



Domino reactions. Asymmetric palladium(II)-catalyzed cyclizations-carbonylations in the synthesis of natural compounds

Jana Dohanosova

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**UNIVERSITE PARIS-SUD 11
U.F.R SCIENTIFIQUE D'ORSAY
and
SLOVAK UNIVERSITY OF TECHNOLOGY
IN BRATISLAVA**

A dissertation submitted for the degree of :

**DOCTOR OF PHILOSOPHY
AT UNIVERSITE PARIS-SUD 11 D'ORSAY**

by

Jana DOHÁŇŠOVÁ

**DOMINO REACTIONS. ASYMMETRIC PALLADIUM(II)-
CATALYZED CYCLIZATIONS-CARBONYLATIONS IN
THE SYNTHESIS OF NATURAL COMPOUNDS**

Defended on 11th of May 2012 in front of the examining committee:

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ABBREVIATIONS

Ac	acetyl
AcOH	acetic acid
Ar	aryl
b	broad
b.p.	boiling point
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
box	bis(oxazoline)
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
c	concentration
calcd.	calculated
cat.	catalyst, catalytic
Cbz	benzyloxycarbonyl
CCD	charge coupled device
config.	configuration
conv.	conversion
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet or day(s)
DACH	1,2-diaminocyclohexane
dba	dibenzylideneacetone
DCM	dichloromethane
dd	doublet of doublets
DIBAL	diisobutyl aluminium hydride
DME	dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
dt	doublet of triplets
ee	enantiomeric excess
EI	electron impact, electron ionization
eq	equation
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
EWG	electron withdrawing group
Fe(Pc)	iron phthalocyanine
FID	flame ionization detector
FLC	flash liquid chromatography
GC	gas chromatography
h	hour(s)
Hex	hexane
HQ	hydroquinone
HRMS	high-resolution mass spectroscopy
id	inner diameter
IL	ionic liquid
ⁱPr	<i>iso</i> -propyl

IR	infra red (spectroscopy)
isol.	isolated
IUCr	International Union of Crystallography
J	coupling constant
L	ligand
LDA	lithium diisopropylamide
M	mol/L
m.p.	melting point
Me	methyl
MS	molecular sieves
Ms	mesyl, methanesulfonyl
MW	microwave or molecular weight
Naph	naphthyl
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
OMe	methoxy
ORTEP	oak ridge thermal ellipsoid plot
OS	operation system
OTf	triflate, trifluoromethanesulfonate
P, PG	protecting group
<i>p</i>-BQ	<i>p</i> -benzoquinone
Ph	phenyl
ppm	parts per million
Pr	propyl
PTSA	<i>p</i> -toluenesulfonic acid
q	quartet
qi	quintet
R	alkyl
<i>R_f</i>	retention factor
ref	reflux
rt	room temperature
s	singlet
sat.	saturated
SFC	supercritical fluid chromatography
sx	sextet
t	triplet
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
^tBu	<i>tert</i> -butyl
TCQN	tetracyanoquinodimethane
temp.	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Tol	tolyl
Ts	tosyl, <i>p</i> -toluenesulfonyl
vol.	volume
y.	yield

ABSTRACT

Intramolecular Wacker-type cyclization of unsaturated polyols and aminopolyols represents a powerful method in the synthesis of oxygen- or nitrogen-containing heterocycles.

The thesis offers an insight into the systematic study of domino intramolecular palladium(II)-catalyzed cyclization and coupling reaction allowing the implementation of side chains into heterocyclic skeletons along with the formation of two stereocenters in a single step. Different types of coupling partners and reaction conditions were examined, the influence of substrate substituents on diastereoselectivity is discussed. The applications in the synthesis of naturally occurring compounds or their analogs are outlined (anisomycin, varitriol).

Palladium(II)-catalyzed oxycarbonylation represents an interesting transformation of unsaturated polyols into bicyclic lactones with tetrahydrofuran structural motif with excellent *cis*-stereoselectivity.

The first example of the use of ionic liquids as reaction media in the asymmetric Pd(II)-catalyzed oxycarbonylation is described. Based on a ligand screening, the chiral bis(oxazoline)-type ligands were successfully used in the Pd(II)-promoted bicyclisation of racemic pent-4-ene-1,3-diol (\pm)-**69a**. The kinetic resolution of (\pm)-**69a** in the presence of chiral catalyst and *p*-benzoquinone under carbon monoxide atmosphere using acetic acid and/or ionic liquid as solvent afforded enantioenriched 2,6-dioxabicyclo[3.3.0]octane-3-ones (*R,R*)-**70a** (57% ee) and (*S,S*)-**70a** (80% ee), respectively.

Key words: Wacker-type cyclization, coupling reaction, oxycarbonylation reaction, bis(oxazoline) ligands, ionic liquids.

PREHLAD

Intramolekulové cyklizácie nenasýtených polyolov a aminopolyolov Wackerovho typu predstavujú významnú metódu prípravy kyslíkatých a dusíkatých heterocyklov.

Predložená dizertačná práca poskytuje nahliadnutie do problematiky domino intramolekulových paládium(II)-katalyzovaných cyklizácií a couplingových reakcií, umožňujúcich zavedenie postranných reťazcov na heterocyklické skelety a tvorbu dvoch stereogénnych centier v rámci jednej syntetickej operácie. Počas systematickej štúdie uvedených domino reakcií boli testované rôzne typy couplingových partnerov a reakčných podmienok, sledoval sa vplyv substituentov substrátu na diastereoselektivitu. Za účelom aplikácie uvedenej stratégie v syntéze prírodných látok a ich analógov bola navrhnutá a realizovaná syntéza vedúca k (-)-anisomycínu, zároveň tiež boli pripravené analógy varitriolu.

Paládium(II)-katalyzované oxykarbonylácie sú považované za jedny z najvýznamnejších reakcií nenasýtených polyolov vedúcich k bicyklickým laktómom obsahujúcim tetrahydrofuránový skelet. Tieto synteticky zaujímavé prekursor prírodných látok vznikajú s excelentnou *cis*-stereoselektivitou.

V predkladanej práci sú popísané vôbec prvé príklady využitia iónových kvapalín v asymetrických paládium(II)-katalyzovaných oxykarbonylačných bicyklizáciách. Na základe rozsiahleho skríningu ligandov sa zistilo, že chirálne Pd(II)-bis(oxazolínové) komplexy účinne katalyzujú bicyklizáciu pent-4-én-1,3-diolu (\pm)-**69a**. Kinetické štiepenie racemického diolu (\pm)-**69a** poskytlo v prítomnosti chirálneho katalyzátora, *p*-benzochinónu a oxidu uhoľnatého v kyseline octovej resp. iónovej kvapaline enantiomérne obohatené 2,6-dioxabicyklo-[3.3.0]oktan-3-óny (*R,R*)-**70a** (57% ee) a (*S,S*)-**70a** (80% ee).

Kľúčové slová: cyklizácia Wackerovho typu, kapling, oxykarbonylácia, bis(oxazolínové) ligandy, iónové kvapaliny.

RÉSUMÉ

La réaction de cyclisation de type Wacker, de composés polyols et aminopolyols insaturés constitue un outil puissant et efficace pour la synthèse d'hétérocycles oxygénés ou azotés.

Dans ce travail de thèse, nous proposons l'étude d'une réaction catalysée par un complexe de palladium(II) de type domino-cyclisation, mettant en jeu une réaction de couplage. Cette séquence catalytique revient à une fonctionnalisation d'un hétérocycle par une chaîne latérale, tout en créant deux centres stéréogènes en une seule étape. L'influence de la nature des réactifs mis en jeu, ainsi que des conditions expérimentales sur l'activité et la diastéréosélectivité de la réaction sont discutées. Les applications vers la synthèse de produits naturels (anisomycine) ou d'analogues (varitriol) sont présentées.

La réaction d'oxycarbonylation catalysée par un complexes de palladium(II) est une transformation intéressante de polyols insaturés en lactones bicycliques, présentant un motif de type tétrahydrofurane avec une excellente stéréosélectivité-*cis*.

Le premier exemple de réaction d'oxycarbonylation catalysée par des complexes de palladium chiraux dans les liquides ioniques est décrit. Une étude approfondie de la nature des ligands démontre que les bis(oxazolines) chirales constituent les meilleurs ligands du palladium pour la cyclisation du pent-4-ène-1,3-diol racémique **69a**. Le dédoublement cinétique du composé **69a** sous atmosphère de monoxyde de carbone, en présence d'un complexe chiral de palladium(II) et de *p*-benzoquinone employant l'acide acétique ou le liquide ionique [bmim]NTf₂ comme solvant, a permis d'isoler le 2,6-dioxabicyclo-[3.3.0]octane-3-ones avec jusqu'à 57% d'excès énantiomérique pour l'énantiomère de configuration (*R,R*)-**70a**, et jusqu'à 80% d'excès énantiomérique pour l'énantiomère de configuration (*S,S*)-**70a**.

Mots clés: Cyclisation de type Wacker, réaction de couplage, réaction d'oxycarbonylation, ligands bis(oxazoline), liquides ioniques.

1. INTRODUCTION

One of the fundamental objectives of organic synthesis is the construction of complex molecules from simpler ones. As the complexity of target molecules has increased considerably, the usual stepwise formation of the individual bonds became insufficient and ineffective. For this reason it has been necessary to develop much more efficient transformations allowing construction of several bonds in one sequence without isolating the intermediates, changing the reaction conditions or adding reagents. It is obvious that such domino reactions could minimize the amount of waste and lead to ecologically and economically favorable production.

The usefulness of a domino reaction is correlated firstly to the number of bonds which are formed in one sequence, i. e. bond-forming efficiency, secondly to the increase in structural complexity and thirdly, to its suitability for a general application.

Palladium-catalyzed transformations have seen a fascinating development in recent years.¹ Moreover, a breakthrough has been achieved with the expansion of asymmetric palladium catalysis.^{1c,1d} Soon after the discovery of the Wacker process^{2,3}, a number of research groups demonstrated that Pd^{II} complexes can facilitate the addition of several different nucleophiles to alkenes, and a variety of oxidative and non-oxidative C–O, C–N and C–C bond-forming transformations has been developed, including intra- and intermolecular reactions. The σ -alkyl-Pd^{II} intermediate formed in nucleopalladation reaction step can participate in a number of subsequent transformations. The opportunities of such palladium(II)-catalyzed domino bisfunctionalizations of unsaturated C–C bonds, together with the broad functional-group compatibility and air- and moisture-tolerance of Pd^{II} catalysts, enable the preparation of hetero- and carbocyclic molecules, important organic building blocks in the synthesis of natural or unnatural compounds with biological interest.

¹ (a) Malleron, J.-L.; Fiaud, J.-C.; Legros, J.-Y. *Handbook of Palladium-Catalyzed Organic Reactions*, Academic Press, London, 1997. (b) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley: Hoboken, NJ, 2002. (c) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453. (d) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981.

² (a) Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Rüttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176. (b) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem., Int. Ed.* **1962**, *1*, 80. (c) Jira, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9034.

³ For reviews see: (a) Takacs, J. M.; Jiang, X. *Curr. Org. Chem.* **2003**, *7*, 369. (b) Cornell, C. N.; Sigman, M. S. *Inorg. Chem.* **2007**, *46*, 1903. (c) Muzart, J. *Tetrahedron* **2007**, *63*, 7505. (d) Keith, J. A.; Henry, P. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9038.

2. BIBLIOGRAPHIC BACKGROUND

2.1. Sequential reactions: key definitions and examples

The nature of sequential reactions, which often involve many distinct steps, can make them hard to define and classify. Nicolaou⁴ noted that a variety of terms, including “cascade“, “domino“, “tandem“ and “sequential“ is often used seemingly interchangeably and indistinguishably in the literature. Indeed, various opinions exist on how such reactions should be classified. According to Tietze⁵, a *domino (or cascade) reaction* is defined as a process involving two or more bond-forming transformations in which the subsequent reaction occurs as a consequence of the functionality formed in previous step. Thus, the intermediate of the previous reaction plays a role of the starting component for the subsequent step and cannot be isolated. Furthermore, no additional reagents, catalysts or additives can be added to the reaction vessel, nor can reaction conditions be changed. A substrate with several functionalities which undergo a transformation individually in the same pot is not a domino reaction.

The name for “domino” was chosen from the game where one puts up several domino pieces in one row. In agreement with the time-resolved succession of the reaction, if one knocks over the first domino piece, all others follow without changing the reaction conditions (Figure 1).



Figure 1. Falling domino pieces.

Denmark⁶ further posited that most of domino reactions, as defined by Tietze, fall under the broader category of *tandem processes*. The dictionary definition of tandem as “one behind the other” is, in itself, insufficient since every reaction sequence would then be a tandem reaction. To specify how the two (or more) reactions follow, Denmark proposed to

⁴ Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G *Angew. Chem., Int. Ed.* **2006**, 45, 7134.

⁵ (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, 32, 131. (b) Tietze, L. F. *Chem. Rev.* **1996**, 96, 115. (c) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006.

⁶ Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, 96, 137.

use the modifiers cascade (or domino), consecutive and sequential and thus, divided tandem reactions (focusing on cycloadditions) into three categories:

(1) *tandem cascade reactions*, wherein the processes take place without the requirement of additional components or reagents, everything necessary is incorporated in the starting materials. The product of the initial stage may be stable under the reaction conditions, however, the intermediate cannot be an isolable species.

(2) *tandem consecutive reactions*, which differ from cascade reactions in that the intermediate is an isolable entity. This intermediate contains the required functionality to perform the second reaction, but additional promotion in the form of energy (heat or light) is necessary to overcome the activation barriers.

(3) *tandem sequential reactions*, which require the addition of the second component for the tandem process in a separate step. To qualify as a tandem reaction, the first stage must create the functionality in the product to enable it to engage in the second reaction.

Others classify domino reactions with even stricter conditions.^{7,8} Contrary to above mentioned Denmark's tandem processes classification, Fogg and dos Santos^{7c} reserve term *tandem catalysis* to describe coupled catalysis in which sequential transformation of the substrate occurs *via* two (or more) mechanistically distinct processes. On the other hand, term *domino catalysis* is stipulated for multiple transformations occurring *via* a single catalytic mechanism. A more detailed classification of one-pot processes involving sequential elaboration of an organic substrate *via* multiple catalytic transformations is depicted in the flowchart (Figure 2).

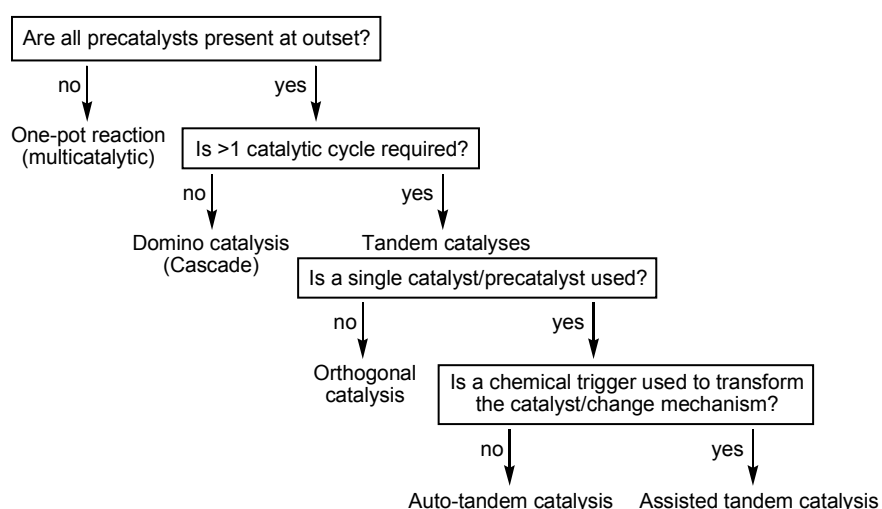


Figure 2. Flowchart for classification of sequential multiple catalytic transformations.

⁷ (a) Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, 67, 9456. (b) Prestat, G.; Poli, G. *Chemtracts - Org. Chem.* **2004**, 17, 97. (c) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, 248, 2365.

⁸ Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1.

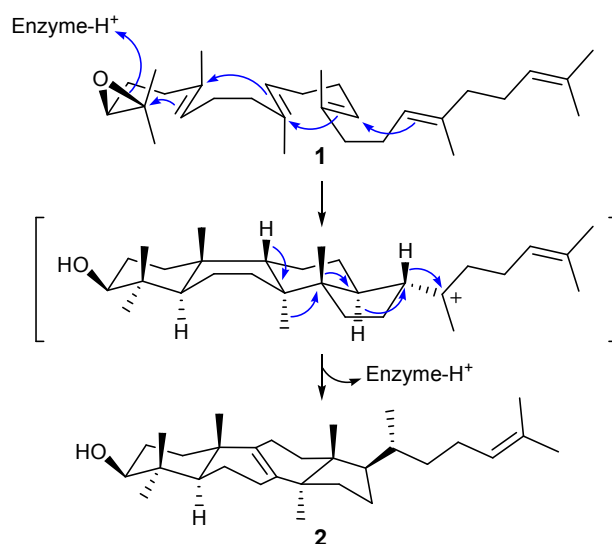
As indicated in the flowchart (Figure 2), Fogg and dos Santos distinguish three subcategories of tandem catalysis:

(1) *orthogonal tandem catalysis*, which involves two or more functionally distinct and noninterfering catalysts or pre-catalysts, all of which are present from the outset of reaction. Orthogonal reactions are characterized by their mutual independence.

(2) *auto-tandem catalysis* involves two or more mechanistically distinct catalyses promoted by a single catalyst precursor. Both cycles occur spontaneously by cooperative interaction of the various species (catalyst, substrate, additional reagents if required) present at the outset of reaction.

(3) *assisted tandem catalysis*, in which a single catalyst species can be expanded by addition of a further reagent to trigger a change in mechanism. The two catalytic processes cannot occur simultaneously, as the two catalysts do not coexist.

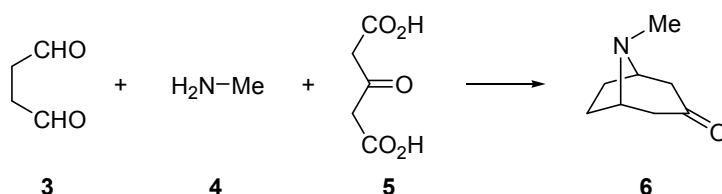
To underline the usefulness of sequential reactions, we can use some textbook examples from the Nature. In Nature domino reactions are rather common, although, a direct comparison to the reactions in the flask is not possible because of the involvement of multienzymes which can allow the catalysis of different steps. A beautiful example, demonstrating elegance, high selectivity and efficiency, is the biosynthesis of steroids from squalene epoxide **1** which is transformed into lanosterol **2** with the formation of four C–C bonds and six stereogenic centers (Scheme 1).⁹



Scheme 1. Biosynthesis of steroids from squalene epoxide

⁹ (a) Corey, E. J.; Russey, W. E.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1966**, *88*, 4750. (b) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 4025. (c) Corey, E. J.; Virgil, S. C.; Sarshar, S. *J. Am. Chem. Soc.* **1991**, *113*, 8171. (d) Corey, E. J.; Virgil, S. C.; Liu, D. R.; Sarshar, S. *J. Am. Chem. Soc.* **1992**, *114*, 1524.

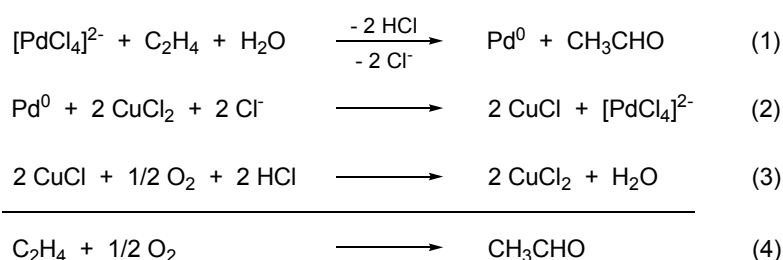
The first domino reaction in the synthesis of a natural product was performed by Schöpf and Robinson¹⁰ putting together a mixture of succindialdehyde **3**, methylamine **4** and acetonedicarboxylic acid **5** to give the bicyclic tropinone **6** which is a structural component of several alkaloids such as cocaine and atropine (Scheme 2). The key step in this synthesis is a double Mannich reaction.



Scheme 2. Biomimetic domino synthesis of tropinone.

2.2. Wacker process and Wacker-type cyclization

The development of catalytic reactions of alkenes transformed the chemical industry in mid-20th century. In 1959, Smidt and co-workers discovered a Pd-catalyzed method for the aerobic oxidative coupling of ethylene and water to produce acetaldehyde (Scheme 3).^{2,3}

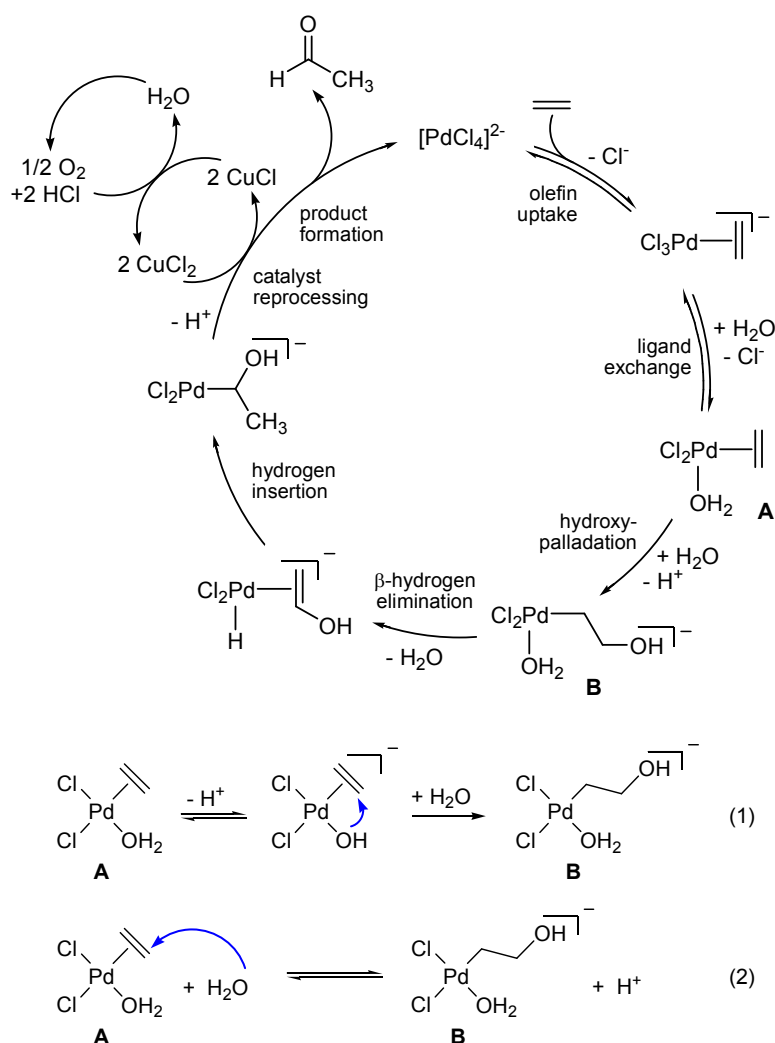


Scheme 3. Individual reactions of the Wacker process.

This transformation, so called Wacker process, represented the starting point for the development of numerous other Pd-catalyzed reactions, ranging from alkene and diene oxidations to cross-coupling reactions of aryl halides. The stoichiometric oxidation reaction (eq 1, Scheme 3) has been known for more than century, however, the industrial Wacker process owes to its success to the recognition that the oxidized Pd^0 catalyst could be regenerated by molecular oxygen in the presence of co-catalytic CuCl_2 (eq 2 and 3). The reaction proceeds through a β -hydroxyethyl- Pd^{II} intermediate **B** (Scheme 4) that is formed *via* the net addition of hydroxide and Pd across the C–C double bond of ethylene. This seemingly

¹⁰ (a) Robinson, R. *J. Chem. Soc.* **1917**, *III*, 762.; *ibid.* **1917**, *III*, 876. (b) Schöpf, C.; Lehmann, G.; Arnold, W. *Angew. Chem.* **1937**, *50*, 779.

straightforward “hydroxypalladation” step has been the subject of extensive mechanistic research and controversy. A major focus of this debate has centered on whether the reaction proceeds by a *cis*-hydroxypalladation pathway, involving migration of a coordinated water or hydroxide to the ethylene molecule (eq 1, Scheme 4), or a *trans*-hydroxypalladation pathway, involving nucleophilic attack of exogenous water or hydroxide on the coordinated ethylene molecule (eq 2).

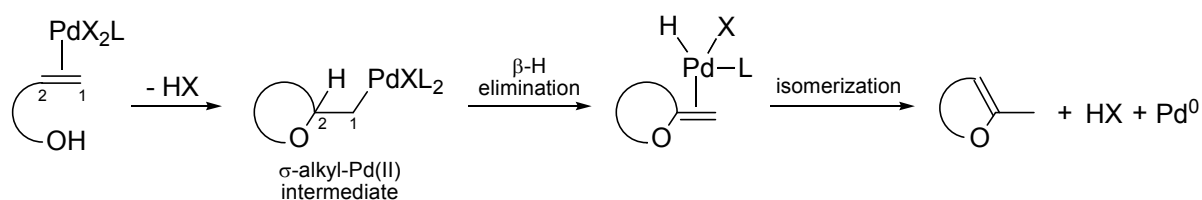


Scheme 4. Overall catalytic cycle of the Wacker process.

The evidence of longstanding kinetic, stereochemical and theoretical studies points out that the Wacker process is quite sensitive and dependent on reaction conditions, specifically Cl⁻ and CuCl₂ concentrations. Experimental results support the conclusion that *syn* hydroxypalladation leading to ethanal is the active mechanism of the Wacker process under industrial conditions (low concentrations of Cl⁻ and CuCl₂) and *anti* hydroxypalladation leading to chlorhydrin byproduct is the active mechanism under conditions with high

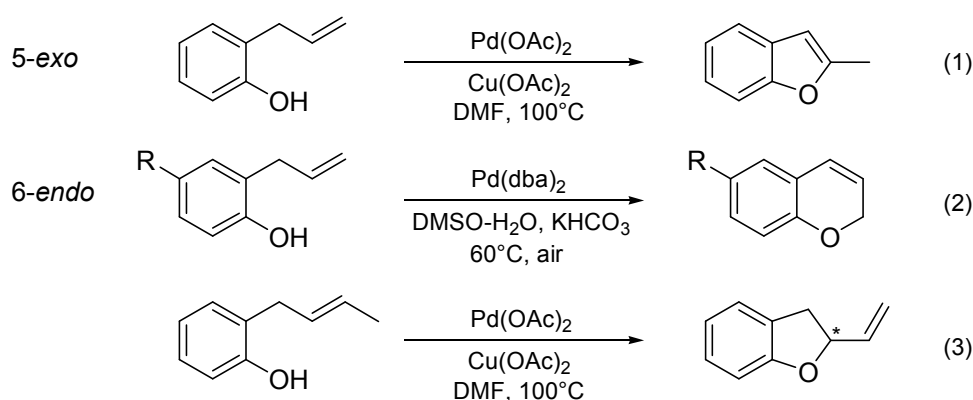
concentrations of Cl^- and CuCl_2 ($[\text{Cl}^-] > 3\text{M}$). Further observation emerged from stereochemical data indicates that in the reaction where Pd^{II} is in the presence of a strongly coordinating ligand such as CO , the nucleophilic attack is *anti* because the second coordination site for *syn* addition is not available.

The intramolecular Wacker-type cyclization using oxygen nucleophiles is one of the most important processes for the preparation of *O*-heterocycles.^{1d,11} The palladium(II) coordinates to the alkene C–C double bond and activates it towards nucleophilic attack. Subsequent β -hydride elimination leads to cyclized product in its thermodynamically stable form (Scheme 5).¹²



Scheme 5. Wacker-type cyclization.

Depending on used catalytic system, 2-allylphenols undergo 5-*exo* and 6-*endo* Wacker-type cyclization, respectively (Scheme 6, eq 1 and 2).¹³ When an alkyl substituent such as methyl group is in the terminal position of allylic side chain (eq 3), the oxypalladated intermediate has two possibilities of β -H-elimination. This intermediate generally produces the energetically favorable vinyl substituent rather than the *exo*-methylene substitution.



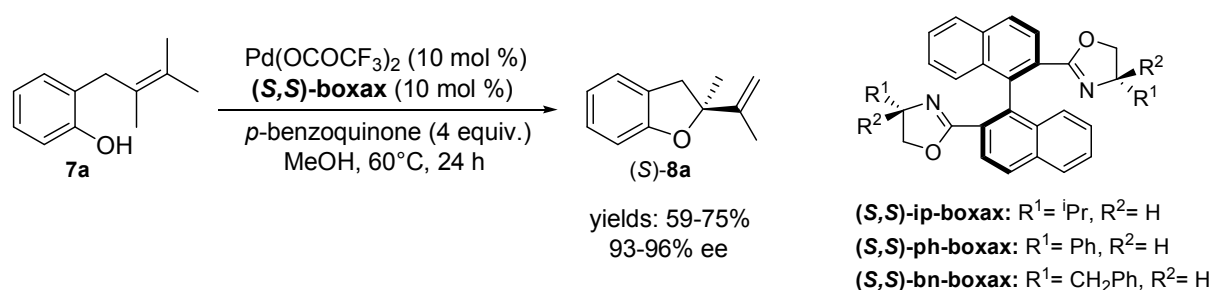
Scheme 6. Wacker-type cyclization of 2-allylphenols.

¹¹ For reviews see: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.

¹² Hosokawa, T.; Maeda, K.; Koga, K.; Moritani, I. *Tetrahedron Lett.* **1973**, *10*, 739.

¹³ Murahashi, S.-I.; Hosokawa, T. *Acc. Chem. Res.* **1990**, *23*, 49.

The first attempts to accomplish the asymmetric version of Wacker-type cyclization were described by Hosokawa and Murahashi,¹⁴ however, the truly effective ligand for this transformation was developed by Hayashi *et al.*¹⁵ 2-(2,3-Dimethylbut-2-enyl)phenol **7a** was cyclized to corresponding dihydrobenzofuran (*S*)-**8a** using (*S,S*)-boxax {(*S,S*)-2,2'-bis[4-(alkyl)oxazolyl]-1,1'-binaphthyl} ligands in the presence of *p*-benzoquinone in methanol (Scheme 7). The best selectivity and efficiency gave (*S,S*)-ip-boxax, the cyclized product was formed with 96% ee in 75% yield. It is noteworthy that the diastereomeric isomer (*R,S*)-ip-boxax ($R^1 = \text{H}$, $R^2 = \text{}^i\text{Pr}$) was much less active and less enantioselective (18% ee, 3% yield).



Scheme 7. Asymmetric intramolecular Wacker-type cyclization of **7a** using (*S,S*)-boxax ligands.

Another significant feature of this transformation is the strong dependence of catalytic activity on the anionic ligands attached to the palladium. The reaction of **7a** was much faster with the palladium catalyst generated from palladium bis(trifluoroacetate) than that from palladium diacetate or dichlorobis(acetonitrile)palladium. Furthermore, this reaction was not catalyzed by chloride complex $\text{PdCl}_2\{(\textit{S,S})\text{-ip-boxax}\}$ at all. Thus, it was expected that a cationic palladium/boxax complex was generated as the active species by dissociation of the relatively stable trifluoroacetate anion from palladium in a polar solvent. Indeed, a dicationic palladium(II)/boxax species generated by addition of 2 equiv of (*S,S*)-ip-boxax to $\text{Pd}(\text{CH}_3\text{CN})_4(\text{BF}_4)_2$ was found to be catalytically much more active than $\text{Pd}(\text{OCOCF}_3)_2\{(\textit{S,S})\text{-ip-boxax}\}$ complex. The reaction of **7a** in the presence of mentioned dicationic species was complete in 50 minutes to give 91% yield of (*S*)-**8a** with 98% ee. Generation of dicationic species by abstraction of chloride from $\text{PdCl}_2\{(\textit{S,S})\text{-ip-boxax}\}$ through treatment with 2 equiv. of a silver(I) salt (AgBF_4 , AgPF_6 or AgSbF_6) was also successful (full conversions of **7a** were achieved in 1 hour to give the product in 86-91% yield with 95-98% ee).

¹⁴ (a) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318. (b) Hosokawa, T.; Okuda, C.; Murahashi, S.-I. *J. Org. Chem.* **1985**, *50*, 1282.

¹⁵ (a) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063. (b) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 5071.

From recent works¹⁶ on enantioselective Wacker-type cyclization, the one worthy of emphasis, published by Zhang,^{16c} reports a new family of tetraoxazoline ligands **9** for the construction of chelation-induced axially chiral catalytic systems (Figure 3). The axially achiral tetraoxazoline ligands **9**, in which four identical chiral oxazoline groups are induced into four ortho positions of biphenyl axis, may produce only one of two possible diastereomeric metal complexes during the coordinating process. As it can be seen in Figure 3, the metal complexes (*S,aS*) are sterically more favorable compared with their diastereomers (*S,aR*). Hence, it is expected that only one diastereomeric metal complex with (*S*)-axial configuration is afforded during the chelation-induced process.

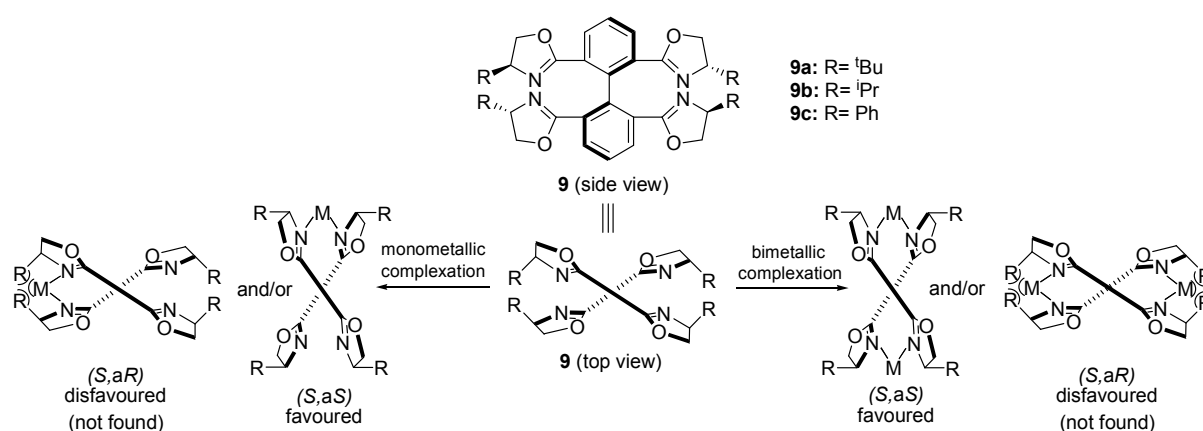
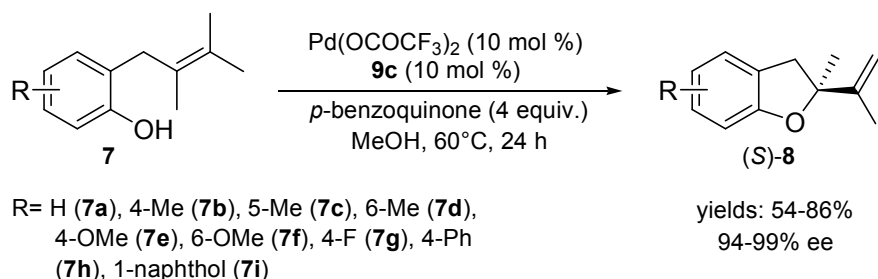


Figure 3. Model figures of diastereomeric monometallic and bimetallic complexes with tetraoxazoline ligands.

Tetraoxazoline ligand **9c** was successfully used in Wacker-type cyclization of substrates **7a-i** (Scheme 8) giving the corresponding chiral 2,3-dihydrobenzofurans **8a-i** in good yields with excellent enantioselectivities (up to 99% ee).



Scheme 8. Asymmetric intramolecular Wacker-type cyclization of **7** using tetraoxazoline **9c**.

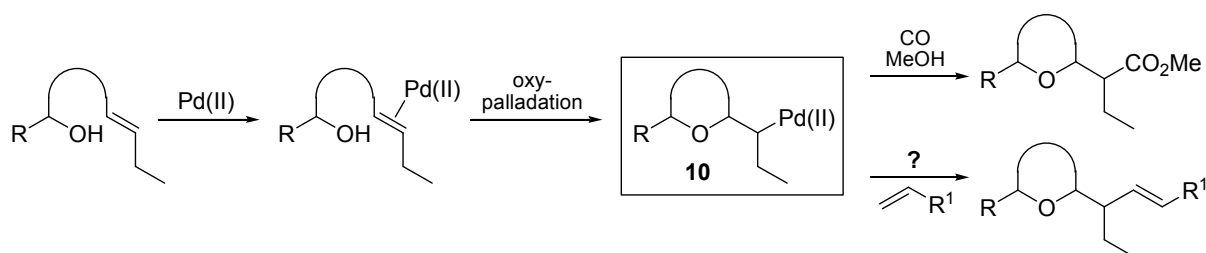
¹⁶ (a) Trend, R. M.; Ramtohl, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778. (b) Wang, F.; Zhang, Y. J.; Yang, G.; Zhang, W. *Tetrahedron Lett.* **2007**, *48*, 4179. (c) Zhang, Y. J.; Wang, F.; Zhang, W. *J. Org. Chem.* **2007**, *72*, 9208. (d) Takenaka, K.; Tanigaki, Y.; Patil, M. L.; Rao, C. V. L.; Takizawa, S.; Suzuki, T.; Sasai, H. *Tetrahedron: Asymmetry* **2010**, *21*, 767. (e) Takenaka, K.; Mohanata, S. C.; Patil, M. L.; Rao, C. V. L.; Takizawa, S.; Suzuki, T.; Sasai, H. *Org. Lett.* **2010**, *12*, 3480.

The σ -alkyl-palladium(II) intermediate formed in oxypalladation reaction step (Scheme 5) can participate in a number of other subsequent transformations. This is only possible in case that considered subsequent reaction is much faster than competitive β -hydride elimination. Following subchapters deal with the most important examples of domino intramolecular palladium(II)-catalyzed cyclizations and coupling or carbonylation reaction in the synthesis of heterocyclic compounds. For this occasion, the definition of domino reaction according to Tietze⁵ is adopted.

2.3. Domino reaction: Intramolecular Pd(II)-catalyzed cyclization and coupling

2.3.1. Coupling with alkenes *via* Heck vinylation

In 1993, Semmelhack¹⁷ raised the question whether the organo-Pd(II) intermediate **10**, formed by intramolecular oxypalladation of hydroxyalkenes, could be trapped in ways other than in that period already well-known CO/MeOH trapping¹⁸, especially *via* carbon chain extension such as Heck vinylation reaction or coupling with organometallic species (Scheme 9).



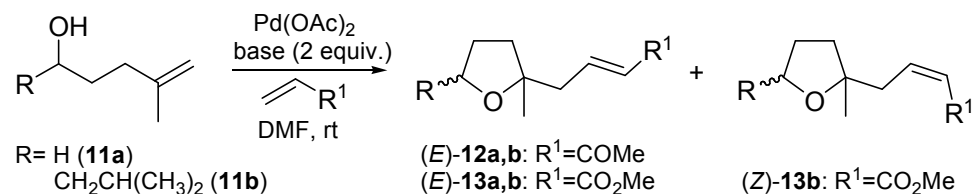
Scheme 9. Alternative fates of organo-Pd(II) intermediate.

To avoid the competitive β -hydride elimination appropriate substrates **11** leading to furans (Table 1) and **14** leading to pyrans (Table 2) with a methyl substitution on double bond were chosen. The first set of experiments was carried out using a stoichiometric amount or little excess of palladium diacetate. The vinyl coupling partner was present in large excess. Indeed, typically to the Heck process, subsequent vinylation produced *E*-disubstituted alkenes as the exclusive or predominant domino product. The *Z*-isomers appeared in minor amounts from methyl acrylate using NaHCO₃ as a base without NaI (Table 1, entry 6 and Table 2,

¹⁷ Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett.* **1993**, 34, 7205.

¹⁸ (a) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, 62, 2035. (b) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, 106, 1496. (c) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, 30, 4925. (d) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, 54, 4483.

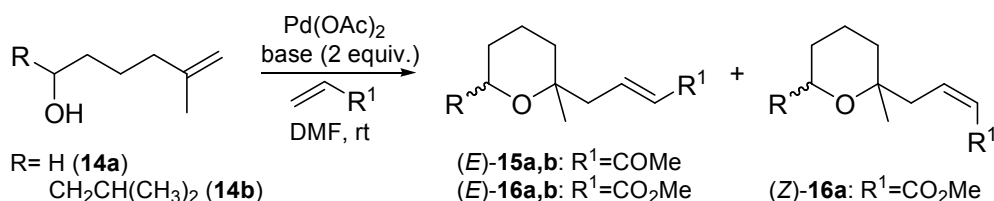
entry 2). The products from **11b** and **14b** were obtained as an inseparable mixture of diastereomers.



entry	substrate	R ¹ (equiv.)	base	time	Pd(OAc) ₂ (equiv.)	product (yield, %)
1	11a	COMe (10)	AcONa ^a	3h	1.25	(E-12a) (84%)
2	11a	CO ₂ Me (10)	AcONa ^a	6h	1.25	(E-13a) (84%)
3	11a	COMe (5)	NaHCO ₃	2h	1	(E-12a) (91%)
4	11b	COMe (10)	AcONa ^a	5 min	1.25	(E-12b) (89%) ^b
5	11b	COMe (5)	NaHCO ₃	3h	1	(E-12b) (91%) ^b
6	11b	CO ₂ Me (5)	NaHCO ₃	4h	1	(E-13b) (86%) ^b , (Z-13b) (9%) ^b

^a NaI (0.2 equiv.) was added. ^b The products are mixtures of 2,5-*cis* and 2,5-*trans* isomers, approx. 1:1.

Table 1. Stoichiometric domino cyclization/Heck vinylation of **11**.



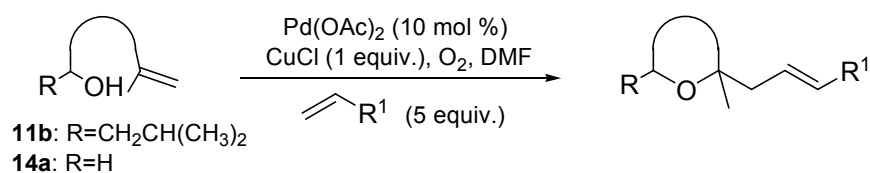
entry	substrate	R ¹ (equiv.)	base	time	Pd(OAc) ₂ (equiv.)	product (yield, %)
1	14a	COMe (5)	NaHCO ₃	2h	1	(E-15a) (91%)
2	14a	CO ₂ Me (5)	NaHCO ₃	5.5h	1	(E-16a) (86%), (Z-16a) (4%)
3	14b	COMe (5)	NaHCO ₃	3h	1	(E-15b) (87%) ^a

^a The products are mixtures of 2,6-*cis* and 2,6-*trans* isomers, approx. 1:1.

Table 2. Stoichiometric domino cyclization/Heck vinylation of **14**.

The catalytic conditions were tested for substrate **11b**. The challenge was to find a suitable reoxidation system for the regeneration of Pd⁰. In this field, *p*-benzoquinone was not an effective reoxidant, and a system with 10 mol % of PdCl₂, 2 equiv. of Cu(II) and oxygen (Wacker conditions) proceeded slowly and gave a moderate yield. Finally, the using of CuCl instead of CuCl₂ led to high turnover numbers, complete conversions and high yields (Table 3). The addition of acetic acid increased the reaction rate in some cases (not shown in

table). Despite of efficiency of the reoxidation system, presented method is limited to substrates which cannot undergo β -hydride elimination from organo-Pd(II) intermediate.

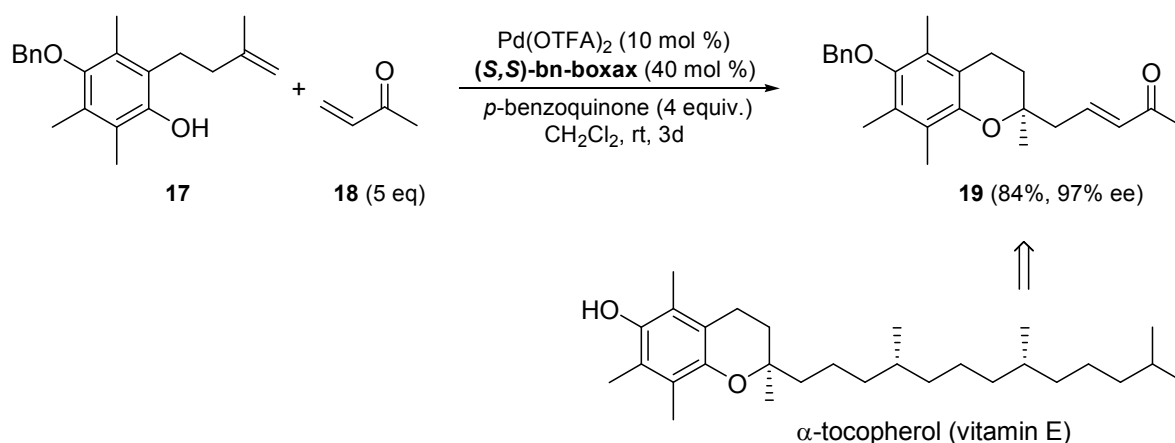


entry	substrate	R ¹	reaction time	product	yield (%)
1	11b	COMe	2h	(<i>E</i>)- 12b ^a	89
2	11b	CO ₂ Me	1.25h	(<i>E</i>)- 13b ^a	82
3	14a	COMe	1.25h	(<i>E</i>)- 15a	92
4	14a	CO ₂ Me	6h	(<i>E</i>)- 16a ^b	85

^a The products are 1:1 mixtures of diastereomers. ^b 5 mol % of Pd(OAc)₂ was used.

Table 3. Catalytic domino cyclization/Heck vinylation of **11b** and **14a**.

The utility of this approach was illustrated in the total synthesis of vitamin E¹⁹ and the synthesis of 4-dehydroxydiversonol,²⁰ a derivative of fungal metabolite diversinol isolated from *Penicillium diversum*.²¹ The chiral chroman framework of vitamin E **19** with concurrently introduced part of a side chain was produced by domino enantioselective palladium-catalyzed Wacker cyclization and Heck reaction of alkylphenol **17** with methyl vinyl ketone **18** (Scheme 10).



Scheme 10. Synthesis of chiral chroman **19**.

¹⁹ (a) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257. (b) Tietze, L. F.; Stecker, F.; Zinngrebe, J.; Sommer, K. *Chem. Eur. J.* **2006**, *12*, 8770.

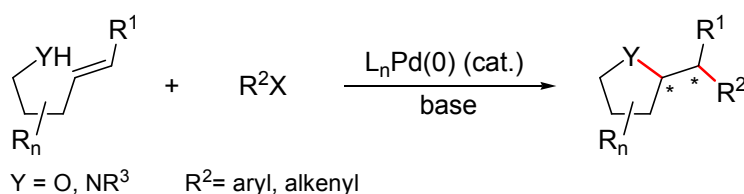
²⁰ Tietze, L. F.; Spiegl, D. A.; Stecker, F.; Major, J.; Raith, C.; Große, C. *Chem. Eur. J.* **2008**, *14*, 8956.

²¹ Turner, W. B. *J. Chem. Soc. Perkin Trans. I* **1978**, 1621.

2.3.2. Coupling with aryl or alkenyl halides

Wolfe and co-workers developed a general strategy for stereoselective synthesis of saturated heterocycles *via* palladium-catalyzed carboetherification and carboamination reactions between aryl or alkenyl halides and alkenes bearing pendant heteroatoms.²² These transformations effect the stereoselective construction of synthetically interesting heterocycles, such as tetrahydrofurans,²³ pyrrolidines,²⁴ imidazolidin-2-ones,²⁵ isoxazolidines,²⁶ oxazolidines,²⁷ pyrazolidines,²⁸ piperazines,²⁹ morpholines³⁰ and diazepines.³¹

Particularly attractive is the formation of substituted tetrahydrofurans and pyrrolidines involving the coupling of a γ -hydroxy- or γ -aminoalkene with an aryl or alkenyl halide, generating carbon–carbon bond, carbon–heteroatom bond, and up to two stereocenters in a single step (Scheme 11).



Scheme 11. Preparation of substituted tetrahydrofurans and pyrrolidines.

The desired products could potentially be formed through five different catalytic cycles (Scheme 12) involving basic organometallic reactions, such as oxidative addition and migratory insertion.

²² For reviews see: (a) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (b) Wolfe, J. P. *Synlett* **2008**, 2913.

²³ (a) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620. (b) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099. (c) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468. (d) Hay, M. B.; Wolfe, J. P. *Tetrahedron Lett.* **2006**, *47*, 2793. (e) Ward, A. F.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1268.

²⁴ (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605. (b) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906. (c) Beaudoin Bertrand, M.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447. (d) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644. (e) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575. (f) Ney, J. E.; Hay, M. B.; Yang, Q.; Wolfe, J. P. *Adv. Synth. Catal.* **2005**, *347*, 1614. (g) Beaudoin Bertrand, M.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353. (h) Beaudoin Bertrand, M.; Leathen, M. L.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 457. (i) Beaudoin Bertrand, M.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, *73*, 8851. (j) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 6276. (k) Rosen, B. R.; Ney, J. E.; Wolfe, J. P. *J. Org. Chem.* **2010**, *75*, 2756. (l) Mai, D. N.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 12157. (m) Lemen, G. S.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 2322. (n) Mai, D. N.; Rosen, B. R.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2932.

²⁵ (a) Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2531. (b) Fritz, J. A.; Wolfe, J. P. *Tetrahedron* **2008**, *64*, 6838.

²⁶ (a) Hay, M. B.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6492. (b) Lemen, G. S.; Giampietro, N. C.; Hay, M. B.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 2533.

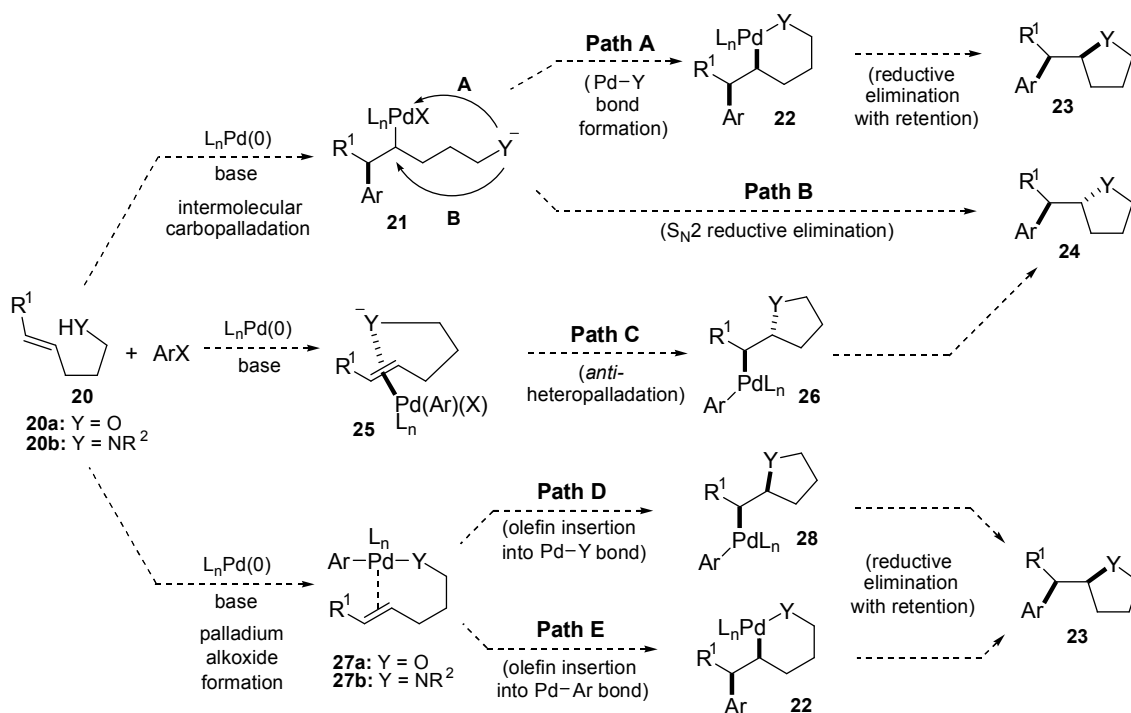
²⁷ Ward, A. F.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 4728.

²⁸ Giampietro, N. C.; Wolfe, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 12907.

²⁹ (a) Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 3279. (b) Nakhla, J. S.; Schultz, D. M.; Wolfe, J. P. *Tetrahedron* **2009**, *65*, 6549.

³⁰ Leathen, M. L.; Rosen, B. R.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 5107.

³¹ Neukom, J. D.; Aquino, A. S.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2196.



Scheme 12. Mechanistic possibilities according to Wolfe.

Two possible mechanisms for the conversion of substrates **20** into heterocyclic products involve the oxidative addition of the aryl halide to palladium(0), followed by an intermolecular Heck-type carbopalladation to provide **21**. The conversion of this intermediate into the desired products **23** or **24** requires either an sp^3 -carbon–heteroatom bond forming reductive elimination from palladium alkoxide or amide **22** (Scheme 12, Path A), or an S_N2 -like reductive elimination directly from **21** (Path B), respectively. Neither of these two pathways is well-precended, as only few examples of sp^3 -carbon–heteroatom bond forming reductive eliminations from late transition metal complexes have been described, most of which involve high oxidation state metal complexes.³²

A third possible mechanism involves the coordination of the alkene to the $Pd(Ar)(X)$ species generated upon oxidative addition of the aryl halide to $Pd(0)$ to provide **25**. This intermediate could undergo *anti*-heteropalladation to afford **26** (Scheme 12, Path C),^{13,33} which would be converted into **24** through the well-known carbon–carbon bond forming reductive elimination. *anti*-Heteropalladation reactions are also well-precended with relatively

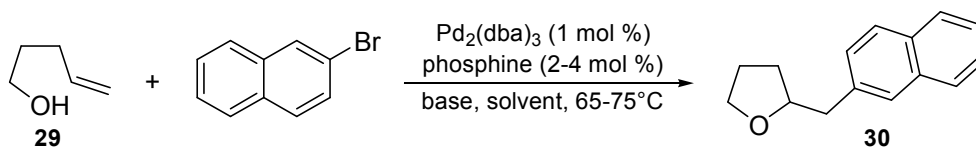
³² (a) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890. (b) Koo, K.; Hillhouse, G. L. *Organometallics* **1995**, *14*, 4421. (c) Matsunaga, P. T.; Hillhouse, G. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 2075. (d) Koo, K.; Hillhouse, G. L. *Organometallics* **1998**, *17*, 2924. (e) Williams, B. S.; Goldberg, K. I. *J. Am. Chem. Soc.* **2001**, *123*, 2576. (f) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868. (g) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.

³³ Hegedus, L. S. *Angew. Chem., Int. Ed.* **1988**, *27*, 1113.

electrophilic PdX_2 complexes. However, these processes are not as common with less-electrophilic $\text{Pd}(\text{Ar})(\text{X})$ intermediates.^{13,33}

The two other mechanistic scenarios involve the formation of an intermediate $\text{Pd}(\text{Ar})(\text{YR})$ complex **27** *via* the oxidative addition of the aryl halide to $\text{Pd}(0)$ followed by palladium–oxygen or palladium–nitrogen bond formation.³⁴ This intermediate could be further transformed *via syn*-intramolecular insertion of the alkene into the palladium–heteroatom bond of **27** to afford **28**.^{35,36} Finally, carbon–carbon bond forming reductive elimination from **28** would provide **23** (Scheme 12, Path D).³⁷ However, insertions of alkenes into late transition metal–heteroatom bonds are rare, and no well-defined examples of insertions of unactivated alkenes into palladium–oxygen or –nitrogen bonds has been reported.^{35,36} Alternatively, the insertion of alkene into the palladium–carbon bond of **27**, followed by the aforementioned sp^3 –carbon–heteroatom bond forming reductive elimination of the resulting complex **22** could also yield **23** (Path E).³²

In preliminary studies on the synthesis of tetrahydrofurans *via* Pd-catalyzed carboetherification reactions, the model coupling of pent-4-en-1-ol **29** with 2-bromonaphthalene was examined (Scheme 13).^{23a,b} To optimize the reaction conditions,



Scheme 13. Optimization studies in synthesis of tetrahydrofurans.

different bases and phosphine ligands were tested. It was found that sodium *tert*-butoxide as relatively strong base most probably provides a greater equilibrium concentration of a nucleophilic alkoxide derived from **29**. The reaction rate of naphthalene side product

³⁴ (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417.

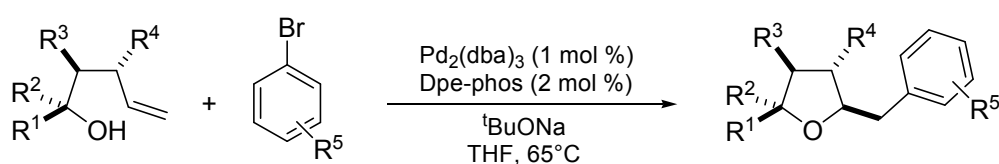
³⁵ (a) Villanueva, L. A.; Abboud, K. A.; Boncella, J. M. *Organometallics* **1992**, *11*, 2963. (b) Van der Lende, D. D.; Abboud, K. A.; Boncella, J. M. *Inorg. Chem.* **1995**, *34*, 5319. (c) Cowan, R. L.; Troglor, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4750. (d) Bryndza, H. E. *Organometallics* **1985**, *4*, 406. (e) Bennett, M. A.; Jin, H.; Li, S.; Rendina, L. M.; Willis, C. A. *J. Am. Chem. Soc.* **1995**, *117*, 8335. (f) Ritter, J. C. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1997**, *119*, 2580. (g) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738. (h) Hamed, O.; Thompson, C.; Henry, P. M. *J. Org. Chem.* **1997**, *62*, 7082. (i) Nelson, D. J.; Li, R.; Brammer, C. *J. Am. Chem. Soc.* **2001**, *123*, 1564.

³⁶ For recent studies on alkene insertion into late transition metal–oxygen or –nitrogen bonds, see: (a) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036. (b) Zhao, P.; Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 12066. (c) see also ref. 16a. (d) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9642.

³⁷ Milstein, D. Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981.

formation was efficiently diminished utilizing bidentate ligand bis[2-(diphenylphosphino)-phenyl] ether (Dpe-phos). Finally, the use of tetrahydrofuran as a solvent and 2 equivalents of both, ^tBuONa and 2-bromonaphthalene afforded domino product **30** in 76% yield.

In general, the tetrahydrofuran-forming reaction is effective with primary, secondary and tertiary alcohols. Good to excellent diastereoselectivities are obtained in the preparation of tetrahydrofurans that are *trans*-2,5- or *trans*-2,3-disubstituted (Table 4, entries 1-3; see also Table 7 and Scheme 59 in Section 4.1.2.). However, the reactions affording 2,4-disubstituted tetrahydrofurans proceed with modest diastereoselectivity (entry 4). A number of electron-neutral or electron-rich aryl bromides are suitable coupling partners in



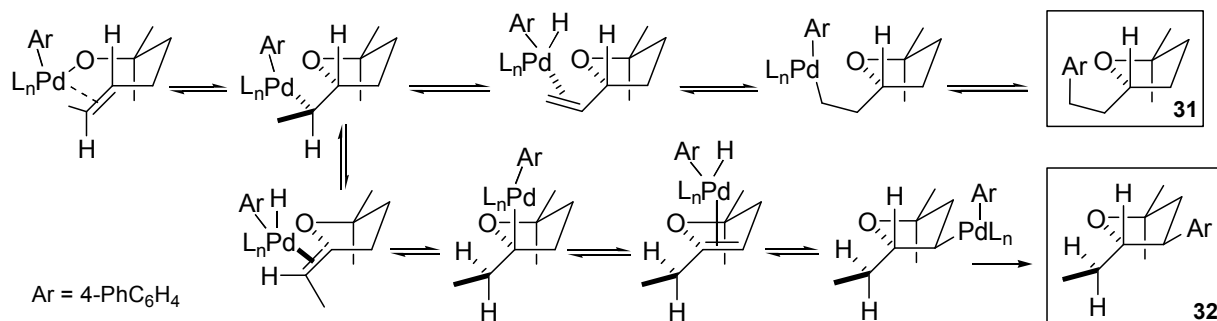
entry	R ¹	R ²	R ³	R ⁴	R ⁵	diastereomeric ratio	yield (%)
1	H	Ph	H	H	4-OMe	>20:1	62
2	Me	Ph	H	H	4- ^t Bu	>20:1	77
3	Me	Me	H	Me	4-Ph	8:1	78
4	H	H	Ph	H	3-OMe	2:1	84
5	(CH ₂) ₄		H	H	2-Me	-	60
6	H	(CH ₂) ₄		H	4-Ph	>20:1	70

^a Conditions: 1.0 equiv. of alcohol, 2.0 equiv. of aryl bromide, 2.0 equiv. of ^tBuONa, 1 mol % Pd₂(dba)₃, 2 mol % Dpe-phos, 0.25 M THF, 65°C.

Table 4. Synthesis of substituted tetrahydrofurans (representative examples).

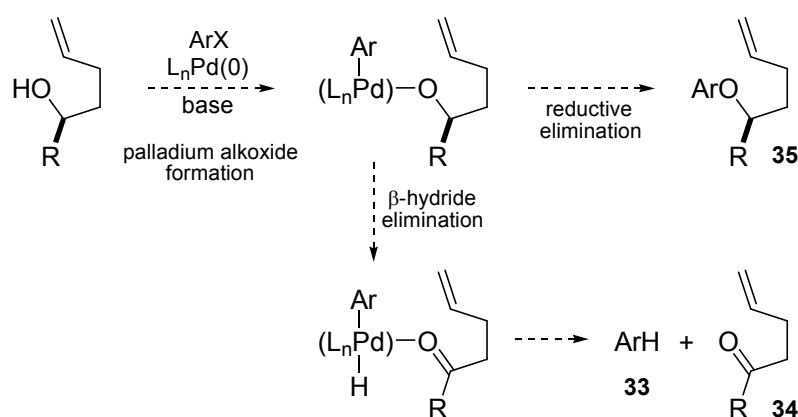
these transformations, but lower yields are obtained with electron-poor aryl bromides because of competing *O*-arylation of the alcohol substrate. The reactions of alkenyl halides with tertiary alcohols proceed in good yield, although modest yields are obtained in the similar reactions of primary or secondary alcohols. The tetrahydrofuran-forming reaction was also effective with tertiary alcohols bearing pendant internal alkenes when slightly modified reaction conditions were employed. The use of 1-2.5 mol % Pd₂(dba)₃, 4-10 mol % P(2-Tol)₃ and a reaction temperature of 110°C provided good results with these more sterically hindered substrates.^{23c,d} Transformations involving acyclic internal alkenes produced corresponding desired tetrahydrofurans with high diastereoselectivities when improved catalytic system (2 mol % Pd₂(dba)₃, 4 mol % S-Phos in xylenes at 140°C)^{23e} was used.

The reaction of acyclic internal alkenes also led to the formation of two additional regioisomers **31** and **32** (Scheme 14) in yields <5%. This fact ultimately provided valuable insight into the mechanism of the tetrahydrofuran-forming carboetherification reaction.



Scheme 14. Formation of regioisomers.

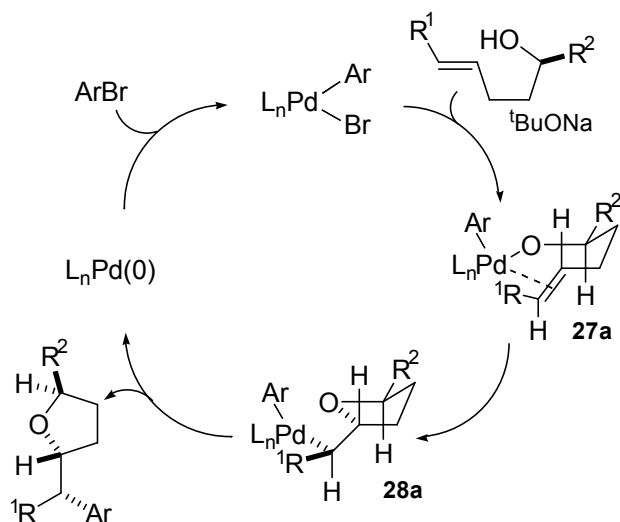
Mechanistic pathways D and E (Scheme 12) both involve arylpalladium alkoxide complexes³⁸ **27a** as key intermediates. Wolfe strongly expects the presence of these complexes in the reaction mixture because beside the formation of main product they can also explain the formation of three frequent side products **33**, **34** and **35** (Scheme 15). Thus, pathways D and E (Scheme 12) both should provide tetrahydrofuran products with the same relative stereochemistry (*syn*-addition). However, the formation of regioisomers **31** and **32** (Scheme 14) cannot be adequately explained by the mechanism of path E leading to the intermediate **22** (Scheme 12). In contrast, their formation can easily be explained if the carboetherification proceeds through alkene insertion into palladium–oxygen bond of **27a** to afford **28a** (Path D).



Scheme 15. Formation of the side-products.

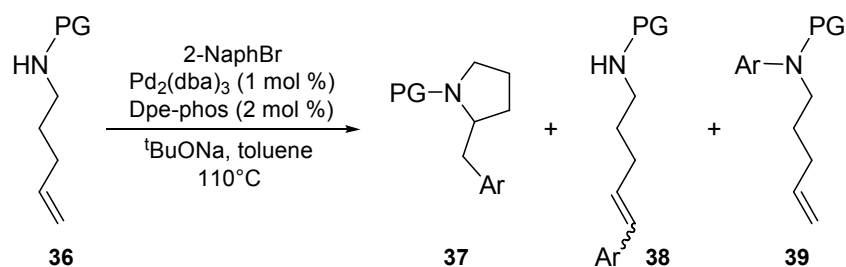
³⁸ (a) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787. (b) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504. (c) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109.

As shown in Scheme 16, mechanistic pathway D (Scheme 12) can, as well, predict and explain the formation of *trans*-2,5- and *trans*-2,3-disubstituted tetrahydrofurans.



Scheme 16. Catalytic cycle and stereochemistry for mechanistic pathway D.

Along with carboetherifications, synthetically interesting are also carboamination reactions of *N*-protected γ -aminoalkenes^{24c,h,i} as the attempts to cyclize primary pent-4-enamine substrates^{24b,e} were unsuccessful or gave undesired *N*-arylated pyrrolidines. The reactivity of pent-4-enamine derivatives **36** bearing different nitrogen-protecting groups was explored in reaction conditions that are typical for carboetherification reactions or carboaminations of *N*-arylated aminoalkenes^{24a,d,f} (Table 5).



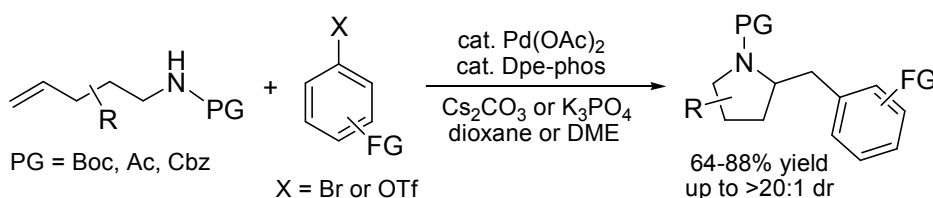
PG	GC ratio (isolated yield)		
	37	38	39
Bn	0	40 ^b	34
Ac	88 (72%)	12	0
Boc	82 (77%)	4 ^b	0
4-MeOC ₆ H ₄ CO	77 (63%)	23	0
Bz	58 (48%)	42	0
4-F ₃ CC ₆ H ₄ CO	0	89 ^b	0

^a Conditions: 1.0 equiv. of amine, 1.2 equiv. of 2-bromonaphthalene, 1.2 equiv. of ^tBuONa, 1 mol % Pd₂(dba)₃, 2 mol % Dpe-phos, 0.25 M toluene, 110°C. ^b Alkene stereoisomers and regioisomers obtained.

Table 5. Protecting group effects.^a

As shown in Table 5, the efficiency of carboamination reaction is highly dependent on the nucleophilicity/basicity of the substrate aminogroup. Varying amounts of the desired pyrrolidine **37** and undesired products that results from Heck arylation (**38**) or *N*-arylation (**39**) of starting material were generated. Pyrrolidines **37** from the reaction of a very electron-rich *N*-benzyl-protected substrate or a very electron-poor 4-(trifluoromethyl)benzoyl-protected substrate were not formed. Satisfactory results were obtained with pent-4-enamines bearing *N*-*tert*-butoxycarbonyl (*N*-Boc) or *N*-acetyl protecting groups.

The efficient palladium-catalyzed carboamination of *N*-protected γ -aminoalkenes with aryl bromides and triflates has been achieved under mild reaction conditions using the weak bases in dioxane solvent (Scheme 17).^{24h}

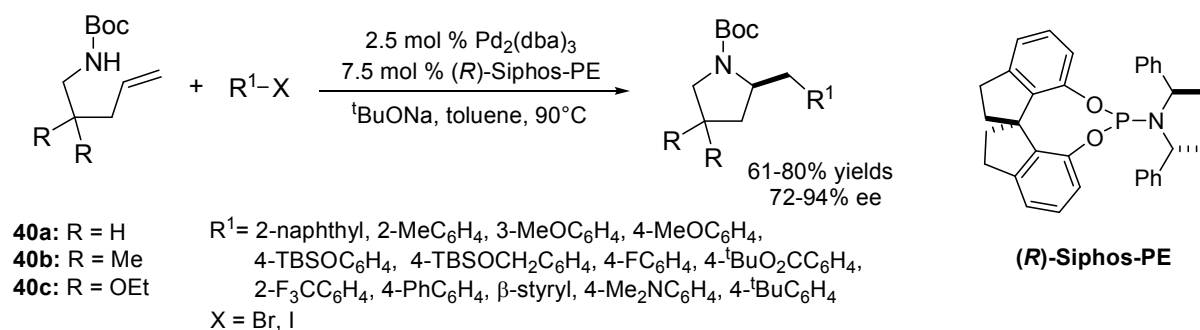


Scheme 17. Synthesis of substituted *N*-protected pyrrolidines.

All products (Scheme 17) were formed as single regioisomers, moreover, this method can be used for synthesis of *cis*-2,5- and *trans*-2,3-disubstituted pyrrolidines with good (12:1) to excellent (>20:1) diastereoselectivities. The reaction can be conducted with a number of aryl bromide coupling partners that are electron rich, electron neutral, electron poor or heteroaromatic. Alkenyl halides can also be employed if dpe-phos ligand is substituted by dppe. The functional group tolerance is greatly improved with the use of cesium carbonate (Cs_2CO_3), comparing with $^t\text{BuONa}$, and products bearing methyl esters, alkyl acetates, enolizable ketones and nitro groups can be prepared. In addition, the use of Cs_2CO_3 allows for transformations of *N*-benzyloxycarbonyl-protected substrates, which rapidly decompose when $^t\text{BuONa}$ is employed as the base. The development of the reaction conditions involving weak bases has also expanded the scope of this method to allow the coupling of aryl triflate electrophiles. These compounds decompose to the corresponding phenols in the presence of $^t\text{BuONa}$ but the use of mild base potassium carbonate (K_2CO_3) allows for the conversion of *N*-protected γ -aminoalkenes and aryl triflates into 2-benzylpyrrolidine derivatives in good yields and diastereoselectivities.

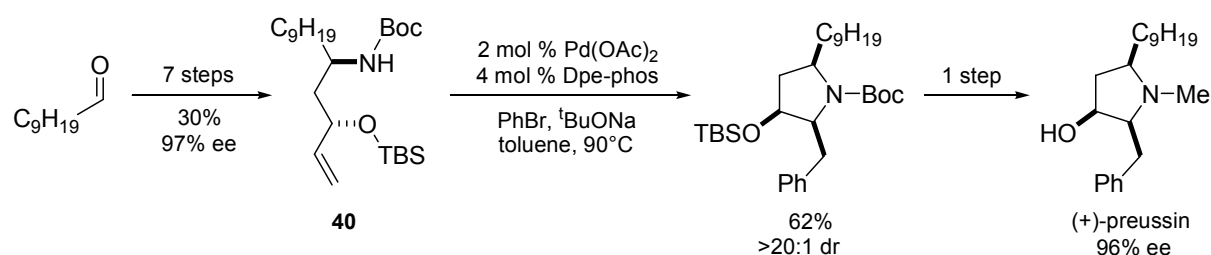
The first asymmetric variant of domino Pd-catalyzed carboamination reactions was described for the coupling between substrates **40a-c** and several different aryl or alkenyl

halides using 2.5 mol % $\text{Pd}_2(\text{dba})_3$ and 7.5 mol % (*R*)-Siphos-PE³⁹ with $^t\text{BuONa}$ as a base in toluene at 90°C (Scheme 18).



Scheme 18. Catalytic asymmetric synthesis of pyrrolidines.

The capability of the diastereoselective carboamidation strategy discussed above was demonstrated in concise synthesis of antifungal and antitumor agent (+)-preussin⁴⁰ (Scheme 19) and its analogues from key substrate **40**.^{24g}



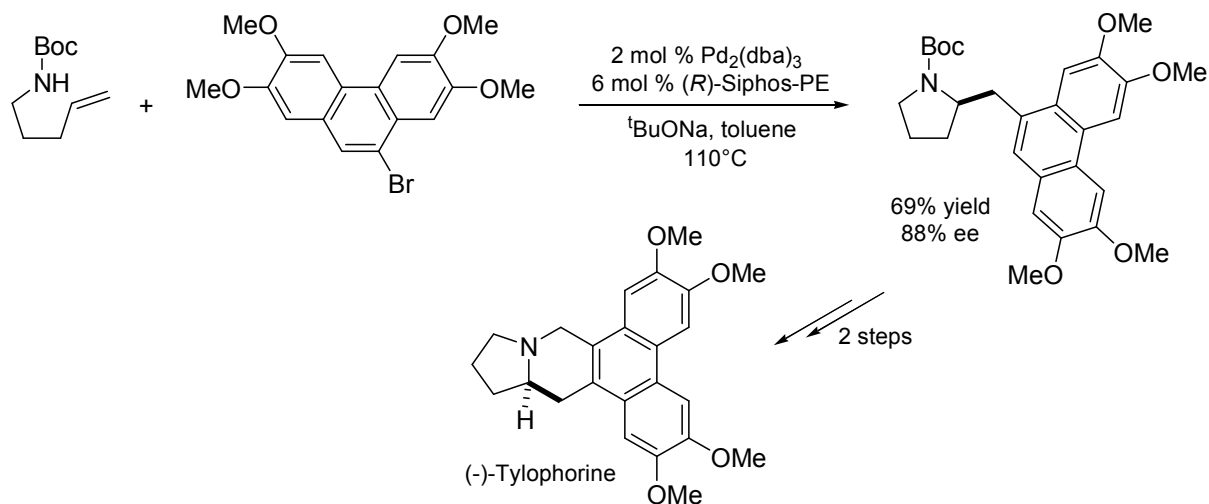
Scheme 19. Synthesis of (+)-preussin.

The synthetic utility of the asymmetric version was illustrated in the synthesis of (-)-tylophorine²⁴¹ (Scheme 20) and (+)-aphanorphine²⁴ⁿ (Scheme 21). The carboamidation reaction of racemic substrate **41** (Scheme 21) afforded the enantiomerically enriched mixture of diastereomers **42a,b** (1:1). The treatment of this mixture with TFA led to cleavage of both the *N*-Boc and *O*-TMS groups, and tosylation of resulting pyrrolidine derivative provided **43a,b** in 83% yield (1:1 dr) over two steps. The enantioconvergent intramolecular

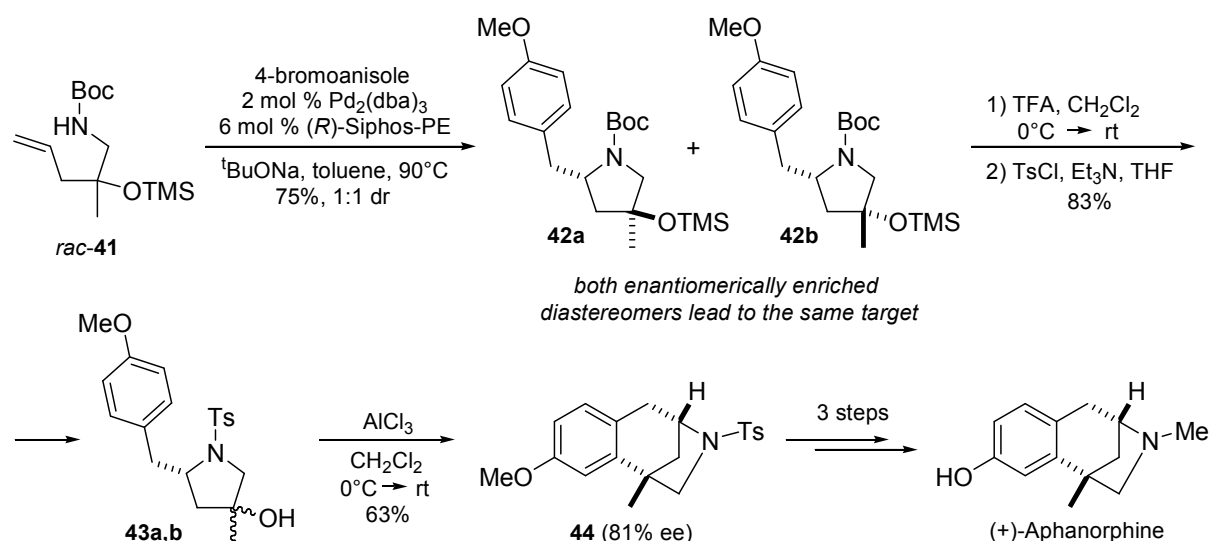
³⁹ Guo, X.-X.; Xie, J.-H.; Hou, G.-H.; Shi, W.-J.; Wang, L.-X.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 2231.

⁴⁰ (a) Schwartz, R. E.; Leisch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. *J. Antibiot.* **1988**, *41*, 1774. (b) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184. (c) Kasahara, K.; Yoshida, M.; Eishima, J.; Takesako, K.; Beppu, T.; Horinouchi, S. *J. Antibiot.* **1997**, *50*, 267. (d) Achenbach, T. V.; Slater, P. E.; Brummerhop, H.; Bach, T.; Müller, R. *Antimicrob. Agents Chemother.* **2000**, *44*, 2794. (e) Kinzy, T. G.; Harger, J. W.; Carr-Schmid, A.; Kwon, J.; Shastry, M.; Justice, M.; Dinman, J. D. *Virology* **2002**, *300*, 60. (f) Okue, M.; Watanabe, H.; Kasahara, K.; Yoshida, M.; Horinouchi, S.; Kitahara, T. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1093.

Friedel-Crafts alkylation of this diastereomeric mixture provided **44** in 63% yield with 81% ee.



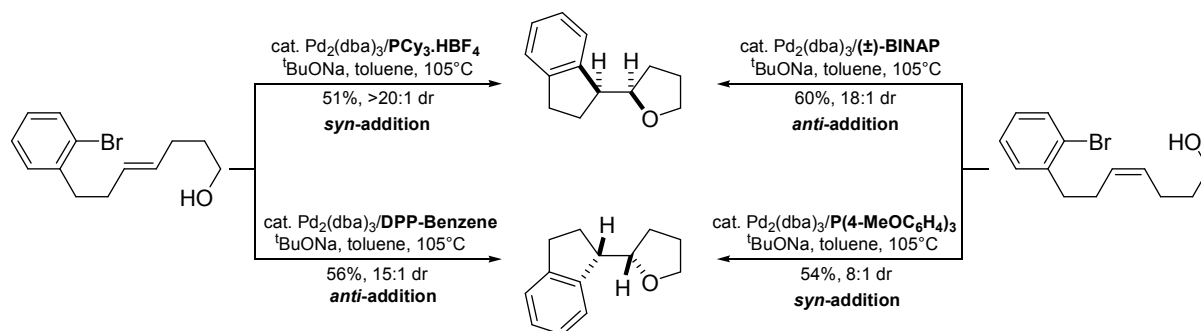
Scheme 20. Synthesis of (-)-tylophorine.



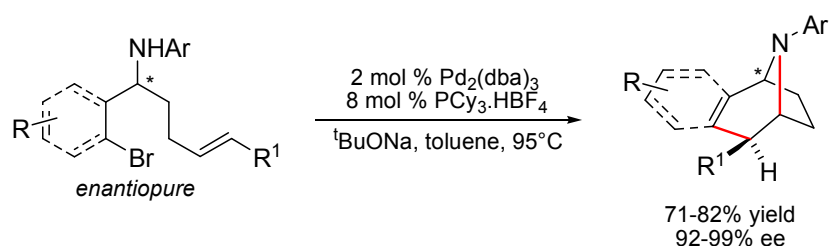
Scheme 21. Synthesis of (+)-aphanorphine.

Intramolecular reactions of unsaturated alcohols or amines bearing tethered aryl halides represent an interesting extension of Wolfe's general carboetherification and carboamination strategy as it allows the synthesis of two rings in a single step (Schemes 22, 23 and 24).⁴¹

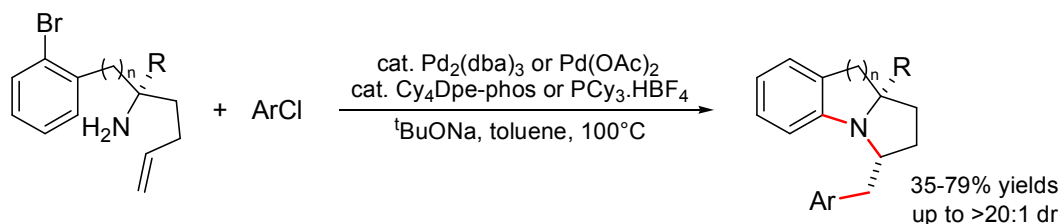
⁴¹ (a) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893. (b) Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2962. (c) Lemen, G. S.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 3218.



