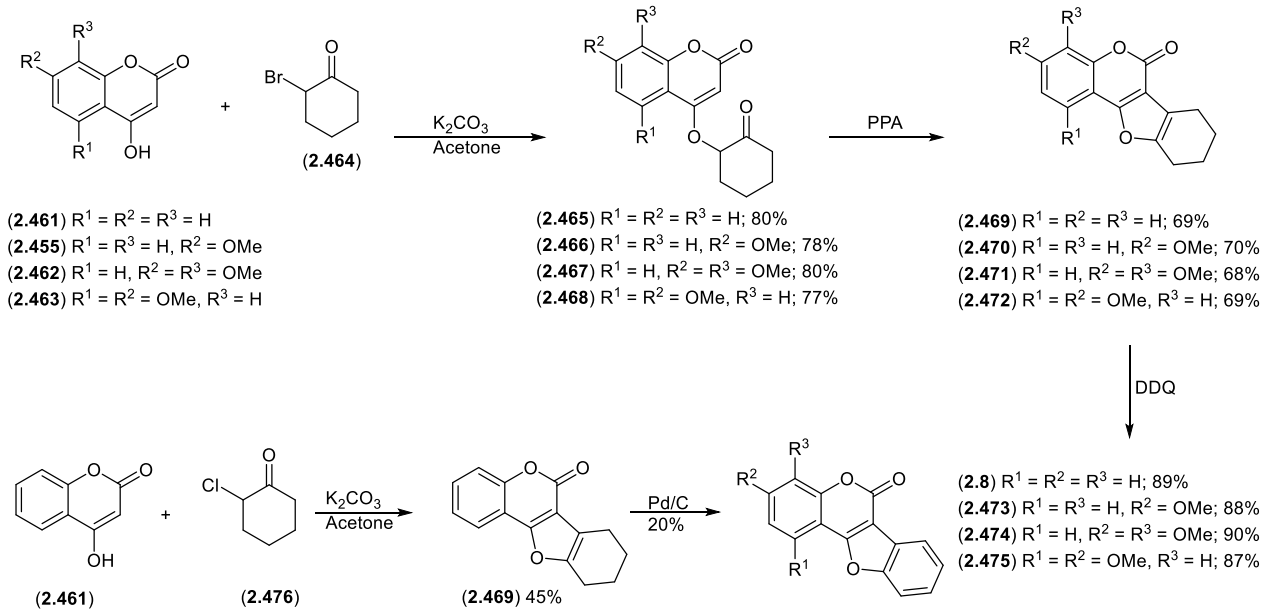
Naturally occurring wedelolactone (**2.459**) and pterocarpin (**2.460**) were respectively prepared by Wanzlick et al.[96] and Fukui et al.[97] via dehydrogenatic condensation from 4-hydroxycoumarin (**2.455** and **2.456**) and catechol (**2.457**), (Scheme 2-33). The condensation is postulated to occur via a double conjugate addition by the coumarin 3-carbon and 4-hydroxy onto the benzoquinone tautomer of the catechol unit.[96] The yield of 40% for **2.458** versus 69% for **2.459** suggests this protocol to be substrate dependent which may translate to limited scope. Pterocarpin (**2.460**) was obtained in 19% overall yield after additional methylenation of the catechol moiety (**2.458**).



Scheme 2-33: Pterocarpin (2.460) *via* dehydrogenatic condensation.

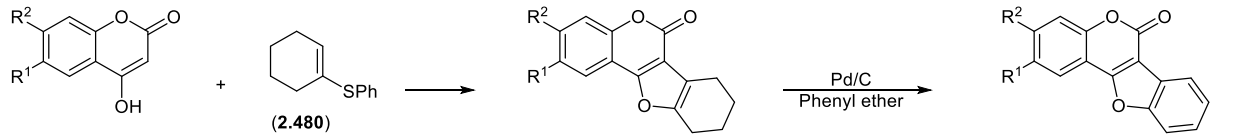
4-Hydroxycoumarins can also be coupled with 2-halocyclohexanones wherein substitution of the halide with the 4-hydroxy unit allows for an intramolecular Claisen-Schmidt type condensation to establish the furan ring (tetrahydrocoumestan), (Scheme 2-34). Dehydrogenation of the original cyclohexanone ring introduces aromaticity to yield coumestans as the final products. Darbarwar et al.[98] reacted 2-chlorocyclohexanone (**2.476**) with 4-hydroxycoumerin (**2.461**) over K_2CO_3 and obtained the tetrahydrocoumestan (**2.469**) in one pot in 45% yield. Subsequent dehydrogenation was achieved with 10% Pd/C to yield 20% unsubstituted coumestan (**2.8**) which translated to a low overall yield (9%). Singh and Singh et al.[99] greatly improved this methodology with three major adjustments: a) the 2-chlorocyclohexanone (**2.476**) was substituted for its bromo counterpart (**2.464**), b) the coupling and cyclisation was effected over two steps, the latter with polyphosphoric

acid (PPA), and c) the oxidation was performed with DDQ. Four coumestans (**2.8**, **2.473-2.475**) were obtained in high yield (68-90%) by employing this strategy. When unsubstituted coumestan (**2.8**) is considered, this methodology is significantly superior with an overall yield of 49% compared to 9% for the Darbarwar protocol.



Scheme 2-34: Synthesis of coumestans from 4-hydroxycoumarins and 2-halocyclohexanones.

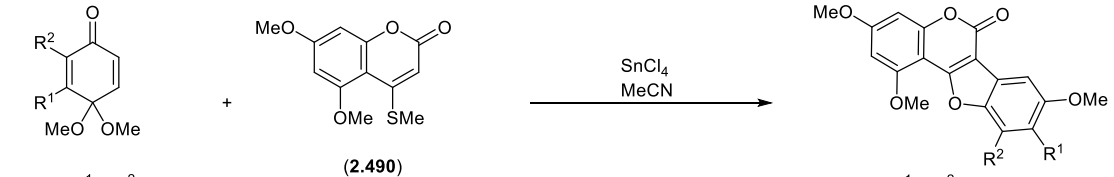
The reaction between 4-hydroxycoumarins (**2.461**, **2.477-2.479**) and vinyl sulfide (**2.480**) in the presence of Fetizon's reagent (Ag_2CO_3/celite) was later reported for the preparation of tetrahydrocoumestans (**2.469**, **2.481-2.483**) in a one-step process (Scheme 2-35).[100] The tetrahydrocoumestan yields for this step were comparable to those obtained with the Singh protocol (vide supra) although compounds displaying different substitution patterns were prepared. The dehydrogenation with palladium on carbon were considerably more efficient when compared to the results obtained by Darbarwar (vide supra), but slightly lower than what was reported by Singh and Singh for DDQ, (cf. Scheme 2.34).



Scheme 2-35: Synthesis of coumestans via tetrahydrocoumestans utilizing a vinyl sulfide.

A single step Lewis acid catalysed protocol for the construction of coumestans has been reported by Liu et al.[101] When 4-thiomethylcoumarin (**2.490**) and the methylketal of benzoquinones (**2.487-2.489**) were combined in the presence of $SnCl_4$, the corresponding coumestans (**2.491**, **2.492** and

2.454) were obtained in less than 60 minutes at ambient temperature (Scheme 2-36). Although moderate to good yields (63-67%) are observed, the presence of a 5-methoxy substituent on the coumarin is often detrimental to coumestan formation. The protocol is, however, limited to the production of 8-alkoxycoumestans as the one ether moiety of the ketal is retained in the final product.



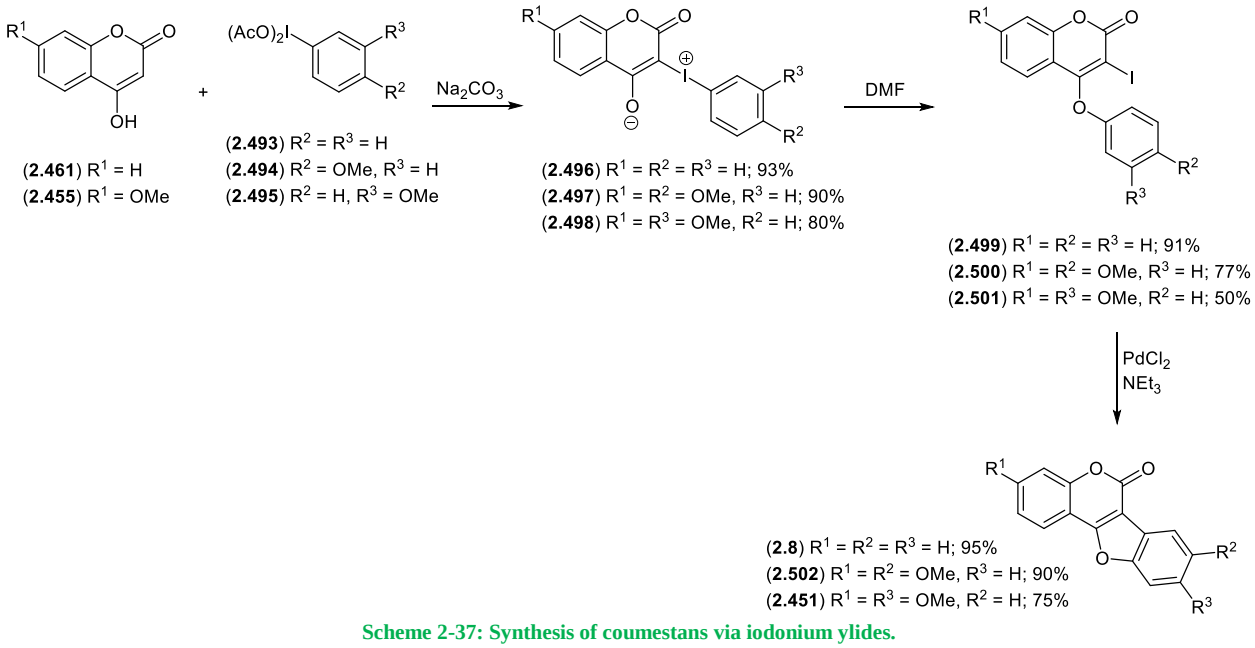
(**2.487**) $R^1 = R^2 = H$
(**2.488**) $R^1 = H$, $R^2 = CH_3$
(**2.489**) $R^1 = OMe$, $R^2 = H$

(**2.490**)

(**2.491**) $R^1 = R^2 = H$; 63%
(**2.492**) $R^1 = H$, $R^2 = CH_3$; 64%
(**2.454**) $R^1 = OMe$, $R^2 = H$; 67%

Scheme 2-36: $SnCl_4$ catalyzed synthesis of coumestans.

Lashober and Kappe[102] were first to report intramolecular Heck cross-coupling for the construction of the furan ring of coumestans. Base assisted coupling between 4-hydroxycoumarins (**2.455** and **2.461**) and (diacetoxy)iodobenzenes (**2.493-2.495**) rendered iodonium ylides (**2.496-2.498**), which could be transformed into the 4-aryloxy-3-iodocoumarins (**2.499-2.501**) by Smiles rearrangement (Scheme 2-37). Formation of the furan ring was realised by treatment with $PdCl_2$ to establish the coumestans (**2.8**, **2.451** and **2.502**). Even though an overall yield of 80% was achieved during the preparation of unsubstituted coumestan (**2.8**), the presence of additional methoxy substituents appear to have a negative effect on the yields with **2.451** and **2.502** being obtained in only 30% and 62% overall yield, respectively.



(**2.461**) $R^1 = H$
(**2.455**) $R^1 = OMe$

(**2.493**) $R^2 = R^3 = H$
(**2.494**) $R^2 = OMe$, $R^3 = H$
(**2.495**) $R^2 = H$, $R^3 = OMe$

(**2.496**) $R^1 = R^2 = R^3 = H$; 93%
(**2.497**) $R^1 = R^2 = OMe$, $R^3 = H$; 90%
(**2.498**) $R^1 = R^3 = OMe$, $R^2 = H$; 80%

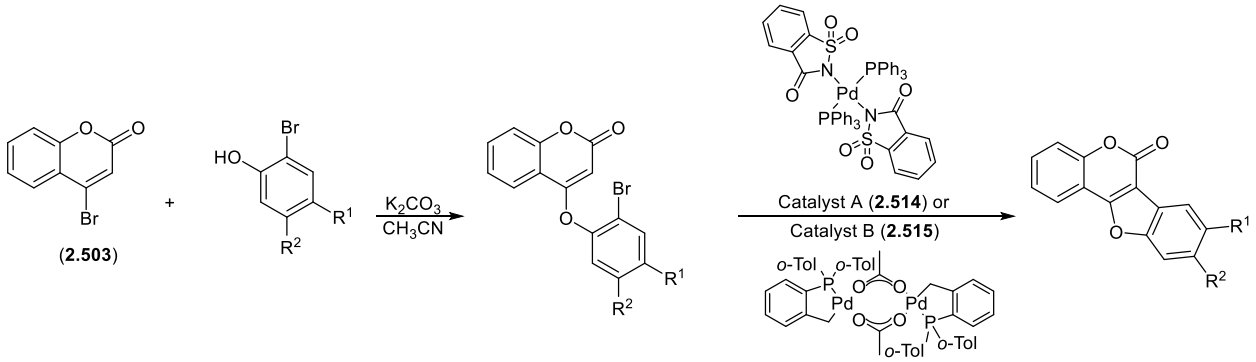
(**2.499**) $R^1 = R^2 = R^3 = H$; 91%
(**2.500**) $R^1 = R^2 = OMe$, $R^3 = H$; 77%
(**2.501**) $R^1 = R^3 = OMe$, $R^2 = H$; 50%

(**2.8**) $R^1 = R^2 = R^3 = H$; 95%
(**2.502**) $R^1 = R^2 = OMe$, $R^3 = H$; 90%
(**2.451**) $R^1 = R^3 = OMe$, $R^2 = H$; 75%

Scheme 2-37: Synthesis of coumestans via iodonium ylides.

Although the halide utilized for the Heck coupling was located on the coumaryl moiety of the aryl coumaryl ether in the Lashober and Kappe protocol, it may also reside on the aryl substituent. Kapdi and co-workers[103,104] demonstrated this with the synthesis of a number of substituted coumestans, in which the 4-(2-bromoaryloxy)coumarin precursors (**2.509-2.513**) were prepared from the corresponding 4-bromocoumarin (**2.503**) and 2-bromophenols (**2.504-2.508**) under alkaline conditions (76-92% yield), (Table 2-11). Although two preformed palladium catalysts, **2.514** and **2.515**, were evaluated for the cross-coupling reaction, both produced the corresponding coumestan in >80% yield, but the Hermann-Beller catalyst (**2.515**) was found to be superior for unsubstituted (entry 1 vs. 2), 8-methyl- (entry 3 vs. 4) and 8-chlorocoumestan (entry 5 vs. 6). The cross-coupling reaction for the formation of the 8-fluorocoumestan (entry 7) also proceeded smoothly (98% yield), however, oxygenation on the D-ring in the case of 8,9-dimethoxycoumestan caused a decrease in yield to 60% (entry 8), which indicates a limitation in the substrate scope. A one-pot transformation of 4-chlorocoumarin and 2-bromophenol (**2.509**) directly to unsubstituted coumestan (**2.8**) was also attempted under microwave conditions, but only 60% yield (vs. 97% for the conventional heating process, entry 2) over the two steps were obtained.

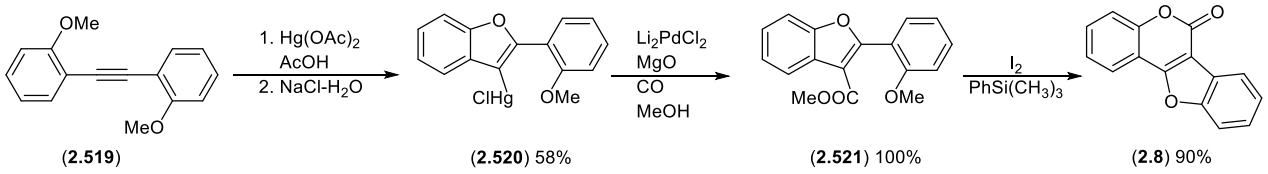
Table 2-11: Synthesis of coumestans utilizing Pd-catalysts 2.514 and 2.515.



Entry	R^1	R^2	2-Bromophenol	4-(2-bromoaryloxy)coumarin	Yield (%)	Coumestan	Catalyst	Yield (%)
1	H	H	(**2.504**)	(**2.509**)	92	(**2.8**)	A	80
2	H	H	(**2.504**)	(**2.509**)	92	(**2.8**)	B	97
3	Me	H	(**2.505**)	(**2.510**)	82	(**2.516**)	A	83
4	Me	H	(**2.505**)	(**2.510**)	82	(**2.516**)	B	95
5	Cl	H	(**2.506**)	(**2.511**)	76	(**2.517**)	A	89
6	Cl	H	(**2.506**)	(**2.511**)	76	(**2.517**)	B	97
7	F	H	(**2.507**)	(**2.512**)	81	(**2.518**)	B	98
8	OMe	OMe	(**2.508**)	(**2.513**)	68	(**2.449**)	B	60

2.5.2. Alkyne and alkene based methods

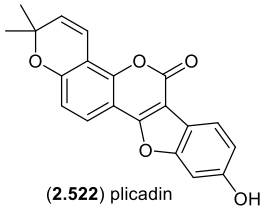
The transformation of 1,2-diphenylacetylenes and stilbenes (1,2-diphenylethenes) into coumestans have also been reported. Larock and Harrison[105] in this regard, performed intramolecular solvomercuration of the 2,2'-dimethoxydiphenylacetylene (**2.519**) leading to the heterocyclic organomercurial (**2.520**), which could be methoxycarbonylated and subjected to demethylative annulation to produce the unsubstituted coumestan (**2.8**) in 52% overall yield (Scheme 2-38).



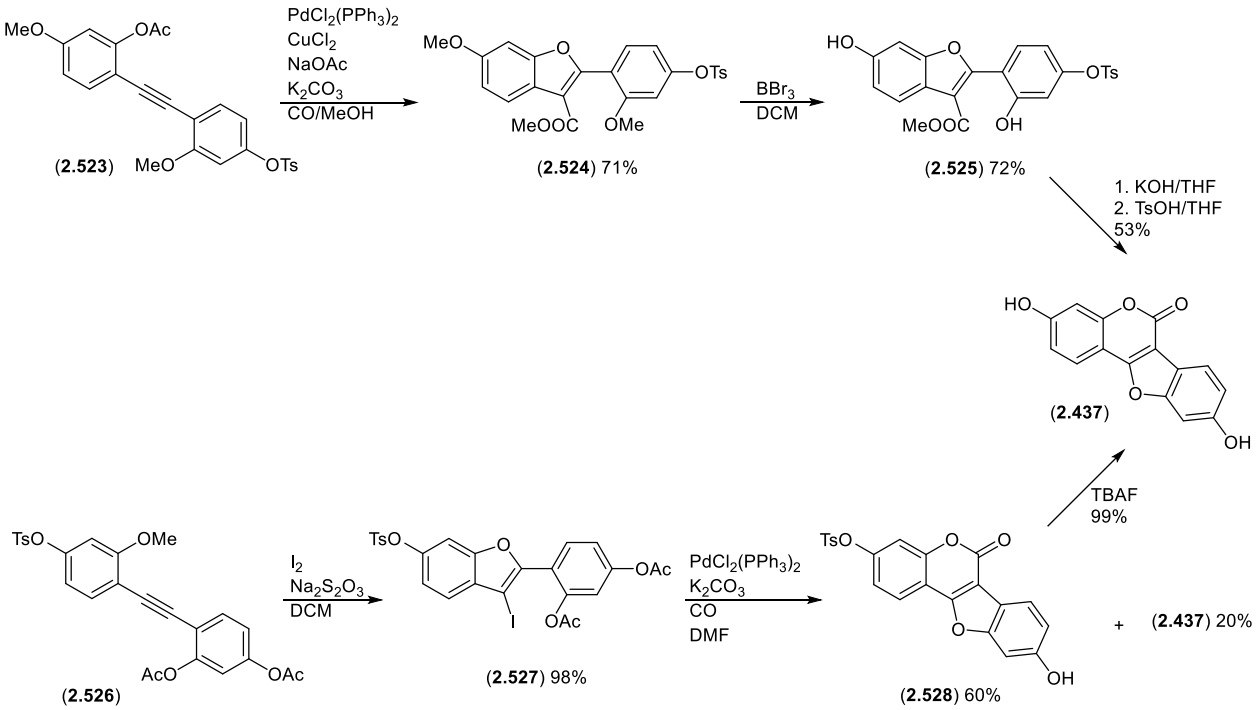
(**2.519**) (**2.520**) 58% (**2.521**) 100% (**2.8**) 90%

Scheme 2-38: Synthesis of coumestan (2.8) from a diphenylacetylene precursor (2.519).

Two methodologies, both employing palladium catalysed carbonylation, were developed by Sakamoto et al.[106] and Larock et al.[107] for the synthesis of coumestrol (**2.437**), (Scheme 2-39). Methoxycarbonylation of substituted 1,2-diphenylacetylene (**2.523** or **2.526**) were used by Sakamoto[106] to produce the benzofuryl carboxylate (**2.524**) in 71% yield, whereas Larock[107] utilized iodine to obtain the 3-iodobenzofuran derivative (**2.527**) in 98% yield. Sakamoto established the B-ring via intramolecular transesterification following demethylation of the carboxylate intermediate (**2.524**), while Larock subjected 3-iodobenzofuran (**2.527**) to carbonylative lactonisation to obtain the 3-*O*-tosyloxycoumestrol (**2.528**) in 60% yield together with coumestrol (**2.437**) in 20% yield. The Sakamoto and Larock routes thus produced coumestrol (**2.437**) in 27% and 58% overall yield, respectively. A similar trend was observed for the production of unsubstituted coumestan (**2.8**) with the same methodologies in overall yields of 24% and 93%. Although the Larock methodology is highly efficient only coumestan (**2.8**), coumestrol (**2.437**) and plicadin (**2.522**, 45% yield) were prepared in this way from the corresponding 1,2-diphenylacetylene.

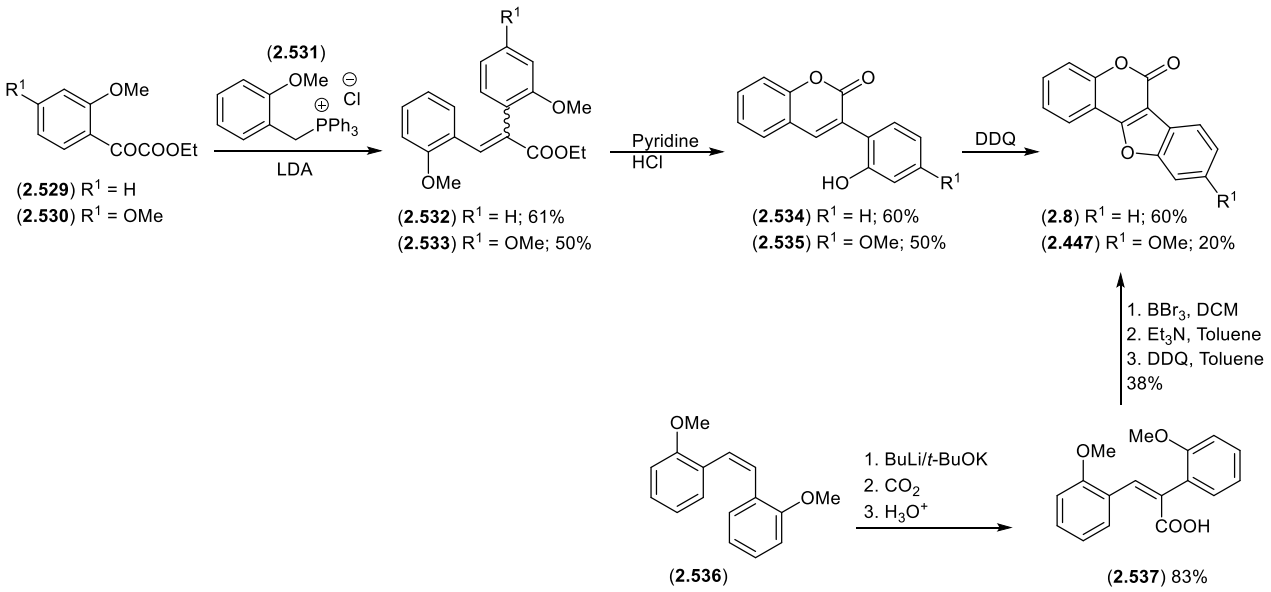


(**2.522**) plicadin



Scheme 2-39: Synthesis of coumestrol (2.437) *via* a diphenylacetylene intermediate.

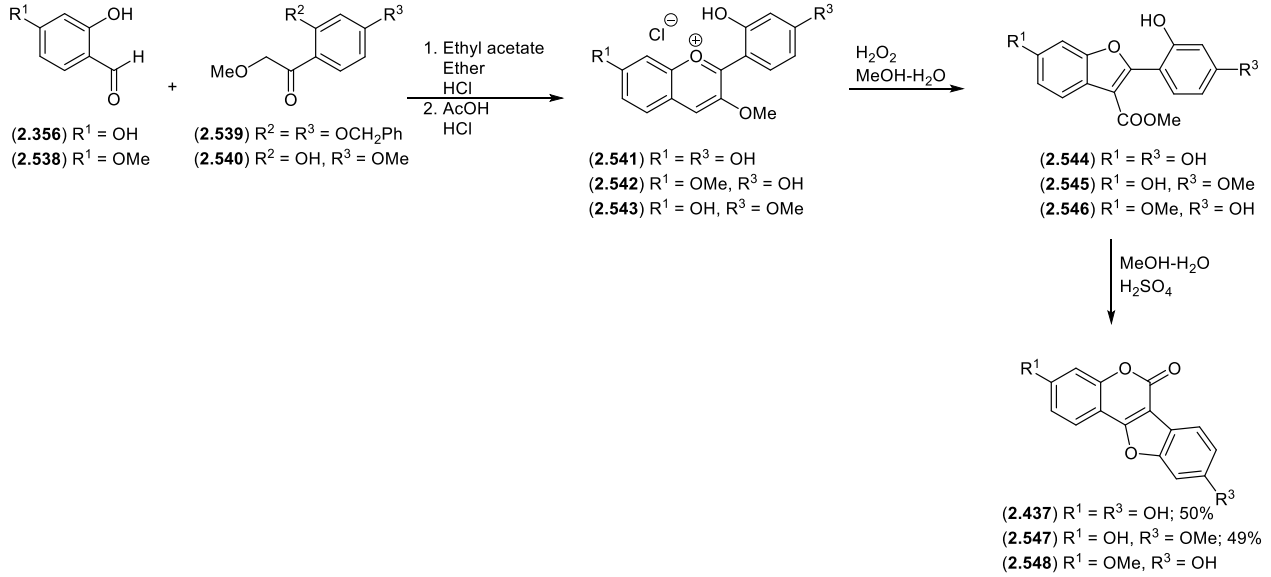
Similar to the protocol for the synthesis of pterocarpans (cf. paragraph 2.4.1.), Mali and Tilve[108] utilized stilbene carboxylates (**2.532** and **2.533**) as precursors to prepare the 3-arylcoumarins (**2.534** and **2.535**) in 60% and 50%, respectively (Scheme 2-40). Treatment of the latter with DDQ afforded unsubstituted coumestan (**2.8**) and 9-methoxycoumestan (**2.447**) in overall yields of 22% and 5%. O'Shea et al.[109] followed a similar approach but employed the stilbene carboxylic acid (**2.537**) instead of the ester (**2.532**), (Scheme 2-40). *Cis*-2,2'-dimethoxystilbene (**2.536**) was carboxylated by means of directed vinyl lithiation followed by quenching with CO_2 and aqueous acid and demethylation with BBr_3 where after the crude product was treated with base and DDQ without isolating any intermediate. Although the overall yield for this method proved to be only 38%, it compares well with the overall yield (36%) for the final two steps in the Mali protocol (vide supra).



Scheme 2-40: Synthesis of coumestans utilizing stilbenes.

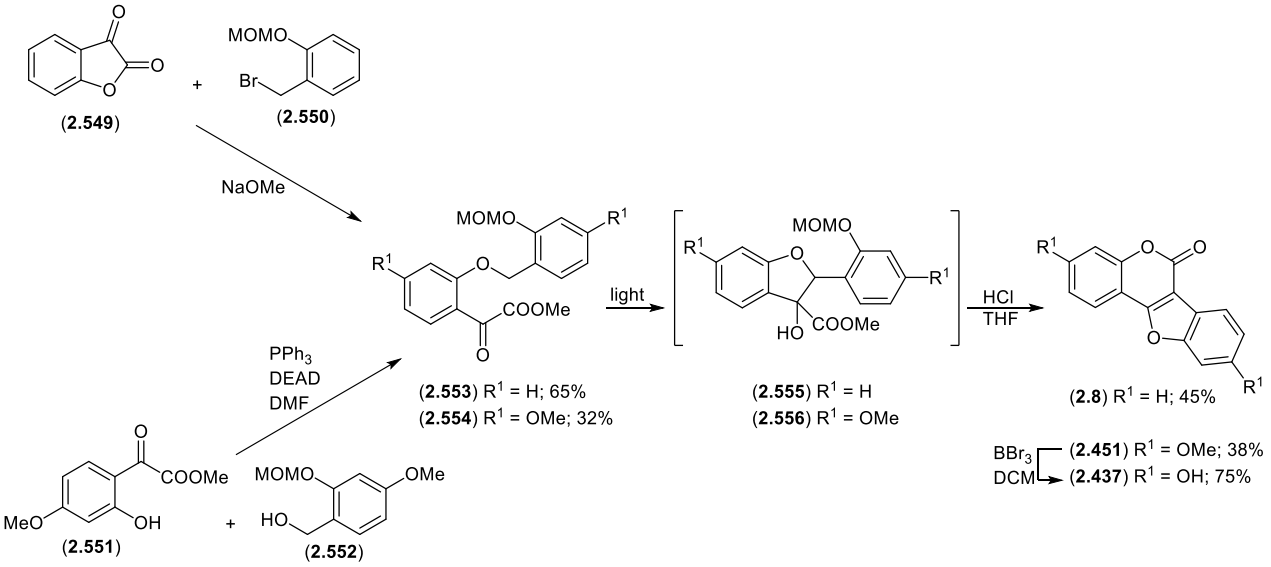
2.5.3. Miscellaneous methods

The synthesis of coumestrol (**2.437**) and its 3- and 9-*O*-methyl analogues (**2.547** and **2.548**) were approached via the flavylium salts (**2.541-2.543**), which became available by aldol condensation between the 2-methoxyacetophenones (**2.539** and **2.540**) and the benzaldehydes (**2.356** and **2.538**), (Scheme 2-41).[110,111] Treatment of the flavylium salts (**2.541-2.543**) with methanoic hydrogen peroxide induced oxidative aryl migration toward intermediary 3-carbomethoxybenzofuran (**2.544-2.546**) which underwent rapid lactonisation upon acidification to render the coumestans (**2.437**, **2.547** and **2.548**) in moderate yields (ca. 50%).



Scheme 2-41: Synthesis of coumestans *via* flavylium salts.

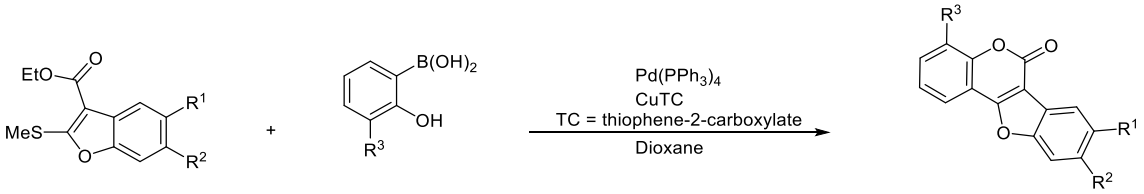
Kraus and Zhang[112] developed methodology for the synthesis of coumestan (**2.8**) and coumestrol (**2.437**) based on the preparation of the benzylated phenylglyoxylate intermediates (**2.553** and **2.554**), followed by photochemical formation of the 3-aryldihydrobenzofuran moieties (**2.555** and **2.556**), (Scheme 2-42). Treatment of the 3-aryldihydrobenzofurans with acid gave coumestan (**2.8**) and coumestrol (**2.437**) in 29% and 9% overall yields, respectively. The glyoxylate key intermediates (**2.553** and **2.554**) may be prepared from the benzylalcohol (**2.552**) and phenylglyoxylate (**2.551**) under Mitsunobu conditions or by coupling the benzyl bromide (**2.550**) with 2,3-dihydro-2,3-dioxobenzofuran (**2.549**).



Scheme 2-42: Synthesis of coumestans via glyoxylates as key intermediates.

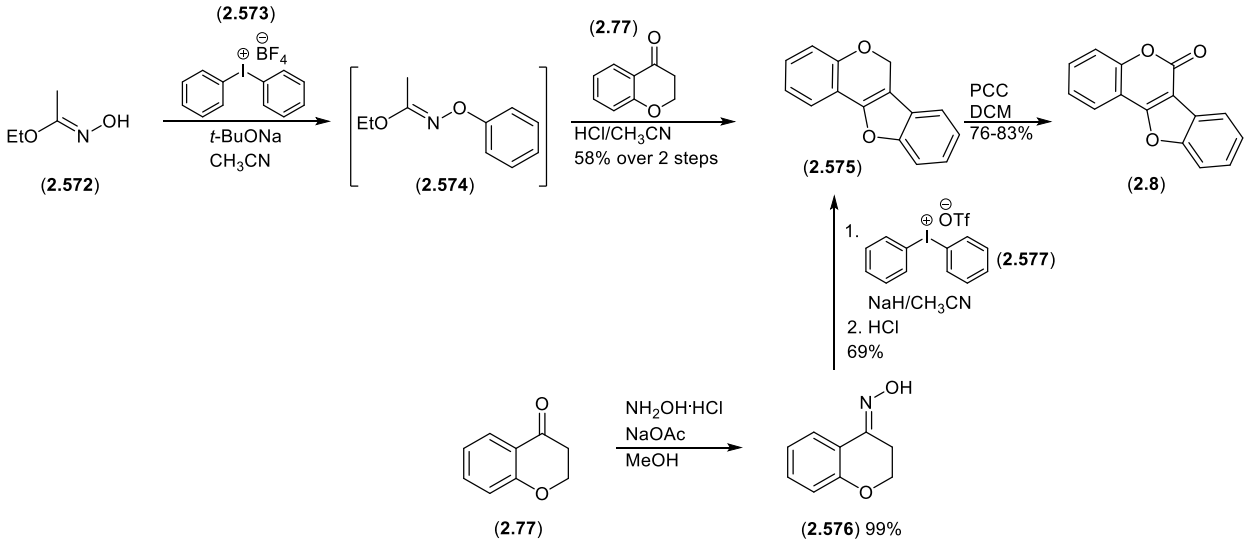
Novel methodology towards the preparation of a series of coumestans (**2.564-2.571**) has been published by Liu et al.[113] This one-step process relies on a [3+3] annulation process where the initial cross-coupling between 4-ethylcarboxy-3-thiomethylbenzofurans (**2.557-2.559**) and phenylboronic acids (**2.560-2.563**) over a $Pd(PPh_3)_4$/CuTC [Cu(I) thiophene-2-carboxylate] system was followed by intramolecular transesterification under Liebeskind-Srogl conditions to give the coumestan products (**2.564-2.571**) in moderate to good yields (48-72%), (Table 2-12).

Table 2-12: Synthesis of coumestans utilizing a Pd/Cu system.



Entry	R^1	R^2	methylthiobenzofuran	R^3	hydroxyphenylboronic acid	Coumestan	Yield (%)
1	OH	H	(**2.557**)	H	(**2.560**)	(**2.564**)	70
2	OMe	H	(**2.558**)	H	(**2.560**)	(**2.565**)	66
3	OMe	OMe	(**2.559**)	H	(**2.560**)	(**2.449**)	57
4	OH	H	(**2.557**)	OMe	(**2.561**)	(**2.566**)	66
5	OMe	H	(**2.558**)	Me	(**2.562**)	(**2.567**)	72
6	OMe	H	(**2.558**)	Br	(**2.563**)	(**2.568**)	48
7	OMe	OMe	(**2.559**)	OMe	(**2.561**)	(**2.569**)	52
8	OMe	OMe	(**2.559**)	Me	(**2.562**)	(**2.570**)	59
9	OMe	OMe	(**2.559**)	Br	(**2.563**)	(**2.571**)	55

Olofsson et al.[114] and Togo et al.[115] independently reported the most recent synthesis routes for unsubstituted coumestan (**2.8**), (Scheme 2-43). Both methodologies employed diaryliodium salts (**2.573** and **2.577**) as arylating agents for acetohydroxamate (**2.572**) and hydroxylamine (**2.576**), respectively, to yield the pterocarpene (**2.575**). Final PCC [$(C_5H_5NH)(CrO_3Cl)$] oxidation of the latter produced unsubstituted coumestan (**2.8**). The Olofsson route entailed formation of an *O*-aryl hydroxylamine (**2.576**) as first step followed by condensation with 4-chromanone (**2.77**) to the pterocarpene (**2.575**). Although these routes are closely related, the overall yield for the Olofsson methodology was 44% whereas the Togo route produced the unsubstituted coumestan (**2.8**) in 57% yield. Even though the coumestan framework was obtained in moderate yield for both methodologies, only unsubstituted coumestan (**2.8**) was prepared whereas substituted derivatives are generally desired.



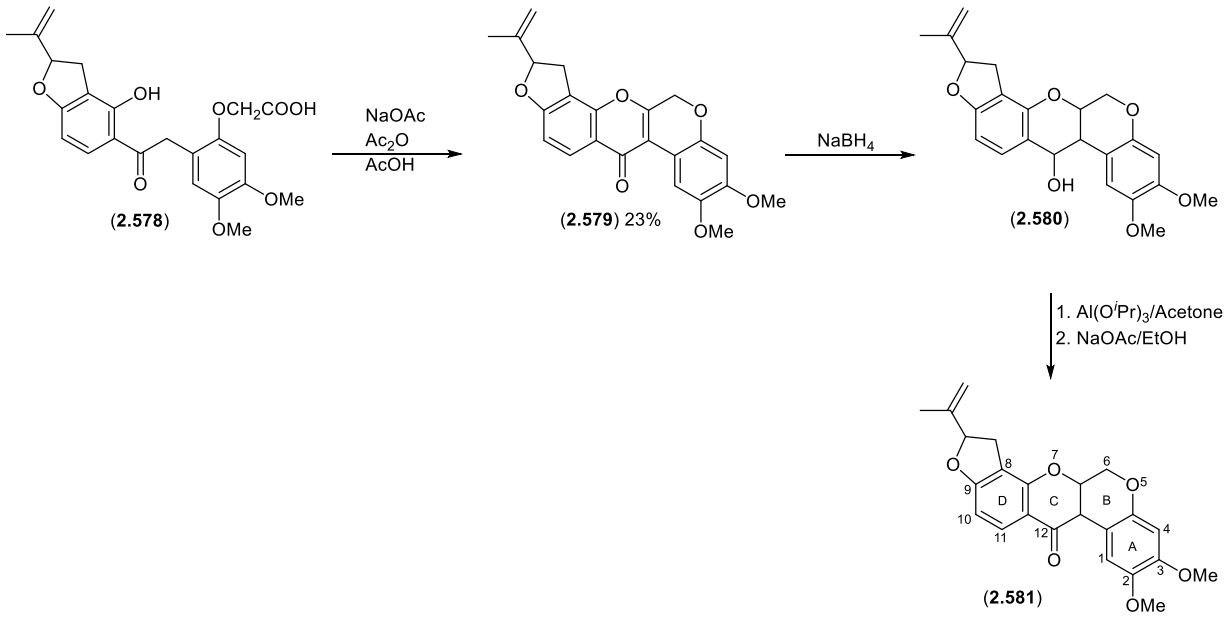
Scheme 2-43: Most recent synthesis of coumestan.

Although various methodologies are discussed, several are limited in their scope and consequently in their applicability toward the preparation of substituted coumestans, e.g. naturally occurring coumestans which generally have oxygenated substitution patterns. In summary, the three step Larock methodology (cf. Scheme 2-38) produced biologically important coumestrol (**2.8**) in the highest yield (58%) when compared to other methodologies. Natural coumestans, wedelolactone and pterocarpin, can be obtained via the Wanslick and Fukui route (cf. Scheme 2-33) in 69% (1 step) and 19% (2 steps), respectively. The most proficient methodologies toward coumestans with oxygenation on both A- and D-rings are those of Zhao (cf. Table 2-10), Liu (cf. Scheme 2-35 and Table 2-12) and Jurd (cf. Scheme 2-36). The iodonium ylide approach by Jurd displayed moderate overall yields (30-62% over 3 steps) but was only applied in the synthesis of two derivatives. Although the $SnCl_4$ transformation reported by Liu (cf. Scheme 2-35) showed promise (ca. 65% yield), the benzoquinone methylketal starting material limits the scope of the reaction to 8-methoxycoumestan analogues. Lui's Pd/Cu cross coupling annulation (cf. Table 2-12), on the other hand, has proven effective for nine derivatives in moderate yield (48-72%). Zhao's $FeCl_3/SiO_2$ conditions also proved proficient for the preparation of a range of substituted coumestans (32-89%). Although these single step transformations reported by Liu and Zhao appear promising, obtaining the respective starting materials, i.e. 4-ethylcarboxy-3-thiomethylbenzofurans and 3-aryl-4-hydroxycoumarins, are not considered and may pose an additional challenge.

2.6. Rotenoids

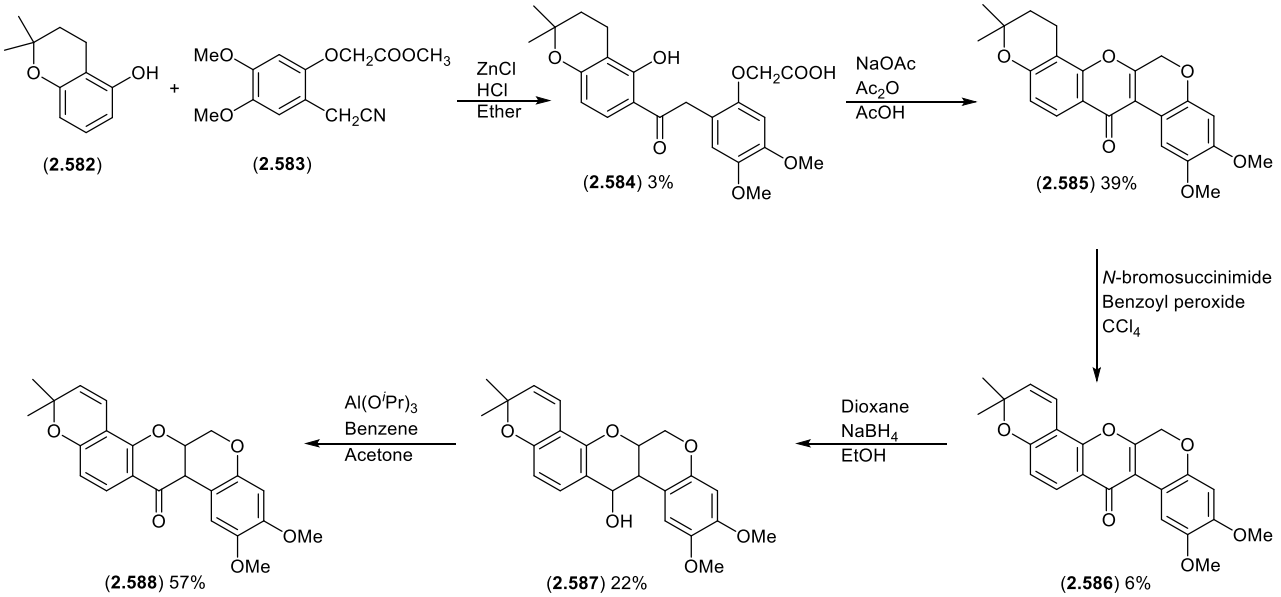
2.6.1. Synthesis of racemic rotenoids

Owing to the insecticidal properties of the rotenoids, rotenone (**2.581**) became the first rotenoid to receive attention as a synthetic target.[116] Initial attempts at the preparation of this compound followed the isoflavone-isoflavanone approach, i.e. addition of a C-1 moiety to the α-position of a suitably substituted deoxybenzoin (cf. paragraph 2.1.1). The deoxybenzoin, derrisic acid (**2.578**), obtained in 7 steps, was therefore subjected to treatment with sodium acetate in a mixture of acetic anhydride and acetic acid which led to intramolecular cyclisation to the unsaturated rotenoid, dehydrorotenone (**2.579**), in 23% yield (Scheme 2-44).[117,118,119,120] Subsequent $NaBH_4$ reduction gave the rotenol (**2.580**), which was transformed into rotenone (**2.581**) by Oppenauer oxidation.



Scheme 2-44: Synthesis of rotenone (2.581).

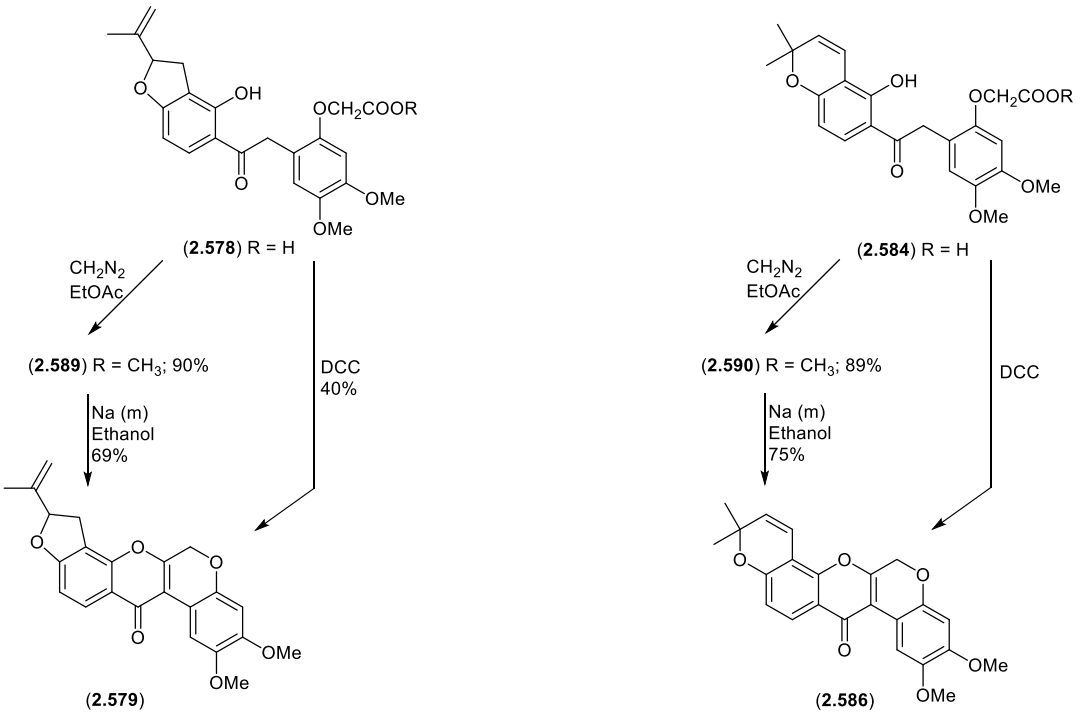
The preparation of the structurally related deguelin (**2.588**) was accomplished in a similar fashion by treating dihydrodeguelinic acid (**2.584**) with the sodium acetate reagent system to form the unsaturated rotenoid, dihydrodehydrodeguelin (**2.585**), in 39% yield (Scheme 2-45).[121] Introduction of the allylic double bond (**2.586**) was achieved through sequential *N*-bromosuccinimide (NBS) bromonation and benzoyl peroxide dehydrobromination, after which $NaBH_4$ reduction and Oppenauer oxidation produced deguelin (**2.588**).



Scheme 2-45: Synthesis of deguelin (2.588).

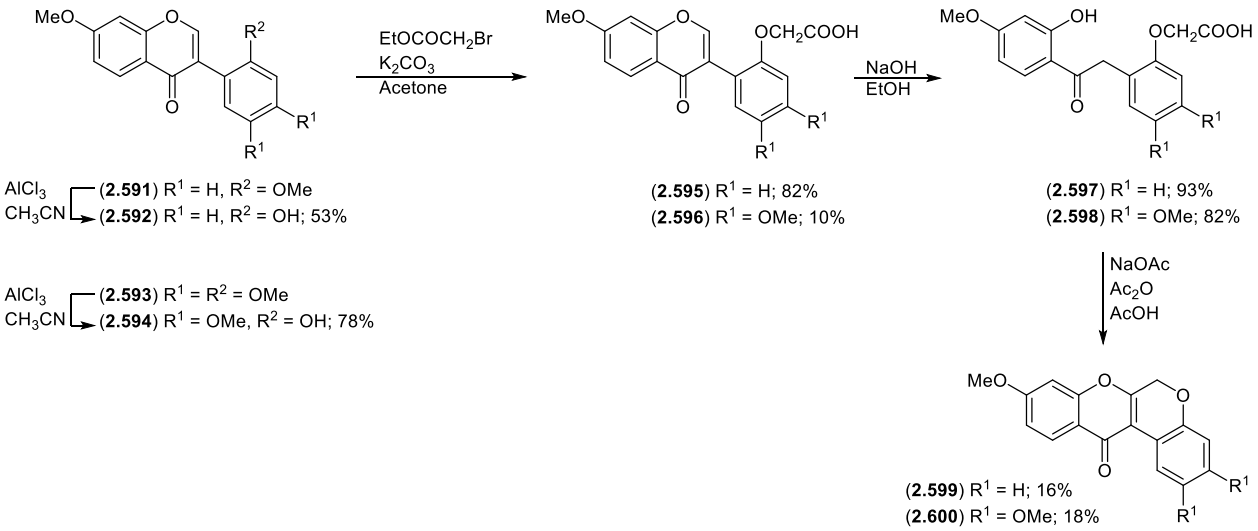
The low yields obtained for the cyclisation of the deoxybenzoin precursors in the rotenone (**2.581**) and deguelin (**2.588**) synthesis (23% and 39%) motivated investigators to improve this step of the methodology. Two alternative methods followed; i) *N*,*N*′-dicyclohexylcarbodiimide (DCC)[122,123] or

ii) sodium metal[124] induced annulation of both derrisic (**2.578**) and deguelinic acid (**2.584**), (Scheme 2-46). Although the DCC cyclisation process proved effective by yielding dehydrorotenone (**2.579**) and dehydrodeguelin (**2.586**) in ca. 40% yield from the respective acid precursors, the sodium procedure proved to be superior yielding dehydrorotenone (**2.586**) and dehydrodeguelin (**2.579**) in 62% and 68%, respectively, despite the required additional esterification of the carboxylic acid moiety.



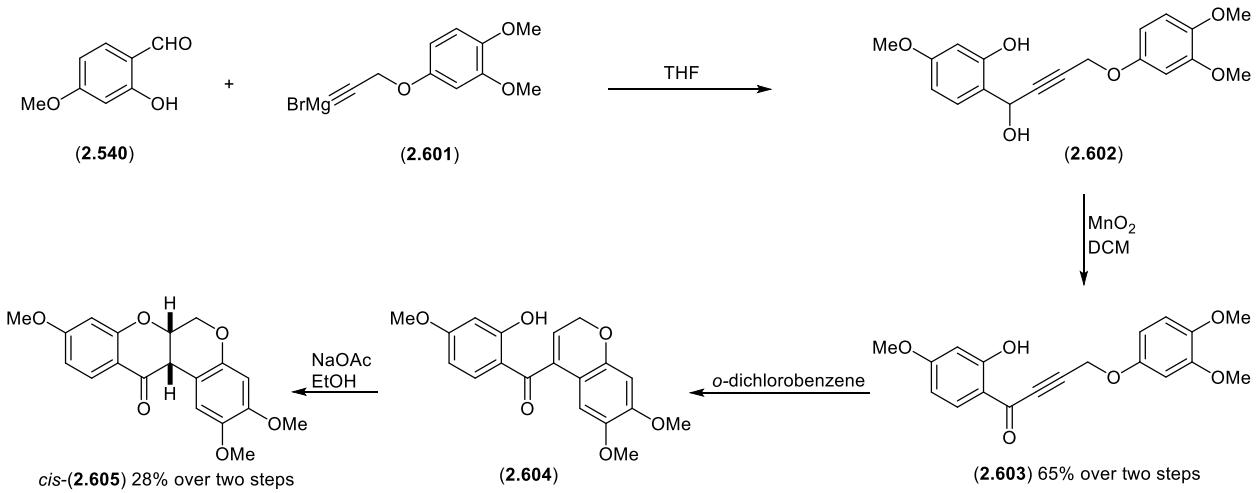
Scheme 2-46: Synthesis of dehydrodeguelin and dehydrorotenone.

During the attempted synthesis of munduserone (**2.605**), the simplest natural occurring rotenoid, Seshadri et al.[125] followed the same route as for the synthesis of rotenone (**2.581**) and deguelin (**2.588**), (vide supra), but due to the tedious preparation of the deoxybenzoin precursors, a biomimetic step, which involved the base catalysed degradation of the appropriate isoflavones (**2.595** and **2.596**), was incorporated into the process (Scheme 2-47). This approach proved to be very effective leading to the deoxybenzoins (**2.597** and **2.598**) in 93% and 82% yields, respectively. The cyclisation of the deoxybenzoins to dehydromunduserone (**2.600**) and 9-methoxydehydrorotenoid (**2.599**), however, gave the products in only 16% and 18% yields leading to overall yields of 1% and 7%. Although the preparation of the deoxybenzoin proved to be much more efficient, it must, however, be kept in mind that this methodology requires the additional preparation of the appropriate isoflavones, which adds a number of steps to the whole process.



Scheme 2-47: Synthesis of dehydrorotenoids from isoflavones.

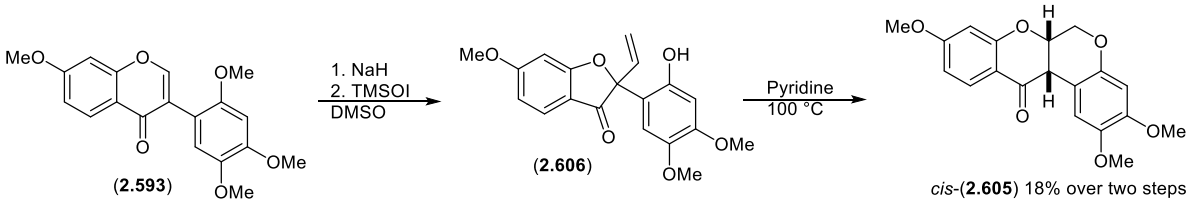
While all the aforementioned methodologies established the B- and C-rings of the rotenoid skeleton simultaneously, an alternative approach, reported by Omokawa and Yamashita,[126,127] envisaged formation of the C-ring toward *cis*-munduserone (**2.605**) as the final step in the synthesis (Scheme 2-48). In this protocol the propargylic alcohol derivative (**2.602**), obtained by reacting the benzaldehyde (**2.540**) with the propargylic Grignard reagent (**2.601**), was oxidised to the ketone analogue (**2.603**), which upon Claisen rearrangement led to the formation of the B-ring of the rotenoid skeleton (**2.604**). Subsequent Michael addition rendered *cis*-munduserone (**2.605**) in 18% overall yield. Although *cis*-munduserone (**2.605**) could be prepared in moderate yield in this way, this approach is limited to analogues with an electron rich A-ring in order to allow for the Claisen rearrangement to be effective.[128] To avoid the use of the Grignard reagent an alternative five step route is possible yielding (±)-munduserone (**2.605**) in 23% overall yield.[129]



Scheme 2-48: Synthesis of (±)-munduserone (2.605) utilizing a Grignard reagent.

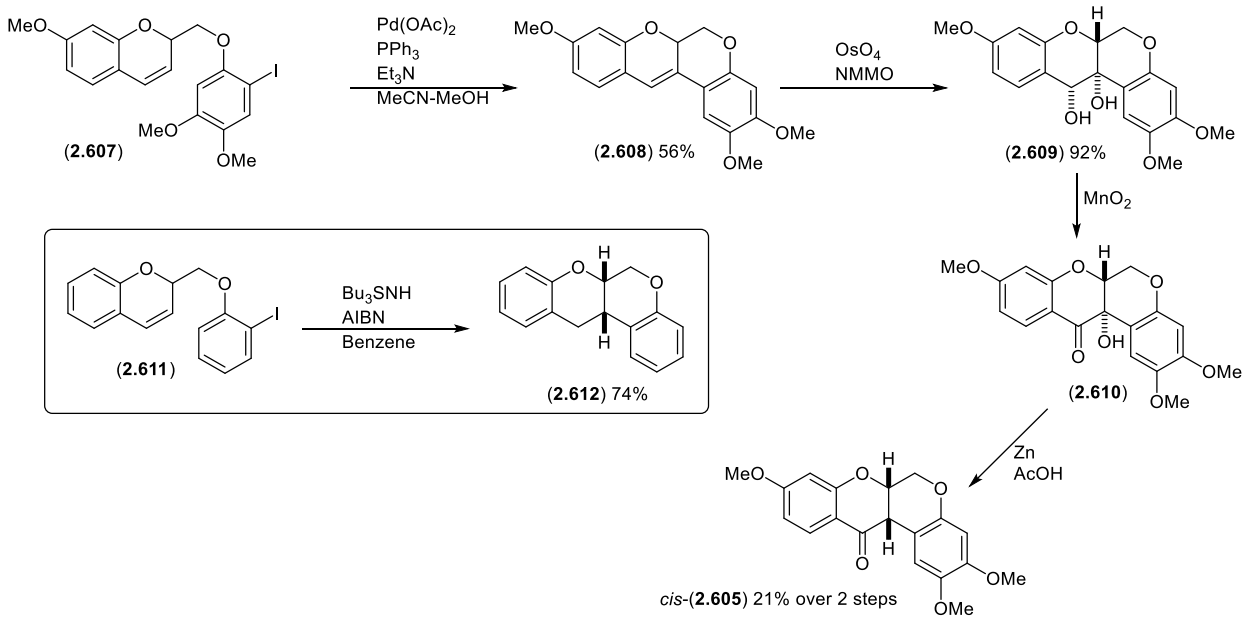
Whiting et al.[29] set out to transform 2',4',5',7-tetramethoxyisoflavone (**2.593**) into *cis*-munduserone (**2.605**), (Scheme 2-49). Following selective demethylation, base catalysed rearrangement of the

isoflavone with trimethylsulphoxonium iodide (TMSOI), yields 2-vinylcoumaran-3-one (**2.606**), which produced *cis*-munduserone (**2.605**) in 8% yield from the isoflavone (**2.593**) upon heating in pyridine. Since formation of the intermediate 2-vinylcoumaran-3-one (**2.606**) proved to be the low yielding step in the process, with only 16% isolated yield, the overall yield could be increased significantly (to 18% overall yield) by performing the process in a single step.



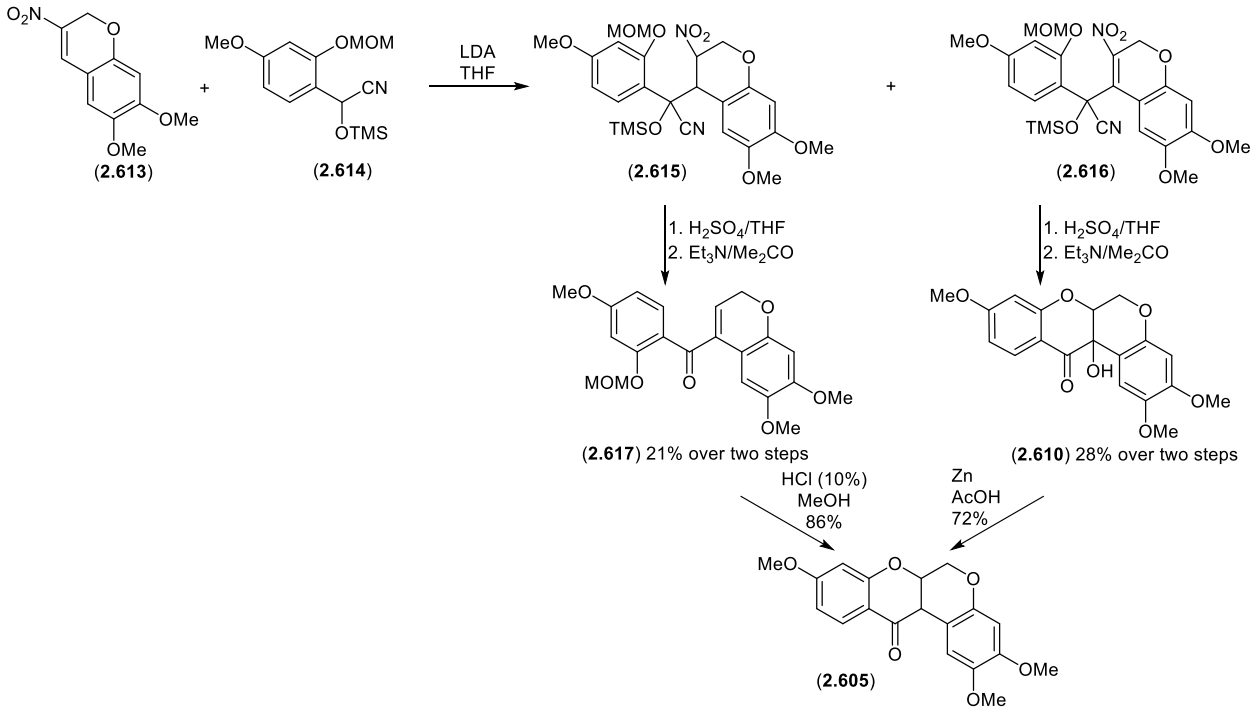
Scheme 2-49: Synthesis of (±)-munduserone (2.605) from isoflavones (2.593).

Whiting and co-workers also pursued the synthesis of *cis*-munduserone (**2.605**) by utilizing the Heck reaction[130,131] or radical cyclisation[132] for the formation of the B-ring of the rotenoid skeleton (Scheme 2-50). During the Heck coupling chromene (**2.607**) was transformed into the chromanochromene (**2.608**) in 58% yield, which was subjected to OsO_4 dihydroxylation, MnO_2 oxidation and Zn/AcOH reduction to yield *cis*-munduserone (**2.605**) in 19% (over the last 3 steps). Even though this process consisted of only 4 steps, the overall yield of 11% was comparable to what was found during the application of the other methodologies. As an alternative to the Heck coupling, it was demonstrated that radical cyclisation of the 2-substituted chromene (**2.611**) could be used to good effect (74% yield) for the formation of the B-ring and thus the wanted chromanochromane (**2.612**). This methodology was, however not applied to the preparation of *cis*-munduserone (**2.605**) itself.



Scheme 2-50: Synthesis of (±)-munduserone (2.605) utilizing the Heck reaction.

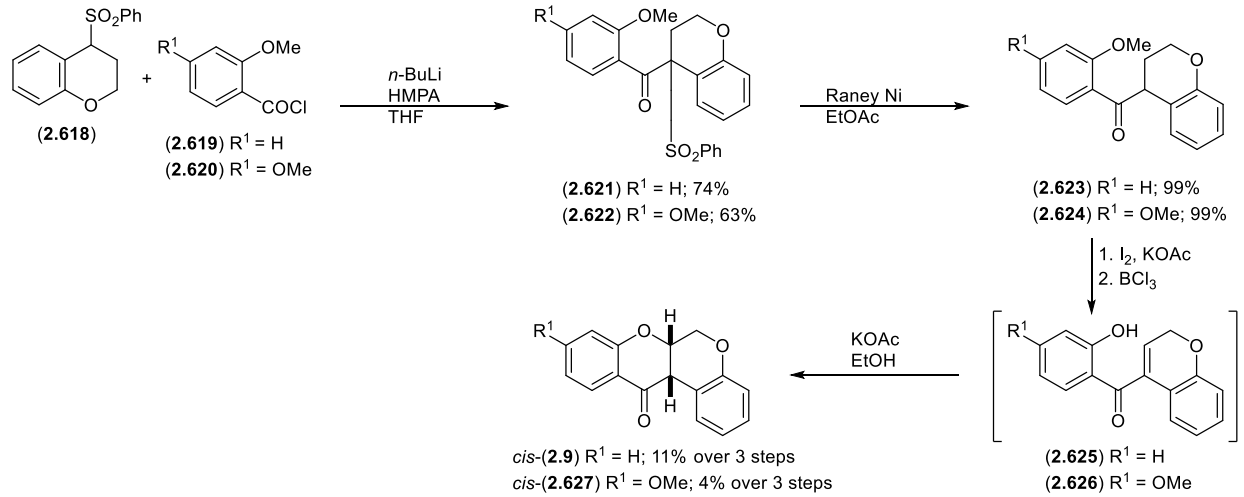
In a different approach towards the synthesis of munduserone (**2.605**), Granados-Covarrubias and Maldonado[133] exploited the conjugate addition of cyanohydrin (**2.614**) to nitrochromene (**2.613**) for the construction of the basic rotenoid skeleton (Scheme 2-51). Subsequent hydrolysis of the reactive intermediates (**2.615** and **2.616**), gave the two intermediate products, **2.617** and **2.610**, in 21 and 28% yield, respectively. Munduserone (**2.605**) could be obtained from either of these substrates by acid catalysed hydrolysis (86%) and/or reduction (72%). Since munduserone (**2.605**) could be obtained in a combined yield of 38% over only 3 steps, this methodology could be regarded as one of the most effective ways for the preparation of this natural product.



Scheme 2-51: Latest synthesis of (±)-munduserone (2.605).

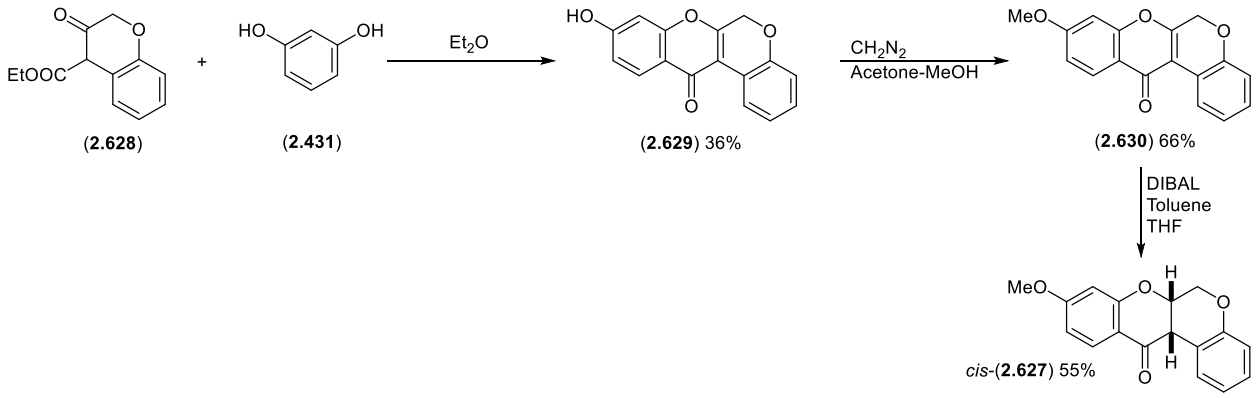
Although most reports on the synthesis of rotenoids aimed at the preparation of the natural products rotenone (**2.581**), deguelin (**2.588**) and munduserone (**2.605**), some methodologies with a general applicability have also been developed. Similar to the preparation of **2.605** (vide supra) Whiting et al.[134] also described the formation of the C-ring of the rotenoid framework by Michael addition of the hydroxy function of the D-ring to the α,β-unsaturated ketone as the final step in the process (Scheme 2-52). The preformed 4-phenylsulfonylchroman (**2.618**) and acyl chloride (**2.620**) fragments were joined together through nucleophilic attack of the sulfonylanion (generated by treatment with BuLi) onto the acyl chloride, after which reductive desulfonylation over Raney Ni and iodine mediated dehydrogenation and subsequent selective demethylation with boron trichloride yielded the α,β-unsaturated ketone (**2.626**). Treatment with KOAc allowed for the formation of the C-ring of the *cis*-rotenoid (**2.627**). Although the initial coupling reaction (63-74%) and reduction process (99%) were high yielding, the low yields (4-11%) obtained during the

sequential dehydrogenation, demethylation and Michael addition reactions renders this methodology not very useful.



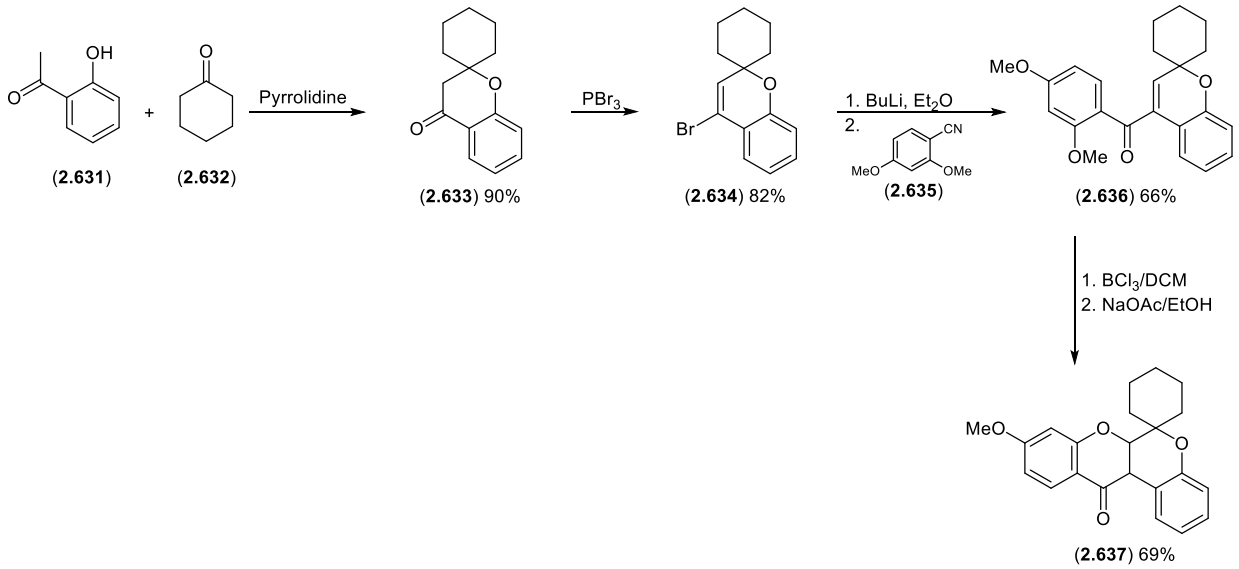
Scheme 2-52: Synthesis of rotenoids via a preformed A- and B-ring system.

