Pure & Appl. Chem., Vol. 68, No. 3, pp. 569–580, 1996.
Printed in Great Britain.

Recent advances in the development of highly enantioselective synthetic methods

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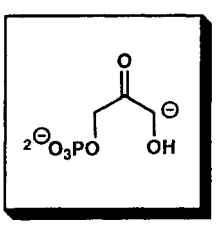
Abstract: In the course of the development of modern synthetic methods in the field of asymmetric synthesis the SAMP-/RAMP-hydrazone method opens a highly diastereo- and enantioselective route to a great variety of carbonyl compounds, alcohols, amines and heterocycles. In this paper recent advances in the development of biomimetic C-C bond formations, such as the synthesis of C_2-symmetric ketodiols, polyhydroxylated piperidines (azasugars), HIV-1 protease inhibitors (AIDS), and the first chiral phosphoenol pyruvate (PEP) equivalent, will be reported. Furthermore, efficient and highly stereoselective 1,2-additions to the CN double bond of hydrazones and imines give rise to various amine compounds of high enantiomeric purity. Asymmetric Michael initiated ring closure (MIRC) reactions afford trans-disubstituted cycloalkanoates with virtually complete control of three contiguous stereogenic centers. Finally, chirality transfer processes mediated by organo iron and palladium complexes allow allylic substitutions with virtually complete regioselectivity and chirality transfer both under stoichiometric (Fe) and catalytic (Pd) conditions.

Biomimetic C-C Bond Formations

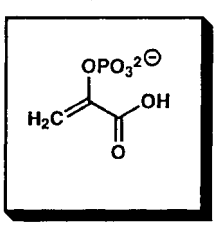
It has always been the dream of chemists to synthesize complex organic molecules in a similar manner, elegance and efficiency as mother nature does it. For a long time, biomimetic strategies have therefore been used successfully in organic synthesis. We would like to report here our first advances in the development of new synthetic equivalents of dihydroxyacetone phosphate (DHAP) enolate **A** and phosphoenol pyruvate (PEP) **B** employing our SAMP-/RAMP-hydrazone method [1, 2].

DHAP



A

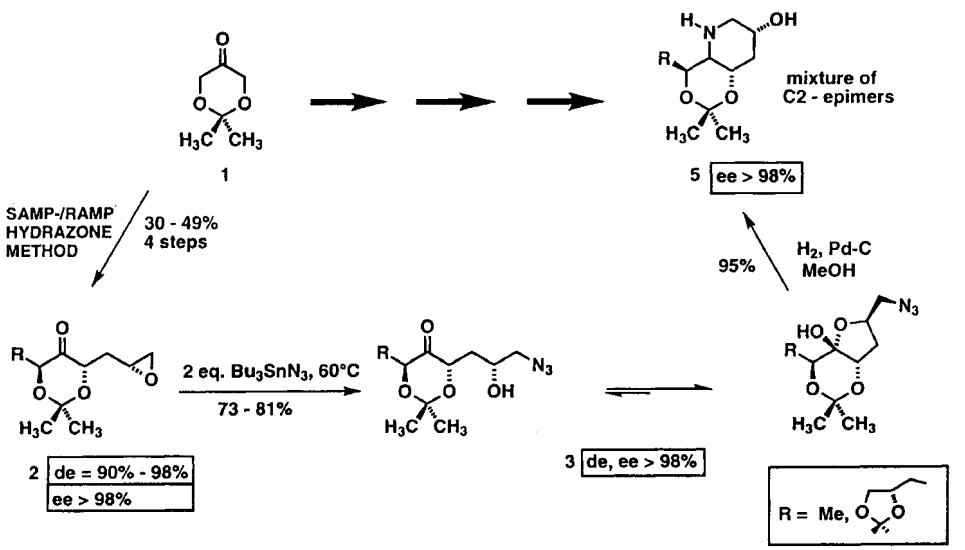
PEP



B

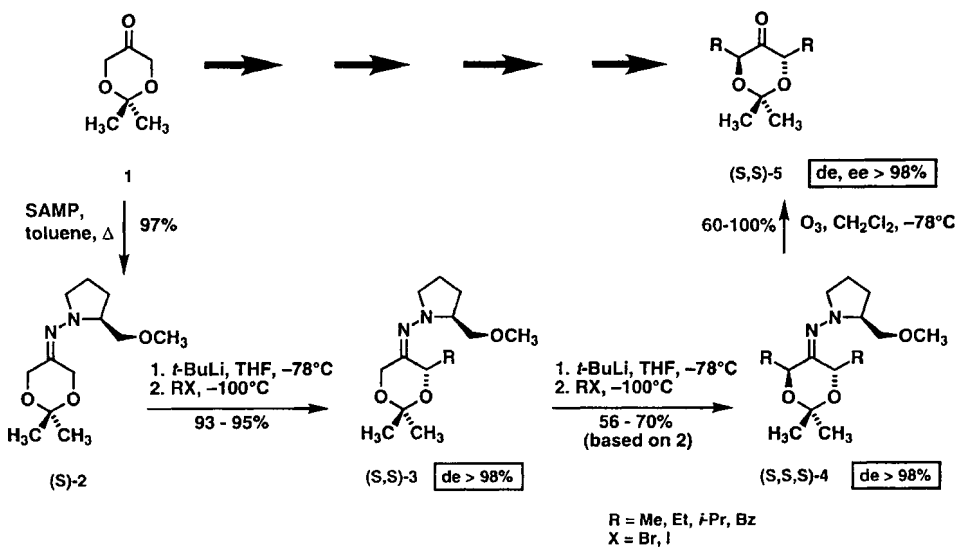
Diastereo- and Enantioselective C-C Bond Formations with a Chiral Dihydroxyacetone phosphate Equivalent

Dihydroxyacetone phosphate (DHAP) is used in nature as a C_3-methylene component in enzyme catalyzed aldol reactions to form 2-ketoses. It turned out that the SAMP-hydrazone of 2,2-dimethyl-1,3-dioxane-5-one, easily prepared in molar quantities from the simple precursors nitromethane, paraformaldehyde and acetone, can be used as a DHAP-enolate equivalent. First test reactions with simple halides showed that indeed the dihydroxyacetone C_3-unit can be transformed to electrophiles with high asymmetric induction [3]. The process revealed a remarkable flexibility, when two different electrophiles were employed to effect α,α'-functionalisation. Scheme 1 shows examples of protected polyfunctional ketodiols of high diastereo- and enantiomeric purity, which can easily be made in gram quantities in 4 steps and good overall yields [4].