Scheme 22. Transformation of alkenes bearing primary alcohols and tethered aryl bromide.^{41a}

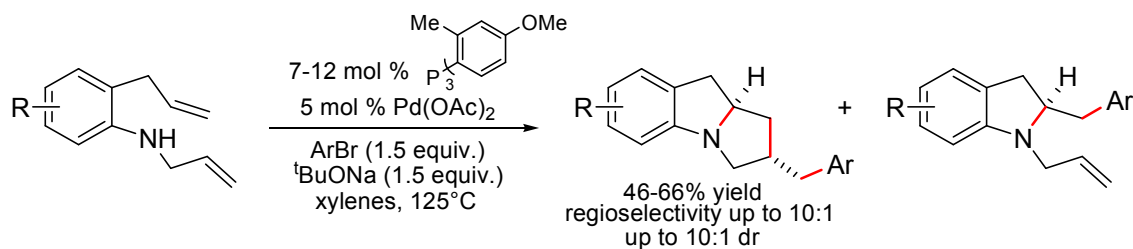


Scheme 23. Transformation of *N*-arylated aminoalkenes bearing tethered aryl bromide into tropanes.^{41b}



Scheme 24. Domino intramolecular *N*-arylation/intramolecular carboamination reaction.^{41c}

The formation of two rings in a single step can be also achieved using *N*,2-diallylaniline derivatives (Scheme 25).⁴²

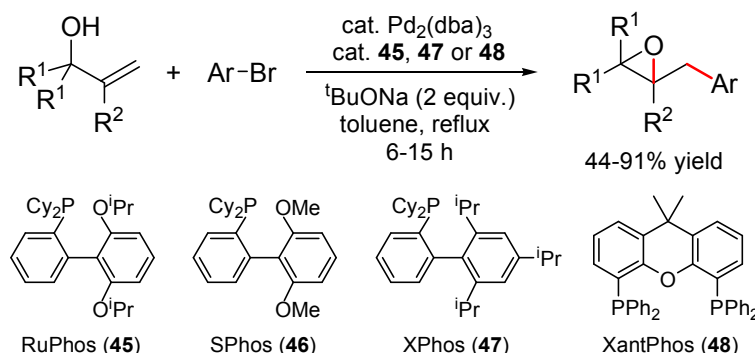


Scheme 25. Domino intramolecular aminopalladation/intramolecular carbopalladation reaction.

Wolfe's general carboetherification and carboamination strategy represents a powerful method for the synthesis of heterocyclic compounds by a domino process, however, it includes a considerable substrate limitations, which will be discussed later.

⁴² Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1028.

Palladium-catalyzed carboetherification reaction of alkenes with aryl bromides is also applicable to more rigid three-membered ring construction (Scheme 26).⁴³



Scheme 26. Palladium-catalyzed epoxidation-arylation reaction in synthesis of substituted epoxides.

Treatment of tertiary allyl alcohols with aryl or alkenyl bromides in the presence of sodium *tert*-butoxide and palladium catalyst provides the corresponding epoxides in moderate to good yields (Scheme 26). The choice of ligand is important, as only using of Buchwald's biaryl phosphines **45-47** and Xantphos **48** led to desired cyclized products. The Mizoroki-Heck reaction of tertiary allyl alcohols predominantly or exclusively proceeded utilizing other phosphine ligands. Reactions proceed smoothly with hydrogen, methyl or phenyl substituent at the internal alkene, however, a bulkier ethyl group in the place of R² caused the decrease of the yields. An electron-withdrawing group on the benzene rings interferes with the formation of epoxides due to competitive Heck reaction. If tertiary allyl alcohol substrates possess a stereogenic center, the diastereoselectivity of cyclization step depends on the bulk of the substituents at α -position (Table 6).

entry	R ^L	R ^S	ligand	dr	yield (%)
1	Ph	Me	47	60:40	43
2	Naph	Me	47	72:28	70
3	<i>i</i> Pr	Ph	47	83:17	57
4	<i>t</i> Bu	Ph	47	>99:1	74
5	<i>t</i> Bu	Me	46	>99:1	65

Table 6. Dependence of the diastereoselectivity on the bulk of α -C-substituents.

⁴³ Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052.

2.4. Domino intramolecular Pd(II)-catalyzed cyclization and carbonylation reaction

The palladium(II)-catalyzed olefin carbonylation reaction⁴⁴ was first reported almost 40 years ago by Stille and co-workers.⁴⁵ The reaction of carbon monoxide with *cis*- and *trans*-but-2-ene in methanol in the presence of palladium(II)-chloride and copper(II)-chloride yielded *threo*- and *erythro*-3-methoxy-2-methylbutanoate, respectively. This domino transformation, based on Wacker process,² which includes oxypalladation of alkenes, migratory insertion of carbon monoxide and alkoxylation, is now broadly defined as palladium(II)-catalyzed oxycarbonylation of unsaturated carbon–carbon bonds.

Despite its well-known toxicity, carbon monoxide is a very valuable and convenient reagent for a variety of reasons. Firstly, it is thermally quite stable and yet chemically reactive. Its relatively high reactivity, especially towards palladium, largely stems from the fact that it can readily provide both a carbon-centered nonbonding pair of electrons and a carbon-centered valence shell empty orbital (Figure 4). Thus, carbon monoxide resembles singlet carbene.

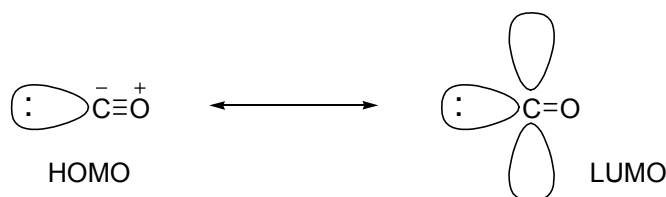
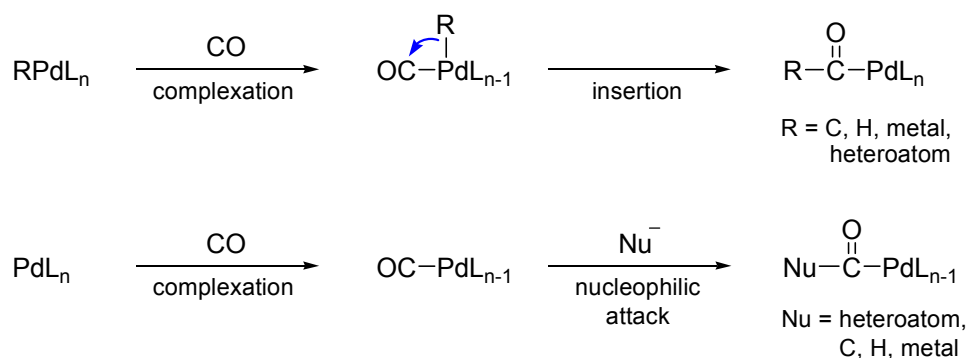


Figure 4. Two resonance structures of carbon monoxide.

Secondly, carbon monoxide is an inexpensive carbon source, which can be incorporated into a variety of organic compounds without producing any undesirable byproducts. Critical processes of carbon-carbon and carbon-heteroatom bond formation can occur *via* either migratory insertion or nucleophilic attack at the carbon atom of the coordinated CO, as shown in Scheme 27. The intramolecular migratory insertion process must involve a concerted [1,2]-shift proceeding with retention of configuration of the migrating group.

⁴⁴ For reviews see: (a) Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415. (b) Hegedus, L. S. *Coord. Chem. Rev.* **1996**, *147*, 443. (c) Heumann, A.; Réglér, M. *Tetrahedron* **1996**, *52*, 9289. (d) Hegedus, L. S. *Coord. Chem. Rev.* **1997**, *161*, 129. (e) Hegedus, L. S. *Coord. Chem. Rev.* **1998**, *175*, 159. (f) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (g) Muzart, J. *Tetrahedron* **2005**, *61*, 5955. (h) Muzart, J. *Tetrahedron* **2005**, *61*, 9423. (i) see ref. 11b. (j) Muzart, J. *J. Mol. Catal. A: Chem.* **2010**, *319*, 1. (k) Beccalli, E. M.; Broggini, G.; Fasana, A.; Rigamonti, M. *J. Organomet. Chem.* **2011**, *696*, 277.

⁴⁵ (a) Stille, J. K.; Jamed, D. E.; Hines, L. F. *J. Am. Chem. Soc.* **1973**, *95*, 5062. (b) James, D. E.; Hines, L. F.; Stille, J. K.; *J. Am. Chem. Soc.* **1976**, *98*, 1806.

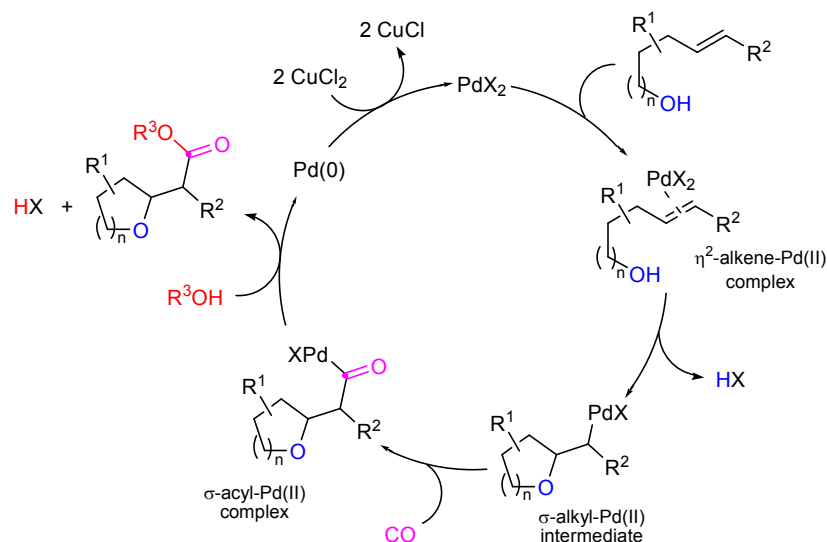


Scheme 27. Two critical processes at carbonylation.

Following sections focus on transformations where the initial oxypalladation step occurs in an intramolecular fashion. Intramolecular palladium(II)-catalyzed oxycarbonylation of unsaturated alcohols is an important transformation giving access to a variety of heterocyclic compounds with diverse functional groups, involving the formation of three new bonds.

2.4.1. Intramolecular alkoxylation-methoxycarbonylation

The intramolecular version of Pd(II)-catalyzed alkoxy carbonylation is widely investigated transformation due to the facility of its exploitation in the stereoselective construction of oxaheterocycles.

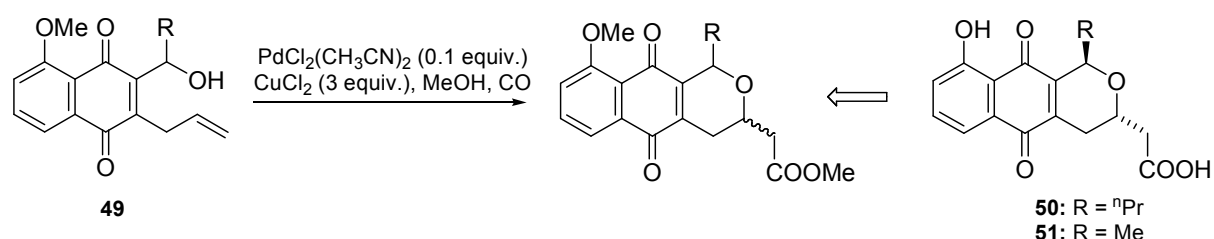


Scheme 28. Proposed catalytic cycle of an intramolecular Pd(II)-catalyzed alkoxy carbonylation.

The generally accepted mechanism of this domino process involves intramolecular nucleophilic attack of hydroxyl group to η^2 -alkene-Pd(II) complex to afford a σ -alkyl-palladium(II) intermediate (Scheme 28). Exposure of this unstable species to the atmospheric

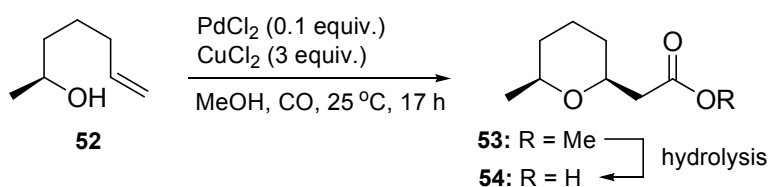
pressure of carbon monoxide results in the insertion of CO into the Pd–C bond to provide σ -acyl-palladium(II) complex, which is finally trapped by alcohol to release the oxaheterocyclic carboxylate. The required catalytic cycle is closed by reoxidation of Pd(0) with CuCl₂ (benzoquinones, manganese(IV) oxide or oxygen, alternatively).

The first application of such Pd-catalyzed alkoxy-methoxycarbonylation reaction to natural product synthesis was described for alkenols **49** providing naphthoquinone antibiotics deoxyfrenolicin **50** and nanaomycin A **51** (Scheme 29), however with only moderate diastereoselectivity (*trans*:*cis*, 3:1).⁴⁶



Scheme 29. Synthesis of deoxyfrenolicin **50** and nanaomycin **51**.

Semmelhack and co-workers systematically studied regio- and stereoselectivity of the cyclization with substituted alkenols.^{18a,b,d;47} The process is efficient for tetrahydropyrans and tetrahydrofurans. While 2,6-disubstituted tetrahydropyrans are formed with a strong preference for the *cis* arrangement, in the several examples of tetrahydrofurans formation, mixtures of diastereomers are produced depending on the relative configuration of substrates. The reaction has been employed for short, stereoselective synthesis of **54**, a component of the African civet cat's glandular marking secretion, starting from (*S*)-hept-6-ene-2-ol **52** (Scheme 30). The key compound **53** was obtained in good yield (74%) and 20:1 (*cis*:*trans*) diastereomeric ratio.^{18b}

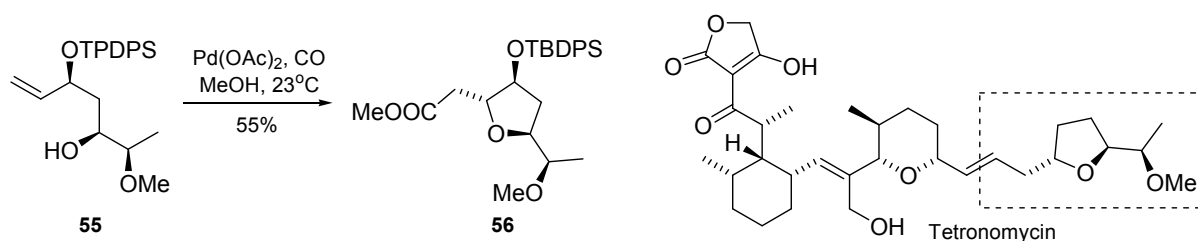


Scheme 30. Synthesis of civet cat compound **54** according to Semmelhack.

⁴⁶ (a) Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulf, W.; Spies, E.; Zask, A. *J. Am. Chem. Soc.* **1982**, *104*, 5850. (b) Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034.

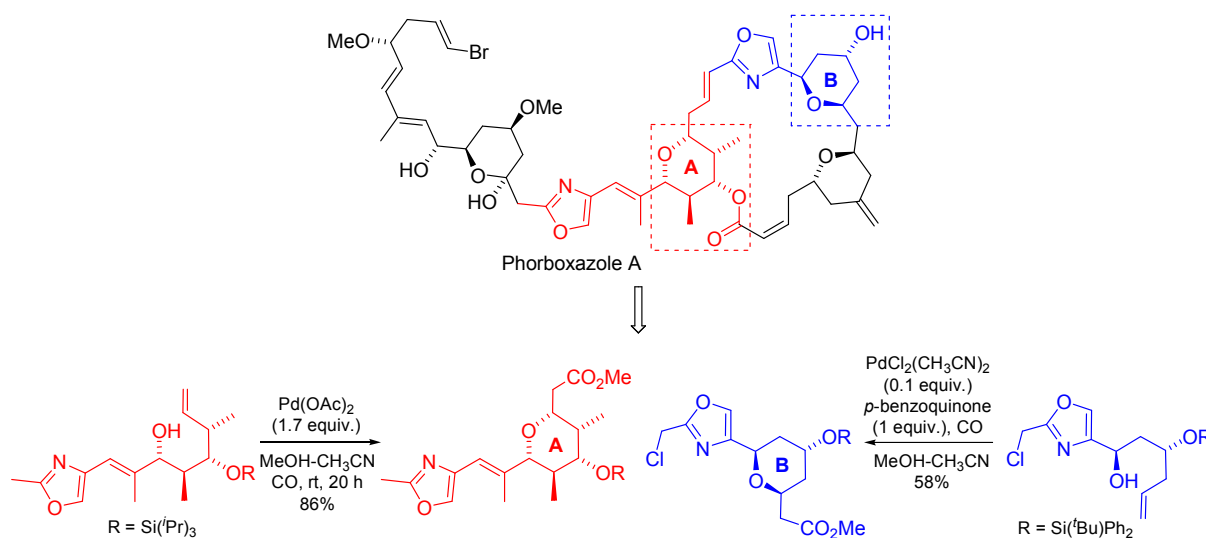
⁴⁷ Semmelhack, M. F.; Epa, W. R.; Cheung, A. W.-H.; Gu, Y.; Kim, C.; Zhang, N.; Lew, W. *J. Am. Chem. Soc.* **1994**, *116*, 2034.

The utility of this approach towards five-membered heterocycles is illustrated by the synthesis of 2,3,5-trisubstituted tetrahydrofuran **56**, which serves as a building block for the synthesis of natural tetronomycin (Scheme 31).⁴⁷ High stereoselectivity of the cyclization of substrate **55** is controlled by removable substituent in the α -allylic position.^{18d}



Scheme 31. Stereoselective cyclization using Pd(II)-catalyzed methoxycarbonylation.

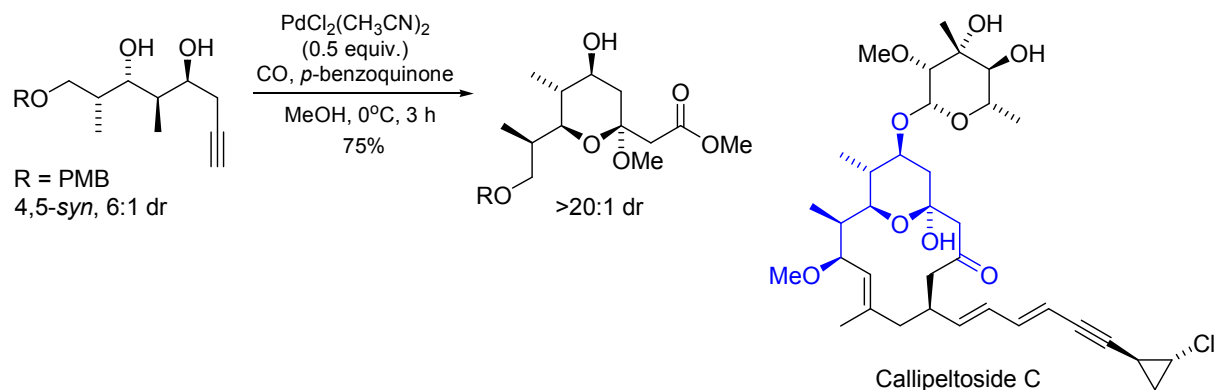
More recently, White et al.⁴⁸ reported the total synthesis of phorboxazole A, one of the most potent cytotoxic natural product yet discovered, which was isolated from a marine sponge of the genus *Phorbas* sp. (Scheme 32). Two subunits containing tetrahydropyrans A and B, respectively, were assembled using Pd-promoted intramolecular 2,6-*cis*-diastereoselective alkoxy carbonylation, however, an excess of $\text{Pd}(\text{OAc})_2$ was needed to complete the conversion in case of the synthesis of ring A.



Scheme 32. Synthesis of phorboxazole A according to White.

⁴⁸ (a) White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Lett.* **2001**, 3, 4003. (b) White, J. D.; Kuntiyong, P.; Lee, T. H. *Org. Lett.* **2006**, 8, 6039.

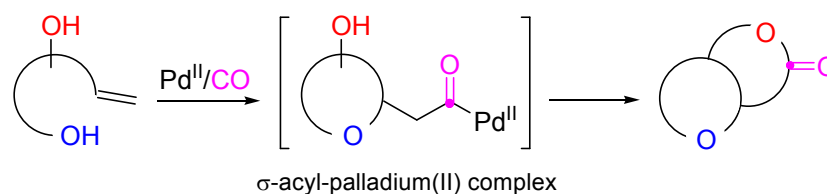
In a similar manner, terminal alkynes cyclize to tetrahydropyrans by an oxycarbonylative reaction, which was demonstrated in the synthesis of complex natural marine macrolide callipeltoside C (Scheme 33).⁴⁹



Scheme 33. Oxycarbonylation of alkynes as the key step in the synthesis of callipeltoside C.

2.4.2. Intramolecular alkoxylation-lactonization

Bicyclization involving oxycarbonylation of hydroxyalkenes has become a powerful tool in target-oriented synthesis. The first examples of this domino reaction: Pd(II)-promoted cyclisation/intramolecular oxycarbonylation were described for 1,4- and 1,3-alkenediols providing *cis*-fused bicyclic lactones involving tetrahydropyran⁵⁰ and tetrahydrofuran⁵¹ structural motif. In these transformations intermediate acylpalladium complexes are trapped intramolecularly by a second hydroxy functionality appropriately placed in the substrate (Scheme 34).



Scheme 34. Intramolecular alkoxylation-lactonization.

Jäger and co-workers⁵² developed a general strategy for the ω -homologation of aldoses using stereocontrolled Pd(II)-catalyzed alkoxylation-lactonization of unsaturated polyols as a key step. The carbon chain of carbohydrate-derived enitols is elongated with

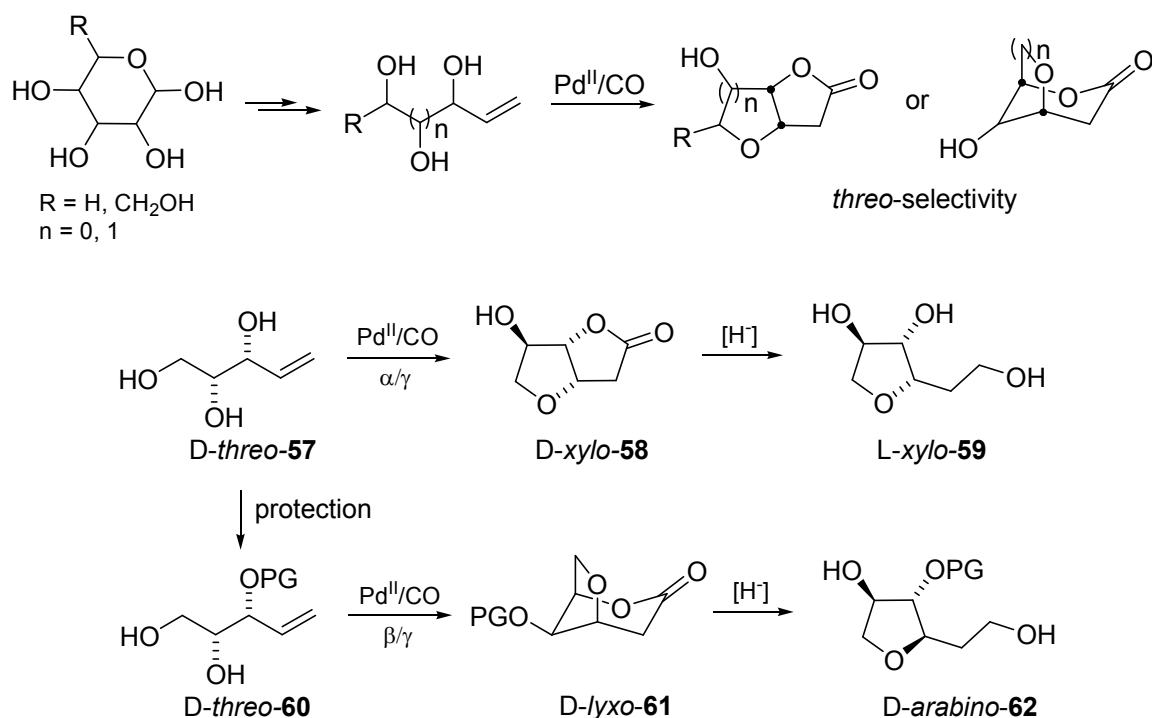
⁴⁹ Carpenter, J.; Northrup, A. B.; Chung, M.; Wiener, J. J. M.; Kim, S.-G.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2008**, 47, 3568.

⁵⁰ Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, 25, 3171.

⁵¹ Tamaru, Y.; Kobayashi, T.; Kawamura, S.-i.; Ochiai, H.; Hojo, M.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, 26, 3207.

⁵² Gracza, T.; Hasenöhl, T.; Stahl, U.; Jäger, V. *Synthesis* **1991**, 1108.

carbon monoxide by actual formation of the new stereogenic centre with defined configuration (Scheme 35). It has been shown that Pd-mediated *O*-cyclization-lactonization transformation of complex *C,C*-unsaturated substrates, loaded with several *a priori* competing nucleophilic functional groups, may turn out high regio- and stereoselectivity which can be controlled by configuration of the substrate and/or partial protection of hydroxyl groups. The regiocontrol of Pd(II)-bicyclization enhances the significance of carbonylation methodology for construction of tetrahydrofurans with defined stereochemistry. For instance, starting from *D*-threo-pentenetriol **57** with free OH groups, via *D*-xylo bicyclic lactone of [3.3.0] type (**58**, α/γ -transformation, Scheme 35), the tetrahydrofuran **59** of *L*-xylo configuration is produced; starting from α -*O*-protected *D*-threo-pentenetriol **60**, via bicycle *D*-lyxo-**61** (product of β/γ -transformation), *D*-arabino-**62** diastereomer is formed.⁵³



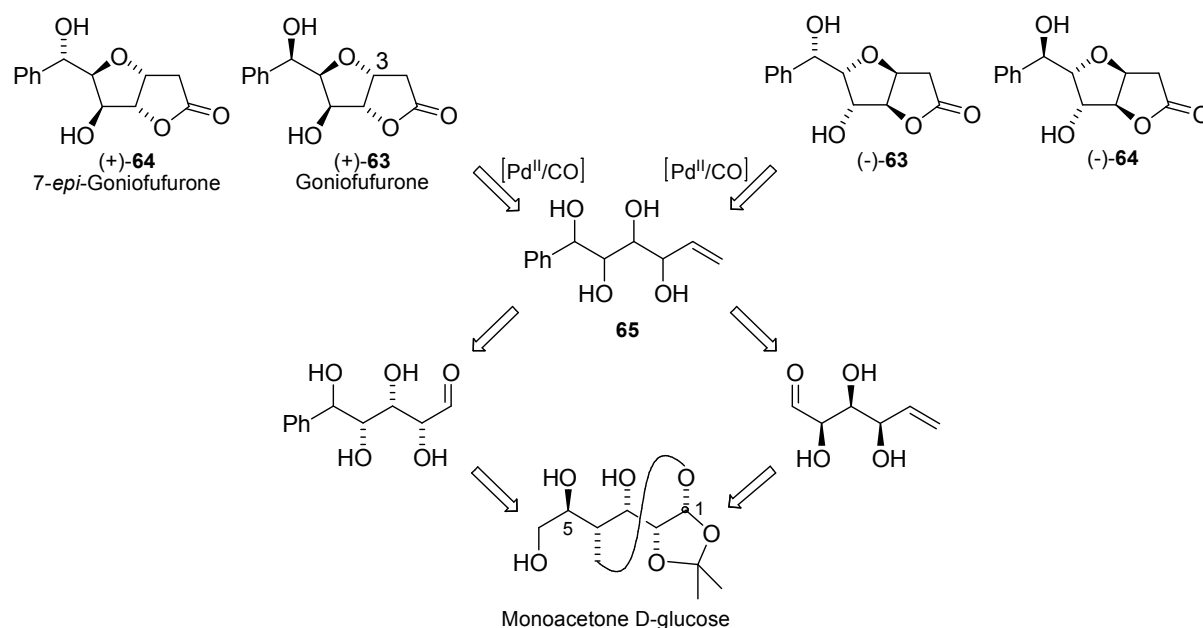
Scheme 35. ω -Homologization of aldoses.

The methodology discussed above was applied in an efficient total synthesis of (-)-**63** and (-)-**64**, and their natural congeners, (+)-goniofufurone (+)-**63** and the 7-epimer (+)-**64**, cytotoxic compounds containing bicyclic lactone as a substructure (Scheme 36).⁵⁴ The crucial step, the Pd(II)-catalyzed oxycarbonylation of corresponding 1-phenyl-5-hexenitols **65**

⁵³ Babjak, M.; Zálupský, P.; Gracza, T. *Arkivoc* **2005**, v, 45.

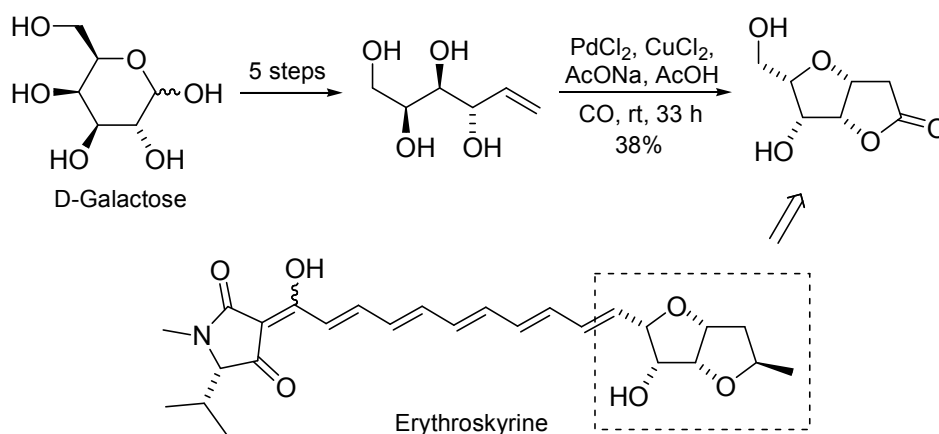
⁵⁴ (a) Gracza, T.; Jäger, V. *Synlett* **1992**, 191. (b) Gracza, T.; Jäger, V. *Synthesis* **1994**, 1359.

provides bicyclic lactones **63**, **64** with high regio-preference and excellent *threo*-selectivity (concerning the newly formed stereocentre at C-3).



Scheme 36. Retrosynthetic analysis of goniofufurones **63** and their epimers **64** according to Gracza and Jäger.

Another convincing application of the homologation strategy represents the total synthesis of erythroskyrine, a polyenoiltetramic acid mycotoxin and principal pigment of *Penicillium Islandicum* (Scheme 37).⁵⁵

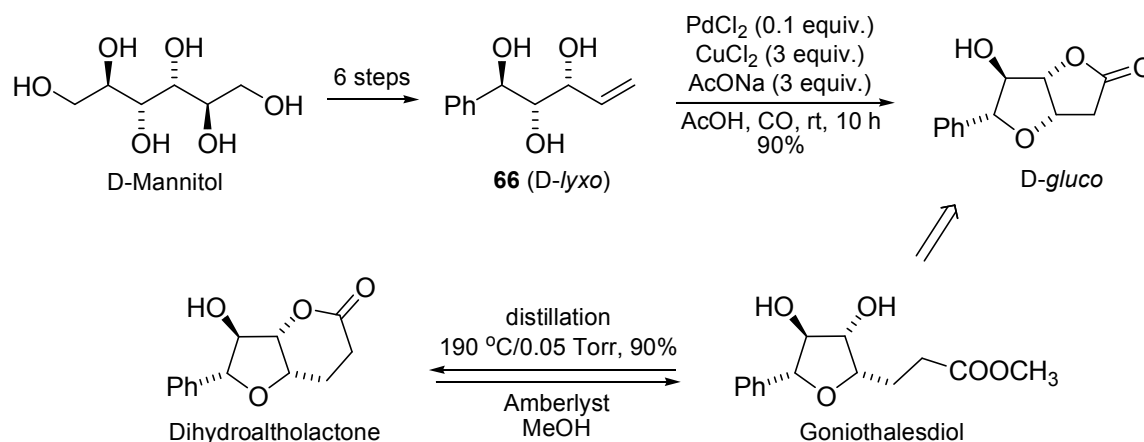


Scheme 37. Intramolecular alkoxy carbonylation-lactonization as the key step in total synthesis of erythroskyrine.

The oxycarbonylation methodology has also been successfully applied in the synthesis of goniothalesdiol and dihydroaltholactone, natural cytotoxic compounds which were isolated

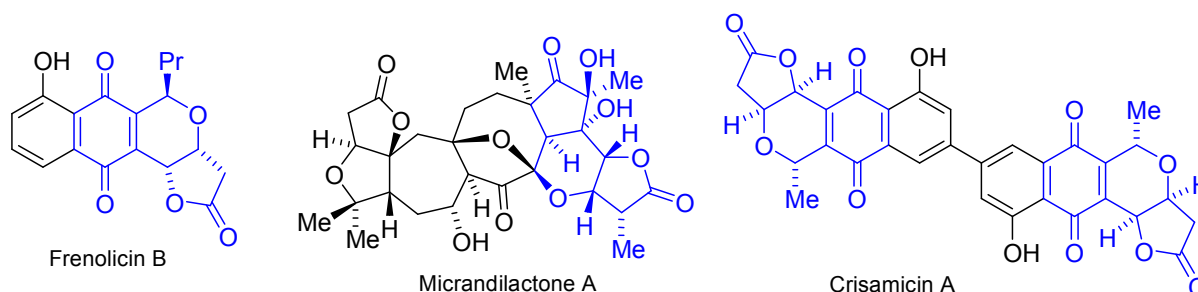
⁵⁵ Dixon, D. J.; Ley, S. V.; Gracza, T.; Szolcsányi, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 8, 839.

from the bark of the Malaysian tree *Goniothalamus borneensis*.⁵⁶ The tetrahydrofuran backbone of both target compounds with D-glucos configuration is generated in high yields from D-lyxose derivative **66** (Scheme 38).



Scheme 38. Key step of goniothalesdiol synthesis according to Gracza.

Further valuable examples of the carbonylation strategy are involved as the key steps in total syntheses of frenolicin B,⁵⁷ micrandilactone A,⁵⁸ crisamicin A,⁵⁹ Hagen's gland lactones,⁶⁰ *trans*-kumausyne,⁶¹ plakortones⁶² and (-)-panacene⁶³ (Figure 5).



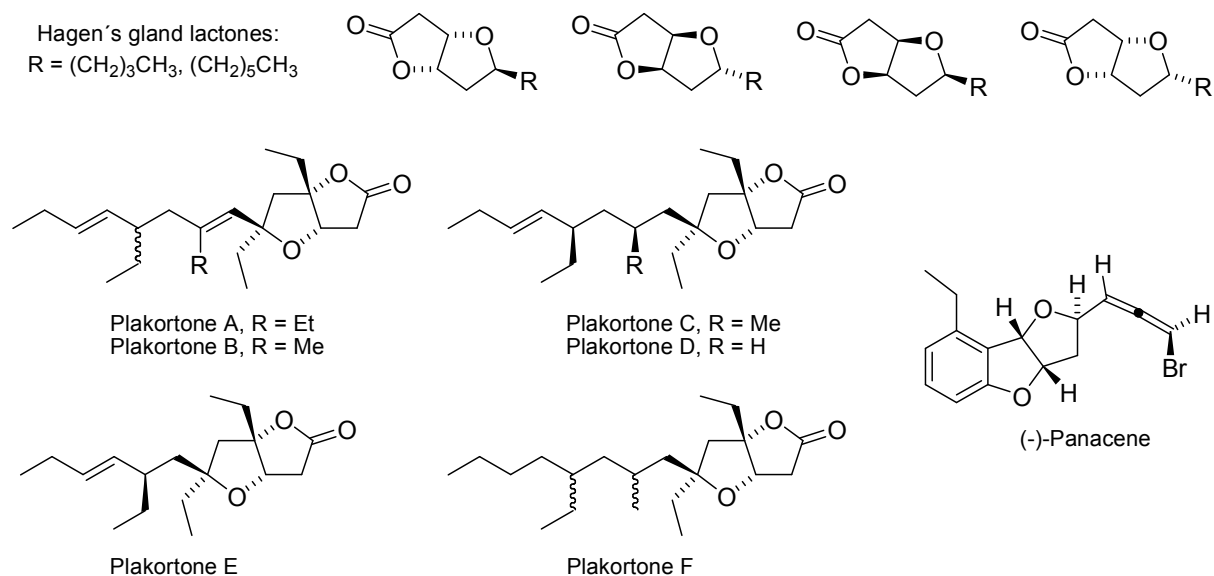
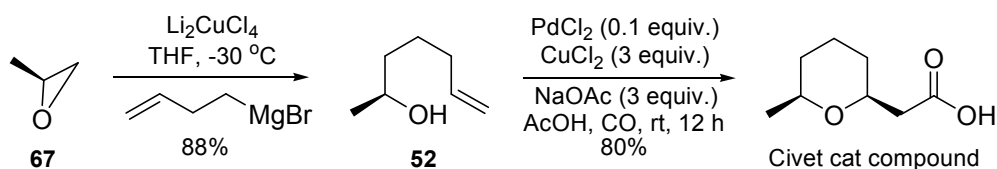


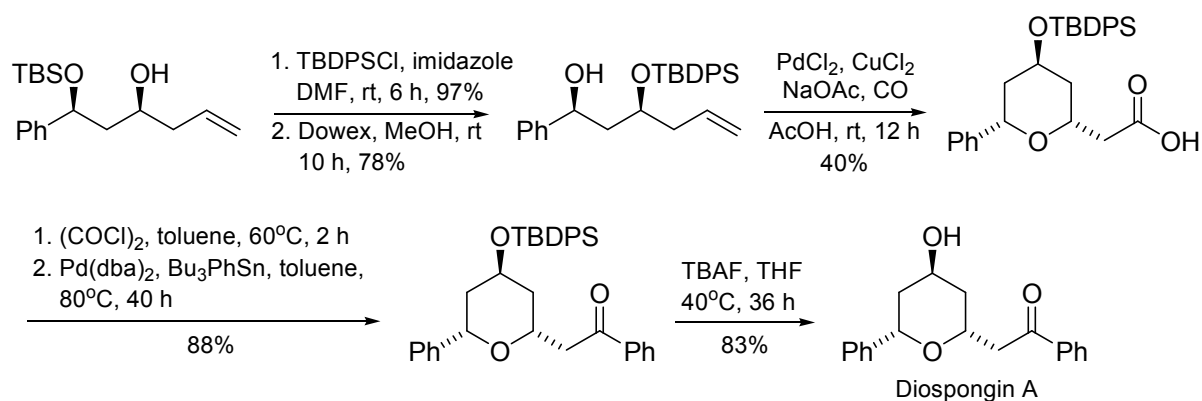
Figure 5b. Structures of Hagen's gland lactones, plakortones and (-)-panacene.

2.4.3. Intramolecular alkoxylation-carboxylation

The capability of Pd-catalyzed cyclization-carboxylation-hydroxylation domino process has been demonstrated in the short and efficient syntheses of two natural products, civet cat compound (2 steps, 70% yield; Scheme 39) and diospongins A (5 steps, 22% from **67**, Scheme 40).⁶⁴



Scheme 39. Total synthesis of civet cat compound.

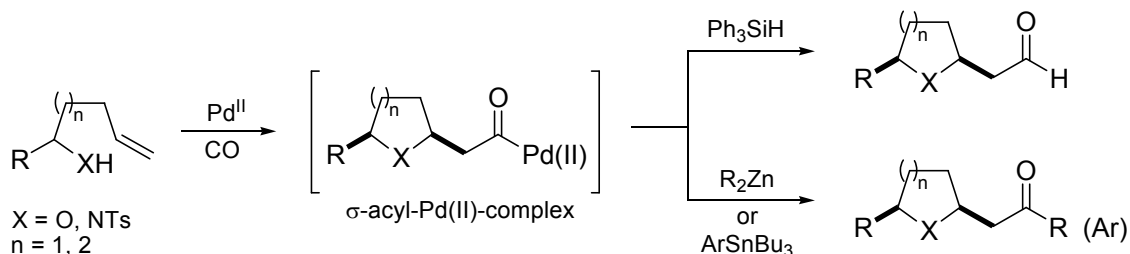


Scheme 40. Total synthesis of diospongins A.

⁶⁴ Karlubíková, O.; Babjak, M.; Gracza, T. *Tetrahedron* **2011**, 67, 4980.

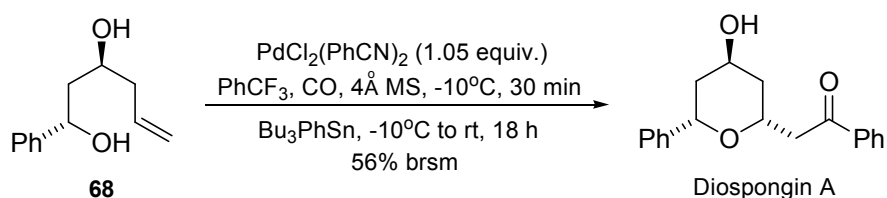
2.4.4. Intramolecular alkoxylation-ketonylation

Recently, Lambert *et al.*⁶⁵ reported a new cascade of reactions incorporating palladium(II)-promoted oxycarbonylation of alkenyl alcohols. Intermediate σ -Pd(II)-acyl species are transmetalated by a suitable organometallic reagent affording ketones or aldehydes. (Scheme 41).



Scheme 41. Oxidative formylation and ketonylation reaction according to Lambert.

These intramolecular oxidative formylation and ketonylation reactions, conceptually related to those described in preceding sections, allow for preparation of carbonyl-bearing complex heterocycles from simple ene-ols, however with the use of stoichiometric amount of palladium reagent. This new oxidative carbonylation method offers new intriguing possibilities and can be incorporated into synthetically productive multicatalytic processes. For example, the transformation of diol **68** under Lambert's reaction conditions (Scheme 42) proceeded smoothly to provide diospongine A with excellent diastereoselectivity (dr > 20:1).⁶⁴



Scheme 42. Pd-catalyzed ketonylation in the synthesis of diospongine A according to Gracza.

2.4.5. Asymmetric intramolecular alkoxylation-carbonylation

In contrast with the impressive evolution of asymmetric reactions with palladium(0) catalyst^{1a,44}, palladium(II)-catalyzed asymmetric Wacker-type oxidations have received only scant attention. For instance, Alper⁶⁶ and Zhang⁶⁷ described asymmetric Pd(II)-catalyzed carbonylation of allylic alcohols. Chiral bis(oxazolines) based on binaphthyl (Boxaxs^{15,68}) or

⁶⁵ Ambrosini, L. M.; Cernak, T. A.; Lambert, T. H. *Synthesis* **2010**, 870.

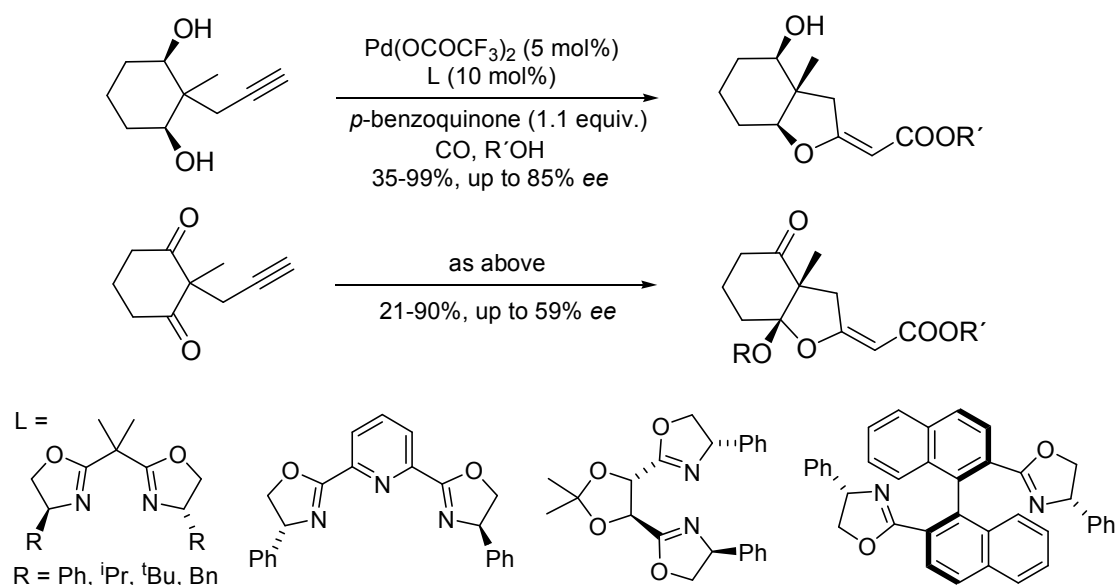
⁶⁶ Alper, H.; Hamel, N. *J. Chem. Soc., Chem. Commun.* **1990**, 135.

⁶⁷ Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1999**, 121, 7708.

⁶⁸ Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **1999**, 64, 1620.

biphenyl backbone^{16b,69} were also successfully applied in the asymmetric Wacker-type cyclization of allylphenols^{14a,16a,70} (section 2.2.). Sasai and co-workers⁷¹ reported oxidative cyclization of alkenyl alcohols with spiro bis(isoxazolines) (SPRIXs).

The first asymmetric variant of a Pd-catalyzed alkoxy-carbonylation was reported by Kato, Akita et al.⁷² accomplishing desymmetrization of cyclic *meso*-2-methyl-2-propargyl-1,3-cyclohexane-diols^{72a,c} and -1,3-diones^{72b} using palladium(II)-complex, bearing chiral bis(oxazoline) ligands (Scheme 43).



Scheme 43. The first asymmetric intramolecular Pd-catalyzed alkoxy-carbonylation reaction.

Recently, Kapitán and Gracza⁷³ have disclosed further oxycarbonylative annulations of unsaturated polyols using chiral palladium(II) complexes. In their initial report,^{73a} the kinetic resolution of pent-4-ene-1,3-diols **69** through asymmetric oxycarbonylative bicyclization has been investigated. The conversion of substrates was controlled by the amount of benzoquinone reoxidant. Besides the chiral ligand, the efficiency of this methodology depends on the anionic part of the catalyst and the solvent. Under optimum

⁶⁹ Wang, F.; Zhang, Y. J.; Wei, H.; Zhang, J.; Zhang, W. *Tetrahedron Lett.* **2007**, 4083.

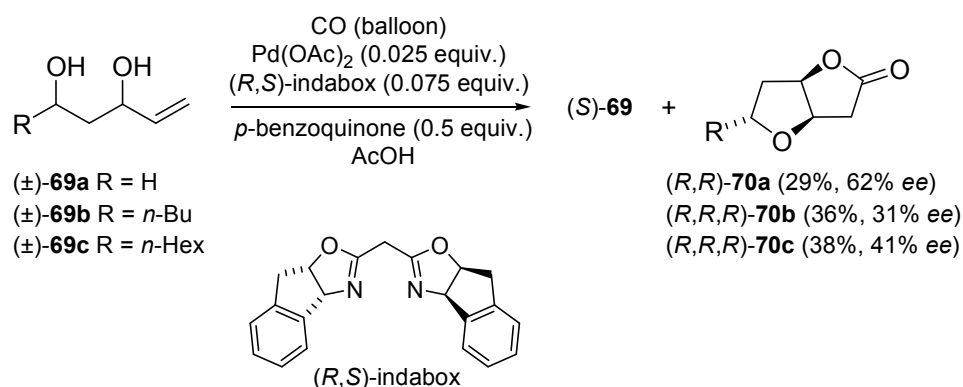
⁷⁰ Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed* **2003**, 42, 2892.

⁷¹ (a) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, 123, 2907. (b) Koranne, P. S.; Tsujihara, T.; Arai, M. A.; Bajracharya, G. B.; Suzuki, T.; Onitsuka, K.; Sasai, H. *Tetrahedron: Asymmetry* **2007**, 18, 919. (c) Takenaka, K.; Akita, M.; Tanigaki, Y.; Takizawa, S.; Sasai, H. *Org. Lett.* **2011**, 13, 3506.

⁷² (a) Kato, K.; Tanaka, M.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, 43, 1511. (b) Kato, K.; Tanaka, M.; Yamamura, S.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2003**, 44, 3089. (c) Kato, K.; Matsuba, C.; Kusakabe, T.; Takayama, H.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T. A.; Vologdin, N. V.; Gusev, O. V. *Tetrahedron* **2006**, 62, 9988.

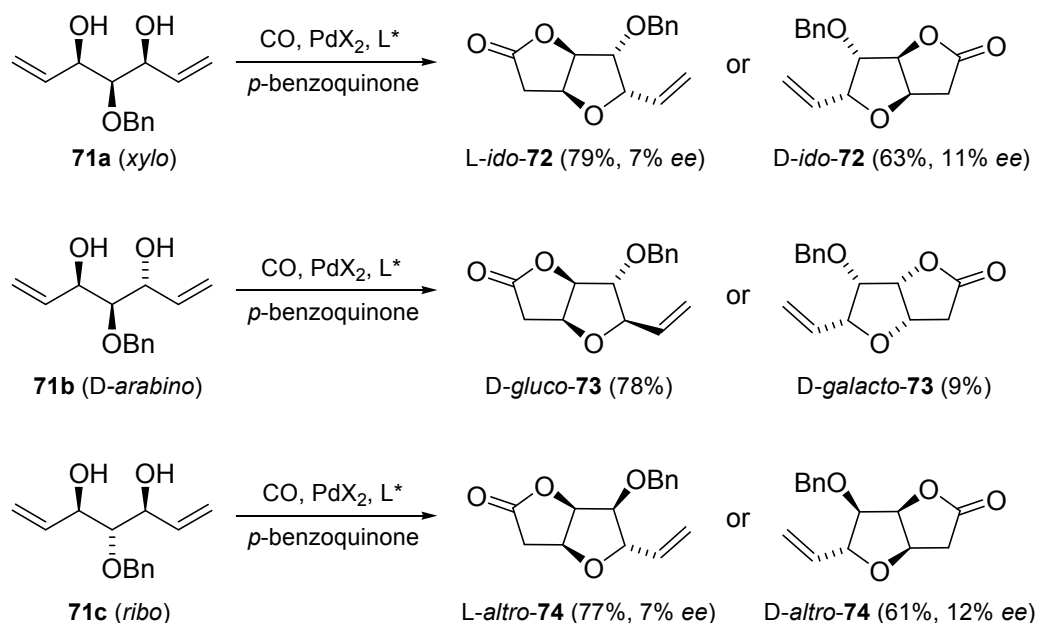
⁷³ (a) Kapitán, P.; Gracza, T. *Arkivoc* **2008**, viii, 8. (b) Kapitán, P.; Gracza, T. *Tetrahedron: Asymmetry* **2008**, 19, 38.

conditions, the lactone **70a** was isolated in 29% yield and 62% ee (Scheme 44). Similarly, the *syn*-diols (±)-**69b** and (±)-**69c** provided the corresponding *exo*-lactones **70b** and **70c**, respectively, with high diastereoselectivity and good yields, however with low enantioselectivities.



Scheme 44. Kinetic resolution of alkene-1,3-diols (±)-**69** via asymmetric Pd(II)-catalyzed oxycarbonylation.

The later study of this transformation with symmetric substrates demonstrated that the *meso*-diols **71a** and **71c** undergo Pd(II)-initiated oxycarbonylative bicyclization to afford bicyclic lactones **72** and **74** in good yields and with excellent *threo*-diastereoselectivity (Scheme 45).^{73b} The applicability of this transformation in the synthesis of natural products illustrates the conversion of **71b** to the optically pure *D*-gluco-**73**, precursor for synthesis of cytotoxic goniofufurone.

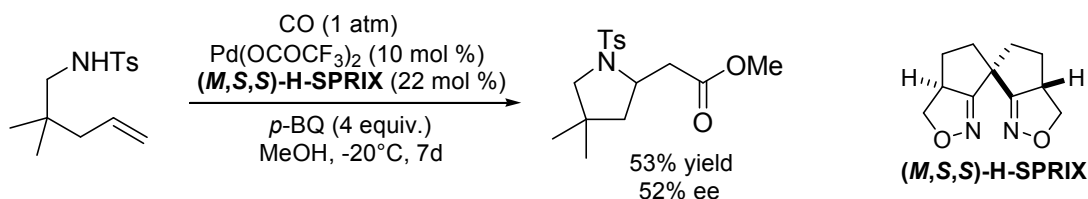


L* = (R,S)-indabox, [(S,S)-bis(4-isopropylloxazol-2-yl)methane]

Scheme 45. Palladium(II)-catalyzed oxycarbonylation of diols **71a-c**.

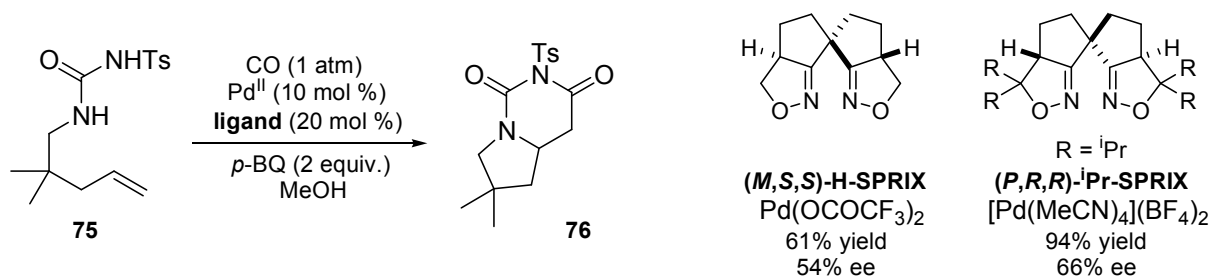
2.4.6. Asymmetric intramolecular aminocarbonylation reaction

The first asymmetric intramolecular aminocarbonylation reaction was reported by Sasai and co-workers using the SPRIX ligands (Scheme 46).⁷⁴ Initial efforts using palladium bis(trifluoroacetate), (*M,S,S*)-**H-SPRIX** ligand and *p*-benzoquinone (4 equiv.) under 1 atmosphere of CO afforded moderate enantioselectivities (up to 65% at -40°C). The reaction did not proceed with BINAP, (*S,S*)-**ip-boxax** nor some bis(oxazolines).



Scheme 46. The first asymmetric intramolecular Pd-catalyzed aminocarbonylation.

Additional studies showed that tosyl urea-derived substrates cyclized under similar reaction conditions with moderate enantioselectivity (Scheme 47). In this case, trapping of the Pd-acyl by a pendant nitrogen nucleophile provided bicyclic 5,6-dihydrouracil derivative **76** with 54% ee. Optimization of reaction conditions for the cyclization of tosyl urea **75** increased enantioselectivity level. Using cationic $\text{Pd}(\text{MeCN})_4(\text{BF}_4)_2$ and the bulkier (*P,R,R*)-**ⁱPr-SPRIX** catalyst provided the product in 94% yield and 66% ee.⁷⁵ Lowering the ligand loading to a Pd/ligand ratio of 1.1:1 allowed the reaction to be performed at -40°C, which resulted in an increase to 88% ee, although the reaction required 7 days to reach total conversion.



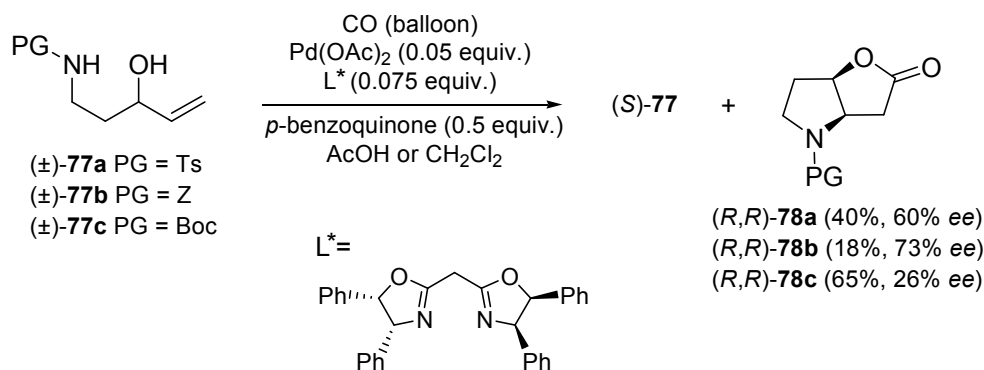
Scheme 47. Asymmetric intramolecular Pd-catalyzed aminocarbonylation of *N*-tosyl ureas.

Analogously with oxycarbonylation of pent-4-ene-1,3-diols **69** shown in Scheme 44, the kinetic resolution of *N*-protected 1-aminopent-4-ene-3-ols (\pm)-**77** through carbonylative

⁷⁴ Shinohara, T.; Arai, M. A.; Wakita, K.; Arai, T.; Sasai, H. *Tetrahedron Lett.* **2003**, *44*, 711.

⁷⁵ Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Org. Chem.* **2009**, *74*, 9274.

bicyclization afforded the corresponding enantiomerically enriched pyrrolidinolactones **78**, *N*-protected Geissman-Waiss lactones (Scheme 48).⁷⁶ Their synthetic utility consists in fact, that Geissman-Waiss lactone is an important intermediate in the syntheses of a number of necine bases.⁷⁷



Scheme 48. Kinetic resolution of (±)-**77** via asymmetric Pd(II)-catalyzed carbonylative bicyclization.

⁷⁶ Koóš, P.; Špánik, I.; Gracza, T. *Tetrahedron: Asymmetry* **2009**, *20*, 2720.

⁷⁷ For synthesis of related structures see: (a) Casiraghi, G.; Zanardi, F.; Rassu, G.; Pinna, L. *Org. Prep. Proced. Int.* **1996**, *28*, 641. (b) Hartmann, T.; Witte, L. *In Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: New York, 1995; pp 155–223. (c) Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic: London, 1986. (d) Niwa, H.; Okamoto, O.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *J. Org. Chem.* **1987**, *52*, 2941. (e) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 5211. (f) Wee, A. G. H. *J. Org. Chem.* **2001**, *66*, 8513.

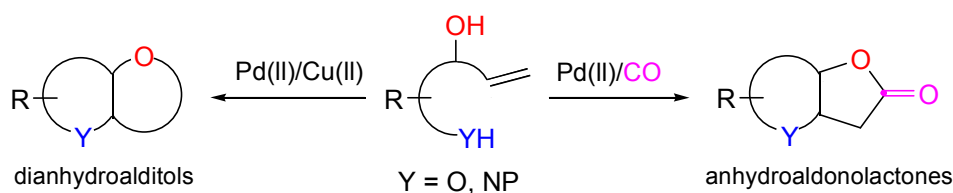
3. OBJECTIVES

The first part of submitted thesis deals with the study of domino intramolecular palladium(II)-catalyzed cyclization of unsaturated polyols and coupling reaction. The second part discusses the kinetic resolution of racemic pentenediols by asymmetric intramolecular palladium(II)-catalyzed oxycarbonylative bicyclization. The main aims and objectives can be summarized as follows:

- preparation and profiling of substrates suitable for the study of mentioned reaction types; synthesis of racemic diol substrates, their α -protection, optically pure triol substrates and aminoalcohols
- development of a general strategy and conditions for successful trapping of σ -alkyl Pd(II)-intermediate by adequate coupling partner, applications directed towards synthesis of naturally occurring compounds or optically pure building blocks
- realization of more extensive ligand screening based on previous results in asymmetric palladium(II)-catalyzed oxycarbonylation, exploration of alternative reoxidation systems; solvent and pressure influence
- improvement of kinetic resolution process, evaluation of ionic liquids and their influence on asymmetric Pd-catalyzed oxycarbonylation; the use of microwave activation in order to accelerate desired transformations

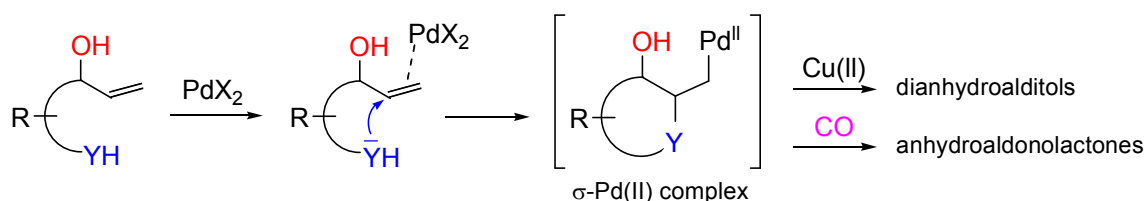
4. RESULTS AND DISCUSSION

Previous studies performed in research group of prof. Gracza have demonstrated the synthetical usefulness of palladium(II)-catalyzed cyclizations of unsaturated polyols and aminopolyols for the construction of biologically interesting heterocyclic skeletons. While such substrates lead to dianhydroalditols under bicyclization conditions ($\text{Pd}^{\text{II}}/\text{Cu}^{\text{II}}$),⁷⁸ in oxy- or amidocarbonylation conditions ($\text{Pd}^{\text{II}}/\text{CO}$)^{52-56,79} they afford anhydroaldonolactones (Scheme 49).



Scheme 49. Pd(II)-catalyzed bicyclizations of (amino) polyols.

The key intermediate of these transformations is an alkyl σ -Pd(II)-complex formed by an intramolecular nucleophilic attack of hydroxyl or amino group on more substituted carbon of double bond activated by palladium (Scheme 50).



Scheme 50. The σ -Pd(II)-complex formation.

4.1. Intramolecular Pd(II)-catalyzed cyclization and coupling reaction

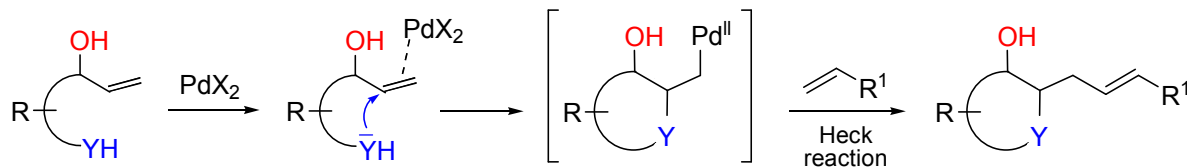
Based on the longstanding studies of Pd(II)-catalyzed cyclization reactions, the main idea of this project was the stereoselective trapping of σ -alkyl Pd(II)-intermediate by suitable coupling partner in the process of side chain extension. Such a domino reaction would present a powerful method for the stereoselective preparation of heterocyclic skeletons with linked side chain functionalities within a single synthetic operation.

⁷⁸ (a) Szolcsányi, P.; Gracza, T. *Chem. Commun.* **2005**, 3948. (b) Babjak, M.; Remeň, I.; Szolcsányi, P.; Zálupský, P.; Mikloš, D.; Gracza, T. *J. Organomet. Chem.* **2006**, 691, 928.

⁷⁹ Szolcsányi, P.; Gracza, T.; Koman, M.; Prónayová, N.; Liptaj, T. *Tetrahedron: Asymmetry* **2000**, 11, 2579.

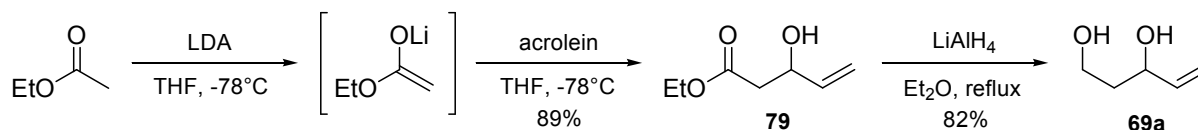
4.1.1. Coupling with alkenes *via* Heck vinylation

At the very beginning of our study, we considered Pd(II)-catalyzed cyclization and coupling with alkenes *via* Heck vinylation⁸⁰ (Scheme 51).



Scheme 51. Trapping of the σ -alkyl Pd(II)-intermediate by alkenes.

In order to study this Wacker-type reaction, we decided to use the simple unsaturated racemic diol **69a** as the model substrate. Pent-4-ene-1,3-diol **69a** was prepared in two steps by the condensation of lithium enolate derived from ethyl acetate with acrolein,^{81a} followed by the reduction of corresponding unsaturated ester **79** with lithiumaluminium hydride^{81b} (Scheme 52). Both, ester **79** and diol **69a** were purified by the distillation under reduced pressure.

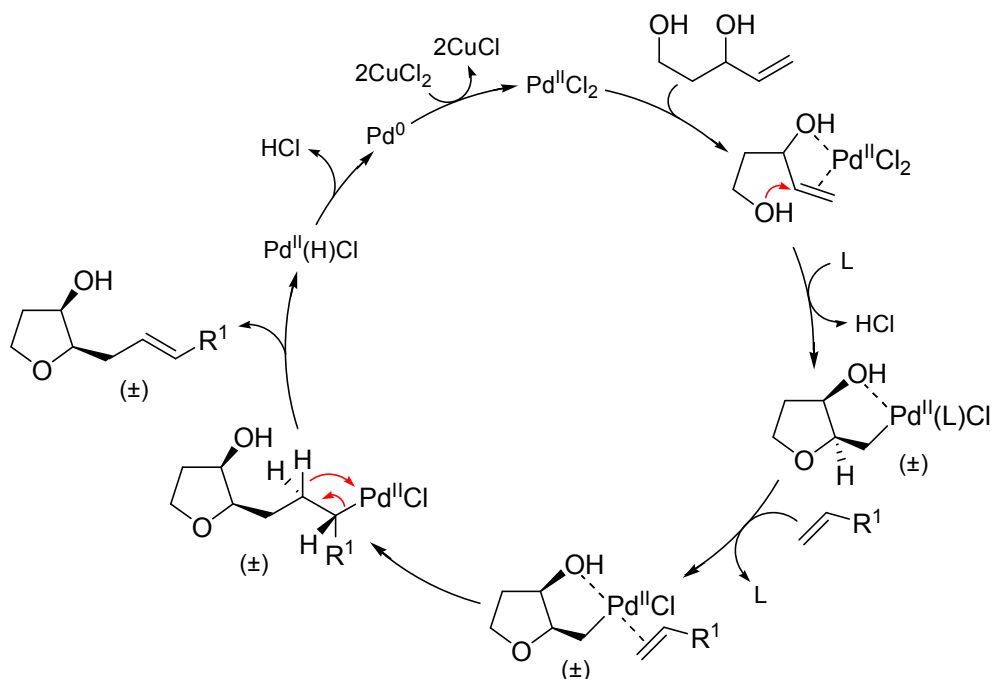


Scheme 52. Preparation of diol **69a**.

We started our investigation according to the reaction conditions which were proven to be the most efficient for Pd(II)-catalyzed bicyclization as well as for oxy- and amidocarbonylation of (amino) polyols, PdCl₂/CuCl₂/AcOH buffered with AcONa.^{52-56,78,79} We supposed the mechanism in which palladium(II) as a soft Lewis acid activates the double bond towards the nucleophilic attack (Scheme 53). We further considered that the free α -hydroxyl group could possibly coordinate with palladium and play an important role in the stereochemistry control of this transformation. The existence of this complexation would prevent the *syn*-alignment of palladium and β -hydrogen and thus, should disallow the competitive β -hydride elimination. σ -Alkyl Pd(II)-intermediate could be then trapped by alkene *via* insertion of the double bond into Pd–C bond. Subsequent β -hydride elimination would afford desired 2,3-*cis*-substituted tetrahydrofuran product.

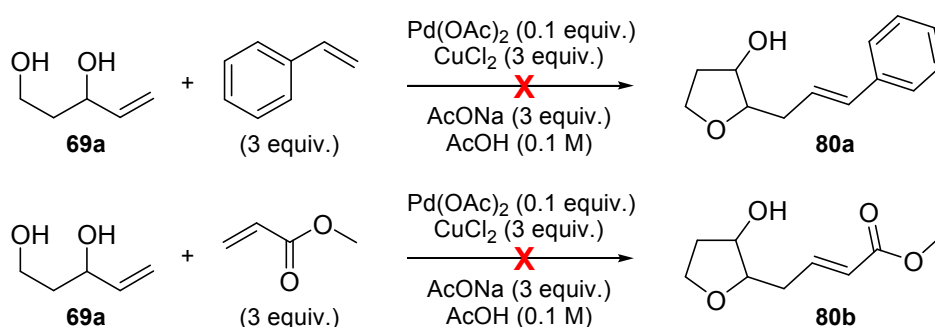
⁸⁰ Holton, R. A. *J. Am. Chem. Soc.* **1977**, *99*, 8083.

⁸¹ (a) Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717. (b) Kelly, D. R.; Nally, J. *Tetrahedron Lett.* **1999**, *40*, 3251.



Scheme 53. Supposed mechanism of domino Wacker-type cyclization–Heck vinylation.

The first experiments were carried out under $\text{Pd}^{\text{II}}/\text{Cu}^{\text{II}}$ conditions in glacial acetic acid with an excess of coupling partner at room temperature (Scheme 54). In both cases, we observed the full conversion of **69a** in 8 hours leading to partially separable mixture of several products. The presence of desired tetrahydrofurans **80a,b** was not confirmed. No improvement occurred when DMF was used instead of acetic acid.

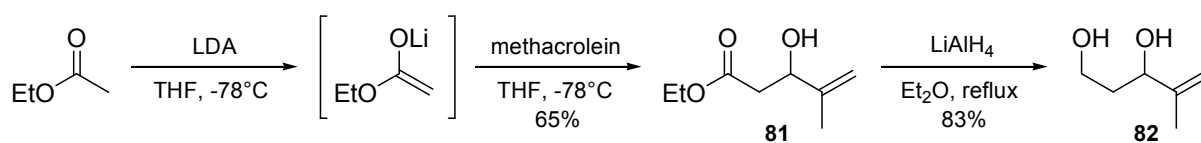


Scheme 54. Attempts at domino reaction under $\text{Pd}^{\text{II}}/\text{Cu}^{\text{II}}/\text{AcOH}$ conditions.

When we subjected the diol substrate **69a** to the same reaction conditions without any coupling partner, surprisingly, the starting material was completely consumed in 2 hours. Moreover, the mixture of products isolated from the reaction mixture was identical with those observed in previous experiments. The failure of desired process was ascribed to the inability of subsequent vinylation reaction efficiently compete with intramolecular β -hydride

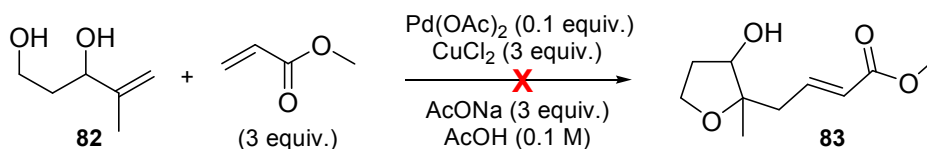
elimination which is much faster. Thus, our idea of α -hydroxyl group and palladium complexation apparently failed in these conditions as well.

The next strategy consisted in a slight modification of the substrate structure. The substitution of C4 hydrogen on double bond by methyl seemed to be the right option how to avoid undesired β -hydride elimination. 4-Methyl-pent-4-ene-1,3-diol **82** was prepared analogously by the condensation^{81a} of lithium enolate derived from ethyl acetate with methacrolein followed by the reduction⁸² of corresponding unsaturated ester **81** with lithium aluminium hydride (Scheme 55).



Scheme 55. Preparation of diol **82**.

Unfortunately, the reaction of **82** with methyl acrylate under identical reaction conditions led to the complex mixture of products (full conversion of substrate in 22 hours) without the presence of desired tetrahydrofuran **83** (Scheme 56). Despite the fact that the β -hydride elimination cannot occur in this case, the reaction of **82** in absence of coupling partner gave complete conversion in 20 hours yielding vague products of substrate homocoupling.



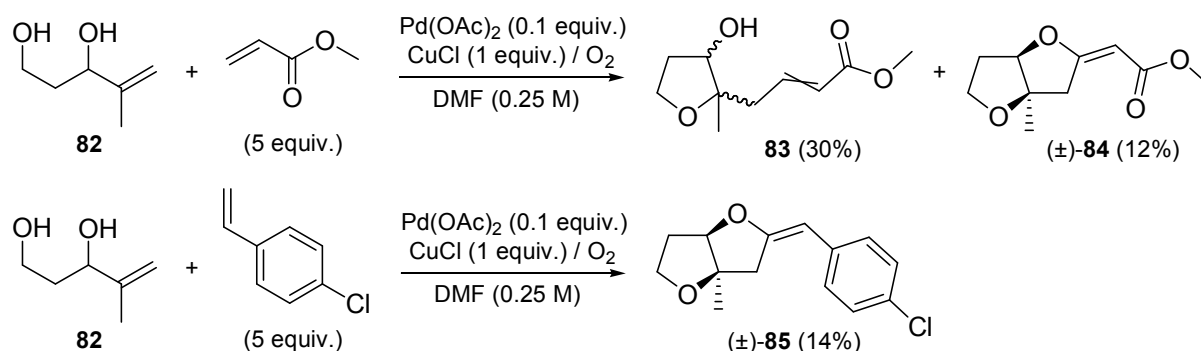
Scheme 56. Attempts at domino reaction under Pd^{II}/Cu^{II}/AcOH conditions.

Based on the pioneering results published by Semmelhack and Epa in the same field (Table 3, Section 2.3.1.),¹⁷ we subsequently turned our attention to Pd^{II}/Cu^I/O₂/DMF system. The substrates described in the literature¹⁷ differed from our model substrate particularly in the absence of hydroxyl group at the α -position.

The reaction of **82** with methyl acrylate using Pd(OAc)₂ as the catalyst and CuCl/O₂ as the reoxidant in DMF at room temperature (Scheme 57) provided the mixture of several products with complete conversion overnight. The desired tetrahydrofuran **83** was isolated in

⁸² Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A.; Oku, A. *J. Org. Chem.* **1992**, 57, 1412.

30% yield as yellowish oil. Based on three analogous sets of signals in ^{13}C NMR, we assume the formation of its stereo- and/or geometric isomers. Simultaneously, a white crystalline compound **84** with an interesting *cis*-bicyclic structure, confirmed by X-ray analysis (Figure 5),⁸³ was isolated in about 12% yield. Similarly, when 4-chlorostyrene was used as coupling partner, the bicyclic compound **85** was isolated in 14% yield (Scheme 57), although, the reaction was much slower (incomplete conversion even after 5 days).



Scheme 57. The formation of bicyclic structures (±)-**84** and (±)-**85**.

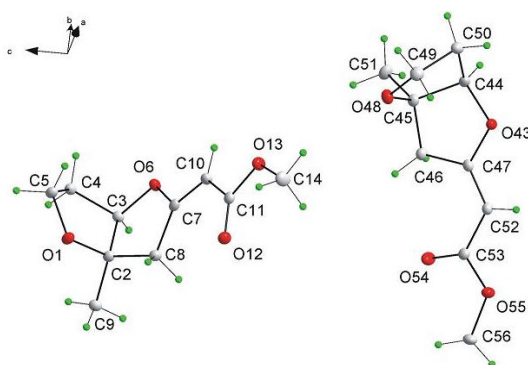
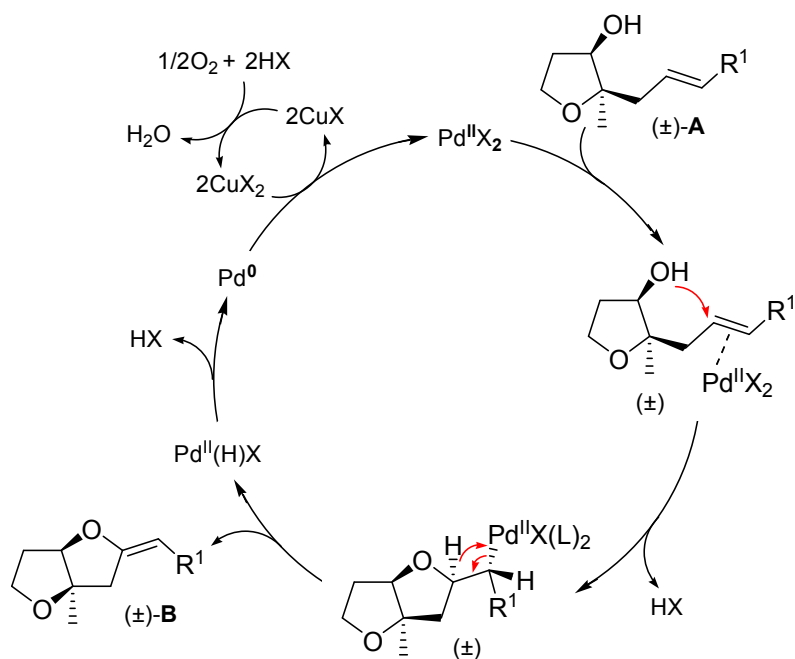


Figure 5. ORTEP view of the structure **84**.

The formation of bicyclic structures **84** and **85** can be explained as follows (Scheme 58). Only (±)-2,3-*cis*-2,2,3-trisubstituted tetrahydrofuran **A**, the product of Pd(II)-catalyzed cyclization and Heck vinylation, can undergo the subsequent reaction – second cyclization *via* nucleophilic attack of free hydroxyl group on the double bond activated by palladium (Scheme 58). The β-H elimination then leads to (±)-*cis*-bicyclic structure **B** as the product of domino reaction sequence: Pd(II)-catalyzed cyclization, Heck reaction, Pd(II)-catalyzed cyclization.

⁸³ Bellovičová, L.; Kožíšek, J.; Doháňšová, J.; Lásiková, A.; Gracza, T. *Acta Crystallographica* **2010**, E66, o2381.

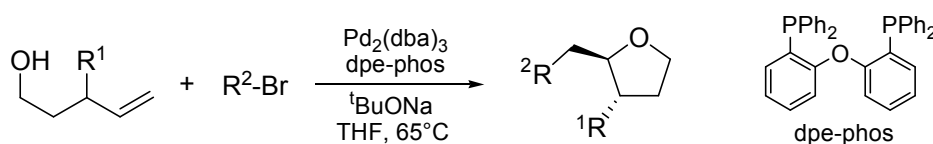


Scheme 58. The proposed mechanism of the formation of bicyclic structures **84** and **85**.

The use of $\text{Pd}(\text{OCOCF}_3)_2$ instead of $\text{Pd}(\text{OAc})_2$ as well as the addition of catalytic amount of acetic or trifluoroacetic acid led to similar results and slightly shorter reaction times.

4.1.2. Coupling with aryl halides

Meanwhile, a detailed study dealing with the domino Pd(II)-catalyzed cyclizations of γ -hydroxy alkenes and coupling with aryl halides appeared in the literature.^{22,23} Wolfe and co-workers found that γ -hydroxy alkenes and aryl halides readily underwent the carboetherification reaction under relatively strong basic conditions using Pd₂(dba)₃/dpe-phos catalytic system with sodium *tert*-butanoate as the base of choice (see Section 2.3.2.). But again, the main difference comparing the described hydroxy alkenes with our model substrates consisted in the absence of free α -hydroxyl group. High *trans*-diastereoselectivities observed in case of 2,3-disubstituted tetrahydrofuran products predominantly relate to alkyl or aryl substitution at the α -carbon of the alcohol substrate.^{23b} The stereocontrol of the formation of 2,3-disubstituted tetrahydrofurans (Table 7) is dependent on the size of 3-substituent (R¹). The stereoselectivity improves as the size increases from methyl (3:1) to *tert*-butyl (>20:1), however, the size of the aryl bromide has a small influence on the diastereoselectivity.



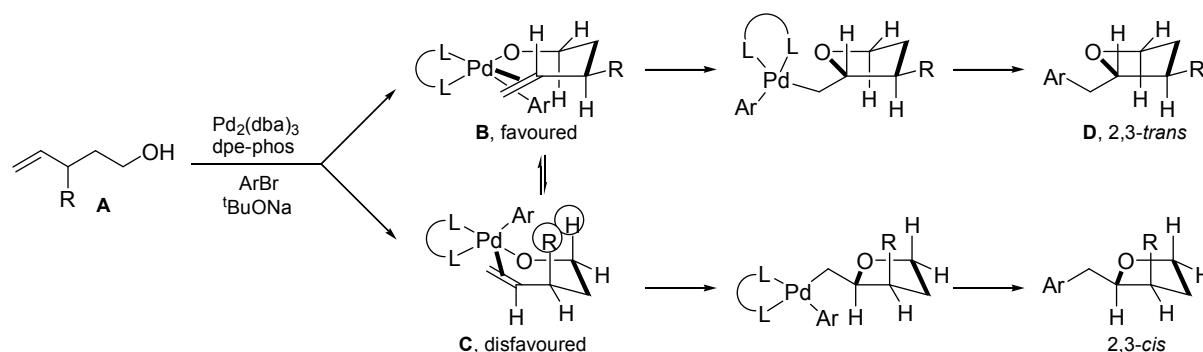
entry	R ¹	R ² -Br	yield	dr
1	H		76%	-
2	Me		78%	3:1
3	Et		66%	6:1
4	Ph		51%	18:1
5	<i>t</i> Bu		55%	>20:1

conditions: substrate (1 equiv.), ArBr (2 equiv.), *t*BuONa (2 equiv.), Pd₂(dba)₃ (0.01 equiv.), dpe-phos (0.02 equiv.), THF, 65°C.

Table 7. 2,3-Disubstituted tetrahydrofurans: dependence of stereocontrol on 3-substituent size.^{23b}

Wolfe proposed that the conversion of a 3-substituted γ -hydroxyalkenes **A** (Scheme 59) to a *trans*-2,3-disubstituted tetrahydrofurans **D** proceeds *via* transition state **B** in which the R group is placed in a pseudoequatorial orientation. The only unfavorable interaction that is present in conformer **C** is developing 1,3-diaxial interaction between the C-3 substituent and the axial C-1 hydrogen. The C-3 carbon is extended out of the coordination plane of the

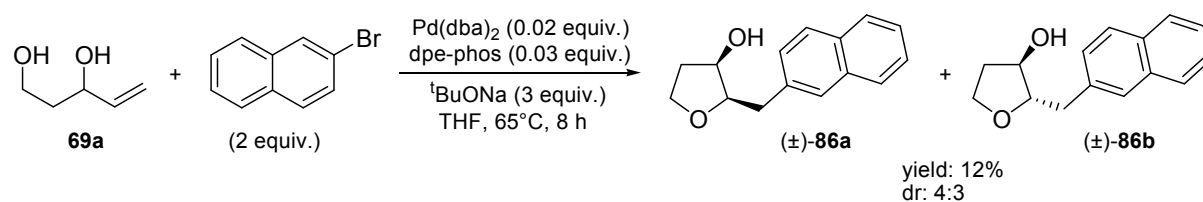
square planar metal complex, which leads to little or no interaction between the C-3 substituent and metal-bound aryl group (or phosphine ligand).