A one-pot coupling-annulation between chroman-3-one-4-carboxylate (**2.628**) and resorcinol (**2.431**) produced dehydrorotenoid (**2.629**) in 36% yield as reported by Crombie et al. (Scheme 2-53).[128] The corresponding *cis*-9-methoxyrotenoid (**2.627**) could be obtained in 13% overall yield, which was significantly better than what was found by Whiting et al.[134] (3% overall) following methylation (with CH_2N_2) and DIBAL reduction of the double bond (cf. Scheme 2-52).



Scheme 2-53: Synthesis of rotenoid 2.627.

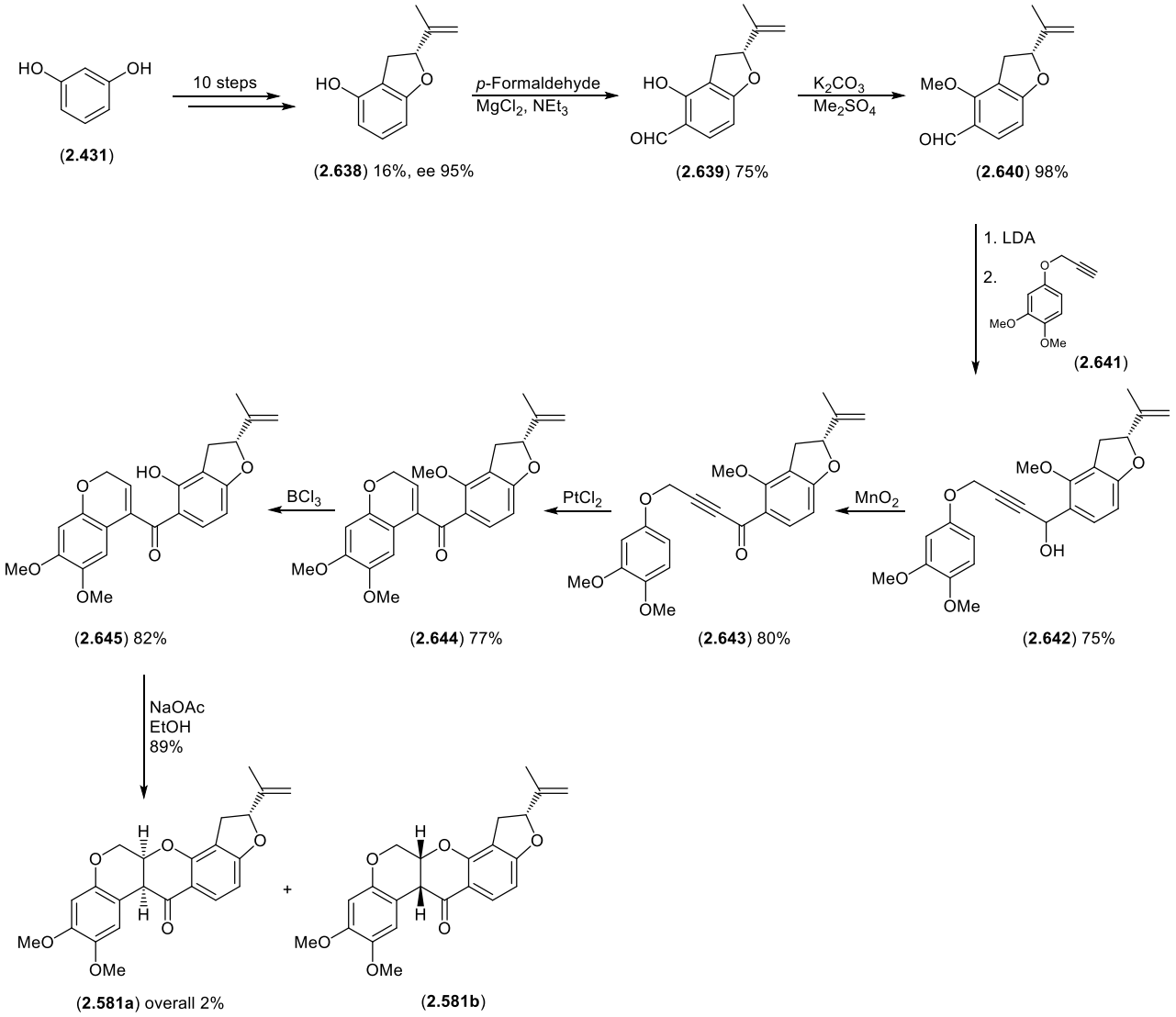
A facile four step general approach to rotenoid **2.637** has been reported by Hepworth et al.[135] (Scheme 2-54). In this process 2'-hydroxyacetophenone (**2.631**) was transformed into the spiro-4-chromanone (**2.633**), which in turn was transformed into the bromochromene (**2.634**) upon treatment with PBr_3. Transmetallation and condensation with benzonitrile (**2.635**) produced the α,β-unsaturated ketone system from which the rotenoid was obtained via demethylation and Michael addition in an overall yield of 34% (4 steps). Although this methodology is very effective and relatively high yielding, it has only been applied to the synthesis of a single rotenoid, i.e. **2.637**.



Scheme 2-54: Four step synthesis of rotenoid 2.637 from 2-hydroxyacetophenone (2.631).

2.6.2. Stereoselective synthesis of rotenoids

The first total stereoselective synthesis of the natural product rotenone (**2.581a**) was published by De Koning et al.[129] starting from the chiral dihydrobenzofuran moiety (**2.638**) which were synthesized previously in ten steps from commercially available resorcinol (**2.431**) in 16% yield and 95% ee.[136] The seven step synthesis protocol (Scheme 2-55) from the dihydrobenzofuran (**2.638**) to rotenone (**2.581a**) involved the formylation of **2.638**, followed by a coupling reaction to **2.641** utilizing LDA and consequently oxidation to the ketone moiety (**2.643**), whereafter the key 6-*endo*-hydroarylation reaction gave chromene intermediate **2.644**. The final transformation was the base-catalyzed intramolecular Michael addition to yield the pentacyclic product as two *cis*-diastereomers, **2.581a** and **2.581b**, resulting in an overall yield of 2% rotenone (**2.581a**).



Scheme 2-55: Total stereoselective synthesis of natural product rotenone (2.581a).

To conclude, the bulk of the research performed on the synthesis of rotenoids focused on the naturally occurring rotenone (**2.581**), deguelin (**2.588**) and munduserone (**2.605**). Rotenone (**2.581**) and deguelin (**2.588**) were obtained with the same protocol from their corresponding deoxybenzoin precursor, derrisic acid (**2.578**) and deguelinic acid (**2.584**), via base catalysed cyclisation to the dehydrorotenoid (**2.579** and **2.586**) followed by reduction and Oppenhauer oxidation. A choice of three conditions exist for the cyclisation, i.e. NaOAc, DCC and sodium metal, of which the latter was the most effective with 62% and 68% yield to the respective dehydrorotenoids (cf. Scheme 2-45). Subsequent reduction and Oppenhauer oxidation proceeded with 13% yield over 2 steps. Dehydromunduserone (**2.600**) was obtained in a similar fashion, but was not converted to munduserone (**2.605**). Omokawa and Whiting, on the other hand, developed 3 alternative pathways toward munduserone utilizing i) a propargylic alcohol intermediate in a 4 step process resulting in 18% overall yield (cf. Scheme 2-47), ii) a one step transformation from 2',4',5',7-tetramethoxyisoflavone with 18% yield (cf. Scheme 2-48), and iii) a chromene intermediate in a 4

step process with 11% overall yield (cf. Scheme 2-49). The highest yielding synthesis toward munduserone (**2.605**) was, however, developed by Granado-Covarrubias and Maldonado (cf. Scheme 2-51) during which the rotenoid skeleton was constructed by means of conjugated addition of a cyanohydrin (**2.614**) and a nitrochromene (**2.613**) to produce munduserone (**2.605**) with 38% overall yield in 3 steps. Only 2 alternative rotenoid syntheses have been reported and the substrate scope of both was limited to only a single *cis*-9-methoxyrotenoid derivative each. The first was reported by Crombie (cf. Scheme 2-53) and prepared *cis*-9-methoxyrotenoid (**2.627**) in 13% overall yield in 3 steps, while the other produced 9-methoxy-6-spirorotenoid (**2.638**) over a 4 step process in an overall yield of 34% (cf. Scheme 2-54). The first stereoselective synthesis of rotenone (**2.581a**) was published by De Koning (cf. Scheme 2-55), reaching the target molecule in 17 steps with an overall yield of 2%.

2.7. References

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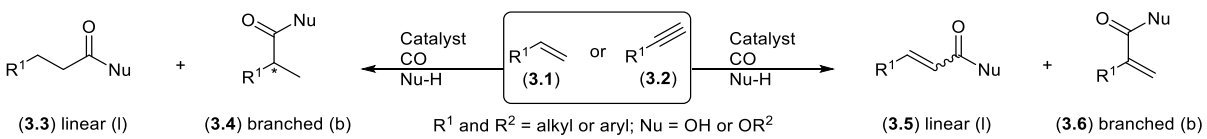
CARBONYLATION 3

The isoelectric nature of carbon monoxide (CO) not only allows reaction with carbocations,[1] carbanions[2] and radical carbon species,[3] but also with transition metals which allows for catalytic carbonyl insertion into a carbon backbone.[4] Since the first report of oxo synthesis in 1938,[5] transition metal catalysed carbonylation has been extensively utilized in organic synthesis chemistry,[6] mainly since i) it entails the insertion of a C=O moiety through the formation of a carbon-carbon bond, ii) the reaction tolerates a wide variety of functional groups, iii) the carbonyl functional group incorporated in the product is renowned for molecular transformations and iv) the catalytic system generally renders good atom economy with low waste production, thus resulting in a relatively environmentally friendly process. Asymmetric carbonylation furthermore provides a one-step synthesis toward optically active carbonyl compounds, including carboxylic acids and esters, from prochiral alkenes.[7]

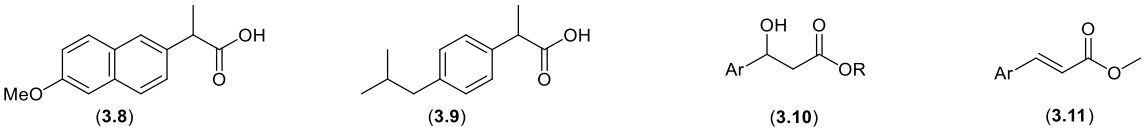
Based on the nucleophile present in the system, carbonylation can be divided into five main transformations, i.e. hydroformylation, hydroxycarbonylation, alkoxycarbonylation (hydroesterification), aminocarbonylation (hydroamidation) and thiocarbonylation (hydrothiocarbonylation), which leads to aldehydes, carboxylic acids, esters, amides and thioesters, respectively.[8] These transformations can be effected by numerous metals, e.g. cobalt, iron, rhodium, ruthenium, platinum and palladium, on a variety of different substrates, e.g. alkenes, alkynes, allenes, alcohols and epoxides.[8]

The discussion in this chapter will, however, be limited to the palladium catalysed hydroxy- and alkoxycarbonylation of alkenes (**3.1**) and alkynes (**3.2**) with CO as source of the carbonyl and water or an alcohol as nucleophile (Scheme 3-1). An important aspect of these reactions is regioselectivity. Unsymmetrical substrates may yield two structural isomers as the carbonyl may be introduced on either of the original sp/sp^2-hybridized carbon atoms. Carbonylation of terminal alkenes and alkynes, for example, consequently result in either Markovnikov or *anti*-Markovnikov addition to yield branched (b) and/or linear (l) products, respectively.



Scheme 3-1: Hydroxy- and alkoxycarbonylation of alkenes and alkynes.

The utilization of catalytic carbonylation of alkenes and alkynes is important in industry as both branched and linear carbonylated products have designated applications. Branched 2-aryl propionic acids/esters include non-steroidal anti-inflammatory agents like naproxen (**3.8**) and ibuprofen (**3.9**), whereas linear derivatives, e.g. 3-aryl propionate (**3.10**) and methyl cinnamate (**3.11**) derivatives, are employed as speciality and commodity chemicals (Figure 3-1).[9,10] In addition, intramolecular hydroesterification are often employed for the synthesis of various lactones in the food, pharmaceutical and polymer industries.



(**3.8**) (**3.9**) (**3.10**) (**3.11**)

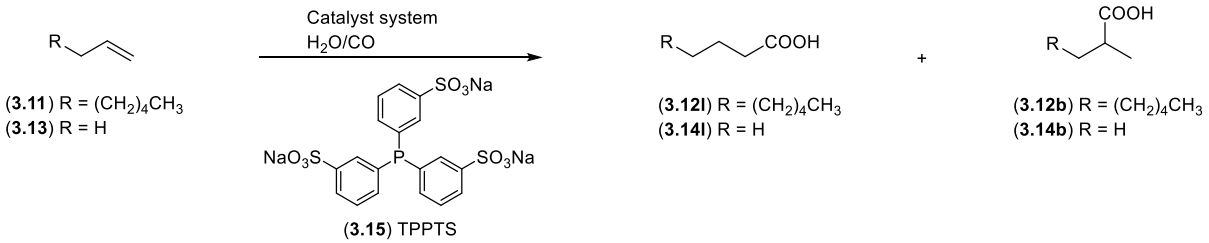
Figure 3-1: Industrially important carbonylated products employed as speciality and commodity chemicals.

Following the discovery of the role of metal carbonyls in the Fischer-Tropsh process, Reppe laid the foundation for carbonylation reactions utilizing firstly $Ni(CO)_4$, followed by various other metal carbonyl catalysts, mostly based on iron, ruthenium, cobalt, rhodium, iridium, palladium and platinum.[4,6] Exploration of other catalytic methods soon followed. One of the catalytic systems that played a fundamental role towards the development of the current palladium based transformations in the presence of CO, was a $H_2PtCl_5/SnCl_2$ couple reported by Kehoe and Schell.[11] Although investigations with regard to hydroxy- and alkoxycarbonylation often occur hand-in-hand or is extrapolated from the one to the other, the two transformations will be discussed separately.

3.1. Alkene hydroxycarbonylation with selectivity toward linear products

Du Pont was one of the first to claim the transformation of olefins to carboxylic acids over palladium.[12] Carbonylation of 1,5-hexadiene was performed utilizing PdF_2 (1 mol%) and HCl (1.1 eq.) under CO (960 bar) at 210 °C for 16 hours to yield the acyl halide which, in turn, was converted during workup to α-propylbutyrolactone (10%). Fenton[13] later reported direct hydroxycarbonylation of 1-octene (**3.11**) under various parameters to nonanoic acid (**3.12l**, linear isomer), and 2-methyloctanoic acid (**3.12b**, branched isomer) (Table 3-1, entry 1). Optimal regioselectivity toward the linear isomer (67:33) was obtained for the $PdCl_2•H_2O/AcOH/PPh_3$ system at 55 bar CO and 125 °C with 1.2 equivalents of water.

Table 3-1: Hydroxycarbonylation of octene (3.11) and propene (3.13) with $PdCl_2$ catalyst systems.*



Entry	Alkene	Catalyst system	P_{CO} (bar) [Temp (°C)]	Conv. (%) [Yield] (%)	Products	Ratio l:b
1[13]	**3.11**	$PdCl_2$•2H_2O/AcOH/PPh_3[a]	55 [125]	77	**3.12**	67:33
2[14]	**3.13**	$PdCl_2$/TPPTS/TsOH[b]	50 [110]	70	**3.14**	58:42
3[15]	**3.13**	$PdCl_2$/TPPTS/HCl[c]	40 [120]	[66]	**3.14**	57:43
4[15]	**3.13**	$PdCl_2$/TPPTS/HCl/LiCl or PVA[c,d]	40 [120]	[100]	**3.14**	57:43

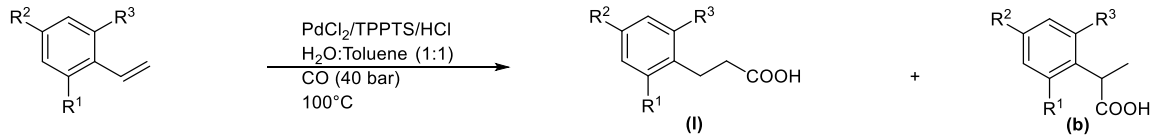
[a]Reaction conditions: $PdCl_2$•2H_2O (5 mmol), PPh_3 (20 mmol), 1-octene (700 mmol), AcOH (400 ml), H_2O (1.2 eq.), 2 h. [b]Reaction conditions: $PdCl_2$ (0.2 mmol), TPPTS (0.8 mmol), TsOH (30 mmol), propene (200 mmol), H_2O (140 ml), 0.5 h. [c]Reaction conditions: $PdCl_2$ (0.08 mmol), TPPTS (0.5 mmol), HCl (adjusted to pH 1.8, ca. 1 mmol), propene (33 mmol), H_2O (12 ml), toluene (12 ml), 1 h. [d]LiCl (0.84 mmol) or PVA (0.125 g).

Since hydroxycarbonylation requires water as a nucleophile, it is often performed in biphasic systems. Consequently, an ionic catalyst was later considered to assist the transformation. Sheldon et al.[14] achieved this by employing sulfonated triphenylphosphine (**3.15**), TPPTS [trisodium tris(3-sulfonatophenyl)phosphine], as ligand. The hydroxycarbonylation of propene (**3.13**) with the $PdCl_2$/TPPTS/TsOH/H_2O system, however, exhibited low regioselectivity (58:42) that slightly favoured *n*-butanoic acid (**3.14l**) as linear product (Table 3-1, entry 2). Monflier et al.[15] proceeded to investigate the influence of additives on the stability and selectivity of the catalyst with propene (**3.13**) as substrate. It was found that the addition of LiCl or polyvinyl alcohol (PVA) to the $PdCl_2$/TPPTS/HCl catalyst system increased the activity of the catalyst significantly (100% vs. 66% after 1 hour), although regioselectivity remained unchanged at 57:43 (Table 3-1, entry 3 vs. 4).

The substrate scope of the $PdCl_2$/TPPTS/HCl system was expanded to include styrene derivatives (Table 3-2).[16] Regioselectivity toward the linear product was achieved in the presence of an *ortho*-substituent. Tolyl (**3.16**) and xylyl (**3.18**) derivatives yielded comparative results (ca. l:b = 70:30; Table 3-2, entries 1 and 2), whereas the double *ortho*-substituted mesityl derivative (**3.20**) exhibited very high regioselectivity, (l:b = 95:5; Table 3-2, entry 3).

*Although the reaction conditions of pressure, temperature, ratio of catalyst to substrate etc. may have some influence on the ratio of products obtained, the ratios in this and future tables are given as reported in the different papers under the prevailing reaction conditions. As is evident from entries 2, 3 and 4 the influence of reaction conditions on product selectivity is not significant, therefore product selectivity may be considered primarily as a function of the catalyst system and substrate structure.

Table 3-2: Hydroxycarbonylation of methylstyrenes (3.16, 3.18 and 3.20) with $PdCl_2$ and TPPTS (3.15) as ligand.[a]

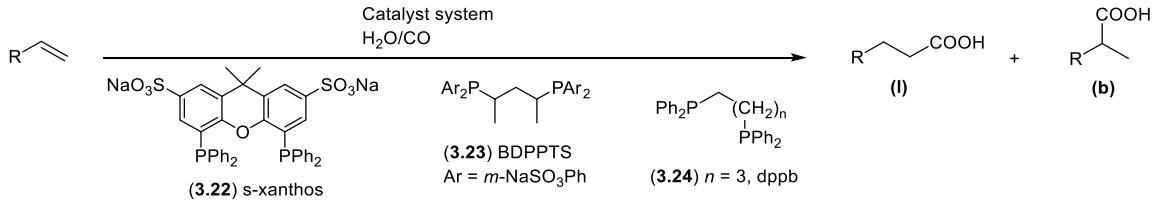


Entry	R^1	R^2	R^3	Alkene	Yield (%) 3h (20h)	Products	Ratio l:b
1[16]	Me	H	H	**3.16**	42 (100)	**3.17**	74:26
2[16]	Me	Me	H	**3.18**	19 (100)	**3.19**	72:27
3[16]	Me	Me	Me	**3.20**	2 (12)	**3.21**	95:5

[a]Reaction conditions: $PdCl_2$ (0.25 mmol), TPPTS (1.5 mmol), HCl (1 mmol), alkene (13 mmol), H_2O (35 ml), toluene (35 ml).

Van Leeuwen et al.[17] extended the philosophy of an ionic catalyst to a cationic bidentate palladium complex. The sulfonated xanthos ligand, s-xanthos (**3.22**), proved effective for the transformation of propene (**3.13**), (Table 3-3, entry 1) with slightly improved linear regioselectivity over the aforementioned TPPTS (**3.15**) system (l:b = 65:35 vs. 58:42). Similar results were obtained when styrene (**3.25**) was subjected to the same conditions, rendering the linear product (**3.26l**) with a 65:35 preference (Table 3-3, entry 2). Increased linear regioselectivity (81:19) was, however, achieved for styrene (**3.25**) when 2,4-bis-(diphenylphosphino)pentane (**3.23**, BDPPTS), was utilized as ligand together with $Pd(OAc)_2$ (Table 3-3, entry 3).[18] Although the bidentate BDPPTS (**3.23**) catalyst system yielded high linear regioselectivity (81:19), the substrate scope is limited as introduction of substitution on the styrene ring decreased regioselectivity to ca. 70:30 (Table 3-3, entry 3 vs. 4 and 5). The pH of the reaction mixture also proved influential with higher yields observed under acidic conditions (Table 3-3, entries 6-8) but at the cost of regioselectivity (Table 3-3, entries 3-5 vs. 6-8).[18]

Table 3-3: Hydroxycarbonylation with catalyst systems utilizing s-xanthos (3.22), BDPPTS (3.23) and dppb (3.24) ligands.



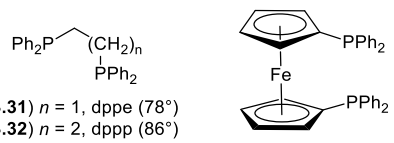
Entry	R	Alkene	Catalyst system	pH	Conv. (%)	Products	Ratio l:b
1[17]	Me	**3.13**	Pd-s-xanthos/TsOH[a]	-	-	**3.14**	65:35
2[17]	Ph	**3.25**	Pd-s-xanthos/TsOH[a]	-	-	**3.26**	65:35
3[18]	Ph	**3.25**	$Pd(OAc)_2$/BDPPTS[b]	12.7	57	**3.26**	81:19
4[18]	4-OMePh	**3.27**	$Pd(OAc)_2$/BDPPTS[b]	12.7	81	**3.28**	70:30
5[18]	4-FPh	**3.29**	$Pd(OAc)_2$/BDPPTS[b]	12.7	74	**3.30**	71:29
6[18]	Ph	**3.25**	$Pd(OAc)_2$/BDPPTS[b]	3.4	94	**3.26**	66:34
7[18]	4-OMePh	**3.27**	$Pd(OAc)_2$/BDPPTS[b]	3.5	96	**3.28**	55:45
8[18]	4-FPh	**3.29**	$Pd(OAc)_2$/BDPPTS[b]	3.5	92	**3.30**	65:35
9[19]	Ph	**3.25**	$Pd_2(dba)_3$/dppb/H_2O[c]	-	79	**3.26**	85:15
10[19]	Ph	**3.25**	$Pd_2(dba)_3$/dppb/$H_2C_2O_4$[c]	-	96	**3.26**	83:17

[a]Reaction conditions: Pd-s-xanthos (16 μmol), TsOH (2.7 mmol), propene (9 bar) or styrene (mmol not specified), H_2O (10 ml), CO (30 bar), 120 °C (propene) or 95 °C (styrene), 30 min (propene) or 180 min (styrene). [b]Reaction conditions: $Pd(OAc)_2$ (0.04 mmol), BDPPTS (0.08 mmol), H_2SO_4 (0.25 M) for pH adjustment, alkene (15 mmol), H_2O (10 ml), CO (20 bar), 120 °C, 16 h. [c]Reaction conditions: $Pd_2(dba)_3$ (0.04 mmol), dppb (0.4 mmol), alkene (2.5 mmol), H_2O (100 mmol) or $H_2C_2O_4$ (2.5 mmol), DME (10 ml), CO (75 bar), 150 °C, 24 h.

Claver et al.[19] reported a comprehensive study on the influence of the counter ion of the added acid (H_2O, TsOH, $H_2C_2O_4$, HCl, HBr and HI) on the hydroxycarbonylation of styrene (**3.25**) with $Pd_2(dba)_3$, in combination with 1,4-bis(diphenylphosphino)butane (**3.24**, dppb), as catalyst. Optimal regioselectivity for this bidentate system was obtained with the use of H_2O (no additional acid) and was comparable to the BDPPTS system (l:b = 85:15 vs. 81:19, Table 3-3, entry 3 vs. 9) but exhibited superior conversion (79% vs. 57%). The conversion was then increased to 96% with the use of oxalic acid ($H_2C_2O_4$), without significantly compromising the regioselectivity (l:b = 85:15 vs. 83:17; Table 3-3, entries 9 and 10).

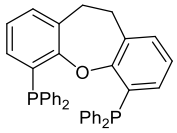
Claver et al.[20] continued to study the effect of the bite angles of different bidentate ligands on the regioselectivity of styrene (**3.25**) hydroxycarbonylation catalysed by $PdCl_2(PhCN)_2$ (Table 3-4). Observations suggested bidentate ligands with bite angles larger than 90° (Table 3-4, entries 3-7) to induce preference (> 80%) for the linear product, 3-phenylpropanoic acid (**3.26l**), whereas 1,2-bis(diphenylphosphino)ethane (**3.31**, dppe), with a bite angle of 78°, didn't impart significant selectivity (Table 3-4, entry 1). The ligand that induced the greatest selectivity toward the linear product (**3.26l**) was bis[2-(diphenylphosphino)ether] (**3.35**, DPEphos) with a bite angle of 103° (Table 3-4, entry 6). In addition to $PdCl_2(PhCN)_2$, other precatalysts, i.e. $Pd(OAc)_2$ and $Pd_2(dba)_3$, were also evaluated and yielded similar results.

Table 3-4: Hydroxycarbonylation of styrene (3.25) utilizing different bidentate ligands.[a]

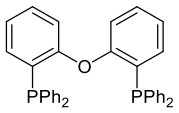


(**3.31**) *n* = 1, dppe (78°)
(**3.32**) *n* = 2, dppp (86°)
(**3.24**) *n* = 3, dppb (98°)

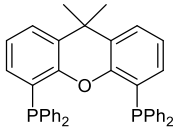
(**3.33**) dppf (99°)



(**3.34**) HomoXanthos (102°)



(**3.35**) DPEphos (103°)



(**3.36**) Xantphos (110°)

Entry	Diphosphine ligand	Bite Angle	Conversion (%)	Regioselectivity **3.26l**:**3.26b**
1	dppe (**3.31**)	78	5	53:47
2	dppp (**3.32**)	86	28	77:23
3	dppb (**3.24**)	98	95	83:17
4	dppf (**3.33**)	99	96	84:16
5	HomoXantphos (**3.34**)	102	98	85:15
6	**DPEphos** (**3.35**)	**103**	**99**	**86:14**
7	Xantphos (**3.36**)	110	99	81:19

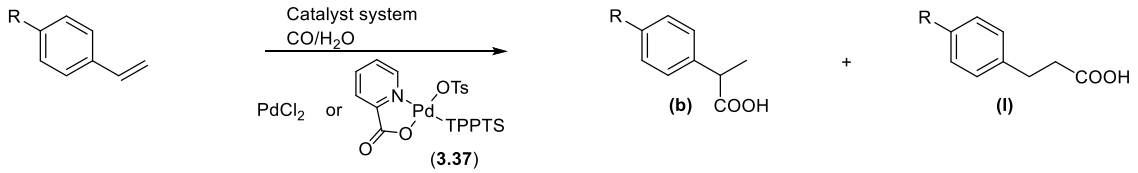
[a]Reaction conditions: $PdCl_2(PhCN)_2$ (0.04 mmol), ligand (0.4 mmol), $H_2C_2O_4$ (8 mmol), styrene (8 mmol), DME (10 ml), CO (75 bar), 150 °C, 24 h.

In conclusion, for propene (**3.13**) some regioselectivity (58:42) toward butanoic acid (**3.14l**), i.e. the linear product, can be achieved by employing a monodentate (**3.15**) catalyst system (cf. Table 3-2), however, the utilization of the bidentate s-xanthos (**3.22**) catalyst system (cf. Table 3-3) increased the regioselectivity to l:b = 65:35. Styrene derivatives seem to require a steric factor, e.g. *ortho*-methyl units, on the substrate to force regioselectivity towards linear product formation when a monodentate ligand is employed. Bidentate ligand systems, on the other hand, tend to favour the linear product in most instances, with the highest reported selectivity for styrene (**3.25**, 86%) being achieved in the presence of DPEphos (**3.35**). Similarly BDPPTS (**3.23**) renders the highest regioselectivity for propene (**3.13**, 67%).

3.2. Alkene hydroxycarbonylation with selectivity toward branched products

One of the earliest catalyst systems to exhibit regioselectivity toward branched products was reported by Alper et al.[21] When this bimetallic $PdCl_2/CuCl_2/HCl$ system was employed, no linear products were detected for 1-decene (**3.80**), 1-octene (**3.11**) or 4-methylstyrene (**3.38**) and the respective branched carboxylic acids (**3.81**, **3.12** and **3.39**) were obtained in 100%, 82% and 58% yield. What makes this system unique, is the presence of O_2 in combination with CO (bubbled through the reaction mixture at 1 atm), together with the mild reaction conditions, i.e. 1 atmosphere pressure and room temperature, utilizing THF as solvent. Lee et al.[22] modified the Pd/Cu system through the addition of PPh_3 and the exclusion of O_2 in the reaction atmosphere. Increase in both pressure (45 bar) and temperature (100 °C) significantly improved the results for 4-methylstyrene (**3.38**) producing a 93% yield of the branched acid (**3.39b**), (Table 3-5, entry 1).

Table 3-5: Hydroxycarbonylation of styrene (3.25) and derivatives with TPPTS (3.15) catalyst systems.



Entry	R	Alkene	Catalyst system	P_{CO} (bar) [Temp (°C)]	Conv. (%) [Yield (%)]	Products	Ratio b:l
1[22]	Me	**3.38**	$PdCl_2/CuCl_2/HCl/PPh_3/H_2O$[a]	45 [100]	100	**3.39**	93:7
2[16]	H	**3.25**	$PdCl_2$/TPPTS/HCl/H_2O[b]	40 [100]	[100]	**3.26**	56:44
3[16]	Me	**3.38**	$PdCl_2$/TPPTS/HCl/H_2O[b]	40 [100]	[100]	**3.39**	59:41
4[16]	Cl	**3.40**	$PdCl_2$/TPPTS/HCl/H_2O[b]	40 [100]	[98]	**3.41**	59:41
5[16]	Br	**3.42**	$PdCl_2$/TPPTS/HCl/H_2O[b]	40 [100]	[70]	**3.43**	59:41
6[16]	F	**3.29**	$PdCl_2$/TPPTS/HCl/H_2O[b]	40 [100]	[100]	**3.30**	53:47
7[14]	H	**3.25**	$PdCl_2$/TPPTS/TsOH/H_2O[c]	140 [65]	100	**3.26**	90:10
8[23]	H	**3.25**	(**3.37**)/TPPTS/TsOH/LiCl/H_2O[d]	55 [115]	95	**3.26**	92:8

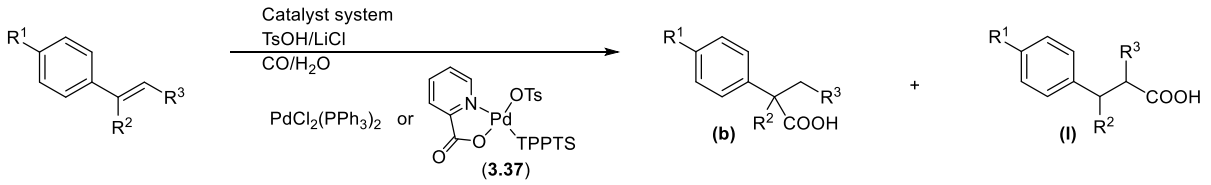
[a]Reaction conditions: $PdCl_2$ (0.5 mmol), $CuCl_2$ (1.5 mmol), PPh_3 (2 mmol), HCl (0.5 ml), alkene (50 mmol), H_2O (9 ml), THF (80 ml), 2 h. [b]Reaction conditions: $PdCl_2$ (0.25 mmol), TPPTS (1.5 mmol), HCl (1 mmol), alkene (13 mmol), H_2O (35 ml), toluene (35 ml), 20 h. [c]Reaction conditions: $PdCl_2$ (0.2 mmol), TPPTS (0.8 mmol), TsOH (7 mmol), styrene (10 mmol), H_2O (140 ml), 10 h. [d]Reaction conditions: Catalyst (63 μmol), TPPTS (0.12 mmol), styrene (30 mmol), TsOH (11 mmol), LiCl (11 mmol), H_2O (6 ml), toluene (16 ml), 1.5 h.

Although the monodentate TPPTS system mentioned previously (cf. Table 3-2) was claimed to give a 95% regioselectivity toward the linear product (**3.21l**) during the hydroxycarbonylation of 2,4,6-trimethylstyrene (**3.20**), the selectivity was hypothesized to be the result of steric crowding around the olefinic double bond.[16] In the absence of any *ortho*-substituents, regioselectivity was inverted, albeit with a very low preference (ca. 60:40) toward the branched acid (**3.21b**), (Table 3-5, entries 2-6). High selectivity (90%) was, however, obtained for styrene (**3.25**) when the HCl was substituted for TsOH and the CO pressure increased from 40 bar to 140 bar (Table 3-5, entry 2 vs. 7).[14] Chaudhari et al.[23] explored an alternative precatalyst to $PdCl_2$ and found that the *N*,*O*-bidentate ligand [2-pyridine carboxylic acid (pyca)] bound catalyst (**3.37**), in combination with TPPTS (**3.15**) and additional LiCl, only required 55 bar of CO to obtain comparable results (Table 3-5, entry 8).

Chaudhari and co-workers[24,25] exchanged the traditional toluene solvent for water miscible methyl ethyl ketone (MEK) which eliminated the need for an ionic catalyst. The TPPTS (**3.15**) was thus replaced by the neutral PPh_3 ligand, but TsOH and LiCl were retained as acid and promoter, respectively. These modifications resulted in excellent regioselectivity (>99%) for styrene (**3.25**) (Table 3-6, entry 1) as well as several *para*-substituted derivatives (Table 3-6, entries 2-6) with $PdCl_2$,[24] while the Pd-*N*,*O* (**3.37**) catalyst gave similar results (Table 3-6, entries 7 and 8).[25] The high regioselectivity prompted Chaudhari et al.[24] to expand the substrate scope to higher substituted alkenes, i.e. α-methylstyrene (**3.48**) and *trans*-β-methylstyrene (**3.50**), (Table 3-6, entries 9 and 10). Although the reaction rates for both these substrates

decreased significantly compared to the monosubstituted analogue (Table 3-6, entry 1 vs. 9 and 10; TOF 2255 h^{-1} vs. 77 and 225 h^{-1}, respectively),[24] formation of the benzylic carboxylic acid products, (**3.49b**) and (**3.51bn**), were still favoured. Regioselectivity towards the branched product in the instance of the sterically more demanding α-methylstyrene (**3.48**) was still an unexpected 61% (Table 3-6, entry 9), whereas *trans*-β-methylstyrene (**3.50**) exhibited regioselectivity of 96% (Table 3-6, entry 10).

Table 3-6: Hydroxycarbonylation of styrene (3.25) and derivatives over $PdCl_2(PPh_3)_2$ or Pd(pyca)(TPPTS)(OTs), (3.37).

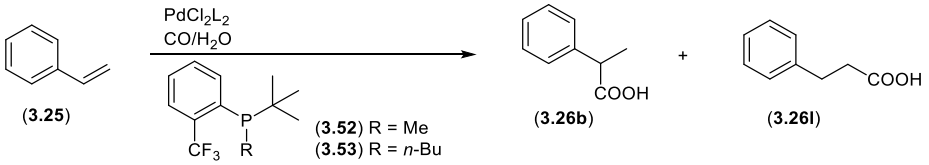


Entry	R^1	R^2	R^3	Alkene	Catalyst system	Conv. (%) [Yield (%)]	Products	Ratio b:l
1[24]	H	H	H	**3.25**	$PdCl_2(PPh_3)_2$[a]	[91]	**3.26**	99:1
2[24]	Me	H	H	**3.38**	$PdCl_2(PPh_3)_2$[a]	[88]	**3.39**	95:5
3[24]	$C(Me)_3$	H	H	**3.44**	$PdCl_2(PPh_3)_2$[a]	[92]	**3.45**	98:2
4[24]	$CH_2CH(CH_3)_2$	H	H	**3.46**	$PdCl_2(PPh_3)_2$[a]	[93]	**3.47**	97:3
5[24]	Cl	H	H	**3.40**	$PdCl_2(PPh_3)_2$[a]	[88]	**3.41**	100:0
6[24]	Br	H	H	**3.42**	$PdCl_2(PPh_3)_2$[a]	[92]	**3.43**	100:0
7[25]	H	H	H	**3.25**	(**3.37**)[b]	97	**3.26**	99:1
8[25]	$CH_2CH(CH_3)_2$	H	H	**3.46**	(**3.37**)[b]	95	**3.47**	99:1
9[24]	H	Me	H	**3.48**	$PdCl_2(PPh_3)_2$[a]	[50]	**3.49**	61:39
10[24]	H	H	Me	**3.50**	$PdCl_2(PPh_3)_2$[a]	[85]	**3.51**	96:4[c]

[a]Reaction conditions: $PdCl_2(PPh_3)_2$ (0.06 mmol), TsOH (6 mmol), LiCl (6 mmol), alkene (30 mmol), H_2O (70 mmol), MEK (20 ml), CO (55 bar), 115 °C, 15-120 min. [b]Reaction conditions: Catalyst (0.06 mmol), TsOH (12 mmol), LiCl (12 mmol), alkene (30 mmol), H_2O (70 mmol), MEK (20 ml), CO (55 bar), 115 °C, 10-60 min. [c]bn:b = benzylic:branched products.

Claver and co-workers[19,20] continued investigations into the homogeneous system, substituting MEK for 1,2-dimethoxyethane (DME). Various PPh_3 derived ligands were evaluated with focus on the electronic and steric effects of the ligand on the regioselective outcome during the carbonylation of styrene (**3.25**), (Table 3-7). No definite trend could be established with respect to the electronic effect of the ligand. While the presence of the electron-donating methyl group on P(*p*-tolyl)$_3$ (Table 3-7, entry 1 vs. 2) exhibited a 15% drop in selectivity, the methoxy derivative, P(*p*-OMePh)$_3$, improved selectivity by 14% up to 98% when compared to PPh_3 (Table 3-7, entry 1 vs. 3). The electron deficient P(*p*-FPh)$_3$ ligand displayed selectivity of 79%, which is comparable to that of PPh_3 (Table 3-7, entry 1 vs. 4). A larger cone angle, however, portrayed a clear influence as PPh_2(*o*-tolyl), with a cone angle of 161° vs. 145° for P(*p*-tolyl)$_3$, exclusively formed the branched product, albeit at a slower rate (Table 3-7, entry 2 vs. 5).

Table 3-7: Hydroxycarbonylation of styrene (3.25) utilizing various monodentate ligands.[a]



Entry	Monophosphine (L)	Cone Angle	Conv. (%) [Yield (%)]	Ratio b:l
1[20]	PPh_3[a]	145	96	84:16
2[20]	P(*p*-tolyl)$_3$[a]	145	98	69:31
3[20]	P(*p*-OMePh)$_3$[a]	145	79	98:2
4[20]	P(*p*-FPh)$_3$[a]	145	96	79:21
5[20]	**PPh_2(*o*-tolyl)**[a]	**161**	**76**	**100:0**
6[26]	(**3.52**) MeP(2-CF_3Ph)[$C(Me)_3$][b]	178	99 [55]	200:1
7[26]	(**3.53**) *n*-BuP(2-CF_3Ph)[$C(Me)_3$][b]	183	69 [32]	200:1

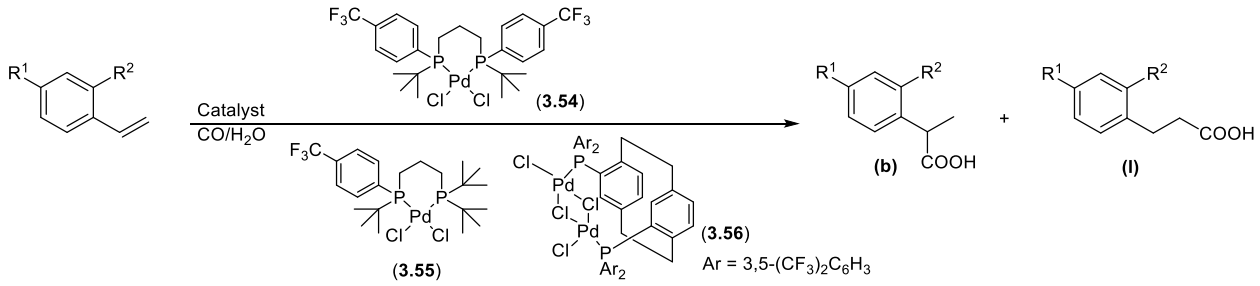
[a]Reaction conditions: $PdCl_2(PhCN)_2$ (0.04 mmol), ligand (0.16 mmol), $H_2C_2O_4$ (2.5 mmol), styrene (2.5 mmol), DME (10 ml), CO (30 bar), 100 °C, 20 h. [b]Reaction conditions: $PdCl_2L_2$ (1%), TsOH (20%), LiCl (20%), styrene (quantity not specified), H_2O (2.5 eq.), MEK (1.5 ml), CO (30 bar), 80 °C.

Clarke et al.[26] further expanded on the cone angle parameter by evaluating ligands **3.52** and **3.53** with respective cone angles of 178° and 183°. The larger cone angles further improved regioselectivity to >200:1 (Table 3-7, entries 6 and 7), though the larger ligands had a detrimental effect on the efficacy of the catalyst. The catalytic system with ligand **3.52** still managed full conversion within 6 hours, but yielded only 55% carboxylic acid product (Table 3-7, entry 6). The effect was even greater with the large 183° cone angle of **3.53**, for which only 69% conversion and a mere 32% yield carboxylic acid was observed over the same period (Table 3-7, entry 7). It is thus clear that, although a larger ligand improves regioselectivity, the rate of the reaction and product selectivity can be greatly compromised if the ligand becomes too bulky.

Although bidentate phosphine ligands tend to favour linear product formation, Clarke and co-workers[27,28,29] envisaged diphosphine palladium complexes which would yield the branched product preferentially (Table 3-8). The LiCl/TsOH/MEK/H_2O system was adopted and several ligands evaluated. The first catalyst to show promise with styrene (**3.25**) as substrate was **3.54** with a 67:1 regioselectivity toward 2-phenylpropionic acid (**3.26b**) (Table 3-8, entry 1).[27] Substituting one of the aryl units for another *tert*-butyl group, as in **3.55**, proved advantageous as regioselectivity was increased to 76:1 (Table 3-8, entry 2).[28] Superior results were, however, obtained when the entire ligand backbone was modified resulting in a dipalladium complex (**3.56**) which carboxylated styrene (**3.25**) to 2-phenylpropionic acid (**3.26b**) with >100:1 selectivity (Table 3-8, entry 3).[29] The substrate scope of the latter was expanded toward substituted styrene derivatives, of which the electron deficient derivatives (**3.40** and **3.57**)

exhibited similar results to unsubstituted styrene (**3.25**), (Table 3-8, entry 3 vs. 4 and 5). The presence of an electron-donating 4-*tert*-butyl substituent (**3.44**) proved detrimental as regioselectivity was decreased to 68:1 (Table 3-8, entry 6). The bulky catalyst also exhibited sensitivity toward steric factors as hydroxycarbonylation of 2-chlorostyrene (**3.59**) only achieved a 57:1 selectivity toward the branched product (**3.60b**) (Table 3-8, entry 7).

Table 3-8: Hydroxycarbonylation of styrene (3.25) and derivatives with Pd-complexes 3.54, 3.55 and 3.56.



Entry	R^1	R^2	Alkene	Catalyst	P_{CO} (bar) [Temp (°C)]	Yield (%)	Products	Ratio b:l
1[27]	H	H	**3.25**	**3.54**[a]	50 [100]	83	**3.26**	67:1
2[28]	H	H	**3.25**	**3.55**[a]	30 [120]	84	**3.26**	76:1
3[29]	H	H	**3.25**	**3.56**[b]	30 [70]	90	**3.26**	>100:1
4[29]	Cl	H	**3.40**	**3.56**[b]	30 [70]	99	**3.41**	>100:1
5[29]	COOH	H	**3.57**	**3.56**[b]	30 [50]	91	**3.58**	>100:1
6[29]	$C(Me)_3$	H	**3.44**	**3.56**[b]	30 [40]	40	**3.45**	68:1
7[29]	H	Cl	**3.59**	**3.56**[b]	30 [60]	89	**3.60**	57:1

[a]Reaction conditions: Catalyst (0.01 mmol), TsOH (0.2 mmol), LiCl (0.2 mmol), styrene (1 mmol), H_2O (2.5 mmol), MEK (1.5 ml), 16 h. [b]Reaction conditions: Catalyst (1 mol%), TsOH (20 mol%), LiCl (20 mol%), alkene (moles not specified), H_2O (2.5 eq.), MEK (1.5 ml), 19-22 h.

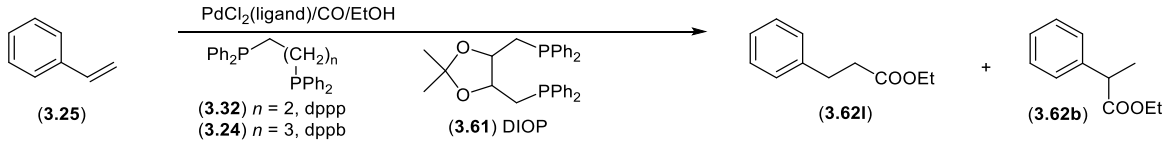
To conclude, although studies were generally limited to styrenes as substrates, MEK proved to be superior to toluene as solvent for the hydroxycarbonylation of these derivatives.[24] A connotation between the cone angle of the monodentate ligand and the regioselectivity induced by that ligand was observed. The highest reported regioselectivity (>200:1) was achieved in the presence of **3.52** with a cone angle of 178°.[26] Bulky bidentate ligands can also be effective with regioselectivity exceeding 100:1 toward the branched product.[29] The latter is, however, sensitive to steric influence in the vicinity of the double bond as well as the presence of electron donating groups on the substrate (vide supra).

3.3. Alkene alkoxycarbonylation with selectivity toward linear products

One of the first reports on the hydroesterification of alkenes toward linear esters was published by Sugi and Bando.[30] A number of bidentate ligands induced moderate regioselectivity when used together with $PdCl_2$ in the ethoxycarbonylation of aromatic olefin, styrene (**3.25**), (Table 3-9). The most promising ligands were 1,3-bis(diphenyl-phosphino)propane [dppp (**3.32**)], 1,4-

bis(diphenylphosphino)butane [dppb (**3.24**)] and 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane [DIOP (**3.61**)] with selectivities toward the linear ester (**3.62l**) of 72%, 68% and 72%, respectively (Table 3-9, entries 1-3). The catalytic system did not employ any acid and thus required 200 bar of CO at 120 °C.

Table 3-9: Ethoxycarbonylation of styrene (3.25) over diphosphine $PdCl_2$(ligand) complexes.[a]



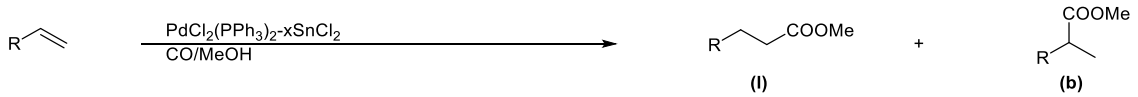
(**3.25**) (**3.62l**) (**3.62b**)

Entry	Catalyst	P_{CO} (bar) [Temp (°C)]	Yield (%)	Ratio l:b
1	$PdCl_2$(dppp)	200 [120]	41	72:28
2	$PdCl_2$(dppb)	200 [120]	70	68:32
3	$PdCl_2$(DIOP)	200 [120]	90	75:25

[a]Reaction conditions: Catalyst (0.15 mmol), styrene (50 mmol), EtOH (100 mmol), benzene (50 ml), 16 h.

In the same year, Knifton[31] evaluated a variety of bimetallic palladium complexes for the methoxycarbonylation of aliphatic olefin 1-heptene (**3.63**). $PdCl_2(PPh_3)_2$-10$SnCl_2$, was the most efficient and produced methyl octanoate (**3.64l**) with 87% regioselectivity at 140 bar CO and 70 °C (Table 3-10, entry 1). The substrate scope of the investigation also included other aliphatic substrates, like propene (**3.13**), 3-methyl-1-pentene (**3.66**) and 4-methyl-1-pentene (**3.68**), which exhibited preferences of 85%, 89% and 98%, respectively, toward the linear ester products (Table 3-10, entries 2-4). In a subsequent study by Kalck et al.,[32] a $PdCl_2(PPh_3)$-2-2.5$SnCl_2$ system also converted allylbenzene (**3.70**) to its linear ester, methyl 4-phenylbutanoate (**3.71l**), with 90% regioselectivity (Table 3-10, entry 5).

Table 3-10: Methoxycarbonylation of various olefins with Pd-Sn catalyst systems.



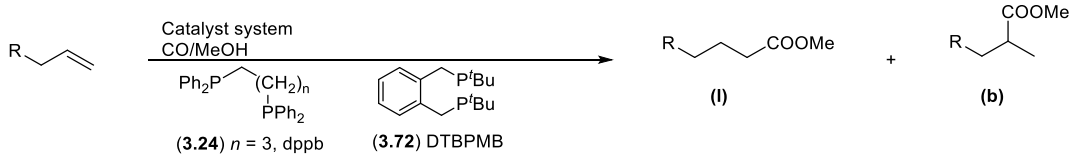
(**l**) (**b**)

Entry	R	Alkene	P_{CO} (bar) [Temp (°C)]	Conv. (%)	Products	Ratio l:b
1[31]	$(CH_2)_4CH_3$	**3.63**	140 [70][a]	96	**3.64**	87:13
2[31]	CH_3	**3.13**	140 [70][a]	90	**3.65**	85:15
3[31]	$CH(CH_3)CH_2CH_3$	**3.66**	140 [70][a]	71	**3.67**	98:2
4[31]	$CH_2CH(CH_3)_2$	**3.68**	140 [70][a]	86	**3.69**	89:11
5[32]	Bn	**3.70**	40 [100][b]	100	**3.71**	90:10

[a]Reaction conditions: $PdCl_2(PPh_3)_2$ (0.5-20 mmol), $SnCl_2$•$2H_2O$ (2.5-20 mmol), MeOH (5-15 ml), alkene (50-200 mmol), methyl isobutyl ketone (75 ml), 3 h. [b]Reaction conditions: $PdCl_2(PPh_3)_2$ (1 mmol), $SnCl_2$ (2.5 mmol), PPh_3 (2 mmol), alkene (100 mmol), MeOH (200 mmol), toluene (25 ml), 6 h.

Huh and Alper[33] followed with a palladium based system in which bidentate ligand dppb (**3.24**) was introduced to a monodentate hydrido precatalyst, $(Cy_3P)_2Pd(H)(H_2O)$, in the presence of TsOH (Tables 3-11 and 3-12). The system exhibited linear regioselectivity of 77% and 88% (Table 3-11, entries 1 and 2) for the methoxycarbonylation of 1-heptene (**3.77**) and 1-octene (**3.11**), respectively, while ca. 80% was observed for styrene (**3.25**), (Table 3-12, entry 1) and styrene derivatives **3.38**, **3.40** and **3.42**, (Table 3-12, entries 8-10). Alper et al.[34] continued to explore alternative catalyst systems and found 5-chloro-borosalicylic acid (5-Cl-BSA), formed in situ from 5-chlorosalicylic acid (5-Cl-SA) and boric acid [$B(OH)_3$], to also be an effective acid promoter in combination with $Pd(OAc)_2$ and P(*p*-tolyl)$_3$. Terminal olefins 1-decene (**3.80**), allylbenzene (**3.70**) and 4-methoxy-allylbenzene (**3.84**) were successfully converted to the respective linear methyl esters, **3.81l**, **3.71l** and **3.86l**, with 97-98% regioselectivity (Table 3-11, entries 3-5).

Table 3-11: Methoxycarbonylation of terminal aliphatic alkenes in various palladium systems.



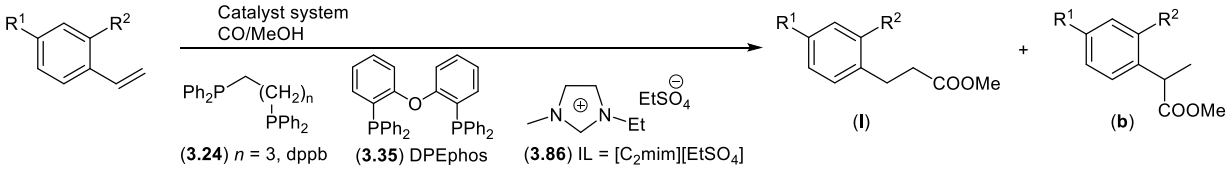
Entry	R	Alkene	Catalyst system	P_{CO} (bar) [T (°C)]	Conv. (%)	Prod.	Ratio l:b
1[33]	$(CH_2)_3CH_3$	**3.77**	$[(PCy_3)_2Pd(H)(H_2O)]BF_4$/TsOH/dppb[a]	20 [100]	82[b]	**3.78**	77:23
2[33]	$(CH_2)_4CH_3$	**3.11**	$[(PCy_3)_2Pd(H)(H_2O)]BF_4$/TsOH/dppb[a]	20 [100]	75[b]	**3.79**	88:12
3[34]	$(CH_2)_6CH_3$	**3.80**	$Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA[c]	30 [100]	92	**3.81**	97:3
4[34]	Ph	**3.70**	$Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA[c]	30 [100]	92[b]	**3.71**	97:3
5[34]	4-OMePh	**3.84**	$Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA[c]	30 [100]	60[b]	**3.85**	98:2
6[35]	$(CH_2)_4CH_3$	**3.11**	$Pd_2(dba)_3$/DTBPMB/MsOH[d]	1 [20]	98	**3.79**	99:1
7[35]	$(CH_2)_2CH_3$	**3.75**	$Pd_2(dba)_3$/DTBPMB/MsOH[d]	4 [20]	100	**3.76**	98:2
8[35]	$(CH_2)_8CH_3$	**3.82**	$Pd_2(dba)_3$/DTBPMB/MsOH[d]	4 [20]	71	**3.83**	99:1
9[36]	CH_2CH_3	**3.73**	$Pd(OAc)_2$/PPh_3/$Al(OTf)_3$[e]	50 [100]	100	**3.74**	78:22
10[37]	$(CH_2)_4CH_3$	**3.11**	$Pd(OAc)_2$/PPh_3/TsOH[f]	35 [80]	n.r.[g]	**3.79**	71:29

[a]Reaction conditions: $[(PCy_3)_2Pd(H)(H_2O)]BF_4$ (0.01 mmol), dppb (0.01 mmol), TsOH (0.02 mmol), alkene (0.1 mmol), MeOH (0.2 ml), THF (5 ml), 48 h. [b]Isolated yield. [c]Reaction conditions: $Pd(OAc)_2$ (0.03 mmol), P(*p*-tolyl)$_3$ (0.3 mmol), 5-chlorosalicylic acid (5-Cl-SA, 0.6 mmol), $B(OH)_3$ (0.3 mmol), alkene (2 mmol), MeOH (3 ml), 18 h. [d]Reaction conditions: $Pd_2(dba)_3$ (0.1 mmol), DTBPMB (0.5 mmol), MsOH (1 mmol), alkene (13 mmol), MeOH (10 ml), 3 h. [e]Reaction conditions: $Pd(OAc)_2$ (0.1 mmol), PPh_3 (0.9 mmol), $Al(OTf)_3$ (0.8 mmol), 1-pentene (50 ml), MeOH (50 ml), 3 h. [f]Reaction conditions: $Pd(OAc)_2$ (0.1 mmol), PPh_3 (0.8 mmol), $Al(OTf)_3$ (0.8 mmol), H_2SO_4 (0.2 mmol), MeOH (50 ml), 1-octene (50 ml). [g]n.r. = Not reported.

The substrate scope of the $Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA catalyst system was expanded to styrene (**3.25**) which was converted to methyl 3-phenylpropanoate (**3.87l**) with 90% selectivity (Table 3-12, entry 2). A variety of styrene derivatives (Table 3-12, entries 11-15) were also subjected to methoxycarbonylation and all exhibited regioselectivity greater than 85%. The cationic palladium complex, $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$, was also proven to be effective for

the methoxycarbonylation of styrene (**3.25**), with a regioselectivity of 73% toward the linear methyl ester (**3.87l**) (Table 3-12, entry 3).[9] Inoue et al.[9] also evaluated a bidentate cationic palladium complex, i.e. $[Pd(PhCN)_2(dppb)](BF_4)_2$, which exhibited superior regioselectivity (82%) to the monodentate version, $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$, (Table 3-12, entry 3 vs. 4). Regioselectivity achieved by this complex is thus identical to the Alper[33] system, albeit with inferior yield (29% vs. 97%, Table 3-12, entry 1 vs. 4). Van Leeuwen et al.[38] reported the palladium catalyst containing phenoxy ether ligand (**3.35**), i.e. $PdCl_2$(DPEphos), to give the linear ester (**3.87l**) from styrene (**3.25**) with 77% regioselectivity (Table 3-12, entry 5). Catalyst systems developed from $Pd_2(dba)_3$ and bis(di-*tert*-butylphosphinomethyl)benzene (**3.72**, DTBPMB) bidentate ligands by Cole-Hamilton et al.[35] exhibited excellent regioselectivity (>98%), though the substrate scope investigated was limited to aliphatic alkenes like 1-octene (**3.11**), 1-hexene (**3.75**) and 1-dodecene (**3.82**), (Table 3-11, entries 6-8). Shaughnessy et al.,[39] explored the effect of various ionic liquids in combination with $Pd(PPh_3)_2Cl_2$ and TsOH on the methoxycarbonylation of styrene (**3.25**). The highest regioselectivity (87%) toward the linear ester (**3.87l**) was observed in combination with 1-ethyl-3-methylimidazolium ethylsulfate $[C_2mim][EtSO_4]$ (Table 3-12, entry 6). Williams et al.[36] substituted the traditional Brønsted acid for a Lewis acid, i.e. $Al(OTf)_3$. It must be noted that although regioselectivity for styrene (**3.25**) was only 74% (Table 3-12, entry 7) this system holds another advantage, i.e. lower PPh_3 quaternization rates are observed when compared to the Brønsted systems, which translate to lower ligand loss during the course of the catalytic process. Williams and co-workers[36,37] also subjected the aliphatic alkenes, 1-pentene (**3.73**) and 1-octene (**3.11**), to this Lewis acid system to yield (**3.74l**) and (**3.79l**), respectively, in 78% and 71% selectivity (Table 3-11, entries 9 and 10).

Table 3-12: Methoxycarbonylation of styrene (3.25) and derivatives in various palladium catalytic systems.



Entry	R^1	R^2	Alkene	Catalyst system	P_{CO} (bar) [Temp (°C)]	Yield (%)	Prod.	Ratio l:b
1[33]	H	H	**3.25**	$[(PCy_3)_2Pd(H)(H_2O)]BF_4$/TsOH/dppb[a]	20 [100]	97	**3.87**	82:18
2[34]	H	H	**3.25**	$Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA[b]	40 [100]	66	**3.87**	90:10
3[9]	H	H	**3.25**	$[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$[c]	2 [80]	88	**3.87**	73:27
4[9]	H	H	**3.25**	$[Pd(PhCN)_2(dppb)](BF_4)_2$[c]	5 [80]	29	**3.87**	82:18
5[38]	H	H	**3.25**	$PdCl_2$(DPEphos)/HCl[d]	70 [100]	94	**3.87**	77:23
6[39]	H	H	**3.25**	$PdCl_2(PPh_3)_2$/PPh_3/TsOH/IL[e]	14 [90]	70	**3.87**	87:13
7[36]	H	H	**3.25**	$Pd(OAc)_2$/Al(OTf)$_3$/PPh_3[f]	35 [80]	95	**3.87**	74:26
8[33]	Me	H	**3.38**	$[(PCy_3)_2Pd(H)(H_2O)]BF_4$/TsOH/dppb[a]	20 [100]	90	**3.88**	79:21
9[33]	Cl	H	**3.40**	$[(PCy_3)_2Pd(H)(H_2O)]BF_4$/TsOH/dppb[a]	20 [100]	90	**3.89**	80:20
10[33]	Br	H	**3.42**	$[(PCy_3)_2Pd(H)(H_2O)]BF_4$/TsOH/dppb[a]	20 [100]	70	**3.90**	81:19
11[34]	Cl	H	**3.40**	$Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA[b]	40 [100]	72	**3.89**	85:15
12[34]	F	H	**3.29**	$Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA[b]	40 [100]	72	**3.91**	90:10
13[34]	^{t}Bu	H	**3.44**	$Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA[b]	40 [100]	91	**3.92**	88:12
14[34]	H	Me	**3.16**	$Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA[b]	40 [100]	60	**3.93**	97:3
15[34]	H	Br	**3.94**	$Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA[b]	40 [100]	65	**3.95**	98:2

[a]Reaction conditions: $[(PCy_3)_2Pd(H)(H_2O)]BF_4$ (0.01 mmol), dppb (0.01 mmol), TsOH (0.02 mmol), alkene (0.1 mmol), MeOH (0.2 ml), THF (5 ml), 48 h. [b]Reaction conditions: $Pd(OAc)_2$ (0.03 mmol), P(*p*-tolyl)$_3$ (0.3 mmol), 5-chlorosalicylic acid (0.6 mmol), $B(OH)_3$ (0.3 mmol), styrene (2 mmol), MeOH (3 ml), 18 h. [c]Reaction conditions: Catalyst (0.04 mmol), styrene (2 mmol), MeOH (2.5 ml), 4 h. [d]Reaction conditions: Pd:HCl:styrene:MeOH:toluene = 1:200:200:2000:8000, 16 h. [e]Reaction conditions: $PdCl_2(PPh_3)_2$ (0.05 mmol), PPh_3 (0.1 mmol), TsOH (0.13 mmol), styrene (2.2 mmol), IL (4 ml), MeOH (4 ml), 3 h. [g]Reaction conditions: $Pd(OAc)_2$ (0.05 mmol), PPh_3 (0.2 mmol), Al(OTf)$_3$ (0.1 mmol), styrene (50 mmol), MeOH (12 ml), 4 h.

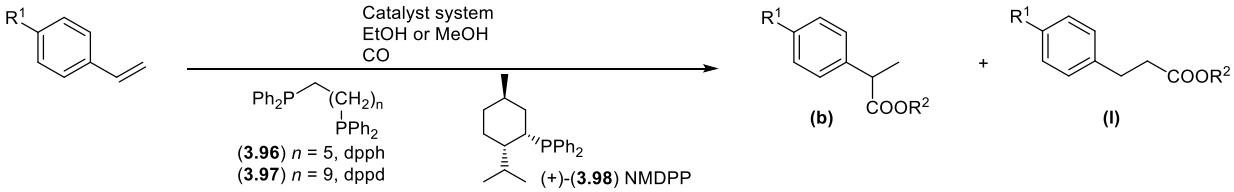
In summary, the alkoxycarbonylation of aliphatic substrates to their linear esters can be achieved in good regioselectivity with either of two systems, i.e. the monodentate $Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA system developed by Alper[34] or the bidentate $Pd(dba)_2$/DTBPMB/MsOH system reported by Cole-Hamilton.[35] The $Pd(OAc)_2$/P(*p*-tolyl)$_3$/ 5-Cl-BSA system displays regioselectivity of >97% for substrates with terminal non-conjugated double bonds like 1-decene (**3.80**), allylbenzene (**3.70**) and 4-methoxy-allylbenzene (**3.84**) (cf. Table 3-11, entries 3-5).[34] Linear ester yields for all these substrates are high (86-89%) with the exception of 4-methoxyallylbenzene (**3.84**) (60%), thus suggesting sensitivity to the electron density of the substrate as only 5% isomerisation is reported. As an alternative, the bidentate $Pd(dba)_2$/DTBPMB/MsOH system also proved to be effective for the transformation of terminal aliphatic alkenes such as 1-hexene (**3.75**), 1-octene (**3.11**) and 1-dodecene (**3.82**) to the linear esters with >98% regioselectivity (cf. Table 3-11, entries 6-8). The Alper system, $Pd(OAc)_2$/P(*p*-tolyl)$_3$/5-Cl-BSA, is also suitable for the alkoxycarbonylation of aromatic substrates and has been proven to transform a range of styrene derivatives (cf. Table 3-12, entries 11-15). Although regioselectivity toward the linear product is high for this system,

chemoselectivity results in only moderate yields of the ester. Linear selectivity for unsubstituted styrene (**3.25**) as well as 4-fluorostyrene (**3.29**) was 90%, with yields of 59% and 65%, respectively. Selectivities for 4-chloro- (**3.40**) and 4-*tert*-butylstyrene (**3.44**) are slightly lower (85% and 88% for the linear esters, respectively), and although the yield for the former (**3.89l**) is comparable to the fluoro analogue (61% vs. 65%), the latter yielded 80% linear ester (**3.92l**). *Ortho*-substituted methyl- (**3.16**) and bromostyrene (**3.94**) exhibited higher regioselectivity, ca. 97%, but yields remained moderate at 58% and 64%, respectively.

3.4. Alkene alkoxycarbonylation with selectivity toward branched products

The system reported by Sugi and Bando[30] in 1976 (cf. paragraph 3.3.) did not only produce linear esters, but could be manipulated toward branched regioselectivity upon modification of the ligand. Although the bidentate ligands, dppp (**3.32**), dppb (**3.24**) and DIOP (**3.61**), exhibited selectivity toward the formation of the linear ester (**3.62**) from styrene (**3.25**), (cf. Table 3-9), 1,2-bis(diphenylphosphino)hexane [dpph (**3.96**)] and 1,2-bis(diphenylphosphino)decane [dppd (**3.97**)] inverted regioselectivity (83% and 94%, respectively) toward ethyl 2-phenylpropanoate (**3.62b**), (Table 3-13, entries 1 and 2). Monodentate ligands, however, proved superior with regioselectivities >98% (Table 3-13, entries 3-7). With the exception of PBu_3 (Table 3-13, entry 7), all monodentate ligands produced the branched ester in >94% yield, with PPh_3 (Table 3-13, entry 3) being the most effective with 99% yield. The introduction of $CuCl_2$ into the $PdCl_2/PPh_3$ system, by Lee et al.,[40] allowed for milder reaction conditions, i.e. 41 bar of CO at 100 °C vs. 200 bar of CO at 120 °C. The $PdCl_2/CuCl_2/PPh_3$ system catalysed methoxycarbonylation of 4-methylstyrene (**3.38**) with 97% regioselectivity toward the branched ester (**3.88b**) in 93% yield (Table 3-13, entry 8). Nozaki et al.[41] achieved 100% selectivity toward methyl 2-phenylpropanoate (**3.62b**) at even milder conditions (20 bar CO and 50 °C) with $PdCl_2$ and neomenthyldiphenylphosphine [NMDPP (**3.98**)], as ligand (Table 3-13, entry 9). High regioselectivity (95%) was also obtained when $CyPPh_2$ was employed as ligand (Table 3-13, entry 10). Cometti[42] managed to perform methoxycarbonylation of styrene (**3.25**) by utilizing $Pd(dba)_2$ and NMDPP (**3.98**) at 2 bar CO when acid, i.e. trifluoroacetic acid (TFA), was added and claimed regioselectivity of 94% towards the branched product (**3.87b**) (Table 3-13, entry 11).

Table 3-13: Methoxycarbonylation of styrene and derivatives in mono- and diphosphine ligated palladium systems.