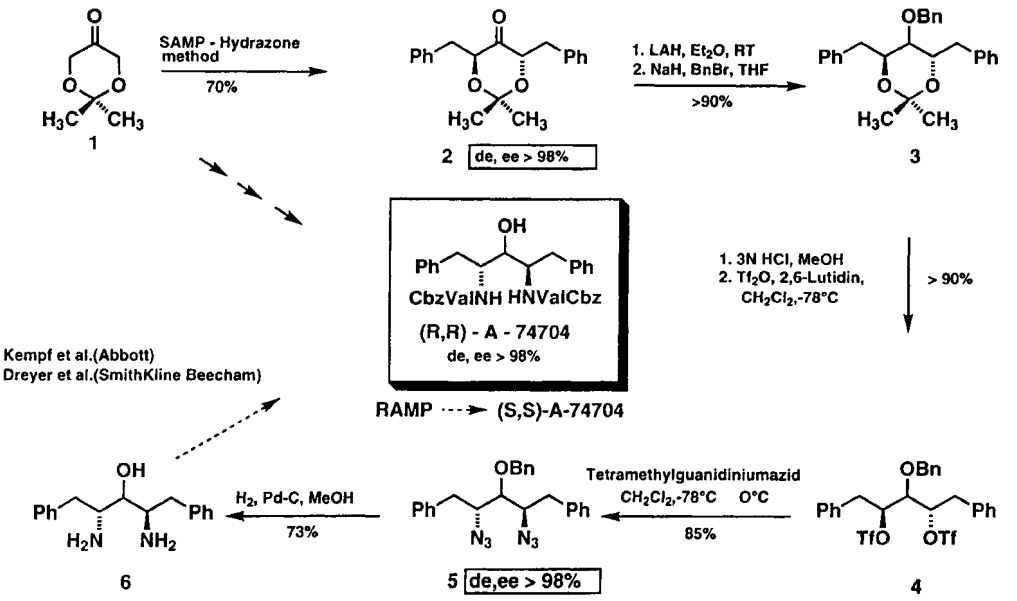
Scheme 1. Diastereo- and enantioselective synthesis of protected, polyfunctional ketodiols from dihydroxyacetone

Since the pioneering work of Kagan in 1972 on catalytic asymmetric hydrogenations using the diphosphine ligand DIOP [5], C_2-symmetric chiral auxiliaries have proven to be particularly useful in asymmetric synthesis [6]. If the same electrophile is used twice in our α,α'-bisalkylation of dihydroxyacetone acetonide 1, one obtains with virtually complete asymmetric induction C_2-symmetric ketones (de, ee ≥ 98 %) [7]. Obviously, the second alkylation occurs regioselectively at the α'-position without epimerization of the α-stereogenic center and the uniform SAMP-hydrazone mechanism of electrophilic substitution α to the carbonyl group [8,9] is not disturbed by the preexisting α-stereocenter (scheme 2).



Scheme 2. Diastereo- and enantioselective synthesis of protected, C_2-symmetric ketodiols using the SAMP-/RAMP-hydrazone method.

A first application of the new, very efficient asymmetric synthesis of C_2-symmetric ketones is described in scheme 3. Since the Center of Disease Control in Atlanta (USA) defined the diagnostic term AIDS (Acquired Immunodeficiency Syndrome) in 1982 [10] many groups and companies have been looking for medications for treatment of AIDS. Most of the medicaments authorized for treatment inhibit the enzyme reverse transcriptase of the human immunodeficiency virus (HIV). Nevertheless, they are only able to prolong somewhat the survival of patients, and lead to considerable side effects and to the generation of more resistant strains of the virus [11].



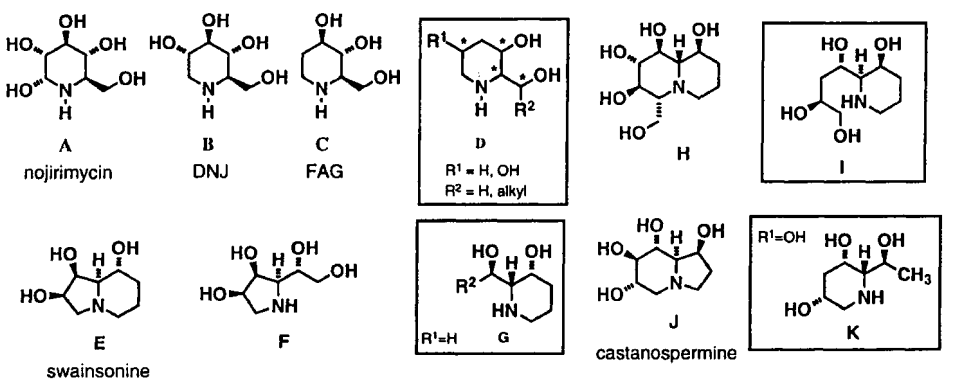
Scheme 3. Diastereo- and enantioselective synthesis of A-74704, a C_2-symmetrical HIV-1 protease inhibitor.

Since the elucidation of its structure in 1989 HIV-1 protease with an unusual homodimeric C_2-symmetrical structure has become a new, highly favored target for chemotherapy [12]. On the basis of enzymatic investigations, Erickson and Kempf et al. [13] developed the C_2-symmetrical, highly selective HIV-1 protease inhibitor A-74704 (scheme 3). They demonstrated that the marked inhibiting effect of the compound relies on its optimal fit in the active center of the C_2-symmetrical protease.

According to our protocol, the α,α'-bisbenzylation of 1 afforded the corresponding C_2-symmetric ketone 2 with practically complete asymmetric induction. In 6 further steps, using well known basic transformations, we reached the diastereo- and enantiomerically pure diamino alcohol 6, which is easily transformed to A-74704 according to Kempf et al. (Abbott) and Dreyer et al. (SmithKline Beecham) (scheme 3) [14]. It is interesting to note that 6 is also the key building block of a HIV-1 protease inhibitor developed by Bayer AG and Hoechst AG [15].

