UNIVERSIDADE FEDERAL DE SÃO CARLOS
CENTRO DE CIÊNCIAS EXATAS E DE TECNOLOGIA
DEPARTAMENTO DE QUÍMICA
PROGRAMA DE PÓS-GRADUAÇÃO EM QUÍMICA

"Multicomponent Approach to Silica-Grafted Peptide Catalysts: A 3 D Continuous-Flow Organocatalytic System with On-line Monitoring of Conversion and Stereo- selectivity"

Gabriel dos Santos Scatena*

Dissertação apresentada como parte dos requisitos para obtenção do título de MESTRE EM QUÍMICA, área de concentração: QUÍMICA ORGÂNICA.

Orientador: Prof. Dr. Márcio Weber Paixão
Coorientadora: Prof. Dr. Quezia Bezerra Cass

*** bolsista CNPq**

São Carlos – SP

2014

Ficha catalográfica elaborada pelo DePT da Biblioteca Comunitária UFSCar
Processamento Técnico
com os dados fornecidos pelo(a) autor(a)

Scatena, Gabriel dos Santos
S287m Multicomponent approach to silica-grafted peptide catalysts : A 3 D continuous-flow organocatalytic system with on-line monitoring of conversion and stereo-selectivity / Gabriel dos Santos Scatena. -- São Carlos : UFSCar, 2016.
84 p.

Dissertação (Mestrado) -- Universidade Federal de São Carlos, 2014.

1. Asymmetric organocatalysis. 2. Flow chemistry. 3. Multicomponent reactions. 4. Microreactor. I. Título.

UNIVERSIDADE FEDERAL DE SÃO CARLOS

Centro de Ciências Exatas e de Tecnologia
Programa de Pós-Graduação em Química

Folha de Aprovação

Assinaturas dos membros da comissão examinadora que avaliou e aprovou a Defesa de Dissertação de Mestrado do candidato Gabriel dos Santos Scatena, realizada em 28/11/2014:

Prof. Dr. Márcio Weber Paixão
UFSCar

Prof. Dr. Tiago de Campos Lourenço
Apex Science

Prof. Dr. Timothy John Brocksom
UFSCar

Dedication

Dedico este trabalho a meus pais,
Vicente e Osmara Scatena, e a toda
minha família por todo amor,
compreensão e apoio ao longo destes
26 anos

.Ao amigo Victor Hugo Faldin “Buzz”.
“Ao infinito e além.”

"Imagination is more important than knowledge. For knowledge is limited, whereas imagination embraces the entire world, stimulating progress, giving birth to evolution."

Albert Einstein

“Success consists of going from failure
to failure without loss of enthusiasm.”

Winston Churchill

“If you don't know where you are going any road can take you there”

Lewis Carroll, Alice in Wonderland

“não discuto
com o destino

o que pintar
eu assino”

Paulo Leminski.

Acknowledgements

Primeiramente gostaria de agradecer aos meus pais, pois sem eles nada disso seria possível, e a toda minha família, pela base criada, a qual me permitiu alcançar meus objetivos.

Ao Professor Márcio Weber Paixão e Professora Quezia Bezerra Cass, por terem aceitado a empreitada de me orientar, por toda paciência, experiências, discussões, aprendizados, compreensão, lições, ensinamentos e paciência.

A Tiago de Campos Lourenço, por me apresentar, por todos ensinamentos sobre cromatografia e, sobretudo, pela amizade.

Ao amigo Eid Buzalaf, pela disponibilidade e revisão ortográfica da dissertação.

Aos amigos Alexander Fernandez de la Torre e Daniel Garcia, pela participação na minha formação científica, ajuda na confecção desta dissertação e pelas discussões intermináveis.

Ao Alexandre Augusto Cruz, pelas dicas e discussões que possibilitaram uma compreensão mais completa da parte de *Hardware* e *Software* dos equipamentos, bem como a montagem do sistema cromatográfico tridimensional.

A todos dos laboratórios de “Síntese Orgânica e Cromatografia Líquida de Alta Eficiência” e “Síntese de Produtos Naturais”, pelas sugestões, auxílios e participação direta ou indireta neste trabalho.

Ao CNPQ pela bolsa concedida, à CAPES e à FAPESP pelo suporte financeiro.

A todos que de alguma forma colaboraram na realização deste trabalho e contribuíram para minha formação.

Abbreviations

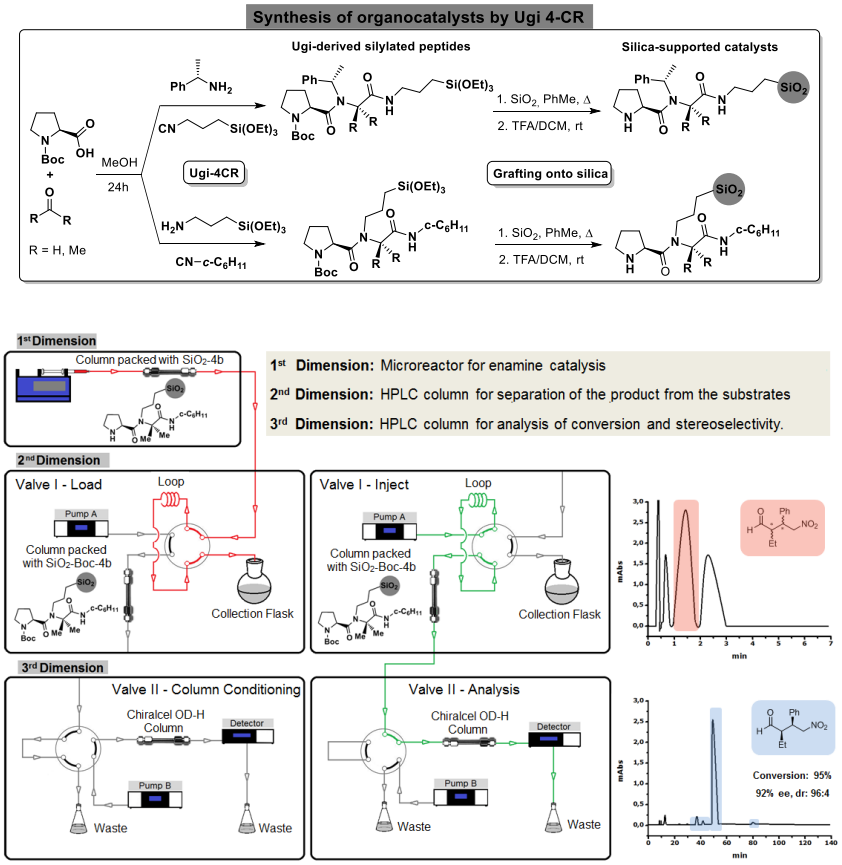
Asp	Asparagine
Boc	*tert*-butyloxycarbonyl
Cbz	Carboxybenzyl
CPMP	Committee for Proprietary Medicinal Products
Cy	Cyclohexyl
DCM	Dichloromethane
DKR	Dynamic Kinetic Resolution
DMSO	Dimethylsulfoxide
EtOAc	Ethyl Acetate
FDA	Food and Drug Administration
HOMO	Highest Occupied Molecular Orbital
HPLC	High Performance Liquid Chromatography
IMCR	Isocyanide Multicomponent Reaction
Karstedt's catalyst	Platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex
KR	Kinetic Resolution
LLE	Liquid-liquid Extraction
MCR	Multicomponent Reaction
MeOH	Methanol
$NaBH_4$	Sodium Borohydride
PEGA	Polyethylene glycol–polyacrylamide
PMP	*p*-Methoxyphenyl
Pro	Proline
RPKA	Reaction-Progress Kinetic Analysis
SFC	Supercritical Fluid Chromatography

SMB	Simulated Moving Bed
SOMO	Singly Occupied Molecular Orbital
SPAR	Polyacrylamide
TBS	*tert*-Butyldimethylsilyl
TentaGel	Polyethylene glycol–polystyrene
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl

List of figures and tables

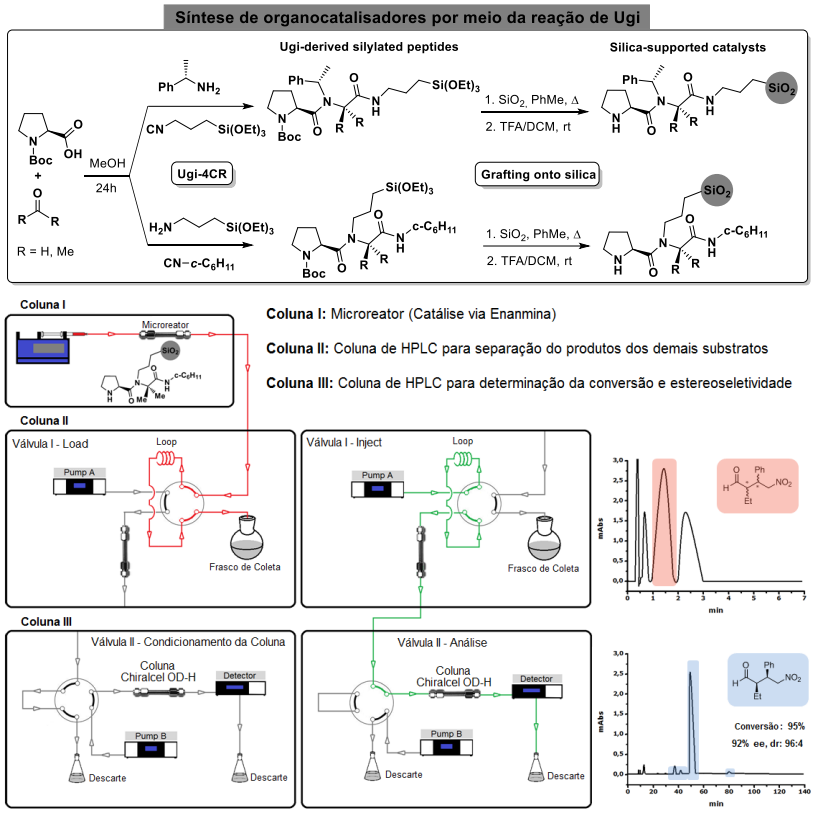
Abstract

MULTICOMPONENT APPROACH TO SILICA-GRAFTED PEPTIDE CATALYSTS: A 3D CONTINUOUS-FLOW ORGANOCATALYTIC SYSTEM WITH ON-LINE MONITORING OF CONVERSION AND STEREO-SELECTIVITY. The derivatization of organocatalysts with functional appendages suitable to anchor onto solid supports is usually achieved by stepwise syntheses. As an alternative to such a strategy, this work describes a one-pot approach to silylated prolyl-peptide catalysts by a multicomponent reaction that enables the simultaneous incorporation of the catalytic and the heterogenizable (triethoxysilane) moieties. A microreactor with high catalytic efficacy and reproducibly in the conjugate addition of aldehydes to nitroolefins was obtained by grafting onto HPLC-grade silica (10 μm) and packing into a column with a selected catalyst. A 3 D continuous-flow system that includes the on-line monitoring of the reaction outcome was set up. For that, the microreactor was coupled to a chromatographic column for the separation of the remaining substrates from the Michael adduct in the second dimension, followed by a chiral polysaccharide column for the analysis of conversion and stereoselectivity. This approach represents a new instrumental setup that combines the advantages of multidimensional chromatography and flow catalysis.



Resumo

MULTICOMPONENT APPROACH TO SILICA-GRAFTED PEPTIDE CATALYSTS: A 3D CONTINUOUS-FLOW ORGANOCATALYTIC SYSTEM WITH ON-LINE MONITORING OF CONVERSION AND STEREO-SELECTIVITY. A derivação de Organocatalisadores com apêndices funcionais adequados para ancorar em suportes sólidos é geralmente obtida por síntese “passo a passo”. Como uma alternativa para tal estratégia, este trabalho descreve uma abordagem de síntese *one-pot* de catalisadores prolil-peptio sililados através de uma reação multicomponentes, que permite a incorporação simultânea do sítio catalítico e o grupo funcional de ancoragem (trietoxisilano). Um micro-reactor foi obtido, tendo elevada eficácia catalítica e reprodutibilidade, na adição conjugada de aldeídos a nitro-olefinas, enxertando sobre sílica de grau HPLC (10 um) e preenchendo uma coluna com um catalisador escolhido. Um sistema de fluxo contínuo 3D que inclui a monitoração em linha do resultado da reação foi ajustado para cima. Para isso, o micro-reator foi acoplado a uma coluna cromatográfica para a separação dos substratos restantes do aduto de Michael na segunda dimensão, seguido por uma coluna de polissacarídeo quiral para a análise de conversão e estereosselectividade. Essa abordagem representa uma nova configuração do instrumento que combina as vantagens de cromatografia multidimensional e reações catálisadas em fluxo.



Objectives

MULTICOMPONENT APPROACH TO SILICA-GRAFTED PEPTIDE CATALYSTS: A 3D CONTINUOUS-FLOW ORGANOCATALYTIC SYSTEM WITH ON-LINE MONITORING OF CONVERSION AND STEREO-SELECTIVITY. Synthesize of a serie of organocatalysts based on proline, by the Ugi multicomponent reaction, then, immobilize them on silica, for evaluation of reaction conditions under batch and continuous flow. As well, development of a three dimensional chromatographic system for on-line monitoring of the reaction parameters.

Objetivos

MULTICOMPONENT APPROACH TO SILICA-GRAFTED PEPTIDE CATALYSTS: A 3D CONTINUOUS-FLOW ORGANOCATALYTIC SYSTEM WITH ON-LINE MONITORING OF CONVERSION AND STEREO-SELECTIVITY. Sintetizar organocatalisadores baseados em prolina, por meio da reação multicomponente de Ugi, imobilizá-los em sílica, para avaliação de condições de reação em batelada e fluxo contínuo. Além disso, desenvolver um sistema cromatográfico tridimensional para monitoramento on-line dos parâmetros reacionais.

SUMARY

INTRODUCTION

1. Chirality, an old concept that is still challenging!

In 1809, begins the concept of enantioresolution, by the crystallographer Hay,[1] but it was Pasteur, in 1848, that discovered the difference of biological activity of enantiomers, (+)-ammonium tartrate and (-)-ammonium tartrate, by Penicillium glaucum.[2]

Pasteur performed the first known enantioresolution. He noticed that the crystals of the racemate ammonium sodium tartrate had two distinct enantiomorphic forms. Using tweezers and a magnifying lens he separated them manually, and demonstrated that the two different types of crystals rotate polarized light in opposite directions. [3]Pasteur's experiment is a landmark of the chiral resolution.

Most racemic mixtures don't have different enantiomorphic forms, even worse, most have almost all physicochemical properties identical. This causes that the separation of enantiomers to be quite a challenge. Usually, the separation of enantiomers was accomplished by the formation of a pair of diastereoisomer, which they have different physicochemical properties and can be easily separated.

Other technique employed as chromatographic resolution was `Paper chromatography´. This technique was first employed in separation of aromatic aminoacids.[4]

Based on that, Dagliesh, in 1952, proposed the model of "three points of interaction" between enantiomers and the selector chiral.[5] The model explains the formation of diastereoisomeric complex. According to this model, three simultaneous interactions of one enantiomer and the chiral selector are required, of which at least one must be dependent on the stereochemistry of the analyte. While the other enantiomer interacts with only two sites of the chiral selector.[1] (FIGURE 1)

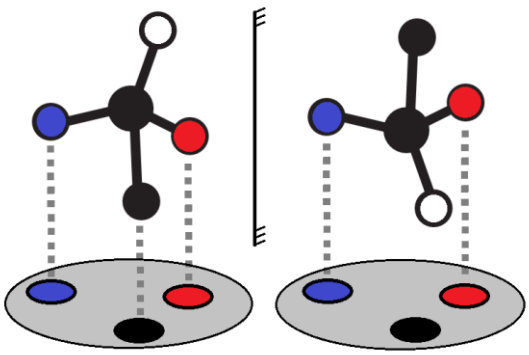


FIGURE 1 - Model proposed by Dagliesh in 1952 of “Three points of interaction”.

Nowadays, it is increasingly important to obtain molecules in an enantioselective way. Chiral molecules are no longer a merely academic interest and became the butt of large corporations, especially pharmaceutical industry. The production of enantiomerically pure substances are given by the need to have compounds with greater activity with less side effects and more efficient procedures of preparation, since in some cases not active enantiomer is considered an impurity.

Besides the search for more effective chiral substance and methods that are more productive, regulation of the Food Drug Administration (FDA) of the United States, 1992, which started to recommend the policy of administering drugs as racemic mixtures, only if pharmacological and toxicological studies of the pure enantiomers were performed. In 1993, the European Union Committee for Proprietary Medical Products (CPMP) created the guidelines “Investigation of Chiral Active Substances”.

Given the current need for obtaining molecules in the form of a single enantiomer, various techniques have been developed in order to get them more efficient and simplified manner. All these techniques basically involves two routes:

1. Achiral synthesis
2. Asymmetric synthesis

Achiral synthesis aways is followed by separation procedures, such as: High Performance Liquid Chromatography (HPLC), Simulated Moving Bed (SMB), Supercritical Fluid Chromatography (SFC), Crystallization, Kinetic Resolution (KR), Dynamic Kinetic Resolution (DKR), Membrane-based and others.

1.1. Asymmetric synthesis.

The IUPAC definition:[6] "*A chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts*." In other words: the formation of a favored stereoisomer by a synthetic procedure.

Stereoselective synthesis can be done under stoichiometric and catalytic conditions. The second one is favorable due to low quantity of catalyst[7] used, reducing the cost and waste of material used. The most used techniques were: Metalocatalysis, Biocatalysis, Organocatalysis, Chiralpools and Chiral auxiliaries (FIGURE 2 **- The three pillars of catalysis.**).

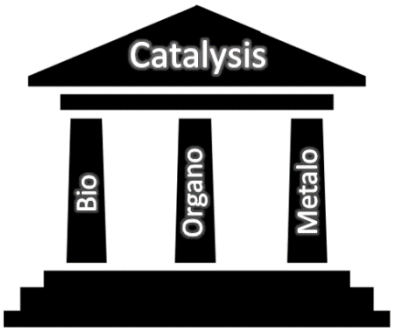


FIGURE 2 - The three pillars of catalysis.

1.2. Organocatalysis in asymmetric synthesis.

The term 'Organocatalysis' was created in 2000,[8] it consists in the use of organic molecules (composed mainly of atoms C, H, O, N, P and S) to catalyze organic transformations in absence of metal in the catalyst structure. The numbers of application and publications is increasing very fast in the past 14 years (FIGURE 3).[9]

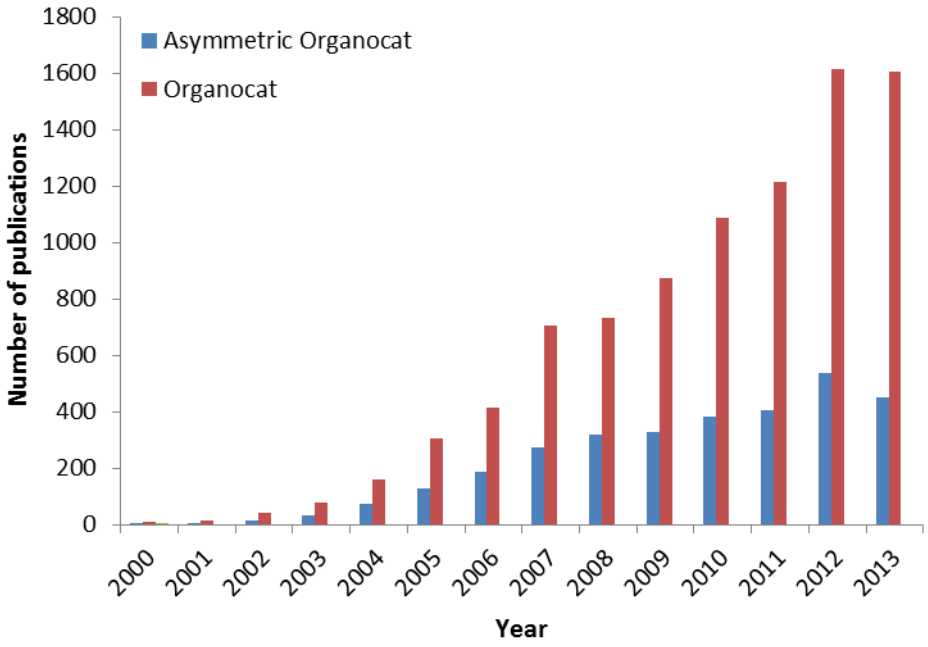


FIGURE 3 - Number of publication in journals published in the last years which math for the keywords: Asymmetric Organocat or Organocat.

1.3. Modes of activation

Organocatalysis can be divided in two types of substrate activation[10] (FIGURE 4):

I. Covalent activation : In the covalent activation, a new covalent bond between the catalyst and the substrate is formed, having kinetic stability and high bond energy (35 to 135 kcal.mol-1). It comprehends the enamine, iminium and SOMO catalysis

II. Non-covalent: Several types of non-covalent interaction are known: electrostatic, van der Waals, hydrogen-bonding,π-π etc. The energy involved in that kind of interaction is lower than the covalent type, about 2 to 20 kcal.mol^{-1}. Counterion and hydrogen-bonding are examples of this mode of activation.

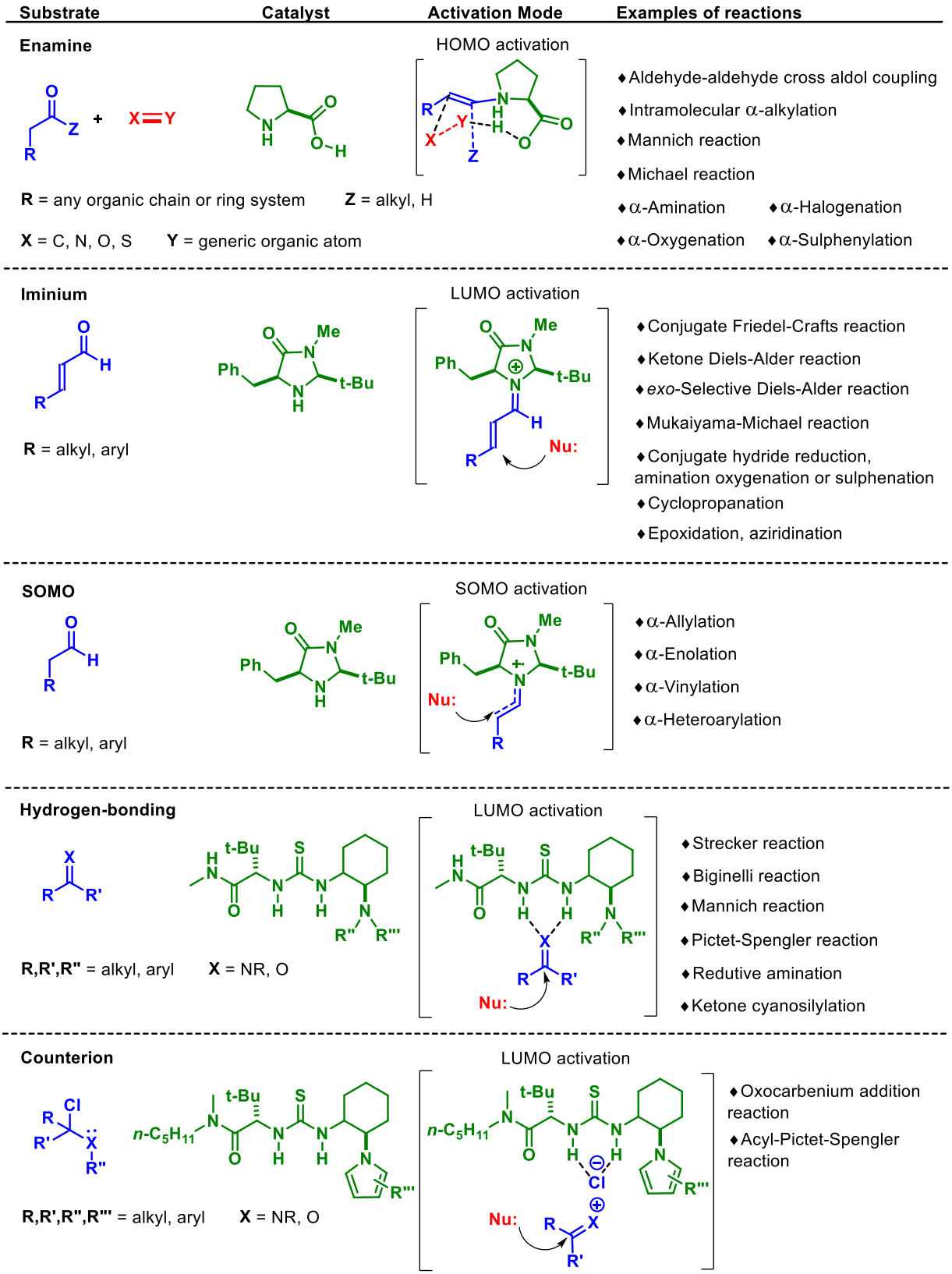


FIGURE 4 - Generic modes of activation in organocatalysis.

The enamine mode of activation is used in a wide range of enantioselective carbonyl α-funcionalization. Generally, the catalyst is a proline based type, it acts in the carbonyl compound, raising the HOMO (Highest Occupied Molecular Orbital), this activation strategy affords high levels of reaction efficiency and enantioselectivity.

The organocatalytic iminium activation strategy has been applied sucefully to a series of reactions. It is viable due to imidazolidinone catalysts' ability to lowering the LUMO (Lowest Unnocuppaid Molecular Orbital) energy of α,β-unstaturated aldehydes, making it appropriate to a great number of conjugate addition reactions.

SOMO (Singly Occupied Molecular Orbital) catalysis is based on one-electron oxidation of an electron-rich enamine that selectively generates a reactive radical cation with three π-electrons. The electrophilicity of the SOMO of the intermediate allows it to react readily with a variety of weakly nucleophilic carbon-based at the α-carbon of the parent enamine.

Hydrogen-bonding donating catalysis is a mimetic of lewis acid activation, also lowering the LUMO energy. Generally, employs ureas or thioureas as the crucial functionality group which can make one or two hydrogen bonds involving the N-H.

Asymmetric counteranion-directed catalysis (ACDC) proceeds through an ionic intermediate by means of ion pairing of the substrate and a chiral catalyst, therefore the energy of the LUMO is reduced.

Interestingly, due to the different modes of catalyst-substrate interaction, those modes of activation can be combined orthogonally or complementary, therefore in a sequential or convergent fashion is possible to obtain a broad range of products. Nowadays, the behavior of these catalysts and especially the mode of activation captivated the research community.

A remarkable example is the first use of organocatalysis is the industrial scale, for synthesis of Tencapengepant, a trial drug for the acute treatment of migraine, developed by Merck & Co.

The Starting from 1,2-difluorobenze, the α,β-unsaturated aldehyde was efficiently prepared. Then the crude intermediary was used without further purification, for the subsequent organocatalytic nitromethane Michael addition under optimal conditions, to obtain the desired γ-nitroaldehyde, described in the FIGURE 5.