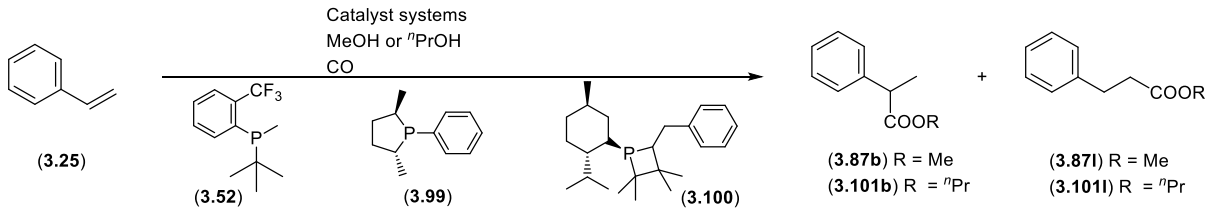


Entry	R^1	R^2	Alkene	Catalyst system	P_{CO} (bar) [Temp (°C)]	Yield (%)	Products	Ratio b:l
1[30]	H	Et	**3.25**	$PdCl_2$(dpph)[a]	200 [120]	78	**3.62**	83:17
2[30]	H	Et	**3.25**	$PdCl_2$(dppd)[a]	200 [120]	88	**3.62**	94:6
3[30]	H	Et	**3.25**	$PdCl_2(PPh_3)_2$[a]	200 [120]	99	**3.62**	99:1
4[30]	H	Et	**3.25**	$PdCl_2(BuPPh_2)_2$[a]	200 [120]	98	**3.62**	98:2
5[30]	H	Et	**3.25**	$PdCl_2(BzPPh_2)_2$[a]	200 [120]	98	**3.62**	98:2
6[30]	H	Et	**3.25**	$PdCl_2(PCy_3)_2$[a]	200 [120]	94	**3.62**	99:1
7[30]	H	Et	**3.25**	$PdCl_2(PBu_3)_2$[a]	200 [120]	76	**3.62**	99:1
8[40]	Me	Me	**3.38**	$PdCl_2/CuCl_2/PPh_3$[b]	40 [100]	96	**3.88**	97:3
9[41]	H	Et	**3.25**	$PdCl_2$/NMDPP[c]	20 [50]	96	**3.62**	100:0
10[41]	H	Et	**3.25**	$PdCl_2$/$CyPPh_2$[c]	40 [50]	76	**3.62**	95:5
11[42]	H	Me	**3.25**	$Pd(dba)_2$/NMDPP[d]	2 [50]	94	**3.87**	94:6

[a]Reaction conditions: Catalyst (0.15 mmol), styrene (50 mmol), EtOH (100 mmol), benzene (50 ml), 16 h. [b]Reaction conditions: $PdCl_2$ (0.5 mmol), $CuCl_2$ (1 mmol), PPh_3 (2 mmol), alkene (50 mmol), MeOH (4 ml), toluene (70 ml), 2 h. [c]Reaction conditions: $PdCl_2$ (0.01 mmol), ligand (0.02 mmol), styrene (1 mmol), MeOH (0.5 ml), acetone (2 ml), 24 h. [d]Reaction conditions: $Pd(dba)_2$ (0.7 mmol), ligand (2 mmol), alkene (15 mL), MeOH (15 mL), TFA (3 mL), 4 h.

Inoue et al.[9] discovered that by increasing CO pressure, the regioselectivity of a specific system may be inverted. Although the linear product (**3.87l**) dominated at 2 bar CO during the methoxycarbonylation of styrene (**3.25**) with $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$ (cf. Table 3-12, entry 1), an increase to 20 bar rendered the branched product (**3.87b**) with 83% regioselectivity (Table 3-14, entry 1). Results were improved by employing PPh_3 with $Pd(OAc)_2$ in the presence of TsOH yielding 95% ester with 93% regioselectivity toward methyl 2-phenylpropanoate (**3.87b**) at room temperature (Table 3-14, entry 2). Similar regioselectivity was observed by Ooka et al.[43] when methylsulfonic acid (MsOH) was employed instead of TsOH (Table 3-14, entry 3), but with greatly diminished yield (43%). The system developed by Clarke et al.[26] for the hydroxycarbonylation of styrene (**3.25**), (cf. Table 3-7, entry 6), also proved effective for alkoxycarbonylation but exhibited inferior regioselectivity when phosphine **3.52** was employed as ligand. The highest regioselectivity (73:1) was achieved during preparation of the *n*-propyl esters (**3.101b** and **3.101l**) of styrene (**3.25**), (Table 3-14, entry 4). Claver and co-workers[44,45] investigated the $PdCl_2$/TsOH system with several NMDPP derived monophosphine ligands for the methoxycarbonylation of styrene (**3.25**). Ligands **3.99** and **3.100** exhibited the best branched regioselectivities for the methoxycarbonylation of styrene (**3.25**) with 99:1 and 96:4 branched to linear ratios, respectively (Table 3-14, entries 5 and 6).

Table 3-14: Alkoxycarbonylation of styrene (3.25) with monophosphine ligated palladium systems.

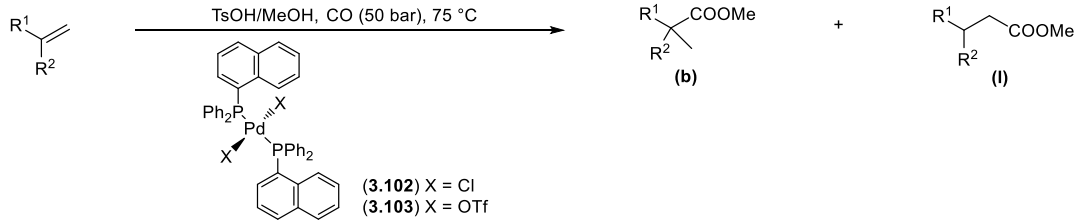


Entry	Catalyst system	P_{CO} (bar) [Temp (°C)]	Yield (%)	Product(s)	Ratio b:l
1[9]	$[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$[a]	20 [50]	55	**3.87**	83:17
2[9]	$Pd(OAc)_2/PPh_3/TsOH$[b]	20 [R.T.]	95	**3.87**	93:7
3[43]	$Pd(OAc)_2/PPh_3/MsOH$[c]	6 [R.T.]	43	**3.87**	91:9
4[26]	$PdCl_2$(**3.52**)$_2$/TsOH/LiCl[d]	30 [80]	73	**3.101**	73:1
5[45]	$PdCl_2$(**3.99**)$_2$/TsOH[e]	35 [50]	>99	**3.87**	99:1
6[45]	$PdCl_2$(**3.100**)$_2$/HCl[f]	50 [90]	95	**3.87**	96:4

[a]Reaction conditions: $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$ (0.04 mmol), MeOH (2.5 ml), styrene (2 mmol), 4 h. [b]Reaction conditions: $Pd(OAc)_2$ (0.04 mmol), PPh_3 (0.08 mmol), TsOH (0.1 mmol), styrene (2 mmol), MeOH (2.5 ml), 4 h. [c]Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), PPh_3 (0.04 mmol), MsOH (0.15 mmol), styrene (10 mmol), MeOH (1 ml), 17 h. [d]Reaction conditions: Catalyst (1%), TsOH (20%), LiCl (20%), nPrOH (1.5 ml), styrene (moles not specified). [e]Catalyst (0.02 mmol), TsOH (0.2 mmol), styrene (3 mmol), MeOH (2.5 ml), THF (2.5 ml), 24 h. [f]Reaction conditions: Catalyst (0.02 mmol), HCl (0.2 mmol), styrene (3 mmol), MeOH (2.5 ml), THF (2.5 ml), 24 h.

Aguirre et al.[46] evaluated naphthyl(diphenyl)phosphine palladium catalysts **3.102** and **3.103** under comparable conditions. Both exhibited excellent regioselectivity for the methoxycarbonylation of styrene (**3.25**), 92% and 93% towards the branched product (**3.87b**), respectively for both the chloride (**3.102**) and triflate (**3.103**) complexes, respectively (Table 3-15, entries 1 and 2). Although these complexes proved effective for the methoxycarbonylation of α-methylstyrene (**3.48**) as well with 88% and 90% branched regioselectivity (Table 3-15, entries 3 and 4), catalyst activity was significantly lower than for styrene (**3.25**). No significant regioselectivity could be observed when 1-hexene (**3.75**) was evaluated (Table 3-15, entries 5 and 6).

Table 3-15: Methoxycarbonylation of styrene (3.25), α-methylstyrene (3.48) and 1-hexene (3.75) over catalysts 3.102 and 3.103.[a]

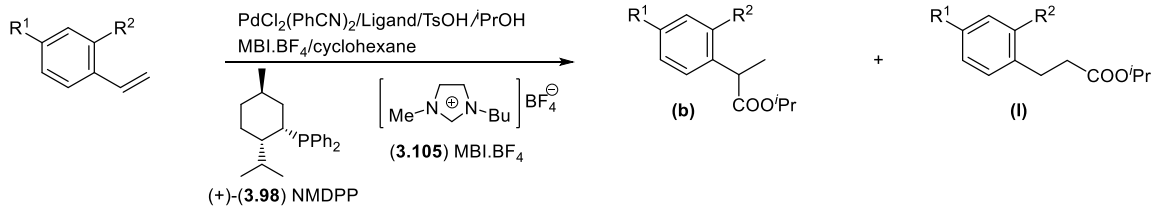


Entry	R^1	R^2	Alkene	Catalyst	Conversion (%)	Products	Ratio b:l
1[46]	Ph	H	**3.25**	**3.102**	93	**3.87**	92:8
2[46]	Ph	H	**3.25**	**3.103**	97	**3.87**	93:7
3[46]	Ph	Me	**3.48**	**3.102**	40	**3.104**	88:22
4[46]	Ph	Me	**3.48**	**3.103**	47	**3.104**	90:10
5[46]	$(CH_2)_3CH_3$	H	**3.75**	**3.102**	61	**3.76**	44:56
6[46]	$(CH_2)_3CH_3$	H	**3.75**	**3.103**	67	**3.76**	48:52

[a]Reaction conditions: Catalyst (0.04 mmol), TsOH (0.4 mmol), alkene (16 mmol), MeOH (5 ml), DCE (15 ml), 4-24 h.

Similar to Shaughnessy[39] (cf. Table 3-12, entry 6), Monteiro et al.[47] explored the effect of ionic liquid on the palladium catalysed hydroesterification of styrene (**3.25**) and its derivatives with isopropanol as nucleophile (Table 3-16). A variety of ligands were evaluated with styrene (**3.25**) as substrate, of which $CyPPh_2$ (Table 3-16, entry 1) induced 89% regioselectivity toward the branched ester (**3.106b**). Regioselectivity of 80% was achieved with PPh_3 at 10 bar (Table 3-16, entry 2), which was improved to 94% at 30 bar (Table 3-16, entry 3). NMDPP (**3.98**) was the most proficient ligand with 99% regioselectivity (Table 3-16, entry 4). The substrate scope was expanded with the NMDPP system to include 4-methyl- (**3.38**), 4-chloro- (**3.40**) and 4-methoxystyrene (**3.27**), while retaining selectivity (Table 3-16, entries 5-7). It must be noted, however, that chemoselectivity is substrate-dependent, with a yield of only 22% ester (**3.109**) being obtained from 4-methoxystyrene (**3.27**), whereas 2-chlorostyrene (**3.59**) yielded 60% ester (**3.110**) (Table 3-16, entries 7 and 8).

Table 3-16: Isopropyloxycarbonylation of styrene (3.25) and derivatives in ionic liquid.[a]



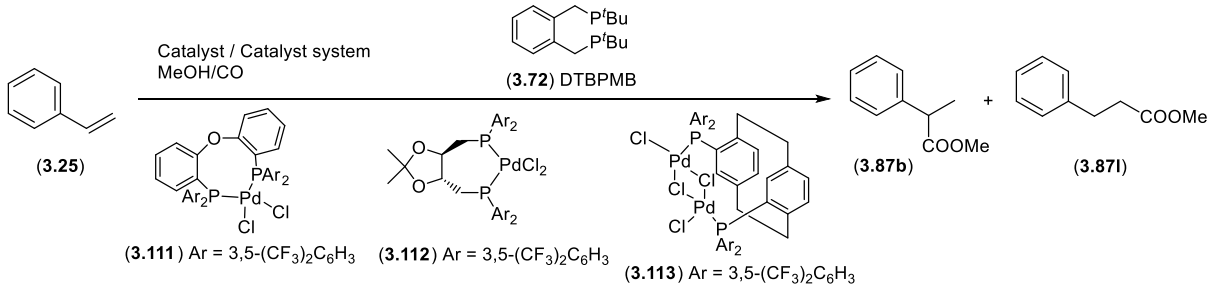
Entry	R^1	R^2	Alkene	Ligand	P_{CO} (bar) [Temp (°C)]	Yield (%)	Products	Ratio b:l
1[47]	H	H	**3.25**	$CyPPh_2$	10 [70]	n.r.[b]	**3.106**	89:11
2[47]	H	H	**3.25**	PPh_3	10 [70]	n.r.[b]	**3.106**	80:20
3[47]	H	H	**3.25**	PPh_3	30 [70]	n.r.[b]	**3.106**	94:6
4[47]	H	H	**3.25**	NMDPP (**3.98**)	10 [70]	89	**3.106**	>99:1
5[47]	Me	H	**3.38**	NMDPP (**3.98**)	10 [70]	76	**3.107**	>99:1
6[47]	Cl	H	**3.40**	NMDPP (**3.98**)	10 [70]	71	**3.108**	>99:1
7[47]	OMe	H	**3.27**	NMDPP (**3.98**)	10 [70]	22	**3.109**	>99:1
8[47]	H	Cl	**3.59**	NMDPP (**3.98**)	10 [70]	60	**3.110**	>99:1

[a]Reaction conditions: $PdCl_2(PhCN)_2$ (0.05 mmol), ligand (0.1 mmol), TsOH (0.25 mmol), styrene (4.5 mmol), IL (4 ml), ^{i}PrOH (8 ml), cyclohexane (12 ml), 20 h. [b]n.r. = Not reported.

Although less reported, bidentate ligands have also been found to induce branched regioselectivity. When the ligand reported by Cole-Hamilton[35] for linear ester formation of aliphatic olefins (cf. Table 3-11, entry 6-8), DTBPMB (**3.72**), was employed with $Pd(OAc)_2$ and TsOH, styrene (**3.25**) was transformed to the branched methyl ester (**3.87b**) with 89% regioselectivity (Table 3-17, entry 1). Two catalysts with CF_3-containing bidentate ligands, **3.111** and **3.112**, evaluated by Van Leeuwen et al.,[38] transformed styrene (**3.25**) into the branched ester (**3.87b**) with 74% and 92% regioselectivity, respectively (Table 3-17, entries 2 and 3). A decrease in pressure (30 bar vs. 70 bar) was, however, required to achieve the higher

selectivity at the cost of reaction rate with only 60% yield for **3.112** (Table 3-17, entry 3) compared to 98% yield for **3.111** (Table 3-17, entry 2). The dipalladium complex (**3.113**) reported by Clarke[29] for hydroxycarbonylation (cf. Table 3-8, entries 3-7) was also proven successful for the methoxycarbonylation of styrene (**3.25**). Similar to hydroxycarbonylation, alkoxycarbonylation was achieved with complete selectivity toward the branched product (**3.87b**) (Table 3-17, entry 4).

Table 3-17: Methoxycarbonylation of styrene (3.25) utilizing palladium complexes 3.111-3.113.

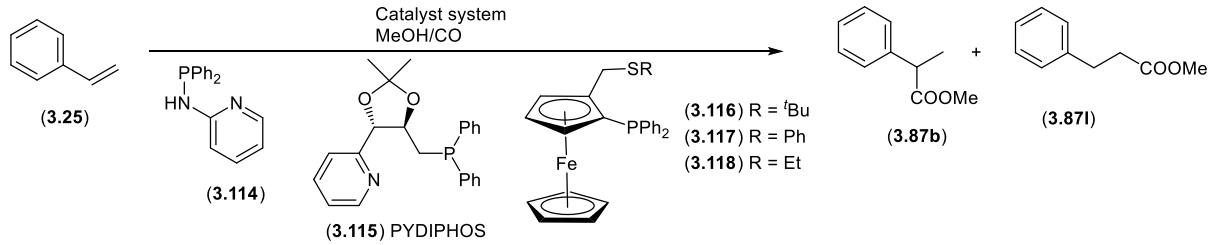


Entry	Catalyst/Catalyst system	P_{CO} (bar) [Temp (°C)]	Yield (%)	Ratio b:l
1[48]	$Pd(OAc)_2$/DTBPMB/MsOH[a]	6 [R.T.]	99	89:11
2[38]	(**3.111**)/HCl[b]	70 [100]	98	74:26
3[38]	(**3.112**)/HCl[b]	30 [90]	60	92:8
4[29]	(**3.113**)/TsOH/LiCl[c]	30 [60]	>99	>100:1

[a]Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), DTBPMB (**3.72**) (0.04 mmol), MsOH (0.15 mmol), styrene (10 mmol), MeOH (1 ml), 17 h. [b]Reaction conditions: Catalyst (0.015 mmol), HCl in Et_2O (2 M, 3 mmol), styrene (3 mmol), MeOH (30 mmol), toluene (5 mL), 16 h. [c]Reaction conditions: Catalyst (1 mol%), TsOH (20 mol%), LiCl (20 mol%), styrene (moles not specified), MeOH (2.5 eq.), MEK (1.5 ml) 22 h.

Diphosphine compounds are mostly employed as bidentate ligands, but several other heteroatomic compounds have also been reported as alternatives. Aguirre et al.[49] and Chelucci et al.[50] reported *P*,*N*-ligands, **3.114** and **3.115**, respectively, whereas Urrutigoity et al.[51] reported ferrocenyl derived *P*,*S*-ligands (**3.116**-**3.118**) for the alkoxycarbonylation of styrene (**3.25**) (Table 3-18). The *P*,*S*-ligands were employed in combination with MsOH and $Pd(OAc)_2$, which afforded >98% regioselectivity (Table 3-18, entries 1-3), albeit in moderate to high yield.[51] *P*,*N*-ligand **3.114** induced methoxycarbonylation with 97% regioselectivity to produce the branched ester (**3.87b**) in 96% yield in the presence of TsOH (Table 3-18, entry 4).[49] Perfect regioselectivity is claimed for the reaction catalysed by $PdCl_2$(**3.115**), although a pressure of 105 bar was required as no acid was introduced (Table 3-18, entry 5).[50]

Table 3-18: Methoxycarbonylation of styrene (3.25) in the presence of heteroatomic bidentate ligands 3.114-3.118.



Entry	Catalyst system	P_{CO} (bar) [Temp (°C)]	Yield (%)	Ratio b:l
1[51]	$Pd(OAc)_2$/(**3.116**)/MsOH[a]	20 [50]	80	98:2
2[51]	$Pd(OAc)_2$/(**3.117**)/MsOH[a]	40 [50]	75	99:1
3[51]	$Pd(OAc)_2$/(**3.118**)/MsOH[a]	20 [50]	69	98:2
4[49]	$PdCl_2$(**3.114**)/TsOH[b]	50 [75]	99	97:3
5[50]	$PdCl_2$(**3.115**)[c]	105 [100]	77	100:0

[a]Reaction conditions: $Pd(OAc)_2$ (0.02 mmol), ligand (0.02 mmol), MsOH (0.13 mmol), styrene (0.86 mmol), MeOH (1 ml), 24 h. [b]Reaction conditions: $PdCl_2$ (0.04 mmol), TsOH (0.4 mmol), styrene (16 mmol), toluene (15 ml), MeOH (5 ml), 6 h. [c]Reaction conditions: Catalyst (0.1 mmol), styrene (30 mmol), EtOH (5 ml), benzene (20 ml), 240 h.

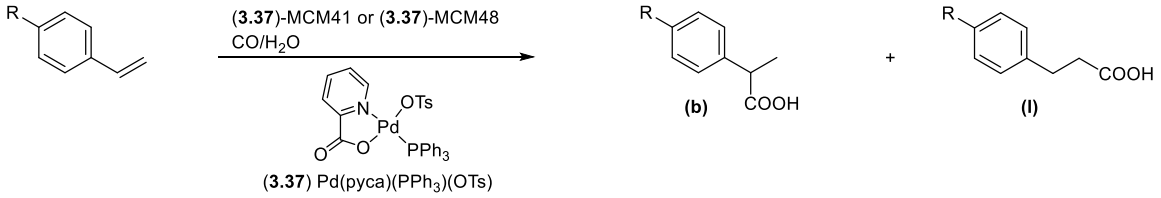
In summary, when styrene (**3.25**) is subjected to alkoxycarbonylation the branched product can be obtained in excellent (>97%) regioselectivity and chemoselectivity (ester yield >95%). When combined with PPh_3[30] or NMDPP[41] as ligand, $PdCl_2$ has shown to effectively catalyse the transformation of styrene (**3.25**) to its branched ester with 99-100% regioselectivity and 96-97% yield in the absence of a Brønsted acid (cf. Table 3-13, entries 1-10). Although the system with PPh_3 required 200 bar and 120 °C, the $PdCl_2$/NMDPP-catalyzed reaction proceeded satisfactory at 20 bar CO and 50 °C. Catalyst systems containing TsOH as acid co-catalyst achieved similar results utilizing NMDPP derived ligands (**3.99**) and (**3.100**)[45] as well as PPh_2NHPy (**3.114**),[49] i.e. 96-99% regioselectivity and 95-99% yield. Alternatively, the dipalladium complex (**3.113**) developed by Clarke[29] exhibited >100:1 regioselectivity and achieved >99% yield but requires the presence of additional LiCl (cf. Table 3-17, entry 4). It must be pointed out that the efficacy of some systems may be influenced by the substrate as is evident by the fact that inversion in regioselectivity to the linear product is observed for aliphatic olefins in the Cole-Hamilton $Pd_2(dba)_3$/DTBPMB system (Table 3-11, entries 6-8 vs. Table 3-17, entry 1).

3.5. Alkene carbonylation with heterogeneous catalyst systems

Heterogeneous catalysis has the major advantage of easy separation of catalyst and product. Consequently a few investigations have been reported where an immobilized palladium source is employed during the carbonylation of olefins. Chaudhari et al.[52] anchored their Pd(pyca)(PPh_3)(OTs) catalyst (**3.37**), (cf. Tables 3-5 and 3-6) on silicates MCM-41 and MCM-48, which proved to be highly active and regioselective for the hydroxycarbonylation, of 4-

methyl- (**3.38**), 4-*tert*-butyl- (**3.44**) and unsubstituted styrene (**3.25**) with >93% conversions and >99% regioselectivities toward the branched isomers (Table 3-19, entries 1-6).

Table 3-19: Hydroxycarbonylation of styrene (3.25) and styrene derivatives utilizing MCM-anchored palladium catalysts.[a]

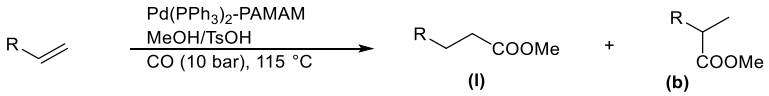


Entry	R	Alkene	Catalyst	Conv. (%)	Products	Ratio b:l
1	H	**3.25**	(**3.37**)-MCM41	98	**3.26**	99:1
2	H	**3.25**	(**3.37**)-MCM48	98	**3.26**	99:1
3	Me	**3.38**	(**3.37**)-MCM41	98	**3.39**	99:1
4	Me	**3.38**	(**3.37**)-MCM48	98	**3.39**	99:1
5	^{t}Bu	**3.44**	(**3.37**)-MCM41	93	**3.45**	99:1
6	^{t}Bu	**3.44**	(**3.37**)-MCM48	95	**3.45**	99:1

[a]Reaction conditions: Catalyst (50 mg; 0.18 wt% Pd for MCM41, 0.20 wt% Pd for MCM48), substrate (5 mmol), LiCl (0.5 mmol), TsOH (0.5 mmol), PPh_3 (0.1 mmol), H_2O (0.01 mmol), MEK (25 mL), CO (30 bar), 115 °C, 12 h.

The only heterogeneous catalyst to exhibit preference toward the linear ester during the methoxycarbonylation of styrene (**3.25**) has been reported by Reynhardt and Alper.[53] The palladium was immobilized by complex formation with PAMAM (polyamidoamine) dendrimers anchored to a silica support and rendered methyl 3-phenylpropanoate (**3.87l**), the linear ester, with 78% regioselectivity (Table 3-20, entry 1). The substrate scope was expanded to include several substituted styrene derivatives (**3.16**, **3.38**, **3.40** and **3.44**) as well as aliphatic olefins (**3.11**, **3.75** and **3.80**). Although moderate regioselectivity toward the linear products was obtained for 4-chlorostyrene (**3.40**) and 4-*tert*-butylstyrene (**3.44**), (Table 3-20, entries 2 and 3, 69% and 67%, respectively), 2-methylstyrene (**3.16**) was transformed with 93% regioselectivity (Table 3-20, entry 4). 1-Hexene (**3.75**), 1-octene (**3.11**) and 1-decene (**3.80**) yielded their respective linear esters, (**3.76l**), (**3.79l**) and (**3.81l**), in moderate regioselectivity, i.e. 71%, 76% and 65%, respectively (Table 3-20, entries 5-7).

Table 3-20: Methoxycarbonylation of aliphatic and aromatic olefins utilizing PAMAM immobilised $Pd(PPh_3)_2$ as catalyst.[a]

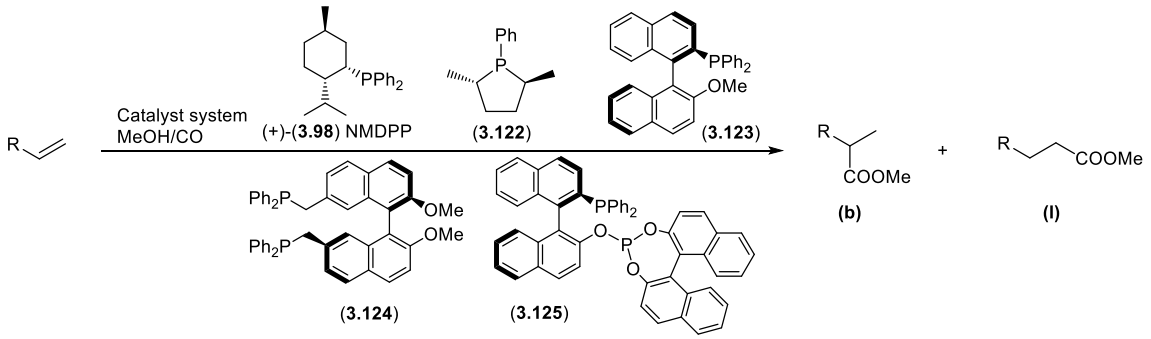


Entry	R	Alkene	Conversion (%)	Products	Ratio l:b
1[53]	Ph	**3.25**	>99	**3.87**	78:22
2[53]	4-ClPh	**3.40**	>99	**3.89**	69:31
3[53]	4-^{t}BuPh	**3.44**	>99	**3.92**	67:33
4[53]	2-MePh	**3.16**	>99	**3.93**	93:7
5[53]	$(CH_2)_3CH_3$	**3.75**	63	**3.76**	71:29
6[53]	$(CH_2)_5CH_3$	**3.11**	75	**3.79**	76:24
7[53]	$(CH_2)_7CH_3$	**3.80**	>99	**3.81**	65:35

[a]Reaction conditions: Catalyst (0.002 mmol Pd), PPh_3 (0.05 mmol), TsOH (0.07 mmol), alkene (2 mmol), MeOH (5 mL), toluene (5 ml), CO (10 bar), 115 °C, 22 h.

Lee and Alper[54] as well as Nozaki et al.[55] employed montmorillonite clay as solid support for $Pd(OAc)_2$ and $PdCl_2$, respectively. In both instances branched regioselectivity was observed. PPh_3 was employed with the Alper[54] system and converted 4-methyl- (**3.38**), 2-methyl- (**3.16**) and 4-isobutylstyrene (**3.119**) to esters **3.88b**, **3.93b** and **3.120b** with 100% regioselectivity (Table 3-21, entries 1-3). 1-Octene (**3.11**) and 1-decene (**3.80**) were also converted with some regioselectivity (ca. 70%), but the activity of this system towards aliphatic substrates was very low with less than 30% of the substrate being converted (Table 3-21, entries 4 and 5). Nozaki et al.[55] explored other mono- and bidentate ligands for clay-supported $PdCl_2$, together with PPh_3, for the methoxycarbonylation of styrene (**3.25**). With the exception of (**3.124**, 86%), ligands **3.98** and **3.121**-**3.123** all rendered >98% branched selectivity (Table 3-21, entries 6-10). The conversion with catalyst systems containing ligands **3.121**, **3.123** and **3.124** were, however, below 50% (Table 3-21, entries 8-10) whereas the efficacy of **3.122** was comparable to NMDPP (**3.98**), (Table 3-21, entries 6 vs. 7). Poly(*N*-vinyl-2-pyrrolidine) (PVP) has also been utilized as support for bimetallic Pd(II)-Ni(II) and Pd(II)-Cu(II) catalysts.[56] Both complexes effectively catalysed the transformation of styrene (**3.25**) to methyl 2-phenylpropanoate (**3.87b**) in excellent (>98%) regioselectivity (Table 3-21, entries 11 and 12).

Table 3-21: Methoxycarbonylation of aliphatic and aromatic olefins utilizing clay and PVP immobilised palladium catalysts.



Entry	R	Alkene	Catalyst system	P_{CO} (bar) [Temp (°C)]	Conv. (%)	Products	Ratio b:l
1[54]	4-MePh	**3.38**	$Pd(OAc)_2$-clay/PPh_3/HCl[a]	40 [125]	100	**3.88**	100:0
2[54]	2-MePh	**3.16**	$Pd(OAc)_2$-clay/PPh_3/HCl[a]	40 [125]	100	**3.93**	100:0
3[54]	4-^{i}BuPh	**3.119**	$Pd(OAc)_2$-clay/PPh_3/HCl[a]	40 [125]	88	**3.120**	100:0
4[54]	$(CH_2)_5CH_3$	**3.11**	$Pd(OAc)_2$-clay/PPh_3/HCl[a]	40 [125]	29	**3.79**	66:34
5[54]	$(CH_2)_7CH_3$	**3.80**	$Pd(OAc)_2$-clay/PPh_3/HCl[a]	40 [125]	25	**3.81**	72:28
6[55]	Ph	**3.25**	$PdCl_2$-clay/**3.98**/HCl[b]	40 [125]	77	**3.87**	100:0
7[55]	Ph	**3.25**	$PdCl_2$-clay/**3.122**/HCl[b]	40 [125]	78	**3.87**	100:0
8[55]	Ph	**3.25**	$PdCl_2$-clay/**3.121**/HCl[b]	40 [125]	49	**3.87**	98:2
9[55]	Ph	**3.25**	$PdCl_2$-clay/**3.123**/HCl[b]	40 [125]	23	**3.87**	100:0
10[55]	Ph	**3.25**	$PdCl_2$-clay/**3.124**/HCl[b]	40 [125]	52	**3.87**	86:14
11[56]	Ph	**3.25**	$PdCl_2$-PVP/4$NiCl_2$/PPh_3[c]	20 [80]	100	**3.87**	99:1
12[56]	Ph	**3.25**	$PdCl_2$-PVP/4$CuCl_2$/5PPh_3[c]	20 [80]	99	**3.87**	98:2

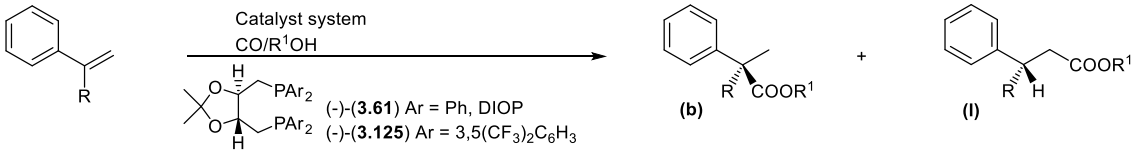
[a]Reaction conditions: Catalyst (0.009 mmol Pd), PPh_3 (0.02 mmol), conc. HCl (0.05 mL), alkene (1.5 mmol), MeOH (9 mmol), benzene (10 ml), 24 h. [b]Reaction conditions: Pd-clay (0.002 mmol Pd), ligand (0.010 mmol), conc. HCl (0.10 mL), styrene (1.0 mmol), MeOH (6.0 mmol), benzene (10 mL), 24 h. [c]Reaction conditions: Catalyst (0.04 mmol Pd), $NiCl_2$ or $CuCl_2$ (0.16 mmol), alkene (1 mmol), MeOH (0.8 mL), benzene (10 mL), 10 h.

3.6. Stereoselective hydroxycarbonylation and alkoxycarbonylation of alkenes

The pioneers of stereoselective hydroxy- and alkoxycarbonylation is Consiglio and Pino.[57] Their initial work focussed on the ethoxycarbonylation of styrene (**3.25**) utilizing bidentate (-)-DIOP (**3.61**) as chiral ligand in combination with $PdCl_2$ and HCl to yield the branched product, (*S*)-ethyl 2-phenylpropanoate (**3.62b**), with an enantiomeric excess (ee) of 2% (Table 3-22, entry 1).[7] When α-methylstyrene (**3.48**) was subjected to the reaction conditions the linear product, (*S*)-ethyl 3-phenylbutanoate (**3.127l**), was formed with an ee of 10% (Table 3-22, entry 2).[7] With isopropanol and methanol as nucleophiles, the ee for the latter was improved to 14% and 19%, respectively (Table 3-22, entries 3 and 4).[7] Consiglio[58] expanded the investigation to the hydroxycarbonylation of α-methylstyrene (**3.48**) with water as nucleophile, which yielded an optical purity of 60% towards (*S*)-3-phenylbutanic acid (**3.49l**), but the reaction suffered from low chemoselectivity (Table 3-22, entry 5). The hydroxycarbonylation of styrene (**3.25**) catalysed by $PdCl_2$/(**3.61**)/HCl was evaluated and gave the branched isomer of the (*S*)-carboxylic acid (**3.26b**) in 10% ee (Table 3-22, entry 6). Similar results were observed when

H_2O was substituted for ^{t}BuOH as nucleophile (Table 3-22, entry 7).[57] The DIOP ligand, (-)-(**3.61**), was later revisited by Van Leeuwen et al.[38] for the methoxycarbonylation of styrene (**3.25**), and although a conversion of only 25% with no regioselectivity was reported, the (*S*)-methyl ester (**3.87b**) was obtained with 30% ee (Table 3-22, entry 8). Conversion was improved to 76% following the introduction of CF_3-substituents (cf. Table 3-17, entry 3) to the DIOP ligand (-)-(**3.125**) and replacing HCl with TsOH, but resulted in a slight drop in ee to 23% (Table 3-22, entry 9).

Table 3-22: Enantioselective carbonylation of styrene (3.25) and α-methylstyrene (3.48) utilizing chiral DIOP ligands.



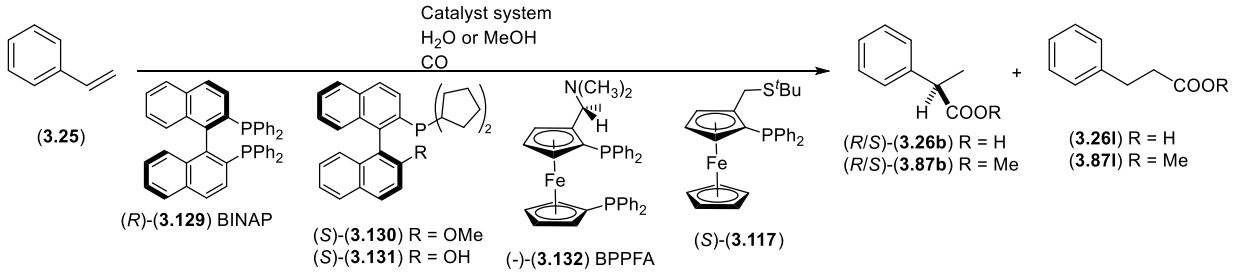
Entry	R	R^1	Alkene	Catalyst system	P_{CO} (bar) [Temp (°C)]	Conv. (%) [Yield (%)]	Product	ee (%)
1[7]	H	Et	**3.25**	$PdCl_2$/(-)-**3.61**/HCl[a]	300 [100]	95 [68]	*S*-**3.62b**	2
2[7]	Me	Et	**3.48**	$PdCl_2$/(-)-**3.61**/HCl[a,b]	300 [100]	70 [40]	*S*-**3.127l**	10
3[7]	Me	^{i}Pr	**3.48**	$PdCl_2$/(-)-**3.61**/HCl[a,c]	300 [100]	90 [80]	*S*-**3.128l**	14
4[57]	Me	Me	**3.48**	$PdCl_2$/(-)-**3.61**/HCl[d]	400 [100]	n.r.[e]	*S*-**3.104l**	19
5[58]	Me	H	**3.48**	$PdCl_2$/(-)-**3.61**/HCl[f]	400 [100]	n.r.[e]	*S*-**3.49l**	60
6[57]	H	H	**3.25**	$PdCl_2$/(-)-**3.61**/HCl[g]	400 [100]	n.r.[e]	*S*-**3.26b**	10
7[57]	H	^{t}Bu	**3.25**	$PdCl_2$/(-)-**3.61**/HCl[g]	700 [100]	n.r.[e]	*S*-**3.126b**	10
8[38]	H	Me	**3.25**	$PdCl_2$/(-)-**3.61**/HCl[h]	30 [90]	25 [19]	*S*-**3.87b**	30
9[38]	H	Me	**3.25**	$PdCl_2$/(-)-**3.125**/TsOH[h]	30 [90]	76 [71]	*S*-**3.87b**	23

[a]Reaction conditions: $PdCl_2$ (0.5 mmol), DIOP (1.0 mmol), alkene (100 mmol), H_2O or MeOH (50 mL), catalytic HCl., 20 h. [b]43 h. [c]117 h. [d]Reaction conditions: $PdCl_2$:DIOP 1:2 (quantity not specified), alkene (100 mmol), MeOH (150 mmol), benzene (40 mL). [e]n.r. = not reported. [f]Reaction conditions: $PdCl_2$:DIOP 1:2, other reaction conditions not specified. [g]No additional reaction conditions reported. [h]Reaction conditions: $PdCl_2$ (0.01 mol%), DIOP (0.02 mol%), HCl or TsOH (1 eq.), alkene, MeOH (10 eq.), THF (10 eq.), 24 h.

(*R*)-BINAP (**3.129**) and (-)-BPPFA (**3.132**) have also been employed for both hydroxy- and methoxycarbonylation of styrene (**3.25**). For the hydroxycarbonylation of styrene (**3.25**), Claver et al.[20] obtained ee values of 11% and 4% with (*R*)-BINAP (**3.129**) and (-)-BPPFA (**3.132**), respectively (Table 3-23, entries 1 and 2), while Inoue et al.[9] reported 12% and 86% ee for methoxycarbonylation (Table 3-23, entries 3 and 4). Although the BINAP yielded similar results for the two transformations (Table 3-23, entry 1 vs. 3), BPPFA resulted in much higher stereoselectivity under methoxycarbonylation conditions (Table 3-23, entry 2 vs. 4). The methoxycarbonylation of styrene was also performed in the presence of modified BINAP and BPPFA ligands, i.e. (*S*)-(**3.117**), (*S*)-(**3.130**) and (*S*)-(**3.131**). Although the ferrocenyl ligand, (*S*)-(**3.117**), evaluated by Urrutigoity et al.[51] (cf. Table 3-18, entries 1-3) proved to be inferior with only 10% ee (Table 3-23, entry 5), the ee value could be increased slightly to 17% (Table 3-23, entry 6), but with compromising effects on the conversion (20% vs. 83%). However,

catalytic systems with BINAP derivatives (*S*)-**3.130** and (*S*)-**3.131**, developed by Nozaki et al.[41] (cf. Table 3-21, entry 9), significantly improved ee values to ca. 47% (Table 3-23, entries 7 and 8).

Table 3-23: Enantioselective carbonylation of styrene (3.25) utilizing various chiral ligands.

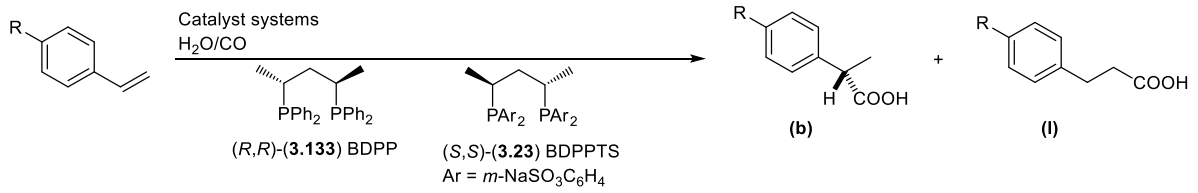


Entry	Catalyst system	P_{CO} (bar) [Temp (°C)]	Conv. (%) [Yield (%)]	Products	Ratio b:l	ee (%)
1[20]	$[PdCl_2(PhCN)_2]$/(*R*)-**3.129**/$H_2C_2O_4$[a]	20 [150]	42	**3.26**	30:70	11 (*R*)
2[20]	$[PdCl_2(PhCN)_2]$/(-)-**3.132**/$H_2C_2O_4$[a]	20 [150]	88	**3.26**	15:85	4 (*R*)
3[9]	$Pd(OAc)_2$/(*S*)-**3.129**/TsOH[b]	20 [RT]	[5]	**3.87**	48:52	12 (*S*)
4[9]	$Pd(OAc)_2$/(+)-**3.132**/TsOH[b]	20 [RT]	[17]	**3.87**	44:56	86 (*S*)
5[51]	$Pd(OAc)_2$/(*S*)-**3.117**/MsOH[c]	20 [50]	83 [80]	**3.87**	98:2	10[e]
6[51]	$Pd(OAc)_2$/(*S*)-**3.117**/MsOH[c,d]	20 [25]	20 [19]	**3.87**	99:1	17[e]
7[41]	$PdCl_2$/(*S*)-**3.130**[f]	30 [40]	[72]	**3.87**	100:0	46 (*S*)
8[41]	$PdCl_2$/(*S*)-**3.131**[f,g]	30 [40]	85	**3.87**	100:0	48 (*S*)

[a]Reaction conditions: $PdCl_2(PhCN)_2$ (0.04 mmol), ligand (0.4 mmol), $H_2C_2O_4$ (2.5 mmol), styrene (2.5 mmol), DME (10 mL), 24h. [b]Reaction conditions: $Pd(OAc)_2$ (0.04 mmol), ligand (0.04 mmol), TsOH (0.10 mmol), styrene (2 mmol), MeOH (2.5 mL), 20 h. [c]Reaction conditions: $Pd(OAc)_2$ (0.017 mmol), ligand (0.017 mmol), MsOH (0.13 mmol), styrene (0.86 mmol), MeOH (1 mL), 24 h. [d]48 h. [e]Enantiomer not reported. [f]Reaction conditions: $PdCl_2$ (0.010 mmol), ligand (0.020 mmol), styrene (1 mmol), MeOH (0.5 mL), benzene (2.0 mL), 19-24 h. [g]THF instead of benzene.

Claver et al.[20] also evaluated the stereoinduction of chiral bidentate ligand (*R*,*R*)-BDPP (**3.133**) on styrene (**3.25**), but obtained only 3% ee (Table 3-24, entry 1). Sulfonated BDPP, i.e. (*S*,*S*)-BDPPTS (**3.23**), as reported by Claver et al.[18] (cf. Table 3-3, entries 3-8), was more effective and converted unsubstituted (**3.25**), 4-methoxy- (**3.27**) and 4-fluorostyrene (**3.29**) to the respective carboxylic acids with 32%, 43% and 36% ee, respectively (Table 3-24, entries 2-4).

Table 3-24: Enantioselective hydroxycarbonylation of styrene (3.25), 4-methoxy- (3.27) and 4-fluorostyrene (3.29).

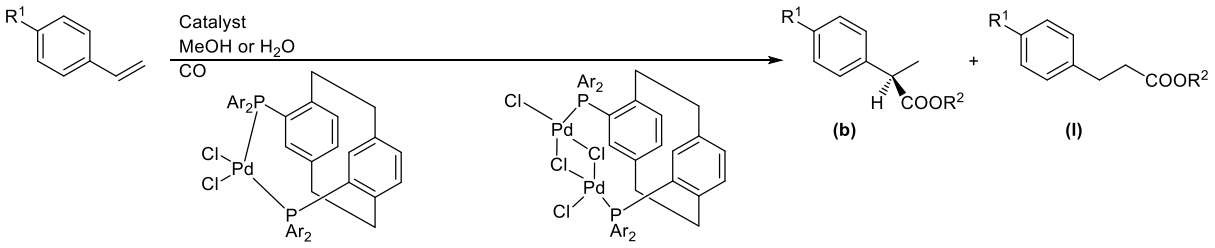


Entry	R	Alkene	Catalyst system	Conv. (%)	Products	Ratio b:l	ee (%)
1[20]	H	**3.25**	$[PdCl_2(PhCN)_2]/(BDPP)/H_2C_2O_4$[a]	35	**3.26**	31:69	3[b]
2[18]	H	**3.25**	$Pd(OAc)_2/(BDPPTS)/H_2SO_4$[c]	99	**3.26**	34:66	32 (*S*)
3[18]	OMe	**3.27**	$Pd(OAc)_2/(BDPPTS)/H_2SO_4$[c,d]	98	**3.28**	45:55	43 (+)
4[18]	F	**3.29**	$Pd(OAc)_2/(BDPPTS)/H_2SO_4$[c,d]	99	**3.30**	35:65	36 (+)

[a]Reaction conditions: $PdCl_2(PhCN)_2$ (0.04 mmol), ligand (0.4 mmol), $H_2C_2O_4$ (2.5 mmol), styrene (2.5 mmol), DME (10 mL), CO (20 bar), 150 °C, 24h. [b]Enantiomer not reported. [c]Reaction conditions: $Pd(OAc)_2$ (0.04 mmol), ligand (0.08 mmol), dil. H_2SO_4 (2.5 M to pH 3.5), substrate (2.5 mmol), H_2O (10 mL), CO (20 bar), 120 °C, 16 h. [d]100 °C.

The system developed by Clarke and co-workers[29,59] (cf. Tables 3-8 and 3-17) has also effectively induced stereoselectivity during the hydroxy- and methoxycarbonylation of styrene (**3.25**). Catalyst (*R*)-**3.135** converted styrene to the branched carboxylic acid, (*R*)-**3.26b**, and methyl ester, (*R*)-**3.87b**, with 80% and 91% ee, respectively (Table 3-25, entries 1 and 2) albeit with no significant regioselectivity. Upon modification of this catalyst to (*R*)-**3.134**, the latter could be addressed. Methoxycarbonylation of styrene (**3.25**) now achieved a 4:1 preference toward the branched ester, (*R*)-**3.87b**, (Table 3-25, entry 3) with 93% ee when the monopalladium species (*R*)-**3.134** was employed. The dipalladium complex, (*R*)-**3.114**, proved superior for hydroxycarbonylation with >100:1 branched regioselectivity and 77% ee (Table 3-25, entry 4). The respective acids of 4-chloro- (*R*)-(**3.40b**), 4-*tert*-butyl- (*R*)-(**3.44b**) and 4-carboxystyrene (*R*)-(**3.57b**) could also be obtained in the same manner with similar success (Table 3-25, entries 5-7).

Table 3-25: Enantioselective carbonylation of styrene (3.25) and derivatives with palladium complexes 3.114, 3.134 and 3.135.



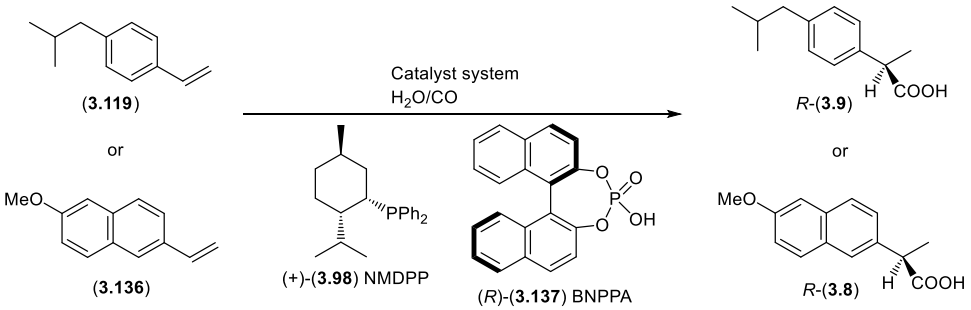
(*R*)-(**3.134**) Ar = 3,5-(^{t}Bu)$_2$-4-(MeO)C$_6$H$_2$ (*R*)-(**3.114**) Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$
(*R*)-(**3.135**) Ar = 3,5-(Me$_2$C$_6$H$_3$)

Entry	R^1	R^2	Alkene	Catalyst	Temp (°C)	Yield (%)	Products	Ratio b:l	ee (%)
1[59]	H	H	**3.25**	(*R*)-**3.135**[a]	50	71	**3.26**	52:48	80 (*R*)
2[59]	H	Me	**3.25**	(*R*)-**3.135**[a,b]	25	71	**3.87**	49:51	91 (*R*)
3[29]	H	Me	**3.25**	(*R*)-**3.134**[a,c]	35	72	**3.87**	80:20	93 (*R*)
4[29]	H	H	**3.25**	(*R*)-**3.114**[a,d]	70	90	**3.26**	>100:1	77 (*R*)
5[29]	Cl	H	**3.40**	(*R*)-**3.114**[a,e]	70	>99	**3.41**	>100:1	66 (*R*)
6[29]	^{t}Bu	H	**3.44**	(*R*)-**3.114**[a,e]	40	40	**3.45**	68:1	62 (*R*)
7[29]	COOH	H	**3.57**	(*R*)-**3.114**[a,e]	50	91	**3.58**	>100:1	66 (*R*)

[a]Reaction Conditions: Catalyst (1 mol%), LiCl (20 mol%), TsOH (20 mol%), alkene (1 mmol), H_2O (2.5 mmol), MEK (1.5 mL), CO (30 bar), 42 h. [b]No H_2O, MeOH instead of MEK. [c]Catalyst (0.5 mol%), MeOH instead of H_2O, 71 h. [d]19 h. [e]22 h.

Some systems have only been evaluated under hydroxycarbonylation conditions. Alper and Hamel,[60] for example, developed a palladium/copper system which employed (*S*)- and (*R*)-BNPPA (**3.137**) as chiral monodentate ligands for the preparation of ibuprofen (**3.9**) and naproxen (**3.8**) from 4-isobutylstyrene (**3.119**) and 2-vinyl-6-methoxynaphthalene (**3.136**), respectively. Both BNPPA stereoisomers were evaluated in the $PdCl_2/CuCl_2$ catalytic hydroxycarbonylation systems and gave comparable results (83-91% ee) for the preparation of both *R* and *S* enantiomers of ibuprofen (Table 3-26, entries 1 and 2) and naproxen (Table 3-26, entries 3 and 4). Cometti and Chiusoli[42] utilized $Pd(dba)_2$ together with (+)-NMDPP (**3.98**) to also convert 2-vinyl-6-methoxynaphthalene (**3.136**) to its corresponding (*S*)-methyl ester (**3.8**) with 42% ee (Table 3-26, entry 5).

Table 3-26: Preparation of enantio-enriched naproxen (3.8) and ibuprofen (3.9) from their respective styrene precursors.

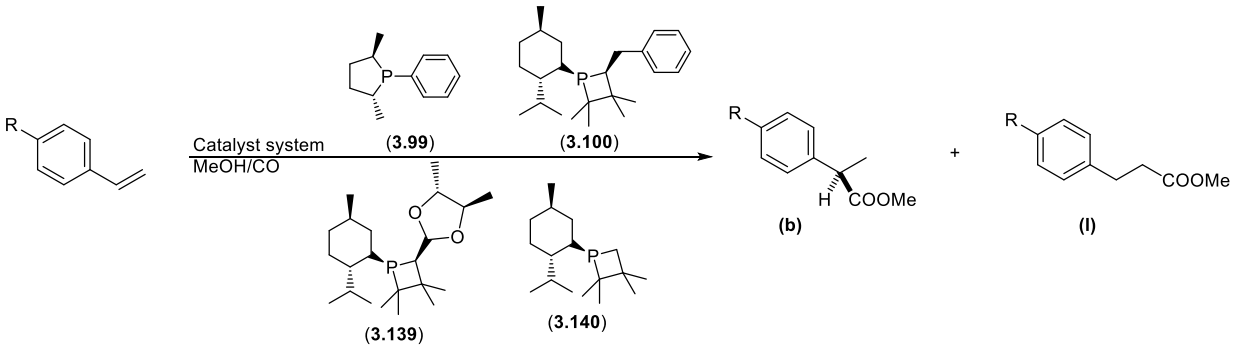


Entry	Alkene	Catalyst system	Ligand (L)	P_{CO} (bar) [Temp (°C)]	Yield (%)	Product	ee (%)
1[60]	**3.119**	$PdCl_2/CuCl_2$/(L)/HCl/O_2[a]	(*S*)-**3.137**	1 [RT]	89	(*S*)-**3.9**	83
2[60]	**3.119**	$PdCl_2/CuCl_2$/(L)/HCl/O_2[a]	(*R*)-**3.137**	1 [RT]	81	(*R*)-**3.9**	84
3[60]	**3.136**	$PdCl_2/CuCl_2$/(L)/HCl/O_2[a,b]	(*S*)-**3.137**	1 [RT]	71	(*S*)-**3.8**	85
4[60]	**3.136**	$PdCl_2/CuCl_2$/(L)/HCl/O_2[a]	(*R*)-**3.137**	1 [RT]	64	(*R*)-**3.8**	91
5[42]	**3.136**	$Pd(dba)_2$/(L)/TFA[c]	(+)-**3.98**	2 [50]	n.r.[d]	(*S*)-**3.8**	42

[a]Reaction conditions: $PdCl_2$ (0.39 mmol), $CuCl_2$ (0.74 mmol), ligand (0.15 mmol), conc. HCl (0.5 mL), alkene (3 mmol), H_2O (0.5 mL), THF (15 mL), CO/O_2 mixture (1 bar), 18 h. [b]Ligand (0.20 mmol), alkene (4 mmol). [c]Reaction conditions: $Pd(dba)_2$ (0.7 mmol), ligand (2 mmol), alkene (15 mL), MeOH (15 mL), trifluoroacetic acid (3 mL), 4 h. [d]n.r.= Not reported.

Claver and co-workers[44,45] followed by preparing some NMDPP-inspired ligands (cf. Table 3-14). $PdCl_2$/TsOH in the presence of ligand **3.100**, as well as complex $PdCl_2$(**3.99**)$_2$, catalysed the formation of (*R*)-**3.87b** and (*S*)-**3.87b** in ca. 10% ee (Table 3-27, entries 1 and 2), whereas 29% ee of the *R*-isomer could be obtained with $PdCl_2$(**3.139**)$_2$ (Table 3-27, entry 3). Although the ee was improved with complex $PdCl_2$(**3.139**)$_2$, a decrease in conversion (26%) was observed when compared to the free ligand system of **3.100** (Table 3-27, entry 1 vs. 3). A similar result was obtained for $PdCl_2$(**3.99**)$_2$ (Table 3-27, entry 1 vs. 2). Enantioselective methoxycarbonylation of 4-methoxy- (**3.27**) and 4-methylstyrene (**3.38**) performed with $PdCl_2$(**3.140**)$_2$/TsOH gave the branched esters, (*S*)-**3.138** and (*S*)-**3.88**, with ee values of 50% and 25%, respectively (Table 3-27, entries 4 and 5).

Table 3-27: Enantioselective methoxycarbonylation of styrene (3.25) and derivatives with chiral NMDPP derived ligands.

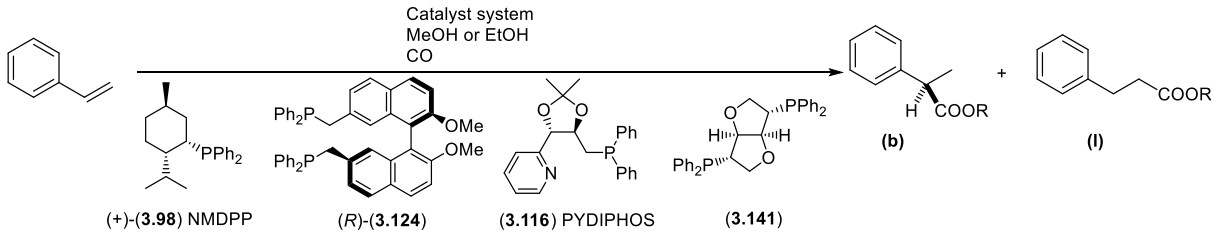


Entry	R	Alkene	Catalyst system	P_{CO} (bar) [Temp (°C)]	Conv. (%)	Products	Ratio b:l	ee (%)
1[44]	H	**3.25**	$PdCl_2$/**3.100**/TsOH[a]	35 [70]	97	**3.26**	98:2	12 (*R*)
2[45]	H	**3.25**	$PdCl_2$(**3.99**)$_2$/TsOH[b]	35 [90]	22	**3.26**	75:25	11 (*S*)
3[44]	H	**3.25**	$PdCl_2$(**3.139**)$_2$/TsOH[b]	35 [70]	26	**3.26**	97:3	29 (*R*)
4[45]	OMe	**3.27**	$PdCl_2$(**3.140**)$_2$/TsOH[b]	35 [60]	71	**3.138**	94:6	50 (*S*)
5[45]	Me	**3.38**	$PdCl_2$(**3.140**)$_2$/TsOH[b]	35 [60]	33	**3.88**	92:8	25 (*S*)

[a]Reaction conditions: $PdCl_2$ (0.015 mmol), ligand (0.030 mmol), TsOH (0.15 mmol), alkene (0.375 mmol), MeOH (2.5 mL), THF (2.5 mL), 24 h. [b]Reaction conditions: $PdCl_2$(ligand)$_2$ (0.015 mmol), TsOH (0.15 mmol), alkene (3 mmol), MeOH (2.5 mL), THF (2.5 mL), 24 h.

Whereas BNPPA (**3.137**), BDPP (**3.133**) and BDPPTS (**3.23**) have only been evaluated as ligands in catalytic systems aimed at hydroxycarbonylation, certain other ligands in palladium catalyst systems have only been evaluated for their effect on alkoxycarbonylation. Chiral NMDPP [(+)-**3.98**] has been utilized as a monodentate ligand in combination with homogeneous palladium[42,55] and palladium heterogenized on montmorillonite[55] (cf. Table 3-21). Although Nozaki et al.[55] claims comparative results for both homogeneous and heterogeneous methoxycarbonylation of styrene in low 12% ee (Table 3-28, entries 1 and 2), Cometti and Chiusoli[42] reported 52% ee utilizing (+)-NMDPP (**3.98**), when a large excess of styrene (**3.25**) is present in combination with $Pd(dba)_2$ (Table 3-28, entry 3). Chelucci et al.[50] reported a *P*,*N*-bidentate ligand (**3.116**) catalyst system for the ethoxycarbonylation of styrene (**3.25**) with excellent regioselectivity toward the branched ester (**3.62b**), (>99%, cf. Table 3-18, entry 5), though only 20% ee was obtained toward the (*R*)-isomer (Table 3-28, entry 4).

Table 3-28: Enantioselective carbonylation of styrene (3.25) utilizing various chiral ligands.



Entry	R	Catalyst system	P_{CO} (bar) [Temp (°C)]	Conv. (%) [Yield (%)]	Products	Ratio b:l	ee (%)
1[55]	Me	$Pd(dba)_2$/**3.98**/TFA[a]	1 [50]	20	**3.87**	94:6	12 (*S*)
2[55]	Me	Pd-clay/**3.124**/HCl[b]	45 [125]	23	**3.87**	100:0	12 (*S*)
3[42]	Me	$Pd(dba)_2$/**3.98**/TFA[c]	2 [50]	100	**3.87**	94:6	52 (+)
4[50]	Et	$PdCl_2$**3.116**[d]	105 [100]	90 [77]	**3.62**	100:0	20 (*R*)
5[61]	Me	$PdCl_2$/$CuCl_2$/**3.141**[e]	50 [80]	100 [99]	**3.87**	93:7	99 (*S*)

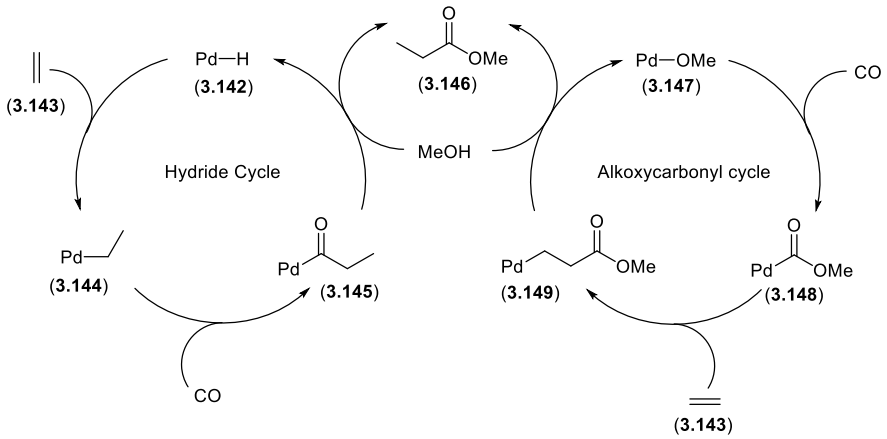
[a]Reaction conditions: $Pd(dba)_2$ (0.007 mmol), ligand (0.02 mmol), conc. TFA (0.03 mL), styrene (1.3 mmol), MeOH (10 mL), 5 h. [b]Reaction conditions: Pd-clay (0.002 mmol), ligand (0.01 mmol), conc. HCl (0.1 mL), styrene (1 mmol), MeOH (6 mmol), benzene (10 mL), 24 h. [c]Reaction conditions: $Pd(dba)_2$ (0.7 mmol), ligand (2 mmol), styrene (15 mL), MeOH (15 mL), TFA (3 mL), 4 h. [d]Reaction conditions: Catalyst (0.1 mmol), styrene (30 mmol), EtOH (5 mL), benzene (20 mL), 240 h. [e]Reaction conditions: $PdCl_2$ (0.08 mmol), $CuCl_2$ (0.185 mmol), ligand (0.24 mmol), styrene (0.5 mL), MeOH (0.5 mL), DME (5.0 mL), 24 h.

The most promising ligand for asymmetric methoxycarbonylation of styrene with Pd(II) catalysts, chiral bisoxalane (**3.141**), was developed by Zhou et al.[61] This diphosphine (**3.141**) was combined with $PdCl_2$ and $CuCl_2$ and produced (*S*)-methyl 2-phenylpropanoate (**3.87b**) with 93% regioselectivity and 99% ee (Table 3-28, entry 5). Although it was only evaluated for ibuprofen and naproxen precursors [(**3.119**) and (**3.136**)], the $PdCl_2$/BNPPA/HCl/O_2 catalytic system has exhibited the highest ee (83-91%) for hydroxycarbonylation (cf. Table 3-26). The dipalladium complex (**3.114**) developed by Clarke (cf. Tables 3-8 and 3-17) is also a viable system for enantioselective hydroxycarbonylation with 77% ee and excellent regioselectivity (>100:1) but only exhibited proficiency on electron deficient styrene derivatives (cf. Table 3-25).

3.7. Catalytic cycle and mechanism for the hydroesterification of alkenes

Two hypothesized mechanistic pathways for alkene hydroesterification, i.e. the hydride cycle and the alkoxycarbonyl cycle, have been under discussion since the 1970's (Scheme 3-2). The hydride cycle initiates with a palladium hydride species (**3.142**) formed via oxidative addition of a hydrogen donor, after which the insertion of the alkene (**3.143**) into the Pd-H bond follows to form an alkyl complex (**3.144**). Subsequent coordination and migratory insertion of CO produces a Pd-acyl species (**3.145**) onto which the alcohol attacks to regenerate the Pd-H complex (**3.142**) and liberate the ester product (**3.146**). In the alkoxycarbonyl cycle, the alkene (**3.143**) is inserted into the Pd-CO bond of the alkoxycarbonyl-palladium complex (**3.148**) to yield **3.149**, followed by alcoholysis to yield an alkoxy-palladium complex (**3.147**) and the ester

product (**3.146**). CO coordination and migratory insertion then regenerates the alkoxycarbonyl-palladium complex (**3.148**). The co-existence of these two cycles is suspected to be the underlying factor influencing the regioselective outcome of the transformation. Steric interactions would favour the terminal complexation of the alkene into the Pd-H species (**3.144**), yielding the linear ester, whereas alkene insertion into the Pd-alkoxycarbonyl species (**3.149**) would render the branched ester in similar fashion.[62,63,64]



Scheme 3-2: Hydride and alkoxycarbonyl catalytic cycles for the methoxycarbonylation of ethene.

Tooze and co-workers[64,65,66,67] consequently launched an investigation into the methoxycarbonylation of ethene catalysed by bidentate complex Pd(DTBPMB)(dba). All of the palladium intermediates for the hydride catalytic cycle, i.e. the Pd-H [Pd(DTBPMB)H(MeOH)][TfO], the Pd-alkyl [Pd(DTBPMB)Et(MeOH)][TfO] and the Pd-acyl [Pd(DTBPMB)(COEt)(THF)][TfO] species, could be isolated. This provided unambiguous ^{1}H and ^{31}P NMR spectroscopic evidence that at least the hydride pathway is followed to produce methyl propanoate (**3.146**).

Toniolo and co-workers[68,69] followed suit by performing a detailed mechanistic study on the methoxycarbonylation of ethene (**3.143**) and styrene (**3.25**) with *cis*-$[Pd(SO_4)(PPh_3)_2]$[68] and in situ generated $Pd(OTs)_2(PPh_3)_2$,[69] respectively, both in the presence of monodentate PPh_3. In both instances the indicative Pd-acyl species, i.e. *trans*-$[Pd(COEt)Cl(PPh_3)_2]$ and *trans*-$[PdCl(COCH_2CH_2\ Ph)(PPh_3)_2]$, were isolated successfully together with other intermediate complexes. Similar to the Tooze[64,65,66,67] study (vide supra), the ^{1}H and ^{31}P NMR and IR spectroscopic data supports the hydride mechanism in both instances. These results thus suggest that the hydride pathway occurs for both aliphatic and aromatic substrates in the presence of either a mono- or bidentate ligand system.

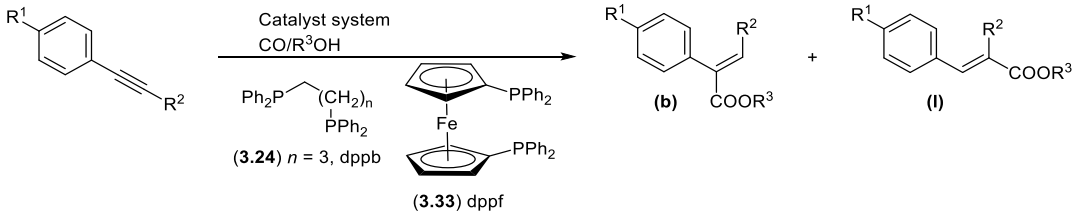
3.8. Carbonylation of alkynes

Carbonylation of alkynes is an industrially relevant process that allows access to α,β-unsaturated carboxylic acids and esters. These compounds are often employed as building blocks for the synthesis of polymers (e.g. Perspex), fine chemicals [e.g. methyl methacrylate (**3.167**)], and pharmaceuticals [e.g. naproxen (**3.8**) and ibuprofen (**3.9**)].[70,71,72] Similar to the carbonylation of olefins, alkyl carbonylation can also produce regioisomers, i.e. linear and branched products (cf. Scheme 3-1).

3.8.1. Alkyne carbonylation with selectivity toward branched products

One of the first reports on the carbonylation of alkyne substrates describe the formation of the *tert*-butyl ester of atropic acid (**3.150**) from phenylacetylene (**2.152**).[73] No Brønsted acid was present in the bidentate $Pd(OAc)_2$/dppb system which consequently required 150-190 °C and 80 atm of CO to yield only 60% of the ester (Table 3-29, entry 1). Although the yield was moderate, the regioselectivity was excellent as no linear product was observed. Miura and co-workers[74,75] exchanged the dppb (**3.24**) ligand for an alternative bidentate ligand, dppf (**3.33**), as well as monodentate PPh_3. Both the catalyst systems with mono- and bidentate ligands converted phenylacetylene (**2.152**) to the esters derived from phenol **3.151**, 4-methylphenol (**3.152**) and 4-chlorophenol (**3.153**) with excellent branched regioselectivity (>93%), (Table 3-29, entries 2-7). The yields were slightly higher for the system with the monodentate ligand (Table 3-29, entries 2-4 vs. 5-7), but extended reaction times (ca. 10 hours vs. 22 hours) were required.[74] Upon addition of TsOH, however, reaction times for the PPh_3 system was significantly reduced (ca. 2 hours), rendering the branched butyl esters of unsubstituted phenylacetylene (**2.152**) as well as phenylacetylenes with electron-donating and electron-withdrawing *p*-substituents (Table 3-29, entries 8-11) with excellent regioselectivity (>94%) and in high yield (>72%). Alternative alcohols, i.e. 1-propanol, 2-butanol and *tert*-pentanol rendered similar results (Table 3-29, entries 12-14). The substrate scope was further expanded to include disubstituted acetylenes, i.e. diphenylacetylene (**3.164**). Although regioselectivity was not relevant, the efficacy of the system was proven by the formation of the *E*-geometrical isomer (**3.165**) in 81% yield (Table 3-29, entry 15).

Table 3-29: Alkoxycarbonylation of phenylacetylene (2.152) and derivatives in various palladium systems.