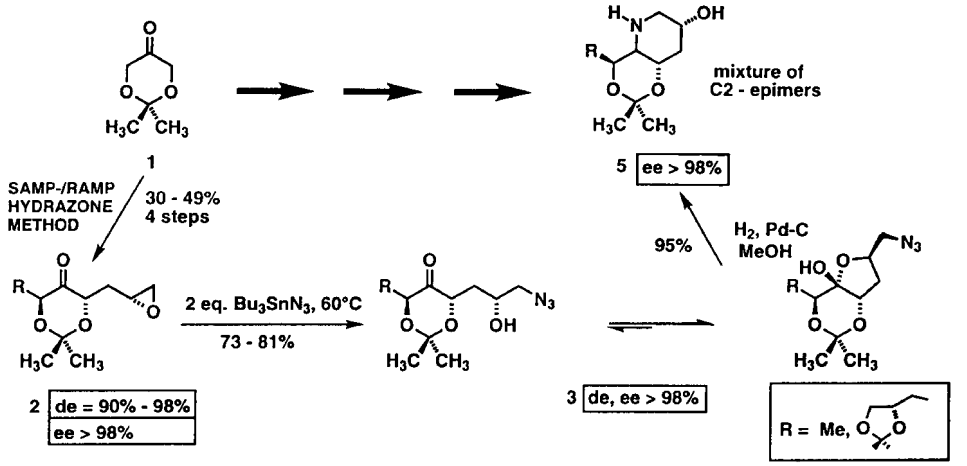
The asymmetric synthesis described in scheme 3 provides an efficient and stereochemically flexible entry to C_2-symmetric HIV-1 protease inhibitors. The inhibiting effect and the pharmacological properties of these new agents may possibly be improved further for the treatment of AIDS, as certain properties can be varied almost at will: the stereogenic centers, which can be selected by the choice of the auxiliary (SAMP/RAMP), the side chain (here $PhCH_2$) by the choice of electrophile and the substituents on the amino group.

With respect to the products represented in scheme 1, it should be possible to introduce amino groups via halogen or oxiran functionalities to get an efficient entry into a series of polyhydroxylated piperidines (azasugars) [16-18]. This class of compounds gained much interest because of its biological activity as potential glycosidase inhibitors [19-21]. Scheme 4 shows a number of polyhydroxy piperidines (boxed) synthesized in our group in comparison with known compounds derived from natural sources.

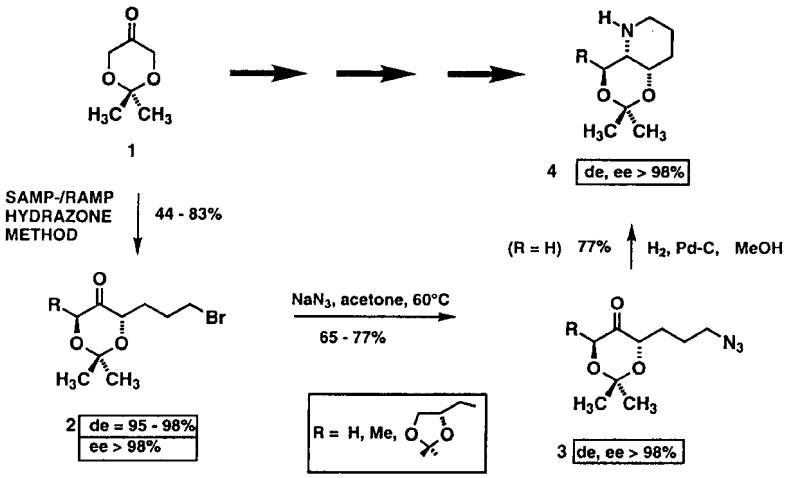


Scheme 4. Novel polyhydroxylated piperidines (azasugars) as potential glycosidase inhibitors.

Scheme 5 and 6 shows two typical synthetic approaches for the highly stereoselective synthesis of polyhydroxylated piperidines. By the azide oxirane ring opening variant piperidine derivatives bearing 4 stereogenic centers are formed with excellent stereoselectives (scheme 5). Only the stereocenter α to nitrogen is not fully controlled and a mixture of C_2-epimers is obtained. The alternative route via bromide azide substitution shown in scheme 6 works with virtually complete asymmetric induction and only one stereoisomer is formed (de,ee ≥ 98%).



Scheme 5. Flexible, diastereo- and enantioselective synthesis of novel polyhydroxylated piperidines (azide oxirane ring opening variant).



Scheme 6. Flexible, diastereo- and enantioselective synthesis of novel polyhydroxylated piperidines (bromide azide substitution variant).

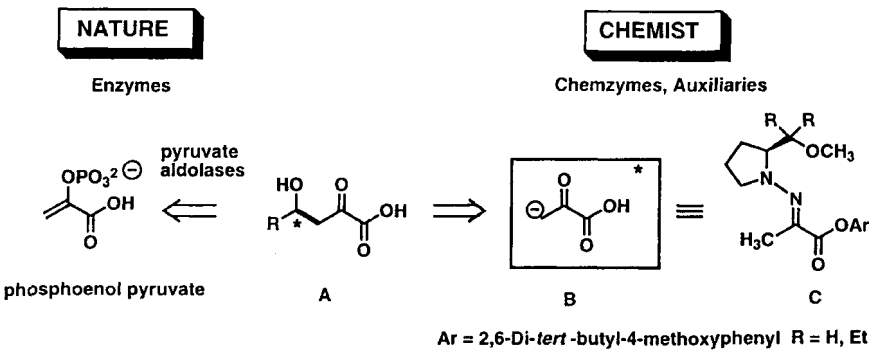
In summary, novel polyhydroxylated piperidine structures of excellent diastereo- and enantiomeric purities can be synthesized in good overall yields. By choosing the right auxiliary (SAMP, RAMP), the absolute configuration of the stereogenic center can be selected. Furthermore a broad range of side chains may be introduced by changing the first eletrophile [7].

Diastereo- and Enantioselective C-C Bond Formations with a Chiral Phosphoenol-pyruvate Equivalent

Many biologically important compounds, like N-acetylneuraminic acid, 3-deoxy-D-*manno*-octulosonic acid (KDO), and 3-deoxy-D-arabino-2-heptulosonic acid 7-phosphate (DAHP), the precursor of shikimic acid, are formed in a C-C bond forming reaction by transfer of phosphoenolpyruvate (PEP) to aldoses resulting in 4-hydroxy-2-oxocarboxylic acid structures.

As the first chemical synthetic equivalent of PEP, transfering the pyruvic acid d^2-synthon (boxed), we have synthesized chiral pyruvate hydrazones form simple chemicals and (S)-proline (scheme 7).