Unfortunately, Merck & Co on July 29, 2011, it was discontinued the clinical development program for telcagepant, based on the findings from a recently completed six-month Phase III study.[11]

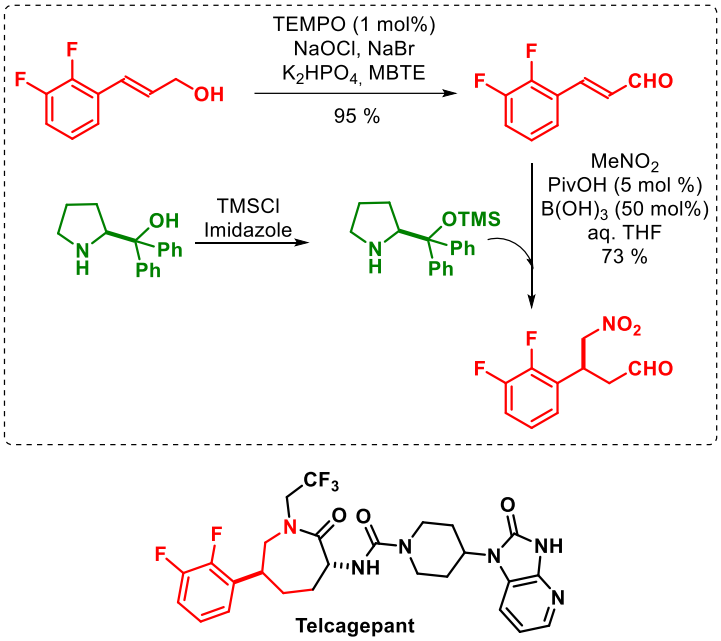


FIGURE 5 - Synthesis of an intermediary of Telcagepant by organocatalytic process.

1.3.1. Enamine Activaion

Specifically the enamine mode of activation is a powerful tool for α-functionalization of carbonyl compounds. It involves the formation of transient enamine intermediates that are more nucleophilic, which have the HOMO (Highest Occupied Molecular Orbital) energy higher than their parent carbonyl compound. It allows reactions that could not proceed without catalysis, enabling formation of new bonds. Even, there are some different stereochemical models for enamine reactivity to explain the stereochemistry of the formed product: A. List-Hook model, a Hydrogen-bonding interaction in which the electrophile has an electronegative heteroatom with an electron pair (lone-pair) acting as hydrogen bond acceptor. B. Steric model takes place when bulky substituents groups are present in the position 2 of pyrrolidine e.g. Jørgensen's Organocatalysts, the electrophile approach is driven by steric interaction, the less steric hindered path is the favored one. C. Seebach model, states that the nucleophilic attack of the enamine proceeds by the electrons in

the carboxylate moiety, not the lone-pair on the enamine nitrogen as in A. [12] [13] [14] [15](FIGURE 6).

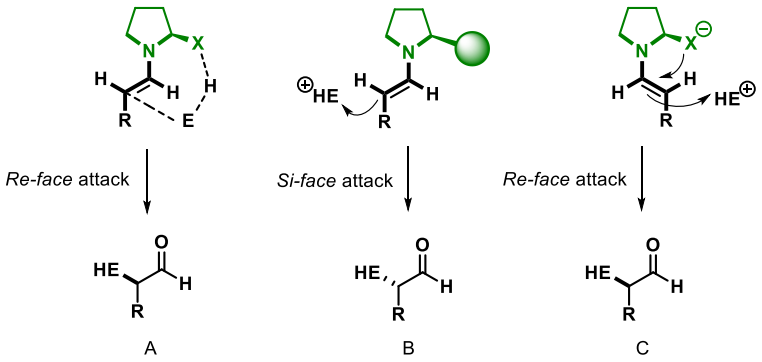


FIGURE 6 - Stereochemical models for enamine reactivity. A: List-Hook model. B: Steric model. C: Seebach model.

A generalization mechanism for enamine pyrrolidine-type catalyst[16] [17] is shown in FIGURE 7.

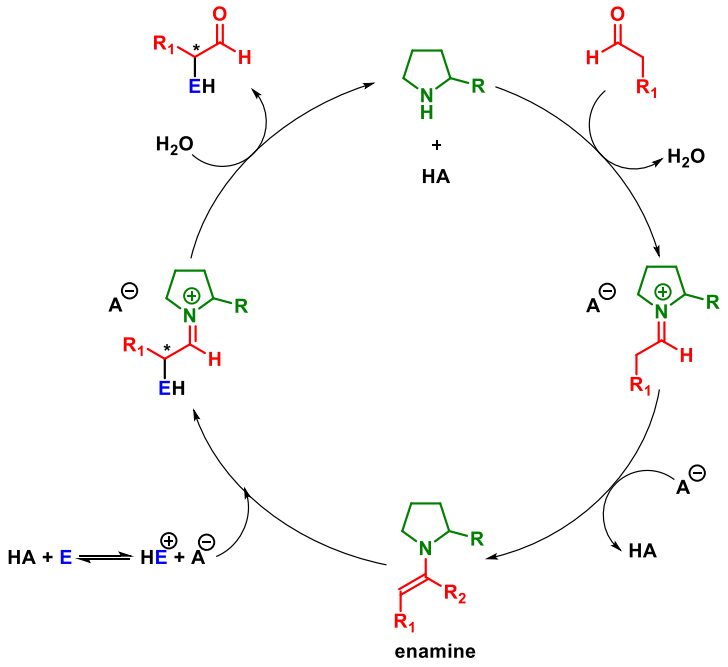


FIGURE 7 - General mechanism for enamine pyrrolidine-type catalyst.

The general mechanism for pyrrolidine-type catalyst consists of the formation of iminium ion by the condensation of carbonyl and the chiral amine catalyst. The iminium ion formation raises the acidity of the α-proton and its deprotonation leads to

the enamine. This reactive enamine attacks the electrophile to form the iminium, then by hydrolysis of it, yields the desired product with regeneration of the catalyst.

Undoubtedly, the most important bond formation in organic chemistry definably is carbon-carbon bond (C-C). The Michael reaction is a benchmark for development of new organocatalysts, in particular, the addition of aldehydes to β-trans-nitrostyrens. New trends to improve and understand the real mechanism were done. Hayashi and Sebach proposed the revised mechanism for pyrrolidine-type catalyst in 2011 (FIGURE 8).[21] In the first step the catalyst reacts with aldehyde to afford the enamine. Then react with correspond nitroalkene to form the zwiterionic intermediate. The zwiterionic intermediate can undergo by two paths: 1) [2+2] reversible cycloaddition to cyclobutane, generating an off-cycle specie in which the catalyst is taken out of the cycle 2) protonation of the nitronate carbon atom and leading to iminium ion, which is hydrolyzes to the desired product or deprotonate to enamine, a epimer of the product.

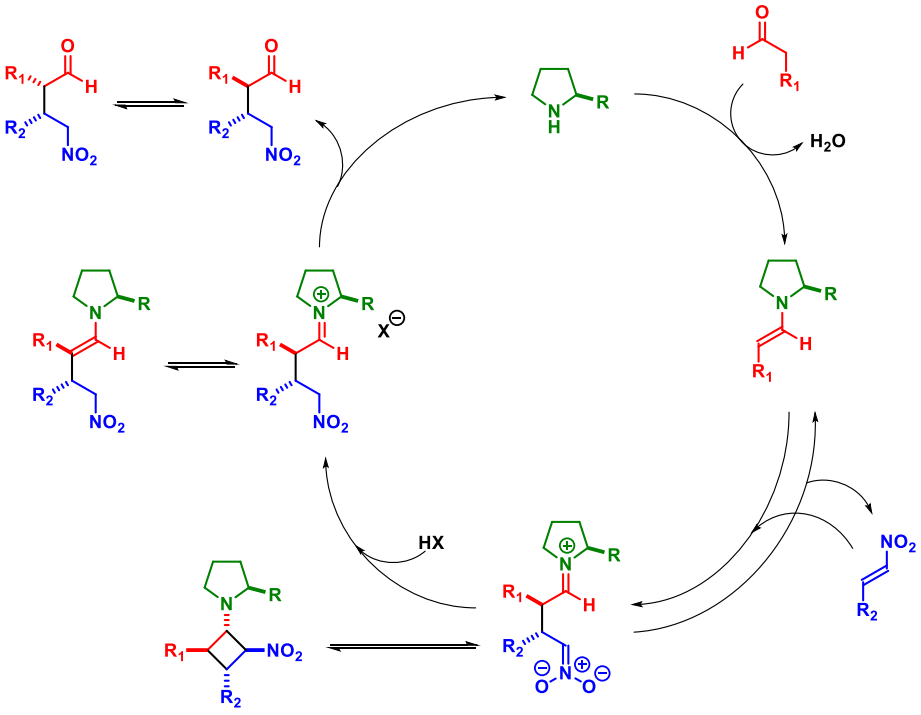


FIGURE 8 - Revised mechanism for pyrrolidine-type catalyst.

Using a combination of kinetic and thermodynamic factors, which illustrates a remarkable Curtin−Hammett scenario. Donna Blackmond and co-workers published

results that leads to the proposal that the stereochemical outcome in the case of the conjugated addition to nitro-olefins is not determined by the transition state of the step in which the stereogenic center is formed from enamine attack on the trans-β-Nitrostyrene. Instead, it is correlated with the relative stability and reactivity of diastereomeric intermediates downstream in the catalytic cycle, a general phenomenon for pyrrolidine-based catalysts lacking an acidic directing proton (FIGURE 9).

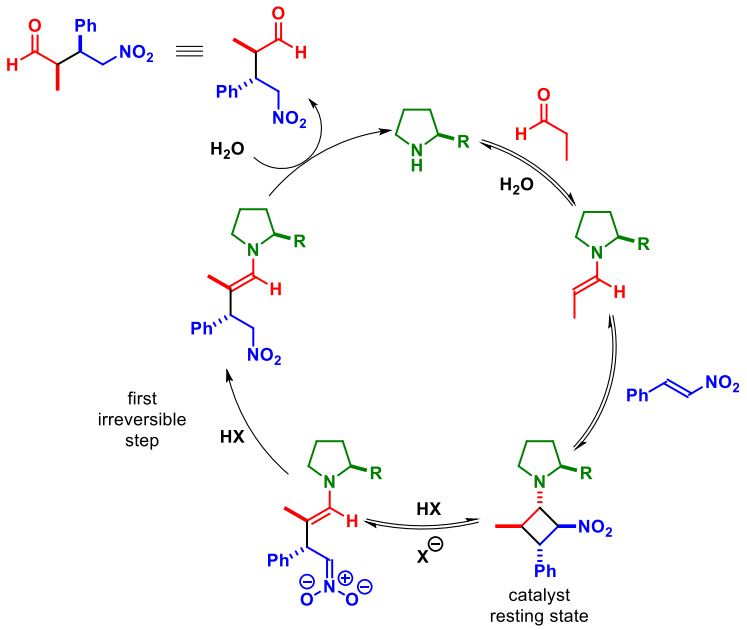


FIGURE 9 - Modified Catalytic Cycle by Donna Blackmond.

All the catalytic species shown in the proposed catalytic cycle have been observed experimentally by NMR studies. Some steps, represents the combination of a sequence of elementary reaction combined into a kinetically significant step.

The formation of the cyclobutane specie represents, the fast initial rate, which rapidly became equilibrated with the enanmine and the trans-β-Nitrostyrene. This cyclobutane, it is called a catalyst resting state and not an *off-cycle* specie as proposed by Hayashi and Seebach.Then the protonation and deprotonation step dominates the remainder reaction, once that it is an irreversible step.

Despite of the enanmine formation destroys the stereocenter formed in the addition step, a highly selective reaction proceeds by this pathway, it suggests that a stereo specific relationship exists between this enamine and the *syn* product.

Seebach and co-workers noticed that α-substituted aldehydes cyclobutane derivatives are very stable, and can act as an irreversible trap for the catalyst, once that the ring opening to the zwitterion is very problematic, which should prevent the product formation (FIGURE 10).

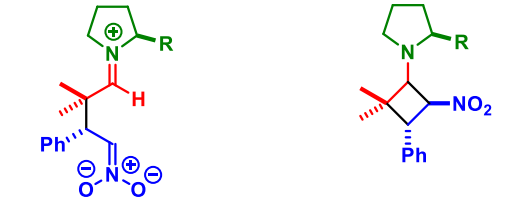


FIGURE 10 - Possible explanations for the low reactivity of α-substituted aldehyde.

Although the controversy of the models regarding the reaction, the comprehension of mechanism can leads to the improvement of reaction parameters and results. Furthermore, in order to enhance the productivity and recyclability of those catalysts, a powerful tool is anchoring or supporting them in a solid support, which permits the easy recovery and reuse. An even more elegant, the variant where the reactional system is automated and the supported catalyst remains in a determined reactor, that is, flow chemistry is an area which gains force nowadays and became a stair-up between laboratorial and industrial process.

1.4. Catalyst heterogenization and flow chemistry.

The “Catalyst Heterogenization” consists of the adsorption (physical process) or covalently bond (chemical process) of a catalyst in a support that is in a difference phase of the reaction media. Once that, in organic chemistry, most reactions are performed in liquid phase, most of the heterogenized catalyst are made by graffiting the catalyst in a solid support. Many types of support can be used: organic (eg. polymers, resins) and inorganic (zeolites, silica). Each one has specific characteristics, thus has unique properties that can act synergistically with the

catalyst. In general, the aim is to have good physical stability (abrasion, pressure, temperature, swelling and shrinking) and chemical (pH, leaching and solubility).

Another important factor to be considered is the total surface area. The larger the surface area for a given mass of particle, the better will usually be the catalyst due its effect on the reaction rate, because it mimics the homogeneous catalysis. In order to obtain optimal results, typically is used small particles with large area to volume ratio and a well-defined pore structure.

Once the heterogeneous catalyst is obtained, the selection of the appropriated synthesis techniques is of paramount importance, although techniques related to organic synthesis have improved a lot in recent years, most of all chemical process still based on batch reactions. The main drawback is that the optimization of reaction is slow and tedious. Each parameter of reaction should be varied independently to obtain the optimal condition; it can increase the time, reagents and money spent in the process.

Continuous flow reactions can be a solution to overcome that problem. Running flow reactions have few advantages:

- ✓ Scaling up: the use of several reactors in parallel (numbering up) allow achieve the same residence time and just recalculating the flow, multiplying the initial flow rate by the total number of columns, obtaining exactly the same results. It is also possible to design a bigger reactor that has the same residence time.
- ✓ Safety: usually smaller volumes, easy handling, anhydrous conditions, sensitive air, dangerous reagents.
- ✓ Heat and mass transfer: Reaction temperature can be controlled very well, due to the small channels and the large area to volume ratio mixing and heat/cooling occurs practically instantly.
- ✓ Automation: the reactor "hyphenation" to detection systems is less effort, facilitating operational and experimental planning, thus reaction parameters can be easily improved (concentration and proportional of reagents, temperature, pressure and flow rate) and it gives a better knowledge of relational system (kinetics and thermodynamic).
- ✓ Multistep reactions: can be arranged in a continuous sequence.

  Purification: Many techniques can be coupled to the flow systems: liquid/liquid extraction, solid phase scavenging, chromatographic separation.

Moreover, continuous flow reaction can easily be combined with heterogeneous catalysis enabling the recycling and reuse of the catalyst, which turns this very important tool for organic synthesis. More interesting result are achieved when all of the process of flow conditions can be operated automatically in a multidimensional way which might result in the effective design of productivity-enhancing improvements.

1.5. Solid supported organocatalysts. Batch and continuous flow.

The field of organocatalysis has been growing constantly. Over the last 14 years, several immobilized organocatalysts have been described due to the greener importance to recovery the catalysts from the reaction or by the possibility to combine with different technologies (ca. microreactors, HPLC, others). In this case, the combination of immobilized organocatalysts with continuous flow has been increasing, due to the possibility to reuse and recycle many times in an automated form. It is worthy note that the choice of the solid support is relevant and many materials are available e.g. resin, polystyrene, and silica. [18, 19]

Pericàs and co-workers [20] described the first example of Mannich reaction of aldehydes and ketones with the *N*-(*p*-methoxylphenyl) ethyl glyoxylate imine catalyzed by (2*S*,4*R*)-hydroxylproline solid-supported in polystyrene beads. The evaluation of different spacers for the incorporation of proline moiety onto the polystyrene beads led the authors to identify that the presence of 1,2,3-triazole linker was crucial for the high catalytic behavior of this supported system. Therefore, catalyst 1 showed better performance (catalytic activity and enantioselectivity) when compared to catalyst 2 and 3 under batch conditions. Despite of the short reaction times required for the reactions proceed under batch conditions, a single-pass, continuous-flow system was set-up using a jacketed omnifit column filled with PS-supported proline derivative 1 connected to a single-piston pump. This system operated at room temperature with a loading of 1.0 g of Catalyst 1 (functionalization; (*f)* = 0.46 mmol.g $^{-1}$) using a flow-rate of 0.20 mLmin^{-1} with a residence time of 6.0 min. Under this condition, the Mannich product could be obtained in highly efficiency and stereoselectivity (yield= >95%, 97% ee, *d.r.* > 97:3) with the advantage that non-further purification is necessary (FIGURE 11).

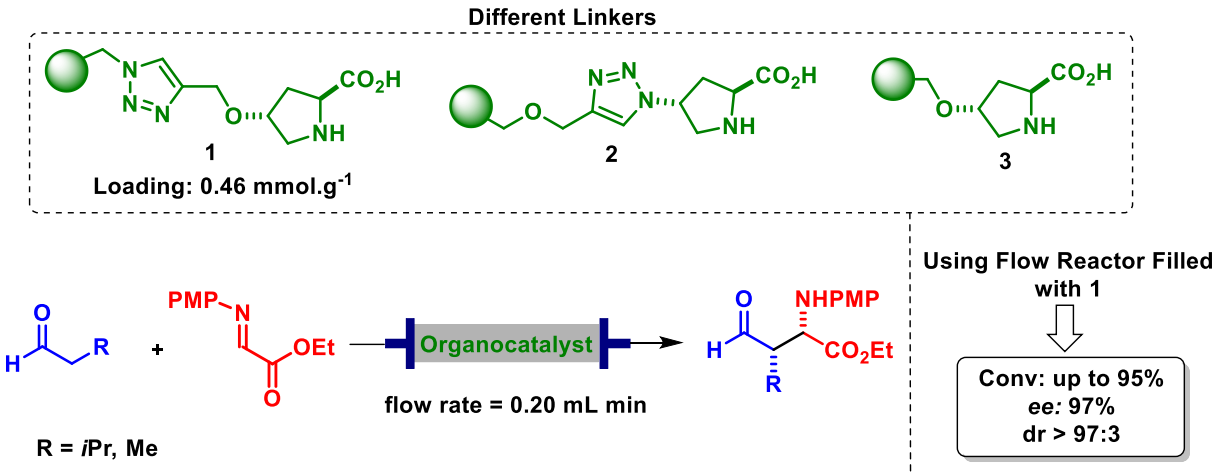


FIGURE 11 - Evaluation of different linkers of the organocatalyst in the Mannich reaction.

Despite its extreme simplicity and very high stereocontrol of the packed-bed continuous-flow reactor 1 was implemented for the direct enantioselective α-aminoxylation of simple aldehydes. [21] Through a simple flow process, involving short residence times, a series of α-oxy-substituted aldehydes was prepared with excellent enantioselectivity (>90% ee). The authors observed that both catalysts showed to be a little instable decreasing the conversion of reaction with time. A low stability of the catalyst under the employed reaction conditions led to slow deactivation after five hours cycle (yield=15–20%). (FIGURE 12)

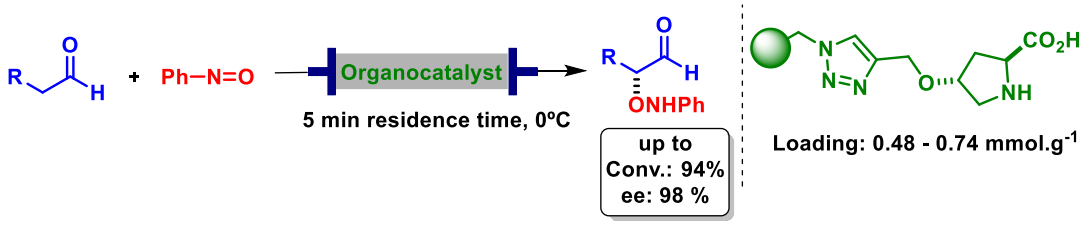


FIGURE 12 - Alpha-aminoxylation of aldehydes.

The lack of shielding groups in the hydroxylproline structure limits considerably its applicability in different asymmetric reactions. To overcome this limiation, new pyrrolidine-type catalysts were designed based on the so-called Jørgensen-Hayashi

organocatalyst. Therefore, Pericàs and co-workers developed a small collection of polystyrene (PS)-supported diphenylprolinol silyl ethers catalysts. In order to avoid silyl group loss from the catalyst during the reaction, they have described the synthesis of a series of silyl protecting groups e.g. TES, TBS and TIPS in place of the more labile TMS (FIGURE 13). Excellent results in α-amination of aldehydes in batch were obtained with an immobilized silyl protected-pyrrolidine catalyst.[22] By using 2 mol% of the organocatalyst containing TBS (*tert*-Butyldimethylsilyl) moiety led to complete conversion in only 45 min with 93% of ee. The polymer-supported organocatalyst was reused for 10 times accumulating a turn over number (TON) of 480, with an overall yield of 96% and 88% *ee*. These results allowed the implementation of a continuous-flow process at a flow rate of 0.15 $mLmin^{-1}$ and residence time of 6 min in a reactor charged with 0.3 g of the catalyst. The devise was kept in operation for 8 h with the production of 7.6 mmol of the desired product (ee: up to 91%). A slight decrease in terms of conversion was observed in the last 2 h of operation.

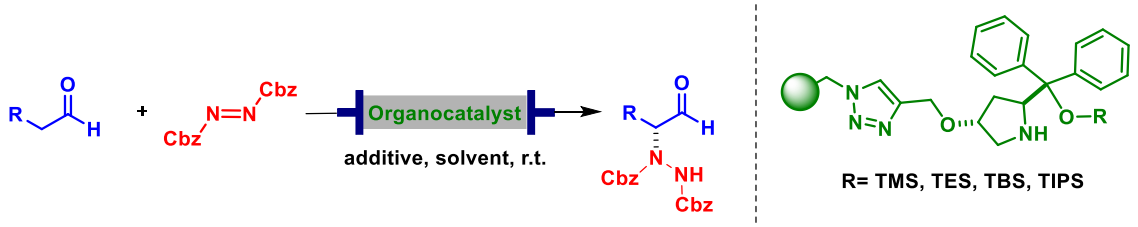


FIGURE 13 - The α-amination of propanaldehydes.

In a similar way, diarylprolinol silyl ethers immobilized onto polystyrene was also employed in the enantioselective a domino Michael-Knoevenagel reaction of dimethyl 3-oxoglutarate and 3-substituted acrolein derivatives (FIGURE 14). On the search of the optimal condition, the authors found out that the addition of benzoic acid as additive increased the yield of the domino process, providing the desired cyclohexanol product as a single isomer in a remarkably shorter reaction time and low catalyst loading.[23] The reaction proceed in continuous flow operation for 72 hours, 8.7 g of pure product were isolated without any deterioration of the enantioselectivity during the process (97% ee). Furthermore, the continuous flow operation allowed the achievement of a TON of 66, approximately tenfold increase with respect to batch conditions, in an easy and practical manner.

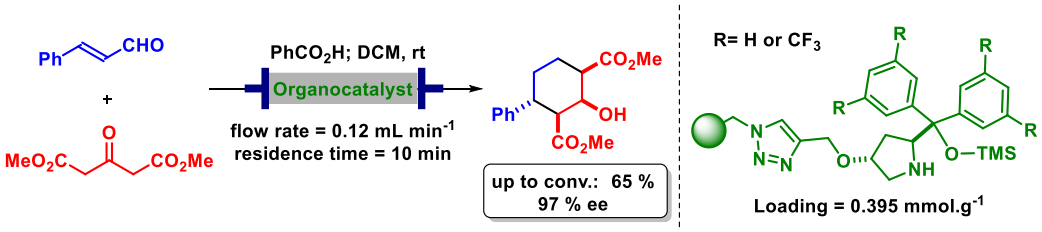


FIGURE 14 - A domino Michael-Knoevenagel reaction.

In addition, Wennemer and co-workers developed peptide based organocatalyst for heterogeneous catalysis systems.[24] The authors identified H-L-Pro-Pro-Asp-NH_2 as best peptide catalyst for asymmetric Aldol reaction.[25] The catalyst was grafted onto four different resins e.g. polystyrene (Ɛ-aminocaproic acid as a spacer), SPAR (polyacrylamide), TentaGel (polyethylene glycol–polystyrene) and PEGA (polyethylene glycol–polyacrylamide). However, when the peptides were immobilized on TentaGel and PEGA showed a similar performance compared to the free peptide, therefore, affording the Aldol product in high yields (90%) and good enantioselectivity 75%. The recyclability was examined during eight identical reactions using 1 mol% of resin. During the three cycles, no significant decrease in the catalytic activity or selectivity of the solid-supported catalyst was observed (yields= 83–95%, 80% *ee*). Thereafter, the catalytic activity was observed to decrease while the enantioselectivity remained high after the fifth cycle (yields= 10–40%, >65% ee) (FIGURE 15).

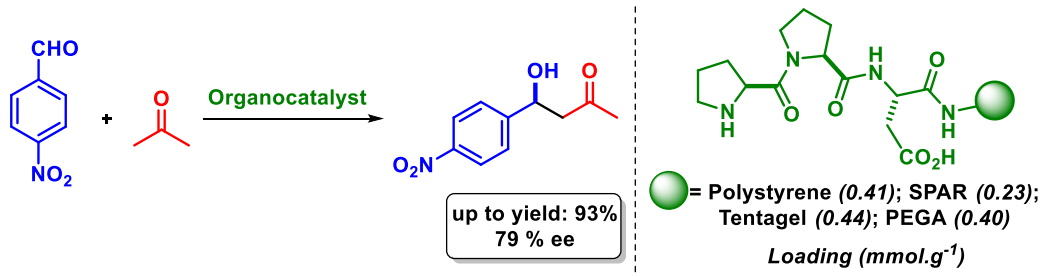


FIGURE 15 - Catalyst H-L-Pro-Pro-Asp-NH_2 grated on different solid support.

Another peptide class of organocatalyst having a sequence of H-D-Pro-Pro-Glu-NH-$(CH_2)_5$CONH-PS was efficiently applied for asymmetric conjugate addition reactions under a flow system. The conjugate addition products were obtained in more than 450 mmol (>100 g) with excellent stereoselectivities using only 0.8 mmol

of the immobilized catalyst. After approximately 400 turnovers, a slight deactivation of the catalyst was observed – however, the activity could be recovered by simply rinsing with mild base. After 610 turnovers the catalyst had still the same high stereoselectivity and a comparable activity as the freshly prepared. This result, suggested that the turnover limit of the catalyst had not yet been reached.[26]

The reaction of nitrostyrene with butanal when pumped through the flow system at a flow rate of ca. 0.23 mL.min^{-1}, provided the γ-nitroaldehyde in excellent yield and high stereoselectivities (syn/anti 25:1, 95% ee) FIGURE 16.

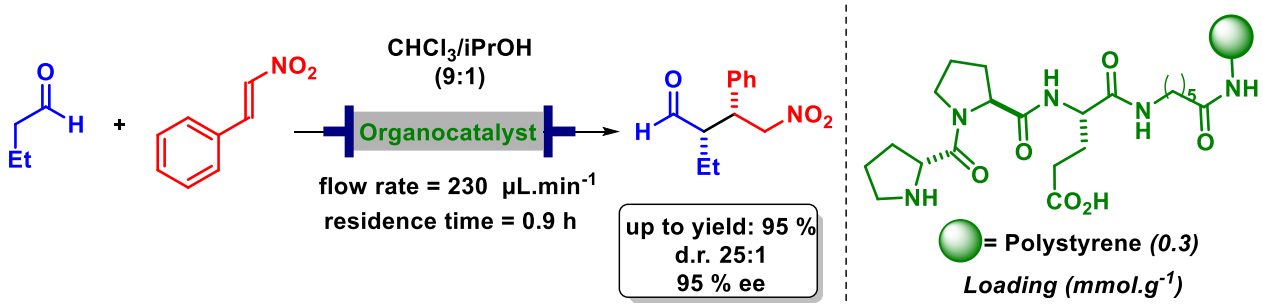


FIGURE 16 - High turnover H-D-Pro-Pro-Glu-NH-$(CH_2)_5$CONH-PS catalyst.

