DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS
48

ASPECTS OF CONDENSATIONS OF CARBONYL COMPOUNDS AND THEIR IMINE ANALOGUES

OLAVI LOOG

TARTU UNIVERSITY
PRESS

Department of Chemistry, University of Tartu, Estonia

Dissertation is accepted for the commencement of the degree of Doctor of Philosophy in Chemistry on Aprill 5, 2005, by the Doctoral Committee of the Department of Chemistry, University of Tartu.

Opponents: Prof. Margus Lopp (Tallinn University of Technology)

Commencement: June 10, 2005, 2 Jakobi Str., room 430

Publication of this dissertation is granted by University of Tartu

ISSN 1406–0299
ISBN 9949–11–061–0 (trükis)
ISBN 9949–11–062–9 (PDF)

Tartu Ülikooli Kirjastus
www.tyk.ee
Tellimus nr 189

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

I Selfcondensation of 2-Methylpropanal with Homochiral BINOL Catalysts as a Model Asymmetric Aldol-Tishchenko Reaction. Loog, O.; Mäeorg, U. *Tetrahedron: Asymmetry* **1999**, 10, 2411–2415.

II Synthesis of Hydrazine with Aromatic Substituents Using Triarylbismuth Reagents. Loog, O.; Mäeorg, U.; Ragnarsson, U. *Synthesis* **2000**, 1591–1597.

III Cu-Catalysed N-Arylation of Hydrazines with Bismuthanes. Synthesis and Pinacol or Imino-Pinacol Coupling of 4-Formylphenylhydrazines and their Phenylimine Derivatives. Loog, O.; Mäeorg, U. *Synlett* **2004**, 2537–2540.

ABBREVIATIONS

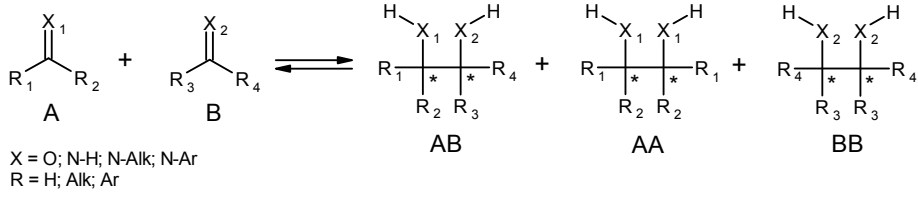
Ac	acetyl
Alk	alkyl
aq.	aqueous
Ar	aryl
BINOL	1,1'-binaphthalene-2,2'-diol
Boc	*t*-butoxycarbonyl
Bu	butyl
cat.	catalyst
Cp	cyclopentadienyl
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
Et	ethyl
GLC	gas-liquid chromatography
i-Pr	2-propyl
Me	methyl
mp	melting point
NMR	nuclear magnetic resonance
Ph	phenyl
Py	pyridine
r.t.	room temperature
ref.	reference
TADDOL	α,α,α',α'-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol
t-Bu	*t*-butyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin leyer chromatography
Ts	*p*-toluenesulfonyl
Z	benzyloxycarbonyl

FOREWORD

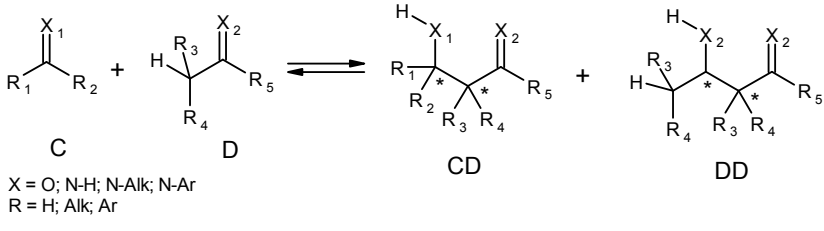
This thesis is based on the results of the studies on two main subjects. The first of these is the stereochemistry and mechanism of homo aldol-Tishchenko reaction, and the second is the pinacol coupling of hydrazinoarylaldehydes and the imino-pinacol coupling of their imine analogues. These two somewhat different subjects are still connected in a wider context, being small parts in a big mosaic which could be called condensation reactions of carbonyl compounds and their imine analogues. In connection to hydrazinoarylaldehydes and their synthsis an additional topic is introduced, namely arylation of hydrazines, which forms the third relevant part of this work.

1. INTRODUCTION

Carbonyl compounds and their imine analogues are very important in synthetic organic chemistry. Central to the numerous reactions of these compounds are condensations that lead to the formation of C-C bonds between two reactant molecules. Classical examples are the pinacol coupling and the aldol condensation of aldehydes and ketones, which give 1,2- and 1,3-diols respectively. There are many different modifications of these reactions involving reactions with derivatives of carbonyl compounds (for example, enolates) as well as sequential (or so called tandem) reactions, where the first formed aldol or pinacol product reacts further (for example, croton condensation, McMurry reaction, aldol-Tishchenko reaction). Most but not all of these reactions occur to a greater or lesser extent in principle between the imine analogues of carbonyl compounds. The best known of those is imino-pinacol coupling, which is used to prepare 1,2-diamines. There are also examples of mixed type of reactions, where one reactant is carbonyl compound (or its enol derivative) and the other is imine. The general schemes of the reactions described here are given in Scheme 1 and Scheme 2.



Scheme 1. General scheme of pinacol-type reactions



Scheme 2. General scheme of aldol-type reactions

Pinacol-type reaction is in principle possible with almost all carbonyl compounds or imines, except if there are very bulky substituents which do not favour the formation of C-C bond. Aldol-type condensations can occur only if there is a hydrogen in α-position next to the carbonyl group (the compound is

enolisabel) in at least one of the reactant molecules. Although aldol condensation is generally more favourable for such compounds, they can undergo pinacol coupling, too. Which reaction occurs depends on the reaction conditions and substituents. Both types of reactions are reversible, which sometimes limits their practical use. In both reactions one or two stereogenic centres may be formed, leading to stereoisomeric products.

The simplest and best-known cases of such reactions are homocondensations, where only one starting compound is used (A or B in Scheme 1 and D in Scheme 2). For pinacol couplings this leads to symmetrical adducts (AA or BB in Scheme 1). If R_1 and R_2 are not the same, three stereoisomers – *SS*- and *RR*-enantiomer (*dl*-isomers) and *meso*-form exist (provided that there are no stereogenic centres in the substituents). Aldol products from homocondensations (DD in Scheme 2) can exist at least as two enantiomers or, if R_3 and R_4 are not the same, then four stereoisomers (two diastereomeric pairs of enantiomers) are possible. Schemes are even more simple when aldehydes (R_2 or R_4 = H in Scheme 1) or aldimines (R_4 = H in Scheme 2) are used as starting compounds. Aldehydes and aldimines can be generally also more easily condensed than ketones and ketimines because they are more reactive and sterically less demanding.

Products from pinacol and aldol reactions are valuable as bioactive compounds, as synthetic intermediates, in homochiral form as ligands for chiral catalysts, and so on.

Aldol condensation and pinacol coupling have been known for more than a century and have been thoroughly studied. A lot of information about reaction mechanisms and different conditions is available in the literature. In recent decades a great deal of efforts has been dedicated to the elucidation of the stereochemical aspects of those reactions and to the development of stereospecific synthetic methods.

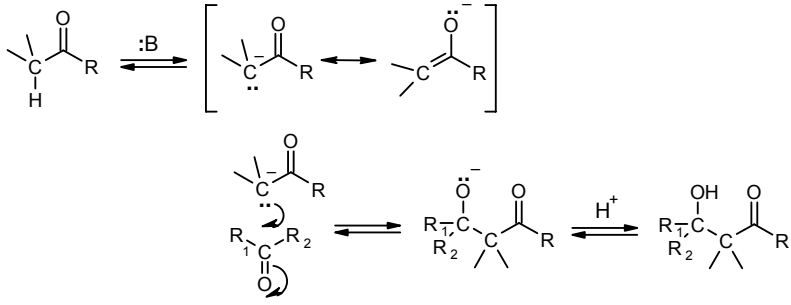
As mentioned above, the general theme "condensation reactions of carbonyl compounds and their imine analogues" also includes the two main subjects of this thesis – stereochemistry and reaction mechanism of the homo aldol-Tishchenko reaction, and hydrazinoarylaldehydes' and their imine analogues' pinacol or imino-pinacol coupling. In the following section the background for those topics is described in more detail. At the end of the section, there is also a short review about the synthesis of hydrazinoarylaldehydes.

2. LITERATURE REVIEW AND THEORETICAL BAC KGROUND

2.1. Aldol condensation

Aldol condensation is a reaction between two carbonyl compound molecules, from which at least one is enolisable (has α-hydrogen next to carbonyl group – see Scheme 2). The reaction is catalysed by acids or bases and is reversible. In some cases (as a prerequisite there must be another α-hydrogen in enolisable starting compound – in Scheme 2, R_3 or/and R_4 must be H) the spontaneous dehydration follows or it can be easily done (for example, by heating) because the double bond formed will be in conjugation with the C=O bond. This process is called crotonisation and it is in principle also reversible [1] (but not as prone to retrograde reaction as aldol adducts are).

In most cases, when the condensation is performed in the presence of base, the reaction starts with the formation of enolate ion, which reacts with the carbonyl group of another molecule producing after protonation β-hydroxyaldehyde (aldol) or β-hydroxyketone (see Scheme 3).



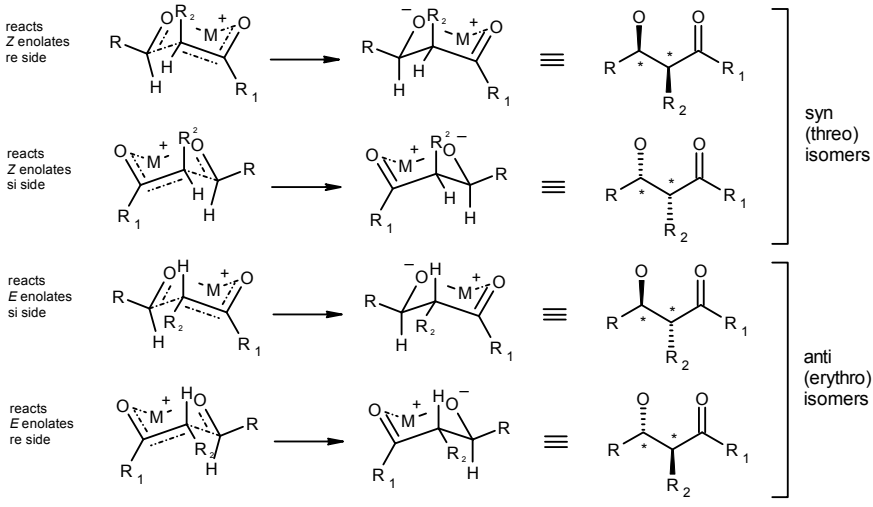
Scheme 3. Base catalysed aldol reaction

The equilibrium between aldol and starting carbonyl compounds lies far on the side of aldol in reactions between two molecules of aldehyde (in Scheme 2, R_2, R_5 = H), whereas in reactions between two molecules of ketone the equilibrium lies on the side of retroaldol products (R_1, R_2, R_5 = Alk, Ar) [1].

In simple cases only one starting carbonyl compound is present, but also mixed reactions, or so called cross-couplings, between different aldehydes or different ketones as well as between aldehyde and ketone are used. In mixed reactions, components are usually selected so that one of them is not enolisable or the cross-coupling is favoured due to the components' different reactivities and concentrations. Especially useful are reactions between ketone and non-

enolisable aldehyde and even if the aldehyde has α-hydrogen, it is usually the α-carbon of the ketone that adds to the carbonyl of the aldehyde, not the other way around [1]. The reaction can be made regioselective by preparing an enol derivative of the ketone separately and then adding the aldehyde (or ketone). A number of these preformed enolates have been used, the most common of which is the silyl enol ether of ketone [1]. Also many different metal enolates have been found to be useful.

The reactions with preformed enol derivatives provide also a way to control the stereoselectivity of the aldol reaction. As already mentioned, in the most general case four stereoisomeric products can be formed in aldol condensation. Those isomers can be represented as two diastereomeric pairs of *syn* (or erythro) and *anti* (or threo) isomers (see Scheme 4).



Scheme 4. Examples of typical activated complexes in aldol reaction explaining the formation of stereoisomers

For many aldol reactions it is believed that the reaction proceeds through the chair conformational activated complex (so called Zimmerman complex), where the bulkiest substituent of the not enolised aldehyde (or ketone) is favourably in the equatorial position [2], as shown in Scheme 4. Scheme 4 also shows the most probable way for the four stereoisomers to be formed. In general, metal *Z*-enolates give the *syn* (or erythro) pair of stereoisomers, and this reaction is highly useful for the diastereoselective synthesis of these products. The *E*

isomers generally react nonselectively*. However, also *anti* (or threo) stereoselectivity has been achieved in a number of cases with different enolates [1].

When the diastereoselectivity of aldol reaction can be controlled, for example, by the configuration of preformed enolate, the enantioselective reaction needs in addition a chiral component in the system – for example, a chiral catalyst or the chirality in the substrate. For aldol reaction quite a number of highly efficient and enantioselective processes have been documented. Majority of them share as a general feature the formation of a silyl enolate in the first step followed by the Lewis acid- or Lewis base-catalysed addition of this species to the aldehyde (also known as Mukaiyama aldol reaction) [3,4]. Only recently, other protocols have emerged. For example, direct catalytic enantioselective aldol reactions of unmodified ketones or aldehydes using organometallic or purely organic catalysts were reported by different workgroups [5].

2.2. Aldol-Tishchenko reaction

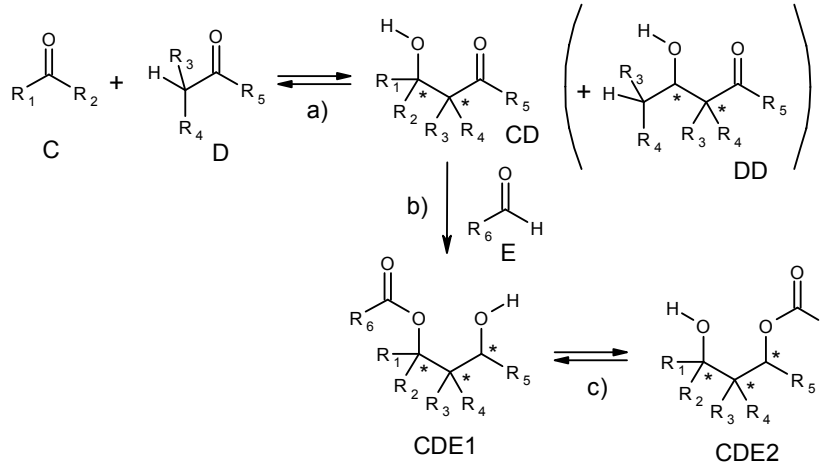
Aldol-Tishchenko reaction is one of the numerous modifications of aldol reaction. The first step in this multistep reaction (see Schemes 5 and 6) is aldol condensation (reaction a), which is followed by Tishchenko reaction (reaction b) where aldol is reduced by aldehyde molecule (E), resulting in the formation of diol monoester (CDE1 or DDE1 – not shown in Scheme 5). In addition, the latter could be subjected to acyl migration (reaction c). Aldol-Tishchenko reaction is catalysed by moderately basic metal compounds (mostly metal hydroxides and alkoxides). Tishchenko reaction is irreversible and assures by this the irreversibility of the whole reaction sequence (as already mentioned, the aldol condensation alone is reversible). It can be seen from Scheme 5 that as a result of Tishchenko reaction, a new stereogenic centre is formed if R_5 is not H. However, in most cases its configuration is already determined by the two stereogenic centres in the aldol compound (see Scheme 6 and its caption). Tishchenko reaction is also usually the speed-limiting step in the process.