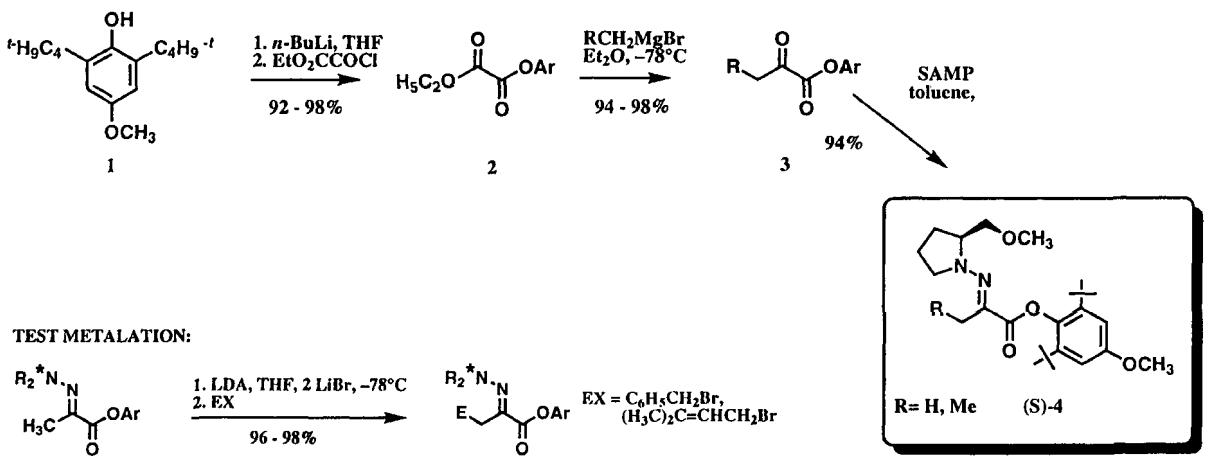
After initially trying to metalate hydrazones of methyl and *tert*-butyl pyruvate and trapping them with electrophiles, which was an unsuccessful attempt leading to self-acylated products, we realized that sterically



Scheme 7. Enzyme catalysed PEP-transfer and chemical mimicry via metalated chiral hydrazones.

blocked esters of 2,6-di-*tert*-butyl-4-methoxyphenol allowed the manipulation of the corresponding azaenolates.

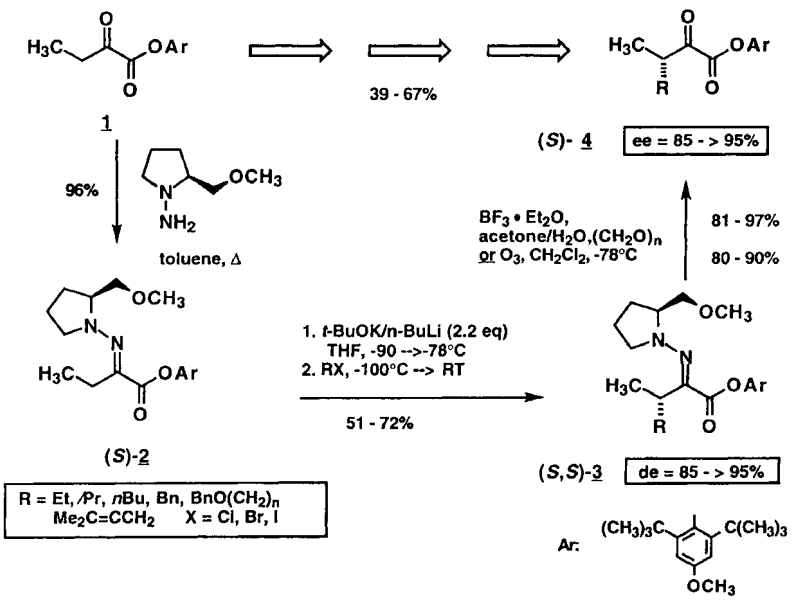
The synthesis of the sterically hindered 2-ketoesters succeeded with excellent yields by esterification of ethyl oxalyl chloride with the lithium salt of 2,6-di-tert-butyl-4-methoxyphenol followed by the chemoselective nucleophilic addition of methyl or ethyl Grignard reagents to the unsymmetrical ethyl aryl oxalate 3. Reaction with (*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) finally gave the aryl pyruvate SAMP-hydrazones as pale yellow solids in almost quantitative yields [22].



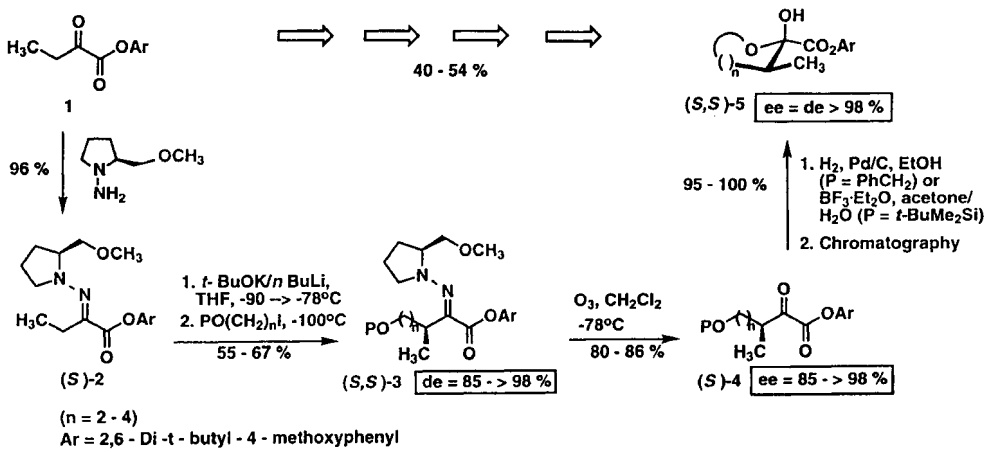
Scheme 8. Synthesis and first reactions of sterically hindered 2-ketoester SAMP-hydrazones as chiral PEP-equivalents.

3-substituted 2-ketoesters could be synthesized in good yields and with high diastereomeric excesses (de = 85 - ≥ 95 %) from the SAMP-hydrazones by metalation with Lochmann-Schlosser base followed by alkylation with alkyl halides at –100 °C. Besides the usual oxidative cleveage with ozone, the 3-substituted 2-ketoesters could be obtained under very mild conditions without racemization with boron trifluoride-ether in acetone/water and the addition of paraformaldehyde (scheme 9). The determination of the absolute configuration of the ketoesters was performed by X-ray structure analysis of the corresponding crystalline benzylated SAMP-hydrazone. In agreement with the postulated mechanism for electrophilic substitutions via SAMP/RAMP-hydrazones [8,9] the absolute configuration was found to be (*S*). Furthermore, the X-ray structure demonstrates nicely that the ester group ist sterically blocked by the two bulky *tert*-butyl-groups.