Pericàs and co-workers studied a polystyrene-supported bifunctional squaramide organocatalyst in the Michael addition of 2-hydroxy-1,4-naphthoquinone, to different nitrostyrene. [27] Under batch conditions, the supported catalyst could be recycled up to 10 times without any decrease in terms of enantioselectivity. The reactions were adapted to continuous flow operation, at a flow rate of 0.2 mL min^{-1} through a column charged with 0.095 mmol of catalyst (f = 0.38 mmol g^{-1}). After 20h, highly selectivity was obtained (96% ee), with a TON of 200 and a productivity of 4.07 mmol.g.resin^{-1}.h^{-1}. Six different nitroalkenes were used in a sequential manner, in a single flow experiment an easily constructed and operated asymmetric Michael machine. This illustrates the unique potential of flow processes based on covalently immobilized organocatalysts for the production of libraries of enantiopure compounds (FIGURE 17).

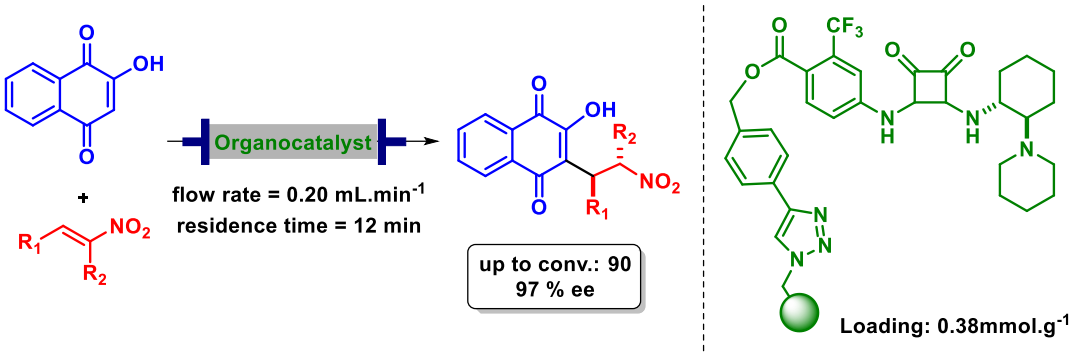


FIGURE 17 - Bifunctional squaramide organocatalyst in the Michael addition

Celentano and coworkers performed the first Continuous-flow organocatalyzed Diels-Alder reaction.[28] A chiral “homemade” HPLC column was employed, filled with a silica-supported MacMillan´s catalyst (FIGURE 18). This methodology results to be efficient and selective for the asymmetric reaction between *α,β*-unsaturated aldehydes and cyclopentadiene (yield = >95%, 85% ee). Besides, in an alternative way, the synthesis of three different substrates were also evaluated and observed that until 150 h the reactor did not lost efficiency and selectivity. Furthermore, the reactor could be regenerated which providing more than 300 operating hours.[29]

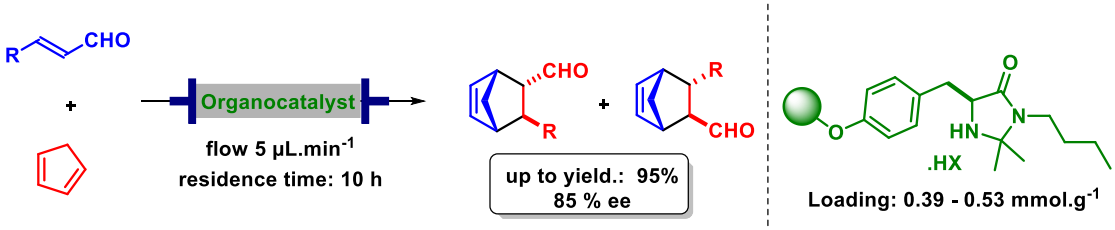


FIGURE 18 - Continuous-flow organocatalyzed Diels-Alder reaction.

Additionally, two silica-supported heterogeneous L-Proline organocatalysts featuring either a carbamate or an ether linker were obtained using a co-condensation sol-gel synthesis (FIGURE 19).[30] Its application in Aldol reaction produced high efficiency, but poor enantioselectivity were obtained (yield = 28-99%, 20-38% *ee*).

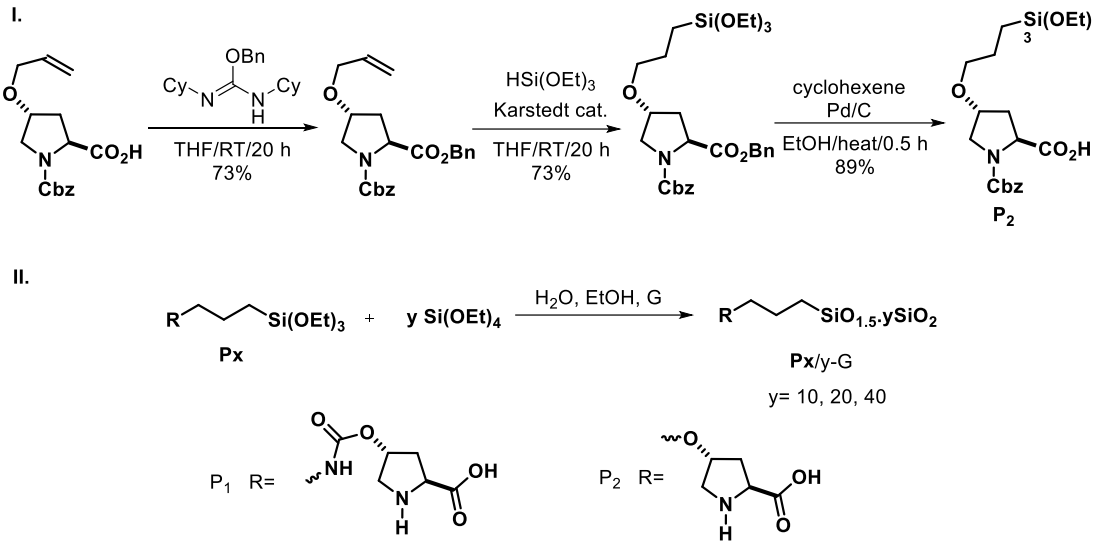


FIGURE 19 - I.)Preparation of the precursor featuring an ether linker P2. II.)Preparation of the hybrid silica via the sol–gel process using P1 or P2.

Bortolini and co-workers developed another efficient Silica-supported catalyst based on 5-(pyrrolidin-2-yl) tetrazole.[31] They prepared the supported organocatalysts by a photoinduced thiol-ene coupling reaction and packed into a short stainless steel column. Initially Aldol reaction of cyclohexanone with p-nitro benzaldehyde was evaluated, where diisopropyl ether as solvent allowed good stereoselectivities, complete conversion, and long term stability of the packing material (yield= >95%, 95% ee, *d.r.* 2:1). The authors also evaluated, under batch conditions, Mannich, Michael and α-amination to gain more information about the potential implementation of continuous-flow heterogeneous catalysis (**Erro! Fonte de referência não encontrada.**). Due to the excellent results obtained on the Aldol reaction in batch conditions, a continuous flow experiment was performed. Where the optimal conditions for flow process was found pumping a 0.03 M solution of aldehyde at 5 μL min^{-1} with residence time t_r = 25 min.

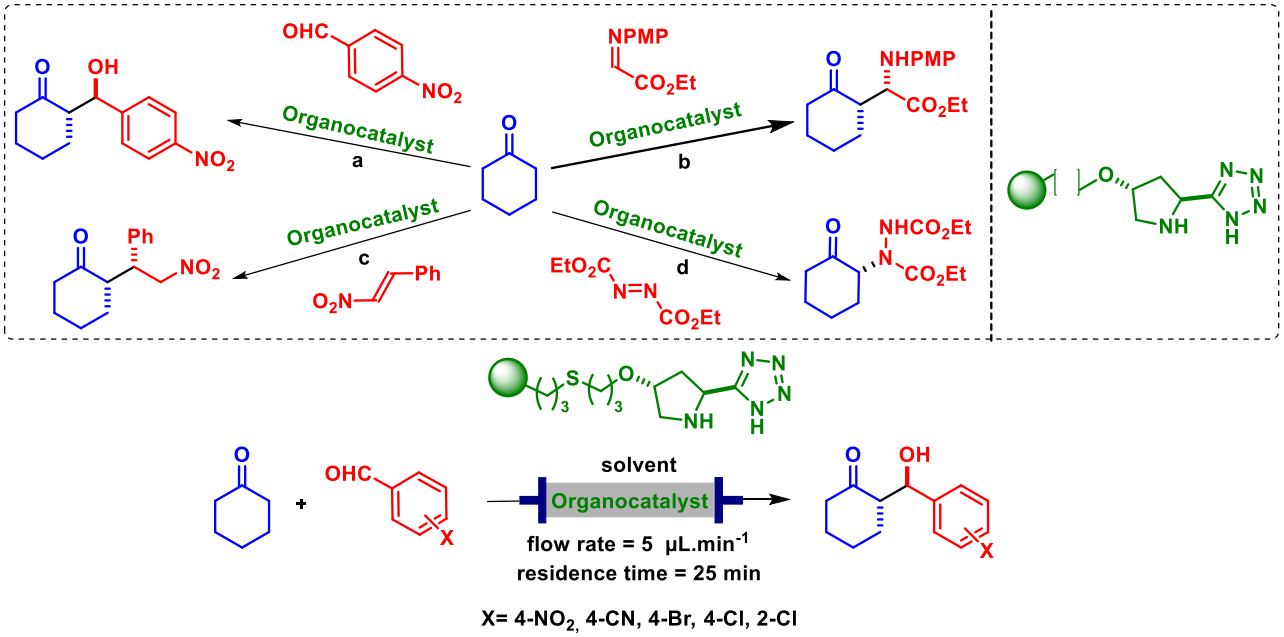


FIGURE 20 - Silica-supported catalyst based on 5-(Pyrrolidin-2-yl) tetrazole application in different reactions.

Single column chromatography, one-dimensional, is widely used for analysis in a broad range of fields, once that separation is imperative for identification, characterization and/or quantification of compounds in complex matrices. However, most of the matrices require a laborious sample pre-treatment that wastes time. Due to a lack of resolution and separation power in one dimensional chromatography, a robust system was necessary in order to circumvent that. Multidimensional has emerged to fill this gap. Using more than one column and a switching valve system is possible to dramatically enhance achievable peak capacity, allowing combination of two or more orthogonal system.

Recently, a Reaction-Progress Kinetic Analysis (RPKA) combined with a two-dimensional chromatography (for online monitoring of reaction) was studied (FIGURE 21).[32] This system allows rapid optimization and comprehension of flow conditions, as well as knowledge of rate determining step of mechanism. A suitable 2D instrumental arrangement for simultaneous flow reaction and online flow-injection analysis was performed. This combination led to the author to study and monitory the optimal variables for kinetic parameters as well as clear understanding of important features of the heterogeneous continuous-flow process, such as the dependence of the reaction order on feed composition and saturation capacity of the catalytic bed.

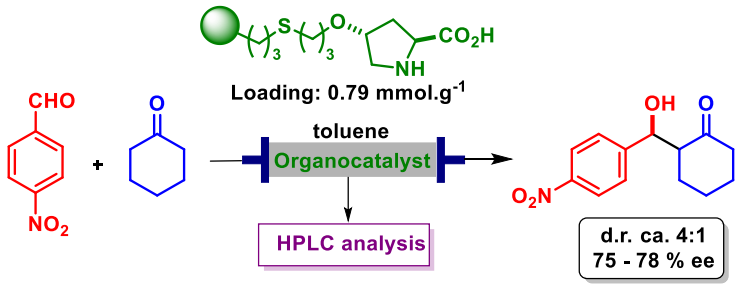


FIGURE 21 - Bidimensional chromatography allied to RPKA

1.6. Multicomponent Reaction.

The synthesis of compounds with highly structural complexity is still a challenge in organic synthesis. It demands many steps of reaction, purification and characterization, a laborious and time consuming process[33]. In the 90th century Combinatorial Chemistry was developed to meet the need of the pharmaceutical industry in the search for new compounds with biological activity. Despite the efforts in this area, long-term experience has demonstrated that in the search for new bioactive molecules, we should look nature‘s compounds or synthetic molecules resembling them. Therefore, new synthesis tools became needed. One of them is multicomponent reactions (MCRs).

This approach consists of a process in which at least three reagents are used to form a single product that contains most of the atoms of the reactants. Such reactions are abbreviated by MC-nR, where n is the number of reagents used to obtain a given product. A single reagent can be counted more than once to determine n, since this reagent is chemically bound to different sites of the product (FIGURE 22).[34 35 36 37]

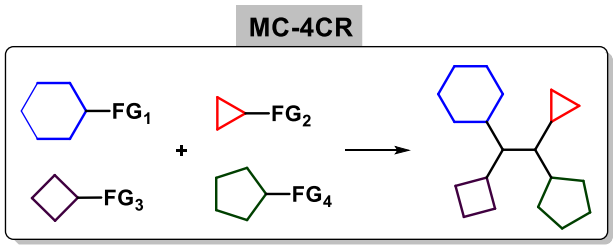


FIGURE 22 – Generic multicomponent reaction.

Multicomponent reactions are well known for a long time. The first reports of this reaction type dates from the early 19th century. The seminal protocol was the amino acids Strecker reaction which was quickly followed by others (FIGURE 23).

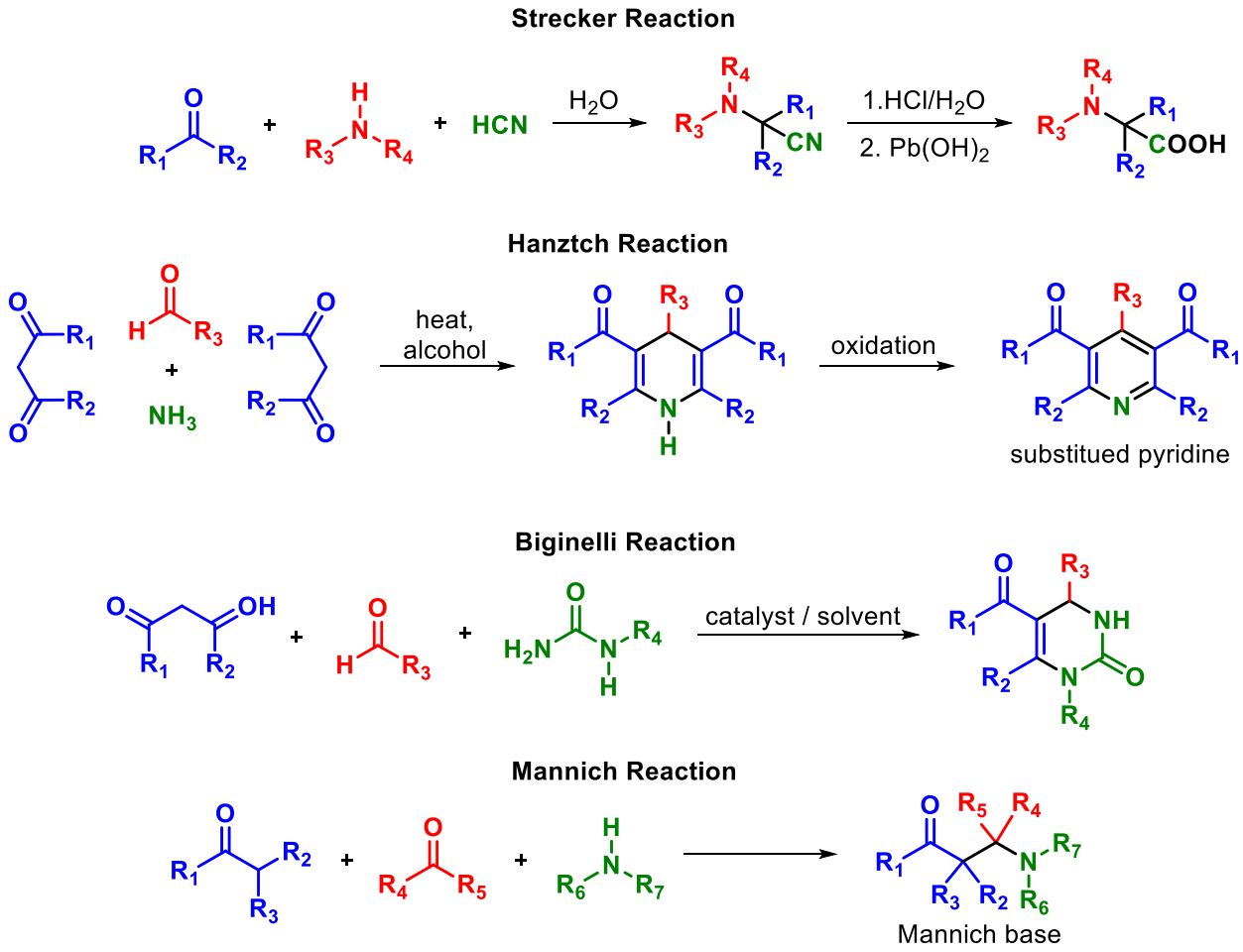


FIGURE 23 - Representative Multicomponent reactions.

UGI REACTION

The Ugi multicomponent reaction is a four component reaction which involves an oxo-compound (aldehyde or ketone), an amine, a carboxylic acid and an isocyanide. It is a powerful tool for rapid generation of a higher complexity structure from simple compounds.

The accepted mechanism starts with the condensation of the amine and carbonyl compound to form the imine with loss of one equivalent of water. Then, a protonation

by the carboxylic acid activates the iminium ion for nucleophilic addition of the isocyanide with its terminal carbon atom to generate the nitrilium ion. [38] A second nucleophilic addition takes place at this intermediate with the carboxylic acid anion to the imidate. The final step is an acyl group transfer the so-called Mumm rearrangement. All reaction steps are reversible except for the Mumm rearrangement, which drives the whole reaction sequence (FIGURE 24).

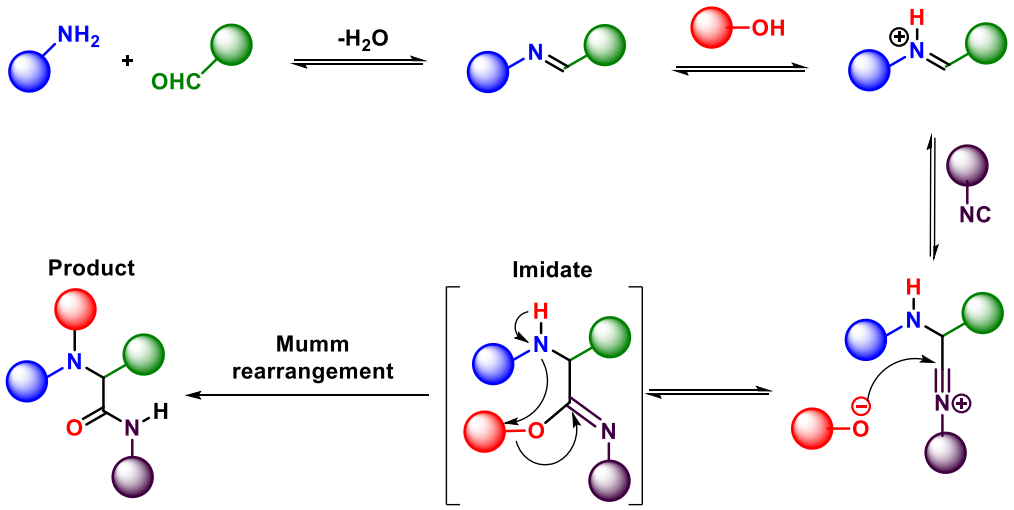


FIGURE 24 - Mechanism of Ugi reaction.

An important work by Orru and co-workers combine a biocatalytic desymmetrization and multicomponent Ugi type 3 component reactions (Ugi 3CR) to obtain a set of organocatalyst. These catalysts were obtained in good yields 75 to 83 %, excellent d.r and ee (>99:1 and >99 % respectively) in 24 to 48 h. All catalysts were evaluated in *Michael reactions of propanaldehyde to β-trans-nitrostyrene and good results could be obtained (*FIGURE 25*).*

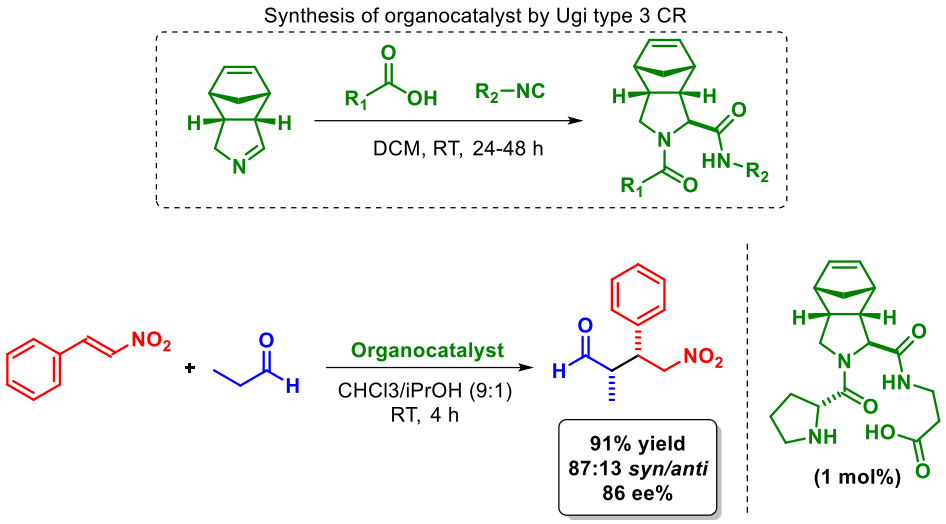


FIGURE 25 - Catalyst prepared from tandem biocatalytic desymmetrization and multicomponent Ugi.

In a previous work, our group reported a solution-phase combinatorial approach based on the Ugi four-component reaction for the development of new prolyl peptide-peptoid hybrid catalysts.[39] Three different components were varied during the creation of the small library of catalysts, i.e., R^2 = *N*-amine component, the oxo component R^1 and the isocyano component R^3. The multicomponent nature of this process enabled the straightforward generation of a series of *pseudo*-peptoid hybrids having the generic sequences. The *N*-amine and isocyanide components were varied either alkyl or amino acid substituents to improve the catalytic properties of the compounds synthesized. These pyrrolidine *pseudo*-peptoid catalysts were evaluated in the asymmetric conjugate addition of aldehydes to β-nitroolefins. Michael adducts were obtained in good to excellent enantio- and diastereoselectivity (98% *ee*, *dr.* 96:4) having toluene as best solvent (FIGURE 26).

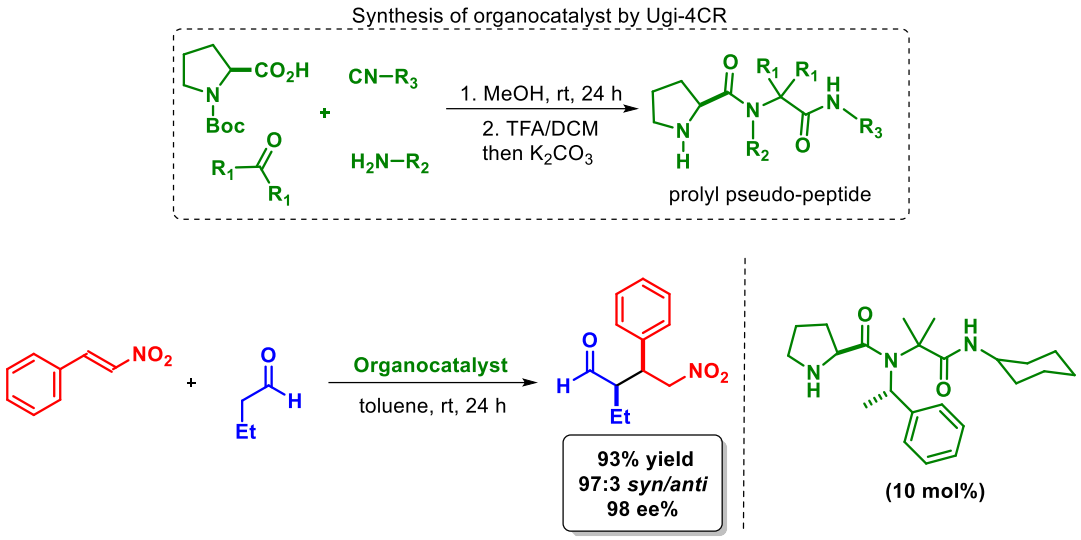


FIGURE 26 - Easy access to a small library of catalysts.

In general, the synthesis and the immobilization of a determined organocatalysts are described in a linear way, until we know (*vide infra*). No record in the literature was found similar to employ Isocyanide Multicomponent Reactions (IMCRs) in the synthesis of a catalyst and linked it in a matrix.

Appendix

Multicomponent Approach to Silica-Grafted Peptide Catalysts:

A 3 D Continuous-Flow Organocatalytic System with On-line Monitoring of Conversion and Stereoselectivity.

Scatena, G. S., de la Torre, A. F., Cass, Q. B., Rivera, D. G., Paixão, M. W.

ChemCatChem, **2014**, 6: 3208

Multicomponent Approach to Silica-Grafted Peptide Catalysts:

A 3D Continuous-Flow Organocatalytic System with On-line Monitoring of Conversion and Stereo- selectivity

Gabriel S. Scatena,[a] Alexander F. de la Torre,[a] Quezia B. Cass,* [a] Daniel G. Rivera,[a,b] and Márcio W. Paixão*[a]

[a]B. Sc. G. S. Scatena, M. Sc. A. F. de la Torre, Prof. Dr. Q. B. Cass, Prof. Dr. M. W. Paixão

Department of Chemistry, Federal University of São Carlos (UFSCar), São Carlos, SP, Brazil. CEP:13565-905. Tel: +55 16 3351 8075 Emails: quezia@dq.ufscar.br, mwpaixao@ufscar.br

[b]Prof. Dr. D. G. Rivera

Center for Natural Products Research, Faculty of Chemistry, University of Havana, Zapata y G, 10400, La Habana, Cuba.

Dedication

In memory of Prof. Carlos Barbas III, for his contribution to the field of Organocatalysis

Abstract

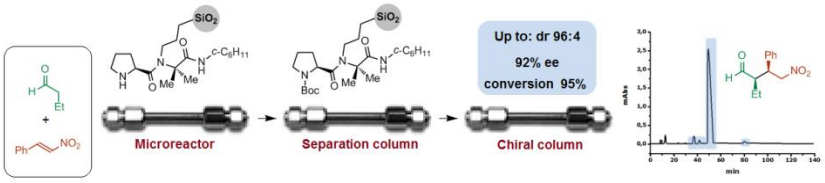
The derivatization of organocatalysts with functional appendages suitable for anchoring onto solid supports is usually achieved by stepwise syntheses. As an alternative to such a strategy, this work describes a one-pot approach to silylated prolyl-peptide catalysts by a multicomponent reaction enabling the simultaneous incorporation of the catalytic and the heterogenizable (triethoxysilane) moieties. Grafting onto HPLC grade silica (10 μm) and packing into a column with a selected catalyst provided a microreactor proving high catalytic efficacy and reproducibly in the conjugate addition of aldehydes to nitroolefins. A three-dimensional continuous-flow system including the on-line monitoring of the reaction outcome was set up. For that, the microreactor was coupled to a chromatographic column for the separation of remaining substrates from the Michael adduct at the second dimension, followed by a chiral polysaccharide column for analysis of conversion and stereoselectivity. This approach represents a new instrumental setup that combines the advantages of multidimensional chromatography and flow catalysis.