Scheme 59. Stereochemistry of 2,3-disubstituted tetrahydrofurans according to Wolfe.^{23b}

4.1.2.1. Diol substrates

In our continuing investigation, we adopted Wolfe's conditions and subjected the model substrate **69a** to the reaction with 2-bromonaphthalene as a coupling partner (Scheme 60).



Scheme 60. Formation of the product **86**.

The reaction proceeded with full conversion in 8 hours leading to a single product, however, tetrahydrofuran **86** was isolated in low yield (Scheme 60). A slight preference for *cis*-isomer **86a** was observed (the relative configuration of **86a** was confirmed by X-ray analysis, Figure 6).⁸⁴

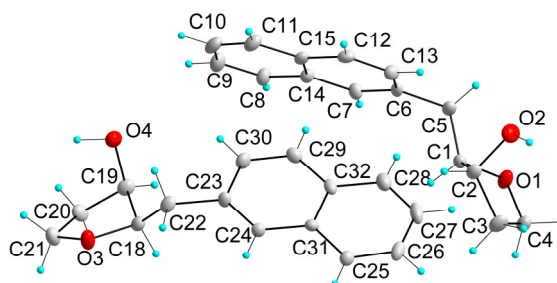
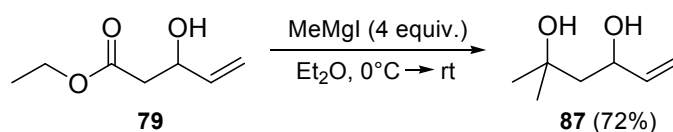


Figure 6. ORTEP view of the structure **86a**.

⁸⁴ Lásiková, A.; Doháňošová, J.; Hlavínová, L.; Toffano, M.; Vo-Thanh, G.; Kožíšek, J.; Gracza, T. *Tetrahedron: Asymmetry* **2012**, accepted.

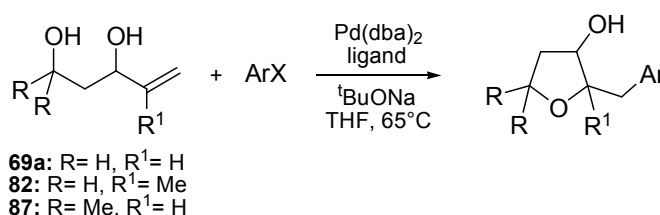
Optimization of reaction conditions

In order to improve the yield and the diastereoselectivity of desired transformation for diol substrates, we attempted to optimize the reaction conditions. At first, we synthesized a model substrate which should exclude the potential β -hydride elimination also in the state of palladium(aryl)(alkoxide) complex **B** (Scheme 59). Corresponding simple 2-methylhex-5-ene-2,4-diol **87** containing two methyl groups at γ -carbon was prepared by the addition of methylmagnesium iodide to the ester **79** (Scheme 61).



Scheme 61. Preparation of the substrate **87**.

Secondly, we tested a different aryl halides, ligands and amounts of the base, coupling partner and catalyst (Table 8).



entry	substrate	ArX (equiv.)	equiv. of ^t BuONa	equiv. of Pd(dba) ₂	ligand (equiv.)	time	conv. ^a (%)	isolated yield (%)	dr ^b (cis/trans)
1	69a	PhI (2)	3	0.1	dppb (0.12)	4 d	90	0	-
2	69a	PhI (2)	3	0.1	dppp (0.12)	4 d	50	0	-
3	69a	2-NaphBr (2)	3	0.02	dpe-phos (0.03)	8 h	100	12	57/43
4	69a	2-NaphBr (1.5)	2	0.02	dpe-phos (0.03)	8 h	100	15	55/45
5	69a	2-NaphBr (1.2)	3	0.02	dppb (0.03)	29 h	100	8	29/71
6	82	2-NaphBr (1.5)	2	0.02	dpe-phos (0.03)	28 h	90	<5	75/25
7	87	2-NaphBr (1.5)	2.2	0.02	dpe-phos (0.03)	30 h	100	traces	-

^a Conversion was determined by ¹H NMR. ^b Diastereomeric ratio was determined by ¹H NMR.

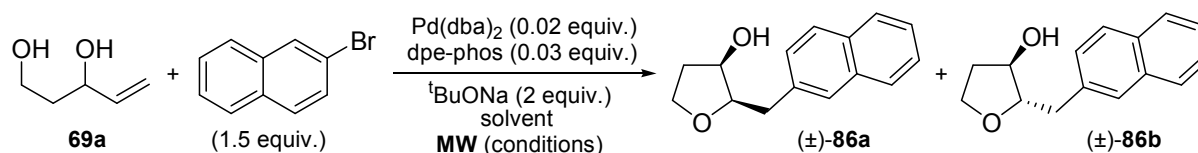
Table 8. Optimization of reaction conditions for diol substrates **69a**, **82** and **87**.

The reaction with phenyl iodide as the coupling partner using different ligands did not afford the desired tetrahydrofuran product (Table 8, entries 1-2). The best yield achieved with substrate **69a** and 2-bromonaphthalene was 15% (entry 4), the diastereoselectivity with a little preference for the *cis*-isomer did not dramatically change by diminishing of coupling partner amount (entry 3 vs. entry 4). Interestingly, the best diastereoselectivity was observed with

1,4-bis(diphenylphosphino)butane (dppb) and was inverted, favoring the *trans*-isomer **86b** (entry 5). The results obtained with substrates **82** and **87** were unsatisfactory (entries 6-7), however, the diastereoselectivity of the reaction of diol **82** using dpe-phos ligand (entry 6) appeared to be better in comparison with **69a** (entries 3-4). Naphthalene formed by the debromination of 2-bromonaphthalene (presumably as the product of undesired β -hydride elimination) was present in high amounts in all of relating reaction mixtures. Appropriate products of the substrate β -H elimination were not detected.

Microwave activation

With a view to accelerate the desired transformation and eventually improve the yield, the experiments under microwave heating conditions were carried out (Table 9).



entry	solvent	conditions	conv. (%)	isolated yield (%)	dr ^a (86a / 86b)
1	-	80°C / 20 min	100	traces	-
2	THF	100°C / 50 min	100	<5%	44/56
3	toluene	80°C / 20 min	100	6% ^b	59/41

^a Diastereomeric ratio was determined by ¹H NMR. ^b Two other unknown products containing terminal double bond were observed in ¹H NMR spectrum of crude mixture.

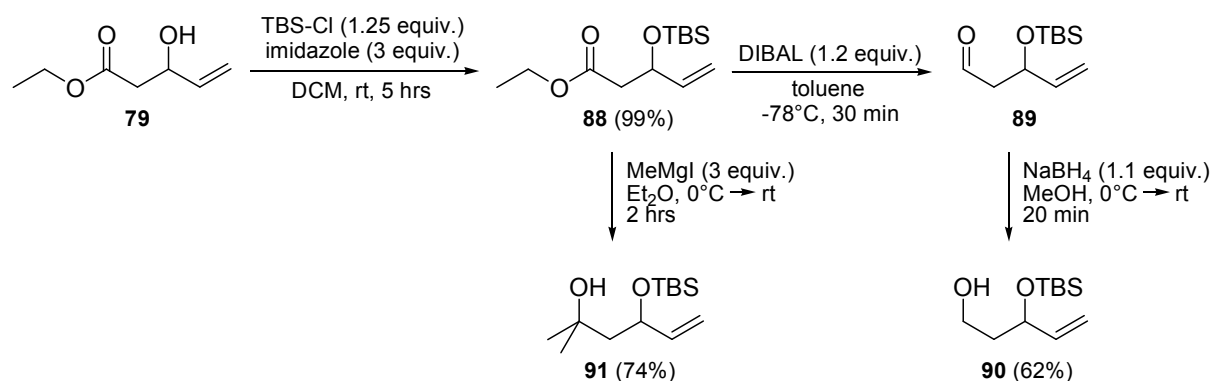
Table 9. Pd(II)-catalyzed cyclization of **69a** and coupling with 2-NaphBr under microwave activation.

The experiment without the solvent led to complete conversion of substrate **69a** but gave only traces of tetrahydrofuran product **86** (Table 9, entry 1). Similarly, the reaction in THF provided the desired product in less than 5% yield with a slight preference for *trans*-isomer **86b** (entry 2), high amount of naphthalene side product was observed in the reaction mixture. When toluene was used as a solvent, no significant improvement was achieved, moreover, two other unidentified products with a terminal double bond were found in the reaction mixture (entry 3).

4.1.2.2. Protection of α -hydroxyl group

It is evident that Wolfe's basic conditions are substrate dependent and do not tolerate the unprotected hydroxyl groups except that participating in cyclization. With above-

described unsatisfactory results in hands, we decided on protecting of the allylic hydroxyl group. Due to the stability in basic conditions, the *tert*-butyldimethylsilyl group was chosen. Thus, new model substrates **90** and **91** were synthesized (Scheme 62). Almost quantitative silylation⁸⁵ of hydroxyester **79** followed by the reduction⁸⁶ of corresponding protected ester **88** by diisobutylaluminium hydride afforded the aldehyde **89**. The reduction⁸⁷ of crude aldehyde **89** with sodium borohydride yielded (±)-3-*tert*-butyldimethylsilyloxy-pent-4-en-1-ol **90**. (±)-2-Methyl-4-*tert*-butyldimethylsilyloxy-hex-5-en-2-ol **91** was prepared by the addition of methylmagnesium iodide to the ester **88**.



Scheme 62. Preparation of α-protected diols **90** and **91**.

Optimization of reaction conditions

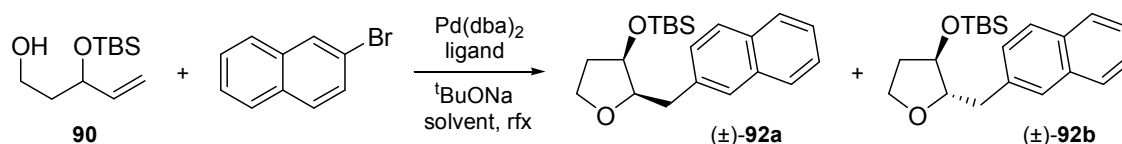
For the purpose to optimize the reaction conditions for the substrate **90**, different phosphine ligands and amounts of coupling partner and base were tested (Table 10).

In general, α-TBS-protected diol substrate **90** afforded higher yields and diastereoselectivities of desired tetrahydrofuran product **92** than the transformations of unprotected diols. The best diastereoselectivity, again in favor of the 'opposite' *trans*-diastereoisomer, was achieved with 1,5-bis(diphenylphosphino)pentane ligand (dppp, Table 10, entry 4), however, the yield was low. 1,4 Bis(diphenylphosphino)-butane (dppb, entry 3) showed almost no diastereoselectivity, in the case of dpe-phos (entries 1-2, 5 and 7-9) and xant-phos (entry 6) the *cis*-diastereoisomer **92a** was formed preferentially (7:3; the relative configuration of isomer **92a** was confirmed by the comparison of the NMR spectra after its TBS-deprotection with the spectra of **86a**). The best yield was achieved in the reaction using 2 equiv. of 2-bromonaphthalene and 1.1 equiv. of the base (entry 8).

⁸⁵ Sannigrahi, M.; Mayhew, D. L.; Clive, D. L. J. *J. Org. Chem.* **1999**, *64*, 2776.

⁸⁶ Tan, C.-H.; Holmes, A. B. *Chem. Eur. J.* **2001**, *7*, 1845.

⁸⁷ Barco, A.; Baricordi, N.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Tetrahedron* **2007**, *63*, 4278.

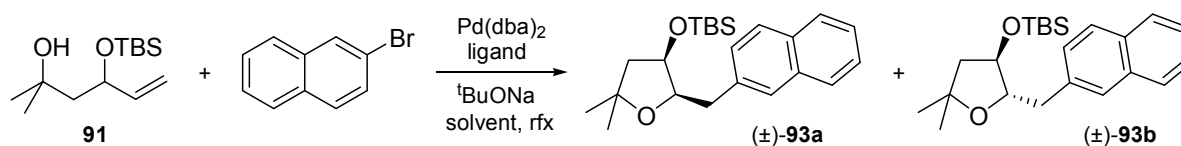


entry	equiv. of 2-NaphBr	equiv. of ^t BuONa	equiv. of Pd(dba) ₂	ligand (equiv.)	solvent	time	conv. ^a (%)	isolated yield (%)	dr ^b (92a/92b)
1	1	1.1	0.05	dpe-phos (0.05)	THF	1 d	100	40	71/29
2	1	1.1	0.1	dpe-phos (0.12)	THF	1 d	100	48	72/28
3	1.5	1.1	0.02	dppb (0.03)	THF	1 d	100	32	45/55
4	1.5	1.1	0.02	dppp (0.03)	THF	2.5 d	95	14	17/83
5	1.5	1.5	0.1	dpe-phos (0.12)	THF	3 h	100	45	72/28
6	1.5	1.5	0.1	xant-phos (0.12)	THF	2 h	100	31	70/30
7	1.5	1.5	0.1	dpe-phos (0.12)	toluene	2 h	100	39	67/33
8	2	1.1	0.1	dpe-phos (0.12)	THF	4 h	100	52	72/28
9	2	2	0.1	dpe-phos (0.12)	THF	3 h	100	49	72/28

^a Conversion was determined by GC. ^b Diastereomeric ratio was determined by GC.

Table 10. Optimization of reaction conditions for α -protected diol substrate **90**.

Analogous optimization for substrate **91** showed the similar results (Table 11).



entry	equiv. of 2-NaphBr	equiv. of ^t BuONa	equiv. of Pd(dba) ₂	ligand (equiv.)	solvent	time	conv. ^a (%)	isolated yield (%)	dr ^b (93a/93b)
1	1	1.1	0.05	dpe-phos (0.05)	THF	1 d	94	48	62/38
2	1.5	1.1	0.02	dpe-phos (0.03)	THF	1.5 d	100	53	56/44
3	1.5	1.1	0.02	dppb (0.03)	THF	1 d	100	40	45/55
4	1.5	1.1	0.02	dppp (0.03)	THF	1 d	100	42	58/52
5	1.5	1.5	0.1	dpe-phos (0.12)	THF	8 h	96	52	66/34
6	1.5	1.5	0.1	xant-phos (0.12)	THF	2.5 h	82	43 ^c	55/45
7	1.5	1.5	0.1	dpe-phos (0.12)	toluene	1.5 h	100	50	55/45
8	2	1.1	0.1	dpe-phos (0.12)	THF	4 d	86	38 ^c	66/34
9	2	2	0.1	dpe-phos (0.12)	THF	8 h	96	51	68/32

^a Conversion was determined by GC. ^b Diastereomeric ratio was determined by GC. ^c The Heck-type side-product was observed.

Table 11. Optimization of reaction conditions for α -protected diol substrate **91**.

All tested bis(phosphine) ligands (dppb, dppp, xant-phos and dpe-phos) provided worse diastereoselectivities comparing to those achieved with the substrate **90**. The highest yields were accomplished with ligand dpe-phos; however, the diastereoselectivities were

moderate (Table 11; entries 2, 5, 7 and 9). The product of Heck-type reaction⁸⁸ **94** (Figure 7) was observed as a byproduct in the case of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene ligand (xant-phos, entry 6; 8% yield), and when the reaction time was extended due to slow conversion in the reaction with 2 equiv. of the base (entry 8; 8% yield). The (*E*)-configuration on the double bond was affirmed by the NMR coupling constant between hydrogens H-5 and H-6 ($J_{5-6} = 15.9$ Hz).

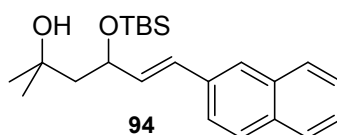
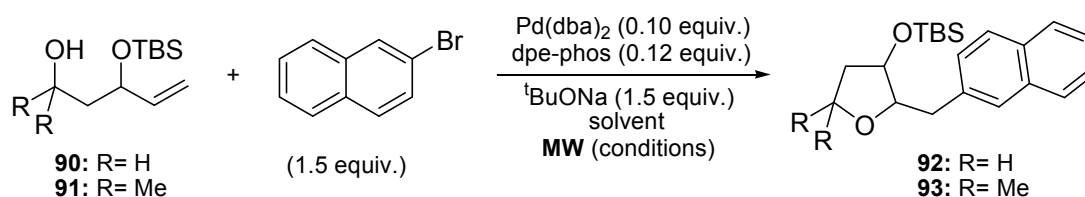


Figure 7. The product of Heck reaction **94** derived from **91**.

Microwave activation

After the optimization in classical heating conditions, we decided to explore the influence of microwave activation on studied domino reaction of **90/91** with 2-naphthyl bromide (Table 12).



entry	substrate	solvent	conditions	conv. (%)	isolated yield (%)	dr ^a (<i>cis/trans</i>)
1	90	THF	65°C / 3 h	<10%	-	-
2	90	toluene	70°C / 1 h	100	57%	44/56
3	91	toluene	70+80°C / 1+1 h	96	42%	59/41

^a Diastereomeric ratio was determined by GC.

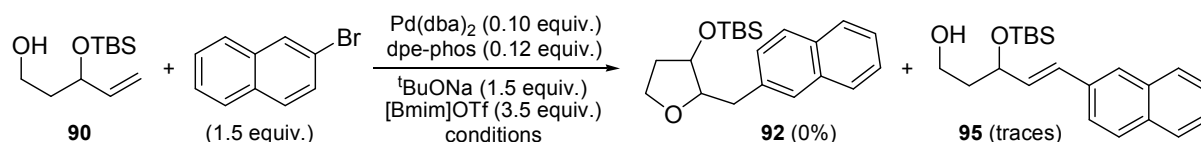
Table 12. Pd(II)-catalyzed cyclization of **90/91** and coupling with 2-NaphBr under MW activation.

As shown in Table 12, the reaction of substrate **90** performed in the microwave reactor in toluene proceeded with slightly better yield, however, with lower diastereoselectivity (Table 12, entry 2 vs. Table 10, entries 5, 7). When tetrahydrofuran was used instead of toluene, the reaction was much slower (entry 1). In the case of the substrate **91**, no improvement occurred in comparison with the results under classical heating (entry 3).

⁸⁸ Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

The use of ionic liquids

Ionic liquids (ILs), or room temperature molten salts, have attracted considerable attention thanks to their ability to serve as effective reaction media for a wide range of organic reactions and other applications in chemistry.⁸⁹ By modifying the structure of cations or anions of ionic liquids, it has been shown that their properties can be altered in order to influence the outcomes of reactions. We were interested in evaluating the effect of ionic liquid used as solvent on transformation. Unfortunately, the conversions of **90** in experiments carried out in 1-butyl-3-methylimidazolium trifluoromethanesulfonate ([Bmim]OTf) were incomplete even after 4 days of classical heating (Table 13, entry 1) or after several cycles in microwave reactor (entry 2). The only product detected in the reaction mixture besides the starting material was the Heck product⁸⁸ **95**.



entry	conditions	conv. (%)	% isol. yield (92)	side products
1	classical heating: 70°C / 4 d	30	-	95
2	MW heating ^a	40	-	95 , naphthalene

^a 70°C / 30 min, 70°C / 30 min, 80°C / 30 min, 100°C / 30 min, 120°C / 30 min, 120°C / 20 min.

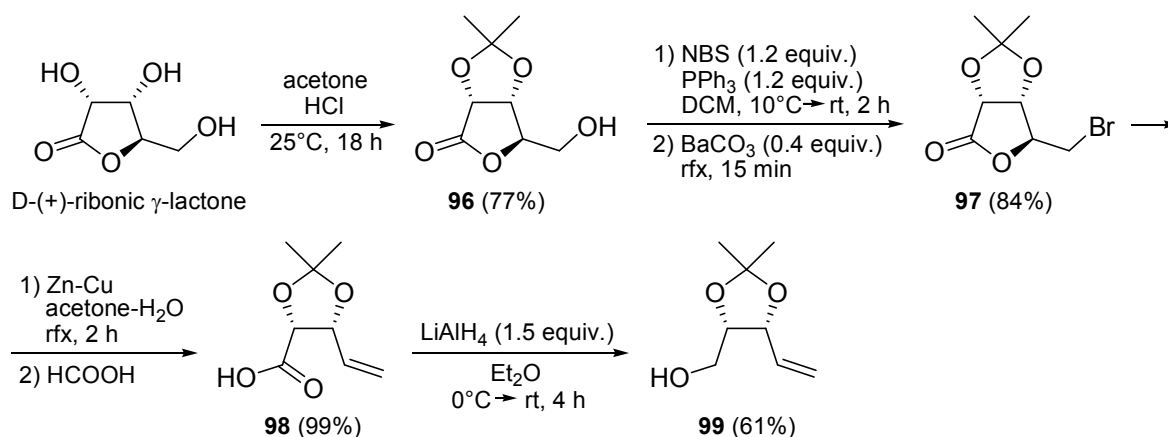
Table 13. Using of [Bmim]OTf instead of organic solvents.

4.1.2.3. Acetonide-protected triol substrates, towards applications in synthesis

As the principal research area of our group is oriented not only towards the study of stereoselective reactions but as well towards their applications in the syntheses of naturally occurring compounds or optically pure building blocks, we were interested in the extension of Pd(II)-catalyzed cyclization and coupling reaction for polysubstituted γ -hydroxy alkenes. For this purpose, (2*S*,3*R*)-2,3-*O*-isopropylidene-pent-4-en-1,2,3-triol⁹⁰ **99** was synthesized in 4 steps starting from commercially available D-(+)-ribonic acid γ -lactone (Scheme 63).

⁸⁹ see Section 4.2.4.

⁹⁰ Jäger, V.; Häfele, B. *Synthesis* **1987**, 801.

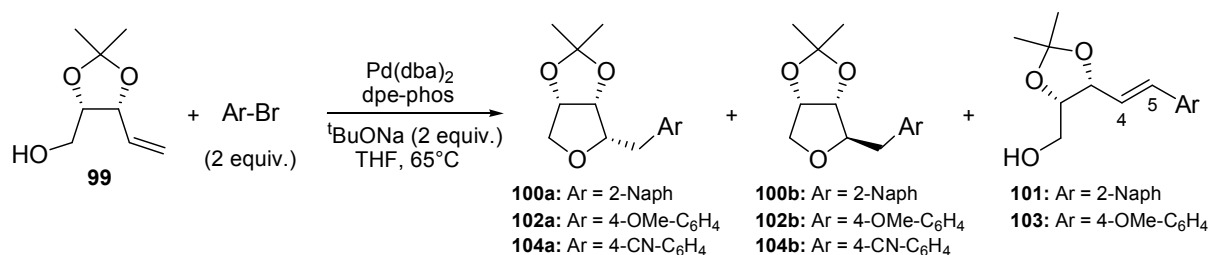


Scheme 63. The synthesis of triol substrate **99**.⁹⁰

In the first step, α - and β -hydroxyl groups of D-(+)-ribonic acid γ -lactone were protected with the acetonide (Scheme 63).⁹¹ The free hydroxyl group of the protected lactone **96** was then substituted with bromide using NBS to give **97**, followed by the reductive ring opening with Zn-Cu complex.⁹⁰ Subsequent reduction of carboxylic acid **98** with lithium aluminium hydride led to corresponding triol **99** in good overall yield.

Experiments under basic conditions

A series of experiments with the substrate **99** was accomplished using different aryl halides as coupling partners and Pd(dba)₃/dpe-phos as the catalytic system (Table 14).



entry	Ar-Br	equiv. of Pd(dba) ₂	equiv. of dpe-phos	time (h)	domino product (isolated yield, %)	Heck product (isolated yield, %)	dr ^a (a/b)
1	2-NaphBr	0.02	0.02	10	100 (30)	101 (8)	71/29 ^b
2	4-Br-C ₆ H ₄ -OCH ₃	0.02	0.02	15	102 (43)	103 (7)	72/28
3	2-NaphBr	0.1	0.1	2	100 (72)	101 (12)	71/29
4	4-Br-C ₆ H ₄ -OCH ₃	0.1	0.1	2	102 (66)	103 (14)	67/33
5	4-CN-C ₆ H ₄ -Br	0.1	0.1	8	104 (72)	-	76/24

^a Diastereomeric ratio was determined from ¹H NMR of crude reaction mixture. ^b Diastereomeric ratio was determined from ¹H NMR of diastereomeric mixture after purification

Table 14. Pd(II)-catalyzed cyclization of **99** and coupling with aryl bromides.

⁹¹ Hough, L.; Jones, J. K. N.; Mitchell, D. L. *J. Can. Chem.* **1958**, *36*, 1720.

The first experiment was carried out with 2-bromonaphthalene using 0.02 equiv. of both, Pd(dba)₂ and dpe-phos, respectively (Table 14, entry 1). The reaction proceeded with full conversion in 10 hours. The desired tetrahydrofuran product **100** was isolated in 30% yield with moderate *cis*-diastereoselectivity (71/29~2.4:1). Moreover, the product of Heck reaction⁸⁸ **101** was isolated from reaction mixture in 8% yield.

The stereochemistry of both diastereomers, **100a** and **100b**, was assigned from the diastereomeric mixture on the basis of NOESY experiment (Figure 8). The nOe enhancement was observed between the hydrogens H-2 and H-3 (*cis*-isomer **100a**), and between the hydrogens H-3 and H-6 (*trans*-isomer **100b**). The (*E*)-configuration on the double bond of product **101** was determined from the NMR coupling constant between hydrogens H-4 and H-5 ($J_{4,5} = 15.9$ Hz).

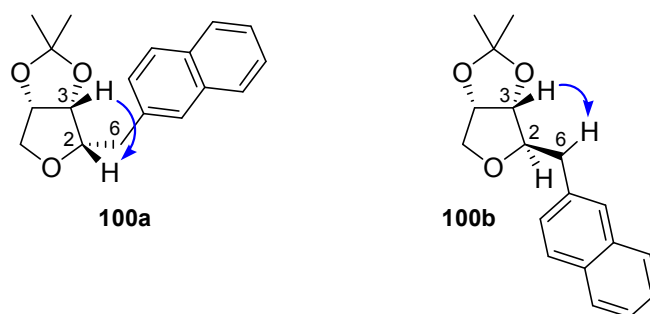


Figure 8. Stereochemistry assignment of **100a** and **100b**.

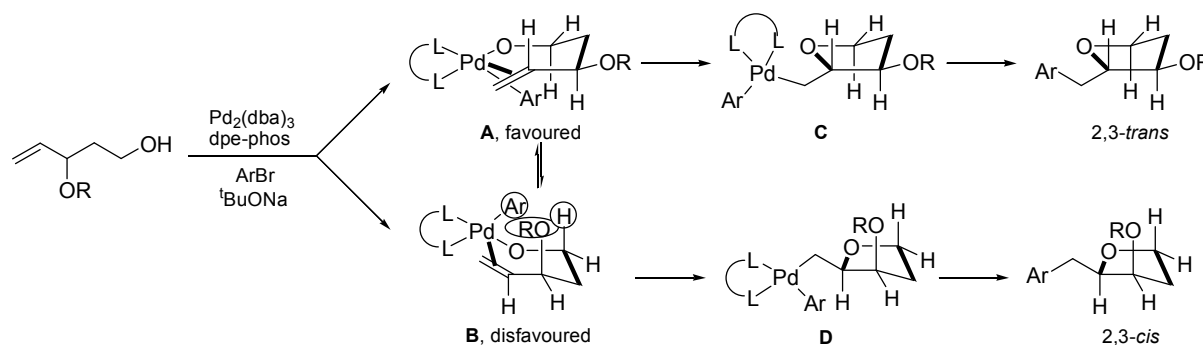
Subsequently, we performed the reaction with 4-bromoanisole as the coupling partner with electron-donating substituent under similar reaction conditions (Table 14, entry 2). The starting substrate **99** was consumed in 15 hours leading to 43% yield of product **102** with almost the same diastereoselectivity as in the previous case (72/28~2.6:1). The amount of side product **103** isolated from the reaction mixture was 7%. The stereochemistry of **102a,b** as well as the geometry of the double bond in **103** was estimated based on analogy to the structures **100a,b** and **101**.

As the yields were relatively low and the reaction times long, we increased the catalyst loading to 10 mol % (Table 14, entries 3-5). This modification led to a considerable decrease in reaction times and higher yields. The reaction with 2-bromonaphthalene (entry 3) provided the desired product **100** in 72% yield with complete conversion in 2 hours. The diastereoselectivity stayed unchanged, the amount of the Heck side-product **101** was higher (12%). A slight drop in yield and selectivity was observed with 4-bromoanisole (entry 4). The experiment with the coupling partner bearing an electron withdrawing substituent gave the

corresponding product **104** in 72% yield with full conversion after 8 hours (entry 5). The diastereoselectivity was little higher (76/24~3.2:1) favoring the *cis*-isomer **104a**. Furthermore, the Heck-type side product was not observed in this case. The relative configurations of **104a,b** were determined analogously as in the previous case.

It is worth emphasizing, that our findings are in contrast to the high *trans*-diastereoselectivity described in the literature for the formation of 2,3-disubstituted tetrahydrofurans.^{23b} To explain the opposite stereochemical outcome of the transformations of our model substrates **69a**, **90**, **91** and **99** bearing an OR function in allylic position, we suggest a duality of the reaction pathway (Scheme 64a vs. Scheme 64b).

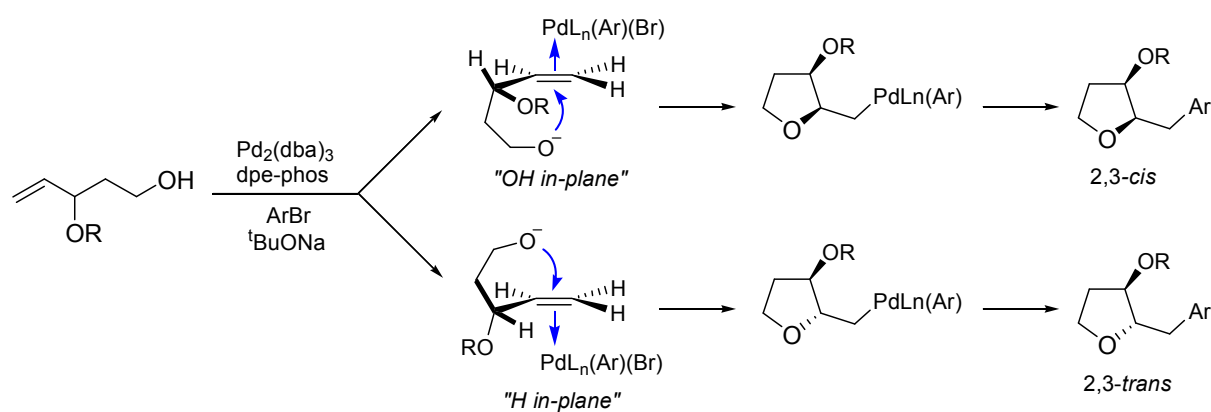
Considering the mechanism as proposed by Wolfe (Scheme 64a), after oxidative addition of the aryl bromide to Pd(0) is resulting σ -aryl Pd(II)-intermediate transformed into palladium(aryl)(alkoxide) **A** and/or **B**. Subsequent *syn*-intramolecular insertion of the alkene into the palladium–heteroatom bond affords σ -alkyl Pd(II)-intermediate (**C** vs. **D**) which undergoes reductive elimination to give desired tetrahydrofuran product. This approach should prefer the formation of *trans*-diastereomer.



Scheme 64a. Proposed mechanism according to Wolfe, *syn*-oxypalladation.

On the other hand, according to Chamberlin's computational studies, the electrophile-promoted intramolecular nucleophilic addition to olefins in the presence of an allylic heteroatom, such as an alcohol derivative, proceeds with the preferential formation of *cis*-2,3-disubstituted tetrahydrofurans.⁹² The electrophilic activation is preferred on the *OH in-plane* conformer, from the face of the π bond *syn* to the allylic hydrogen (Scheme 64b). In this conformation, the internal nucleophile is constrained to reside in a nearly ideal position for antarafacial attack on the activated π bond.

⁹² Chamberlin, A. R.; Mulholland Jr., R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, 109, 672.



Effect of C-1 substitution

Thus, the substrate **99** containing the acetonide-protected hydroxyl substituents in C-2 and C-3 positions affords 2,3,4-trisubstituted tetrahydrofuran products with moderate 2,3-*cis*-diastereoselectivity, which is presumably diminished by the contribution of *syn*-oxypalladation pathway (Scheme 64a). However, beside high 2,3-*trans*-diastereoselectivity observed in the transformations of 3-alkyl- or 3-aryl-substituted γ -hydroxy alkenes, Wolfe describes that also 1-substituted γ -hydroxy alkenes lead to desired products with high 2,5-*trans*-diastereoselectivities (Table 15).^{23b}

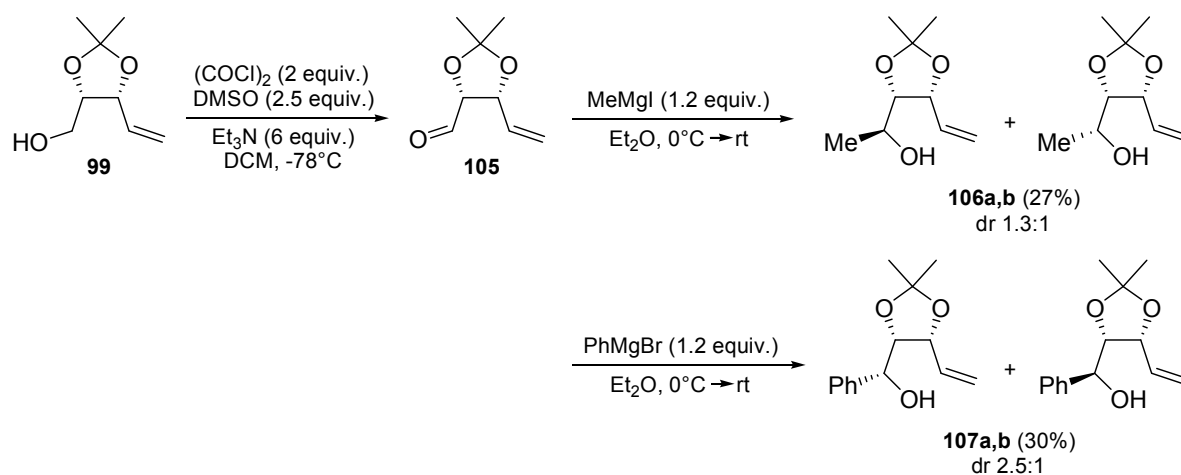
entry	R ¹	R ² -Br	yield (%)	dr
1	Me		43	>20:1
2	Et		37	>20:1
3	^t Bu		no reaction	-
4	Ph		69	>20:1
5	Ph		60	>20:1

conditions: substrate (1 equiv.), ArBr (2 equiv.), ^tBuONa (2 equiv.), Pd₂(dba)₃ (0.01 equiv.), dpe-phos (0.02 equiv.), THF, 65°C

Table 15. Stereocontrol in the formation of 2,5-disubstituted tetrahydrofuran products.^{23b}

In the reactions of aryl bromides with some pent-4-en-1-ol derivatives bearing C-1 substituents, a single tetrahydrofuran product was formed with >20:1 diastereoselectivity favoring the *trans*-stereoisomer (Table 15).^{23b} The size of the R group did not have any impact on the stereoselectivity of the transformations, but had a pronounced effect on chemical yield (entries 1-3). Also, the yield of tetrahydrofuran products was decreased and larger amounts of ketone side products were formed as the size of the alkyl group increased. The nature of the aryl bromide did not have a noticeable effect on the stereoselectivity of these transformations.

Therefore, in order to examine the effect of C-1 substitution on the diastereoselectivity, we introduced the R group (R = Me, Ph) into the chain of the substrate **99** (Scheme 65).



Scheme 65. Synthesis of C-1 substituted substrates **106** and **107**.

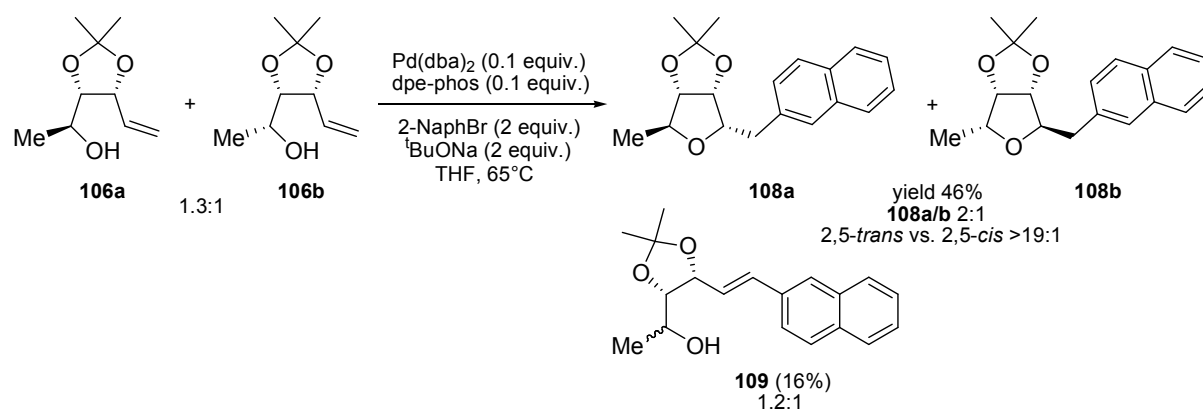
The alcohol **99** was converted to the corresponding aldehyde **105** via Swern oxidation (Scheme 65).⁹³ (3*S*,4*R*)-3,4-*O*-Isopropylidene-hex-5-ene-2,3,4-triol⁹⁴ **106** was prepared by addition of methylmagnesium iodide to aldehyde **105** in 27% yield over two steps with low diastereoselectivity (1:1.3 *syn* vs. *anti*). In the same way, using phenylmagnesium bromide, (2*S*,3*R*)-2,3-*O*-isopropylidene-1-phenyl-pent-4-en-1,2,3-triol⁹⁵ **107** was isolated in 30% yield in two steps with the diastereoselectivity 2.5:1 (*syn* vs. *anti*). The low yields of Grignard additions were caused by the volatility of starting material.

⁹³ (a) Hall, A.; Meldrum, K. P.; Therond, P. R.; Wightman, R. H. *Synlett* **1997**, 123. (b) Yang, M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, 69, 3993. (c) Va, P.; Roush, W. R. *Tetrahedron* **2007**, 63, 5768.

⁹⁴ Gallos, J. K.; Stathakis, C. I.; Salapassidou, M. J.; Grammatoglou, C. E.; Koumbis, A. E. *Carbohydrate Research* **2007**, 342, 744.

⁹⁵ Robertson, J.; Unsworth, W. P.; Lamont, S. G. *Tetrahedron* **2010**, 66, 2363.

A set of experiments with C-1 substituted triol substrates **106** and **107** was conducted using Pd(dba)₂/dpe-phos as the catalytic system. The reaction of **106** (1.3:1 diastereomeric mixture) with 2-bromonaphthalene proceeded with full conversion in 2.5 hours (Scheme 66). The desired tetrahydrofuran **108** was isolated in 46% yield. From four possible diastereoisomers, only 2,3-*cis*-/2,5-*trans*-isomer **108a** and 2,3-*trans*-/2,5-*trans*-isomer **108b** were detected in the reaction mixture in ratio 2:1. The Heck product⁸⁸ **109** was isolated in 16% yield as a diastereomeric mixture (1.2:1). The abundance of the stereoisomers **108a** and **108b** after the transformation depends on the composition of the starting diastereomeric mixture. In other words, the reaction is controlled by the C-1 substituent and proceeds with excellent 2,5-*trans*-diastereoselectivity (>19:1).



Scheme 66. Pd(II)-catalyzed cyclization of **106** and coupling with 2-NaphBr.

The absolute configuration of **108a** was determined by X-ray analysis (Figure 9).⁸⁴ The relative configuration of **108b** was determined from the diastereomeric mixture on the basis of NOESY experiment and the analogy with **110a** (Figure 10).

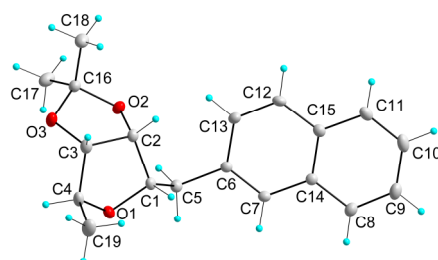
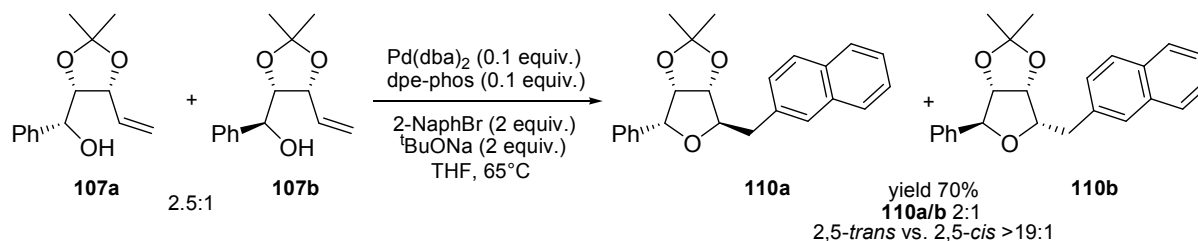


Figure 9. ORTEP view of the structure **108a**.

In the case of diastereomeric mixture **107a,b**, both 2-bromonaphthalene as well as 4-bromoanisole were tested as the coupling partners. The reaction with 2-bromonaphthalene afforded only two diastereoisomers of four possible (2,3-*trans*-/2,5-*trans*-isomer **110a** and

2,3-*cis*-/2,5-*trans*-isomer **110b**) in 70% yield and complete conversion within 3.5 hours (Scheme 67). The product of Heck reaction was not detected. The **110a** and **110b** ratio (2:1) is dependent on the composition of the starting material; the products were formed with excellent 2,5-*trans*-diastereoselectivity (>19:1).



Scheme 67. Pd(II)-catalyzed cyclization of **107** and coupling with 2-NaphBr.

Both diastereoisomers, **110a** and **110b**, were separated by flash chromatography; their stereochemistry was assigned on the basis of NOESY experiments and by the comparison of the coupling constants. In the case of isomer **110a**, the nOe enhancement was observed between the hydrogens H-4 and H-5, confirming the 4,5-*cis*-configuration; and between the hydrogens H-5 and H-6 proofing the 2,5-*trans*-stereochemistry (Figure 10). Moreover, the 2,3-*trans*-configuration was affirmed from the NMR coupling constant between the hydrogens H-2 and H-3 ($J_{2-3} = 0$ Hz); the value of J_{4-5} (3.8 Hz) was in agreement with proposed 4,5-*cis*-configuration. In the case of isomer **110b**, the nOe enhancement was observed between the hydrogens H-2 and H-3, confirming the 2,3-*cis*-stereochemistry. The same configuration was also proven from the NMR coupling constant ($J_{2-3} = 3.6$ Hz), which was identical with the analogous coupling constant in **108a** (the absolute stereochemistry of which was established by X-ray analysis). The 4,5-*trans*-stereochemistry of **110b** was determined on the basis of the coupling constant J_{4-5} (0 Hz, the analogy with **108a**); the nOe enhancement was observed between H-5 and the hydrogen of methyl group opposite to that giving an interaction with H-3 and H-4 (Figure 10).

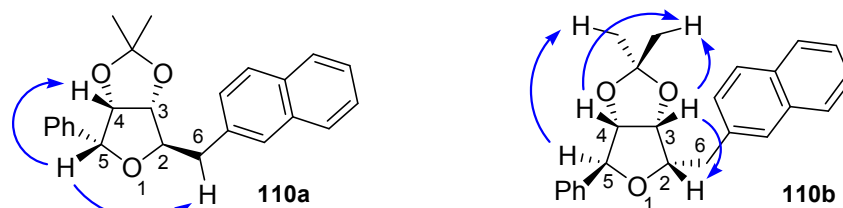
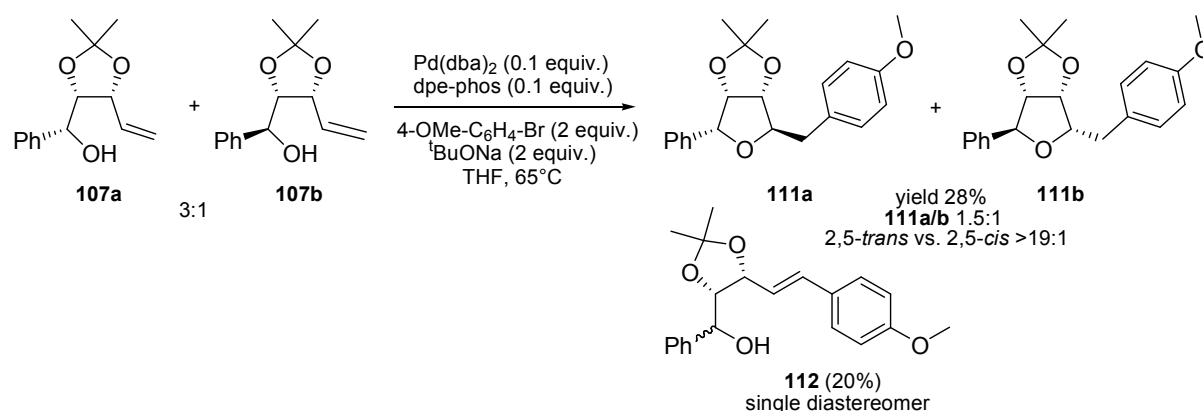


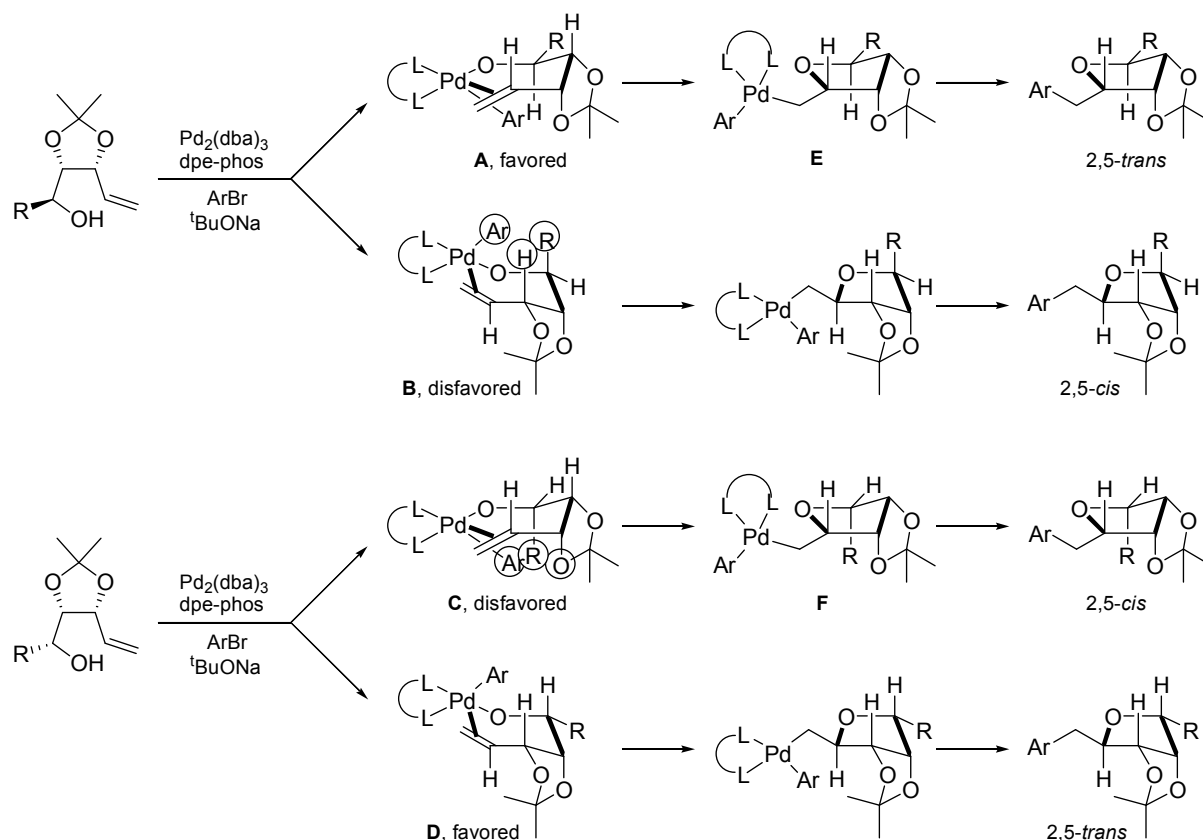
Figure 10. Stereochemistry assignment of **110a** and **110b**.

The reaction with 4-bromoanisole was accomplished using different diastereomeric mixture of **107a,b** (Scheme 68). The starting material was fully consumed in 5 hours providing the product **111** in 28% isolated yield. Analogously with two previous cases, only two of four isomers were detected in the reaction mixture, **111a** and **111b** were formed with wonderful 2,5-*trans*-diastereoselectivity. The product of Heck-type reaction **112** was isolated in relatively high amount (20% yield) as a single diastereomer. The stereochemistry of **111a** and **111b** was established on the basis of analogy to the previous analogs.



Scheme 68. Pd(II)-catalyzed cyclization of **107** and coupling with 4-bromoanisole.

Taken as a whole, the transformations of C-1 substituted triol substrates **106** and **107** proceeded with high 2,5-*trans*-diastereoselectivity. We suppose the preferential formation of conformers **A** and **D** (Scheme 69) in which the R substituent is oriented in a pseudoequatorial position to minimize nonbonding interactions with the C-3 hydrogen substituent and the aryl group or phosphine ligand bound to the Pd complex. The combination of these two interactions would disfavor the reaction through conformers **B** and **C** in which the R group is oriented in a pseudoaxial position. The alkene insertion *via* conformers **A** and **D** affords intermediates **E** and **F**, which provide the observed *trans*-2,5-disubstituted products upon C-C bond-forming reductive elimination. Ether substituents at C-2 and C-3 carbons of the substrate seem to have no influence on diastereocontrol.



Scheme 69. Stereochemistry of 2,3,4,5-tetrasubstituted tetrahydrofurans.

Varitriol structural analogs

Natural tetrahydrofuran derivative (+)-varitriol (Figure 11) was isolated from a marine-derived strain of fungus *Emericella varicolor* and was found to have significant activity against a variety of tumors (particularly renal, CNS and breast cancer cell lines).⁹⁶

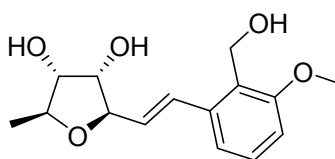


Figure 11. (+)-Varitriol.

Noteworthy cytotoxic activity generated considerable interest among synthetic chemists and resulted in the development of several total syntheses of (+)-varitriol^{97,98} and

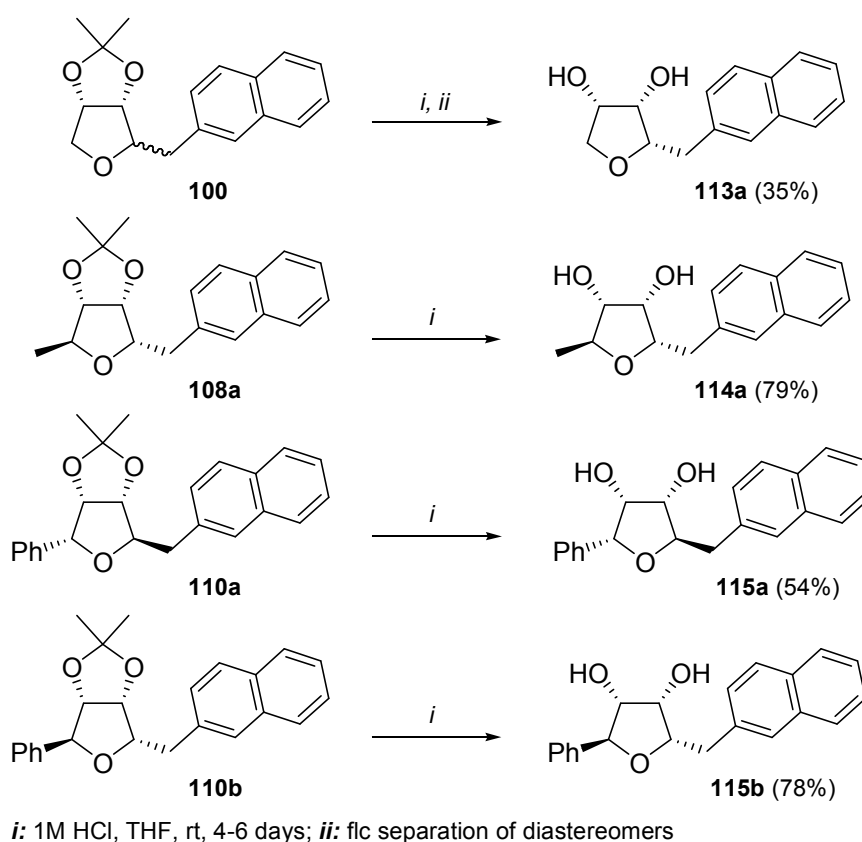
⁹⁶ (a) Malmström, J.; Christophersen, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. *J. Nat. Prod.* **2002**, 65, 364. (b) Mayer, A. M. S.; Gustafson, K. R. *Eur. J. Cancer* **2004**, 40, 2676.

⁹⁷ First total synthesis: V. Kumar, A. K. Shaw, *J. Org. Chem.* **2008**, 73, 7526.

⁹⁸ Synthesis employing the diastereoselective Pd(II)-catalyzed bicyclization: Palík, M.; Karlubíková, O.; Lásíková, A.; Kožíšek, J.; Gracza, T. *Eur. J. Org. Chem.* **2009**, 709.

unnatural (-)-varitriol,⁹⁹ respectively. The analogs with modified aromatic part were also prepared and tested for *in vitro* cytotoxicity towards certain human tumors and NCI₆₀ cancer cell line panel.¹⁰⁰

The deprotection of 2,3,4-trisubstituted and 2,3,4,5-tetrasubstituted tetrahydrofuran domino products (**100**, **108a**, **110a** and **110b**) was carried out in order to examine a potential activity of related 3,4-dihydroxylated tetrahydrofurans **113-115** as the varitriol analogs with modified furanoside and side chain part (Scheme 70). The testing their *in vitro* cytotoxicity is under way.



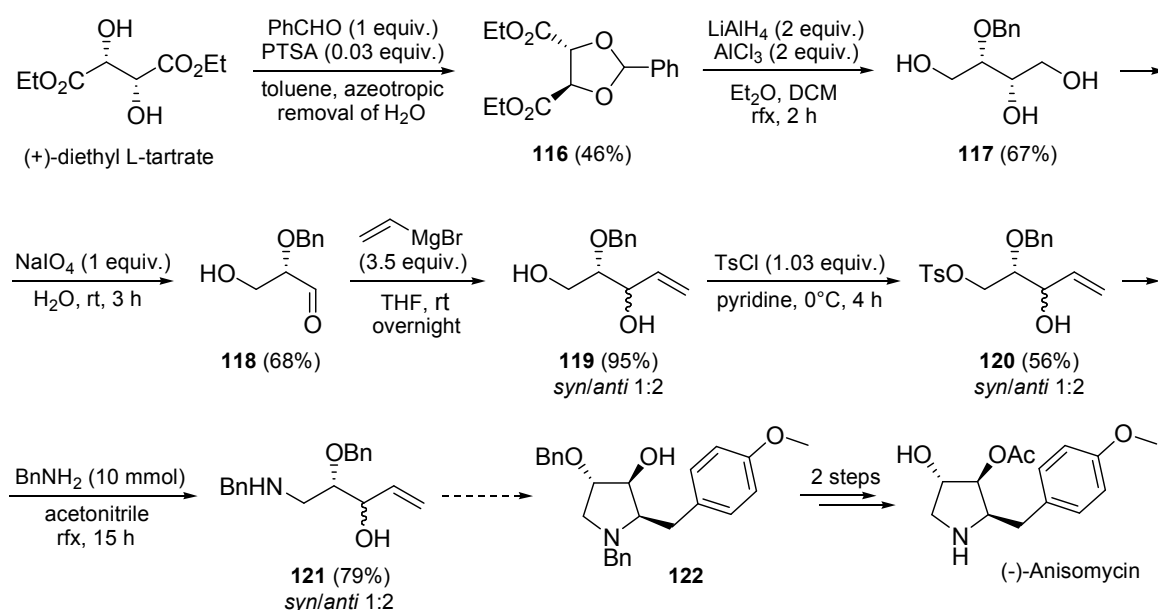
Scheme 70. Acetonide-deprotection of 2,3,4-trisubstituted and 2,3,4,5-tetrasubstituted tetrahydrofurans.

⁹⁹ (a) Clemens, R. T.; Jennings, M. P. *Chem. Commun.* **2006**, 2720. (b) McAllister, G. D.; Robinson, J. E.; Taylor, R. J. K. *Tetrahedron* **2007**, 63, 12123.

¹⁰⁰ Caletková, O.; Lásiková, A.; Hajdúch, M.; Džubák, P.; Gracza, T. *Bioorg. Med. Chem. Lett.* **2012**, accepted.

4.1.2.4. γ -Aminoalkene substrates, towards application in synthesis

With the purpose to apply the studied transformation, domino Pd(II)-catalyzed cyclization and coupling reaction in total synthesis, we turned our attention to polyhydroxylated γ -aminoalkene substrates. In 2007, Wolfe and co-workers described a new mild reaction conditions for carboamidation of *N*-protected γ -aminoalkenes with aryl bromides using the weak base Cs₂CO₃ (see section 2.3.2.).^{24h} Based on these promising results, we designed a new model substrate **121** leading to anisomycin precursor¹⁰¹ **122**, starting from (+)-diethyl L-tartrate (Scheme 71).



Scheme 71. Synthesis of *N*-protected γ -aminoalkene substrate **121**.

(*S,S*)-2-Benzyloxy-butane-1,3,4-triol **117** was prepared by the reaction of (+)-diethyl L-tartrate with benzaldehyde in the presence of catalytic amount of PTSA, followed by the reduction and benzyldiene ring opening of **116**.¹⁰² The critical step of the synthesis was the addition of vinylmagnesium bromide to the aldehyde¹⁰³ **118**, which was prepared by the cleavage of vicinal diols in **117** with NaIO₄. Despite of the efforts to find the conditions for selective *syn*-addition (chelation, low temperatures, protocol modifications), in all cases we obtained only 1:2 diastereomeric mixture of *syn*-**119** vs. *anti*-**119**. The best yield afforded the reaction at room temperature with 3.5 equiv. of vinylmagnesium bromide. Subsequent tosylation in pyridine and the nucleophilic substitution with benzylamine led to desired

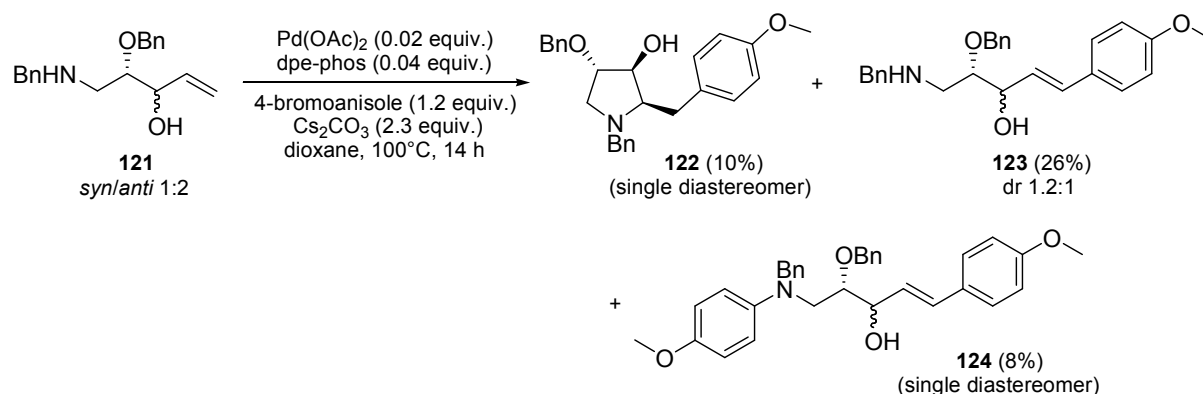
¹⁰¹ Hulme, A. N.; Rosser, E. M. *Org. Lett.* **2002**, *4*, 265.

¹⁰² Sánchez-Sancho, F.; Valverde, S.; Herradón, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209.

¹⁰³ Steuer, B.; Wehner, V.; Lieberknecht, A.; Jäger, V. *Org. Synth.* **1998**, *9*, 39.

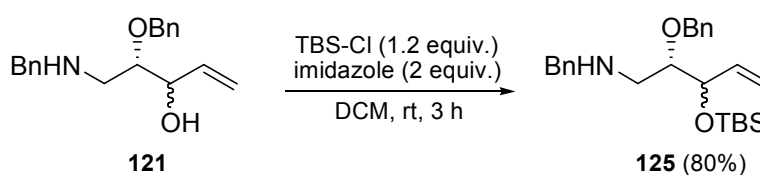
N-protected γ -aminoalkene **121** as the diastereomeric mixture (1:2, *syn* vs. *anti*). Lower yield of **120** in tosylation reaction was observed due to the formation of bis(tosylated) side product.

The diastereomeric mixture **121** was subjected to the carboamidation with 4-bromoanisole using Pd(OAc)₂/dpe-phos as the catalyst, Cs₂CO₃ as the base in dioxane at 100°C (Scheme 72).



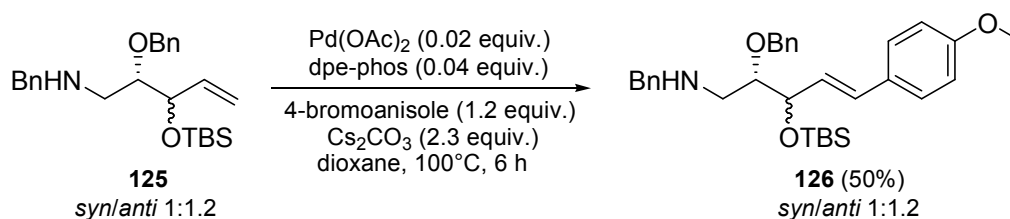
Scheme 72. Pd(II)-catalyzed cyclization of **121** and coupling with 4-bromoanisole.

The reaction proceeded with full conversion in 14 hours to give the desired pyrrolidine **122** in low yield (10%) as the single diastereomer (Scheme 72). Based on the known stereochemistry on C-4 carbon (bearing *O*-benzyl) and the ¹H and ¹³C NMR spectra, which were identical with the spectra of natural anisomycin precursor described in the literature,¹⁰¹ the absolute configuration of **122** was determined to be (2*R*,3*S*,4*S*). The major product isolated from the reaction mixture was the product of Heck reaction **123** (26%), which was formed as the mixture of *syn*- and *anti*-diastereomer with (*E*)-configuration on the double bond (*J*_{4,5} = 15.9 Hz). A small amount of *N*-arylated derivative **124** was also identified. With respect to these results we assumed, that even mild basic conditions for the carboamidation of *N*-protected γ -aminoalkenes with aryl bromides do not tolerate free α -hydroxyl group in the substrate. Thus, following our previous experience, we decided for the protection of corresponding α -hydroxyl with *tert*-butyldimethylsilyl group (Scheme 73).



Scheme 73. Preparation of the substrate **125**.

(2*S*)-*N*-Benzyl-2-benzyloxy-3-*tert*-butyldimethylsilyloxy-pent-4-en-1-amine **125** (1:1.2 *syn/anti* diastereomeric mixture after the purification on column chromatography) was submitted to the same Wolfe's carboamidation conditions (Scheme 74). To our surprise, the Heck product **126** with (*E*)-configuration on the double bond ($J_{4,5} = 15.9$ Hz) was generated as the exclusive product of this reaction.



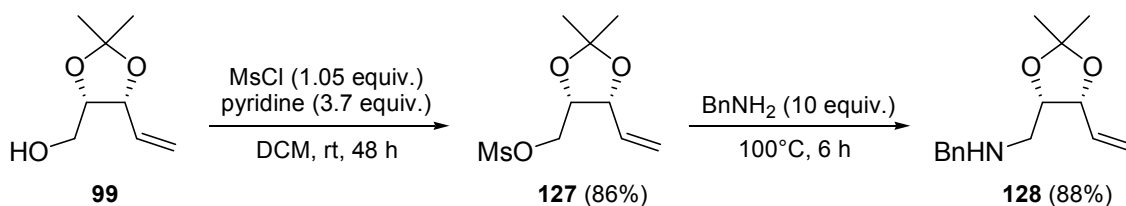
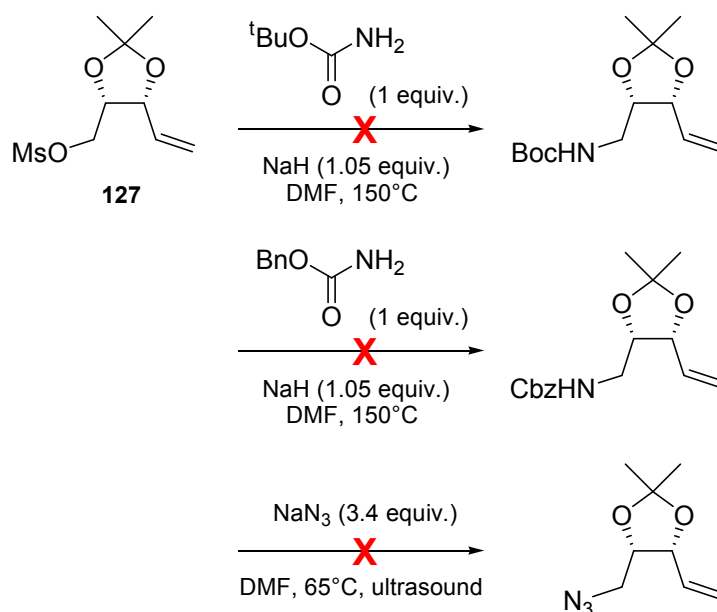
Scheme 74. The formation of Heck product **126**.

Two important aspects can be highlighted. First, the TBS-protection of free hydroxyl group in α -position did not improve the yield of desired product in case of *N*-protected γ -aminoalkenes (contrary to γ -hydroxyalkenes), furthermore, this approach completely failed to give the cyclized product. Secondly, the *N*-benzyl protection, which was introduced into the molecule of substrate to simplify the synthesis of target structure - anisomycin¹⁰⁴ (Scheme 71), appeared to be incompatible with desired transformation. Anisomycin can be prepared in high purity as its hydrochloride salt in two steps from pyrrolidine **122** by the acetylation of C-3 hydroxyl group and subsequent parallel debenzylation of C-4 hydroxyl and N-1 amino group.¹⁰¹

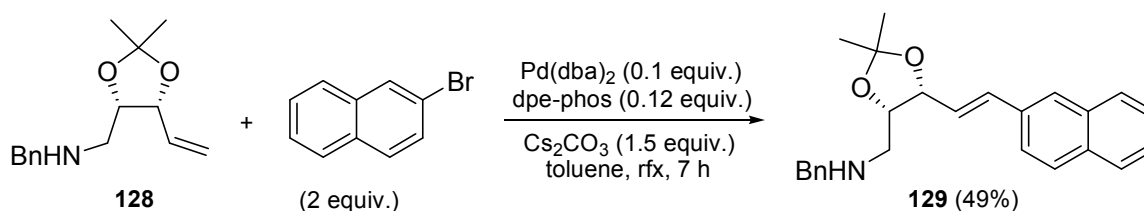
In order to investigate the behavior of aminoalkene substrates analogous to the alcohol **99** (Scheme 64) in studied reaction conditions, we wished to synthesize a new set of *N*-protected γ -aminoalkenes. While the substrate **128** was prepared smoothly by the mesylation¹⁰⁵ of (2*S*,3*R*)-2,3-*O*-isopropylidene-1-phenyl-pent-4-en-1,2,3-triol **99** followed by the nucleophilic substitution with benzylamine (Scheme 75), we had considerable difficulties obtaining the appropriate *N*-*tert*-butoxycarbonyl and *N*-benzyloxycarbonyl derivatives (Scheme 76).

¹⁰⁴ Sobin, B. A.; Tanner, F. W., Jr. *J. Am. Chem. Soc.* **1954**, 76, 4053.

¹⁰⁵ Jäger, V.; Hümmer, W.; Stahl, U.; Gracza, T. *Synthesis* **1991**, 769.

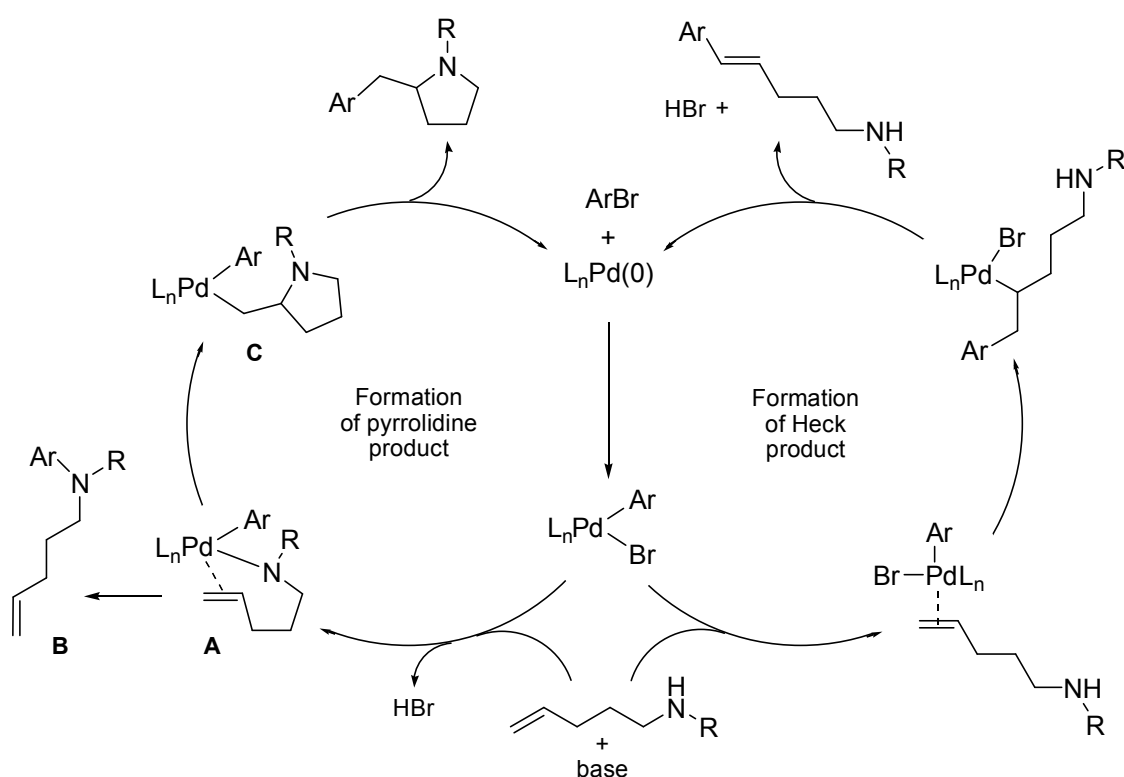
Scheme 75. Preparation of aminopentenediol **128**.Scheme 76. Efforts to prepare different *N*-protected aminopentenediols.

In accordance with the previous observation, the reaction of **128** with 2-bromonaphthalene employing $\text{Pd}(\text{dba})_2/\text{dpe-phos}$ and cesium carbonate provided amine **129** as the sole product (Scheme 77). This result represents an additional point demonstrating the unsuitability of *N*-benzyl protection with Wolfe's conditions for the formation of pyrrolidines.

Scheme 77. The formation of Heck-type product **129**.

The incompatibility of *N*-benzyl protection very likely relates to the different nucleophilicity of amine (*N*-Bn) vs. amide (*N*-Boc, *N*-Ac) nitrogen. According to the literature,^{22b,24c} the efficiency of carboamination reaction is highly dependent on the nucleophilicity/basicity of the substrate aminogroup (Section 2.3.2), satisfactory results were

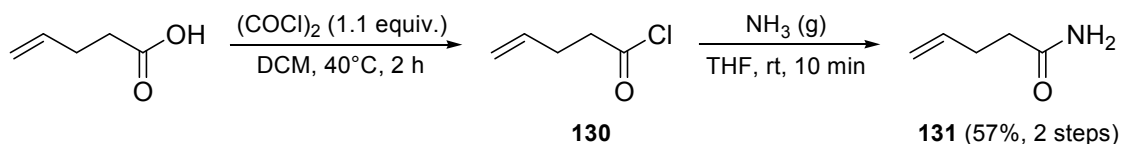
obtained predominantly with pent-4-enamines bearing *N*-*tert*-butoxycarbonyl (*N*-Boc) or *N*-acetyl protecting groups.²⁴ This fact is elucidated by the stabilization of σ -alkyl Pd(II)-intermediate **C** (Scheme 78) through the chelation of the metal to the carbonyl of the amide or carbamate, or by the observation that C–N bond-forming reductive elimination (**A** \rightarrow **B**) slows as the nucleophilicity of amine, amide or carbamate decreases.^{24c} Additional plausible explanation may include the hypothesis that the higher nucleophilicity of benzyl-protected amine causes its complexation with another molecule of palladium (another than that which activates the double bond), and the amine becomes inactive towards the nucleophilic attack.



Scheme 78. Proposed mechanism of pyrrolidine^{24c} and competing Heck products⁸⁷ formation.

With a view to probe the feasibility of carboamidation reaction in the presence of free amidic group, the substrate **131** containing no additional functional groups was prepared from pent-4-enoic acid (Scheme 79).¹⁰⁶

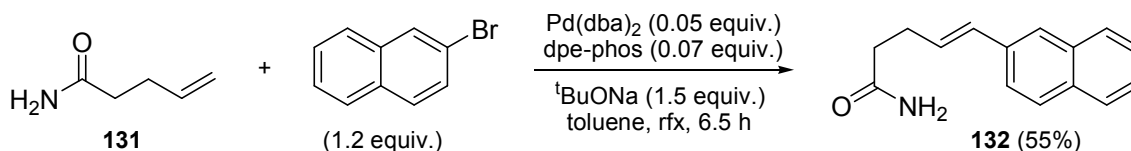
¹⁰⁶ (a) Rosenbulm, S.B.; Huynh, T.; Afonso, A.; Davis Jr., H. R. *Tetrahedron* **2000**, 56, 5735. (b) Gaudreault, P.; Drouin, C.; Lessard, J. *Can. J. Chem.* **2005**, 83, 543.



Scheme 79. Synthesis of the substrate **131**.

Gaseous ammoniac was bubbled in tetrahydrofuran solution of crude acid chloride **130** (Scheme 79), prepared by the reaction of oxalyl chloride with pent-4-enoic acid, to give the amide **131** as a white precipitate.

We can only conclude that pent-4-enamide **131** in the presence of 2-bromonaphthalene, $\text{Pd}(\text{dba})_2$, dpe-phos and $^t\text{BuONa}$ in toluene was converted to corresponding Heck product **132** in 55% yield (Scheme 80) and did not provide the desired product of domino $\text{Pd}(\text{II})$ -catalyzed cyclization and coupling reaction.



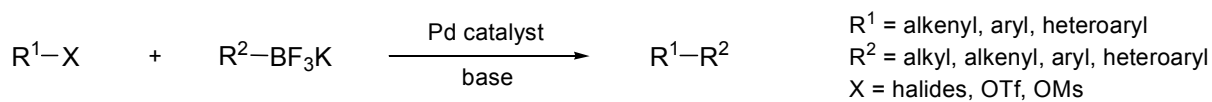
Scheme 80. The formation of undesired **132**.

4.1.3. Coupling with organotrifluoroborates

In the broad field of carbon–carbon bond-forming chemistry, the Suzuki-Miyaura reaction has proven to be a particularly attractive method.¹⁰⁷ The standard organoborane nucleophiles (boronic acids and boronate esters) readily undergo cross-coupling under mild reaction conditions, in the presence of several functional groups (e.g. OH, CO₂H, CHO, CN, etc.). However, both boronic acids and boronate esters suffer from limitations, such as purification difficulty, uncertain stoichiometry due to trimerization and/or lack of atom economy.

On the other hand, potassium organotrifluoroborates R–BF₃K are typically crystalline solids insensitive to air and moisture which are easily stored, have known stoichiometry and low molecular weight.¹⁰⁸

In general, potassium alkyl-, alkenyl-, aryl- and heteroaryltrifluoroborate participate in Suzuki-Miyaura cross-coupling reaction affording biaryls, 1,3-dienes, styrenes and functionalized heterocycles (Scheme 81).^{109,110}



Scheme 81. Suzuki-Miyaura cross-coupling with organotrifluoroborates.

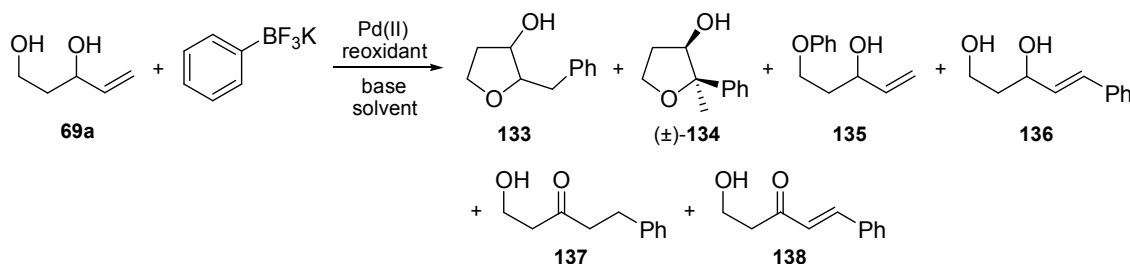
¹⁰⁷ For reviews see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

¹⁰⁸ For reviews see: (a) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313. (b) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49. (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (d) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288.

¹⁰⁹ (a) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393. (b) Molander, G. A.; Rodrigues Rivero, M. *Org. Lett.* **2002**, *4*, 107. (c) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424. (d) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867. (e) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302. (f) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534. (g) Molander, G. A.; Petrillo, D. E.; Landzberg, N. R.; Rohanna, J. C.; Biolatto, B. *Synlett* **2005**, 1763. (h) Molander, G. A.; Fumagalli, T. *J. Org. Chem.* **2006**, *71*, 5743. (i) Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198. (j) Molander, G. A.; Vargas, F. *Org. Lett.* **2007**, *9*, 203. (k) Molander, G. A.; Ham, J.; Seapy, D. G. *Tetrahedron* **2007**, *63*, 768. (l) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2007**, *9*, 1597. (m) Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2007**, *72*, 8422. (n) Molander, G. A.; Petrillo, D. E. *Org. Lett.* **2008**, *10*, 1795. (o) Molander, G. A.; Canturk, B. *Org. Lett.* **2008**, *10*, 2135. (p) Molander, G. A.; Gormisky, P. E.; Sandrock, D. L. *J. Org. Chem.* **2008**, *73*, 2052. (q) Molander, G. A.; Gormisky, P. E. *J. Org. Chem.* **2008**, *73*, 7481. (r) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257. (s) Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2009**, *74*, 1297. (t) Dreher, S. D.; Lim, S.-E.; Sandrock, D. L.; Molander, G. A. *J. Org. Chem.* **2009**, *74*, 3626. (u) Molander, G. A.; Beaumard, F. *Org. Lett.* **2011**, *13*, 1242. (v) Molander, G. A.; Fleury-Brégeot, N.; Hiebel, M.-A. *Org. Lett.* **2011**, *13*, 1694. (w) Molander, G. A.; Beaumard, F.; Niethamer, T. K. *J. Org. Chem.* **2011**, *76*, 8126.

¹¹⁰ (a) Fang, G.-H.; Yan, Z.-J.; Deng, M.-Z. *Org. Lett.* **2004**, *6*, 357. (b) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649. (c) Charette, A. B.; Mathieu, S.; Fournier, J.-F. *Synlett* **2005**, 1779. (d) Kabalka, G. W.; Al-Masum, M. *Tetrahedron Lett.* **2005**, *46*, 6329. (e) Arvela, R. K.; Leadbeater, N. E.; Mack, T. L.; Kormos, C. M. *Tetrahedron Lett.* **2006**, *47*, 217. (f) Kabalka, G. W.; Zhou, L.-L.; Naravane, A. *Tetrahedron Lett.* **2006**, *47*, 6887. (g) Zhang, L.; Meng, T.; Wu, J. *J. Org. Chem.* **2007**, *72*, 9346. (h) Harker, R. L.; Crouch, R. D. *Synthesis* **2007**, 25.

Based on our previous studies on domino cyclization-coupling reaction, we started our investigation under PdCl₂/CuCl₂/AcONa reaction conditions considering the transformation with potassium phenyltrifluoroborate as the model coupling partner with diol substrate **69a** (Table 16, entry 1). Subsequently, the reaction conditions were modified with respect to solvent, reoxidant, additive and palladium salt (Table 16).



entry	equiv. of PhBF ₃ K	Pd(II) (equiv.)	reoxidant (equiv.)	base (equiv.)	solvent	temp.	time	isolated yield (%)				
								134	135	136	137	138
1	2	PdCl ₂ (0.1)	CuCl ₂ (3)	AcONa (3)	THF	rt	6 h	52	-	-	-	-
2 ^a	2	PdCl ₂ (0.1)	CuCl ₂ (3)	AcONa (3)	THF-MeOH 1:1	rt	3 h	17	-	5	12	-
3	2	PdCl ₂ (1)	-	AcONa (3)	THF	rt	3 h	-	36	-	-	-
4	2	PdCl ₂ (1)	-	AcONa (3)	THF	65°C	3 h	-	34	17	-	-
5 ^a	1.5	Pd(OAc) ₂ (0.1)	CuCl ₂ (3)	AcONa (3)	THF	rt	3 h	5	-	-	-	-
6	1.5	Pd(OAc) ₂ (0.1)	CuCl ₂ (3)	AcONa (3)	THF	65°C	1 h	-	22	-	-	-
7	1	PdCl ₂ (1)	-	Cs ₂ CO ₃ (3)	THF-H ₂ O 10:1	77°C	15 min	-	28	18	6	6
8	1.1	PdCl ₂ (0.1)	CuCl ₂ (2)	AcONa (2)	CH ₃ CN-H ₂ O 1:1	rt	5 d	24	-	-	-	-
9	1.1	PdCl ₂ (0.1)	CuCl ₂ (1)	AcONa (1)	CH ₃ CN-H ₂ O 1:1	rt	2 h	32	-	-	-	-
10	1.1	PdCl ₂ (0.1)	<i>p</i> -BQ (1)	-	CH ₃ CN-H ₂ O 1:1	rt	2 h	53	-	-	-	-

^a Conversion was not complete.