As a first extension of the new overall enantioselective α-alkylation of 2-ketoesters we developed an efficient asymmetric synthesis of 3-substituted cyclic hemiketals of ω-hydroxy-2-oxoesters [23]. As is shown in scheme 10, the metalated SAMP-hydrazones were trapped with various O-benzyl- and O-silyl-protected ω-hydroxy-1-iodoalkanes, which after hydrazone cleveage and deprotection afforded the cyclic hemiketals (de,ee > 98 %), structurally modified deoxygenated analogs of ulosonic acid. The relative and absolute configuration shown are based on Nuclear Overhauser experiments and an X-ray structure analysis.



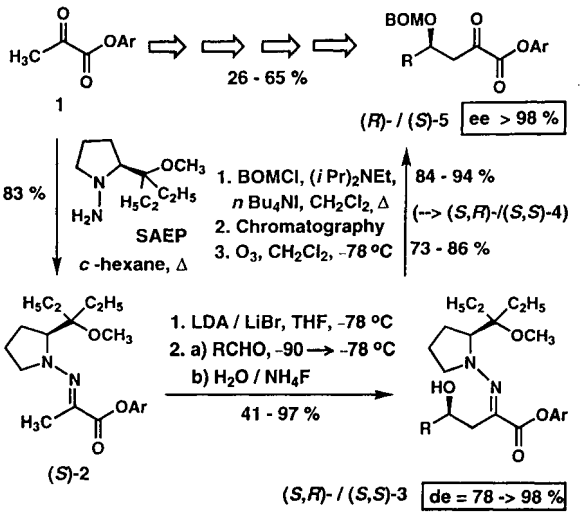
Scheme 9. Enantioselective synthesis of 3-substituted 2-ketoesters.



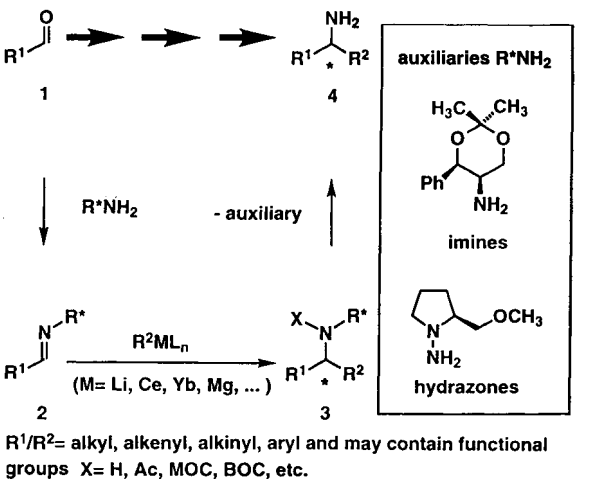
Scheme 10. Diastereo- and enantioselective synthesis of structurally modified deoxygenated analogs of ulosonic acid

As the real biomimetic reaction sequence in this respect, we could perform a stereoselective aldol reaction with a broad range of aldehydes as electrophiles with high overall enantioselectivity. Starting with aryl pyruvate the benzyloxymethyl (BOM) protected 4-hydroxy-2-oxocarboxylic acid esters 5 could be prepared in high enantiomeric purity (ee > 98 %) and in good overall yields [24]. In order to get such very high asymmetric inductions it was necessary to exchange SAMP for the sterically more demanding auxiliary (*S*)-1-amino-2-(1-ethyl-1-methoxy-propyl)pyrrolidine (SAEP) [25] and to metalate the corresponding SAEP-hydrazone with lithium diisopropylamide (LDA) in the presence of two equivalents of lithium bromide (scheme 11).

In this manner, for instance, the protected natural product 2-keto-3-deoxygluconate (KDG) [26] starting from isopropylidene-protected (*R*)-glyceraldehyde was obtained in diastereo- and enantiomerically pure form. The absolute configurations given are based again on a crystal structure analysis of a single crystal of a hydrazone adduct (R = Me_2CHCH_2) and by assumption of an uniform reaction mechanism. The relative topicity found is in agreement with the stereochemical outcome previously observed in aldol reactions with SAMP/RAMP-hydrazones [27,28,9]. Beside the synthetic value of the highly enantioselective and generally applicable PEP-transfer, it is especially noteworthy that virtually complete asymmetric inductions could be obtained with a methyl ketone as methylene component, a stereochemical situation notoriously difficult to control in aldol and aldol type reactions ("acetat problem") [29].



Scheme 11. Enantioselective aldol reaction with the first chiral PEP-equivalent.

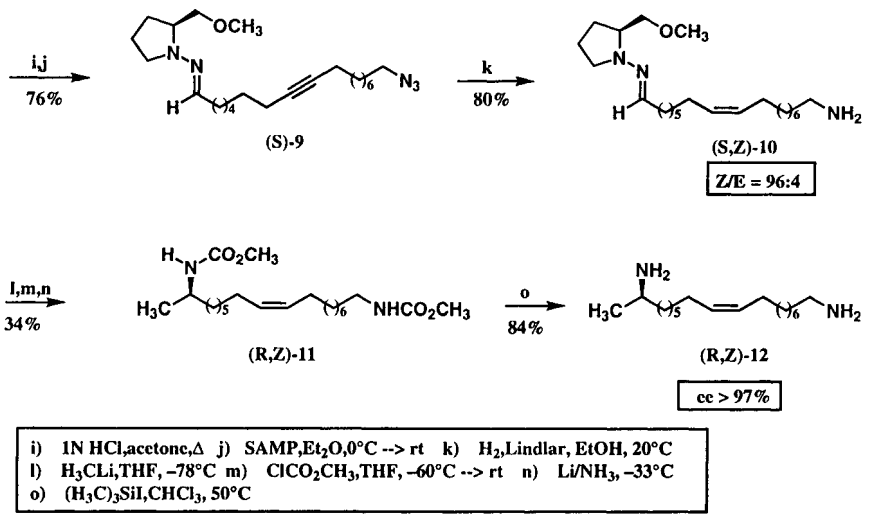


Scheme 12. Asymmetric synthesis of amines by 1,2-addition to the CN-double bond of imines and hydrazones

Enantioselective Synthesis of Amines by Stereoselective 1,2-Addition to the CN Double Bond of Hydrazones and Imines