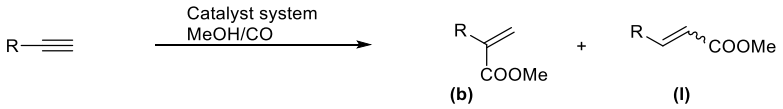
Entry	Alkyne	R^1	R^2	R^3	Catalyst system	P_{CO} (bar) [T (°C)]	Yield (%)	Products	Ratio b:l
1[73]	**2.152**	H	H	$C(Me)_3$	$Pd(OAc)_2$/dppb[a]	80 [150]	60	**3.150**	100:0
2[74]	**2.152**	H	H	Ph	$Pd(OAc)_2$/dppf[b]	15 [100]	85	**3.151**	95:5
3[74]	**2.152**	H	H	4-MePh	$Pd(OAc)_2$/dppf[b]	15 [100]	99	**3.152**	96:4
4[74]	**2.152**	H	H	4-ClPh	$Pd(OAc)_2$/dppf[b]	15 [100]	85	**3.153**	95:5
5[74]	**2.152**	H	H	Ph	$Pd(PPh_3)_4$[c]	1 [100]	74	**3.151**	95:5
6[74]	**2.152**	H	H	4-MePh	$Pd(PPh_3)_4$[c]	1 [100]	89	**3.152**	93:7
7[74]	**2.152**	H	H	4-ClPh	$Pd(PPh_3)_4$[c]	1 [100]	82	**3.153**	93:7
8[75]	**2.152**	H	H	Bu	$Pd(dba)_2/PPh_3/TsOH$[d]	1 [100]	93	**3.154**	96:4
9[75]	**3.155**	Me	H	Bu	$Pd(dba)_2/PPh_3/TsOH$[d]	1 [100]	77	**3.156**	97:3
10[75]	**3.157**	OMe	H	Bu	$Pd(dba)_2/PPh_3/TsOH$[d]	1 [100]	93	**3.158**	99:1
11[75]	**3.159**	Cl	H	Bu	$Pd(dba)_2/PPh_3/TsOH$[d]	1 [100]	92	**3.160**	96:4
12[75]	**2.152**	H	H	*n*-Pr	$Pd(dba)_2/PPh_3/TsOH$[d]	1 [100]	89	**3.161**	96:4
13[75]	**2.152**	H	H	*sec*-Bu	$Pd(dba)_2/PPh_3/TsOH$[d]	1 [100]	75	**3.162**	96:4
14[75]	**2.152**	H	H	*tert*-Pent	$Pd(dba)_2/PPh_3/TsOH$[d]	1 [100]	94	**3.163**	94:6
15[75]	**3.165**	H	Ph	Bu	$Pd(dba)_2/PPh_3/TsOH$[d]	1 [100]	81	**3.165**	n.a.[e]

[a]Reaction conditions: $Pd(OAc)_2$ (0.1 mmol), dppb (0.1 mmol), alkyne (2.5 mmol), ^{t}BuOH (2.5 mmol), DME (2.5 ml), 3 d. [b]Reaction conditions: $Pd(OAc)_2$ (0.04 mmol), dppf (0.04 mmol), alkyne (1 mmol), alcohol (4 mmol), benzene (5 ml), 22-30 h. [c]Reaction conditions: $Pd(PPh_3)_4$ (0.04 mmol), alkyne (1 mmol), alcohol (4 mmol), toluene (5 ml), 10 h. [d]Reaction conditions: $Pd(dba)_2$ (0.04 mmol), PPh_3 (0.16 mmol), TsOH (0.04 mmol), alkyne (1 mmo), alcohol (4 mmol), toluene (5 ml), 2 h. [e]n.a. = Not applicable.

Drent and co-workers[76,77] adopted the Pd(II)/TsOH/monophosphine approach and investigated the system's ability to transform propyne (**3.166**) to methyl methacrylate (**3.167**), i.e. the branched isomer (Table 3-30). Although the system with PPh_3 as ligand rendered 89% selectivity (Table 3-30, entry 1), the investigation was continued by substituting one phenyl ring on PPh_3 for a pyridyl ring. The relative orientation of the *P*,*N*-heteroatoms influences the efficacy of the ligand as was evident from the fact that 4-$PyPPh_2$ rendered similar selectivity (ca. 90%) and activity (TOF 10 h^{-1}) to PPh_3, while 2-$PyPPh_2$ increased the selectivity and activity of the catalyst system to 99% and 40000 TOF h^{-1} (Table 3-30, entries 1-3). The *ortho*- and *meta*-derivatives, i.e. 2-$PyPPh_2$ and 3-$PyPPh_2$, resulted in comparable selectivity (ca. 99%), but the activity of the system with 2-$PyPPh_2$ was significantly higher (TOF 1000 h^{-1} vs. 40000 h^{-1}, Table 3-30, entry 3 vs. 4). In addition, 45 °C was sufficient for the 2-$PyPPh_2$ system, whereas the reactions with 3-$PyPPh_2$, 4-$PyPPh_2$ and PPh_3 systems were performed at 70, 90 and 115 °C, respectively (Table 3-30, entries 1-4). The substrate scope of the 2-$PyPPh_2$ system was expanded to phenylacetylene (**2.152**) by Cole-Hamilton et al.,[78] who claimed a quantitative

yield for the ester (**3.168**) with 97% regioselectivity toward the branched product (**3.168b**) (Table 3-30, entry 5).

Table 3-30: Methoxycarbonylation of acetylene (3.166) and diphenylacetylene (2.152) with pyridyl monophosphine systems.

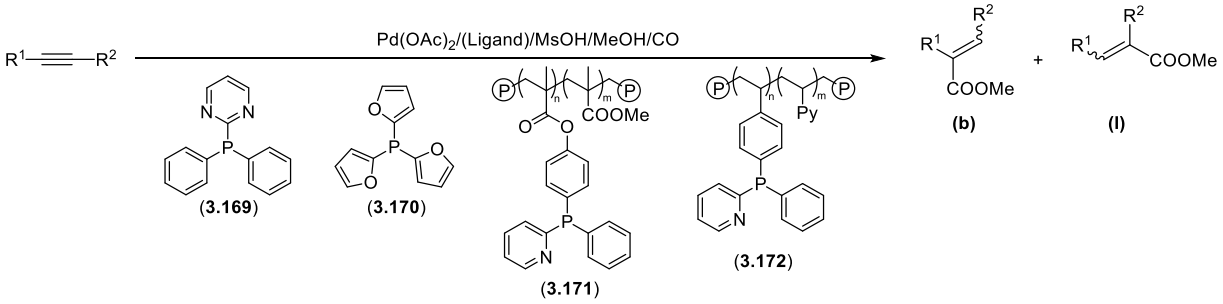


Entry	Alkyne	R	Catalyst system	P_{CO} (bar) [T (°C)]	TOF (h^{-1})	Products	Ratio b:l
1[76]	**3.166**	Me	$Pd(OAc)_2/PPh_3/MsOH$[a]	60 [115]	10	**3.167**	89:11
2[76]	**3.166**	Me	$Pd(OAc)_2$/4-$PyPPh_2$/MsOH[a]	60 [90]	10	**3.167**	90:10
3[76]	**3.166**	Me	$Pd(OAc)_2$/2-$PyPPh_2$/MsOH[a,b]	60 [45]	40000	**3.167**	99:1
4[76]	**3.166**	Me	$Pd(OAc)_2$/3-$PyPPh_2$/MsOH[a]	60 [70]	1000	**3.167**	99:1
5[78]	**2.152**	Ph	$Pd(OAc)_2$/2-$PyPPh_2$/TsOH[c]	55 [60]	n.r.[d]	**3.168**	97:3

[a]Reaction conditions: $Pd(OAc)_2$ (0.1 mmol), ligand (3 mmol), MsOH (2 mmol), propyne (30 ml), MeOH (50 ml). [b]$Pd(OAc)_2$ (0.01 mmol). [c]Reaction conditions: $Pd(OAc)_2$ (0.1%), ligand 2-$PyPPh_2$ (2%), TsOH (4%), phenylacetylene (quantity not specified). [d]n.r. = Not reported.

Reetz et al.[79] introduced an additional heteroatom into the *P*,*N*-ligand by substituting the pyridyl ring for a pyrimidyl unit. The diphenyl 2-pyrimidylphosphine ligand **3.169** combined with $Pd(OAc)_2$ in the methoxycarbonylation of phenylacetylene (**2.152**) also gave the branched ester (**3.169b**) in 100% regioselectivity and 97% yield (Table 3-31, entry 1). This system proved just as effective for the transformation of 1-hexyne (**3.173**), (Table 3-31, entry 2) and diphenylacetylene (**3.164**), (Table 3-31, entry 3). Scrivanti and co-workers[80,81] further modified the ligand by substituting the pyrimidyl ring for an *N-tert*-butylphenylmethanimine unit,[81] however promising results were only obtained with another ligand, tri(2-furyl)phosphine (**3.170**),[80] which enabled 97% conversion with 95% regioselectivity (Table 3-31, entry 4). The success of the system with the 2-$PyPPh_2$ ligand motivated Doherty et al.[82] to immobilize the ligand. 2-$PyPPh_2$ was therefore anchored to a methacrylate homopolymer (**3.171**) as well as a polyvinylpyridine support (**3.172**). The methacrylate system led to excellent regioselectivity (ca. 98%) for both phenylacetylene (**2.152**) and propyne (**3.166**) (Table 3-31, entries 5 and 7) whereas >99% regioselectivity could be achieved with the polyvinylpyridine system (Table 3-31, entries 6 and 8), though at the expense of activity.

Table 3-31: Methoxycarbonylation of acetylene derivatives with $Pd(OAc)_2$ in the presence of various phosphorous ligands.

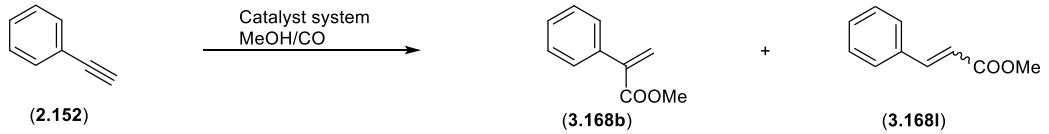


Entry	R^1	R^2	Alkyne	Ligand	P_{CO} (bar) [T (°C)]	Yield (%)	Products	Ratio b:l
1[79]	Ph	H	**2.152**	**3.169**[a]	60 [60]	97	**3.168**	100:0
2[79]	*n*-C_4H_9	H	**3.173**	**3.169**[a]	60 [60]	97	**3.174**	100:0
3[79]	Ph	Ph	**3.164**	**3.169**[a]	60 [60]	97	**3.175**	n.a.[b]
4[80]	Ph	H	**2.152**	**3.170**[c]	40 [50]	89	**3.168**	95:5
5[82]	Ph	H	**2.152**	**3.171**[d]	40 [50]	n.r.[e]	**3.168**	98:2
6[82]	Ph	H	**2.152**	**3.172**[d]	40 [50]	n.r.[e]	**3.168**	>99:1
7[82]	Me	H	**3.166**	**3.171**[d,f]	40 [50]	n.r.[e]	**3.167**	98:2
8[82]	Me	H	**3.166**	**3.172**[d,f]	40 [50]	n.r.[e]	**3.167**	>99:1

[a]Reaction conditions: $Pd(OAc)_2$ (0.03 mmol), ligand (1 mmol), MsOH (2.3 mmol), alkyne (43.5 mmol), MeOH (30 ml), *N*-methyl-pyrrolidone (10 ml). [b]n.a. = Not applicable. [c]Reaction conditions: $Pd(OAc)_2$ (0.013 mmol), ligand (0.26 mmol), MsOH (0.4 mmol), alkyne (2 mmol), MeOH (30 ml), 18 h. [d]Reaction conditions: $Pd(OAc)_2$ (0.01 mmol), ligand (0.1 mmol), MsOH (0.3 mmol), alkyne (10 mmol), MeOH (30 ml). [e]n.r. = Not reported. [f]alkyne (2 bar).

Another *P*,*N*-bidentate system which was adopted from the carbonylation of olefins, is the PPh_3/pyca/TsOH system (cf. Tables 3-5, 3-6 and 3-19). Chaudhari et al.[70] evaluated PPh_3, P(*p*-FPh)$_3$ and P(*p*-ClPh)$_3$ as ligands with $Pd(OAc)_2$ and pyca for the butoxycarbonylation of phenylacetylene (**2.152**) (Table 3-32). Under similar conditions, the three catalyst systems exhibited comparative selectivity (ca. 97%) toward the branched product (**3.168b**), (Table 3-32, entries 1-3). The activity of the system based on the electron deficient P(*p*-FPh)$_3$ ligand was, however, superior with 95% conversion relative to the 90% and 85% for P(*p*-ClPh)$_3$ and PPh_3, respectively.

Table 3-32: Methoxycarbonylation of phenylacetylene (2.152) with $Pd(OAc)_2$/pyca catalyst systems.[a]



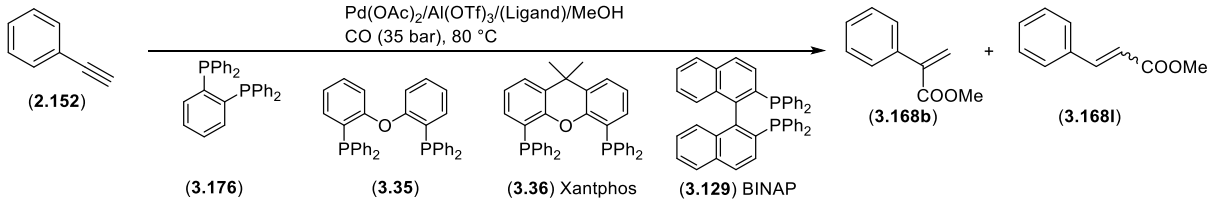
(**2.152**) (**3.168b**) (**3.168l**)

Entry	Catalyst system	P_{CO} (bar) [T (°C)]	Conversion (%)	Ratio b:l
1	$Pd(OAc)_2$/PPh_3/pyca/TsOH	2 [100]	85	97:3
2	$Pd(OAc)_2$/P(*p*-FPh)$_3$/pyca/TsOH[b]	2 [100]	95	98:2
3	$Pd(OAc)_2$/ P(*p*-ClPh)$_3$/pyca/TsOH[b]	2 [100]	90	96:4

[a]Reaction conditions: $Pd(OAc)_2$ (0.03 mmol), ligand (0.12 mmol), pyca (0.06 mmol), TsOH (0.3 mmol), alkyne (0.015 mmol), BuOH (3.75 ml), toluene (19 ml), 8-43 minutes. [b]ligand (0.9 mmol), pyca (0.45 mmol), TsOH (1.2 mmol).

Williams et al.[83] also evaluated their Lewis acid system (cf. Tables 3-11, entries 9 and 10, Table 3-12, entry 7) for the methoxycarbonylation of phenylacetylene (**2.152**), (Table 3-33). Although $Ph(PPh_2)_2$ (**3.176**) as ligand in this system proved ineffective (Table 3-33, entry 1), the system with BINAP (**3.129**) yielded 99% ester (**3.168b**) with >99:1 branched regioselectivity (Table 3-33, entry 4). Other diphosphine ligands that were investigated include 2,2'-diphenyl-phosphinophenyl ether (**3.35**) and Xantphos (**3.36**) which yielded the methoxycarbonylation products (**3.169**) in 85% and 42%, respectively (Table 3-33, entries 2 and 3). Alternative additives such as $La(OTf)_3$, $Hf(OTf)_4$, TsOH and TfOH were also screened, but were all found inferior to $Al(OTf)_3$.

Table 3-33: Methoxycarbonylation of phenylacetylene (2.152) with $Pd(OAc)_2/Al(OTf)_3$ and various bidentate phosphine ligands.[a]



Entry	Ligand	Bite angle	Yield (%)	Ratio b:l
1	**3.176**	83	0	n.a.[b]
2	**3.35**	102	85	62:38
3	**3.36**	112	42	71:29
4	**3.129**	92	99	>99:1

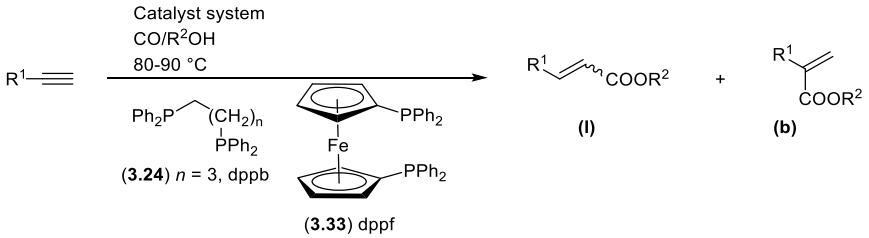
[a]Reaction conditions: $Pd(OAc)_2$ (0.01 mmol), ligand (0.04 mmol), $Al(OTf)_3$ (0.02 mmol), phenylacetylene (11 mmol), MeOH (4.7 ml), 3 h.
[b]n.a. = Not applicable.

3.8.2. Alkyne carbonylation with selectivity toward linear products

The cationic palladium complex originally reported by Inoue for the linear ester formation from olefins (cf. Table 3-12, entries 3 and 4), was also applied to terminal alkynes.[84] The $[Pd(dppf)(PhCN)_2](BF_4)_2$ complex converted 1-octyne (**3.177**) and phenylacetylene (**2.152**) to their respective α,β-unsaturated linear esters, (**3.178l**) and (**3.168l**), with 85% (Table 3-34, entry 1) and 89% (Table 3-34, entry 3) regioselectivity, respectively. $PdCl_2(dppf)$ displayed similar efficacy with 92% and 87% (Table 3-34, entries 2 and 4) linear selectivity for the respective alkynes. Ali et al.[85] employed dppb (**3.24**) as diphosphine ligand in combination with borosalicylic acid (BSA), similar to the system originally reported by Alper (cf. Tables 3-11 and 3-12). At 15 bar CO, a regioselectivity of 92% was achieved toward the linear methoxycarbonylation product (**3.169l**) of phenylacetylene (**2.152**) (Table 3-34, entry 5). Although $Pd(OAc)_2$ was the preferred source of palladium, 5% Pd-C yielded similar results (Table 3-34, entry 6). Longer chain alcohols like 1-heptanol (Table 3-34, entry 8) as well as a

branched alcohol, 2-propanol (Table 3-34, entry 7), was also employed with comparable efficacy.

Table 3-34: Alkoxycarbonylation of 1-octyne (3.177) and phenylacetylene (2.152) with various dppb (3.24) and dppf (3.33) systems.

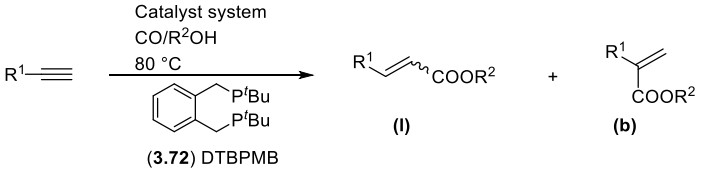


Entry	Alkyne	R^1	R^2	Catalyst system	P_{CO} (bar)	Yield (%)	Products	Ratio l:b
1[84]	**3.177**	$(CH_2)_5CH_3$	Me	$[Pd(dppf)(PhCN)_2](BF_4)_2$[a]	60	100	**3.178**	85:15
2[84]	**3.177**	$(CH_2)_5CH_3$	Me	$PdCl_2(dppf)$[a]	60	100	**3.178**	92:8
3[84]	**2.152**	Ph	Me	$[Pd(dppf)(PhCN)_2](BF_4)_2$[a,b]	40	71	**3.168**	89:11
4[84]	**2.152**	Ph	Me	$PdCl_2(dppf)$[a,c]	40	41	**3.168**	87:13
5[85]	**2.152**	Ph	Me	$Pd(OAc)_2$/dppb/BSA[d]	15	99[e]	**3.168**	92:8
6[85]	**2.152**	Ph	Me	Pd-C/dppb/BSA[d]	15	97[e]	**3.168**	90:10
7[85]	**2.152**	Ph	$CH(CH_3)_2$	$Pd(OAc)_2$/dppb/BSA[d]	15	99[e]	**3.179**	91:9
8[85]	**2.152**	Ph	$(CH_2)_6CH_3$	$Pd(OAc)_2$/dppb/BSA[d]	15	100[e]	**3.180**	89:11

[a]Reaction conditions: Catalyst (0.04 mmol), alkyne (2 mmol), MeOH (3 ml), MeCN (10 ml), 80 °C, 3h. [b]120 °C, 2 h. [c]2h. [d]Reaction conditions: Catalyst (0.02 mmol), dppb (0.08 mmol), $B(OH)_3$ (0.3 mmol), salicylic acid (0.6 mmol), alkyne (2 mmol), alcohol (8 mmol), CH_3CN (10 ml), 90 °C, 3 h. [e]Conversion (%).

Cole-Hamilton et al.[86] also revised their DTBPMB (**3.72**) system, which was developed for the methoxycarbonylation of olefins (cf. Tables 3-11 and 3-17, entry 1), for the carbonylation of alkynes (Table 3-35). Although regioselectivity for the olefinic substrates favoured branched esters, phenylacetylene (**2.152**) was transformed with 99% regioselectivity (Table 3-35, entry 1) to linear methyl cinnamate (**3.168l**). Cinnamic acid (**3.181l**) was obtained with similar selectivity (Table 3-35, entry 2) in the presence of water as nucleophile, albeit with slightly lower yield (88% vs. 93%). The system, however, proved less efficient for the methoxycarbonylation of aliphatic 1-butyne (**3.182**), 1-pentyne (**3.184**) and 1-octyne (**3.177**) for which only 83%, 73% and 75% linear regioselectivities were obtained, respectively (Table 3-35, entries 3-5).

Table 3-35: Carbonylation of terminal alkynes with DTBPMB (3.72) catalyst systems.



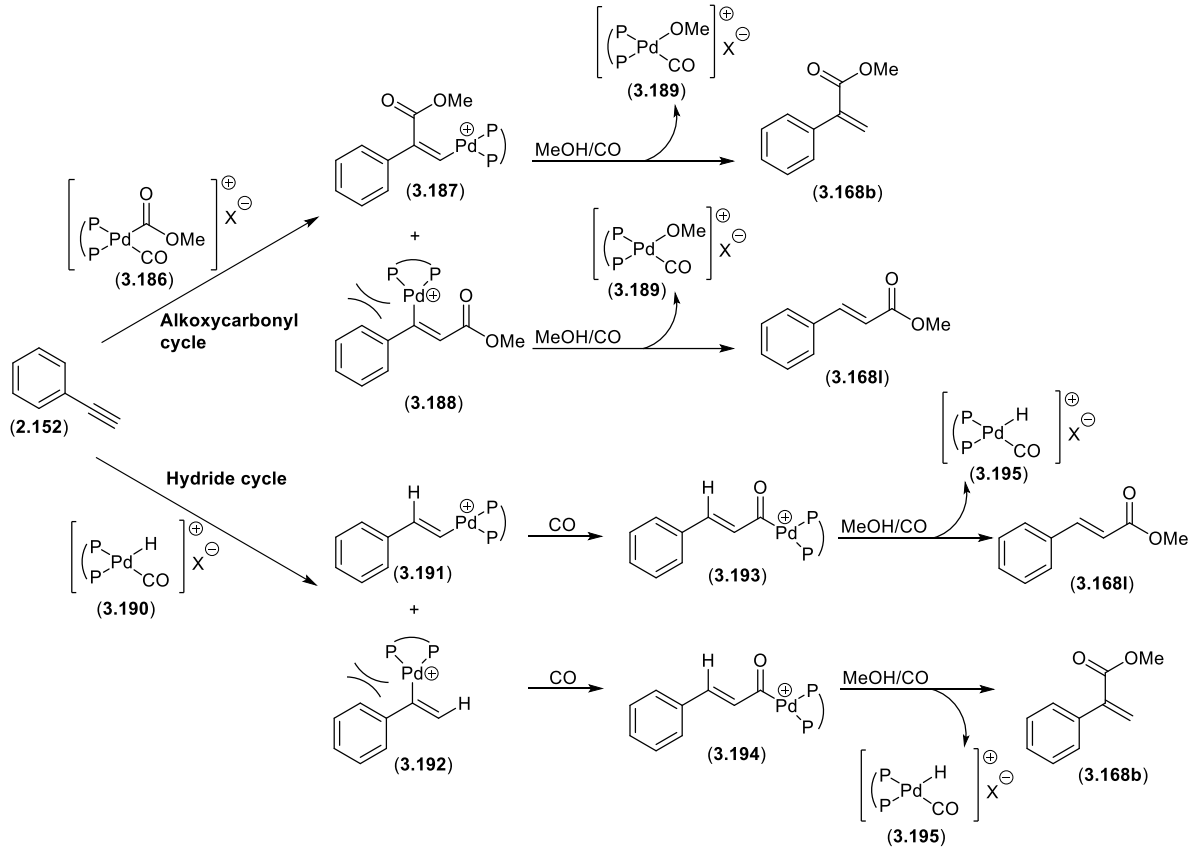
Entry	Alkyne	R^1	R^2	Catalyst system	P_{CO} (bar)	Yield (%)	Products	Ratio l:b
1	**2.152**	Ph	Me	Pd_2dba_3/DTBPMB/MsOH[a]	30	93	**3.168**	99:1
2	**2.152**	Ph	H	$[PdCl_2(MeCN)_2]$/DTBPMB/MsOH[b]	70	88	**3.181**	96:4
3	**3.182**	CH_2CH_3	Me	Pd_2dba_3/DTBPMB/MsOH[c,d]	30	100	**3.183**	83:17
4	**3.184**	$(CH_2)_2CH_3$	Me	Pd_2dba_3/DTBPMB/MsOH[c]	30	90	**3.185**	73:27
5	**3.177**	$(CH_2)_5CH_3$	Me	Pd_2dba_3/DTBPMB/MsOH[c]	30	87	**3.178**	75:25

[a]Reaction conditions: Catalyst (0.02 mmol), DTBPMB (0.3 mmol), MsOH (0.6 mmol), alkyne (9 mmol), MeOH (10 ml), 3 h. [b]Reaction conditions: Catalyst (0.09 mmol), DTBPMB (0.46 mmol), MsOH (2.7 mmol), alkyne (9 mmol), H_2O (2 ml), dioxane (10 ml), 5 h. [c]Catalyst (0.009 mmol), DTBPMB (0.05 mmol), MsOH (0.3 mmol) , alkyne (9 mmol), MeOH (10 ml), 3 h. [d]0.5 h.

For the production of geminal disubstituted olefins from terminal alkynes, i.e. the branched product, two systems provided excellent regioselectivity. The 2-$PyPPh_2$ ligand in combination with $Pd(OAc)_2$ and MsOH has shown to be versatile as it retained selectivity of >99% even when immobilized (cf. Tables 3-30 and 3-31). This system was also proven effective for the carbonylation of aliphatic propyne (**3.166**)[76] and aromatic phenylacetylene (**2.152**).[78] Alternatively, the $Pd(OAc)_2$/$Al(OTf)_3$/BINAP system also yields >99% regioselectivity during the transformation of phenylacetylene (**2.152**) and does not require the presence of a strong Brønsted acid for the reaction to proceed smoothly (cf. Table 3-33).[83] In contrast to the latter, the $Pd_2(dba)_3$ system with diphosphine DTBPMB (**3.72**) in combination with MsOH renders the cinnamate ester (**3.168l**) with 96% regioselectivity (cf. Table 3-35).[86] Although regioselectivity is slightly lower, Pd-C and $Pd(OAc)_2$ systems with dppb (**3.24**) in combination with BSA is also effective with >90% selectivity toward the linear product (cf. Table 3-34).[85]

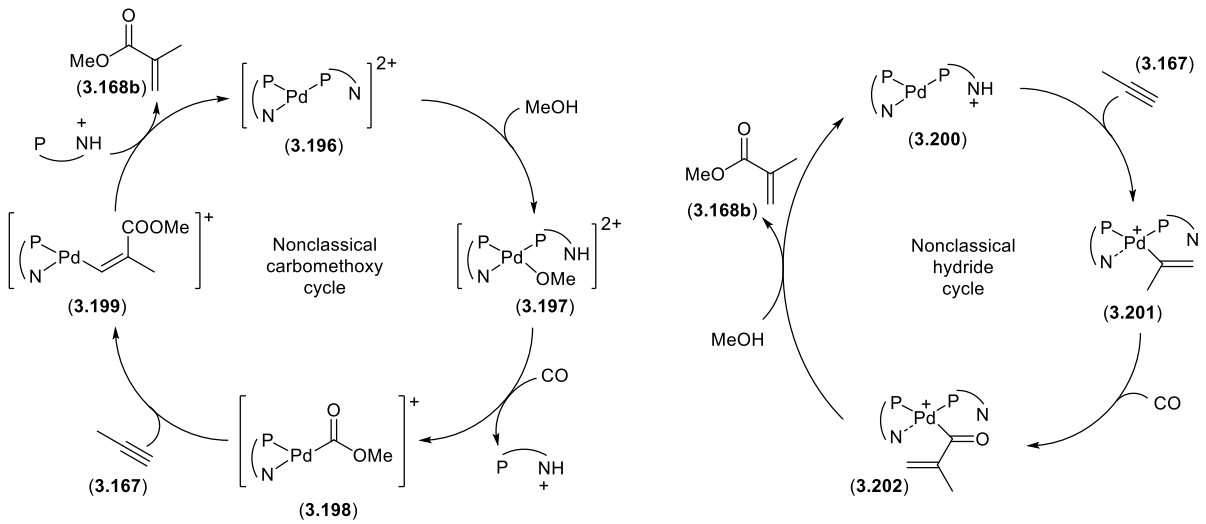
3.8.3. Catalytic cycle and mechanism for the hydroesterification of alkynes

Two basic mechanisms for the hydroesterification of alkynes have been proposed. These are similar to the hypothesized mechanisms for olefins (cf. paragraph 3.7), i.e. the hydride and alkoxycarbonyl mechanisms (Scheme 3-3).[86] When the intermediate palladium species for both routes are considered, the *trans*-orientation with the phenyl ring on the distal carbon relative to the palladium centre (**3.187** and **3.191**) is expected to be the most stable. Consequently the hydride mechanism is hypothesized to preferentially form the linear product (**3.168l**) whereas the branched product (**3.168b**) is the result of the alkoxycarbonyl route.[72,86] For diphosphine systems, this effect is expected to be enhanced as the increased bulk of the ligand would further disfavour the geminal phenyl-palladium species (**3.188** and **3.192**).[84,86,87]



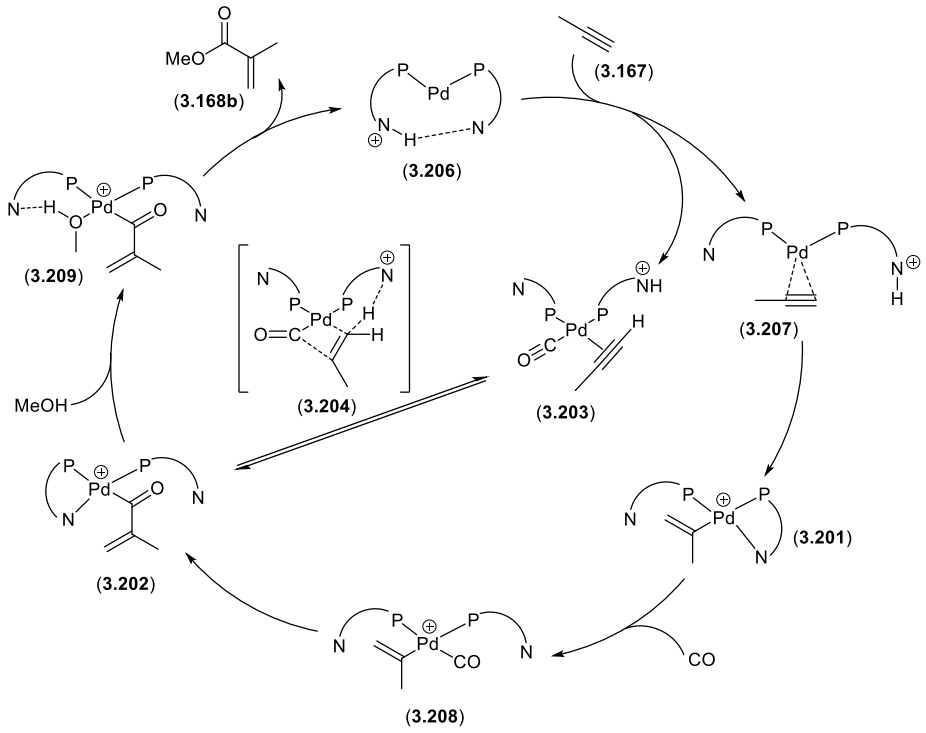
Scheme 3-3: Hydride and alkoxycarbonyl mechanisms for the hydroesterification of phenylacetylene (2.152).

The *P*,*N*-bidentate systems, however, yield branched selectivity. Speculations that explain this phenomenon have led to the proposal of nonclassical carbomethoxy and hydride mechanisms by Drent et al.[76] and Scrivanti et al.,[88] respectively (Scheme 3-4). The pyridyl ring is believed to either act as a rate enhancer during protonolysis in the carbomethoxy cycle (**3.196** to **3.197**) or as an in situ base in the solvolysis step of the hydride cycle to yield a Pd(0) species (**3.200**).



Scheme 3-4: Nonclassical carbomethoxy and hydride mechanisms for *P*,*N*-ligated palladium systems.

Cole-Hamilton et al.[72] on the other hand suggested propyne (**3.167**) to be coordinated to a Pd(0)CO species (**3.203**), where after concerted CO insertion and protonation (**3.204**) would render the Pd-acyl species (**3.202**) (Scheme 3-5). Although such a transition was supported by DFT studies, no experimental evidence could be obtained for this hypothesis. An alternative stepwise approach, emerging from DFT calculations entails the co-catalytic action of the pyridyl unit and explains the high regioselectivity observed for this system (**3.207** to **3.208** via **3.201**). Although these mechanisms explain the general observations for *P*,*P*- and *P*,*N*-systems, no mechanistic proposal has been reported for the inverted regioselectivity obtained in systems which do not contain any Brønsted acid. The Miura[74] system employs dppb (**3.24**) or dppf (**3.33**) as diphosphine ligand (cf. Table 3-29), whereas the Williams[83] system incorporates BINAP (**3.129**) (cf. Table 3-33) to render 93% and 99% branched selectivity, respectively.



Scheme 3-5: Catalytic cycle for the hydroesterification of alkynes with *P*,*N*-ligands as proposed by Cole-Hamilton et al.

3.9. References

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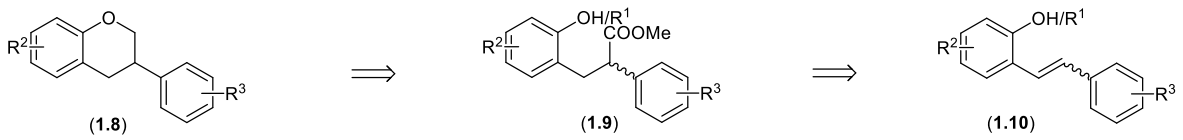
RESULTS AND DISCUSSION 4

4.1. Introduction

As indicated in the literature review, isoflavonoids are an important class of natural products with diverse physiological properties and activities. Despite their importance, the availability of flavonoids with a series of substitution patterns is limited due to tedious preparative protocols and/or the utilization of poisonous reagents in stoichiometric quantities. In order to bring the preparation of isoflavonoids in line with modern synthetic methodologies in which catalysis plays a major role, a study towards the synthesis of isoflavonoids from easily obtainable starting materials through the application of catalytic processes was embarked upon. As indicated in Scheme 4-1, it was envisaged that the isoflavonoid skeleton (**1.8**) could become available through hydroesterification of a substituted stilbene (**1.10**) followed by a cyclization step. For construction of the isoflavonoid C-ring to be possible, the carboxylate entity would be required to be delivered to the distal position of the stilbene double bond as indicated in (**1.9**). The primary aim of this investigation therefore centred around the utilization of electronic parameters to direct the mode of carbonyl attack towards the desired double bonded carbon of the stilbene. In order to induce the required regioselectivity, a range of diarylalkenes with various electron-donating and/or electron-withdrawing substituents on the phenyl rings were to be subjected to palladium catalysed hydroesterification. To study the influence, if any, of electronic effects on the activity and regioselectivity of the hydroesterification reaction, stilbene molecules were to be targeted as the final substrates in this methodology and therefore subjected to the methoxycarbonylation process.

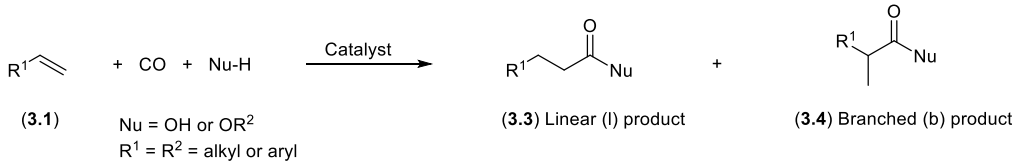


$R^1 = R^2 = R^3$ = oxygenated substituents

Scheme 4-1: Retrosynthesis for the new catalytic pathway towards isoflavonoids.

Since different applications of the products from alkene (**3.1**) hydroesterification reactions required either the linear (l, **3.3**) or branched (b, **3.4**) product, obtaining the desired regioselectivity during the reaction presented a challenge to researchers as from the early stages

of the development of hydroesterification methodology (Scheme 4-2). In this regard, Knifton, one of the pioneers in the field of hydroesterification technology, studied the effect of the ligand and olefin structure on the regioselective outcome of the reaction as early as 1976.[1,2] Subsequent studies evaluated the effect of various metals, like iron, cobalt, nickel, ruthenium, rhodium, palladium and platinum, as well as immobilized catalysts, reaction conditions, co-catalysts and solvents on the activity and regioselectivity of hydroesterification reactions, while phosphine ligands differing in bite angle, electronic and steric properties, like monodentate, bidentate and diphosphine complexes, were also investigated in this regard (cf. chapter 3).



Scheme 4-2: General carbonylation reaction.

4.2. Hydroesterification of alkenes

Although the electronic effect of electron-donating and electron-withdrawing substituents on the phenyl ring were already assessed to some extent for methylstyrene substrates during the candidate's MSc studies, a catalyst system based on $PdCl_2$ was used in those investigations.[3] Since repeatability and consistency of results were found to be problematic with the $PdCl_2$ catalyst system, it was decided to rather utilize $Pd(OAc)_2$ as source of palladium, thus requiring the re-optimization of reaction conditions with the Williams $Pd(OAc)_2/Al(OTf)_3/PPh_3$ hydroesterification catalyst system.[4]

4.2.1. Optimization of reaction conditions with *trans*-β-methylstyrene (3.50) as model substrate

In order to optimise the reaction conditions with regard to temperature, CO pressure and CO concentration in the reaction mixture (influenced by the speed of stirring with a mechanical gas-entrainment stirrer), the model substrate, *trans*-β-methylstyrene (**3.50**), was treated with the $Pd(OAc)_2/Al(OTf)_3/PPh_3$ catalyst system in a 25 ml autoclave reactor. As is evident from Figure 4-1, raising the temperature from 85 °C to 95 °C caused a drastic increase in the conversion (77-95%), while further increases in temperature to 100 °C and 105 °C did not have a significant effect on conversion values. Changing the external CO pressure and the speed of the gas-entrainment stirrer, on the other hand, had little effect on the conversion, and it was thus

decided to perform all future reactions at 95 °C, 35 bar CO pressure and a stirrer speed of 500 rpm.

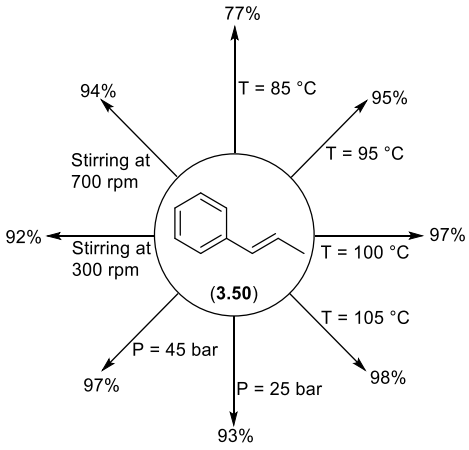
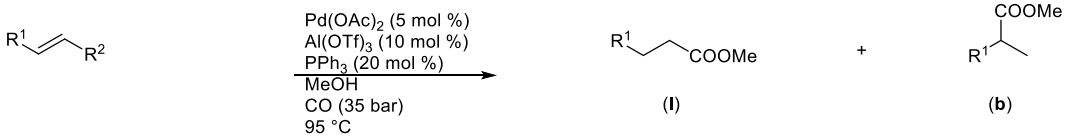


Figure 4-1: Optimization of reaction conditions for the methoxycarbonylation of *trans*-β-methylstyrene (3.50). Reaction conditions: $Pd(OAc)_2$ (5 mol%), $Al(OTf)_3$ (10 mol%), PPh_3 (20 mol%) in MeOH (8 ml) for 3 h at 95°C, 35 bar of CO pressure and 500 rpm stirring speed, unless indicated otherwise.

4.2.2. Validation of the reactor and reaction parameters with octenes and styrene

In order to validate and compare the current results against literature values, two substrates widely used in the development of methoxycarbonylation methodologies and catalyst systems, i.e. 1-octene (**3.11**) and styrene (**3.25**), were subsequently subjected to the optimized reaction conditions. As indicated in Table 4-1 (entries 1 and 3), both these substrates gave high conversions (100% and 91%, respectively) to mainly the linear products, **3.79l** and **3.87l**, both with a l:b ratio of 3:1. The 91% conversion obtained for styrene (**3.25**, entry 3) was in good agreement with the results reported by Williams et al.[4] (81-98%), which confirmed the reactivity of the catalyst system and the integrity of the reaction setup. As expected, the internal alkene, 2-octene (**4.1**), displayed substantial lower reactivity giving only 83% conversion after 100 minutes of reaction time (entry 2).

Table 4-1: Methoxycarbonylation of 1-octene (3.11), 2-octene (4.1) and styrene (3.25).



Entry	R^1	R^2	Alkene	Time (min)	Conversion (%)[a]	Yield (%)[a]	Products	Ratio (l:b)	TOF (h^{-1})[b]
1	$(CH_2)_5CH_3$	H	**3.11**	25	100	76	**3.79**	3:1	104
2	$(CH_2)_4CH_3$	CH_3	**4.1**	100	83	68	**3.79**	2:1	15
3	Ph	H	**3.25**	12	91	87	**3.87**	3:1	113

[a]Determined by GC analysis with xylene as internal standard. [b]Turnover frequency based on $Pd(OAc)_2$.

The same linear and branched products, methyl nonanoate (**3.79l**) and methyl 2-methyloctanoate (**3.79b**), were formed during the methoxycarbonylation of both 1- (**3.11**) and 2-octene (**4.1**) and could unambiguously be identified by EIMS and NMR spectroscopic (^{1}H, ^{13}C and 2D) analysis (Tables 4-2 and 4-3).

Table 4-2: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 3.79l and 3.79b.

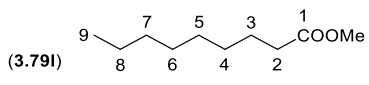
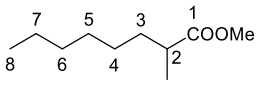
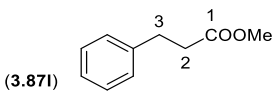
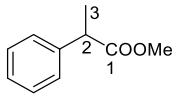
Diagnostic Data	 (3.79l)		 (3.79b)	
EIMS	*m/z* 172 (M^+, 2%)		*m/z* 172 (M^+, 1%)	
Plate nr.	1a-e		1a-e	
^{1}H/^{13}C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2-CH_2 or CH_3	0.87 (t, *J* = 7.0)	14.2	1.13 (d, *J* = 7.0)	17.2
OMe	3.66 (s)	51.5	3.67 (s)	51.3
C=O	-	174.4	-	177.5

Table 4-3: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 3.87l and 3.87b.

Diagnostic Data	 (3.87l)		 (3.87b)	
EIMS	*m/z* 164 (M^+, 35%)		*m/z* 164 (M^+, 23%)	
Plate nr.	2a-e		2a-e	
^{1}H/^{13}C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.63 (t, *J* = 7.9)	35.8	3.72 (q, *J* = 7.2)	45.6
3	2.95 (t, *J* = 7.9)	31.1	1.50 (d, *J* = 7.2)	18.7
OMe	3.67 (s)	51.7	3.65 (s)	52.2
C=O	-	173.5	-	175.1

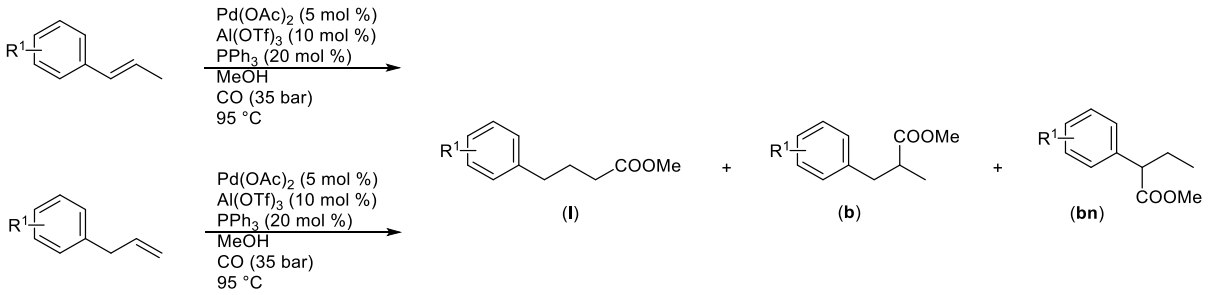
The formation of the linear product (**3.79l**) from 2-octene (**4.1**) as well as the differences in the conversion (100% and 83%, respectively) and yield (76% and 68%, respectively) for 1- (**3.11**) and 2-octene (**4.1**) reflected in Table 4-1 (entry 1 and 2), are explicable in terms of isomerization of the double bond, an inherent property of palladium.[5,6] Under the prevailing reaction conditions, the 3- and 4-octene isomers did not give any observable hydroesterification products, which can be explained by the higher reactivity of mono- vs. disubstituted alkenes.[7,8,9]

4.2.3. Effect of the electronic and steric environment around the double bond on product distribution and reaction rate

In order to determine the electronic effect, if any, of the substituents attached to the aromatic ring on product distribution and reaction rate, it was subsequently decided to subject a series of *trans*-β-methylstyrenes, **3.50**, **4.2**, and **4.3**, and allylbenzenes, **3.70**, **3.84**, **4.4**, **4.6**, and **4.8**, with

electron-donating and electron-withdrawing groups to the methoxycarbonylation conditions, while the steric effect of substituents attached to the double bond was investigated through substituted styrenes, **3.48** and **4.26** (Tables 4-4 and 4-12).

Table 4-4: Methoxycarbonylation of arylalkenes.

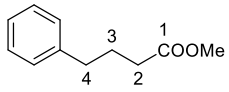
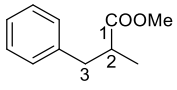
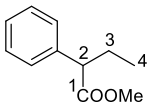


Entry	Methylstyrene R^1	Allylbenzene R^1	Alkene	Time (min.)	Conv. (%)[a]	Yield (%)[a]	Products	Ratio (l:b:bn)[b]	TOF (h^{-1})[c]
1	H	-	**3.50**	180	95	89	**3.71**	3:2:1	10
2	-	H	**3.70**	90	96	88	**3.71**	8:2:1	30
3	*p*-OMe	-	**4.2**	240	49	48	**3.85**	2:1:1	7
4	*o*-OMe	-	**4.3**	120	95	85	**4.5**	10:4:1	11
5	-	*p*-OMe	**3.84**	240	66	54	**3.85**	7:2:1	20
6	-	*o*-OMe	**4.4**	90	95	80	**4.5**	15:5:1	25
7	-	*p*-CF_3	**4.6**	360	88	66	**4.7**	9:2:1	32
8	-	*o*-OTf	**4.8**	40	93	86	**4.9**	5:1:nd	31

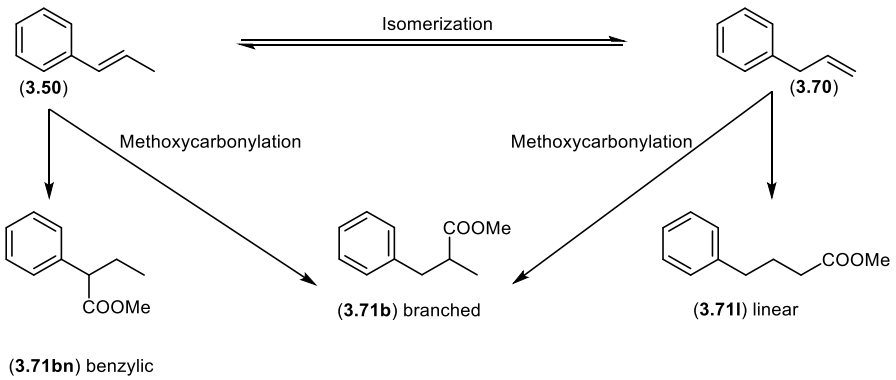
[a]Determined by GC analysis with Xylene as internal standard. [b]Repetition of reactions indicated a variation of 0.2 in product ratios. [c]Turnover frequency based on $Pd(OAc)_2$.

When *trans*-β-methylstyrene (**3.50**) was exposed to the catalyst system, $Pd(OAc)_2/Al(OTf)_3/PPh_3$, and reaction conditions (35 bar CO pressure, 95 °C), three products with R_T values 19.8, 17.3 and 16.7 minutes were obtained in a combined yield of 89% (conversion = 95% and l:b:bn ratio = 3:2:1) after three hours of reaction time (Table 4-4, entry 1). The main product (R_T = 19.8 minutes) was identified as the linear (l) ester, methyl 4-phenylbutanoate (**3.71l**), while the second and third products (R_T = 17.3 and 16.7 minutes, respectively) could be recognised as the branched (b), methyl 2-methyl-3-phenylpropanoate (**3.71b**), and benzylic (bn), methyl 2-phenylbutanoate (**3.71bn**), isomers, respectively. The structures of all three products, **3.71l**, **3.71b** and **3.71bn**, were unambiguously confirmed by EIMS and NMR spectroscopic (^1H, ^{13}C and 2D) analysis (diagnostic resonances are shown in Table 4-5).

Table 4-5: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 3.71l, 3.71b and 3.71bn.

Diagnostic Data	(**3.71l**) 		(**3.71b**) 		(**3.71bn**) 	
EIMS	*m/z* 178 (M^+, 37%)		*m/z* 178 (M^+, 18%)		*m/z* 178 (M^+, 18%)	
Plate nr.	3a-e		3a-e		3a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.33 (t, *J* = 7.6)	33.5	2.77-2.71 (m)	41.6	3.46 (t, *J* = 7.7)	53.5
3	1.96 (p, *J* = 7.6)	26.6	3.03 (dd, *J* = 6.8, 13.4) 2.66 (dd, *J* = 6.8, 13.4)	39.8	2.14-2.06 (m) 1.83-1.76 (m)	26.9
4/2-CH_3	2.65 (t, *J* = 7.6)	35.2	1.15 (d, *J* = 6.9)	16.9	0.94 (t, *J* = 7.4)	12.3
OMe	3.66 (s)	51.65	3.64 (s)	51.72	3.65 (s)	52.0
C=O	-	174.1	-	176.7	-	174.7

The formation of the linear product (**3.71l**) can again be attributed to the ability of palladium to isomerize the double bond to the sterically less demanding terminal position.[5,6] In the reaction mixture two processes, i.e. isomerization and carbonylation, are therefore operating in tandem. The *trans*-β-methylstyrene (**3.50**) is thus carbonylated to form the benzylic (**3.71bn**) and branched (**3.71b**) products, whereas isomerization of the internal double bond to the terminal position (**3.70**) and subsequent carbonylation once again form the linear (**3.71l**) and branched (**3.71b**) products (Scheme 4-3).



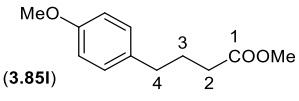
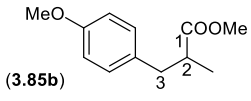
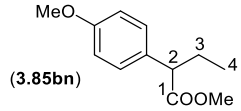
Scheme 4-3: Formation of linear, branched and benzylic products via isomerization of internal double bonds and carbonylation.

In an effort to minimize the isomerization and determine the real efficacy of the catalyst system and reaction conditions with regards to the methoxycarbonylation, the reaction was subsequently extended to allylbenzene (**3.70**), which resulted in the formation of the same three products **3.71l**, **3.71b** and **3.71bn** in 88% combined yield (conversion 96%) after only 90 minutes, albeit in a l:b:bn ratio of 8:2:1 (Table 4-4, entry 2). Although more of the linear product (**3.71l**) than the other two products, **3.71b** and **3.71bn**, was observed, the fact that some of the benzylic product (**3.71bn**) was indeed formed, served as proof that palladium once again

catalysed some isomerization of the double bond, this time to the internal position. The higher reactivity and therefore shorter reaction time of allylbenzene (**3.70**), when compared to *trans*-β-methylstyrene (**3.50**), 90 vs. 180 minutes, is explicable in terms of the generally accepted fact that terminal double bonds are more reactive than internal ones towards carbonylation.[8,9]

With the preliminary experiments completed, the methoxycarbonylation of arylalkenes with electron-donating or electron-withdrawing substituents were embarked upon to determine the effect of these substituents on the product distribution and/or reactivity of the substrate. When the *para*-methoxy carrying substrates, *trans*-*p*-methoxy-β-methylstyrene (anethole, **4.2**) and *p*-methoxyallylbenzene (4-allylanisole, **3.84**), were subjected to the catalyst system, $Pd(OAc)_2/Al(OTf)_3/PPh_3$, and standard reaction conditions (35 bar CO pressure, 95 °C), longer reaction times [4 hours for both vs. 3 hours and 1.5 hours for β-methylstyrene (**3.50**) and allylbenzene (**3.70**), respectively] were required for the methoxycarbonylation reaction to reach completion (Table 4-4). A mixture of the respective linear (**3.85l**), branched (**3.85b**) and benzylic (**3.85bn**) products in combined yields of 48% [vs. 89% for β-methylstyrene (**3.50**)] and 54% [vs. 88% for allylbenzene (**3.70**)] with conversions 49% and 66% vs. 95% and 96%, respectively (Table 4-4 entries 3 vs. 1 and 5 vs. 2) were obtained. The structures of the three products, **3.85l**, **3.85b** and **3.85bn**, were confirmed by ^1H and ^{13}C NMR, whereas mass spectrometry attested to the presence of the appropriate molecular ions with *m/z* 208 (Table 4-6). As expected, the l:b:bn ratios (2:1:1 and 7:2:1, respectively) were close to those observed for *trans*-β-methylstyrene (**3.50**) and allylbenzene (**3.70**), respectively, with the linear product dominating for the allylbenzene analogue (**3.84**) as was observed previously.

Table 4-6: Diagnostic EIMS, ^1H and ^{13}C NMR data for the structure elucidation of products 3.85l, 3.85b and 3.85bn.

Diagnostic Data						
EIMS	*m/z* 208 (M^+, 39%)		*m/z* 208 (M^+, 13%)		*m/z* 208 (M^+, 21%)	
Plate nr.	4a-e		4a-e		4a-e	
$^1H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.34 (t, *J* = 7.5)	33.3	2.75-2.69 (m)	41.7	3.43 (t, *J* = 7.7)	52.5
3	1.94 (p, *J* = 7.5)	26.7	2.98 (dd, *J* = 6.9, 13.5) 2.65-2.63 (m)	38.9	2.11-2.07 (m) 1.81-1.76 (m)	26.8
4/2-CH_3	2.61 (t, *J* = 7.5)	34.2	1.16 (d, *J* = 6.9)	16.7	0.90 (t, *J* = 7.3)	12.2
OMe	3.68 (s)	51.5	3.66 (s)	51.6	3.67 (s)	51.9
C=O	-	174.0	-	176.7	-	174.8

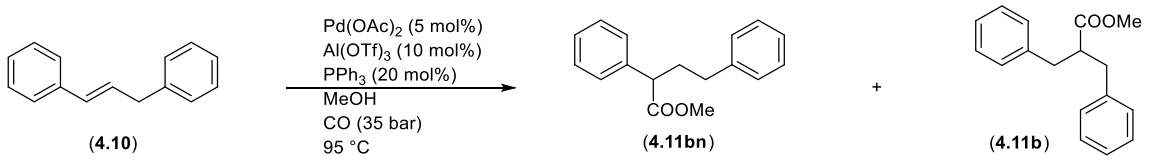
When comparing the methoxycarbonylation reaction of *trans*-β-methylstyrene (**3.50**) with that of its *p*-methoxy-substituted analogue (**4.2**), it is evident that the presence of an electron-donating substituent (methoxy) in the *para*-position of the aromatic ring causes an overall decrease in the reactivity of the substrate (TOF of 10 h^{-1} vs. 7 h^{-1}; reaction times of 180 min. vs. 240 min. to reach conversions of 95% vs. 49%, Table 4-4 entries 1 and 3). This result contradicts the results on styrene (**3.25**) with other catalyst systems as reported by Claver et al.[10] and Alper et al.,[11] though, it must be kept in mind that both *trans*-β-methylstyrenes, (**3.50**) and (**4.2**), are prone to isomerization, which may have a significant influence on the reaction.

It was further noticed that the influence of the electron-richer double bond was extended to the regioselectivity of the reaction where a slight decrease in the formation of the linear (**3.85l**) and branched (**3.85b**) products and therefore an increase in the benzylic (**3.85bn**) product were found for the methoxy substituted analogue (**4.2**), 3:2:1 vs. 2:1:1, 33% vs. 25% branched, 17% vs. 25% benzylic for **3.50** and **4.2**, respectively (Table 4-4, entries 1 and 3). Since the branched product can be formed from the 1-propene isomer (**3.84**) as well as the internal alkene (**4.2**), the fact that a 1:1 ratio for the b:bn products in the latter case (OMe-analogue) (Table 4-4, entry 3) was found, indicates that the hydropalladation step in the mechanism (cf. paragraph 3.7.) shows a preference towards attaching the palladium to the benzylic carbon (also see the methoxycarbonylation of **4.10** below).

Even though the methoxy substituent attached to the aromatic ring, in principle, should not have any influence on the terminal bond, a similar trend of a decrease in reactivity was observed for the methoxycarbonylation of 4-allylanisole (**3.84**), TOF 20 h^{-1} vs. 30 h^{-1} for the unsubstituted allylbenzene (**3.70**), with reaction times of 240 min. vs. 90 min. to reach conversions of 66% vs. 96% respectively (Table 4-4, entry 2 vs. 5). When the product ratios, 8:2:1 vs. 7:2:1, for the methoxycarbonylation of allylbenzene (**3.70**) and 4-allylanisole (**3.84**) are compared, a slight relative increase in the formation of the benzylic (**bn**) product compared to the branched (**b**) and linear (**l**) products were also observed (9% vs. 10%), which indicates that the electronic properties of the aromatic substituent has some influence on the regioselectivity of this reaction as well.

Since the isomerization of the double bond in 1,3-diphenylpropene (**4.10**) would not have any influence on the branched vs. benzylic product distribution, this substrate was subsequently subjected to the reaction conditions and catalyst system in an effort to confirm the preference

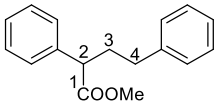
for the formation of the benzylic product (**4.11bn**) over the branched product (**4.11b**), (Scheme 4-4).



Scheme 4-4: Methoxycarbonylation of 1,3-diphenylpropene (4.10).

While a conversion and yield of 64% for the formation of the benzylic product, methyl 2,4-diphenylbutanoate (**4.11bn**), was found, (NMR and MS data in Table 4-7), the branched analogue, methyl 2-benzyl-3-phenylpropanoate (**4.11bn**), was only observable by GC and GCMS, bn:b ratio 21:1. If the statistical effect of the two benzylic positions vs. one branched position is taken into account, a 10:1 preference for carbonylation at the benzylic centre was therefore evident.

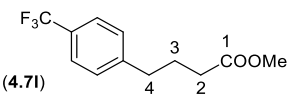
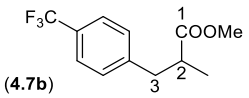
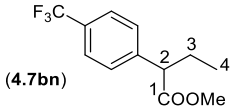
Table 4-7: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of product 4.11bn.

Diagnostic Data	(4.11bn) 	
EIMS	*m/z* 254 (M^+, 2%)	
Plate nr.	5a-e	
^{1}H/^{13}C	δ_H (*J* in Hz)	δ_C
2	3.56 (t, *J* = 7.7)	50.9
3	2.44-2.38 (m) 2.13-2.07 (m)	35.0
4	2.56 (t, *J* = 7.8)	33.6
OMe	3.63 (s)	52.1
C=O	-	174.4

The fact that a reduction in reaction rate was observed for both compounds with a methoxy substituent in the *para*-position of the aromatic ring, i.e. anethole (**4.2**) and 4-allylanisole (**3.84**), when compared to their unsubstituted analogues (**3.50**) and (**3.70**), (Table 4-4, entries 3 vs. 1 and 5 vs. 2), points towards the rate of alkene insertion into the Pd-H bond or another step in the catalytic cycle being slowed down slightly by the more electron-rich double bond or more electron-rich benzylic position, although isomerization of the double bond to the terminal position of the alkene chain to be supressed by the presence of the electron-donating substituent cannot be excluded completely.

To verify this hypothesis, *p*-trifluoromethylallylbenzene (**4.6**), with an electron-withdrawing CF_3-group in the *para*-position, was subjected to the methoxycarbonylation reaction, which led to a conversion of 88% and 66% yield (l:b:bn product ratio 9:2:1) to be obtained (Table 4-4, entry 7). The linear (**4.7l**), branched (**4.7b**) and benzylic (**4.7bn**) product structures could be confirmed by NMR and EIMS analysis (Table 4-8). Since the isomerization of the double bond to the terminal position of the alkene chain can be viewed as the alleviation of steric strain rather than electronic effects, the improved reaction rate obtained for this substrate (**4.6**) when compared to that of the methoxy analogue (**3.84**), (TOF of 32 h^{-1} vs. 20 h^{-1}, Table 4-4, entry 7 vs. 5), confirms that the rate of the alkene insertion into the Pd-H bond or another step in the catalytic cycle is slowed down by an increased electron density on the double bond and/or benzylic position.

Table 4-8: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.7l, 4.7b and 4.7bn.

Diagnostic Data	 (**4.7l**)		 (**4.7b**)		 (**4.7bn**)	
EIMS	*m/z* 246 (M^+, 8%)		*m/z* 246 (M^+, 15%)		*m/z* 246 (M^+, 10%)	
Plate nr.	6a-e		6a-e		6a-e	
^{1}H/^{13}C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.34 (t, *J* = 7.6)	33.3	2.75-2.69 (m)	41.3	3.53 (t, *J* = 7.7)	53.3
3	1.97 (p, *J* = 7.6)	26.3	3.09-3.06 (m) 2.78-2.73 (m)	39.5	2.15-2.07 (m) 1.88-1.79 (m)	26.8
4/2-CH_3	2.71 (t, *J* = 7.6)	35.0	1.18 (d, *J* = 6.8)	17.0	0.89 (t, *J* = 7.4)	12.1
OMe	3.67 (s)	51.7	3.64 (s)	51.8	3.64 (s)	52.2
C=O	-	173.8	-	176.2	-	173.9

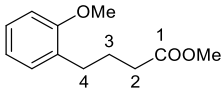
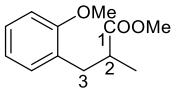
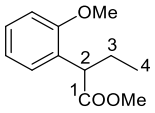
In order to evaluate the possible additional steric effect of a methoxy substituent in the *ortho*-position of the substrates, *trans*-*o*-methoxy-β-methylstyrene (**4.3**) and *o*-methoxyallylbenzene (**4.4**) were subsequently subjected to the standard methoxycarbonylation methodology. As previously found for *trans*-β-methylstyrene (**3.50**) and allylbenzene (**3.70**), a similar set of linear (**4.5l**), branched (**4.5b**) and benzylic (**4.5bn**) products were obtained during these reactions. Once again, the structures of products, **4.5l**, **4.5b** and **4.5bn**, could be confirmed by NMR (^{1}H, ^{13}C and 2D) as well as EIMS analysis (Table 4-9). Substrates **4.3** and **4.4** both gave high conversions (95% for both) and yields (85% and 80%, respectively) in reaction times of only 120 minutes and 90 minutes, respectively. It was also clear from both reactions that the effect of a methoxy-substituent in the *ortho*-position exceeds that of the same substituent in the *para*-position. The TOF value obtained for the compounds with *ortho*-methoxy substituents

increased from 7 h^{-1} to 11 h^{-1} and 20 h^{-1} to 25 h^{-1}, respectively, for the β-methylstyrene (**4.3**) and allylbenzene (**4.4**) analogues when compared to the *para*-substituted isomers, **4.2** and **3.84**, which corresponds to longer reaction times and lower conversions for the *p*-substituted compounds (Table 4-4 entries 3 vs. 4 and 5 vs. 6). The fact that the conversions and yields increased for the *o*-methoxy substituted β-methylstyrene (**4.3**) and allylbenzene (**4.4**) analogues when compared to the *p*-substituted compounds, **4.2** and **3.84**, was unexpected and needs further comment. Although the donating electronic effect of the *ortho*-methoxy substituent could be expected to be comparable to that of a *para*-methoxy group, the NMR chemical shift values of the alkene protons in the *trans*-β-methylstyrene analogues **4.2** and **4.3**, (δ_H 6.33 and 6.08 vs. 6.71 and 6.22)[13,14] as well as Hirshfeld calculations[15] indicate a *para*-methoxy group to be more electron-donating than its *ortho*-methoxy counterpart. So, while it could be expected that the reaction rate and therefore conversion should be somewhat higher for the *ortho*-methoxy analogues (**4.3** and **4.4**), it could also be anticipated that the steric hinderance of the *ortho*-substituent should have a negative effect on the conversion and yields of the *ortho*-substituted compounds. Since a fairly large increase in reaction rate (reaction times of 90 and 120 min. vs. 240 min.) and conversions (both 95% vs. 66 and 49%) were found for the *ortho*-substituted analogues, it can be concluded that the steric hindrance between the palladium catalyst and substrate results in less isomerization to the less reactive internal olefin (**4.3**) in the case of the allylbenzene analogue (**4.4**) and more facile reverse isomerization to the α-olefin (**4.4**) for the β-methylstyrene compound (**4.3**). This hypothesis was supported by an increase in the formation of the linear product (**4.5l**) and a concomitant substantial decrease in the formation of the benzylic analogue (**4.4**) for the *o*-substituted substrates when compared to the *p*-substituted substrates (Table 4-4, 10:4:1 vs. 2:1:1 l:b:bn, 67% vs. 50% linear, 7% vs. 25% benzylic for *o*- (**4.2**) and *p*-methoxy-β-methylstyrene (**4.3**); 15:5:1 vs. 7:2:1 l:b:bn, 71% vs. 70% linear, 5% vs. 10% benzylic for *o*- (**4.4**) and *p*-methoxyallylbenzene (**3.84**), respectively). The formation of chelated structures **4.12** (Figure 4-2) between the palladium catalyst, the *ortho*-methoxy group and the double bond may also bring the catalyst in close proximity to the double bond which could also lead to an increase in reaction rate.

(**4.12a**) (**4.12b**) (**4.13a**) (**4.13b**)

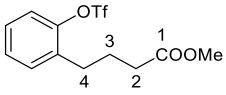
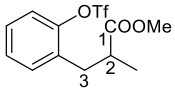
Figure 4-2: Possible complex formations between different substituents and the palladium catalyst.

Table 4-9: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.5l, 4.5b and 4.5bn.

Diagnostic Data	(4.5l) 		(4.5b) 		(4.5bn) 	
EIMS	*m/z* 208 (M^+, 40%)		*m/z* 208 (M^+, 22%)		*m/z* 208 (M^+, 34%)	
Plate nr.	7a-e		7a-e		7a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.32 (t, *J* = 7.6)	33.6	2.86-2.80 (m)	39.5	3.93 (t, *J* = 7.6)	45.7
3	1.92 (p, *J* = 7.6)	25.0	2.98 (dd, *J* = 7.1, 13.2) 2.70 (dd, *J* = 7.6, 13.2)	34.6	2.08-2.03 (m) 1.78-1.73 (m)	25.7
4/2-CH_3	2.65 (t, *J* = 7.6)	29.5	1.13 (d, *J* = 7.0)	17.0	0.89 (t, *J* = 7.4)	12.2
OMe	3.64 (s)	51.45	3.61 (s)	51.47	3.63 (s)	51.8
C=O	-	174.2	-	177.1	-	175.0

Since a more bulky substituent should have an even more profound steric influence on the incoming palladium catalyst, *ortho*-triflate substituted allylbenzene (**4.8**) was subjected to the methoxycarbonylation reaction conditions, which resulted in an excellent conversion (93%) and yield (86%) in only 40 minutes of reaction time (Table 4-4, entry 8). In addition to the excellent yield and reaction rate, only the linear (**4.9l**) and the branched (**4.9b**) products (5:1:0 vs. 15:5:1 for the *o*-methoxyallylbenzene) were isolated from this reaction and characterized by NMR spectrometry and EIMS analysis (Table 4-10).

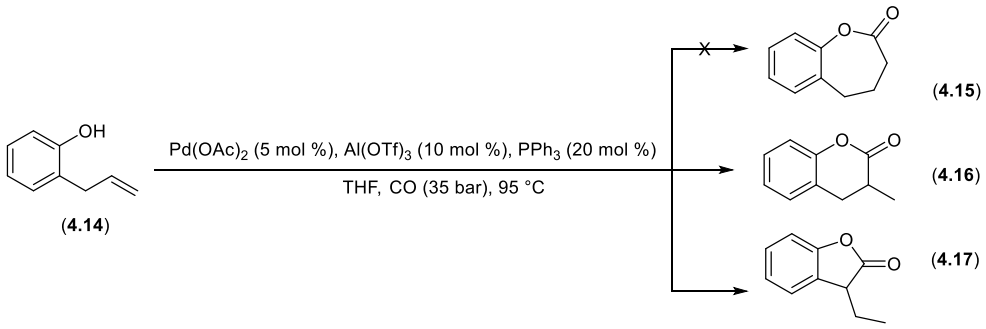
Table 4-10: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.9l and 4.9b.

Diagnostic Data	(4.9l) 		(4.9b) 	
EIMS	*m/z* 326 (M^+, 4%)		*m/z* 326 (M^+, 5%)	
Plate nr.	8a-f		8a-f	
^{19}F NMR	δ_F -76.84		δ_F -76.87	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.36 (t, *J* = 7.6)	33.2	3.72 (q, *J* = 7.2)	39.9
3	1.98 (p, *J* = 7.6)	25.0	3.12-3.07 (m) 2.86-2.81 (m)	33.9
4/2-CH_3	2.76 (t, *J* = 7.6)	29.1	1.20 (d, *J* = 6.6)	17.0
OMe	3.66 (s)	51.6	3.61 (s)	51.4
C=O	-	173.3	-	175.7

The reactivity of the allylbenzene with an *ortho*-triflate substituent (**4.8**), which is electron-withdrawing compared to the allylbenzene substrate with an *ortho*-methoxy substituent (**4.4**), also increased drastically from 25 h^{-1} to 31 h^{-1}, with a corresponding decrease of reaction time from 90 minutes to 40 minutes to reach similar conversion values (Table 4-4, entry 6 vs. 8).