Table 16. Efforts for the Pd(II)-catalyzed cyclization of **69a** and coupling with PhBF₃K.

The desired cyclization product **133** was not isolated at all under tested reaction conditions (Table 16). To our surprise, product **134** was isolated in the reaction using catalytic PdCl₂ reoxidized by CuCl₂ in the presence of AcONa in THF at room temperature (entry 1). When the mixture of THF-MeOH 1:1 was employed instead of THF, the amount of **134** decreased (entry 2). Moreover, the product of Heck reaction⁸⁸ **136** along with linear ketone **137** was acquired. The reaction with 1.1 equiv. of PhBF₃K in acetonitrile-water 1:1 also led to **134** even when lower CuCl₂ loadings were used (entries 8, 9). The best yield of cyclization product **134** gave the reaction with *p*-benzoquinone reoxidant (entry 10). In all of the cases, **134** was formed as the single diastereomer with 2,3-*cis*-configuration of hydroxyl and phenyl substituents (the relative stereochemistry was assigned on the basis of nOe enhancement between the hydrogen of the methyl group and H-3 hydrogen, Figure 12). The reactions

carried out with stoichiometric PdCl_2 (entries 3, 4 and 7) and/or at higher temperature (entry 6) provided ether **135** as the major product. When cesium carbonate was used as the base, conjugated ketone **138** was found in the reaction mixture besides the other products (entry 7).

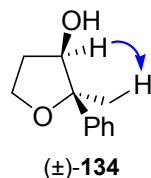
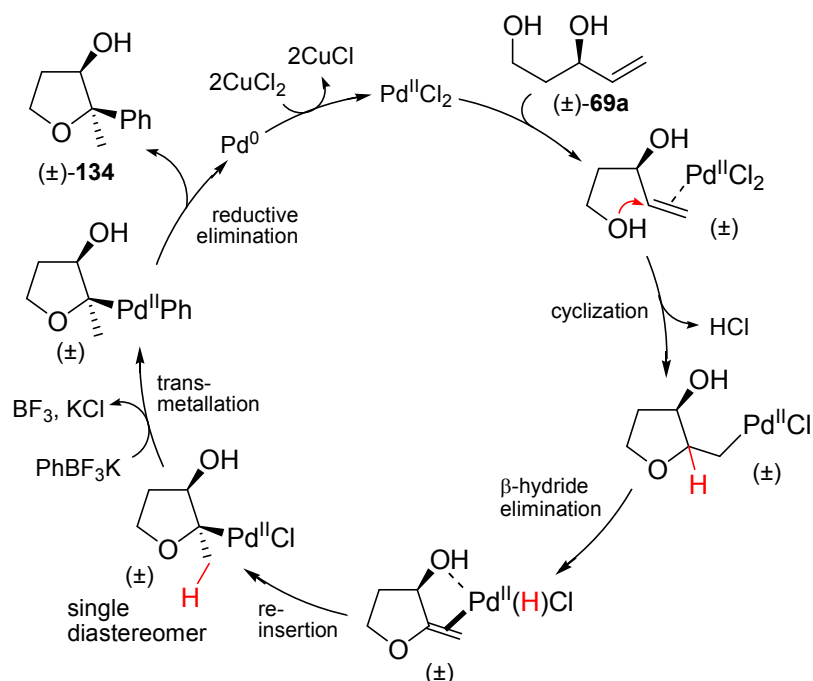


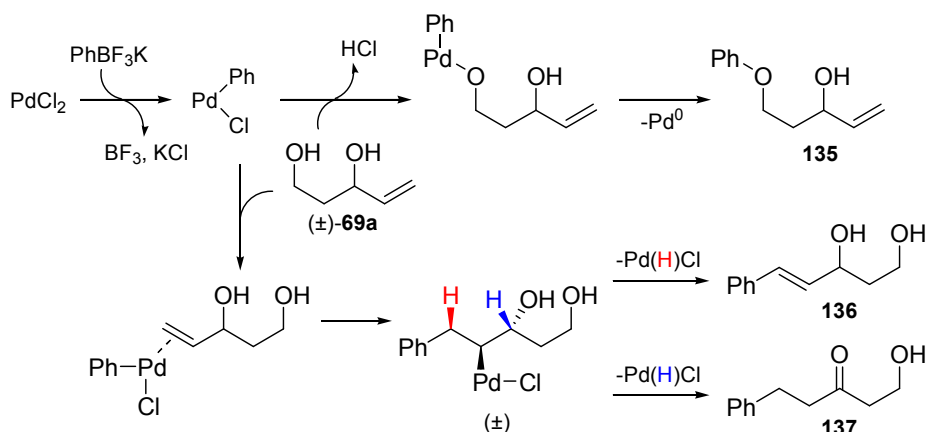
Figure 12. Assignment of the relative stereochemistry of **134**.

As it was highlighted, the product **134** was formed as the single diastereomer with 2,3-*cis*-geometry. The proposed mechanism of its formation is outlined in Scheme 83. After the cyclization and β -hydride elimination, the reinsertion of the double bond into Pd–H bond is believed to be the stereochemistry determining step, proceeding from *Re* diastereotopic face presumably due to the complexation of the α -hydroxyl group with palladium. Subsequent transmetalation and reductive elimination then releases the tetrahydrofuran **134**.

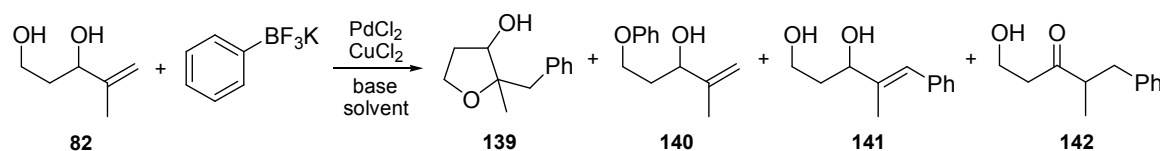


Scheme 83. Formation of **134**, proposed mechanism.

The mechanistic propositions for the formation of **135**, **136** and **137** are shown in Scheme 84.

Scheme 84. Formation of side products **135**, **136** and **137**.

Similar set of experiments was accomplished with diol substrate **82** (Table 17):



entry	equiv. of PhBF ₃ K	equiv. of PdCl ₂	equiv. of CuCl ₂	base (equiv.)	solvent	temp.	time	isolated yield (%)			
								139	140	141	142
1	2	0.1	3	AcONa (3)	THF	65°C	6 h	-	45	-	-
2 ^a	2	0.1	3	AcONa (3)	THF-MeOH 1:1	rt	8 h	-	-	7	36
3	2	1	-	AcONa (3)	THF	rt	6 h	-	5	14	-
4	2	1	-	AcONa (3)	THF	65°C	30 min	-	71	-	-
5 ^a	1	1	-	Cs ₂ CO ₃ (3)	THF-H ₂ O 10:1	77°C	15 min	7	-	8	8
6	1.1	0.1	3	AcONa (3)	CH ₃ CN-H ₂ O 1:1	rt	3 d	-	-	-	38
7	1.1	0.1	3	AcONa (3)	THF-H ₂ O 1:1	rt	4 d	-	-	-	43
8	1.1	0.1	3	AcONa (3)	acetone	rt	1 d	-	15	-	-

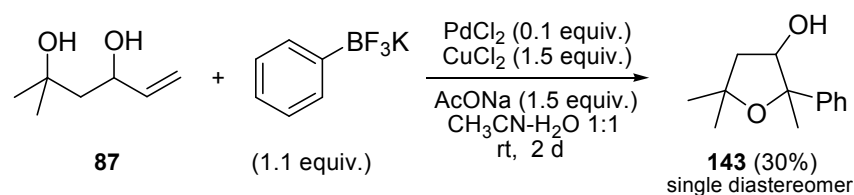
^a Conversion was not complete.

Table 17. Pd(II)-catalyzed cyclization of **82** and coupling with PhBF₃K.

The σ -alkyl Pd(II)-intermediate formed after the cyclization of substrate **82** can not undergo β -hydride elimination; thus, the untypical cyclization product, analogous to **134**, can not be observed. The desired tetrahydrofuran **139** was isolated in low yield only in a single case, when the reaction was conducted with stoichiometric PdCl₂ and cesium carbonate in THF-water 10:1 (Table 17, entry 5). Analogously with the previous observation concerning **134**, the desired product **139** was isolated as a single diastereomer (unfortunately, NOESY experiment did not provide the explicit confirmation of relative stereochemistry). Ether **140** was found in the reaction mixture as the sole product when the reaction was carried out in THF at reflux (entries 1, 4) or in acetone at room temperature (entry 8). Ketone **142** was

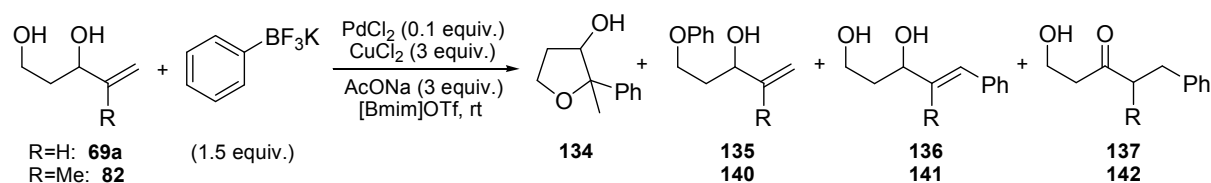
isolated from the reactions using solvent mixtures with water or methanol at room temperature (entries 2, 6 and 7).

Finally, the experiment with the substrate **87** using catalytic PdCl₂, 1.1 equiv. PhBF₃K, 1.5 equiv. of CuCl₂ and AcONa in acetonitrile-water at room temperature afforded the untypical cyclization product **143** in 30% yield (Scheme 85). Analogously with previous case (**134**), we suppose the formation of 2,3-*cis*-diastereomer.



Scheme 85. Pd(II)-catalyzed cyclization of **87** and coupling with PhBF₃K.

In order to explore the feasibility of studied transformation in alternative solvents, the pioneering experiments in ionic liquids were accomplished (Table 18).



entry	substrate	equiv. of [Bmim]OTf	time	conversion	products (yield, %)
1	69a	3.5	2 h	100	134 (25)
2	82	3.5	2 h	100	140 (30)

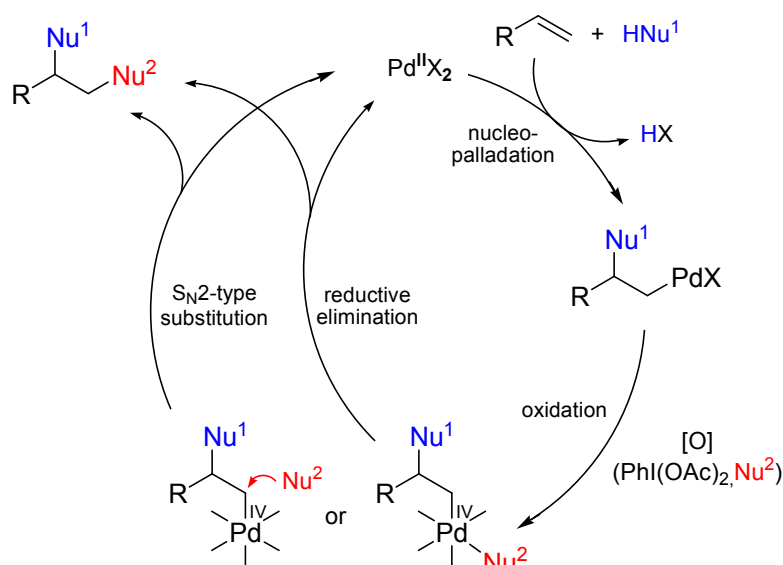
Table 18. Using of [Bmim]OTf ionic liquid.

The use of 1-butyl-3-methylimidazolium trifluoromethanesulfonate as the reaction medium did not indicate any positive influence and led to lower yield of desired product comparing with results in THF (Table 18, entry 1 vs. Table 16, entry 1). We suppose that the origin of the difficulties consisted in the isolation of products from the reaction mixture by the extraction with diethyl ether due to high viscosity of the ionic liquid.

The intramolecular Pd(II)-catalyzed cyclization of unsaturated alcohols and coupling with potassium organotrifluoroborates could represent a stereoselective method for the preparation of substituted tetrahydrofurans. However, with respect to low yields and a wide range of the byproducts formation, it needs a further optimization of reaction conditions.

4.1.4. “Coupling” with iodobenzene diacetate, Pd^{II}/Pd^{IV} catalysis

As it was pointed out earlier, the trapping of σ -alkyl Pd(II)-intermediate by suitable coupling partner can be efficient only if it proceeds faster than competitive β -hydride elimination. Another strategy how to avoid β -hydride elimination, that is receiving growing attention, is the rapid oxidation of σ -alkyl Pd-intermediate from Pd(II) to Pd(IV).¹¹⁹ Sanford and co-workers have shown, that PhI(OAc)₂ can oxidize square-planar organometallic Pd(II) complexes to the corresponding octahedral Pd(IV) complexes to facilitate subsequent bond-forming process.¹²⁰ Depending on the nucleophile and substrate, the second bond-forming step is hypothesized to proceed *via* either a reductive elimination of C–Nu² from Pd(IV), resulting in retention of stereochemistry, or by nucleophilic attack of an external nucleophile, with Pd(II) as the leaving group, resulting in inversion of stereochemistry (Scheme 86).¹²¹



Scheme 86. Proposed mechanism for Pd-catalyzed bisfunctionalization involving Pd^{II}-Pd^{IV} oxidation.

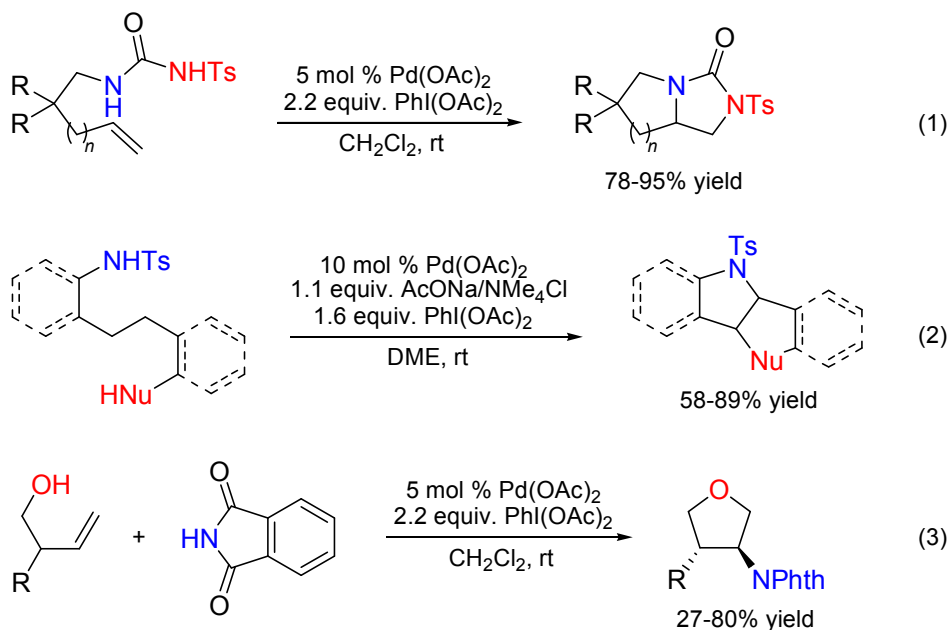
The second nucleophile may either be incorporated into the substrate leading to bicyclic products¹²² (Scheme 87, eq 1 and eq 2) or an external nucleophile¹²³ can be used (eq 3).

¹¹⁹ For reviews see: (a) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, 39, 712. (b) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, 110, 824.

¹²⁰ (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, 126, 2300. (b) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, 126, 9542. (c) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, 127, 12790.

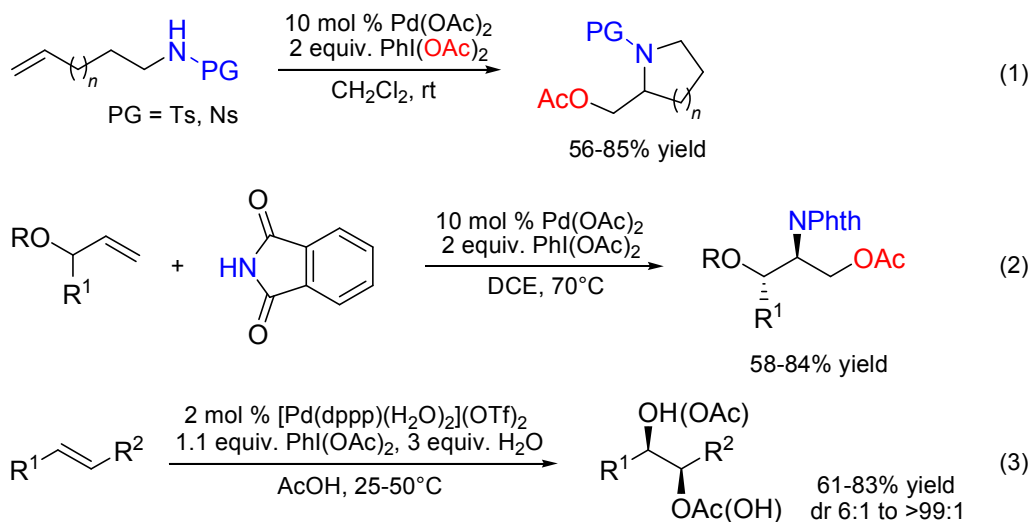
¹²¹ Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, 6, 4083.

¹²² (a) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.*, **2005**, 127, 14586. (b) Muñiz, K. *J. Am. Chem. Soc.*, **2007**, 129, 14542.



Scheme 87. Intramolecular Pd-catalyzed bisfunctionalization reactions.

Particularly interesting are examples when the nucleophile is derived from $\text{PhI}(\text{OAc})_2$ (Scheme 88). The first aminoacetoxylation reaction utilizing iodobenzene diacetate as both, the oxidizing agent and nucleophile, was reported by Sorensen and co-workers (eq 1).¹²⁴



Scheme 88. Pd-catalyzed bisfunctionalization reactions with second nucleophile derived from $\text{PhI}(\text{OAc})_2$.

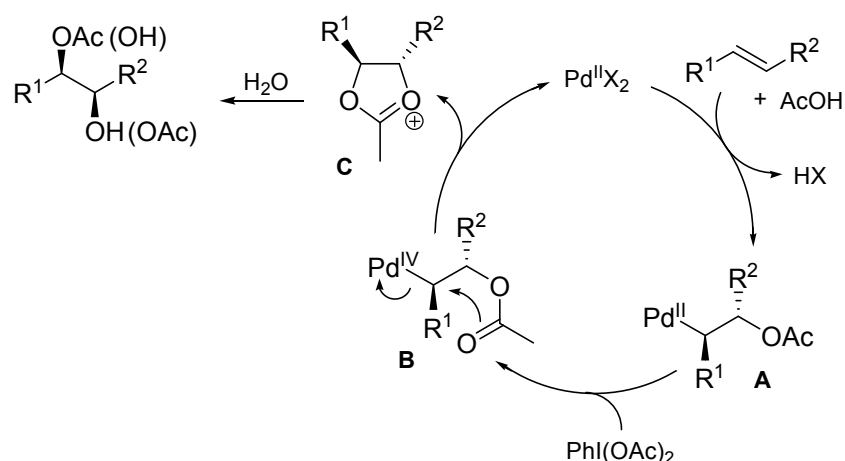
Stahl and Liu published a Pd-catalyzed aminoacetoxylation reaction of allylic ethers with phthalimide and acetate as the nucleophiles (Scheme 88, eq 2).¹²⁵

¹²³ Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, 46, 5737.

¹²⁴ Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, 127, 7690.

¹²⁵ Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, 128, 7179.

Recently, Song and Dong reported a Pd-catalyzed alkene dioxygenation reaction (Scheme 88, eq 3).¹²⁶ Mono-, di- and trisubstituted alkene substrates react to give *cis*-hydroxyacetates with good to high diastereoselectivity. However, the mixtures are due to insufficient regioselectivity subsequently acetylated by the addition of acetic anhydride to form corresponding diacetates. Initial *anti*-oxypalladation, followed by Pd oxidation is proposed to afford intermediate **B** (Scheme 89). Intramolecular S_N2-type substitution, followed by hydrolysis of **C** leads to regioisomeric mixture of hydroxyacetates.



Scheme 89. Pd-catalyzed dioxygenation of alkenes.

In the same paper, Dong and Song described the initial study on an intramolecular Pd-catalyzed dioxygenation of olefins for construction of tetrahydrofurans and lactones (Table 19).¹²⁶ Treatment of 1-phenylbut-3-en-1-ol with [Pd(dppp)(H₂O)₂](OTf)₂ in wet AcOH afforded corresponding tetrahydrofuran as a mixture of diastereomers (78% yield, 1.1:1 dr, entry 1). Substrates bearing tertiary hydroxyl group also underwent 5-*endo*-cyclization (entries 2 and 3), while 5-phenylpent-4-en-1-ol preferentially gave 5-*exo*-cyclization (entry 4). When Pd(OCOCF₃)₂/1,3-bis(diphenylphosphino)propane (dppp) was used as the catalyst, an oxidative cyclization occurred to yield appropriate lactone (entry 5).

¹²⁶ Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 2962.

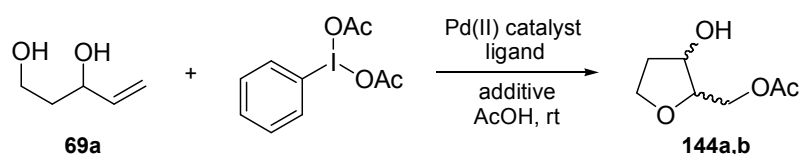
entry	substrate ^a	product	yield (%) ^b	dr
1			78	1.1:1
2			90	1.1:1
3 ^c			80	-
4			90	2.3:1
5 ^d			85	1.3:1

^a 0.25 mmol scale (0.1 M in wet AcOH), 1.1 equiv. of PhI(OAc)₂, 2 mol % of [Pd(dppp)(H₂O)₂](OTf)₂.

^b Isolated yield. ^c 1.5 equiv. of PhI(OAc)₂ was used. ^d 5 mol % Pd(OCOCF₃)₂ and 5.5 mol % dppp were used.

Table 19. Intramolecular Pd-catalyzed oxidative tetrahydrofuran ring formation.¹²⁶

Based on these promising reports, we decided to subject our model substrates to PhI(OAc)₂ oxidizing conditions. The diol substrate **69a** was allowed to react with iodobenzene diacetate, acting also as the second nucleophile, using corresponding catalytic system in acetic acid (Table 20).



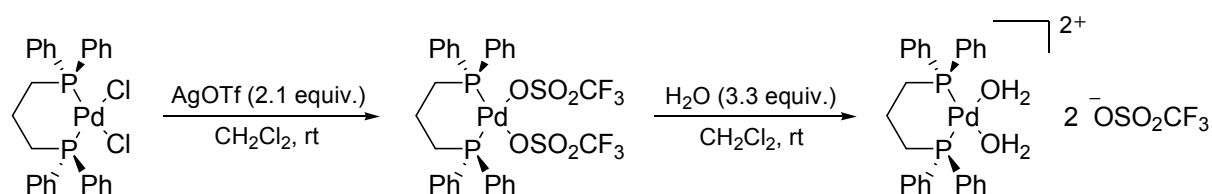
entry	equiv. of PhI(OAc) ₂	Pd(II) (equiv.)	ligand (equiv.)	additive (equiv.)	time (h)	isolated yield (%)	dr ^a (a/b)
1	1.5	Pd(OAc) ₂ (0.1)	-	AcONa (1.5)	3	42	3:1
2	1.1	Pd(OCOCF ₃) ₂ (0.05)	dppp (0.055)	-	2	46	3.5:1
3	1.1	[Pd(dppp)(H ₂ O) ₂](OTf) ₂ (0.05)	-	H ₂ O (3 equiv.)	10 ^b	29	2.5:1

^a Diastereomeric ratio was determined from ¹H NMR of crude reaction mixture. ^b The reaction mixture was heated to 50°C.

Table 20. Intramolecular Pd^{II}/Pd^{IV}-catalyzed oxidative tetrahydrofuran ring formation.

The reaction in the presence of Pd(OAc)₂ and 1.5 equiv. of AcONa (conditions derived from classical Pd(II)-catalyzed bicyclization)⁷⁸ provided the desired tetrahydrofuran

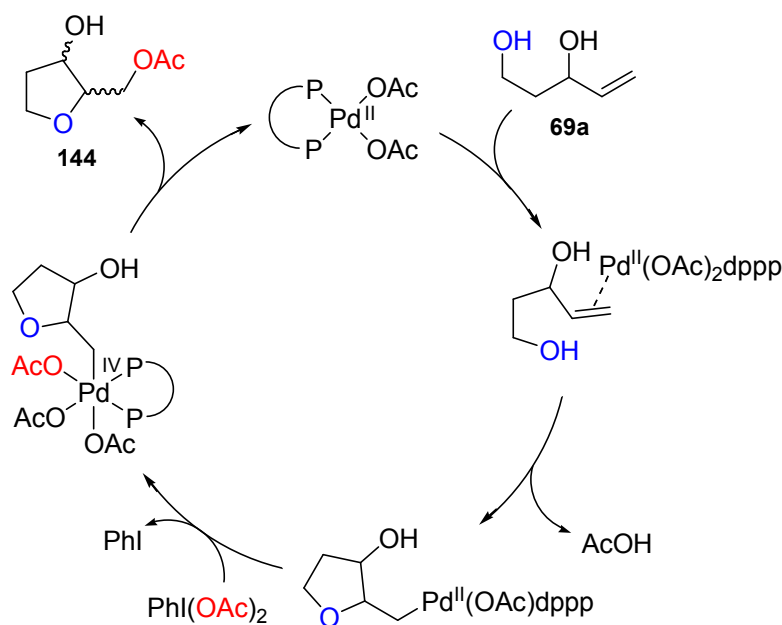
144 in 42% yield with diastereoselectivity 3:1 (Table 20, entry 1). Having obtained this moderate result we turned our attention to Dong and Song's conditions described for lactonization of 5-phenylpent-4-en-1-ol (Table 19, entry 5). The reaction of (\pm)-**69a** and $\text{PhI}(\text{OAc})_2$ using $\text{Pd}(\text{OCOCF}_3)_2/\text{dppp}$ catalytic system without any base led to a slight improvement in both, yield (46%) and diastereoselectivity (3.5:1) of **144** (Table 20, entry 2). Finally, we prepared the cationic complex $[\text{Pd}(\text{dppp})(\text{H}_2\text{O})_2](\text{OTf})_2$ ¹²⁷ (Scheme 90) that was proposed to be the catalyst of choice concerning analogous substrates (Table 19, entries 1-4).



Scheme 90. Preparation of cationic complex $[\text{Pd}(\text{dppp})(\text{H}_2\text{O})_2](\text{OTf})_2$.

Unfortunately, the cationic complex $[\text{Pd}(\text{dppp})(\text{H}_2\text{O})_2](\text{OTf})_2$ failed to give the product **144** in a satisfactory yield, moreover the reaction proceeded much slower even at higher temperature (Table 20, entry 3).

Proposed mechanism of the formation of **144** is outlined in Scheme 91.



Scheme 91. Proposed mechanism of the formation of **144**.

¹²⁷ (a) Olivier, D. L.; Anderson, G. K. *Polyhedron* **1992**, *11*, 2415. (b) Stang, P. J.; Cao, D. H. *J. Am. Chem. Soc.* **1994**, *116*, 4981. (c) Stang, P. J.; Cao, D. H.; Poulter, G. T.; Arif, A. M. *Organometallics* **1995**, *14*, 1110. (d) Yuan, H.; Thomas, L.; Woo, L. K. *Inorg. Chem.* **1996**, *35*, 2808.

In further investigation, the α -protected substrates **90** and **99** were exposed to $\text{Pd}(\text{OCOCF}_3)_2/1,3\text{-bis}(\text{diphenylphosphino})\text{propane}$ (dppp) catalytic conditions (Table 21).

entry	equiv. of $\text{PhI}(\text{OAc})_2$	$\text{Pd}(\text{II})$ (equiv.)	ligand (equiv.)	additive (equiv.)	time (h)	isolated yield (%)	dr ^a
1	1.1	$\text{Pd}(\text{OCOCF}_3)_2$ (0.05)	dppp (0.055)	-	18	39	3:1
2	1.1	$\text{Pd}(\text{OCOCF}_3)_2$ (0.05)	dppp (0.055)	-	48	mixture of unidentified products	-

^a Diastereomeric ratio was determined from ^1H NMR of crude reaction mixture.

Table 21. Intramolecular $\text{Pd}^{\text{II}}/\text{Pd}^{\text{IV}}$ -catalyzed cyclization of substrates **90** and **99**.

As it can be seen in the Table 21, the α -*tert*-butyldimethylsilyl-protected diol **90** afforded the desired product of domino $\text{Pd}(\text{II})$ -catalyzed cyclization and $\text{Pd}(\text{IV})$ -mediated coupling with acetate: **145**, however, in moderate yield (39%, entry 1). On the other hand, (2*S*,3*R*)-2,3-*O*-isopropylidene-pent-4-en-1,2,3-triol **99** provided the mixture of several products (entry 2). Based on ^1H and ^{13}C NMR spectra of the partially separated reaction mixture we suppose the presence of both, 5-*exo*- and 6-*endo*-cyclization products.

Intramolecular $\text{Pd}(\text{II})$ -catalyzed cyclization of model substrates **69a**, **90** and **99**, and subsequent oxidation with $\text{Ph}(\text{OAc})_2$ leading to C–O bond formation, showed only moderate diastereoselectivity and low yields. The protection of free α -hydroxyl group did not lead to any improvement. Thus, present method, which would lead to the analogs of glycosidases inhibitors,¹²⁸ is not suitable for the synthetical use.

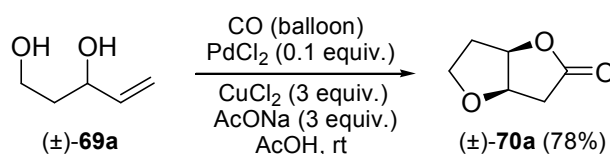
¹²⁸ (a) Winchester, B.; Fleet, G. W. J. *Glycobiol.* **1992**, 2, 199. (b) Sinnott, M. L. *Chem. Rev.* **1990**, 90, 1171.

4.2. Asymmetric intramolecular Pd(II)-catalyzed cyclization and carbonylation reaction

As it was highlighted earlier, catalytic carbonylation chemistry is widely used in organic synthesis and represents a powerful method for bisfunctionalisation of the unsaturated carbon–carbon bonds (see Section 2.4.).⁴⁴ Palladium-catalyzed cyclization of unsaturated alcohols and amines accompanied by the insertion of carbon monoxide is considered to be one of the most interesting and synthetically useful carbonylation reactions.

Having obtained preliminary success with the use of chiral Pd(II)-complexes in an enantioselective oxy- and amidocarbonylative bicyclisation reaction (Sections 4.2.5. and 4.2.6.),^{73,76} we wished to focus on the improvement of asymmetric catalyst performance. In order to reach an advancement, we decided to accomplish a more extensive ligand screening, explore an alternative reoxidation systems, investigate the influence of solvent, temperature and alternative reaction media on the target transformation.

First, the racemic 2,6-dioxabicyclo[3.3.0]octan-3-one (\pm)-**70a** (Scheme 92) was synthesized under standard oxycarbonylation conditions (palladium(II) chloride, copper(II) chloride and sodium acetate in acetic acid under CO atmosphere) with excellent *cis*-selectivity as the racemic reference sample for the determination of enantiomeric excesses.

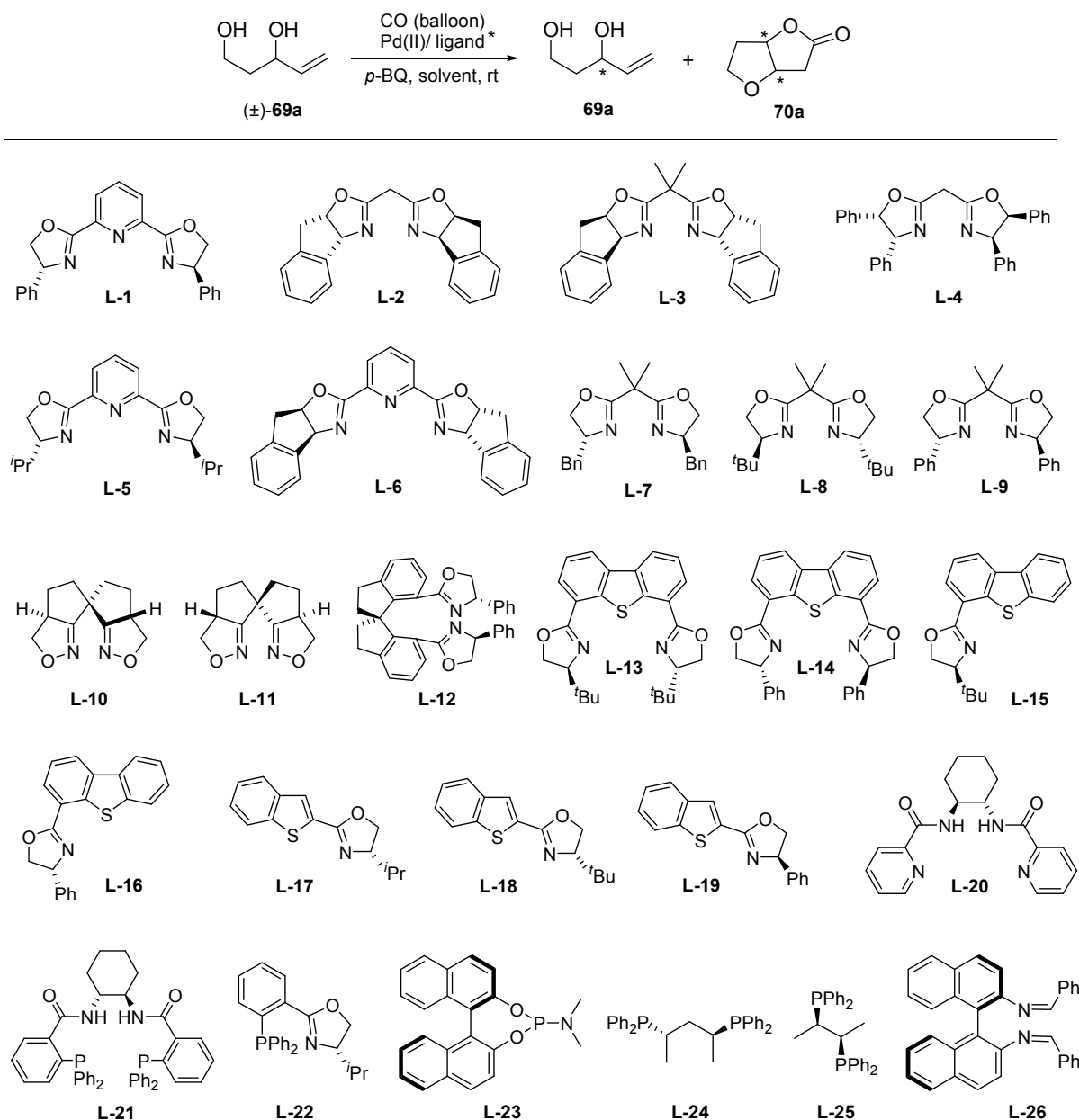


Scheme 92. Preparation of racemic 2,6-dioxabicyclo[3.3.0]octan-3-one (\pm)-**70a**.

4.2.1. Ligand screening

We began our investigation with screening of several types of chiral ligands in the kinetic resolution of pent-4-ene-1,3-diol (\pm)-**69a** (Scheme 93). Initially, the standard catalytic system for the kinetic resolution of unsaturated 1,3-diols was examined.⁷³ The reaction was carried out with different chiral PdX₂–(L^{*}) complexes using *p*-benzoquinone as the reoxidant in acetic acid (0.1–0.2 mol/L with respect to substrate) under carbon monoxide atmosphere (balloon). Chiral palladium(II)-complexes were prepared prior to use in dichloromethane from palladium(II) salt and an excess of ligand. In accordance with the kinetic resolution process, the 50% conversion was maintained by use of 0.5 equiv. of *p*-benzoquinone (Table 22). Conversion control was made by GC analysis using methyl benzoate as an internal standard. The bicyclic product **70a** and the remaining diol **69a** were separated by flash chromatography and their enantiomeric excesses were determined by chiral GC analysis using Chiraldex

B-PM capillary column. Due to more efficient separation on GC column, the enantiomeric excess of **69a** was determined after its conversion into 1-acetyl derivative **146**. The absolute configuration of **70a** was assigned by comparison of the specific rotation values with the literature data ($[\alpha]_D^{20} = +62$ (c 0.9, CHCl₃) for (*R,R*)-**70a** prepared from D-glucose;¹²⁹ $[\alpha]_D^{20} = -67$ (c 0.639, CHCl₃) for (*S,S*)-**70a** prepared by microbial regiodivergent Baeyer-Villiger oxidation with 99% ee¹³⁰).



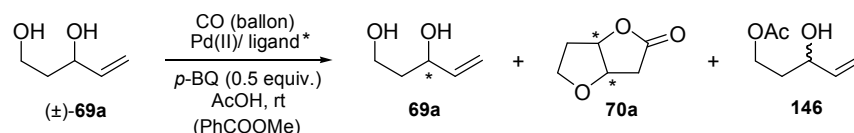
Scheme 93. Kinetic resolution of (±)-**69a** in asymmetric Pd(II)-catalyzed oxycarbonylation, ligand screening.

¹²⁹ Gurjar, M. K.; Patil, V. J.; Pawar, S. M. *Carbohydr. Res.* **1987**, 165, 313.

¹³⁰ Mihovilovic, M. D.; Kapitan, P. *Tetrahedron Lett.* **2004**, 45, 2751.

General screening

As mentioned above, the principal way of conversion control was the utilization of 0.5 equiv. of *p*-benzoquinone reoxidant. The first set of results is summarized in Table 22.



entry	Pd(II) (mol %)	ligand (mol %)	conv. ^a (%)	time	% GC ^b yield (70a)	% isol. yield (70a)	% ee (70a) ^c (config.)	% reisol. yield (69a)	% ee (69a) ^d (config.)	70a / 146 ratio
1	Pd(OAc) ₂ (4)	L-1 (12)	50	3 d	-	22	49 (<i>S,S</i>)	46	27 (<i>R</i>)	1.5:1
2	Pd(OAc) ₂ (2.5)	L-2 (7.5)	40	2 d	25	19	43 (<i>R,R</i>)	45	10 (<i>S</i>)	5.6:1
3	Pd(OAc) ₂ (3)	L-4 (9)	28	3 d	22	16	36 (<i>R,R</i>)	57	10 (<i>S</i>)	3:1
4	Pd(OAc) ₂ (4)	L-5 (12)	33	4 d	24	22	6 (<i>S,S</i>)	55	1 (<i>R</i>)	1.5:1
5	Pd(OAc) ₂ (4)	L-6 (12)	29	5 d	13	-	0 ^e	-	-	1:1
6	Pd(OCOCF ₃) ₂ (4)	L-6 (12)	0	1 d	-	-	-	-	-	-
7	Pd(PhCN) ₂ Cl ₂ (4)	L-6 (12)	5	2 d	-	-	-	-	-	-
8	Pd(OAc) ₂ (4)	L-7 (12)	50	4 d	40	27	9 (<i>R,R</i>)	36	3 (<i>S</i>)	4.5:1
9	Pd(OAc) ₂ (4)	L-13 (12)	39	4 d	8	-	4 (<i>S,S</i>) ^e	-	-	1:1.7 ^f
10	[Pd(π -allyl)Cl] ₂ (4)	L-13 (16)	50	5 d	11	-	5 (<i>S,S</i>) ^e	-	-	1:1.7 ^f
11	Pd(OAc) ₂ (3)	L-14 (9)	54	2 d	14	-	5 (<i>R,R</i>) ^e	-	-	2.3:1 ^f
12	[Pd(π -allyl)Cl] ₂ (4)	L-14 (16)	48	5 d	21	16	0	-	-	2:1
13	Pd(PhCN) ₂ Cl ₂ (5)	L-20 (6)	45	3.5 d	35	32	2 (<i>S,S</i>)	-	-	4.6:1
14	Pd(PhCN) ₂ Cl ₂ (5)	L-21 (6)	5	1 d	0	-	-	-	-	-
15	Pd(PhCN) ₂ Cl ₂ (5)	L-22 (6)	5	2 d	0	-	-	-	-	only 146
16	Pd(CH ₃ CN) ₂ Cl ₂ (6)	L-23 (12)	10	3 d	0	-	-	-	-	only 146
17	Pd(PhCN) ₂ Cl ₂ (5)	L-24 (6)	10	3 d	0	-	-	-	-	only 146
18	Pd(PhCN) ₂ Cl ₂ (5)	L-25 (6)	22	5 d	20	-	4 (<i>S,S</i>) ^e	-	-	1.5:1
19	Pd(OAc) ₂ (4)	L-26 (12)	33	15 h	8	-	2 (<i>S,S</i>) ^e	-	-	6.3:1 ^f

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined by GC with methyl benzoate as internal standard.

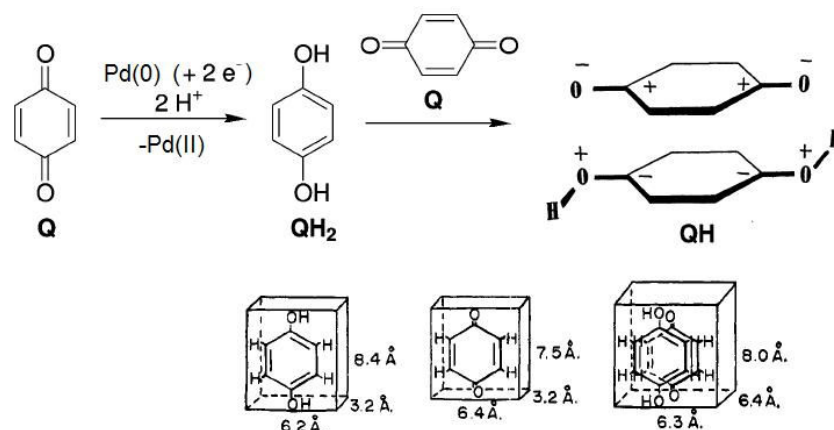
^c Enantiomeric excess of isolated lactone **70a** determined by GC with chiral stationary phase. ^d Enantiomeric excess of reisolated substrate **69a** after its conversion to **146**, determined by GC with chiral stationary phase. ^e Enantiomeric excess of **70a** determined from crude reaction mixture using GC with stationary phase. ^f Another side products observed in the reaction mixtures.

Table 22. Chiral ligand screening using 0.5 equiv. of *p*-benzoquinone.

Generally, palladium(II)-complexes with bis(oxazoline) ligands, except **L-6**, were proven to be the most suitable catalysts for studied kinetic resolution process; however, slightly extended reaction times were necessary to approximate 50% conversion comparing with previously published data⁷³ (Table 22, entries 1-4 and 8). The best result in term of enantioselectivity was reached with PyBox-type ligand **L-1** (49% ee, entry 1). (*R,S*)-Indabox **L-2** showed similar reactivity and comparable enantioselectivity (entry 2), ligands **L-5** and **L-7** were less selective (entries 4 and 8). Surprisingly, (bis)oxazoline **L-6** absolutely failed to give any satisfactory achievement (entries 5-7). A promising group of sulfur-containing

dibenzothiophene bis(oxazoline) ligands (DBT-Box)¹³¹ **L-13** and **L-14** provided good catalytic activity accompanied by poor chemo- and enantioselectivity (entries 9-12), an additional unknown product was observed besides desired lactone **70a** and undesired product of substrate acetylation **146**. (*S,S*)-DACH-Pyridyl Trost ligand **L-20**¹³² also provided relatively good catalytic activity, though was completely non-selective (entry 13). Other tested structures like (*R,R*)-DACH-phenyl Trost **L-21**, phosphoramidite **L-23** and phosphines **L-22**, **L-24** and **L-25** were not accepted in the system with *p*-benzoquinone as Pd(0)/Pd(II)-reoxidant (entries 15, 17 and 18), most probably due to their oxidation¹³³ into phosphine oxides. Benzaldehyde derived bis(imine) **L-26** (entry 19) showed no selectivity.

Based on the data collected in Table 22 we assumed, that the main idea of conversion control (the use of 50 mol % of Pd(0)-reoxidant *p*-benzoquinone in respect of substrate) could fail as the complete consumption of *p*-benzoquinone was observed in several cases at conversions of (±)-**69a** lower than 25%. This was most probably caused due to the formation of charge-transfer quinhydrone complex (QH), which is an equimolar complex of hydroquinone (H₂Q) and *p*-benzoquinone (Q) (Scheme 94).¹³⁴ Quinhydrone is inactive in Pd(0)/Pd(II)-reoxidation process, the charge transfer interactions between the electron donor (hydroquinone) and the electron acceptor (*p*-benzoquinone) stabilize the complex while additional stability may also be provided by hydrogen bonds.



Scheme 94. The charge-transfer quinhydrone complex formation.

¹³¹ (a) Voituriez, A.; Schulz, E. *Tetrahedron: Asymmetry* **2003**, *14*, 339. (b) Schulz, E.; Voituriez, A. *Rus. Chem. Bull., Int. Ed.* **2003**, *52*, 2588.

¹³² Trost, B. M.; Van Vranken, D. L. *Angew. Chem. Int. Ed.* **1992**, *31*, 228.

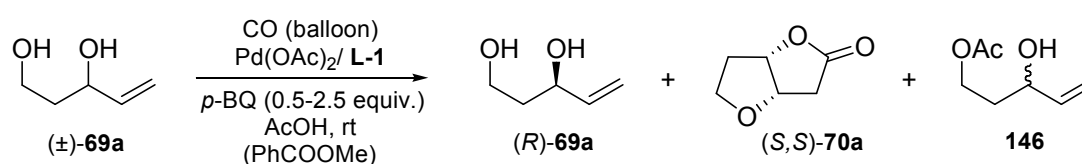
¹³³ (a) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177. (b) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, *14*, 1818.

¹³⁴ (a) Moser, R. E.; Cassidy, H. G. *J. Am. Chem. Soc.* **1965**, *87*, 3463. (b) Kruif, C. G.; Smit, E. J.; Govers, H. A. *J. J. Chem. Phys.* **1981**, *74*, 5838. (c) Karr, P. A.; Zandler, M. E.; Beck, M.; Jaeger, J. D.; McCarty, A. L.; Smith, P. M.; D'Souza, F. *J. Mol. Struct. (THEOCHEM)* **2006**, *765*, 91. (d) Quan, M.; Sanchez, D.; Wasylikiw, M. F.; Smith, D. K. *J. Am. Chem. Soc.* **2007**, *129*, 12847.

Thus, hydroquinone (H₂Q) as a product of Pd(0)/Pd(II) reoxidation forms the charge-transfer complex with unreacted *p*-benzoquinone (Q). After 25% conversion of *p*-benzoquinone to hydroquinone, exactly 1:1 H₂Q/Q mixture is present in the reaction milieu and additional *p*-benzoquinone is required to resume the catalytic cycle processes.

Dependence of conversion on *p*-benzoquinone amount

To explore the conversion dependence on *p*-benzoquinone amount in detail, we accomplished the experiments with different portions of the reoxidant. The results obtained with Pd–L-1 complex are outlined in Table 23.



<i>p</i> -BQ (equiv.)	time (days)	conversion (%)	% ee (S,S)-70a	(S,S)-70a /146 ratio
0.5	2	24	62	3.6:1
	3	30	50	4:1
	4	43	40	2:1
	6	50	37	1.5:1
1	1	14	54	3:1
	2	30	48	3.3:1
	3	47	27	4:1
	6	73	21	3.1:1
1.5	1	10	58	-
	2	29	46	3.8:1
	3	47	33	3.7:1
	6	75	21	3.8:1
2	1	12	59	-
	2	24	45	3:1
	3	39	31	3.4:1
	6	74	19	3.4:1
2.5	1	9	58	-
	2	21	37	2.9:1
	3	40	33	3.4:1
	6	74	20	3.6:1

Table 23. Dependence of conversion on *p*-benzoquinone amount using Pd(OAc)₂/L-1 catalyst.

In general, a noticeable differences in conversions of (\pm)-**69a** were observed when the amount of *p*-benzoquinone increased from 0.5 to 2.5 equivalents (Table 23). The optimal conversion (47%) was reached after 3 days using 1 and 1.5 equiv. of *p*-BQ (in contrast to 30% conversion using 0.5 equiv.). However, the enantioselectivity significantly decreased (27% and 33% ee) comparing to 0.5 equivalent-experiment (40% ee at 43% conversion). The ratios of desired lactone (*S,S*)-**70a** and undesired acylation product **146** ranged from 4:1 to 3:1 except the reaction with 0.5 equiv. of reoxidant, where at 50% conversion the contribution of the side product increased to 1:1.5. Analogous experiments with ligand **L-4** showed comparable results, when the conversion of (\pm)-**69a** after 3 days increased from 24% (using 0.5 equiv. *p*-BQ) to 41% (by the use of 1 equiv. *p*-BQ), the enantioselectivity kept unchanged.

Sulphur-containing mono(oxazolines)

In further screening we continued with the sulfur-containing mono(oxazoline) ligands: dibenzothiophene oxazolines (DBT-Mox)¹³¹ **L-15**, **L-16** and benzothiophene oxazolines (BT-Mox)¹³¹ **L-17**, **L-18** and **L-19**. To avoid a potential lost of catalytic system reoxidation ability due to quinhydrone charge-transfer complex formation, all the experiments were performed with 1 equiv. of *p*-benzoquinone (Table 24).

entry	ligand	conv. ^a (%)	time (days)	% GC ^b yield (70a)	% isol. yield (70a)	% ee (70a) ^c (config.)	% reisol. yield (69a)	% ee (69a) ^d (config.)	70a / 146 ^e ratio
1	L-15	55	2	16	-	12 (<i>S,S</i>)	-	-	1.8:1
2	L-16	63	2	26	-	12 (<i>R,R</i>)	-	-	2.7:1
3	L-17	50	2	8	-	4 (<i>R,R</i>)	-	-	1:1.4
4	L-18	26	2	7	-	7 (<i>R,R</i>)	-	-	1:1.3
5	L-19	56	2	13	-	4 (<i>S,S</i>)	-	-	1.2:1

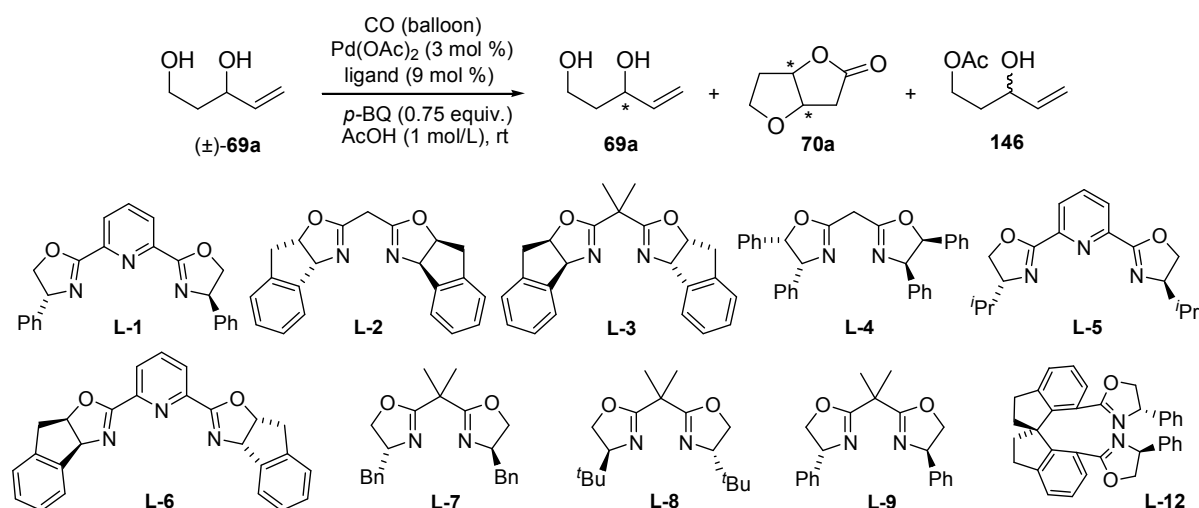
^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined by GC with methyl benzoate as internal standard. ^c Enantiomeric excess of **70a** determined from crude reaction mixture by GC with chiral stationary phase. ^d Enantiomeric excess of reisolated substrate **69a** after its conversion to **146**, determined by GC with chiral stationary phase. ^e Other two side products observed in the reaction mixtures.

Table 24. Pd(II)-catalyzed oxycarbonylative bicyclization using DBT-Mox a BT-Mox ligands.

Both, DBT-Mox and BT-Mox ligands showed moderate to good catalytic activity but poor chemoselectivity, as more than 4 products were detected in the reaction mixtures. Slightly higher enantioselectivities (12% ee) were attained with dibenzothiophene oxazolines **L-15** and **L-16** (Table 24, entries 1 and 2). Benzothiophene oxazolines (entries 3-5) led only to low GC yields and poor enantioselectivities. The structure of side products was not further explored as the reaction mixtures were analyzed without purification.

Bis(oxazoline) ligands, modified reaction conditions

Due to quite long reaction times necessary for reaching 50% conversion (Tables 22, 23) and the potential presence of charge-transfer quinhydrone complex, we acceded to a mild modification of the reaction conditions. The concentration of the substrate was increased from 0.2 to 1 mol/L, and the amount of *p*-benzoquinone was enlarged to 0.75 equiv. (Table 25).



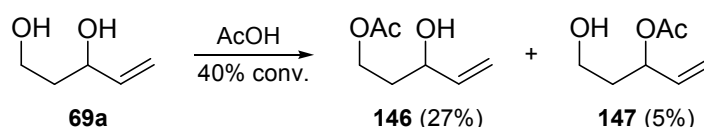
entry	ligand	conv. ^a (%)	time	% GC ^b yield (70a)	% isol. yield (70a)	% ee (70a) ^c (config.)	% reisol. yield (69a)	% ee (69a) ^d (config.)	70a / 146 ratio
1	L-1	42	29 h	38	19	43 (<i>S,S</i>)	40	26 (<i>R</i>)	7:1
2	L-2	42	24 h	27	26	57 (<i>R,R</i>)	57	21 (<i>S</i>)	11:1
3 ^e	L-2	56	24 h	36	28	57 (<i>R,R</i>)	44	27 (<i>S</i>)	10:1
4 ^f	L-3	36	27 h	32	22	61 (<i>S,S</i>)	61	26 (<i>R</i>)	11:1
5	L-4	46	55 h	23	21	37 (<i>R,R</i>)	54	14 (<i>S</i>)	4.1:1
6	L-5	42	30 h	22	17	0	48	0	6.8:1
7	L-6	49	8 d	24	19	15 (<i>R,R</i>)	36	5 (<i>S</i>)	1.2:1
8	L-7	48	24 h	34	28	5 (<i>R,R</i>)	37	0	13:1
9	L-8	37	48 h	13	12	10 (<i>S,S</i>)	54	4 (<i>R</i>)	2.6:1
10	L-9	61	21 h	45	39	18 (<i>R,R</i>)	37	10 (<i>S</i>)	>20:1
11	L-12	56	20 h	24	13	41 (<i>S,S</i>)	42	12 (<i>R</i>)	14:1

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC with methyl benzoate as internal standard. ^c Enantiomeric excess of isolated lactone **70a** determined by GC with chiral stationary phase. ^d Enantiomeric excess of reisolated substrate **69a** after its conversion to **146**, determined by GC with chiral stationary phase. ^e 4 Å molecular sieves were used. ^f Concentration 0.5 mol/L instead of 1 mol/L was used.

Table 25. Pd(II)-catalyzed oxycarbonylative bicyclization using bis(oxazoline) ligands.

As it can be seen in the Table 25, the enhancement of reaction concentration and the use of 0.75 equiv. of *p*-BQ instead of 0.5 equiv. led to shorter reaction times (from 3 days to about 24 hours) and reduced production of acetylated side product **146**. The best enantioselectivity was obtained with (*R,S*)-indabox **L-2** (57% ee, entries 2 and 3) and dimethyl-substituted (*S,R*)-indabox **L-3** (61% ee, entry 4), isolated yields ranged between 22-28%. The best isolated yield (39%) as well as high chemoselectivity (>20:1) was reached using Pd(OAc)₂/**L-9** catalyst, unfortunately, the enantioselectivity was low (18% ee, entry 10). To our surprise, ligand **L-5** was absolutely non-selective, while its Ph-analogue **L-1** provided relatively good enantioselectivity (entry 6 vs. entry 1). The output of entry 6 confirmed the previous finding, that bis(oxazoline) **L-6** is completely unsuitable ligand for studied kinetic resolution process.

Another critical point is significant from Table 25. If we compare the entries 2, 5 and 7 (24 hours, 55 hours and 8 days), it is evident that the prolonged reaction times lead to higher amounts of **146** (from 11:1 to 1.2:1 **70a/146** ratio). Indeed, when the alcohol substrate **69a** was stirred in acetic acid without any additional reagents, its slow conversion to γ -acetylated diol **146** and α -acetylated diol **147** was observed (Scheme 95; approx. 50% conversion in 10 days when glacial acetic acid was used; 30% conversion in 10 days when wet acetic acid was used). This fact also elucidates the increasing conversion of **69a** with prolonged reaction time even after the total consumption of *p*-BQ in some cases (e.g. Table 22, entries 10 and 12).



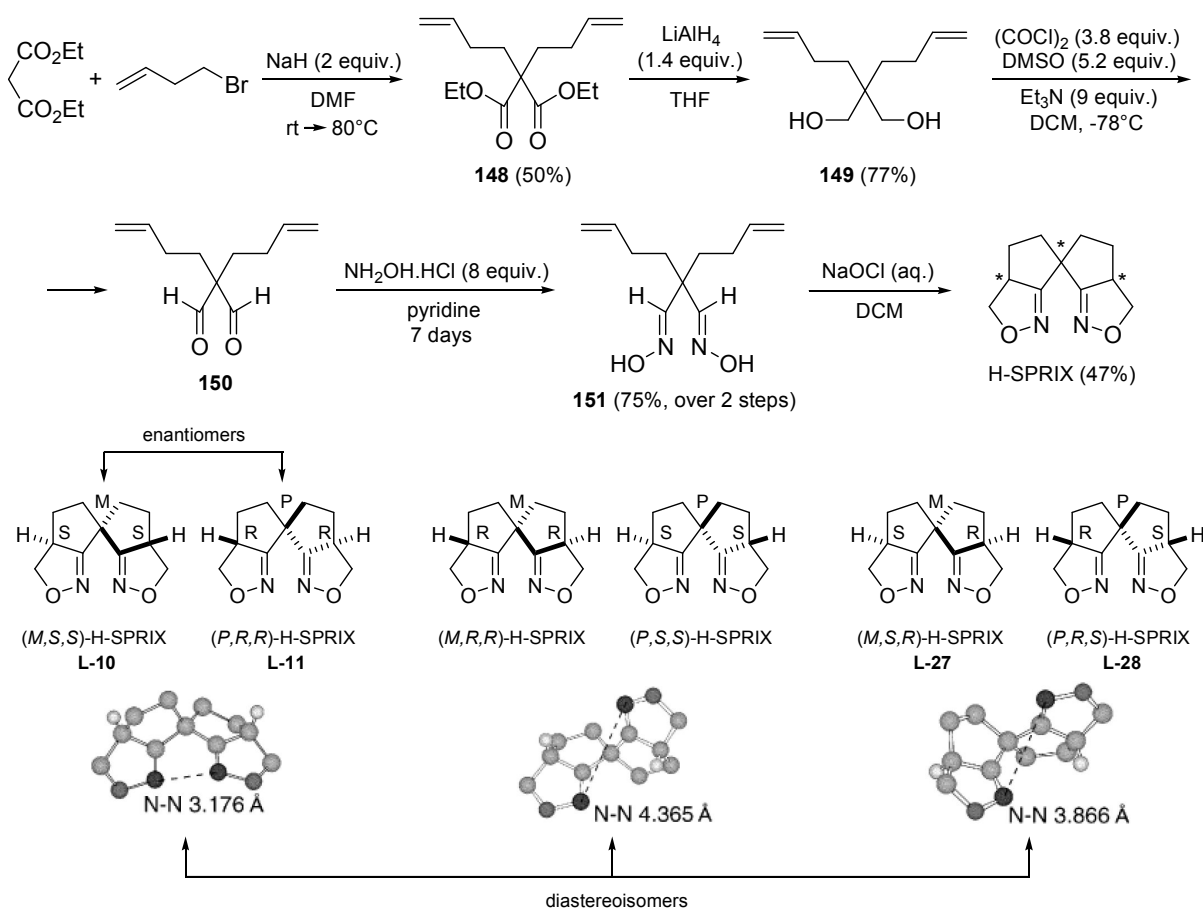
Scheme 95. Formation of side products **146** and **147**.

Isoxazoline-type ligands

Subsequently, we turned our attention to isoxazoline-type ligands, SPRIXs,^{71a,135} as they were successfully used in asymmetric amidocarbonylation reactions^{74,75} (Section 2.4.6.). H-SPRIX and ^{*i*}Pr-SPRIX were synthesized according to the procedures described in the literature (Scheme 96 and 97; depicted yields are isolated yields obtained during our syntheses).^{71a,135} Three diastereomers of H-SPRIX: (*M,S,S*)-/(*P,R,R*)-, (*M,R,R*)-/(*P,S,S*)- and (*M,S,R*)-/(*P,R,S*)-H-SPRIX were separated by flash chromatography; the two enantiomers of

¹³⁵ Arai, M. A.; Arai, T.; Sasai, H. *Org. Lett.* **1999**, *1*, 1795.

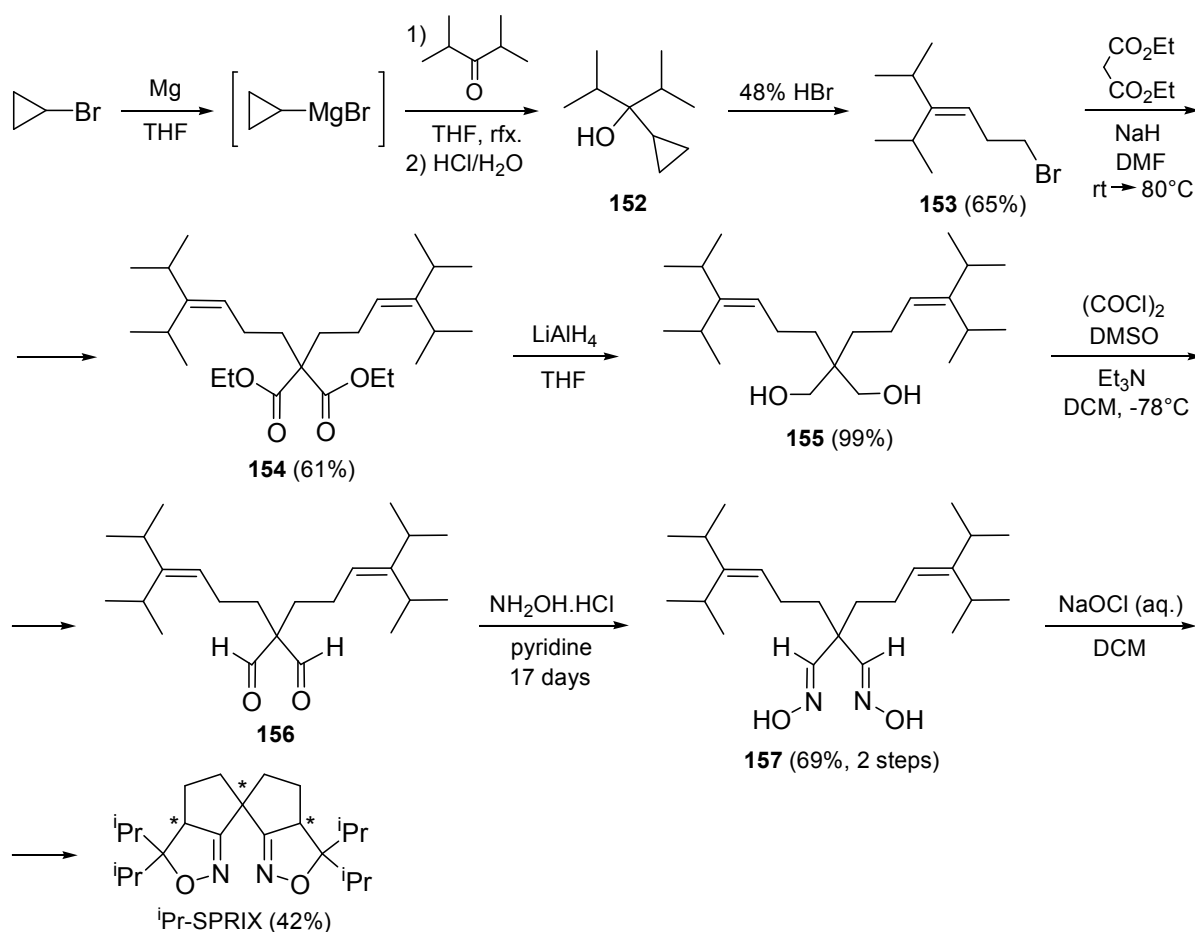
each (*M,S,S*)- vs. (*P,R,R*)- (**L-10** vs. **L-11**) and (*M,S,R*)- vs. (*P,R,S*)-H-SPRIX (**L-27** vs. **L-28**), respectively, were separated using semipreparative supercritical fluid chromatography (SFC) with chiral stationary phase. Unfortunately, we did not succeed in separation of *i*Pr-SPRIX as we were not able to separate its three diastereomers by FLC. The attempts to reach the separation of two enantiomers (*M,S,S*)- and (*P,R,R*)- (**L-29**, **L-30**) of the major *i*Pr-SPRIX diastereoisomer from the mixture of six isomers using SFC were not effective as well.



Scheme 96. Synthesis of H-SPRIX.

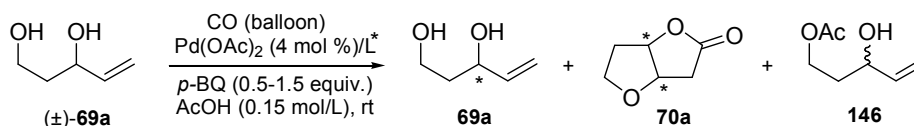
The synthesis of H-SPRIX started from diethyl malonate and 4-bromobut-1-ene (Scheme 96). Double nucleophilic substitution afforded unsaturated diethyl ester¹³⁶ **148** in 50% isolated yield, whereas the product of monosubstitution (25%) was also generated. The reduction with lithium aluminium hydride gave corresponding diol **149** in 77% yield. Swern oxidation followed by the condensation with hydroxylamine led to dioxime **151**, which was cyclized with sodium hypochlorite to desired bis(isoxazoline) ligand H-SPRIX.

¹³⁶ Bien, S.; Ovadia, D. *J. Org. Chem.* **1974**, *39*, 2258.

Scheme 97. Synthesis of *i*Pr-SPRIX.

The *i*Pr-SPRIX was synthesized analogously (Scheme 97), however the corresponding unsaturated bromide (1-bromo-4-isopropyl-5-methylhex-3-ene) **153** is not commercially available. Therefore, it had to be prepared in two steps by the Grignard addition of cyclopropylmagnesium bromide to diisopropyl ketone, followed by cyclopropane ring opening and elimination of water from **152**.^{71a} The critical step of synthesis was the preparation of oxime **157** which took 17 days, the conversion was controlled by NMR. Finally, the cyclization with sodium hypochlorite led to partially separable mixture of *i*Pr-SPRIX diastereomers. Although, we obtained the diastereomerically enriched mixture after flash chromatography, the final separation on SFC was unsuccessful.

With ligands **L-10**, **L-11** (both enantiopure) and **L-27**, **L-28** (enantioenriched, 71% and 73% ee) in hands, we examined their catalytic activity in oxycarbonylative bicyclization reaction (Table 26).



entry	ligand	Pd/L*	p-BQ (equiv.)	conv. ^a (%)	time	% GC ^b yield (70a)	% isol. yield (70a)	% ee (70a) ^c (config.)	70a / 146 ratio
1	L-10	1/3	1.5	52	50 min	23	-	6 (S,S)	>20:1
2	L-10	1/3	1.5	80	90 min	40	-	3 (S,S)	>20:1
3	L-11	1/3	1.5	97	3 h	55	-	1 (R,R)	>20:1
4	L-11	1/2	0.5	53	90 min	25	-	5 (R,R)	>20:1
5	L-28	1/3.5	1	24	24 h	11	-	6 (R,R)	2.5:1 ^d

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC analysis with methyl benzoate as internal standard. ^c Enantiomeric excess of **70a** determined from crude reaction mixture by GC with chiral stationary phase. ^d Another side product observed in the reaction mixture.

Table 26. Pd(II)-catalyzed oxycarbonylative bicyclization using H-SPRIX ligands.

The first experiments were carried out with 1.5 equiv. of *p*-benzoquinone reoxidant (Table 26, entries 1-3). To our surprise, (*M,S,S*)-/(*P,R,R*)-H-SPRIX ligands **L-10/L-11** abounded in great catalytic activity, as approx. 50% conversion was reached in 50 minutes (entry 1). Moreover, high chemoselectivity was observed (>20:1). Almost complete consumption of the diol substrate was achieved in 3 hours (entry 3). When 0.5 equiv. of reoxidant was used and the amount of the ligand was reduced from 3 to 2 equiv. with respect to palladium, 53% conversion was accomplished in 90 minutes (entry 4). Unfortunately, the enantioselectivities were poor and moved between 5-6% ee. On the other hand, when (*M,S,R*)-/(*P,R,S*)-H-SPRIX **L-27/L-28** was employed, the reactivity considerably decreased (entry 5). This fact can be explained by the different distance and torsion angle between two nitrogen atoms in each of three possible diastereomers (Scheme 96); ligands **L-10/L-11** possess the shortest distance (3.18 Å) and smallest torsion angle (45.6°) between two coordination centers, what enables the coordination with palladium.¹³⁵

Bis(phosphine)-palladium(II) complexes

As mentioned above, phosphine ligands were not proven to be suitable for Pd(II)-catalyzed oxycarbonylative bicyclisation using *p*-benzoquinone as Pd(0)/Pd(II) reoxidant (Table 22, entries 14-18). Nevertheless, we carried out an additional study using the simple achiral complexes 1,2-bis(diphenylphosphino)ethane-palladium(II) dichloride **C-1** and bis(triphenylphosphine)palladium(II) dichloride **C-2** previously prepared (Table 27).

entry	Pd-complex	reoxidant (equiv.)	additive (equiv.)	conv. ^a (%)	time	% GC ^b yield (70a)	70a / 146 ratio
1	C-1	<i>p</i> -BQ (0.5)	-	0	24 h	-	-
2	C-2	<i>p</i> -BQ (0.5)	-	9	4 d	0	only 146
3	C-1	<i>p</i> -BQ (0.5)	AgBF ₄ (0.12)	21	4 d	0	only 146
4	C-1	CuCl ₂ (0.5)	-	0	24 h	-	-
5	C-1	CuCl ₂ (0.5)	AcONa (0.5)	0	24 h	-	-
6	C-1	CuCl ₂ (3)	AcONa (3)	36	40 h	2	1:2 ^c
7	C-1	PhI(OAc) ₂ (0.5)	-	45	48 h	3	1:3.5 ^c

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC with methyl benzoate as internal standard. ^c Another side product observed in the reaction mixture.

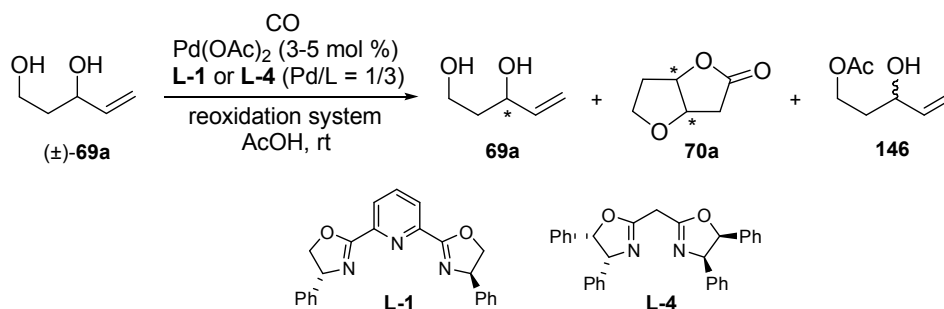
Table 27. Bis(phosphine)-palladium complexes as the catalysts for oxycarbonylative bicyclization.

Initially, we remained under *p*-benzoquinone reoxidation conditions (Table 27, entries 1-3). As shown in the table, the reactions employing **C-1** and **C-2** with 0.5 equiv. of *p*-BQ proceeded very slowly and did not lead to desired cyclization product (entry 1, 2). In order to facilitate the ligand exchange, AgBF₄ was used as an additive (entry 3) which caused a slight improvement in conversion (21%). But again, only acetylated product **146** was detected. The use of CuCl₂ (0.5 equiv.) without any additive or with AcONa (0.5 equiv.) resulted in no reaction (entries 4, 5). The increasing of CuCl₂/AcONa amount to 3 equiv. accelerated the reaction, however provided the mixture of products with (±)-**70a** as the minor compound (entry 6). Similar result was obtained using PhI(OAc)₂ as oxidant (entry 7).

4.2.2. Alternative reoxidation systems

Despite the fact, that *p*-benzoquinone worked quite well as the Pd(0)/Pd(II) reoxidant using bis(oxazoline) ligands, we were interested in exploration of alternative reoxidation systems, which could possibly extend the ligand scope and acceptance. The results obtained with ligands **L-1** and **L-4** are summarized in Table 28.

When iodobenzene diacetate was used (Table 28, entry 1), the reaction proceeded with 31% conversion in 5 days, enantioselectivity 16% and products ratio 1:1 (**70a**/**146**). Thus, comparing to previously obtained result (24% conversion in 3 days, 36% ee and 3:1 ratio; Table 22, entry 3) we did not reach any considerable improvement.



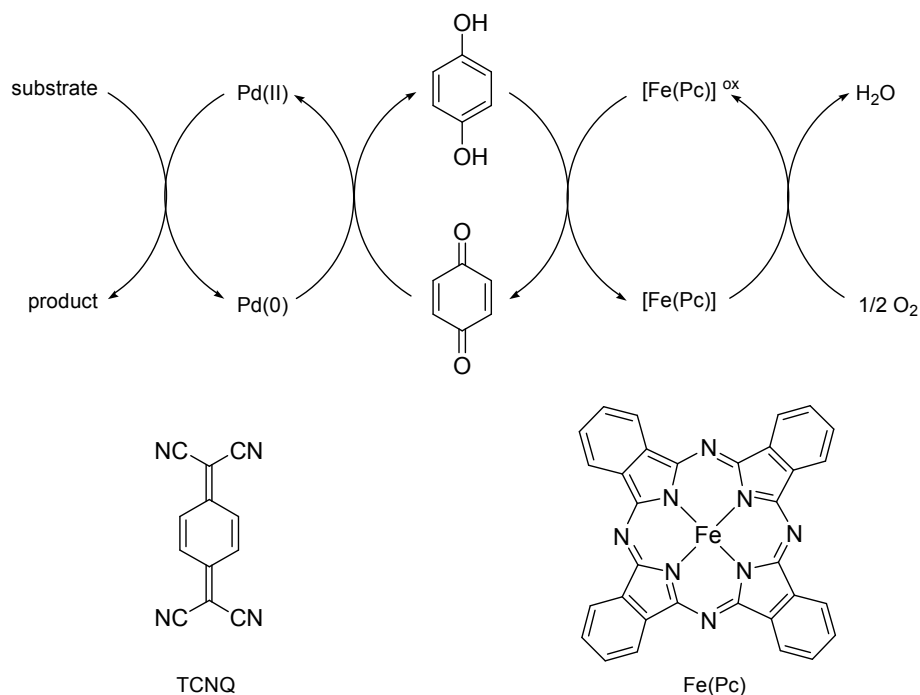
entry	ligand	reoxidant (equiv.)	conv. ^a (%)	time	% GC ^b yield (70a)	% ee (70a) ^c (config.)	70a / 146 ratio
1	L-4	PhI(OAc) ₂ (0.5)	31	5 d	12	16 (<i>R,R</i>)	1.2:1
2	L-4	CuCl ₂ (0.5)	60	3 d	30	0	1.5:1 ^d
3	L-4	Cu(OAc) ₂ (0.5)	10	3 d	3	39 (<i>R,R</i>)	1:1.5
4	L-4	<i>p</i> -BQ (0.5), TCNQ (0.5)	37	5 d	14	3 (<i>R,R</i>)	1.5:1
5	L-1	HQ (0.2), Fe(Pc) (0.05), O ₂	46	3 d	22	39 (<i>S,S</i>)	3:1
6	L-1	<i>p</i> -BQ (0.2), Fe(Pc) (0.05), O ₂	38	5 d	22	33 (<i>S,S</i>)	2.2:1

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC analysis with methyl benzoate as internal standard. ^c Enantiomeric excess of **70a** determined from crude reaction mixture by GC with chiral stationary phase. ^d Other 4 side products observed in the reaction mixture.

Table 28. Alternative reoxidants for Pd(II)-catalyzed oxycarbonylative cyclization.

When the reaction was carried out with 0.5 equivalent of CuCl₂, 50% conversion was accomplished in less than 3 days (entry 2, Table 28). However, several products were detected in reaction mixture and bicycle **70a** was formed with no enantioselectivity. On the other hand, poor conversion (about 10%) was achieved with Cu(OAc)₂ (entry 3). This fact can be explained by the nitrophilic properties of Cu(II) salts^{78a} and by consequent formation of Cu-(bis)oxazoline instead of chiral Pd-(bis)oxazoline complex. The equimolar mixture of *p*-benzoquinone and tetracyanoquinodimethane (TCNQ, Scheme 98) was employed with a view to avoid the quinhydrone (*p*-BQ and HQ 1:1 mixture) charge-transfer complex formation, as TCNQ is a stronger electron-acceptor than *p*-benzoquinone. But in fact, the reaction proceeded slowly with no selectivity (3% ee). An interesting reoxidation system using iron phthalocyanine Fe(Pc)¹³⁷ and *p*-benzoquinone or hydroquinone in catalytic amount with O₂ (Scheme 98) was also tested (entries 5-6). Better conversion (46% in 3 days), chemo- (3:1 mixture **70a/146**) and enantioselectivity (39% ee) were achieved with Fe(Pc)/hydroquinone/O₂ (entry 5). However, the experiment using 0.5 equiv. of *p*-benzoquinone (Table 22, entry 1) led to more satisfactory result (50% conversion in 3 days, 49% ee, **70a/146** 1.5:1).

¹³⁷ (a) Bäckvall, J.-E.; Hopkins, R. B. *Tetrahedron Lett.* **1988**, 29, 2885. (b) Bäckvall, J.-E.; Hopkins, R. B.; Grennberg, H.; Mader, M. M.; Awasthi, A. K. *J. Org. Chem.* **1990**, 112, 5160. (c) Piera, J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2008**, 47, 3506.



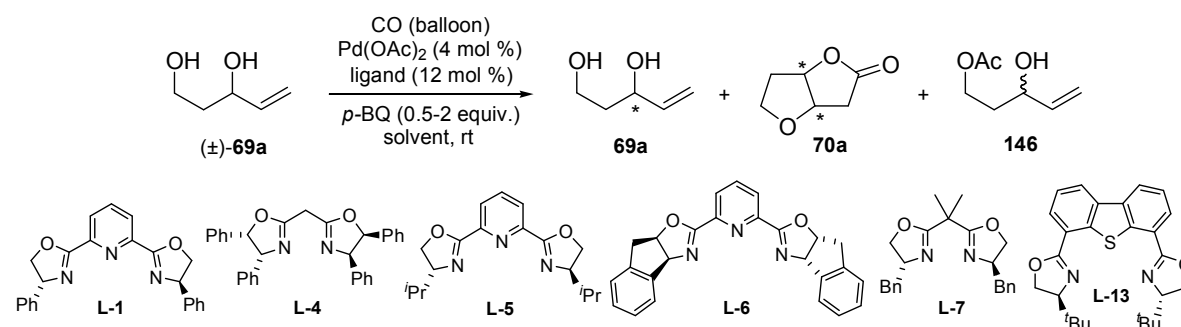
Scheme 98. Reoxidation system using iron phthalocyanine; structure of TCNQ.

4.2.3. Solvent, temperature and pressure influence

Kapitán in his thesis described, that along the strong dependence on anionic ligands attached to palladium (acetate anions were proven to be the most suitable), the catalytic activity in asymmetric oxycarbonylative bicyclization strongly depends on solvent.¹³⁸ He found that glacial acetic acid represents a key component to accomplish the desired type of transformation, whereas employment of tetrahydrofuran or dichloromethane led to low conversion of substrates.

One of the limitations of acetic acid as the solvent is its melting point (16.6°C) which disables to carry out the experiments at lower temperature. Therefore, we decided to perform an additional screening of solvents and solvent mixtures. The first set of experiments was effected with bis(oxazoline) ligands (Table 29).