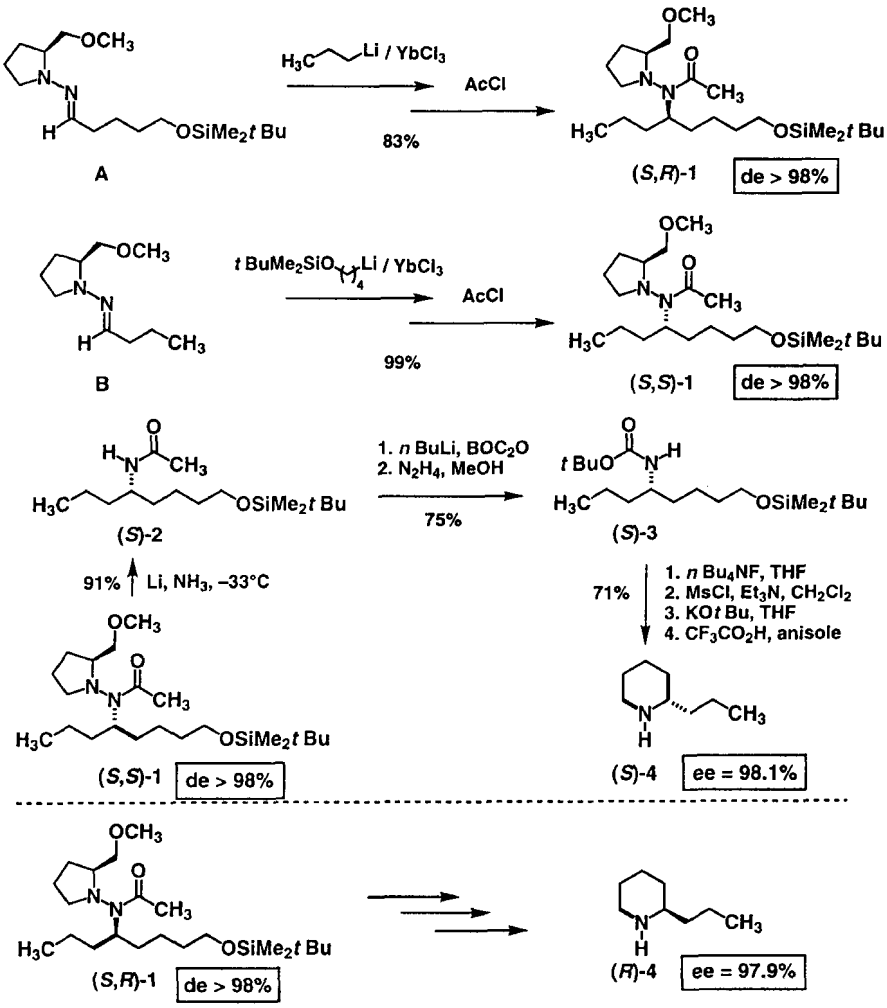
Amine compounds of high enantiomeric purity are of enormous importance as chiral building blocks used for the synthesis of natural and biologically active substances, as auxiliaries, ligands etc.. Therefore much work has been carried out recently to develop efficient asymmetric synthesis of amines. In 1982 we initiated a programme with this goal by applying nucleophilic 1,2-additions of organometallic compounds to the CN double bond of chiral hydrazones and imines [30] (scheme 12).

Based on this method, we were able, for instance, to achieve an efficient and highly enantioselective (ee ≥ 97 %) total synthesis of the ladybug defence alkaloid (17*R*,9*Z*)-1,17-diaminooctadec-9-ene [(*R*,*Z*)-12, harmonine)]. The key step was to generate the stereogenic center by nucelophilic 1,2-addition of methyllithium to an aldehyde-SAMP-hydrazone. The last steps of the harmonine synthesis are shown in scheme 13 [31].



Scheme 13. Enantioselective total synthesis of harmonine - a ladybug defence alkaloid.

As another natural compound, which was for instance used by ancient greeks to execute "condemned criminals" (e.g. Socrates), we were able to synthesize both enantiomers of coniine, a toxic piperidine alkaloid of the hemlock plant *Conium maculatum*. In this case, organoytterbium reagents were added in a 1,2-fashion to aldehyde SAMP-hydrazones with virtually complete asymmetric induction and in excellent yields. By choosing the proper building blocks of nucleophile and electrophile, both epimers of the SAMP-hydrazines 1 could be obtained. Reductive N-N bond cleavage led to the amino compounds 2, from which by standard reaction both enantiomers of coniine (ee = 97.9 % and 98.1 % respectively) could be synthesized via cyclization (enantioselectivity through synthon control) (scheme 14) [32].



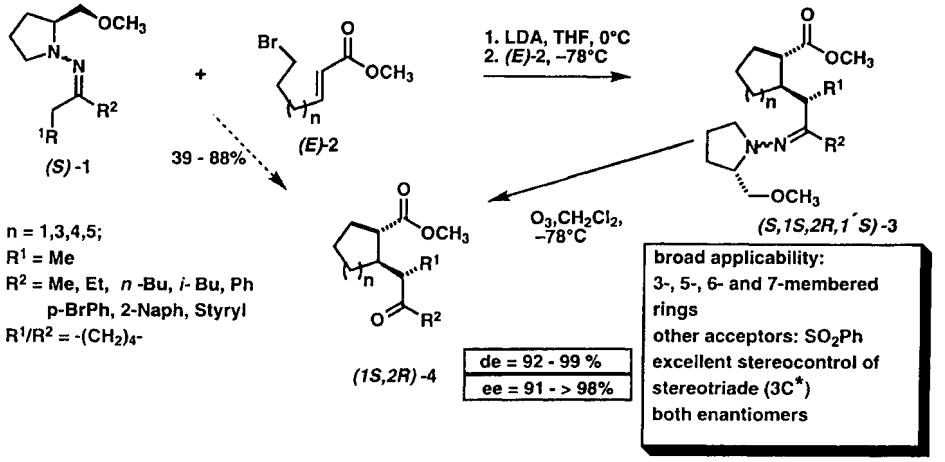
Scheme 14. Asymmetric synthesis of both enantiomers of coniine.

Furthermore, we have used the same 1,2-addition technique to synthesize α-aminoacetals and the corresponding α-aminoacids by employing organocerium nucleophils and reached ee-values of 90 - 96 % [33]. The same is true, if the acetal moiety is placed in β-position to the hydrazone group. Again excellent asymmetric inductions with RM/CeCl3 (M = Li, MgBr) of up to 98 % ee were reached for the corresponding β-aminoacetals and β-aminoacids [34].