The classic aldol-Tishchenko reaction [6] is used to obtain 1,3-diol monoesters from the selfcondensation of enolisable aldehydes (only aldehyde D, where R_5 is H, is present). In the first step of this reaction, two molecules of aldehyde are condensed to aldol (DD), which is further reduced by the third molecule of aldehyde (E = D) to give secondary 1,3-diol monoester (CDE1 = DDD1), which may isomerise to primary monoester (CDE2 = DDD2).

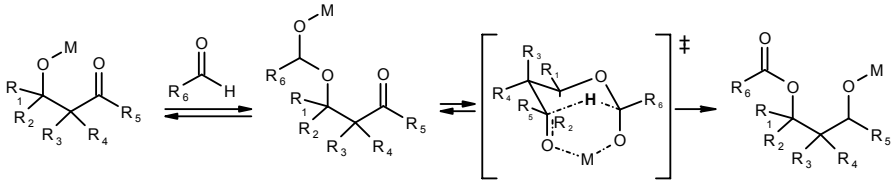
More recently, different mixed reactions (heteroreactions) with even bigger practical value than the classical aldol-Tishchenko reaction have been developed. In mixed reactions the aldol is formed from two different aldehydes [7,8]

* Although the most favourable activated complexes for *E* enolates in Scheme 4 suggest the preferential formation of the *anti* isomers, the equatorial position of the aldehydes substituent R is probably not so important here, especially when the R is small.

or from aldehydes and ketones [3,8–11], followed by reduction of aldol adduct in Tishchenko reaction. Tishchenko reaction has also been used as an independent reaction for the *anti*-diastereoselective reduction of β-hydroxyketones [8,10,12,13] or in one occasion for the oxidation of aldehyde group to ester group with cheap β-hydroxyketone in complex structure, with oxidatively labile dithione moiety [14].



Scheme 5. The general scheme of aldol-Tishchenko reaction (reaction with DD is not presented)



It is proposed that in the activated complex the bulkiest substituents are preferably in the equatorial positions.

Scheme 6. Formation of the activated complex in Tishchenko reaction [12,15]

Although the aldol-Tishchenko reaction is known for more than 100 years [6a], and the aldol condensation is thoroughly studied, the mechanism and stereochemistry of the Tishchenko reaction* was not clear until Burkhardt [15] and Evans [12] proposed in 1990 the idea of 6+6 bicyclic activated complex, where the hydride transfer occurs intramolecularly in hemiacetal formed from

* Because of confusing usage of the term "Tishchenko reaction" in the literature, it should be clarified that here is meant the intramolecular reaction, sometimes also called Evans-Tishchenko reaction, as showed in the Scheme 6.

aldehyde and β-hydroxy carbonyl compound (see Scheme 6). This idea was later supported by other authors, because it can explain the high *anti*-diastereoselectivity observed in many Tishchenko reductions of β-hydroxy carbonyl compounds [8,10,12,13]. In recent years, a few examples of catalytic enantioselective versions of aldol-Tishchenko reaction have also been published [3,7,9,I]. Tishchenko reaction is usually the main (or only) stereoselective step in the reaction sequence, because it's not reversible and goes through the highly organised activated complex coordinated on a central metal atom. This gives good presumptions for enantiodiscrimination if there is a chiral auxiliary in the system [7,9,I]. However, there is also a contrary example described where non-selective Tishchenko reaction was used to "frozen" the enantiomeric excess obtained by enantioselective aldol reaction [3].

The acyl migration in first formed monoester (CDE1 in Scheme 5) after disproportionation is often described [3,7,8,10-12,13a-d,15,16a,b], but the mechanism and stereochemistry of this isomerisation is discussed only in few occasions [8,16]. In connection to this work, it has been shown that the isomerisation can be modestly enantioselective in the presence of a chiral catalyst [16c].

2.2.1. Side reactions

Most common side reactions that may accompany aldol-Tishchenko reaction are:

1) Formation of simple esters when two aldehyde molecules disproportionate without remarkable formation of aldol product (Claisen-Tishchenko reaction*) [6d,17]. For the formation of simple esters higher temperatures and aldehydes with only one α-hydrogen are favourable. Disproportionation between two aldol molecules has not been observed.
2) Crotonisation or croton condensation – elimination of water from aldol when there is an α-hydrogen next to carbonyl group (enolisable starting aldehyde must have 2 α-hydrogen atoms, see also Paragraph 2.1.) [6d,g,h]. Elimination is favourable at higher temperatures and when strong bases are used.
3) Depending on the reaction conditions and the nature of aldehyde, the acetalisation between aldol and aldehyde may lead to the formation of cyclic aldoxanes [17,18] (see also Scheme 12). Process is favoured at lower temperatures. It has also been observed that even two molecules of aldol may form cyclic aldoxanes, so called paraldols, in quite remarkable amounts when aldols are stored for longer periods [18].
4) Verley-Meerwein-Panndorf reaction may occur if aluminumalkoxides are used as catalyst [6e,17].

* When no difference is made between the intra- and intermolecular reactions, then this disproportionation reaction is also often called Tishchenko reaction.

2.3. Imino-aldol reaction

Although the aldol reaction of carbonyl compounds is easily attained with the aid of Lewis acids or bases, an aldol-type reaction of imines (in Scheme 2, X = N-Alk or N-Ar) is difficult to carry out because of the lower acidity of the α-proton of imines than that of carbonyl compounds [19]. Moreover, due to the difference in electronegativity of oxygen and nitrogen, imines are also generally less reactive toward nucleophilic additions than carbonyl compounds [20]. Other possible drawbacks for condensation of imines may include the fast retro-aldol reaction or further reactions of the aldol-type adducts (their unstability). In fact, only in a few cases aldol-type dimers of imines, β-aminoimines, have been isolated and characterised as individual compounds [21,22]. More often they have been described as unstable intermediates, as for example, in homo-condensation of aliphatic imines when α,β-unsaturated imines are obtained as a result of elimination of an amine from dimeric imine adducts [19,23] (like crotonisation in condensation of carbonyl compounds). An aldol-type condensation has also been postulated as the first step in thermal polymerisation of aliphatic imines to pyridine derivatives [24], and in formation of cyclic dimers of arylaldimines (formed from arylamines and aliphatic aldehydes), which in turn can be converted to quinolines at higher temperatures [21,22,25].

More practical are Lewis acid catalysed mixed aldol-type condensations (Mannich-type reactions – Mukaiyama aldol reaction analogue for imines), where imines are coupled with ketene silyl acetals or silyl enolates to form β-aminoesters or β-aminoketones (or aminoenoxysilanes), respectively [4,26]. Also several asymmetric versions of this reaction have been described [4].

The mixed condensation reactions of carbonyl compounds and imines could also be directed in the opposite way. For example, by using $LiN(i\text{-}Pr)_2$ or BuLi as a base, imines are α-lithiated and can react with ketones to give β-hydroxyimines, which after hydrolysis give corresponding aldol products (β-hydroxyketones) [27,28]. Other reagents used for the activation of imines include Grignard reagents and Lewis acid-amine base reagents [28]. This reaction (sometimes called directed aldol reaction or imine aldol reaction) is synthetically useful alternative to the carbonyl aldol reactions.

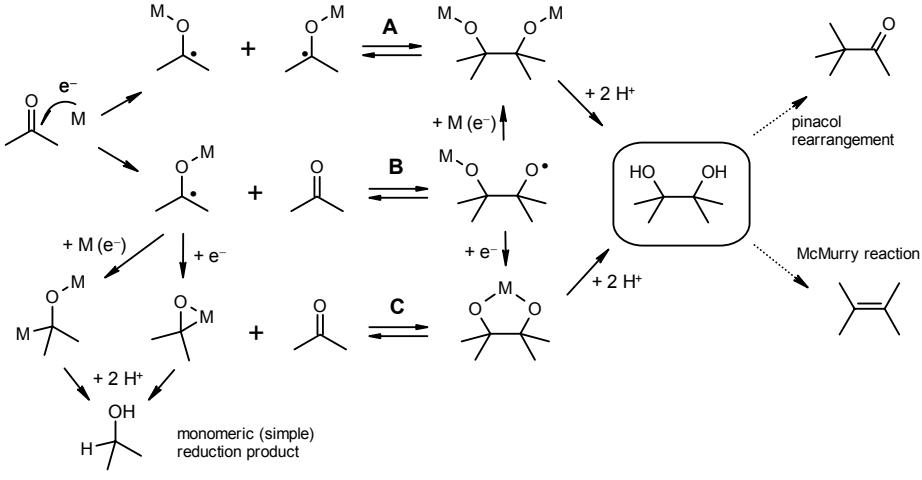
2.4. Pinacol coupling

Another well-known reaction of aldehydes and ketones is their reductive dimerisation – the pinacol coupling – which is used to prepare vicinal diols (Scheme 1, X = O) (for reviews, see ref. [29]). Reductive dimerisation can also be performed with imines. In this case coupling leads to the formation of vicinal diamines (for reviews, see ref. [30] and references therein). Both vicinal diols and diamines, especially in the homochiral form, are used as ligands in

catalysts, as complexing agents and as versatile synthetic intermediates [29–31]. Intramolecular pinacol coupling of dicarbonyl compounds (or diimines) is also a valuable tool for the synthesis of various functionalised cyclic compounds [29c,32–34].

Pinacol coupling of carbonyl compounds can be induced photochemically [35], electrochemically [32], or most commonly, by use of various metals or their salts [36]. In last decades various low-valent metal species such as Al, Ce, Cr, Fe, Mg, Mn, Nb, Ni, Sm, Si, Ti, V, Yb, and Zr were developed as reducing metal reagents for this reaction (see ref. [29,36,37] and references therein). Among these, the most extensively used reagents are different low-valent Ti compounds.

Three typical reaction mechanisms proposed for pinacol coupling are shown in Scheme 7 [29c,38,39]. Most often the reaction is thought to proceed as dimerisation of two ketyl radicals, formed after single electron transfer from low-valent transition metal complexes, metal powders, or electrodes to the carbonyl group (path A) [40]. However, in some cases the path B or C seems to be more probable. For example, in condensation of aliphatic aldehydes or ketones the concentration of ketyl radicals can be relatively low and therefore the coupling of two radicals is very unlikely. Instead, ketyl radical addition to the carbonyl substrate and formation of oxoradical, which is subsequently reduced (path B), or initial reduction of the ketyl radical to its dianion, which adds to the carbonyl compound (path C), could dominate in these reactions [38]. Formation of metal oxiranes with carbonyl compounds and Zr, Nb, and Yb and also the structure analysis of reaction intermediates support Path C in reactions with some transition metals [29c].



Scheme 7. Reaction mechanisms proposed for pinacol coupling and its most common side reactions

Depending on reaction conditions and substrates, the pinacol may be subjected further to pinacol rearrangement, giving ketones, or deoxygenation (McMurry reaction), giving alkenes (see Scheme 7). Although both reactions have synthetical importance, they are still more often just unwanted side reactions accompanying formation of diols. Whether the reductive coupling leads to diols or to the deoxygenated or rearranged products depends on the oxygen affinity of the reducing agent employed [29c]. Also reactions with aliphatic ketones often give rearranged and deoxygenated products, because their lower reactivity requires more severe reaction conditions [41]. Another common side reaction in pinacol couplings is the monomeric (simple) reduction of the carbonyl compound to alcohol, which involves reduction of radical anion to dianion (by another electron transfer from metal, but at higher potential than the first electron transfer) and following hydrogen abstraction from solvent or other proton source in the system [39,42]. If carbonyl compound has α-hydrogens, then also aldol reaction may occur as a side reaction.

Two adjacent stereocentres are created as a result of the pinacol coupling and therefore lots of efforts have been made to develop stereoselective reactions. In recent years quite a many highly diastereoselective reactions have been achieved with different reagents and substrates (for example, see [37,40,43–46]), and also some enantioselective pinacol couplings have been described [37,46,47]. Stereoselectivity is generally more easily controlled in condensations of aromatic aldehydes or ketones, but also a few diastereoselective [45,46b] and in one case even enantioselective [37] reactions with aliphatic aldehydes have been described.

Another goal in stereoselective reactions is to develop efficient catalytic reactions, where selective catalyst is regenerated by a cheap reductant, as for example Zn, Mg, or Mn. Indeed, there are many examples of such catalytic reactions [36,40,44,45a], including enantioselective catalytic reactions [37,46,47a,d]. In order to regenerate the catalyst in catalytic systems, there must be also present, in addition to the stoichiometric reductant, a stoichiometric reagent that replaces catalyst(metal)-oxygen bonds. In most cases this additive is trimethylsilylchloride (or triethylsilylchloride [37]), which silylates the oxygen atoms in formed dimers. Corresponding diols are obtained after hydrolytic work-up. A different concept was developed by Gansäuer and Bauer [44b], who used the protonation of the metal-oxygen bond by acid addition salts of organic bases instead of silylation.

When homo-coupling of carbonyl compounds has already been thoroughly studied, as referred above, then only a little has been reported about the mixed pinacol coupling of different carbonyl compounds (see ref. [32,33,35] and references therein). If mixed aldol condensations of different carbonyl compounds are easily obtained by using one non-enolisable component or pre-formed enolates (see Paragraph 2.1.), then in mixed pinacol couplings, the homo-couplings can be suppressed only by the substantial differences in components' reactivity towards reduction. Therefore, the two chosen components must have reduction

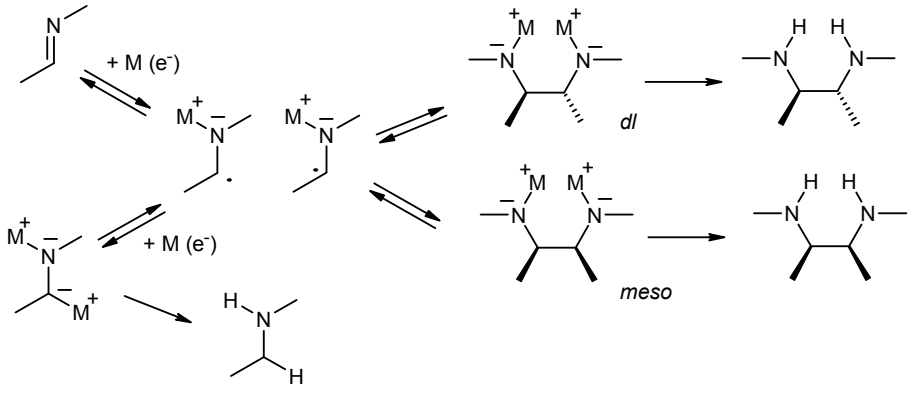
potentials different enough for the selective reduction of only one component to the ketyl radical, which then reacts with another component according to path B or C in Scheme 7. For example, arylketones, which have generally much lower reduction potentials than aliphatic ketones (for example, acetophenon –2.10 V *vs* acetone –2.96 V[*]), have been coupled with aliphatic ketones to unsymmetrical pinacols in moderate to good yields by Mg/trimethylsilylchloride [33]. If such ”aromatic” and ”aliphatic” carbonyl groups are in the same molecule, then unsymmetrical cyclic diols can be obtained [32,33]. In principle, the selective reaction could be achieved also due to the sterical differences of reactants.