¹³⁸ Kapitán P. *Enantioselective Palladium(II)-Catalyzed Oxycarbonylation in the Synthesis of Bicyclic Lactones. Synthesis of Natural Products*, Slovak University of Technology in Bratislava, Thesis 2005.



entry	ligand	equiv. of <i>p</i> -BQ	conv. ^a (%)	time (days)	solvent	% GC ^b yield (70a)	% ee (70a) ^c (config.)	70a / 146 ratio
1	L-1	0.5	<5	4	DMF	-	-	-
2	L-1	1	15	2	H ₂ O	10	67 (S,S)	10:1
3	L-1	1	37	2	AcOH-H ₂ O 1:2	16	51 (S,S)	8.5:1
4	L-1	2	58	4	AcOH-H ₂ O 1:2	41	41 (S,S)	9:1
5	L-4	0.5	19	2	AcOH-toluene 1:1	10	36 (R,R)	3.5:1
6 ^d	L-4	1.5	100	1	CF ₃ COOH	-	-	-
7	L-4	2	20	5	AcOH-H ₂ O 1:2	13	20 (R,R)	1.5:1
8	L-5	2	49	3	AcOH-H ₂ O 1:2	21	5 (S,S)	7.5:1
9	L-6	0.5	<5	2	AcOH-DMF 1:2	-	-	-
10	L-6	2	60	5	AcOH-H ₂ O 1:2	27	9 (R,R)	5.5:1 ^e
11	L-7	2	50	3	AcOH-H ₂ O 1:2	24	0	9:1
12	L-13	2	57	3	AcOH-H ₂ O 1:2	21	0	3:1 ^e

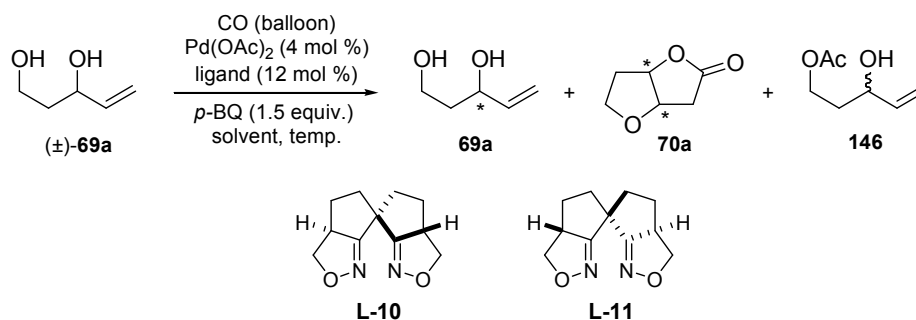
^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC with methyl benzoate as internal standard. ^c Enantiomeric excess of lactone **70a** determined from crude reaction mixture by GC with chiral stationary phase. ^d Substrate decomposition. ^e Another unknown products observed in crude reaction mixture.

Table 29. Solvent screening using bis(oxazoline) ligands.

Polar aprotic dimethylformamide completely failed to give desired transformation (Table 29, entry 1), even in the mixture with acetic acid (entry 9). The use of trifluoroacetic acid led to substrate decomposition (trifluoroacetic acid is almost 10⁵-fold more acidic than acetic acid, *pK_a* (TFA) = 0.23, *pK_a* (AcOH) = 4.76), desired lactone **70a** was not observed (entry 6). An interesting result was obtained using water as the solvent (entry 2), however the conversion could not be determined correctly due to not complete solubility of methyl benzoate, internal standard, in water. At approximately 15% conversion, the bicyclic lactone **70a** was formed with good enantioselectivity (67% ee) and chemoselectivity (10:1). To insure a good solubility of methylbenzoate in reaction medium, the 1:2 mixture of acetic acid-water was studied (entries 3, 4, 7, 8, 10-12). A notable improvement in yield was attained with ligand **L-1** using 2 equiv. of *p*-benzoquinone (entry 4).

Specifically challenging task was to find a suitable solvent for the transformation using (*M,S,S*)-/(*P,R,R*)-H-SPRIX ligands (**L-10/L-11**). As it was pointed earlier, Pd(OAc)₂-**L-10**/Pd(OAc)₂-**L-11** complexes demonstrated a high catalytic activity in studied

kinetic resolution process (52% conversion in 50 minutes; Table 26, entry 1), however the desired lactone **70a** was generated with low enantioselectivity (6% ee). Thus, the main idea was to conduct the experiments at low temperature and increase the level of asymmetric induction (Table 30).



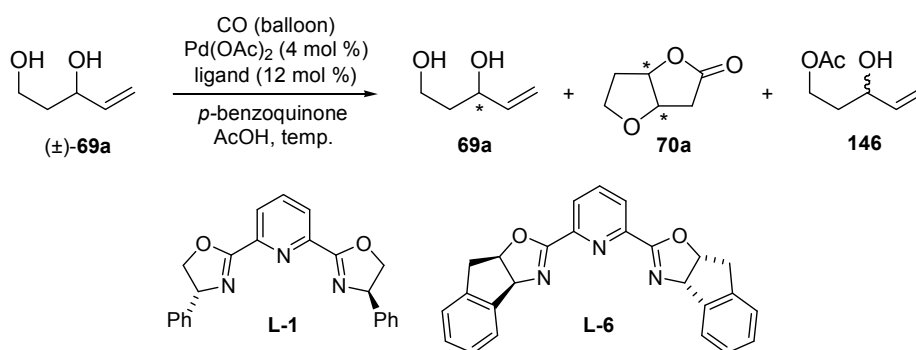
entry	ligand	solvent	temperature	conv. ^a (%)	time	% GC ^b yield (70a)	% ee (70a) ^c (config.)	70a / 146 ratio
1	L-10	AcOH-DCM 1:8	-60°C to rt	12	overnight	9	3 (S,S)	>20:1
2	L-11	THF	rt	0	3 d	-	-	-
3	L-11	acetonitrile	rt	0	3 d	-	-	-
4	L-10	AcOH-AcOEt 1:4	rt	4	2 h	4	6 (S,S)	>20:1
5	L-11	CH ₃ CH ₂ CO ₂ H	rt	57	24 h	30	3 (R,R)	>20:1

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC with methyl benzoate as internal standard. ^c Enantiomeric excess of lactone **70a** determined from crude reaction mixture by GC with chiral stationary phase.

Table 30. Solvent screening using H-SPRIX **L-10/L-11**.

As it can be seen in the table, the reaction in dichloromethane-acetic acid 8:1 mixture provided low conversion and was unselective (Table 30, entry 1), tetrahydrofuran and acetonitrile absolutely failed to give desired transformation (entries 2 and 3). If 1:4 mixture of acetic acid and ethyl acetate was used (entry 4), 4% conversion was reached in 2 hours. The reaction in propionic acid gave 57% conversion in 24 hours (entry 5) and could be potentially performed at lower temperature, however the catalytic activity was considerably lower.

The temperature influence was checked in a system using bis(oxazolines) **L-1** and **L-6** in acetic acid (Table 31). In general, increasing of the temperature to 40°C and 60°C led to higher reaction rates and rising of acetylation side product amounts. Higher temperature seemed to have no influence on enantioselectivity (entry 1 vs. 2; 3 vs. 4).

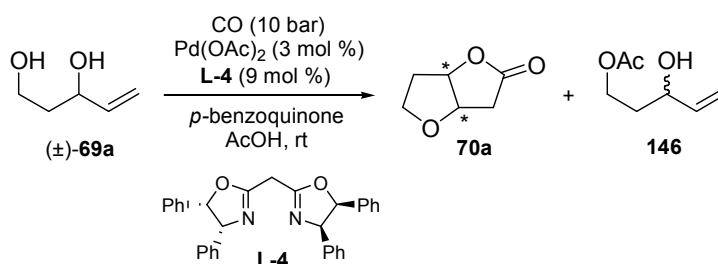


entry	ligand	<i>p</i> -BQ (equiv.)	temperature	conv. ^a (%)	time	% GC ^b yield (70a)	% ee (70a) ^c (config.)	70a / 146 ratio
1	L-1	1	rt	47	3 d	28	27 (S,S)	4:1
2	L-1	1	40°C	48	24 h	25	30 (S,S)	2:1
3	L-6	0.5	rt	29	5 d	13	0	1:1.1
4	L-6	0.5	60°C	49	18 h	11	0	1:3.3

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC with methyl benzoate as internal standard. ^c Enantiomeric excess of lactone **70a** determined from crude reaction mixture by GC with chiral stationary phase.

Table 31. Influence of temperature on Pd(II)-catalyzed oxycarbonylative bicyclization.

Finally, we examined the pressure influence (Table 32). The reaction was carried out with chiral Pd(OAc)₂–**L-4** complex using *p*-benzoquinone in acetic acid under 10 bar pressure of carbon monoxide. Initially, 0.5 equiv. of reoxidant was used and the conversion was checked after 24 hours (Table 32, entry 1). To our surprise, *p*-benzoquinone was completely consumed during this period at 25% conversion of substrate.



entry	<i>p</i> -BQ (equiv.)	time (hours)	conv. ^a (%)	% GC ^b yield (70a)	% ee (70a) ^c (config.)	70a / 146 ratio
1	0.5	24	25	14	45 (R,R)	2.5:1
2	+1	+16	30	18	41 (R,R)	2:1
3	-	+18	40	25	41 (R,R)	2:1

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC with methyl benzoate as internal standard. ^c Enantiomeric excess of lactone **70a** determined from crude reaction mixture by GC with chiral stationary phase.

Table 32. Influence of pressure on Pd(II)-catalyzed oxycarbonylative bicyclization.

Thus, a new portion of reoxidant (1 equiv.) was added. After additional 16 hours (Table 32, entry 2) the conversion was found to be 30% (*p*-benzoquinone was still present in the reaction mixture). Further stirring of the reaction mixture at 10 bar pressure for 18 hours led to 40% conversion of the substrate (entry 3). The enantioselectivity of the formation of **70a** did not dramatically change during the reaction process. We can conclude, that the reaction carried out under 10 bar pressure of carbon monoxide proceeded with slightly better enantioselectivity comparing to previously observed results (Table 22, entry 3; Table 25, entry 5), the reaction rate and yield were comparable to the experiment with 0.75 equiv. of *p*-benzoquinone and acetic acid concentration 1 mol/L (Table 25, entry 5).

4.2.4. Influence of ionic liquids

Ionic liquids, or room temperature molten salts, not only have the potential to increase chemical reactivity and thus lead to more efficient processes, but are also non-flammable and less toxic than conventional solvents due to their low vapor pressure.^{139,140} By modifying the structure of cations or anions, it has been shown that their properties can be altered in order to influence the outcomes of reactions.

Many applications of ionic liquids as a clean media for green catalytic transformations have been reported,¹⁴¹ there are only few examples of Pd(II)-catalyzed oxycarbonylative cyclization using ILs in the literature.¹⁴² So far, no asymmetric Pd(II)-catalyzed oxycarbonylative cyclization using ILs has been reported.

Thus, we decided to explore if the use of ionic liquids as the reaction media could have some positive influence on kinetic resolution of (\pm)-**69a** by Pd(II)-catalyzed oxycarbonylation. Imidazolium- and pyridinium-type ILs, chosen for our study, were prepared easily in two steps using microwave activation (Scheme 99).¹⁴³ Ionic liquids were purified by simple filtration of the inorganic byproduct (MBr, M = Li, K, Na) followed by washing of the crude IL with diethyl ether to remove residual reagents.

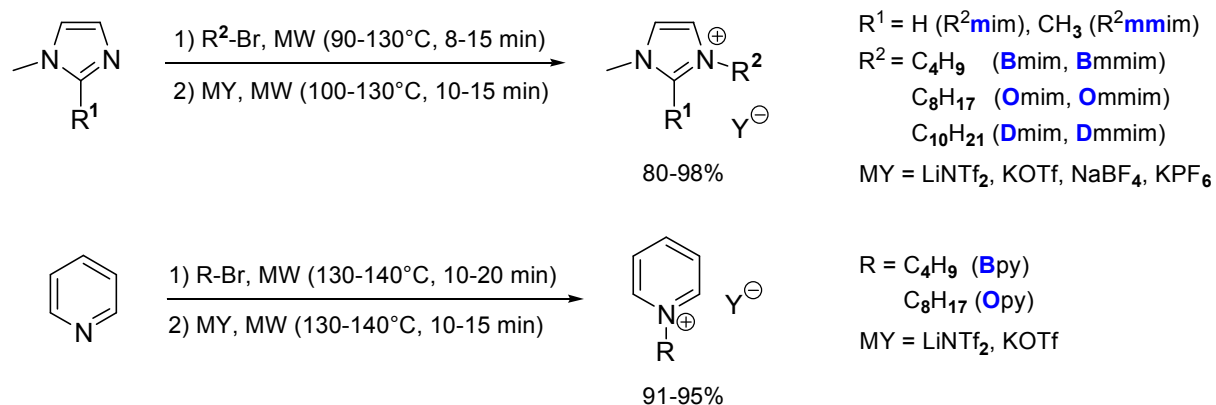
¹³⁹ Wasserscheid, P.; Welton, T. *Ionic liquids in synthesis*; 2nd Edition, Wiley-VCH: Weinheim, 2008.

¹⁴⁰ (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772. (c) Sheldon, R. *Chem. Commun.* **2001**, 2399. (d) Hallett, J. P.; Welton, T. *Chem. Rev.* **2011**, *111*, 3508.

¹⁴¹ For reviews see: (a) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *61*, 1015. (b) Pârvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, *107*, 2615. (c) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonaccorso, H. G. *Chem. Rev.* **2008**, *108*, 2015.

¹⁴² (a) Consorti, C. S.; Ebeling, G.; Dupont, J. *Tetrahedron Lett.* **2002**, *43*, 753. (b) Gabriele, B.; Mancuso, R.; Lupinacci, E.; Salerno, G.; Veltri, L. *Tetrahedron* **2010**, *66*, 6156.

¹⁴³ Aupoix, A. *Les sels d'azolium précurseurs de carbènes N-hétérocycliques: Synthèse et applications en catalyse*, Université Paris-Sud 11, Thesis 2010.



Scheme 99. Preparation of imidazolium- and pyridinium-type ionic liquids.

All tested ionic liquids were prepared in above-described manner and used without further purification.

The initial trial was performed with $\text{Pd}(\text{OAc})_2/\text{L-1}$ or **L-4** catalyst using 0.5 equiv. of *p*-benzoquinone and 3 equiv. of ionic liquid under atmosphere of carbon monoxide (Table 33). As illustrated in the table, experiments performed in pure ionic liquids led to subtle conversions of (\pm)-**69a** and afforded only traces of lactone **70a**, even after several days of vigorous stirring (entries 1, 4-6, 8-10). In some cases, putative conversions were observed. This phenomenon was chiefly apparent when very viscous ionic liquids were used (entries 5 and 9; conversion data in parentheses). Despite of the fact that no product, even any trace, was detected in the reaction mixture (GC analysis), the conversions obtained after the calculation (in respect to methylbenzoate) were positive. We expect, that this defect occurred due to a loss of starting material during the extraction of products from viscous ionic liquid with diethyl ether.

As it was underlined earlier, glacial acetic acid represents a key component to accomplish asymmetric Pd-catalyzed oxycarbonylative bicyclization. Therefore, the experiments with acetic acid as an additive were conducted. In comparison with experiments in pure ionic liquid, the reactions with 0.5 equiv. of acetic acid proceeded with slightly better conversion (Table 33, entries 2 and 7). A crucial improvement occurred, when 1:1 mixture of ionic liquid and acetic acid was employed. The reaction of (\pm)-**69a** using $\text{Pd}(\text{OAc})_2/\text{L-1}$ catalytic system and 0.5 equiv. of *p*-benzoquinone reoxidant in 3 equiv. of 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide and 3 equiv. of acetic acid under carbon monoxide atmosphere proceeded with 32% conversion and afforded (*S,S*)-**70a** with 80% ee (entry 3).

$(\pm)\text{-69a}$
 $\xrightarrow[\text{IL (3 equiv.) additive}]{\text{CO (balloon), Pd(OAc)}_2 \text{ (4 mol \%), ligand (12 mol \%), } p\text{-BQ (0.5 equiv.)}}$
 70a + 146

$[\text{Bmim}]\text{NTf}_2$
 $[\text{Bmim}]\text{BF}_4$
 $[\text{Bmim}]\text{PF}_6$
 $[\text{Bmim}]\text{Br}$
 $[\text{Dmim}]\text{OTf}$

entry	ligand	ionic liquid	additive (equiv.)	conv. ^a (%)	time (days)	% GC ^b yield (70a)	% ee (70a) ^c (config.)	70a / 146 ratio
1	L-1	[Bmim]NTf ₂	-	<5	3	2	-	-
2	L-1	[Bmim]NTf ₂	AcOH (0.5)	15	3	4	39 (S,S)	10:1
3	L-1	[Bmim]NTf ₂	AcOH (3)	32	3	18	80 (S,S)	9.5:1
4	L-1	[Bmim]BF ₄	-	<10	7	4	-	-
5	L-1	[Bmim]Br	-	<5 (68)	2	0	-	-
6	L-4	[Bmim]NTf ₂	-	<5	3	2	-	-
7	L-4	[Bmim]NTf ₂	AcOH (0.5)	9	3	3	38 (R,R)	-
8	L-4	[Bmim]BF ₄	-	<5	7	3	-	-
9	L-4	[Bmim]PF ₆	-	0 (59)	5	-	-	-
10	L-4	[Dmim]OTf	-	<5	5	3	-	-

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC with methyl benzoate as internal standard. ^c Enantiomeric excess of isolated lactone **70a** determined by GC with chiral stationary phase.

Table 33. Asymmetric Pd-catalyzed oxycarbonylation in ionic liquids.

With this encouraging result in hands, we accomplished a broader ILs screening.¹⁴⁴ First, the ionic liquids with different anions and *N*-alkyl chains were tested. The outcomes are summarized in Table 34, divided into four parts according to anionic part of tested ionic liquid (NTf₂, BF₄, PF₆ and OTf). The best results in regard to enantioselectivity are highlighted in gray.

¹⁴⁴ Doháňošová, J.; Lásiková, A.; Toffano, M.; Gracza, T.; Vo-Thanh, G. *New J. Chem.* **2012**, submitted.

(±)-**69a** $\xrightarrow[\text{IL / AcOH, rt}]{\text{CO (balloon), Pd(OAc)}_2 \text{ (4 mol \%), ligand (12 mol \%), } p\text{-BQ (0.5 equiv.)}}$ **70a** + **146**

L-1 **L-2** **L-3** **L-4**

entry	ligand	IL (equiv.)	AcOH (equiv.)	<i>p</i> -BQ (equiv.)	conv. ^a (%)	time (d)	% GC ^b y. (70a)	% isol. y. (70a)	% ee (70a) ^c (config.)	% ee (69a) ^d (config.)	70a / 146 ratio
1	L-1	BmimNTf ₂ (3)	3	0.5	55	4	27	14	68 (S,S)	55 (R)	12:1
2	L-1	BmimNTf ₂ (3)	3	1	49	4	28	16	65 (S,S)	56 (R)	12:1
3	L-1	BmimNTf ₂ (10)	3	0.5	26	9	7	-	78 (S,S) ^e	-	7.5:1
4	L-1	BmimNTf ₂ (10)	10	0.5	49	7	17	14	80 (S,S)	49 (R)	5.3:1
5	L-2	BmimNTf ₂ (3)	3	0.5	19	2	8	-	44 (R,R) ^e	-	>20:1
6	L-3	BmimNTf ₂ (3)	3	0.5	42	2	21	16	40 (S,S)	20 (R)	>20:1
7	L-1	OmimNTf ₂ (3)	3	0.5	20	6	5	-	28 (S,S) ^e	-	2:1
8	L-1	DmimNTf ₂ (3)	3	0.5	47	3	19	18	68 (S,S)	42 (R)	8.5:1
9	L-1	BpyNTf ₂ (3)	3	0.5	48	3	24	20	71 (S,S)	43 (R)	8:1
10	L-1	OpyNTf ₂ (3)	3	0.5	30	3	16	10	46 (S,S) ^e	-	1.2:1
11	L-1	BmimBF ₄ (4)	3	0.5	42	6	15	13	72 (S,S)	38 (R)	5:1
12	L-1	BmimBF ₄ (3)	3	0.5	38	3	18	15	77 (S,S)	38 (R)	5.7:1
13	L-3	BmimBF ₄ (4)	3	0.5	41	2	21	16	42 (S,S)	20 (R)	>20:1
14	L-3	BmimBF ₄ (3)	3	0.5	41	3	18	19	45 (S,S)	24 (R)	>20:1
15	L-2	BmimBF ₄ (3)	3	1	41	6	12	-	12 (R,R) ^e	-	8.7:1
16	L-4	BmimBF ₄ (3)	3	1	63	6	10	-	7 (R,R) ^e	-	8:1
17	L-1	OmimBF ₄ (3)	3	0.5	42	3	15	17	71 (S,S)	39 (R)	5.5:1
18	L-1	BmimOTf (3)	3	0.5	5	6	1	-	-	-	1.4:1
19	L-2	BmimOTf (3)	3	0.5	5	6	1	-	-	-	1:1.7
20	L-1	OmimOTf (3)	3	0.5	0	3	-	-	-	-	-
21	L-1	OmimPF ₆ (3)	3	0.5	55	3	27	20	79 (S,S)	60 (R)	7.5:1

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC with methyl benzoate as internal standard. ^c Enantiomeric excess of isolated lactone **70a** determined by GC with chiral stationary phase. ^d Enantiomeric excess of reisolated substrate **69a** after its conversion to **146**, determined by GC with chiral stationary phase. ^e Enantiomeric excess of **70a** determined from crude reaction mixture by GC with chiral stationary phase.

[Bmim] **[Omim]** **[Dmim]** **[Bpy]** **[Opy]** | ⁻NTf₂ ⁻BF₄ ⁻OTf ⁻PF₆

Table 34. Asymmetric Pd-catalyzed oxycarbonylation in ionic liquids.

Four key points are significant for asymmetric Pd-catalyzed oxycarbonylation in ionic liquids (Table 34). At first, ionic liquids had positive influence on enantioselectivity only in the case of ligand **L-1**. Comparing to the results obtained in acetic acid, the employment

of other ligands (**L-2**, **L-3**, **L-4**) led to lower enantioselectivities. Secondly, no relationship between different *N*-alkyl substituents ($-\text{C}_4\text{H}_9$, $-\text{C}_8\text{H}_{17}$, $-\text{C}_{10}\text{H}_{21}$) and enantioselectivity was observed. At third, ionic liquids with trifluoromethanesulfonate anionic part were proven to be absolutely unsuitable for desired transformation (entries 18-20). Fourthly, when the amount of ionic liquid was increased to 10 equivalents, the reaction was considerably inhibited (entry 3). Using of 10 equiv. of IL and the same amount of acetic acid extended the reaction time from usual 2-4 days to 7 days, however the bicyclic product **70a** was formed in similar isolated yield (entry 4 vs.1).

In general, good enantioselectivities (up to 80% ee) were observed with ligand **L-1** using [Bmim]NTf₂ and [Bmim]BF₄ (Table 34, entries 1-4 and 11-12). Comparable results were obtained also with [Dmim]NTf₂, [Omim]BF₄ and [Omim]PF₆ (entries 8, 17 and 21). Surprisingly, [Omim]NTf₂ completely failed and the desired bicyclic product **70a** was formed in low yield with poor enantioselectivity (entry 7). Among pyridinium-type ILs, a plausible result was achieved with [Bpy]NTf₂ (entry 9).

In order to explore a potential relationship between acidic C-2 hydrogen on imidazolium core (Figure 13) and the reaction mechanism, 1-alkyl-2,3-dimethylimidazolium-type ILs were also tested (Table 35).

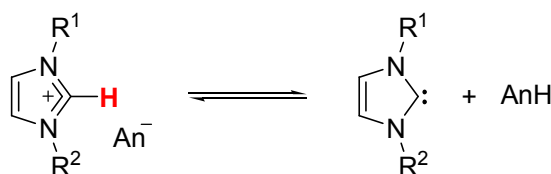


Figure 13. Acidic hydrogen of 1,3-dialkylimidazolium-type ILs.

As it can be seen in Table 35, the reactions carried out in ionic liquids without C-2 hydrogen proceeded with poor conversion and low enantioselectivity. We assume that a hydrogen bond which presumably exists between [mim]-type IL (Scheme 99, $\text{R}^1=\text{H}$) and alcohol substrate in transition state, plays an important role in the mechanism of this transformation. Its absence then may lead to retardation or catalytic inactivity.

entry	ionic liquid	conv. ^a (%)	% GC ^b yield (70a)	% ee (<i>S,S</i>)- 70a ^c	70a / 146 ratio
1	[Bmmim]NTf ₂	9	7	21	3:1
2	[Ommim]NTf ₂	10	7	32	3.7:1
3	[Dmmim]NTf ₂	16	6	17	3.5:1
4	[Ommim]BF ₄	<5	1	26	1:1.3
5	[Ommim]PF ₆	<5	1	24	1.2:1

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC with methyl benzoate as internal standard. ^c Enantiomeric excess of isolated lactone **70a** determined by GC with chiral stationary phase.

Table 35. Asymmetric Pd-catalyzed oxycarbonylation in [mmim]-type ionic liquid.

Microwave activation

As shown in Table 36, microwave irradiation of the reaction mixture exhibited expected rate enhancement, the oxycarbonylative bicyclization of (±)-**69a** catalyzed by Pd(OAc)₂/L-1 complex in the presence of [Bmim]NTf₂-AcOH (both of 3 equiv.) afforded (*S,S*)-**70a** in 16% isolated yield with untouched enantioselectivity (73% ee) in 2 hours instead of several days (entry 2).

entry	MW conditions	conv. ^a (%)	time (h)	% GC ^b yield (70a)	% isol. yield (70a)	% ee (70a) ^c (config.)	70a / 146 ratio
1	80°C, 10W, cooling	39	4	13	11	77 (<i>S,S</i>)	7:1
2	100°C, 12W, cooling	50	2	19	16	73 (<i>S,S</i>)	4:1

^a Conversion was determined by GC using methyl benzoate as internal standard. ^b Yield of **70a** determined from crude reaction mixture by GC with methyl benzoate as internal standard. ^c Enantiomeric excess of isolated lactone **70a** determined by GC with chiral stationary phase.

Table 36. Asymmetric Pd-catalyzed oxycarbonylation in IL under MW activation.

Based on these results, further studies to improve the performance of asymmetric catalysts using ionic liquids are now under way. The use of chiral ionic liquids as chiral reaction media for this transformation will be also studied.

5. EXPERIMENTAL PART

5.1. Chemicals, techniques and instrumentation

Reagents: Unless otherwise noted, all reagents, catalysts and additives were purchased from commercial suppliers and used without further purification.

Solvents: The solvents were distilled prior to use from sodium/benzophenone (diethyl ether, tetrahydrofuran), calcium hydride (acetonitrile, dichloromethane, toluene), phosphorus pentoxide (acetone) or under reduced pressure after being stirred with activated 4Å molecular sieves (dimethylformamide, dimethyl sulfoxide); or used without further drying in declared purity (glacial acetic acid).

Gases: Argon used for manipulation under inert atmosphere was of the purity of 99.998%. Carbon monoxide used in carbonylation reactions was of the purity of 99.997%. Oxygen used for reoxidation was of the purity of 99.995%.

TLC: Thin layer chromatography was performed on aluminium plates pre-coated with silica gel 60 F₂₅₄ with thickness of 200 µm (Merck). The plates were visualized by UV light (254 nm) and/or by dipping in oxidizing reagents ('Mostain', KMnO₄, PMA) with subsequent heating to 250°C. The oxidizing reagents were prepared as follows:

- Mostain: Ce(SO₂)₄ (5 g), (NH₄)₆Mo₇O₂₄·4H₂O (25 g), conc. H₂SO₄ (50 mL), H₂O (450 mL)
- KMnO₄: KMnO₄ (1.5 g), K₂CO₃ (10 g), 5% NaOH (2.5 mL), H₂O (150 mL)
- PMA: phosphomolibdic acid hydrate (12MoO₃·H₃PO₄·xH₂O, 10 g), ethanol (200 mL)

FLC: Flash column chromatography was performed on silica gel 60 from Merck (40-63 µm, 230-400 mesh).

GC: Gas chromatography analyses were performed on a Fisons Instruments GC 8000 Series chromatograph using BP-1 capillary column with 100% dimethylpolysiloxane stationary phase (30 m, id 0.32 mm, film thickness 0.25 µm) or on a Varian 430-GC chromatograph using Varian VF-1ms capillary column with 100% dimethylpolysiloxane stationary phase (15 m, id 0.25 mm, film thickness 0.25 µm), using helium as a carrier gas.

Chiral gas chromatography analyses were performed on a Fisons Instruments GC 8000 Series Top chromatograph using ChiralDEX B-PM capillary column with 2,3,6-tri-*O*-methyl-β-

cyclodextrin stationary phase (50 m, id 0.25 mm, film thickness 0.12 μm) or on a Carlo Erba Fractovap chromatograph using β -DEX 225 capillary column with 25% 2,3-di-*O*-acetyl-6-*O*-TBDMS- β -cyclodextrin stationary phase (30 m, id 0.25 mm, film thickness 0.25 μm), using hydrogen as a carrier gas.

The samples were injected to the system by a micro syringe using air/sample/air (each of 1 μL) injection method and vaporized utilizing split injection technique. The analyses were performed using either isothermal program or program with thermal gradient. The detection was provided by FID detector. Either Data Jet Integrator or Azur software operating under Windows OS were used for the signals integration.

SFC: Supercritical fluid chromatography was performed on a Berger Instruments chromatograph system consisting of Berger Instruments 719 Series AutoSampler, Berger Instruments FCM-1100/1200 Fluid Control Module (Supercritical dual pump) and Berger Instruments TCM-2000 Thermal Control Module using Chiralpak IA column based on the 3,5-dimethylphenylcarbamate derivative of amylose respectively, with supercritical CO_2/MeOH mobile phase using analytical or semi preparative injection loop.

NMR: The ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-250 (250 MHz for ^1H , 62.5 MHz for ^{13}C), Bruker DRX-300 and Varian VXR-300 (300 MHz for ^1H , 75 MHz for ^{13}C), Bruker Avance DRX-360 (360 MHz for ^1H , 90 MHz for ^{13}C), and Varian Inova 600 (600 MHz for ^1H , 150 MHz for ^{13}C) spectrometers in chloroform- d_1 , acetone- d_6 or dimethylsulfoxide- d_6 with TMS as an internal standard. Chemical shifts (δ) are reported in ppm (parts per million) relative to TMS ($\delta = 0$ ppm) or CDCl_3 ($\delta = 7.26$ ppm) for ^1H and CDCl_3 ($\delta = 77$ ppm) for ^{13}C . Coupling constants (J) are given in Hz, splitting patterns are described as s (singlet), d (doublet), t (triplet), q (quartet), qi (quintet), sx (sextet), sep (septet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublets of doublets), b (broad).

1D NOESY, 2D COSY and 2D HSQC experiments were recorded on a Varian Inova 600 spectrometer.

The ^{19}F NMR spectra were recorded on a Bruker DPX-250 spectrometer.

Melting point: Melting points were determined using a Büchi Melting Point B-540 instrument and are uncorrected.

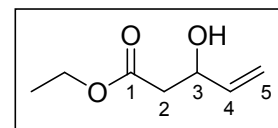
FTIR: Fourier transform infra-red spectra were recorded on a Philips Analytical PU9800 FTIR spectrometer or Perkin Elmer Spectrum One FT-IR spectrometer as thin films on KBr or NaCl discs.

Optical rotation: Optical rotations were measured using an IBZ Messtechnik POLAR L- μ P polarimeter or a Perkin Elmer 341 polarimeter with the sodium D line (289 nm) in a water jacketed cell of length 10.000 cm. Specific rotation values $[\alpha]_D$, given in units of $10^{-1}\text{deg.cm}^2.\text{g}^{-1}$, were calculated from equation $[\alpha]_D = \alpha^*100/c^*l$ where α is a measured value in degrees, c is concentration in g/100 mL and l is the length of a cell in dm.

HRMS: High resolution mass spectra were recorded on a Bruker MicrOTOF-Q spectrometer using electrospray ionization (ESI) and tandem quadrupole coupled with a time-of-flight mass analyzer.

X-ray analysis: X-ray crystal analyses were performed on an Oxford Diffraction Gemini R single crystal diffractometer equipped with an CCD detector with Mo K_{α} radiation ($\lambda = 0.71070 \text{ \AA}$) and graphite monochromator.

Microwave activation: Microwave experiments were conducted on a CEM Discover or a CEM Discover S-Class microwave reactor operating in single mode at 2.45 GHz. The monitoring was performed using a Synergy software operating under Windows OS. The temperature was measured by optical fiber and maintained at a constant value by power modulation (0-200 W). Stirring was provided by an in situ magnetic variable speed stirrer or with a mechanical stirrer. Reactions were performed in glass vessels (capacity 10 mL or 38 mL) either sealed with a septum or in open ones.

5.2. Synthesis of substrates**(±)-3-Hydroxy-pent-4-enoic acid ethyl ester^{81a} (79)****C₇H₁₂O₃**MW: 144.17 g.mol⁻¹

n-BuLi (36 mL, 2.5 M in hexane, 89 mmol) was added to the solution of diisopropylamine (12.5 mL, 89 mmol, dried over KOH and freshly distilled) in dry THF (60 mL) at 10°C. The mixture was stirred for 30 min at 10°C, then cooled to -78°C and ethyl acetate (8.7 mL, 89 mmol, dried over K₂CO₃ and freshly distilled) was added dropwise. The solution was kept at -78°C for 1 h, acrolein (5 mL, 66 mmol) was added and stirred at -78°C for additional 1 h. Diethyl ether (100 mL) was added and the mixture was subsequently quenched with saturated NH₄Cl, and extracted with Et₂O (3 x 40 mL). Combined organic extracts were dried over MgSO₄ and concentrated. The crude product **79** was distilled under reduced pressure.

yield: 8.50 g (89%)

R_f = 0.65 (AcOEt/hexanes 1:1)

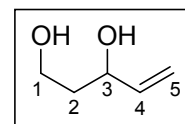
b.p. = 105°C / 28 mbar

colorless liquid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.24 (t, CH₃, *J* = 7.2 Hz, 3H); 2.51 (dd, H-2a, *J* = 16.2 Hz, 1H); 2.52 (dd, *J* = 16.8 Hz, H-2b, 1H); 3.13 (d, OH, *J* = 4.5 Hz, 1H); 4.14 (q, OCH₂, *J* = 7.2 Hz, 2H); 4.47-4.55 (m, H-3, 1H); 5.12 (dt, H-5a, *J* = 10.5, 1.5 Hz, 1H); 5.28 (dt, H-5b, *J* = 15.6, 1.5 Hz, 1H); 5.85 (ddd, H-4, *J* = 15.6, 10.5, 5.7 Hz, 1H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 14.1 (q, CH₃); 41.2 (t, C-2); 60.7 (t, OCH₂); 68.9 (d, C-3); 115.2 (t, C-5); 138.8 (d, C-4); 172.1 (s, C-1); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 3449, 2984, 2938, 1736, 1179.

(±)-Pent-4-ene-1,3-diol^{81b} (69a)**C₅H₁₀O₂**MW: 102.13 g.mol⁻¹

The solution of ester **79** (8.73 g, 60.6 mmol) in dry Et₂O (100 ml) was added dropwise to the suspension of lithium aluminium hydride (3.79 g, 99.9 mmol) in dry Et₂O (100 mL) at 0°C. The mixture was then refluxed for 2 h, cooled to 0°C and Glauber salt (32 g) was slowly added. The mixture was filtered through a pad of celite, the filtrate was washed with dichloromethane and the solution of diol **69a** was concentrated to give crude yellowish liquid which was distilled under reduced pressure.

yield: 5.09 g (82%)

R_f = 0.11 (AcOEt/cyclohexane 1:1)

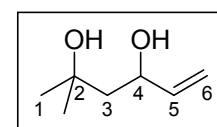
b.p. = 120°C / 20 mbar

colorless liquid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.71-1.80 (m, H-2, 2H); 3.13 (t, OH, *J* = 5.1 Hz, 1H); 3.25 (d, OH, *J* = 3.9 Hz, 1H); 3.73-3.89 (m, H-1, 2H), 4.32-4.39 (m, H-3, 1H), 5.11 (dt, H-5a, *J* = 10.5, 1.5 Hz, 1H), 5.25 (dt, H-5b, *J* = 17.1, 1.5 Hz, 1H), 5.88 (ddd, H-4, *J* = 17.1, 10.5, 5.7 Hz, 1H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 38.1 (t, C-2); 60.8 (t, C-1); 72.4 (d, C-3); 114.5 (t, C-5); 140.5 (d, C-4); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 3367, 2927, 2875, 1718, 1428.

(±)-2-Methylhex-5-ene-2,4-diol (87)**C₇H₁₄O₂**MW: 130.18 g.mol⁻¹

An oven dried flask was purged with argon and charged with MeMgI (23 mL, 3.0 M in diethyl ether, 69 mmol). Additional ether (46 mL) was added to provide a 1.0 M solution of MeMgI, which was then cooled to 0°C. The ester **79** (2.5 g, 17.3 mmol) was added dropwise *via* syringe, the resulting mixture was then warmed to rt and stirred for 4 h. A saturated solution of aqueous NH₄Cl (100 mL) was added dropwise and the resulting mixture was then diluted with ethyl acetate (70 mL). The layers were separated, and the aqueous layer was

extracted with diethyl ether (2 x 20 mL). The combined organic layers were dried over anhydrous MgSO_4 , filtered and concentrated *in vacuo*. The crude tertiary alcohol **87** was then purified by flash chromatography (45 g of silica gel, ethyl acetate/pentane 1:2).

yield: 1.62 g (72%)

$R_f = 0.42$ (AcOEt/hexanes 1:1)

yellowish liquid

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.25 (s, H-1, 3H); 1.32 (s, CH_3 , 3H); 1.54 (dd, H-3a, $J = 14.4, 2.7$ Hz, 1H); 1.71 (dd, H-3b, $J = 14.4, 10.8$ Hz, 1H); 3.55 (bs, 2x OH, 2H); 4.45-4.51 (m, H-4, 1H); 5.06 (dt, H-6a, $J = 10.2, 1.5$ Hz, 1H); 5.23 (d, $J = 17.1, 1.5$ Hz, 1H), 5.84 (ddd, $J = 17.1, 10.2, 5.7$ Hz, 1H); relative to CDCl_3 ($\delta = 7.26$ ppm).

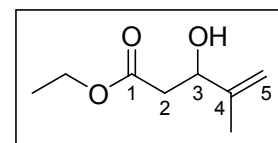
^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 27.6 (q, C-1); 31.7 (q, CH_3); 47.5 (t, C-3); 70.8 (d, C-4); 71.5 (s, C-2); 114.1 (t, C-6); 140.9 (d, C-5); relative to CDCl_3 ($\delta = 77$ ppm).

IR (film on KBr): ν (cm^{-1}) = 3320, 2971, 1381, 1366, 1150, 989, 910, 850.

(±)-3-Hydroxy-4-methylpent-4-enoic acid ethyl ester^{81a} (**81**)

$\text{C}_8\text{H}_{14}\text{O}_3$

MW: 158.19 $\text{g}\cdot\text{mol}^{-1}$



$n\text{-BuLi}$ (51 mL, 1.3 M in hexane, 66.5 mmol) was added to the solution of diisopropylamine (9.4 mL, 66.5 mmol, dried over KOH and freshly distilled) in dry THF (60 mL) at 10°C . The mixture was stirred for 30 min at 10°C , then cooled to -78°C and ethyl acetate (5.9 mL, 60.5 mmol, dried over K_2CO_3 and freshly distilled) was added dropwise. The solution was kept at -78°C for 1 h, methacrolein (5 mL, 60.5 mmol) was added and stirred at -78°C for additional 1 h. Diethyl ether (100 mL) was added, and the mixture was subsequently quenched with saturated NH_4Cl (100 mL) and extracted with Et_2O (3 x 50 mL). Combined organic extracts were dried over MgSO_4 and concentrated. The crude product **81** was distilled under reduced pressure.

yield: 5.92 g (65%)

$R_f = 0.37$ (AcOEt/hexanes 1:3)

b.p. = $63\text{--}67^\circ\text{C}$ / 1 mbar

yellowish liquid

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.28 (t, CH_3CH_2 , J = 7.2 Hz, 3H); 1.76 (s, $\text{CH}_3\text{C}=\text{CH}_2$, 3H); 2.56 (dd, H-2a, J = 16.2 Hz, 1H); 2.58 (dd, J = 16.5 Hz, H-2b, 1H); 3.01 (bs, OH, 1H); 4.18 (q, OCH_2 , J = 7.2 Hz, 2H); 4.48 (m, H-3, 1H); 4.88 (s, H-5a, 1H); 5.04 (s, H-5b, 1H); relative to TMS (δ = 0 ppm).

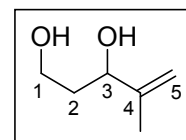
^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 14.2 (q, CH_3CH_2); 18.2 (q, $\text{CH}_3\text{C}=\text{CH}_2$); 40.1 (t, C-2); 60.8 (t, OCH_2); 71.5 (d, C-3); 111.4 (t, C-5); 145.5 (s, C-4); 172.6 (s, C-1); relative to TMS (δ = 0 ppm).

IR (film on KBr): ν (cm^{-1}) = 3463, 1734, 1163, 1025.

(\pm)-4-Methylpent-4-ene-1,3-diol⁸² (82**)**

$\text{C}_6\text{H}_{12}\text{O}_2$

MW: 116.16 $\text{g}\cdot\text{mol}^{-1}$



The solution of ester **81** (5.12 g, 32.4 mmol) in dry Et_2O (30 ml) was added dropwise to the suspension of lithium aluminium hydride (1.23 g, 32.4 mmol) in dry Et_2O (65 ml) at 0°C . The mixture was then refluxed for 2 h, cooled to 0°C and Glauber salt (16 g) was slowly added. The mixture was filtered through a pad of celite, the filtrate was washed with dichloromethane and the solution of diol **82** was concentrated to give crude yellowish oil which was distilled under reduced pressure.

yield: 3.12 g (83%)

R_f = 0.38 (AcOEt/cyclohexane 3:1)

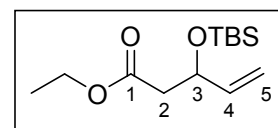
b.p. = $80\text{--}85^\circ\text{C}$ / 1 mbar

colorless oil

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.74 (s, CH_3 , 3H); 1.77–1.82 (m, H-2, 2H); 3.23 (bs, 2x OH, 2H); 3.78–3.84 (m, H-1, 2H); 4.27–4.31 (m, H-3, 1H); 4.86 (s, H-5a, 1H); 5.01 (s, H-5b, 1H); relative to TMS (δ = 0 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 18.2 (q, CH_3); 36.5 (t, C-2); 61.0 (t, C-1); 75.1 (d, C-3); 110.6 (t, C-5); 147.3 (s, C-4); relative to TMS (δ = 0 ppm).

IR (film on KBr): ν (cm^{-1}) = 3315, 2947, 1438, 1053, 897, 568.

(±)-3-*tert*-Butyldimethylsilyloxy-pent-4-enoic acid ethyl ester⁸⁵ (88)**C₁₃H₂₆O₃Si**MW: 258.43 g.mol⁻¹

The solution of ester **79** (6 g, 41.6 mmol) in dichloromethane (120 mL) was stirred for 5 h with imidazole (8.5 g, 125 mmol) and *tert*-butyldimethylsilylchloride (7.84 g, 52 mmol). The reaction was quenched with saturated NH₄Cl (80 mL) and the aqueous phase was extracted with dichloromethane (3x 20 mL). The combined organic phases were dried over MgSO₄ and concentrated *in vacuo*. The crude ester **88** was then purified by flash chromatography (300 g of silica gel, ethyl acetate/pentane 1:10).

yield: 10.6 g (99%)

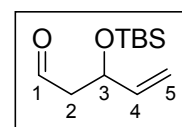
R_f = 0.57 (AcOEt/hexanes 1:9)

colorless liquid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.04 (s, SiCH₃, 3H); 0.05 (s, SiCH₃, 3H); 0.87 (s, C(CH₃)₃, 9H); 1.26 (t, CH₃, *J* = 7.2 Hz, 3H); 2.42 (dd, H-2a, *J* = 14.4, 5.4 Hz, 1H); 2.52 (dd, H-2b, *J* = 14.4, 8.1 Hz, 1H); 4.07-4.18 (m, OCH₂, 2H); 4.55-4.61 (m, H-3, 1H); 5.06 (dt, H-5a, *J* = 10.2, 1.5 Hz, 1H); 5.22 (dt, H-5b, *J* = 17.1, 1.5 Hz, 1H); 5.84 (ddd, H-4, *J* = 17.1, 10.2, 6.3 Hz, 1H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = -5.2 (q, SiCH₃); -4.5 (q, SiCH₃); 14.1 (q, CH₃); 18.0 (s, C(CH₃)₃); 25.6 (3xq, C(CH₃)₃); 43.7 (t, C-2); 60.3 (t, OCH₂); 70.8 (d, C-3); 114.5 (t, C-5); 140.3 (d, C-4); 171.1 (s, C-1); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 2945, 1727, 1473, 1348, 1255.

(±)-3-*tert*-Butyldimethylsilyloxy-pent-4-enal⁸⁶ (89)**C₁₁H₂₂O₂Si**MW: 214.38 g.mol⁻¹

A solution of diisobutylaluminium hydride (19 mL, 1.1 M in cyclohexane, 20.9 mmol) was added dropwise to a solution of **88** (4.5 g, 17.4 mmol) in toluene (95 mL) at -78°C. Following the addition, the reaction was stirred for 1 h. The reaction was quenched by dropwise addition of a saturated NH₄Cl (10 mL). After allowing the reaction mixture to reach

rt, a saturated solution of Rochelle salt (40 mL) was added. The mixture was poured into brine (50 mL) and more Rochelle solution was added (30 mL) before it was extracted with ethyl acetate. The combined organic phases were dried and concentrated *in vacuo*. The crude aldehyde **89** was used in a subsequent step without purification.

crude yield: 3.35 g (90%)

$R_f = 0.40$ (AcOEt/hexanes 1:9)

yellowish liquid

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 0.05 (s, SiCH_3 , 3H); 0.07 (s, SiCH_3 , 3H); 0.88 (s, $\text{C}(\text{CH}_3)_3$, 9H); 2.52 (ddd, H-2a, $J = 15.9, 5.1, 2.4$ Hz, 1H); 2.61 (ddd, H-2b, $J = 15.9, 6.9, 2.7$ Hz, 1H); 4.62-4.68 (m, H-3, 1H); 5.12 (dt, H-5a, $J = 10.2, 1.5$ Hz, 1H); 5.26 (dt, H-5b, $J = 17.1, 1.5$ Hz, 1H); 5.87 (ddd, H-4, $J = 17.1, 10.2, 5.7$ Hz, 1H); 9.77 (t, H-1, $J = 2.4$ Hz, 1H); relative to CDCl_3 ($\delta = 7.26$ ppm).

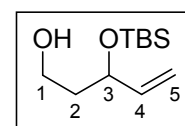
^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = -5.1 (q, SiCH_3); -4.4 (q, SiCH_3); 18.0 (s, $\text{C}(\text{CH}_3)_3$); 25.7 (3xq, $\text{C}(\text{CH}_3)_3$); 51.2 (t, C-2); 69.3 (d, C-3); 114.8 (t, C-5); 139.9 (d, C-4); 201.5 (s, C-1); relative to CDCl_3 ($\delta = 77$ ppm).

IR (film on KBr): ν (cm^{-1}) = 2990, 1728, 1470, 1256.

(±)-3-*tert*-Butyldimethylsilyloxy-pent-4-en-1-ol⁸⁷ (90)

$\text{C}_{11}\text{H}_{24}\text{O}_2\text{Si}$

MW: 216.39 $\text{g}\cdot\text{mol}^{-1}$



The crude aldehyde **89** (3.35 g) was dissolved in MeOH (65 mL), and the resulting solution cooled at 0°C . Sodium borohydride (0.72 g, 19.2 mmol) was added portionwise, and the mixture stirred at room temperature for 20 min. Removal of the solvent *in vacuo* was followed by column chromatography (120 g of silica gel, diethyl ether/pentane 1:4) afforded protected diol **90**.

yield: 2.33 g (62%) over 2 steps from **88**

$R_f = 0.21$ (ether/isohexane 1:4)

yellowish liquid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.05 (s, SiCH₃, 3H); 0.09 (s, SiCH₃, 3H); 0.90 (s, C(CH₃)₃, 9H); 1.65-1.76 (m, H-2a, 1H); 1.79-1.90 (m, H-2b, 1H); 2.51 (bs, OH, 1H); 3.67-3.74 (m, H-1a, 1H); 3.77-3.85 (m, H-1b, 1H); 4.38-4.44 (m, H-3, 1H); 5.09 (dt, H-5a, J = 10.5, 1.5 Hz, 1H); 5.21 (dt, H-5b, J = 17.1, 1.5 Hz, 1H); 5.84 (ddd, H-4, J = 17.1, 10.5, 5.7 Hz, 1H); relative to CDCl₃ (δ = 7.26 ppm).

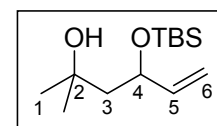
¹³C NMR (75 MHz, CDCl₃): δ (ppm) = -5.1 (q, SiCH₃); -4.4 (q, SiCH₃); 18.1 (s, C(CH₃)₃); 25.8 (3xq, C(CH₃)₃); 39.1 (t, C-2); 60.1 (t, C-1); 73.2 (d, C-3); 114.4 (t, C-5); 140.6 (d, C-4); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 2928, 2856, 1252, 1082, 1021, 920, 835, 775.

(±)-2-Methyl-4-*tert*butyldimethylsilyloxy-hex-5-en-2-ol (91)

C₁₃H₂₈O₂Si

MW: 244.45 g.mol⁻¹



An oven dried flask was purged with argon and charged with MeMgI (11.6 mL, 3.0 M in diethyl ether, 34.8 mmol). Additional ether (24 mL) was added to provide a 1.0 M solution of MeMgI, which was then cooled to 0°C. The ester **88** (3.0 g, 11.6 mmol) was added dropwise via syringe, the resulting mixture was then warmed to rt and stirred for 5 h. A saturated solution of aqueous NH₄Cl (70 mL) was added dropwise and the resulting mixture was then diluted with ethyl acetate (50 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 20 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude tertiary alcohol **91** was then purified by flash chromatography (60 g of silica gel, ethyl acetate/pentane 1:20).

yield: 2.11 g (74%)

R_f = 0.20 (AcOEt/pentane 1:40)

colorless liquid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.07 (s, SiCH₃, 3H); 0.12 (s, SiCH₃, 3H); 0.89 (s, C(CH₃)₃, 9H); 1.19 (s, H-1, 3H); 1.29 (s, CH₃, 3H); 1.49 (dd, H-3a, J = 14.4, 3.0 Hz, 1H); 1.81 (dd, H-3b, J = 14.4, 10.5 Hz, 1H); 4.14 (bs, OH, 1H); 4.46-4.53 (m, H-4, 1H); 5.05 (d, H-6a, J = 10.2 Hz, 1H); 5.13 (d, H-6b, J = 17.1 Hz, 1H); 5.80 (ddd, H-5, J = 17.1, 10.2, 7.8 Hz, 1H); relative to CDCl₃ (δ = 7.26 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = -4.8 (q, SiCH_3); -3.3 (q, SiCH_3); 17.9 (s, $\text{C}(\text{CH}_3)_3$); 25.8 (3xq, $\text{C}(\text{CH}_3)_3$); 27.9 (q, C-1); 31.1 (q, CH_3); 48.6 (t, C-3); 70.4 (s, C-2); 74.1 (d, C-4); 114.8 (t, C-6); 141.6 (d, C-5); relative to CDCl_3 ($\delta=77$ ppm).

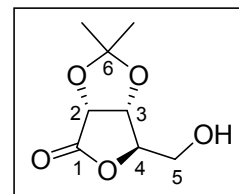
IR (film on KBr): ν (cm^{-1}) = 2930, 1252, 1073, 921, 835, 776.

HRMS (ESI): calcd. for $\text{C}_{13}\text{H}_{28}\text{O}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 267.1756; found $[\text{M}+\text{Na}]^+$ 267.1747.

2,3-*O*-Isopropylidene-D-ribo-1,4-lactone⁹¹ (**96**)

$\text{C}_8\text{H}_{12}\text{O}_5$

MW: 188.18 $\text{g}\cdot\text{mol}^{-1}$



Concentrated HCl (1.2 mL) was added to the solution of D-(+)-ribonic γ -lactone (3.0 g, 20.3 mmol) in acetone (120 mL) and the reaction mixture was stirred for 22 h. The solution was neutralized by solid K_2CO_3 , the inorganic salts were filtered through sintered glass funnel and the filtrate was concentrated *in vacuo*. After trituration with cold hexane the crystals of product **96** were collected on a suction filter.

yield: 2.91 g (77%)

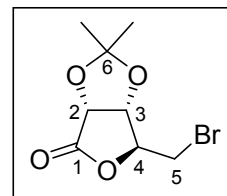
R_f = 0.33 (AcOEt/hexanes 2:1)

m.p. = 134-136°C (lit.⁹¹ m.p. = 138-139°C)

white crystals

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.39 (s, CH_3 , 3H); 1.48 (s, CH_3 , 3H); 2.61 (t, OH, J = 5.1 Hz, 1H); 3.81 (dd, H-5a, J = 12.3, 3.9 Hz, 1H); 4.00 (ddd, H-5b, J = 12.3, 4.5, 2.1 Hz, 1H); 4.64 (t, H-4, J = 2.1 Hz, 1H); 4.79 (d, H-3, J = 5.7 Hz, 1H); 4.85 (d, H-2, J = 5.7 Hz, 1H); relative to TMS ($\delta=0$ ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 25.5 (q, CH_3); 26.7 (q, CH_3); 62.0 (t, C-5); 75.6 (d, C-3); 78.2 (d, C-2); 82.6 (d, C-4); 113.2 (s, C-6); 174.8 (s, C-1); relative to CDCl_3 ($\delta=77$ ppm).

5-Bromo-5-deoxy-2,3-*O*-isopropylidene-D-ribono-1,4-lactone⁹⁰ (97)**C₈H₁₁BrO₄**MW: 251.07 g.mol⁻¹

Triphenylphosphine (4.84 g, 18.5 mmol) was slowly added to the solution of protected D-(+)-ribonic γ -lactone **96** (2.89 g, 15.4 mmol) and *N*-bromosuccinimide (3.28 g, 18.5 mmol) in dichloromethane (100 mL) at 10°C. After reaching rt, the reaction mixture was stirred for 2.5 h. Following the addition of BaCO₃ (1.16 g, 5.9 mmol) the solution was heated to reflux for 15 minutes. After the cooling to rt, the solid phase was collected on a suction filter and washed with water (5x 4 mL). The aqueous layer was extracted with dichloromethane (10 mL), the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product **97** was purified by flash chromatography (250 g of silica gel, ethyl acetate/hexanes 1:1).

yield: 3.24 g (84%)

R_f = 0.66 (AcOEt/hexanes 1:1)m.p. = 87-88°C (lit.⁹⁰ m.p. = 88.5-89.5°C)

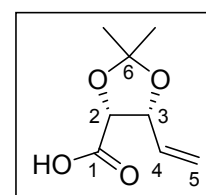
white crystals

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.40 (s, CH₃, 3H); 1.49 (s, CH₃, 3H); 3.65 (dd, H-5a, *J* = 11.6 Hz, 1H); 3.66 (dd, H-5b, *J* = 11.6 Hz, 1H); 4.71 (d, H-3, *J* = 6.0 Hz, 1H); 4.88 (t, H-4, *J* = 3.0 Hz, 1H); 4.95 (d, H-2, *J* = 6.0 Hz, 1H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 25.4 (q, CH₃); 26.5 (q, CH₃); 32.8 (t, C-5); 75.3 (d, C-3); 79.1 (d, C-2); 80.5 (C-4); 113.9 (s, C-6); 173.1 (s, C-1); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 1775, 1168, 1070, 1049, 979, 855, 545, 516.

Specific rotation: $[\alpha]_D$ (25°C) = -40.8 (c 1.80, CHCl₃), (lit.⁹⁰ -43.5, c 2.37, CHCl₃)

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-pent-4-enoic acid⁹⁰ (98)**C₈H₁₂O₄**MW: 172.18 g.mol⁻¹

Zinc-copper couple for reductive ring opening of **97** was prepared from zinc dust (100 g), which was washed with 2M HCl (3x) followed by washing with water (1x) and methanol

(1x). Activated zinc dust was subsequently washed with saturated solution of $\text{Cu}(\text{OAc})_2$ in methanol (6x or until no color change appeared). Finally, Zn-Cu couple was washed with methanol (1x), diethyl ether (1x) and dried *in vacuo*.

Zn-Cu couple (6.7 g) was added to the solution of bromide **97** (3.22 g, 12.8 mmol) in acetone/water 4:1 (30 mL) and the reaction mixture was heated to reflux for 2 hours. After cooling to rt the suspension was filtered through a bed of celite and the filtrate was concentrated *in vacuo*. The crude was dissolved in chloroform and conc. formic acid (1.1 mL) was added. After being stirred, the reaction mixture was washed with brine (20 mL). The aqueous layer was extracted with chloroform (4x 15 mL), the combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude acid **98** was used in a subsequent step without purification.

crude yield: 2.19 g (99%)

$R_f = 0.22$ (AcOEt/hexanes 1:1)

colorless oil

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.42 (s, CH_3 , 3H); 1.62 (s, CH_3 , 3H); 4.69 (d, H-2, $J = 7.4$ Hz, 1H); 4.84 (t, H-3, $J = 7.2$ Hz, 1H); 5.30 (d, H-5a, $J = 10.4$ Hz, 1H); 5.45 (d, H-5b, $J = 17.0$ Hz, 1H); 5.79 (ddd, H-4, $J = 17.2, 10.3, 7.0$ Hz, 1H); 8.57 (bs, COOH, 1H); relative to TMS ($\delta = 0$ ppm).

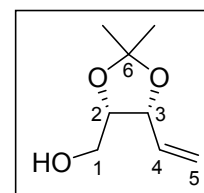
IR (film on KBr): ν (cm^{-1}) = 3368, 1720, 1205, 1112, 1046, 932.

Specific rotation: $[\alpha]_D$ (20°C) = -22.8 (c 1.35, CHCl_3), (lit.⁹⁰ -24.6, c 1.56, CHCl_3)

(2*S*,3*R*)-2,3-*O*-Isopropylidene-pent-4-en-1,2,3-triol⁹⁰ (99**)**

$\text{C}_8\text{H}_{14}\text{O}_3$

MW: 158.19 g.mol⁻¹



Lithium aluminium hydride (0.58 g, 15.3 mmol) was slowly added to the solution of acid **98** (1.76 g, 10.2 mmol) in dry diethyl ether (50 mL) at 0°C. After reaching rt the suspension was stirred for 4 h. The reaction mixture was then cooled to 0°C and Glauber salt (10 g) was added portionwise. The completion of hydrolysis was indicated through the color change from grey to white. The mixture was filtered through a pad of celite, inorganic salts

were washed with dichloromethane and the filtrate was concentrated *in vacuo*. The crude triol **99** was distilled under reduced pressure.

yield: 0.99 g (61%)

$R_f = 0.45$ (AcOEt/hexanes 1:1)

b.p. = 81-83°C / 4 mbar

colorless oil

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.40 (s, CH_3 , 3H); 1.52 (s, H CH_3 , 3H); 2.07 (bs, OH, 1H); 3.58 (d, H-1, $J = 5.6$ Hz, 2H); 4.27 (dd, H-2, $J = 12.2, 5.7$ Hz, 1H); 4.65 (t, H-3, $J = 7.1$ Hz, 1H); 5.28 (dt, H-5a, $J = 10.3, 1.0$ Hz, 1H); 5.40 (dt, H-5b, $J = 17.1, 1.3$ Hz, 1H); 5.87 (ddd, H-4, $J = 17.1, 10.3, 7.3$ Hz); relative to TMS ($\delta = 0$ ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 25.2 (q, CH_3); 27.8 (q, CH_3); 55.4 (d, C-2); 62.0 (t, C-1); 78.2 (d, C-3); 108.8 (s, C-6); 119.0 (t, C-5); 132.9 (d, C-4); relative to CDCl_3 ($\delta = 77$ ppm).

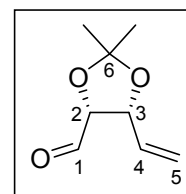
IR (film on KBr): ν (cm^{-1}) = 3354, 2933, 1722, 1035, 931.

Specific rotation: $[\alpha]_D$ (20°C) = -42.5 (c 2.15, CHCl_3), (lit.⁹⁰ -44.0, c 4.89, CHCl_3)

(2*R*,3*R*)-2,3-Dihydroxy-2,3-*O*-isopropylidene-pent-4-enal⁹³ (105**)**

$\text{C}_8\text{H}_{12}\text{O}_3$

MW: 156.18 $\text{g}\cdot\text{mol}^{-1}$



To a -78°C solution of oxalyl chloride (0.55 mL, 6.4 mmol) in dichloromethane (13 mL) was added DMSO (0.6 mL, 8.0 mmol) in dichloromethane (1.6 mL). The reaction was stirred at -78°C for 15 min, then alcohol **99** (500 mg, 3.2 mmol) in dichloromethane (1.6 mL) was added. The reaction was stirred for 20 min at -78°C followed by the addition of triethylamine (2.7 mL, 19.2 mmol). The mixture was stirred at -78°C for 10 min and allowed to warm to 0°C. After 30 min, the reaction was diluted with diethyl ether (50 mL) upon which a white precipitate of triethylamine hydrochloride was formed. The slurry was filtered through a pad of celite and concentrated to afford the crude aldehyde **105** which was immediately used in the next reaction without purification.

crude yield: 485 mg (contaminated with DMSO)

$R_f = 0.65$ (AcOEt/hexanes 1:1)

yellowish volatile oil

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.45 (s, CH_3 , 3H); 1.63 (s, CH_3 , 3H); 4.42 (dd, H-2, $J = 7.5, 3.1$ Hz, 1H); 4.87 (t, H-3, $J = 7.2$ Hz, 1H); 5.33 (dt, H-5a, $J = 10.4, 1.1$ Hz, 1H); 5.47 (dt, H-5b, $J = 17.2, 1.2$ Hz, 1H); 5.76 (ddd, H-4, $J = 17.2, 10.4, 7.2$ Hz, 1H); 9.56 (d, H-1, $J = 3.1$ Hz, 1H); relative to TMS ($\delta = 0$ ppm).

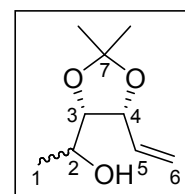
^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 25.3 (q, CH_3); 27.3 (q, CH_3); 79.0 (d, C-3); 82.2 (d, C-2); 111.2 (s, C-6); 119.7 (t, C-5); 131.2 (d, C-4); 200.6 (d, C-1); relative to CDCl_3 ($\delta = 77$ ppm).

IR (film on KBr): ν (cm^{-1}) = 3307, 1715, 1405, 1005, 949.

(3*S*,4*R*)-3,4-*O*-Isopropylidene-hex-5-ene-2,3,4-triol⁹⁴ (106)

$\text{C}_9\text{H}_{16}\text{O}_3$

MW: 172.22 $\text{g}\cdot\text{mol}^{-1}$



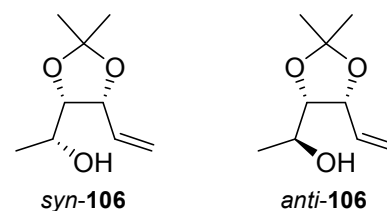
Three-necked round-bottomed flask equipped with a condenser was filled with magnesium chips (45 mg, 1.8 mmol) under argon and small iodine grain was added. To activate the magnesium surface, iodine grain was heated with a heat gun until it sublimed. Then iodomethane (0.11 mL, 1.8 mmol) in diethyl ether (3.5 mL) was added via syringe. The mixture was heated to reflux with a heat gun, the discoloration of reaction mixture indicated the start of the reaction. The mixture was stirred at room temperature until complete consumption of magnesium. The crude aldehyde **105** (168 mg, 1.1 mmol) was then added to the solution of methylmagnesium iodide at 0°C . The reaction mixture was stirred for 1 h and quenched with saturated NH_4Cl (10 mL). The water phase was extracted with diethyl ether (3 x 5 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude alcohol **106** was purified by flash chromatography (2 g of silica gel, ethyl acetate/hexanes 1:3).

yield: 50 mg (27%) over two steps from **99**

dr: *anti*-**107** vs. *syn*-**107** 1.3:1 (after purification)

$R_f = 0.50$ (AcOEt/hexanes 1:2)

yellowish oil



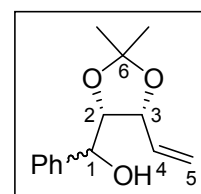
^1H NMR (600 MHz, CDCl_3): δ (*anti*, ppm) = 1.28 (d, H-1, J = 6.6 Hz, 3H); 1.38 (s, CH_3 , 3H); 1.48 (s, CH_3 , 3H); 3.82-3.87 (m, H-2, 1H); 3.93 (dd, H-3, J = 9.6, 6.5 Hz, 1H); 4.66 (dd, H-4, J = 7.4, 6.5 Hz, 1H); 5.32 (ddd, H-6a, J = 10.8, 1.3, 1.0 Hz, 1H); 5.44 (dt, H-6b, J = 17.4, 1.3 Hz, 1H); 6.04 (ddd, H-5, J = 17.4 Hz, 10.2 Hz, 7.8 Hz, 1H). δ (*syn*, ppm) = 1.16 (d, H-1, J = 6.6 Hz, 3H); 1.40 (s, CH_3 , 3H); 1.52 (s, CH_3 , 3H); 3.74-3.79 (m, H-2, 1H); 3.95 (dd, H-3, J = 8.2, 6.5 Hz, 1H); 4.56 (t, H-4, J = 6.5 Hz, 1H); 5.29 (ddd, H-6a, J = 10.2, 1.3, 1.0 Hz, 1H); 5.34 (dt, H-6b, J = 17.3, 1.3 Hz, 1H); 5.93 (ddd, H-5, J = 17.3 Hz, 10.2 Hz, 8.1 Hz, 1H); relative to TMS (δ = 0 ppm).

IR (film on KBr): ν (cm^{-1}) = 3367, 2960, 2924, 1259, 1016, 797.

(2*S*,3*R*)-2,3-*O*-Isopropylidene-1-phenyl-pent-4-en-1,2,3-triol⁹⁵ (107**)**

$\text{C}_{14}\text{H}_{18}\text{O}_3$

MW: 234.29 $\text{g}\cdot\text{mol}^{-1}$



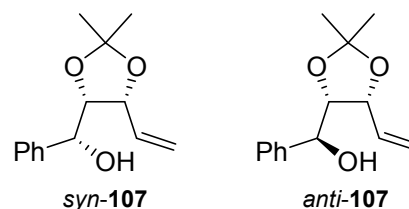
A three-necked flask equipped with a condenser was filled with magnesium chips (45 mg, 1.8 mmol) and a small iodine grain. After the activation, bromobenzene (0.19 mL, 1.8 mmol) in diethyl ether (3.5 mL) was added. The discoloration of reaction mixture indicated the start of the reaction. The mixture was stirred at rt until complete consumption of magnesium. The crude aldehyde **105** (240 mg, 1.5 mmol) was then added to the solution of phenylmagnesium bromide at 0°C. The reaction mixture was stirred for 2 h and quenched with sat. NH_4Cl (10 mL). The water phase was extracted with diethyl ether (3 x 5 mL). Combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The crude alcohol **107** was purified by flash chromatography (4.5 g of silica gel, ethyl acetate/hexanes 1:6).

yield: 108 mg (30%) over two steps from **99**

dr: *syn*-**107** vs. *anti*-**107** 2.5:1 (after purification)

R_f = 0.28 (AcOEt/hexanes 1:5)

colorless oil



^1H NMR (600 MHz, CDCl_3): δ (*syn*, ppm) = 1.42 (s, CH_3 , 3H); 1.60 (s, CH_3 , 3H); 2.75 (d, OH, J = 4.6 Hz, 1H); 4.41 (dd, H-2, J = 6.5, 5.7 Hz, 1H); 4.55 (dd, H-3, J = 7.2, 6.6 Hz, 1H);

4.64 (t, H-1, J = 4.8 Hz, 1H); 5.25 (dt, H-5a, J = 10.2, 1.0 Hz, 1H); 5.29 (dt, H-5b, J = 17.4, 1.1 Hz, 1H); 5.96 (ddd, H-4, J = 17.4, 10.2, 7.5 Hz, 1H); 7.32-7.40 (m, Ph, 5H). δ (*anti*, ppm) = 1.31 (s, CH₃, 3H); 1.47 (s, CH₃, 3H); 2.05 (d, OH, J = 3.4 Hz, 1H); 4.31 (dd, H-2, J = 8.7, 6.2 Hz, 1H); 4.68 (dd, H-1, J = 8.7, 3.2 Hz, 1H); 4.75 (dd, H-3, J = 7.2, 6.2 Hz, 1H); 5.35 (dt, H-5a, J = 10.4, 1.0 Hz, 1H); 5.49 (dt, H-5b, J = 17.2, 1.4 Hz, 1H); 6.16 (ddd, H-4, J = 17.4, 10.4, 7.2 Hz, 1H); 7.32-7.40 (m, Ph, 5H); relative to TMS (δ = 0 ppm).

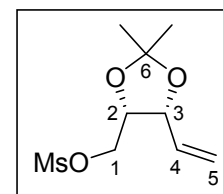
¹³C NMR (150 MHz, CDCl₃): δ (*syn*, ppm) = 25.1 (q, CH₃); 27.5 (q, CH₃); 72.2, 78.8, 81.4 (3xd, C-1,2,3); 108.9 (s, C-6); 119.2 (t, C-5); 127.3 (2xd, Ph); 128.0 (d, Ph); 128.3 (2xd, Ph); 133.7 (d, C-4); 140.4 (s, Ph). δ (*anti*, ppm) = 25.2 (q, CH₃); 27.8 (q, CH₃); 72.4, 78.9, 80.8 (3xd, C-1,2,3); 108.9 (s, C-6); 118.3 (t, C-5); 127.0 (2xd, Ph); 128.0 (d, Ph); 128.3 (2xd, Ph); 134.1 (d, C-4); 141.2 (s, Ph); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 3369, 1452, 1214, 1025, 992, 699.

(2*S*,3*R*)-2,3-*O*-Isopropylidene-1-mesyloxy-pent-4-ene-2,3-diol¹⁰⁵ (127)

C₉H₁₆O₅S

MW: 236.29 g.mol⁻¹



Methanesulfonyl chloride (0.2 mL, 2.7 mmol) was added to a stirred solution of **99** (400 mg, 2.5 mmol) in dry pyridine (0.75 mL, 9.3 mmol) and dry dichloromethane (15 ml) at 0°C. After stirring for 48 h at rt, the reaction mixture was washed with water, brine and extracted with dichloromethane. The combined organic layers were dried over MgSO₄, concentrated *in vacuo* and re-concentrated from toluene (2x). The crude mesylate **127** was used in subsequent reaction without purification.

crude yield: 517 mg (86%)

R_f = 0.58 (AcOEt/toluene 2:3)

yellowish liquid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.40 (s, CH₃, 3H); 1.53 (s, CH₃, 3H); 3.06 (s, SCH₃, 3H); 4.13 (dd, H-1a, J = 10.8, 7.5 Hz, 1H), 4.20 (dd, H-1b, J = 10.8, 4.2 Hz, 1H), 4.43 (ddd, H-2, J = 7.1, 6.8, 4.2 Hz, 1H), 4.71 (tt, H-3, J = 6.8, 1.0 Hz, 1H), 5.33 (dt, H-5a, J = 10.4, 1.2 Hz, 1H), 5.46 (dt, H-5b, J = 17.1, 1.3 Hz, 1H), 5.81 (ddd, H-4, J = 17.1, 10.4, 7.0 Hz, 1H); relative to TMS (δ = 0 ppm).

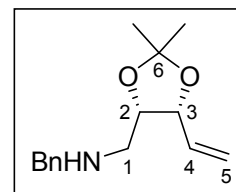
^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 25.2 (q, CH_3); 27.7 (q, CH_3); 37.7 (q, SCH_3); 68.5 (t, C-1); 75.4 (d, C-2); 77.8 (d, C-3); 109.6 (s, C-6); 119.5 (t, C-5); 131.7 (d, C-4); relative to CDCl_3 ($\delta=77$ ppm).

IR (film on KBr): ν (cm^{-1}) = 1352, 1171, 962, 830, 527.

(2*S*,3*R*)-1-(Benzylamino)-2,3-*O*-isopropylidene-pent-4-ene-2,3-diol (128**)**

$\text{C}_{15}\text{H}_{21}\text{NO}_2$

MW: 247.33 $\text{g}\cdot\text{mol}^{-1}$



A solution of mesylate **127** (581 mg, 2.46 mmol) in benzylamine (2.7 mL, 24.6 mmol) was heated to 100°C for 6 h until TLC control indicated complete conversion. The crude product **128** was purified by flash chromatography (74 g of silica gel, ethyl acetate/hexanes 1:1 with NH_3).

yield: 537 mg (88%)

$R_f = 0.18$ (AcOEt/hexanes 2:3 with NH_3)

yellow liquid

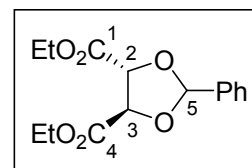
^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.37 (s, CH_3 , 3H); 1.46 (s, CH_3 , 3H); 1.69 (bs, NH, 1H); 2.60 (dd, H-1a, $J = 12.0, 4.1$ Hz, 1H); 2.69 (dd, H-1b, $J = 12.0, 8.7$ Hz, 1H); 3.81 (s, CH_2Ph , 2H); 4.34 (ddd, H-2, $J = 8.7, 6.5, 4.1$ Hz, 1H); 4.57 (dd, H-3, $J = 7.4, 6.5$ Hz, 1H); 5.22 (ddd, H-5a, $J = 10.3, 1.4, 1.0$ Hz, 1H); 5.33 (dt, H-5b, $J = 17.1, 1.4$ Hz, 1H); 5.80 (ddd, H-4, $J = 17.1$ Hz, 10.3 Hz, 7.4 Hz, 1H); 7.23-7.33 (m, Ph, 5H); relative to TMS ($\delta = 0$ ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 25.4 (q, CH_3); 28.0 (q, CH_3); 49.6 (t, C-1); 54.0 (t, CH_2Ph); 77.5, 78.8 (2xd, C-2,3); 108.6 (s, C-6); 118.5 (t, C-5); 126.9, 128.1, 128.4 (5xd, Ph); 133.6 (d, C-4); 140.0 (s, Ph); relative to CDCl_3 ($\delta = 77$ ppm).

IR (film on KBr): ν (cm^{-1}) = 1454, 1370, 1213, 1043, 925, 735, 698.

Specific rotation: $[\alpha]_D$ (20°C) = -30.4 (c 1.034, CHCl_3)

HRMS (ESI): Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 248.1645; found $[\text{M}+\text{H}]^+$ 248.1643. Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{Na}]^+$ 270.1465; found $[\text{M}+\text{Na}]^+$ 270.1463.

Diethyl (–)-2,3-*O*-benzylidene-L-tartrate¹⁰² (116)**C₁₅H₁₈O₆**MW: 294.30 g.mol⁻¹

A 500 mL round-bottomed flask equipped with a Dean-Stark trap was charged with diethyl L-tartrate (51.5 g, 250 mmol), benzaldehyde (26.6 g, 250 mmol), toluene (300 mL) and *p*-toluensulfonic acid monohydrate (1.40 g, 7.35 mmol). The stirred mixture was heated with azeotropic removal of water for 20 h. The solution was allowed cooling to rt and concentrated *in vacuo*. The residual dark liquid was dissolved in diethyl ether (200 mL), transferred to a separatory funnel and washed with saturated aqueous potassium bicarbonate (100 mL) and with water (2 x 100 mL). The ethereal layer was dried over MgSO₄ and concentrated *in vacuo*, followed by removal of solvent (and residual benzaldehyde) at 0.1 mm Hg at rt. The crude product **116** was collected by suction filtration through a glass-sintered funnel. Trituration of the product with hexanes and its collection by suction filtration gave purified product **116**.

yield: 33.8 g (46%)

R_f = 0.40 (AcOEt/hexanes 1:4)m.p. = 40–42°C (lit.¹⁴⁵ m.p. = 47°C)

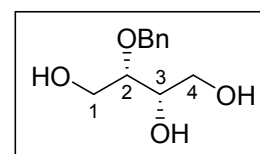
ochrous solid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.31 (t, CH₃, *J* = 7.1 Hz, 3H); 1.35 (t, CH₃, *J* = 7.1 Hz, 3H); 4.28 (q, OCH₂, *J* = 7.1 Hz, 2H); 4.33 (q, OCH₂, *J* = 7.1 Hz, 2H); 4.83, 4.95 (2xd, H-2,3, *J* = 4.0 Hz, 2H); 6.16 (s, H-5, 1H); 7.39–7.41 (m, Ph, 3H); 7.57–7.60 (m, Ph, 2H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 14.0 (q, CH₃); 14.1 (q, CH₃); 62.0 (2xt, OCH₂); 77.3, 77.6 (2xd, C-2,3); 106.7 (d, C-5); 127.2 (2xd, Ph); 128.3 (2xd, Ph); 129.9 (d, Ph); 135.5 (s, Ph); 169.0, 169.6 (2xs, C-1,4); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 3394, 3325, 1732, 1705, 1184, 1128, 1079, 940, 662, 574.

¹⁴⁵ Jäger, V.; Wehner, V. *Angew. Chem.* **1989**, *101*, 512.

(*S,S*)-2-Benzyloxy-butane-1,3,4-triol¹⁰³ (117)**C₁₁H₁₆O₄**MW: 212.24 g.mol⁻¹

A 1 L three-necked, sulfonation flask was oven-dried and flushed with argon. The flask was equipped with mechanical stirrer, a 250 mL addition funnel and reflux condenser equipped with an oil bubbler. A slight pressure of gas was maintained in the apparatus throughout the course of the reaction. The flask was charged with lithium aluminium hydride (8.14 g, 215 mmol) and cooled to -30°C. Then dry diethyl ether (90 mL) was added with vigorous stirring and a solution of aluminium chloride (28.6 g, 215 mmol) in dry diethyl ether (70 mL) was added dropwise during 40 min. Dry dichloromethane (70 mL) was placed in the addition funnel and added rapidly, while the temperature was allowed to rise to 0°C. A solution of protected diethyl L-tartrate **116** (32.0 g, 109 mmol) in dry dichloromethane (70 mL) was added dropwise during 30 min. The mixture was stirred for 1 h at rt and heated to reflux for additional 2 h. The mixture was cooled to -20 °C as above, and deionized water (7 mL), followed by a solution of potassium hydroxide (15.6 g, 277 mmol) in deionized water (23 mL) was added cautiously. The cooling bath was removed and the mixture was stirred at room temperature overnight. Then tetrahydrofuran (100 mL) was added and the mixture was heated to reflux for 1 h. The mixture was filtered through a glass-sintered funnel containing a 2 cm pad of celite. Filtrate was concentrated *in vacuo*. As the Soxhlet extraction was totally ineffective, water, Glauber salt and ethyl acetate were added to an inorganic precipitate (collected during filtration) and this mixture was stirred for several hours. Organic phase was decanted, a new portion of ethyl acetate was added, and the mixture was stirred for further few hours. The combined organic layers were concentrated *in vacuo* to give the product **117**.

yield: 15.4 g (67%)

 $R_f = 0.41$ (dichloromethane/methanol 9:1)m.p.= 72-74°C (lit.¹⁴⁶ m.p.= 71-73°C)

white crystals

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 2.83 (bs, 3xOH, 3H); 3.51- 3.88 (4xdd, H-1,2,3,4, 6H); 4.56 (d, CH₂Ph-a, $J = 11.7$ Hz, 1H); 4.69 (d, CH₂Ph-b, $J = 11.7$ Hz, 1H); 7.31-7.39 (m, Ph, 5H); relative to TMS ($\delta = 0$ ppm).

¹⁴⁶ Dumont, R.; Pfander, H. *Helv. Chim. Acta* **1983**, 66, 814.

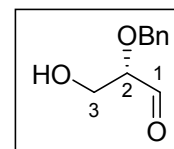
^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 60.7, 63.1 (2xt, C-1,4); 71.7 (d, C-3); 72.4 (t, CH_2Ph); 79.1 (d, C-2); 128.0 (2xd, Ph); 128.1 (d, Ph); 128.6 (2xd, Ph); 137.6 (s, Ph); relative to CDCl_3 ($\delta=77$ ppm).

IR (film on KBr): ν (cm^{-1}) = 3251, 2940, 1450, 1124, 1083, 1035, 991, 737, 692, 595.

(S)-2-O-Benzylglyceraldehyde¹⁰³ (118)

$\text{C}_{10}\text{H}_{12}\text{O}_3$

MW: 180.20 $\text{g}\cdot\text{mol}^{-1}$



A solution of triol **117** (5.0 g, 23.6 mmol) in water (50 mL) was stirred vigorously, while sodium periodate (5.04 g, 23.6 mmol) was added over 45 min. The mixture was stirred for 2 h at rt, then the pH was adjusted to 7.0 by the addition of solid potassium carbonate. The mixture was transferred to a separatory funnel and extracted with dichloromethane (3x 75 mL). The combined organic layers were dried over MgSO_4 for 15 min and concentrated in *vacuo* (30 mm, 30°C). The remaining crude oil was transferred to a round-bottomed flask and purified by short-path distillation in a preheated 160°C oil bath to give the aldehyde **118**.

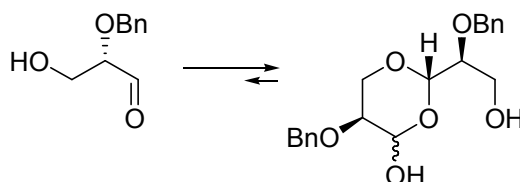
yield: 2.91 g (68%)

$R_f = 0.77$ (AcOEt/hexanes 3:1)

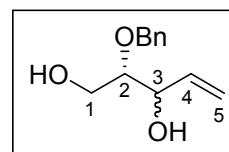
b.p. = $100\text{--}102^\circ\text{C}$ / 0.04–0.05 Torr

colorless oil (turns more and more viscous, after several weeks at rt it forms waxy solid)

Due to fast oligomerization of **118** (Scheme 100) exact spectral characterizations cannot be given.



Scheme 100. Oligomerization of **118**.