In addition, we showed that organocerium reagents add to the CN double bond of new chiral α,β-unsaturated imines, which opens an efficient entry to allylamines and propargylamines of very high enantiomeric purity (ee ≥ 97 %) [35]. Recently, we were able to add allylic Grignard-reagents or cerium reagents to aldehyde SAMP-hydrazones, which lead to homoallylamines and after subsequent oxidative cleavage of the double bond to β-aminoacids and β-aminodiacids with excellent enantiomeric excesses (ee = 90 - 98 %) [36].

Asymmetric MIRC-Reactions via SAMP-/RAMP-Hydrazones

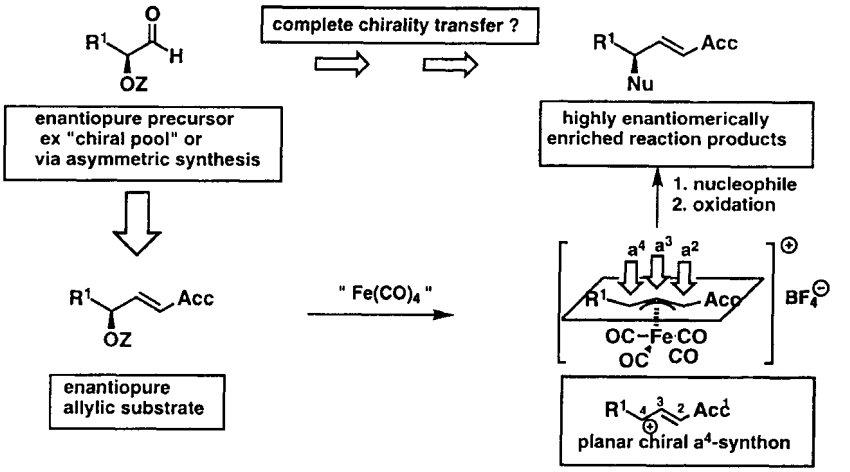
One elegant way to construct carbocycles is the combination of a Michael-addition, followed by an intramolecular trapping of the resulting acceptor enolate and called MIRC reactions (Michael Initiated Ring Closure) [37]. Because metalated SAMP-/RAMP-hydrazones have proven to be excellent chiral Michael donors in a broad range of reactions [38], adapting the MIRC reaction method opened a highly diastereo- and enantioselective route to trans-disubstituted cyclopentanoates (scheme 15). For instance, metalation of the hydrazones with LDA followed by addition to the ω-functionalized Michael-acceptor (*E*)-6-bromo-hex-2-enoate led after oxidative cleavage with ozone to the trans-disubstituted cyclopentanoates in good overall yields with excellent diastereo- and enantioselectivities (de,ee ≥ 95 %) [39,40]. The new method has a broad applicability, because 3-, 5-, 6- and 7-membered rings are available this way, other Michael acceptors such as sulfones can be used and excellent control of three contiguous stereocenters is achieved. Needless to mention that both enantiomers can be prepared at will by changing from SAMP to RAMP.



Scheme 15. Asymmetric MIRC reactions via SAMP-/RAMP-hydrazones; diastereo- and enantioselective synthesis of *trans*-disubstituted cycloalkanoates.

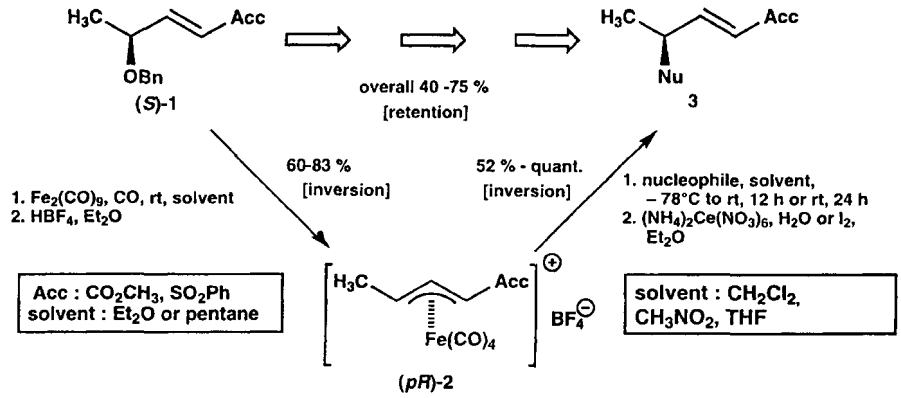
Asymmetric Chirality Transfer Processes Mediated via Organo Iron and Palladium Complexes

Organo transitionmetal complexes gain more and more importance in both stoichiometric and catalytic asymmetric synthesis. In the early eighties we initiated a programme directed towards the application of allylic organo iron cation complexes, which constitute planar chiral a^4-synthons and thus allow the Umpolung of the classical d^4-reactivity [41]. As is depicted in scheme 16, the concept is based on a complete chirality transfer starting from easily available enantiopure allylic substrates of natural source or prepared by enzyme reactions, their conversion to η^3-tetracarbonyl iron cation complexes and reaction with various nucleophiles.



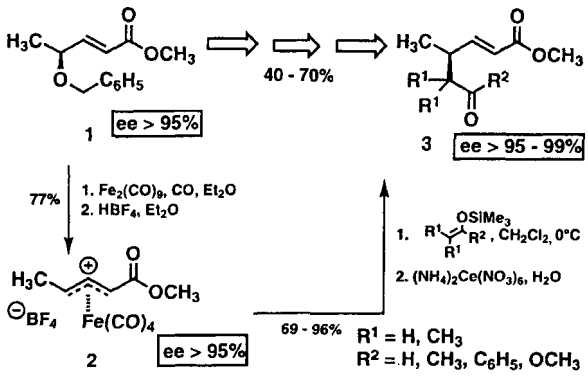
Scheme 16. New general concept: iron mediated chirality transfer. a^4-umpolung employing enantiopure cationic iron complexes.

A typical reaction procedure is given in scheme 17, indicating a complete chirality transfer for the allylic substitution from central over planar to central chirality with overall retention (double inversion), complete regioselectivity and conservation of the (*E*)-double bond geometry in good overall yields.