Keywords

organocatalysis, multicomponent reactions, flow chemistry, heterogeneous catalysis, microreactor

Table of Contents

Graphical Abstract



Short Text

FULLY Automated: A three-dimensional continuous-flow organocatalytic system was designed by integration of microreactor and multidimensional chromatography technologies. This enamine catalysis platform enables the production of chiral γ-nitroaldehydes with on-line monitoring of the reaction parameters

Introduction

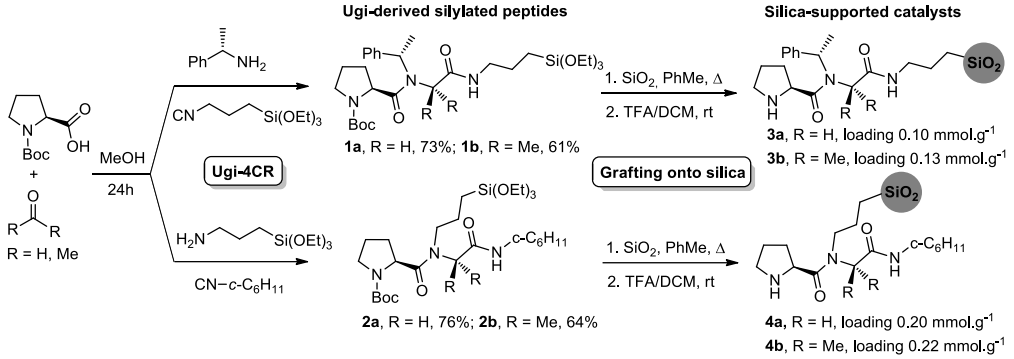
The immobilization of organocatalysts onto solid supports, such as organic polymers and inorganic materials (e.g., silica gel), has emerged as a powerful and sustainable strategy that integrates the advantages of heterogeneous and organocatalysis.[40] Heterogenization of organocatalysts allows not only for catalyst recovery and reuse,[41] but also the implementation of continuous-flow catalytic systems permitting the uninterrupted production of chiral building blocks and fine chemicals.[40,42] Excellent reports have recently proven the potential of continuous-flow catalytic systems based on supported pyrrolidine[43] and imidazolidinone[44] chiral catalysts (e.g., proline and its derivatives, Wennermers and MacMillan catalysts). Traditionally, approaches to prepare organocatalysts properly functionalized for heterogenization (i.e., anchoring to a resin, grafting onto inorganic materials or polymerization) require multistep syntheses wherein the assembly of the catalytic motif is done separately from the installation of the heterogenizable appendage.[43,44] In our endeavor to facilitate access to immobilized organocatalysts, we propose the utilization of multicomponent reactions (MCRs) for the simultaneous incorporation of both the catalytic and the heterogenizable moieties in a one-pot process. Recently, we have described a combinatorial approach based on the Ugi four-component reaction (Ugi-4CR) for the development of new prolyl-peptides proving success in enamine catalysis.[45] Our interest on applying MCRs to catalyst discovery derives from their tremendous diversity-generation capacity,[46] which enables direct and tunable variation of functionalities around a known organocatalytic motif.[47] Herein we report on the utilization of a multicomponent approach for the one-pot synthesis of silylated prolyl-peptide catalysts and their further grafting onto silica, thus enabling the construction of an organocatalytic microreactor for continuous-flow enamine catalysis. A key feature of this strategy is the utilization of the Ugi-4CR to introduce in one step all structural fragments leading to the heterogenizable organocatalyst, i.e., the chiral pyrrolidine and triethoxysilane moieties, thus providing a significant advance over all previously known multi-steps approaches comprising the separate assembly and derivatization of the organocatalytic core. Another innovation of this work is the combination, for the first time, of flow organocatalysis with multidimensional chromatography. The separation capacity of connecting orthogonal chromatographic columns has previously proven success on the analysis of complex mixtures.[48] Herein we take advantage of this capability for the design of a three-dimensional

catalytic/chromatographic system enabling the online monitoring of the asymmetric transformation. The system comprises: *i*) the microreactor packed with a silica-supported organocatalyst, *ii*) a first chromatographic column enabling the separation of the reaction product from the substrates and solvent, and *iii*) a second chiral stationary-phase chromatographic column for analysis of conversion and stereoselectivity.

Results and Discussion

Because of the feasible covalent derivatization of silica gel as well as its intrinsic properties (i.e., high surface area, thermal and mechanical stability etc.), this material has been widely used as solid support in heterogeneous catalysis either in batch[49] or in continuous-flow reactors.[43c,44b] As shown in scheme 1, two distinctive types of triethoxysilylated prolyl-peptide catalysts were prepared by means of the Ugi-4CR, followed by grafting onto Luna silica gel (pore diameter, 100 Å; mean particle size, 10 µm; surface area, 400 $m^2.g^{-1}$). The classic Ugi-4CR is the one-pot condensation of a primary amine, an oxo compound (i.e., ketone or aldehyde), a carboxylic acid, and an isocyanide to produce an *N*-substituted dipeptide backbone.[50] Taking advantage of the multicomponent nature of the process, a variation of three components (i.e., the amine, the oxo and the isocyanide) was made based on the knowledge gained in the previous catalytic screening of Ugi-derived propyl-peptides catalysts having an internal *N*-substitution.[45] Such a combinatorial approach provided important information regarding which are the key structural elements for this new family of hybrid peptide-peptoid catalysts to be effective in asymmetric conjugate addition reactions relying on enamine catalysis. Those results aided in the selection of the most suitable Ugi-components for the preparation of the silylated prolyl-peptide catalyst descried in this work. For example, it was demonstrated that the utilization of acetone as oxo-component leads to catalysts providing greater stereoselection than those derived from paraformaldehyde.[45] As proven by a molecular modeling study, the reason for this is the greater conformational rigidity and better shielding of one of the faces in enamines derived from catalysts having the sequence Pro-*N*-alkyl-Aib (Aib is α-aminoisobutyric acid) compared to those having the sequence Pro-*N*-alkyl-Gly.[45] Nevertheless, we decided to prepare catalysts derived from acetone and paraformaldehyde to enable addressing their catalytic efficacy also in heterogeneous enamine catalysis. Thus, the other two tunable components (i.e., amine and

isocyanide) were selected to allow for the incorporation of the heterogenizable triethoxysilane moiety, since proline is a fixed component required for enamine formation. As illustrated in scheme 1, such a rational selection of the components led to the one-pot synthesis of silylated organocatalysts **1a**-**b** and **2a**-**b**, derived from *N*-Boc-proline and either paraformaldehyde or acetone, in combination with (*S*)-α-methylbenzylamine and 3-isocyanoprolpyltriethoxysilane as well as 3-aminoprolpyltriethoxysilane and cyclohexylisocyanide, respectively.



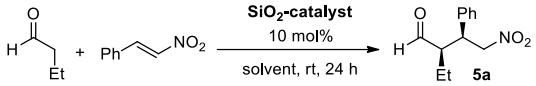
Scheme 1. Multicomponent one-pot synthesis of triethoxysilylated prolyl-peptide catalysts and subsequent grafting onto silica for applications in heterogeneous catalysis.

Grafting onto silica Luna was accomplished by conventional means based on mixing upon heating the silylated organocatalyst with commercially available silica, followed by *N*-terminal deprotection of the peptide moiety to render the silica-supported prolyl-peptides **3** and **4**. Catalysts loading onto the silica was determined to range from 0.1 mmol.g^{-1} for **3a** to 0.22 mmol.g^{1} for **4b**, showing that anchoring of catalysts **2a-b** derived from the 3-aminoprolpyltriethoxysilane was more effective than that of 3-isocyanopropyltriethoxysilane-derived catalysts **1a-b**. To seek preliminary information of the catalytic efficiency and stereoselectivity, the four silica-supported catalysts (**3a-b** and **4a-b**) were screened in batch for the asymmetric Michael addition relying on heterogeneous enamine catalysis. For this, the model organocatalytic system comprising the conjugate addition of *n*-butanal to *trans*-*β*-nitrostyrene was studied using 10 mol% of the solid-supported catalysts and toluene as solvent. As depicted in table 1, the best results (entry 4) in terms of conversion and stereocontrol were obtained for catalyst **SiO$_2$-4b** (96:4 dr, 90% ee,). It must be noticed that Ugi-based peptide catalysts derived from acetone (i.e., **3b** and **4b**) showed higher catalytic

efficiency than those derived from paraformaldehyde, which agrees with our previous studies of this type of catalysts in homogeneous catalysis.[45]

It is intriguing the fact that catalyst **4b** having a *C*-terminal cyclohexyl carboxamide and propylsilica as *N*-substituent provided greater enantioselectivity than **3b,** which on the other hand has the propylsilica linked at the *C*-terminus and (*S*)-α-methylbenzyl as *N*-substituent. This may be mostly due to a conformational difference between the *anti* enamines derived from **3b** and **4b**, by which the latter one allows for a better shielding to one of the faces (i.e., the *Re*-face according to the resulting 2*R*,3*S* configuration, see the Experimental Part) during the attack to the nitroolefin. The effectiveness of catalyst **4b** was further assessed in a variety of solvents, providing good enantio- and excellent diastereoselectivity in quite different reaction media, including both apolar and polar protic solvents (Table 1, entries 5-11). This behavior is quite different from that of homogeneous organocatalytic Michael reactions described with similar prolyl-peptide catalysts, in which the catalyst efficacy and enantioselection is highly dependent on the solvent of choice.[45,51]

Table 1. Screening of silica-supported prolyl-peptide catalysts and reaction conditions in batch heterogeneous Michael addition.



Entry[a]	Catalyst	Solvent	Conversion (%)[b]	dr (*syn*/*anti*)[b]	ee (%)[b]
1	SiO_2-**3a**	PhMe	55	94:6	18
2	SiO_2-**3b**	PhMe	80	91:9	14
3	SiO_2-**4a**	PhMe	68	95:5	72
4	SiO_2-**4b**	PhMe	91	96:4	90
5	SiO_2-**4b**	THF	93	94:6	88
6	SiO_2-**4b**	$CHCl_3$	92	97:3	87
7	SiO_2-**4b**	Et_2O	91	97:3	90
8	SiO_2-**4b**	*i*-PrOH	96	91:9	88
9	SiO_2-**4b**	EtOH	92	93:7	89
10	SiO_2-**4b**	CH_3CN	94	92:8	90
11[c]	SiO_2-**4b**	Hexane/*i*-PrOH	95	96:4	86

[a]Reactions conducted using 3 equiv of aldehyde. [b]Determined by chiral stationary-phase HPLC analysis. [c]Solvent mixture 9:1 (*v*/*v*).

Having established which silica-supported catalyst provides the best results under batch heterogeneous conditions, we focused on implementing the three-dimensional flow system integrating the microreactor and the multidimensional chromatography platform. Thus, the immobilized catalyst SiO_2-**4b** was employed for preparing the packed-bed microreactor using an HPLC column (2.1 mm internal diameter × 50 mm length). In general, previously reported on-flow catalytic systems lack the integration of an analytical platform for monitoring the reaction progress.[43,44] Recently, a catalytic microreactor was used coupled to a chromatographic system in a two-dimensional setup for on-line analysis of the reaction kinetics by nonlinear chromatography.[52] The three-dimensional continuous-flow system[53] herein described is a further advance in the field of flow asymmetric catalysis, as it allows for the real-time investigation of important reaction parameters such as conversion and stereoselectivity.

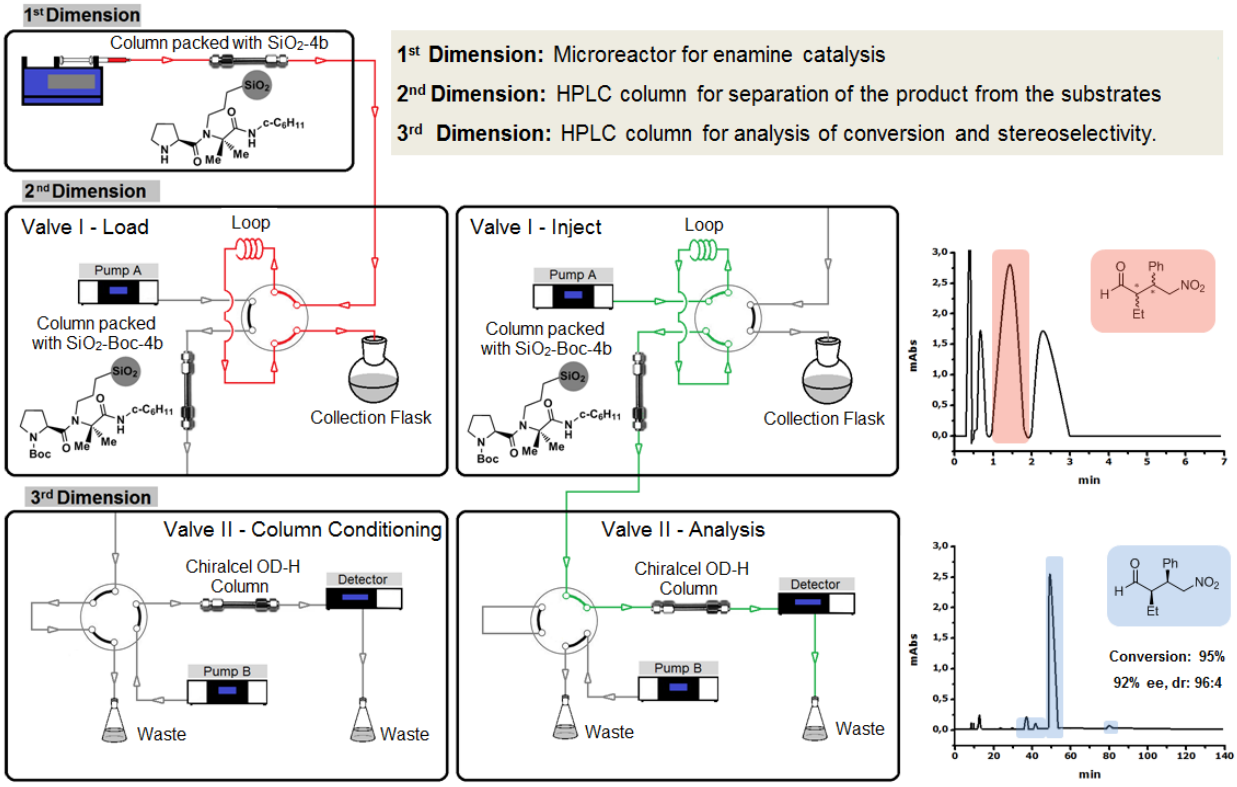


Figure 1. Three-dimensional continuous-flow catalytic system for the production and on-line analysis of chiral γ-nitroaldehydes.

Figure 1 illustrates the three-dimensional catalytic flow system designed for the simultaneous production and analysis of chiral γ-nitroaldehydes. The system comprises the utilization of a sample loop interface that storages the microreactor outflow and couples it to a chromatographic column for the purification of the reaction product. The band of the pure product is then heart-cut transferred by a switching valve system to a polysaccharide chiral column for analysis of the stereoselectivity and conversion. A typical procedure includes the continuous injection of a solution of β-nitrostyrene (0.25 M, 1 equiv) and butanal (0.75 M, 3 equiv) in *n*-hexane/*i*-PrOH (9:1, *v*/*v*) to the organocatalytic microreactor (filled with catalyst SiO_2-**4b**) by means of a syringe pump. To seek the most favorable conditions, various flow rates were tested to reach a compromise between retention time and reaction yield. Finally, a flow rate of 1 μL/min was set, upon which the steady-state regime was reached at 18 h. These conditions were kept for the first during 48 h to continuously produce the Michael adduct in 95% yield, 96:4 dr and 92% ee. The outflow of the microreactor was accumulated at the sample loop (*ca.* 2 μL) and then by means of pump A injected at the Boc-protected peptide SiO_2-**4b** homemade column. It must be mentioned that the selection of the same peptide in a protected form (SiO_2-Boc-**4b**) as stationary phase for the second dimension was not arbitrary. Instead, it was the one that furnished adequate retention for the Michael adduct showing selectivity with respect to β-nitrostyrene. As depicted in figure 1, the direct analysis is accomplished at the third dimension by a heart-cut transfer[54] of the γ-nitroaldehyde chromatographic band (*ca.* 2 μL) to the chiral column by means of a switching valve. Such a first-hand analysis of the reaction progress allows stopping the continuous-flow when the reaction parameters reach undesired values, e.g. drop in the conversion and stereoselection. This feature represents an important operational

advanced in terms of cost and time, as it enables circumventing the conventional collection, purification and analysis of the chiral product in separate operations.

Table 2 depicts the main characteristics of the packed-bed microreactor, as determined by pycnometry and elemental analysis (see the Supporting Information). To assess the robustness of the microreactor and the reproducibility of the catalytic process, seven consecutive rounds were initially carried out with the same substrates and reaction flow, albeit varying the operation time. After each round, the microreactor was flushed thoroughly with EtOH and then rinsed again with *n*-hexane/*i*-PrOH, a solvent mixture not affecting the integrity of the chiral-stationary phase. As shown in table 3, during those independent rounds, the microreactor was able to produce γ-nitroaldehyde **5a** in high yield and excellent stereoselectivity, corresponding to a turnover number (TON) of 218 for this product.

Table 2. Main characteristics of the catalytic microreactor.

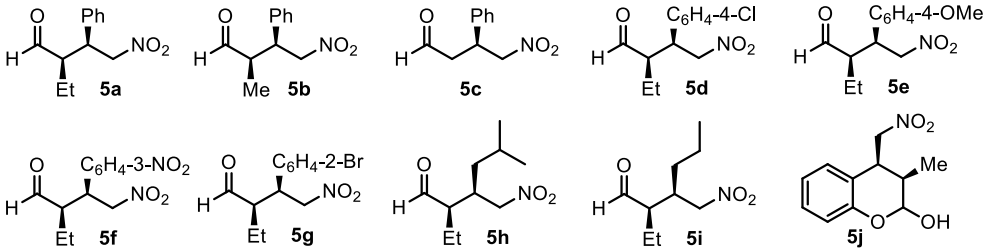
Loading of **4b** (mmol.g^{-1})[a]	Amount (mg)	V_0 (μL)	V_G (μL)[b]	V_{bed} (μL)[c]	T (min)[d]	Total Porosity[e]
0.217	143	140	173	33	140	0.81

[a]Determined by elemental analysis. [b]Geometric volume. [c]V_{bed}= V_G-V_0. [d]Residence time calculated at 1 μL.min^{-1}. [e]Total porosity $\varepsilon_{tot}=V_0/V_G$

Interestingly, the enantioselectivity was slightly higher using the flow microreactor than under batch conditions, while the diastereoselectivity remained invariable. The yield of isolated pure products – collected at the second dimension – was eventually compared with the conversion calculated at the third dimension using the calibration curve method, resulting in very similar results. The reproducibility of the microreactor was subsequently evaluated in the continuous-flow production of enantiomerically enriched γ-nitroaldehydes (**5b-j**). Importantly, the microreactor proved capability to catalyze reaction between dissimilar aldehydes and both aliphatic and aromatic

nitroolefins, featuring a variety of substitution patterns at the phenyl rings (i.e., electron-donating and withdrawing groups).

Table 3. Scope of the catalytic conjugate of aldehydes to β-nitroolefins in a continuous-flow system with online monitoring of the reaction outcome.



Round[a,b]	Operation time (h)	Product	Amount of **5** (mmol)	dr[c] (*syn*/*anti*)	ee[c] (%)	TON	Yield[d] (%)
1	48	**5a**	0.68	96:4	92	22	95
2	96	**5a**	1.36	96:4	92	44	95[e]
3	96	**5a**	1.36	96:4	92	44	95
4	48	**5a**	0.68	96:4	92	22	95
5	96	**5a**	1.34	96:4	92	43	93
6	48	**5a**	0.67	96:4	92	21	93[e]
7	48	**5a**	0.66	96:4	92	21	92
8	24	**5b**	0.32	95:5	88	10	90
9	24	**5c**	0.24	-	82	8	67
10	24	**5d**	0.33	88:12	91	11	93
11	24	**5e**	0.28	94:6	86	9	78
12	24	**5f**	0.31	96:4	86	10	86
13	24	**5g**	0.33	95:5	86	11	91
14	24	**5h**	0.30	94:6	84	10	84
15	24	**5i**	0.31	94:6	85	10	87
16[f]	24	**5j**	0.26	97:3	91	8	72

[a]Solutions of the β-nitroolefin (0.25 M) and the aldehyde (0.75 M) dissolved in *n*-hexane/*i*-PrOH (9:1) were pumped into the microreactor packed with SiO_2-**4b**. [b]The microreactor column was flushed with EtOH and rinsed with *n*-hexane/*i*-PrOH before each new round. [c]Determined by chiral stationary-phase HPLC analysis. [d]Yield of isolated pure product at second dimension. [e]Conversion determined by calibration curve. [f]Enantio and diastereoselectivity determined for the reduced product as reported in reference [55] (see ESI).

To extend the substrate scope of the continuous-flow catalytic microreactor, we explored the possibility of carrying out a tandem process comprising the conjugate addition of an aldehyde to *trans*-2-hydroxy-β-nitrostyrene followed by acetalyzation to produce adduct **5j** in reasonable yield. This compound was collected at the second dimension and further reduced to facilitate the assessment of the stereoselectivity, exactly as described in the original report.[55]

Michael adducts were obtained in good enantio and diastereoselectivity, albeit in some cases with lower yields than the model γ-nitroaldehyde **5a**. To determine whether the drop in the catalytic efficiency was due either to the microreactor itself or to the structural differences in the aldehydes and the nitroolefins, the original combination of butanal and β-nitrostyrene was submitted to an additional run. Notably, adduct **5a** was produced once again in excellent yield (94%) and stereoselectivity (94:6 dr and 91% ee), proving the robustness of the microreactor. At the end of this study, the microreactor had been working for eleven rounds, corresponding to a total TON of 304 and still showing good efficiency and stereoselectivity. For all γ-nitroaldehydes, the absolute configuration of the major diastereomer were established to be 2*R*,3*S,* based on chemical correlation with previous reports.[51a,56]

Conclusions

We have introduced a multicomponent strategy for the one-pot assembly of organocatalysts suitably functionalized for immobilization onto solid supports. Four silylated prolyl-peptide catalysts were produced by means of the Ugi-4CR through variation of the oxo, the amine and the isocyanide components. They were all grafted onto HPLC silica and after batch screening for the heterogeneous catalytic Michael addition, SiO_2-**4b** was selected as the most effective catalyst. The SiO_2-**4b** flow microreactor showed high catalytic efficiency, excellent stereoselectivity and reproducibility in the organocatalytic conjugates addition for a series of aldehydes to nitroolefins. Neither deactivation of the catalytic microreactor nor significant drop in the stereoselectivity was observed even after 16 rounds. A novel instrumental setup that combines the power of multidimensional chromatography and microreactor technologies was designed with success. This consists of a three-dimensional continuous-flow system that couples the microreactor to a column for separation of the γ-nitroaldehyde from the remaining starting materials, followed by a chiral column for analysis of the conversion ratio and stereoselectivity. We believe that both the exploitation of the MCR chemical efficiency in the assembly of heterogenizable organocatalysts and the design of the multidimensional platform represent important innovations that may encourage further progress in the field of flow catalysis.

Experimental Section

General. All reagents and solvents were purchased and used as received. Enantiomeric excess and diastereoisomeric ratio were determined by HPLC. Flash column chromatography was carried out using silica gel 60 (F_{254} 230-400 mesh) and analytical thin layer chromatography (TLC) was performed using silica gel aluminum sheets (0.2 mm F_{254}), which were developed using visualizing agents: UV fluorescence (254 nm), iodine, potassium permanganate/Δ. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent signals chemical shifts are given relative to tetramethylsilane (TMS), and coupling constants (*J*) are reported in hertz. High resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) (Hybrid linear ion trap–orbitrap FT-MS and QqTOF/MS – Microtof – QII models). HPLC chromatograms were obtained on an apparatus with two LC-10AT Pumps, FCV-10ALvp Low Pressure Gradient Valve, DGU-14A degasser unit, CTO-10A oven, SIL-10ADvp, SPD-10A UV-Vis Detector, SCL-10Avp System Controller, using a Chiralpak OD-H (4,6 mmØ × 250 mmL, particle size 5 µm), Chiralpak AD-H (4.6 mmØ × 250 mmL, particle size 5 µm), Chiralpak IC (2.1 mmØ × 150 mmL, particle size 3 µm), Chiralpak AS-H (4.6 mmØ × 250 mmL, particle size 5 µm) and SiO_2-4a-Boc (2,1 mmØ × 150 mmL, particle size 10 µm) under reported conditions. Two valves of six port *VICI* Valco**.** Optical rotations were measured with a Schmidt + Haensch Polartronic H Polarimeter at 589 nm, 25 °C. Silica used was purchased from Phenomenex, Luna NH_2 (particle size: 10 µm, pore size: 100 Å, surface area 400 $m^2.g^{-1}$, calculated bonded phase coverage 5.80 $\mu mol.m^{-2}$, loading of NH_2 2.32 $mmol.g^{-1}$). A high-pressure slurry packer fitted with a Haskel 780-3 pump was used for the analytical column packing. Microanalyses were performed with a *CHNS* analyzer Model *EA 1108* from *Fisons* Instruments. A *FEI Inspect F50* field emission scanning electron microscopy (FESEM) was used to image the morphology of silica before and after grafting of the organocatalysts (see Supporting Information).

General Ugi-4CR-based procedure: A suspension of the amine (1.0 mmol) and the aldehyde (or ketone) (1.0 mmol) in MeOH (5 mL) was stirred for 1 h at room temperature. The carboxylic acid (1.0 mmol) and the isocyanide (1.0 mmol) were then added and the reaction mixture was stirred at room temperature for 24 h. The

volatiles were concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography.

Silylated proly-peptide 1a: (*S*)-α-Methylbenzylamine (514 µL, 4 mmol, 1.0 equiv.), paraformaldehyde (120 mg, 4 mmol, 1.0 equiv.), Boc-L-Pro-OH (862 mg, 4 mmol, 1.0 equiv.) and 3-isocyanopropyltriethoxysilane[57] (928, 4 mmol, 1.0 equiv.) were reacted in MeOH (10 ml) according to the general procedure for Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded prolyl-peptide **1a** (1.63 g, 73%) as a colorless oil. R_f = 0.30 (*n*-hexane/EtOAc 1:1). $[\alpha]_D^{25}$ -0.044 (*c* 0.48, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (m, 1H, N*H*); 7.20-7.50 (m, 5H); 5.40, 6.11 (2×q, 1H); 4.34, 4.88 (2×m, 1H); 3.80 (q, *J*=7.0 Hz, 6H); 3.51-3.66 (m, 2H); 3.45 (m, 2H); 3.03-3.29 (m, 1H); 2.11 (m, 2H); 1.88 (m, 3H); 1.64 (m, 2H); 1.51 (d, 3H, *J*=7.2 Hz); 1.47 (s, 9H, Boc); 1.22 (t, *J*=7.0 Hz, 9H); 0.49, 0.63 (2×m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 168.9, 154.9, 140.5, 128.6, 127.8, 127.6, 127.1, 80.1, 60.4, 58.3, 57.3, 55.2, 51.3, 47.3, 47.2, 42.6; 29.3, 28.5, 24.7, 22.7, 18.3, 8.0. HRMS (ESI-FT-QQTOF) *m/z*: 580.34076 $[M+H]^+$; calcd. for $C_{29}H_{50}N_3O_7Si$: 580.34125.