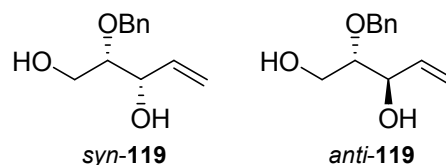
(2S)-2-Benzyloxy-pent-4-ene-1,3-diol (119)**C₁₂H₁₆O₃**MW: 208.25 g.mol⁻¹

A 250 mL three-necked round-bottomed flask equipped with addition funnel and condenser was air-heated, flushed with argon and charged with magnesium (1.37 g, 56.4 mmol) and a grain of iodine. After activation, the solution of vinylbromide (6.2 mL, 86.6 mmol) in THF (30 mL) was added dropwise. The reaction mixture was stirred for 1 h until complete consumption of magnesium. The solution of vinylmagnesium bromide was cooled to 0°C and the solution of aldehyde **118** (2.91 g, 16.1 mmol) in THF (30 mL) was added dropwise. The reaction mixture was stirred overnight followed by the addition of NH₄Cl saturates solution (100 mL). The aqueous layer was extracted with diethyl ether and combined organic layers were concentrated *in vacuo*. The crude alcohol **119** was used in the next reaction without purification.

crude yield: 3.17 g (95%)

diastereomeric ratio: *syn*-**119** vs. *anti*-**119** ~1:2R_f = 0.25 (AcOEt/hexanes 1:1)

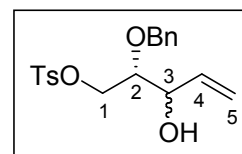
yellow oil



¹H NMR (300 MHz, CDCl₃): δ (*anti*, ppm) = 2.24 (s, OH, 1H); 2.68 (s, OH, 1H); 3.46 (dd, H-2, *J* = 9.8, 4.7 Hz, 1H); 3.67 (dd, H-1a, *J* = 11.8, 4.7 Hz, 1H); 3.80 (dd, H-1b, *J* = 13.6, 4.5 Hz, 1H); 4.27 (t, H-3, *J* = 5.4 Hz, 1H); 4.65 (d, CH₂Ph-a, *J* = 11.5 Hz, 1H); 4.70 (d, CH₂Ph-b, *J* = 11.5 Hz, 1H); 5.25 (dt, H-5a, *J* = 10.5, 1.4 Hz, 1H); 5.39 (dt, H-5b, *J* = 17.2, 1.5 Hz, 1H); 5.91 (ddd, H-4, *J* = 17.2, 10.5, 6.0 Hz, 1H); 7.30-7.39 (m, Ph, 5H). δ (*syn*, ppm) = 2.37 (s, OH, 1H); 2.71 (s, OH, 1H); 3.46 (dd, H-2, *J* = 9.8, 4.7 Hz, 1H); 3.73-3.79 (m, H-1, 2H); 4.40 (t, H-3, *J* = 4.9 Hz, 1H); 4.64 (d, CH₂Ph-a, *J* = 11.6 Hz, 1H); 4.69 (d, CH₂Ph-b, *J* = 11.6 Hz, 1H); 5.24 (dt, H-5a, *J* = 10.5, 1.5 Hz, 1H); 5.38 (dt, H-5b, *J* = 17.1, 1.8 Hz, 1H); 5.92 (ddd, H-4, *J* = 17.1, 10.5, 5.4 Hz, 1H); 7.30-7.39 (m, Ph, 5H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (*anti*, ppm) = 61.5 (t, C-1); 72.9 (d, C-3); 73.1 (t, CH₂Ph); 81.7 (d, C-2); 117.1 (t, C-5); 127.9, 128.0, 128.6 (5xd, Ph); 137.0 (d, C-4); 137.8 (s, Ph). δ (*syn*, ppm) = 61.3 (t, C-1); 72.2 (t, CH₂Ph); 72.8 (d, C-3); 81.2 (d, C-2); 116.4 (t, C-5); 127.9, 128.0, 128.5 (5xd, Ph); 136.7 (d, C-4); 137.8 (s, Ph); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 3386, 2880, 1454, 1099, 1058, 994, 738, 699.

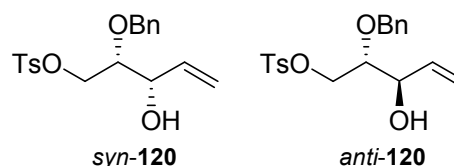
(2S)-2-(Benzyloxy)-3-hydroxypent-4-enyl 4-methylbenzenesulfonate (120)**C₁₉H₂₂O₅S**MW: 362.44 g.mol⁻¹

The diol substrate **119** (3.12 g, 15.0 mmol) was dissolved with stirring in pyridine (15 mL) and cooled to -20°C. *p*-Toluenesulfonyl chloride (2.95 g, 15.5 mmol) was added and the solution was stirred at 0°C for 4 h. The reaction mixture was diluted with diethyl ether (90 mL), washed with several portions of aqueous CuSO₄ (150 mL) and finally with water (50 mL). The organic phase was dried over MgSO₄, concentrated *in vacuo* and the crude tosylate **120** purified by flash chromatography (164 g of silica gel, ethyl acetate/toluene 1:5).

crude yield: 3.07 g (56%)

diastereomeric ratio: *syn*-**120** vs. *anti*-**120** ~1:2R_f = 0.33 (AcOEt/toluene 1:5)

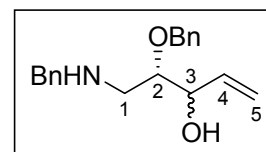
greenish-yellow oil



¹H NMR (300 MHz, CDCl₃): δ (*anti*, ppm) = 2.31 (d, OH, *J* = 5.7 Hz, 1H); 2.44 (s, CH₃, 3H); 3.60 (td, H-2, *J* = 5.6, 4.8 Hz, 1H); 4.07 (dd, H-1a, *J* = 10.6, 5.9 Hz, 1H); 4.09-4.16 (m, H-3, 1H); 4.22 (dd, H-1b, *J* = 10.6, 4.3 Hz, 1H); 4.53 (d, CH₂Ph-a, *J* = 11.3 Hz, 1H); 4.66 (d, CH₂Ph-b, *J* = 11.3 Hz, 1H); 5.21 (dt, H-5a, *J* = 10.5, 1.3 Hz, 1H); 5.31 (dt, H-5b, *J* = 17.2, 1.3 Hz, 1H); 5.80 (ddd, H-4, *J* = 17.2, 10.5, 6.0 Hz, 1H); 7.24-7.36 (m, Ph, C₆H₄, 7H); 7.77 (d, C₆H₄, *J* = 8.3 Hz, 2H). δ (*syn*, ppm) = 2.18 (d, OH, *J* = 4.5 Hz, 1H); 2.44 (s, CH₃, 3H); 3.65 (ddd, H-2, *J* = 6.7, 4.7, 3.9 Hz, 1H); 4.13 (dd, H-1a, *J* = 10.7, 6.4 Hz, 1H); 4.20 (dd, H-1b, *J* = 10.7, 3.6 Hz, 1H); 4.25-4.28 (m, H-3, 1H); 4.56 (d, CH₂Ph-a, *J* = 11.5 Hz, 1H); 4.62 (d, CH₂Ph-b, *J* = 11.5 Hz, 1H); 5.20 (dt, H-5a, *J* = 10.6, 1.4 Hz, 1H); 5.29 (dt, H-5b, *J* = 17.2, 1.4 Hz, 1H); 5.81 (ddd, H-4, *J* = 17.2, 10.6, 5.7 Hz, 1H); 7.24-7.36 (m, Ph, C₆H₄, 7H); 7.77 (d, C₆H₄, *J* = 8.3 Hz, 2H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (*anti*, ppm) = 21.6 (q, CH₃); 68.9 (t, C-1); 71.9 (d, C-3); 73.6 (t, CH₂Ph); 79.2 (d, C-2); 117.6 (t, C-5); 127.9, 128.0, 128.4, 129.9 (9xd, Ph, C₆H₄); 136.2 (d, C-4); 132.6, 137.2, 145.0 (3xs, Ph, C₆H₄). δ (*syn*, ppm) = 21.6 (q, CH₃); 69.3 (t, C-1); 72.0 (d, C-3); 73.0 (t, CH₂Ph); 79.4 (d, C-2); 117.3 (t, C-5); 127.8, 127.9, 128.0, 128.4, 129.8 (9xd, Ph, C₆H₄); 135.6 (d, C-4); 132.7, 137.5, 144.9 (3xs, Ph, C₆H₄); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 3531, 2876, 1360, 1177, 1097, 980, 815, 666, 555.

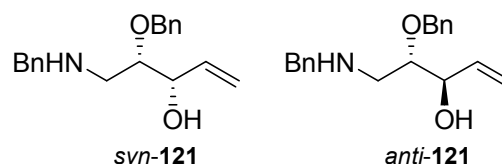
(2S)-1-(Benzylamino)-2-(benzyloxy)pent-4-en-3-ol (121)**C₁₉H₂₃NO₂**MW: 297.39 g.mol⁻¹

A solution of tosylate **120** (1.0 g, 2.76 mmol) and benzylamine (3.0 mL, 27.6 mmol) in dry acetonitrile (40 mL) was heated to reflux for 15 h. The solvent was removed, the crude was dissolved in ethyl acetate (80 mL) and washed with water (3x 50 mL). Aqueous layers were extracted with diethyl ether (3x 40 mL), combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude product **121** was purified by flash chromatography (82 g of silica gel, ethyl acetate/toluene 3:1 sat. with NH₃).

yield: 0.65 g (79%)

diastereomeric ratio: *syn*-**121** vs. *anti*-**121** ~1:2R_f = 0.54 (AcOEt/toluene 3:1 sat. with NH₃)

yellow oil



¹H NMR (300 MHz, CDCl₃): δ (*anti*, ppm) = 2.78 (dd, H-1a, *J* = 12.3, 3.7 Hz, 1H); 2.98 (dd, H-1b, *J* = 12.3, 6.0 Hz, 1H); 3.16 (bs, OH, NH, 2H); 3.54 (td, H-2, *J* = 6.0, 3.8 Hz, 1H); 3.74 (s, NCH₂Ph, 2H); 4.37 (dd, H-3, *J* = 5.1, 3.9 Hz, 1H); 4.57 (d, OCH₂Ph-a, *J* = 11.9 Hz, 1H); 4.62 (d, OCH₂Ph-b, *J* = 11.9 Hz, 1H); 5.20 (dt, H-5a, *J* = 10.6, 1.6 Hz, 1H); 5.38 (dt, H-5b, *J* = 17.2, 1.6 Hz, 1H); 5.97 (ddd, H-4, *J* = 17.2, 10.6, 5.2 Hz, 1H); 7.25-7.35 (m, 2xPh, 10H). δ (*syn*, ppm) = 2.88 (dd, H-1a, *J* = 12.3, 3.5 Hz, 1H); 2.94 (dd, H-1b, *J* = 12.3, 4.1 Hz, 1H); 3.16 (bs, OH, NH, 2H); 3.41 (dd, H-2, *J* = 8.0, 4.0 Hz, 1H); 3.69 (d, NCH₂Ph-a, *J* = 13.1 Hz, 1H); 3.76 (d, NCH₂Ph-b, *J* = 13.1 Hz, 1H); 4.49 (t, H-3, *J* = 4.3 Hz, 1H); 4.55 (d, OCH₂Ph-a, *J* = 11.8 Hz, 1H); 4.70 (d, OCH₂Ph-b, *J* = 11.8 Hz, 1H); 5.16 (dt, H-5a, *J* = 10.5, 1.7 Hz, 1H); 5.38 (dt, H-5b, *J* = 17.2, 1.6 Hz, 1H); 5.84 (ddd, H-4, *J* = 17.1, 10.5, 4.9 Hz, 1H); 7.25-7.35 (m, 2xPh, 10H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (*anti*, ppm) = 49.6 (t, C-1); 53.9 (t, NCH₂Ph); 72.4 (t, OCH₂Ph); 74.8 (d, C-3); 78.7 (d, C-2); 115.8 (t, C-5); 127.2, 127.8, 128.1, 128.4, 128.5 (10xd, 2xPh); 137.7 (d, C-4); 138.1, 139.2 (2xs, 2xPh). δ (*syn*, ppm) = 48.7 (t, C-1); 53.9 (t, NCH₂Ph); 71.4 (t, OCH₂Ph); 74.3 (d, C-3); 78.7 (d, C-2); 115.5 (t, C-5); 127.2, 127.8, 128.2, 128.4, 128.5 (10xd, 2xPh); 138.4 (d, C-4); 138.1, 139.1 (2xs, 2xPh); relative to CDCl₃ (δ = 77 ppm).

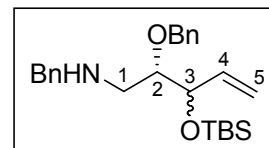
IR (film on KBr): ν (cm⁻¹) = 3312, 3029, 2863, 1454, 1098, 1070, 737, 698.

HRMS (ESI): Calcd. for $C_{19}H_{23}NO_2$ $[M+H]^+$ 298.1802; found $[M+H]^+$ 298.1803. Calcd. for $C_{19}H_{23}NO_2$ $[M+Na]^+$ 320.1621; found $[M+Na]^+$ 320.1620.

(2*S*)-*N*-Benzyl-2-(benzyloxy)-3-*tert*-butyldimethylsilyloxy-pent-4-en-1-amine (125**)**

$C_{25}H_{37}NO_2Si$

MW: 411.65 g.mol⁻¹



A 10 mL round-bottomed flask was charged with substrate **121** (100 mg, 0.34 mmol) and dichloromethane (3 mL). Then imidazole (46 mg, 0.67 mmol) and *tert*-butyldimethylsilyl chloride (61 mg, 0.40 mmol) were added. The reaction mixture was stirred at rt for 3 h. Water (1.5 mL) was added, phases were separated, aqueous layer was extracted with dichloromethane (3x 2 mL), and combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product **125** was purified by flash chromatography (4.4 g of silica gel, ethyl acetate/hexanes 1:10 + 1 vol. % Et_3N).

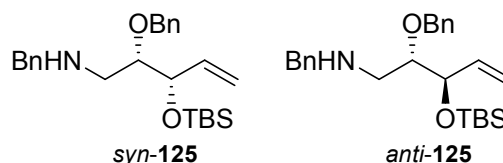
yield: 110 mg (80%)

diastereomeric ratio: *syn*-**125** vs. *anti*-**125** ~1:1.6

R_f (*syn*) = 0.44 (AcOEt/hexanes 1:3 with NH_3)

R_f (*anti*) = 0.57 (AcOEt/hexanes 1:3 with NH_3)

colorless oil



1H NMR (300 MHz, $CDCl_3$): δ (*anti*, ppm) = 0.02 (s, $SiCH_3$, 3H); 0.03 (s, $SiCH_3$, 3H); 0.88 (s, $C(CH_3)_3$, 9H); 1.68 (bs, NH, 1H); 2.64 (dd, H-1a, J = 12.3, 8.0 Hz, 1H); 2.79 (dd, H-1b, J = 12.3, 3.7 Hz, 1H); 3.59 (ddd, H-2, J = 9.0, 5.4, 3.7 Hz, 1H); 3.71 (s, NCH_2Ph , 2H); 4.33 (t, H-3, J = 5.4 Hz, 1H); 4.61 (d, OCH_2Ph -a, J = 11.7 Hz, 1H); 4.73 (d, OCH_2Ph -b, J = 11.7 Hz, 1H); 5.14 (dt, H-5a, J = 10.5, 1.6 Hz, 1H); 5.25 (dt, H-5b, J = 17.2, 1.8 Hz, 1H); 5.92 (ddd, H-4, J = 17.2, 10.5, 5.3 Hz, 1H); 7.20-7.34 (m, 2xPh, 10H). δ (*syn*, ppm) = 0.03 (s, $SiCH_3$, 3H); 0.06 (s, $SiCH_3$, 3H); 0.89 (s, $C(CH_3)_3$, 9H); 1.62 (bs, NH, 1H); 2.75 (d, H-1, J = 5.8 Hz, 2H); 3.58 (dd, H-2, J = 10.0, 5.7 Hz, 1H); 3.72 (s, NCH_2Ph , 2H); 4.25 (dd, H-3, J = 5.9, 4.5 Hz, 1H); 4.54 (d, OCH_2Ph -a, J = 11.5 Hz, 1H); 4.78 (d, OCH_2Ph -b, J = 11.5 Hz, 1H); 5.17 (dt, H-5a, J = 10.4, 1.3 Hz, 1H); 5.26 (dt, H-5b, J = 17.2, 1.5 Hz, 1H); 5.92 (ddd, H-4, J = 17.2, 10.5, 6.2 Hz, 1H); 7.23-7.33 (m, 2xPh, 10H); relative to TMS (δ = 0 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (*anti*, ppm) = -4.9 (q, SiCH_3); -4.7 (q, SiCH_3); 18.2 (s, $\text{C}(\text{CH}_3)_3$); 25.8 (3xq, $\text{C}(\text{CH}_3)_3$); 49.1 (t, C-1); 53.9 (t, NCH_2Ph); 73.0 (t, OCH_2Ph); 73.5 (d, C-3); 81.7 (d, C-2); 115.5 (t, C-5); 126.7, 127.7, 127.9, 128.0, 128.3, 128.4 (10xd, 2xPh); 137.2 (d, C-4); 138.7, 140.4 (2xs, 2xPh). δ (*syn*, ppm) = -4.9 (q, SiCH_3); -4.4 (q, SiCH_3); 18.2 (s, $\text{C}(\text{CH}_3)_3$); 25.8 (3xq, $\text{C}(\text{CH}_3)_3$); 49.7 (t, C-1); 53.9 (t, NCH_2Ph); 73.1 (t, OCH_2Ph); 75.1 (d, C-3); 82.3 (d, C-2); 116.0 (t, C-5); 126.8, 127.6, 127.9, 128.1, 128.3, 128.4 (10xd, 2xPh); 138.5 (d, C-4); 138.7, 140.3 (2xs, 2xPh); relative to CDCl_3 ($\delta=77$ ppm).

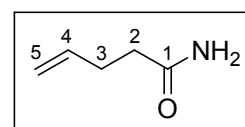
IR (film on KBr): ν (cm^{-1}) = 2927, 2854, 1454, 1251, 1073, 1028, 834, 775, 733, 696.

HRMS (ESI): Calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 412.2666; found $[\text{M}+\text{H}]^+$ 412.2688. Calcd. for $\text{C}_{25}\text{H}_{37}\text{NO}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 434.2486; found $[\text{M}+\text{Na}]^+$ 434.2474.

Pent-4-enamide¹⁰⁶ (**131**)

$\text{C}_5\text{H}_9\text{NO}$

MW: 99.13 $\text{g}\cdot\text{mol}^{-1}$



A solution of the pent-4-enoic acid (3 g, 30 mmol) in dichloromethane (15 mL) was stirred under argon at rt and oxalyl chloride (2.8 mL, 33 mmol) was added dropwise over 15 minutes. The solution was stirred at 40°C for 2 h. The reaction mixture was concentrated *in vacuo*, additional dichloromethane (5 mL) was added and reconstituted to give a yellow liquid. The crude acid chloride **130** was diluted in dry tetrahydrofuran (25 mL) and gaseous ammoniac was bubbled in the resulting solution for 10 minutes at rt along with precipitation of amide **131**. Tetrahydrofuran was removed *in vacuo* and a white solid was dissolved in ethyl acetate (25 mL). Aqueous sat. Na_2CO_3 (20 mL) was added and the aqueous layer was extracted with ethyl acetate (3x 10 mL). The combined organic layer was washed with sat. Na_2CO_3 (20 mL), dried over MgSO_4 and concentrated *in vacuo* to give the amide **131**.

yield: 1.7 g (57%) over two steps

R_f = 0.17 (AcOEt/hexanes 7:1)

m.p. = 103-104°C (lit.^{106b} m.p. = 102-103°C)

white crystals

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 2.29-2.41 (m, H-2, H-3, 4H); 5.02 (ddd, H-5a, J = 10.3, 2.7, 1.2 Hz, 1H); 5.09 (ddd, H-5b, J = 17.2, 3.3, 1.7 Hz, 1H); 5.78 (bs, NH₂, 1H); 5.84 (tdd, H-4, J = 17.0, 10.2, 6.2 Hz, 1H); 6.18 (bs, NH₂, 1H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 29.3 (t, C-3); 35.0 (t, C-2); 115.6 (t, C-5); 136.8 (d, C-4); 175.2 (s, CO); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 3349, 3169, 1629, 1414, 908, 643.

5.3. Intramolecular Pd(II)-catalyzed cyclization and Heck vinylation reaction

5.3.1. General procedure

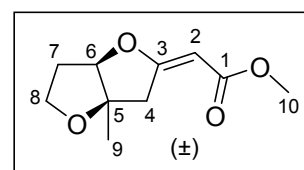
A mixture of alcohol substrate (1 equiv.) and CuCl (1 equiv.) in dry DMF was stirred at rt for 10 minutes under oxygen atmosphere (balloon). An appropriate vinylic coupling partner (5 equiv.) and palladium(II) catalyst (0.1 equiv.) were then added. In special cases, a catalytic amount of acetic or trifluoroacetic acid (0.2 equiv.) was added and the mixture was stirred at rt until the alcohol substrate was consumed as monitored by TLC. After the dilution with ethyl acetate, the organic layer was washed with sat. NH₄Cl, dried over MgSO₄ and concentrated *in vacuo*. The residue was separated by flash chromatography.

5.3.2. Characterization data of synthesized compounds

(±)-(3a*R*,6a*R*)-(E)-Methyl 2-(3a-methylperhydrofuro[3,2-*b*]furan-2-ylidene)-acetate⁸³ (84)

C₁₀H₁₄O₄

MW: 198.22 g.mol⁻¹



A reaction of (±)-4-methylpent-4-en-1,3-diol **82** (200 mg, 1.72 mmol) and CuCl (170 mg, 1.72 mmol) in dry DMF (7 mL) with methyl acrylate (740 mg, 8.6 mmol) and palladium acetate (39 mg, 0.17 mmol) following the general procedure afforded in 56 h the mixture of products which was separated by flash chromatography (10 g of silica gel, ethyl acetate/hexanes 1:3). The title compound **84** was crystallized from hexane.

yield: 40 mg (12%)

R_f = 0.35 (AcOEt/hexanes 1:3)

m.p. = 65-67°C⁸³

white crystals

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.43 (s, H-9, 3H); 2.14 (ddd, H-7a, *J* = 10.3, 8.2, 4.6 Hz, 1H); 2.24 (ddd, H-7b, *J* = 13.8, 5.9, 2.3 Hz, 1H); 2.99 (dd, H-4a, *J* = 19.2, 2.3 Hz, 1H); 3.61 (d, H-4b, *J* = 19.2 Hz, 1H); 3.66 (s, H-10, 3H); 3.82 (ddd, H-8a, *J* = 8.7, 8.4, 5.1 Hz, 1H); 4.00 (dt, H-8b, *J* = 8.4, 2.4 Hz, 1H); 4.67 (d, H-6, *J* = 4.4 Hz, 1H); 5.28 (dd, H-2, *J* = 2.1, 1.6 Hz, 1H); relative to TMS (δ = 0 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 22.7 (q, C-9); 32.7 (t, C-7); 44.2 (t, C-4); 50.7 (q, C-10); 66.9 (t, C-8); 87.7 (s, C-5); 89.9 (d, C-6); 91.2 (d, C-2); 168.7 (s, C-1); 175.7 (s, C-3); relative to CDCl_3 ($\delta = 77$ ppm).

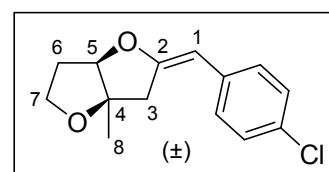
IR (film on KBr): ν (cm^{-1}) = 2951, 1705, 1645, 1437, 1364, 1148, 1106, 1039, 822.

X-ray analysis: An ORTEP view of the crystal and molecular structure of **84** is shown in Figure 5 (Section 4.1.1.), the supplementary data are available from the IUCr electronic archives (Reference: BV2142).⁸³

(\pm)-(3a*R*,6a*R*)-2(*E*)-(4-Chlorobenzylidene)-hexahydro-3a-methylfuro[3,2-*b*]furan (85**)**

$\text{C}_{14}\text{H}_{15}\text{ClO}_2$

MW: 250.72 $\text{g}\cdot\text{mol}^{-1}$



A reaction of (\pm)-4-methylpent-4-en-1,3-diol **82** (100 mg, 0.86 mmol) and CuCl (85 mg, 0.86 mmol) in dry DMF (5 mL) with 4-chlorostyrene (596 mg, 4.3 mmol), palladium acetate (20 mg, 0.09 mmol) and acetic acid (10 μL , 0.17 mmol) following the general procedure afforded in 5 days the mixture of products which was separated by flash chromatography (10 g of silica gel, ethyl acetate/hexanes 1:3).

yield (**85**): 31 mg (14%)

$R_f = 0.47$ (AcOEt/hexanes 1:3)

yellow oil

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.41 (s, H-8, 3H); 2.18 (ddd, H-6a, $J = 10.3, 8.3, 4.5$ Hz, 1H); 2.30 (ddd, H-6b, $J = 13.7, 5.9, 2.3$ Hz, 1H); 2.88 (dd, H-3a, $J = 16.9, 1.8$ Hz, 1H); 2.96 (d, H-3b, $J = 16.9$ Hz, 1H); 3.89 (ddd, H-7a, $J = 10.3, 8.5, 5.9$ Hz, 1H); 4.02 (dt, H-7b, $J = 8.4, 2.2$ Hz, 1H); 4.76 (d, H-5, $J = 4.3$ Hz, 1H); 5.11 (s, H-1, 1H); 7.21 (d, H-Ar, $J = 8.6$ Hz, 2H); 7.44 (d, H-Ar, $J = 8.6$ Hz, 2H); relative to TMS ($\delta = 0$ ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 22.7 (q, C-8); 33.4 (t, C-6); 44.5 (t, C-3); 67.4 (t, C-7); 87.3 (s, C-4); 91.6 (d, C-5); 96.8 (d, C-1); 128.1, 128.4 (4xd, 4xCH-Ar); 128.9, 129.7 (2xs, 2xC-Ar); 157.3 (s, C-3); relative to CDCl_3 ($\delta = 77$ ppm).

5.4. Intramolecular Pd(II)-catalyzed cyclization and coupling with aryl halides

5.4.1. General procedures

General procedure A1 for unprotected diol substrates (classical)

An oven-dried Schlenk tube was cooled under a stream of argon and charged with Pd(dba)₂ (0.02 or 0.1 equiv.), bis(phosphine) ligand (0.03 or 0.12 equiv.), ^tBuONa (2-3 equiv.) and aryl halide (1.5-2 equiv.). The tube was purged with argon and the alcohol substrate (1 equiv.) in THF (4 mL/mmol of aryl bromide) was added. The reaction mixture was heated to 65°C until the alcohol substrate was consumed as judged by TLC. The reaction mixture was cooled to rt and treated with either sat. NH₄Cl or 0.1 M HCl (to pH 5) and ethyl acetate was added. After the separation, the aqueous layer was extracted with ethyl acetate, dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography.

General procedure A2 for unprotected diol substrates (microwave activation)

An oven-dried vessel for microwave heating was cooled under a stream of argon and charged with Pd(dba)₂ (0.02 equiv.), dpe-phos (0.03 equiv.), ^tBuONa (2 equiv.) and 2-bromonaphthalene (1.5 equiv.). The vessel was purged with argon and the alcohol substrate (1 equiv.) with or without appropriate solvent was added. The reaction mixture was irradiated under corresponding MW conditions (temperature, power, pressure, time) and worked up following the classical heating conditions procedure A1.

General procedure B1 for TBS-protected diol substrates (classical)

An oven-dried Schlenk tube was cooled under a stream of argon and charged with Pd(dba)₂ (0.02, 0.05 or 0.1 equiv.), bis(phosphine) ligand (0.03, 0.05 or 0.12 equiv.), ^tBuONa (1.1-2 equiv.) and aryl halide (1-2 equiv.). The tube was purged with argon and the alcohol substrate (1 equiv.) in THF (4 mL/mmol of aryl bromide) was added. The reaction mixture was heated to 65°C until the alcohol substrate was consumed as judged by TLC. The reaction mixture was cooled to rt and saturated aqueous NH₄Cl (2 mL) and ethyl acetate (10 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography.

General procedure B2 for TBS-protected diol substrates (microwave activation)

An oven-dried vessel for microwave heating was cooled under a stream of argon and charged with Pd(dba)₂ (0.1 equiv.), dpe-phos (0.12 equiv.), ^tBuONa (1.5 equiv.) and 2-bromonaphthalene (1.5 equiv.). The vessel was purged with argon and the alcohol substrate (1 equiv.) in THF or toluene (0.5 M or 1 M) was added. The reaction mixture was irradiated under corresponding MW conditions (temperature, power, pressure, time) and worked up following the classical heating conditions procedure B1.

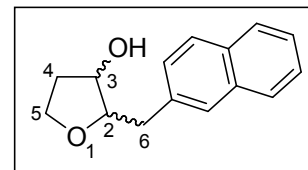
General procedure B3 for TBS-protected diol substrates (ionic liquids)

An oven-dried Schlenk tube (or MW vessel) was cooled under a stream of argon and charged with Pd(dba)₂ (0.1 equiv.), dpe-phos (0.12 equiv.), ^tBuONa (1.5 equiv.) and 2-bromonaphthalene (1.5 equiv.). The tube was purged with argon and [Bmim]OTf (3.5 equiv.) and the alcohol substrate (1 equiv.) was added. The reaction mixture was heated to 65°C with stirring (or heated under MW conditions) and extracted with diethyl ether. The combined extracts were concentrated *in vacuo*.

General procedure C for acetonide-protected triol substrates

An oven-dried Schlenk tube was cooled under a stream of argon and charged with Pd(dba)₂ (0.01 or 0.02 equiv.), dpe-phos (0.01 or 0.02 equiv.), ^tBuONa (2 equiv.) and aryl halide (2 equiv.). The tube was purged with argon and the alcohol substrate (1 equiv.) in THF (4 mL/mmol of aryl bromide) was added. The reaction mixture was heated to 65°C until the alcohol substrate was consumed as judged by TLC. The reaction mixture was cooled to rt and filtered through a pad of celite. After the addition of silica gel (1g/1mmol of alcohol substrate) the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography.

5.4.2. Characterization data of tetrahydrofuran products and side products

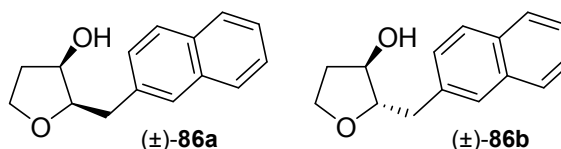
(±)-2-(Naphthalen-2'-ylmethyl)tetrahydrofuran-3-ol (86)**C₁₅H₁₆O₂**MW: 228.29 g.mol⁻¹

A reaction of Pd(dba)₂ (17 mg, 0.029 mmol), dpe-phos (24 mg, 0.044 mmol), ^tBuONa (282 mg, 2.94 mmol) and 2-bromonaphthalene (456 mg, 2.20 mmol) with the alcohol substrate **69a** (150 mg, 1.47 mmol) in THF (5 mL) following the general procedure A1 afforded in 8 h the crude product **86** which was purified by flash chromatography (14 g of silica gel, ethyl acetate/pentane 1:2).

yield: 51 mg (15%)

R_f = 0.26 (AcOEt/hexanes 1:2)diastereomeric ratio: **86a** vs. **86b** ~4:3

yellowish oil



Further purification involving the protection of the hydroxyl group with *tert*-butyldimethylsilyl chloride, separation of the diastereomers **92a** and **92b** by flash chromatography and deprotection with Dowex 50 (acidic H⁺ form) afforded **86a** as a white solid, which was recrystallized from hexane (m.p. 76-79°C), and **86b** as a colorless oil.

(±)-2,3-*cis*-2-(Naphthalen-2'-ylmethyl)tetrahydrofuran-3-ol (86a)

¹H NMR (600 MHz, CDCl₃): δ (ppm) = 1.89 (bs, OH, 1H); 1.94 (dddd, H-4a, *J* = 13.7, 7.8, 4.6, 1.3 Hz, 1H); 2.16 (dddd, H-4b, *J* = 13.4, 9.4, 7.8, 5.4 Hz, 1H); 3.15 (d, H-6, *J* = 7.1 Hz, 2H); 3.79 (ddd, H-5a, *J* = 9.3, 8.7, 4.6 Hz, 1H); 3.91 (ddd, H-2, *J* = 7.1, 7.1, 3.0 Hz, 1H); 4.10 (dd, H-5b, *J* = 16.2, 7.9 Hz, 1H); 4.17 (m, H-3, 1H); 7.40-7.45 (m, Naph, 3H); 7.73 (s, Naph, 1H); 7.77-7.80 (m, Naph, 3H); relative to TMS (δ = 0 ppm).

¹³C NMR (150 MHz, CDCl₃): δ (ppm) = 35.3 (t, C-6); 35.6 (t, C-4); 65.8 (t, C-5); 72.1 (d, C-3); 83.8 (d, C-2); 125.3, 125.9, 127.4, 127.5, 127.6, 127.6, 128.0 (7xd, Naph); 132.2, 133.6, 136.2 (3xs, Naph); relative to CDCl₃ (δ = 77 ppm).

IR (film on NaCl): ν (cm⁻¹) = 3419, 2944, 2882, 1601, 1508, 1126, 1052, 820, 751.

HRMS (ESI): Calcd. for C₁₅H₁₆O₂ [M+Na]⁺ 251.1048; found [M+Na]⁺ 251.1038.

X-ray analysis: An ORTEP view of the crystal and molecular structure of **86a** is shown in Figure 6 (Section 4.1.2.1.), the supplementary data were submitted to Cambridge Crystallographic Data Center and will be available online.

(±)-2,3-*trans*-2-(Naphthalen-2'-ylmethyl)tetrahydrofuran-3-ol (86b)

¹H NMR (600 MHz, CDCl₃): δ (ppm) = 1.78 (dddd, H-4a, *J* = 10.2, 6.9, 6.9, 3.5 Hz, 1H); 1.96 (bs, OH, 1H); 2.02 (dddd, H-4b, *J* = 13.1, 8.6, 8.5, 6.5 Hz, 1H); 2.88 (dd, H-6a, *J* = 13.9, 6.6 Hz, 1H); 2.97 (dd, H-6b, *J* = 13.9, 6.8 Hz, 1H); 3.89 (ddd, H-5a, *J* = 8.7, 8.6, 6.9 Hz, 1H); 3.93 (ddd, H-5b, *J* = 8.4, 8.4, 3.8 Hz, 1H); 4.01 (ddd, H-2, *J* = 6.7, 6.7, 3.3, 1H); 4.11 (ddd, H-3, *J* = 6.3, 3.1, 3.1 Hz, 1H); 7.35 (dd, Naph, *J* = 8.4, 1.7 Hz, 1H); 7.40-7.45 (m, Naph, 2H); 7.65 (s, Naph, 1H); 7.75-7.79 (m, Naph, 3H); relative to TMS (δ = 0 ppm).

¹³C NMR (150 MHz, CDCl₃): δ (ppm) = 34.6 (t, C-4); 39.9 (t, C-6); 66.4 (t, C-5); 75.3 (d, C-3); 86.6 (d, C-2); 125.4, 126.0, 127.5, 127.5, 127.6, 127.6, 128.0 (7xd, Naph); 132.2, 133.5, 135.5 (3xs, Naph); relative to CDCl₃ (δ = 77 ppm).

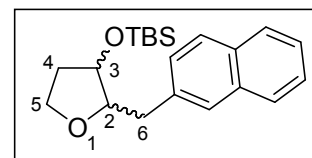
IR (film on NaCl): ν (cm⁻¹) = 3419, 2944, 2882, 1601, 1508, 1126, 1052, 820, 751.

HRMS (ESI): Calcd. for C₁₅H₁₆O₂ [M+Na]⁺ 251.1048; found [M+Na]⁺ 251.1041.

(±)-3-(*tert*-Butyldimethylsilyloxy)-2-(naphthalen-2'-ylmethyl)tetrahydrofuran (92)

C₂₁H₃₀O₂Si

MW: 342.55 g.mol⁻¹



A reaction of Pd(dba)₂ (40 mg, 0.069 mmol), dpe-phos (45 mg, 0.083 mmol), ^tBuONa (74 mg, 0.76 mmol) and 2-bromonaphthalene (287 mg, 1.39 mmol) with the alcohol substrate **90** (150 mg, 0.69 mmol) in THF (4 mL) following the general procedure B1 afforded in 4 h the crude product **92**, which was purified by flash chromatography (16 g of silica gel, ethyl acetate/pentane 1:40). The diastereomers **92a** and **92b** were partially separated.

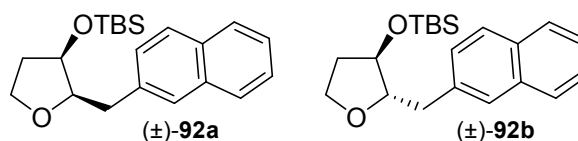
combined yield: 123 mg (52%)

R_f (**92a**) = 0.50 (ether/hexanes 1:10)

R_f (**92b**) = 0.60 (ether/hexanes 1:10)

diastereomeric ratio: **92a** vs. **92b** ~7:3

both are yellowish oils



(±)-2,3-*cis*-3-(*tert*-Butyldimethylsilyloxy)-2-(naphthalen-2'-ylmethyl)tetrahydrofuran (92a)

¹H NMR (600 MHz, CDCl₃): δ (ppm) = 0.08 (s, SiCH₃, 3H); 1.00 (s, SiCH₃, 3H); 0.96 (s, C(CH₃)₃, 9H); 1.89-1.93 (m, H-4a, 1H); 2.07-2.13 (m, H-4b, 1H); 3.03 (dd, H-6a, *J* = 14.3, 4.9 Hz, 1H); 3.09 (dd, H-6b, *J* = 14.3, 8.2 Hz, 1H); 3.78 (ddd, H-5a, *J* = 12.8, 8.4, 4.4 Hz, 1H); 4.01 (ddd, H-2, *J* = 8.3, 4.8, 3.7 Hz, 1H); 4.07 (dd, H-5b, *J* = 15.6, 8.0 Hz, 1H); 4.32 (m, H-3, 1H); 7.38-7.44 (m, Naph, 3H); 7.71 (s, Naph, 1H); 7.76-7.79 (m, Naph, 3H); relative to TMS (δ = 0 ppm).

¹³C NMR (150 MHz, CDCl₃): δ (ppm) = -4.9 (q, SiCH₃); -4.4 (q, SiCH₃); 18.2 (s, C(CH₃)₃); 25.9 (3xq, C(CH₃)₃); 36.0, 36.1 (2xt, C-4,6); 66.0 (t, C-5); 73.1 (d, C-3); 83.8 (d, C-2); 125.1, 125.7, 127.3, 127.5, 127.5, 127.8, 127.8 (7xd, Naph); 132.1, 133.6, 137.2 (3xs, Naph); relative to CDCl₃ (δ = 77 ppm).

IR (film on NaCl): ν (cm⁻¹) = 3419, 2943, 2882, 1601, 1508, 1441, 1052, 751.

HRMS (ESI): Calcd. for C₂₁H₃₀O₂Si [M+Na]⁺ 365.1913; found [M+Na]⁺ 365.1890.

(±)-2,3-*trans*-3-(*tert*-Butyldimethylsilyloxy)-2-(naphthalen-2'-ylmethyl)tetrahydrofuran (92b)

¹H NMR (600 MHz, CDCl₃): δ (ppm) = -0.09 (s, SiCH₃, 3H); -0.05 (s, SiCH₃, 3H); 0.82 (s, C(CH₃)₃, 9H); 1.75-1.79 (m, H-4a, 1H); 1.96-2.02 (m, H-4b, 1H); 2.93 (dd, H-6a, *J* = 14.0, 7.0 Hz, 1H); 2.96 (dd, H-6b, *J* = 14.0, 5.9 Hz, 1H); 3.91 (ddd, H-5a, *J* = 15.2, 8.5, 7.0 Hz, 1H); 3.95 (ddd, H-5b, *J* = 12.2, 8.3, 4.0 Hz, 1H); 4.00 (ddd, H-2, *J* = 6.8, 6.2, 3.7 Hz, 1H); 4.09 (m, H-3, 1H); 7.38 (dd, Naph, *J* = 8.4, 1.6 Hz, 1H); 7.40-7.45 (m, Naph, 2H); 7.66 (s, Naph, 1H); 7.76-7.80 (m, Naph, 3H); relative to TMS (δ = 0 ppm).

¹³C NMR (150 MHz, CDCl₃): δ (ppm) = -4.9 (q, SiCH₃); -4.7 (q, SiCH₃); 17.9 (s, C(CH₃)₃); 25.7 (3xq, C(CH₃)₃); 35.2 (t, C-4); 40.0 (t, C-6); 66.8 (t, C-5); 75.7 (d, C-3); 86.7 (d, C-2); 125.2, 125.8, 127.5, 127.5, 127.6, 127.8, 127.9 (7xd, Naph); 132.2, 133.6, 136.1 (3xs, Naph); relative to CDCl₃ (δ = 77 ppm).

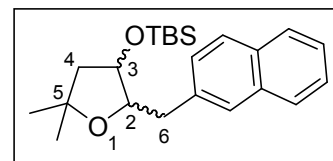
IR (film on NaCl): ν (cm⁻¹) = 3419, 2943, 2882, 1601, 1508, 1441, 1052, 751.

HRMS (ESI): Calcd. for C₂₁H₃₀O₂Si [M+Na]⁺ 365.1913; found [M+Na]⁺ 365.1891.

(±)-3-(*tert*-Butyldimethylsilyloxy)-5,5-dimethyl-2-(naphthalen-2'-ylmethyl)-tetrahydrofuran (93**)**

C₂₃H₃₄O₂Si

MW: 370.60 g.mol⁻¹



A reaction of Pd(dba)₂ (38 mg, 0.067 mmol), dpe-phos (43 mg, 0.080 mmol), ^tBuONa (96 mg, 1.00 mmol) and 2-bromonaphthalene (208 mg, 1.00 mmol) with the alcohol substrate **91** (150 mg, 0.61 mmol) in THF (4 mL) following the general procedure B1 afforded in 8 h the crude product **93** which was purified by flash chromatography (13 g of silica gel, ethyl acetate/pentane 1:80). The diastereomer **93a** was partially separated.

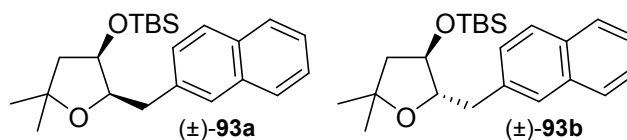
combined yield: 119 mg (52%)

R_f (**93a**) = 0.47 (AcOEt/pentane 1:40)

R_f (**93b**) = 0.55 (AcOEt/pentane 1:40)

diastereomeric ratio: **93a** vs. **93b** ~7:3

both are yellowish oils



¹H NMR (300 MHz, CDCl₃): δ (**93a**, ppm) = 0.02 (s, SiCH₃, 3H); 0.07 (s, SiCH₃, 3H); 0.97 (s, C(CH₃)₃, 9H); 1.25 (s, CH₃, 3H); 1.43 (s, CH₃, 3H); 1.88 (dd, H-4a, *J* = 13.2, 2.3 Hz, 1H); 1.97 (dd, H-4b, *J* = 13.2, 5.1 Hz, 1H); 3.08 (dd, H-6a, *J* = 14.2, 6.7 Hz, 1H); 3.14 (dd, H-6b, *J* = 14.2, 6.1 Hz, 1H); 4.21 (dd, H-2, *J* = 10.2, 6.5 Hz, 1H); 4.28 (m, H-3, 1H); 7.40-7.44 (m, Naph, 3H); 7.70-7.71 (m, Naph, 1H); 7.74-7.80 (m, Naph, 3H). δ (**93b**, ppm) = -0.15 (s, SiCH₃, 3H); -0.06 (s, SiCH₃, 3H); 0.82 (s, C(CH₃)₃, 9H); 1.25 (s, CH₃, 3H); 1.36 (s, CH₃, 3H); 1.71 (dd, H-4a, *J* = 12.7, 4.3 Hz, 1H); 1.86 (dd, H-4b, *J* = 12.7, 6.9 Hz, 1H); 2.99 (d, H-6, *J* = 6.0 Hz, 2H); 4.07 (ddd, H-2, *J* = 6.8, 4.5, 4.5 Hz, 1H); 4.15-4.23 (m, H-3, 1H); 7.38-7.47 (m, Naph, 3H); 7.68-7.69 (m, Naph, 1H); 7.73-7.82 (m, Naph, 3H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (**93a**, ppm) = -5.1 (q, SiCH₃); -4.2 (q, SiCH₃); 18.2 (s, C(CH₃)₃); 25.9 (3xq, C(CH₃)₃); 29.3 (q, CH₃); 30.1 (q, CH₃); 36.3 (t, C-6); 48.1 (t, C-4); 74.2 (d, C-3); 79.6 (s, C-5); 82.9 (d, C-2); 125.0, 125.7, 127.3, 127.4, 127.5, 127.6, 128.0 (7xd, Naph); 132.0, 133.5, 137.2 (3xs, Naph). δ (**93b**, ppm) = -5.1 (q, SiCH₃); -4.7 (q, SiCH₃); 17.8 (s, C(CH₃)₃); 25.6 (3xq, C(CH₃)₃); 28.5 (q, CH₃); 30.1 (q, CH₃); 40.3 (t, C-6); 47.4 (t, C-4); 76.2 (d, C-3); 80.5 (s, C-5); 85.8 (d, C-2); 125.1, 125.7, 127.4, 127.5, 127.6, 127.8, 128.3 (7xd, Naph); 132.2, 133.5, 136.0 (3xs, Naph); relative to CDCl₃ (δ = 77 ppm).

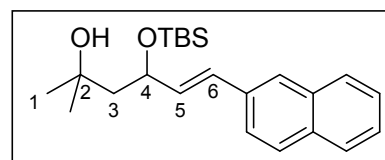
IR (film on NaCl): ν (cm⁻¹) = 2959, 2929, 2896, 1472, 1362, 1256, 1140, 1063, 836, 776.

HRMS (ESI): Calcd. for C₂₃H₃₄O₂Si [M+Na]⁺ 393.2220; found [M+Na]⁺ 393.2208.

(±)-(E)-4-tert-Butyldimethylsilyloxy-2-methyl-6-(naphthalen-2'-yl)hex-5-ene-2-ol (94)

C₂₃H₃₄O₂Si

MW: 370.60 g.mol⁻¹



Compound **94** with an internal double bond was formed as a side product in the reaction of formation of tetrahydrofuran **93**.

yield: 19 mg (8%)

R_f = 0.07 (AcOEt/pentane 1:40)

yellow oil

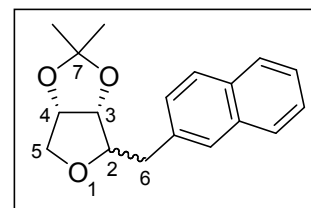
¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.09 (s, SiCH₃, 3H); 0.18 (s, SiCH₃, 3H); 0.93 (s, C(CH₃)₃, 9H); 1.25 (s, H-1, 3H); 1.37 (s, CH₃, 3H); 1.63 (dd, H-3a, J = 14.3, 3.1 Hz, 1H); 1.98 (dd, H-3b, J = 14.3, 10.6 Hz, 1H); 4.27 (bs, OH, 1H); 4.76 (ddd, H-4, J = 10.6, 8.0, 2.9 Hz, 1H); 6.27 (dd, H-5, J = 15.9, 8.0 Hz, 1H); 6.64 (d, H-6, J = 15.9 Hz, 1H); 7.44-7.48 (m, Naph, 2H); 7.58 (dd, Naph, J = 8.6, 1.7 Hz, 1H); 7.71-7.73 (m, Naph, 1H); 7.79-7.83 (m, Naph, 3H); relative to CDCl₃ (δ = 7.26 ppm).

IR (film on NaCl): ν (cm⁻¹) = 3516, 2959, 2930, 2857, 1471, 1257, 1150, 965, 837, 666.

(3*R*,4*S*)-3,4-*O*-Isopropylidene-2-((naphthalene-2'-yl)methyl)tetrahydrofuran-3,4-diol
(100)

C₁₈H₂₀O₃

MW: 284.35 g.mol⁻¹



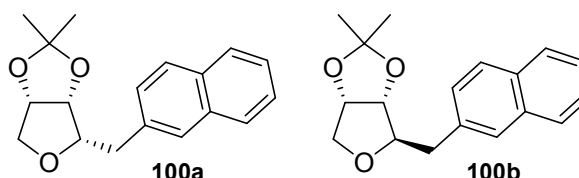
A reaction of Pd(dba)₂ (73 mg, 0.126 mmol), dpe-phos (68 mg, 0.126 mmol), ^tBuONa (243 mg, 2.53 mmol) and 2-bromonaphthalene (524 mg, 2.53 mmol) with the alcohol substrate **99** (200 mg, 1.26 mmol) in THF (10 mL) following the general procedure C afforded in 2 h the crude product **100** which was purified by flash chromatography (20 g of silica gel, ethyl acetate/toluene 1:6).

yield: 258 mg (72%)

R_f = 0.62 (AcOEt/toluene 1:2)

diastereomeric ratio: **100a** vs. **100b** ~ 2.5:1

yellowish solid

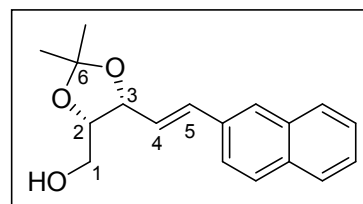


¹H NMR (300 MHz, CDCl₃): δ (**100a**, ppm) = 1.37 (s, CH₃, 3H); 1.60 (s, CH₃, 3H); 3.18 (dd, H-6a, *J* = 13.8, 7.1 Hz, 1H); 3.26 (dd, H-6b, *J* = 13.8, 6.5 Hz, 1H); 3.46 (dd, H-5a, *J* = 10.8, 3.7 Hz, 1H); 3.70 (ddd, H-2, *J* = 6.8, 6.8, 3.5 Hz, 1H); 4.05 (d, H-5b, *J* = 10.8 Hz, 1H); 4.57 (dd, H-3, *J* = 6.1, 3.6 Hz, 1H); 4.76 (dd, H-4, *J* = 6.1, 3.7 Hz, 1H); 7.42-7.49 (m, Naph, 3H); 7.77-7.82 (m, Naph, 4H). δ (**100b**, ppm) = 1.31 (s, CH₃, 3H); 1.50 (s, CH₃, 3H); 2.88 (dd, H-6a, *J* = 14.1, 7.0 Hz, 1H); 2.97 (dd, H-6b, *J* = 14.1, 7.6 Hz, 1H); 3.95 (dd, H-5a, *J* = 10.6, 3.6 Hz, 1H); 4.00 (dd, H-5b, *J* = 10.6, 2.0 Hz, 1H); 4.42 (ddd, H-2, *J* = 7.4, 7.4, 1.6 Hz, 1H); 4.56-4.59 (m, H-3, 1H); 4.82 (ddd, H-4, *J* = 6.0, 3.7, 2.2 Hz, 1H); 7.35-7.49 (m, Naph, 3H); 7.77-7.82 (m, Naph, 4H).; relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (**100a**, ppm) = 25.0, 26.2 (2xq, 2xCH₃); 35.0 (t, C-6); 72.9 (t, C-5); 80.8, 81.1 (2xd, C-3,4); 83.6 (d, C-2); 112.0 (s, C-7); 125.3, 125.8, 127.5, 127.6, 127.6, 127.8, 127.9 (7xd, Naph); 132.2, 133.5, 136.1 (3xs, Naph). δ (**100b**, ppm) = 25.1, 26.6 (2xq, 2xCH₃); 37.3 (t, C-6); 72.1 (t, C-5); 81.0 (d, C-4); 84.1 (s, C-3); 85.1 (d, C-2); 112.8 (s, C-7); 125.5, 126.0, 127.4, 127.5, 127.6, 128.2, 128.2 (7xd, Naph); 132.2, 133.5, 135.0 (3xs, Naph); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 2935, 1375, 1210, 1081, 990, 860, 828, 752, 474.

HRMS (ESI): Calcd. for C₁₈H₂₀O₃ [M+Na]⁺ 307.1305; found [M+Na]⁺ 307.1301.

(E)-(2*S*,3*R*)-2,3-*O*-Isopropylidene-5-(naphthalene-2'-yl)pent-4-ene-1,2,3-triol (101)**C₁₈H₂₀O₃**MW: 284.35 g.mol⁻¹

Compound **101** with an internal double bond was formed as a side product in the reaction of formation of tetrahydrofuran **100**.

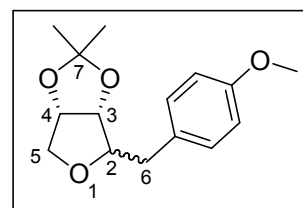
yield: 41 mg (11%)

 $R_f = 0.32$ (AcOEt/toluene 1:2)

yellow oil

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.46 (s, CH₃, 3H); 1.59 (s, CH₃, 3H); 3.69 (d, H-1, $J = 5.5$ Hz, 2H); 4.36 (dt, H-2, $J = 6.6, 5.5$ Hz, 1H); 4.89 (ddd, H-3, $J = 7.8, 6.6, 0.8$ Hz, 1H); 6.35 (dd, H-4, $J = 15.9, 7.8$ Hz, 1H); 6.86 (d, H-5, $J = 15.9$ Hz, 1H); 7.44-7.48 (m, Naph, 2H); 7.60 (dd, Naph, $J = 8.6, 1.7$ Hz, 1H); 7.75-7.82 (m, Naph, 4H); relative to TMS ($\delta = 0$ ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 25.2, 27.8 (2xq, 2xCH₃); 62.1 (t, C-1); 78.2, 78.6 (2xd, C-2,3); 108.9 (s, C-6); 123.6, 124.2, 126.1, 126.4, 126.9, 127.7, 128.0 (9xd, C-4, C-5, Naph); 132.1, 133.5, 134.2 (3xs, Naph); relative to CDCl₃ ($\delta = 77$ ppm).

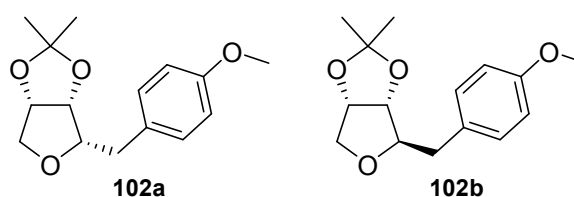
(3*R*,4*S*)-3,4-*O*-Isopropylidene-2-(4'-methoxybenzyl)tetrahydrofuran-3,4-diol (102)**C₁₅H₂₀O₄**MW: 264.32 g.mol⁻¹

A reaction of Pd(dba)₂ (73 mg, 0.126 mmol), dpe-phos (68 mg, 0.126 mmol), ^tBuONa (243 mg, 2.53 mmol) and 4-bromoanisole (473 mg, 2.53 mmol) with the alcohol substrate **99** (200 mg, 1.26 mmol) in THF (10 mL) following the general procedure C afforded in 2 h the crude product **102** which was purified by flash chromatography (20 g of silica gel, ethyl acetate/toluene 1:6).

yield: 221 mg (66%)

 $R_f = 0.58$ (AcOEt/toluene 1:2)diastereomeric ratio: **102a** vs. **102b** ~ 2:1

yellow oil



¹H NMR (300 MHz, CDCl₃): δ (**102a**, ppm) = 1.35 (s, CH₃, 3H); 1.55 (s, CH₃, 3H); 2.95 (dd, H-6a, *J* = 13.9, 7.0 Hz, 1H); 3.04 (dd, H-6b, *J* = 13.9, 6.7 Hz, 1H); 3.44 (dd, H-5a, *J* = 10.7, 3.8 Hz, 1H); 3.56 (ddd, H-2, *J* = 6.8, 6.8, 3.5 Hz, 1H); 3.79 (s, OCH₃, 3H); 4.02 (d, H-5b, *J* = 10.7 Hz, 1H); 4.53 (dd, H-3, *J* = 6.1, 3.5 Hz, 1H); 4.74 (dd, H-4, *J* = 6.1, 3.7 Hz, 1H); 6.84 (d, H-Ar, *J* = 8.7 Hz, 2H); 7.24 (d, H-Ar, *J* = 8.7 Hz, 2H). δ (**102b**, ppm) = 1.31 (s, CH₃, 3H); 1.49 (s, CH₃, 3H); 2.65 (dd, H-6a, *J* = 14.2, 7.0 Hz, 1H); 2.73 (dd, H-6b, *J* = 14.2, 7.6 Hz, 1H); 3.79 (s, OCH₃, 3H); 3.89 (dd, H-5a, *J* = 10.7, 4.1 Hz, 1H); 3.95 (dd, H-5b, *J* = 10.7, 1.8 Hz, 1H); 4.25 (ddd, H-2, *J* = 7.4, 7.4, 1.6 Hz, 1H); 4.50-4.52 (m, H-3, 1H); 4.79 (ddd, H-4, *J* = 6.0, 4.1, 1.8 Hz, 1H); 6.84 (d, H-Ar, *J* = 8.6 Hz, 2H); 7.12 (d, H-Ar, *J* = 8.6 Hz, 2H); relative to TMS (δ = 0 ppm).

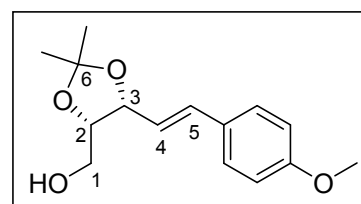
¹³C NMR (75 MHz, CDCl₃): δ (**102a**, ppm) = 25.0, 26.1 (2xq, 2xCH₃); 33.9 (t, C-6); 55.2 (q, OCH₃); 72.8 (t, C-5); 80.7 (d, C-3); 81.1 (d, C-4); 83.9 (d, C-2); 112.0 (s, C-7); 113.8, 130.2 (4xd, C-Ar); 130.5 (s, C-Ar); 158.1 (s, C-Ar). δ (**102b**, ppm) = 25.1, 26.6 (2xq, 2xCH₃); 36.2 (t, C-6); 55.2 (q, OCH₃); 72.0 (t, C-5); 80.9 (d, C-4); 84.1 (s, C-2); 85.3 (d, C-3); 112.8 (s, C-7); 114.0, 130.0 (4xd, C-Ar); 130.5 (s, C-Ar); 158.2 (s, C-Ar); relative to CDCl₃ (δ = 77 ppm).

IR (film on NaCl): ν (cm⁻¹) = 2935, 2852, 1375, 1212, 1081, 990, 860, 828, 752, 474.

HRMS (ESI): Calcd. for C₁₅H₂₀O₄ [M+Na]⁺ 287.1254; found [M+Na]⁺ 287.1246.

(*E*)-(2*S*,3*R*)-2,3-*O*-Isopropylidene-5-(4'-methoxybenzyl)pent-4-ene-1,2,3-triol (103**)**

C₁₅H₂₀O₄
MW: 264.32 g.mol⁻¹



Compound **103** with an internal double bond was formed as a side product in the reaction of formation of tetrahydrofuran **102**.

yield: 46 mg (14%)

R_f = 0.29 (AcOEt/toluene 1:2)

yellow oil

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.43 (s, CH₃, 3H); 1.56 (s, CH₃, 3H); 1.86 (t, OH, *J* = 6.1 Hz, 1H); 3.65 (t, H-1, *J* = 5.7 Hz, 2H); 3.81 (s, OCH₃, 3H); 4.31 (dt, H-2, *J* = 6.7, 5.5

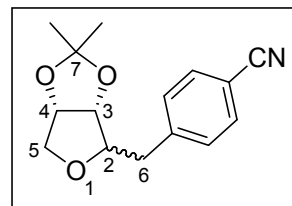
Hz, 1H); 4.82 (ddd, H-3, $J = 7.7, 7.1, 0.5$ Hz, 1H); 6.08 (dd, H-4, $J = 15.8, 8.0$ Hz, 1H); 6.64 (d, H-5, $J = 15.8$ Hz, 1H); 6.86 (d, H-Ar, $J = 8.8$ Hz, 2H); 7.33 (d, H-Ar, $J = 8.8$ Hz, 2H); relative to TMS ($\delta = 0$ ppm).

IR (film on KBr): ν (cm^{-1}) = 3400, 2918, 1603, 1511, 1246, 1027, 697.

(3*R*,4*S*)-3,4-*O*-Isopropylidene-2-(4'-cyanobenzyl)tetrahydrofuran-3,4-diol (104**)**

C₁₅H₁₇NO₃

MW: 259.30 g.mol⁻¹



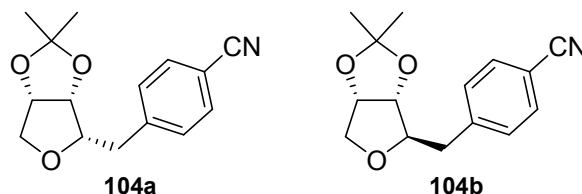
A reaction of Pd(dba)₂ (73 mg, 0.126 mmol), dpe-phos (68 mg, 0.126 mmol), ^tBuONa (243 mg, 2.53 mmol) and 4-bromobenzonitrile (460 mg, 2.53 mmol) with the alcohol substrate **99** (200 mg, 1.26 mmol) in THF (10 mL) following the general procedure C afforded in 8 h the crude product **104** which was purified by flash chromatography (20 g of silica gel, ethyl acetate/toluene 1:6).

yield: 237 mg (72%)

$R_f = 0.51$ (AcOEt/toluene 1:2)

diastereomeric ratio: **104a** vs. **104b** ~ 3:1

yellow oil



¹H NMR (300 MHz, CDCl₃): δ (**104a**, ppm) = 1.35 (s, CH₃, 3H); 1.55 (s, CH₃, 3H); 3.03-3.15 (m, H-6, 2H); 3.45 (dd, H-5a, $J = 10.8, 3.7$ Hz, 1H); 3.59 (ddd, H-2, $J = 6.7, 6.6, 3.6$ Hz, 1H); 4.03 (d, H-5b, $J = 10.8$ Hz, 1H); 4.54 (dd, H-3, $J = 6.1, 3.6$ Hz, 1H); 4.77 (dd, H-4, $J = 6.1, 3.6$ Hz, 1H); 7.43 (d, H-Ar, $J = 8.4$ Hz, 2H); 7.59 (d, H-Ar, $J = 8.4$ Hz, 2H). δ (**104b**, ppm) = 1.33 (s, CH₃, 3H); 1.50 (s, CH₃, 3H); 2.80-2.83 (m, H-6, 2H); 3.93 (dd, H-5a, $J = 10.7, 3.9$ Hz, 1H); 3.97 (dd, H-5b, $J = 10.7, 2.3$ Hz, 1H); 4.24 (ddd, H-2, $J = 7.8, 7.8, 2.1$ Hz, 1H); 4.49 (dd, H-3, $J = 6.3, 2.1$ Hz, 1H); 4.83 (ddd, H-4, $J = 6.2, 3.9, 2.2$ Hz, 1H); 7.33 (d, H-Ar, $J = 8.4$ Hz, 2H); 7.60 (d, H-Ar, $J = 8.4$ Hz, 2H); relative to TMS ($\delta = 0$ ppm).

¹³C NMR (75 MHz, CDCl₃): δ (**104a**, ppm) = 24.9, 26.0 (2xq, 2xCH₃); 35.1 (t, C-6); 72.8 (t, C-5); 80.7 (d, C-3); 81.0 (d, C-4); 82.7 (d, C-2); 110.1 (s, C-Ar); 112.2 (s, C-7); 119.0 (s, CN); 130.2, 132.1 (4xd, C-Ar); 144.3 (s, C-Ar). δ (**104b**, ppm) = 25.1, 26.6 (2xq, 2xCH₃); 37.2 (t, C-6); 71.9 (t, C-5); 80.8 (d, C-4); 84.3 (s, C-2); 84.5 (d, C-3); 110.4 (s, C-Ar); 113.2

(s, C-7); 118.9 (s, CN); 129.9, 132.2 (4xd, C-Ar); 143.4 (s, C-Ar); relative to CDCl₃ (δ = 77 ppm).

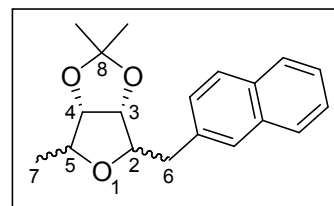
IR (film on KBr): ν (cm⁻¹) = 2985, 2935, 2852, 2226, 1608, 1372, 1207, 1093, 859.

HRMS (ESI): Calcd. for C₁₅H₁₇NO₃ [M+Na]⁺ 282.1101; found [M+Na]⁺ 282.1089.

(3*R*,4*S*)-3,4-*O*-Isopropylidene-5-methyl-2-((naphthalene-2'-yl)methyl)tetrahydrofuran-3,4-diol (108**)**

C₁₉H₂₂O₃

MW: 298.38 g.mol⁻¹



A reaction of Pd(dba)₂ (13 mg, 0.023 mmol), dpe-phos (12 mg, 0.023 mmol), ^tBuONa (45 mg, 0.465 mmol) and 2-bromonaphthalene (96 mg, 0.465 mmol) with the alcohol substrate **101** (40 mg, 0.232 mmol) in THF (3 mL) following the general procedure C afforded in 3.5 h the crude product **108** which was purified by flash chromatography (4 g of silica gel, ethyl acetate/hexanes 1:10). The diastereomers **108a** and **108b** were partially separated.

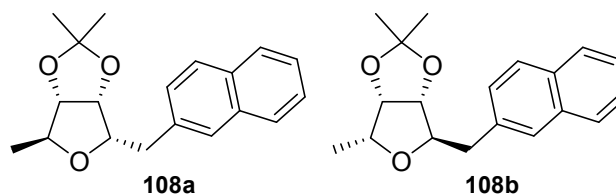
combined yield: 32 mg (46%)

R_f (**108a**) = 0.39 (AcOEt/hexanes 1:5)

R_f (**108b**) = 0.34 (AcOEt/hexanes 1:5)

ratio: **108a** vs. **108b** ~ 2:1

yellowish solid recrystallized from hexane (**108a**, m.p. 93-95°C) and yellow oil (**108b**)



(2*S*,3*R*,4*S*,5*S*)-3,4-*O*-Isopropylidene-5-methyl-2-((naphthalene-2'-yl)methyl)tetrahydrofuran-3,4-diol (108a**)**

¹H NMR (600 MHz, CDCl₃): δ (ppm) = 1.11 (d, H-7, J = 7.0 Hz, 3H); 1.35 (s, CH₃, 3H); 1.60 (s, CH₃, 3H); 3.12 (dd, H-6a, J = 13.8, 6.5 Hz, 1H); 3.25 (dd, H-6b, J = 13.8, 7.1 Hz, 1H); 4.10 (ddd, H-2, J = 6.8, 6.8, 3.7 Hz, 1H); 4.28 (q, H-5, J = 6.9 Hz, 1H); 4.43 (dd, H-4, J = 6.1, 0.5 Hz, 1H); 4.58 (dd, H-3, J = 6.0, 3.7 Hz, 1H); 7.40-7.47 (m, Naph, 3H); 7.75-7.80 (m, Naph, 4H); relative to TMS (δ = 0 ppm).

¹³C NMR (150 MHz, CDCl₃): δ (ppm) = 16.9 (q, C-7); 25.1, 26.4 (2xq, 2xCH₃); 35.3 (t, C-6); 79.6 (d, C-5); 80.3 (d, C-2); 81.2 (d, C-3); 86.3 (d, C-4); 112.3 (s, C-8); 125.2, 125.8,

127.5, 127.6, 127.8, 127.9 (7xd, Naph); 132.1, 133.5, 136.2 (3xs, Naph); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 3059, 2964, 1373, 1267, 1207, 1072, 749.

Specific rotation: $[\alpha]_D$ (26°C) = +77.2 (c 0.246, CHCl₃)

HRMS (ESI): Calcd. for C₁₉H₂₂O₃ [M+Na]⁺ 321.1461; found [M+Na]⁺ 321.1456.

X-ray analysis: An ORTEP view of the crystal and molecular structure of **108a** is shown in Figure 9 (Section 4.1.2.3.), the supplementary data were submitted to Cambridge Crystallographic Data Center and will be available online.

(2R,3R,4S,5R)-3,4-O-Isopropylidene-5-methyl-2-((naphthalene-2'-yl)methyl)tetrahydrofuran-3,4-diol (108b)

¹H NMR (600 MHz, CDCl₃): δ (ppm) = 1.30 (s, CH₃, 3H); 1.33 (d, H-7, J = 6.3 Hz, 3H); 1.48 (s, CH₃, 3H); 2.84 (dd, H-6a, J = 14.0, 7.8 Hz, 1H); 3.00 (dd, H-6b, J = 14.0, 7.6 Hz, 1H); 4.10 (dd, H-5, J = 7.5, 3.8 Hz, 1H); 4.42 (t, H-2, J = 7.7 Hz, 1H); 4.62-4.65 (m, H-3, H-4, 2H); 7.40-7.47 (m, Naph, 3H); 7.75-7.80 (m, Naph, 4H); relative to TMS (δ = 0 ppm).

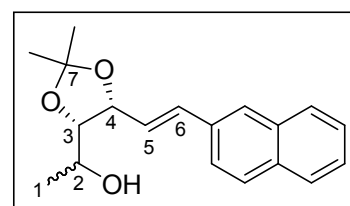
¹³C NMR (150 MHz, CDCl₃): δ (ppm) = 14.0 (q, C-7); 25.2, 26.3 (2xq, 2xCH₃); 37.4 (t, C-6); 75.8 (d, C-5); 82.3 (d, C-4); 84.4 (d, C-2); 84.9 (d, C-3); 119.8 (s, C-8); 125.2, 125.8, 127.5, 127.6, 127.8, 127.9 (7xd, Naph); 132.2, 134.5, 135.1 (3xs, Naph); relative to CDCl₃ (δ = 77 ppm).

IR (film on NaCl): ν (cm⁻¹) = 3059, 2964, 1373, 1267, 1207, 1072, 749.

HRMS (ESI): Calcd. for C₁₉H₂₂O₃ [M+Na]⁺ 321.1461; found [M+Na]⁺ 321.1456.

(E)-(3S,4R)-3,4-O-Isopropylidene-6-(naphthalene-2'-yl)hex-5-ene-2,3,4-triol (109)

C₁₉H₂₂O₃
MW: 298.38 g.mol⁻¹



Compound **109** with an internal double bond was formed as a side product in the reaction of formation of tetrahydrofuran **108**.

yield: 11 mg (16%)

R_f = 0.13 (AcOEt/hexanes 1:5)

diastereomeric ratio ~ 1.2:1

yellow oil

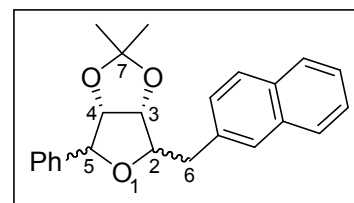
¹H NMR (300 MHz, CDCl₃): δ (major, ppm) = 1.20 (d, H-1, *J* = 6.3 Hz, 3H); 1.46 (s, CH₃, 3H); 1.60 (s, CH₃, 3H); 3.87 (qi, H-2, *J* = 6.2 Hz, 1H); 4.03 (dd, H-3, *J* = 6.3, 4.3 Hz, 1H); 4.81 (ddd, H-4, *J* = 8.4, 6.6, 0.5 Hz, 1H); 6.40 (dd, H-5, *J* = 15.8, 8.5 Hz, 1H); 6.81 (d, H-6, *J* = 15.8 Hz, 1H); 7.45-7.48 (m, Naph, 2H); 7.62-7.63 (m, Naph, 1H); 7.76-7.82 (m, Naph, 4H).
δ (minor, ppm) = 1.31 (d, H-1, *J* = 6.1 Hz, 3H); 1.44 (s, CH₃, 3H); 1.56 (s, CH₃, 3H); 3.96 (q, H-2, *J* = 6.2 Hz, 1H); 4.22 (dd, H-3, *J* = 5.9, 3.7 Hz, 1H); 4.90 (ddd, H-4, *J* = 7.4, 6.3, 0.9 Hz, 1H); 6.49 (dd, H-5, *J* = 15.9, 7.8 Hz, 1H); 6.89 (d, H-6, *J* = 15.9 Hz, 1H); 7.45-7.48 (m, Naph, 2H); 7.59-7.60 (m, Naph, 1H); 7.76-7.82 (m, Naph, 4H); relative to TMS (δ = 0 ppm).

IR (film on KBr): ν (cm⁻¹) = 3379, 2978, 1371, 1170, 814.

HRMS (ESI): Calcd. for C₁₉H₂₂O₃ [M+Na]⁺ 321.1461; found [M+Na]⁺ 321.1451.

(3*R*,4*S*)-3,4-*O*-Isopropylidene-5-phenyl-2-((naphthalene-2'-yl)methyl)tetrahydrofuran-3,4-diol (110**)**

C₂₄H₂₄O₃
MW: 360.45 g.mol⁻¹



A reaction of Pd(dba)₂ (22 mg, 0.039 mmol), dpe-phos (21 mg, 0.039 mmol), ^tBuONa (75 mg, 0.785 mmol) and 2-bromonaphthalene (163 mg, 0.785 mmol) with the alcohol substrate **102** (92 mg, 0.393 mmol) in THF (4 mL) following the general procedure C afforded in 3.5 h the crude product **110** which was purified by flash chromatography (8 g of silica gel, ethyl acetate/hexanes 1:10). The diastereomers **110a** and **110b** were separated.

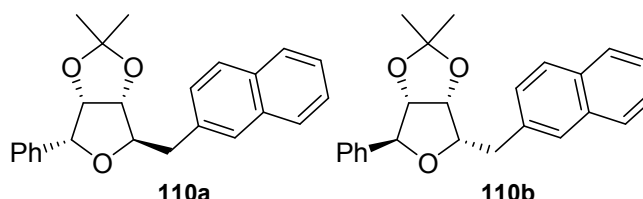
combined yield: 100 mg (70%)

R_f (**110a**) = 0.32 (AcOEt/hexanes 1:6)

R_f (**110b**) = 0.52 (AcOEt/hexanes 1:6)

ratio: **110a** vs. **110b** ~ 2:1

yellowish oil (**110a**) and yellowish solid recrystallized from hexane (**110b**, m.p. 105-107°C)



(2*R*,3*R*,4*S*,5*R*)-3,4-*O*-Isopropylidene-5-phenyl-2-((naphthalene-2'-yl)methyl)tetrahydrofuran-3,4-diol (110a**)**

¹H NMR (600 MHz, CDCl₃): δ (ppm) = 1.22 (s, CH₃, 3H); 1.42 (s, CH₃, 3H); 2.96 (dd, H-6a, *J* = 14.0, 7.9 Hz, 1H); 3.12 (dd, H-6b, *J* = 14.0, 7.3 Hz, 1H); 4.63 (t, H-2, *J* = 7.6 Hz, 1H); 4.75 (d, H-3, *J* = 5.9 Hz, 1H); 4.84 (dd, H-4, *J* = 5.8, 3.9 Hz, 1H); 5.05 (d, H-5, *J* = 3.7

Hz, 1H); 7.27-7.30 (m, Naph, 1H); 7.34-7.46 (m, Naph, Ph, 7H); 7.68 (bs, Naph, 1H); 7.77-7.80 (m, Naph, 3H); relative to TMS ($\delta = 0$ ppm).

^{13}C NMR (150 MHz, CDCl_3): δ (ppm) = 24.8, 26.1 (2xq, 2x CH_3); 37.3 (t, C-6); 82.0 (d, C-5); 82.6 (d, C-4); 84.6 (2xd, C-2,3); 112.6 (s, C-7); 125.5, 126.0, 127.4, 127.5, 127.6, 127.7, 127.8, 127.9, 128.3 (12xd, Naph, Ph); 132.3, 133.6, 134.9, 136.1 (4xs, Naph, Ph); relative to CDCl_3 ($\delta = 77$ ppm).

IR (film on KBr): ν (cm^{-1}) = 2931, 1371, 1206, 1070, 717, 696.

Specific rotation: $[\alpha]_{\text{D}}$ (25°C) = -19.5 (c 0.830, CHCl_3)

HRMS (ESI): Calcd. for $\text{C}_{24}\text{H}_{24}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 383.1618; found $[\text{M}+\text{Na}]^+$ 383.1604.

(2*S*,3*R*,4*S*,5*S*)-3,4-*O*-Isopropylidene-5-phenyl-2-((naphthalene-2'-yl)methyl)tetrahydrofuran-3,4-diol (110b)

^1H NMR (600 MHz, CDCl_3): δ (ppm) = 1.41 (s, CH_3 , 3H); 1.69 (s, CH_3 , 3H); 3.27 (dd, H-6a, $J = 14.0, 7.1$ Hz, 1H); 3.32 (dd, H-6b, $J = 14.0, 6.6$ Hz, 1H); 4.17 (ddd, H-2, $J = 6.8, 6.7, 3.6$ Hz, 1H); 4.60 (dd, H-3, $J = 6.0, 3.6$ Hz, 1H); 4.96 (d, H-4, $J = 6.0$ Hz, 1H); 5.23 (s, H-5, 1H); 7.22-7.34 (m, Ph, 5H); 7.42-7.52 (m, Naph, 3H); 7.78-7.83 (m, Naph, 4H); relative to TMS ($\delta = 0$ ppm).

^{13}C NMR (150 MHz, CDCl_3): δ (ppm) = 25.3, 26.5 (2xq, 2x CH_3); 35.4 (t, C-6); 81.7 (d, C-3); 81.8 (d, C-2); 84.6 (d, C-5); 87.5 (d, C-4); 112.6 (s, C-7); 125.3, 125.5, 125.8, 127.3, 127.6, 127.6, 127.8, 127.9, 128.5 (12xd, Naph, Ph); 132.2, 133.5, 136.0, 138.8 (4xs, Naph, Ph); relative to CDCl_3 ($\delta = 77$ ppm).

IR (film on KBr): ν (cm^{-1}) = 2979, 2935, 1379, 1208, 1064, 1038, 858, 751, 700.

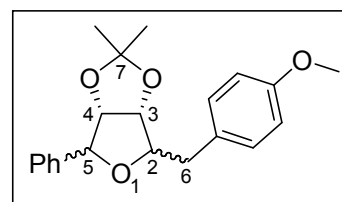
Specific rotation: $[\alpha]_{\text{D}}$ (26°C) = +26.8 (c 0.310, CHCl_3)

HRMS (ESI): Calcd. for $\text{C}_{24}\text{H}_{24}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 383.1618; found $[\text{M}+\text{Na}]^+$ 383.1610.

(3*R*,4*S*)-3,4-*O*-Isopropylidene-5-phenyl-2-(4'-methoxybenzyl)tetrahydrofuran-3,4-diol (111)

$\text{C}_{21}\text{H}_{24}\text{O}_4$

MW: 360.41 $\text{g}\cdot\text{mol}^{-1}$



A reaction of $\text{Pd}(\text{dba})_2$ (49 mg, 0.085 mmol), dpe-phos (46 mg, 0.085 mmol), $^t\text{BuONa}$ (164 mg, 1.71 mmol) and 4-bromoanisole (320 mg, 1.71 mmol) with the alcohol substrate **102**

(200 mg, 0.854 mmol) in THF (7 mL) following the general procedure C afforded in 5 h the crude product **111** which was purified by flash chromatography (25 g of silica gel, ethyl acetate/hexanes 1:10). The diastereomers **111a** and **111b** were separated.

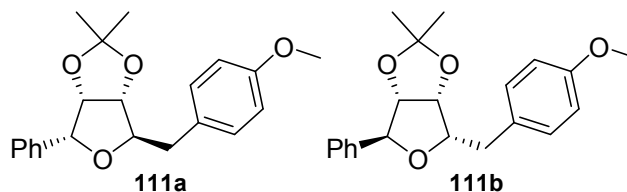
combined yield: 81 mg (28%)

R_f (**111a**) = 0.33 (AcOEt/hexanes 1:6)

R_f (**111b**) = 0.54 (AcOEt/hexanes 1:6)

ratio: **111a** vs. **111b** ~ 1.5:1

both are yellow oils



(2*R*,3*R*,4*S*,5*R*)-3,4-*O*-Isopropylidene-5-phenyl-2-(4'-methoxybenzyl)tetrahydrofuran-3,4-diol (111a**)**

^1H NMR (600 MHz, CDCl_3): δ (ppm) = 1.24 (s, CH_3 , 3H); 1.42 (s, CH_3 , 3H); 2.74 (dd, H-6a, J = 14.1, 7.9 Hz, 1H); 2.91 (dd, H-6b, J = 14.1, 7.3 Hz, 1H); 3.77 (s, OCH_3 , 3H); 4.47 (t, H-2, J = 7.6 Hz, 1H); 4.70 (dd, H-3, J = 5.9, 0.8 Hz, 1H); 4.82 (dd, H-4, J = 5.9, 3.9 Hz, 1H); 4.98 (d, H-5, J = 3.8 Hz, 1H); 6.85 (d, H-Ar, J = 8.7 Hz, 2H); 7.15 (d, H-Ar, J = 8.7 Hz, 2H); 7.27-7.30 (m, Ph, 1H); 7.33-7.36 (m, Ph, 2H); 7.39-7.42 (m, Ph, 2H); relative to TMS (δ = 0 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 24.8, 26.1 (2xq, 2x CH_3); 36.2 (t, C-6); 55.2 (q, OCH_3); 81.8 (d, C-5); 82.5 (d, C-4); 84.5, 84.8 (2xd, C-2,3); 112.5 (s, C-7); 114.1, 127.4, 127.8, 127.9 (7xd, C-Ar, Ph); 129.4 (s, C-Ar); 130.1 (2xd, C-Ar); 136.1 (s, Ph); 158.3 (s, C-Ar); relative to CDCl_3 (δ = 77 ppm).

IR (film on NaCl): ν (cm^{-1}) = 2933, 1512, 1245, 1068, 1027, 711, 698.

Specific rotation: $[\alpha]_D$ (25°C) = +13.4 (c 0.380, CHCl_3)

HRMS (ESI): Calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_4$ $[\text{M}+\text{Na}]^+$ 363.1567; found $[\text{M}+\text{Na}]^+$ 363.1561.