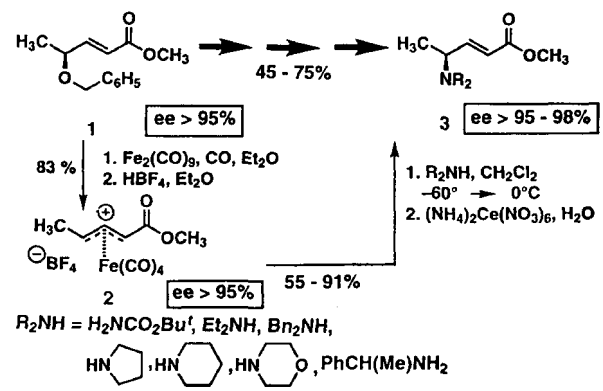


Scheme 17. Typical reaction procedure.

Starting from lactic acid we used this efficient iron mediated chirality transfer process to prepare 4-methyl-6-oxo-enoates using silyl enolethers as nucleophiles in 40 - 70 % overall yield and with ee-values of ≥95 - 99 % (scheme 18) [42].

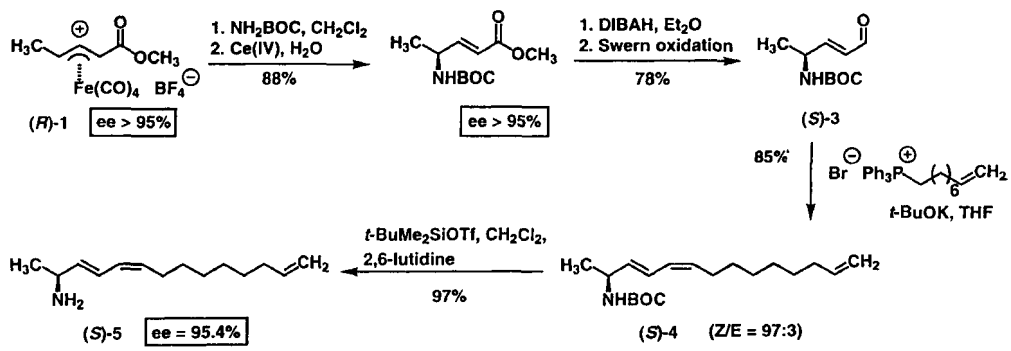


Scheme 18. Iron mediated synthesis of 4-methyl-6-oxo-enoates of high enantiomeric purity.

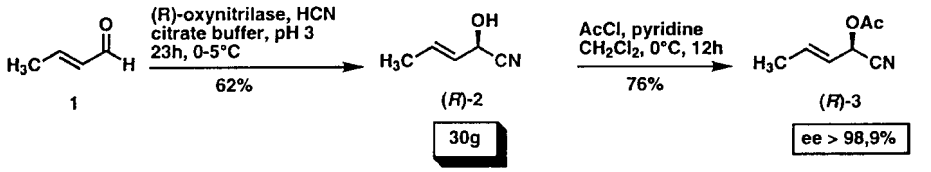


Scheme 19. Iron mediated synthesis of 4-amino-enoates of high enantiomeric purity.

In an extension of this method various nitrogen nucelophiles could be added leading to 4-amino enoates in good yields with high enantiomeric excesses (ee ≥95 - 97 %) (scheme 19) [43]. Based on these results, we were able to carry out the first total synthesis of the natural product 2-amino-3,5,13-tetradecatriene, a cytotoxic and antifungal component of the new zeeland ascidian *Pseudodistoma novaezelandiae* (scheme 20) [44]. Recently we could further extend the technique by employing α,β-unsaturated sulfones as starting materials [45, 46].

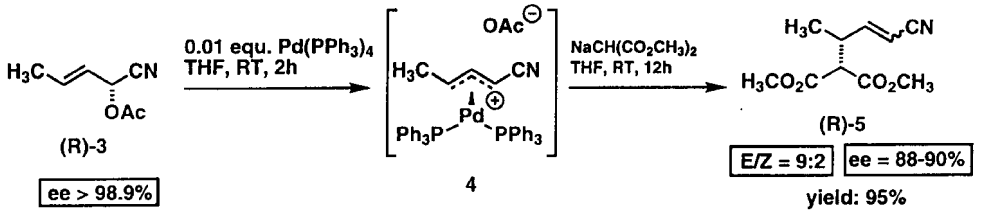


Scheme 20. First total synthesis of the cytotoxic and antifungal C14-amine isolated from the New Zealand ascidian *Pseudodistoma noveazelandiae*.



Scheme 21. Enzyme catalyzed asymmetric C-C-bond formation; large scale enantioselective synthesis of cyanohydrins (batch process).

Finally, we were able to combine an efficient enzymatic C-C bond formation with palladium catalysis as an alternative to the iron mediated chirality transfer processes mentioned above. As is schown in scheme 21, (R)-oxynitrilase was used in a batch process to prepare 30 g of crotonaldehyde cyanohydrin, which turned out to be almost enantiopure (ee > 98.9 %). The usual palladium catalyzed allylic substitution protocol with sodium malonate as the nucleophile provided γ-substituted α,β-unsaturated nitriles with good chirality transfer and in excellent yield (scheme 22) [47].



Scheme 22. Pd-catalyzed allylic alkylation of cyanohydrin acetates; virtually complete 1,3-chirality transfer in the formation of γ-substituted α,β-unsaturated nitriles.

Conclusion

The new biomimetic C-C bond formations reported here demonstrated that in a broad range of applications stereoselectivities can be reached, which compare well with the corresponding enzyme reactions. Because a large number of new structures as both pure enantiomers are available this way in gram quantities, the classical chemical synthesis may offer advantages over enzymatic processes. Together with the exciting recent developments in asymmetric 1,2-additions to the CN double bond of hydrazones and imines, the asymmetric MIRC-reactions and the efficient iron and palladium mediated chirality transfer processes described, the synthetic arsenal for the stereoselective synthesis of natural products and bioactive compounds has been further broadened.

Acknowledgement. I would like to thank my able coworkers, whose names are given in the list of references for their hard work and skill and their enthusiasm to join me in the projects described. This work was supported by the Deutsche Forschungsgemeinschaft (SFB 380, Leibniz-Prize), Volkswagenstiftung, European Union (Human Captal and Mobility network "Metal-Mediated and Catalyzed Organic Synthesis"), Land Nordrhein-Westfalen and the Fonds der Chemischen Industrie. We thank the companies Degussa AG, BASF AG, Bayer AG, Hoechst AG, Wacker Chemie, Boehringer Mannheim und Henkel KG for providing us with chemicals.

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