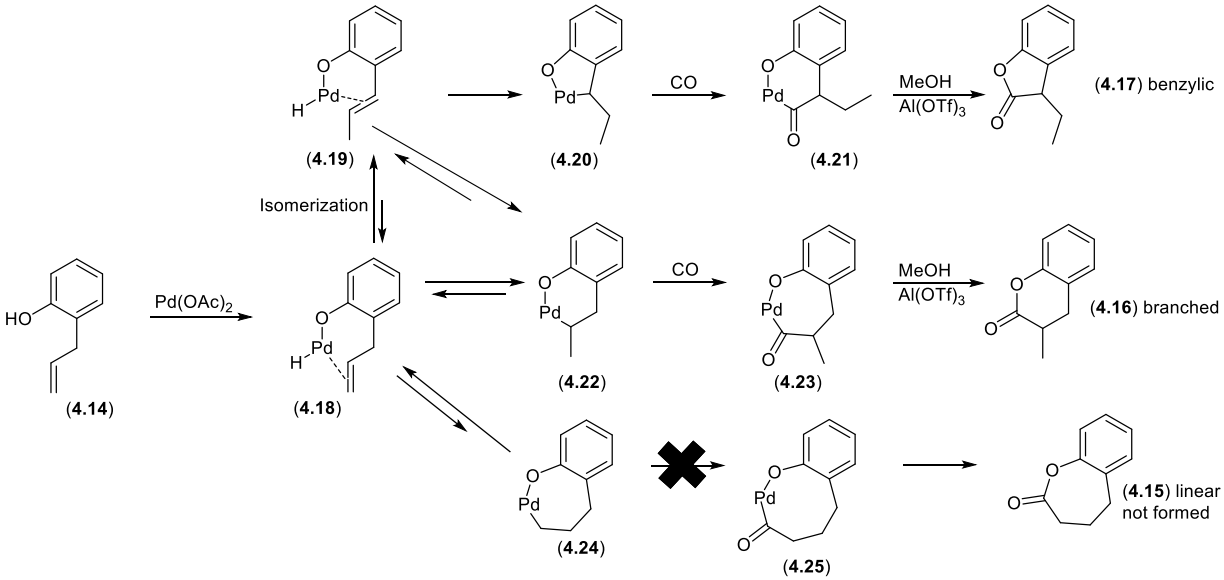
Although this could be due to suppression of the isomerization to the less reactive internal olefin, an agostic interaction between the methoxy hydrogens and the palladium catalyst could also have a stabilizing effect on one of the transition states, and cannot be ignored as alternative cause for the higher reactivity observed for *ortho*-methoxy (**4.4**) and *ortho*-triflate (**4.8**) substituted compounds. The formation of chelated structures **4.13** (Figure 4-2) between the palladium catalyst, the *ortho*-triflate group and the double bond may also bring the catalyst in close proximity to the double bond which could have led to the increased reaction rate.

In order to reduce the steric bulk of the *ortho*-electron donating substituent and maybe reach even higher reactivity, *o*-hydroxyallylbenzene (**4.14**) was subsequently subjected to the alkoxycarbonylation reaction. While three products, **4.15**, **4.16** and **4.17**, could in principle be formed through intramolecular cyclization during the carbonylation process, only the five- and six-membered cyclic compounds, **4.17** and **4.16**, were isolated in a 55% combined yield, 60% conversion and a ratio of 1:1 (Scheme 4-5).



Scheme 4-5: Intramolecular alkoxycarbonylation of *o*-hydroxyallylbenzene (4.14).

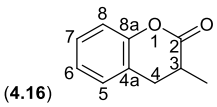
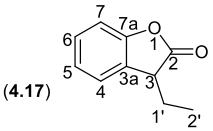
Although the linear isomers (**3.71l**, **3.85l**, **4.5l**, **4.7l** and **4.9l**) were the major products during all of the preceding reactions, the fact that **4.15** was not detected in the product mixture of this reaction is probably explicable in terms of the unfavourable eight-membered ring structure (**4.25**). Since the five- and six-membered cyclic products, 3-ethylbenzofuran-2(3*H*)-one (**4.17**) and 3-methylchroman-2-one (**4.16**), were formed in a 1:1 ratio, it could be concluded that the *ortho*-OH substituent enhances isomerization of the double bond to the internal position, while it also directs the carbonylation towards the more stable incipient benzylic carbocation intermediate (Scheme 4-6). If this is not the case, the six-membered ring product (**4.17**) should be the major product as it may originate from the more reactive mono-substituted α-olefin (**4.18**) as well as the branched position of the in situ formed internal alkene (**4.19**), (Scheme 4-6).



Scheme 4-6: Formation of cyclic products during the intramolecular carbonylation of *o*-hydroxyallylbenzene (4.14).

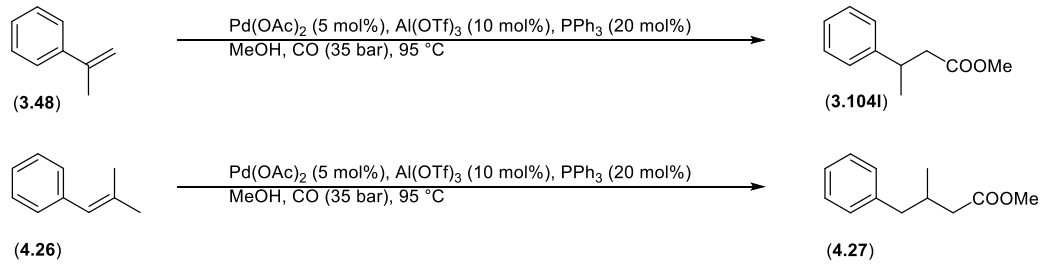
The reactivity of *o*-hydroxyallylbenzene (**4.14**), compared to that of the *o*-methoxy (**4.4**) and *o*-triflate (**4.8**) analogues, decreased [60% conversion after 90 min. vs. 93% after 40 min. and 95% after 90 min. for the *o*-triflate- (**4.8**) and *o*-methoxyallylbenzene (**4.4**), respectively] and may be due to a rate determining isomerization of the double bond to the thermodynamically favourable position in order to form the more stable six- and five-membered ring products, (**4.16**) and (**4.17**). Changing the solvent for the intramolecular methoxycarbonylation reaction of (**4.14**) from MeOH to THF can also have an influence on the reactivity of the reaction. The structures of the products were confirmed by the ^{1}H and ^{13}C NMR spectra (Table 4-11).

Table 4-11: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.16 and 4.17.

Diagnostic Data	 (4.16)		 (4.17)	
EIMS	*m/z* 162 (M^+, 100%)		*m/z* 162 (M^+, 100%)	
Plate nr.	9a-e		10a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
3	2.86-2.76 (m)	34.3	3.71 (t, *J* = 5.9)	44.7
4	2.98 (dd, *J* = 14.9, 5.4) 2.86-2.76 (m)	31.8	7.27 (br dd, *J* = 7.6)	124.3 or 124.2
5	7.18 (br d, *J* = 7.5)	128.1	7.15 (br dd, *J* = 7.6, 1.0)	124.3 or 124.2
6	7.09 (br dd, *J* = 8.5, 7.5, 1.1)	124.4	7.32-7.29 (m)	128.9
7	7.26 (br dd, *J* = 8.5, 8.2)	128.3	7.11 (br dd, *J* = 8.0, 1.0)	110.8
8	7.04 (br dd, *J* = 8.2, 1.1)	116.7	-	-
CH_3/CH_2CH_3	1.38 (d, *J* = 6.5)	15.5	2.09-2.04 (m) 0.97 (t, *J* = 7.5)	24.4 10.3
C=O	-	171.8	-	177.4

In order to assess the effect of steric hindrance in a 1,1-disubstituted olefin and since the isomerization factor could not play a role in the product distribution of this substrate, the methoxycarbonylation reaction with the current catalyst system, $Pd(OAc)_2/Al(OTf)_3/PPh_3$, was extended to α-methylstyrene (**3.48**). As could be expected, only the linear product, **3.104l** was formed in 63% yield with 85% conversion after a period of 4 hours (Table 4-12, entry 1), whereas the extended reaction time (4 h) when compared to that of styrene (12 minutes) confirmed the detrimental effect of steric hindrance towards methoxycarbonylation with the current catalyst system. The structure of the product (**3.104l**) could unambiguously be confirmed by EIMS and NMR analysis (Table 4-13).

Table 4-12: Methoxycarbonylation of di- (3.48) and trisubstituted (4.26) alkenes.

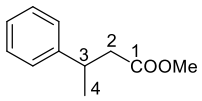
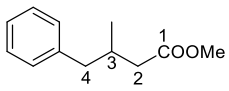


Entry	Alkene	Time (min.)	Conversion (%)[a]	Yield (%)[a]	Product	TOF (h^{-1})[b]
1	**3.48**	240	85	63	**3.104l**	6
2	**4.26**	360	38	26	**4.27**	2

[a]Determined by GC analysis with Xylene as internal standard. [b]Turnover frequency based on $Pd(OAc)_2$.

An increase in the steric bulk of the substrate to the trisubstituted double bond analogue (**4.26**) resulted in an extremely low reactivity (TOF = 2 h^{-1}) with the linear isomer (**4.27**) being obtained as the sole product in only 26% yield after six hours of reaction time (Table 4-12, entry 2). The formation of only the linear product, (**4.27**, Table 4-13), indicates double bond isomerization to the terminal position prior to methoxycarbonylation and the isomerization to be a more facile process than methoxycarbonylation in higher substituted alkenes.

Table 4-13: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 3.104 and 4.27.

Diagnostic Data	(**3.104**) 		(**4.27**) 	
EIMS	*m/z* 178 (M^+, 22%)		*m/z* 192 (M^+, 2%)	
Plate nr.	11a-e		12a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.62 (dd, *J* = 15.2, 6.9) 2.54 (dd, *J* = 15.2, 8.3)	42.8	2.33 (dd, *J* = 14.6, 5.8) 2.14 (dd, *J* = 14.6, 7.8)	41.0
3	3.31-3.25 (m)	36.5	2.31-2.25 (m)	32.4
4	1.29 (d, *J* = 7.0)	21.8	2.62 (dd, *J* = 13.5, 6.7) 2.50 (dd, *J* = 13.5, 7.4)	43.1
CH_3	-	-	0.94 (d, *J* = 6.6)	19.8
OMe	3.60 (s)	51.5	3.64 (s)	51.5
C=O	-	172.9	-	173.6

4.2.4. Effect of mass transfer enhancement on the reaction rate of different substrates

Although the optimization process discussed in paragraph 4.2.1 indicated the external CO pressure (25-45 bar) and stirrer speed (300-700 rpm) to have little effect on the methoxycarbonylation of *trans*-β-methylstyrene (**3.50**), the availability of CO and thus the CO concentration in solution logically should have a significant influence on the rate of the reaction unless CO is not involved in the rate limiting step of the process. The CO concentration in solution is, however, not only dependent on the CO pressure above the liquid inside the reactor (Henry's law), but also on how well the CO is transferred into the liquid phase where the reaction occurs. Since the equilibrium CO concentration in solution can be reached and maintained more efficiently by improving the transfer of CO from the head space of the reactor into the reaction mixture by utilizing a gas-entrainment stirrer, this aspect of the reaction was subsequently investigated. For the set of alkenes, [1-octene (**3.11**), styrene (**3.25**), *trans*-β-methylstyrene (**3.50**), *trans-p*-methoxy-β-methylstyrene (**4.2**), α-methylstyrene (**3.48**), allylbenzene (**3.70**), *p*-methoxyallylbenzene (**3.84**) and *o*-methoxyallylbenzene (**4.4**)] selected for this study, all the reactions were thus repeated under optimized conditions with- and without mass transfer limitations in order to study the possibility of mass-transfer being the rate limiting step in the reactions.

The first substrate, 1-octene (**3.11**), renowned for high reactivity in hydroesterification reactions, showed virtually no reaction rate effect originating from mass-transfer limitations (Table 4-14 and Figure 4-2), while the product distribution was found to be slightly more in

favour of the linear product (**3.79l**) for the less well-stirred reaction. A slightly lower conversion (84% vs. 91%) and yield (73% vs. 87%) were observed for styrene (**3.25**) and the product ratio also increased from 3:1 (l:b) under proper mass-transfer conditions to 4:1 when mass-transfer limitations were present.

The reduction in the formation of the linear vs. branched products for the two substrates, **3.11** and **3.25**, for the reactions performed under proper mass-transfer conditions can probably be explained by the fact that under conditions of lower CO concentration, the rate of CO insertion into the C-Pd bond is slowed down. Under these circumstances, the more stable incipient 2° carbocation as well as carbopalladation towards the less hindered primary position will be favoured and lead to more of the linear product to be formed.

Table 4-14: Methoxycarbonylation of oct-1-ene (3.11) and styrene (3.25) with and without proper mass transfer conditions.

Entry	Alkene	Time (min)	Conversion (%)[a,b]	Yield (%)[a,b]	Products	Ratio l:b[a]
1	1-octene (**3.11**)	25	100 (98)	76 (77)	**3.79**	3:1 (4:1)
2	styrene (**3.25**)	12	91 (84)	87 (73)	**3.87**	3:1 (4:1)

[a]Values in brackets are for reactions under conditions of mass transfer limitations, without utilizing a gas-entrainment stirrer. [b]Determined by GC analysis with Xylene as internal standard.

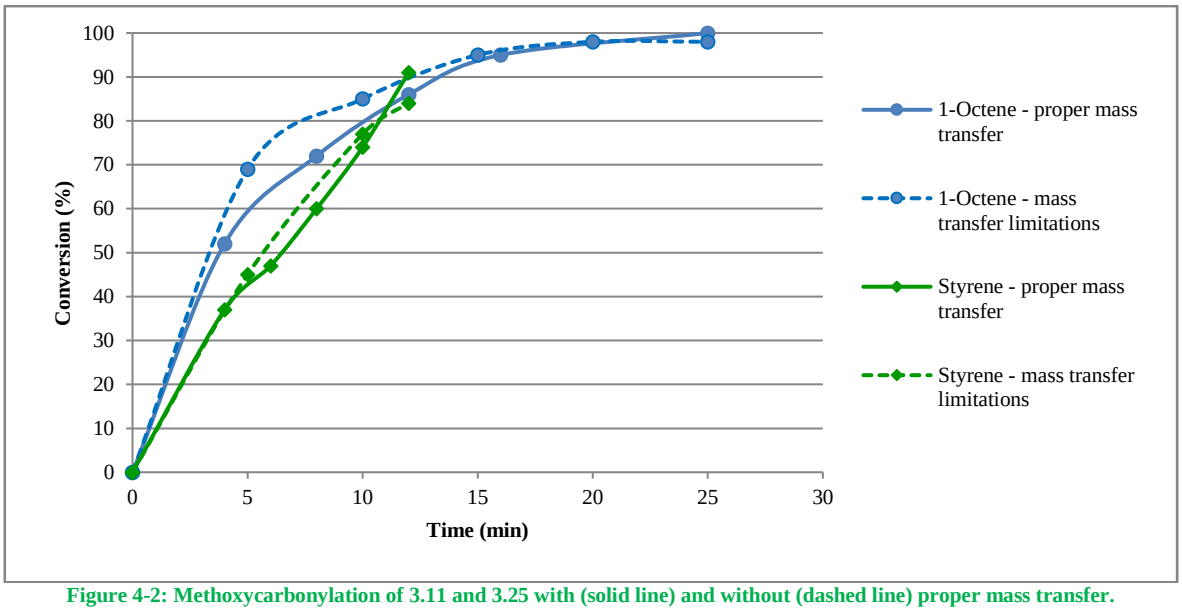


Figure 4-2: Methoxycarbonylation of 3.11 and 3.25 with (solid line) and without (dashed line) proper mass transfer.

When the effect of mass-transfer limitations were investigated for *trans*-β-methylstyrene (**3.50**) and its substituted analogues, **4.2** and **3.48**, it was found that the conversions for all three substrates, **3.50**, **4.2** and **3.48**, remained unchanged, while the yields for the *p*-methoxy- and α-methyl-analogues, **4.2** and **3.48**, did not change significantly (Table 4-15, entries 1-3, Figure 4-3). It is also evident from the similarity in the reaction rate curves in Figure 4-3 that mass-transfer does not have a profound effect on the rates of these reactions under the prevailing

conditions, or it may indicate that another step in the mechanism, probably isomerization of the double bond to the terminal position, could be the rate determining step in the process. The latter is corroborated by the fact that a decrease in the formation of the linear products, **3.71l**, and **3.85l**, were observed during the reactions under proper mass-transfer conditions. In this instance, it could be envisaged that CO insertion into the C-Pd bond would be retarded by low CO concentration allowing for an increase in the isomerization to the terminal position.

Table 4-15: Methoxycarbonylation of arylalkenes with and without proper mass transfer conditions.

Entry	Arylalkene	Time (min.)	Conv. (%)[a,b]	Yield (%)[a,b]	Product	Ratio l:b:bn[a,c]
1	β-methylstyrene (**3.50**)	180	95 (95)	89 (76)	**3.71**	3:2:1 (5:2:1)
2	*p*-OMe-methylstyrene (**4.2**)	180	50 (51)	47 (46)	**3.85**	2:1:1 (3:1:1)
3	α-methylstyrene (**3.48**)	180	76 (75)	63 (62)	**3.104**	n.a.
4	Allylbenzene (**3.70**)	90	96 (78)	88 (68)	**3.71**	8:2:1 (7:2:1)
5	*p*-OMe-allylbenzene (**3.84**)	180	66 (58)	54 (50)	**3.85**	7:2:1 (5:1:1)
6	*o*-OMe-allylbenzene (**4.4**)	120	98 (93)	80 (72)	**4.5**	15:5:1 (26:5:1)

[a]Values in brackets are for reactions under conditions of mass transfer limitations without utilizing a gas-entrainment stirrer. [b]Determined by GC analysis with Xylene as internal standard. [c]n.a. = not applicable.

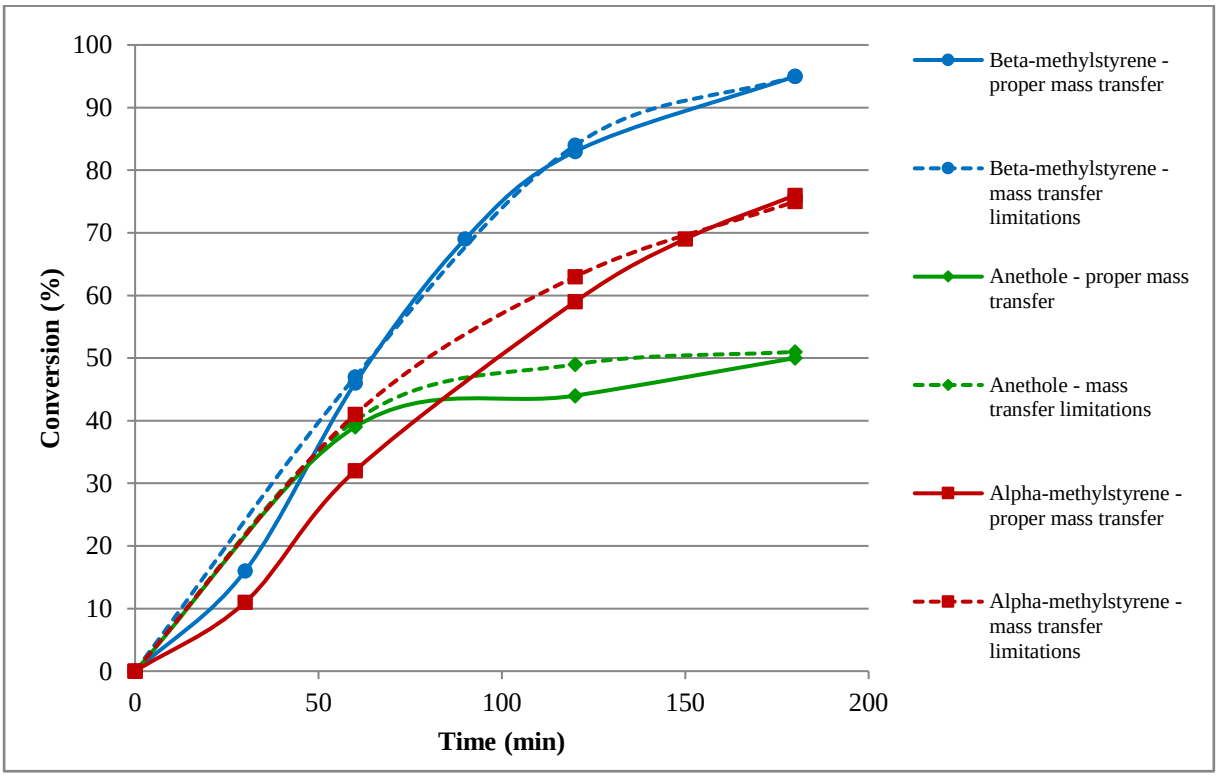


Figure 4-3: Methoxycarbonylation of 3.50, 4.2 and 3.48 with (solid line) and without (dashed line) proper mass transfer.

Extending the comparative study to the allylbenzene analogues, **3.70**, **3.84** and **4.4**, a substantial increase in conversion (78% to 96% and 58% to 66% and 93% to 98%, respectively) was observed for allylbenzene (**3.70**), *p*-methoxyallylbenzene (**3.84**) and *o*-methoxyallylbenzene (**4.4**) during the reactions without mass-transfer limitations (Table 4-15, entries 4-6). Contrary

to what was found for the β-methylstyrene analogues, the allylbenzenes, **3.70** and **3.84**, displayed a significant enhancement of the reaction rate, especially during the early stages of the reactions, when proper mass-transfer conditions were present (Figure 4-4), so it could be concluded that the availability of CO in fact is the rate limiting step in these reactions, which makes sense when taken into account that the isomerization of the double bond to the more reactive α-position is not an issue anymore. The fact that in the case of *o*-methoxyallylbenzene (**4.4**), virtually no difference in the reaction rate with and without mass transfer limitations was found, confirms the point made earlier (vide supra) that some other step in the reaction sequence, like the formation of a chelated intermediate between the palladium catalyst and the methoxy group and the double bond or an agostic interaction between the hydrogen atoms of the methoxy group and the palladium catalyst, might be the rate determining point in the mechanism.

For the allylbenzene analogues, **3.70** and **3.84**, the product ratios were also slightly more in favour of the linear isomers (8:2:1 vs. 7:2:1 and 7:2:1 and 5:1:1, respectively) under conditions of no mass transfer limitations, while the opposite (15:5:1 vs. 26:5:1) was found for the *o*-methoxyallylbenzene analogue (**4.4**). The fact that for the former two substrates, **3.70** and **3.84**, the formation of the linear product is enhanced over the branched and benzylic isomers is probably explicable in terms of a higher CO concentration in solution leading to more efficient CO insertion into the C-Pd bond and thus less opportunity for isomerization of the double bond to the internal position. For *o*-methoxyallylbenzene (**4.4**), the inverse situation, i.e. a decrease in the formation of the linear product, 26:5:1 vs. 15:5:1, as the availability of CO in the reaction mixture was increased, may be an indication that isomerization to the internal isomer is largely inhibited by the steric effect of the methoxy group, which allowed for the product from the lower energy transition state (hydride transfer to the more stable incipient carbocation and carbopalladation to the more favourable terminal position) to be formed preferentially when the availability of CO is limited.

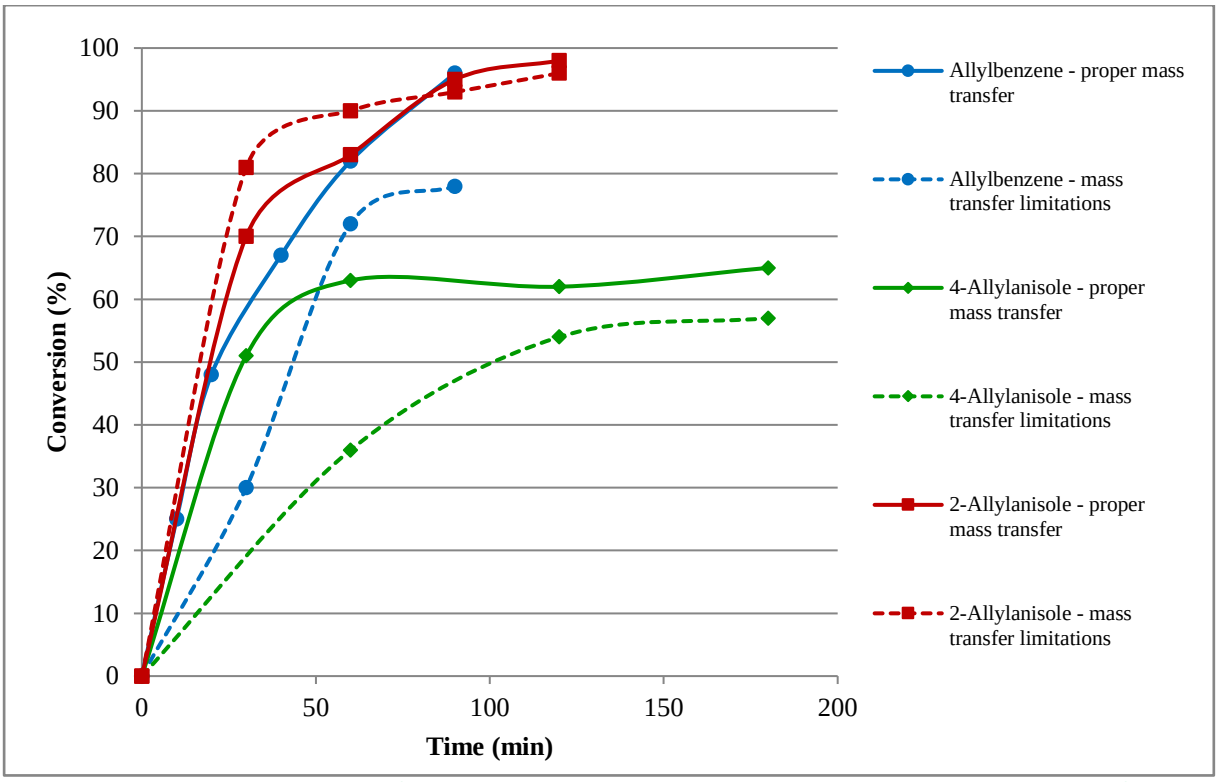


Figure 4-4: Methoxycarbonylation of 3.70, 3.84 and 4.4 with (solid line) and without (dashed line) proper mass transfer.

4.2.5. Methoxycarbonylation under conditions of microwave heating

While the Pd-catalyzed alkoxycarbonylation of alkenes has been well documented for a plethora of catalyst systems (cf. Chapter 3), these reactions are usually performed in autoclave (AC) reactors at CO pressures ranging from ca. 1-70 bar. Since it is generally known that microwave heating has the ability to accelerate some chemical reactions[16] and a microwave reactor equipped with a continuous gas-inlet system became available, it was subsequently decided to evaluate the effect, if any, of microwave heating (150 W) on the methoxycarbonylation reaction with the current catalyst system, $Pd(OAc)_2/Al(OTf)_3/PPh_3$, and compare it with the results obtained under autoclave conditions (35 bar CO pressure) as discussed in paragraph 4.2.2.-4.2.4. Although it was determined previously that the optimum pressure for this methoxycarbonylation system was 35 bar, the glass vessels in the microwave reactor were rated for a maximum of 12 bar only, so the alkoxycarbonylation reactions were repeated in the autoclave reactor at the same pressure (12 bar) in order to be in a position to draw a direct comparison between the two methods of heating and stirring with a stirrer bar for the microwave reactions and ordinary mechanical stirring (no gas-entrainment) for the autoclave reactions.

The first two substrates, 1-octene (**3.11**) and styrene (**3.25**), were therefore subjected to methoxycarbonylation methodology with microwave heating (12 bar, 95 °C) as well as under conventional autoclave conditions (12 bar, 95 °C) with the standard catalyst system, $Pd(OAc)_2/Al(OTf)_3/PPh_3$, and samples taken at intervals of 10 and 30 minutes (Table 4-16). For both substrates, (**3.11** and **3.25**), a substantial increase in conversion of ca. 20% and 30%, respectively, were found even after only 10 minutes into the reaction for the microwave reaction when compared to the autoclave equivalent at the same pressure (12 bar), while virtually complete conversion of the starting material (96-99%) were observed after 30 minutes under microwave irradiation as well as conventional heating conditions (Table 4-16, entries 2 vs. 3 and 5 vs. 6). The fact that the final yield for the microwave reactions are somewhat lower than those of the reactions in the autoclave reactor under the same conditions (82% vs. 91% and 72% vs. 92%) is probably explicable in terms of unwanted side reactions, like polymerization in the case of styrene (**3.25**), and/or subsequent hydrolysis of the ester products, **3.79** and **3.87**, by water present in the methanol, which were exposed to the microwave conditions for an extended period of time since the MW reactions were already 99% and 89% completed after only 10 minutes (Table 4-16, entries 3 and 6).

Table 4-16: Methoxycarbonylation of 1-octene (3.11) and styrene (3.25) under reaction conditions A, B and C.[a]

Entry	Alkene	Method	Conversion (%)[b]		Yield (%)[b,c]	Product	Ratio l:b[b,c]
			10 min.	30 min.			
1	1-octene (**3.11**)	A (AC, 35 bar)	85	95	92	**3.79**	4:1
2		B (AC, 12 bar)	80	94	91	**3.79**	4:1
3		C (MW, 12 bar)	99	99	82	**3.79**	4:1
4	styrene (**3.25**)	A (AC, 35 bar)	77	96	93	**3.87**	4:1
5		B (AC, 12 bar)	58	96	92	**3.87**	4:1
6		C (MW, 12 bar)	89	99	72	**3.87**	4:1

[a]Method A - Conventional heating in autoclave reactor system (AC) under 35 bar of CO, 95 °C, no gas-entrainment; Method B - Conventional heating in autoclave reactor system (AC) under 12 bar of CO, 95 °C, no gas-entrainment; Method C - Microwave irradiation (150 W) with ordinary magnetic stirring under 12 bar of CO, 95 °C. [b]Determined by GC analysis with Xylene as internal standard. [c]Determined after 30 minutes.

When the substituted arylalkenes, allylbenzene (**3.70**), 4-allylanisole (**3.84**), 2-allylanisole (**4.4**) and *trans*-β-methylstyrene (**3.50**) were subjected to methoxycarbonylation under the conditions of microwave heating over the standard catalyst system, $Pd(OAc)_2/Al(OTf)_3/PPh_3$, it was found that allylbenzene (**3.70**) performed equally well under both methods of heating (Table 4-17, entries 1, 2 and 3). A substantial improvement in conversion (20% vs. 28% and 70% vs. 86%, respectively) after only one hour was obtained for the methoxy substituted allylbenzene analogues, **3.84** and **4.4**, during conditions of MW irradiation over conventional heating at the same pressure (Table 4-17, entry 5 vs. 6 and 8 vs. 9). The improved conversion rates obtained

for these substrates were accompanied by an increase in final product yield of 20% to 37% and 73% to 89%, respectively, for the microwave reactions when compared to the reactions in the autoclave reactor. For the *trans*-β-methylstyrene (**3.50**) reactant an even more profound increase in conversion (29% to 65% after one hour) and final yield (66% to 82%) were obtained under microwave conditions (Table 4-17, entry 11 vs. 12). With regard to the regioselectivity of the reactions, a general decrease in the formation of the linear products is evident for all the substrates during the microwave reactions when compared to the conventional heating experiments under the same pressure (Table 4-17 entry 2 vs. 3, 5 vs. 6, 8 vs. 9 and 11 vs. 12). The reduced formation of the linear products is probably explicable in terms of a more facile hydroesterification reaction and thus lower tendency towards isomerization to the corresponding internal olefins for the allylbenzene substrates, while isomerization of the β-methylstyrene to the sterically less hindered allylbenzene isomer may also be accelerated by the microwave conditions.

Table 4-17: Methoxycarbonylation of arylalkenes under reaction conditions A, B and C.[a]

Entry	Alkene	Method	Conv. (%)[b]		Yield (%)[b,c]	Product	Ratio l:b:bn[b,c]
			1 h	3 h			
1	allylbenzene (**3.70**)	A (AC, 35 bar)	72	97	80	**3.71**	7:2:1
2		B (AC, 12 bar)	57	87	80	**3.71**	12:2:1
3		C (MW, 12 bar)	57	90	81	**3.71**	9:2:1
4	*p*-OMe-allylbenzene (**3.84**)	A (AC, 35 bar)	38	60	51	**3.85**	5:2:1
5		B (AC, 12 bar)	20	21	20	**3.85**	15:2:1
6		C (MW, 12 bar)	28	40	37	**3.85**	6:1:1
7	*o*-OMe-allylbenzene (**4.4**)	A (AC, 35 bar)	88	-	75	**4.5**	26:5:1
8		B (AC, 12 bar)	70	90	73	**4.5**	28:6:1
9		C (MW, 12 bar)	86	96	89	**4.5**	27:5:1
10	β-methylstyrene (**3.50**)	A (AC, 35 bar)	47	95	76	**3.71**	5:2:1
11		B (AC, 12 bar)	29	74	66	**3.71**	10:2:1
12		C (MW, 12 bar)	65	94	82	**3.71**	8:2:1

[a]Method A - Conventional heating in autoclave reactor system (AC) under 35 bar of CO, 95 °C, no gas-entrainment; Method B - Conventional heating in autoclave reactor system (AC) under 12 bar of CO, 95 °C, no gas-entrainment; Method C - Microwave irradiation (150 W) with ordinary magnetic stirring under 12 bar of CO, 95 °C. [b]Determined by GC analysis with Xylene as internal standard. [c]Determined after 3 hours.

Finally, for 1-octene (**3.11**) and styrene (**3.25**), a definite reaction rate increasing effect was observed with the conversion after 10 minutes under microwave conditions at 12 bar being almost the same or better than what was obtained after 30 minutes at 35 bar with conventional heating in an autoclave reactor. Although no dramatic reaction rate enhancing effect was observed for the other substrates, both the substituted allylbenzene analogues (**3.84** and **4.4**) and β-methylstyrene (**3.50**) showed improvements in conversion and yield under microwave conditions when compared to conventional heating at the same pressure. The fact that only a

very slight improvement in conversion and yield could be detected for allylbenzene (**3.70**) is currently inexplicable.

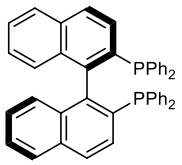
4.3. Aminocarbonylation

4.3.1. Introduction

Although palladium catalysed alkoxycarbonylation, which entails the reaction of an alkene with CO followed by nucleophilic attack of an alcohol nucleophile under palladium catalysis, is a well-studied reaction, reports on the utilization of nitrogen nucleophiles in this type of reaction is completely lacking.[*17,18] It was therefore decided during the candidate's MSc study[3] to extend the current investigation to include nitrogen nucleophiles in the carbonylation of alkene substrates with the $Pd(OAc)_2/Al(OTf)_3/PPh_3$ catalyst system. This led to the successful formation of linear and branched amides from β-methylstyrene (**3.50**) and aniline (**4.28**). Owing to the potential of the new reaction, it was subsequently decided to extend the scope of the reaction to other aryl substituted alkenes as well as amines during the candidate's PhD research. Although two papers[17,18] on the subject appeared since the initial demonstration of the palladium catalysed aminocarbonylation reaction, the published reports utilized different palladium catalysts and did not include aluminium triflate as acid co-catalyst. It is also important to note that in all of these methodologies, the amine was used as the limiting reagent with the alkenes in sometimes large excess, while the reported reactions was also restricted to aniline derivatives as nucleophiles.

4.3.2. Catalyst (ligand) and substrate variation

In order to be able to compare the results obtained during the current investigation with literature values, the study was started with the aminocarbonylation of styrene (**3.25**) and allylbenzene (**3.70**) with different ligands and co-catalysts being evaluated (Table 4-18). As indicated in Table 4-18 entry 1, results similar to those published by Liu et al.[18] (99% conversion, yield and regioselectivity towards the branched product were obtained. Changing the catalyst system to include $Al(OTf)_3$ and using the alkene (**3.25**) as limiting reagent resulted in a decrease in yield and conversion to ca. 70%, while a 20% formation of the linear product was also observed (Table 4-18, entry 2). When the monodentate PPh_3 ligand was replaced with the bidentate BINAP (**3.129**),

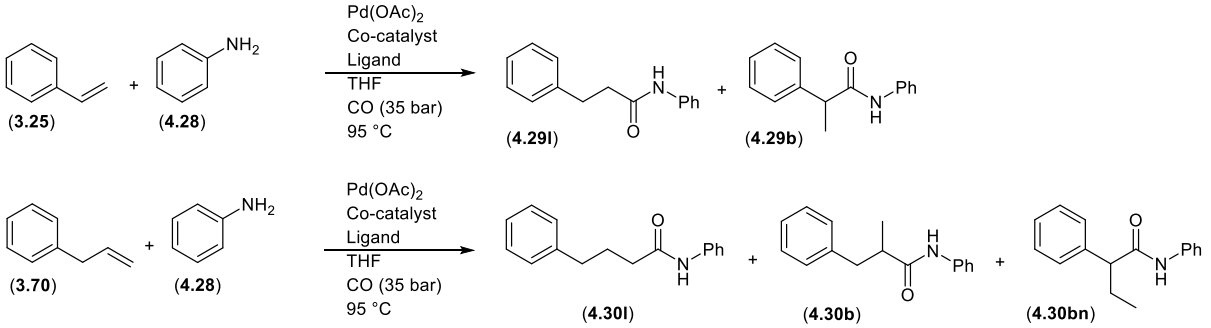


(**3.129**) (*R*)-BINAP

[*] During the course of this investigation, two communications describing utilization of nitrogen nucleophiles in carbonylation reactions was published by Beller et al.[17] and Liu et al.[18]

however, the conversion returned to 90% with a combined yield of the linear (**4.29l**) and branched (**4.29b**) products of 86% (Table 4-18, entry 3). When the concentration of the BINAP (**3.129**) ligand was reduced to two equivalents, however, an interesting swop in regioselectivity to the formation of the linear analogue (**4.29l**) as major product (l:b 2:1) was found, although the yield and conversion came down to only 69% and 58%, respectively (Table 4-18, entry 4).

Table 4-18: Preliminary aminocarbonylation reactions with model substrates styrene (3.25) and allyl benzene (3.70).[a]



Entry	Alkene	Co-cat.	Ligand	Ratio Alkene:Amine	Time (h)	Conv. (%) [Yield (%)][b]	Product(s)	Ratio l:b:bn
1[c]	**3.25**	-	PPh_3	11:1	2	99 [99]	**4.29**	only **4.29b**
2	**3.25**	$Al(OTf)_3$	PPh_3	1:9	4	72 [69]	**4.29**	1:4:na
3	**3.25**	$Al(OTf)_3$	BINAP	1:9	5	90 [86]	**4.29**	1:4:na
4[d]	**3.25**	$Al(OTf)_3$	BINAP	1:9	5	69 [58]	**4.29**	2:1:na
5	**3.70**	$Al(OTf)_3$	PPh_3	1:9	24	64 [56]	**4.30**	4:1:1
6	**3.70**	$Al(OTf)_3$	BINAP	1:9	24	97 [92]	**4.30**	8:2:1
7	**3.70**	TfOH	PPh_3	1:9	24	47 [46]	**4.30**	10:6:1
8	**3.70**	$Al(OTf)_3$	PPh_3	11:1	20	10 [9]	**4.30**	1:1:1

[a]$Pd(OAc)_2$/Co-cat./Ligand was used in a ratio of 1:2:4. [b]Determined by GC analysis with xylene as internal standard. [c]$PdCl_2$ and conditions similar to those published by Liu et al.[18] [d]$Pd(OAc)_2$/$Al(OTf)_3$/BINAP was used in a ratio of 1:2:2.

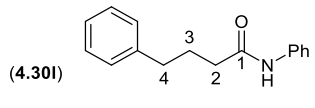
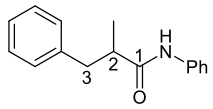
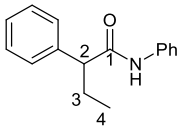
Table 4-19: Diagnostic EIMS, ^1H and ^{13}C NMR data for the structure elucidation of products 4.29l and 4.29b.

Diagnostic Data	(4.29l)		(4.29b)	
EIMS	*m/z* 225 (M^+, 15%)		*m/z* 225 (M^+, 37%)	
Plate nr.	13a-e		14a-e	
$^1H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	1.75 (t, *J* = 7.8)	39.4	3.85 (q, *J* = 7.0)	47.8
3	2.07 (t, *J* = 7.8)	32.0	1.49 (d, *J* = 7.0)	19.3
N-H	8.24 (br s)	-	9.31 (br s)	-
C=O	-	171.1	-	172.9

The aminocarbonylation of allylbenzene (**3.70**) led to the formation of the anticipated linear, branched and benzylic products, *N*,4-diphenylbutanamide (**4.30l**), 2-methyl-*N*,3-

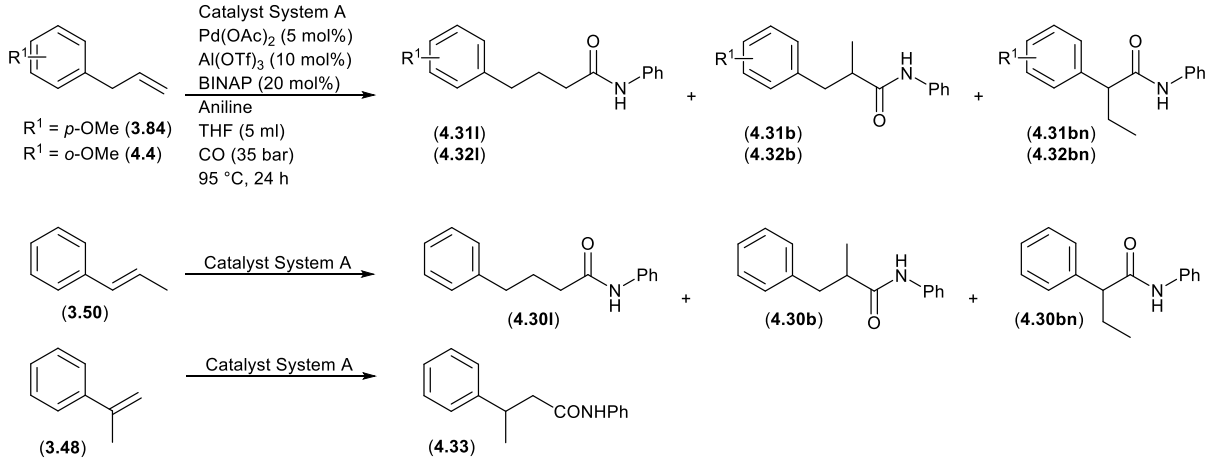
diphenylpropanamide (**4.30b**) and *N*,2-diphenylbutanamide (**4.30bn**), the structures of which were confirmed by EIMS and NMR analysis (Table 4-20). An extended reaction time of 24 hours, vs. 5 hours for styrene (**3.25**), was required for the reaction to reach completion. The same trend as for styrene (**3.25**), i.e. a drastic increase in conversion (64% to 97%) and yield (56% to 92%), were observed for allylbenzene (**3.70**) when the ligand was changed from PPh_3 to BINAP (Table 4-18, entry 5 vs. 6), while a substantial increase in the formation of the linear (**4.30l**) and branched (**4.30b**) products (8:2:1 vs. 4:1:1) was also found. Replacing $Al(OTf)_3$ with TfOH to ensure that $Al(OTf)_3$ and not triflic acid was the active co-catalyst, resulted in low values for the conversion (47%) and yield (46%), confirming the fact that $Al(OTf)_3$ plays a pivotal role in these aminocarbonylation reactions. In contrast to the catalyst system used by Liu et al.,[18] very low values for the conversion (10%) and yield (9%) were obtained with the current catalyst system, $Pd(OAc)_2/Al(OTf)_3/PPh_3$, when the aminocarbonylation of allylbenzene (**3.70**) was repeated with excess allylbenzene (allylbenzene:aniline ratio of 11:1) (Table 4-18, entry 8).

Table 4-20: Diagnostic EIMS, ^1H and ^{13}C NMR data for the structure elucidation of products 4.30l, 4.30b and 4.30bn.

Diagnostic Data	(**4.30l**) 		(**4.30b**) 		(**4.30bn**) 	
EIMS	*m/z* 239 (M^+, 14%)		*m/z* 239 (M^+, 24%)		*m/z* 239 (M^+, 25%)	
Plate nr.	15a-e		16a-e		17a-d	
$^1H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.31 (t, *J* = 7.5)	36.8	2.62-2.58 (m)	44.9	3.40 (t, *J* = 7.6)	56.2
3	2.02 (p, *J* = 7.5)	27.0	3.02 (dd, *J* = 8.4, 13.5) 2.75 (dd, *J* = 6.4, 13.5)	40.7	2.31-2.24 (m) 1.90-1.83 (m)	26.5
4/2-CH_3	2.66 (t, *J* = 7.5)	35.2	1.26 (d, *J* = 6.8)	17.9	0.92 (t, *J* = 7.4)	12.5
N-H	7.61 (br s)	-	7.07-7.05 (m)	-	7.30-7.24 (m)	-
C=O	-	171.4	-	174.1	-	171.9

In an effort to determine the scope and limitations of the current catalyst system, $Pd(OAc)_2/Al(OTf)_3$/BINAP, for aminocarbonylation, the reaction was subsequently expanded to include the methoxy substituted allylbenzenes, **3.84** and **4.4**, as well as internal (**3.50**) and 1,1-disubstituted alkenes (**3.48**), (Table 4-21).

Table 4-21: Aminocarbonylation of arylalkenes with aniline (4.28).



Entry	R^1	Allylbenzene	β-methylstyrene	α-methylstyrene	Conv. (%)[a]	Yield (%)	Product	Ratio l:b:bn
1	*p*-OMe	**3.84**	-	-	93	93[a]	**4.31**	4:1:1
2	*o*-OMe	**4.4**	-	-	98	94[a]	**4.32**	15:5:1
3	-	-	**3.50**	-	18	18[a]	**4.30**	3:3:1
4	-	-	-	**3.48**	-	16[b]	**4.33**	Only **4.33**

[a]Determined by GC analysis with xylene as internal standard. [b]Isolated yield.

As indicated in Table 4-21 (entries 1 and 2) both 4- (**3.84**) and 2-allylanisole (**4.4**) gave excellent conversions (>92%) and yields (>92%) to the linear, **4.31l** and **4.32l** and branched products **4.31b** and **4.32b**, respectively (Tables 4-22 and 4-23), while only trace amounts of the benzylic products, **4.31bn** and **4.32bn**, respectively, which could only be identified by GC and EIMS analysis, were formed. Although the linear products (**4.31l** and **4.32l**) were favoured in both of these reactions, a drastic increase in the formation of the linear isomer was observed for the reaction of the *o*-methoxyallylbenzene analogue (**4.4**) when compared to 4-allylanisole (**3.84**) and unsubstituted allylbenzene (**3.70**), l:b:bn 15:5:1 vs. 4:1:1 vs. 8:2:1. This trend was also seen for the methoxycarbonylation of *o*-allylanisole (**4.4**) with PPh_3, which is caused by the palladium chelation effect as explained in paragraph 4.2.3. *Para*-methoxyallylbenzene (**3.84**) also showed a lower tendency towards the formation of the linear isomer (4:1:1 vs. 8:2:1) when compared to the unsubstituted allylbenzene analogue (**3.70**), probably due to isomerization of the double bond being a more facile process for the electron-rich substrate than the aminocarbonylation reaction.

Table 4-22: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.31l, 4.31b and 4.31bn.

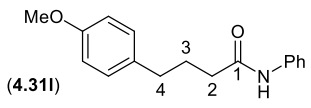
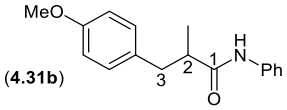
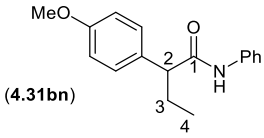
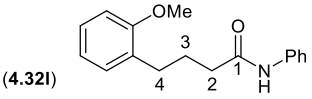
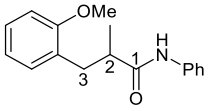
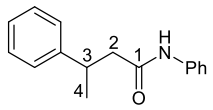
Diagnostic Data	 (**4.31l**)		 (**4.31b**)		 (**4.31bn**)	
EIMS	*m/z* 269 (M^+, 18%)		*m/z* 269 (M^+, 12%)		*m/z* 269 (M^+, 13%)	
Plate nr.	18a-e		18a-e		18a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.32 (t, *J* = 7.4)	36.9	2.57-2.51 (m)	45.2	3.34 (t, *J* = 7.6)	55.4
3	2.03 (p, *J* = 7.4)	27.2	2.97 (dd, *J* = 8.6, 13.7) 2.71 (dd, *J* = 6.2, 13.7)	39.9	2.27-2.23 (m) 1.85-1.80 (m)	26.5
4/2-CH_3	2.64 (t, *J* = 7.4)	34.3	1.26 (d, *J* = 6.8)	17.8	0.91 (t, *J* = 7.4)	12.5
N-H	7.18 (br s)	-	6.97 (br s)	-	7.21 (br s)	-
C=O	-	171.2	-	174.2	-	172.3

Table 4-23: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.32l and 4.32b.

Diagnostic Data	 (**4.32l**)		 (**4.32b**)	
EIMS	*m/z* 269 (M^+, 27%)		*m/z* 269 (M^+, 24%)	
Plate nr.	19a-e		20a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.34 (t, *J* = 7.4)	37.1	2.70-2.66 (m)	42.7
3	2.02 (p, *J* = 7.4)	25.8	3.02 (dd, *J* = 7.7, 13.3) 2.76 (dd, *J* = 6.6, 13.3)	35.6
4/2-CH_3	2.70 (t, *J* = 7.4)	29.6	1.25 (d, *J* = 6.8)	17.6
N-H	7.51-7.50 (m)	-	7.08 (s)	-
C=O	-	171.6	-	174.6

When the double bond was moved from the terminal (allylbenzene, **3.70**) to the internal position (*trans*-β-methylstyrene, **3.50**), a drastic decrease in the reaction rate was found, with both the conversion and yield of the three products, **4.30l**, **4.30b** and **4.30bn**, falling to only 18% (Table 4-21, entry 3). Aminocarbonylation of the disubstituted α-methylstyrene (**3.48**), gave the expected low yield (16%) and only the linear product, *N*,3-diphenylbutanamide (**4.33**). The structure of which was confirmed by NMR analysis, with the diagnostic resonances originating from C-1, *N*-H, H-2, H-3 and H-4 being clearly visible (Table 4-24).

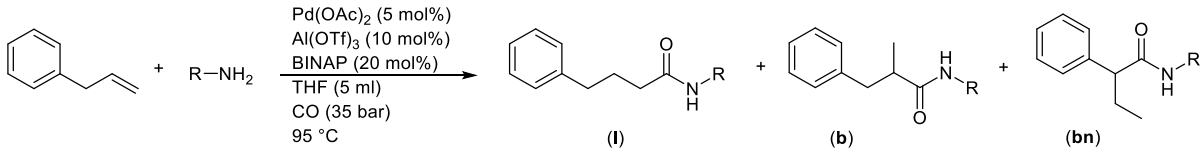
Table 4-24: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of product 4.33.

Diagnostic Data	(**4.33**) 	
EIMS	*m/z* 239 (M^+, 18%)	
Plate nr.	21a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C
2	2.62 (dd, *J* = 7.5, 14.1) 2.56 (dd, *J* = 7.3, 14.1)	46.8
3	3.38-3.34 (m)	37.2
4	1.35 (d, *J* = 7.0)	21.8
N-H	7.26-7.21 (m)	-
C=O	-	170.3

4.3.3. Variation of the nitrogen nucleophile

Since aniline derivatives were the only amines utilized in the aminocarbonylation of a variety of alkenes as reported by Beller et al.[17] and Liu et al.,[18] it was subsequently decided to investigate the scope and limitations of different amines (Table 4-25) in the aminocarbonylation reaction with the current catalyst system, $Pd(OAc)_2/Al(OTf)_3$/BINAP.

Table 4-25: Aminocarbonylation of allylbenzene (3.70) with various *N*-nucleophiles.



Entry	*N*-nucleophile	R	Conv. (%)[a]	Yield (%)[a]	Prod.	Ratio (l:b:bn)	Amine pK_a value[b,19]
1	Aniline (**4.28**)	Ph	97	92	**4.30**	8:2:1	4.87 (4.61)
2	Anisidine (**4.34**)	4-OMe-Ph	95	87	**4.35**	8:2:1	5.36 (5.21)
3	4-Chloroaniline (**4.36**)	4-Cl-Ph	99	97	**4.37**	12:2:1	3.98 (3.97)
4	2,4-Dichloroaniline (**4.38**)	2,4-diCl-Ph	n.d.	n.a.	n.a.	n.a.	2.05 (2.02)
5	4-Nitroaniline (**4.39**)	4-NO_2-Ph	n.d.	n.a.	n.a.	n.a.	1.02 (1.01)
6	Butylamine (**4.40**)	$(CH_2)_3CH_3$	n.d.	n.a.	n.a.	n.a.	10.60 (10.69)
7[c]	Butylamine (**4.40**)	$(CH_2)_3CH_3$	n.d.	n.a.	n.a.	n.a.	10.60 (10.69)
8	Acetamide (**4.41**)	$COCH_3$	n.d.	n.a.	n.a.	n.a.	15.1 (16.60)[d]
9[e]	Acetamide (**4.41**)	$COCH_3$	n.d.	n.a.	n.a.	n.a.	15.1 (16.60)[d]
10	Benzylamine (**4.42**)	Bn	n.d.	n.a.	n.a.	n.a.	9.34 (9.06)
11	4-Chlorobenzylamine (**4.43**)	4-Cl-Bn	25	23	**4.44**	25:9:1	9.14[20] (8.85)

[a]Conversion and yield determined by GC analysis with xylene as internal standard. n.d. = Not detected. n.a. = Not applicable. [b]Value in parenthesis was calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2018 ACD/Labs) with a standard deviation of ±0.10. [c]Reaction was performed without $Al(OTf)_3$. [d]Standard deviation for calculated value is ±0.40. [e]Reaction was performed with TsOH instead of $Al(OTf)_3$.

In order to investigate the effect of an electron-donating and electron-withdrawing substituent on the aromatic ring of the aniline, anisidine (**4.34**) and 4-chloroaniline (**4.36**) were the first two nucleophiles to be subjected to the aminocarbonylation utilizing the $Pd(OAc)_2/Al(OTf)_3$/BINAP catalyst system under 35 bar of CO and 95 °C. As found earlier, three sets of products, i.e. the linear (**4.35l** and **4.37l**), branched (**4.35b** and **4.37b**), and benzylic (**4.35bn** and **4.37bn**) amides, were obtained in 8:2:1 and 12:2:1 ratio in 87% and 97% yield, respectively, after 24 hours of reaction time (Table 4-25, entries 2 and 3). The structures of the products were confirmed by EIMS and NMR (^1H, ^{13}C and 2D) analysis (Tables 4-26 and 4-27). The high reactivity of the 4-chloroaniline (**4.36**) when compared to the methoxy substituted analogue (**4.34**), 99% vs. 95% conversion, might again be the reason for the slightly increased formation of the linear product (**4.37l**).

Table 4-26: Diagnostic EIMS, ^1H and ^{13}C NMR data for the structure elucidation of products 4.35l, 4.35b and 4.35bn.

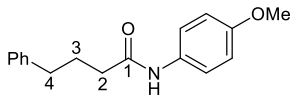
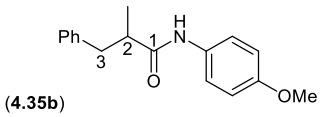
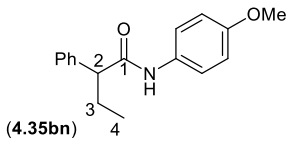
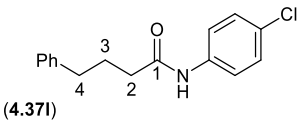
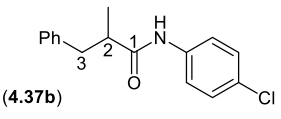
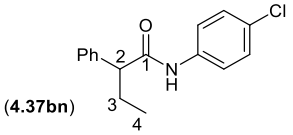
Diagnostic Data	 (**4.35l**)		 (**4.35b**)		 (**4.35bn**)	
EIMS	*m/z* 269 (M^+, 34%)		*m/z* 269 (M^+, 30%)		*m/z* 269 (M^+, 28%)	
Plate nr.	22a-e		22a-e		22a-e	
$^1H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.31 (t, *J* = 7.5)	Hidden	2.60-2.54 (m)	44.6	3.37 (t, *J* = 7.6)	55.9
3	2.04 (p, *J* = 7.5)	Hidden	3.01 (dd, *J* = 8.5, 13.5) 2.74 (dd, *J* = 6.4, 13.5)	40.6	2.27-2.23 (m) 1.87-1.82 (m)	26.5
4/2-CH_3	2.68 (t, *J* = 7.5)	Hidden	1.25 (d, *J* = 6.8)	17.8	0.91 (t, *J* = 7.4)	12.4
N-H	Hidden	-	7.04 (br s)	-	Hidden	-
C=O	-	Hidden	-	173.9	-	171.7

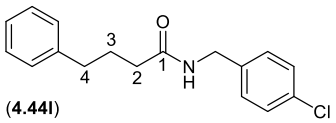
Table 4-27: Diagnostic EIMS, ^1H and ^{13}C NMR data for the structure elucidation of products 4.37l, 4.37b and 4.37bn.

Diagnostic Data	 (**4.37l**)		 (**4.37b**)		 (**4.37bn**)	
EIMS	*m/z* 273 (M^+, 25%)		*m/z* 273 (M^+, 27%)		*m/z* 273 (M^+, 19%)	
Plate nr.	23a-e		23a-e		23a-e	
$^1H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	2.31 (t, *J* = 7.5)	36.7	2.61-2.55 (m)	44.7	3.38 (t, *J* = 7.6)	56.0
3	2.03 (p, *J* = 7.5)	26.8	2.99 (dd, *J* = 8.7, 13.5) 2.75 (dd, *J* = 6.2, 13.5)	40.6	2.26-2.21 (m) 1.87-1.82 (m)	26.4
4/2-CH_3	2.67 (t, *J* = 7.5)	35.0	1.26 (d, *J* = 6.8)	17.7	0.90 (t, *J* = 7.4)	12.3
N-H	7.46 (br s)	-	7.12 (br s)	-	Hidden	-
C=O	-	171.2	-	174.1	-	172.0

When the reaction was extended to the 2,4-dichloro- (**4.38**) and 4-nitroaniline (**4.39**) analogues, no reaction whatsoever was observed (Table 4-25 entries 4 and 5). Since it might be ascribed to the nucleophilicity of the two deactivated aniline derivatives, **4.38** and **4.39**, being too low (pK_a values of 2.05 and 1.02, respectively), the reaction was repeated with an aliphatic amine, butylamine (**4.40**), but once again no product formation could be detected (Table 4-25 entries 6 and 7). Since butylamine (**4.40**) is known to be a good nucleophile and strong base (pK_a 10.60), complexation of butylamine to the $Al(OTf)_3$ will form an ammonium ion with such a high stability that the formation of the palladium hydride species is probably inhibited to such an extent that the aminocarbonylation reaction cannot occur. In an effort to remove the unproductive interaction of the Lewis acid, $Al(OTf)_3$, with the nucleophile, $BuNH_2$, and since the catalyst system reported by Liu et al.[18] did not include an acid co-catalyst, the reaction with butylamine (**4.40**) was repeated, but without the $Al(OTf)_3$. The reaction, however, did not give any of the desired products, and it was thus decided to change the nucleophile to a less nucleophilic equivalent. Treating allylbenzene (**3.70**) with acetamide (**4.41**) and $Al(OTf)_3$ and repeating the reaction with TsOH instead of $Al(OTf)_3$, analogues to the protocol reported by Beller et al.;[17] both failed to give any product formation (Table 4-25 entries 8 and 9).

The failure of all the reactions with nitrogen nucleophiles displaying high pK_a values >10, as well as very low pK_a values <3, led to the idea that the nucleophile required for this reaction to be successful should be of intermediate basicity (pK_a of ca. 4-7). Since amine nucleophiles of this nature, apart from aniline analogues, are not readily available, benzylamine (**4.42**) with pK_a 9.34 and subsequently 4-chlorobenzylamine (**4.43**) with pK_a 9.14 were subjected to the standard aminocarbonylation catalyst system and reaction conditions. Whereas the aminocarbonylation of benzylamine (**4.42**) gave no reaction whatsoever (Table 4-25 entry 10), the reaction of the 4-chloro-analogue (**4.43**) resulted in the formation of the expected three products, **4.44l**, **4.44b** and **4.44bn**, in a 23% combined yield with a l:b:bn product ratio of 25:9:1 (Table 4-25 entry 11). Although the branched (**4.44b**) and benzylic (**4.44bn**) products could be identified by GC and EIMS, these compounds were obtained in very small amounts, and only the linear isomer (**4.44l**) could be isolated and characterized by NMR (^1H, ^{13}C and 2D) analysis (Table 4-28).

Table 4-28: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of product 4.44l.

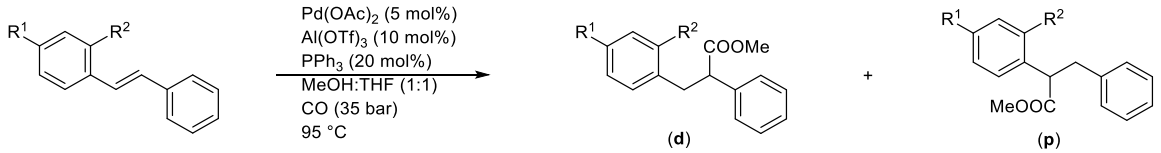
Diagnostic Data	 (**4.44l**)	
EIMS	*m/z* 287 (M^+, 22%)	
Plate nr.	24a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C
2	2.25 (t, *J* = 7.6)	35.94
3	1.92 (p, *J* = 7.6)	28.2
4	2.62 (t, *J* = 7.6)	35.87
CH_2	4.37 (d, *J* = 6.1)	42.7
N-H	7.68 (br s)	-
C=O	-	172.9

Although the pK_a value of 4-chlorobenzylamine (**4.43**) is only slightly lower than that of the unsubstituted equivalent, it seems as if it is true that the success of the reaction is dependent on the basicity of the nucleophile, which should not be too high (as that may lead to unproductive complexation to the Lewis acid present in the catalyst system) or too low (as that would render nucleophilic displacement of the palladium from the palladium acyl species impossible), (cf. paragraph 3.7.). Confirmation of this hypothesis would follow from the preparation and testing of more amines with pK_a values in the 4-7 range, so this aspect of the investigation will receive more attention in a follow-up investigation.

4.4. Methoxycarbonylation of stilbenes

With all the model reactions completed, the investigation was subsequently extended to the original objective, i.e. the methoxycarbonylation of stilbenes, on route to isoflavonoids (Scheme 4-1, Table 4-29). Since the solubility of these substrates, **4.45**, **4.47** and **4.49**, in pure methanol and ethanol is very low (solvent study performed in candidate's M.Sc.),[3] a mixture of MeOH and THF (1:1) had to be used as solvent system for these reactions.

Table 4-29: Methoxycarbonylation of stilbenes.

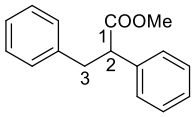


Entry	R^1	R^2	Stilbene	Time (h)	Conv. (%)[a]	Yield (%)[b]	Product	Ratio (d:p)[c]	TOF (h^{-1})[d]
1	H	H	**4.45**	24	17	6	**4.46**	-	0.14
2	OMe	H	**4.47**	24	16	2	**4.48**	1.3:1	0.08
3	H	OMe	**4.49**	24	19	4	**4.50**	4:1	0.39

[a]Due to the insolubility of the stilbenes substrates in the cold solvent system, the large difference in conversion and yield might be ascribed to some starting material precipitating inside the internals of the reactor; thus leading to inflated conversion values. [b]Isolated yield. [c]d:p = distal:proximal. [d]Turnover frequency based on $Pd(OAc)_2$.

When *trans*-stilbene (**4.45**) was subjected to the reaction conditions, $Pd(OAc)_2/Al(OTf)_3/PPh_3$ under 35 bar of CO pressure and 95 °C, the reduced methanol concentration and conjugated nature of the double bond led to a severe reduction in reactivity (TOF 0.14 h^{-1}) and conversion (17%) together with an increase in reaction time to 24 h, (Table 4-29 entry 1). Even with prolonged reaction times exceeding 24 hours, only small amounts of the product (**4.46**) was found (Table 4-30).

Table 4-30: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of product 4.46.

Diagnostic Data	(**4.46**) 	
EIMS	*m/z* 240 (M^+, 15%)	
Plate nr.	25a-e	
^{1}H/^{13}C	δ_H (*J* in Hz)	δ_C
2	3.95 (dd, *J* = 8.9, 6.8)	54.2
3	3.37 (dd, *J* = 13.7, 8.9) 3.02 (dd, *J* = 13.7, 6.8)	40.5
OMe	3.55 (s)	52.1
C=O	-	174.2

Extending the reaction to **4.47** and **4.49** led to the same dismal results of 2-4% yields and 16-19% conversion. The structures of the products, **4.48d**, **4.48p**, **4.50d** and **4.50p**, were confirmed by EIMS and NMR (^{1}H, ^{13}C and 2D) analysis (Tables 4-31 and 4-32).

Table 4-31: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.48d and 4.48p.

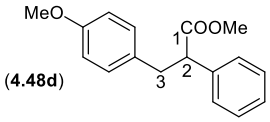
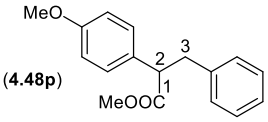
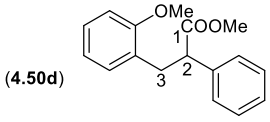
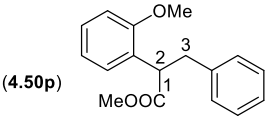
Diagnostic Data	 (**4.48d**)		 (**4.48p**)	
EIMS	*m/z* 270 (M^+, 13%)		*m/z* 270 (M^+, 10%)	
Plate nr.	26a-e		26a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	3.81-3.79 (m)	53.9	3.81-3.79 (m)	52.7
3	3.35 (dd, *J* = 8.9, 13.9) 2.96 (dd, *J* = 6.7, 13.9)	39.0	3.38 (dd, *J* = 8.7, 13.8) 2.99 (dd, *J* = 6.9, 13.8)	39.9
OMe	3.60 (br s)	52.0	3.60 (br s)	52.0
C=O	-	173.9	-	174.1

Table 4-32: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.50d and 4.50p.

Diagnostic Data	 (**4.50d**)		 (**4.50p**)	
EIMS	*m/z* 270 (M^+, 9%)		*m/z* 270 (M^+, 35%)	
Plate nr.	27a-e		27a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	3.99 (dd, *J* = 6.4, 8.7)	51.2	4.30 (dd, *J* = 6.9, 8.3)	46.4
3	3.36-3.33 (m) 3.07 (dd, *J* = 6.4, 13.5)	34.9	3.36-3.33 (m) 2.97 (dd, *J* = 6.9, 13.7)	38.7
OMe	3.59 (br s)	51.9	3.60 (br s)	51.9
C=O	-	174.2	-	174.3

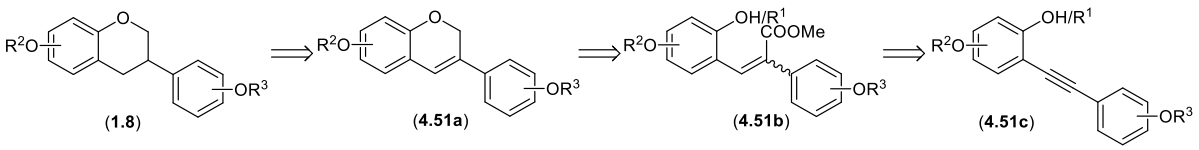
Despite the low reactivity, the desired isomers, **4.48d** and **4.50d**, with the newly introduced carbonyl in the distal position to the oxygenated phenyl ring was found to be the major product from both methoxy-substituted substrates (**4.47** and **4.49**), [1.3:1 and 4:1, distal (d):proximal (p), respectively], thus it could be concluded that the introduction of an electron-donating methoxy-group to one of the phenyl rings directs the carbonylation to the distal position. This electronic effect was complemented by the steric effect of the *ortho*-substituent as is evident from the product distribution observed for the 2-methoxystilbene (**4.49**), 4:1. Since the effect of isomerization is irrelevant for the stilbene substrates (**4.47** and **4.49**), the somewhat enhanced reactivity (4% vs. 2%) of the *o*-substituted analogue (**4.49**) may indicate that an agostic interaction or coordination between the *o*-methoxy and the palladium may stabilize the σ-Pd intermediate in the distal position. The fact that the distal product (**4.50d**) is preferred (4:1) for the *o*-methoxy analogue may be explained by the sterically congested environment around the centre of the reaction due to a doubly substituted double bond together with an *o*-methoxy

group, which could be responsible for directing the Pd, and therefore the carboxylation, to the distal position. Since some selectivity (1.3:1) was also observed for the *p*-substituted isomer, it, however, seems as if the electron donating properties of the methoxy substituents are also influencing the point of carbonylation with the more stable incipient carbocation being the point of choice for hydride acceptance.

Although the desired methoxycarbonylation products were obtained from stilbene substrates, **4.47** and **4.49**, and the desired distal isomers were indeed formed as the preferred products, the reactivity of the stilbene substrates in this application were too low for this process to be a generally acceptable and viable method for the synthesis of isoflavonoids. It was therefore decided to investigate alternative substrates that could be utilized in a catalytic process for the synthesis of isoflavonoids.