(2*S*,3*R*,4*S*,5*S*)-3,4-*O*-Isopropylidene-5-phenyl-2-(4'-methoxybenzyl)tetrahydrofuran-3,4-diol (111b**)**

^1H NMR (600 MHz, CDCl_3): δ (ppm) = 1.39 (s, CH_3 , 3H); 1.64 (s, CH_3 , 3H); 3.04 (dd, H-6a, J = 13.9, 6.8 Hz, 1H); 3.10 (dd, H-6b, J = 13.9, 7.0 Hz, 1H); 3.79 (s, OCH_3 , 3H); 4.03 (dddd, H-2, J = 6.8, 6.8, 3.6, 0.5 Hz, 1H); 4.56 (dd, H-3, J = 6.0, 3.6 Hz, 1H); 4.93 (dd, H-4, J = 6.0, 1.0 Hz, 1H); 5.19 (s, H-5, 1H); 6.85 (d, H-Ar, J = 8.7 Hz, 2H); 7.22-7.33 (m, H-Ar, Ph, 7H); relative to TMS (δ = 0 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 25.3, 26.4 (2xq, 2x CH_3); 34.3 (t, C-6); 55.2 (q, OCH_3); 81.5 (d, C-3); 82.1 (d, C-2); 84.6 (d, C-5); 87.5 (d, C-4); 112.6 (s, C-7); 113.7, 125.5, 127.2, 128.5, 130.2 (9xd, C-Ar, Ph); 130.5 (s, C-Ar); 138.9 (s, Ph); 158.1 (s, C-Ar); relative to CDCl_3 (δ = 77 ppm).

IR (film on NaCl): ν (cm^{-1}) = 2935, 1512, 1245, 1070, 1027, 717, 696.

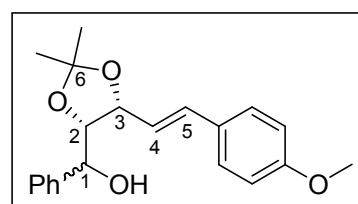
Specific rotation: $[\alpha]_{\text{D}}(25^\circ\text{C}) = +7.1$ (c 0.270, CHCl_3)

HRMS (ESI): Calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_4$ $[\text{M}+\text{Na}]^+$ 363.1567; found $[\text{M}+\text{Na}]^+$ 363.1554.

(*E*)-(2*S*,3*R*)-2,3-*O*-Isopropylidene-1-phenyl-5-(4'-methoxybenzyl)pent-4-ene-1,2,3-triol
(112)

$\text{C}_{21}\text{H}_{24}\text{O}_4$

MW: 340.41 $\text{g}\cdot\text{mol}^{-1}$



Compound **112** with an internal double bond was formed as a side product in the reaction of formation of tetrahydrofuran **111**.

yield: 58 mg (20%)

R_f = 0.15 (AcOEt/hexanes 1:6)

yellow oil

single diastereomer

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.45 (s, CH_3 , 3H); 1.64 (s, CH_3 , 3H); 2.89 (d, OH, J = 4.1 Hz, 1H); 3.77 (dd, H-1, J = 7.2, 6.1 Hz, 1H); 3.81 (s, OCH_3 , 3H); 4.45 (t, H-2, J = 6.3 Hz, 1H); 4.69 (t, H-3, J = 6.7 Hz, 1H); 6.06 (dd, H-4, J = 15.9, 7.9 Hz, 1H); 6.45 (d, H-5, J = 15.9 Hz, 1H); 6.85 (d, H-Ar, J = 8.8 Hz, 2H); 7.23-7.30 (m, H-Ar, Ph, 7H); relative to TMS (δ = 0 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 25.7, 27.7 (2xq, 2x CH_3); 55.2 (q, OCH_3); 72.6 (d, C-1); 78.7, 81.9 (2xd, C-2, C-3); 108.8 (s, C-6); 113.9 (2xd, Ar); 122.2, 127.5, 127.9, 128.0, 128.3, 128.9, 130.1, 133.4 (s, 9xd, C-4, C-5, Ph, Ar); 140.3 (s, Ph); 159.5 (s, Ar); relative to CDCl_3 (δ = 77 ppm).

IR (film on KBr): ν (cm^{-1}) = 3435, 2933, 1604, 1511, 1245, 1027, 698.

HRMS (ESI): Calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_4$ $[\text{M}+\text{Na}]^+$ 363.1567; found $[\text{M}+\text{Na}]^+$ 363.1553.

5.4.3. Deprotection of tetrahydrofuran products

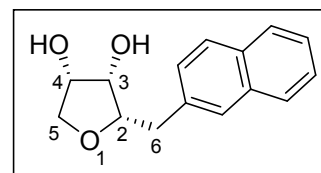
General procedure

Acetonide-protected tetrahydrofuran in THF was stirred at rt with 1M HCl until it was consumed as judged by TLC. The reaction mixture was treated with sat. Na₂CO₃, the aqueous layer was extracted with DCM (2x 10 mL), combined extracts were dried over MgSO₄ and concentrated *in vacuo*. The crude free diol was purified by flash chromatography.

Characterization data of deprotected tetrahydrofuran-3,4-diols

(2*S*,3*S*,4*S*)-2-((Naphthalen-2'-yl)methyl)tetrahydrofuran-3,4-diol (**113a**)

C₁₅H₁₆O₃
MW: 224.29 g.mol⁻¹



The reaction of protected tetrahydrofuran **103** (189 mg, 0.66 mmol) in THF (20 mL) with 1M HCl (20 mL) afforded in 4 days the crude mixture of diols **113a** and **113b** which was partially separated by flash chromatography (16 g of silica gel, ethyl acetate/hexanes 1:2).

yield (**113a**): 57 mg (35%)

R_f = 0.13 (AcOEt/toluene 1:2)

m.p. = 124.0-125.5°C

white solid

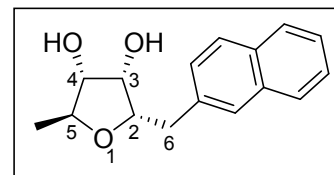
¹H NMR (600 MHz, acetone-d₆): δ (ppm) = 2.88 (bs, 2xOH, 2H); 3.04 (dd, H-6a, *J* = 13.8, 7.4 Hz, 1H); 3.20 (dd, H-6b, *J* = 13.8, 5.9 Hz, 1H); 3.68 (dd, H-5a, *J* = 8.7, 6.0 Hz, 1H); 3.80 (dd, H-5b, *J* = 8.7, 6.8 Hz, 1H); 4.00-4.02 (m, H-3, 1H); 4.02-4.04 (m, H-2, 1H); 4.38 (dt, H-4, *J* = 11.5, 6.0, 1H); 7.41-7.47 (m, Naph, 2H); 7.49 (dd, Naph, *J* = 8.4, 1.6 Hz, 1H); 7.78-7.85 (m, Naph, 4H); relative to TMS (δ = 0 ppm).

¹³C NMR (150 MHz, acetone-d₆): δ (ppm) = 37.6 (t, C-6); 73.4 (d+s, C-3, C-5); 73.7 (d, C-4); 84.5 (d, C-2); 127.0, 127.6, 129.3, 129.3, 130.0 (7xd, Naph); 134.1, 135.6, 139.2 (3xs, Naph); relative to acetone-d₆ (δ = 30.83 ppm).

IR (film on KBr): ν (cm⁻¹) = 3332, 2951, 2883, 1028, 822, 752, 472.

Specific rotation: [α]_D (27°C) = +25.3 (c 0.215, CHCl₃)

HRMS (ESI): Calcd. for C₁₅H₁₆O₃ [M+Na]⁺ 267.0992; found [M+Na]⁺ 267.0991.

(2*S*,3*S*,4*R*,5*S*)-5-Methyl-2-((naphthalen-2'-yl)methyl)tetrahydrofuran-3,4-diol (114a)**C₁₆H₁₈O₃**MW: 258.31 g.mol⁻¹

The reaction of protected tetrahydrofuran **108a** (22 mg, 0.074 mmol) in THF (4 mL) with 1M HCl (3 mL) afforded in 6 days the crude diol **114a** which was purified by flash chromatography (1 g of silica gel, ethyl acetate/hexanes 4:1).

yield: 15 mg (79%)

 $R_f = 0.33$ (AcOEt/hexanes 1:1)

m.p. = 76.0-78.0°C

yellowish solid

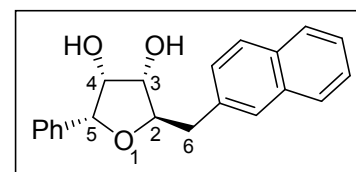
¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.30 (d, CH₃, J = 6.2 Hz, 3H); 2.51-2.55 (m, 2xOH, 2H); 3.10 (dd, H-6a, J = 13.7, 6.7 Hz, 1H); 3.20 (dd, H-6b, J = 13.6, 7.9 Hz, 1H); 3.75-3.81 (m, H-4, 1H); 3.94-4.02 (m, H-3, H-5, 2H); 4.32 (ddd, H-2, J = 7.6, 7.4, 3.4 Hz, 1H); 7.40-7.47 (m, Naph, 3H); 7.72-7.81 (m, Naph, 4H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 18.9 (q, CH₃); 35.9 (t, C-6); 72.3, 77.4 (2xd, C-3, C-5); 78.6 (d, C-4); 80.8 (d, C-2); 125.4, 126.0, 127.5, 127.5, 127.6, 127.7, 128.0 (7xd, Naph); 132.2, 133.6, 135.7 (3xs, Naph); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 3427, 2925, 2870, 1057, 823, 748, 473.

Specific rotation: $[\alpha]_D$ (27°C) = -22.9 (c 0.15, MeOH)

HRMS (ESI): Calcd. for C₁₆H₁₈O₃ [M+Na]⁺ 281.1148; found [M+Na]⁺ 281.1120. Calcd. for C₁₆H₁₈O₃ [M-H]⁻ 257.1183; found [M-H]⁻ 257.1172.

(2*R*,3*S*,4*R*,5*R*)-2-((Naphthalen-2'-yl)methyl)-5-phenyltetrahydrofuran-3,4-diol (115a)**C₂₁H₂₀O₃**MW: 320.38 g.mol⁻¹

The reaction of protected tetrahydrofuran **110a** (65 mg, 0.18 mmol) in THF (6 mL) with 1M HCl (5.2 mL) afforded in 4 days the crude diol **115a** which was purified by flash chromatography (2.2 g of silica gel, ethyl acetate/hexanes 1:1).

yield: 31 mg (54%)

$R_f = 0.37$ (AcOEt/hexanes 1:1)

m.p. = 118.0-119.0°C

yellowish solid

^1H NMR (600 MHz, CDCl_3): δ (ppm) = 1.84 (bs, OH, 1H); 2.52 (bs, OH, 1H); 3.09 (dd, H-6a, $J = 14.3, 6.3$ Hz, 1H); 3.28 (dd, H-6b, $J = 14.2, 4.4$ Hz, 1H); 4.05-4.08 (m, H-3, H-4, 2H); 4.34-4.37 (m, H-2, 1H); 4.99 (s, H-5, 1H); 7.26-7.35 (m, Ph, 5H); 7.41-7.48 (m, Naph, 3H); 7.77-7.81 (m, Naph, 4H); relative to TMS ($\delta = 0$ ppm).

^{13}C NMR (150 MHz, CDCl_3): δ (ppm) = 39.0 (t, C-6); 73.5, 76.3 (2xd, C-3, C-4); 81.9 (d, C-5); 82.6 (d, C-2); 125.4, 125.9, 126.6, 127.6, 127.6, 127.8, 127.9, 128.1, 128.3, 128.5 (12xd, Ph, Naph); 132.2, 133.4, 135.4 (3xs, Naph); 137.0 (s, Ph); relative to CDCl_3 ($\delta = 77$ ppm).

IR (film on KBr): ν (cm^{-1}) = 3556, 3389, 2925, 1016, 817, 745, 701, 479.

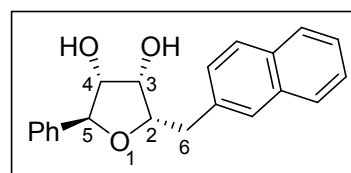
Specific rotation: $[\alpha]_D$ (27°C) = -55.6 (c 0.2577, MeOH)

HRMS (ESI): Calcd. for $\text{C}_{21}\text{H}_{20}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 343.1305; found $[\text{M}+\text{Na}]^+$ 343.1304. Calcd. for $\text{C}_{21}\text{H}_{20}\text{O}_3$ $[\text{M}-\text{H}]^-$ 319.1340; found $[\text{M}-\text{H}]^-$ 319.1366.

(2*S*,3*S*,4*R*,5*S*)-2-((Naphthalen-2'-yl)methyl)-5-phenyltetrahydrofuran-3,4-diol (115b**)**

$\text{C}_{21}\text{H}_{20}\text{O}_3$

MW: 320.38 $\text{g}\cdot\text{mol}^{-1}$



The reaction of protected tetrahydrofuran **110b** (27 mg, 0.075 mmol) in THF (4 mL) with 1M HCl (3 mL) afforded in 6 days the crude diol **115b** which was purified by flash chromatography (1 g of silica gel, ethyl acetate/hexanes 1:1).

yield: 18.6 mg (78%)

$R_f = 0.48$ (AcOEt/hexanes 1:1)

m.p. = 129.5-130.5°C

yellowish solid

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 2.61-2.66 (m, 2xOH, 2H); 3.22 (dd, H-6a, $J = 13.7, 6.7$ Hz, 1H); 3.31 (dd, H-6b, $J = 13.7, 7.9$ Hz, 1H); 4.04-4.10 (m, H-3, H-4, 2H); 4.51 (ddd,

H-2, $J = 7.7, 7.6, 2.9$ Hz, 1H); 4.88 (d, H-5, $J = 7.2$ Hz, 1H); 7.25-7.37 (m, Ph, 5H); 7.43-7.48 (m, Naph, 3H); 7.77-7.82 (m, Naph, 4H); relative to TMS ($\delta = 0$ ppm).

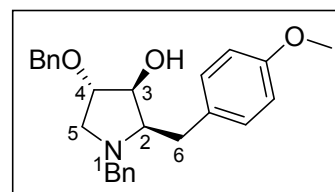
^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 36.0 (t, C-6); 72.6 (d, C-3); 79.8 (d, C-4); 82.2 (d, C-2); 82.8 (d, C-5); 125.4, 125.6, 126.0, 127.5, 127.6, 127.6, 127.8, 128.0, 128.5 (12xd, Ph, Naph); 132.2, 133.6, 135.6 (3xs, Naph); 140.9 (s, Ph); relative to CDCl_3 ($\delta = 77$ ppm).

IR (film on KBr): ν (cm^{-1}) = 3535, 3506, 3373, 2916, 1010, 817, 745, 708, 478.

Specific rotation: $[\alpha]_{\text{D}} (27^\circ\text{C}) = -39.6$ (c 0.1932, MeOH)

HRMS (ESI): Calcd. for $\text{C}_{21}\text{H}_{20}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 343.1305; found $[\text{M}+\text{Na}]^+$ 343.1295. Calcd. for $\text{C}_{21}\text{H}_{20}\text{O}_3$ $[\text{M}-\text{H}]^-$ 319.1340; found $[\text{M}-\text{H}]^-$ 319.1330.

5.4.4. Characterization data of pyrrolidine products and side products

(2*R*,3*S*,4*S*)-1-Benzyl-4-(benzyloxy)-3-hydroxy-2-(4'-methoxybenzyl)pyrrolidine¹⁰¹ (122**)****C₂₆H₂₉NO₃**MW: 403.51 g.mol⁻¹

A 10 mL round-bottom flask with stopcock equipped with condenser was flame-dried and flushed with argon. The flask was charged with the 4-bromoanisole (470 mg, 2.51 mmol), Pd(OAc)₂ (9 mg, 0.042 mmol), dpe-phos (45 mg, 0.084 mmol) and Cs₂CO₃ (1.57 g, 4.81 mmol). The flask was purged with argon and the solution of substrate **121** (620 mg, 2.08 mmol) in dioxane (10.5 mL) was then added *via* syringe. The resulting mixture was heated to 100°C until the starting material was consumed (14 h). The reaction mixture was cooled to rt and saturated aqueous NH₄Cl (5 mL) and ethyl acetate (5 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3x15 mL) and the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product **122** was purified by flash chromatography (26 g of silica gel, ethyl acetate/hexanes 1:2 sat. with NH₃).

yield: 80 mg (10%)

 R_f = 0.58 (AcOEt/hexanes 1:1 sat. with NH₃)

yellow oil

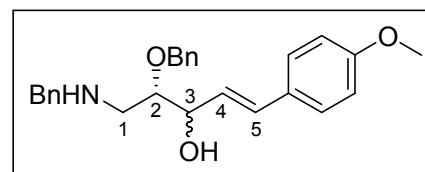
¹H NMR (600 MHz, CDCl₃): δ (ppm) = 2.25 (dd, H-5a, J = 10.8, 4.3 Hz, 1H); 2.61 (bs, OH, 1H); 2.85-2.96 (m, H-2, H-6, 3H); 3.33 (d, NCH₂Ph-a, J = 12.9 Hz, 1H); 3.36 (dd, H-5b, J = 10.6, 6.9 Hz, 1H); 3.79 (s, OCH₃, 3H); 3.80-3.85 (m, H-3, H-4, 2H); 4.14 (d, NCH₂Ph-b, J = 12.9 Hz, 1H); 4.39 (d, OCH₂Ph-a, J = 11.9 Hz, 1H); 4.46 (d, OCH₂Ph-b, J = 11.9 Hz, 1H); 6.84 (d, H-Ar, J = 8.7 Hz, 2H); 7.19-7.33 (m, 2xPh, H-Ar, 12H); relative to TMS (δ = 0 ppm).

¹³C NMR (150 MHz, CDCl₃): δ (ppm) = 32.5 (t, C-6); 55.2 (q, OCH₃); 57.9 (t, NCH₂Ph); 58.3 (t, C-5); 68.5 (d, C-2); 71.3 (t, OCH₂Ph); 75.4 (d, C-3); 82.7 (d, C-4); 113.9 (2xd, C-Ar); 127.2, 127.6, 128.3, 128.5, 128.9, 130.2 (12xd, 2xPh, C-Ar); 130.7 (s, C-Ar); 137.8, 138.0 (2xs, 2xPh); 158.0 (s, C-Ar); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 3396, 2932, 1610, 1512, 1454, 1247, 1177, 1112, 735, 699.

Specific rotation: $[\alpha]_D$ (25°C) = -64.1 (c 0.66, CHCl₃), lit.¹⁰¹ -96.1 (c 0.4, CHCl₃)

HRMS (ESI): Calcd. for C₂₆H₂₉NO₃ [M+H]⁺ 404.2220; found [M+H]⁺ 404.2217.

(2S)-(E)-1-(Benzylamino)-2-(benzyloxy)-5-(4'-methoxyphenyl)pent-4-en-3-ol (123)**C₂₆H₂₉NO₃**MW: 403.51 g.mol⁻¹

Compound **123** with an internal double bond was formed as the main but undesired product in the reaction of the formation of pyrrolidine **122**.

yield: 219 mg (26%)

 $R_f = 0.26$ (AcOEt/hexanes 1:1 sat. with NH₃)

diastereomeric ratio: ~ 1.2:1 (after separation)

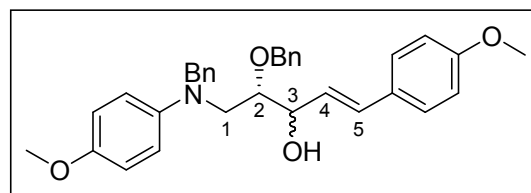
yellow oil

¹H NMR (300 MHz, CDCl₃): δ (major, ppm) = 2.04 (bs, OH, 1H); 2.81 (dd, H-1a, $J = 12.4, 3.6$ Hz, 1H); 3.03 (dd, H-1b, $J = 12.4, 5.7$ Hz, 1H); 3.59 (td, H-2, $J = 5.7, 3.8$ Hz, 1H); 3.70 (d, NCH₂Ph-a, $J = 12.9$ Hz, 1H); 3.78 (d, NCH₂Ph-b, $J = 12.9$ Hz, 1H); 3.80 (s, OCH₃, 3H); 4.52 (ddd, H-3, $J = 5.5, 4.2, 1.3$ Hz, 1H); 4.62 (s, OCH₂Ph, 2H); 6.13 (dd, H-4, $J = 15.9, 5.7$ Hz, 1H); 6.64 (d, H-5, $J = 15.9$ Hz, 1H); 6.85 (d, H-Ar, $J = 8.7$ Hz, 2H); 7.25-7.34 (m, H-Ar, 2xPh, 12H). δ (minor, ppm) = 2.04 (bs, OH, 1H); 2.94 (d, H-1a, $J = 10.6$ Hz, 1H); 2.96 (d, H-1b, $J = 10.6$ Hz, 1H); 3.47 (dd, H-2, $J = 8.3, 4.1$ Hz, 1H); 3.75 (s, NCH₂Ph, 2H); 3.80 (s, OCH₃, 3H); 4.45 (dd, H-3, $J = 15.8, 5.9$ Hz, 1H); 4.58 (d, OCH₂Ph-a, $J = 11.8$ Hz, 1H); 4.71 (d, OCH₂Ph-b, $J = 11.8$ Hz, 1H); 6.01 (dd, H-4, $J = 15.9, 5.5$ Hz, 1H); 6.62 (dd, H-5, $J = 15.9, 0.9$ Hz, 1H); 6.83 (d, H-Ar, $J = 8.7$ Hz, 2H); 7.25-7.34 (m, H-Ar, 2xPh, 12H); relative to TMS ($\delta = 0$ ppm).

¹³C NMR (75 MHz, CDCl₃): δ (major, ppm) = 49.6 (t, C-1); 53.9 (t, NCH₂Ph); 55.2 (q, OCH₃); 72.3 (t, OCH₂Ph); 74.8 (d, C-3); 79.1 (d, C-2); 113.8 (2xd, C-Ar); 127.2 (d, C-4); 127.6, 127.8, 127.9, 128.2, 128.4, 128.5 (12xd, C-Ar, 2xPh); 129.8 (s, C-Ar); 130.3 (d, C-5); 138.1, 139.2 (2xs, Ph); 159.0 (s, C-Ar). δ (minor, ppm) = 48.9 (t, C-1); 53.9 (t, NCH₂Ph); 55.2 (q, OCH₃); 71.5 (t, OCH₂Ph); 74.4 (d, C-3); 79.0 (d, C-2); 113.8 (2xd, C-Ar); 126.9 (d, C-4); 127.2, 127.6, 127.8, 127.9, 128.1, 128.4 (12xd, C-Ar, 2xPh); 129.7 (s, C-Ar); 130.1 (d, C-5); 138.1, 139.0 (2xs, 2xPh); 159.0 (s, C-Ar); relative to CDCl₃ ($\delta = 77$ ppm).

IR (film on KBr): ν (cm⁻¹) = 3307, 3063, 2933, 1607, 1512, 1250, 1030, 699.

HRMS (ESI): Calcd. for C₂₆H₂₉NO₃ [M+H]⁺ 404.2220; found [M+H]⁺ 404.2211. Calcd. for C₂₆H₂₉NO₃ [M+Na]⁺ 426.2040; found [M+Na]⁺ 426.2029.

(2S)-(E)-1-[N-Benzyl-N-(4'-methoxyphenyl)amino]-2-(benzyloxy)-5-(4''-methoxyphenyl)-pent-4-en-3-ol (124)**C₃₃H₃₅NO₄**MW: 509.64 g.mol⁻¹

Compound **124** with an internal double bond was formed as a side product in the reaction of formation of pyrrolidine **122**.

yield: 81 mg (8%)

 $R_f = 0.85$ (AcOEt/hexanes 1:1 sat. with NH₃)

single diastereomer

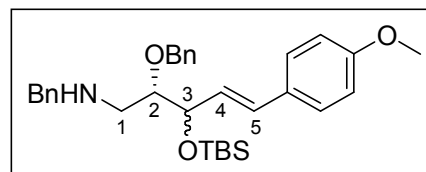
yellow oil

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 2.56 (dd, H-1a, $J = 12.0, 10.7$ Hz, 1H); 3.28 (d, NCH₂Ph-a, $J = 13.7$ Hz, 1H); 3.32 (dd, H-1b, $J = 12.2, 4.7$ Hz, 1H); 3.53 (d, NCH₂Ph-b, $J = 13.8$ Hz, 1H); 3.60 (ddd, H-2, $J = 10.3, 10.3, 4.7$ Hz, 1H); 3.81, 3.83 (2xs, 2xOCH₃, 6H); 4.17 (dd, H-3, $J = 8.4, 6.7$ Hz, 1H); 4.47 (d, OCH₂Ph-a, $J = 11.8$ Hz, 1H); 4.51 (d, OCH₂Ph-b, $J = 11.7$ Hz, 1H); 6.24 (dd, H-4, $J = 15.9, 6.4$ Hz, 1H); 6.74 (d, H-5, $J = 15.9$ Hz, 1H); 6.87 (d, H-Ar, $J = 8.7$ Hz, 2H); 6.95 (d, H-Ar, $J = 8.8$ Hz, 2H); 7.20-7.30 (m, 2xPh, 10H); 7.47 (d, H-Ar, $J = 8.8$ Hz, 2H); 7.61 (d, H-Ar, $J = 8.7$ Hz, 2H); relative to TMS ($\delta = 0$ ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 52.7, 53.5 (2xt, C-1, NCH₂Ph); 55.2, 55.3 (2xq, 2xOCH₃); 71.9 (d, C-3); 72.2 (t, OCH₂Ph); 82.1 (d, C-2); 113.9, 114.1 (4xd, C-Ar); 125.0 (d, C-4); 126.9, 127.4, 127.8, 127.9, 128.2, 128.3, 128.5 (14xd, C-Ar, 2xPh); 129.7 (s, C-Ar); 131.9 (d, C-5); 138.0, 138.7, 138.8 (3xs, C-Ar, 2xPh); 158.6, 159.2 (2xs, C-Ar); relative to CDCl₃ ($\delta = 77$ ppm).

IR (film on KBr): ν (cm⁻¹) = 3334, 2929, 1605, 1510, 1245, 1075, 1027, 696.

HRMS (ESI): Calcd. for C₃₃H₃₅NO₄ [M+H]⁺ 510.2639; found [M+H]⁺ 510.2587.

(2S)-(E)-1-(Benzylamino)-2-(benzyloxy)-3-tert-butyltrimethylsilyloxy-5-(4'-methoxyphenyl)pent-4-ene (126)**C₃₂H₄₂NO₃Si**MW: 517.77 g.mol⁻¹

A 10 mL round-bottom flask with stopcock equipped with condenser was flame-dried and flushed with argon. The flask was charged with the 4-bromoanisole (41 mg, 0.219 mmol), Pd(OAc)₂ (1 mg, 0.004 mmol), dpe-phos (4 mg, 0.007 mmol) and Cs₂CO₃ (137 mg, 0.419 mmol). The flask was purged with argon and the solution of substrate **125** (75 mg, 0.182 mmol) in dioxane (1.5 mL) was then added via syringe. The resulting mixture was heated to 100°C until the starting material was consumed (6 h). The reaction mixture was cooled to rt and saturated aqueous NH₄Cl (2 mL) and ethyl acetate (2 mL) were added. The layers were separated, the aqueous layer was extracted with ethyl acetate (3x5 mL) and the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product **126** was purified by flash chromatography (2.8 g of silica gel, acetone/hexanes 1:15 sat. with NH₃).

yield: 47 mg (50%)

R_f = 0.28 (acetone/hexanes 1:8 sat. with NH₃)diastereomeric ratio: ~ 1:1.2 (syn-**126** vs. anti-**126**)

yellow oil

¹H NMR (300 MHz, CDCl₃): δ (*anti*, ppm) = -0.01 (s, SiCH₃, 3H); 0.04 (s, SiCH₃, 3H); 0.90 (s, C(CH₃)₃, 9H); 2.68 (dd, H-1a, *J* = 12.3, 7.7 Hz, 1H); 2.82 (dd, H-1b, *J* = 12.5, 3.9 Hz, 1H); 3.62-3.66 (m, H-2, 1H); 3.73 (s, NCH₂Ph, 2H); 3.81 (s, OCH₃, 3H); 4.47 (dt, H-3, *J* = 5.3, 1.1 Hz, 1H); 4.56 (d, OCH₂Ph-a, *J* = 11.5 Hz, 1H); 4.77 (d, OCH₂Ph-b, *J* = 11.4 Hz, 1H); 6.10 (dd, H-4, *J* = 15.9, 5.8 Hz, 1H); 6.49 (d, H-5, *J* = 15.9 Hz, 1H); 6.86 (d, H-Ar, *J* = 8.8 Hz, 2H); 7.25-7.35 (m, H-Ar, 2xPh, 12H). δ (*syn*, ppm) = 0.06 (s, SiCH₃, 3H); 0.07 (s, SiCH₃, 3H); 0.90 (s, C(CH₃)₃, 9H); 2.77-2.81 (m, H-1, 2H); 3.60-3.64 (m, H-2, 1H); 3.70 (s, NCH₂Ph, 2H); 3.81 (s, OCH₃, 3H); 4.35-4.39 (m, H-3, 1H); 4.64 (d, OCH₂Ph-a, *J* = 11.7 Hz, 1H); 4.77 (d, OCH₂Ph-b, *J* = 11.7 Hz, 1H); 6.10 (dd, H-4, *J* = 15.9, 7.0 Hz, 1H); 6.49 (d, H-5, *J* = 15.9 Hz, 1H); 6.85 (d, H-Ar, *J* = 8.7 Hz, 2H); 7.25-7.35 (m, H-Ar, 2xPh, 12H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (*anti*, ppm) = -4.8 (q, SiCH₃); -4.1 (q, SiCH₃); 18.2 (s, C(CH₃)₃); 25.9 (3xq, C(CH₃)₃); 49.9 (t, C-1); 54.0 (t, NCH₂Ph); 55.3 (q, OCH₃); 73.2 (t,

OCH₂Ph); 75.2 (d, C-3); 82.6 (d, C-2); 113.9 (2xd, C-Ar); 126.8 (d, C-4); 126.8, 127.6, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4, 128.8 (12xd, C-Ar, 2xPh); 129.7 (s, C-Ar); 130.6 (d, C-5); 138.7, 140.4 (2xs, 2xPh); 159.1 (s, C-Ar). δ (*syn*, ppm) = -4.8 (q, SiCH₃); -4.5 (q, SiCH₃); 18.2 (s, C(CH₃)₃); 25.9 (3xq, C(CH₃)₃); 49.4 (t, C-1); 54.0 (t, NCH₂Ph); 55.3 (q, OCH₃); 73.2 (t, OCH₂Ph); 73.9 (d, C-3); 82.3 (d, C-2); 113.9 (2xd, C-Ar); 126.8 (d, C-4); 126.8, 127.6, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4, 128.8 (12xd, C-Ar, 2xPh); 129.8 (s, C-Ar); 130.0 (d, C-5); 138.6, 140.4 (2xs, 2xPh); 159.1 (s, C-Ar); relative to CDCl₃ (δ = 77 ppm).

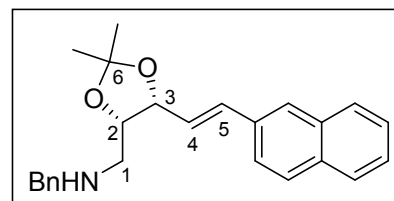
IR (film on KBr): ν (cm⁻¹) = 2927, 1606, 1510, 1245, 1028, 832, 734, 697.

HRMS (ESI): Calcd. for C₃₂H₄₂NO₃Si [M+2H]²⁺ 518.3085; found [M+2H]²⁺ 518.3064.

(2*S*,3*R*)-(E)-1-(Benzylamino)-2,3-*O*-isopropylidene-5-(naphthalene-2'-yl)pent-4-ene-2,3-diol (129)

C₂₅H₂₇NO₂

MW: 373.49 g.mol⁻¹



An oven-dried Schlenk tube was cooled under a stream of argon and charged with Pd(dba)₂ (28 mg, 0.049 mmol), dpe-phos (31 mg, 0.058 mmol), 2-bromonaphthalene (201 mg, 0.970 mmol) and cesium carbonate (237 mg, 0.728 mmol). The tube was purged with argon and the substrate **128** (120 mg, 0.485) in toluene (5 mL) was added. The reaction mixture was heated to reflux for 7 h, quenched with sat. NH₄Cl (2 mL) and diluted with ethyl acetate (10 mL). The aqueous phase was extracted with ethyl acetate, the organic phase was dried over MgSO₄ and concentrated *in vacuo*. The crude product **129** was purified by flash chromatography (10 g of silica gel, acetone/hexanes 1:4 with NH₃).

yield: 82 mg (49%)

R_f = 0.29 (acetone/hexanes 1:4 with NH₃)

m.p. = 114-116°C

yellow solid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.42 (s, CH₃, 3H); 1.54 (s, CH₃, 3H); 1.70 (bs, NH, 1H); 2.70 (dd, H-1a, *J* = 12.0, 4.4 Hz, 1H); 2.80 (dd, H-1b, *J* = 12.0, 8.2 Hz, 1H); 3.79 (s, NCH₂Ph, 2H); 4.43 (ddd, H-2, *J* = 8.1, 6.6, 4.4 Hz, 1H); 4.82 (t, H-3, *J* = 7.2 Hz, 1H); 6.29 (dd, H-4, *J* = 15.8, 7.9 Hz, 1H); 6.80 (d, H-5, *J* = 15.8 Hz, 1H); 7.23-7.28 (m, Ph, 5H); 7.43-

7.48 (m, Naph, 2H); 7.57 (dd, Naph, J = 8.6, 1.6 Hz, 1H); 7.72-7.74 (m, Naph, 1H); 7.77-7.82 (m, Naph, 3H); relative to TMS (δ = 0 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 25.5 (q, CH_3); 28.1 (q, CH_3); 49.6 (t, C-1); 54.0 (t, NCH_2Ph); 77.9, 78.7 (2xd, C-2, C-3); 108.7 (s, C-6); 123.6, 125.1, 126.0, 126.3, 126.7, 127.0, 127.6, 128.0, 128.1, 128.2, 128.4 (13xd, C-4, Ph, Naph); 133.1, 133.5 (2xs, Naph); 133.6 (d, C-5); 133.7 (s, Naph); 139.8 (s, Ph); relative to CDCl_3 (δ = 77 ppm).

IR (film on KBr): ν (cm^{-1}) = 3327, 2987, 2827, 1380, 1268, 1037, 973, 815, 743, 700.

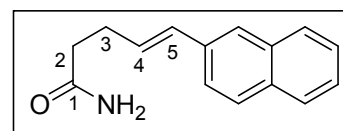
Specific rotation: $[\alpha]_{\text{D}}$ (20°C) = -10.2 (c 1.198, CHCl_3)

HRMS (ESI): Calcd. for $\text{C}_{25}\text{H}_{27}\text{NO}_2$ $[\text{M}+\text{H}]^+$ 374.2115; found $[\text{M}+\text{H}]^+$ 374.2105. Calcd. for $\text{C}_{25}\text{H}_{27}\text{NO}_2$ $[\text{M}+\text{Na}]^+$ 396.1934; found $[\text{M}+\text{Na}]^+$ 396.1923.

(*E*)-5-(Naphthalen-2'-yl)pent-4-enamide (**132**)

$\text{C}_{15}\text{H}_{15}\text{NO}$

MW: 225.29 $\text{g}\cdot\text{mol}^{-1}$



An oven-dried Schlenk tube was cooled under a stream of argon and charged with $\text{Pd}(\text{dba})_2$ (44 mg, 0.076 mmol), dpe-phos (57 mg, 0.106 mmol), 2-bromonaphthalene (376 mg, 1.82 mmol) and sodium *tert*-butanoate (218 mg, 2.27 mmol). The tube was purged with argon and the substrate **131** (150 mg, 1.51 mmol) in toluene (6 mL) was added. The reaction mixture was heated to reflux with stirring for 6.5 h. The reaction mixture was diluted with ethyl acetate (10 mL) and quenched with sat. NH_4Cl (2 mL). The aqueous phase was extracted with ethyl acetate, the organic phase was washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The crude product **132** was purified by flash chromatography (11 g of silica gel, ethyl acetate).

yield: 186 mg (55%)

R_f = 0.25 (AcOEt)

m.p. = 167-169°C

ochrous solid

^1H NMR (600 MHz, DMSO-d_6): δ (ppm) = 2.21 (t, H-2, J = 7.5 Hz, 2H); 2.40 (q, H-3, J = 7.2 Hz, 2H); 6.37 (td, H-4, J = 15.8, 6.7 Hz, 1H); 6.52 (d, H-5, J = 15.9 Hz, 1H); 6.73 (bs,

NH₂, 1H); 7.28 (bs, NH₂, 1H); 7.37-7.44 (m, Naph, 2H); 7.58 (dd, Naph, $J = 8.6, 1.3$ Hz, 1H); 7.71-7.72 (m, Naph, 1H); 7.77-7.80 (m, Naph, 3H); relative to TMS ($\delta = 0$ ppm).

¹³C NMR (75 MHz, DMSO-d₆): δ (ppm) = 28.5 (t, C-3); 34.7 (t, C-2); 123.4, 125.0, 125.6, 126.2, 127.4, 127.6, 127.9, 129.7, 130.4, 132.2, 133.2, 134.7 (3xs, 9xd, C-4, C-5, Naph); 173.4 (s, C-1); relative to DMSO-d₆ ($\delta = 39.43$ ppm).

IR (film on KBr): ν (cm⁻¹) = 3363, 3182, 3055, 2925, 1647, 1410, 962, 813, 739.

HRMS (ESI): Calcd. for C₁₅H₁₅NO [M+H]⁺ 226.1226; found [M+H]⁺ 226.1223. Calcd. for C₁₅H₁₅NO [M+Na]⁺ 248.1046; found [M+Na]⁺ 248.1041.

5.5. Intramolecular Pd(II)-catalyzed cyclization and coupling with potassium phenyltrifluoroborate

5.5.1. General procedures

General procedure A (catalytic)

An oven-dried Schlenk tube was cooled under a stream of argon and charged with PdCl₂ or Pd(OAc)₂ (0.1 equiv.), PhBF₃K (1.1-2 equiv.), reoxidant (1-3 equiv.) and eventually with a base (1-3 equiv.). The tube was re-flushed with argon and the solvent (5 mL/1 mmol of substrate) was added. Finally, the alcohol substrate (1 equiv.) in a solvent (5 mL/1 mmol of substrate) was added and the reaction mixture was stirred at appropriate temperature until the alcohol substrate was consumed as judged by TLC. The reaction mixture was either filtered through a pad of celite followed by washing of the filtrate with ethyl acetate or diluted with ethyl acetate, quenched with sat. aqueous NH₄Cl and extracted with ethyl acetate. After the concentration *in vacuo*, the crude products were separated by flash chromatography.

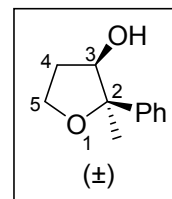
General procedure B (stoichiometric)

An oven-dried Schlenk tube was cooled under a stream of argon and charged with PdCl₂ (1 equiv.), PhBF₃K (2 equiv.) and with a base (3 equiv.). The tube was re-flushed with argon and the solvent (5 mL/1 mmol of substrate) was added. Finally, the alcohol substrate (1 equiv.) in a solvent (5 mL/1 mmol of substrate) was added and the reaction mixture was stirred at appropriate temperature until the alcohol substrate was consumed as judged by TLC. The reaction mixture was filtered through a pad of celite followed by washing of the filtrate with ethyl acetate and concentrated *in vacuo*. The crude products were purified by flash chromatography.

General procedure C (in ionic liquid)

An oven-dried Schlenk tube was cooled under a stream of argon and charged with PdCl₂ (0.1 equiv.), PhBF₃K (1.1-2 equiv.), reoxidant (3 equiv.), base (3 equiv.) and with the alcohol substrate (1 equiv.). The tube was re-flushed with argon and the ionic liquid (3.5 equiv.). The reaction mixture was stirred at rt temperature or under microwave heating until the alcohol substrate was consumed as judged by TLC. The reaction mixture was extracted with diethyl ether and concentrated *in vacuo*. The crude products were separated by flash chromatography.

5.5.2. Characterization data of synthesized compounds

(±)-2-Methyl-2-phenyltetrahydrofuran-3-ol (134)**C₁₁H₁₄O₂**MW: 178.23 g.mol⁻¹

A reaction of PdCl₂ (17 mg, 0.098 mmol), PhBF₃K (198 mg, 1.08 mmol) and *p*-benzoquinone (106 mg, 0.979 mmol) with the alcohol substrate (±)-**69a** (100 mg, 0.979 mmol) in CH₃CN-H₂O 1:1 (6 mL) following the general procedure A afforded in 2 h at rt the crude product **134** which was purified by flash chromatography (5.7 g of silica gel, ethyl acetate/hexanes 1:2).

yield: 93 mg (53%)

R_f = 0.59 (AcOEt/hexanes 1:2)

yellowish liquid

single diastereomer

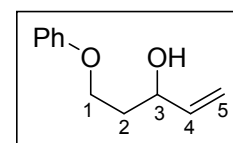
¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.63 (s, CH₃, 3H); 1.98-2.05 (m, H-4, 2H); 3.73-3.82 (m, H-5a, 1H); 3.93-3.99 (m, H-5b, 1H); 4.60-4.63 (m, H-3, 1H); 7.28-7.33 (m, Ph, 2H); 7.38-7.44 (m, Ph, 1H); 7.76 (dd, Ph, *J* = 8.0, 1.4 Hz, 2H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 24.0 (q, CH₃); 34.3 (t, C-4); 65.8 (t, C-5); 84.7 (d, C-3); 114.1 (s, C-2); 127.8 (2xd, Ph); 131.7 (d, Ph); 135.0 (2xd, Ph); relative to CDCl₃ (δ = 77 ppm).*

* Not all of the quaternary carbons are visible in the spectrum.

IR (film on KBr): ν (cm⁻¹) = 3442, 2990, 1601, 1355, 1104, 702, 644.

HRMS (ESI): Calcd. for C₁₁H₁₄O₂ [M+Na]⁺ 201.0885; found [M+Na]⁺ 201.0886.

(±)-1-Phenoxy-4-penten-3-ol (135)**C₁₁H₁₄O₂**MW: 178.23 g.mol⁻¹

A reaction of Pd(OAc)₂ (22 mg, 0.098 mmol), PhBF₃K (270 mg, 1.47 mmol), CuCl₂ (395 mg, 2.94 mmol) and AcONa (241 mg, 2.94 mmol) with the alcohol substrate **69a** (100

mg, 0.979 mmol) in tetrahydrofuran (8 mL) following the general procedure A afforded in 1 h at 65°C the crude product **135** which was purified by flash chromatography (2.5 g of silica gel, ethyl acetate/hexanes 1:1).

yield: 39 mg (22%)

R_f = 0.82 (AcOEt/hexanes 1:1)

colorless liquid

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.83-1.93 (m, H-2a, 1H); 2.11-2.18 (m, H-2b, 1H); 4.10-4.22 (m, H-1, 2H); 4.68-4.73 (m, H-3, 1H); 5.24 (dt, H-5a, J = 10.8, 1.4 Hz, 1H); 5.41 (dt, H-5b, J = 16.9, 1.4 Hz, 1H); 5.97 (ddd, H-4, J = 16.9, 10.8, 4.7 Hz, 1H); 7.33-7.45 (m, Ph, 3H); 7.84 (dd, Ph, J = 7.9, 1.4 Hz, 2H); relative to CDCl_3 (δ = 7.26 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 32.4 (t, C-2); 60.4 (t, C-1); 71.2 (d, C-3); 115.0 (t, C-5); 127.5 (2xd, Ph); 130.6 (d, Ph); 133.7 (2xd, Ph); 138.4 (d, C-4); 152.8 (s, Ph); relative to CDCl_3 (δ = 77 ppm).

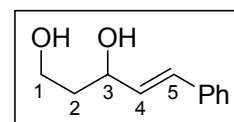
IR (film on NaCl): ν (cm^{-1}) = 3436, 2956, 1602, 1442, 1312, 1161, 701, 644.

HRMS (ESI): Calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_2$ $[\text{M}+\text{Na}]^+$ 201.0885; found $[\text{M}+\text{Na}]^+$ 201.0882.

(±)-(E)-5-Phenylpent-4-ene-1,3-diol (**136**)

$\text{C}_{11}\text{H}_{14}\text{O}_2$

MW: 178.23 $\text{g}\cdot\text{mol}^{-1}$



A reaction of PdCl_2 (206 mg, 1.47 mmol), PhBF_3K (270 mg, 1.47 mmol) and Cs_2CO_3 (1435 mg, 4.41 mmol) with the alcohol substrate **69a** (150 mg, 1.47 mmol) in THF- H_2O 10:1 (15 mL) following the general procedure B afforded in 15 min at 77°C the crude **136** as a side product which was purified by flash chromatography (3.5 g of silica gel, ethyl acetate/hexanes 1:3).

yield: 48 mg (18%)

R_f = 0.80 (AcOEt/hexanes 1:1)

colorless liquid

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.93-2.04 (m, H-2a, 1H); 2.17-2.25 (m, H-2b, 1H); 4.19-4.25 (m, H-1, 2H); 4.84-4.90 (m, H-3, 1H); 6.31 (dd, H-4, J = 15.9, 5.2 Hz, 1H); 6.73

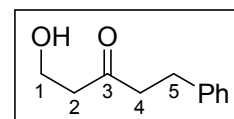
(dd, H-5, $J = 15.9, 0.9$ Hz, 1H); 7.31-7.45 (m, Ph, 3H); 7.87 (dd, Ph, $J = 7.9, 1.4$ Hz, 2H); relative to CDCl_3 ($\delta = 7.26$ ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 32.9 (t, C-2); 60.6 (t, C-1); 71.3 (d, C-3); 126.5 (d, C-4); 127.6 (2xd, Ph); 128.6 (d, C-5); 130.7 (d, Ph); 133.8 (2xd, Ph); 136.5 (s, Ph); relative to CDCl_3 ($\delta = 77$ ppm).

1-Hydroxy-5-phenylpentan-3-one (137)

$\text{C}_{11}\text{H}_{14}\text{O}_2$

MW: 178.23 g.mol $^{-1}$



Compound **137** was formed as a side product in the reaction of formation of undesired Heck product **136**.

yield: 18 mg (6%)

$R_f = 0.29$ (AcOEt/hexanes 1:1)

yellow liquid

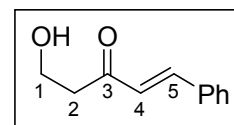
^1H NMR (300 MHz, CDCl_3): δ (ppm) = 2.25 (s, OH, 1H); 2.58 (t, H-2, $J = 5.4$ Hz, 2H); 2.68-2.73 (m, H-4, 2H); 2.82-2.87 (m, H-5, 2H); 3.77 (t, H-1, $J = 5.4$ Hz, 2H); 7.09-7.15 (m, Ph, 3H); 7.18-7.24 (m, Ph, 2H); relative to TMS ($\delta = 0$ ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 29.5 (t, C-5); 44.6 (t, C-2); 44.7 (t, C-4); 57.8 (t, C-1); 126.2 (d, Ph); 128.2 (2xd, Ph); 128.5 (2xd, Ph); 140.7 (s, Ph); 210.6 (s, CO); relative to CDCl_3 ($\delta = 77$ ppm).

(E)-1-Hydroxy-5-phenylpent-4-en-3-one (138)

$\text{C}_{11}\text{H}_{12}\text{O}_2$

MW: 176.21 g.mol $^{-1}$



Compound **138** was formed as a side product in the reaction of formation of undesired Heck product **136**.

yield: 18 mg (6%)

$R_f = 0.29$ (AcOEt/hexanes 1:1)

yellow liquid

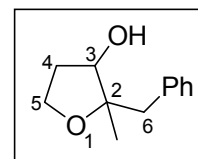
¹H NMR (300 MHz, CDCl₃): δ (ppm) = 2.25 (s, OH, 1H); 2.88 (t, H-2, J = 5.4 Hz, 2H); 3.89 (t, H-1, J = 5.4 Hz, 2H); 6.67 (d, H-4, J = 16.3 Hz, 1H); 7.33-7.35 (m, Ph, 3H); 7.47-7.49 (m, Ph, 2H); 7.51 (d, H-5, J = 16.4 Hz, 1H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 42.1 (t, C-2); 58.1 (t, C-1); 126.1 (d, C-4); 128.4 (2xd, Ph); 129.0 (2xd, Ph); 130.7 (d, Ph); 134.1 (s, Ph); 143.6 (d, C-5); 200.5 (s, CO); relative to CDCl₃ (δ = 77 ppm).

(±)-2-Benzyl-2-methyltetrahydrofuran-3-ol (139)

C₁₂H₁₆O₂

MW: 192.25 g.mol⁻¹



A reaction of PdCl₂ (183 mg, 1.03 mmol), PhBF₃K (190 mg, 1.03 mmol) and Cs₂CO₃ (1010 mg, 3.10 mmol) with the alcohol substrate **82** (120 mg, 1.03 mmol) in THF-H₂O 10:1 (11 mL) following the general procedure B afforded in 3 h at 77°C the mixture of products which was purified by flash chromatography (4.7 g of silica gel, ethyl acetate/hexanes 1:3). Tetrahydrofuran **139** was isolated as the minor product.

yield: 13 mg (7%)

R_f = 0.43 (AcOEt/hexanes 1:1)

orange liquid

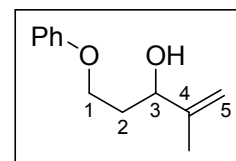
single diastereomer

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.93 (s, CH₃, 3H); 1.65 (bs, OH, 1H); 1.85 (dddd, H-4a, J = 13.2, 8.0, 4.8, 3.0 Hz, 1H); 2.29 (dddd, H-4b, J = 13.3, 9.1, 7.3, 6.0 Hz, 1H); 2.86 (s, H-6, 2H); 3.83 (ddd, H-5a, J = 8.9, 8.9, 4.9 Hz, 1H); 3.96 (dd, H-3, J = 5.7, 2.8 Hz, 1H); 4.01 (dt, H-5b, J = 8.4, 8.0 Hz, 1H); 7.14-7.26 (m, Ph, 5H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 22.8 (q, CH₃); 34.7 (t, C-4); 40.4 (t, C-6); 64.2 (t, C-5); 77.4 (d, C-3); 84.8 (s, C-2); 126.1, 128.1, 130.5 (5xd, Ph); 138.2 (s, Ph); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 3394, 3026, 2970, 2929, 2881, 1453, 1086, 1029, 700.

HRMS (ESI): Calcd. for C₁₂H₁₆O₂ [M+Na]⁺ 215.1043; found [M+Na]⁺ 215.1043.

(±)-4-Methyl-1-phenoxy-pent-4-en-3-ol (140)**C₁₂H₁₆O₂**MW: 192.25 g.mol⁻¹

A reaction of PdCl₂ (153 mg, 0.861 mmol), PhBF₃K (317 mg, 1.72 mmol) and AcONa (212 mg, 2.58 mmol) with the alcohol substrate **82** (100 mg, 0.979 mmol) in tetrahydrofuran (8 mL) following the general procedure B afforded in 30 min at 65°C the crude product **140** which was purified by flash chromatography (8 g of silica gel, ethyl acetate/hexanes 1:1).

yield: 118 mg (71%)

R_f = 0.92 (AcOEt/hexanes 1:1)

yellowish oil

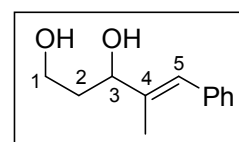
¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.82 (s, CH₃, 3H); 1.94 (dtd, H-2a, *J* = 13.9, 8.7, 5.2 Hz, 1H); 2.12 (dtd, H-2b, *J* = 14.1, 8.0, 3.8 Hz, 1H); 4.14-4.19 (m, H-1, 2H); 4.58 (dd, H-3, *J* = 8.7, 3.6 Hz, 1H); 4.97 (d, H-5a, *J* = 1.2 Hz, 1H); 5.11 (d, H-5b, *J* = 0.5 Hz, 1H); 7.33-7.46 (m, Ph, 3H); 7.83 (dd, Ph, *J* = 7.9, 1.5 Hz, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 18.4 (q, CH₃); 31.2 (t, C-2); 60.9 (t, C-1); 74.0 (d, C-3); 110.9 (t, C-5); 127.5 (2xd, Ph); 130.6 (d, Ph); 133.7 (2xd, Ph); 144.9 (s, C-4); relative to CDCl₃ (δ = 77 ppm).*

* Not all of the quaternary carbons are visible in the spectrum.

IR (film on NaCl): ν (cm⁻¹) = 3452, 2970, 1442, 1311, 1148, 700.

HRMS (ESI): Calcd. for C₁₁H₁₄O₂ [M+Na]⁺ 215.1043; found [M+Na]⁺ 215.1061.

(±)-(E)-4-Methyl-5-phenylpent-4-ene-1,3-diol (141)**C₁₂H₁₆O₂**MW: 192.25 g.mol⁻¹

Compound **141** was formed as a side product in the reaction of formation of tetrahydrofuran **139**.

yield: 15 mg (8%)

R_f = 0.15 (AcOEt/hexanes 1:1)

yellowish oil

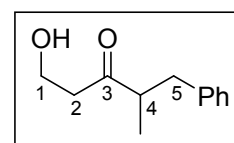
^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.77-1.83 (m, H-2, 2H); 1.80 (d, CH_3 , J = 1.3 Hz, 3H); 3.01 (bs, 2xOH, 2H); 3.77-3.81 (m, H-1, 2H); 4.33 (dd, H-3, J = 7.5, 4.8 Hz, 1H); 6.48 (s, H-5, 1H); 7.18-7.28 (m, Ph, 5H); relative to TMS (δ = 0 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 13.9 (q, CH_3); 36.7 (t, C-2); 61.3 (t, C-1); 77.4 (d, C-3); 125.1 (d, C-5); 126.4 (d, Ph); 128.1 (2xd, Ph); 128.9 (2xd, Ph); 137.4 (s, Ph); 140.0 (s, C-4); relative to CDCl_3 (δ = 77 ppm).

(\pm)-1-Hydroxy-4-methyl-5-phenylpentan-3-one (142)

$\text{C}_{12}\text{H}_{16}\text{O}_2$

MW: 192.25 $\text{g}\cdot\text{mol}^{-1}$



A reaction of PdCl_2 (23 mg, 0.130 mmol), PhBF_3K (265 mg, 1.44 mmol), CuCl_2 (528 mg, 3.93 mmol) and AcONa (360 mg, 3.93 mmol) with the alcohol substrate **82** (152 mg, 1.31 mmol) in $\text{THF-H}_2\text{O}$ 1:1 (10 mL) following the general procedure A afforded in 4 days at rt the crude product **142** which was purified by flash chromatography (5.9 g of silica gel, ethyl acetate/hexanes 1:3).

yield: 107 mg (43%)

R_f = 0.34 (AcOEt /hexanes 1:1)

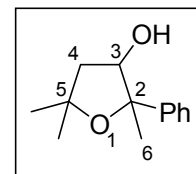
colorless oil

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.04 (d, CH_3 , J = 6.9 Hz, 3H); 2.43 (ddd, H-2a, J = 18.1, 5.9, 4.7 Hz, 1H); 2.52 (dd, H-5a, J = 13.3, 7.3 Hz, 1H); 2.62 (ddd, H-2b, J = 18.1, 6.3, 4.7 Hz, 1H); 2.78 (sx, H-4, J = 7.0 Hz, 1H); 2.92 (dd, H-5b, J = 13.3, 7.1 Hz, 1H); 3.70 (t, H-1, J = 4.7 Hz, 2H); 7.06-7.24 (m, Ph, 5H); relative to TMS (δ = 0 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 16.2 (q, CH_3); 38.9 (t, C-5); 43.5 (t, C-2); 48.4 (d, C-4); 57.7 (t, C-1); 126.3 (d, Ph); 128.4 (2xd, Ph); 128.8 (2xd, Ph); 139.3 (s, Ph); 215.0 (s, CO); relative to CDCl_3 (δ = 77 ppm).

IR (film on KBr): ν (cm^{-1}) = 3400, 3026, 2933, 1702, 1453, 1046, 743, 700.

HRMS (ESI): Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_2$ $[\text{M}+\text{H}]^+$ 193.1223; found $[\text{M}+\text{H}]^+$ 193.1223. Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_2$ $[\text{M}+\text{Na}]^+$ 215.1043; found $[\text{M}+\text{Na}]^+$ 215.1037.

(±)-2,5,5-Trimethyl-2-phenyltetrahydrofuran-3-ol (143)**C₁₃H₁₈O₂**MW: 206.28 g.mol⁻¹

A reaction of PdCl₂ (14 mg, 0.079 mmol), PhBF₃K (155 mg, 0.842 mmol), CuCl₂ (165 mg, 1.23 mmol) and AcONa (101 mg, 1.23 mmol) with the alcohol substrate **87** (100 mg, 0.768 mmol) in CH₃CN-H₂O 1:1 (6 mL) following the general procedure A afforded in 2 days at rt the crude product **143** which was purified by flash chromatography (6 g of silica gel, ethyl acetate/hexanes 1:3).

yield: 47 mg (30%)

R_f = 0.66 (AcOEt/hexanes 1:1)

yellow oil

single diastereomer

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.24, 1.25 (2xs, 2xCH₃, 6H); 1.60 (s, H-6, 3H); 2.00 (dd, H-4a, *J* = 14.2, 7.0 Hz, 1H); 2.15 (dd, H-4b, *J* = 14.2, 0.8 Hz, 1H); 4.68 (dd, H-3, *J* = 6.9, 0.8 Hz, 1H); 7.29-7.44 (m, Ph, 3H); 7.77 (dd, Ph, *J* = 8.0, 1.4 Hz, 2H); relative to TMS (δ = 0 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 25.8 (q, C-6); 28.7, 30.6 (2xq, 2xCH₃); 45.4 (t, C-4); 84.1 (d, C-3); 87.0 (s, C-5); 114.7 (s, C-2); 127.8 (2xd, Ph); 131.7 (d, Ph); 134.9 (2xd, Ph); relative to CDCl₃ (δ = 77 ppm).*

* Not all of the quaternary carbons are visible in the spectrum.

IR (film on KBr): ν (cm⁻¹) = 3323, 3237, 1643, 1062.

5.6. Intramolecular Pd(II)-catalyzed cyclization and coupling with iodobenzene diacetate

5.6.1. General procedure

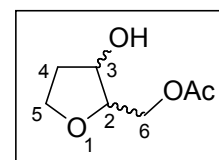
An oven-dried round-bottom flask with stopcock was cooled under a stream of argon and charged with $\text{Pd}(\text{OCOCF}_3)_2$ (0.05 equiv.), 1,3-bis(diphenylphosphino)propane (0.055 equiv.) and acetic acid (6.5 mL/1 mmol of substrate). The catalytic system was stirred at rt for 30 minutes. Then the alcohol substrate (1 equiv.) in acetic acid (3.5 mL/1 mmol of substrate) and $\text{PhI}(\text{OAc})_2$ (1.1 equiv.) were added. The reaction mixture was then stirred at rt until the alcohol substrate was consumed as judged by TLC. The reaction mixture was concentrated *in vacuo* and the crude product was purified by flash chromatography.

5.6.2. Characterization data of synthesized compounds

(±)-(3-Hydroxytetrahydrofuran-2-yl)methyl acetate¹⁴⁷ (**144**)

$\text{C}_7\text{H}_{12}\text{O}_4$

MW: 160.17 g.mol⁻¹



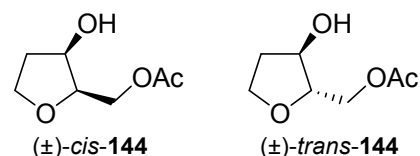
A reaction of $\text{Pd}(\text{OCOCF}_3)_2$ (24 mg, 0.073 mmol), 1,3-bis(diphenylphosphino)propane (33 mg, 0.081 mmol) and $\text{PhI}(\text{OAc})_2$ (520 mg, 1.61 mmol) with the alcohol substrate **69a** (150 mg, 1.47 mmol) in AcOH (15 mL) following the general procedure afforded in 20 h the crude product **144** (as a diastereomeric mixture of *cis*-**144** and *trans*-**144**) which was purified by flash chromatography (10 g of silica gel, ethyl acetate/hexanes 6:1). The major diastereomer was partially separated.

combined yield: 109 mg (46%)

R_f = 0.26 (AcOEt/hexanes 6:1)

diastereomeric ratio: ~ 4:1

yellowish oil



¹H NMR (300 MHz, acetone-d₆): δ (major, ppm) = 1.89 (dddd, H-4a, *J* = 13.1, 7.0, 4.2, 2.0 Hz, 1H); 2.00 (s, OAc, 3H); 2.07-2.19 (m, H-4b, 1H); 3.00 (bs, OH, 1H); 3.73 (ddd, H-5a, *J* = 8.6, 8.2, 4.2 Hz, 1H); 3.85 (ddd, H-2, *J* = 8.4, 7.2, 4.5 Hz, 1H); 3.96 (dt, H-5b, *J* = 8.2, 7.1 Hz,

¹⁴⁷ Koole, L. H.; van Genderen, M. H. P.; Buck, H. M. *J. Org. Chem.* **1988**, 53, 5266.

1H); 4.12 (dd, H-6a, $J = 11.5, 7.3$ Hz, 1H); 4.28 (dd, H-6b, $J = 11.5, 4.6$ Hz, 1H); 4.38-4.44 (m, H-3, 1H); relative to TMS ($\delta = 0$ ppm).

^{13}C NMR (75 MHz, acetone- d_6): δ (major, ppm) = 21.8 (q, CH_3); 37.4 (t, C-4); 65.3 (t, C-6); 67.6 (t, C-5); 73.1 (d, C-3); 81.9 (d, C-2); 172.1 (s, CO). δ (minor, ppm) = 21.9 (q, CH_3); 34.9 (t, C-4); 61.8 (t, C-6); 67.5 (t, C-5); 75.7 (d, C-3); 83.6 (d, C-2); 171.8 (s, CO); relative to acetone- d_6 ($\delta = 30.8$ ppm).

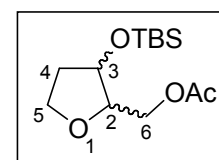
IR (film on KBr): ν (cm^{-1}) = 3412, 2951, 2884, 1734, 1233, 1039.

HRMS (ESI): Calcd. for $\text{C}_7\text{H}_{12}\text{O}_4$ $[\text{M}+\text{Na}]^+$ 183.0628; found $[\text{M}+\text{Na}]^+$ 183.0627.

(\pm)-(3-*tert*-Butyldimethylsilyloxytetrahydrofuran-2-yl)methyl acetate (145**)**

$\text{C}_{13}\text{H}_{26}\text{O}_4\text{Si}$

MW: 274.43 $\text{g}\cdot\text{mol}^{-1}$



A reaction of $\text{Pd}(\text{OCOCF}_3)_2$ (12 mg, 0.035 mmol), 1,3-bis(diphenylphosphino)propane (16 mg, 0.038 mmol) and $\text{PhI}(\text{OAc})_2$ (246 mg, 0.763 mmol) with the alcohol substrate **90** (150 mg, 0.693 mmol) in AcOH (7 mL) following the general procedure afforded in 18 h the crude product **145** which was purified by flash chromatography (6 g of silica gel, ethyl acetate/hexanes 1:8). The major diastereomer was partially separated.

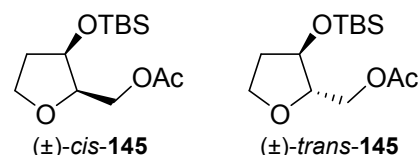
combined yield: 74 mg (39%)

R_f (major) = 0.50 (AcOEt/hexanes 1:4)

R_f (minor) = 0.56 (AcOEt/hexanes 1:4)

diastereomeric ratio: $\sim 3:1$

colorless oil



^1H NMR (300 MHz, acetone- d_6): δ (major, ppm) = 0.07 (s, $2\times\text{SiCH}_3$, 6H); 0.89 (s, $\text{C}(\text{CH}_3)_3$, 9H); 1.84 (dddd, H-4a, $J = 12.6, 5.4, 5.4, 3.7$ Hz, 1H); 1.99-2.06 (m, H-4b, 1H); 2.09 (s, OAc, 3H); 3.87 (ddd, H-2, $J = 5.9, 4.2, 4.2$ Hz, 1H); 3.96 (dd, H-5, $J = 8.3, 5.5$ Hz, 2H); 4.03 (dd, H-6a, $J = 11.6, 6.0$ Hz, 1H); 4.13 (dd, H-6b, $J = 11.6, 4.6$ Hz, 1H); 4.16 (dd, H-3, $J = 6.6, 3.6$ Hz, 1H); relative to TMS ($\delta = 0$ ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (major, ppm) = -4.9 (q, SiCH_3); -4.7 (q, SiCH_3); 17.9 (s, $\text{C}(\text{CH}_3)_3$); 20.9 (q, OAc); 25.7 ($3\times\text{q}$, $\text{C}(\text{CH}_3)_3$); 35.4 (t, C-4); 64.5 (t, C-6); 67.2 (t, C-5); 73.7 (d, C-3); 83.7 (d, C-2); 170.9 (s, CO). δ (minor, ppm) = -4.8 (q, SiCH_3); -3.6 (q, SiCH_3); 17.9

(s, C(CH₃)₃); 21.1 (q, OAc); 25.6 (3xq, C(CH₃)₃); 32.1 (t, C-4); 64.0 (t, C-6); 66.2 (t, C-5); 71.9 (d, C-3); 83.7 (d, C-2); 170.2 (s, CO); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 2953, 2929, 2857, 1744, 1231, 1116, 1041, 834, 775.

HRMS (ESI): Calcd. for C₁₃H₂₆O₄Si [M+Na]⁺ 297.1493; found [M+Na]⁺ 297.1484.

5.7. Asymmetric intramolecular Pd(II)-catalyzed oxycarbonylation of unsaturated diols

5.7.1. General procedure A (classical)

Chiral ligand (0.09 or 0.12 equiv.) and Pd(OAc)₂ (0.03 or 0.04 equiv.) were stirred in dichloromethane (0.5 mL) under argon atmosphere for 15 min. Resulting Pd-complex solution was transferred into a Schlenk tube and dichloromethane was removed *in vacuo*. The Pd-complex was dissolved in glacial acetic acid* and the solution of alcohol substrate **69a** (1 equiv.) and methyl benzoate (internal standard, 0.5 equiv.) in glacial acetic acid* was added. Finally, *p*-benzoquinone (0.5 or 0.75 equiv.) was added and the Schlenk tube was purged with CO from balloon (5x vacuum–CO cycle). The reaction mixture was vigorously stirred at room temperature until approx. 50% conversion of alcohol substrate **69a** as judged by GC. The reaction mixture was filtered through a short celite column and concentrated *in vacuo*. Both, enantiomerically enriched lactone **70a** and alcohol **69a** were separated by flash chromatography.

Concerning the screening of other reaction parameters, general procedure A was modified in respect of palladium salt, solvent, temperature, pressure and reoxidation system.

5.7.2. General procedure B (microwave activation)

Chiral ligand (0.09 equiv.) and Pd(OAc)₂ (0.03 equiv.) were stirred in dichloromethane (0.5 mL) under argon atmosphere for 15 min. Resulting Pd-complex solution was transferred into a Schlenk tube and dichloromethane was removed *in vacuo*. The Pd-complex was dissolved in glacial acetic acid** and the solution of alcohol substrate **69a** (1 equiv.) and methyl benzoate (internal standard, 0.5 equiv.) in glacial acetic acid** was added. Finally, *p*-benzoquinone (0.75 equiv.) was added and the reaction mixture was transferred into a special MW vessel which was purged with CO from balloon (5x vacuum–CO cycle). The reaction mixture was irradiated under corresponding microwave conditions (temperature, power, time) until approx. 50% conversion of alcohol substrate **69a** as judged by GC. The reaction mixture was filtered through a short celite column and concentrated *in vacuo*. Both, enantiomerically enriched lactone **70a** and alcohol **69a** were separated by flash chromatography.

*Overall concentration of **69a** in acetic acid at the beginning of reaction ranged between 0.2-1.0 mmol/mL.

Overall concentration of **69a in acetic acid at the beginning of reaction was 1.0 mmol/mL.

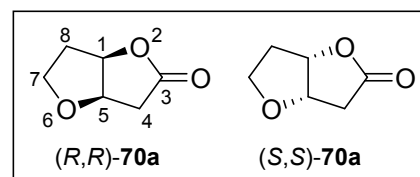
5.7.3. General procedure C (in ionic liquid)

Chiral ligand (0.12 equiv.) and Pd(OAc)₂ (0.04 equiv.) were stirred in dichloromethane (0.5 mL) under argon atmosphere for 15 min. Resulting Pd-complex solution was transferred into a Schlenk tube and dichloromethane was removed *in vacuo*. The mixture of alcohol substrate **69a** (1 equiv.), methyl benzoate (internal standard, 0.5 equiv.), ionic liquid (3 equiv.) and glacial acetic acid (3 equiv.) was then added to the solid Pd-complex. Finally, *p*-benzoquinone (0.5 equiv.) was added and the Schlenk tube was purged with CO from balloon (5x vacuum–CO cycle). The reaction mixture was vigorously stirred at room temperature until approx. 50% conversion of alcohol substrate **69a** as judged by GC. The reaction mixture was extracted with diethyl ether and combined extracts were concentrated *in vacuo*. Both, enantiomerically enriched lactone **70a** and alcohol substrate **69a** were separated by flash chromatography.

5.7.4. General procedure D (in ionic liquid under microwave activation)

Chiral ligand (0.12 equiv.) and Pd(OAc)₂ (0.04 equiv.) were stirred in dichloromethane (0.5 mL) under argon atmosphere for 15 minutes. Resulting Pd-complex solution was transferred into a Schlenk tube and dichloromethane was removed *in vacuo*. The mixture of alcohol substrate **69a** (1 equiv.), methyl benzoate (internal standard, 0.5 equiv.), ionic liquid (3 equiv.) and glacial acetic acid (3 equiv.) was then added to the solid Pd-complex. Finally, *p*-benzoquinone (0.5 equiv.) was added and the reaction mixture was transferred into a special MW vessel which was purged with CO from a balloon (5x vacuum–CO cycle). The reaction mixture was irradiated under corresponding microwave conditions (temperature, power, time) until approx. 50% conversion of alcohol substrate **69a** as judged by GC. The reaction mixture was extracted with diethyl ether and combined extracts were concentrated *in vacuo*. Both, enantiomerically enriched lactone **70a** and alcohol **69a** were separated by flash chromatography.

5.7.5. Characterization data of products

(*R,R*)- and (*S,S*)-2,6-Dioxabicyclo[3.3.0]octan-3-one⁵¹ (70a)**C₆H₈O₃**MW: 128.13 g.mol⁻¹

A reaction of Pd(OAc)₂ (3.4 mg, 0.015 mmol), {(3*aR*,8*aS*)-bis(8,8*a*-dihydro-3*aH*-indeno[1,2-*d*]oxazol-2-yl)}methane [(*R,S*)-indabox] (14.9 mg, 0.045 mmol), methyl benzoate as an internal standard (34.0 mg, 0.250 mmol) and *p*-benzoquinone (40.5 mg, 0.375 mmol) with the alcohol substrate **69a** (51.1 mg, 0.500 mmol) in glacial acetic acid (0.5 mL) following the general procedure A afforded in 24 h at 42% conversion of substrate **69a** the crude lactone **70a** which was purified by flash chromatography (3.8 g of silica gel, ethyl acetate/cyclohexane 1:3).

yield: 16.5 mg (26%)

enantiomeric excess: 57% (*R,R*)-**70a***R_f* = 0.50 (AcOEt/cyclohexane 3:1)

colorless liquid

¹H NMR (360 MHz, CDCl₃): δ (ppm) = 2.07-2.17 (m, H-8*a*, 1H); 2.24-2.31 (m, H-8*b*, 1H); 2.61 (d, H-4*a*, *J* = 18.7 Hz, 1H); 2.74 (dd, H-4*b*, *J* = 18.7, 6.1 Hz, 1H); 3.86-3.96 (m, H-7, 2H); 4.65 (ddd, H-5, *J* = 5.0, 5.0, 0.9 Hz, 1H); 5.08 (ddd, H-1, *J* = 4.7, 4.7, 0.9 Hz, 1H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 32.9 (t, C-8); 36.2 (t, C-4); 66.9 (t, C-7); 78.0 (d, C-5); 84.3 (d, C-1); 175.8 (s, C-3); relative to CDCl₃ (δ = 77 ppm).

IR (film on KBr): ν (cm⁻¹) = 2951, 2869, 1767, 1148, 1068, 1026.

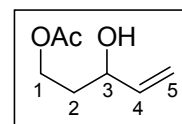
MS (EI): Calcd. for C₆H₈O₃ [M]⁺ 128.05; found [M]⁺ 128.0.

HRMS (ESI): Calcd. for C₆H₈O₃ [M+Na]⁺ 151.0366; found [M+Na]⁺ 151.0363.

Specific rotation:

(*R,R*)-**70a**: [α]_D (25°C) = +20 (c 0.098, CHCl₃) at 45% ee (lit.^{73a} +20, c 0.40, CH₃Cl, 45% ee);

(*S,S*)-**70a**: [α]_D (25°C) = -18 (c 0.038, CHCl₃) at 43% ee (lit.^{73a} -20, c 0.28, CH₃Cl, 45% ee).

(±)-1-Acetoxypent-4-en-3-ol (146)**C₇H₁₂O₃**MW: 144.17 g.mol⁻¹

Acetic acid (4 mL) was added to the alcohol substrate **69a** (170 mg, 1.66 mmol) and the solution was stirred for 13 days at rt with 40% conversion. Acetic acid was removed *in vacuo* and the product of primary hydroxyl group acetylation **146** was separated from the mixture by flash chromatography (8 g of silica gel, ethyl acetate-cyclohexane 1:4).

yield: 65 mg (27%)

 $R_f = 0.50$ (AcOEt/cyclohexane 1:1)

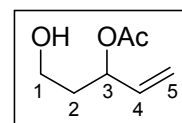
colorless liquid

¹H NMR (250 MHz, CDCl₃): δ (ppm) = 1.79-1.90 (m, H-2, 2H); 1.97 (d, OH, $J = 4.1$ Hz, 1H); 2.06 (s, CH₃, 3H); 4.10-4.19 (m, H-1a, 1H); 4.20-4.24 (m, H-3, 1H); 4.29 (ddd, H-1b, $J = 11.3, 7.6, 5.9$ Hz, 1H); 5.14 (ddd, H-5a, $J = 10.4, 1.2, 1.0$ Hz, 1H); 5.27 (ddd, H-5b, $J = 17.2, 1.2, 1.1$ Hz, 1H); 5.82 (ddd, H-4, $J = 17.2, 10.4, 6.0$ Hz, 1H); relative to CDCl₃ ($\delta = 7.26$ ppm).

¹³C NMR (62.5 MHz, CDCl₃): δ (ppm) = 20.9 (q, CH₃); 35.9 (t, C-2); 61.3 (t, C-1); 69.9 (d, C-3); 115.1 (t, C-5); 140.3 (d, C-4); 171.2 (s, CO); relative to CDCl₃ ($\delta = 77$ ppm).

IR (film on KBr): ν (cm⁻¹) = 3430, 2963, 1740, 1369, 1246, 1043.

HRMS (ESI): Calcd. for C₇H₁₂O₃ [M+Na]⁺ 167.0679; found [M+Na]⁺ 167.0681.

(±)-3-Acetoxypent-4-en-1-ol (147)**C₇H₁₂O₃**MW: 144.17 g.mol⁻¹

The acetylated product **147** was formed as a minor product in the reaction of formation of the acetate **146**.

yield: 12 mg (5%)

 $R_f = 0.34$ (AcOEt/cyclohexane 1:1)

colorless liquid

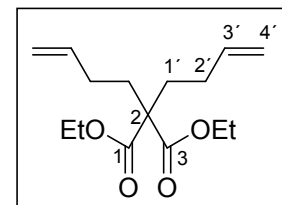
¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.68 (bs, OH, 1H); 1.78-1.92 (m, H-2, 2H); 2.10 (s, CH₃, 3H); 3.63 (dd, H-1a, $J = 8.2, 4.8$ Hz, 1H); 3.70 (dd, H-1b, $J = 11.3, 5.6$ Hz, 1H); 5.19

(ddd, H-5a, $J = 10.5, 1.2, 1.2$ Hz, 1H); 5.29 (ddd, H-5b, $J = 17.3, 1.3, 1.2$ Hz, 1H); 5.42-5.49 (m, H-3, 1H); 5.84 (ddd, H-4, $J = 17.3, 10.5, 6.2$ Hz, 1H); relative to CDCl_3 ($\delta = 7.26$ ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 20.9 (q, CH_3); 37.2 (t, C-2); 58.4 (t, C-1); 72.0 (d, C-3); 116.7 (t, C-5); 136.1 (d, C-4); 171.3 (s, CO); relative to CDCl_3 ($\delta = 77$ ppm).

IR (film on KBr): ν (cm^{-1}) = 3426, 2961, 2924, 2853, 1740, 1369, 1260, 1042.

HRMS (ESI): Calcd. for $\text{C}_7\text{H}_{12}\text{O}_3$ $[\text{M}+\text{Na}]^+$ 167.0679; found $[\text{M}+\text{Na}]^+$ 167.0677.

5.8. Synthesis of bis(isoxazoline) ligands**Diethyl 2,2-bis(but-3'-enyl)malonate¹³⁶ (148)****C₁₅H₂₄O₄**MW: 268.35 g.mol⁻¹

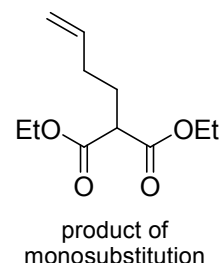
Diethyl malonate (2.73 g, 17 mmol) was added dropwise with stirring to a suspension of sodium hydride (0.68 g, 17 mmol) in dry DMF (10 mL). Stirring was continued until all NaH had reacted and then, 4-bromobut-1-ene (2.30 g, 17 mmol) was added dropwise. After addition, the solution was stirred for 30 min at rt. Then NaH (0.68 g, 17 mmol) was added again in portions, followed by 4-bromobut-1-ene (2.30 g, 17 mmol). After stirring at 80°C for 2 h, the reaction mixture was poured into a cold water (75 mL) and extracted with ether (3x 50 mL). The ether solution was washed with water and dried over MgSO₄. The solvent was removed *in vacuo* and the crude mixture was distilled under reduced pressure. The main fraction consisted in the desired product of disubstitution **148** and the product of monosubstitution in molar ratio 2:1 (determined from ¹H NMR). This inseparable mixture was used in subsequent reaction.

combined yield: 3.20 g

calculated yield (**148**): 2.29 g (50%)R_f (**148**) = 0.69 (AcOEt/cyclohexane 1:4)R_f (*mono*) = 0.56 (AcOEt/cyclohexane 1:4)

b.p. = 150°C / 20 mbar

colorless liquid



¹H NMR (300 MHz, CDCl₃): δ (**148**, ppm) = 1.23 (t, CH₃, J = 7.1 Hz, 6H); 1.95-2.01 (m, H-1', H-2', 8H); 4.17 (q, OCH₂, J = 7.1 Hz, 4H); 4.95 (dd, H-4'a, J = 10.2, 1.1 Hz, 2H); 5.02 (dd, H-4'b, J = 17.2, 1.4 Hz, 2H); 5.71-5.83 (m, H-3', 2H). δ (*mono*, ppm) = 1.25 (t, CH₃, J = 7.1 Hz, 6H); 1.99-2.12 (m, H-1', H-2', 4H); 3.34 (t, H-2, J = 7.3 Hz, 1H); 4.18 (q, OCH₂, J = 7.1 Hz, 4H); 4.98-5.06 (m, H-4', 2H); 5.69-5.81 (m, H-3', 1H); relative to CDCl₃ (δ = 7.26 ppm).

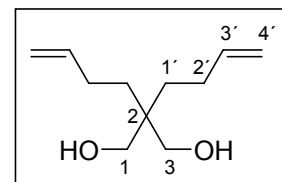
¹³C NMR (75 MHz, CDCl₃): δ (**148**, ppm) = 14.0 (2xq, CH₃); 28.3 (2xt, C-2'); 31.5 (2xt, C-1'); 57.0 (s, C-2); 61.1 (2xt, OCH₂); 114.9 (2xt, C-4'); 137.5 (2xd, C-3'); 171.4 (2xs, C-1,

C-3). δ (*mono*, ppm) = 14.0 (2xq, CH₃); 27.8 (t, C-1'); 31.3 (t, C-2'); 51.2 (d, C-2); 61.3 (2xt, OCH₂); 115.9 (t, C-4'); 136.8 (d, C-3'); 169.4 (2xs, C-1, C-3); relative to CDCl₃ (δ = 77 ppm).

2,2-Bis(but-3'-enyl)propane-1,3-diol¹³⁵ (**149**)

C₁₁H₂₀O₂

MW: 184.28 g.mol⁻¹



Lithiumaluminium hydride (0.68 g, 17.9 mmol) was added to a solution of the above-described mixture (3.20 g; 8.5 mmol of **148**, 4.3 mmol of monoproduct) in THF (40 mL) at 0°C and the reaction mixture was stirred for 8 h at rt. The suspension was cooled to 0°C, diluted with diethyl ether (40 mL) and Glauber salt (8 g) was slowly added. The mixture was filtered through a pad of celite, the filtrate was washed with dichloromethane and the solution was concentrated *in vacuo* to give a mixture of desired diol **149** and monosubstituted diol. The crude mixture was separated by flash chromatography (60 g of silica gel, ethyl acetate/cyclohexane 2:3).

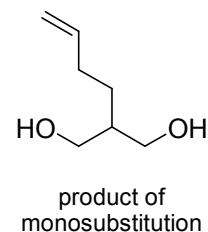
combined yield: 2.11 g

isolated yield (**149**): 1.20 g (77%)

R_f (**149**) = 0.66 (AcOEt/cyclohexane 2:1)

R_f (mono) = 0.30 (AcOEt/cyclohexane 2:1)

colorless liquid



¹H NMR (300 MHz, CDCl₃): δ (**149**, ppm) = 1.36-1.42 (m, H-1', 4H); 1.97-2.04 (m, H-2', 4H); 2.44 (s, OH, 2H); 3.58 (s, H-1, H-3, 4H); 4.95 (ddd, H-4'a, J = 10.2, 1.5, 1.4 Hz); 5.03 (ddd, H-4'b, J = 17.1, 1.6, 1.6 Hz); 5.82 (tdd, H-3', J = 17.1, 10.2, 6.5 Hz); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (**149**, ppm) = 27.3 (2xt, C-1'); 30.1 (2xt, C-2'); 41.1 (s, C-2); 68.7 (2xt, C-1, C-3); 114.4 (2xt, C-4'); 138.9 (2xd, C-3'); relative to CDCl₃ (δ = 77 ppm).