2.5. Imino-pinacol coupling

Pinacol-type coupling of imines to vicinal diamines (Scheme 1, X = N-H, N-Alk, N-Ar) is in many aspects very similar to the pinacol coupling of carbonyl compounds. Often the same reagents and reaction conditions are used and the same mechanisms are proposed for both couplings (see Scheme 7, for the imine coupling, O should be replaced with N-R). So the coupling of imines can be accomplished by the action of low valent metals and their salts (see ref. [30,34] and references therein), as well as electrochemically [48] or photochemically [49]. However, imines are generally less reactive than corresponding carbonyl compounds because of the higher reduction potentials and sterical reasons (substituent at nitrogen atom), and tend to give more simple reduction products. Reactions with imines are also generally less stereoselective compared to couplings of carbonyl compounds in similar conditions. In addition, formed vicinal diamines are quite sensitive to oxidative cleavage (retrograde reaction), especially in the presence of acids [50].

Fast retrograde reaction may affect the diamine’s yield as well as its isomeric ratio. It has been observed that diamine dianions (generated, for example, with strong base as BuLi or with active metals like Li and Na) are easily cleaved to radical anions [30b,51], and consequently the yield of diamine depends on the equilibrium between the coupling and the cleavage reactions (see Scheme 8). Such reversibility of coupling also shifts the product isomeric ratio to the thermodynamically controlled (favoured) ratio [51]. For example, the thermodynamically controlled isomerisation has been used for conversion of *meso*-diamine to its *dl*-isomer [30b]. By the same principle, unsymmetrical diamines could be obtained as a result of cleavage of diamine and subsequent coupling of formed radical anion with another imine added to the mixture [51].

[*] Potential *vs* Ag/AgCl electrode in 1%Bu_4NC1O_4/DMF [33].



Scheme 8. Reversible imine coupling via dimerisation of radical anions

Similarly to the pinacol couplings of carbonyl compounds, the imino-pinacol couplings are usually performed with aryl derivatives (in Scheme 1 R_1 is Ar). The most common substrates are arylimines derived from arylaldehydes. The amine portion has been varied more, but still simple aryl or alkyl groups are preferred as *N*-substituents. Imino-pinacol couplings of ketimines are very rear, obviously because of sterical bulk, and give usually monomeric reduction products as main products [42,52]. Highly diastereoselective couplings (towards useful *dl*-isomer) are rear as well, and in most of these cases nontrivial imine substrates are required [30a,53]. There is also an example of enantioselective imino-pinacol coupling [53a], but so far has this method, using an excess of homochiral champersulfonic acid, remained to be the only asymmetric version documented[*].

Coupling of imines gives *N*,*N'*-disubstituted 1,2-diamines and therefore, in order to obtain *N*,*N'*-unsubstituted diamines, it is necessary to remove the substituents from the nitrogen atoms. As an alternative, the direct synthesis of *N*,*N'*-unsubstituted diamines could be performed by coupling of aryl oximes (X = N-OH in Scheme 1) or azines [54]. Also silylimines [55] and dibenzylidenesulfamides [56] are suitable for this purpose.

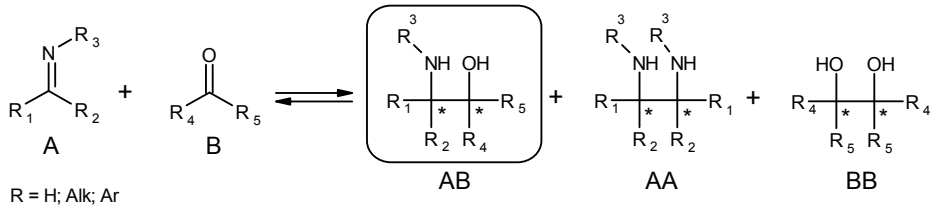
Intermolecular coupling of imines is generally limited to the preparation of symmetrical 1,2-diamines, although a couple of reports on synthesis of unsymmetrical diamines has been published [51,57]. The reactivity of two imines must be different in order to avoid the formation of statistical mixture of homo- and cross-condensation products, and in addition, the reaction conditions or the nature of imines must favour the cross-coupling. As a single example, quite a remarkable chemoselectivity is achieved in coupling of arylimines

[*] Attempts to repeat this enantioselective synthesis in our workgroup were unsucessful, indicating that the reaction is probably very sensitive to the alterations in composition or form of heterogeneous Zn/Cu couple, used as reductant.

having electron-donating substituents in *N*-aryl group with arylimines having electron-withdrawing substituents [57]. Selectivity is thought to be due to the differential coordination of imines with slightly different basicity with two centres in bimetallic complex formed from boron trifluoride etherate and trichloromethylsilane.

2.6. Cross-coupling of aldehydes and imines

In addition to the above described couplings, there is still another possibility – coupling of carbonyl compounds with imines (see ref. [33,58,59] and references therein). Depending on the ratio of reactants, their reactivity, and other reaction conditions, varying amounts of 1,2-aminoalcohols and homo-coupling products are obtained as a result (see Scheme 9).



Scheme 9. Coupling of aldehydes and carbonyl compounds

Again, the key to reasonable yields of cross-coupling products is the different reactivity of components and supporting reaction conditions (in general, the principle is the same as for above described mixed pinacol couplings of different carbonyl compounds or different imines). For example, methods based on the different reactivity of arylimines and alkylketones (e.g. reduction potentials for Ph(C=N-Ph)Me is –2,23 V and for acetone –2,96 V[*]) have been used for cross-couplings with modest to good chemoselectivity [33,59]. In used reaction conditions, the homo-coupling of aliphatic ketones didn't occur (because of the higher reduction potential), and the homo-coupling of imine was suppressed in one occasion by its slow addition into the reaction mixture containing ketone in excess [59]. In another work the suppression of homo-coupling of imines was achieved by the use of ketimines, which generally do not form dimerisation products due to the sterical reasons, as an imine component [33]. Also in those experiments, the cross-coupling was additionally supported by the ketone's excess. A different approach was used for coupling of arylaldimines with arylaldehydes by Shimizu et al. [58], in which case the selectivity was believed to arise from bimetallic complex, formed from boron trifluoride etherate and

[*] Potential *vs* Ag/AgCl electrode in 1%Bu_4NC1O_4/DMF [33].

methyltrichlorosilane. On the basis of affinity and sterical repulsion, the oxygen atom (of aldehyde) is coordinated with the more Lewis acidic silicon atom of methyltrichlorosilane, whereas the nitrogen atom (of imine) is coordinated with the boron trifluoride. Imine and aldehyde, which are coordinated on the same bimetallic complex, are then reduced with zinc, and the subsequent coupling of radical species gives the cross-adduct.

2.7. Synthesis of hydrazinoarylaldehydes

Hydrazinoarylaldehydes are compounds which are from one side derivatives of arylaldehydes (for example, benzaldehyde), and from the other derivatives of hydrazines (see Figure 1). Among other possible uses of hydrazinoarylaldehydes, they are also potential substrates for pinacol and imino-pinacol condensation to yield multifunctional compounds, which may found use, for example, as multidentate chelating chiral ligands for catalysts, as starting compounds for construction of heterocyclic structures, and so on.

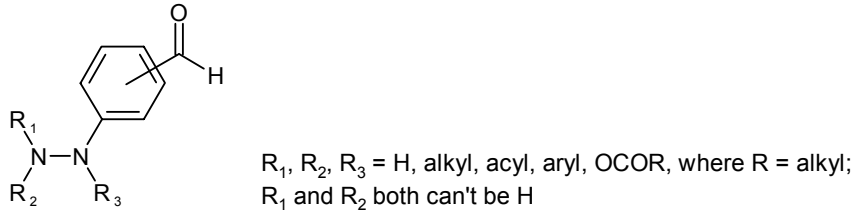
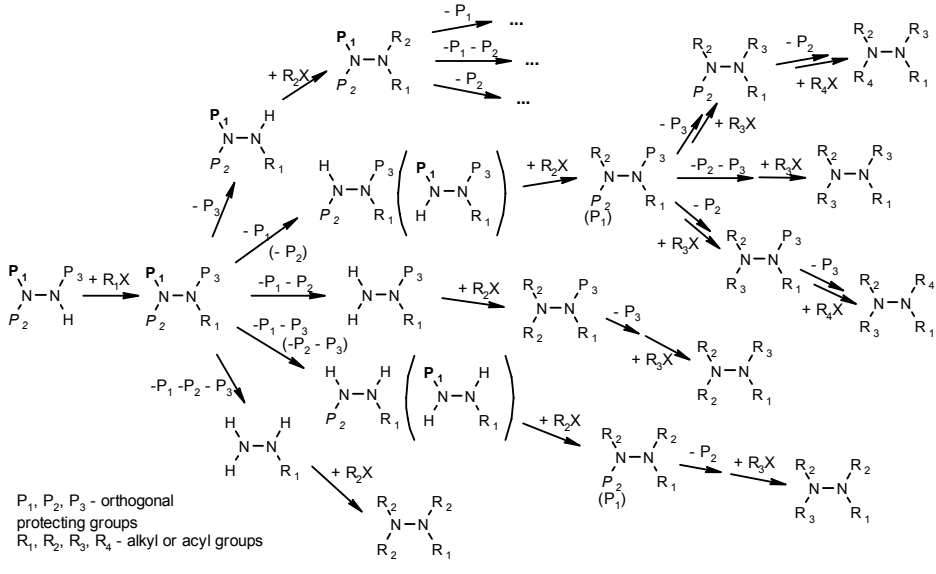


Figure 1. General formula of hydrazinobenzaldehydes

The hydrazine derivatives are found in drugs, pesticides, different types of reagents, and constitute starting materials for the synthesis of heterocycles (for a review, see ref. [60]). If many hydrazines, including aryl hydrazines, are common chemicals, which are produced and used in big quantities, then arylhydrazines and their derivatives (hydrazones, hydrazides) bearing an aldehyde group are relatively unknown compounds. For example, agaritinal, a derivative of 4-formylphenylhydrazine, is often accompanied with agaritine [61] (a derivative of 4-hydroxymethylphenylhydrazine, which is considered a potential health risk) in mushrooms from genus Agaricus, at least one of which (*Agaricus bisporus*) is widely cultivated. Formylarylhydrazones have also been used as intermediates in synthesis of compounds with non-linear optical properties [62], heterodiradicals [63], and heterocyclic compounds [64]. Other possible uses of formylphenylhydrazine derivatives include, for example, photothermographic materials [65], electrophotographic photoreceptors [66], diagnostic agents for urobilinogen detection [67], and antibiotics [68].

Different strategies and numerous methods can be used for the synthesis of substituted hydrazines [60]. However, most of the methods are generally not very selective and have limited scope (like, they can be used only for certain type of starting compounds or they yield only certain type of products). The most general and in many aspects very convenient way to obtain differentially substituted hydrazines is to use directed stepwise substitution-deprotection strategy, starting with a suitably protected hydrazine derivative [60,69] (see Scheme 10).



Scheme 10. General scheme for the directed stepwise synthesis of substituted hydrazines

By this approach hydrazines with desired substitution pattern, including hydrazines with four different substituents, can be easily obtained. However, until recently, the substituents which have been introduced included only alkyl and acyl groups. When the target was hydrazine with one or more aryl substituents in addition to alkyl and/or acyl group(s), then it was necessary to start with the suitable protected aryl hydrazine. In many cases this is not a serious problem, because simple phenylhydrazine derivatives are accessible from commercial sources or by simple synthetic procedures, but sometimes the use of aryl hydrazines as the starting compounds is not possible or not convenient, as for example, when aryl substituent does not tolerate the following substitution or deprotection reactions, or there are no reasonable methods for preparing such hydrazine. Also in combinatorial chemistry and screening studies this restriction may complicate the process. Therefore, a method for direct arylation of

protected hydrazines was needed to extend the scope of the directed stepwise substitution-deprotection strategy.

Direct arylation of hydrazines could also be used for obtaining hydrazinoarylaldehydes if the arylation was performed with the reagent containing aryl group, which was substituted with the suitable aldehyde group precursor.

2.7.1. Direct arylation of hydrazines

As hydrazines' chemical properties are very similar to those of amines, then it is logical to assume that methods for arylation of amines are also applicable for hydrazines. In fact, there are a few earlier reports where *N*-arylation has also performed, among other amine substrates, with some simple hydrazine derivatives [70,71]. Following the same logic, we were able to show in 2000 that trisubstituted hydrazines can be arylated under mild conditions and in very good yields with triarylbismuthanes in the presence of $Cu(OAc)_2$ and Et_3N [II] by the method used previously for *N*-arylation of amines [72]. At the same time another paper appeared [73], where *N*-arylaminophthalimides were phenylated with triphenylbismuthane under similar conditions. In the following years the interest in arylation of hydrazines has grown considerably (for the recent review, see ref. [74] and references therein, see also ref. [71,75–77]).

At the moment, the methods used for *N*-arylation, including arylation of hydrazines, can be divided into four main groups:

1) Pd-catalysed arylation with aryl halogenides [71,77,78];
2) Cu-catalysed arylation with aryl halogenides (Jourdan-Ullmann-Goldberg synthesis) [76,79,80a];
3) Cu-mediated arylation with arylbismuthanes (for reviews see ref. [80], see also ref. [74]);
4) Cu-catalysed arylation with aryl boric acids (or with their esters or cyclic anhydrides) [75,81].

Each method has its advantages and disadvantages. Advantages of arylation with trivalent or pentavalent triarylbismuthanes (Ar_3Bi or Ar_3BiX_2, where X is OCOR or Cl, respectively) include mild reaction conditions, usually high yields, simple preparation of arylbismuthanes from arylhalogenides by standard methods of organometallic chemistry, and low toxicity of bismuth compounds [82]. On the other hand, synthesis of arylbismuthanes is limited to aryl compounds substituted with groups tolerating lithiation or Grignard reagent preparations [80b], and in addition, the synthesis of arylbismuthanes with electron-withdrawing substituents is not so straight forward, although there are a few examples of such bismuthanes [83]. The main shortcoming of the method is that only one aryl group out of three in triarylbismuthane can be used for arylation, and therefore the use of triarylbismuthanes with "expensive" aryl groups is not

very economical. However, compared to other methods, arylation with bismuthanes is a method of choice in many cases.