4.5. Hydroesterification of alkynes

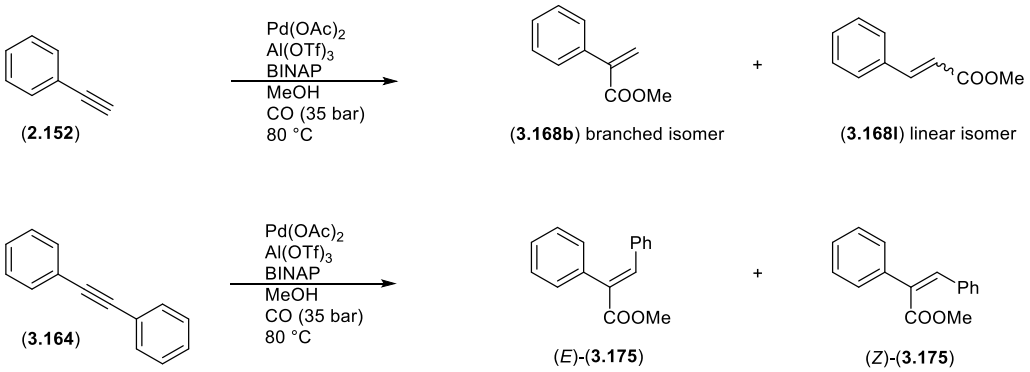
Since the hydroesterification of diarylalkynes is a well-documented process[21,22,23] and could easily be adapted to serve the same purpose as the alkoxycarbonylation of stilbenes, as indicated in Scheme 4-7, it was therefore decided to investigate this reaction as alternative method for the synthesis of isoflavonoids, although this methodology would entail an additional process step.



Scheme 4-7: Retrosynthesis of isoflavonoids through the hydroesterification of alkynes.

4.5.1. Model reactions for the hydroesterification of alkynes

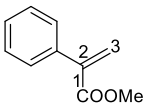
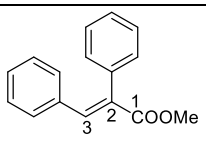
Since the formation of the desired regioisomer would again play a pivotal role in the viability of this methodology, phenylacetylene (**2.152**) was picked as model substrate to investigate this option for the synthesis of isoflavonoids. Unsubstituted phenylacetylene (**2.152**) was therefore subjected to the reaction conditions as described by Williams et al.,[24] $Pd(OAc)_2/Al(OTf)_3$/BINAP under 35 bar of CO at 80 °C, and although two product isomers, **3.168b** and **3.168l**, are possible, only the branched product (**3.168b**) was obtained in 94% yield after 90 minutes of reaction time (Scheme 4-8).



Scheme 4-8: Possible products to be formed in the preliminary methoxycarbonylation of alkynes.

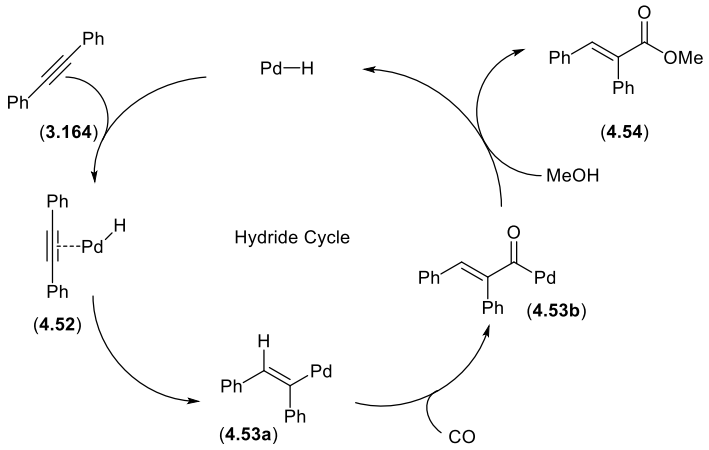
When the reaction was extended to 1,2-diphenylacetylene (**3.164**), the same conditions led to a substrate conversion of 72% after six hours of reaction time with an (*E*)-methyl 2,3-diphenylprop-2-enoate (**3.175**) yield of 62%. The structures of the products, **3.168b** and (*E*)-**3.175**, were confirmed by EIMS and NMR (^{1}H, ^{13}C and 2D) analysis, where the methoxy resonances could be detected at δ_H 3.86 and 3.79 ppm, respectively and the CO signals at δ_C 167.4 and 168.5 ppm (Table 4-33).

Table 4-33: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 3.168b and (*E*)-(3.175).

Diagnostic Data	(3.168b) 		(*E*)-(3.175) 	
EIMS	*m/z* 162 (M^+, 57%)		*m/z* 238 (M^+, 82%)	
Plate nr.	43a-e		44a-f	
^{1}H/^{13}C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	-	141.4 or 136.8	-	132.6
3	6.41 (d, *J* = 1.2) 5.93 (d, *J* = 1.2)	127.0	7.85 (s)	140.7
OMe	3.86 (br s)	52.3	3.79 (br s)	52.5
C=O	-	167.4	-	168.5

While the *E*- and/or *Z*-isomer of methyl 2,3-diphenylprop-2-enoate (**3.175**) could, in principle, be formed, 1D NOE NMR (plate 44f) proved the geometry of the product to be the *E*-isomer by means of a NOE effect observed between H-3 and -COOMe; no Z-isomer was detected whatsoever.[22,23,25] The hydride mechanistic pathway proved by Tooze and co-workers[26,27,28,29] for the methoxycarbonylation of ethene (cf. paragraph 3.7) also explains the formation of only the *E*-product during the methoxycarbonylation of 1,2-diphenylacetylene, since hydrogen transfer in the π-complex (**4.52**) must occur from the Pd-face of the triple bond in order to form (**4.53a**), due to *syn*-addition (Scheme 4-9). The two alkoxycarbonylation pathways proposed

by Cole-Hamilton[21] (cf. paragraph 3.8.3.) should lead to both the *Z*- and *E*-isomers during the methoxycarbonylation of 1,2-diphenylacetylene and can thus be considered as less likely.



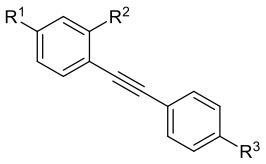
Scheme 4-9: Catalytic cycle for the methoxycarbonylation of alkynes.

Although the reaction conditions obtained from the Williams[24] paper gave acceptable conversions and yields, those authors focussed on the effect of different catalyst systems (ligands and co-catalysts) and did not pay much attention to the determination of the optimum conditions for the reaction. In an effort to improve the yield and conversion rate, it was therefore decided to change the reaction conditions for the hydroesterification of diphenylacetylene (**3.164**) to those found to be the optimum during the methoxycarbonylation of alkenes (cf. paragraph 4.2.1.) as the starting point in an optimization process for this reaction. When the hydroesterification of diphenylacetylene (**3.164**) was repeated at 95 °C with the $Pd(OAc)_2/Al(OTf)_3$/BINAP catalyst system in a 1:2:4 ratio and a catalyst loading of 2 mol%, 97% conversion with a product yield of 82% was found after only 40 minutes of reaction time, and it was decided that further efforts into finding the absolute optimized conditions was not worth a while. With good reaction conditions at hand, it was decided to again investigate the effect of electron-withdrawing and/or electron-donating substituents on the phenyl rings of the diphenylacetylene on the reactivity and regioselectivity of this hydroesterification reaction to establish if the desired regioisomer for the subsequent cyclization process in the synthesis of isoflavonoids, would in fact be formed.

4.5.2. Synthesis of substituted diphenylacetylenes

Since diphenylacetylene molecules with different electron-donating and/or electron-withdrawing substituents are not commercially available, the envisaged substituted substrates (**4.55-4.60**), (Figure 4-5) had to be prepared. Although the Sonogashira reaction which

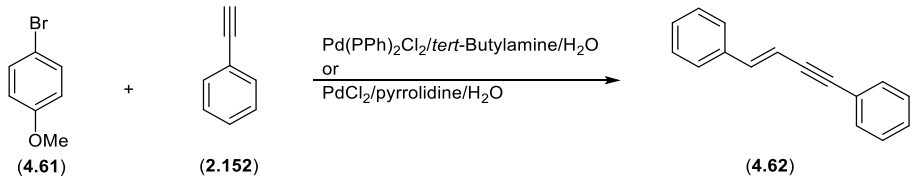
traditionally utilizes a Pd-Cu catalyst system,[30] can be viewed as the standard method for the preparation of substituted alkynes, many variations on the basic reaction, including Pd-free[31] and Cu-free[32,33] methods, have been published.



(**4.55**) R^1 = OMe, R^2 = R^3 = H
(**4.56**) R^1 = R^3 = H, R^2 = OMe
(**4.57**) R^1 = R^2 = OMe, R^2 = H
(**4.58**) R^1 = OTf, R^2 = R^3 = H
(**4.59**) R^1 = OTf, R^2 = H, R^3 = OMe
(**4.60**) R^1 = R^2 = OTf, R^2 = OMe

Figure 4-5: Envisaged substituted diphenylacetylenes.

The first attempts at the preparation of (4-methoxyphenyl)phenylacetylene (**4.55**) was therefore based on the papers by Roman et al.[34] [$Pd(PPh_3)_2Cl_2$/*t*-butylamine/H_2O] and Liang et al.[35] ($PdCl_2$/pyrrolidine/H_2O), who claimed that the formation of unwanted products due to the homocoupling of the terminal alkynes could be eliminated through the utilization of these methods. Despite these claims, none of the desired (4-methoxyphenyl)phenylacetylene (**4.55**) could, however, be isolated from either of these reactions, whereas only the reductive homo-coupled diphenylacetylene by-product (**4.62**), (NMR spectra plate 28a-e), was observed in the reaction utilizing the $PdCl_2$/pyrrolidine/H_2O catalyst system (Scheme 4-10).†

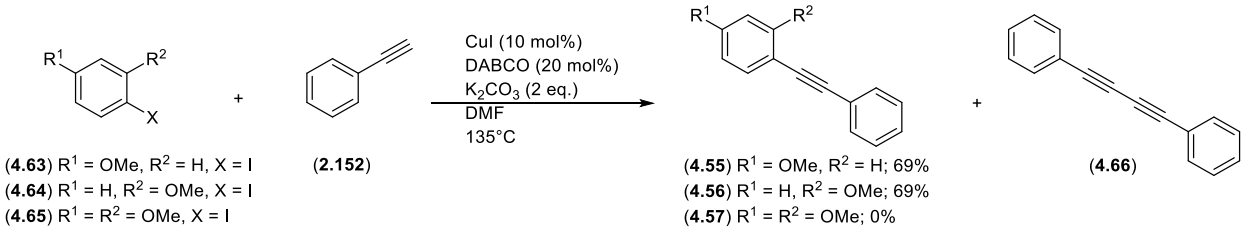


(**4.61**) (**2.152**) (**4.62**)

Scheme 4-10: Sonogashira reactions catalysed with Cu-free catalyst systems.

Since Li et al.[38] published a CuI/DABCO/Z_2CO_3/DMF catalyst system with either Cs_2CO_3 or K_2CO_3 for the synthesis of diphenylacetylenes through the coupling of arylhalides with phenylacetylenes, it was decided to apply these reagents to the synthesis of (4-methoxyphenyl)phenylacetylene (**4.55**), (Scheme 4-11).

† The same product was also obtained by Chow et al.[36] and Ho et al.[37]



(**4.63**) R^1 = OMe, R^2 = H, X = I
(**4.64**) R^1 = H, R^2 = OMe, X = I
(**4.65**) R^1 = R^2 = OMe, X = I

(**2.152**)

(**4.55**) R^1 = OMe, R^2 = H; 69%
(**4.56**) R^1 = H, R^2 = OMe; 69%
(**4.57**) R^1 = R^2 = OMe; 0%

(**4.66**)

Scheme 4-11: Successful synthesis of 4.55 and 4.56 with 4.66 as byproduct.

When 4-iodoanisole (**4.63**) was reacted with phenylacetylene (**2.152**) utilizing K_2CO_3 as base, the desired (4-methoxyphenyl)phenylacetylene (**4.55**) was obtained in 69% yield, although it was accompanied by 27% of the homocoupled phenylacetylene by-product (**4.66**), (Scheme 4-9). The structures of both products, **4.55** and **4.66**, were confirmed by ^{1}H and ^{13}C NMR analysis, which showed the characteristic resonances as summarized in Table 4-34. Applying the same reagents and conditions to the reaction of 2-iodoanisole (**4.64**) with phenylacetylene (**2.152**) led to the isolation of the intended product, (2-methoxyphenyl)phenylacetylene (**4.56**), only, in 69% yield. The structure of the product was again elucidated with NMR analysis (Table 4-35). The preparation of (2,4-dimethoxyphenyl)phenylacetylene (**4.57**) through the application of the same reagents and conditions, however, failed and no product formation was observed.

Table 4-34: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.55 and 4.66.

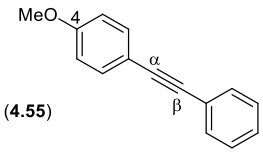
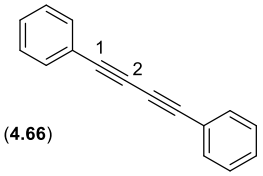
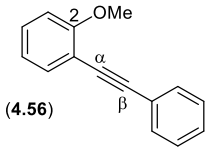
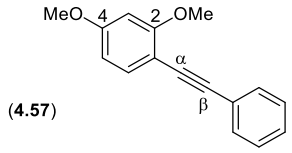
Diagnostic Data	 (**4.55**)		Diagnostic Data	 (**4.66**)
EIMS	*m/z* 208 (M^+, 100%)		EIMS	*m/z* 208 (M^+, 100%)
Plate nr.	30a-e		Plate nr.	29a-e
^{1}H/^{13}C	δ_H (*J* in Hz)	δ_C	^{13}C	δ_C
OMe	3.82 (s)	55.4	1	81.7
α	-	89.5	2	74.1
β	-	88.2		

Table 4-35: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of product 4.56.

Diagnostic Data	 (**4.56**)	
EIMS	*m/z* 208 (M^+, 100%)	
Plate nr.	31a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C
OMe	3.94 (s)	55.9
α	-	85.8
β	-	93.5

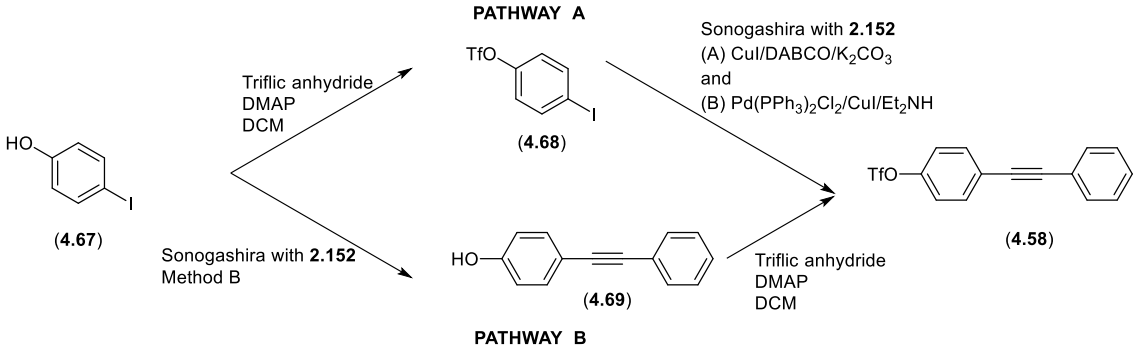
Since a microwave irradiation method utilizing the $Pd(PPh_3)_2Cl_2/CuI/Et_2NH/DMF$ catalyst system was reported to give high yields of substituted acetylenes, this process was used in the next attempt to synthesize (2,4-dimethoxyphenyl)phenylacetylene (**4.57**). The reagents were added together and submitted to 200 W microwave irradiation at 120 °C for a total of 5 minutes where after the desired product (**4.57**) was isolated as a yellow oil in an excellent yield (91%). The structure of the product (**4.57**) was confirmed with EIMS and NMR analysis (Table 4-36).

Table 4-36: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of product 4.57.

Diagnostic Data	 (**4.57**)	
EIMS	*m/z* 238 (M^+, 100%)	
Plate nr.	32a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C
OMe	3.88 (s)	56.0
OMe	3.81 (s)	55.5
α	-	85.9
β	-	92.1

With the diphenylacetylene analogues containing electron-donating groups, **4.55**, **4.56** and **4.57**, available, attention was subsequently turned towards the synthesis of those compounds containing one or more electron-withdrawing substituents, like triflate groups, attached to the phenyl ring. Since the hydroxy function of the product had to be protected by trifluoromethanesulfonylation, two routes towards the final product, i.e. (A) protection of the OH-function followed by Sonogashira coupling or (B) Sonogashira coupling followed by protection of the OH-group, could be envisaged for the preparation of the desired triflate

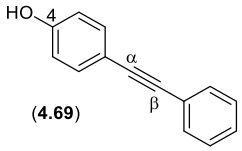
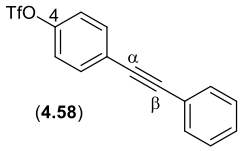
protected substrate (Scheme 4-12). Since the second route (B) would entail a Sonogashira reaction on a free phenolic substrate, which could lead to complications, it was decided to embark on route A as the preferred option for the preparation of the required (4-trifluoromethanesulfonyloxyphenyl)phenylacetylene (**4.58**). Treatment of 4-iodophenol (**4.67**) with triflic anhydride and DMAP in DCM led to the formation of the desired product (**4.68**), (^{1}H, ^{13}C and ^{19}F NMR analysis, plate 33a-f) in an excellent yield (96%). Unfortunately the Sonogashira coupling between the synthesized 4-iodotrifluoromethanesulfonyloxybenzene (**4.68**) and phenylacetylene (**2.152**) gave only trace amounts of the desired product (**4.58**), irrespective of whether conventional heating methodology with the CuI/DABCO/K_2CO_3/DMF catalyst system (Method A) or microwave irradiation with $Pd(PPh_3)_2Cl_2$/CuI/Et_2NH/DMF (Method B) were used.



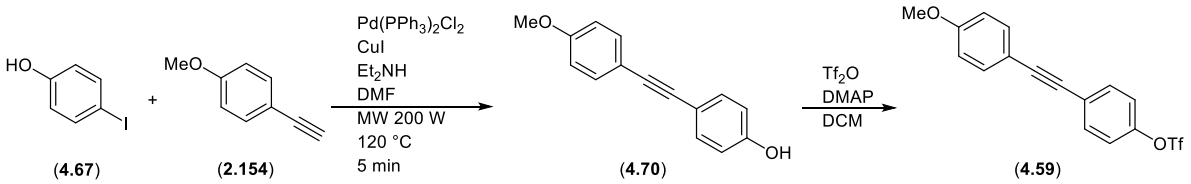
Scheme 4-12: Pathways A and B for the synthesis of 4.58.

Despite the potential problems with the unprotected free hydroxy group, it was therefore decided to investigate route B towards the wanted product, thus the Sonogashira coupling between 4-iodophenol (**4.67**) and phenylacetylene (**2.152**) were attempted over the $Pd(PPh_3)_2Cl_2$/CuI/Et_2NH/DMF catalyst system under microwave irradiation conditions (200 W, 120 °C, 5 minutes) and the product, (4-hydroxyphenyl)phenylacetylene (**4.69**), obtained in an excellent yield (94%). With the free-phenolic acetylene in hand, the desired (4-trifluoromethanesulfonyloxyphenyl)phenylacetylene (**4.58**) could easily be obtained by performing a simple protecting reaction with triflic anhydride and DMAP to give the protected acetylene (**4.58**) in 93% yield. The structures of both **4.69** and **4.58** were confirmed by EIMS and NMR (^{1}H, ^{13}C, ^{19}F and 2D) analysis (Table 4-37).

Table 4-37: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.69 and 4.58.

Diagnostic Data	 (**4.69**)	 (**4.58**)	
EIMS	*m/z* 194 (M^+, 100%)	*m/z* 326 (M^+, 59%)	
Plate nr.	34a-e	35a-f	
Carbon/Fluorine	δ_C	δ_C	δ_F
α	89.4	87.5	-
β	88.2	91.4	-
CF_3	-	118.9 (q, *J* = 320.9 Hz)	-75.86

In order to have a more profound difference between the two aromatic rings of the acetylene substrate and thus enhance any electronic effect during the subsequent hydroesterification reaction, substrates with one ring being deactivated by one or more triflate groups and the other ring activated by methoxy substituents were required. The synthesis of 4-methoxyphenyl-4'-trifluoromethanesulfonyloxyphenylacetylene (**4.59**) was therefore performed by reacting 4-iodophenol (**4.67**) with 4-ethynylanisole (**2.154**) using the reaction sequence and conditions described for the preparation of (4-trifloromethanesulfonyloxyphenyl)phenylacetylene (**4.58**), (Scheme 4-13).

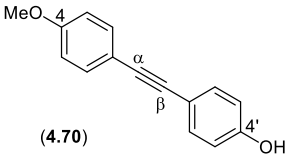
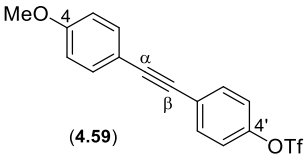


(**4.67**) (**2.154**) (**4.70**) (**4.59**)

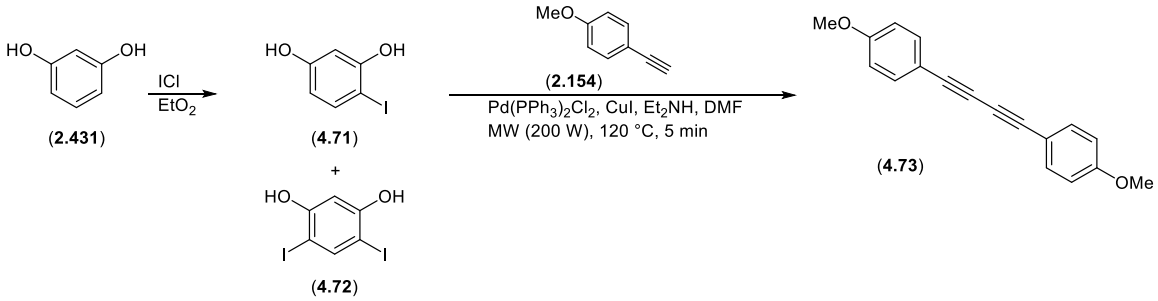
Scheme 4-13: Two step synthesis of 4-methoxyphenyl-4'-trifluoromethanesulfonyloxyphenylacetylene (4.59).

Sonogashira coupling of 4-iodophenol (**4.67**) with *p*-methoxyphenylacetylene (**2.154**) over the $Pd(PPh_3)_2Cl_2$/CuI catalyst system under microwave heating conditions (200 W and 120 °C) for 5 minutes gave the 4'-hydroxyphenyl-4-methoxyphenylacetylene (**4.70**) in 88% yield (Scheme 4-13), the structure of which was confirmed by EIMS and NMR (^{1}H, ^{13}C and 2D) analysis (Table 4-38). Treatment of the intermediate product (**4.70**) with triflic anhydride and DMAP in DCM resulted in the formation of the desired hydroesterification substrate (**4.59**) in 92% yield (Table 4-38).

Table 4-38: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.70 and 4.59.

Diagnostic Data	 (**4.70**)		 (**4.59**)		
EIMS/HRMS	*m/z* 224 (M^+, 100%)		*m/z* 357.0406 $(M + H)^+$		
Plate nr.	36a-e		37a-f		
$^{1}H/^{13}C/^{19}F$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_F
OMe	3.82 (s)	55.5	3.83 (s)	55.5	
OH	3.16 (br s)	-	-	-	
α	-	87.9	-	91.5	
β	-	88.8	-	86.3	
C=O	-	167.4	-	168.5	
CF_3	-	-	-	118.9 (q, *J* = 321.1 Hz)	-75.87

For the same synthetic protocol to be applicable to the preparation of the last substrate to be subjected to the hydroesterification reaction, i.e. 4-methoxy-2',4'-bis(trifluoromethane-sulfonyloxy)phenylacetylene (**4.60**), 2,4-dihydroxyiodobenzene (**4.71**) would be required as primary starting material for the disubstituted ring of the diphenylacetylene (**4.60**). Since this compound could not be obtained commercially, it had to be prepared and therefore resorcinol (**2.431**) was subjected to an iodination reaction with ICl (Scheme 4-14).



Scheme 4-14: Attempted synthesis of 4-methoxyphenyl-2',4'-bis(trifluoromethanesulfonyloxy)phenylacetylene (4.73).

Although the desired product (**4.71**) was obtained in 58% yield, it was unfortunately accompanied by 14% of the diiodo analogue (**4.72**). The structures of both products were confirmed by EIMS and NMR (^{1}H, ^{13}C and 2D) analysis (Table 4-39). Sonogashira coupling of the iodophenol (**4.71**) with *p*-methoxyphenylacetylene (**2.154**), however, led to the formation of only the homocoupled product, 1,4-bis(4-methoxyphenyl)but-1,3-diyne (**4.73**), (Scheme 4-14, Table 4-40).

Table 4-39: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.71 and 4.72.

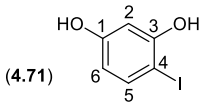
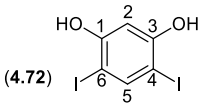
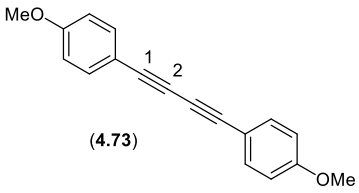
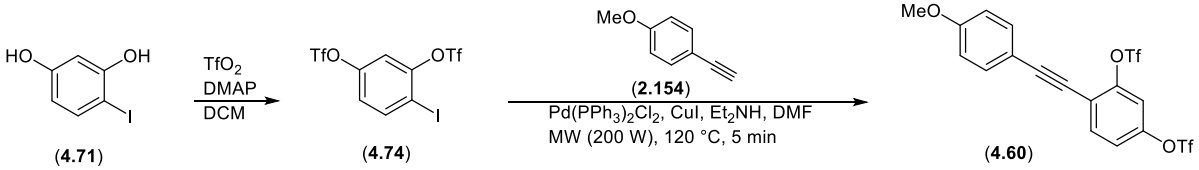
Diagnostic Data	 (**4.71**)		 (**4.72**)	
EIMS	*m/z* 236 (M^+, 100%)		*m/z* 362 (M^+, 100%)	
Plate nr.	38a-e		39a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
2	6.54 (d, *J* = 2.8)	102.8	6.68 (s)	103.0
5	7.46 (d, *J* = 8.6)	138.5	7.91 (s)	147.3
6	6.27 (dd, *J* = 8.6, 2.8)	110.6	-	73.1
1-OH and 3-OH	5.12 (br s)	-	9.22 (br s)	-
4	-	74.8	-	73.1

Table 4-40: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of product 4.73.

Diagnostic Data	 (**4.73**)	
EIMS	*m/z* 262 (M^+, 100%)	
Plate nr.	40a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C
OMe	3.81 (s)	55.5
1	-	81.4
2	-	73.1

In order to avoid the unwanted coupling reaction, it was decided to revisit the application of the Sonogashira coupling between the methoxyacetylene (**2.154**) and, in this instance, the ditriflate protected iodobenzene analogue (**4.74**). 2,4-Bis(trifluoromethanesulfonyloxy)iodo-benzene (**4.74**) was therefore formed from 2,4-dihydroxyiodobenzene (**4.71**) by reacting it with triflic anhydride and DMAP in DCM to give the ditriflate analogue (**4.74**) in 71% yield (Scheme 4-15).

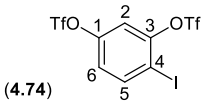
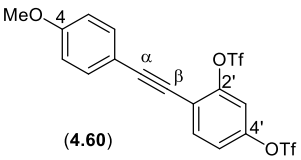


Scheme 4-15: Successful synthesis of 4-methoxyphenyl-2',4'-bis(trifluoromethanesulfonyloxy)phenylacetylene (4.60).

The Sonogashira coupling of 2,4-bis(trifluoromethanesulfonyloxy)iodobenzene (**4.74**) with *p*-methoxyacetylene (**2.154**) gave the desired product (**4.60**), albeit in only 19% yield (Scheme 4-

15). Both the structures of **4.74** and **4.60** were elucidated with HRMS and NMR (^{1}H, ^{13}C, ^{19}F and 2D) analysis (Table 4-41). Although the yield proved to be rather low, it was at this point decided to continue with the hydroesterification investigation and, if successful, to return to method development for the preparation of the acetylene substrates.

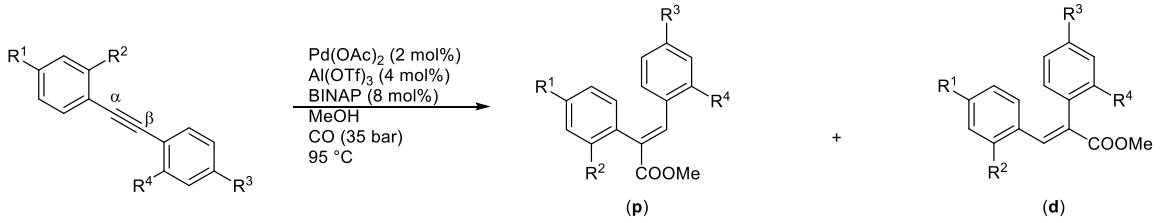
Table 4-41: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.74 and 4.60.

Diagnostic Data	 (**4.74**)		 (**4.60**)		
HRMS	*m/z* 499.8330 $(M + H)^+$		*m/z* 504.9841 $(M + H)^+$		
Plate nr.	41a-f		42a-f		
^{1}H/^{13}C/^{19}F	δ_C	δ_F	δ_H (*J* in Hz)	δ_C	δ_F
OMe	-	-	3.84 (s)	55.5	-
α	-	-	-	99.1	-
β	-	-	-	80.1	-
CF_3	118.8 (q, *J* = 321.2 Hz)	-75.51 -76.01	-	Hidden	-75.50 -76.48

4.5.3. Hydroesterification of substituted diphenylacetylenes

The hydroesterification of the substituted diphenylacetylenes was started by subjecting (4-methoxyphenyl)phenylacetylene (**4.55**) to the established methoxycarbonylation reaction conditions, $Pd(OAc)_2$/$Al(OTf)_3$/BINAP under 35 bar of CO at 95 °C, (Table 4-42). After only 40 minutes, the two methyl ester products, methyl 2-(4'-methoxyphenyl)-3-phenylprop-2-enoate (**4.75p**) and methyl 3-(4'-methoxyphenyl)-2-phenylprop-2-enoate (**4.75d**), were obtained in a combined yield of 89% (97% conversion) and a ratio of 2:1 in favour of the proximal product (**4.75p**), (Table 4-42, entry 1).

Table 4-42: Methoxycarbonylation of substituted diphenylacetylenes.

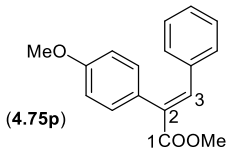
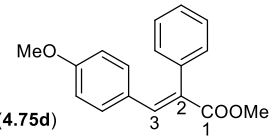


Entry	R^1	R^2	R^3	R^4	Alkyne	Time (min)	Conv. (%)[a]	Yield (%)[a]	Products	Ratio (p:d)[b]
1	OMe	H	H	H	**4.55**	40	97	89	**4.75**	2:1
2	H	OMe	H	H	**4.56**	40	98	89	**4.76**	2:1
3	OMe	OMe	H	H	**4.57**	10	92	35	**4.77**	7:1
4	H	H	OTf	H	**4.58**	40	99	71	**4.78**	1:1
5	OMe	H	OTf	H	**4.59**	20	95	71	**4.79**	3:1
6	OMe	H	OTf	OTf	**4.60**	30	76	72	**4.80**	18:1

[a]Determined by GC analysis with xylene as internal standard. [b]p:d = proximal:distal.

The product structures, **4.75p** and **4.75d**, were elucidated with the use of ^{1}H and ^{13}C NMR analysis, which showed the characteristic ester OMe resonances at δ_H 3.79 and 3.77 ppm, respectively, as well as the CO resonances at δ_C 168.7 and 168.6, respectively (Table 4-43). The HMBC 2D NMR experiment (plate 45e) indicated the main product (**4.75p**) to be the proximal isomer by means of a correlation between H-3 and the B-ring carbons. Further confirmation of the structure of the proximal isomer was obtained by an NOE (plate 45f) effect observable between H-3 and only the B-ring protons. The geometry of both products (**4.75p**) and (**4.75d**) were determined through a 1D NOE NMR experiment (plate 45f), where NOE effects between H-3 and the ester methoxy groups were observable. It could therefore be concluded that the *E*-isomers, and not the Z-isomers, were formed. This is analogous to the case for the methoxycarbonylation of diphenylacetylene (**3.164**), (cf. paragraph 4.3.1).

Table 4-43: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.75p and 4.75d.

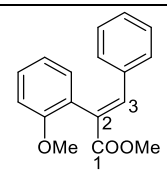
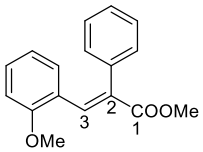
Diagnostic Data	 (4.75p)		 (4.75d)	
EIMS	*m/z* 268 (M^+, 99%)		*m/z* 268 (M^+, 100%)	
Plate nr.	45a-f		45a-f	
^{1}H/^{13}C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
3	7.81 (s)	140.29	7.81 (s)	140.34
C=O	-	168.7	-	168.6
COOMe	3.79 (s)	52.5	3.77 (s)	52.3

The preferred formation of the proximal isomer (**4.75p**) can be explained by the stability of the α-carbocation when compared to the β-carbocation entity during reaction with the electrophilic palladium species. The electron-donating methoxy substituent would have a stabilizing effect on the incipient α-carbocation species, which is in agreement with the dominant formation of the benzylic methoxycarbonyl product (**4.11bn**) over the branched (**4.11b**) isomer (21:1) during the methoxycarbonylation of 1,3-diphenylpropene (**4.10**), (cf. paragraph 4.2.3.).

Since PPh_3 is an order of magnitude cheaper than BINAP, the methoxycarbonylation of (4-methoxyphenyl)phenylacetylene (**4.55**) was repeated with PPh_3 instead of BINAP to evaluate the effect, if any, of the cheaper ligand on the outcome of the reaction. Although it was found that the yield could be improved from 89% to 93% in this way, no selectivity as to one of the regioisomers was observed (product distribution 1:1). It was therefore decided to rather continue with the more expensive, but regioselective, bidentate BINAP ligand.

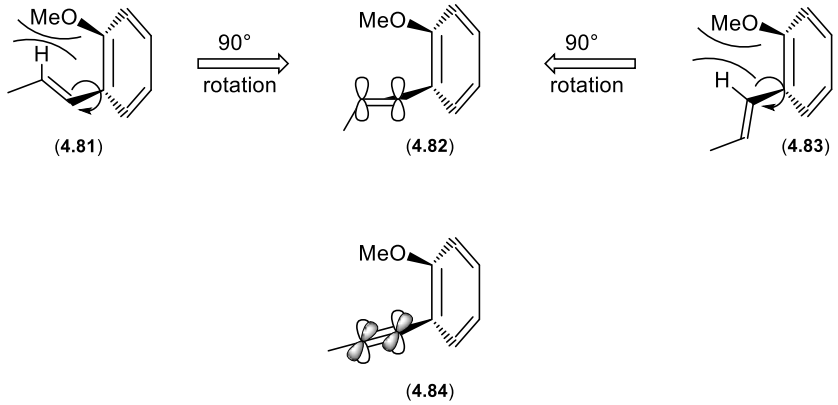
Extending the methoxycarbonylation reaction to (2-methoxyphenyl)phenylacetylene (**4.56**), led to the formation of the expected esters, **4.76p** and **4.76d**, in 89% yield (98% conversion) and again in a 2:1 ratio in favour of the proximal product (**4.76p**), (Table 4-42, entry 2). The structures of the products were established by ^{1}H and ^{13}C NMR spectroscopy (Table 4-44), with HMBC (plate 46e) correlation between H-3 and the B-ring carbons confirming the main product to be the proximal isomer (**4.76p**). An NOE (plate 46f) experiment once again indicated both products to be the *E*-isomers.

Table 4-44: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.76p and 4.76d.

Diagnostic Data	(**4.76p**) 		(**4.76d**) 	
EIMS	*m/z* 268 (M^+, 100%)		*m/z* 268 (M^+, 100%)	
Plate nr.	46a-g		46a-g	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
H-3	7.83 (s)	140.6	8.16 (s)	135.7
C=O	-	168.7	-	168.6
COOMe	3.77 (s)	55.8	3.80 (s)	55.6

Contrary to what was found during the methoxycarbonylation of the alkene derivatives (cf. paragraph 4.2.3.), the 2-methoxy substituent (**4.56**) in this instance had no significant effect on the reactivity or regioselectivity of the reaction when compared to that of the 4-methoxy isomer

(**4.55**). This phenomenon is probably explicable in terms of two sets of π-bonding electrons being available for complexation to the metal species. While the preferred conformation in the case of the alkene substrates would be one where the *ortho*-methoxy substituent is in an orthogonal position with regard to the plane of the double bond (**4.82**) and thus have a profound influence on the formation of the metal complex (Scheme 4-16), the methoxy substituent would always be parallel to one of the π-bonding electron clouds and orthogonal to the other one in the case of alkyne substrates (**4.84**). One π-bond would therefore always be available for complexation to the metal without being influenced by the *ortho*-substituent.

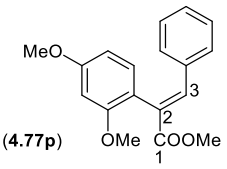
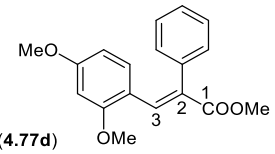
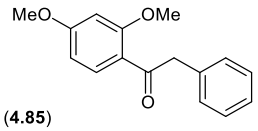


(**4.81**) (**4.82**) (**4.83**) (**4.84**)

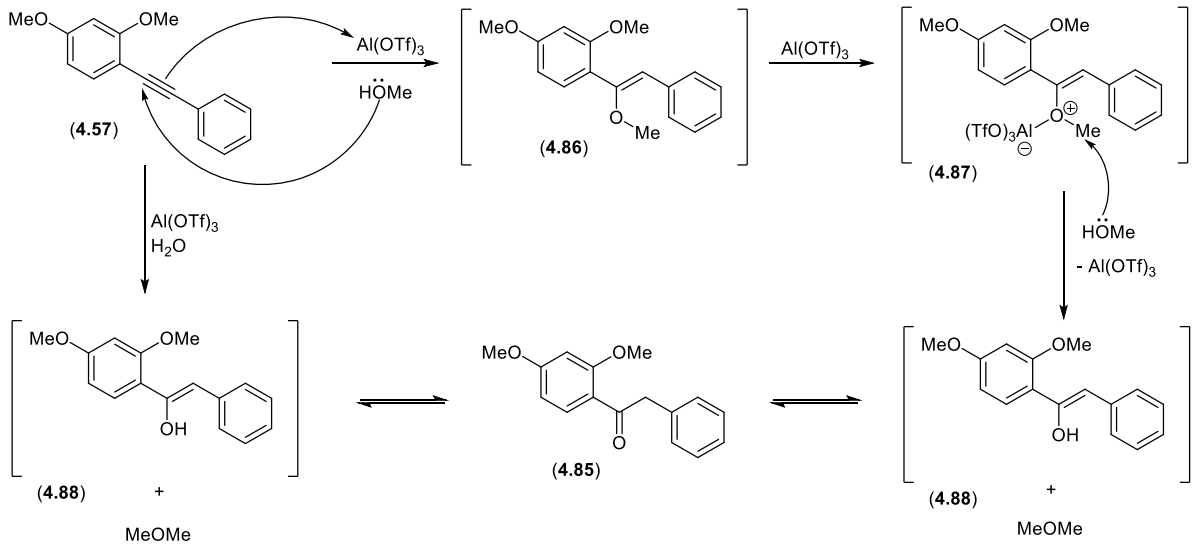
Scheme 4-16: Steric interaction of an *ortho*-methoxy substituent on an alkene vs. alkyne with regards to regioselectivity.

The methoxycarbonylation of (2,4-dimethoxyphenyl)phenylacetylene (**4.57**) required only 10 minutes of reaction time to reach a conversion of 92%. The desired ester products, **4.77p** and **4.77d**, which were obtained in 35% yield and a 7:1 ratio (Table 4-42, entry 3) was, however, accompanied by 46% of the 2,4-dimethoxydeoxybenzoin (**4.85**). The structure of products, **4.77p**, **4.77d** and **4.85**, were confirmed by EIMS and NMR analysis (Table 4-45). The increased stability of the benzylic α-carbocation also resulted in an increase in the formation of the proximal carbonylation product (**4.77p**), since a 7:1 ratio of the two ester isomers, (**4.77p** and **4.77d**), was obtained (Table 4-42, entry 3).

Table 4-45: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.77p, 4.77d and 4.85.

Diagnostic Data	 (**4.77p**)		 (**4.77d**)		 (**4.85**)	
EIMS	*m/z* 298 (M^+, 100%)		*m/z* 298 (M^+, 100%)		*m/z* 256 (M^+, 1%)	
Plate nr.	47a-e		48a-e		49a-e	
$^{1}H/^{13}C$	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
3	7.79 (s)	140.4	8.15 (s)	135.1	-	-
C=O	-	168.85	-	168.94	-	197.8
COOMe	3.76 (s)	52.4	3.78 (s)	52.3	-	-
CH_2	-	-	-	-	4.27 (s)	50.1

The formation of 2,4-dimethoxydeoxybenzoin (**4.85**) may be explained by Lewis acid catalysed addition of methanol to the triple bond to form the methyl enol ether (**4.86**), (Scheme 4-17). Subsequent $Al(OTf)_3$ catalysed demethylation of the enol ether (**4.87**) would lead to the ketone (**4.85**) through keto-enol tautomerism. This hypothesis was supported by repeating the reaction without any $Pd(OAc)_2$ and PPh_3, i.e. refluxing (2,4-dimethoxyphenyl)phenylacetylene (**4.57**) with $Al(OTf)_3$ in MeOH. A 71% yield of the 2,4-dimethoxybenzoin (**4.85**) was obtained after 5 hours of reaction time. Since no deoxybenzoin formation was observed during the reactions of the monomethoxylated diphenylacetylenes, it could be concluded that the activating properties of two electron-donating methoxy substituents on one phenyl ring is enough to allow for the weak Lewis acid to interact with the triple bond to the extent of catalysing the addition of methanol to the multiple bond, thus leading to the enol ether product (**4.86**). Alternatively, the H_2O present in the methanol can act as nucleophile to give the enol-ether (**4.88**) directly (Scheme 4-17).



Scheme 4-17: Lewis acid catalysed formation of 2,4-dimethoxydeoxybenzoin (4.85).

Methoxycarbonylation of the diphenylacetylenes with an electron-withdrawing group in the *para*-position of the B-ring, (4-trifluoromethanesulfonyloxyphenyl)phenylacetylene (**4.58**) and 4-methoxyphenyl-4'-trifluoromethanesulfonyloxyphenylacetylene (**4.59**) gave the two expected products from each substrate, **4.78p** and **4.78d** as well as **4.79p** and **4.79d**, respectively, both in 71% yield (99% and 95% conversion, respectively, Table 4-42 entries 4 and 5). The structures of the products were again confirmed by EIMS and NMR (^{1}H, ^{13}C, ^{19}F and 2D) analysis (Tables 4-46 and 4-47), while the position of the ester function and geometries of the compounds were assigned as before (vide supra).

Table 4-46: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.78p and 4.78d.

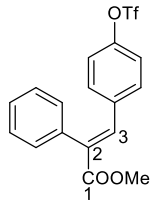
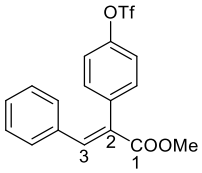
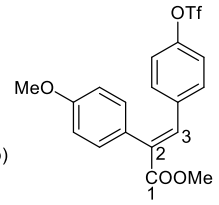
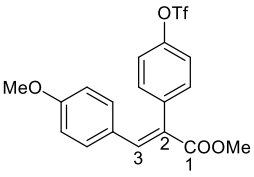
Diagnostic Data	(4.78p) 			(4.78d) 		
HRMS	*m/z* 387.0507 (M + H)$^{+}$			*m/z* 387.0507 (M + H)$^{+}$		
Plate nr.	50a-f			50a-f		
^{1}H/^{13}C/^{19}F	δ_H	δ_C (*J* in Hz)	δ_F	δ_H	δ_C (*J* in Hz)	δ_F
3	7.81 (s)	138.1	-	7.92 (s)	141.9	-
C=O	-	167.9	-	-	167.6	-
COOMe	3.79 (s)	52.6	-	3.81 (s)	52.7	-
CF_3	-	118.8 (q, *J* = 320.6)	-75.82 or -76.00		118.8 (q, *J* = 321.1)	-75.82 or -76.00

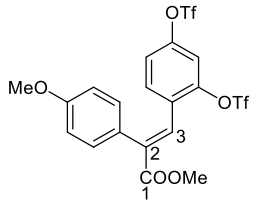
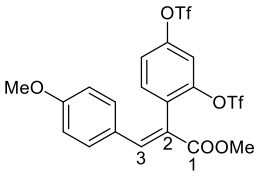
Table 4-47: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.79p and 4.79d.

Diagnostic Data	(**4.79p**) 			(**4.79d**) 		
HRMS	*m/z* 417.0617 $(M + H)^+$			*m/z* 417.0617 $(M + H)^+$		
Plate nr.	51a-f			51a-f		
$^{1}H/^{13}C/^{19}F$	δ_H	δ_C (*J* in Hz)	δ_F	δ_H	δ_C (*J* in Hz)	δ_F
3	7.77 (s)	137.7	-	7.86 (s)	141.5	-
C=O	-	168.1	-	-	167.8	-
COOMe	3.79 (s)	52.5	-	3.78 (s)	52.4	-
CF_3	-	118.8 (q, *J* = 320.8)	-76.01		118.8 (q, *J* = 321.0)	-75.86

It was clear from the product ratios of the methoxy substituted acetylenes **4.55**, **4.56** and **4.57** that the proximal position was the preferred site for carbonylation due to the enhanced stability of the incipient carbocation in the presence of electron-donating (methoxy) substituents (product ratios of 2:1 and 7:1, Table 4-42 entries 1-3). In the case of the diphenylacetylene carrying an electron-withdrawing triflate substituent (**4.58**), a 1:1 ratio of the proximal (**4.78p**) vs. distal (**4.78d**) products was found, thus indicating almost no difference in the stabilities of the two incipient carbocations that would be formed in the hydroesterification reaction. The hypothesis that the stability of the incipient carbocation is playing an important role during the hydroesterification reaction, was further confirmed by the 3:1 ratio in favour of the compound with the carbonyl moiety in the benzylic position next to the methoxy carrying A-ring when 4-methoxyphenyl-4'-trifluoromethanesulfonyloxy-phenylacetylene (**4.59**) was subjected to methoxycarbonylation (Table 4-42 entry 5).

Since it was clear from the results discussed above that a deactivating group attached to the B-ring of the acetylene has an enhancing effect towards the formation of the ester (**4.79**) proximal to the electron-rich A-ring, it was decided to evaluate the effect of the two triflate groups attached to the B-ring as a final experiment. 4-Methoxyphenyl-2',4'-bis(trifluoromethane-sulfonyloxy)phenylacetylene (**4.60**) was therefore subjected to the standard methoxycarbonylation conditions and the ester products, **4.80p** and **4.80d**, obtained in 72% yield (76% conversion, Table 4-42 entry 6) after only 30 minutes of reaction time. The structures of the products, **4.80p** and **4.80d**, were confirmed and elucidated again by EIMS and NMR (^{1}H, ^{13}C, ^{19}F and 2D) analysis (Table 4-48).

Table 4-48: Diagnostic EIMS, ^{1}H and ^{13}C NMR data for the structure elucidation of products 4.80p and 4.80d.

Diagnostic Data	(**4.80p**) 			(**4.80d**) 		
HRMS	*m/z* 565.0067 $(M + H)^+$			*m/z* 565.0067 $(M + H)^+$		
Plate nr.	52a-f			52a-f		
$^{1}H/^{13}C/^{19}F$	δ_H	δ_C (*J* in Hz)	δ_F	δ_H	δ_C (*J* in Hz)	δ_F
3	7.78 (s)	129.4	-	8.02 (s)	144.6	-
C=O	-	167.3	-	-	166.4	-
COOMe	3.86 (s)	52.8	-	3.79 (s)	52.6	-
CF_3	-	118.9 (q, *J* = 321.0)	-75.75		118.9 (q, *J* = 321.0)	-75.53 -75.51

In this instance, an excellent 18:1 product ratio, 95% regioselectivity, in favour of the ester attached to the α-position of the acetylene substrate (**4.80p**) was found. It could therefore be concluded that the stability of the incipient carbocation in fact is the dominating factor with regard to product selectivity during the hydroesterification reaction of substituted diphenylacetylenes over the $Pd(OAc)_2/Al(OTf)_3$/BINAP catalyst system evaluated in the current investigation, although the steric effect of the bulky triflate group pushing the palladium to the 'other side' could not be excluded completely.

4.6. Conclusions and future work

Since the aim of this project was to study the influence of the electronic environment around the double bond of alkenes on the reactivity and regioselectivity of the methoxycarbonylation reaction for developing new methodology towards the synthesis of isoflavonoids, several aryl substituted alkenes were subjected to the reaction with CO and MeOH over a $Pd(OAc)_2/Al(OTf)_3/PPh_3$ catalyst at the optimum conditions of 35 bar CO pressure at 95 °C. During these investigations it was found that isomerization of the double bond to the terminal position of the β-methylstyrene analogues represents a facile side reaction. The same products, i.e. linear (l), branched (b) and benzylic (bn) substituted compounds, were formed from β-methylstyrenes and the corresponding allylbenzenes. It was also found that a *p*-methoxy substituent on the aryl ring of the β-methylstyrene or allylbenzene results in a decrease in reaction rate as manifested in the conversions and yields when compared to the unsubstituted analogues, while an *o*-methoxy substituent increases the reaction rate substantially in comparison to the *p*-methoxy analogues. As could be expected, an *o*-substituent (methoxy or

triflate group) also has a profound influence on the product distribution with a drastic increase in the linear products being observed for both the allylbenzene and β-methylstyrene isomers. It was also determined that a more electron-rich aromatic ring has a slight enhancing effect on the formation of the benzylic products. The preference for methoxycarbonylation at the more electron-rich benzylic position was confirmed by the methoxycarbonylation of 1,3-diphenylpropene. For this substrate, isomerization of the double bond is irrelevant and methoxycarbonylation becomes the only reaction to be considered.

Since the availability of CO and thus the CO concentration in solution should have a significant influence on the rate of the reactions unless CO is not involved in the rate limiting step of the process, the effect of mass transfer limitations on the reaction rate of β-methylstyrenes and allylbenzenes were studied. This investigation resulted in an 8-18% increase in reaction rate being observed under conditions of proper mass transfer for the allylbenzene substrates where isomerization of the double bond plays a minor role.

Research into the effect of microwave vs. thermal heating was limited by the pressure limit (12 bar) of the glass reaction vessel in the microwave reactor, but resulted in the first successful microwave hydroesterification reactions being recorded. For 1-octene and styrene, a definite increase in reaction rate was achieved, with the conversion after 10 minutes under microwave conditions at 12 bar being almost the same or better than what was obtained after 30 minutes at 35 bar with conventional heating. Although a general increase in reaction rate was not found for the allylbenzene substrate, a ca. 15% increase in yield was observed for *p*-methoxyallylbenzene, *o*-methoxyallylbenzene and β-methylstyrene as substrates when the microwave reactions were compared to those performed under conventional heating at the same pressure.

When the nucleophile in the carbonylation reactions was changed from oxygen to nitrogen species and the ligand to BINAP, the first aminocarbonylation of the *o*- and *p*-methoxy substituted allylbenzenes with aniline resulted in the successful formation of the linear and branched amides (anilides) in >90% yield. Although the same reaction has been published recently with different catalyst systems, those methods require large excesses of the alkene (up to 11:1), thus rendering the methodologies less useful. Extending our methodology to β-methylstyrene and α-methylstyrene with aniline, however, gave the amides in only 18% and 16% yield, respectively, while the reactions of allylbenzene with deactivated anilines (2,4-dichloro and 4-nitroaniline) were unsuccessful. Since the success of the reaction may be

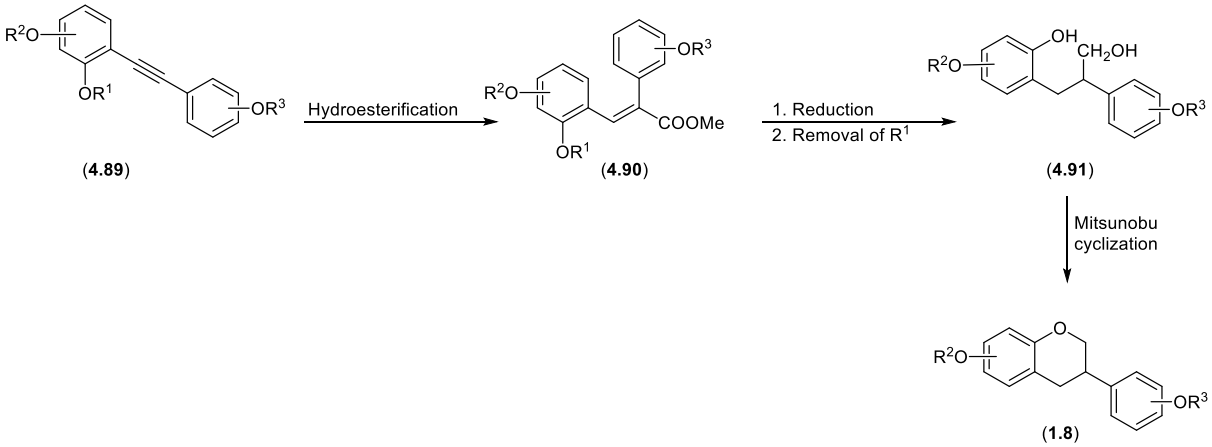
dependent on the pK_a of the amine, various commercially available amines were included in the investigation. Preliminary results suggest that amines with pK_a-values below 3 are not nucleophilic enough to attack the palladium acyl species, whereas amines with pK_a-values above 9 are basic enough to form stable ammonium ions and presumably does not allow the formation of the palladium hydride species required for aminocarbonylation. Although the reaction was repeated with 4-chlorobenzylamine which gave some conversion (25%) to the desired amide product, confirmation of this hypothesis was, however, limited by the commercial availability of amines with pK_a values in the 5-7 range. This aspect of the investigation will therefore receive more attention in a follow-up investigation.

Finally, attention was turned towards the original aim of this project, i.e. carbonylation of stilbenes. The reactions were poor though, stilbenes with methoxy substituents gave conversions of 16-19% and yields of only 2-6%, although some selectivity towards the formation of the distal isomer was observed.

Since the alkoxycarbonylation of alkynes is a well-documented reaction and these substrates could also function as starting material for the synthesis of isoflavonoids, albeit with an additional reduction step being necessary, the investigation was changed to the methoxycarbonylation of diphenylacetylenes. The methoxy and triflate substituted diphenylacetylenes, with the exception of (2,4-dimethoxyphenyl)phenylacetylene, were excellent substrates for the methoxycarbonylation reaction catalysed by $Pd(OAc)_2/Al(OTf)_3$/BINAP and good to excellent conversions and yields could be obtained in reaction times of 40 minutes or less. Owing to Lewis acid catalysed methanol addition to the triple bond and subsequent demethylation, (2,4-dimethoxyphenyl)phenylacetylene gave only 35% of the desired product, which was accompanied by 46% of the corresponding deoxybenzoin.

While some selectivity towards the proximal isomer of the esters were generally found for monomethoxy substituted diphenylacetylene (2:1, proximal:distal) and the substrate with a methoxy on one aromatic ring and a triflate group on the other ring (3:1), excellent regioselectivity towards hydroesterification at the benzylic position proximal to the methoxy substituted phenyl ring was found for the methoxycarbonylation of 4-methoxyphenyl-2',4'-bis(trifluoromethanesulfonyloxy)phenylacetylene (18:1 or 95%). It was thus demonstrated that substituted diphenylacetylenes can be methoxycarbonylated successfully and that high selectivity towards the isomer that would allow cyclization to the 6-membered heterocyclic ring

of the isoflavonoid nucleus is possible. Method development for the preparation of diphenylacetylenes with substitution patterns resembling those found in naturally occurring isoflavonoids could be embarked upon with confidence. The development of the envisaged catalytic methodology towards the synthesis of real examples of isoflavonoids, as indicated in Scheme 4-18, will receive further attention in a follow-up investigation.



Scheme 4-18: Future synthesis of isoflavonoids.

4.7. References

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EXPERIMENTAL 5

5.1. Chromatography

5.1.1. Thin Layer Chromatography (TLC)

Qualitative TLC was conducted on Macherey-Nagel Alugram Xtra Sil G UV_{254} (0.2 mm layer) divided into strips (2.5 cm x 5 cm). Eluent was prepared v/v. R_f values are those observed in these qualitative TLC assessments.

5.1.2. Preparative Layer Chromatography (PLC)

PLC was conducted on glass plates (20 cm x 20 cm) coated with a layer (1 mm) of Merck Kieselgel 60 PF_{254} that had been air-dried overnight at room temperature. Eluent was prepared v/v. Crude mixture was applied (15-20 mg per plate) and after development, in the appropriate solvent system, the plates were air-dried in a fume hood. Bands were distinguished by making use of UV light (254 nm) after which the bands were scraped off and the isolated product washed out using acetone or ethyl acetate. The solvent was then removed under reduced pressure on a water bath at ca. 40 °C.

5.1.3. Flash Column Chromatography (FCC)

FCC was conducted on 100 g of Macherey-Nagel Silica 60 (0.063-0.2 mm) per gram of crude mixture in a glass column. The silica was suspended in the appropriate eluent and packed into a glass column. Air was discharged with the use of N_2-pressure (ca. 50 kPa). The crude mixture was dissolved in a minimum amount of eluent and applied to the top of the silica column. In the case of low solubility, the crude mixture was adsorbed on a minimum amount of silica and loaded onto the top of the silica column. The purified products were recovered by elution under N_2-pressure and collected in fractions. Clean fractions were combined and concentrated under reduced pressure at ca. 40 °C.

5.1.4. Cyclograph Chromatography (CC)

A CycloGraph^{TM} Centrifugal Chromatography System was used for CC performed on a round glass plate coated with silica of different thicknesses (2 mm, 4 mm, 6mm or 8 mm). The

crude mixture (300 mg, 600 mg, 1200 mg or 2500 mg) was dissolved in a minimum amount of eluent and applied to the middle of the rotating cyclograph plate. Bands were eluted at 700-1480 rpm and visualised by fluorescence when irradiated with UV-light (254 nm). Clean fractions were combined and concentrated under reduced pressure at ca. 40 °C.

5.1.5. Gas Chromatography with Flame Ionisation Detection (GC)

Gas chromatography was used to analyse carbonylation reactions utilizing a Shimadzu chromatograph (GC-2010) fitted with a flame ionisation detector (FID), an auto sampler (AOC-20i+s), a J&W HP-5 capillary column (30 m, 0.32 mm ID, 0.25 µm film thickness) by employing hydrogen (H_2) as carrier gas at a linear velocity of 12 cm/s. Injection port and detector temperatures were set at 300 °C.

Table 5-1: GC column temperature programmes used in the determination of conversions and yields of carbonylation reactions.

Programme	Ramp (°C/min)	Temperature (°C)	Hold time (min)
A	-	70	0
	5	150	2
	10	250	10
B	-	40	0
	2	70	2
	20	160	0
	10	250	10
C	-	70	0
	10	170	2
	5	300	12
D	-	50	0
	2	100	2
	20	160	0
	10	250	12
E	-	60	0
	4	150	2
	10	250	11
F	-	60	0
	10	150	2
	5	300	10
G	-	60	0
	7	150	2
	15	300	10

Single point internal standard protocol was used for quantification by including a known amount of xylene in all the experiments as an internal standard. The equation below was used

to calculate response factors (RF) from standard solutions containing the internal standard (IS) and the desired analyte (DA).

$$RF = \frac{A_{IS}\ x\ n_{DA}}{A_{DA}\ x\ n_{IS}}$$

5.2. Spectroscopic and Spectrometric Methods

5.2.1. Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR experiments were performed on a Bruker AM 300 or Bruker AVANCE II AM 600 FT-spectrometer at 293 K, with deuterochloroform ($CDCl_3$) as solvent, unless specified otherwise. Chemical shifts are reported in parts per million (ppm) with the solvent residual peak at 7.26 ppm for proton spectra and 77.16 ppm for carbon spectra on the δ-scale, whereas coupling constants are given in Hz.[1] Standard references added for ^{31}P and ^{19}F NMR experiments are phosphoric acid and hexafluorobenzene which resonates at 0.00 ppm and -164.9 ppm, respectively. The chemical impurity resonating as a singlet at 1.56 ppm in proton spectra is identified as moisture according to Gottlieb *et al*.[1] Additional experiments utilized for structure elucidation and peak assignment were distortionless enhancement by polarisation transfer (DEPT) at a 135° angle, heteronuclear single-quantum correlation (HSQC), heteronuclear multiple-bond correlation (HMBC) and nuclear Overhauser effect (NOE).

5.2.2. Electron-Impact Ionisation Mass Spectrometry (EIMS)

Mass spectrometry of compounds and reaction mixtures were performed by means of electron impact (EI) ionization making use of a Shimadzu gas chromatograph (GC-2010) fitted with a mass spectrometer (GCMS-QP2010), an auto sampler injection unit (AOC-20i) and a J&W DB-5 MS capillary-column (30 m, 0.32 mm ID, 0.25 µm film thickness) with helium (He) as carrier gas. The mass spectrometer (GCMS-QP2010) includes a direct sample inlet unit (DI 2010) for direct injections.

5.2.3. High-Resolution Mass Spectrometry (HRMS)

HRMS analyses were conducted at the University of KwaZulu-Natal (UKZN), Pietermaritzburg, South Africa.

5.3. Melting Points

Melting points were determined with a Barloworld Scientific Stuart Melting Point (SMP 3) apparatus and are uncorrected.

5.4. General procedures for the hydroesterification of alkenes

5.4.1. Parr reactor (thermal heating)

Reactions were performed in a 4590 Parr reactor (25 ml vessel), with or without the use of a gas entrainment stirrer as explained in paragraphs 4.2.1-4.2.2. The CO used were passed through a CrO_3 silica bed for purification purposes. $Al(OTf)_3$ (10 mol%), PPh_3 (20 mol%), xylene (0.5 g) and the alkene (4 mmol) were added together in the Parr reactor and dissolved in MeOH (6 ml). The reactor was degassed and allowed to heat up to 95 °C. $Pd(OAc)_2$ (5 mol%) dissolved in MeOH (2 ml) was injected, whereafter the pressure was adjusted to 35 bar of CO.

5.4.2. Microwave reactor (microwave irradiation)

$Pd(OAc)_2$ (5 mol%), $Al(OTf)_3$ (10 mol%), PPh_3 (20 mol%), xylene (0.25 g) and the alkene (2 mmol) were added together in a MW vial (10 ml) and dissolved in MeOH (4 ml). The vial was sealed and degassed whereafter the pressure was adjusted to 12 bar of CO (purified with CrO_3). After inserting the temperature probe, the reaction was performed in the CEM® Corporation Discover SP microwave reactor, irradiating the reaction mixture with microwaves (150 W) to 95 °C by utilizing the fixed power method.

5.5. General procedure for the methoxycarbonylation of alkynes

$Pd(OAc)_2$ (2 mol%), $Al(OTf)_3$ (4 mol%), BINAP (8 mol%), xylene (0.5 g) and the alkyne (1 mmol) were added together in the Parr reactor and dissolved in MeOH (7 ml). The reactor was degassed and allowed to heat up to 95 °C, whereafter the pressure was adjusted to 35 bar of CO.

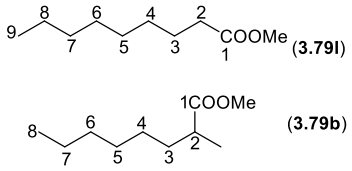
5.6. General procedure for the aminocarbonylation reactions

$Pd(OAc)_2$ (5 mol%), $Al(OTf)_3$ (10 mol%), BINAP (20 mol%), xylene (0.5 g), the alkene (4 mmol) and the *N*-nucleophile (9 eq.) were added together in the Parr reactor and dissolved in THF (5 ml). The reactor was degassed and allowed to heat up to 95 °C, whereafter the pressure was set to 35 bar of CO.

5.7. Methoxycarbonylation of alkenes utilizing thermal heating

5.7.1. Methoxycarbonylation of 1-octene (3.11)

Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0476 g, 0.212 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.425 mmol, 10 mol%), PPh_3 (0.223 g, 0.851 mmol, 20 mol%), xylene (0.504 g, 4.74 mmol) and 1-octene (**3.11**), (0.474 g, 4.23 mmol).



Methyl nonanoate (**3.79l**)[2] and methyl 2-methyloctanoate (**3.79b**)[2] were formed (in a ratio of 3:1) as a very light yellow oil: GC determined yield 76% (isolated 0.037 g, 5%); Programme A: R_T 15.1 (**3.79l**) and 13.4 min (**3.79b**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 1a): δ_H 3.67 [0.7H, s, OMe, (**3.79b**)], 3.66 [3H, s, OMe, (**3.79l**)], 2.44-2.41 [0.2H, m, H-2, (**3.79b**)], 2.29 [2H, t, *J* = 7.6 Hz, H-2, (**3.79l**)], 1.64-1.59 [2H, m, H-3, (**3.79l**)], 1.32-1.22 [10H, m, H-4, H-5, H-6, H-7, H-8 (**3.79l**)], 1.32-1.22 [2.2H, m, H-3, H-4, H-5, H-6, H-7, (**3.79b**)], 1.13 [0.7H, d, *J* = 7.0 Hz, 2-CH_3, (**3.79b**)], 0.87 [0.7H, t, *J* = 7.0 Hz, H-8, (**3.79b**)], 0.87 [3H, t, *J* = 7.0 Hz, H-9, (**3.79l**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 1b): δ_C 177.5 [C-1 (**3.79b**)], 174.4 [C-1 (**3.79l**)], 51.5 [OMe (**3.79l**)], 51.3 [OMe (**3.79b**)], 39.6 [C-2 (**3.79b**)], 34.2 [C-2 (**3.79l**)], 33.9 (**3.79b**), 31.9 (**3.79l**), 31.8, (**3.79b**), 29.32 (**3.79l**), 29.27 (**3.79b**), 29.26 (**3.79l**), 29.2 (**3.79l**), 27.3 (**3.79b**), 25.1 [C-3, (**3.79l**)], 22.74 (**3.79l**), 22.69 (**3.379b**), 17.2 [2-CH_3, (**3.79b**)], 14.2 [C-9, (**3.79l**)], 14.1 [C-8, (**3.79b**)]; EIMS (70 eV) *m/z* 172 [M^+, 2% (**3.79l**)], 172 [M^+, 1% (**3.79b**)].

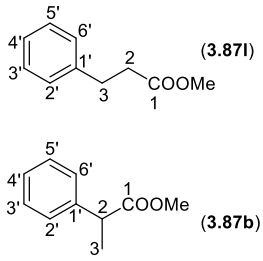
5.7.2. Methoxycarbonylation of 2-octene (4.1)

Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0469 g, 0.209 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.425 mmol, 10 mol%), PPh_3 (0.222 g, 0.845 mmol, 20 mol%), xylene (0.501 g, 4.72 mmol) and 2-octene (**4.1**) (0.475 g, 4.24 mmol). Methyl nonanoate (**3.79l**) and methyl 2-methyloctanoate (**3.79b**) (cf. paragraph 5.7.1.) were formed in a ratio of 2:1; GC determined yield 68%.

5.7.3. Methoxycarbonylation of styrene (3.25)

Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0476 g, 0.212 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.424 mmol, 10 mol%), PPh_3 (0.224 g, 0.854 mmol, 20 mol%), xylene (0.499 g, 4.70 mmol) and styrene (**3.25**), (0.442 g, 4.25 mmol).

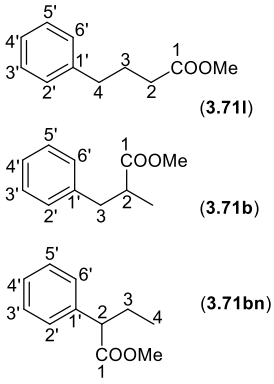
Methyl 3-phenylpropanoate (**3.87l**)[3] and methyl 2-phenylpropanoate (**3.87b**)[4] were formed (in a ratio of 3:1) as a colourless oil: GC determined yield 87% (isolated 0.538 g, 77%); purified with FCC utilizing petroleum ether:ether 7:3 (R_f 0.595); Programme A: R_T 16.8 (**3.87l**) and 14.9 min (**3.87b**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 2a): δ_H 7.34-7.26 [2.7H, m, H-Ar, (**3.87l**) and (**3.87b**)], 7.22-7.19 [2.9H, m, H-Ar, (**3.87l**) and (**3.87b**)], 3.72 [0.2H, q, *J* = 7.2 Hz, H-2, (**3.87b**)], 3.67 [3H, s, OMe, (**3.87l**)], 3.65 [0.5H, s, OMe, (**3.87b**)], 2.95 [2H, t, *J* = 7.9 Hz, H-3, (**3.87l**)] 2.63 [2H, t, *J* = 7.9 Hz, H-2, (**3.87l**)], 1.5 [0.5H, d, *J* = 7.2 Hz, H-3, (**3.87b**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 2b): δ_C 175.1 [C-1, (**3.87b**)], 173.5 [C-1, (**3.87l**)], 140.7 [C-1', (**3.87b**)], 140.6 [C-1', (**3.87l**)], 128.8 [C-4', (**3.87b**)], 128.6 [C-Ar, (**3.87l**)], 128.4 [C-Ar, (**3.87l**)], 127.6 [C-Ar, (**3.87b**)], 127.3 [C-Ar, (**3.87b**)], 126.4 [C-4' (**3.87l**)], 52.2 [OMe, (**3.87b**)], 51.7 [OMe (**3.87l**)], 45.6 [C-2, (**3.87b**)], 35.8 [C-2, (**3.87l**)], 31.1 [C-3 (**3.87l**)], 18.7 [C-3, (**3.87b**)]; EIMS (70 eV) *m/z* 164 [M^+, 35% (**3.87l**)], 164 [M^+, 23% (**3.87b**)].