¹H NMR (300 MHz, CDCl₃): δ (*mono*, ppm) = 1.32-1.38 (m, H-1', 2H); 1.72-1.82 (m, H-2, 1H); 2.06-2.13 (m, H-2', 2H); 2.79 (s, OH, 2H); 3.64 (dd, H-1a, H-3a, J = 10.7, 7.4 Hz, 2H); 3.80 (dd, H-1b, H-3b, J = 10.7, 3.8 Hz, 2H); 4.96 (ddt, H-4'a, J = 10.1, 1.7, 1.4 Hz); 5.02 (ddt,

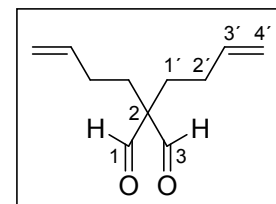
H-4'b, $J = 17.1, 1.7, 1.6$ Hz); 5.79 (tdd, H-3', $J = 17.1, 10.2, 6.6$ Hz); relative to CDCl_3 ($\delta = 7.26$ ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (mono, ppm) = 26.8 (t, C-1'); 31.2 (t, C-2'); 41.2 (s, C-2); 65.9 (2xt, C-1, C-3); 114.8 (t, C-4'); 138.3 (d, C-3'); relative to CDCl_3 ($\delta = 77$ ppm).

2,2-Bis(but-3'-enyl)malonaldehyde¹³⁵ (**150**)

$\text{C}_{11}\text{H}_{16}\text{O}_2$

MW: 180.24 g.mol⁻¹



A solution of DMSO (2.4 mL, 33.9 mmol) in dichloromethane (7 mL) was slowly added to a solution of oxalyl chloride (2.1 mL, 24.7 mmol) in dichloromethane (20 mL) at -78°C , and the reaction mixture was stirred for 30 min. Then, diol **149** (1.2 g, 6.5 mmol) in DCM (6 mL) was added at -78°C and the resulting milky solution was stirred for 30 min. To the above mixture was added triethylamine (8.2 mL, 58.6 mmol) at -78°C and the reaction mixture was stirred for 10 min at -78°C . The reaction mixture was allowed to warm to rt, diluted with DCM (10 mL) and stirred for 1.5 h. Then, sat. aqueous NH_4Cl (25 mL) was added and the reaction mixture was extracted with DCM (3x 20 mL), dried over MgSO_4 and concentrated *in vacuo*. The crude malonaldehyde **150** was directly used in the next reaction.

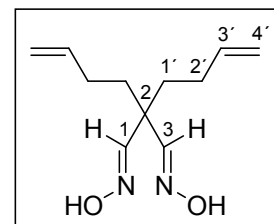
yield: 2.63 g

$R_f = 0.72$ (AcOEt/cyclohexane 1:4)

yellow slurry

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 1.89-2.02 (m, H-1', H-2', 8H); 4.99 (d, H-4'a, $J = 10.1$ Hz, 2H); 5.02 (d, H-4'b, $J = 17.1$ Hz, 2H); 5.66-5.79 (m, H-3', 2H); 9.74 (s, H-1, H-3, 2H); relative to CDCl_3 ($\delta = 7.26$ ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 28.1 (2xt, C-1'), 30.3 (2xt, C-2'); 64.7 (s, C-2); 116.0 (2xt, C-4'); 136.9 (2xd, C-3'); 201.3 (2xd, C-1, C-3); relative to CDCl_3 ($\delta = 77$ ppm).

2,2-Bis(but-3'-enyl)malonodioxime¹³⁵ (151)**C₁₁H₁₈N₂O₂**MW: 210.27 g.mol⁻¹

Hydroxylamine hydrochloride (1.8 g, 26.0 mmol) was added to the solution of crude malonaldehyde **150** (2.63 g) in pyridine (20 mL) at 0°C. The reaction mixture was stirred for 7 days at rt (additional 2 g of NH₂OH.HCl were added during the reaction; the conversion was controlled by ¹H and ¹³C NMR). The reaction mixture was diluted with ethyl acetate (150 mL), washed with 1N aq. HCl (80 mL) to remove pyridine, washed with sat. aq. NaHCO₃ (60 mL), brine (70 mL); dried over MgSO₄ and concentrated *in vacuo*. The crude malonodioxime **151** was purified by flash chromatography (60 g of silica gel, ethyl acetate/cyclohexane 1:4).

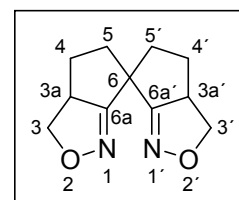
yield: 1.03 g (75% over two steps)

R_f = 0.36 (AcOEt/cyclohexane 1:3)

yellowish liquid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.75-1.79 (m, H-1', 4H); 2.01-2.08 (m, H-2', 4H); 4.97 (d, H-4'a, *J* = 10.2 Hz, 2H); 5.02 (dd, H-4'b, *J* = 17.1, 1.6 Hz, 2H); 5.71-5.84 (m, H-3', 2H); 7.43 (s, H-1, H-3, 2H); 7.60 (bs, OH, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 28.3 (2xt, C-1'); 35.3 (2xt, C-2'); 45.5 (s, C-2); 115.0 (2xt, C-4'); 137.8 (2xd, C-3'); 153.9 (2xd, C-1, C-3); relative to CDCl₃ (δ = 77 ppm).

3,3',3a,3a',4,4',5,5'-Octahydro-6,6'-spirobi[6*H*-cyclopent[*c*]isoxazole]¹³⁵ (H-SPRIX)**C₁₁H₁₄N₂O₂**MW: 184.28 g.mol⁻¹

Aqueous 12-15% sodium hypochlorite (7 mL) was added to a solution of malonodioxime **151** (1.03 g, 4.9 mmol) in dichloromethane (100 mL) at 0°C and stirred for 3 h at rt. The reaction was quenched by the addition of water, extracted with DCM, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The mixture of three diastereomers was separated by flash chromatography (30 g of silica gel, ethyl acetate/cyclohexane 1:3-2:1).

combined yield: 0.47 g (47%)

isolated yield (*M,S,S*-H-SPRIX): 200 mg (15%)

isolated yield (*M,S,R*-H-SPRIX): 130 mg (10%)

isolated yield (*M,R,R*-H-SPRIX): 80 mg (6%)

R_f (*M,S,S*-H-SPRIX) = 0.15 (AcOEt/cyclohexane 1:1)

R_f (*M,S,R*-H-SPRIX) = 0.41 (AcOEt/cyclohexane 1:1)

R_f (*M,R,R*-H-SPRIX) = 0.49 (AcOEt/cyclohexane 1:1)

white crystals

The enantiomers of (*M,S,S*)-H-SPRIX and (*M,S,R*)-H-SPRIX were separated by semipreparative supercritical fluid chromatography using Chiralpak IA column (150 bar, 15% MeOH in CO₂, 4 mL/min).

(*M,S,S*)-H-SPRIX:

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.71-1.84 (m, H-4A, H-4'A, 2H); 2.07-2.16 (m, H-4B, H-4'B, 2H); 2.18-2.29 (m, H-5A, H-5'A, 2H); 2.61 (dd, H-5B, H-5'B, J = 13.1, 7.2, 1.4 Hz, 2H); 3.76-3.95 (m, H-3a, H-3a', H-3A, H-3'A, 4H); 4.51-4.57 (m, H-3B, H-3'B, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 27.1 (2xt, C-4, C-4'); 40.5 (s, C-6); 44.0 (2xt, C-5, C-5'); 55.1 (2xd, C-3a, C-3a'); 75.0 (2xt, C-3, C-3'); 175.2 (C-6a, C-6a'); relative to CDCl₃ (δ = 77 ppm).

(*M,S,R*)-H-SPRIX:

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.52-1.81 (m, H-4A, H-4'A, 2H); 2.06-2.31 (m, H-4B, H-4'B, H-5A, H-5'A, 4H); 2.40-2.50 (m, H-5B, 1H); 2.83 (ddd, H-5'B, J = 13.3, 7.5, 1.7 Hz, 1H); 3.78-3.94 (m, H-3a, H-3A, H-3'A, 3H); 4.05-4.19 (m, H-3a', 1H); 4.25-4.62 (H-3B, H-3'B, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 24.9 (t, C-4); 27.3 (t, C-4'); 40.6 (t, C-5); 41.3 (t, C-5'); 41.4 (s, C-6); 53.1 (d, C-3a); 55.0 (d, C-3a'); 75.1 (t, C-3); 76.2 (t, C-3'); 171.8 (s, C-6a); 173.9 (s, C-6a'); relative to CDCl₃ (δ = 77 ppm).

(*M,R,R*)-H-SPRIX:

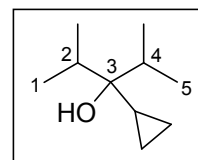
¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.47-1.61 (m, H-4A, H-4'A, 2H); 2.16-2.30 (m, H-4B, H-4'B, H-5A, H-5'A, 4H); 2.71-2.82 (m, H-5B, H-5'B, 2H); 3.85-3.96 (m, H-3a, H-3a', H-3A, H-3'A, 4H); 4.55-4.60 (m, H-3B, H-3'B, 2H); relative to CDCl₃ (δ = 7.26 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 26.3 (2xt, C-4, C-4'); 40.8 (s, C-6); 41.8 (2xt, C-5, C-5'); 53.8 (2xd, C-3a, C-3a'); 75.9 (2xt, C-3, C-3'); 172.8 (2xs, C-6a, C-6a'); relative to CDCl_3 ($\delta = 77$ ppm).

3-Cyclopropyl-2,4-dimethylpentan-3-ol^{71a} (**152**)

$\text{C}_{10}\text{H}_{20}\text{O}$

MW: 156.27 g.mol⁻¹



Magnesium turnings (0.86 g, 35.4 mmol; activated by I_2) in THF (5 mL) were treated with cyclopropyl bromide (5.0 g, 41.3 mmol) in THF (5 mL); the reaction was initiated by few drops and gentle heating followed by the discoloration of the solution. The reaction mixture was then heated to reflux for 30 min and THF (10 mL, at warm) was introduced. After cooling to rt, a solution of diisopropylketone (4.2 mL, 29.5 mmol) in THF (8 mL) was added dropwise. The reaction mixture was heated to reflux for 1.5 h, cooled to rt, and water was carefully introduced. The pH of the aqueous phase was adjusted to 3 with 4 N aq. HCl and the phases were separated. The aqueous phase was extracted with ethyl acetate, combined organic layers were washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The crude alcohol **152** was in the next step without further purification.

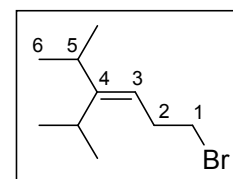
yield: 4.95 g

$R_f = 0.51$ (AcOEt/cyclohexane 1:9)

yellow liquid

^1H NMR (300 MHz, CDCl_3): δ (ppm) = 0.30-0.36 (m, CH_2CH_2 , 4H); 0.60-0.67 (m, CH, 1H); 0.72 (bs, OH, 1H); 0.95, 0.98 (2xd, $2\times\text{CH}_3$, H-1, H-5, $J = 6.9$ Hz, 12H); 1.97 (sep, H-2, H-4, $J = 6.9$ Hz, 2H); relative to CDCl_3 ($\delta = 7.26$ ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 0.1 (2xt, CH_2CH_2); 13.1 (d, CH); 17.5, 17.9 (4xq, $2\times\text{CH}_3$, C-1, C-5); 35.8 (2xd, C-2, C-4); 74.3 (s, C-3); relative to CDCl_3 ($\delta = 77$ ppm).

1-Bromo-4-isopropyl-5-methylhex-3-ene^{71a} (153)**C₁₀H₁₉Br**MW: 219.16 g.mol⁻¹

48% aq. HBr (10 mL) was added to the crude alcohol **152** (4.95 g) dropwise at 0°C. The solution was stirred for 2 h at rt and the reaction mixture was extracted with *n*-pentane. The organic layer was successively washed with brine, sat. aq. NaHCO₃, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by distillation under reduced pressure to give the bromide **153**.

yield: 4.22 g (65% over two steps)

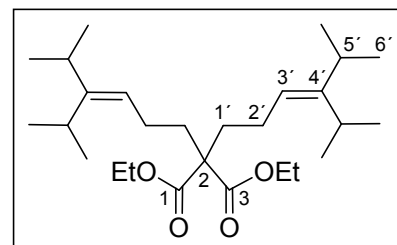
R_f = 0.84 (AcOEt/cyclohexane 1:9)

b.p. = 92°C / 8 mbar

colorless liquid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 1.01 (d, 3xCH₃, H-6, *J* = 7.0 Hz, 12H); 2.30 (sep, H-5, *J* = 6.8 Hz, 1H); 2.61 (q, H-2, *J* = 7.4 Hz, 2H); 2.76 (sep, CH, *J* = 7.0 Hz, 1H); 3.32 (t, H-1, *J* = 7.4 Hz, 2H); 5.10 (t, H-3, *J* = 7.3 Hz, 1H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 21.1, 24.5 (4xq, 3xCH₃, C-6); 28.7 (t, C-2); 29.5, 31.0 (2xd, C-5, CH); 33.1 (t, C-1); 117.4 (d, C-3); 155.0 (s, C-4); relative to CDCl₃ (δ = 77 ppm).

Diethyl 2,2-bis(4'-isopropyl-5'-methylhex-3'-enyl)malonate^{71a} (154)**C₂₇H₄₈O₄**MW: 436.67 g.mol⁻¹

Diethyl malonate (1.62 g, 10.1 mmol) was added dropwise with stirring to a suspension of sodium hydride (405 mg, 10.1 mmol) in dry DMF (10 mL). Stirring was continued until all NaH had reacted and then bromide **153** (2.22 g, 10.1 mmol) was added dropwise. After addition, the solution was stirred for 3 h at rt. Then NaH (405 mg, 10.1

mmol) was added again in portions, followed by the addition of bromide **153** (2.22 g, 10.1 mmol). After the stirring at 80°C for 2 h, the reaction mixture was poured into a cold water (75 mL) and extracted with diethyl ether (3x 50 mL). The ether solution was washed with water and dried over MgSO₄. The solvent was removed *in vacuo* and the crude reaction mixture, containing malonate **154** and the product of monosubstitution, was separated by flash chromatography (75 g of silica gel, AcOEt/cyclohexane 1:50).

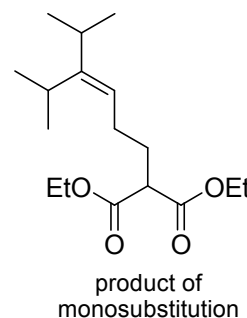
yield (**154**): 2.68 g (61%)

yield (mono): 0.51 g (17%)

R_f (**154**) = 0.38 (AcOEt/cyclohexane 1:20)

R_f (mono) = 0.26 (AcOEt/cyclohexane 1:20)

colorless oil



Compound **154**:

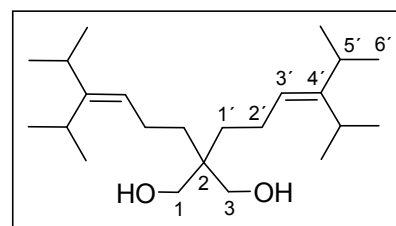
¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.98 (d, H-6', H-6'', 6xCH₃, *J* = 6.9 Hz, 24H); 1.25 (t, 2xCH₃CH₂O, *J* = 7.1 Hz, 6H); 1.89-1.91 (m, H-1', H-1'', H-2', H-2'', 8H); 2.26, 2.71 (2x sep, H-5', H-5'', 2xCH, *J* = 6.9 Hz, 4H); 4.19 (q, 2xCH₃CH₂O, *J* = 7.1 Hz, 4H); 5.04-5.11 (m, H-3', H-3'', 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 14.1 (2xq, 2xCH₃CH₂O); 21.2 (4xq, C-6', C-6'', 2xCH₃); 22.0 (2xt, C-2', C-2''); 24.5 (4xq, 4xCH₃); 28.8, 29.3 (4xd, C-5', C-5'', 2xCH); 32.7 (2xt, C-1', C-1''); 57.4 (s, C-2); 61.0 (2xt, 2xCH₃CH₂O); 119.8 (2xd, C-3', C-3''); 152.1 (2xs, C-4', C-4''); 171.8 (2xs, C-1, C-3); relative to CDCl₃ (δ = 77 ppm).

Product of monosubstitution:

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.98, 0.99 (2xd, C-6', 3xCH₃, *J* = 6.9 Hz, 12H); 1.26 (t, 2xCH₃CH₂O, *J* = 7.1 Hz, 6H); 1.92 (q, H-1', *J* = 7.3 Hz, 2H), 2.08 (q, H-2', *J* = 7.1 Hz, 2H); 2.27, 2.72 (2xsep, H-5', CH, *J* = 6.9 Hz, 2H); 3.32 (t, H-2, *J* = 7.3 Hz, 1H); 4.19 (q, 2xCH₃CH₂O, *J* = 7.0 Hz, 4H); 5.06 (t, H-3', *J* = 7.1 Hz, 1H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 14.0 (2xq, 2xCH₃CH₂O); 21.1, 24.5 (4xq, C-6', 3xCH₃); 24.9 (t, C-2'); 28.6 (t, C-1'); 29.2 (2xd, C-5', CH); 51.4 (d, C-2); 61.2 (2xt, 2xCH₃CH₂O); 119.1 (d, C-3'); 153.1 (s, C-4'); 169.5 (2xs, C-1, C-3); relative to CDCl₃ (δ = 77 ppm).

2,2-Bis(4'-isopropyl-5'-methylhex-3'-enyl)propane-1,3-diol^{71a} (155)**C₂₃H₄₄O₂**MW: 352.59 g.mol⁻¹

Lithiumaluminium hydride (202 mg, 5.31 mmol) was added to a solution of malonate **154** (1.16 g, 2.66 mmol) in dry THF (15 mL) at 0°C and the reaction mixture was stirred at rt for 6 h. After the dilution with diethyl ether, Galuber salt (2 g) was added at 0°C and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through a pad of celite, the celite was washed with diethyl ether and the filtrate was concentrated to give the crude diol **155** which was used in the next step without further purification.

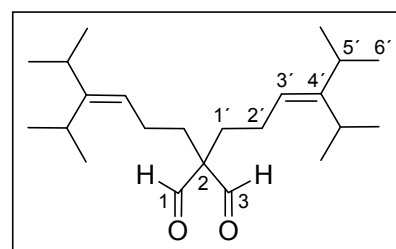
yield: 0.93 g (99%)

 $R_f = 0.49$ (AcOEt/cyclohexane 1:2)

white solid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.99, 1.00 (2xd, C-6', C-6'', 6xCH₃, $J = 6.9$ Hz, 24H); 1.29-1.34 (m, H-1', H-1'', 4H); 1.95-2.03 (m, H-2', H-2'', 4H); 2.27 (sep, H-5', H-5'', $J = 6.8$ Hz, 2H); 2.35 (bs, OH, 2H); 2.78 (sep, 2xCH, $J = 6.9$ Hz, 2H); 3.60 (s, H-1, H-3, 4H); 5.09 (t, H-3', H-3'', $J = 7.1$ Hz, 2H); relative to CDCl₃ ($\delta = 7.26$ ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 20.9 (2xt, C-2', C-2''); 21.3, 24.5 (8xq, C-6', C-6'', 6xCH₃); 28.6, 29.4 (4xd, C-5', C-5'', 2xCH); 31.5 (2xt, C-1', C-1''); 41.4 (s, C-2); 69.2 (2xt, C-1, C-3); 121.0 (2xd, C-3', C-3''); 151.6 (2xs, C-4', C-4''); relative to CDCl₃ ($\delta = 77$ ppm).

2,2-Bis(4'-isopropyl-5'-methylhex-3'-enyl)malonaldehyde^{71a} (156)**C₂₃H₄₀O₂**MW: 348.56 g.mol⁻¹

A solution of DMSO (3.2 mL, 45.7 mmol) in dichloromethane (10 mL) was slowly added to a solution of oxalyl chloride (2.8 mL, 33.4 mmol) in dichloromethane (40 mL) at

-78°C and the reaction mixture was stirred for 30 min. Then, diol **155** (2.92 g, 8.28 mmol) in DCM (15 mL) was added at -78°C and resulting milky solution was stirred for 30 min. To the above mixture was added triethylamine (11.0 mL, 79.1 mmol) at -78°C and the reaction mixture was stirred for 30 min at -78°C. Then the temperature was allowed to increase to rt and the reaction mixture was stirred for 2.5 h. Then, sat. aq. NH₄Cl (75 mL) was added, the layers were separated and the water phase was extracted with dichloromethane. After the washing with water to eliminate Et₃N.HCl, combined organic layers were dried over MgSO₄ and concentrated *in vacuo* to give the crude malonaldehyde **156** which was directly used in the next reaction.

yield: 3.0 g

R_f = 0.80 (AcOEt/cyclohexane 1:8)

yellow liquid

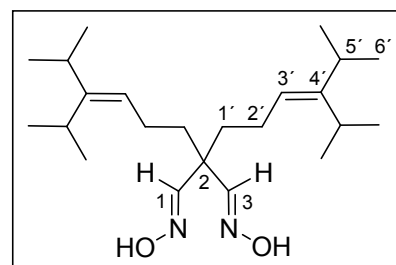
¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.97 (2xd, C-6', C-6'', 6xCH₃, *J* = 7.0 Hz, 24H); 1.83-1.88 (m, H-1', H-1'', 4H); 1.95-2.04 (m, H-2', H-2'', 4H); 2.26, 2.68 (2xsep, H-5', H-5'', 2xCH, *J* = 6.9 Hz, 4H); 5.00 (t, H-3', H-3'', *J* = 7.0 Hz, 2H); 9.75 (s, H-1, H-3, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 21.0 (4xq, C-6', C-6'', 2xCH₃); 22.0 (2xt, C-2', C-2''); 24.4 (4xq, 4xCH₃); 28.5, 29.4 (4xd, C-5', C-5'', 2xCH); 31.9 (2xt, C-1', C-1''); 65.1 (s, C-2); 119.3 (d, C-3', C-3''); 153.2 (2xs, C-4', C-4''); 201.8 (2xd, C-1, C-3); relative to CDCl₃ (δ = 77 ppm).

2,2-Bis(4'-isopropyl-5'-methylhex-3'-enyl)malonodioxime^{71a} (**157**)

C₂₃H₄₂N₂O₂

MW: 378.59 g.mol⁻¹



Hydroxylamine hydrochloride (3.2 g, 33.1 mmol) was added to the solution of crude malonaldehyde **156** (3.0 g) in pyridine (30 mL) at 0°C. The reaction mixture was stirred for 17 days at rt (additional 9 g of NH₂OH.HCl were added during the reaction period; the conversion was monitored by ¹H and ¹³C NMR). The reaction mixture was diluted with ethyl

acetate (100 mL), successively washed with 1N aq. HCl (50 mL) to remove pyridine, washed with sat. aq. NaHCO₃ (50 mL) and brine (50 mL); dried over MgSO₄ and concentrated *in vacuo*. The crude malonodioxime **157** was purified by flash chromatography (80 g of silica gel, ethyl acetate/cyclohexane 1:15).

yield: 2.15 g (69%, over two steps)

R_f = 0.19 (AcOEt/cyclohexane 1:9)

white solid

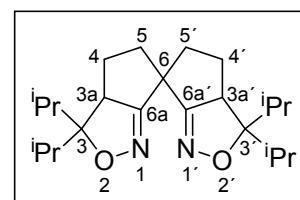
¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.98 (d, C-6', C-6'', 6xCH₃, *J* = 6.9 Hz, 24H); 1.66-1.72 (m, H-1', H-1'', 4H); 2.00-2.07 (m, H-2', H-2'', 4H); 2.25, 2.73 (2xsep, C-5', C-5'', 2xCH, *J* = 6.9 Hz, 4H); 5.03 (t, H-3', H-3'', *J* = 7.1 Hz, 2H); 7.44 (s, H-1, H-3, 2H); 8.17 (bs, OH, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 21.2 (4xq, C-6', C-6'', 2xCH₃); 21.9 (2xt, C-2', C-2''); 24.5 (4xq, 4xCH₃); 28.6, 29.3 (4xd, C-5', C-5'', 2xCH); 36.5 (2xt, C-1', C-1''); 45.8 (s, C-2); 120.1 (2xd, C-3', C-3''); 152.1 (2xs, C-4', C-4''); 154.2 (2xd, C-1, C-3); relative to CDCl₃ (δ = 77 ppm).

3,3',3a,3a',4,4',5,5'-Octahydro-3,3,3',3'-tetraisopropyl-6,6'-spirobi[6*H*-cyclopent[*c*]isoxazole]^{71a} (iPr-SPRIX)

C₁₇H₂₄N₂O₂

MW: 288.38 g.mol⁻¹



Aqueous 12-15% sodium hypochlorite (7 mL) was added to a solution of malonodioxime **157** (2.10 g, 5.55 mmol) in dichloromethane (100 mL) at 0°C and stirred for 3 days at rt. The reaction was quenched by the addition of water, extracted with DCM, washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The mixture of three diastereomers was partially separated by flash chromatography (50 g of silica gel, DCM/MeOH 300:1).

combined yield: 0.88 g (42%)

R_f = 0.34-0.41 (AcOEt/hexane 1:8)

yellowish solid

The separation of enantiomers by semi preparative SFC using several chiral stationary phases was not successful.

(*M,S,S*)-ⁱPr-SPRIX:

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.88, 0.91, 0.97, 1.03 (4xd, 8xCH₃, J = 6.8 Hz, 24H); 1.69-1.76 (m, H-4A, H-4'A, 2H); 1.83-2.26 (m, H-4B, H-4'B, H-5A, H-5'A, 4xCH, 8H); 2.49-2.55 (m, H-5B, H-5'B, 2H); 3.62 (dd, H-3a, H-3a', J = 11.7, 7.6 Hz, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 17.7, 18.2, 18.6, 18.7 (8xq, 8xCH₃); 23.9 (2xt, C-4, C-4'); 31.0, 31.3 (4xd, 4xCH); 40.5 (s, C-6); 44.4 (2xt, C-5, C-5'); 56.6 (2xd, C-3a, C-3a'); 95.4 (2xs, C-3, C-3'); 172.8 (2xs, C-6a, C-6a'); relative to CDCl₃ (δ = 77 ppm).

(*M,S,R*)-ⁱPr-SPRIX and (*M,R,R*)-ⁱPr-SPRIX:

¹H NMR (300 MHz, CDCl₃): δ (*M,S,R*; ppm) = 0.82-1.01 (4xd, 8xCH₃, J = 6.8 Hz, 24H); 1.80-1.92 (m, H-4, H-4', H-5A, H-5'A, 6H); 2.16-2.31 (m, 4xCH, 4H); 2.66-2.82 (m, H-5B, H-5'B, 2H); 3.69 (dd, H-3a, J = 11.5, 7.9 Hz, 1H); 4.01 (t, H-3a', J = 9.4 Hz, 1H). δ (*M,R,R*; ppm) = 0.82-1.01 (4xd, 8xCH₃, J = 6.8 Hz, 24H); 1.67-1.92 (m, H-4, H-4', H-5A, 5H); 2.03-2.45 (m, H-5'A, H-5B, 4xCH, 6H); 2.71-2.81 (m, H-5'B, 1H); 3.77 (t, H-3a, H-3a', J = 9.7 Hz, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (*M,S,R*; ppm) = 17.0, 17.6, 17.8, 17.8, 18.0, 18.4, 18.9 (8xq, 8xCH₃); 20.3, 23.7 (2xt, C-4, C-4'); 31.1, 31.5, 31.6, 31.8 (4xd, 4xCH); 40.2, 40.9 (2xt, C-5, C-5'); 42.4 (s, C-6); 53.1, 56.1 (2xd, C-3a, C-3a'); 95.7, 96.9 (2xs, C-3, C-3'); 169.6, 172.1 (2xs, C-6a, C-6a'). δ (*M,R,R*; ppm) = 17.3, 17.9, 18.2; 18.8 (8xq, 8xCH₃); 21.8 (2xt, C-4, C-4'); 31.7, 31.8 (4xd, 4xCH); 41.9 (2xt, C-5, C-5'); 42.4 (s, C-6); 54.5 (2xd, C-3a, C-3a'); 96.7 (2xs, C-3, C-3'); 171.0 (2xs, C-6a, C-6a'); relative to CDCl₃ (δ = 77 ppm).

5.9. Preparation of ionic liquids

5.9.1. Imidazolium-based IL

General procedure¹⁴³

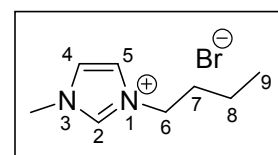
A mixture of 1-methylimidazole or 1,2-dimethylimidazole (1 equiv.) and 1-bromoalkane (1 equiv.) was irradiated by microwaves under corresponding conditions (specified for each compound, step A). Appropriate alkaline salt (1 equiv.) was added and the resulting mixture was irradiated under microwaves for additional period (step B). The reaction mixture was cooled to rt and dichloromethane was added. After filtration, the solvent was removed, the crude product was washed with diethyl or diisopropyl ether, concentrated *in vacuo* and used without further purification.

Characterization data

1-Butyl-3-methylimidazolium bromide ([Bmim]Br)

$C_8H_{15}BrN_2$

MW: 219.12 g.mol⁻¹



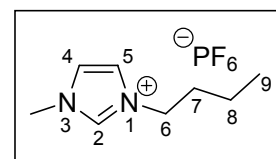
A reaction of 1-methylimidazole (821 mg, 10 mmol) and 1-bromobutane (1.37 g, 10 mmol) under MW irradiation (90°C, 8 min) following the general procedure (step A) afforded the crude **[Bmim]Br** which was washed with diethyl ether and concentrated *in vacuo*.

yield: 2.04 g (93%)

yellowish viscous liquid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.93 (t, H-9, J = 7.3 Hz, 3H); 1.36 (sx, H-8, J = 7.3 Hz, 2H); 1.89 (qi, H-7, J = 7.6 Hz, 2H); 4.11 (s, CH₃, 3H); 4.33 (t, H-6, J = 7.4 Hz, 2H); 7.56, 7.69 (2xt, H-4, H-5, J = 1.8, 1.8 Hz, 2H); 10.29 (s, H-2, 1H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 13.2 (q, C-9); 19.2 (t, C-8); 31.9 (t, C-7); 36.4 (q, CH₃); 49.5 (t, C-6); 122.0, 123.5 (2xd, C-4, C-5); 136.9 (d, C-2); relative to CDCl₃ (δ = 77 ppm).

1-Butyl-3-methylimidazolium hexafluorophosphate ([Bmim]PF₆)**C₈H₁₅F₆N₂P**MW: 284.18 g.mol⁻¹

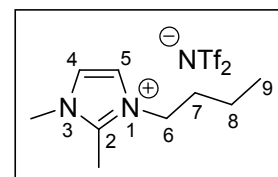
A reaction of 1-methylimidazole (1.23 mg, 15 mmol) and 1-bromobutane (2.06 g, 15 mmol) under MW irradiation (90°C, 8 min), followed by the addition of potassium hexafluorophosphate (2.76 g, 15 mmol) and MW irradiation (100°C, 15 min) following the general procedure afforded the crude [Bmim]PF₆ which was washed with diethyl ether and concentrated *in vacuo*.

yield: 3.32 g (78%)

yellowish viscous liquid

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.93 (t, H-9, *J* = 7.4 Hz, 3H); 1.35 (sx, H-8, *J* = 7.4 Hz, 2H); 1.82-1.92 (m, H-7, 2H); 4.03 (s, CH₃, 3H); 4.26 (t, H-6, *J* = 7.4 Hz, 2H); 7.45, 7.51 (2xt, H-4, H-5, *J* = 1.8, 1.8 Hz, 2H); 9.68 (s, H-2, 1H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 13.2 (q, C-9); 19.2 (t, C-8); 31.8 (t, C-7); 36.3 (q, CH₃); 49.6 (t, C-6); 122.0, 123.5 (2xd, C-4, C-5); 136.5 (d, C-2); relative to CDCl₃ (δ = 77 ppm).

1-Butyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide ([Bmmim]NTf₂)**C₁₁H₁₇F₆N₃O₄S₂**MW: 433.39 g.mol⁻¹

A reaction of 1,2-dimethylimidazole (480 mg, 5 mmol) and 1-bromobutane (685 mg, 5 mmol) under MW irradiation (90°C, 15 min) followed by the addition of lithium bis(trifluoromethylsulfonyl)imide (1435 mg, 5 mmol) and MW irradiation (100°C, 15 min) following the general procedure afforded the crude [Bmmim]NTf₂ which was washed with diethyl ether and concentrated *in vacuo*.

yield: 1.82 g (84%)

yellowish liquid

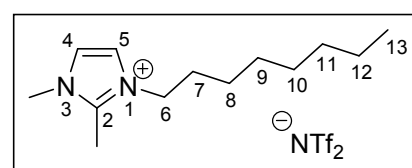
¹H NMR (250 MHz, CDCl₃): δ (ppm) = 0.95 (t, H-9, J = 7.4 Hz, 3H); 1.36 (sx, H-8, J = 7.3 Hz, 2H); 1.71-1.83 (m, H-7, 2H); 2.59 (s, CH₃, 3H); 3.79 (s, NCH₃, 3H); 4.03 (t, H-6, J = 7.5 Hz, 2H); 7.16, 7.20 (2xd, H-4, H-5, J = 2.2, 2.2 Hz, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (62.5 MHz, CDCl₃): δ (ppm) = 9.5 (q, CH₃); 13.3 (q, C-9); 19.5 (t, C-8); 31.4 (t, C-7); 35.3 (q, NCH₃); 48.6 (t, C-6); 120.8, 122.5 (2xd, C-4, C-5); 143.7 (s, C-2); relative to CDCl₃ (δ = 77 ppm).

¹⁹F NMR (235 MHz, CDCl₃): δ (ppm) = -79.04 (CF₃); relative to CFCl₃ (0 ppm).

1-Octyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide ([Ommim]NTf₂)

C₁₅H₂₅F₆N₃O₄S₂
MW: 489.50 g.mol⁻¹



A reaction of 1,2-dimethylimidazole (480 mg, 5 mmol) and 1-bromooctane (966 mg, 5 mmol) under MW irradiation (120°C, 10 min) followed by the addition of lithium bis(trifluoromethylsulfonyl)imide (1435 mg, 5 mmol) and MW irradiation (120°C, 15 min) following the general procedure afforded the crude [Ommim]NTf₂ which was washed with diethyl ether (partially soluble) and concentrated *in vacuo*.

yield: 2.07 g (85%)

slightly yellowish liquid

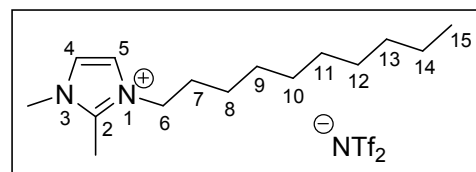
¹H NMR (250 MHz, CDCl₃): δ (ppm) = 0.86 (t, H-13, J = 7.0 Hz, 3H); 1.22-1.33 (m, H-8, H-9, H-10, H-11, H-12, 10H); 1.71-1.83 (m, H-7, 2H); 2.58 (s, CH₃, 3H); 3.78 (s, NCH₃, 3H); 4.02 (t, H-6, J = 7.5 Hz, 2H); 7.15, 7.20 (2xd, H-4, H-5, J = 2.2, 2.1 Hz, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 9.5 (q, CH₃); 13.9 (q, C-13); 22.5, 26.2, 28.8, 28.9, 29.5, 31.6 (6xt, C-7,8,9,10,11,12); 35.2 (q, C-6); 48.8 (t, C-6); 120.7, 122.5 (2xd, C-4, C-5); 143.6 (s, C-2); relative to CDCl₃ (δ = 77 ppm).

¹⁹F NMR (235 MHz, CDCl₃): δ (ppm) = -79.03 (CF₃); relative to CFCl₃ (0 ppm).

1-Decyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide ([Dmmim]NTf₂)

C₁₇H₂₉F₆N₃O₄S₂
 MW: 517.55 g.mol⁻¹



A reaction of 1,2-dimethylimidazole (480 mg, 5 mmol) and 1-bromodecane (1106 mg, 5 mmol) under MW irradiation (130°C, 10 min) followed by the addition of lithium bis(trifluoromethylsulfonyl)imide (1435 mg, 5 mmol) and MW irradiation (130°C, 10 min) following the general procedure afforded the crude [Dmmim]NTf₂ which was washed with diisopropyl ether (soluble in Et₂O) and concentrated *in vacuo*.

yield: 2.07 g (80%)

yellowish liquid

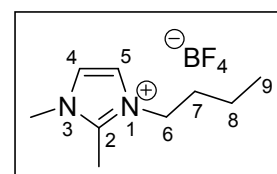
¹H NMR (300 MHz, CDCl₃): δ (ppm) = 0.87 (t, H-15, *J* = 6.9 Hz, 3H); 1.23-1.33 (m, H-8, H-9, H-10, H-11, H-12, H-13, H-14, 14H); 1.73-1.83 (m, H-7, 2H); 2.59 (s, CH₃, 3H); 3.79 (s, NCH₃, 3H); 4.02 (t, H-6, *J* = 7.5 Hz, 2H); 7.16, 7.21 (2xd, H-4, H-5, *J* = 2.2, 2.1 Hz, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 9.6 (q, CH₃); 14.0 (q, C-15); 22.6, 26.3, 28.9, 29.2, 29.3, 29.4, 29.5, 31.8 (8xt, C-7,8,9,10,11,12,13,14); 35.3 (q, NCH₃); 48.8 (t, C-6); 120.7, 122.5 (2xd, C-4, C-5); 143.6 (s, C-2); relative to CDCl₃ (δ = 77 ppm).

¹⁹F NMR (235 MHz, CDCl₃): δ (ppm) = -79.03 (CF₃); relative to CFCl₃ (0 ppm).

1-Butyl-2,3-dimethylimidazolium tetrafluoroborate ([Bmmim]BF₄)

C₉H₁₇BF₄N₂
 MW: 240.05 g.mol⁻¹



A reaction of 1,2-dimethylimidazole (480 mg, 5 mmol) and 1-bromobutane (685 mg, 5 mmol) under MW irradiation (90°C, 15 min) followed by the addition of sodium tetrafluoroborate (549 mg, 5 mmol) and MW irradiation (100°C, 15 min) following the general procedure afforded the crude [Bmmim]BF₄ which was washed with diethyl ether and concentrated *in vacuo*.

yield: 518 mg (43%)

yellowish solid

^1H NMR (250 MHz, CDCl_3): δ (ppm) = 0.94 (t, H-9, J = 7.3 Hz, 3H); 1.38 (sx, H-8, J = 7.3 Hz, 2H); 1.73-1.85 (m, H-7, 2H); 2.76 (s, CH_3 , 3H); 3.97 (s, NCH_3 , 3H); 4.19 (t, H-6, J = 7.3 Hz, 2H); 7.48, 7.66 (2xd, H-4, H-5, J = 2.1, 2.1 Hz, 2H); relative to CDCl_3 (δ = 7.26 ppm).

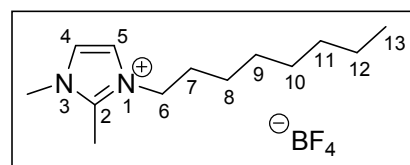
^{13}C NMR (62.5 MHz, CDCl_3): δ (ppm) = 10.5 (q, CH_3); 13.4 (q, C-9); 19.5 (t, C-8); 31.6 (t, C-7); 35.9 (q, NCH_3); 48.6 (t, C-6); 121.0, 122.9 (2xd, C-4, C-5); 143.6 (s, C-2); relative to CDCl_3 (δ = 77 ppm).

^{19}F NMR (235 MHz, CDCl_3): δ (ppm) = -152.63 (BF_4); relative to CFCl_3 (0 ppm).

1-Octyl-2,3-dimethylimidazolium tetrafluoroborate ([Ommim] BF_4)

$\text{C}_{13}\text{H}_{25}\text{BF}_4\text{N}_2$

MW: 296.16 g.mol $^{-1}$



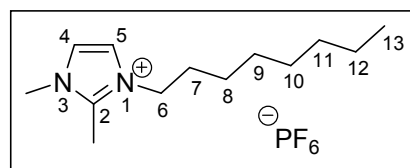
A reaction of 1,2-dimethylimidazole (480 mg, 5 mmol) and 1-bromooctane (966 mg, 5 mmol) under MW irradiation (120°C, 10 min) followed by the addition of sodium tetrafluoroborate (549 mg, 5 mmol) and MW irradiation (120°C, 10 min) following the general procedure afforded the crude [Ommim] BF_4 which was washed with diethyl ether and concentrated *in vacuo*.

yield: 1.27 g (86%)

yellowish very viscous liquid which solidified after several weeks of standing

^1H NMR (250 MHz, CDCl_3): δ (ppm) = 0.86 (t, H-13, J = 6.9 Hz, 3H); 1.22-1.34 (m, H-8, H-9, H-10, H-11, H-12, 10H); 1.75-1.85 (m, H-7, 2H); 2.78 (s, CH_3 , 3H); 4.00 (s, NCH_3 , 3H); 4.18 (t, H-6, J = 7.5 Hz, 2H); 7.46, 7.71 (2xd, H-4, H-5, J = 2.1, 2.1 Hz, 2H); relative to CDCl_3 (δ = 7.26 ppm).

^{13}C NMR (75 MHz, CDCl_3): δ (ppm) = 10.7 (q, CH_3); 13.9 (q, C-13); 22.4, 26.2, 28.8, 28.9, 29.7, 31.5 (6xt, C-7,8,9,10,11,12); 36.0 (q, NCH_3); 48.9 (t, C-6); 120.9, 123.0 (2xd, C-4, C-5); 143.6 (s, C-2); relative to CDCl_3 (δ = 77 ppm).

1-Octyl-2,3-dimethylimidazolium hexafluorophosphate ([Ommim]PF₆)**C₁₃H₂₅F₆N₂P**MW: 354.32 g.mol⁻¹

A reaction of 1,2-dimethylimidazole (480 mg, 5 mmol) and 1-bromooctane (966 mg, 5 mmol) under MW irradiation (120°C, 10 min) followed by the addition of potassium hexafluorophosphate (920 mg, 5 mmol) and MW irradiation (120°C, 10 min) following the general procedure afforded the crude [Ommim]PF₆ which was washed with diethyl ether and concentrated *in vacuo*.

yield: 1.18 g (67%)

very viscous brown liquid

¹H NMR (250 MHz, CDCl₃): δ (ppm) = 0.86 (t, H-13, *J* = 6.9 Hz, 3H); 1.21-1.34 (m, H-8, H-9, H-10, H-11, H-12, 10H); 1.75-1.84 (m, H-7, 2H); 2.72 (s, CH₃, 3H); 3.94 (s, NCH₃, 3H); 4.13 (t, H-6, *J* = 7.5 Hz, 2H); 7.39, 7.58 (2xd, H-4, H-5, *J* = 2.0, 2.0 Hz, 2H); relative to CDCl₃ (δ = 7.26 ppm).

¹³C NMR (75 MHz, CDCl₃): δ (ppm) = 10.3 (q, CH₃); 13.9 (q, C-13); 22.4, 26.2, 28.8, 28.9, 29.7, 31.5 (6xt, C-7,8,9,10,11,12); 35.7 (q, NCH₃); 48.8 (t, C-6); 120.9, 122.9 (2xd, C-4, C-5); 143.6 (s, C-2); relative to CDCl₃ (δ = 77 ppm).

¹⁹F NMR (235 MHz, CDCl₃): δ (ppm) = -71.61, -74.64 (PF₆); relative to CFCl₃ (0 ppm).

6. CONCLUSION

6.1. Intramolecular Pd(II)-catalyzed cyclization and coupling reaction

In order to study the domino intramolecular Pd-catalyzed cyclization and coupling reaction, a series of model substrates, involving free alkenediols **69a**, **82** and **87**; α -protected alkenediols **90** and **91**; acetonide-protected alkenetriols **99**, **106** and **107**; *N*-protected γ -amino alkenols **121**, **125** and **128**; and pent-4-enamide **131** was prepared.

Wacker-type cyclization and coupling reaction with alkenes under classical bicyclization conditions ($\text{PdCl}_2/\text{CuCl}_2/\text{AcONa}/\text{AcOH}$) did not proceed; the employment of Semmelhack's reoxidation conditions (CuCl/O_2) using $\text{Pd}(\text{OAc})_2$ in DMF led to the isolation of desired tetrahydrofuran product **83** as the mixture of diastereo- and geometric isomers, and the bicyclic structures **84** and **85** as the products of domino reaction: Intramolecular Pd(II)-catalyzed cyclization, Heck reaction and second intramolecular Pd(II)-catalyzed cyclization with excellent *cis*-selectivity, however, in low yield.

The protection of free α -hydroxyl group appeared to be crucial for successful realization of domino Pd(II)-catalyzed cyclization and coupling with aryl halides in the synthesis of tetrahydrofurans using basic conditions ($\text{Pd}(\text{dba})_2/\text{dpe-phos}^t/\text{BuONa}/\text{THF}$). While pent-4-ene-1,3-diol **69a** afforded the desired product **86** at most in 15% yield with poor diastereoselectivity (4:3), the α -*tert*-butyldimethylsilyl-protection considerably increased the yields (up to 53%) and provided better selectivities (up to 5:1). In both cases, 2,3-*cis*-disubstituted tetrahydrofurans were formed as the major products, which was in contrast with the results reported for analogous 3-alkyl/arylsubstituted γ -hydroxy alkenes. Acetonide-protected substrate **99** gave the corresponding tetrahydrofurans in 66-72% yield with similar diastereoselectivity (up to 3:1), again favoring the *cis*-isomers. The reaction of alkenetriols **106** and **107** afforded appropriate 2,3,4,5-tetrasubstituted tetrahydrofuran products (46-70%) with excellent 2,5-*trans*-diastereoselectivity (>19:1). The C-1 substituent showed the significant impact on stereocontrol of the reaction, additional C-2 and C-3 ether substituents had no effect on the selectivity. Therefore, intramolecular Pd(II)-catalyzed cyclization of C-1 substituted protected alkene polyols and coupling with aryl halides can be used for synthetic planning.

Domino palladium(II)-catalyzed cyclization of *N*-benzyl γ -amino alcohol **121** and coupling with 4-bromoanisole in mild conditions ($\text{Pd}(\text{OAc})_2/\text{dpe-phos}/\text{Cs}_2\text{CO}_3/\text{dioxane}$) provided pyrrolidine **122** (leading to natural (-)-anisomycin) in 10% yield as the single diastereomer; the product of Heck vinylation was formed as the major compound. The protection of free α -hydroxyl group as well as the use of acetone-protected *N*-benzyl γ -amino alcohol **128** did not improve the yield of desired pyrrolidine; moreover, the Heck products were formed exclusively.

The attempts to develop a new strategy employing potassium organotrifluoroborates as the coupling partners represented a challenging task. When alkenediols **69a** and **87** with unsubstituted terminal double bond were cyclized and coupled with potassium phenyltrifluoroborate, the unexpected cyclization products **134** and **143** were isolated in 17-53% yield as the single 2,3-*cis*-diastereoisomers. The reaction of the substrate **82**, which cannot be transformed into above-mentioned untypical cyclized structure due to methyl substitution on the double bond, afforded the desired tetrahydrofuran **139** in 7% yield when stoichiometric palladium with Cs_2CO_3 were used. The main undesired products observed in these transformations were ethers formed by *O*-arylation, Heck products and ketones formed by insertion of double bond into the Pd–C bond followed by β -hydride elimination.

Intramolecular Pd(II)-catalyzed cyclization and Pd(IV)/Pd(II)-catalyzed C–O coupling methodology utilizing $\text{PhI}(\text{OAc})_2$ led to desired tetrahydrofuran products **144** and **145** in 29-46% yield exhibiting moderate diastereoselectivity.

6.2. Asymmetric intramolecular Pd(II)-catalyzed oxycarbonylative bicyclization

Palladium-catalyzed cyclization of unsaturated alcohols and amines accompanied by the insertion of carbon monoxide is considered to be one of the most interesting and synthetically useful carbonylation reactions. Based on previous results of our research group in asymmetric palladium(II)-catalyzed oxycarbonylation, a more extensive ligand screening was performed. Generally, palladium(II)-complexes with C_2 -symmetric bis(oxazoline) ligands were proven to be the most suitable catalysts for studied kinetic resolution process. The catalysts with sulphur-containing ligands such as dibenzothiophene bis(oxazolines)

(DBT-box), dibenzothiophene oxazolines (DBT-mox) and benzothiophene oxazolines (BT-mox) showed moderate to good catalytic activity without chemo- and enantiocontrolling ability. Similarly, Pd(II)-salts with (*S,S*)-DACH-pyridyl Trost ligand and binaphthyl derived bis(imines) did catalyze the oxycarbonylation but were unselective. Bidentate phosphorus-containing ligands, such as (*R,R*)-DACH-phenyl Trost ligands, phosphoramidites or bisphosphines significantly misbehaved in this catalytic system. The best results concerning the kinetic resolution of (\pm)-**69a** were reached in conditions using Pd(OAc)₂-{(*S,R*)-indabox (**L-3**)} providing enantioenriched lactone (*S,S*)-**70a** (22% yield, 61% ee) and with Pd(OAc)₂-{(*R,S*)-indabox (**L-2**)} giving (*R,R*)-**70a** (26% yield, 57% ee).

It is notable that the use of Pd-H-SPRIX complexes efficiently promoted the reaction. The 50% conversion of the racemic diol (\pm)-**69a** was reached with both enantiomers **L-10** and **L-11** in about 1 hour (contrary to usual 1-3 days), albeit with low enantioselectivity. The attempts to find an alternative solvent, which would allow carrying out the reaction at low temperature and possibly increasing the level of asymmetric induction, were not successful.

An alternative reoxidation system using iron phthalocyanine and hydroquinone in catalytic amount under O₂ atmosphere was found to be potentially usable; nevertheless, it was again compatible mostly with bis(oxazoline) ligands. In the case of phosphorus-containing ligands, a really well-working reoxidant was not found. Glacial acetic acid represents the key component to accomplish the asymmetric oxycarbonylation, but on the other hand, it leads to the formation of undesired substrate acylation product **146**. It was found that the utilization of acetic acid-water (1:2) solvent mixture markedly decreased the amount of the byproduct **146**. Surprisingly, the reaction carried out under 10 bar CO pressure was neither significantly faster nor more chemoselective.

In order to improve the kinetic resolution of diol (\pm)-**69a** by asymmetric Pd(II)-catalyzed oxycarbonylation, the influence of imidazolium- and pyridinium-based ionic liquids was evaluated. The experiments performed in pure ionic liquids afforded only traces of lactone **70a**. A crucial improvement occurred, when 1:1 mixture of ionic liquid and acetic acid was employed. The reaction of (\pm)-**69a** using Pd(OAc)₂/**L-1** (pybox) catalytic system, 0.5 equiv. of *p*-benzoquinone reoxidant, 3 equiv. of 1-alkyl-3-methylimidazolium-based ionic liquid and 3 equiv. of acetic acid under carbon monoxide atmosphere afforded lactone

(*S,S*)-**70a** with enantioselectivities up to 80% ee. To the best of our knowledge, this is the first example of the use of ionic liquids as reaction media in the asymmetric Pd(II)-catalyzed oxycarbonylation.

No correlation between different *N*-alkyl substituents of IL and enantioselectivity was observed; the ionic liquids with trifluoromethanesulfonate anionic part were proven to be absolutely inappropriate for desired transformation. The reactions carried out in imidazolium-type ionic liquids missing C-2 hydrogen resulted in both, low conversion and enantioselectivity. This fact was most probably caused due to loss of hydrogen-bonding ability, playing an important role in the reaction mechanism. Microwave irradiation of the reaction mixture exhibited expected rate enhancement and diminished the reaction time from several days to 2 hours.

REFERENCES

1. (a) Malleron, J.-L.; Fiaud, J.-C.; Legros, J.-Y. *Handbook of Palladium-Catalyzed Organic Reactions*, Academic Press, London, 1997. (b) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley: Hoboken, NJ, 2002. (c) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453. (d) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981.
2. (a) Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Rüttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176. (b) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *Angew. Chem., Int. Ed.* **1962**, *1*, 80. (c) Jira, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9034.
3. For reviews see: (a) Takacs, J. M.; Jiang, X. *Curr. Org. Chem.* **2003**, *7*, 369. (b) Cornell, C. N.; Sigman, M. S. *Inorg. Chem.* **2007**, *46*, 1903. (c) Muzart, J. *Tetrahedron* **2007**, *63*, 7505. (d) Keith, J. A.; Henry, P. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9038.
4. Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.
5. (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed.* **1993**, *32*, 131. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006.
6. Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.
7. (a) Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456. (b) Prestat, G.; Poli, G. *Chemtracts - Org. Chem.* **2004**, *17*, 97. (c) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365.
8. Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1.
9. (a) Corey, E. J.; Russey, W. E.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1966**, *88*, 4750. (b) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1991**, *113*, 4025. (c) Corey, E. J.; Virgil, S. C.; Sarshar, S. *J. Am. Chem. Soc.* **1991**, *113*, 8171. (d) Corey, E. J.; Virgil, S. C.; Liu, D. R.; Sarshar, S. *J. Am. Chem. Soc.* **1992**, *114*, 1524.
10. (a) Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762.; *ibid.* **1917**, *111*, 876. (b) Schöpf, C.; Lehmann, G.; Arnold, W. *Angew. Chem.* **1937**, *50*, 779.
11. For reviews see: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (b) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.
12. Hosokawa, T.; Maeda, K.; Koga, K.; Moritani, I. *Tetrahedron Lett.* **1973**, *10*, 739.
13. Murahashi, S.-I.; Hosokawa, T. *Acc. Chem. Res.* **1990**, *23*, 49.
14. (a) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318. (b) Hosokawa, T.; Okuda, C.; Murahashi, S.-I. *J. Org. Chem.* **1985**, *50*, 1282.
15. (a) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063. (b) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 5071.
16. (a) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778. (b) Wang, F.; Zhang, Y. J.; Yang, G.; Zhang, W. *Tetrahedron Lett.* **2007**, *48*, 4179. (c) Zhang, Y. J.; Wang, F.; Zhang, W. *J. Org. Chem.* **2007**, *72*, 9208. (d) Takenaka, K.; Tanigaki, Y.; Patil, M. L.; Rao, C. V. L.; Takizawa, S.; Suzuki, T.; Sasai, H. *Tetrahedron: Asymmetry* **2010**, *21*, 767. (e) Takenaka, K.; Mohanata, S. C.; Patil, M. L.; Rao, C. V. L.; Takizawa, S.; Suzuki, T.; Sasai, H. *Org. Lett.* **2010**, *12*, 3480.
17. Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett.* **1993**, *34*, 7205.
18. (a) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035. (b) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496. (c) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925. (d) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483.

19. (a) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257. (b) Tietze, L. F.; Stecker, F.; Zinngrebe, J.; Sommer, K. *Chem. Eur. J.* **2006**, *12*, 8770.
20. Tietze, L. F.; Spiegl, D. A.; Stecker, F.; Major, J.; Raith, C.; Große, C. *Chem. Eur. J.* **2008**, *14*, 8956.
21. Turner, W. B. *J. Chem. Soc. Perkin Trans. I* **1978**, 1621.
22. For reviews see: (a) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (b) Wolfe, J. P. *Synlett* **2008**, 2913.
23. (a) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620. (b) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099. (c) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468. (d) Hay, M. B.; Wolfe, J. P. *Tetrahedron Lett.* **2006**, *47*, 2793. (e) Ward, A. F.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1268.
24. (a) Ney, J. E.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3605. (b) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906. (c) Beaudoin Bertrand, M.; Wolfe, J. P. *Tetrahedron* **2005**, *61*, 6447. (d) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644. (e) Yang, Q.; Ney, J. E.; Wolfe, J. P. *Org. Lett.* **2005**, *7*, 2575. (f) Ney, J. E.; Hay, M. B.; Yang, Q.; Wolfe, J. P. *Adv. Synth. Catal.* **2005**, *347*, 1614. (g) Beaudoin Bertrand, M.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353. (h) Beaudoin Bertrand, M.; Leathen, M. L.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 457. (i) Beaudoin Bertrand, M.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, *73*, 8851. (j) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 6276. (k) Rosen, B. R.; Ney, J. E.; Wolfe, J. P. *J. Org. Chem.* **2010**, *75*, 2756. (l) Mai, D. N.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 12157. (m) Lemen, G. S.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 2322. (n) Mai, D. N.; Rosen, B. R.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2932.
25. (a) Fritz, J. A.; Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2531. (b) Fritz, J. A.; Wolfe, J. P. *Tetrahedron* **2008**, *64*, 6838.
26. (a) Hay, M. B.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 6492. (b) Lemen, G. S.; Giampietro, N. C.; Hay, M. B.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 2533.
27. Ward, A. F.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 4728.
28. Giampietro, N. C.; Wolfe, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 12907.
29. (a) Nakhla, J. S.; Wolfe, J. P. *Org. Lett.* **2007**, *9*, 3279. (b) Nakhla, J. S.; Schultz, D. M.; Wolfe, J. P. *Tetrahedron* **2009**, *65*, 6549.
30. Leathen, M. L.; Rosen, B. R.; Wolfe, J. P. *J. Org. Chem.* **2009**, *74*, 5107.
31. Neukom, J. D.; Aquino, A. S.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2196.
32. (a) Lin, B. L.; Clough, C. R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 2890. (b) Koo, K.; Hillhouse, G. L. *Organometallics* **1995**, *14*, 4421. (c) Matsunaga, P. T.; Hillhouse, G. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 2075. (d) Koo, K.; Hillhouse, G. L. *Organometallics* **1998**, *17*, 2924. (e) Williams, B. S.; Goldberg, K. I. *J. Am. Chem. Soc.* **2001**, *123*, 2576. (f) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868. (g) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.
33. Hegedus, L. S. *Angew. Chem., Int. Ed.* **1988**, *27*, 1113.
34. (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. *Pure Appl. Chem.* **1999**, *71*, 1417.
35. (a) Villanueva, L. A.; Abboud, K. A.; Boncella, J. M. *Organometallics* **1992**, *11*, 2963. (b) Van der Lende, D. D.; Abboud, K. A.; Boncella, J. M. *Inorg. Chem.* **1995**, *34*, 5319. (c) Cowan, R. L.; Trogler, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4750. (d) Bryndza, H. E. *Organometallics* **1985**, *4*, 406. (e) Bennett, M. A.; Jin, H.; Li, S.; Rendina, L. M.; Willis, C. A. *J. Am. Chem. Soc.* **1995**, *117*, 8335. (f) Ritter, J. C. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1997**, *119*, 2580. (g) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. J.

- Am. Chem. Soc.* **1988**, *110*, 6738. (h) Hamed, O.; Thompson, C.; Henry, P. M. *J. Org. Chem.* **1997**, *62*, 7082. (i) Nelson, D. J.; Li, R.; Brammer, C. *J. Am. Chem. Soc.* **2001**, *123*, 1564.
36. For recent studies on alkene insertion into late transition metal–oxygen or –nitrogen bonds, see: (a) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036. (b) Zhao, P.; Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 12066. (c) see also ref. 16a. (d) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9642.
 37. Milstein, D. Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4981.
 38. (a) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787. (b) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504. (c) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109.
 39. Guo, X.-X.; Xie, J.-H.; Hou, G.-H.; Shi, W.-J.; Wang, L.-X.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 2231.
 40. (a) Schwartz, R. E.; Leisch, J.; Hensens, O.; Zitano, L.; Honeycutt, S.; Garrity, G.; Fromtling, R. A.; Onishi, J.; Monaghan, R. *J. Antibiot.* **1988**, *41*, 1774. (b) Johnson, J. H.; Phillipson, D. W.; Kahle, A. D. *J. Antibiot.* **1989**, *42*, 1184. (c) Kasahara, K.; Yoshida, M.; Eishima, J.; Takesako, K.; Beppu, T.; Horinouchi, S. *J. Antibiot.* **1997**, *50*, 267. (d) Achenbach, T. V.; Slater, P. E.; Brummerhop, H.; Bach, T.; Müller, R. *Antimicrob. Agents Chemother.* **2000**, *44*, 2794. (e) Kinzy, T. G.; Harger, J. W.; Carr-Schmid, A.; Kwon, J.; Shastry, M.; Justice, M.; Dinman, J. D. *Virology* **2002**, *300*, 60. (f) Okue, M.; Watanabe, H.; Kasahara, K.; Yoshida, M.; Horinouchi, S.; Kitahara, T. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1093.
 41. (a) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893. (b) Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 2962. (c) Lemen, G. S.; Wolfe, J. P. *Org. Lett.* **2011**, *13*, 3218.
 42. Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1028.
 43. Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052.
 44. For reviews see: (a) Hegedus, L. S. *Tetrahedron* **1984**, *40*, 2415. (b) Hegedus, L. S. *Coord. Chem. Rev.* **1996**, *147*, 443. (c) Heumann, A.; Réglér, M. *Tetrahedron* **1996**, *52*, 9289. (d) Hegedus, L. S. *Coord. Chem. Rev.* **1997**, *161*, 129. (e) Hegedus, L. S. *Coord. Chem. Rev.* **1998**, *175*, 159. (f) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (g) Muzart, J. *Tetrahedron* **2005**, *61*, 5955. (h) Muzart, J. *Tetrahedron* **2005**, *61*, 9423. (i) see ref. 11b. (j) Muzart, J. *J. Mol. Catal. A: Chem.* **2010**, *319*, 1. (k) Beccalli, E. M.; Brogini, G.; Fasana, A.; Rigamonti, M. *J. Organomet. Chem.* **2011**, *696*, 277.
 45. (a) Stille, J. K.; Jamed, D. E.; Hines, L. F. *J. Am. Chem. Soc.* **1973**, *95*, 5062. (b) James, D. E.; Hines, L. F.; Stille, J. K.; *J. Am. Chem. Soc.* **1976**, *98*, 1806.
 46. (a) Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulf, W.; Spies, E.; Zask, A. *J. Am. Chem. Soc.* **1982**, *104*, 5850. (b) Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034.
 47. Semmelhack, M. F.; Epa, W. R.; Cheung, A. W.-H.; Gu, Y.; Kim, C.; Zhang, N.; Lew, W. *J. Am. Chem. Soc.* **1994**, *116*, 2034.
 48. (a) White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Lett.* **2001**, *3*, 4003. (b) White, J. D.; Kuntiyong, P.; Lee, T. H. *Org. Lett.* **2006**, *8*, 6039.
 49. Carpenter, J.; Northrup, A. B.; Chung, M.; Wiener, J. J. M.; Kim, S.-G.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3568.
 50. Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, *25*, 3171.
 51. Tamaru, Y.; Kobayashi, T.; Kawamura, S.-i.; Ochiai, H.; Hojo, M.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, *26*, 3207.
 52. Gracza, T.; Hasenöhrl, T.; Stahl, U.; Jäger, V. *Synthesis* **1991**, 1108.

53. Babjak, M.; Zálupský, P.; Gracza, T. *Arkivoc* **2005**, v, 45.
54. (a) Gracza, T.; Jäger, V. *Synlett* **1992**, 191. (b) Gracza, T.; Jäger, V. *Synthesis* **1994**, 1359.
55. Dixon, D. J.; Ley, S. V.; Gracza, T.; Szolcsányi, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 8, 839.
56. (a) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron Lett.* **2002**, 43, 6983. (b) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron* **2005**, 61, 2471.
57. (a) Kraus, G. A.; Li, J.; Gordon, M. S.; Jensen, J. H. *J. Am. Chem. Soc.* **1993**, 115, 5859. (b) Kraus, G. A.; Li, J.; Gordon, M. S.; Jensen, J. H. *J. Org. Chem.* **1995**, 60, 1154.
58. Tang, Y.; Zhang, Y.; Dai, M.; Luo, T.; Deng, L.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, 7, 885.
59. Li, Z.; Gao, Y.; Tang, Y.; Dai, M.; Wang, G.; Wang, Z.; Yang, Z. *Org. Lett.* **2008**, 10, 3017.
60. a) Paddon-Jones, G. C.; Moore, C. J.; Brecknell, D. J.; König, W. A.; Kitching, W. *Tetrahedron Lett.* **1997**, 38, 3479. (b) Paddon-Jones, G. C.; McErlean, C. S. P.; Hayes, P.; Moore, C. J.; König, W. A.; Kitching, W. *J. Org. Chem.* **2001**, 66, 7487.
61. Boukouvalas, J.; Fortier, G.; Radu, I.-I. *J. Org. Chem.* **1998**, 63, 916.
62. (a) Paddon-Jones, G. C.; Hungerford, N.; Hayes, P.; Kitching, W. *Org. Lett.* **1999**, 1, 1905. (b) Hayes, P. Y.; Kitching, W. *J. Am. Chem. Soc.* **2002**, 124, 9718. (c) Hayes, P. Y.; Kitching, W. *Heterocycles* **2004**, 62, 173. (d) Hayes, P. Y.; Chow, S.; Rahm, F.; Bernhardt, P. V.; De Voss, J. J.; Kitching, W. *J. Org. Chem.* **2010**, 75, 6489. (e) Semmelhack, M. F.; Shanmugam, P. *Tetrahedron Lett.* **2000**, 41, 3567. (f) Semmelhack, M. F.; Hooley, R. J.; Kraml, C. M. *Org. Lett.* **2006**, 8, 5203.
63. Boukouvalas, J.; Pouliot, M.; Robichaud, J.; MacNeil, S.; Snieckus, V. *Org. Lett.* **2006**, 8, 3597.
64. Karlubíková, O.; Babjak, M.; Gracza, T. *Tetrahedron* **2011**, 67, 4980.
65. Ambrosini, L. M.; Cernak, T. A.; Lambert, T. H. *Synthesis* **2010**, 870.
66. Alper, H.; Hamel, N. *J. Chem. Soc., Chem. Commun.* **1990**, 135.
67. Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1999**, 121, 7708.
68. Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **1999**, 64, 1620.
69. Wang, F.; Zhang, Y. J.; Wei, H.; Zhang, J.; Zhang, W. *Tetrahedron Lett.* **2007**, 4083.
70. Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed* **2003**, 42, 2892.
71. (a) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, 123, 2907. (b) Koranne, P. S.; Tsujihara, T.; Arai, M. A.; Bajracharya, G. B.; Suzuki, T.; Onitsuka, K.; Sasai, H. *Tetrahedron: Asymmetry* **2007**, 18, 919. (c) Takenaka, K.; Akita, M.; Tanigaki, Y.; Takizawa, S.; Sasai, H. *Org. Lett.* **2011**, 13, 3506.
72. (a) Kato, K.; Tanaka, M.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, 43, 1511. (b) Kato, K.; Tanaka, M.; Yamamura, S.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2003**, 44, 3089. (c) Kato, K.; Matsuba, C.; Kusakabe, T.; Takayama, H.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T. A.; Vologdin, N. V.; Gusev, O. V. *Tetrahedron* **2006**, 62, 9988.
73. (a) Kapitán, P.; Gracza, T. *Arkivoc* **2008**, viii, 8. (b) Kapitán, P.; Gracza, T. *Tetrahedron: Asymmetry* **2008**, 19, 38.
74. Shinohara, T.; Arai, M. A.; Wakita, K.; Arai, T.; Sasai, H. *Tetrahedron Lett.* **2003**, 44, 711.
75. Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Org. Chem.* **2009**, 74, 9274.
76. Kooš, P.; Špánik, I.; Gracza, T. *Tetrahedron: Asymmetry* **2009**, 20, 2720.

77. For synthesis of related structures see: (a) Casiraghi, G.; Zanardi, F.; Rassu, G.; Pinna, L. *Org. Prep. Proced. Int.* **1996**, 28, 641. (b) Hartmann, T.; Witte, L. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: New York, 1995; pp 155–223. (c) Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic: London, 1986. (d) Niwa, H.; Okamoto, O.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *J. Org. Chem.* **1987**, 52, 2941. (e) Nagao, Y.; Dai, W.-M.; Ochiai, M.; Shiro, M. *J. Org. Chem.* **1989**, 54, 5211. (f) Wee, A. G. H. *J. Org. Chem.* **2001**, 66, 8513.
78. (a) Szolcsányi, P.; Gracza, T. *Chem. Commun.* **2005**, 3948. (b) Babjak, M.; Remeň, Ľ; Szolcsányi, P.; Zálupský, P.; Mikloš, D.; Gracza, T. *J. Organomet. Chem.* **2006**, 691, 928.
79. Szolcsányi, P.; Gracza, T.; Koman, M.; Prónayová, N.; Liptaj, T. *Tetrahedron: Asymmetry* **2000**, 11, 2579.
80. Holton, R. A. *J. Am. Chem. Soc.* **1977**, 99, 8083.
81. (a) Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, 54, 4717. (b) Kelly, D. R.; Nally, J. *Tetrahedron Lett.* **1999**, 40, 3251.
82. Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A.; Oku, A. *J. Org. Chem.* **1992**, 57, 1412.
83. Bellovičová, L.; Kožíšek, J.; Doháňošová, J.; Lásiková, A.; Gracza, T. *Acta Crystallographica* **2010**, E66, o2381.
84. Lásiková, A.; Doháňošová, J.; Hlavínová, L.; Toffano, M.; Vo-Thanh, G.; Kožíšek, J.; Gracza, T. *Tetrahedron: Asymmetry* **2012**, accepted.
85. Sannigrahi, M.; Mayhew, D. L.; Clive, D. L. J. *J. Org. Chem.* **1999**, 64, 2776.
86. Tan, C.-H.; Holmes, A. B. *Chem. Eur. J.* **2001**, 7, 1845.
87. Barco, A.; Baricordi, N.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Tetrahedron* **2007**, 63, 4278.
88. Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, 100, 3009.
89. –
90. Jäger, V.; Häfele, B. *Synthesis* **1987**, 801.
91. Hough, L.; Jones, J. K. N.; Mitchell, D. L. *J. Can. Chem.* **1958**, 36, 1720.
92. Chamberlin, A. R.; Mulholland Jr., R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, 109, 672.
93. (a) Hall, A.; Meldrum, K. P.; Therond, P. R.; Wightman, R. H. *Synlett* **1997**, 123. (b) Yang, M.; Ye, W.; Schneller, S. W. *J. Org. Chem.* **2004**, 69, 3993. (c) Va, P.; Roush, W. R. *Tetrahedron* **2007**, 63, 5768.
94. Gallos, J. K.; Stathakis, C. I.; Salapassidou, M. J.; Grammatoglou, C. E.; Koumbis, A. E. *Carbohydrate Research* **2007**, 342, 744.
95. Robertson, J.; Unsworth, W. P.; Lamont, S. G. *Tetrahedron* **2010**, 66, 2363.
96. (a) Malmstrøm, J.; Christophersen, C.; Barrero, A. F.; Oltra, J. E.; Justicia, J.; Rosales, A. *J. Nat. Prod.* **2002**, 65, 364. (b) Mayer, A. M. S.; Gustafson, K. R. *Eur. J. Cancer* **2004**, 40, 2676.
97. First total synthesis: V. Kumar, A. K. Shaw, *J. Org. Chem.* **2008**, 73, 7526.
98. Synthesis employing the diastereoselective Pd(II)-catalyzed bicyclization: Palík, M.; Karlubíková, O.; Lásiková, A.; Kožíšek, J.; Gracza, T. *Eur. J. Org. Chem.* **2009**, 709.
99. (a) Clemens, R. T.; Jennings, M. P. *Chem. Commun.* **2006**, 2720. (b) McAllister, G. D.; Robinson, J. E.; Taylor, R. J. K. *Tetrahedron* **2007**, 63, 12123.
100. Caletková, O.; Lásiková, A.; Hajdúch, M.; Džubák, P.; Gracza, T. *Bioorg. Med. Chem. Lett.* **2012**, accepted.
101. Hulme, A. N.; Rosser, E. M. *Org. Lett.* **2002**, 4, 265.
102. Sánchez-Sancho, F.; Valverde, S.; Herradón, B. *Tetrahedron: Asymmetry* **1996**, 7, 3209.

103. Steuer, B.; Wehner, V.; Lieberknecht, A.; Jäger, V. *Org. Synth.* **1998**, 9, 39.
104. Sobin, B. A.; Tanner, F. W., Jr. *J. Am. Chem. Soc.* **1954**, 76, 4053.
105. Jäger, V.; Hümmer, W.; Stahl, U.; Gracza, T. *Synthesis* **1991**, 769.
106. (a) Rosenbulm, S.B.; Huynh, T.; Afonso, A.; Davis Jr., H. R. *Tetrahedron* **2000**, 56, 5735. (b) Gaudreault, P.; Drouin, C.; Lessard, J. *Can. J. Chem.* **2005**, 83, 543.
107. For reviews see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, 95, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, 576, 147. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, 58, 9633.
108. For reviews see: (a) Darses, S.; Genet, J.-P. *Eur. J. Org. Chem.* **2003**, 4313. (b) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, 38, 49. (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, 40, 275. (d) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, 108, 288.
109. (a) Molander, G. A.; Ito, T. *Org. Lett.* **2001**, 3, 393. (b) Molander, G. A.; Rodrigues Rivero, M. *Org. Lett.* **2002**, 4, 107. (c) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, 67, 8424. (d) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, 4, 1867. (e) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, 68, 4302. (f) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, 68, 5534. (g) Molander, G. A.; Petrillo, D. E.; Landzberg, N. R.; Rohanna, J. C.; Biolatto, B. *Synlett* **2005**, 1763. (h) Molander, G. A.; Fumagalli, T. *J. Org. Chem.* **2006**, 71, 5743. (i) Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, 71, 9198. (j) Molander, G. A.; Vargas, F. *Org. Lett.* **2007**, 9, 203. (k) Molander, G. A.; Ham, J.; Seapy, D. G. *Tetrahedron* **2007**, 63, 768. (l) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2007**, 9, 1597. (m) Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2007**, 72, 8422. (n) Molander, G. A.; Petrillo, D. E. *Org. Lett.* **2008**, 10, 1795. (o) Molander, G. A.; Canturk, B. *Org. Lett.* **2008**, 10, 2135. (p) Molander, G. A.; Gormisky, P. E.; Sandrock, D. L. *J. Org. Chem.* **2008**, 73, 2052. (q) Molander, G. A.; Gormisky, P. E. *J. Org. Chem.* **2008**, 73, 7481. (r) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, 130, 9257. (s) Molander, G. A.; Jean-Gérard, L. *J. Org. Chem.* **2009**, 74, 1297. (t) Dreher, S. D.; Lim, S.-E.; Sandrock, D. L.; Molander, G. A. *J. Org. Chem.* **2009**, 74, 3626. (u) Molander, G. A.; Beaumard, F. *Org. Lett.* **2011**, 13, 1242. (v) Molander, G. A.; Fleury-Brégeot, N.; Hiebel, M.-A. *Org. Lett.* **2011**, 13, 1694. (w) Molander, G. A.; Beaumard, F.; Niethamer, T. K. *J. Org. Chem.* **2011**, 76, 8126.
110. (a) Fang, G.-H.; Yan, Z.-J.; Deng, M.-Z. *Org. Lett.* **2004**, 6, 357. (b) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, 6, 2649. (c) Charette, A. B.; Mathieu, S.; Fournier, J.-F. *Synlett* **2005**, 1779. (d) Kabalka, G. W.; Al-Masum, M. *Tetrahedron Lett.* **2005**, 46, 6329. (e) Arvela, R. K.; Leadbeater, N. E.; Mack, T. L.; Kormos, C. M. *Tetrahedron Lett.* **2006**, 47, 217. (f) Kabalka, G. W.; Zhou, L.-L.; Naravane, A. *Tetrahedron Lett.* **2006**, 47, 6887. (g) Zhang, L.; Meng, T.; Wu, J. *J. Org. Chem.* **2007**, 72, 9346. (h) Harker, R. L.; Crouch, R. D. *Synthesis* **2007**, 25.
111. Kuriyama, M.; Shimazawa, R.; Enomoto, T.; Shirai, R. *J. Org. Chem.* **2008**, 73, 6939.
112. Kabalka, G. W.; Venkataiah, B.; Dong, G. *Org. Lett.* **2003**, 5, 3803.
113. Ge, H.; Niphakis, M. J.; Georg, G. I. *J. Am. Chem. Soc.* **2008**, 130, 3708.
114. Zhao, J.; Zhang, Y.; Cheng, K. *J. Org. Chem.* **2008**, 73, 7428.
115. (a) Pucheault, M.; Darses, S.; Genet, J.-P. *J. Am. Chem. Soc.* **2004**, 126, 15356. (b) Chuzel, O.; Roesch, A.; Gener, J.-P.; Darses, S. *J. Org. Chem.* **2008**, 73, 7800.
116. Martinez, R.; Voica, F.; Genet, J.-P.; Darses, S. *Org. Lett.* **2007**, 9, 3213.
117. (a) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, 5, 1381. (b) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, 5, 4397.
118. (a) Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2004**, 45, 343. (b) Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2004**, 45, 1417.

119. For reviews see: (a) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, 39, 712. (b) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, 110, 824.
120. (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, 126, 2300. (b) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, 126, 9542. (b) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, 127, 12790.
121. Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, 6, 4083.
122. (a) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.*, **2005**, 127, 14586. (b) Muñiz, K. *J. Am. Chem. Soc.*, **2007**, 129, 14542.
123. Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, 46, 5737.
124. Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, 127, 7690.
125. Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, 128, 7179.
126. Li, Y.; Song, D.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, 130, 2962.
127. (a) Olivier, D. L.; Anderson, G. K. *Polyhedron* **1992**, 11, 2415. (b) Stang, P. J.; Cao, D. H. *J. Am. Chem. Soc.* **1994**, 116, 4981. (c) Stang, P. J.; Cao, D. H.; Poulter, G. T.; Arif, A. M. *Organometallics* **1995**, 14, 1110. (d) Yuan, H.; Thomas, L.; Woo, L. K. *Inorg. Chem.* **1996**, 35, 2808.
128. (a) Winchester, B.; Fleet, G. W. J. *Glycobiol.* **1992**, 2, 199. (b) Sinnott, M. L. *Chem. Rev.* **1990**, 90, 1171.
129. Gurjar, M. K.; Patil, V. J.; Pawar, S. M. *Carbohydr. Res.* **1987**, 165, 313.
130. Mihovilovic, M. D.; Kapitán, P. *Tetrahedron Lett.* **2004**, 45, 2751.
131. (a) Voituriez, A.; Schulz, E. *Tetrahedron: Asymmetry* **2003**, 14, 339. (b) Schulz, E.; Voituriez, A. *Rus. Chem. Bull., Int. Ed.* **2003**, 52, 2588.
132. Trost, B. M.; Van Vranken, D. L. *Angew. Chem. Int. Ed.* **1992**, 31, 228.
133. (a) Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177. (b) Amatore, C.; Carré, E.; Jutand, A.; M'Barki, M. A. *Organometallics* **1995**, 14, 1818.
134. (a) Moser, R. E.; Cassidy, H. G. *J. Am. Chem. Soc.* **1965**, 87, 3463. (b) Kruif, C. G.; Smit, E. J.; Govers, H. A. J. *J. Chem. Phys.* **1981**, 74, 5838. (c) Karr, P. A.; Zandler, M. E.; Beck, M.; Jaeger, J. D.; McCarty, A. L.; Smith, P. M.; D'Souza, F. *J. Mol. Struct. (THEOCHEM)* **2006**, 765, 91. (d) Quan, M.; Sanchez, D.; Wasylkiw, M. F.; Smith, D. K. *J. Am. Chem. Soc.* **2007**, 129, 12847.
135. Arai, M. A.; Arai, T.; Sasai, H. *Org. Lett.* **1999**, 1, 1795.
136. Bien, S.; Ovadia, D. *J. Org. Chem.* **1974**, 39, 2258.
137. (a) Bäckvall, J.-E.; Hopkins, R. B. *Tetrahedron Lett.* **1988**, 29, 2885. (b) Bäckvall, J.-E.; Hopkins, R. B.; Grennberg, H.; Mader, M. M.; Awasthi, A. K. *J. Org. Chem.* **1990**, 112, 5160. (c) Piera, J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2008**, 47, 3506.
138. Kapitán P. *Enantioselective Palladium(II)-Catalyzed Oxycarbonylation in the Synthesis of Bicyclic Lactones. Synthesis of Natural Products*, Slovak University of Technology, Thesis 2005.
139. Wasserscheid, P.; Welton, T. *Ionic liquids in synthesis*; 2nd Edition, Wiley-VCH: Weinheim, 2008.
140. (a) Welton, T. *Chem. Rev.* **1999**, 99, 2071. (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, 39, 3772. (c) Sheldon, R. *Chem. Commun.* **2001**, 2399. (d) Hallett, J. P.; Welton, T. *Chem. Rev.* **2011**, 111, 3508.
141. For reviews see: (a) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, 61, 1015. (b) Pârvulescu, V. I.; Hardacre, C. *Chem. Rev.* **2007**, 107, 2615. (c) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. *Chem. Rev.* **2008**, 108, 2015.
142. (a) Consorti, C. S.; Ebeling, G.; Dupont, J. *Tetrahedron Lett.* **2002**, 43, 753. (b) Gabriele, B.; Mancuso, R.; Lupinacci, E.; Salerno, G.; Veltri, L. *Tetrahedron* **2010**, 66, 6156.

143. Aupoix, A. *Les sels d'azolium précurseurs de carbènes N-hétérocycliques: Synthèse et applications en catalyse*, Université Paris-Sud 11, Thesis 2010.
144. Doháňošová, J.; Lásiková, A.; Toffano, M; Gracza, T.; Vo-Thanh, G. *New J. Chem.* **2012**, submitted.
145. Jäger, V.; Wehner, V. *Angew. Chem.* **1989**, *101*, 512.
146. Dumont, R.; Pfander, H. *Helv. Chim. Acta* **1983**, *66*, 814.
147. Koole, L. H.; van Genderen, M. H. P.; Buck, H. M. *J. Org. Chem.* **1988**, *53*, 5266.