As already mentioned, both trivalent and pentavalent arylbismuthanes can be used for arylation. Trivalent arylbismuthanes are usually prepared from $BiCl_3$ and corresponding arylmagnesium halogenide or aryllithium derivative. The most common pentavalent bismuth reagents, triarylbismuth diacetates, are readily obtained from Ar_3Bi by oxidation using $NaBO_3$/AcOH [84]. For the arylation with trivalent bismuthanes, stoichiometric amount (or even excess) of copper salt [usually $Cu(OAc)_2$] is used, whereas if pentavalent bismuthanes are used, only catalytic amount of copper salt or metallic copper is needed. Also the reactivity of tri- and pentavalent bismuthanes is different. For example, trivalent reagents react faster with di- and trisubstituted hydrazines than pentavalent reagents, whereas pentavalent reagents exhibit high chemoselectivity for amino over amide functions [74].

2.7.2. Other methods

Preparative methods used so far for obtaining formylarylhydrazine derivatives include, according to the literature, following examples. Reduction of cyano group with DIBAL-H was used for the conversion of 4-cyanophenylhydrazine derivative to the corresponding aldehyde [63]. In another method [62], substituted phenylhydrazone was metallated with *t*-BuLi and then treated with PhN(Me)CHO. 4-Formylhydrazobenzenes formed as a result of untypical alkyl-nitrogen cleavage when acetamidomethylsubstituted diaryl azocompounds were treated with KOH in alcohol [85]. One very specific example comprises direct substitution of pentafluorobenzaldehyde diethylacetal with hydrazine, treatment of formed *p*-substituted arylhydrazine with pentafluorobenzaldehyde to give corresponding hydrazone, and deprotection of latter to *p*-formylarylhydrazine arylhydrazone [86]. Another specific examples include photoinduced deoxygenation and dimerisation of 4-nitrobenzaldehyde with *t*-BuHgI/KI [87], formation of 1-methyl-1-(3-chloro-4-formylphenyl)hydrazone of 2,4-dichlorobenzaldehyde when 2,4-dichlorobenzaldehyde was treated with methylhydrazine [88], and coupling of 4-diazobenzaldehyde with ethyl N-(2-cyanoacetyl)-carbamate [64]. Antibiotic XK-90 (*N*-acetyl-*N'*-(3-formyl-4-hydroxyphenyl)-hydrazine) has been produced microbiologically from *Streptomyces chibasis* [68].

3. AIMS OF THE STUDY

The main goals of the present thesis were:

1) To investigate the mechanism and stereochemical aspects of the homo aldol-Tishchenko reaction and to evaluate its suitability for the enantioselective synthesis of 1,3-diol derivatives on the basis of selfcondensation of simple aldehyde, 2-methylpropanal.

2) To contribute to the development of an effective method for direct arylation of substituted hydrazines, applicable in the stepwise substitution-deprotection strategy of synthesis of hydrazines, and to examine the suitability of this method for the synthesis of hydrazinoarylaldehydes.

3) To synthesise functionalised 1,2-diol derivatives with hydrazinoaryl moieties by pinacol coupling of hydrazinoarylaldehydes and to synthesise functionalised 1,2-diamine derivatives with hydrazinoaryl moieties by imino-pinacol coupling of hydrazinoarylaldehydes phenylimine derivatives.

4. RESULTS AND DISCUSSION

4.1. Stereochemical aspects of the aldol-Tishchenko reaction on the basis of selfcondensation of 2-methylpropanal [I]

When this investigation was started, there were no examples of enantioselective version of aldol-Tishchenko or Tishchenko* reaction published in the literature and also the mechanism of this process was not completely clear. However, the selfcondensation reaction of simple aldehydes to 1,3-diol monoesters seemed to us very attractive as a potential tool for obtaining chiral diols and their derivatives. In order to focus only on enantiodiscrimination and to simplify the analysis of results, we chose 2-methylpropanal (**1**) as the aldehyde substrate. By this selection only one chiral centre is formed in aldol as well as in monoesters, and this means that no diastereomers will be present in products.

As chiral selector, homochiral binaphtholate catalysts were used. They were chosen because in earlier reports phenolates had been used as catalyst for non-stereoselective aldol-Tishchenko reactions [6g-i,16b] and homochiral binaphthol is easily accessible. Preliminary experiments with different naphtholates in different solvents (THF, DMF and DMSO) gave the best results in terms of reaction time and products' ees with monolithium (*S*)-2,2'-binaphtholate (**7**) in THF. The results also indicated that at least two steps in this reaction sequence were asymmetrical with different, very probably even with the opposite enantiomeric discrimination, as can be concluded from the data given in the Table 1.

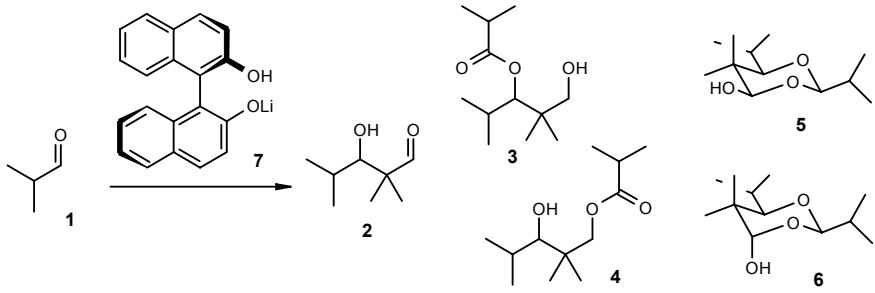
Table 1. Results of selfcondensation of 1[a]

Entry (time)	**a** (214 h)[b]		**b** (1.2 h)	
Compound	**%**[c]	**ee%**	**%**[c]	**ee%**
2	5	–	76	12.9 *R*
3	24	3.5 *S*	7	–
4	28	18.7 *S*	–	–
5 + **6**	43	19.4 *R*	11	–

[a] Products were isolated from the catalyst by vacuum distillation using DMSO as the aiding media. The distillate was partitioned between water and Et_2O and the organic layer was dried ($MgSO_4$) and concentrated at reduced pressure, to give products mixture as colourless oil. For further details see the following discussion.
[b] Conversion of aldehyde 76%.
[c] Compound relative content in the product mixture.

* As already mentioned (see footnotes on p. 14), here only intramolecular disproportionation is considered as Tishchenko reaction. For intermolecular disproportionation of aldehydes to simple esters, there are two earlier reports where enantioselective reactions are claimed [89,90].

In all experiments varying amounts of aldol **2**, regioisomeric monoesters **3** and **4,** and aldoxanes **5** and **6** were obtained (see Scheme 11). Their ratio depended on the reaction time and conditions, but usually monoesters and aldoxanes were the main products in more or less comparable amounts. The presence of substantial amount of aldoxanes (cyclic acetals of aldol and aldehyde, considered as by-products of aldol-Tishchenko reaction [17,18]) in product mixture complicated the analytical procedures as well as mechanistic considerations. On the other hand, this gave us additional information about stereochemistry of 2-methypropanale selfcondensation. Such large amounts of aldoxanes could be explained by their relative stability at ambient temperature.



Scheme 11. 2-Methylpropanale selfcondensation products

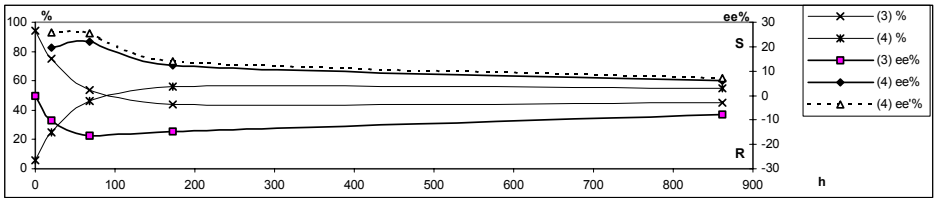
Before continuing, a few words about experimental and analytical methods. All experiments were performed at room temperature under argon in the presence of 10 mol% (in acyl migration experiments 33 mol%) of catalyst. Catalyst **7** was prepared from 1 equivalent of (*S*)-2,2'-binaphthol and 1 equivalent of granulated lithium in THF immediately before the condensation or acyl migration experiments. After lithium was dissolved, aldehyde **1** (or in acyl migration experiments monoester **3** or **4**) was added and the reaction mixture was kept in the sealed vessel. Reaction mixture or sample aliquots were quenched with saturated NH_4Cl and extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated at reduced pressure. Relative composition of the residue* was determined by GLC and the components were separated with column chromatography on silica gel. Diastereomeric aldoxanes **5** and **6** were not separable by column chromatography. According to ^1H NMR, the ratio of **5** and **6** was approximately 3:2 in all studied samples. For the determination of enantiomeric excess, all the separated compounds were converted to 2,2,4-trimethylpentane-1,3-diol **10** by following procedures: 1) aldol **2** was reduced with $NaBH_4$ in EtOH; 2) monoesters **3** and **4** were hydrolysed with KOH in

* After 200–300 h the conversion of aldehyde to condensation products was generally 65–77% in experiments where the whole reaction mixture was worked-up and the products were separated from catalyst by vacuum distillation (see for example footnote a in Table 1).

EtOH at reflux; and 3) aldoxanes **5** and **6** were reduced with $LiAlH_4$ in Et_2O. Diol **10** was then converted to diacetate (with excess of Ac_2O in CH_2Cl_2 at 90 °C in a sealed vial) and its enantiomeric ratio was determined by GLC on a chiral capillary column (Chiraldex™ B-PH). The absolute configuration of enantiomers was assigned according to their retention times, based on comparison with the retention time of the enantiomer with known configuration ((*S*)-**10** was prepared by Harada [91] method and converted into the diacetate as all other samples).

In the first condensation experiments with catalyst **7** we also observed that the enantiomeric composition of monoesters **3** and **4** was not identical (see Table 1), indicating probable enantiodiscrimination in acyl migration step. For further confirmation of this observation, an independent acyl migration experiment was carried out [16c], and as a result of this experiment we proved that the chiral catalyst **7** can, indeed, affect the stereochemistry of reversible acyl migration between **3** and **4**. In both direction, starting either from **3** or **4**, the migration was faster with *S* isomers, as it was observed after 120 or 160 h, respectively. However, because the migration is reversible, the enantiomeric excess should decrease and reach ultimately zero as the reaction approaches to the equilibrium. This was clearly demonstrated later, when the time dependence of the enantiomeric excess and regioisomers ratio was monitored in acyl migration experiment, as shown in Table **2** and its illustrating chart.

Table 2. The changes in regioisomeric and enantiomeric composition in acyl migration[a]

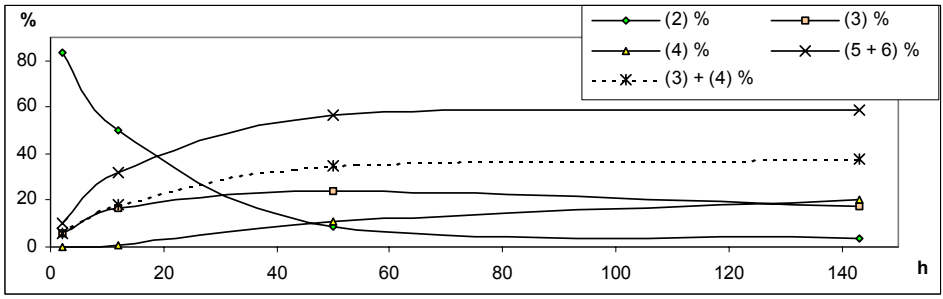


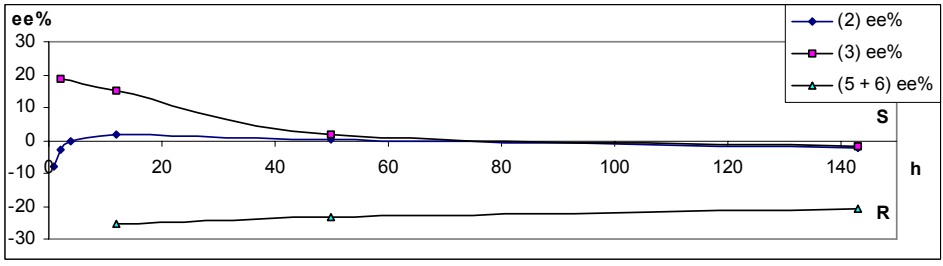
h	(3) %[b]	(3) ee%	(4) %[b]	(4) ee%	(4) ee'%[c]
0	94	0	6	(0)	–
20	75	10.1 *R*	25	19.5 *S*	25.8
68	54	16.6 *R*	46	22.1 *S*	25.4
172	44	14.8 *R*	56	12.4 *S*	13.9
862	45	7.7 *R*	55	6.2 *S*	7.0

[a] Experimental details are given in discussion above.
[b] Relative content in the product mixture.
[c] Adjusted ee% considering 6% of racemic **4** in starting material.

The next step in the study was to monitor the course of the whole selfcondensation reaction in time by determining the changes in proportion of components and in their ee after different time intervals. The results with illustrating charts are shown in Table 3.

Table 3. Changes in relative composition of reaction products and in their ee%[a]





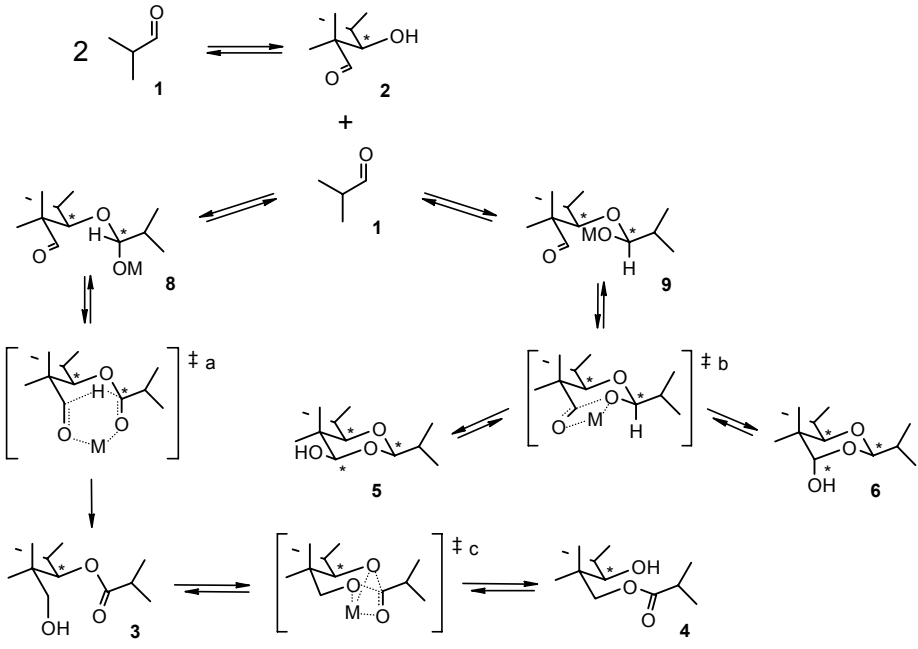
Time (h)	1		2	4	12		50		143	
Compound	**ee%**	**%**[b]	**ee%**	**ee%**	**%**[b]	**ee%**	**%**[b]	**ee%**	**%**[b]	**ee%**
2	8 *R*	84	2.9 *R*	0.3 *R*	50	1.7 *S*	9	0.3 *S*	3.5	2.4 *R*
3	–	6	18.6 *S*	–	17	15.1 *S*	24	2.0 *S*	17	1.7 *R*
4	–	0	–	–	1	–	11	–	20.5	33.0 *S*
5 + **6**	–	10	–	–	32	25.6 *R*	56	23.4 *R*	59	21.0 *R*
(**3** + **4**)		6			18		35		37.5	

[a] Experimental details are given in discussion above.
[b] Compound relative content in the product mixture.