5.7.4. Methoxycarbonylation of *trans*-β-methylstyrene (3.50)

Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0481 g, 0.214 mmol, 5 mol%), $Al(OTf)_3$ (0.202 g, 0.425 mmol, 10 mol%), PPh_3 (0.226 g, 0.861 mmol, 20 mol%), xylene (0.155 g, 1.46 mmol) and *trans*-β-methylstyrene (**3.50**), (0.501 g, 4.24 mmol).

Methyl 4-phenylbutanoate (**3.71l**),[5] methyl 2-methyl-3-phenylpropanoate (**3.71b**)[6] and methyl 2-phenylbutanoate (**3.71bn**)[7] were formed (in a ratio of 3:2:1) as a light yellow oil: GC determined yield 89% (isolated 0.480 g, 64%) after FCC utilizing H:T:A 4:4:2 (R_f 0.784); Programme A: R_T 19.8 (**3.71l**), 17.3 (**3.71b**) and 16.7 min (**3.71bn**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 3a): δ_H 7.33-7.24 [4.8H, m, H-Ar, (**3.71l**), (**3.71b**) and (**3.71bn**)], 7.22-7.15 [4.5H, m, H-Ar, (**3.71l**), (**3.71b**) and (**3.71bn**)], 3.66 [3H, s, OMe (**3.71l**)], 3.65 [1H, s, OMe (**3.71bn**)], 3.64 [1.8H, s, OMe (**3.71b**)], 3.46 [0.3H, t, *J* = 7.7 Hz, H-2, (**3.71bn**)], 3.03 [0.6H, dd, *J* = 6.8 and 13.4 Hz, H-3a/b, (**3.71b**)], 2.77-2.71 [0.6H, m, H-2, (**3.71b**)], 2.66 [0.6H, dd, *J* = 7.8 and 13.4 Hz, H-3a/b, (**3.71b**)], 2.65 [2H, t, *J* = 7.6 Hz, H-4, (**3.71l**)], 2.33 [2H, t, *J* = 7.6 Hz, H-2, (**3.71l**)], 2.14-2.06 [0.3H, m, H-3a/b, (**3.71bn**)], 1.96 [2H, p, *J* = 7.6 Hz, H-3, (**3.71l**)], 1.83-1.76 [0.3H, m, H-3a/b, (**3.71bn**)], 1.15 [1.7H, d, *J* = 6.9 Hz, 2-CH_3,



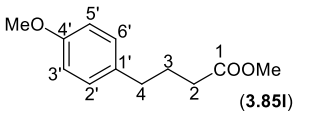
(**3.71b**)], 0.94 [1H, t, *J* = 7.4 Hz, H-4, (**3.71bn**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 3b): δ_C 176.7 [C-1, (**3.71b**)], 174.7 [C-1, (**3.71bn**)], 174.1 [C-1, (**3.71l**)], 141.5 [C-1', (**3.71l**)], 139.5 [C-1', (**3.71b**)], 139.2 [C-1', (**3.71bn**)], 129.1, 128.7, 128.6, 128.51, 128.48, 128.1, 127.3, 126.4, 126.1, 53.5 [C-2, (**3.71bn**)], 52.0 [OMe, (**3.71bn**)], 51.72 [OMe, (**3.71b**)], 51.65 [OMe (**3.71l**)], 41.6 [C-2, (**3.71b**)], 39.8 [C-3 (**3.71b**)], 35.2 [C-4, (**3.71l**)], 33.5 [C-2, (**3.71l**)], 26.9 [C-3 (**3.71bn**)], 26.6 [C-3, (**3.71l**)], 16.9 [2-CH_3 (**3.71b**)], 12.3 [C-4, (**3.71bn**)]; EIMS (70 eV) *m/z* 178 [M^+, 37% (**3.71l**)], 178 [M^+, 18% (**3.71b**)], 178 [M^+, 18% (**3.71bn**)].

5.7.5. Methoxycarbonylation of allylbenzene (3.70)

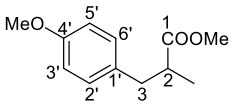
Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0496 g, 0.221 mmol, 5 mol%), $Al(OTf)_3$ (0.202 g, 0.425 mmol, 10 mol%), PPh_3 (0.225 g, 0.857 mmol, 20 mol%), xylene (0.151 g, 1.42 mmol) and allylbenzene (**3.70**), (0.502 g, 4.25 mmol). Methyl 4-phenylbutanoate (**3.71l**), methyl 2-methyl-3-phenylpropanoate (**3.71b**) and methyl 2-phenylbutanoate (**3.71bn**) (cf. paragraph 5.7.4.) were formed in a ratio of 8:2:1; GC determined yield 88%.

5.7.6. Methoxycarbonylation of anethole (4.2)

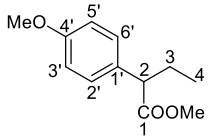
Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0476 g, 0.212 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.425 mmol, 10 mol%), PPh_3 (0.225 g, 0.858 mmol, 20 mol%), xylene (0.501 g, 4.72 mmol) and anethole (**4.2**), (0.628 g, 4.24 mmol).



(**3.85l**)



(**3.85b**)



(**3.85bn**)

Methyl 4-(4-methoxyphenyl)butanoate (**3.85l**),[5] methyl 3-(4-methoxyphenyl)-2-methylpropanoate (**3.85b**)[6] and methyl 2-(4-methoxyphenyl)butanoate (**3.85bn**)[8] were formed (in a ratio of 2:1:1) as a light yellow oil: GC determined yield 48% (isolated 0.318 g, 36%); purified with FCC utilizing petroleum ether:ether 7:3 (R_f 0.639); Programme A: R_T 25.1 (**3.85l**), 23.5 (**3.85b**) and 23.1 min (**3.85bn**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 4a): δ_H 7.25 [0.2H, d, *J* = 8.7 Hz, H-2' and H-6', (**3.85bn**)], 7.11 [2H, d, *J* = 8.7 Hz, H-2' and H-6', (**3.85l**)], 7.10 [0.4H, d, *J* = 8.6 Hz, H-2' and H-6', (**3.85b**)], 6.88-6.87 [0.2H, d, *J* = 8.7 Hz, H-3' and H-5', (**3.85bn**)], 6.86-6.83 [0.4H, m, H-3' and H-5', (**3.85b**)], 6.85 [2H, d, *J* = 8.7 Hz, H-3' and H-5', (**3.85l**)], 3.81-3.80 [3.9H, s, 4'-OMe, (**3.85l**), (**3.85b**) and (**3.85bn**)], 3.68 [3H, s, COOMe, (**3.85l**)], 3.67 [0.3H, s, COOMe, (**3.85bn**)], 3.66 [0.6H, s, COOMe (**3.85b**)], 3.43 [0.1H, t, *J* = 7.7 Hz, H-2, (**3.85bn**)], 2.98 [0.2H, dd, *J* = 6.9 and

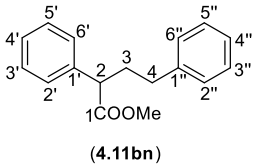
13.5 Hz, H-3a/b, (**3.85b**)], 2.75-2.69 [0.2H, m, H-2, (**3.85b**)], 2.65-2.63 [0.2H, m, H-3a/b, (**3.85b**)], 2.61 [2H, t, *J* = 7.5 Hz, H-4, (**3.85l**)], 2.34 [2H, t, *J* = 7.5 Hz, H-2, (**3.85l**)], 2.11-2.07 [0.1H, m, H-3a/b, (**3.85bn**)], 1.94 [2H, p, *J* = 7.5 Hz, H-3, (**3.85l**)], 1.81-1.76 [0.1H, m, H-3a/b, (**3.85bn**)], 1.16 [0.6H, d, *J* = 6.9 Hz, 2-CH_3, (**3.85b**)], 0.90 [0.3H, t, *J* = 7.3 Hz, H-4, (**3.85bn**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 4b): δ_C 176.7 [C-1, (**3.85b**)], 174.8 [C-1, (**3.85bn**)], 174.0 [C-1, (**3.85l**)], 158.7 [C-4', (**3.85bn**)], 158.1 [C-4', (**3.85b**)], 157.9 [C-4', (**3.85l**)], 133.4 [C-1', (**3.85l**)], 131.4 [C-1', (**3.85b**)], 131.2 [C-1', (**3.85bn**)], 129.9 [C-2' and C-6', (**3.85b**)], 129.4 [C-2' and C-6', (**3.85l**)], 128.9 [C-2' and C-6', (**3.85bn**)], 113.9 [C-3' and C-5', (**3.85bn**)], 113.8 [C-3' and C-5', (**3.85l**)], 113.7 [C-3' and C-5', (**3.85b**)], 55.2 [4'-OMe, (**3.85l**), (**3.85b**) and (**3.85bn**)], 52.5 [C-2, (**3.85bn**)], 51.9 [COOMe, (**3.85bn**)], 51.6 [COOMe, (**3.85b**)], 51.5 [COOMe (**3.85l**)], 41.7 [C-2, (**3.85b**)], 38.9 [C-3 (**3.85b**)], 34.2 [C-4, (**3.85l**)], 33.3 [C-2, (**3.85l**)], 26.8 [C-3 (**3.85bn**)], 26.7 [C-3, (**3.85l**)], 16.7 [2-CH_3 (**3.85b**)], 12.2 [C-4, (**3.85bn**)]; EIMS (70 eV) *m/z* 208 [M^+, 39% (**3.85l**)], 208 [M^+, 13% (**3.85b**)], 208 [M^+, 21% (**3.85bn**)].

5.7.7. Methoxycarbonylation of 1-allyl-4-methoxybenzene (3.84)

Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0478 g, 0.213 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.424 mmol, 10 mol%), PPh_3 (0.223 g, 0.851 mmol, 20 mol%), xylene (0.500 g, 4.71 mmol) and 1-allyl-4-methoxybenzene (**3.84**), (0.629 g, 4.24 mmol). Methyl 4-(4-methoxyphenyl)butanoate (**3.85l**), methyl 3-(4-methoxyphenyl)-2-methylpropanoate (**3.85b**) and methyl 2-(4-methoxyphenyl)butanoate (**3.85bn**), (cf. paragraph 5.7.6.) were formed in a ratio of 7:2:1; GC determined yield 54%.

5.7.8. Methoxycarbonylation of 1,3-diphenylpropene (4.10)

Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0480 g, 0.214 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.424 mmol, 10 mol%), PPh_3 (0.227 g, 0.864 mmol, 20 mol%), xylene (0.502 g, 4.73 mmol) and 1,3-diphenylpropene (**4.10**), (0.600 g, 3.06 mmol).



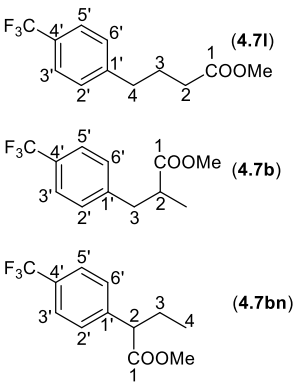
(**4.11bn**)

Methyl 2,4-diphenylbutanoate (**4.11bn**)[9] was formed as a colourless oil: GC determined yield 64% (isolated 0.187 g, 24%); purified with FCC utilizing H:T:Et_2O 8:1:1 (R_f 0.472); Programme A: R_T 29.3 min; ^{1}H NMR (600 MHz, $CDCl_3$, plate 5a): δ_H 7.33-7.24 (7H, m, H-Ar), 7.18 (1H, br t, *J* = 7.4 Hz, H-Ar), 7.14 (2H, br d, *J* = 7.6 Hz, H-Ar), 3.63 (3H, s, OMe), 3.56 (1H, t,

J = 7.7 Hz, H-2), 2.56 (2H, t, *J* = 7.8 Hz, H-4), 2.44-2.38 (1H, m, H-3a/b), 2.13-2.07 (1H, m, H-3a/b); ^{13}C NMR (151 MHz, $CDCl_3$, plate 5b): δ_C 174.4 (C-1), 141.4 (C-1''), 138.9 (C-1'), 128.8 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 128.1 (C-Ar), 127.4 (C-Ar), 126.1 (C-Ar), 52.1 (OMe), 50.9 (C-2), 35.0 (C-3), 33.6 (C-4); EIMS (70 eV) *m/z* 254 (M^+, 2%).

5.7.9. Methoxycarbonylation of 1-allyl-4-(trifluoromethyl)benzene (4.6)

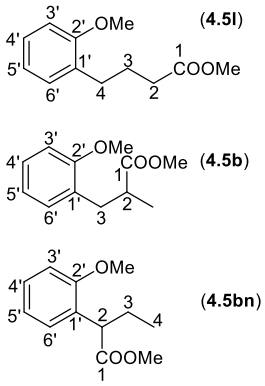
Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0480 g, 0.214 mmol, 5 mol%), $Al(OTf)_3$ (0.200 g, 0.422 mmol, 10 mol%), PPh_3 (0.226 g, 0.861 mmol, 20 mol%), xylene (0.500 g, 4.72 mmol) and 1-allyl-4-(trifluoromethyl)benzene (**4.6**), (0.787 g, 4.23 mmol).



Methyl 4-(4-trifluoromethylphenyl)butanoate (**4.7l**), *methyl 2-methyl-3-(4-trifluoromethylphenyl)propanoate* (**4.7b**) and *methyl 2-(4-trifluoromethylphenyl)butanoate* (**4.7bn**) were formed (in a ratio of 9:2:1) as a light yellow oil: GC determined yield 66% (isolated 0.398 g, 38%); purified with FCC utilizing petroleum ether:Et_2O 7:3 (R_f 0.389); Programme A: R_T 20.4 (**4.7l**), 17.7 (**4.7b**) and 16.9 min (**4.7bn**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 6a): δ_H 7.58 [0.04H, d, *J* = 8.1 Hz, H-3' and H-5', (**4.7bn**)], 7.54-7.53 [2.2H, m, H-3' and H-5', (**4.7l**) and (**4.7b**)], 7.43 [0.04H, d, *J* = 8.2 Hz, H-2' and H-6', (**4.7bn**)], 7.3-7.27 [2.2H, m, H-2' and H-6', (**4.7l**) and (**4.7b**)], 3.67 [3H, s, OMe, (**4.7l**)], 3.64 [0.06H, s, OMe, (**4.7bn**)], 3.64 [0.4H, s, OMe, (**4.7b**)], 3.53 [0.02H, t, *J* = 7.7 Hz, H-2, (**4.7bn**)], 3.09-3.06 [0.14H, m, H-2, (**4.7b**)], 2.78-2.73 [0.26H, m, H-3a and H-3b, (**4.7b**)], 2.71 [2H, t, *J* = 7.6 Hz, H-4, (**4.7l**)], 2.34 [2H, t, *J* = 7.6 Hz, H-2, (**4.7l**)], 2.15-2.07 [0.02H, m, H-3a/b, (**4.7bn**)], 1.97 [2H, p, *J* = 7.6 Hz, H-3, (**4.7l**)], 1.88-1.79 [0.02H, m, H-3a/b, (**4.7bn**)], 1.18 [0.4H, d, *J* = 6.8 Hz, 2-CH_3, (**4.7b**)], 0.89 [0.06H, t, *J* = 7.4 Hz, H-4, (**4.7bn**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 6b): δ_C 176.2 [C-1, (**4.7b**)], 173.9 [C-1, (**4.7bn**)], 173.8 [C-1, (**4.7l**)], 145.6 [C-1', (**4.7l**) and (**4.7bn**)], 143.6 [C-1', (**4.7b**)], 129.4, 128.9 [C-2' and C-6', (**4.7l**)], 128.8, 128.7, 128.6, 128.5, 128.4, 128.2, 125.4 [C-3' and C-5', (**4.7l**)], 124.4 [q, *J* = 271.76 Hz, CF_3, (**4.7l**), (**4.7b**) and (**4.7bn**)], 53.3 [C-2, (**4.7bn**)], 52.2 [OMe (**4.7bn**)], 51.8 [OMe, (**4.7b**)], 51.7 [OMe, (**4.7l**)], 41.3 [C-2, (**4.7b**)], 39.5 [C-3 (**4.7b**)], 35.0 [C-4, (**4.7l**)], 33.3 [C-2, (**4.7l**)], 26.8 [C-3 (**4.7bn**)], 26.3 [C-3, (**4.7l**)], 17.0 [2-CH_3 (**4.7b**)], 12.1 [C-4, (**4.7bn**)]; EIMS (70 eV) *m/z* 246 [M^+, 8% (**4.7l**)], 246 [M^+, 15% (**4.7b**)], 246 [M^+, 10% (**4.7bn**)]; HRMS *m/z* Calcd for $C_{12}H_{13}F_3O_2$ 246.23; found, 246.2351.

5.7.10. Methoxycarbonylation of *trans*-2-methoxy-β-methylstyrene (4.3)

Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0473 g, 0.211 mmol, 5 mol%), $Al(OTf)_3$ (0.203 g, 0.427 mmol, 10 mol%), PPh_3 (0.225 g, 0.857 mmol, 20 mol%), xylene (0.504 g, 4.75 mmol) and *trans*-2-methoxy-β-methylstyrene (**4.3**), (0.606 g, 4.09 mmol).



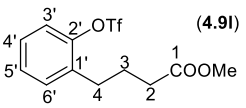
Methyl 4-(2-methoxyphenyl)butanoate (**4.5l**),[10] methyl 3-(2-methoxyphenyl)-2-methylpropanoate (**4.5b**)[6] and methyl 2-(2-methoxyphenyl)butanoate (**4.5bn**) were formed (in a ratio of 10:4:1) as a light yellow oil: GC determined yield 85% (isolated 0.435 g, 51%); purified with FCC utilizing petroleum ether:ether 7:3 (R_f 0.583); Programme A: R_T 24.3 (**4.5l**), 22.5 (**4.5b**) and 22.0 min (**4.5bn**); ^1H NMR (600 MHz, $CDCl_3$, plate 7a): δ_H 7.25 [0.04H, dd, *J* = 7.5 and 1.7 Hz, H-6', (**4.5bn**)], 7.22 [0.04H, ddd, *J* = 8.2, 7.5 and 1.7 Hz, H-4', (**4.5bn**)], 7.19-7.15 [1.2H, m, H-4', (**4.5l**) and (**4.5b**)], 7.10 [1H, dd, *J* = 7.4 and 1.7 Hz, H-6', (**4.5l**)], 7.08 [0.2H, dd, *J* = 7.5 and 1.7 Hz, H-6', (**4.5b**)], 6.93 [0.04H, ddd, *J* = 7.5, 7.5 and 1.1 Hz, H-5', (**4.5bn**)], 6.87 [1H, ddd, *J* = 8.4, 7.4 and 1.1 Hz, H-5', (**4.5l**)], 6.85 [0.2H, ddd, *J* = 8.5, 7.5 and 1.1 Hz, H-5', (**4.5b**)], 6.83-6.81 [1.24H, m, H-3', (**4.5l**), (**4.5b**) and (**4.5bn**)], 3.93 [0.04H, t, *J* = 7.6 Hz, H-2, (**4.5bn**)], 3.8 [0.12H, s, 2'-OMe, (**4.5bn**)], 3.79 [0.6H, s, 2'-OMe, (**4.5b**)], 3.78 [3H, s, 2'-OMe, (**4.5l**)], 3.64 [3H, s, COOMe, (**4.5l**)], 3.63 [0.12H, s, COOMe, (**4.5bn**)], 3.61 [0.6H, s, COOMe (**4.5b**)], 2.98 [0.2H, dd, *J* = 7.1 and 13.2 Hz, H-3a/b, (**4.5b**)], 2.86-2.8 [0.2H, m, H-2, (**4.5b**)], 2.7 [0.2H, dd, *J* = 7.6 and 13.2 Hz, H-3a/b, (**4.5b**)], 2.65 [2H, t, *J* = 7.6 Hz, H-4, (**4.5l**)], 2.32 [2H, t, *J* = 7.6 Hz, H-2, (**4.5l**)], 2.08-2.03 [0.04H, m, H-3a/b, (**4.5bn**)], 1.92 [2H, p, *J* = 7.6 Hz, H-3, (**4.5l**)], 1.78-1.73 [0.04H, m, H-3a/b, (**4.5bn**)], 1.13 [0.6H, d, *J* = 7.0 Hz, 2-CH_3, (**4.5b**)], 0.89 [0.12H, t, *J* = 7.4 Hz, H-4, (**4.5bn**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 7b): δ_C 177.1 [C-1, (**4.5b**)], 175.0 [C-1, (**4.5bn**)], 174.2 [C-1, (**4.5l**)], 157.6 [C-2', (**4.5b**)], 157.5 [C-2', (**4.5l**)], 156.9 [C-2', (**4.5bn**)], 130.8 [C-6', (**4.5b**)], 131.0 [C-6', (**4.5l**)], 129.7 [C-1', (**4.5l**)], 129.4, 128.4, 128.1, 127.72, 127.69 [C-4', (**4.5b**)], 127.3 [C-4' (**4.5l**)], 120.7 [C-5', (**4.5bn**)], 120.4 [C-5', (**4.5l**)], 120.3 [C-5', (**4.5b**)], 110.7 [C-3', (**4.5bn**)], 110.2 [C-3', (**4.5l**) and (**4.5b**)], 55.7 [2'-OMe, (**4.5bn**)], 55.2 [2'-OMe, (**4.5l**) and (**4.5b**)], 51.8 [COOMe, (**4.5bn**)], 51.47 [COOMe, (**4.5b**)], 51.45 [COOMe (**4.5l**)], 45.7 [C-2, (**4.5bn**)], 39.5 [C-2, (**4.5b**)], 34.6 [C-3 (**4.5b**)], 33.6 [C-2, (**4.5l**)], 29.5 [C-4, (**4.5l**)], 25.7 [C-3 (**4.5bn**)], 25.0 [C-3, (**4.5l**)], 17.0 [2-CH_3 (**4.5b**)], 12.2 [C-4, (**4.5bn**)]; EIMS (70 eV) *m/z* 208 [M^+, 40% (**4.5l**)], 208 [M^+, 22% (**4.5b**)], 208 [M^+, 34% (**4.5bn**)].

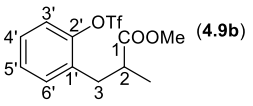
5.7.11. Methoxycarbonylation of 1-allyl-2-methoxybenzene (4.4)

Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0477 g, 0.212 mmol, 5 mol%), $Al(OTf)_3$ (0.202 g, 0.425 mmol, 10 mol%), PPh_3 (0.224 g, 0.853 mmol, 20 mol%), xylene (0.501 g, 4.72 mmol) and 1-allyl-2-methoxybenzene (**4.4**), (0.627 g, 4.23 mmol). Methyl 4-(2-methoxyphenyl)butanoate (**4.5l**), methyl 3-(2-methoxyphenyl)-2-methylpropanoate (**4.5b**) and methyl 2-(2-methoxyphenyl)butanoate (**4.5bn**) (cf. paragraph 5.7.6.) were formed (in a ratio of 15:5:1); GC determined yield 80%.

5.7.12. Methoxycarbonylation of 1-allyl-2-(trifluoromethanesulfonyloxy)benzene (4.8)

Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0474 g, 0.211 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.424 mmol, 10 mol%), PPh_3 (0.224 g, 0.854 mmol, 20 mol%), xylene (0.504 g, 4.75 mmol) and 1-allyl-2-(trifluoromethanesulfonyloxy)benzene (**4.8**), (1.125 g, 4.22 mmol).



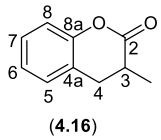


Methyl 4-(2-trifluoromethanesulfonyloxyphenyl)butanoate (**4.9l**) and *methyl 2-methyl-3-(2-trifluoromethanesulfonyloxyphenyl)propanoate* (**4.9b**) were formed (in a ratio of 5:1) as a colourless oil: GC determined yield 86% (isolated 0.509 g, 37%); purified with FCC utilizing H:T:A 8:1:1 (R_f 0.432); Programme A: R_T 24.6 (**4.9l**) and 22.4 min (**4.9b**); ^1H NMR (600 MHz, $CDCl_3$, plate 8a): δ_H 7.34 [1H, br dd, *J* = 7.5 and 1.6 Hz, H-6', (**4.9l**)], 7.32-7.24 [3.4H, m, H-Ar, (**4.9l**) and (**4.9b**)], 3.66 [3H, s, OMe, (**4.9l**)], 3.61 [0.3H, s, OMe, (**4.9b**)], 3.12-3.07 [0.1H, m, H-3a/b, (**4.9b**)], 2.86-2.81 [0.3H, m, H-2 and H-3a/b, (**4.9b**)], 2.76 [2H, t, *J* = 7.6 Hz, H-4, (**4.9l**)], 2.36 [2H, t, *J* = 7.6 Hz, H-2, (**4.9l**)], 1.98 [2H, p, *J* = 7.6 Hz, H-3, (**4.9l**)], 1.2 [0.3H, d, *J* = 6.6 Hz, CH_3, (**4.9b**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 8b): δ_C 175.7 [C-1, (**4.9b**)], 173.3 [C-1, (**4.9l**)], 148.2 [C-2', (**4.9b**)], 148.0 [C-2', (**4.9l**)], 134.1 [C-1', (**4.9b**)], 132.2 [C-1', (**4.9l**)], 131.9 [C-6', (**4.9b**)], 131.2 [C-6', (**4.9l**)], 128.5, 128.4, 128.3, 128.0, 121.3, 118.6 [q, *J* = 319.9 Hz, OTf (**4.9l**) and (**4.9b**)], 51.6 [OMe, (**4.9l**)], 51.4 [OMe, (**4.9b**)], 39.9 [C-2, (**4.9b**)], 33.9 [C-3, (**4.9b**)], 33.2 [C-2 (**4.9l**)], 29.1 [C-4, (**4.9l**)], 25.0 [C-3 (**4.9l**)], 17.0 [2-CH_3 (**4.9b**)]; ^{19}F NMR (565 MHz, $CDCl_3$, plate 8f): δ_F -76.84 (**4.9l**), -76.87 (**4.9b**); EIMS (70 eV) *m/z* 326 [M^+, 4% (**4.9l**)], 326 [M^+, 5% (**4.9b**)]; HRMS *m/z* Calcd for $C_{12}H_{13}F_3O_5S$ 326.29; found, 326.2897.

5.7.13. Methoxycarbonylation of 2-allylphenol (4.14)

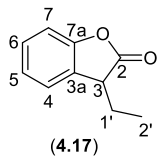
Performed according to the general procedure (cf. paragraph 5.4.1.), however utilizing THF instead of MeOH as solvent. $Pd(OAc)_2$ (0.0484 g, 0.216 mmol, 5 mol%), $Al(OTf)_3$ (0.203 g, 0.427 mmol, 10 mol%), PPh_3 (0.224 g, 0.853 mmol, 20 mol%), xylene (0.504 g, 4.74 mmol) and 2-allylphenol (**4.14**), (0.569 g, 4.24 mmol).

3-Methylchroman-2-one (**4.16**) and 3-ethylbenzofuran-2(3*H*)-one (**4.17**) were formed in 55% GC yield; Programme A: R_T 20.7 (**4.16**) and 18.6 min (**4.17**), respectively. Purified by FCC (H:T:A 8:1:1).



(**4.16**)

3-Methylchroman-2-one (**4.16**)[11] was isolated as a white solid (0.027 g, 4%): R_f 0.432 (H:T:A 8:1:1); ^{1}H NMR (600 MHz, $CDCl_3$, plate 9a): δ_H 7.26 (1H, br dd, *J* = 8.5 and 8.2 Hz, H-7), 7.18 (1H, br d, *J* = 7.5 Hz, H-5), 7.09 (1H, br dd, *J* = 8.5, 7.5 and 1.1 Hz, H-6), 7.04 (1H, br dd, *J* = 8.2 and 1.1 Hz, H-8), 2.98 (1H, dd, *J* = 14.9 Hz and 5.4 Hz, H-4a/b), 2.86-2.76 (2H, m, H-3 and H-4a/b), 1.38 (3H, d, *J* = 6.5 Hz, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$, plate 9b): δ_C 171.8 (C-2), 151.9 (C-8a), 128.3 (C-7), 128.1 (C-5), 124.4 (C-6), 123.0 (C-4a), 116.7 (C-8), 34.3 (C-3), 31.8 (C-4), 15.5 (CH_3); EIMS (70 eV) *m/z* 162 (M^+, 100%).



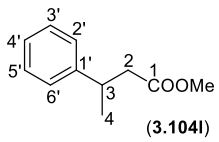
(**4.17**)

3-Ethylbenzofuran-2(3*H*)-one (**4.17**)[12] was isolated as a white solid (0.022 g, 3%): R_f 0.541 (H:T:A 8:1:1); ^{1}H NMR (600 MHz, $CDCl_3$, plate 10a): δ_H 7.32-7.29 (1H, m, H-6), 7.27 (1H, br dd, *J* = 7.6 Hz, H-4), 7.15 (1H, br dd, *J* = 7.6 Hz and 1.0 Hz, H-5), 7.11 (1H, br dd, *J* = 8.0 Hz and 1.0 Hz, H-7), 3.71 (1H, t, *J* = 5.9 Hz, H-3), 2.09-2.04 (2H, m, CH_2), 0.97 (3H, t, *J* = 7.5 Hz, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$, plate 10b): δ_C 177.4 (C-2), 154.1 (C-7a), 128.9 (C-6), 127.3 (C-3a), 124.3 (C-4 or C-5), 124.2 (C-4 or C-5), 110.8 (C-7), 44.7 (C-3), 24.4 (CH_2), 10.3 (CH_3); EIMS (70 eV) *m/z* 162 (M^+, 100%).

5.7.14. Methoxycarbonylation of α-methylstyrene (3.48)

Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0478 g, 0.213 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.424 mmol, 10 mol%), PPh_3 (0.224 g, 0.852 mmol, 20 mol%), xylene (0.499 g, 4.70 mmol) and α-methylstyrene (**3.48**), (0.501 g, 4.24 mmol).

Methyl 3-phenylbutanoate (**3.104l**)[13] was formed as a colourless oil: GC determined yield 63% (isolated 0.463 g, 61%); purified by FCC utilizing petroleum ether:Et_2O 7:3 (R_f 0.676); Programme A: R_T 17.9 min; ^1H NMR (600 MHz, $CDCl_3$, plate 11a): δ_H 7.30-7.27 (2H, m, H-3' and H-5'), 7.22-7.20 (2H, m, H-2' and H-6'), 7.20-7.17 (1H, m, H-4'), 3.60 (3H, s, OMe), 3.31-3.25 (1H, m, H-3), 2.62 (1H, dd, *J* = 6.9 and 15.2 Hz, H-2a/b), 2.54 (1H, dd, *J* = 8.3 and 15.2 Hz, H-2a/b), 1.29 (3H, d, *J* = 7.0 Hz, H-4); ^{13}C NMR (151 MHz, $CDCl_3$, plate 11b): δ_C 172.9 (C-1), 145.8 (C-1'), 128.6 (C-3' and C-5'), 126.8 (C-2' and C-6'), 126.5 (C-4'), 51.5 (OMe), 42.8 (C-2), 36.5 (C-3), 21.8 (C-4); EIMS (70 eV) *m/z* 178 (M^+, 22%).

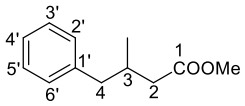


(**3.104l**)

5.7.15. Methoxycarbonylation of 1-phenyl-2-methylprop-1-ene (4.26)

Performed according to the general procedure (cf. paragraph 5.4.1.). $Pd(OAc)_2$ (0.0488 g, 0.217 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.424 mmol, 10 mol%), PPh_3 (0.226 g, 0.863 mmol, 20 mol%), xylene (0.504 g, 4.74 mmol) and 1-phenyl-2-methylprop-1-ene (**4.26**), (0.559 g, 4.23 mmol).

Methyl 3-methyl-4-phenylbutanoate (**4.27**)[14] was formed as a yellow oil: GC determined yield 26% (isolated 0.163 g, 20%); purified with FCC utilizing petroleum ether:Et_2O 7:3 (R_f 0.676); Programme A: R_T 20.8 min; ^1H NMR (600 MHz, $CDCl_3$, plate 12a): δ_H 7.28 (2H, br dd, *J* = 7.5 and 7.4 Hz, H-3' and H-5'), 7.19 (1H, br t, *J* = 7.4 Hz, H-4'), 7.16 (2H, br d, *J* = 7.5 Hz, H-2' and H-6'), 3.64 (3H, s, OMe), 2.62 (1H, dd, *J* = 13.5 and 6.7 Hz, H-4a/b), 2.50 (1H, dd, *J* = 13.5 and 7.4 Hz, H-4a/b), 2.33 (1H, dd, *J* = 14.6 and 5.8 Hz, H-2a/b), 2.31-2.25 (1H, m, H-3), 2.14 (1H, dd, *J* = 14.6 and 7.8 Hz, H-2a/b), 0.94 (3H, d, *J* = 6.6 Hz, 3-CH_3); ^{13}C NMR (151 MHz, $CDCl_3$, plate 12b): δ_C 173.6 (C-1), 140.3 (C-1'), 129.3 (C-2' and C-6'), 128.4 (C-3' and C-5'), 126.2 (C-4'), 51.5 (OMe), 43.1 (C-4), 41.0 (C-2), 32.4 (C-3), 19.8 (3-CH_3); EIMS (70 eV) *m/z* 192 (M^+, 2%).



(**4.27**)

5.8. Methoxycarbonylation of alkenes utilizing microwave irradiation

Utilizing the general procedure described in paragraph 5.4.2. the following alkenes were converted to produce the following esters under microwave conditions.

Table 5-2: Methoxycarbonylation reactions under microwave conditions.

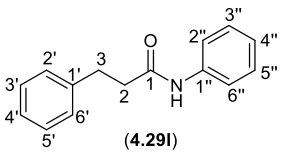
Alkene	1-Octene (**3.11**)	Styrene (**3.25**)	β-methylstyrene (**3.50**)
$Pd(OAc)_2$	0.0251 g, 0.112 mmol	0.0246 g, 0.110 mmol	0.0239 g, 0.106 mmol
$Al(OTf)_3$	0.102 g, 0.215 mmol	0.102 g, 0.214 mmol	0.102 g, 0.216 mmol
PPh_3	0.114 g, 0.433 mmol	0.114 g, 0.436 mmol	0.112 g, 0.427 mmol
Xylene	0.260 g, 2.45 mmol	0.254 g, 2.39 mmol	0.253 g, 2.39 mmol
Products	**3.79l** and **3.79b**	**3.87l** and **3.87b**	**3.71l**, **3.71b** and **3.71bn**
Ratio	4:1	4:1	8:2:1
Yield[a]	82%	72%	82%
Alkene	Allylbenzene (**3.70**)	1-allyl-4-methoxybenzene (**3.84**)	1-allyl-2-methoxybenzene (**4.3**)
$Pd(OAc)_2$	0.0254 g, 0.131 mmol	0.0251 g, 0.112 mmol	0.0235 g, 0.105 mmol
$Al(OTf)_3$	0.101 g, 0.213 mmol	0.102 g, 0.214 mmol	0.102 g, 0.215 mmol
PPh_3	0.114 g, 0.435 mmol	0.111 g, 0.422 mmol	0.112 g, 0.429 mmol
Xylene	0.253 g, 2.39 mmol	0.253 g, 2.38 mmol	0.253 g, 2.38 mmol
Products	**3.71l**, **3.71b** and **3.71bn**	**3.85l**, **3.85b** and **3.85bn**	**4.5l**, **4.5b** and **4.5bn**
Ratio	9:2:1	6:1:1	27:5:1
Yield[a]	81%	37%	89%

[a]Determined by GC analysis with xylene as internal standard.

5.9. Aminocarbonylation of alkenes

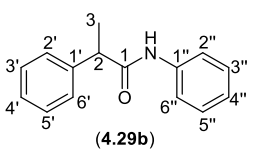
5.9.1. Aminocarbonylation of styrene (3.25)

Performed according to the general procedure (cf. paragraph 5.6.). $Pd(OAc)_2$ (0.025 g, 0.112 mmol, 5 mol%), $Al(OTf)_3$ (0.101 g, 0.214 mmol, 10 mol%), BINAP (0.269 g, 0.431 mmol, 20 mol%), xylene (0.260 g, 2.45 mmol), styrene (**3.25**), (0.222 g, 2.13 mmol) and aniline (**4.28**), (3.5 ml, 38.33 mmol, 9 eq.). The crude mixture was separated by CC (H:DCM:EtOAc 48:48:2) to give *N*,3-diphenylpropanamide (**4.29l**) and *N*,2-diphenylpropanamide (**4.29b**) in a ratio of 1:4; GC determined yield 86%.



(**4.29l**)

N,3-diphenylpropanamide (**4.29l**)[36] was isolated as a light yellow solid (0.063 g, 13%), R_f 0.081 (H:DCM:EtOAc 48:48:2); m.p. 93.8-95.0 °C; Programme E: R_T 38.6 min; ^{1}H NMR [600 MHz, $(CD_2)_3CO$, plate 13a]: δ_H 8.24 (1H, br s, *N*-H), 6.72 (2H, d, *J* = 7.4 Hz, H-2" and H-6"), 6.36-6.33 (6H, m, H-2', H-3', H-5', H-6', H-3" and H-5"), 6.26-6.24 (1H, m, H-4'), 6.11 (1H, t, *J* = 7.4 Hz, H-4"), 2.07 (2H, t, *J* = 7.8 Hz, H-3), 1.75 (2H, t, *J* = 7.8 Hz, H-2); ^{13}C NMR [151 MHz, $(CD_2)_3CO$, plate 13b]: δ_C 171.1 (C-1), 142.3 (C-1'), 140.4 (C-1"), 129.4, 129.2, 126.8 (C-4'), 123.9 (C-4"), 112.0 (C-2" and C-6"), 39.4 (C-2), 32.0 (C-3); EIMS (70 eV) *m/z* 225 (M^+, 15%).



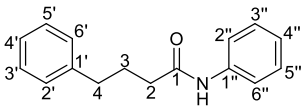
(**4.29b**)

N,2-diphenylpropanamide (**4.29b**)[36] was isolated as an off-white solid (0.269 g, 56%), R_f 0.162 (H:DCM:EtOAc 48:48:2); m.p. 128.1-130.2 °C; Programme E: R_T 36.3 min; ^{1}H NMR [600 MHz, $(CD_2)_3CO$, plate

14a]: δ_H 9.31 (1H, br s, *N*-H), 7.66 (2H, br d, *J* = 7.7 Hz, H-2" and H-6"), 7.43 (2H, br d, *J* = 8.0 Hz, H-2' and H-6'), 7.31 (2H, dd, *J* = 8.0 and 7.4 Hz, H-3' and H-5'), 7.26 (2H, dd, *J* = 7.7 and 7.4 Hz, H-3" and H-5"), 7.23 (1H, br t, *J* = 7.4 Hz, H-4'), 7.02 (1H, br t, *J* = 7.4 Hz, H-4"), 3.85 (1H, q, *J* = 7.0 Hz, H-2), 1.49 (3H, d, *J* = 7.0 Hz, H-3); ^{13}C NMR [151 MHz, $(CD_2)_3CO$, plate 14b]: δ_C 172.9 (C-1), 142.9 (C-1'), 140.2 (C-1"), 129.3 (C-Ar), 129.1 (C-Ar), 128.1 (C-2' and C-6'), 127.5 (C-4'), 124.0 (C-4"), 120.0 (C-2" and C-6"), 47.8 (C-2), 19.3 (C-3); EIMS (70 eV) *m/z* 225 (M^+, 37%).

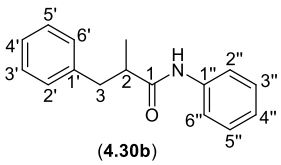
5.9.2. Aminocarbonylation of allylbenzene (3.70)

Performed according to the general procedure (cf. paragraph 5.6.). $Pd(OAc)_2$ (0.048 g, 0.213 mmol, 5 mol%), $Al(OTf)_3$ (0.202 g, 0.425 mmol, 10 mol%), BINAP (0.525 g, 0.843 mmol, 20 mol%), xylene (0.501 g, 4.72 mmol), allylbenzene (**3.70**), (0.500 g, 4.23 mmol) and aniline (**4.28**), (3.5 ml, 38.33 mmol, 9 eq.). The crude mixture was separated by CC (H:DCM:EtOAc 48:48:2) to give *N*,4-diphenylbutanamide (**4.30l**), 2-methyl-*N*,3-diphenylpropanamide (**4.30b**) and *N*,2-diphenylbutanamide (**4.30bn**) in a ratio of 8:2:1; GC determined yield 92%.



(**4.30l**)

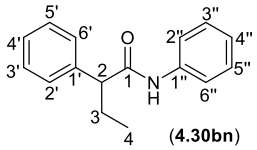
N,4-diphenylbutanamide (**4.30l**)[37] was isolated as an off-white solid (0.040 g, 4%), R_f 0.054 (H:DCM:EtOAc 48:48:2); m.p. 96.7-97.7 °C; Programme E: R_T 41.1 min; ^{1}H NMR [600 MHz, $CDCl_3$, plate 15a]: δ_H 7.61 (1H, br s, *N*-H), 7.49 (2H, d, *J* = 7.8 Hz, H-2" and H-6"), 7.29-7.25 (4H, m, H-3', H-3", H-5' and H-5"), 7.18 (1H, t, *J* = 7.4 Hz, H-4'), 7.15 (2H, d, *J* = 7.3 Hz, H-2' and H-6'), 7.07 (1H, t, *J* = 7.4 Hz, H-4"), 2.66 (2H, t, *J* = 7.5 Hz, H-4), 2.31 (2H, t, *J* = 7.5 Hz, H-2), 2.02 (2H, p, *J* = 7.5 Hz, H-3); ^{13}C NMR [151 MHz, $CDCl_3$, plate 15b]: δ_C 171.4 (C-1), 141.4 (C-1'), 138.0 (C-1"), 129.0 (C-Ar), 128.6 (C-Ar), 128.5 (C-Ar), 126.1 (C-4'), 124.3 (C-4"), 120.1 (C-2" and C-6"), 36.8 (C-2), 35.2 (C-4), 27.0 (C-3); EIMS (70 eV) *m/z* 239 (M^+, 14%).



(**4.30b**)

2-Methyl-*N*,3-diphenylpropanamide (**4.30b**)[38] was isolated as an off-white solid (0.029 g, 3%), R_f 0.108 (H:DCM:EtOAc 48:48:2); m.p. 96.7-97.7 °C; Programme E: R_T 37.7 min; ^{1}H NMR [600 MHz, $CDCl_3$, plate 16a]: δ_H 7.35 (2H, d, *J* = 7.7 Hz, H-2" and H-6"), 7.28-7.24 (4H, m, H-3', H-3", H-5' and H-5"), 7.21-7.20 (1H, m, H-4'), 7.18 (2H, d, *J* = 7.2 Hz, H-2' and H-6'), 7.07-7.05 (2H, m, H-4" and *N*-H), 3.02 (1H, dd, *J* = 8.4 and 13.5 Hz, H-3a/b), 2.75 (1H, dd, *J* = 6.4 and 13.5 Hz, H-3a/b), 2.62-2.58 (1H, m, H-2), 1.26 (3H, d, *J* = 6.8 Hz, 2-CH_3); ^{13}C NMR [151 MHz, $CDCl_3$, plate 16b]: δ_C 174.1 (C-1), 139.8 (C-1'), 137.8 (C-1"),

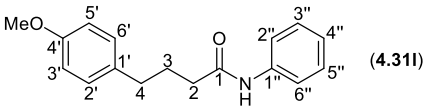
129.1 (C-Ar), 129.0 (C-Ar), 128.7 (C-Ar), 126.6 (C-4'), 124.4 (C-4"), 120.2 (C-2" and C-6"), 44.9 (C-2), 40.7 (C-3), 17.9 (2-CH_3); EIMS (70 eV) *m/z* 239 (M^+, 24%).

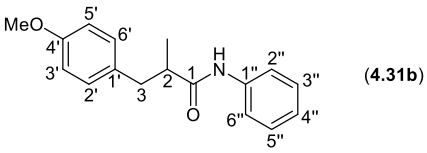

(**4.30bn**)

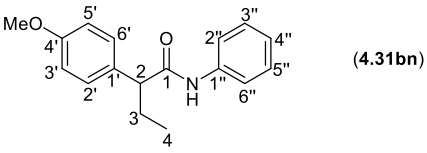
N,2-diphenylbutanamide (**4.30bn**)[39] was isolated as an off-white solid (0.024 g, 2%), R_f 0.189 (H:DCM:EtOAc 48:48:2); m.p. 96.7-97.7 °C; Programme E: R_T 37.1 min; ^{1}H NMR [600 MHz, $CDCl_3$, plate 17a]: δ_H 7.44 (2H, d, *J* = 8.0 Hz, H-2" and H-6"), 7.36-7.35 (4H, m, H-2', H-3', H-5' and H-6'), 7.30-7.24 (4H, m, H-3", H-4', H-5" and *N*-H), 7.06 (1H, t, *J* = 7.4 Hz, H-4"), 3.40 (1H, t, *J* = 7.6 Hz, H-2), 2.31-2.24 (1H, m, H-3a/b), 1.9-1.83 (1H, m, H-3a/b), 0.92 (3H, t, *J* = 7.4 Hz, H-4); ^{13}C NMR [151 MHz, $CDCl_3$, plate 17b]: δ_C 171.9 (C-1), 139.6 (C-1'), 138.0 (C-1"), 129.1 (C-Ar), 129.0 (C-Ar), 128.2 (C-Ar), 127.6 (C-4'), 124.4 (C-4"), 119.9 (C-2" and C-6"), 56.2 (C-2), 26.5 (C-3), 12.5 (C-4); EIMS (70 eV) *m/z* 239 (M^+, 25%).

5.9.3. Aminocarbonylation of 4-allylanisole (3.84)

Performed according to the general procedure (cf. paragraph 5.6.). $Pd(OAc)_2$ (0.048 g, 0.212 mmol, 5 mol%), $Al(OTf)_3$ (0.204 g, 0.429 mmol, 10 mol%), BINAP (0.526 g, 0.846 mmol, 20 mol%), xylene (0.501 g, 4.72 mmol), 4-allylanisole, (**3.84**) (0.628 g, 4.24 mmol) and aniline (**4.28**), (3.5 ml, 38.33 mmol, 9 eq.).


(**4.31l**)


(**4.31b**)

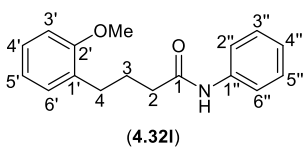

(**4.31bn**)

4-(4'-Methoxyphenyl)-*N*-phenyllbutanamide (**4.31l**),[40] 2-methyl-3-(4'-methoxyphenyl)-*N*-phenylpropanamide (**4.31b**)[40] and 2-(4'-methoxy-phenyl)-*N*-phenyllbutanamide (**4.31bn**)[41] were formed (in a ratio of 4:1:1) as a light yellow oil: GC determined yield 93% (isolated 0.2058 g, 18%); purified with CC utilizing H:DCM 1:1 (R_f 0.257); Programme F: R_T 37.7 (**4.31l**), 34.2 (**4.31b**) and 33.8 min (**4.31bn**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 18a): δ_H 7.49 [1.1H, d, *J* = 8.0 Hz, H-2" and H-6" (**4.31l**)], 7.43 [2H, d, *J* = 7.8 Hz, H-2" and H-6" (**4.31bn**)], 7.37 [1.8H, d, *J* = 7.6 Hz, H-2" and H-6" (**4.31b**)], 7.32-7.29 [1.1H, m, H-3" and H-5", (**4.31l**)], 7.28-7.25 [6.2H, m, H-2', H-3", H-6' and H-5" (**4.31b**), H-3" and H-5" (**4.31bn**), H-4" (**4.31l**)], 7.21 [0.6H, br s, *N*-H, (**4.31bn**)], 7.18 [1H, br s, *N*-H, (**4.31l**)], 7.12-7.09 [3.1H, m, H-2' and H-6', (**4.31l**) and (**4.31bn**)], 7.08-7.05 [1.9H, m, H-4", (**4.31b**) and (**4.31bn**)], 6.97 [0.9H, br s, *N*-H, (**4.31b**)], 6.89 [2H, d, *J* = 8.6 Hz, H-3' and H-5' (**4.31bn**)], 6.83 [1.1H, d, *J* = 8.5 Hz, H-3' and H-5' (**4.31l**)], 6.81 [1.8H, d, *J* = 8.6 Hz, H-3' and H-5' (**4.31b**)], 3.80 [3H, s, OMe (**4.31bn**)], 3.78

[1.7H, s, OMe (**4.31l**)], 3.77 [2.7H, s, OMe (**4.31b**)], 3.34 [1H, t, *J* = 7.6 Hz, H-2 (**4.31bn**)], 2.97 [0.9H, dd, *J* = 8.6 and 13.7 Hz, H-3a/b (**4.31b**)], 2.71 [0.9H, dd, *J* = 6.2 and 13.7 Hz, H-3a/b (**4.31b**)], 2.64 [1.1H, t, *J* = 7.4 Hz, H-4 (**4.31l**)], 2.57-2.51 [0.9H, m, H-2 (**4.31b**)], 2.32 [1.1H, t, *J* = 7.4 Hz, H-2 (**4.31l**)], 2.27-2.23 [1H, m, H-3a/b (**4.31bn**)], 2.03 [1.1H, p, *J* = 7.4 Hz, H-3 (**4.31l**)], 1.85-1.80 [1H, m, H-3a/b (**4.31bn**)], 1.26 [2.7H, d, *J* = 6.8 Hz, 2-CH_3 (**4.31b**)] and 0.91 [3H, t, *J* = 7.4 Hz, H-4 (**4.31bn**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 18b): δ_C 174.2 [C-1, (**4.31b**)], 172.3 [C-1, (**4.31bn**)], 171.2 [C-1, (**4.31l**)], 159.1 [C-4', (**4.31b**)], 158.3 [C-4', (**4.31bn**)], 158.0 [C-4', (**4.31l**)], 138.0 [C-1", (**4.31bn**)], 137.8 [C-1", (**4.31l**) and (**4.31b**)], 133.5 [C-1', (**4.31l**)], 131.8 [C-1', (**4.31bn**)], 131.6 [C-1', (**4.31b**)], 130.1, 129.6, 129.3, 129.1, 129.0, 124.38 [C-4", (**4.31l**)], 124.35 [C-4", (**4.31b**)], 124.3 [C-4", (**4.31bn**)], 120.1 [C-2" and C-6", (**4.31b**)], 119.9 [C-2" and C-6", (**4.31l**)], 119.8 [C-2" and C-6", (**4.31bn**)], 114.5 [C-2' and C-6', (**4.31b**)], 114.1 [C-3' and C-5', (**4.31bn**)], 114.0 [C-3' and C-5', (**4.31l**)], 55.4 [4'-OMe, (**4.31l**), (**4.31b**) and (**4.31bn**), C-2 (**4.31bn**)], 45.2 [C-2, (**4.31b**)], 39.9 [C-3 (**4.31b**)], 36.9 [C-2, (**4.31l**)], 34.3 [C-4, (**4.31l**)], 27.2 [C-3 (**4.31l**)], 26.5 [C-3, (**4.31bn**)], 17.8 [2-CH_3 (**4.31b**)], 12.5 [C-4, (**4.31bn**)]; EIMS *m/z* 269 [M^+, 18% (**4.31l**)], 269 [M^+, 12% (**4.31b**)], 269 [M^+, 13%, (**4.31bn**)].

5.9.4. Aminocarbonylation of 2-allylanisole (4.4)

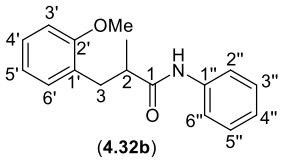
Performed according to the general procedure (cf. paragraph 5.6.). $Pd(OAc)_2$ (0.048 g, 0.215 mmol, 5 mol%), $Al(OTf)_3$ (0.202 g, 0.425 mmol, 10 mol%), BINAP (0.526 g, 0.845 mmol, 20 mol%), xylene (0.500 g, 4.71 mmol), 2-allylanisole (**4.4**), (0.627 g, 4.23 mmol) and aniline (**4.28**), (3.5 ml, 38.33 mmol, 9 eq.). The crude mixture was purified with FCC to obtain the following three products, 4-(2'-methoxyphenyl)-*N*-phenyllbutanamide (**4.32l**), 2-methyl-3-(2'-methoxyphenyl)-*N*-phenylpropanamide (**4.32b**) and 2-(2'-methoxy-phenyl)-*N*-phenyllbutanamide (**4.32bn**) in a ratio of 15:5:1; GC determined yield 94%.



(**4.32l**)

4-(2-Methoxyphenyl)-*N*-phenyllbutanamide (**4.32l**)[40] was isolated as a yellow amorphous solid (0.223 g, 20%), R_f 0.23 (H:DCM:A 50:48:2); Programme G: R_T 27.9 min; ^{1}H NMR [600 MHz, $CDCl_3$, plate 19a]: δ_H 7.51-7.50 (3H, m, H-2", H-6" and *N*-H), 7.30 (2H, br dd, *J* = 7.9 and 7.5 Hz, H-3" and H-5"), 7.19 (1H, br dd, *J* = 8.2 and 7.4 Hz, H-4'), 7.12 (1H, br d, *J* = 7.1 Hz, H-6'), 7.08 (1H, br t, *J* = 7.5 Hz, H-4"), 6.88 (1H, br dd, *J* = 7.4 and 7.1 Hz, H-5'), 6.84 (1H, br d, *J* = 8.2 Hz, H-3'), 3.79 (3H, s, OMe), 2.70 (2H, t, *J* = 7.4 Hz, H-4), 2.34 (2H, t, *J* = 7.4 Hz, H-2), 2.02 (2H, p, *J* = 7.4 Hz, H-3); ^{13}C NMR [151 MHz, $CDCl_3$, plate 19b]: δ_C 171.6 (C-1), 157.6 (C-

2'), 138.2 (C-1"), 130.2 (C-6'), 129.8 (C-1'), 129.0 (C-3" and C-5"), 127.4 (C-4'), 124.2 (C-4"), 120.6 (C-5'), 120.0 (C-2" and C-6"), 110.5 (C-3'), 55.4 (OMe), 37.1 (C-2), 29.6 (C-4), 25.8 (C-3); EIMS (70 eV) *m/z* 269 (M^+, 27%).

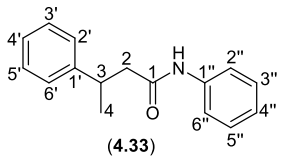


(**4.32b**)

2-Methyl-3-(2-methoxyphenyl)-*N*-phenylpropanamide (**4.32b**)[40] was isolated as a yellow amorphous solid (0.051 g, 4%), R_f 0.392 (H:DCM:A 50:48:2); Programme G: R_T 26.4 min; ^{1}H NMR [600 MHz, $CDCl_3$, plate 20a]: δ_H 7.38 (2H, br d, *J* = 7.9 Hz, H-2" and H-6"), 7.27 (2H, br dd, *J* = 7.9 and 7.5 Hz, H-3" and H-5"), 7.21 (1H, br dd, *J* = 8.0 and 7.2 Hz, H-4'), 7.13 (1H, br d, *J* = 7.6 Hz, H-6'), 7.08 (1H, s, *N*-H), 7.06 (1H, br t, *J* = 7.5 Hz, H-4"), 6.88-6.85 (2H, br dd, *J* = 8.0 and 7.6 Hz, H-3' and H-5'), 3.82 (3H, s, OMe), 3.02 (1H, dd, *J* = 13.3 and 7.7 Hz, H-3a/b), 2.76 (1H, dd, *J* = 13.3 and 6.6 Hz, H-3a/b), 2.70-2.66 (1H, m, H-2), 1.25 (3H, d, *J* = 6.8 Hz, 2-CH_3); ^{13}C NMR [151 MHz, $CDCl_3$, plate 20b]: δ_C 174.6 (C-1), 157.4 (C-2'), 138.1 (C-1"), 131.1 (C-6'), 129.0 (C-3" and C-5"), 128.09 (C-1'), 127.98 (C-4'), 124.1 (C-4"), 120.8 (C-5'), 119.9 (C-2" and C-6"), 110.5 (C-3'), 55.5 (OMe), 42.7 (C-2), 35.6 (C-3), 17.6 (2-CH_3); EIMS (70 eV) *m/z* 269 (M^+, 24%).

5.9.5 Aminocarbonylation of α-methylstyrene (3.48)

Performed according to the general procedure (cf. paragraph 5.6.). $Pd(OAc)_2$ (0.048 g, 0.212 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.424 mmol, 10 mol%), BINAP (0.527 g, 0.846 mmol, 20 mol%), xylene (0.502 g, 4.72 mmol), α-methylstyrene (**3.48**), (0.502 g, 4.25 mmol) and aniline (**4.28**), (3.5 ml, 38.33 mmol, 9 eq.).

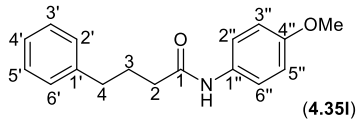


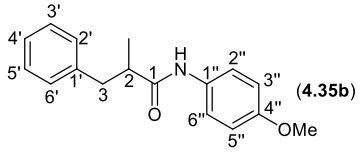
(**4.33**)

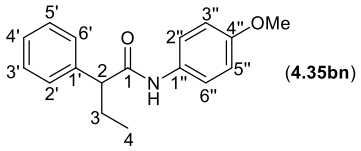
PLC (H:T:A 6:2:2) gave *N*,4-diphenylbutanamide (**4.33**)[42] as a yellow amorphous solid (0.094 g, 16%): R_f 0.446; ^{1}H NMR (600 MHz, $CDCl_3$, plate 21a) δ_H 7.34 (2H, br d, *J* = 7.9 Hz, H-2" and H-6"), 7.31 (2H, br dd, *J* = 7.6 and 7.5 Hz, H-3' and H-5'), 7.26-7.21 (6H, m, H-2', H-3", H-4', H-5", H-6' and *N*-H), 7.06 (1H, br t, *J* = 7.2 Hz, H-4"), 3.38-3.34 (1H, m, H-3), 2.62 (1H, dd, *J* = 14.1 and 7.5 Hz, H-2a/b), 2.56 (1H, dd, *J* = 14.1 and 7.3 Hz, H-2a/b), 1.35 (3H, d, *J* = 7.0 Hz, H-4); ^{13}C NMR (151 MHz, $CDCl_3$, plate 21b): δ_C 170.3 (C-1), 145.8 (C-1'), 137.8 (C-1"), 129.0 (C-Ar), 128.9 (C-Ar), 126.9 (C-2' and C-6'), 126.7 (C-4'), 124.4 (C-4"), 120.2 (C-3" and C-5"), 46.8 (C-2), 37.2 (C-3), 21.8 (C-4); EIMS (70 eV) *m/z* 239 (M^+, 18%).

5.9.6 Aminocarbonylation of allylbenzene (3.70) with anisidine (4.34)

Performed according to the general procedure (cf. paragraph 5.6.). $Pd(OAc)_2$ (0.048 g, 0.213 mmol, 5 mol%), $Al(OTf)_3$ (0.202 g, 0.425 mmol, 10 mol%), BINAP (0.526 g, 0.845 mmol, 20 mol%), xylene (0.505 g, 4.76 mmol), allylbenzene (**3.70**), (0.502 g, 4.25 mmol) and anisidine (**4.34**), (4.67 g, 37.96 mmol, 9 eq.).


(**4.35l**)


(**4.35b**)

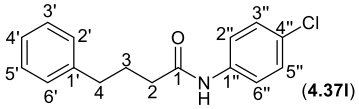

(**4.35bn**)

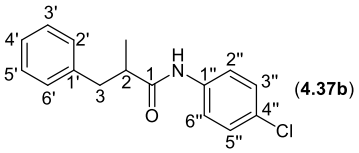
PLC (H:EtOAc 8:2) gave *N*-(4''-methoxyphenyl)-4-phenyllbutanamide (**4.35l**),[43] 2-methyl-*N*-(4''-methoxyphenyl)-3-phenylpropanamide (**4.35b**)[44] and *N*-(4''-methoxyphenyl)-2-phenyllbutanamide (**4.35bn**)[45] were formed (in a ratio of 8:2:1) as a light brown amorphous solid: GC determined yield 87% (isolated 0.099 g, 9%); m.p. 104.7-106.8 °C; R_f 0.257; Programme G: R_T 29.0 (**4.35l**), 27.2 (**4.35b**) and 26.8 min (**4.35bn**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 22a): δ_H 7.47-7.44 [0.15H, m, H-Ar (**4.35l**)], 7.39-7.38 [0.14H, m, H-Ar (**4.35l**)], 7.35-7.34 [0.8H, m, H-2' and H-6' (**4.35bn**)], 7.33-7.32 [0.8H, m, H-2'' and H-6'' (**4.35bn**)], 7.29-7.28 [0.8H, m, H-3' and H-5' (**4.35bn**)], 7.27-7.25 [2H, m, H-3' and H-5' (**4.35b**)], 7.23 [2H, d, *J* = 9.0 Hz, H-2'' and H-6'' (**4.35b**)], 7.22-7.20 [1H, m, H-4' (**4.35b**)], 7.19-7.18 [2.4H, m, H-2' and H-6' (**4.35b**) and H-4' (**4.35bn**)], 7.04 [1H, br s, *N*-H (**4.35b**)], 6.89-6.88 [0.15H, m, H-Ar (**4.35l**)], 6.83-6.82 [0.15H, m, H-Ar (**4.35l**)], 6.79-6.77 [2.8H, m, H-3'' and H-5'' (**4.35b**) and (**4.35bn**)], 3.77 [0.21H, s, OMe (**4.35l**)], 3.75 [3H, s, OMe (**4.35b**)], 3.74 [1.2H, s, OMe (**4.35bn**)], 3.37 [0.4H, t, *J* = 7.6 Hz, H-2 (**4.35bn**)], 3.01 [1H, dd, *J* = 8.5 and 13.5 Hz, H-3a/b (**4.35b**)], 2.74 [1H, dd, *J* = 6.4 and 13.5 Hz, H-3a/b (**4.35b**)], 2.68 [0.14H, t, *J* = 7.5 Hz, H-4 (**4.35l**)], 2.60-2.54 [1H, m, H-2 (**4.35b**)], 2.31 [0.14H, t, *J* = 7.5 Hz, H-2 (**4.35l**)], 2.27-2.23 [0.4H, m, H-3a/b (**4.35bn**)], 2.04 [0.14H, p, *J* = 7.5 Hz, H-3 (**4.35l**)], 1.87-1.82 [0.4H, m, H-3a/b (**4.35bn**)], 1.25 [3H, d, *J* = 6.8 Hz, 2-CH_3 (**4.35b**)] and 0.91 [1.22H, t, *J* = 7.4 Hz, H-4 (**4.35bn**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 22b): δ_C 173.9 [C-1, (**4.35b**)], 171.7 [C-1, (**4.35bn**)], 156.4 [C-4'', (**4.35b**)], 156.3 [C-4'', (**4.35bn**)], 139.8 [C-1', (**4.35b**)], 139.7 [C-1', (**4.35bn**)], 131.0 [C-1'', (**4.35bn**)], 130.8 [C-1'', (**4.35b**)], 129.0 [C-2' and C-6', (**4.35b**)], 128.9 [C-3' and C-5', (**4.35bn**)], 128.5 [C-3' and C-5', (**4.35b**)], 128.1 [C-2' and C-6', (**4.35bn**)], 127.4 [C-4', (**4.35bn**)], 126.4 [C-4', (**4.35b**)], 122.1 [C-2'' and C-6'', (**4.35b**)], 121.7 [C-2'' and C-6'', (**4.35bn**)], 114.0 [C-3'' and C-5'', (**4.35b**) and (**4.35bn**)], 55.9 [C-2, (**4.35bn**)], 55.5 [4''-OMe, (**4.35b**) and (**4.35bn**)], 44.6 [C-2, (**4.35b**)], 40.6 [C-3 (**4.35b**)], 26.5 [C-3,

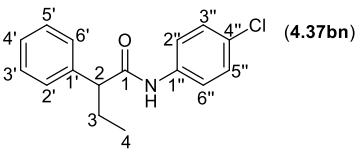
(**4.35bn**)], 17.8 [2-CH_3 (**4.35b**)], 12.4 [C-4, (**4.35bn**)]; EIMS (70 eV) *m/z* 269 [M^+, 34% (**4.35l**)], 269 [M^+, 30% (**4.35b**)], 269 [M^+, 28% (**4.35bn**)].

5.9.7 Aminocarbonylation of allylbenzene (3.70) with 4-chloroaniline (4.36)

Performed according to the general procedure (cf. paragraph 5.6.). $Pd(OAc)_2$ (0.048 g, 0.212 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.423 mmol, 10 mol%), BINAP (0.524 g, 0.841 mmol, 20 mol%), xylene (0.505 g, 4.76 mmol), allylbenzene (**3.70**), (0.500 g, 4.23 mmol) and 4-chloroaniline (**4.36**), (4.86 g, 38.11 mmol, 9 eq.).



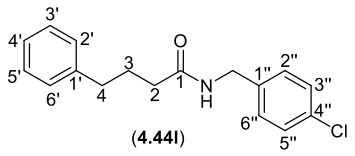




FCC (H:EtOAc 8:2) gave *N*-(4''-chlorophenyl)-4-phenyllbutanamide (**4.37l**), 2-methyl-*N*-(4''-chlorophenyl)-3-phenylpropanamide (**4.37b**)[34] and *N*-(4''-chloro-phenyl)-2-phenyllbutanamide (**4.37bn**) were formed (in a ratio of 12:2:1) as a light brown amorphous solid: GC determined yield 97% (isolated 0.584 g, 51%); m.p. 73.5-78.2 °C; R_f 0.378; Programme G: R_T 31.4 (**4.37l**), 29.4 (**4.37b**) and 29.0 min (**4.37bn**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 23a): δ_H 7.46 [1H, br s, *N*-H (**4.37l**)], 7.44-7.42 (2H, m, H-Ar), 7.38-7.36 (1H, m, H-Ar), 7.35-7.32 (1.7H, m, H-Ar), 7.30-7.18 (11.4H, m, H-Ar), 7.17-7.16 [3.4H, m, H-2' and H-6' (**4.37l**) and (**4.37b**)], 7.12 [1H, br s, *N*-H (**4.37b**)], 3.38 [0.4H, t, *J* = 7.6 Hz, H-2 (**4.37bn**)], 2.99 [0.7H, dd, *J* = 8.7 and 13.5 Hz, H-3a/b (**4.37b**)], 2.75 [0.7H, dd, *J* = 6.2 and 13.5 Hz, H-3a/b (**4.37b**)], 2.67 [2H, t, *J* = 7.5 Hz, H-4 (**4.37l**)], 2.61-2.55 [0.7H, m, H-2 (**4.37b**)], 2.31 [2H, t, *J* = 7.5 Hz, H-2 (**4.37l**)], 2.26-2.21 [0.4H, m, H-3a/b (**4.37bn**)], 2.03 [2H, p, *J* = 7.5 Hz, H-3 (**4.37l**)], 1.87-1.82 [0.4H, m, H-3a/b (**4.37bn**)], 1.26 [3H, d, *J* = 6.8 Hz, 2-CH_3 (**4.37b**)] and 0.90 [1.2H, t, *J* = 7.4 Hz, H-4 (**4.37bn**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 23b): δ_C 174.1 [C-1, (**4.37b**)], 172.0 [C-1, (**4.37bn**)], 171.2 [C-1, (**4.37l**)], 141.2 [C-1', (**4.37b**)], 139.5 [C-1', (**4.37l**)], 139.3 [C-1', (**4.37bn**)], 136.5 [C-1'', (**4.37l**)], 136.4 [C-1'', (**4.37bn**)], 136.2 [C-1'', (**4.37b**)], 129.24, 129.20, 129.1, 129.04, 128.97, 128.93, 128.87, 128.6, 128.51, 128.49, 128.0, 127.6, 126.6, 126.1, 121.4 [C-2'' and C-6'', (**4.37b**)], 121.13 [C-2'' and C-6'', (**4.37bn**)], 121.10 [C-2'' and C-6'', (**4.37l**)], 56.0 [C-2, (**4.37bn**)], 44.7 [C-2, (**4.37b**)], 40.6 [C-3 (**4.37b**)], 36.7 [C-2, (**4.37l**)], 35.0 [C-4, (**4.37l**)], 26.8 [C-3 (**4.37l**)], 26.4 [C-3, (**4.37bn**)], 17.7 [2-CH_3 (**4.37b**)], 12.3 [C-4, (**4.37bn**)]; EIMS (70 eV) *m/z* 273 [M^+, 25% (**4.37l**)], 273 [M^+, 27% (**4.37b**)], 273 [M^+, 19% (**4.37bn**)].

5.9.8 Aminocarbonylation of allylbenzene (3.70) with 4-chlorobenzylamine (4.43)

Performed according to the general procedure (cf. paragraph 5.6.). $Pd(OAc)_2$ (0.048 g, 0.214 mmol, 5 mol%), $Al(OTf)_3$ (0.201 g, 0.423 mmol, 10 mol%), BINAP (0.527 g, 0.847 mmol, 20 mol%), xylene (0.504 g, 4.75 mmol), allylbenzene (**3.70**), (0.500 g, 4.23 mmol) and 4-chlorobenzylamine (**4.43**), (4.6 ml, 37.81 mmol, 9 eq.).