Silylated proly-peptide 1b: 3-aminopropyltriethoxysilane (936 µL, 4 mmol, 1.0 equiv.), paraformaldehyde (120 mg, 4 mmol, 1.0 equiv.), Boc-L-Pro-OH (862 mg, 4 mmol, 1.0 equiv.) and cyclohexylisonitrile (500 µL, 4 mmol, 1.0 equiv.) were reacted in MeOH (10.0 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded prolyl-peptide **1b** (1.43 g, 61%) as an colorless oil. R_f = 0.35 (*n*-hexane/EtOAc 1:1). $[\alpha]_D^{25} = -0.030$ (c 0.47, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, *J*=8.3 Hz, 1H, N*H*); 4.75, 4.60 (2×d, *J*=16.4 Hz, 1H); 4.54 (m, 1H); 3.67-3.87 (m, 8H); 3.40-3.60 (m, 4H); 3.09-3.21 (m, 1H); 2.07-2.15 (m, 2H); 1.53-1.99 (m, 10H); 1.46 (s, 9H, Boc); 1.06-1.37 (m, 14H); 0.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 168.1, 154.6, 79.7, 60.4, 58.5, 56.5, 55.4, 51.0, 48.5, 47.2, 32.8, 30.3, 28.6, 25.5, 25.2, 24.4, 18.2, 14.2, 7.4. HRMS (ESI-FT-QQTOF) *m/z*: 580.33997 $[M+Na]^+$; calcd. for $C_{27}H_{51}N_3NaO_7Si$: 580.33885.

Silylated proly-peptide 2a: (*S*)-α-Methylbenzylamine (485 µL, 4 mmol, 1.0 equiv.), acetone (294 µL, 4 mmol, 1.0 equiv.), Boc-L-Pro-OH (862 mg, 4 mmol, 1.0 equiv.) and 3-isocyanopropyltriethoxysilane[57] (925 mg, 4 mmol, 1.0 equiv.) were reacted in MeOH (10.0 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded prolyl-peptide **2a** (1.78 g,

76%) as an colorless oil. R_f = 0.25 (*n*-hexane/EtOAc 1:1). $[\alpha]_D^{25} = -0.035$ (c 0.44, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.20 (m, 5H); 6.43 (m, 1H, N*H*); 5.09 (m, 1H); 3.80 (q, *J*=7.0 Hz, 6H); 3.51-3.10 (m, 4H); 2.88 (m, 1H); 1.91 (m, 2H); 1.71-1.51 (m, 12H); 1.42 (s, 9H, Boc); 1.22 (t, *J*=7.0 Hz, 9H); 0.63 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.3, 168.9, 154.5, 142.7, 128.7, 127.2, 79.2, 64.6, 60.4, 58.3, 47.5, 47.2, 42.3; 29.3, 28.5, 26.6, 23.9, 22.7, 18.3, 7.7. HRMS (ESI-FT-QQTOF) *m/z*: 608.37943 $[M+H]^+$; calcd. for $C_{31}H_{54}N_3O_7Si$: 608.37255.

Silylated proly-peptide 2b: 3-aminopropyltriethoxysilane (936 µL, 4 mmol, 1.0 equiv.), acetone (300 µL, 4 mmol, 1.0 equiv.), Boc-L-Pro-OH (862 mg, 4 mmol, 1.0 equiv.) and cyclohexylisonitrile (500 µL, 4 mmol, 1.0 equiv.) were reacted in MeOH (10.0 mL) according to the general procedure for the Ugi-4CR. Flash column chromatography purification (*n*-hexane/EtOAc 1:1) afforded prolyl-peptide **2b** (1.56 g, 64%) as an colorless oil. R_f = 0.25 (*n*-hexane/EtOAc 1:1. $[\alpha]_D^{25} = -0.093$ (c 0.39, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (m, 1H, N*H*); 4.50 (m, 1H); 3.84 (m, 3H); 3.52-3.70 (m, 7H); 3.40 (m, 2H); 3.28 (m, 1H); 2.11 (m, 2H); 1.57-2.10 (m, 10H); 1.46, 1.47 (2×s, 6H); 1.44, 1.45 (2×s, 9H, Boc); 1.20-1.37 (m, 8H); 0.94-1.19 (m, 3H); 0.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =174.1, 173.5, 154.5 (*C*=O); 79.3 (*C*); 62.8 (*C*); 60.4 (*C*H); 58.5, 56.9 (CH_2); 48.6 (*C*H); 47.2, 33.0, 30.3 (CH_2); 18.2 (CH_3); 25.5, 25.2, 24.4, 23.1 (CH_2); 28.6 (CH_3); 14.2 (CH_3). HRMS (ESI-FT-QQTOF) *m/z*: 608.36749 $[M+Na]^+$; calcd. for $C_{29}H_{55}N_3NaO_7Si$: 608.37015.

General procedure for grafting the silylated peptide catalysts onto silica: Silica (2.60 g) was added to a rounded bottom flask containing the Ugi-derived silylated peptide (1.0 mmol, 1.0 equiv) dissolved in toluene (6 ml). Pyridine (0.10 mmol, 0.1 equiv.) was then added and the reaction mixture was gently stirred at reflux for 24 h. The Boc-protected silica-supported catalyst was filtered and washed consecutively with 25 ml of hexane, isopropanol, methanol/water (1:1), isopropanol, *n*-hexane and dicloromethane, and then added into a mixture TFA/DCM (1:1) (10 mL) and stirred for 12 h. The corresponding silica-supported catalyst was filtered and washed consecutively with 25 mL of hexane, isopropanol, methanol/water (1:1), isopropanol, *n*-hexane and dicloromethane.

General procedure for the 1,4-addition of aldehydes to nitroolefins under batch condition: The nitroolefin (0.25 mmol, 1.0 equiv.) and the aldehyde (0.75 mmol, 3.0 equiv.) were added to a solution of the silica-supported catalysts (0.025 mmol, 0.01

equiv.) in an appropriate solvent (1 ml). The reaction mixture was stirred for 24 h and then concentrated under reduced pressure. The conversion of the crude product was determined by HPLC. The enantiomeric excess was determined by chiral-phase HPLC analysis through comparison with the authentic racemic material. Assignment of the stereoisomers configuration was performed by comparison with literature data.[56]

Packing of the Microreactor Column: A slurry of SiO_2-**4b** (300 mg, suspended in 15 ml of isopropanol) was packed into a stainless steel column (2.1 mmØ × 50 mmL, particle size 10 μm). Slurry-packing was carried out under constant pressure (6000 psi) using 150 ml of isopropanol as solvent by means of an air driven liquid pump.

Packing the Chromatographic Column: A slurry of SiO_2-Boc-**4b** (500 mg, excess, suspended in 25 ml of isopropanol) was packed into stainless steel column (2.1 mmØ × 150 mmL, particle size 10 μm). Slurry-packing was performed under constant pressure (6000 psi) using 250 ml of isopropanol as solvent by means of an air driven liquid pump.

General procedure for the organocatalytic addition of aldehydes to nitroolefins under flow condition: A solution of the aldehyde (0.75 M) and the nitroolefin (0.25 M) in *n*-hexane/*i*-PrOH (9:1) was pumped with a flow rate of 1 μL.min^{-1} into the microreactor column packed with catalyst SiO_2-**4b** during a defined period of time (see table 3). Every each 140 min (residence time), a volume of about 2.0 μL of the microreactor outflow was injected into the HPLC SiO_2-Boc-**4b** column. The γ-nitroaldehyde chromatographic band was then transferred to a chiral polysaccharide column for analysis of the stereoselectivity by comparison with authentic racemic material and literature data[56] (see Supporting Information).

Supporting Information. ^{1}H and ^{13}C NMR spectra of silylated prolyl-peptide catalysts. Spectroscopic data, NMR spectra and chiral-phase HPLC analysis of Michael adducts. Elemental and microscopy analysis of silica-supported catalysts. Evaluation data of the microreactor and chromatography columns.

Acknowledgments. D. G. Rivera is grateful to FAPESP for a Visiting Professor grant (2013/21599-8). We also gratefully acknowledge financial support from CNPq (INCT-Catálise), CAPES (MES/Cuba Program) and FAPESP.

Supporting Information

Multicomponent Approach to Silica-Grafted Peptide Catalysts:

A 3D Continuous-Flow Organocatalytic System with On-line Monitoring of Conversion and Stereo- selectivity

Gabriel S. Scatena,[a] Alexander F. de la Torre,[a] Quezia B. Cass,* [a] Daniel G. Rivera,[a,b] and Márcio W. Paixão*[a]

[a]Department of Chemistry, Federal University of São Carlos (UFSCar), São Carlos, SP, Brazil. CEP:13565-905. Tel: +55 16 3351 8215

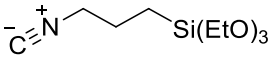
[b]Center for Natural Products Research, Faculty of Chemistry, University of Havana, Zapata y G, 10400, La Habana, Cuba.

Corresponding Authors* quezia@dq.ufscar.br (Q. B. Cass); mwpaixao@ufscar.br (M. W. Paixão).

General procedure for the reduction of lactol.

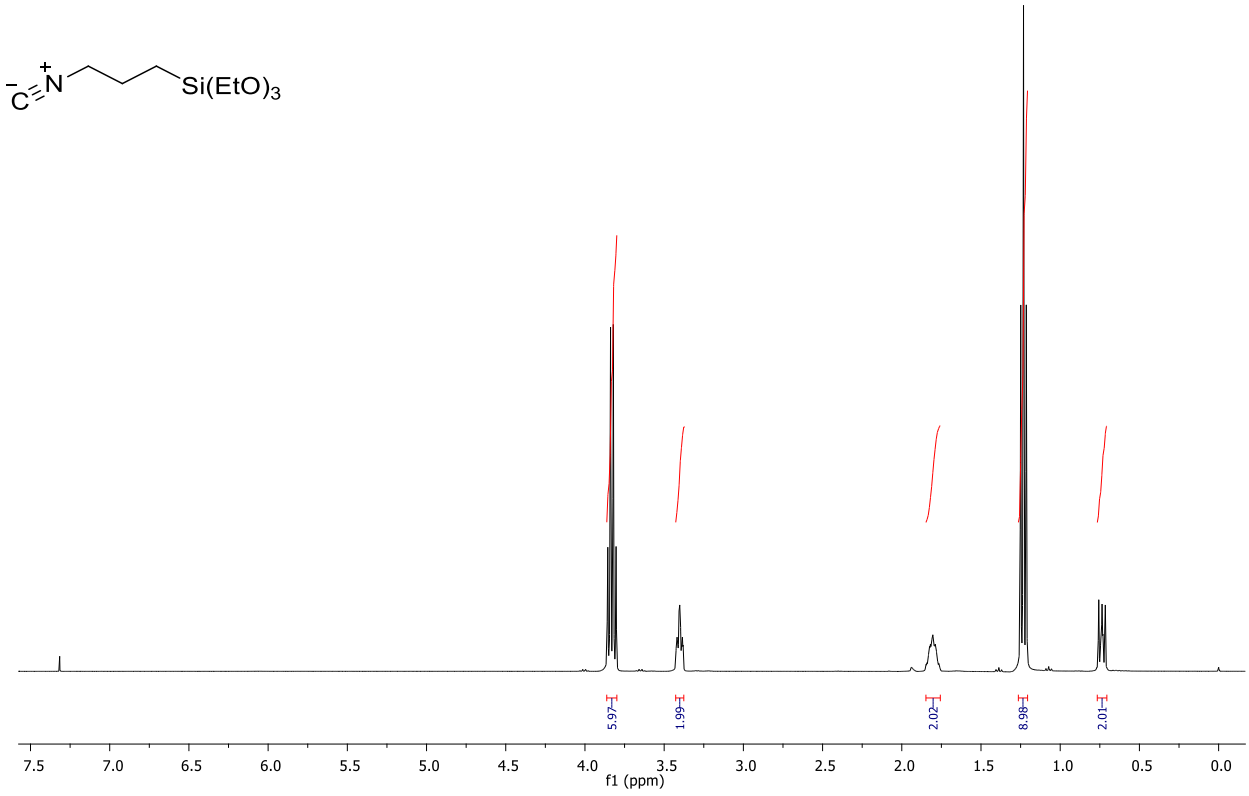
In an oven dried round bottom flask, to the lactol (0.3 mmol), dry MeOH (3.0 mL), and $NaBH_4$ (0.45 mmol, 1.5 equiv.) was added. After stirring the reaction mixture at 0 °C for 0.5 h, it was brought to 25 °C and the crude reaction mixture was worked up with aqueous NH_4Cl saturated solution. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure chiral product was obtained by column chromatography .

Synthesis of 3-isocyanopropyltriethoxysilane. [57]

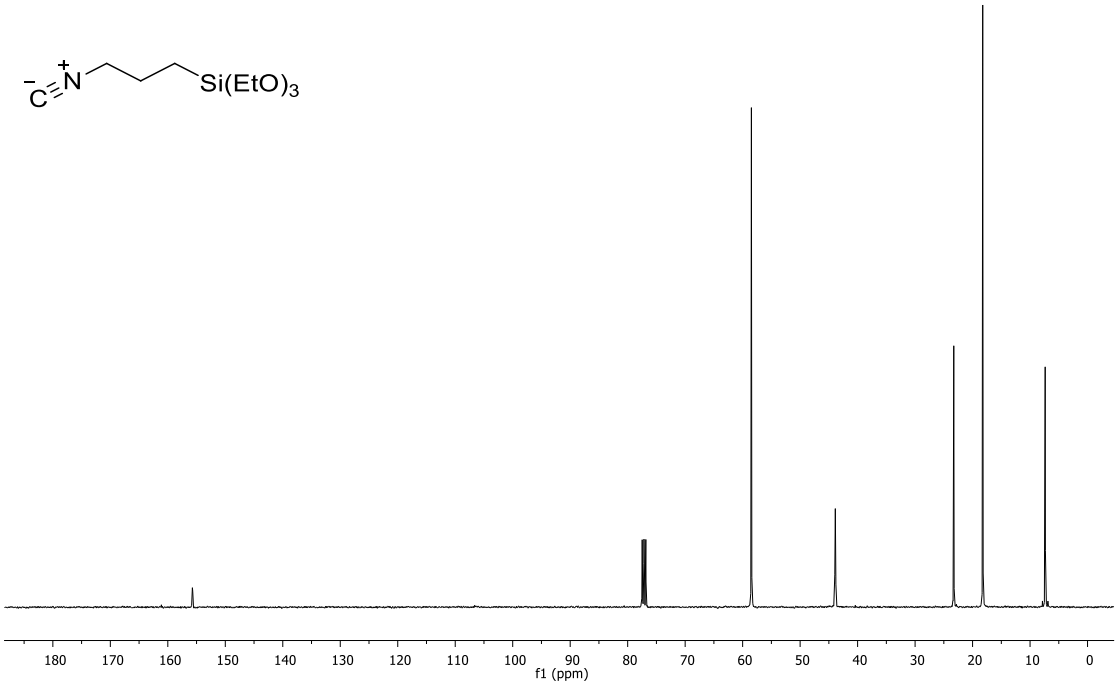


In a 15 mL flask were placed a mixture of 3-aminopropyl triethoxysilane (APTS, 7 ml, 30 mmol, 1.0 equiv.) and ethyl formate (3.6 ml, 45 mmol, 1.5 equiv.). The reaction mixture was stirred at 60 ºC for 24 h. All volatiles were then removed using rotary vacuum evaporation and the crude mixture was re-dissolved in 1,2-dicloroethane (25 ml). PPh_3 (9.83 g, 37.5 mmol, 1.25 equiv.), CCl_4 (2.92 ml, 30 mmol, 1.0 equiv) and TEA (4.0 ml, 30 mmol, 1.0 equiv.) were added and the mixture was stirred at 70 ºC for 24 h. All volatiles were removed in a rotary vacuum evaporation system and the crude mixture, a stick pale yellow solid, was filtered and then washed with hexane (5 × 50 ml). Solvent evaporation, followed by vacuum distillation gave a colorless liquid (4.18 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (q, *J* = 7 Hz, 6H); 3.40 (m, 2H); 1.80 (m, 2H); 1.23 (t, *J* = 7 Hz, 9H); 0.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 58.5, 43.9, 23.3, 18.2, 7.4.

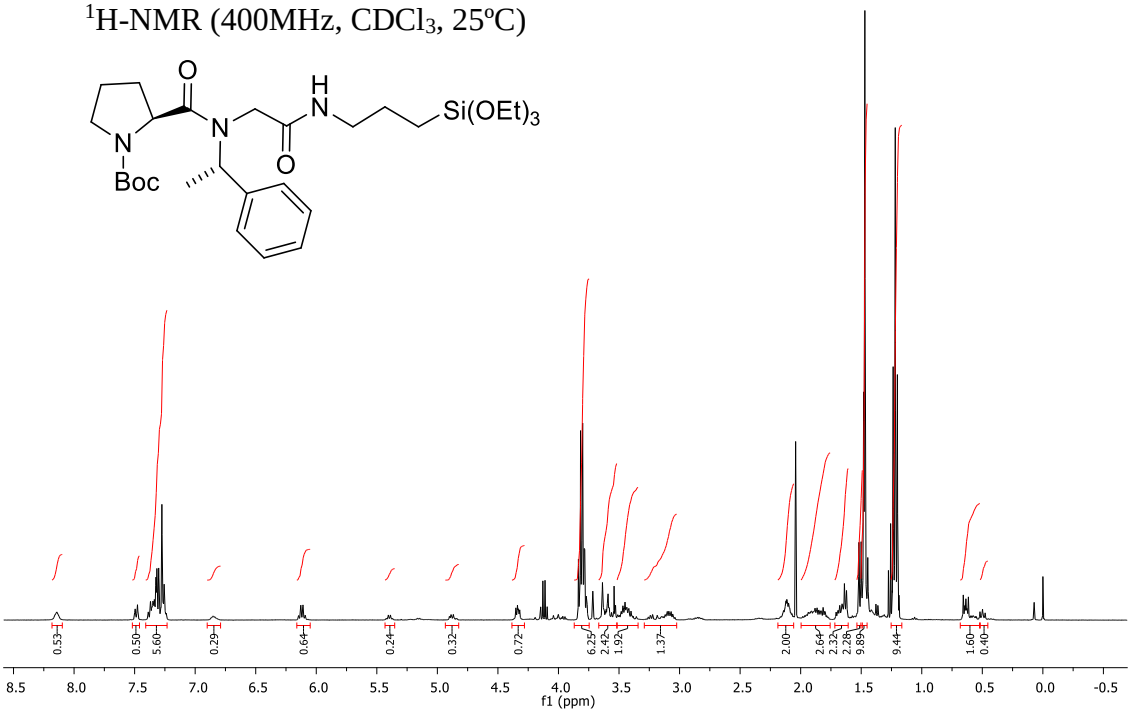
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



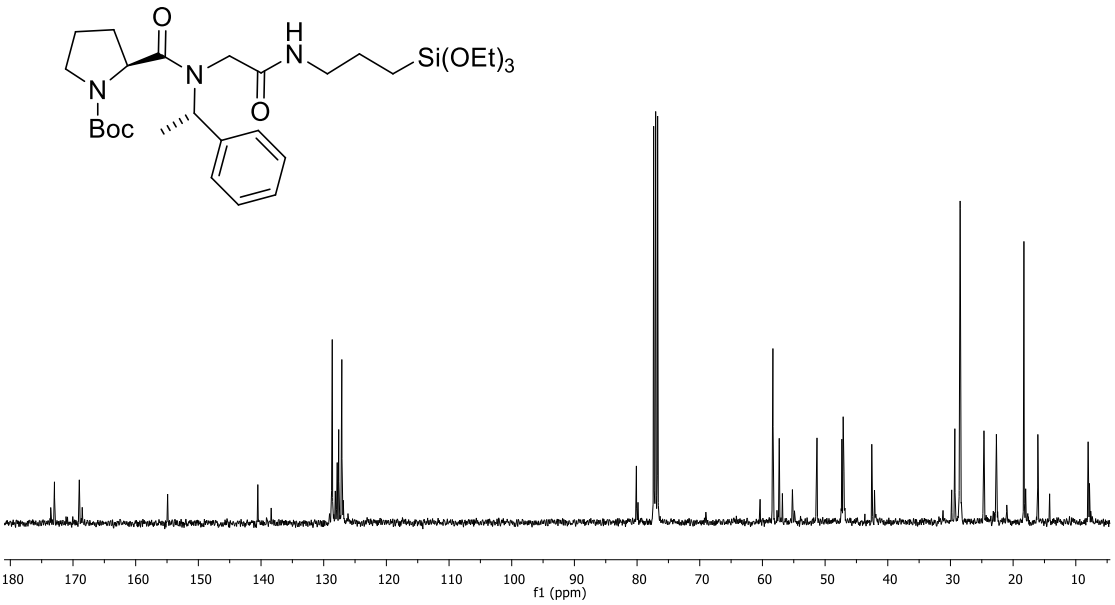
^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



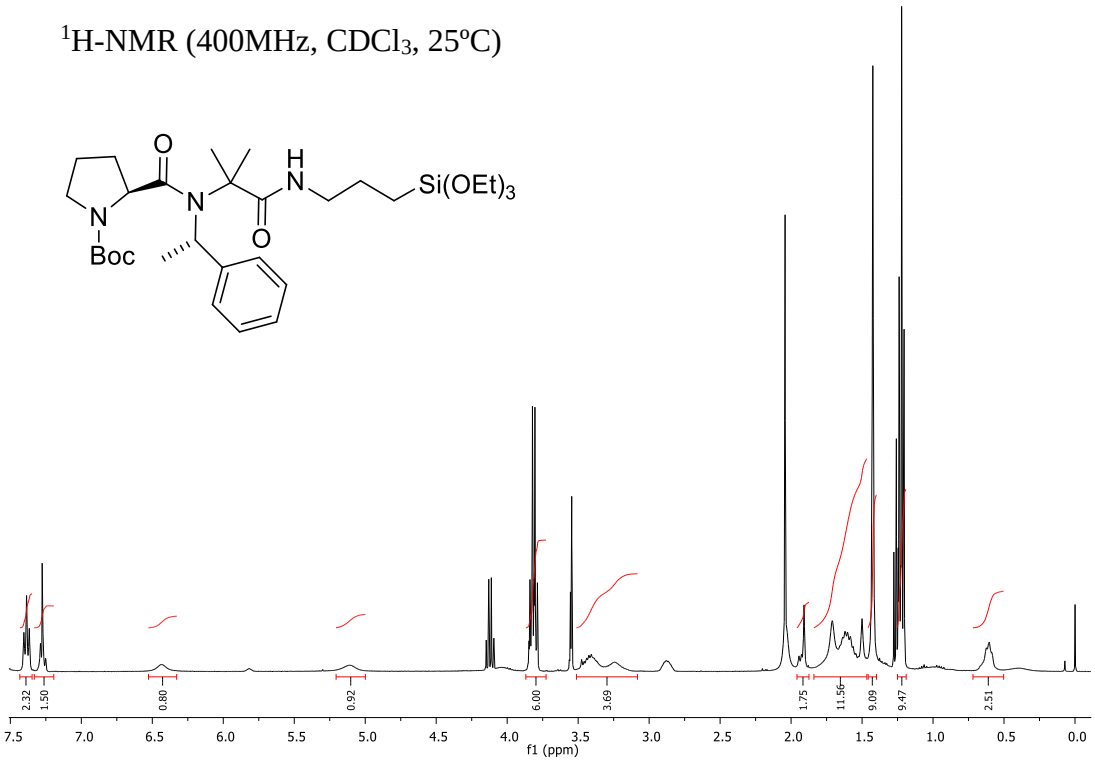
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



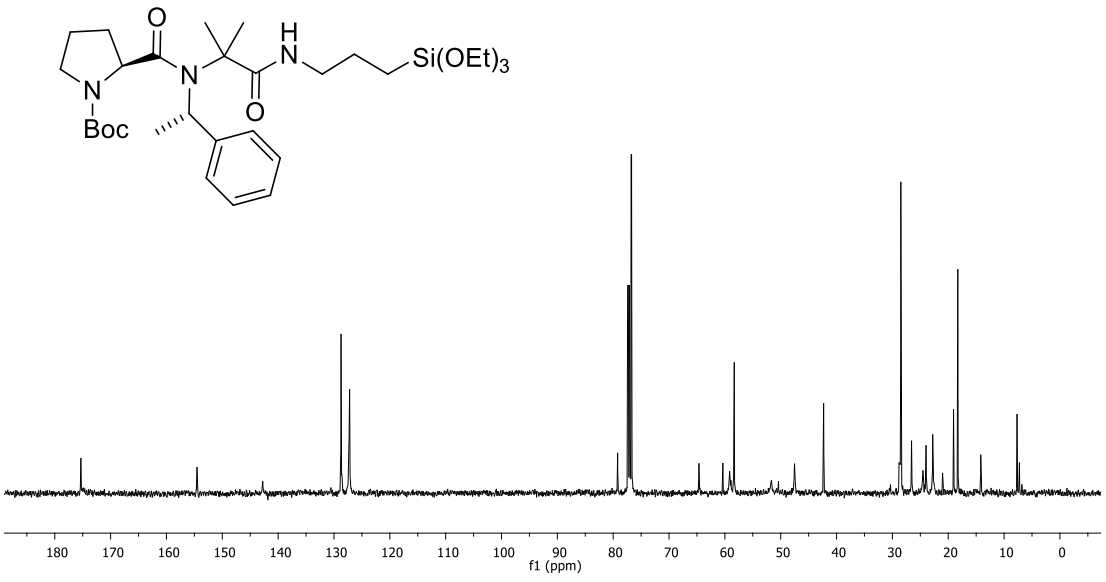
^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



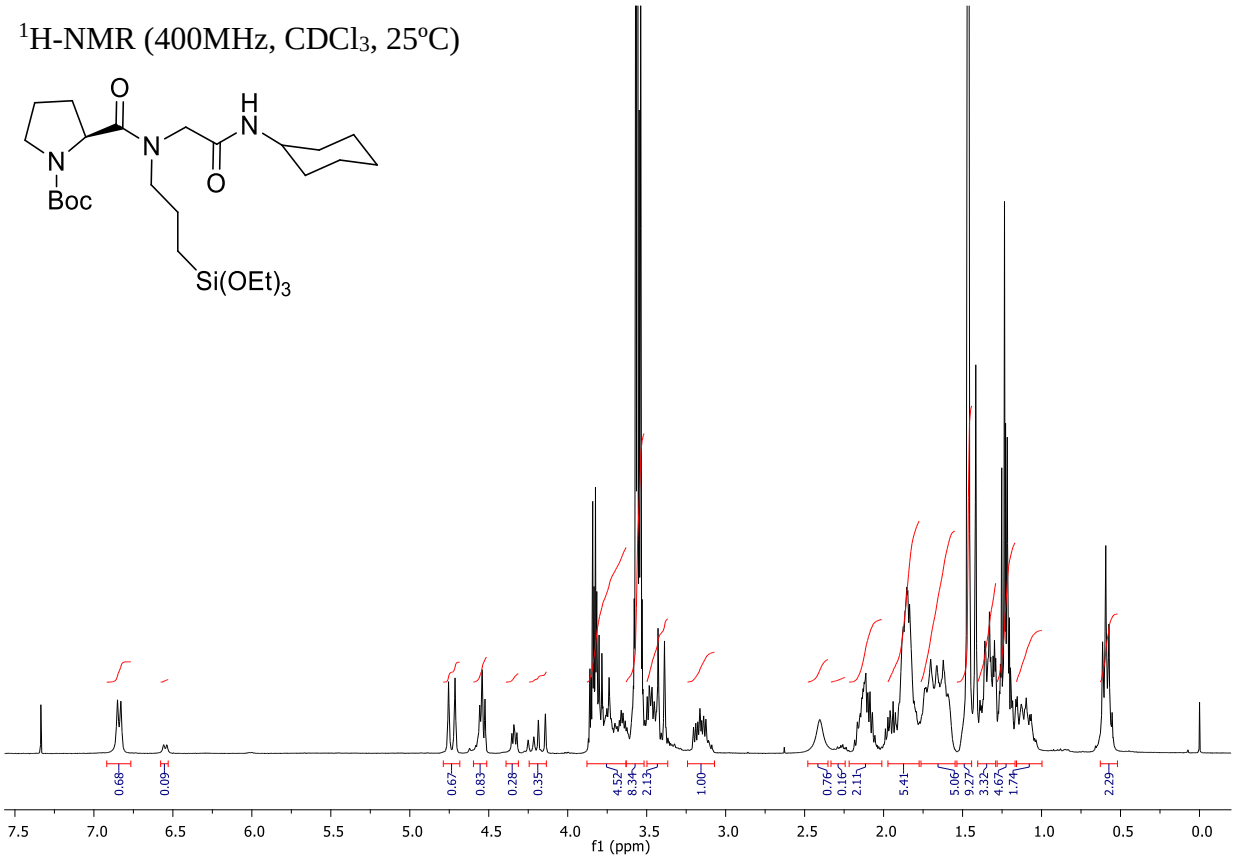
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