In the first few hours, when the major condensation product was **2**, its *R* isomer initial slight exess (ee%) decreased rapidly, most probably due to the fast retroaldol reaction. After 12 h, **2** was already enriched very slightly in the *S* isomer, probably because of the quicker formation of (*R*)-aldoxanes. Afterwards, as the amount of **2** decreased, the ee changed very slowly towards a very slight excess of the *R* isomer. This may be explained assuming that a certain amount of **2** originated from the degradation of aldoxanes. The changes in percentages of monoesters and aldoxanes with time are quite similar, only the percentage of aldoxanes is proportionally larger than that of monoesters. However, a closer examination reveals that the ratio gradually increased in favour of the monoesters relative to the aldoxanes, once the rapid increase of both the materials was ceased (at about 50 h). This could be expained by the slow degradation of aldoxanes or by the reversibility of their formation. The latter proposal is also supported by the slow decrease in the ees of the aldoxanes with time. The changes of amounts of **3** and **4** in the reaction mixture and the change in the ees

of **3** and also the relatively high ee of **4** (at 143 h) are in good agreement with the results of the acyl migration experiment described above.

Based on the results of these experiments and previous reports [10b,12,15], the following scheme (Scheme 12) can be drawn for the selfcondensation of **1** in the presence of **7**. The reaction starts with the rapid formation of **2**, so that the rate of formation of the *R* isomer is somewhat higher. Soon excess of the *R* enantiomer decreases close to zero because of the reverse aldol reaction. At the same time **2** starts to react with **1** to form two diastereomeric hemiacetals **8** and **9**. We propose that both diastereomers react differently: **8** seems to be more able to form the activated complex **‡a** for hydride transfer (as proposed by Evans [12] and Burkhardt [15] for Tishchenko-type reactions) and gives **3**, while **9** is more suitable to form the hypothetical activated complex **‡b** for the formation of aldoxanes. The ratio of aldoxanes and monoesters in the experiments is about 3:2, but it is not clear whether this arises from the diastereoselectivity of the formation of hemiacetals or from the limitations in hydride transfer. Theoretically the hemiacetal **9** leading to aldoxanes is more favourable because of the equatorial position of the OM group, which could explain the small excess of aldoxanes compared to monoesters. Both trimerisation paths



Scheme 12. Detailed scheme of selfcondensation of **1** (only the *R* series of **2**–**8** is depicted)

also have opposite enantioselectivities, so that **3** is enriched with the *S* isomer and the aldoxanes with the *R* isomer. The possibility that only one of them is enantioselective and the other uses the starting material left enriched with the opposite enantiomer is avoided because of the rapid equilibration of the aldol reaction. This is also consistent with the observed ee of **2** throughout most of the reaction. However, it is not obvious from these experiments at which point exactly the discrimination takes place – at the hemiacetal formation or at the following Tishchenko reaction and aldoxane formation. The intramolecular acyl migration, preferring the *S* isomer, begins after the formation of **3** and leads to the formation of a mixture of **3** and **4** in the reaction products. In the beginning it also causes quite large differences in the ee values of **3** and **4**, but afterwards the differences slowly decrease due to the reversibility of this isomerisation.

With these results we showed that several steps in the selfcondensation of **1** proceed with low to moderate enantioselectivity in the presence of catalyst **7**, but the use of this multi-step condensation to prepare enantiomerically pure 1,3-diol derivatives seems to be limited (at least under the conditions described) because of the various equilibrium reactions and opposite selectivities. However, it was concluded that some single steps of this condensation could be useful separately under other conditions, or the reaction toward the aldoxanes may be more promising to obtain products with high ee. The latter would be especially promising if the retro-aldol reaction was suppressed, or the following acetalisation was faster than retro-aldol reaction. In this case, both steps will support the products' enantiomeric enrichment in one direction (provided the direction of selectivity for both steps will remain the same as observed here). Based on these results, a suggestion was also made about the diastereomeric nature of acetalisation reaction, which leads to two trimerisation paths.

Additional comments: If there were reaction conditions where the enantioselectivities of Tishchenko reaction and acyl migration were higher than achieved here (but separately still not high enough) and both selectivities were still in the same direction, then in theory, it could be possible that the enantioselective acyl migration amplifies the initial ee of secondary monoester **3** to the acceptable ee levels in primary monoester **4**. Additionally, it must be provided that the acyl migration is not reversible in those conditions, or that the reaction is stopped far before reaching the equilibrium. In latter case, the yield will suffer, of course.

Another interesting aspect is that aldoxanes and secondary monoester are formed with opposite selectivity. In case of higher selectivity this could, in principle, give access to precursors for both 1,3-diol enantiomers with one catalytic synthesis. However, the fine tuning of this complicated multistep process is inherently not very trivial and also the separation of numerous reaction products is not very convenient.

Speaking of the direction of the reaction towards monoesters (or aldoxanes), it can be reasoned as follows. If activated complexes **‡a** and **‡b** are compared, then **‡b** is more tight (4-membered cycle versus 6-membered cycle in **‡a**) and

can be formed only if the coordinating metal atom is relatively small (like Li and Mg). Consequently, the formation of aldoxanes should be suppressed if catalysts with bigger coordinating metal atom were used.

And, finally, although only one model substrate was used here, it is quite probable that similar trends would be true for other similar aldehydes if catalyst **7** or its close derivative was used.

4.1.1. Later developments

Shortly after our report an interesting paper was published [7], where catalytic hetero (mixed) aldol-Tishchenko reaction of benzaldehyde or some of its derivatives and 2-methylpropanale gave monoesters with up to 70% yield and 74% ee. With α,β-unsaturated aldehyde only 50% yield of monoesters with 10% ee was obtained. The complex of $Y_5O(O\textit{i}\text{-Pr})_{13}$ and homochiral salen was used as the catalyst. It was shown that only Tishchenko reaction was responsible for enantioselectivity, whereas aldol condensation and acyl migration were non-selective. The authors proposed that the preferential formation of less sterically crowded activated complex with chiral catalyst for hydride transfer determines which enantiomer is obtained in excess. Homocondensation of 2-methyl-propanale was not mentioned in those conditions (probably, because the benzaldehyde is much more electrophilic than aliphatic 2-methylpropanale and reacts faster with enolate).

A different strategy for enantioselective aldol-Tishchenko reaction was described in another recent paper [3]. In this work preformed aldol adducts of acetone or acetone and some other methyl ketones were used for the generation of metal enolates by retro-aldol reaction. The enolates reacted then with an aldehyde, present in excess, and formed enantioselectively new aldols, which were disproportionated in the following diastereoselective Tishchenko reaction to secondary diol monoesters. With chiral Zr-TADDOL-ate* catalysts quite high yields and moderate ees were obtained. Acyl migration was completely suppressed in most of the cases studied.

So far the best results of asymmetric aldol-Tishchenko reaction have been described for mixed condensation of some para- or meta-substituted arylalkyl-ketones with non-enolisable arylaldehydes [9]. In this very recent report very good yields (60–96%) and high ees (84–95%) (also the diastereoselectivity was very high) were obtained with catalyst formed from $La(OTf)_3$/BINOL/BuLi. In these conditions, only the Tishchenko step was found to be enantioselective.

In conclusion, below are listed some general features for those three recent reports:

- specific reactions where only certain narrow classes of substrates were used;

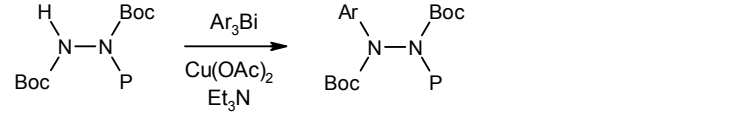
* TADDOL's - α,α,α',α'-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanols - tartaric acid derivatives.

- single enantioselective step;
- heteroreactions where one component is either non-enolisable aromatic aldehyde or metal enolate of the ketone (formed *in situ* from the corresponding aldol by retro-aldol reaction);
- catalyst contains late transition metal atoms (Y, Zr, La) and except for one case (BINOL in ref. [9]), the chiral ligands are big and complex molecules.

4.2. Arylation of substituted hydrazines with triarylbismuthanes [II, III]

After the development of stepwise substitution-deprotection strategy for the synthesis of alkyl- and acyl-substituted hydrazines [69a], a method for direct arylation of protected hydrazines was needed to extend the scope of the strategy. It was shown by Barton et al. that with triphenylbismuthane *N*-phenylation of a variety of amines takes place under mild conditions in the presence of copper salts as catalysts [70]. More recently, Chan demonstrated that also many derivatives of amines including amides, sulfonamides, and carbamates with a free NH undergo this reaction when an additional tertiary amine is added to the reaction mixture [72]. Triphenylbismuthane is nowadays a commercially available reagent with several additional applications in synthetic chemistry and many other triarylbismuthanes have been described and are easy to make [84]. Therefore it was decided to test this synthetic methodology for stepwise introduction of aromatic substituents into hydrazines.

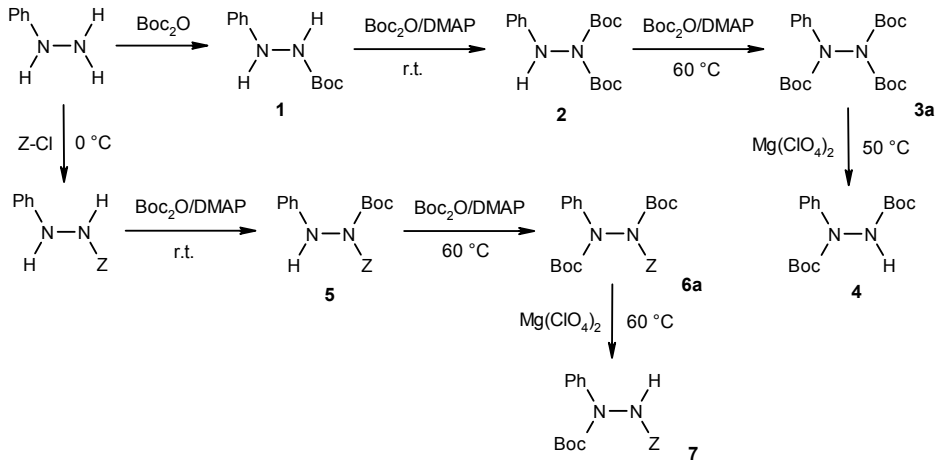
The first arylation experiments with triarylbismuthanes were carried out using hydrazine reagents **A4** and **A1** resulting in monoarylated products **3** and **6** (Scheme 13). Anhydrous $Cu(OAc)_2$ and triethylamine were used as additives [72]. No side-product was detectable chromatographically or spectroscopically in those experiments. Compounds **3a** and **6a** were compared with the reference samples previously prepared from phenylhydrazine by an independent route (Scheme 14). In addition to affording reference samples for this work, the synthetic route depicted in Scheme 14 could also be used as an alternative for the synthesis of some substituted arylhydrazines.



A4: P = Boc
A1: P = Z

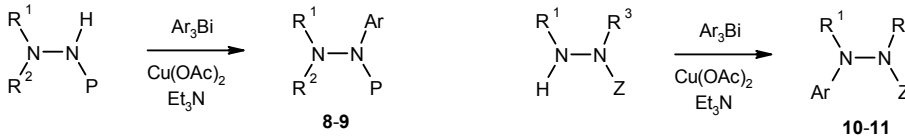
3: P = Boc;
Ar = Ph (**a**), 4-Me-C_6H_4 (**b**), 4-MeO-C_6H_4 (**c**)
6: P = Z;
Ar = Ph (**a**), 4-Me-C_6H_4 (**b**), 4-MeO-C_6H_4 (**c**)

Scheme 13. Arylation of hydrazine reagents **A4** and **A1** with triarylbismuthanes



Scheme 14. Synthesis of Boc or/and Z protected phenylhydrazine derivatives

After monoarylation of **A4** and **A1** with triarylbismuthanes had been demonstrated to proceed efficiently, arylation on N^2 was examined and from compound **4** was made compound **8** with nonidentical aryl moieties on its two nitrogens (Scheme 15, left part). In the same mode, from two previously made monoalkylated derivatives of **A1** the corresponding N^2-arylated compounds **9** were prepared (Scheme 15, left part). Arylation on *N*-alkyl nitrogens **(10)** and in one case also on an *N*-aryl nitrogen **(11)** has also been effected (Scheme 15, right part).



8: R^1 = Ph, R^2 = Boc, P = Boc, Ar = 4-Me-C_6H_4,
9a: R^1 = C_3H_5, R^2 = Boc, P = Z, Ar = Ph,
9b: R^1 = $EtOCOCH_2$, R^2 = Boc, P = Z, Ar = Ph

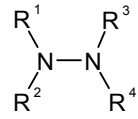
10a: R^1 = Me, R^3 = Bn, Ar = 4-Me-C_6H_4,
10b: R^1 = C_3H_5, R^3 = $EtOCOCH_2$, Ar = 4-Me-C_6H_4,
11: R^1 = Ph, R^3 = Boc, Ar = 4-Me-C_6H_4

Scheme 15. Arylation of trisubstituted hydrazines with triarylbismuthanes

In conclusion, several examples were provided on the application of triarylbismuthanes for the direct arylation of triprotected hydrazine reagents or diprotected monosubstituted hydrazines. The reactions took place under mild conditions and no side-products were detected, as a result of which the yields were quantitative or essentially quantitative. Results are summarized in Table 4. One drawback of the procedure is that only one aromatic residue of the bismuthane seems to be available for arylation. Furthermore, as long as the

bismuthanes are made via Grignard reagents or via lithiation, the restrictions with respect to the functional groups tolerated by those methods, at present, limit the scope of this procedure [80b]. Nevertheless, many new multisubstituted hydrazines are now in sight by simple stepwise synthesis and this methodology should also be applicable for other related reagents.

Table 4. Results of the arylation of hydrazines with triarylbismuthanes[a]



Entry	Compound	R^1	R^2	R^3	R^4	%
1	**3a**	Boc	Boc	Boc	Ph	100
2	**3b**	Boc	Boc	Boc	4-Me-C_6H_4	98
3	**3c**	Boc	Boc	Boc	4-MeO-C_6H_4	97
4	**6a**	Boc	Z	Boc	Ph	98
5	**6b**	Boc	Z	Boc	4-Me-C_6H_4	98
6	**6c**	Boc	Z	Boc	4-MeO-C_6H_4	97
7	**8**	Boc	Ph	Boc	4-Me-C_6H_4	96
8	**9a**	Boc	C_3H_5	Z	Ph	96
9	**9b**	Boc	$EtOCOCH_2$	Z	Ph	97
10	**10a**	Bn	Z	Me	4-Me-C_6H_4	98
11	**10b**	$EtOCOCH_2$	Z	C_3H_5	4-Me-C_6H_4	97
12	**11**	Boc	Z	Ph	4-Me-C_6H_4	96

[a] Yields are for isolated materials.