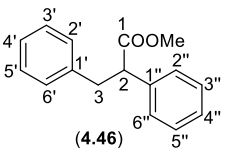
(**4.44l**)

FCC (H:T:A 6:2:2) gave *N*-(4''-chlorobenzyl)-4-phenylbutanamide (**4.44l**) was formed as a white amorphous solid: GC determined yield 23% (isolated 0.118 g, 10%); R_f 0.351; Programme G: R_T 31.5 min; ^{1}H NMR (600 MHz, $CDCl_3$, plate 24a) δ_H 7.68 (1H, br s, *N*-H), 7.33-7.30 (4H, m, H-2'', H-3'', H-5'' and H-6''), 7.27-7.25 (2H, m, H-3' and H-5'), 7.19-7.15 (3H, m, H-2', H-4' and H-6'), 4.37 (2H, d, *J* = 6.1 Hz, CH_2), 2.62 (2H, t, *J* = 7.6 Hz, H-4), 2.25 (2H, t, *J* = 7.6 Hz, H-2), 1.92 (2H, p, *J* = 7.6 Hz, H-3); ^{13}C NMR [151 MHz, $CO(CD_3)_2$, plate 24b]: δ_C 172.9 (C-1), 142.8 (C-1'), 139.8 (C-1''), 132.8 (C-4''), 130.0 (C-2'' and C-6''), 129.2 (C-Ar), 129.1 (C-Ar), 126.6 (C-4'), 42.7 (CH_2), 35.94 (C-2), 35.87 (C-4), 28.2 (C-3); EIMS (70 eV) *m/z* 287 (M^+, 22%).

5.10. Methoxycarbonylation of *trans*-stilbenes (4.45, 4.47 and 4.49)

5.10.1. Methoxycarbonylation of *trans*-stilbene (4.45)

Performed according to the general procedure (cf. paragraph 5.4.1.), however MeOH:THF (1:1) was used as solvent instead of pure methanol. $Pd(OAc)_2$ (0.0487 g, 0.217 mmol, 5 mol%), $Al(OTf)_3$ (0.202 g, 0.426 mmol, 10 mol%), PPh_3 (0.224 g, 0.852 mmol, 20 mol%), xylene (0.501 g, 4.72 mmol) and *trans*-stilbene (**4.45**), (0.763 g, 4.24 mmol).



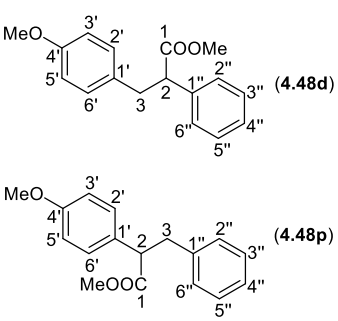
(**4.46**)

Methyl 2,3-diphenylpropanoate (**4.46**)[15] was formed as a yellow oil: GC determined yield 6% (isolated 0.037 g, 4%); purified with FCC utilizing H:DCM:A 6:2:2 (R_f 0.622); Programme A: R_T 29.3 min; ^{1}H NMR (600 MHz, $CDCl_3$, plate 25a): δ_H 7.36-7.34 (2H, m, H-2' and H-6' or H-2'' and H-6''), 7.33-7.3 (2H, m, H-3' and H-5' or H-3'' and H-5''), 7.27-7.24 (1H, m, H-4' or H-4''), 7.24-7.22 (2H, m, H-3' and H-5' or H-3'' and H-5''), 7.20-7.18 (2H, m, H-2' and H-6' or H-2'' and H-6''), 7.17-7.14 (1H, m, H-4' or H-4''), 3.95 (1H, dd, *J* = 8.9 and 6.8 Hz, H-2), 3.55 (3H, s, OMe), 3.37 (1H, dd, *J* = 13.7 and 8.9 Hz, H-3a/b), 3.02 (1H, dd, *J* = 13.7 and 6.8 Hz, H-3a/b); ^{13}C NMR (151 MHz, $CDCl_3$, plate 25b): δ_C 174.2 (C-1), 140.2 (C-1' or C-1''), 140.0 (C-

1' or C-1"), 129.9 (C-Ar), 129.5 (C-Ar), 129.1 (C-Ar), 128.9 (C-Ar), 128.2 (C-Ar), 127.2 (C-Ar), 54.2 (C-2), 52.1 (OMe), 40.5 (C-3); EIMS (70 eV) *m/z* 240 (M^+, 15%).

5.10.2. Methoxycarbonylation of 4-methoxystilbene (4.47)

Performed according to the general procedure (cf. paragraph 5.4.1.), however MeOH:THF (1:1) was used as solvent instead of pure methanol. $Pd(OAc)_2$ (0.0477 g, 0.212 mmol, 5 mol%), $Al(OTf)_3$ (0.202 g, 0.426 mmol, 10 mol%), PPh_3 (0.222 g, 0.846 mmol, 20 mol%), xylene (0.503 g, 4.70 mmol) and 4-methoxystilbene (**4.47**), (0.800 g, 3.81 mmol).

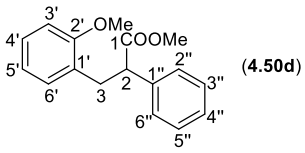


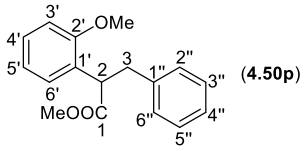
Methyl 3-(4-methoxyphenyl)-2-phenylpropanoate (**4.48d**)[16,17] and methyl 2-(4-methoxyphenyl)-3-phenylpropanoate (**4.48p**)[17] were formed (in a ratio of 1:1) as a light yellow oil: GC determined yield 2% (isolated 0.011 g, 1%); purified with PLC utilizing H:$CHCl_3$:MeOH 6:2:2 (R_f 0.297); Programme A: R_T 33.4 min; ^{1}H NMR (600 MHz, $CDCl_3$, plate 26a): δ_H 7.31-7.29 [2.8H, m, H-Ar, (**4.48d**)], 7.27-7.26 [0.7H, m, H-Ar, (**4.48d**)], 7.24-7.21 [4H, m, H-Ar, (**4.48p**)], 7.18-7.16 [1H, m, H-4" (**4.48p**)], 7.11 [2H, d, *J* = 7.2 Hz, H-2" and H-6" (**4.48p**)], 7.03 [1.4H, d, *J* = 8.5 Hz, H-2' and H-6' (**4.48d**)], 6.84 [2H, d, *J* = 8.6 Hz, H-3' and H-5' (**4.48p**)], 6.77 [1.4H, d, *J* = 8.5 Hz, H-3' and H-5' (**4.48d**)], 3.81-3.79 [1.7H, m, H-2 (**4.48d**) and (**4.48p**)], 3.79 [3H, s, 4'-OMe (**4.48p**)], 3.76 [2.1H, s, 4'-OMe (**4.48d**)], 3.60 [2.1H, s, COOMe (**4.48d**)], 3.60 [3H, s, COOMe (**4.48p**)], 3.38 [1H, dd, *J* = 13.8 and 8.7 Hz, H-3a/b (**4.48p**)], 3.35 [0.7H, dd, *J* = 13.9 and 8.9 Hz, H-3a/b (**4.48d**)], 2.99 [1H, dd, *J* = 13.8 and 6.9 Hz, H-3a/b (**4.48p**)], 2.96 [0.7H, dd, *J* = 13.9 and 6.7 Hz, H-3a/b (**4.48d**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 26b): δ_C 174.1 [C-1 (**4.48p**)], 173.9 [C-1 (**4.48d**)], 158.9 [C-4' (**4.48p**)], 158.1 [C-4' (**4.48d**)], 139.1 [C-1"(**4.48p**)], 138.7 [C-1"(**4.48d**)], 131.1 [C-1'(**4.48d**)], 130.7 [C-1'(**4.48p**)], 129.9 [C-2' and C-6' (**4.48d**)], 129.0, 128.9, 128.6, 128.3, 128.0, 127.4 [C-4"(**4.48d**)], 126.3 [C-4"(**4.48p**)], 114.0 [C-3' and C-5' (**4.48p**)], 113.7 [C-3' and C-5' (**4.48d**)], 55.2 [4'-OMe (**4.48p**)], 55.2 [4'-OMe (**4.48d**)], 53.9 [C-2 (**4.48d**)], 52.7 [C-2 (**4.48p**)], 52.0 [COOMe (**4.48d**) and (**4.48p**)], 39.9 [C-3 (**4.48p**)], 39.0 [C-3 (**4.48d**)]; EIMS (70 eV) *m/z* 270 [M^+, 13% (**4.48d**)], 270 [M^+, 10% (**4.48p**)].

5.10.3. Methoxycarbonylation of 2-methoxystilbene (4.49)

Performed according to the general procedure (cf. paragraph 5.4.1.), however MeOH:THF (1:1) was used as solvent instead of pure methanol. $Pd(OAc)_2$ (0.0477 g, 0.212 mmol, 5

mol%), $Al(OTf)_3$ (0.201 g, 0.424 mmol, 10 mol%), PPh_3 (0.223 g, 0.852 mmol, 20 mol%), xylene (0.501 g, 4.72 mmol) and 2-methoxystilbene (**4.49**), (0.884 g, 4.20 mmol).

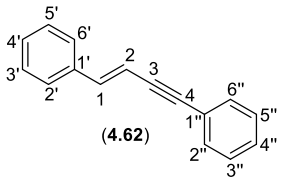




Methyl 3-(2-methoxyphenyl)-2-phenylpropanoate (**4.50d**)[18] and methyl 2-(2-methoxyphenyl)-3-phenylpropanoate (**4.50p**) were formed (in a ratio of 4:1) as a light yellow oil: GC determined yield 4% (isolated 0.020 g, 2%); purified with FCC utilizing H:$CHCl_3$:MeOH 80:14:6 (R_f 0.649); Programme A: R_T 33.2 (**4.50d**) and 33.1 min (**4.50p**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 27a): δ_H 7.30-7.28 [4H, m, H-Ar, (**4.50d**)], 7.24-7.20 [3.5H, m, H-Ar, (**4.50d**) and/or (**4.50p**)], 7.18-7.15 [1.6H, m, H-Ar, (**4.50d**) and/or (**4.50p**)], 7.12-7.11 [1.2H, m, H-Ar, (**4.50d**) and (**4.50p**)], 7.00 [1H, br d, *J* = 7.4 Hz, H-6' (**4.50d**)], 6.92-6.89 [0.6H, m, H-5' (**4.50p**)], 6.85 [0.6H, br d, *J* = 8.1 Hz, H-3' (**4.50p**)], 6.82 [1H, br d, *J* = 8.1 Hz, H-3' (**4.50d**)], 6.79-6.77 [1H, m, H-5' (**4.50d**)], 4.30 [0.6H, dd, *J* = 6.9 and 8.3 Hz, H-2 (**4.50p**)], 3.99 [1H, dd, *J* = 6.4 and 8.7 Hz, H-2 (**4.50d**)], 3.82 [3H, s, 2'-OMe (**4.50d**)], 3.76 [1.8H, s, 2'-OMe (**4.50p**)], 3.60 [1.8H, s, COOMe (**4.50p**)], 3.59 [3H, s, COOMe (**4.50d**)], 3.36-3.33 [1.6H, m, H-3a/b (**4.50d**) and (**4.50p**)], 3.07 [1H, dd, *J* = 13.5 and 6.4 Hz, H-3a/b (**4.50d**)], 2.97 [0.6H, dd, *J* = 13.7 and 6.9 Hz, H-3a/b (**4.50p**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 27b): δ_C 174.3 [C-1 (**4.50p**)], 174.2 [C-1 (**4.50d**)], 157.6 [C-2' (**4.50d**)], 156.7 [C-2' (**4.50p**)], 139.7 [C-1" (**4.50d**) or (**4.50p**)], 139.3 [C-1" (**4.50d**) or (**4.50p**)], 130.8 [C-6' (**4.50d**)], 129.0, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.3, 127.1, 126.1, 120.7 [C-5' (**4.50p**)], 120.2 [C-5' (**4.50d**)], 110.8 [C-3' (**4.50p**)], 110.1 [C-3' (**4.50d**)], 55.6 [2'-OMe (**4.50p**)], 55.2 [2'-OMe (**4.50d**)], 51.9 [COOMe (**4.50d**) and (**4.50p**)], 51.2 [C-2 (**4.50d**)], 46.4 [C-2 (**4.50p**)], 38.7 [C-3 (**4.50p**)], 34.9 [C-3 (**4.50d**)]; EIMS (70 eV) *m/z* 270 [M^+, 9% (**4.50d**)], 270 [M^+, 35% (**4.50p**)].

5.11. Synthesis of (4-methoxyphenyl)phenylacetylene (4.55)

5.11.1. *Trans*-but-1-en-3-yne-1,4-diyldibenzene (4.62)[19]

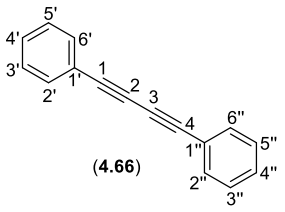


$PdCl_2$ (3.50 mg, 0.0276 mmol, 1.4 mol%) was dissolved in H_2O (2.5 ml) and 4-bromoanisole (**4.61**), (0.25 ml, 2.00 mmol) followed by pyrrolidine (0.82 ml, 9.98 mmol, 5 eq.) was added. The reaction mixture was stirred for 5 minutes at 50 °C, whereafter phenylacetylene (0.28 ml, 2.55 mmol, 1.3 eq.) was added. After 24 h of reaction time, additional aliquots of $PdCl_2$ (5.00 mg, 0.0282 mmol, 1.4 mol%) and phenylacetylene (**2.152**), (0.28 ml, 2.55 mmol, 1.3 eq.) were added. The reaction was stopped after another 24 h of

reaction time and the reaction mixture extracted into EtOAc (3 x 10 ml). The organic layers were combined, washed with brine (3 x 10 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified with PLC (H:T 1:1) to give only *trans*-but-1-en-3-yne-1,4-diyldibenzene (**4.62**) as a yellow solid (0.016 g, 7%); R_f 0.595; ^{1}H NMR (600 MHz, $CDCl_3$, plate 28a): δ_H 7.48-7.46 (2H, m, H-2" and H-6"), 7.42-7.40 (2H, m, H-2' and H-6'), 7.34-7.26 (6H, m, H-3', H-4', H-5', H-3", H-4" and H-5"), 7.03 (1H, d, *J* = 16.2 Hz, H-1), 6.38 (1H, d, *J* = 16.2 Hz, H-2); ^{13}C NMR (151 MHz, $CDCl_3$, plate 28b): δ_C 141.4 (C-1), 136.4 (C-1'), 131.6 (C-2" and C-6"), 128.9 (C-3' and C-5'), 128.8 (C-4'), 128.5 (C-3" and C-5"), 128.3 (C-4"), 126.4 (C-2' and C-6'), 123.5 (C-1"), 108.2 (C-2), 91.9 (C-4), 89.0 (C-3); EIMS (70 eV) *m/z* 204 (M^+, 100%).

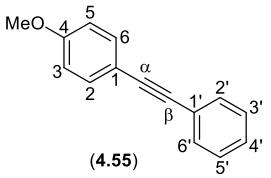
5.11.2. 1,4-Diphenylbutan-1,3-diyne (4.66) and (4-methoxyphenyl)phenylacetylene (4.55)

CuI (0.049 g, 0.255 mmol, 10 mol%), DABCO (0.057 g, 0.505 mmol, 20 mol%), K_2CO_3 (0.699 g, 5.06 mmol, 2 eq.) and 4-iodoanisole (**4.63**), (0.586 g, 2.50 mmol) were dissolved in anhydrous DMF (10 ml). The reaction mixture was stirred for 10 minutes, whereafter phenylacetylene (**2.152**), (0.33 ml, 3.01 mmol, 1.2 eq.) was added and the reaction mixture heated to reflux. After 20 h the workup procedure explained in paragraph 5.8.1. was performed, followed by purification with PLC (H:T:E 97:2:1) to give:



(**4.66**)

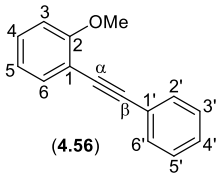
1,4-Diphenylbutan-1,3-diyne (**4.66**)[20] as a white solid (0.139 g, 27%); R_f 0.541; ^{1}H NMR (600 MHz, $CDCl_3$, plate 29a): δ_H 7.57 (4H, d, *J* = 6.9 Hz, H-2', H-6', H-2" and H-6"), 7.37-7.32 (6H, m, H-3', H-4', H-5', H-3", H-4" and H-5"); ^{13}C NMR (151 MHz, $CDCl_3$, plate 29b): δ_C 132.6 (C-2', C-6', C-2" and C-6"), 129.3 (C-4' and C-4"), 128.6 (C-3', C-5', C-3" and C-5"), 121.9 (C-1' and C-1"), 81.7 (C-1 and C-4), 74.1 (C-2 and C-3); EIMS (70 eV) *m/z* 202 (M^+, 100%).



(**4.55**)

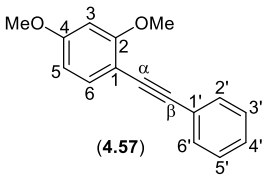
(4-Methoxyphenyl)phenylacetylene (**4.55**)[19] as a yellow solid (0.417 g, 69%); R_f 0.270; ^{1}H NMR (600 MHz, $CDCl_3$, plate 30a): δ_H 7.52-7.50 (2H, m, H-2' and H-6'), 7.47 (2H, br d, *J* = 8.9 Hz, H-2 and H-6), 7.35-7.30 (3H, m, H-3', H-4' and H-5'), 6.87 (2H, br d, *J* = 8.9 Hz, H-3 and H-5), 3.82 (3H, s, OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 30b): δ_C 159.7 (C-4), 133.2 (C-2 and C-6), 131.6 (C-2' and C-6'), 128.4 (C-3' and C-5'), 128.1 (C-4'), 123.7 (C-1'), 115.5 (C-1), 114.1 (C-3 and C-5), 89.5 (C-α), 88.2 (C-β), 55.4 (OMe); EIMS (70 eV) *m/z* 208 (M^+, 100%).

5.12. Synthesis of (2-methoxyphenyl)phenylacetylene (4.56)[21]



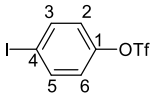
CuI (0.100 g, 0.523 mmol, 10 mol%), DABCO (0.118 g, 1.05 mmol, 20 mol%), K_2CO_3 (1.42 g, 10.3 mmol, 2 eq.) and 2-iodoanisole (**4.64**) (0.67 ml, 5.15 mmol) were dissolved in anhydrous DMF (10 ml). The reaction mixture was heated to 135°C while stirring whereafter phenylacetylene (**2.152**) (0.68 ml, 6.66 mmol, 1.2 eq.) was added in three separate aliquots. The reaction mixture was allowed to reflux for two days, whereafter the workup procedure explained in paragraph 5.8.1. was performed. The crude extract was purified by FCC (H:T:E 97:2:1). The wanted product, (2-methoxyphenyl)phenylacetylene (**4.56**) was obtained as a yellow oil (0.738 g, 69%); R_f 0.216; ^{1}H NMR (600 MHz, $CDCl_3$, plate 31a): δ_H 7.63-7.61 (2H, m, H-2' and H-6'), 7.56 (1H, dd, *J* = 7.5 and 1.6 Hz, H-6), 7.40-7.33 (4H, m, H-4, H-3', H-4' and H-5'), 6.99 (1H, br dd, *J* = 8.0 and 7.5 Hz, H-5), 6.94 (1H, br d, *J* = 8.4 Hz, H-3), 3.94 (3H, s, OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 31b): δ_C 160.0 (C-2), 133.6 (C-6), 131.7 (C-2' and C-6'), 129.9 (C-4), 128.3 (C-3' and C-5'), 128.2 (C-4'), 123.6 (C-1'), 120.6 (C-5), 112.5 (C-1), 110.8 (C-3), 93.5 (C-β), 85.8 (C-α), 55.9 (OMe); EIMS (70 eV) *m/z* 208 (M^+, 100%).

5.13. Synthesis of (2,4-dimethoxyphenyl)phenylacetylene (4.57)[22]



$Pd(PPh_3)_2Cl_2$ (0.065 g, 0.0925 mmol, 0.02 eq.), CuI (0.058 g, 0.305 mmol, 0.06 eq.), 1-iodo-2,4-dimethoxybenzene (**4.65**) (1.19 g, 4.52 mmol), Et_2NH (7.5 ml), DMF (2.5 ml) and phenylacetylene (**2.152**) (0.55 ml, 5.01 mmol, 1.1 eq.) were added together and submitted to microwave irradiation (200 W, 120 °C) for 5 minutes. HCl (50 ml, 0.15 M) was added to the reaction mixture, whereafter the product was extracted into Et_2O (3 x 50 ml). The organic layers were combined, washed with brine (3 x 50 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by PLC (H:DCM 1:1). The desired product, (2,4-dimethoxyphenyl)phenylacetylene (**4.57**) was obtained as a yellow oil (0.904 g, 84%); R_f 0.514; ^{1}H NMR (600 MHz, $CDCl_3$, plate 32a): δ_H 7.54-7.52 (2H, m, H-2' and H-6'), 7.42 (1H, d, *J* = 8.4 Hz, H-6), 7.33-7.27 (3H, m, H-3', H-4' and H-5'), 6.47 (1H, dd, *J* = 8.4 and 2.3 Hz, H-5), 6.45 (1H, d, *J* = 2.3 Hz, H-3), 3.88 (3H, s, OMe), 3.81 (3H, s, OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 32b): δ_C 161.3 (C-2 or C-4), 161.2 (C-2 or C-4), 134.4 (C-6), 131.6 (C-2' and C-6'), 128.3 (C-3' and C-5'), 127.9 (C-4'), 124.0 (C-1'), 105.1 (C-1), 104.9 (C-5), 98.5 (C-3), 92.1 (C-β), 85.9 (C-α), 56.0 (OMe), 55.5 (OMe); EIMS (70 eV) *m/z* 238 (M^+, 100%).

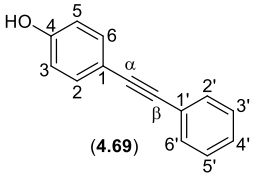
5.14. Synthesis of 4-iodophenyltrifluoromethanesulfonate (4.68)[23]



(**4.68**)

4-Iodophenol (**4.67**) (2.00 g, 9.10 mmol) was dissolved in dry DCM (40 ml) and the reaction mixture was cooled to 0 °C. DMAP (1.34 g, 10.9 mmol, 1.2 eq.) was added and the reaction mixture was stirred for 5 minutes, whereafter triflic anhydride (1.9 ml, 11.29 mmol, 1.2 eq.) was added. The reaction mixture was stirred at 0 °C for 1 h, warmed to room temperature and stirred until completion. Purification was performed by passing the reaction mixture through a short silica column (DCM), whereafter the solvent was removed under vacuum. The desired 4-iodophenyltrifluoromethanesulfonate (**4.68**) was obtained as a colourless oil (3.08 g, 96%); ^{1}H NMR (600 MHz, $CDCl_3$, plate 33a): δ_H 7.77 (2H, d, *J* = 9.0 Hz, H-3 and H-5), 7.03 (2H, d, *J* = 9.0 Hz, H-2 and H-6); ^{13}C NMR (151 MHz, $CDCl_3$, plate 33b): δ_C 149.5 (C-1), 139.5 (C-3 and C-5), 123.5 (C-2 and C-6), 118.8 (q, *J* = 320.9 Hz, CF_3), 93.3 (C-4); ^{19}F NMR (565 MHz, $CDCl_3$): δ_F -75.83; EIMS (70 eV) *m/z* 352 (M^+, 100%).

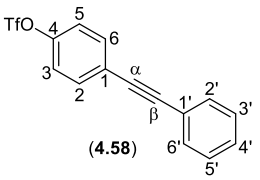
5.15. Synthesis of (4-hydroxyphenyl)phenylacetylene (4.69)[19]



(**4.69**)

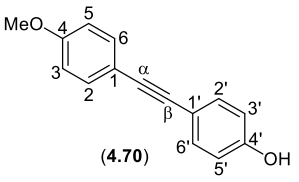
$Pd(PPh_3)_2Cl_2$ (0.085 g, 0.121 mmol, 0.02 eq.), CuI (0.051 g, 0.269 mmol, 0.04 eq.), 4-iodophenol (**4.67**) (1.20 g, 5.43 mmol), Et_2NH (9 ml), DMF (3 ml) and phenylacetylene (**2.152**) (0.66 ml, 6.01 mmol, 1.1 eq.) were added together and submitted to microwave irradiation (200 W, 120 °C) for 5 minutes. HCl (10 ml, 0.15 M) was added to the reaction mixture, whereafter the product was extracted into Et_2O (3 x 10 ml). The organic layers were combined, washed with brine (3 x 10 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified with FCC (H:T:EtOAc, 5:3:2). The desired product, (4-hydroxyphenyl)phenylacetylene (**4.69**) was obtained as a light yellow solid (0.994 g, 94%); R_f 0.432; m.p. 122.6-123.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$, plate 34a): δ_H 7.51-7.50 (2H, m, H-2' and H-6'), 7.41 (2H, d, *J* = 8.4 Hz, H-2 and H-6), 7.34-7.28 (3H, m, H-3', H-4' and H-5'), 6.82 (2H, d, *J* = 8.4 Hz, H-3 and H-5); ^{13}C NMR (151 MHz, $CDCl_3$, plate 34b): δ_C 155.8 (C-4), 133.4 (C-2 and C-6), 131.6 (C-2' and C-6'), 128.5 (C-3' and C-5'), 128.1 (C-4'), 123.6 (C-1 or C-1'), 115.7 (C-1 or C-1'), 115.7 (C-3 and C-5), 89.4 (C-α), 88.2 (C-β); EIMS (70 eV) *m/z* 194 (M^+, 100%).

5.16. Synthesis of (4-trifluoromethanesulfonyloxyphenyl)phenylacetylene (4.58)[21]



(4-Hydroxyphenyl)phenylacetylene (**4.69**) (0.640 g, 3.29 mmol) was dissolved in dry DCM (20 ml) and the reaction mixture was cooled to 0 °C. DMAP (0.493 g, 4.04 mmol, 1.2 eq.) was added and the reaction mixture was stirred for 5 minutes, whereafter triflic anhydride (0.7 ml, 4.16 mmol, 1.2 eq.) was added. The reaction mixture was stirred at 0 °C for 1 h, warmed to room temperature and stirred until completion. Purification was performed by passing the reaction mixture through a short silica column (DCM) whereafter the solvent was removed under vacuum. The desired product, (4-trifluoromethanesulfonyloxyphenyl)phenylacetylene (**4.58**), was obtained as a white solid (1.00 g, 93%); m.p. 61.5-62.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$, plate 35a): δ_H 7.59 (2H, d, *J* = 8.9 Hz, H-2 and H-6), 7.54-7.52 (2H, m, H-2' and H-6'), 7.37-7.35 (3H, m, H-3', H-4' and H-5'), 7.26 (2H, d, *J* = 8.9 Hz, H-3 and H-5); ^{13}C NMR (151 MHz, $CDCl_3$, plate 35b): δ_C 149.1 (C-4), 133.5 (C-2 and C-6), 131.8 (C-2' and C-6'), 129.0 (C-4'), 128.6 (C-3' and C-5'), 124.2 (C-1), 122.7 (C-1'), 121.6 (C-3 and C-5), 118.9 (q, *J* = 320.9 Hz, CF_3), 91.4 (C-β), 87.5 (C-α); ^{19}F NMR (565 MHz, $CDCl_3$, plate 35f): δ_F -75.86; EIMS (70 eV) *m/z* 326 (M^+, 59%).

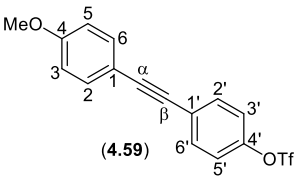
5.17. Synthesis of 4'-hydroxyphenyl-4-methoxyphenylacetylene (4.70)[24]



$Pd(PPh_3)_2Cl_2$ (0.088 g, 0.125 mmol, 0.02 eq.), CuI (0.055 g, 0.290 mmol, 0.05 eq.), 4-iodophenol (**4.67**) (1.21 g, 5.50 mmol), Et_2NH (9 ml), DMF (3 ml) and 4-ethynylanisole (**2.154**) (0.8 ml, 6.17 mmol, 1.1 eq.) were added together and submitted to microwave irradiation (200 W, 120 °C) for 5 minutes. HCl (50 ml, 0.15 M) were added to the reaction mixture whereafter the product was extracted into Et_2O (3 x 50 ml). The organic layers were combined, washed with brine (3 x 50 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by FCC (H:DCM:A, 50:48:2). The desired product, 4'-hydroxyphenyl-4-methoxyphenylacetylene (**4.70**) was obtained as a light yellow solid (1.08 g, 88%); R_f 0.243; m.p. 145.7-147.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$, plate 36a): δ_H 7.43 (2H, br d, *J* = 8.9 Hz, H-2 and H-6), 7.37 (2H, br d, *J* = 8.7 Hz, H-2' and H-6'), 6.94 (2H, br d, *J* = 8.9 Hz, H-3 and H-5), 6.87 (2H, br d, *J* = 8.7 Hz, H-3' and H-5'), 3.82 (3H, s, OMe), 3.16 (1H, br s, OH); ^{13}C NMR (151 MHz, $CDCl_3$, plate 36b): δ_C 160.4 (C-4), 158.4 (C-4'), 133.6 (C-2 and C-6 or C-2' and C-6'), 133.4 (C-2 and C-6 or C-2' and C-6'), 116.4 (C-1

or C-1'), 116.3 (C-3' and C-5'), 115.1 (C-1 or C-1'), 114.8 (C-3 and C-5), 88.8 (C-β), 87.9 (C-α), 55.5 (OMe); EIMS (70 eV) *m/z* 224 (M^+, 100%).

5.18. Synthesis of *4-methoxyphenyl-4'-trifluoromethanesulfonyloxyphenylacetylene (4.59)*

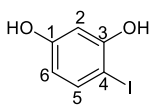


(**4.59**)

4'-Hydroxyphenyl-4-methoxyphenylacetylene (**4.70**) (0.553 g, 2.47 mmol) was dissolved in dry DCM (10 ml) and the reaction mixture was cooled to 0 °C. DMAP (0.369 g, 3.02 mmol, 1.2 eq.) was added and the reaction mixture was stirred for 5 minutes, whereafter triflic anhydride (0.52 ml, 3.09 mmol, 1.2 eq.) dissolved in DCM (7 ml) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, warmed to room temperature and stirred until completion. Purification was performed by passing the reaction mixture through a short silica column (DCM) whereafter the solvent was removed under vacuum. The desired product *4-methoxyphenyl-4'-trifluoromethanesulfonyloxyphenylacetylene (**4.59**)* was obtained as a colourless solid (0.807 g, 92%); m.p. 75.3-76.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$, plate 37a): δ_H 7.57 (2H, d, *J* = 8.9 Hz, H-2' and H-6'), 7.47 (2H, d, *J* = 8.9 Hz, H-2 and H-6), 7.25 (2H, d, *J* = 8.9 Hz, H-3' and H-5'), 6.89 (2H, d, *J* = 8.9 Hz, H-3 and H-5), 3.83 (3H, s, OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 37b): δ_C 160.2 (C-4), 148.8 (C-4'), 133.3 (C-2, C-6, C-2' and C-6'), 124.5 (C-1'), 121.6 (C-3' and C-5'), 118.9 (q, *J* = 321.06 Hz, CF_3), 114.7 (C-1), 114.2 (C-3 and C-5), 91.5 (C-α), 86.3 (C-β), 55.5 (OMe); ^{19}F NMR (565 MHz, $CDCl_3$, plate 37f): δ_F -75.87; HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{16}H_{12}O_4F_3S$, 357.0408; found, 357.0406.

5.19. Synthesis of 4-iodobenzene-1,3-diol (4.71)

Resorcinol (**2.431**) (1.11 g, 10.1 mmol) was dissolved in dry Et_2O (10 ml) and cooled to 0 °C. ICl (1.95 g, 12.0 mmol, 1.2 eq.) was dissolved in dry Et_2O (20 ml) and added dropwise to the reaction mixture over 30 minutes. After 1 h of reaction time the reaction mixture was allowed to warm up to room temperature. After completion Na_2SO_4 (0.216 g, 1.71 mmol, 0.2 eq.) was dissolved in H_2O (20 ml) and added to the reaction mixture. The product was extracted into Et_2O (3 x 50 ml), whereafter the ether fractions were combined, washed with brine (3 x 50 ml) and dried over anhydrous Na_2SO_4. The crude mixture was concentrated under vacuum and purified with FCC ($CHCl_3$:AcOH, 9:1) to obtain the following two products:

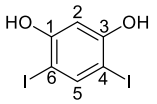


(**4.71**)

4-Iodobenzene-1,3-diol (**4.71**)[25] was isolated as an off-white solid (0.840 g, 35%); R_f 0.270; m.p. 65.6-67.2 °C; ^{1}H NMR [600 MHz, $(CD_3)_2CO$, plate 38a]: δ_H 7.46 (1H, d, *J* = 8.6 Hz, H-5), 6.54 (1H, d, *J* = 2.8 Hz, H-2), 6.27 (1H, dd, *J*

= 8.6 and 2.8 Hz, H-6), 5.13 (2H, br s, 1-OH and 3-OH); ^{13}C NMR [151 MHz, $(CD_3)_2CO$, plate 38b]: δ_C 157.7 (C-1 or C-3), 155.8 (C-1 or C-3), 138.5 (C-5), 110.6 (C-6), 102.8 (C-2), 74.8 (C-4); EIMS (70 eV) *m/z* 236 (M^+, 100%).

4,6-Diiodobenzene-1,3-diol (**4.72**)[26] was isolated as a tan amorphous solid (0.431 g, 12%); R_f 0.351; ^{1}H NMR [600 MHz, $(CD_3)_2CO$, plate 39a]: δ_H 9.22 (2H, br s, 1-OH and 3-OH), 7.91 (1H, s, H-5), 6.68 (1H, s, H-2); ^{13}C NMR [151 MHz, $(CD_3)_2CO$, plate 39b]: δ_C 158.6 (C-1 and C-3), 147.3 (C-5), 103.0 (C-2), 73.1 (C-4 and C-6); EIMS (70 eV) *m/z* 362 (M^+, 100%).



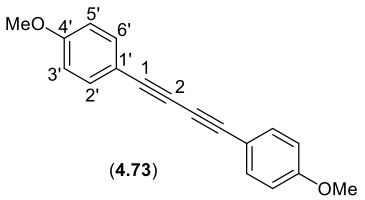
(**4.72**)

5.20. Attempted synthesis of 2,4-dihydroxyphenyl-4'-methoxyphenylacetylene

$Pd(PPh_3)_2Cl_2$ (0.041 g, 0.0581 mmol, 0.02 eq.), CuI (0.035 g, 0.184 mmol, 0.06 eq.), 4-iodobenzene-1,3-diol (**4.71**) (0.659 g, 2.79 mmol), Et_2NH (7.5 ml), DMF (2.5 ml) and 4-ethynylanisole (**2.154**) (0.430 g, 3.25 mmol, 1.2 eq.) were added together and submitted to microwave irradiation (200 W, 120 °C) for 5 minutes. HCl (50 ml, 0.15 M) was added to the reaction mixture, whereafter the product was extracted into Et_2O (3 x 10 ml). The organic layers were combined, washed with brine (3 x 10 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. The only product detected was 1,4-bis(4-methoxyphenyl)but-1,3-diyne (**4.73**).

5.20.1. 1,4-Bis(4-methoxyphenyl)but-1,3-diyne (4.73)[27]

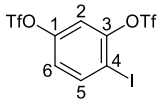
1,4-Bis(4-methoxyphenyl)but-1,3-diyne (**4.73**) was isolated as a brown amorphous solid (0.375 g, 44%); ^{1}H NMR (600 MHz, $CDCl_3$, plate 40a): δ_H 7.46 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 6.85 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 3.81 (3H, s, OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 40b): δ_C 160.4 (C-4'), 134.2 (C-2' and C-6'), 114.3 (C-3' and C-5'), 114.0 (C-1'), 81.4 (C-1), 73.1 (C-2), 55.5 (OMe); EIMS (70 eV) *m/z* 262 (M^+, 100%).



(**4.73**)

5.21. Synthesis of *2,4-Bis(trifluoromethanesulfonyloxy)iodobenzene (4.74)*

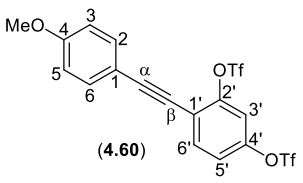
4-Iodobenzene-1,3-diol (**4.71**) (2.01 g, 8.53 mmol) was dissolved in dry DCM (10 ml) and the reaction mixture was cooled to 0 °C. DMAP (2.19 g, 17.9 mmol, 2 eq.) was added and the reaction mixture was stirred for 5 minutes, whereafter triflic anhydride (3.30 ml, 19.6 mmol, 2 eq.) dissolved in DCM (20 ml) was added dropwise. The reaction was deemed complete after 40 minutes. Purification was performed



(**4.74**)

by passing the reaction mixture through a short silica column (DCM), whereafter the solvent was removed under vacuum. The desired product, *2,4-bis(trifluoromethanesulfonyloxy)iodobenzene (**4.74**)*, was obtained as a colourless oil (3.04 g, 71%); ^{1}H NMR (600 MHz, $CDCl_3$, plate 41a): δ_H 8.03 (1H, d, *J* = 8.8 Hz, H-5), 7.29 (1H, d, *J* = 2.7 Hz, H-2), 7.12 (1H, dd, *J* = 8.8 and 2.7 Hz, H-6); ^{13}C NMR (151 MHz, $CDCl_3$, plate 41b): δ_C 150.8 (C-3), 149.6 (C-1), 141.8 (C-5), 122.8 (C-6), 118.8 (q, *J* = 321.18 Hz, 1-OTf and 3-OTf), 116.3 (C-2), 89.2 (C-4); ^{19}F NMR (565 MHz, $CDCl_3$, plate 41f): δ_F -75.51, -76.01; HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_8H_3O_6F_6S_2I$, 499.8320; found, 499.8330.

5.22. Synthesis of *4-methoxyphenyl-2',4'-bis(trifluoromethanesulfonyloxy)phenylacetylene (4.60)*



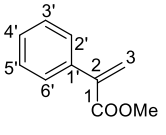
(**4.60**)

$Pd(PPh_3)_2Cl_2$ (0.057 g, 0.0805 mmol, 0.02 eq.), CuI (0.032 g, 0.0.167 mmol, 0.04 eq.), 2,4-bis(trifluoromethanesulfonyloxy)iodobenzene (**4.74**) (2.01 g, 4.01 mmol), Et_2NH (9 ml), DMF (3 ml) and 4-ethynylanisole (**2.154**) (0.6 ml, 4.63 mmol, 1.1 eq.) were added together and submitted to microwave irradiation (200 W, 80 °C) for 5 minutes. HCl (50 ml, 0.15 M) was added to the reaction mixture, whereafter the product was extracted into Et_2O (3 x 50 ml). The organic layers were combined, washed with brine (3 x 50 ml) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by PLC (H:T:Et_2O, 60:38:2). The desired product, *4-methoxyphenyl-2',4'-bis(trifluoromethanesulfonyloxy)phenylacetylene (**4.60**)*, was obtained as an off-white solid (0.388 g, 19%); R_f 0.541; m.p. 65.5-70.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$, plate 42a): δ_H 7.69 (1H, d, *J* = 8.7 Hz, H-6'), 7.53 (2H, d, *J* = 8.8 Hz, H-2 and H-6), 7.32 (1H, dd, *J* = 8.7 and 2.4 Hz, H-5'), 7.26 (1H, d, *J* = 2.4 Hz, H-3'), 6.91 (2H, d, *J* = 8.8 Hz, H-3 and H-5), 3.84 (3H, s, OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 42b): δ_C 160.8 (C-4), 149.5 (C-2'), 148.0 (C-4'), 134.4 (C-6'), 133.7 (C-2 and C-6), 121.6 (C-5'), 119.9 (C-1'), 116.0 (C-3'), 114.4 (C-3 and C-5), 113.7 (C-1), 99.1 (C-α), 80.1 (C-β), 55.5 (OMe); ^{19}F NMR (565 MHz, $CDCl_3$, plate 42f): δ_F -75.50, -76.48; HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{11}O_7F_6S_2$, 504.9850; found, 504.9841.

5.23. Methoxycarbonylation of alkynes

5.23.1. Methoxycarbonylation of phenylacetylene (2.152)

$Pd(OAc)_2$ (0.007 g, 0.0294 mmol, 0.2 mol%), $Al(OTf)_3$ (0.023 g, 0.0477 mmol, 0.4 mol%), BINAP (0.057 g, 0.0907 mmol, 0.8 mol %), xylene (0.302



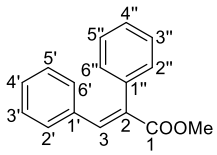
(**3.168b**)

g, 2.85 mmol, 25 mol%) and phenylacetylene (**2.152**), (1.15 g, 11.3 mmol) were added together in the Parr reactor and dissolved in MeOH (6 ml). The reactor was degassed and allowed to heat up to 80 °C, whereafter the pressure was adjusted to 35 bar of CO.

Methyl 2-phenylprop-2-ene (**3.168b**)[28] was formed as a yellow oil: GC determined yield 94% (isolated 0.578 g, 32%); purified with FCC utilizing H:T:A 6:2:2 (R_f 0.622); Programme B: R_T 33.5 min; ^{1}H NMR (600 MHz, $CDCl_3$, plate 43a): δ_H 7.46-7.44 (2H, m, H-Ar), 7.41-7.36 (3H, m, H-Ar), 6.41 (1H, d, *J* = 1.2 Hz, H-3a/b), 5.93 (1H, d, *J* = 1.2 Hz, H-3a/b), 3.86 (3H, s, OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 43b): δ_C 167.4 (C-1), 141.4 (C-1' or C-2), 136.8 (C-1' or C-2), 128.38 (C-Ar), 128.28 (C-Ar), 128.2 (C-Ar), 127.0 (C-3), 52.3 (OMe); EIMS (70 eV) *m/z* 162 (M^+, 57%).

5.23.2. Methoxycarbonylation of diphenylacetylene (3.164)

$Pd(OAc)_2$ (0.007 g, 0.0294 mmol, 1 mol%), $Al(OTf)_3$ (0.025 g, 0.0521 mmol, 2 mol%), BINAP (0.057 g, 0.0912 mmol, 4 mol %), xylene (0.302 g, 2.85 mmol) and diphenylacetylene (**3.164**) (0.400 g, 2.25 mmol) were added together in the Parr reactor and dissolved in MeOH (6 ml). The reactor was degassed and allowed to heat up to 80 °C, whereafter the pressure was adjusted to 35 bar of CO.



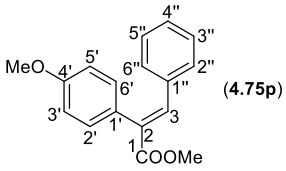
(**3.175**)

(*E*)-methyl 2,3-diphenylprop-2-enoate (**3.175**)[29] was formed as a yellow oil: GC determined yield 94% (isolated 0.243 g, 45%); purified with FCC utilizing H:T:A 6:2:2 (R_f 0.622); Programme B: R_T 31.7 min; ^{1}H NMR (600 MHz, $CDCl_3$, plate 44a): δ_H 7.85 (1H, s, H-3), 7.39-7.34 (3H, m, H-3", H-4" and H-5"), 7.22 (2H, dd, *J* = 7.6 and 1.8 Hz H-2" and H-6"), 7.20 (1H, br d, *J* = 7.3 Hz, H-4'), 7.15 (2H, br dd, *J* = 7.8 and 7.3 Hz, H-3' and H-5'), 7.03 (2H, br d, *J* = 7.6 Hz, H-2' and H-6'), 3.79 (3H, s, OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 44b): δ_C 168.5 (C-1), 140.7 (C-3), 136.0 (C-1"), 134.7 (C-1'), 132.6 (C-2), 130.7 (C-2' and C-6'), 129.9 (C-Ar), 129.2 (C-4'), 128.8 (C-Ar), 128.3 (C-Ar), 128.0 (C-4"), 52.5 (OMe); EIMS (70 eV) *m/z* 238 (M^+, 82%).

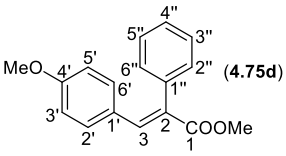
5.23.3. Methoxycarbonylation of (4-methoxyphenyl)phenylacetylene (4.55)

Performed according to the general procedure (cf. paragraph 5.5.). $Pd(OAc)_2$ (0.007 g, 0.031 mmol, 2 mol%), $Al(OTf)_3$ (0.028 g, 0.059 mmol, 4 mol%), BINAP (0.064 g, 0.102 mmol, 8 mol%), xylene (0.501 g, 4.72 mmol) and 4-methoxyphenylphenylacetylene (**4.55**), (0.252 g, 1.21 mmol).

(*E*)-methyl 2-(4-methoxyphenyl)-3-phenylprop-2-enoate (**4.75p**)[30] and (*E*)-methyl 3-(4-methoxyphenyl)-2-phenylprop-2-enoate (**4.75d**)[31] were formed (in a ratio of 1:2) as a yellow oil: GC determined yield 89% (isolated 0.213 g, 66%); purified with FCC utilizing H:T:A 4:4:2 (R_f 0.730); Programme B: R_T 35.4 (**4.75p**) and 34.9 min (**4.75d**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 45a): δ_H 7.81 [1.4H, s, H-3, (**4.75p**) and (**4.75d**)], 7.40-7.36 [1.4H, m, H-Ar, (**4.75p**) and (**4.75d**)], 7.25-7.15 [4.20H, m, H-Ar, (**4.75p**) and (**4.75d**)], 7.14 [2H, d, *J* = 8.6 Hz, H-2' and H-6', (**4.75p**)], 7.07 [2H, br d, *J* = 7.2 Hz, H-2" and H-6", (**4.75p**)], 6.97 [0.8H, d, *J* = 8.9 Hz, H-2' and H-6', (**4.75d**)], 6.90 [2H, d, *J* = 8.6 Hz, H-3' and H-5', (**4.75p**)], 6.67 [0.8H, d, *J* = 8.9 Hz, H-3' and H-5', (**4.75d**)], 3.83 [3H, s, 4'-OMe, (**4.75p**)], 3.79 [3H, s, COOMe, (**4.75p**)], 3.77 [1.2H, s, COOMe, (**4.75d**)], 3.74 [1.2H, s, 4'-OMe, (**4.75d**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 45b): δ_C 168.7 [C-1, (**4.75p**)], 168.6 [C-1, (**4.75d**)], 160.3 [C-4', (**4.75d**)], 159.2 [C-4', (**4.75p**)], 140.3 [C-3, (**4.75d**)], 140.3 [C-3, (**4.75p**)], 136.3, 134.8, 132.4 [C-2' and C-6', (**4.75d**)], 132.0, 131.0 [C-2' and C-6', (**4.75p**)], 130.6 [C-2" and C-6", (**4.75p**)], 129.8, 129.0, 128.8, 128.2 [C-3" and C-5", (**4.75p**)], 127.9, 127.8, 127.2, 114.1 [C-3' and C-5', (**4.75p**)], 113.7 [C-3' and C-5', (**4.75d**)], 55.2 [4'-OMe, (**4.75p**) and (**4.75d**)], 52.5 [COOMe, (**4.75p**)], 52.3 [COOMe, (**4.75d**)]; EIMS (70 eV) *m/z* 268 [M^+, 99% (**4.75p**)], 268 [M^+, 100% (**4.75d**)].



(**4.75p**)

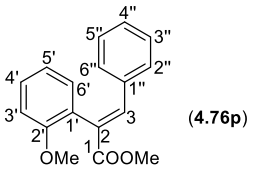


(**4.75d**)

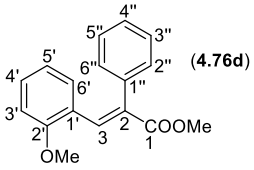
5.23.4. Methoxycarbonylation of (2-methoxyphenyl)phenylacetylene (4.56)

Performed according to the general procedure (cf. paragraph 5.5.). $Pd(OAc)_2$ (0.007 g, 0.033 mmol, 2 mol%), $Al(OTf)_3$ (0.028 g, 0.058 mmol, 4 mol%), BINAP (0.070 g, 0.112 mmol, 8 mol%), xylene (0.502 g, 4.73 mmol) and (2-methoxyphenyl)phenylacetylene (**4.56**), (0.294 g, 1.41 mmol).

(*E*)-methyl 2-(2-methoxyphenyl)-3-phenylprop-2-enoate (**4.76p**)[32] and (*E*)-methyl 3-(2-methoxyphenyl)-2-phenylprop-2-enoate (**4.76d**)[32] were formed (in a ratio of 1:2) as a yellow oil: GC determined yield 89% (isolated 0.227 g, 60%); purified with FCC utilizing H:T:A 4:4:2 (R_f 0.676); Programme B: R_T 34.1 (**4.76p**) and 33.4 min (**4.76d**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 46a): δ_H 8.16 [0.4H, s, H-3, (**4.76d**)], 7.83 [1H, s, H-3, (**4.76p**)], 7.37-7.34 [1H, m, H-4', (**4.76p**)], 7.33-7.29 [1.4H, m, H-Ar, (**4.76p**) and (**4.76d**)], 7.21-7.14 [4H, m, H-Ar, (**4.76p**) and (**4.76d**)], 7.08 [2H, br d, *J* =



(**4.76p**)

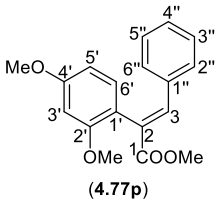


(**4.76d**)

7.3 Hz, H-2'' and H-6'', (**4.76p**)], 7.05 [1H, dd, *J* = 7.4 and 1.7 Hz, H-6', (**4.76p**)], 6.96 [1H, d, *J* = 7.0 Hz, H-3', (**4.76p**)], 6.92 [1H, td, *J* = 7.4 and 1.0 Hz, H-5', (**4.76p**)], 6.84 [0.4H, d, *J* = 8.3 Hz, H-3', (**4.76d**)], 6.67 [0.4H, dd, *J* = 7.7 and 1.6 Hz, H-6', (**4.76d**)], 6.57 [0.4H, t, *J* = 7.7 Hz, H-5', (**4.76d**)], 3.86 [1.2H, s, 2'-OMe, (**4.76d**)], 3.80 [1.2H, s, COOMe, (**4.76d**)], 3.77 [3H, s, COOMe, (**4.76p**)], 3.74 [3H, s, 2'-OMe, (**4.76p**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 46b): δ_C 168.7 [C-1, (**4.76p**)], 168.6 [C-1, (**4.76d**)], 158.4 [C-2', (**4.76d**)], 157.6 [C-2', (**4.76p**)], 140.6 [C-3, (**4.76p**)], 136.1, 135.7 [C-3, (**4.76d**)], 135.0, 132.4, 130.9, 130.7, 130.3, 130.1, 129.72, 129.65, 129.0, 128.5, 128.3, 127.7, 125.3 [C-1', (**4.76p**)], 123.9 [C-1', (**4.76d**)], 121.1 [C-5', (**4.76p**)], 120.0 [C-5', (**4.76d**)], 111.3 [C-3', (**4.76p**)], 110.6 [C-3', (**4.76d**)], 55.8 [COOMe, (**4.76p**)], 55.6 [COOMe, (**4.76d**)], 52.4 [2'-OMe, (**4.76p**) and (**4.76d**)]; EIMS (70 eV) *m/z* 268 [M^+, 100% (**4.76p**)], 268 [M^+, 100% (**4.76d**)].

5.23.5. Methoxycarbonylation of (2,4-dimethoxyphenyl)phenylacetylene (4.57)

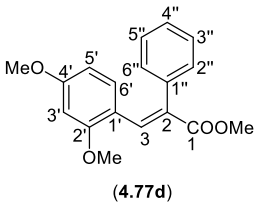
Performed according to the general procedure (cf. paragraph 5.5.). $Pd(OAc)_2$ (0.007 g, 0.032 mmol, 2 mol%), $Al(OTf)_3$ (0.028 g, 0.059 mmol, 4 mol%), BINAP (0.074 g, 0.118 mmol, 8 mol%), xylene (0.502 g, 4.72 mmol) and 2,4-dimethoxyphenylphenylacetylene (**4.57**), (0.364 g, 1.53 mmol). The crude mixture was purified with PLC and 2,4-dimethoxydioxybenzoin (**4.85**), methyl 2-(2',4'-dimethoxyphenyl)-3-phenylprop-2-enoate (**4.77p**) and methyl 3-(2',4'-dimethoxyphenyl)-2-phenylprop-2-enoate (**4.77d**) were obtained in a ratio of 10:7:1; GC determined yield 77%.



(**4.77p**)

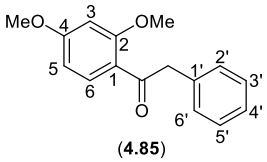
(*E*)-methyl 2-(2',4'-dimethoxyphenyl)-3-phenylprop-2-enoate (**4.77p**)[34] was isolated as a light yellow oil (0.071 g, 16%), R_f 0.338 (H:T:EtOAc 5:4:1); Programme C: R_T 30.3 min; ^{1}H NMR (600 MHz, $CDCl_3$, plate 47a): δ_H 7.79 (1H, s, H-3), 7.19-7.15 (3H, m, H-3'', H-4'' and H-5''), 7.12-7.10 (2H, m, H-2'' and H-6''), 6.95 (1H, d, *J* = 8.3 Hz, H-6'), 6.53 (1H, d, *J* = 2.4 Hz, H-3'), 6.46 (1H, dd, *J* = 8.3 and 2.4 Hz, H-5'), 3.83 (3H, s, 4'-OMe), 3.76 (3H, s, COOMe), 3.70 (3H, s, 2'-OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 47b): δ_C 168.9 (C-1), 161.1 (C-4'), 158.6 (C-2'), 140.4 (C-3), 135.2 (C-1''), 131.3 (C-6'), 130.3 (C-2'' and C-6''), 128.9 (C-2), 128.2 (C-3'', C-4'' and C-5''), 117.8 (C-1'), 104.9 (C-5'), 99.1 (C-3'), 55.7 (2'-OMe or 4'-OMe), 55.4 (2'-OMe or 4'-OMe), 52.4 (COOMe)[a]; EIMS (70 eV) *m/z* 298 (M^+, 100%). [a]Spectrum contaminated with 2,4-dimethoxydeoxybenzoin (**4.85**): see plate 49.

(*E*)-methyl 3-(2',4'-dimethoxyphenyl)-2-phenylprop-2-enoate (**4.77d**)[35] was isolated as a light yellow solid (0.001 g, 0.2%); R_f 0.405 (H:T:EtOAc 5:4:1); Programme C: R_T 31.6 min; ^{1}H NMR (600 MHz, $CDCl_3$, plate 48a): δ_H 8.15 (1H, s, H-3), 7.36-7.31 [3H, m, H-3", H-4" and H-5"), 7.23-7.21 (2H, m, H-2" and H-6"), 6.59 (1H, d, *J* = 8.8 Hz, H-6'), 6.39 (1H, d, *J* = 2.4 Hz, H-3'), 6.12 (1H, dd, *J* = 8.8 and 2.4 Hz, H-5'), 3.85 (3H, s, 2'-OMe), 3.78 (3H, s, COOMe), 3.74 (3H, s, 4'-OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 48b): δ_C 168.9 (C-1), 161.9 (C-4'), 159.9 (C-2'), 136.8 (C-1"), 135.1 (C-3), 131.7 (C-6'), 130.2 (C-2" and C-6"), 130.0 (C-2), 128.6 (C-3' and C-5"), 127.6 (C-4"), 116.7 (C-1'), 104.5 (C-5'), 98.1 (C-3'), 55.7 (2'-OMe or 4'-OMe), 52.3 (COOMe); EIMS (70 eV) *m/z* 298 (M^+, 100%).



(**4.77d**)

2,4-Dimethoxydeoxybenzoin (**4.85**)[33] was isolated as a light yellow solid (0.102 g, 26%), m.p. 47.5-48.1 °C; R_f 0.270 (H:A 8:2); Programme C: R_T 29.4 min; ^{1}H NMR (600 MHz, $CDCl_3$, plate 49a): δ_H 7.81 (1H, d, *J* = 8.7 Hz, H-6), 7.30-7.27 (2H, m, H-3' and H-5'), 7.22-7.19 (3H, m, H-2', H-4' and H-6'), 6.50 (1H, dd, *J* = 8.7 and 2.3 Hz, H-5), 6.43 (1H, d, *J* = 2.3 Hz, H-3), 4.27 (2H, s, CH_2), 3.87 (3H, s, 2-OMe), 3.82 (3H, s, 4-OMe); ^{13}C NMR (151 MHz, $CDCl_3$, plate 49b): δ_C 197.8 (C-1), 164.6 (C-4), 160.8 (C-2), 135.8 (C-1'), 133.2 (C-6), 129.7 (C-2' and C-6'), 128.4 (C-3' and C-5'), 126.5 (C-4'), 120.9 (C-1), 105.3 (C-5), 98.4 (C-3), 55.6 (2-OMe or 4-OMe), 55.5 (2-OMe or 4-OMe), 50.1 (CH_2); EIMS (70 eV) *m/z* 256 (M^+, 1%).

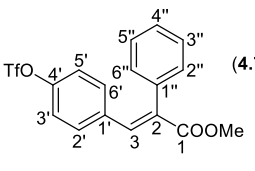


(**4.85**)

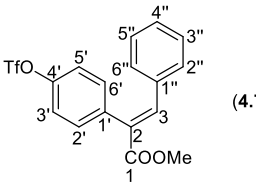
5.23.6. Methoxycarbonylation of (4-trifluoromethanesulfonyloxyphenyl)phenylacetylene (4.58)

Performed according to the general procedure (cf. paragraph 5.5.). $Pd(OAc)_2$ (0.01 g, 0.044 mmol, 2 mol%), $Al(OTf)_3$ (0.027 g, 0.058 mmol, 4 mol%), BINAP (0.073 g, 0.117 mmol, 8 mol%), xylene (0.499 g, 4.70 mmol) and 4-trifluoromethanesulfonyloxyphenylphenylacetylene (**4.58**), (0.465 g, 1.43 mmol).

(E)-methyl 2-phenyl-3-(4'-trifluoromethanesulfonyloxyphenyl)prop-2-enoate (**4.78d**) and *(E)-methyl 3-phenyl-2-(4'-trifluoromethane-sulfonyloxyphenyl)prop-2-enoate* (**4.78p**) were formed (in a ratio of 1:1) as an off-white solid: GC determined yield 71% (isolated 0.117 g, 21%); m.p. 60.0-61.2 °C; purified with FCC utilizing H:T:Et_2O 4:4:2 (R_f 0.703); Programme C: R_T 27.3 (**4.78d**) and 27.6 min (**4.78p**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 50a): δ_H 7.92 [1H, s, H-3, (**4.78p**)], 7.81 [1H, s, H-3, (**4.78d**)], 7.39-7.37 [3H, m, H-Ar, (**4.78d**) and (**4.78p**)], 7.31 [2H,



(**4.78d**)

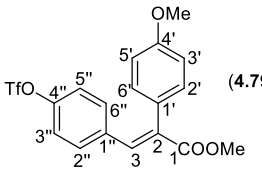


(**4.78p**)

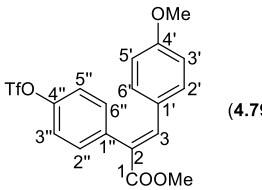
d, *J* = 8.9 Hz, H-2' and H-6', (**4.78p**)], 7.28 [2H, d, *J* = 8.9 Hz, H-3' and H-5', (**4.78p**)], 7.24-7.21 [1H, m, H-4", (**4.78p**)], 7.20-7.16 [4H, m, H-Ar, (**4.78d**) and (**4.78p**)], 7.10 [2H, d, *J* = 8.9 Hz, H-2' and H-6', (**4.78d**)], 7.06 [2H, d, *J* = 8.9 Hz, H-3' and H-5', (**4.78d**)], 6.98 [2H, d, *J* = 7.3 Hz, H-2" and H-6", (**4.78p**)], 3.81 [3H, s, OMe, (**4.78p**)], 3.79 [3H, s, OMe, (**4.78d**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 50b): δ_C 167.9 [C-1, (**4.78d**)], 167.6 [C-1, (**4.78p**)], 149.4 [C-4', (**4.78d**) or (**4.78p**)], 149.1 [C-4', (**4.78d**) or (**4.78p**)], 141.9 [C-3, (**4.78p**)], 138.1 [C-3, (**4.78d**)], 136.5 [C-1', (**4.78p**)], 135.13, 135.10 [C-1', (**4.78d**)], 134.4, 134.1, 132.4 [C-2' and C-6', (**4.78d**)], 132.1 [C-2' and C-6', (**4.78p**)], 130.7, 130.6 [C-2" and C-6", (**4.78p**)], 129.61, 129.59, 129.0, 128.5, 128.4, 121.7 [C-3' and C-5', (**4.78p**)], 121.3 [C-3' and C-5', (**4.78d**)], 118.8 [q, *J* = 321.1 Hz, CF_3, (**4.78p**)], 118.8 [q, *J* = 320.60 Hz, CF_3, (**4.78d**)], 52.7 [OMe, (**4.78p**)], 52.6 [OMe, (**4.78d**)]; ^{19}F NMR (565 MHz, $CDCl_3$, plate 50f): δ_F -75.82, -76.00; HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{14}O_5F_3S$, 387.0514; found, 387.0507.

5.23.7. Methoxycarbonylation of 4-methoxyphenyl-4'-trifluoromethanesulfonyloxy-phenyl-acetylene (4.59)

Performed according to the general procedure (cf. paragraph 5.5.). $Pd(OAc)_2$ (0.007 g, 0.031 mmol, 2 mol%), $Al(OTf)_3$ (0.028 g, 0.058 mmol, 4 mol%), BINAP (0.071 g, 0.115 mmol, 8 mol%), xylene (0.504 g, 4.75 mmol) and 4-methoxyphenyl-4'-trifluoromethanesulfonyloxyphenylacetylene (**4.59**) (0.503 g, 1.41 mmol).



(**4.79p**)



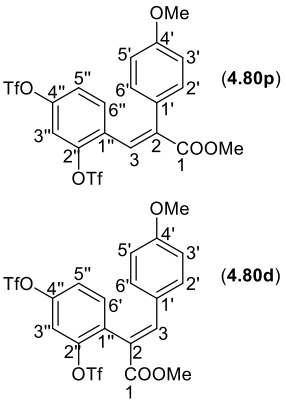
(**4.79d**)

(E)-methyl 2-(4'-methoxyphenyl)-3-(4''-trifluoromethanesulfonyloxy-phenyl)prop-2-enoate (**4.79p**) and *(E)-methyl 3-(4'-methoxyphenyl)-2-(4''-trifluoromethanesulfonyloxyphenyl)prop-2-enoate* (**4.79d**) were formed (in a ratio of 3:1) as a light yellow oil: GC determined yield 71% (isolated 0.057 g, 10%); purified with CC utilizing H:EtOAc 92:8 (R_f 0.135); Programme D: R_T 46.3 (**4.79p**) and 46.7 min (**4.79d**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 51a): δ_H 7.86 [0.3H, s, H-3, (**4.79d**)], 7.77 [1H, s, H-3, (**4.79p**)], 7.33-7.29 [1.2H, m, H-2", H-3", H-5" and H-6", (**4.79d**)], 7.14 [2H, d, *J* = 8.9 Hz, H-2" and H-6", (**4.79p**)], 7.11 [2H, d, *J* = 8.7 Hz, H-2' and H-6', (**4.79p**)], 7.08 [2H, d, *J* = 8.9 Hz, H-3" and H-5", (**4.79p**)], 6.93 [0.6H, d, *J* = 8.9 Hz, H-2' and H-6', (**4.79d**)], 6.91 [2H, d, *J* = 8.7 Hz, H-3' and H-5', (**4.79p**)], 6.69 [0.6H, d, *J* = 8.9 Hz, H-3' and H-5', (**4.79d**)], 3.82 [3H, s, 4'-OMe, (**4.79p**)], 3.79 [3H, s, COOMe, (**4.79p**)], 3.78 [0.9H, s, COOMe, (**4.79d**)], 3.74 [0.9H, s, 4'-OMe, (**4.79d**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 51b): δ_C 168.1 [C-1, (**4.79p**)], 167.8 [C-1, (**4.79d**)], 160.7 [C-4', (**4.79d**)], 159.6

[C-4', (**4.79p**)], 149.2 [C-4", (**4.79p**)], 149.0 [C-4", (**4.79d**)], 141.5 [C-3, (**4.79d**)], 137.7 [C-3, (**4.79p**)], 137.0, 135.4, 134.0, 132.4 [C-2' and C-6', (**4.79d**)], 132.3 [C-2' and C-6', (**4.79p**)], 132.1 [C-Ar, (**4.79d**)], 130.9 [C-2" and C-6", (**4.79p**)], 128.1, 127.0, 126.4, 121.7 [C-Ar, (**4.79d**)], 121.2 [C-3" and C-5", (**4.79p**)], 114.4 [C-3' and C-5', (**4.79p**)], 113.9 [C-3' and C-5', (**4.79d**)], 118.8 [q, J = 321.0 Hz, CF_3, (**B**)], 118.8 [q, J = 320.8 Hz, CF_3, (**4.79p**)], 55.23 [4'-OMe, (**4.79d**)], 55.19 [4'-OMe, (**4.79p**)], 52.5 [COOMe, (**4.79p**)], 52.4 [COOMe, (**4.79d**)]; ^{19}F NMR (565 MHz, $CDCl_3$, plate 51f): δ_F -75.86 (**4.79d**), -76.01 (**4.79p**); HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{18}H_{16}O_6F_3S$, 417.0620; found, 417.0617.

5.23.8. Methoxycarbonylation of 4-methoxyphenyl-2',4'-bis(trifluoromethanesulfonyloxy)phenylacetylene (4.60)

Performed according to the general procedure (cf. paragraph 5.5.). $Pd(OAc)_2$ (0.005 g, 0.020 mmol, 2 mol%), $Al(OTf)_3$ (0.013 g, 0.026 mmol, 4 mol%), BINAP (0.033 g, 0.053 mmol, 8 mol%), xylene (0.501 g, 4.72 mmol) and 4-methoxyphenyl-2',4'-bis(trifluoromethanesulfonyloxy)phenylacetylene (**4.60**), (0.328 g, 0.650 mmol).



(E)-methyl 2-(4'-methoxyphenyl)-3-[bis(2'',4''-trifluoromethanesulfonyloxy)phenyl]prop-2-enoate (**4.80p**) and *(E)-methyl 3-(4'-methoxyphenyl)-2-[bis(2'',4''-trifluoromethanesulfonyloxy)phenyl]-prop-2-enoate* (**4.80d**) were formed (in a ratio of 18:1) as a light yellow solid: GC determined yield 72% (isolated 0.175 g, 65%); purified by FCC utilizing H:EtOAc 9:1 (R_f 0.176); m.p. 68.8-73.0 °C; Programme D: R_T 45.9 (**4.80p**) and 46.4 min (**4.80d**); ^{1}H NMR (600 MHz, $CDCl_3$, plate 52a): δ_H 8.02 [0.4H, s, H-3, (**4.80d**)], 7.78 [1H, s, H-3, (**4.80p**)], 7.45 [0.4H, d, J = 8.6 Hz, H-6", (**4.80d**)], 7.35 [0.4H, dd, J = 8.6 and 2.4 Hz, H-5", (**4.80d**)], 7.33 [0.4H, d, J = 2.4 Hz, H-3", (**4.80d**)], 7.23 [1H, d, J = 2.3 Hz, H-3", (**4.80p**)], 7.10 [2H, d, J = 8.8 Hz, H-2' and H-6', (**4.80p**)], 7.03 [1H, dd, J = 8.9 and 2.3 Hz, H-5", (**4.80p**)], 7.00 [1H, d, J = 8.9 Hz, H-6", (**4.80p**)], 6.97 [0.8H, d, J = 8.8 Hz, H-2' and H-6', (**4.80d**)], 6.86 [2H, d, J = 8.8 Hz, H-3' and H-5', (**4.80p**)], 6.74 [0.8H, d, J = 8.8 Hz, H-3' and H-5', (**4.80d**)], 3.86 [3H, s, COOMe, (**4.80p**)], 3.82 [3H, s, 4'-OMe, (**4.80p**)], 3.80 [1.2H, s, 4'-OMe, (**4.80d**)], 3.79 [1.2H, s, COOMe, (**4.80d**)]; ^{13}C NMR (151 MHz, $CDCl_3$, plate 52b): δ_C 167.3 [C-1, (**4.80p**)], 166.4 [C-1, (**4.80d**)], 161.6 [C-4', (**4.80d**)], 160.2 [C-4', (**4.80p**)], 149.1 [C-4", (**4.80d**)], 148.8 [C-4", (**4.80p**)], 147.8 [C-2", (**4.80p**) and (**4.80d**)], 144.6 [C-3, (**4.80d**)], 138.2 [C-2, (**4.80p**)], 134.3 [C-6", (**4.80d**)], 132.9 [C-6", (**4.80p**)], 132.4 [C-2' and

C-6', (**4.80d**)], 131.33 [C-1", (**4.80d**)], 131.26 [C-2' and C-6', (**4.80p**)], 130.3 [C-1", (**4.80p**)], 129.4 [C-3, (**4.80p**)], 126.2 [C-1', (**4.80p**)], 126.1 [C-1', (**4.80d**)], 121.7 [C-5", (**4.80d**)], 121.1 [C-5", (**4.80p**)], 116.0 [C-3", (**4.80d**)], 115.9 [C-3", (**4.80p**)], 114.5 [C-3' and C-5', (**4.80p**)], 114.4 [C-3' and C-5', (**4.80d**)], 118.9 [q, J = 321.0 Hz, CF_3, (**4.80p**) and (**4.80d**)], 55.5 [4'-OMe, (**4.80d**)], 55.4 [4'-OMe, (**4.80p**)], 52.8 [COOMe, (**4.80p**)], 52.6 [COOMe, (**4.80d**)]; ^{19}F NMR (565 MHz, $CDCl_3$): δ_F -75.75 (**4.80p**), -75.53 (**4.80d**), -76.51 (**4.80d**); HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{19}H_{15}O_9F_6S_2$, 565.0062; found, 565.0067.

5.24. References

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