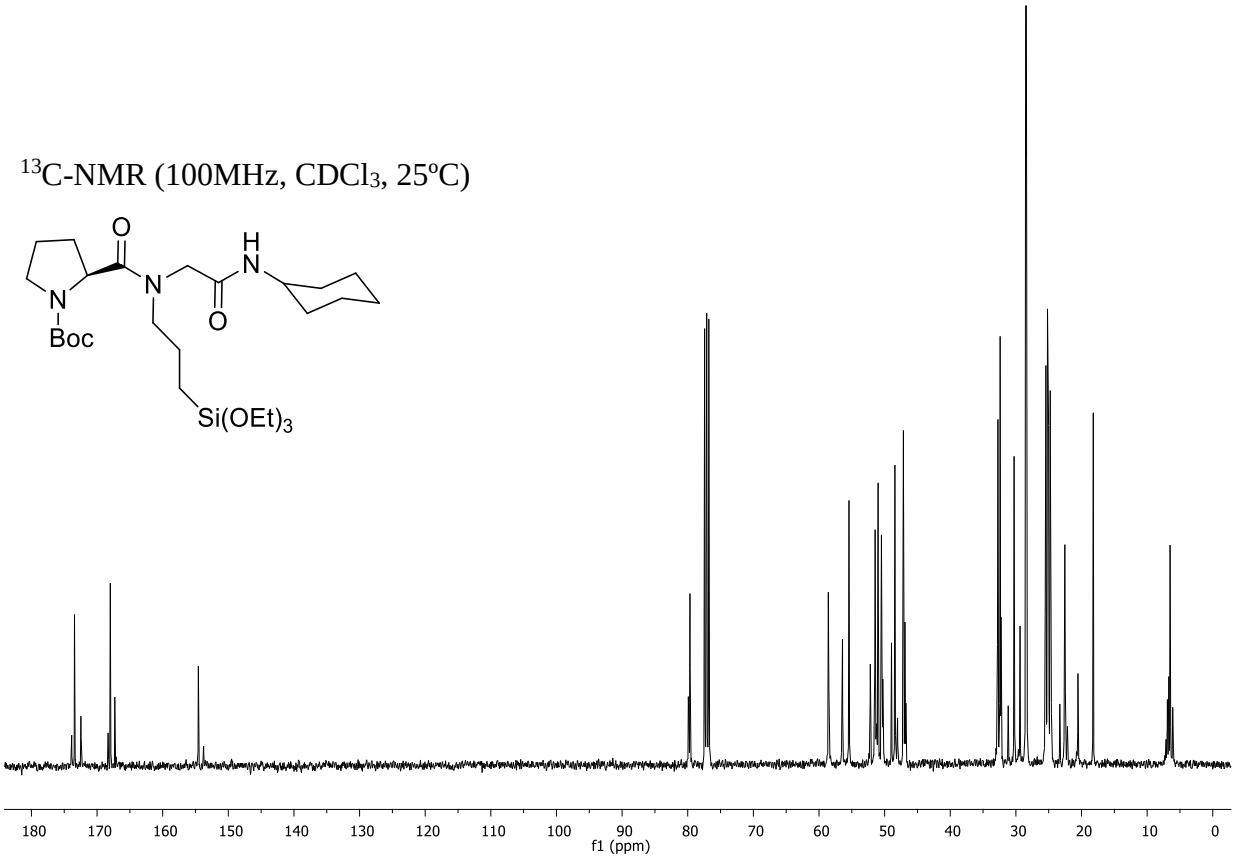
^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



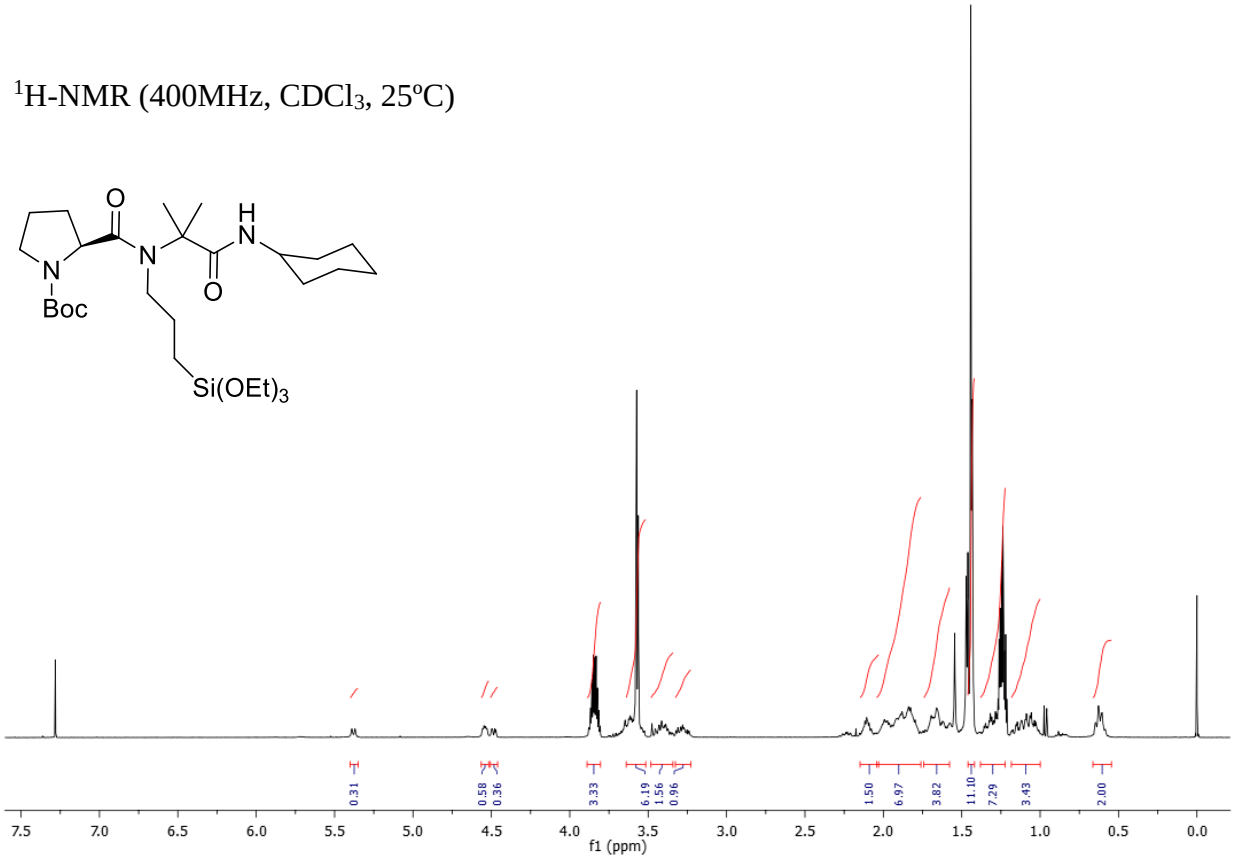
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



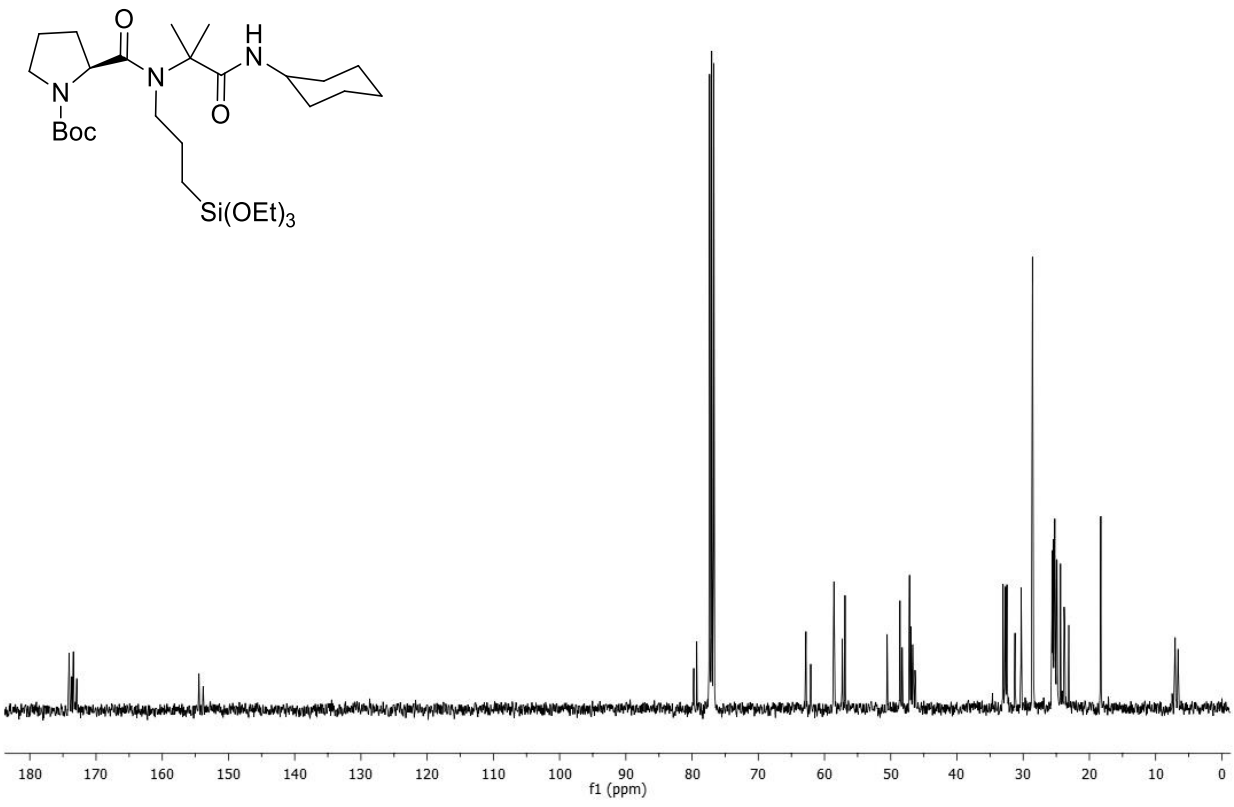
^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



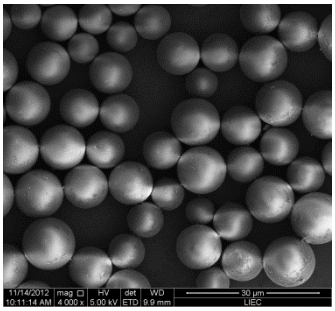
Microanalysis of silica-grafted catalysts

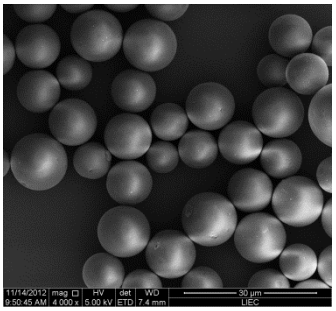
Catalysts	N(%)	C (%)	H (%)	S (%)	Loading(mmol.g^{-1})*
SiO_2-3a	0.4310	4.267982	1.019812	0	0.10
SiO_2-3b	0.5568	4.522238	0.917261	0	0.13
SiO_2-4a	0.8238	5.781246	1.247870	0	0.20
SiO_2-4b	0.9123	7.062346	1.355790	0	0.22

*Loading (mmol of catalyst per gram of silica) determined based on the content of nitrogen.

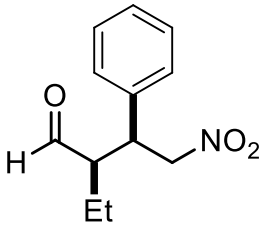
Microscopy analysis of SiO_2-4b

High resolution image of the organocatalyst after grafting and deprotection (left). Silica without functionalization (right):

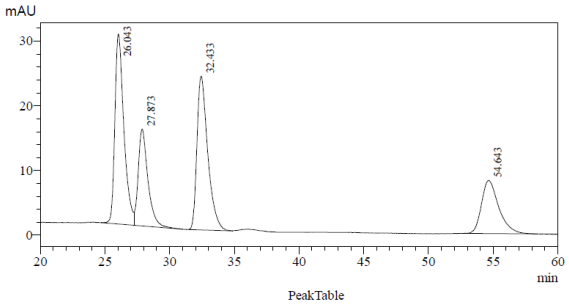




(2*R*,3*S*)-2-ethyl-4-nitro-3-phenylbutanal (5a):

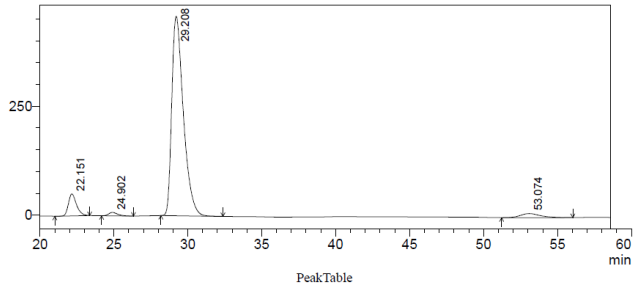


Prepared by reaction of *n*-butanal with *trans*-β-nitrostyrene according to the general flow procedure. The enantiomeric excess and diastereoisomeric ratio were determined by chiral-phase HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH 9:1, 25°C) at 1.0 ml/min, UV detection at 210 nm. Analytical data for major diastereoisomer were in agreement with the published data.[58] **^{1}H NMR** (400 MHz,$CDCl_3$, 25°C) δ = 9.73, 9.48 (2×d, *J* = 2.6 Hz, 1H), 7.37- 7.31 (m, 3H), 7.19-7.17 (m, 2H), 4.72 (dd, *J* = 5.0 Hz, 12.7 Hz, 1H), 4.63 (dd, *J* = 9.6 Hz, 12.7 Hz, 1H), 3.79 (td, *J* = 5.0 Hz, 9.8 Hz, 1H), 2.68 (m, 1H), 1.51(m, 2H), 0.84 (t, *J* = 0.83 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 25°C) δ **=** 203.2, 136.8, 129.1, 128.2, 128.0, 78.5, 55.0, 42.7, 20.4, 10.7 ppm.



PeakTable

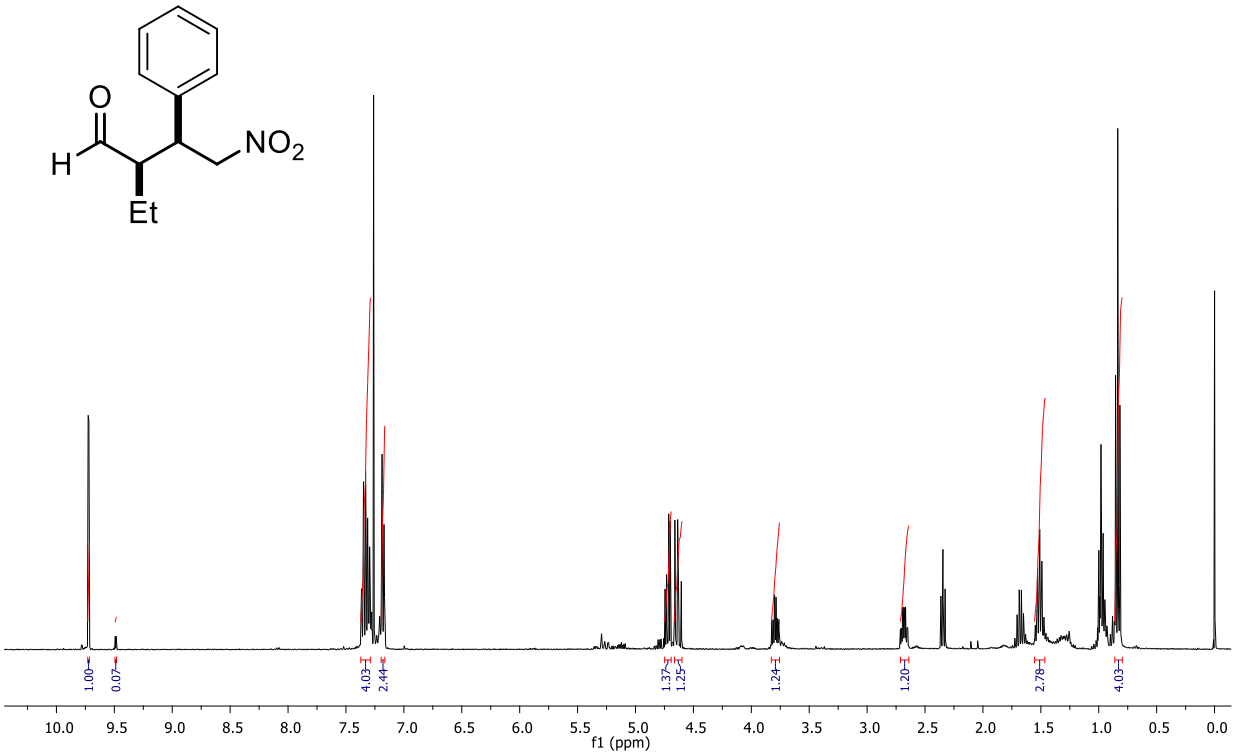
Peak#	Ret. Time	Area	Height	Area %	Height %
1	26.043	14207419	292653	32.706	38.488
2	27.873	7812575	149166	17.985	19.618
3	32.433	13798543	236450	31.765	31.097
4	54.643	7621276	82100	17.544	10.797
Total		43439814	760369	100.000	100.000



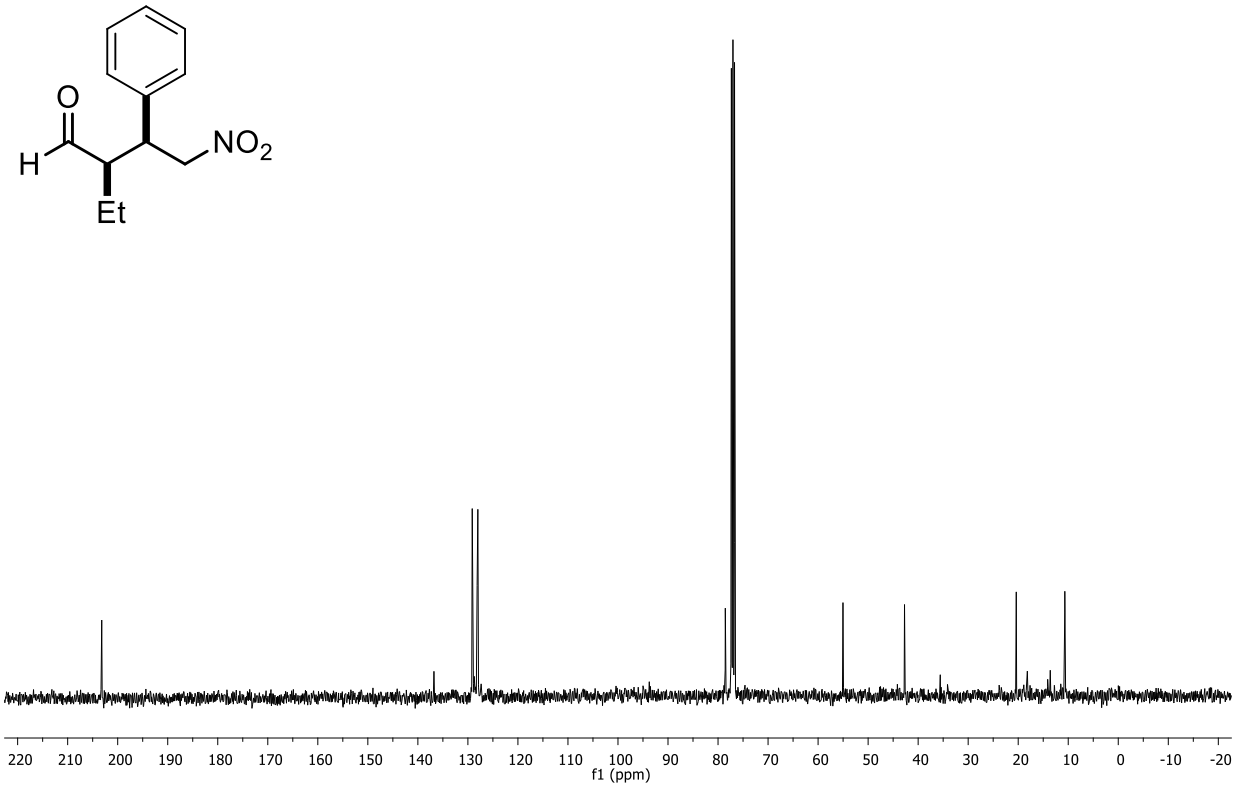
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.151	1917782	50478	6.826	9.606
2	24.902	338621	8019	1.205	1.526
3	29.208	24973439	457652	88.894	87.089
4	53.074	863724	9348	3.074	1.779
Total		28093566	525498	100.000	100.000

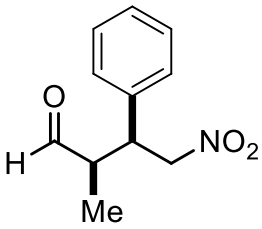
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



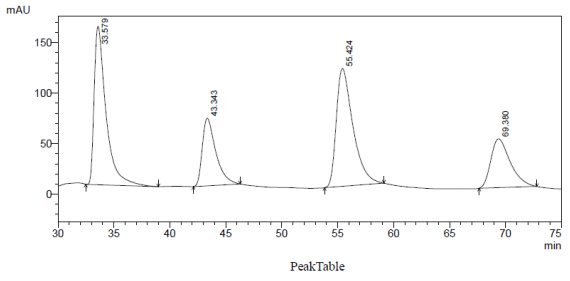
^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



(2*R*,3*S*)-2-methyl-4-nitrobutanal (5b):

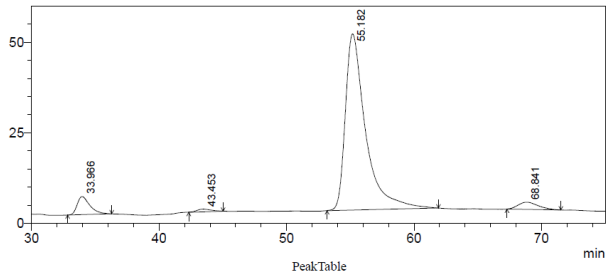


Prepared by reaction of *n*-propanal with *trans*-β-nitrostyrene according to the general flow procedure. The enantiomeric excess and diastereoisomeric ratio were determined by chiral-phase HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH 95:5, 25°C) at 1.0 ml/min, UV detection at 210 nm. Analytical data for major diastereoisomer were in agreement with the published data.[58] **^{1}H NMR** (400 MHz,$CDCl_3$, 25°C) δ = 9.72, 9.54 (2×d, *J* = 2.6 Hz, 1H), 7.36- 7.29 (m, 3H), 7.17-7.16 (m, 2H), 4.80 (dd, *J* = 5.5 Hz, 12.7 Hz, 1H), 4.68 (dd, *J* = 9.3 Hz, 12.7 Hz, 1H), 3.81 (td, *J* = 5.5 Hz, 9.13 Hz, 1H), 2.78 (ddd, *J* = 1.7 Hz, 7.2 Hz, 8.9 Hz, 1H), 1.00(d, *J* = 7.3 Hz, 3 H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 25°C) δ **=** 202.4, 136.7, 129.2, 128.3, 78.3, 48.6, 44.2, 12.3.



PeakTable

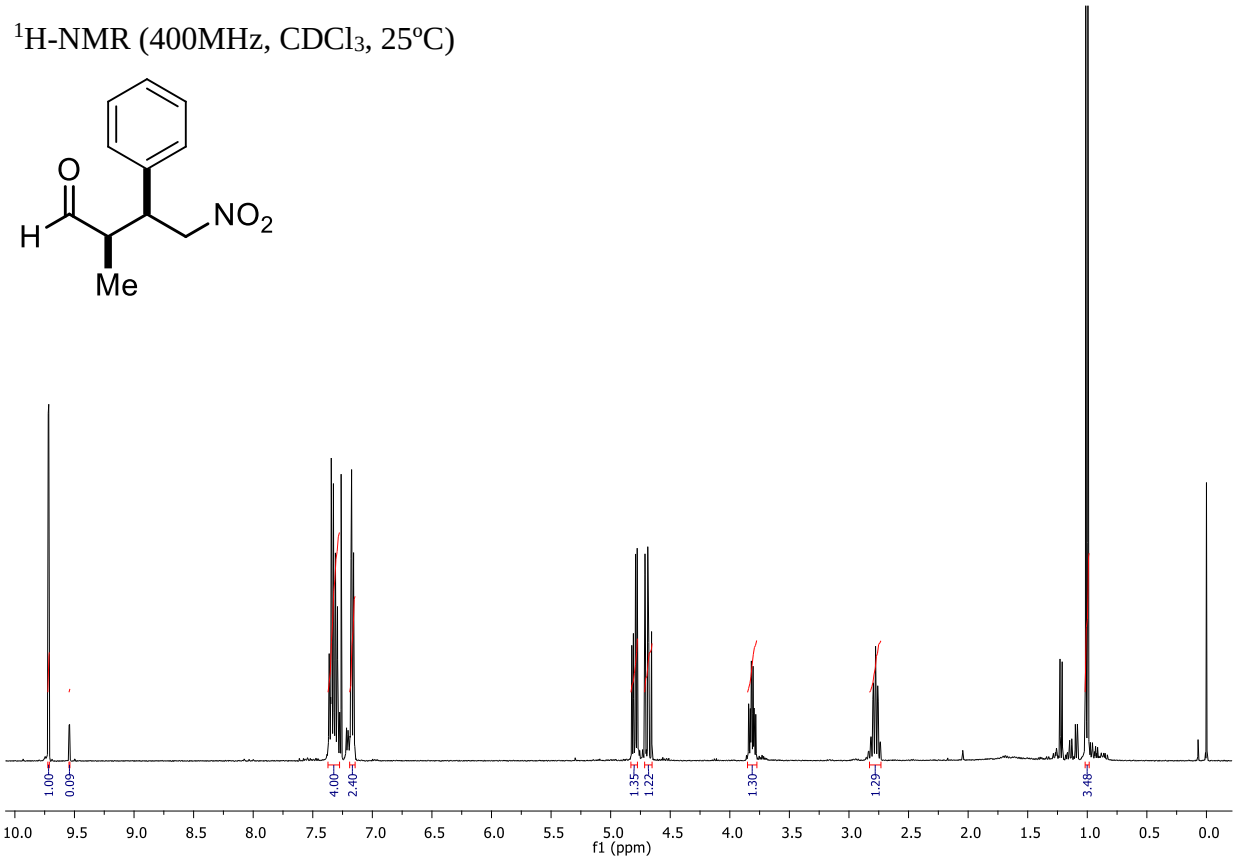
Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.579	11591503	156538	32.937	40.308
2	43.343	5648014	66829	16.049	17.208
3	55.424	12106873	116676	34.401	30.044
4	69.380	5846517	48311	16.613	12.440
Total		35192907	388354	100.000	100.000