As a typical procedure, the synthesis of 1,2,2-tri-*t*-butyloxycarbonyl-1-phenylhydrazine **(3a)** from **A4** with triphenylbismuthane is described: To a magnetically stirred mixture of **A4** (166 mg, 0.5 mmol), anhydrous $Cu(OAc)_2$ (137 mg, 0.75 mmol), and triethylamine (103 μL, 0.75 mmol) in dichloromethane (1.0 mL), under nitrogen, was added triphenylbismuthane (330 mg, 0.75 mmol, commercial origin) in one portion. The mixture was stirred at room temperature until all **A4** had been consumed, as indicated by TLC, which took about 23 h, whereupon the solvent was evaporated and the remainder mixed with 3–4 mL of silica. This was placed on top of a short silica column which was eluted first with EtOAc/light petroleum 1:20 to remove the excess of bismuthane used. Then the EtOAc/light petroleum ratio was changed to 1:5, as a result of which pure **3a** could be eluted from the column to give, after evaporation, a colourless oil (210 mg, 100%). It could be crystallized, although with massive loss of material, from light petroleum; mp 64–65°C.

Other arylating reagents, tri(4-methylphenyl)bismuthane and tri(4-methoxyphenyl)bismuthane, were made according to Combes and Finet [84] in 68% yield (which could be increased to 90% by chromatography of the mother liquor in $CHCl_3$/light petroleum 1:10 on a short silica column) and 77% yield (modest

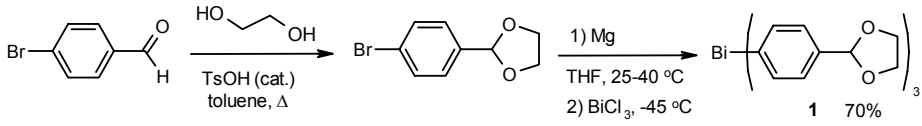
initial yield was substantially increased after extraction of the Celite filter cake in a Soxhlet apparatus) respectively.

Details for the synthesis of phenylhydrazine derivatives presented in Scheme 14 are given in Paper II. It should be noted that Pozdnev prepared **4** directly from **1** with Boc_2O in boiling benzene without addition of DMAP [92], whereas in the presence of this catalyst **2** is formed before **3a** and **5** before **6a** as indicated in Scheme 14. To investigate whether **2** could also be converted to **3a** without DMAP, a separate, small-scale experiment with an excess of Boc_2O in boiling benzene for several hours was carried out with positive result. Obviously the reaction with Boc_2O at the phenyl-substituted nitrogen is rather slow both with and without addition of DMAP and requires heating, whereas in the presence of catalyst smooth dual protection occurs at the other nitrogen. As an advantage, following the Scheme 15 protected phenylhydrazines with either free N-H on N^1 (compounds **2** and **5**) or on N^2 (compounds **4** and **7**) are easily available. Product **4** could also be obtained in considerably higher yield directly from phenylhydrazine by a convenient one-pot reaction.

4.2.1. Synthesis of hydrazinoarylaldehydes [III]

In order to provide a method for the synthesis of substituted hydrazines with arylaldehyde functionality and to extend the choice of substituents available for hydrazines stepwise substitution strategy, the introduction of arylaldehyde functionality by direct arylation was then investigated. Because of its reactivity the aldehyde group can not be present unprotected in aryl derivative when the bismuthane is made or used for arylation as described in previous paragraph. To protect aldehyde functionality, its conversion to 1,3-dioxolane with 1,2-ethandiol was chosen. Accordingly, 4-bromobenzaldehyde* was converted to 4-bromophenyl-1,3-dioxolane following a simple procedure [93], and the latter was then used for the preparation of triarylbismuthane **1**. The arylbismuthane **1** was obtained in good yield via standard aryl Grignard chemistry using slightly modified method described by Combes and Finet [84] under mild conditions in the final step (Scheme 16, for experimental details, see ref. [26] in Paper III). It should be noted that the mild conditions, especially keeping the reaction mixture temperature far below zero (–45°C) in the last step, were crucial for the successful preparation of bismuthane **1**. The reason for this could be the relatively low stability of 1,3-dioxolane protecting group when it is in the para position to electron-donating substituents (like in Grignard reagent as well as in starting *p*-bromo derivative). For example, even the 4-bromophenyl-1,3-dioxolane itself was not very stable on standing at room temperature and its fine needles became soon sticky and some degradation was determined by TLC.

* 4-bromobenzaldehyde was obtained from 4-bromotoluene by treatment with CrO_3/Ac_2O [94].

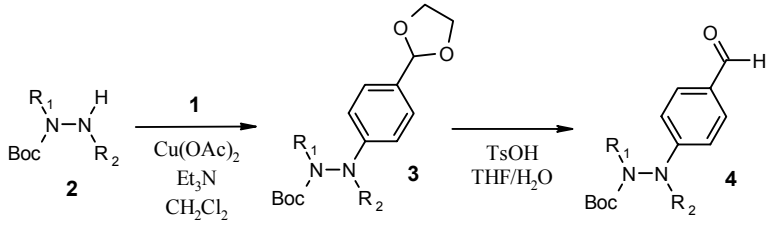


Scheme 16. Synthesis of bismuthane **1**

In contrast to this, the bismuthane **1** is stable and could be stored for months without remarkable degradation.

Arylation of hydrazines with **1** in the presence of $Cu(OAc)_2$ and Et_3N [72] proceeded under mild conditions and gave good yields for trisubstituted hydrazines (see Table 5, compounds **3a-c**). When all three substituents were Boc or Boc and acyl groups (synthesis of **3b** and **3c**), then a double amount of $Cu(OAc)_2$ and Et_3N (3 equivalents of both) were needed to complete the reaction. The reaction times were also longer than usual in those cases. When 1,2-diacetylhydrazine was used, the arylation gave complicated mixture of unidentified products. So it seems that the choice of substrates is limited to trisubstituted hydrazines.

Table 5. Synthesis of hydrazinoarylaldehydes using bismuthane **1**[a]



Entry	R_1	R_2	**3**		**4**	
			t (h)	%	t (h)	%
a	Ph	Boc	28	96	3	92
b	Boc	Boc	52	94	1.5	96
c	Ac	Ac	49	85	1	92

[a] Yields are for isolated materials. For experimental details, see ref. [28] in Paper III.

Acetal group removal from compounds **3a-c** proceeded in high yields by treatment with substoichiometric amounts of TsOH in aqueous THF (see Table 5). The procedure was essentially the same as described previously [93], only 0.4 equivalents of TsOH instead of 0.2 equivalents were used and the water content in solvent mixture (THF/water) was raised from 2% to 4%. Under these conditions Boc groups, even on the same nitrogen in **3b**, were not affected.

Under the same conditions it was also possible to remove acetal protecting groups from bismuthane **1** to give the corresponding bismuthane with free aldehyde groups, which ^1H NMR and ^{13}C NMR spectra were identical with

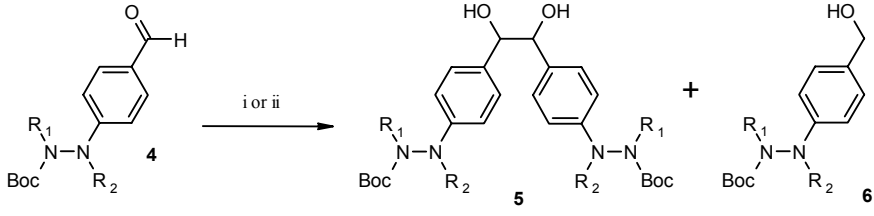
those described in another work [83], but which was not obtained as a solid because of its substantial degradation after work-up when its solution was concentrated, even at room temperature.

In conclusion, it was shown that 4-formylphenylgroup can be introduced under mild conditions and in good yields into trisubstituted hydrazines. In principle, numerous other trisubstituted hydrazines and also secondary amines/ amides could probably be used as substrates, and also bismuthanes of other benzaldehyde derivatives could be prepared and used in the similar manner for arylation.

4.3. Pinacol coupling of 4-formylphenylhydrazines and imino-pinacol coupling of their phenylimine derivatives [III]

Next goal in this study was to use 4-formylphenylhydrazines, described in previous chapter, for the synthesis of multifunctional 1,2-diol derivatives containing two hydrazine moieties (see Table 6). First experiment was performed with hydrazinobenzaldehyde **4a** using inexpensive and easy to make Zn/Cu couple as coupling reagent in refluxing ethanol (see Table 6, entry a'). This reagent has been used for coupling of benzaldehyde derivatives and imines [53a,95], however for **4a**, the treatment resulted mainly in the formation of simple reduction product **6a**.

Table 6. Coupling of hydrazinobenzaldehydes[a]



Conditions: i) Zn/Cu, EtOH, Δ[b]; ii) Mn, Cp_2TiCl_2, 2,4,6-Me_3Py·HCl, THF.

Entry	R_1	R_2	Conditions	t (h)	**5**% (dl/meso)	**6**%
a	Ph	Boc	ii	23	65 (4/1)	(15)[c]
a'	Ph	Boc	i	29	8 (1/1)	65
b	Boc	Boc	ii	61	48 (4/1)	22
c	Ac	Ac	ii	23	51 (10/1)	10

[a] Yields are for isolated materials. Products were separated by silica gel column chromatography (EtOAc/hexane). Ratios of *dl*-/*meso*-isomers were estimated on the basis of C_{18} HPLC and ^{1}H NMR, *dl*- and *meso*-isomers were assigned based on signals of benzylic protons in ^{1}H NMR spectra as described in the literature [96].

[b] Zn/Cu couple was prepared and used as described in ref. [95a].

[c] Yield estimated on the basis of C_{18} HPLC.

Our next choice for coupling reagent was catalytic system described by Gansäuer and Bauer [44b]. They used Mn powder as inexpensive reductant, collidine hydrochloride as proton source, and titanocene dichloride as catalyst for highly *dl*-selective coupling of numerous benzaldehyde derivatives. Coupling of hydrazinobenzaldehydes **4a-c** under the same conditions gave the corresponding diols **5a-c** in moderate yields and with moderate (**5a,b**) to good (**5c**) diastereoselectivity (see Table 6). Reaction times were considerably longer and the yields lower than for simple benzaldehyde derivatives [44b], probably due to the bulky substituents in hydrazino moiety. For example, the lowest yield and longest reaction time were observed when all three substituents in hydrazine were Boc groups (entry 2). Long reaction times may also be responsible for the moderate diastereoselectivity, which is in accordance with the observation of Gansäuer and Bauer [44b]. They found that in order to obtain good *dl*-selectivity, the concentration of aldehyde must be kept low, which was achieved by its very slow addition. When the coupling reaction is slow, aldehyde concentration will be high even at its very slow addition rate, and so the competitive nonselective coupling will probably take place.

Hydrazinobenzaldehydes **4a-c** could be easily converted to their phenylimine derivatives **7a-c** by treatment with aniline (1.2–2 equiv.) in CH_2Cl_2 at room temperature in the presence of $MgSO_4$ followed by filtration through the pad of Celite and concentration at reduced pressure (see Table 7). Imines **7a** and **7b** were isolated in high yields as crystalline solids, only the yield of imine 7c was moderate, mainly because its degradation during the chromatographic purification on silica gel.

The coupling of phenylimine derivatives **7a** and **7b** to the corresponding diamines was then investigated (see Table 7). Here only two test experiments were performed using above described Zn/Cu couple. In these conditions diamines **8a** and **8b** were obtained in 71% and ~29% yields respectively, but with no diastereoselectivity. As for aldehydes' pinacol coupling, it seems that bulky substituents in hydrazine portion (Boc *vs.* Ph as R_1) decrease the yield of coupling product (or at least reaction speed) considerably.

It should be noted that attempts to remove two or three Boc groups attached to one hydrazino moiety in products (**5b**, **6a**, **6b**, **8a**) simultaneously under different deprotection conditions[*] led in all cases to degradation or polymerisation[**]. Hence it is advisable that the hydrazine derivative into which the 4-formylphenyl group is to be introduced is selected so that there is no further

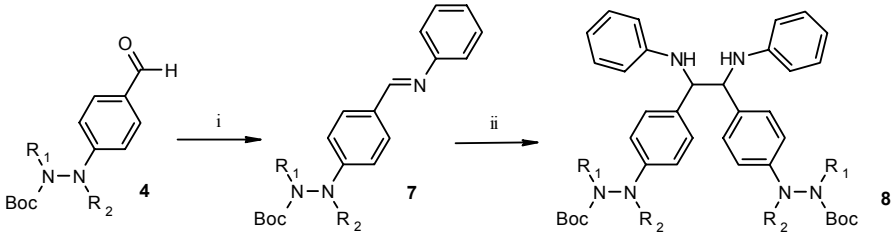
---

[*] Deprotection conditions for Boc groups which were probed: (a) CF_3COOH in CH_2Cl_2, see for example ref. [98a], (b) aq. HCl in CH_3CN, (c) $BF_3{\cdot}Et_2O$ in AcOH [98c], (d) $SnCl_4$ in EtOAc [98d].

[**] Similarly it has been found that removal of Boc groups from 1,2-di-Boc-1,2-diarylhydrazines under usual conditions resulted in the cleavage of N-N bond, to give rise to the corresponding arylamines [76b].

need for removal of Boc groups. Alternatively different protecting groups (for example Z) should be considered.

Table 7. Synthesis of hydrazinobenzaldehydes phenylimine derivatives and their imino-pinacol coupling[a]



Conditions: i) $PhNH_2$, $MgSO_4$, CH_2Cl_2; ii) Zn/Cu, EtOH, Δ[b].

	R_1	R_2	**7**		**8**	
			t (h)	%	t (h)	% (dl/meso)
a	Ph	Boc	23	98	1	71 (1/1)
b	Boc	Boc	50	91	6	~29[c] (1/1)
c	Ac	Ac	26	47[d]		

[a] Yields are for isolated materials. Ratios of *dl*-/*meso*-isomers were estimated on the basis of C_{18} HPLC and ^{1}H NMR, *dl*- and *meso*-isomers were assigned based on signals of benzylic protons in ^{1}H NMR spectra as described in the literature [97].

[b] Zn/Cu couple was prepared and used as described in ref. [95a].

[c] Calculated on the basis of the yield of isolated material (44%), which contained ~15% of starting material **7b**.

[d] Initial yield of raw product was almost quantitative, but the attempts to crystallise the raw product and finally its purification by silica gel column chromatography lowered the yield considerably.

In conclusion, we have shown that formylphenylhydrazines undergo coupling reaction to diols containing two substituted hydrazino moieties (**5a-c**) and the corresponding phenylimine derivatives undergo coupling to corresponding diamines (**8a,b**). Thus, these two new types of compounds are now, in principle, available by not very complicated synthetic procedures, although, there is still room for further studies to improve the yields and stereoselectivities.

5. CONCLUSIONS

Based on the results presented in this thesis, the following conclusions were made about the three main subjects studied.

1) The mechanism and stereochemical aspects of the homo aldol-Tishchenko reaction.

It was shown that several steps in the selfcondensation of 2-methylpropanale proceed with low to moderate enantioselectivity in the presence of homochiral lithium binaphtholate catalyst, but the use of this multi-step condensation to prepare enantiomerically pure 1,3-diol derivatives seems to be limited (at least under the conditions described here) because of the various equilibrium reactions and opposite selectivities. However, it was concluded that some single steps of this condensation could be useful separately under other conditions, or the reaction toward the aldoxanes may be more promising to obtain products with high ee. A suggestion was also made about the diastereomeric nature of acetalisation reaction, which leads to two trimerisation paths.

2) Direct arylation of substituted hydrazines and the synthesis of hydrazino-arylaldehydes.

Several examples were provided on the application of triarylbismuthanes for the direct arylation of triprotected hydrazine reagents or diprotected mono-substituted hydrazines. The reactions took place under mild conditions and no by-products were detected, as a result of which the yields were quantitative or essentially quantitative. Despite some limitations, many new multisubstituted hydrazines are now in sight by a simple stepwise synthesis, and this methodology should also be applicable for other related reagents. In addition, an alternative synthetic path for some di- and triprotected phenylhydrazines was also provided.

As an extension to the arylation method, it was shown that 4-formylphenyl-group can be introduced under mild conditions and in good yields into trisubstituted hydrazines when the formyl group is protected as acetal during the preparation of triarylbismuthane and the following arylation reaction. It was proposed that in the same way also other arylaldehyde groups can be introduced into triprotected hydrazines as well as into numerous other protected amine derivatives.

3) Pinacol coupling of hydrazinoarylaldehydes and imino-pinacol coupling of hydrazinoarylaldehydes phenylimine derivatives.

It was shown that formylphenylhydrazines undergo coupling reaction to diols containing two substituted hydrazino moieties in moderate yields and with moderate to good diastereoselectivity when titanocene dichloride catalyst is used in combination with Mn powder and collidine hydrochloride. Coupling of the corresponding phenylimine derivatives to diamines was achieved with Zn/Cu couple in two occasions, but without diastereoselectivity.

REFERENCES

1. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure,* 4th ed.; John Wiley & Sons Inc: New York, **1992**, 937–942.
2. (a) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, 56, 2499. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, 103, 3099.
3. Schneider, C.; Hansch, M. *Synlett* **2003**, 837; and references therein.
4. Kobayashi, S.; Ishitani, H.; Yamashita, Y.; Ueno, M.; Shimizu, H. *Tetrahedron* **2001**, 57, 861; and references therein.
5. (a) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, 121, 4168. (b) List, B. *Synlett* **2001**, 1675. (c) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, 122, 12003. (d) Juhl, K.; Gathergood, N.; Jorgensen, K. A. *Chem. Commun.* **2000**, 2211. (e) Northrup, A. B.; McMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, 124, 6798.
6. (a) Brauchbar, M.; Kohn, L. *Monatsh. Chem.* **1898**, 19, 16. (b) Kirchbaum, F. M. A. *Monatsh. Chem*. **1904**, 25, 249. (c) Tishchenko, V. E. *Zhurnal' Russkago Fiziko-Khimicheskago Obshchestva* **1906**, 38, 355–418, 482. (d) Villani, F. J.; Nord, F. F. *J. Am. Chem. Soc.* **1947**, 69, 2605. (e) Hesse, G.; Maurer, M. *Lieb. Ann. Chem*. **1962**, 658, 21. (f) Milton, P. A.; Hugh, H. J. US 3291821, **1966**; *Chem. Abstr.* **1966**, 66, 37420q. (g) Casnati, G.; Pochini, A.; Salerno, G.; Ungaro, R. *Tetrahedron Lett*. **1974**, 12, 959. (h) Casnati, G.; Pochini, A.; Salerno, G.; Ungaro, R. *J. Chem. Soc., Perkin Trans. I* **1975**, 1527. (i) Pochini, A.; Salerno, G.; Ungaro, R. *Synthesis* **1975**, 164.
7. Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **2001**, 40, 601.
8. Lu, L.; Chang, H.-Y.; Fang, J.-M. *J. Org. Chem.* **1999**, 64, 843.
9. Gnanadesikan, V.; Horiuchi, Y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, 126, 7782.
10. (a) Mahrwald, R.; Costisella, B. *Synthesis* **1996**, 1087. (b) Bodnar, P. M.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, 62, 5674.
11. Simpura, I.; Nevalainen, V. *Tetrahedron* **2003**, 59, 7535.
12. Evans, D. A.; Hoveyda, A. H *J. Am. Chem. Soc.* **1990**, 112, 6447.
13. (a) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, 115, 7906. (b) Umekawa, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem* **1997**, 62, 3409. (c) Hulme, A. N.; Howells, G. E. *Tetrahedron Lett*. **1997**, 38, 8245. (d) Schöning, K.-U.; Hayashi, R. K.; Powell, D. R.; Kirschning, A. *Tetrahedron: Asymmetry* **1999**, 10, 817. (e) Ooi, T.; Miura, T.; Takaya, K.; Maruoka, K. *Tetrahedron Lett.* **1999**, 40, 7695. (f) Gillespie, K. M.; Munslow, I. J.; Scott, P. *Tetrahedron Lett.* **1999**, 40, 9371.
14. Smith, A. B., III; Adams, C. M.; Lodise Barbosa, S. A.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, 125, 350.
15. Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. *Organometallics* **1990**, 9, 30.
16. (a) Abu-Hasanayn, F.; Streitwieser, A. *J. Org. Chem.* **1998**, 63, 2954. (b) Peterson, J.; Timotheus, H.; Mäeorg, U. *Proc. Estonian Acad. Sci. Chem.* **1997**, 46, 93. (c) Loog, O.; Mäeorg, U. *Proc. Estonian Acad. Sci. Chem.* **1998**, 47, 193.
17. Häusermann, M. *Helv. Chim. Acta* **1951**, 34, 2172.
18. Nielsen, A. T.; Houlihan, W. J. *Org. Reac.* **1968**, 16, 58.

19. Shiraishi, H.; Kawasaki, Y.; Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. *Tetrahedron Lett.* **1996**, 37, 7291.
20. Dai, L.-X.; Lin, Y.-R.; Hou, X.-L.; Zhou, Y.-G. *Pure Appl. Chem.* **1999**, 71, 1033.
21. Kharasch, M. S.; Richlin, I., Mayo, F. R. *J. Am. Chem. Soc.* **1940**, 62, 494.
22. Minkin, V. I.; Nivorozhkin, L. E.; Bren, V. A. *Zh. Obsh. Khim.* **1965**, 35, 1270.
23. Emerson, W. S.; Hess, S. M.; Uhle, F. C. *J. Am. Chem. Soc.* **1941**, 63, 872.
24. Strain, H. H. *J. Am. Chem. Soc.* **1932**, 54, 1221.
25. Minkin, V. I.; Tumakova, Zh. A. *Zh. Obsh. Khim.* **1963**, 33, 642.
26. Gil, R.; Eternot, M.; Guillerez, M.-G.; Collin, J. *Tetrahedron* **2004**, 60, 3085; and references therein.
27. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure,* 4th ed.; John Wiley & Sons Inc: New York, **1992**, 942–943.
28. Hayashi, K.; Kogiso, H.; Nagao, Y. *Synlett* **1996**, 1203; and references therein.
29. (a) G. M. Robertson. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 563. (b) Gansäuer, A.; Bluhm, H. *Chem. Rev.* **2000**, 100, 2771. (c) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 61.
30. (a) Mercer, G. J.; Sigman, M. S. *Org. Lett.* **2003**, 5, 1591; and references therein. (b) Alexakis, A.; Aujard, I.; Mangeney, P. *Synlett* **1998**, 873. (c) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 2580.
31. (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, 97, 3161; and references therein. (b) Matsubara, S.; Hashimoto, Y.; Okano, T.; Utimoto, K. *Synlett* **1999**, 1411. (c) Reedijk, J. *Chem. Commun.* **1996**, 801. (d) Kim, Y. H. *Acc. Chem. Res.* **2001**, 34, 955. (e) Pietruszka, J.; Witt, A. *Synlett* **2003**, 91.
32. Kise, N.; Shiozawa, Y.; Ueda, N. *Tetrahedron Lett.* **2004**, 45, 7599.
33. Maekawa, H.; Yamamoto, Y.; Shimada, H.; Yonemura, K.; Nishiguchi, I. *Tetrahedron Lett.* **2004**, 45, 3869.
34. Annunziata, R.; Benaglia, M.; Caporale, M.; Raimondi, L. *Tetrahedron: Asymmetry* **2002**, 13, 2727.
35. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure,* 4th ed.; John Wiley & Sons Inc: New York, **1992**, 1225–1226; and references therein.
36. Shi, L.; Fan, C.-A.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M. *Tetrahedron* **2004**, 60, 2851; and references therein.
37. Takenaka, N.; Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, 126, 13198.
38. Pedersen, H. L.; Christensen, T. B.; Enemærke, R. J.; Daasbjerg, K.; Skrydstrup, T. *Eur. J. Org. Chem.* **1999**, 565.
39. Barrero, A. F.; Rosales, A.; Cuerva, J. M.; Gansäuer, A.; Oltra, J. E. *Tetrahedron Lett.* **2003**, 44, 1079.
40. Gansäuer, A.; Moschioni, M.; Bauer, D. *Eur. J. Org. Chem.* **1998**, 1923.
41. Mukaiyama, T.; Kagayama, A.; Shiia, I. *Chem. Lett.* **1998**, 1107.
42. Talukdar, S.; Banerji, A. *J. Org. Chem.* **1998**, 63, 3468.
43. Taniguchi, N.; Kaneta, N.; Uemura, M. *J. Org. Chem.* **1996**, 61, 6088.
44. (a) Gansäuer, A. *Synlett* **1997**, 363. (b) Gansäuer, A.; Bauer, D. *J. Org. Chem.* **1998**, 63, 2070. (c) Bandini, M.; Cozzi, P. G.; Morganti, S.; Umani-Ronchi, A. *Tetrahedron Lett.* **1999**, 40, 1997.
45. (a) Groth, U.; Jeske, M. *Synlett* **2001**, 129. (b) Mukaiyama, T.; Yoshimura, N.; Igarashi, K.; Kagayama, A. *Tetrahedron* **2001**, 57, 2499.

46. (a) Chatterjee, A.; Bennur, T. H.; Joshi, N. N. *J. Org. Chem.* **2003**, 68, 5668. (b) Li, Y.-G.; Tian, Q.-S.; Zhao, J.; Feng, Y.; Li, M.-J.; You, T.-P. *Tetrahedron: Asymmetry* **2004**, 15, 1707.
47. (a) Dunlap, M. S.; Nicholas, K. M. *Synth. Commun.* **1999**, 29, 1097. (b) Matsubara, S.; Hashimoto, Y.; Okano, T.; Utimoto, K. *Synlett* **1999**, 1411. (c) Enders, D.; Ullrich, E. C. *Tetrahedron: Asymmetry* **2000**, 11, 3861. (d) Halterman, R. L.; Zhu, C.; Chen, Z.; Dunlap, M. S.; Khan, M. A.; Nicholas, K. M. *Organometallics* **2000**, 19, 3824.
48. (a) Horner, L.; Skaletz, D. H. *Liebigs Ann. Chem.* **1975**, 1210–1228. (b) Shono, T.; Kise, N.; Shirakawa, E.; Matsumoto, H.; Okazaki, E. *J. Org. Chem.* **1991**, 56, 3063. (c) Tanaka, H.; Nakahara, T.; Dhimane, H.; Torii, S. *Synlett* **1989**, 51.
49. (a) Padwa, A.; Bergmark, W.; Pashayan, D. *J. Am. Chem. Soc.* **1969**, 91, 2653. (b) Campos, P. J.; Arranz, J.; Rodríguez, M. A. *Tetrahedron* **2000**, 56, 7285.
50. Shimizu, M.; Makino, H. *Tetrahedron Lett.* **2001**, 42, 8865.
51. Smith, J. G.; Ho, I. *J. Org. Chem.* **1972**, 37, 653.
52. Kim, M.; Knettle, B. W.; Dahlén, A.; Hilmersson, G.; Flowers, R. A., II. *Tetrahedron* **2003**, 59, 10397.
53. (a) Shimizu, M.; Iida, T.; Fujisawa, T. *Chem. Lett.* **1995**, 24, 609. (b) Yanada, R.; Negoro, N.; Okaniwa, M.; Miwa, Y.; Taga, T.; Yanada, K.; Fujita, T. *Synlett* **1999**, 537.
54. Kise, N.; Ueda, N. *Tetrahedron Lett.* **2001**, 42, 2365.
55. (a) Roscamp, E. J.; Pedersen, S. F. *J. Am. Chen. Soc.* **1987**, 109, 3152. (b) Betschart, C. A.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, 71, 1999.
56. Pansare, S. V.; Malusare, M. G. *Tetrahedron Lett.* **1996**, 37, 2859.
57. Shimizu, M.; Suzuki, I.; Makino, H. *Synlett* **2003**, 1635.
58. Shimizu, M.; Iwata, A.; Makino, H. *Synlett* **2002**, 1538.
59. Machrouhi, F.; Namy, J.-L. *Tetrahedron Lett.* **1999**, 40, 1315.
60. Ragnarsson, U. *Chem. Soc. Rev.* **2001**, 30, 205; and references therein.
61. (a) Stijve, T.; Pittet, A. *Deutsche Lebensmittel-Rundschau* **2000**, 96, 251; *Chem. Abstr.* **2000**, 133, 134478. (b) Chulija, A. J.; Bernillon, J.; Favre-Bovin, J.; Kaouadji, M.; Arpin, N. *Phytochemistry* **1988**, 27, 929.
62. Gompper, R.; Walther, P. *Tetrahedron* **1996**, 52, 14607.
63. Ionita, P.; Whitwood, A. C; Gilbert, B. C. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1453.
64. Slouka, J. *Pharmazie* **1971**, 26, 466.
65. Yanagisawa, H.; Ho, K. S. Eur. Pat. Appl. EP 1168066, **2002**; *Chem. Abstr.* **2002**, 136, 61567.
66. Nagata, M.; Kunieda, M.; Kanemaru, T. Jpn. Kokai Tokkyo Koho JP 2000314972, **2000**; *Chem. Abstr.* **2000**, 133, 357222.
67. Rittersdorf, W.; Rey, H.; Rieckmann, P. S. African ZA 6806903, **1969**; *Chem. Abstr.* **1970**, 72, 29743.
68. Takai, H.; Yoshida, M.; Iida, T.; Matsubara, I.; Shirahata, K. *J. Antibiot.* **1976**, 29, 1253.
69. (a) Mäeorg, U.; Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 2626. (b) Brosse, N.; Jamart-Grégorie, B. *Tetrahedron Lett.* **2002**, 43, 249. (c) Tšubrik, O.; Mäeorg, U. *Org. Lett.* **2001**, 3, 2297.
70. (a) Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1987**, 28, 887. (b) Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1986**, 27, 3615.