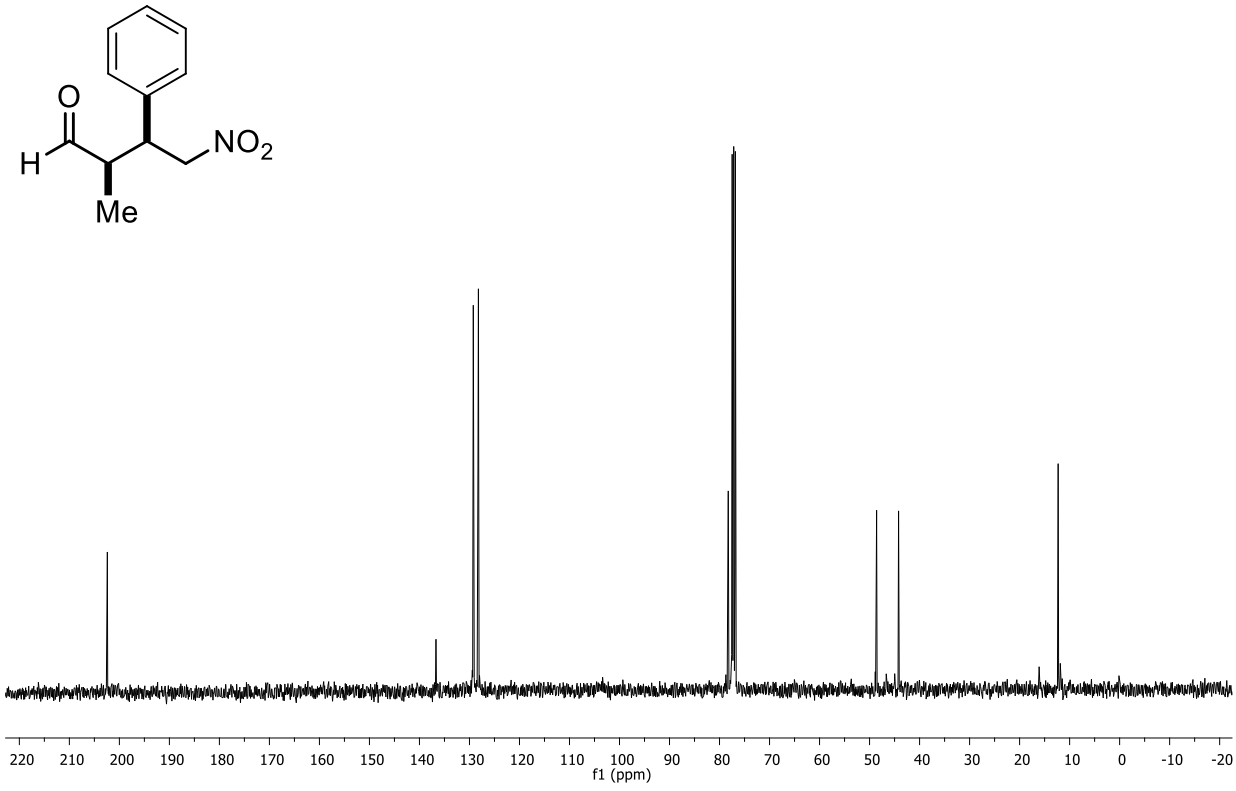
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.966	346235	4988	5.765	8.866
2	43.453	59200	751	0.986	1.335
3	55.182	5379124	48545	89.572	86.294
4	68.841	220780	1972	3.676	3.505
Total		6005339	56256	100.000	100.000

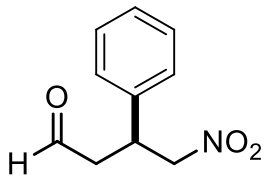
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



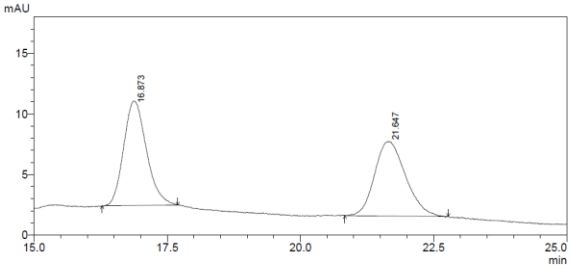
^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



(S)-4-nitro-3-phenylbutanal-(5c):

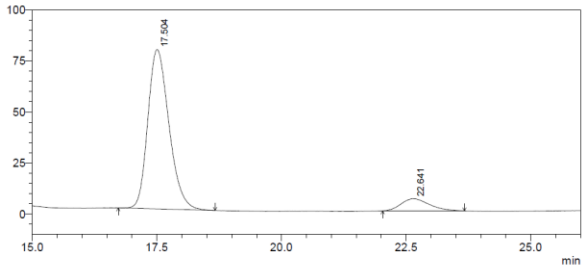


Prepared by reaction of acetaldehyde with *trans*-β-nitrostyrene according to the general flow procedure. The enantiomeric excess and diastereoisomeric ratio were determined by chiral-phase HPLC (Chiralpak AS-H, *n*-hexane/*i*-PrOH 70:30, 25°C) at 1.0 ml/min, UV detection at 210 nm. Analytical data for major diastereoisomer were in agreement with the published data.[58] **^{1}H NMR** (400 MHz,$CDCl_3$, 25°C) δ = 9.62 (s, 1H), 7.29- 7.21 (m, 3H), 7.17-7.15 (m, 2H), 4.57 (qd, *J* = 7.4 Hz, 12.5 Hz; 2H), 4.0 (p, *J* = 7.2 Hz, 1H), 2.93- 2.82 (m, 2H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 25°C) δ **=** 198.8, 138.2, 129.2, 128.1, 127.4, 79.4, 46.4, 37.9 ppm.



PeakTable

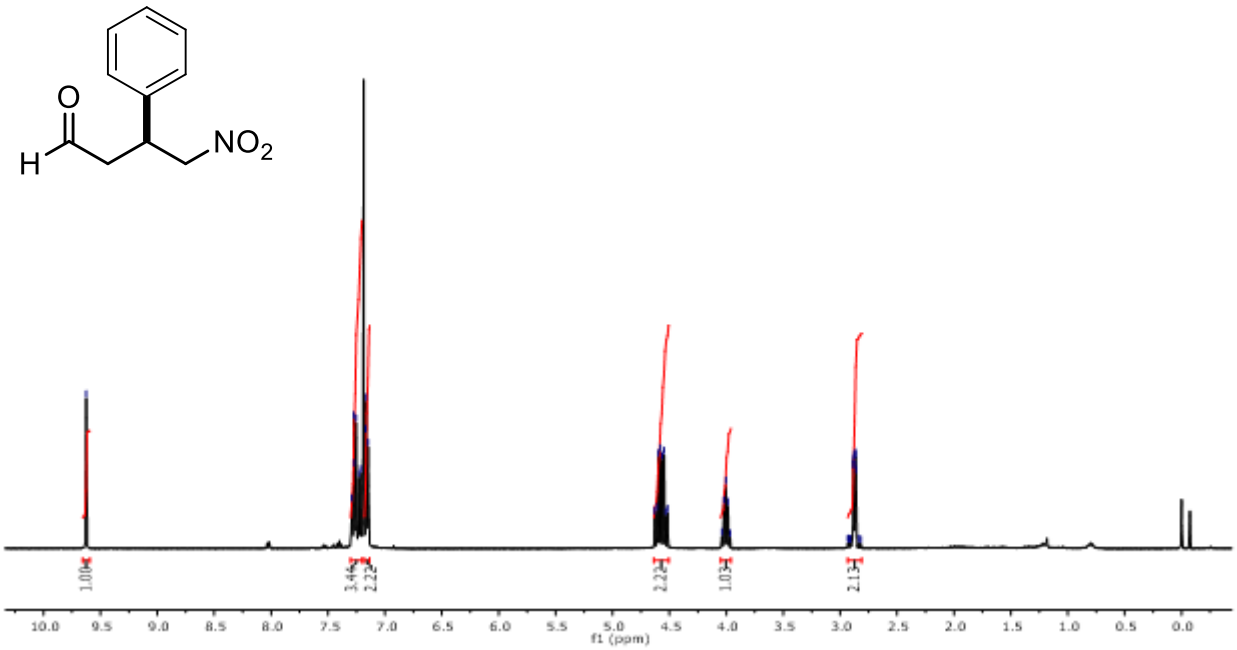
Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.873	257119	8440	50.768	58.049
2	21.647	249345	6100	49.232	41.951
Total		506464	14540	100.000	100.000



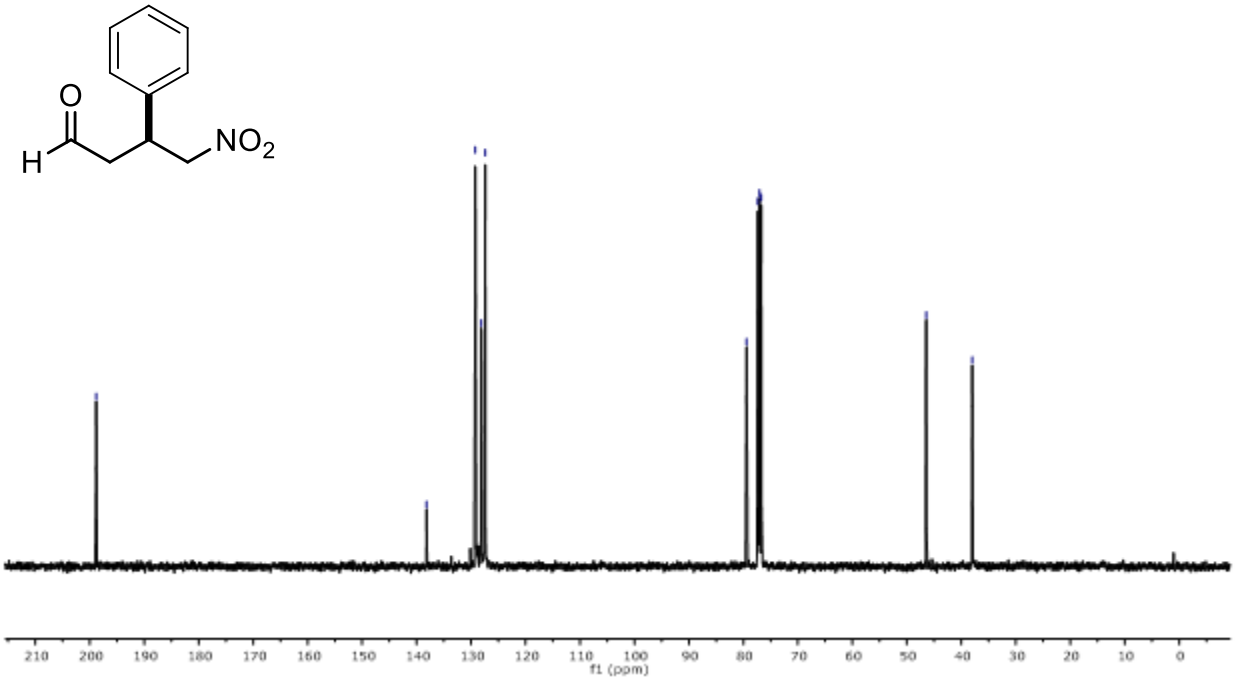
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	17.504	2306245	77584	90.790	92.972
2	22.641	233948	5865	9.210	7.028
Total		2540193	83448	100.000	100.000

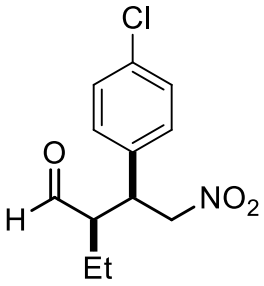
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



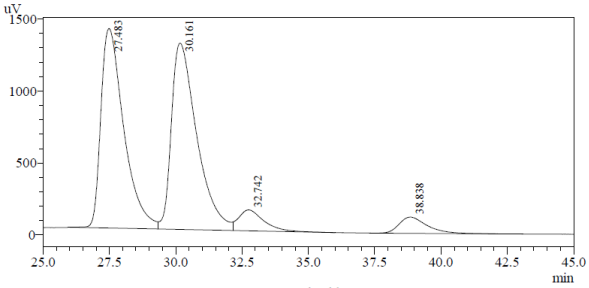
^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



(*2R,3S*)-3-(4-chlorophenyl)-2-ethyl-4-nitrobutanal (5d):

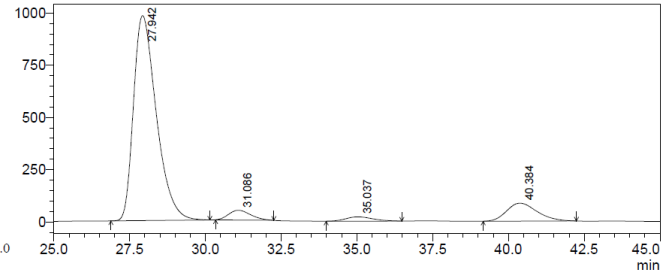


Prepared by reaction of *n*-butanal with *trans*-4-chloro-β-nitrostyrene according to the general flow procedure. The enantiomeric excess and diastereoisomeric ratio were determined by chiral-phase HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH 95:5, 25°C) at 1.0 ml/min, UV detection at 210 nm. Analytical data for major diastereoisomer were in agreement with the published data.[58] **^{1}H NMR** (400 MHz,$CDCl_3$, 25°C) δ = 9.72, 9.50 (2×d, *J* = 2.8 Hz, 1H), 7.34-7.32 (m, 2H), 7.14-7.12 (m, 2H), 4.72 (dd, *J* = 4.8 Hz, 12.8 Hz, 1H), 4.60 (dd, *J* = 9.9 Hz, 12.8 Hz, 1H), 3.82 (dt, *J* = 4.8 Hz, 10.0 Hz, 1H), 2.67 (m, 1H), 1.52 (m, 2H), 0.84 (t, *J* = 7.5 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 25°C) δ **=** 202.8, 135.5, 134.2, 129.8, 129.5, 54.9, 42.2, 20.5, 10.7 ppm.



PeakTable

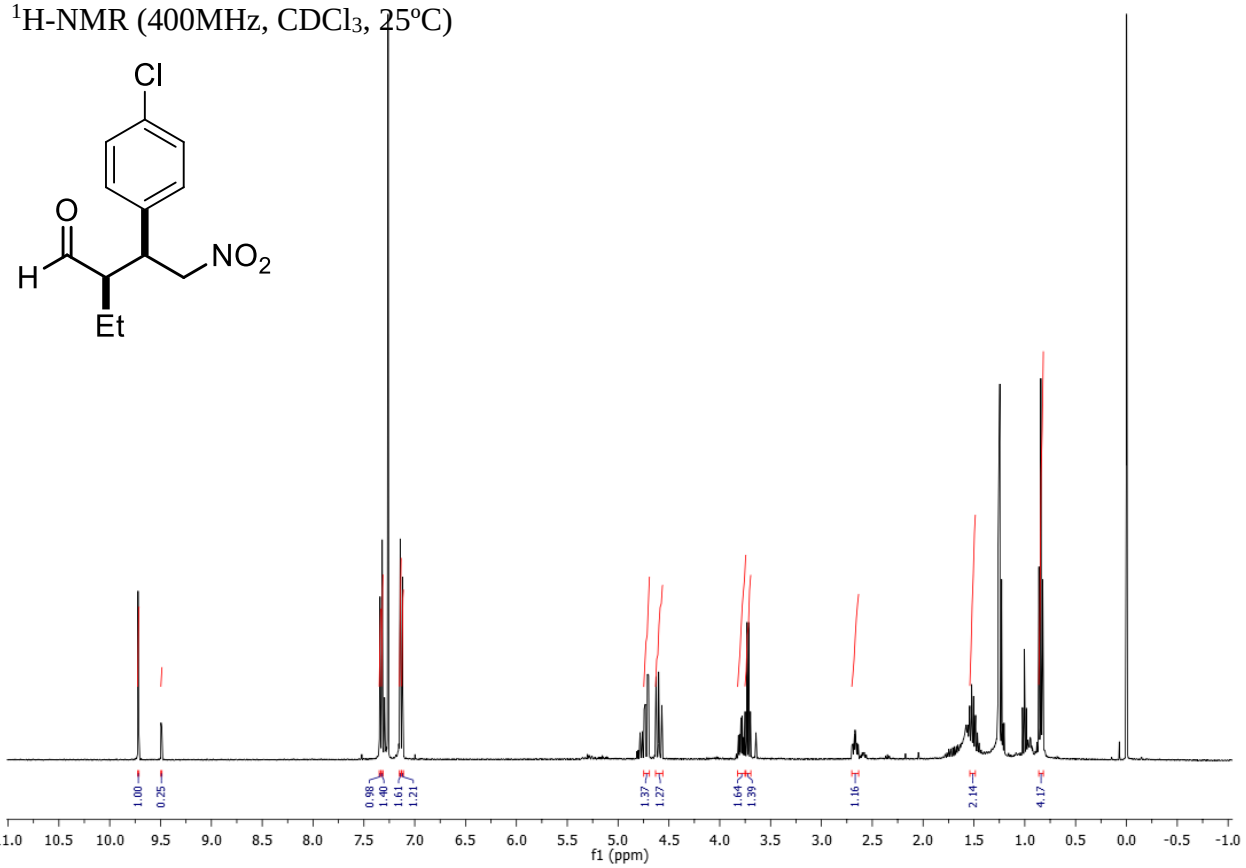
Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.483	83363463	1380994	44.421	47.187
2	30.161	86357607	1287927	46.017	44.007
3	32.742	9626245	144769	5.129	4.947
4	38.838	8318231	112925	4.432	3.859
Total		187665546	2926615	100.000	100.000



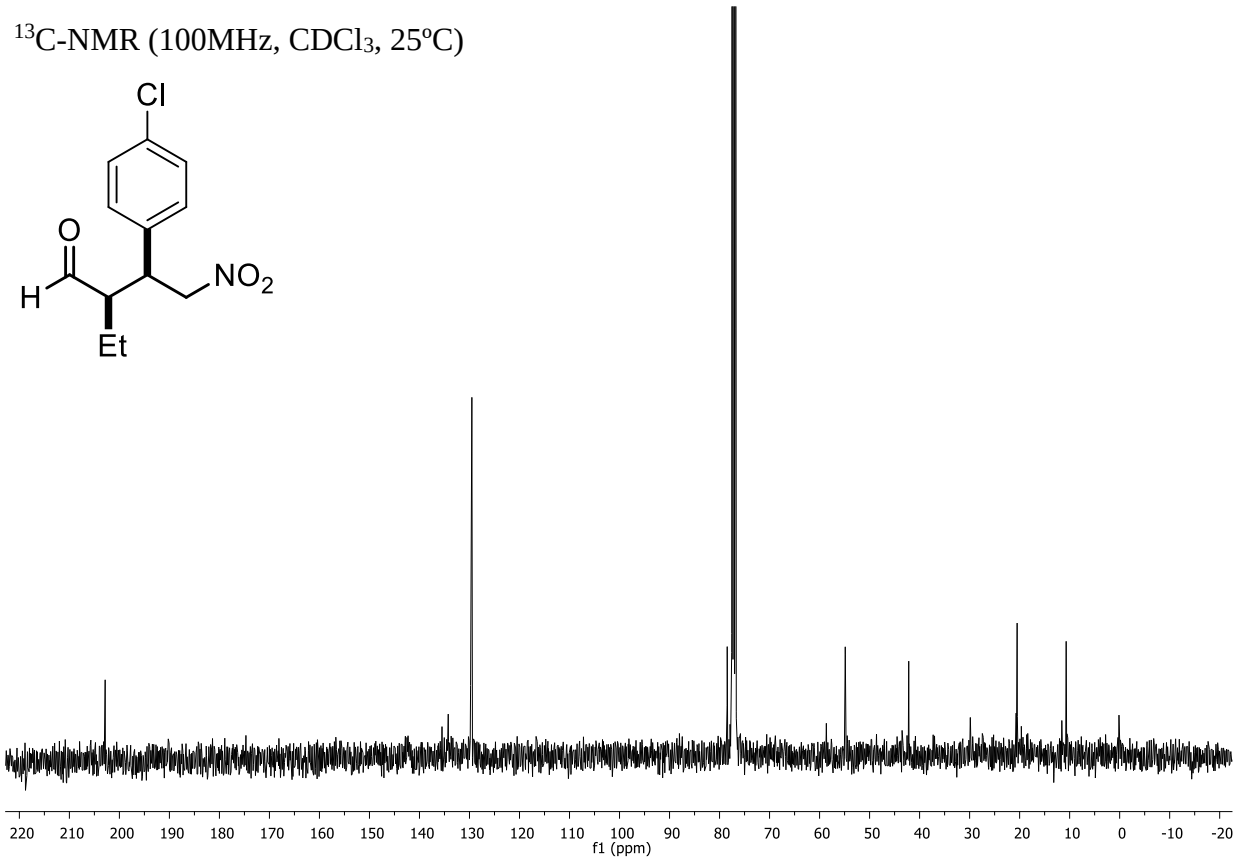
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.942	51453935	967740	84.206	86.507
2	31.086	2353651	44765	3.852	4.002
3	35.037	1262028	20607	2.065	1.842
4	40.384	6035141	85568	9.877	7.649
Total		61104756	1118679	100.000	100.000

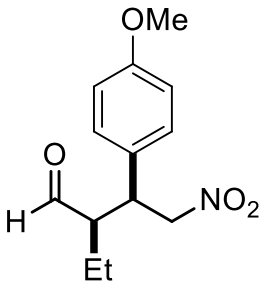
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)

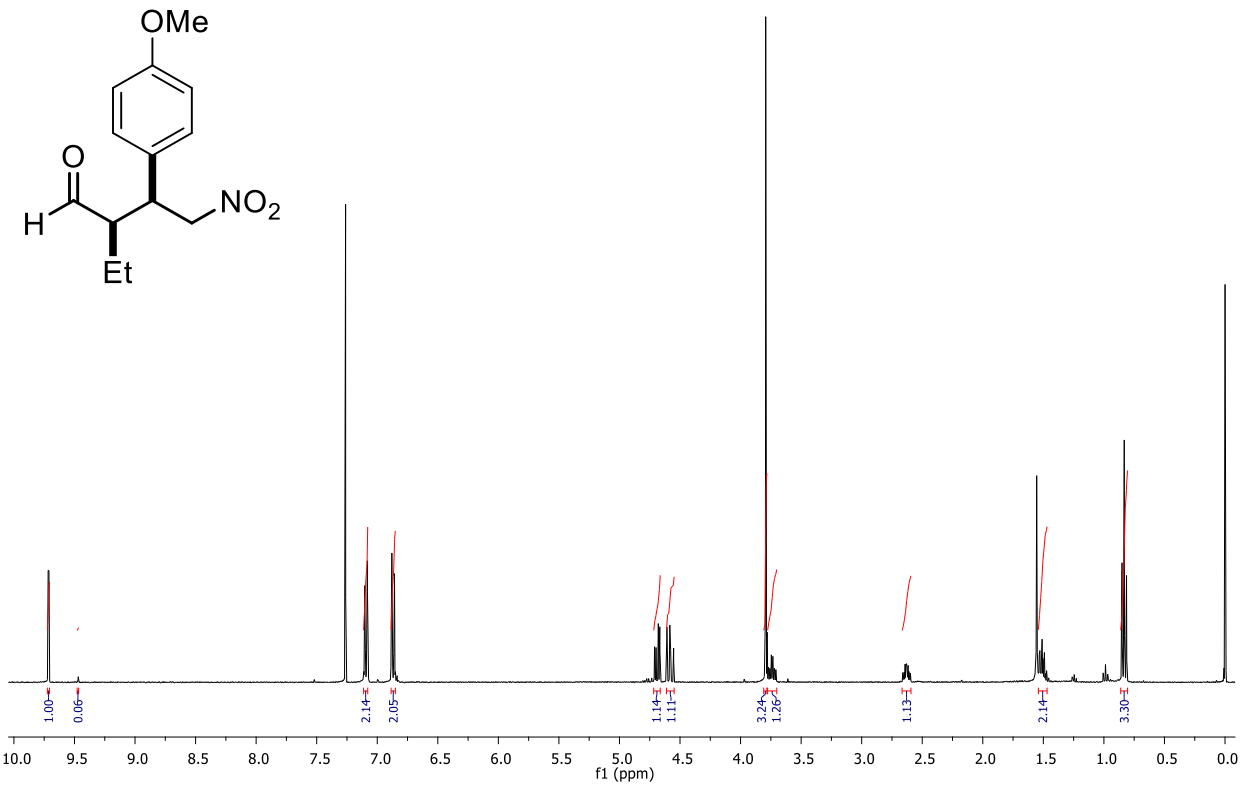


(*2R,3S*)-3-(4-methoxyphenyl)-2-ethyl-4-nitrobutanal (5e):

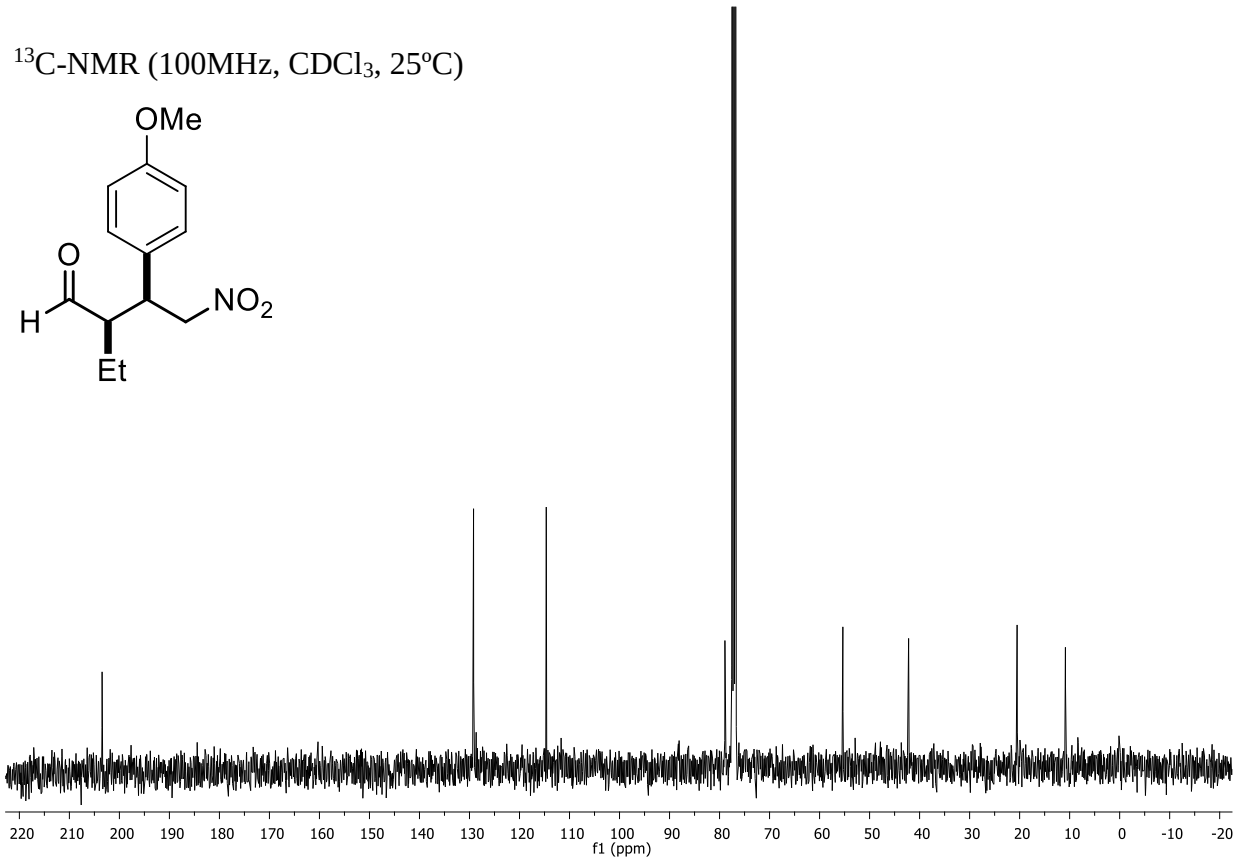


Prepared by reaction of *n*-butanal with *trans*-4-methoxy β-nitrostyrene according to the general flow procedure. The compound was purified by flash column chromatography *n*-hexane/EtOAc 8:2 *v/v*). The enantiomeric excess and diastereoisomeric ratio were determined by chiral-phase HPLC (Chiralpak IC, *n*-hexane/*i*-PrOH 95:5, 25°C) at 0.2 ml/min, UV detection at 210 nm. Analytical data for major diastereoisomer were in agreement with the published data.[58] **^{1}H NMR** (400 MHz,$CDCl_3$, 25°C) δ = 9.72, 9.47 (2×d, *J* = 2.6 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 6.87 (m, 2H), 4.69 (dd, *J* = 4.9 Hz, 12.5 Hz, 1H), 4.58 (m, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 2.63 (m, 1H), 1.50 (m, 2H), 0.83 (t, *J* = 7.5 Hz, 3H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 25°C) δ **=** 203.4, 129.4, 129.2, 114.6, 78.9, 55.4, 55.3, 42.2, 20.5, 10.8 ppm.