71. (a) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, 120, 9722. (b) Buchwald, S. L.; Wagaw, S.; Geis, O. PCT Int. Appl. WO 9943643, **1999**. (c) Wang, Z.; Skerlj, R. T.; Bridger, G. J. *Tetrahedron Lett.* **1999**, 40, 3543.
72. Chan, D. M. T. *Tetrahedron Lett.* **1996**, 37, 9013.
73. Aoki, Y.; Saito, Y.; Sakamoto, T.; Kikugawa, Y. *Synth. Commun.* **2000**, 39, 131.
74. Tšubrik, O.; Mäeorg, U.; Sillard, R.; Ragnarsson, U. *Tetrahedron.* **2004**, 60, 8363.
75. Kabalka, G. W.; Guchhait, S. K. *Org. Lett.* **2003**, 5, 4129.
76. (a) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, 3, 3803. (b) Kim, K.-Y.; Shin, J.-T.; Lee, K.-S.; Cho, C.-G. *Tetrahedron Lett.* **2004**, 45, 117.
77. Arteburn, J. B.; Rao, K. V.; Ramdas, R.; Dible, B. R. *Org. Lett.* **2001**, 3, 1351.
78. (a) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 2046. (b) Hartwig, J. F. *Synlett* **1997**, 329. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, 31, 805.
79. Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.
80. (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed. Engl.* **2003**, 42, 5400. (b) Elliott, G. I.; Konopelski, J. P. *Tetrahedron* **2001**, 57, 5683. (c) Suzuki, H.; Matano, Y. Eds., *Organobismuth Chemistry*, Elsevier: Amsterdam, 2001. (d) Finet, J.-P. *Chem. Rev.* **1989**, 89, 1487.
81. (a) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, 39, 2933. (b) Chan, D. M. T.; Monaco, K. L.; Li, R.; Bonne, D.; Clark, G. C.; Lam, P. Y. S. *Tetrahedron Lett.* **2003**, 44, 3863. (c) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, 5, 4397.
82. Matano, Y.; Aratani, Y.; Miyamatsu, T.; Kurata, H.; Miyaji, K.; Sasako, S.; Suzuki, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2511.
83. Murafuji, T.; Nishino, K.; Nagasuke, M.; Tanabe, A.; Aono, M.; Sugihara, Y. *Synthesis* **2000**, 1208; and references therein.
84. Combes, S; Finet, J.-P. *Synth. Commun.* **1996**, 26, 4569.
85. Stodola, F. H. *J. Org. Chem.* **1972**, 37, 178.
86. Vysochin, V. I.; Barkhash, V. A.; Vorozhtsov, N. N. *Zh. Obsh. Khim.* **1969**, 39, 1607.
87. Russel, G. A.; Yao, C. F. *Heteroat. Chem.* **1993**, 4, 433.
88. Wiley, R. H.; Irick, G. *J. Org. Chem.* **1959**, 24, 1925.
89. Maslinska-Solich, J.; Rudnicka, I. Jedlinski, Z. J. *J. Chem. Soc., Perkin Trans. 2* **1981**, 3034.
90. Choi, S. H.; Yashima, E.; Okamoto, Y. *Enantiomer* **1997**, 2, 105.
91. Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A.; Oku, A. *J. Org. Chem.* **1992**, 57, 1412.
92. Pozdnev, V.F. *Zh. Org. Khim.* **1977**,*13*, 2531
93. Hon, Y.-S.; Lee, C.-F.; Chen, R.-J.; Szu, P.-H. *Tetrahedron* **2001**, 57, 5991.
94. Lieberman, S. V.; Connor, R. *Org. Synth.* **1938**, 18, 61.
95. (a) Vellemäe, E.; Tšubrik, O.; Loog, O.; Mäeorg, S.; Mäeorg, U. *Proc. Estonian Acad. Sci. Chem.* **2003**, 52, 91. (b) Sergeeva, E. V.; Rozenberg, V. I.; Antonov, D. Yu.; Vorontsov, E. V.; Starikova, Z. A.; Hopf, H. *Tetrahedron: Asymmetry* **2002**, 13, 1121.
96. Tsukinoki, T.; Kawaij, T.; Hashimoto, I.; Mataka, S.; Tashiro, M. *Chem. Lett.* **1997**, 26, 235; and references there in.

97. (a) Eisch, J. J.; Kaska, D. D.; Peterson, C. J. *J. Org. Chem.* **1966**, 31, 453. (b) Periasamy, M.; Srinivas, G.; Karunakar, G. V.; Bharathi, P. *Tetrahedron Lett.* **1999**, 40, 7577.
98. (a) Mäeorg, U.; Pehk, T.; Ragnarsson, U. *Acta. Chem. Scand.* **1999**, 53, 1127. (b) Beacham, L. M., III; Matl, V. G.; Smith, J. N.; Williams, E. B., Jr.; Thomas, A. M.; Wolters, E. T. *J. Org. Chem.* **1971**, 36, 488. (d) Miel, H.; Rault, S. *Tetrahedron Lett.* **1997**, 38, 7865.

SUMMARY IN ESTONIAN

Karbonüülühendite ja nende imiinanaloogide kondensatsioonide mõningaid aspekte

Käesolev väitekiri põhineb kolmel mõnevõrra erineval uurimusel, mille ühiseks siduvaks nimetajaks on aldehüüdide ja nende imiinanaloogide kondensatsioonireaktsioonid. Esimene teema käsitleb homo-aldool-Tištšenko reaktsiooni mehhanismi ja stereokeemiaga seotud aspekte. Teiseks peateemaks on hüdrasinoarüülaldehüüdide pinakoolkondensatsioonid ja nende imiinanaloogide iminopinakoolkondensatsioonid. Seoses hüdrasiinoarüülaldehüüdide ja nende sünteesiga on töös kolmanda olulisema teemana põhjalikumalt uuritud hüdrasiinide arüülimist.

Töö tulemuste põhjal tehti kolme peamise uurimisobjekti kohta järgmised järeldused:

1) Aldool-Tištšenko reaktsiooni mehhanism ja stereokeemilised aspektid.

Näidati, et 2-metüülpropanaali homokondensatsiooni mitmed etapid kulgevad homokiraalse liitiumbinaftolaatkatalüsaatori juuresolekul madala kuni mõõduka enantioselektiivsusega. Samas leiti, et selle mitmeetapilise kondensatsiooni kasutamisvõimalused enantiomeerselt puhaste 1,3-diooli derivaatide valmistamiseks näivad olevat piiratud, tulenevalt erinevatest tasakaalureaktsioonidest ja vastandlikest selektiivsustest. Ühtlasi järeldati, et kõrge ee-ga produktide saamiseks võib sobivamaks osutuda selle kondensatsiooni mõnede etappide kasutamine iseseisvalt või reaktsiooni suunamine aldoksaanide moodustumise suunas. Samuti tehti oletus atsetaliseerumisreaktsiooni diastereomeerse olemuse kohta, millest tulenevad kaks võimalikku trimerisatsiooni teed.

2) Asendatud hüdrasiinide arüülimine ja hüdrasinoarüülaldehüüdide süntees.

Toodi mitmeid näiteid triarüülbismutaanide edukast kasutamisest tri-kaitstud hüdrasiinreagentide või üht asendajat sisaldavate di-kaitstud hüdrasiinide arüülimisel. Reaktsioonid toimusid pehmetes tingimustes ja kõrvalsaaduste teket ei täheldatud, mistõttu saagised olid kvantitatiivsed või peaaegu kvantitatiivsed. Vaatamata mõningatele piirangutele, on paljud multiasendatud hüdrasiinid nüüd valmistatavad lihtsa etapiviisilise sünteesi abil. Sama meetodika peaks olema rakendatav ka teiste sarnaste reagentide korral. Lisaks töötati välja alternatiivne sünteesiskeem mõnede di- ja tri-kaitstud fenüülhüdrasiinide sünteesiks.

Arüülimismeetodi võimalusi avardavalt näidati, et tri-asendatud hüdrasiinidesse saab sisestada 4-formüülfenüülrühma pehmetes tingimustes, kui

formüülrühm on triarüülbismutaani valmistamise ja järgneva arüülimisreaktsiooni käigus kaitstud atsetaalina. Oletati, et samal moel on tri-asendatud hüdrasiinidesse, nagu ka mitmetesse teistesse amiini derivaatidesse, võimalik asendajatena sisse viia ka teisi arüülaldehüüdrühmi.

3) Hüdrasinoarüülaldehüüdide pinakoolkondensatsioon ja hüdrasinoarüülaldehüüdide fenüüliminoderivaatide imino-pinakoolkondensatsioon.

Näidati, et formüülfenüülhüdrasiine on võimalik kondenseerida mõõduka saagise ja mõõduka kuni hea diastereoselektiivsusega dioolideks, mis sisaldavad kahte hüdrasinorühma, kasutades titanotseendikloriidkatalüsaatorit koos pulbrilise Mn ja kollidiinvesinikkloriidiga. Vastavate fenüülimiinderivaatide mittediastereoselektiivne kondensatsioon diamiinideks saavutati kahel juhul Zn/Cu-paari abil.

ACKNOWLEDGEMENTS

First of all I would like to thank my supervisor Dr. Uno Mäeorg for his enthusiastic guidance and support in performing this study.

I am also very grateful to Dr. Ulf Ragnarsson for his support and collaboration, and for the opportunity to work in his laboratory at Uppsala University as well as for the pleasant stay there.

I would also like to thank:

Dr. Vahur Mäemets
Ms. Olga Tšubrik
Mr. Aleksei Bredihhin
Dr. Leif Grehn
Mrs. Sirje Mäeorg
Dr. Tõnis Pehk
Dr. Koit Herodes
Prof. Ivo Leito
for helping with the analysis,

Mrs. Vaike Timotheus
for assisting with experiments,

Prof. Victor Snieckus
Mrs. Louise Pile
for good advice.

For financial support, I wish to thank the ERASMUS programme and the Estonian Science Foundation (grant no. 5255).

And finally, my special thanks to Ms. Terje Loogus and her family for all their support and patience.

PUBLICATIONS

Selfcondensation of 2-Methylpropanal with Homochiral BINOL Catalysts as a Model Asymmetric Aldol-Tishchenko Reaction.
Loog, O.; Mäeorg, U. *Tetrahedron: Asymmetry* **1999**, 10, 2411–2415.

Synthesis of Hydrazine with Aromatic Substituents Using Triarylbismuth Reagents.
Loog, O.; Mäeorg, U.; Ragnarsson, U. *Synthesis* **2000**, 1591–1597.

Cu-Catalysed N-Arylation of Hydrazines with Bismuthanes. Synthesis and Pinacol or Imino-Pinacol Coupling of 4-Formylphenylhydrazines and their Phenylimine Derivatives.
Loog, O.; Mäeorg, U. *Synlett* **2004**, 2537–2540.

CURRICULUM VITAE

Olavi Loog

Born:	August 27, 1969, Tallinn, Estonia
Citizenship:	Estonian
Marital status:	single
Address:	Institute of Organic and Bioorganic Chemistry University of Tartu 2 Jakobi St., 51014 Tartu, Estonia
Phone:	+372 7 375 240
E-mail:	olavi.loog@ut.ee

Education

1998–2004	University of Tartu, Department of Chemistry, *Ph.D.* student
1996–1998	University of Tartu, Department of Chemistry, *M.Sc.* (organic chemistry) 1998
1991–1996	University of Tartu, Department of Chemistry, *B.Sc.* (chemistry) 1996

Professional employment

2005–	Pharmasynth AS, chemist
2001–	University of Tartu, Institute of Organic and Bioorganic Chemistry, researcher
1999–2001	University of Tartu, Institute of Organic and Bioorganic Chemistry, assistant

Main scientific publications

1. Loog, O.; Mäeorg, U. Enantioselectivity of Acyl Migration in 2,2,4-Trimethylpentane-1,3-diol Monoesters in the Presence of Chiral BINOL Catalyst. *Proc. Estonian Acad. Sci. Chem.* 1998, 47, 193–195.
2. Loog, O.; Mäeorg, U. Selfcondensation of 2-methylpropanal with homochiral BINOL catalysts as a model asymmetric aldol-Tishchenko reaction. *Tetrahedron: Asymmetry* 1999, 10, 2411–2415.
3. Loog, O. Mäeorg, U, Ragnarsson, U. Synthesis of Hydrazine with Aromatic Substituents Using Triarylbismuth Reagents. *Synthesis* 2000, 1591–1597.
4. Loog, O.; Mäeorg, U. Cu-Catalysed N-Arylation of Hydrazines with Bismuthanes. Synthesis and Pinacol or Imino-Pinacol Coupling of 4-Formylphenylhydrazines and their Phenylimine Derivatives. *Synlett* 2004, 2537–2540.

CURRICULUM VITAE

Olavi Loog

Sündinud:	27. august 1969, Tallinn, Eesti
Kodakondsus:	Eesti
Perekonnaseis:	vallaline
Aadress:	Orgaanilise ja bioorgaanilise keemia instituut Tartu Ülikool Jakobi 2, 51014 Tartu, Eesti
Tel.:	+372 7 375 240
E-post:	olavi.loog@ut.ee

Haridus

1998–2004	Tartu Ülikooli keemiaosakonna doktorant
1996–1998	Tartu Ülikooli keemiaosakonna magistrant, *M.Sc.* (orgaaniline keemia) 1998
1991–1996	Tartu Ülikooli keemiaosakonna üliõpilane, *B.Sc.* (keemia) 1996

Teenistuskäik

2005–	Pharmasynth AS, keemik
2001–	Tartu Ülikooli orgaanilise ja bioorgaanilise keemia instituudi teadur
1999–2001	Tartu Ülikooli orgaanilise ja bioorgaanilise keemia instituudi assistent

Tähtsamad teaduspublikatsioonid

1. Loog, O.; Mäeorg, U. Enantioselectivity of Acyl Migration in 2,2,4-Trimethylpentane-1,3-diol Monoesters in the Presence of Chiral BINOL Catalyst. *Proc. Estonian Acad. Sci. Chem.* 1998, 47, 193–195.
2. Loog, O.; Mäeorg, U. Selfcondensation of 2-methylpropanal with homochiral BINOL catalysts as a model asymmetric aldol-Tishchenko reaction. *Tetrahedron: Asymmetry* 1999, 10, 2411–2415.
3. Loog, O. Mäeorg, U, Ragnarsson, U. Synthesis of Hydrazine with Aromatic Substituents Using Triarylbismuth Reagents. *Synthesis* 2000, 1591–1597.
4. Loog, O.; Mäeorg, U. Cu-Catalysed N-Arylation of Hydrazines with Bismuthanes. Synthesis and Pinacol or Imino-Pinacol Coupling of 4-Formylphenylhydrazines and their Phenylimine Derivatives. *Synlett* 2004, 2537–2540.