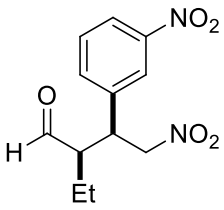
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



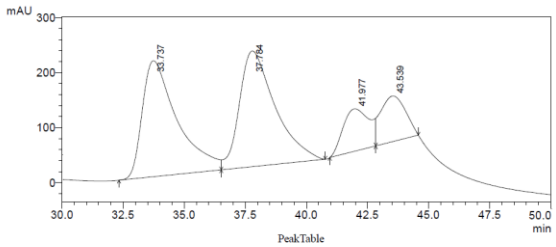
^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



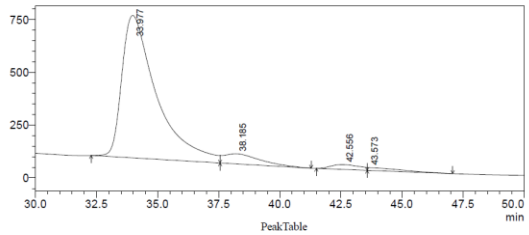
(2R,3S)-2-ethyl-4-nitro-3-(3-nitrophenyl)butanal (5f):



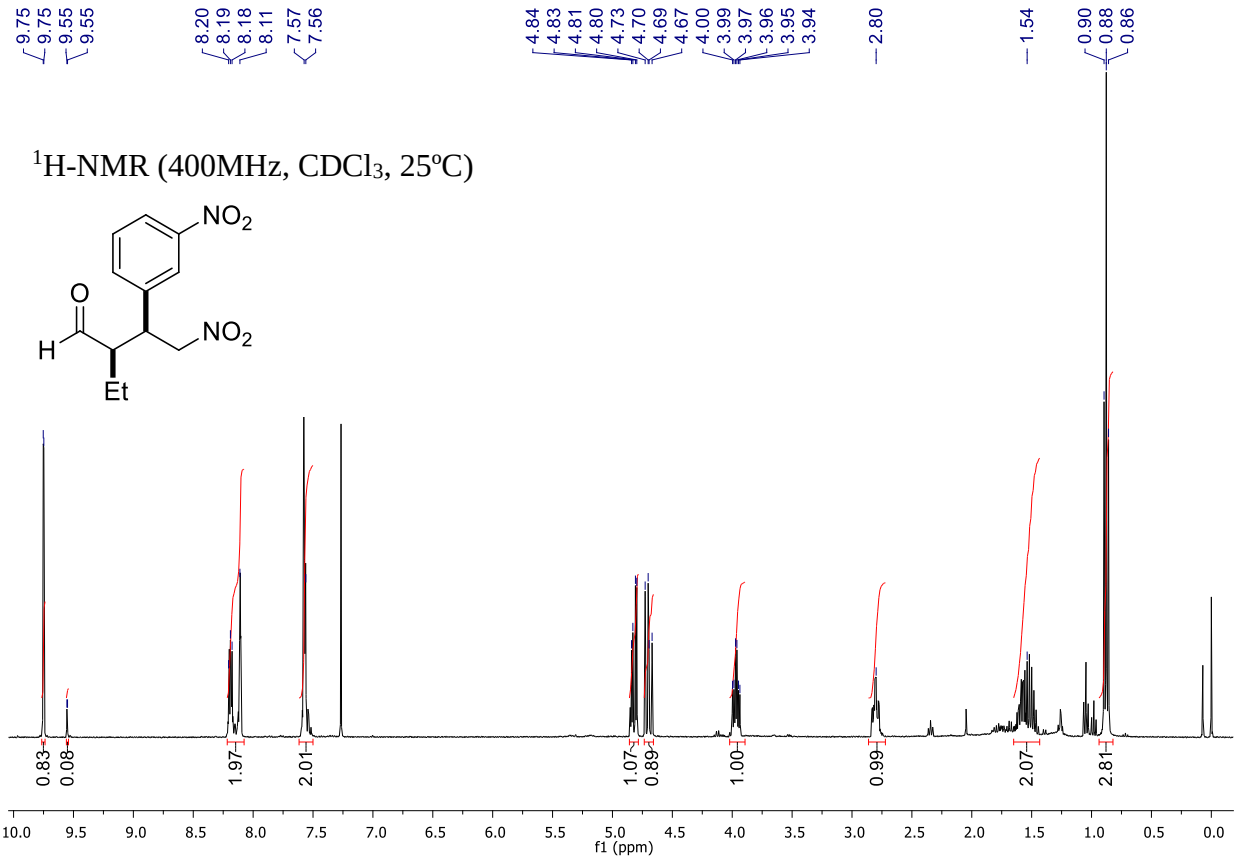
Prepared by reaction of *n*-butanal with *trans*-3-nitro β-nitrostyrene according to the general flow procedure. The compound was purified by flash column chromatography *n*-hexane/EtOAc 8:2 *v/v*). The enantiomeric excess and diastereoisomeric ratio were determined by chiral-phase HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH 90:10, 30°C) at 1.0 ml/min, UV detection at 210 nm. Analytical data for major diastereoisomer were in agreement with the published data.[58] **^{1}H NMR** (400 MHz,$CDCl_3$, 25°C) δ = 9.68, 9.48 (2xd, *J* = 2.8 Hz, 1H; CHO), 8.12-8.04 (m, 2H; Ph), 7.56-7.47 (m, 2H; Ph), 4.74 (dd, *J* = 4.8 Hz, 12.8 Hz, 1H; CH_2NO_2), 4.63 (dd, *J* = 9.9 Hz, 12.8 Hz, 1H; CH_2NO_2), 3.89 (dt, *J* = 4.8 Hz, 10.0 Hz, 1H; CHPh), 2.77-2.71 (m, 1H; CHCHO), 1.57-1.38 (m, 2H; CH_2CH_3), 0.80 (t, *J* = 7.5 Hz, 3H; CH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$, 25°C) δ = 202.2, 148.8, 139.5, 134.6, 130.3, 123.4, 123.0, 78.0, 54.4, 42.2, 20.5, 10.5 ppm.



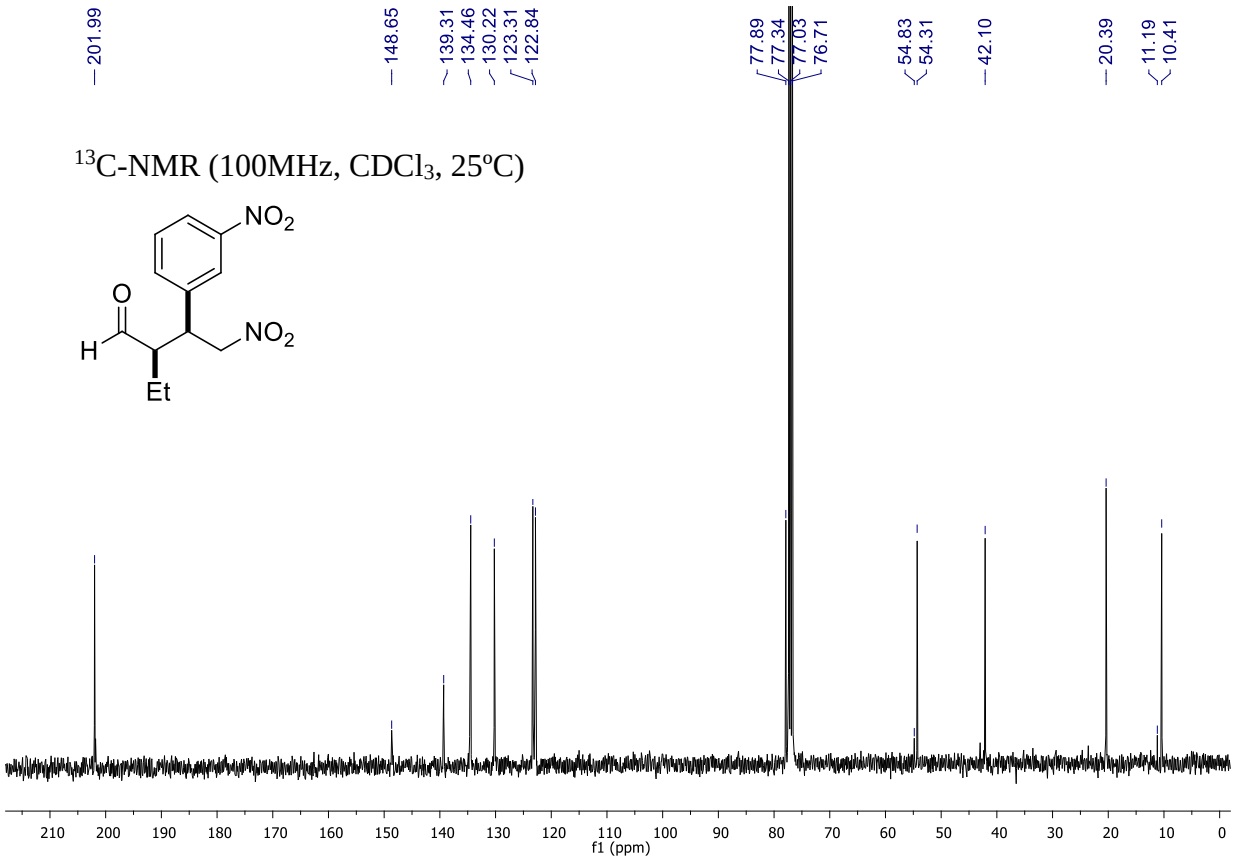
Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.737	20874317	211015	38.698	36.300
2	37.784	21483955	210340	39.828	36.184
3	41.977	5746894	77087	10.654	13.261
4	43.539	5836728	82859	10.820	14.254
Total		53941895	581302	100.000	100.000



Peak#	Ret. Time	Area	Height	Area %	Height %
1	33.977	66725175	675456	89.079	88.841
2	38.185	5017872	47845	6.699	6.293
3	42.556	1893655	23225	2.528	3.055
4	43.573	1269246	13776	1.694	1.812
Total		74905947	760302	100.000	100.000

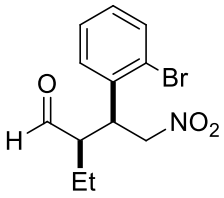


^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)

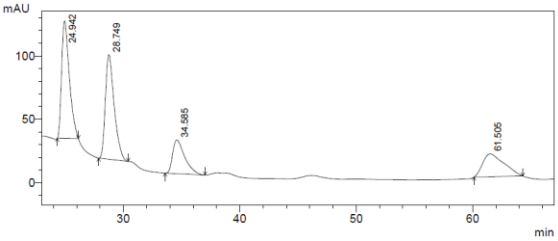


^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)

(2R,3S)-3-(2-bromophenyl)-2-ethyl-4-nitrobutanal (5g):

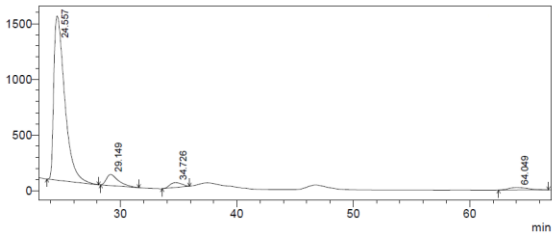


Prepared by reaction of *n*-butanal with *trans*-2-bromo β-nitrostyrene according to the general flow procedure. The compound was purified by flash column chromatography *n*-hexane/EtOAc 8:2 *v/v*). The enantiomeric excess and diastereoisomeric ratio were determined by chiral-phase HPLC (Chiralpak OD-H, *n*-hexane/*i*-PrOH 95:5, 30°C) at 1.0 ml/min, UV detection at 210 nm. Analytical data for major diastereoisomer were in agreement with the published data.[58] **^{1}H NMR** (400 MHz,$CDCl_3$, 25°C) δ = 9.74, 9.60 (2xd, *J* = 2.4 Hz, 1H, CHO), 7.61 (dd, *J* = 1.3 Hz, 1H, Ph), 7.34- 7.30 (m, 1H, Ph), 7.21-7.15 (m, 2H, Ph), 4.89- 4.83 (m, 1H,CH_2NO_2), 4.69, 4.67 (dd, *J* = 4.6 Hz, 13 Hz, 1H, CH_2NO_2), 4.41- 4.32 (m, 1H, CHPh), 2.94 (m, 1H, CHCHO), 1.70- 1.45 (m, 2H, CH_2CH_3), 0.88 (t, *J* = 0.9 Hz, 3H, CH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 202.93, 136.36, 134.05, 129.65, 129.37, 128.25, 77.03, 54.45, 41.39, 20.60, 10.97 ppm.



PeakTable

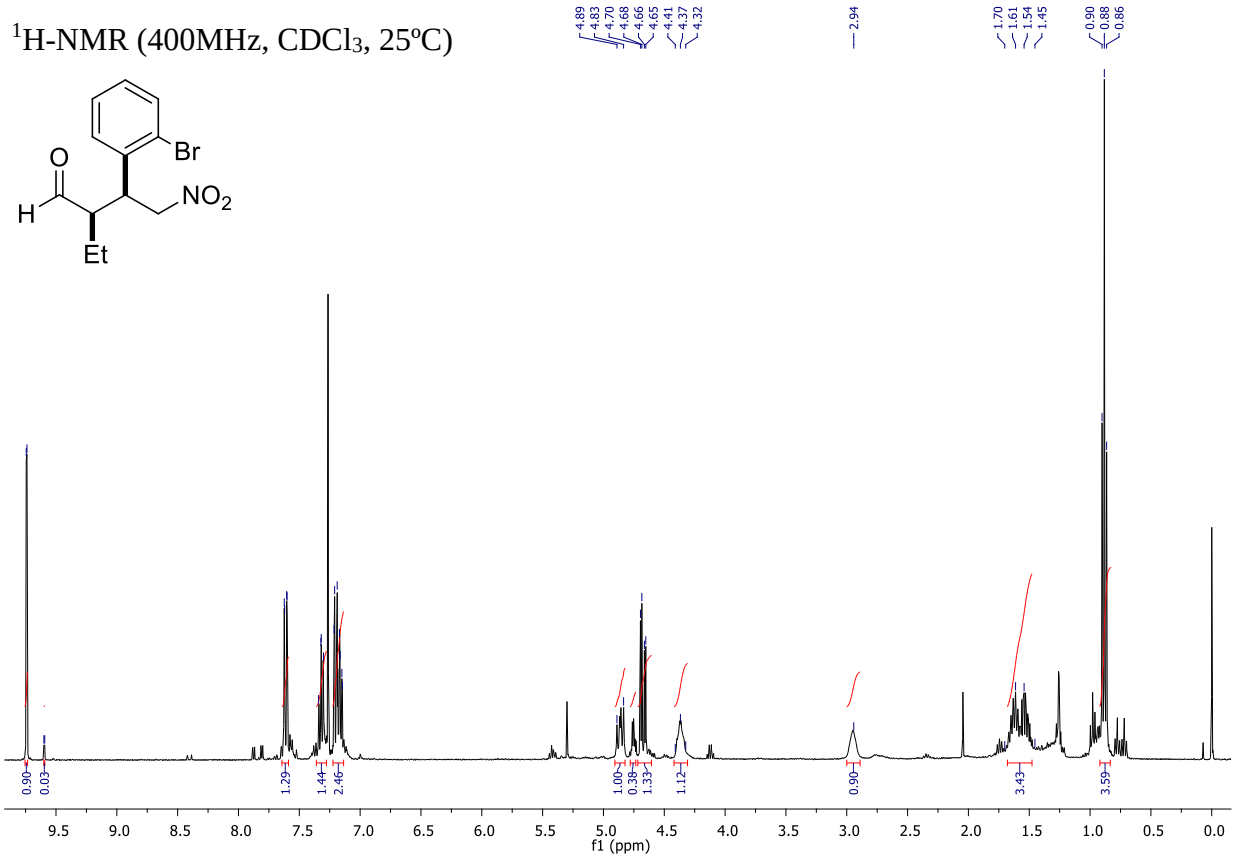
Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.942	4259763	92597	33.185	42.106
2	28.749	4344873	82544	33.848	37.535
3	34.585	1937742	26732	15.096	12.156
4	61.505	2293965	18039	17.871	8.203
Total		12836344	219912	100.000	100.000



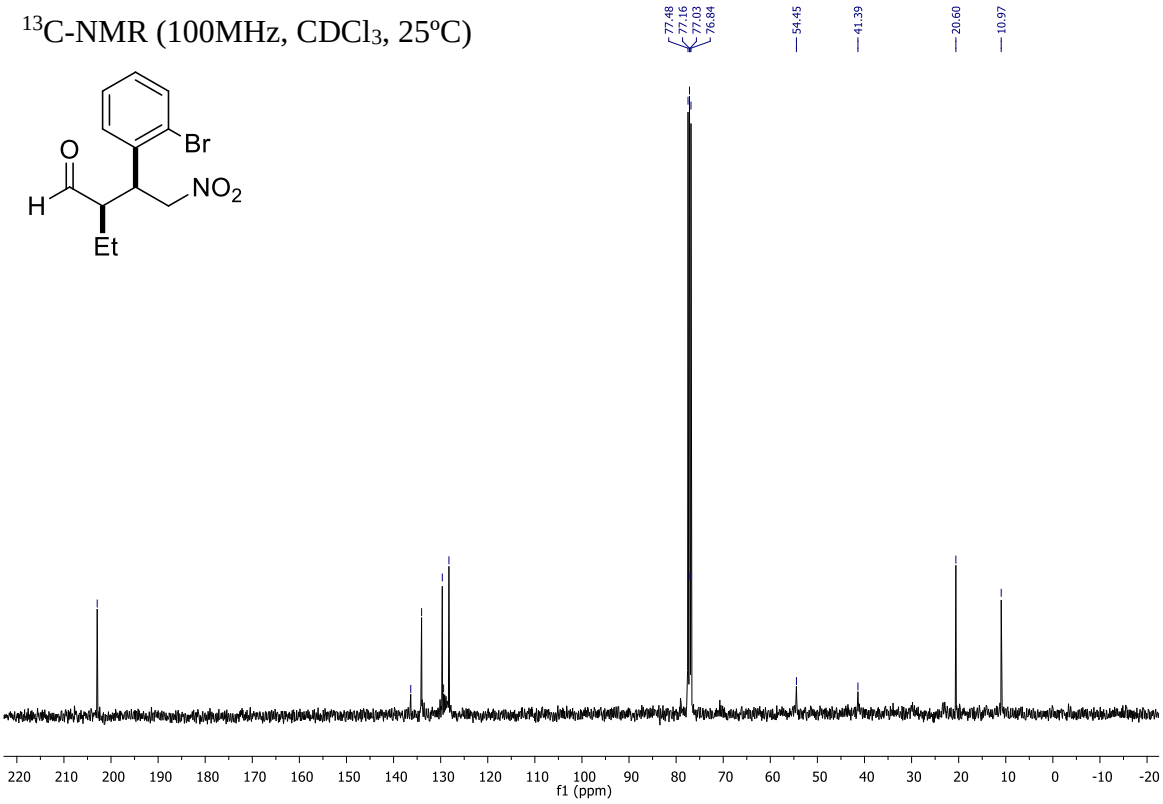
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	24.557	96375289	1474723	88.221	89.936
2	29.149	7224942	99666	6.614	6.078
3	34.726	3045788	43028	2.788	2.624
4	64.049	2596419	22327	2.377	1.362
Total		109242439	1639744	100.000	100.000

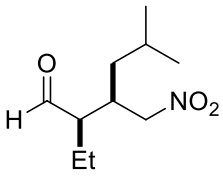
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



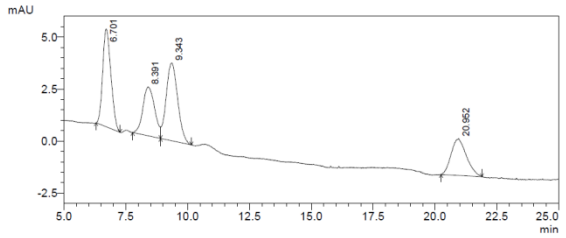
^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



(2R,3R)-2-ethyl-5-methyl-3-(nitromethyl)hexanal (5h):

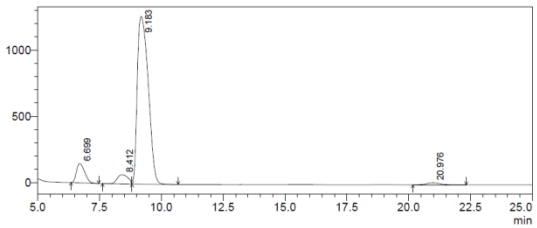


Prepared by reaction of *n*-butanal with 4-methyl-1-nitropent-1-ene according to the general flow procedure. The compound was purified by flash column chromatography *n*-hexane/EtOAc 9:1 *v/v*). The enantiomeric excess and diastereoisomeric ratio were determined by chiral-phase HPLC (Chiralpak IC, *n*-hexane/*i*-PrOH 90:10, 30°C) at 0.2 ml/min, UV detection at 210 nm. Analytical data for major diastereoisomer were in agreement with the published data.[58] **^{1}H NMR** (400 MHz,$CDCl_3$, 25°C) δ = ppm; δ = 9.72 (d, 1H; CHO), 4.49- 4.40 (m, 2H, CH_2NO_2), 2.76- 2.69 (m, 1H; CH_2CH_3), 2.45- 2.40 (m, *J* = 1.23 Hz, 1H, CH_2CH_3), 1.85- 1.74 (m, 1H, CHCHO), 1.65- 1.53 (m, 1H, $CH(CH_3)_2$), 1.53- 1.46 (m, 1H, $CHCH_2CH(CH_3)_2$), 1.25- 1.21 (m, 2H, $CH_2CH(CH_3)_2$), 1.01 (t, *J* = 7.43 Hz, 3H, CH_3), 0.91 (2xd, *J* = 4.87, 6.52 Hz, 6H, CH_3) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 203.22, 77.23, 54.21, 38.43, 34.83, 25.35, 22.82, 22.20, 18.63, 12.31 ppm.



PeakTable

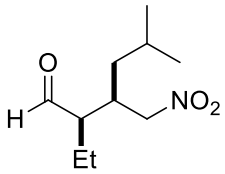
Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.701	108691	4702	28.382	37.416
2	8.391	78360	2351	20.462	18.705
3	9.343	120363	3733	31.429	29.702
4	20.952	75548	1782	19.727	14.177
Total		382961	12567	100.000	100.000



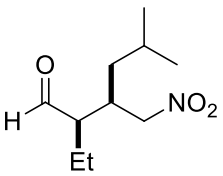
PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.699	3391266	145331	7.513	9.835
2	8.412	2150940	69388	4.765	4.696
3	9.183	39012900	1248185	86.431	84.467
4	20.976	582760	14811	1.291	1.002
Total		45137866	1477715	100.000	100.000

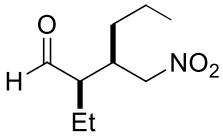
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



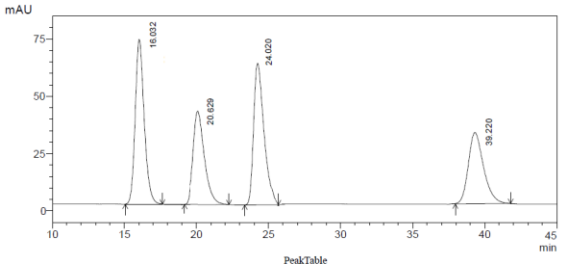
^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



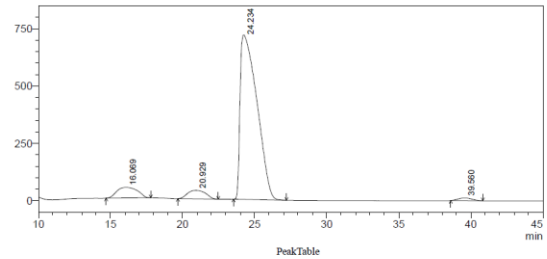
(2R,3R)-2-ethyl-3-(nitromethyl)hexanal (5i):



Prepared by reaction of *n*-butanal with 1-nitropent-1-ene according to the general flow procedure. The compound was purified by flash column chromatography *n*-hexane/EtOAc 9:1 *v/v*). The enantiomeric excess and diastereoisomeric ratio were determined by chiral-phase HPLC (Chiralpak IC, *n*-hexane/*i*-PrOH 99:1, 30°C) at 0.2 ml/min, UV detection at 210 nm. Analytical data for major diastereoisomer were in agreement with the published data.[58] **^{1}H NMR** (400 MHz,$CDCl_3$, 25°C) δ = 9.71 (d, *J* = 1.47 Hz, 1H; CHO), 4.50-4.40 (m, 2H, CH_2NO_2), 2.69-2.65 (m, 1H; CH_2CH_3), 2.43-2.38 (m, 1H, CH_2CH_3), 1.83-1.70 (m, 1H, CHCHO), 1.55- 1.51 (m, 1H, $CH(CH_2)_2CH_3$), 1.40- 1.35 (m, 4H, $(CH_2)_2CH_3$), 1.01 (t, *J* = 7.43 Hz, 3H, CH_3), 0.95- 0.90 (m, 3H, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$, 25°C) δ = 203.29, 77.16, 54.04, 36.70, 31.41, 20.12, 18.72, 14.05, 12.22 ppm.

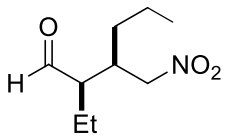


Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.032	1209526	35277	28.838	34.950
2	20.629	883222	20048	21.058	19.862
3	24.020	1208860	30347	28.822	30.066
4	39.220	892659	15264	21.283	15.122
Total		4194267	100936	100.000	100.000

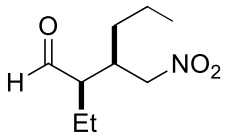


Peak#	Ret. Time	Area	Height	Area %	Height %
1	16.069	4633042	46522	6.945	5.729
2	20.929	3215845	36804	4.821	4.532
3	24.234	58090945	717152	87.078	88.308
4	39.560	771228	11624	1.156	1.431
Total		66711060	812102	100.000	100.000

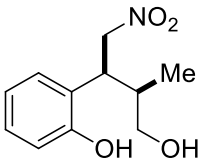
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)



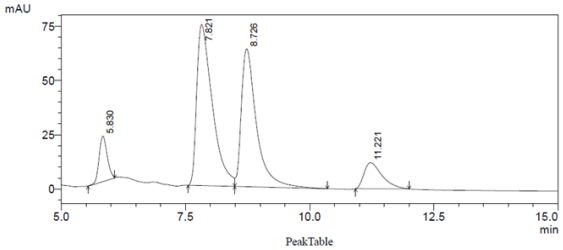
^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)



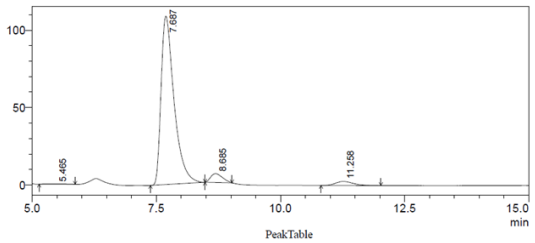
2-((2S,3R)-4-hydroxy-3-methyl-1-nitrobutan-2-yl)phenol (5f-red):



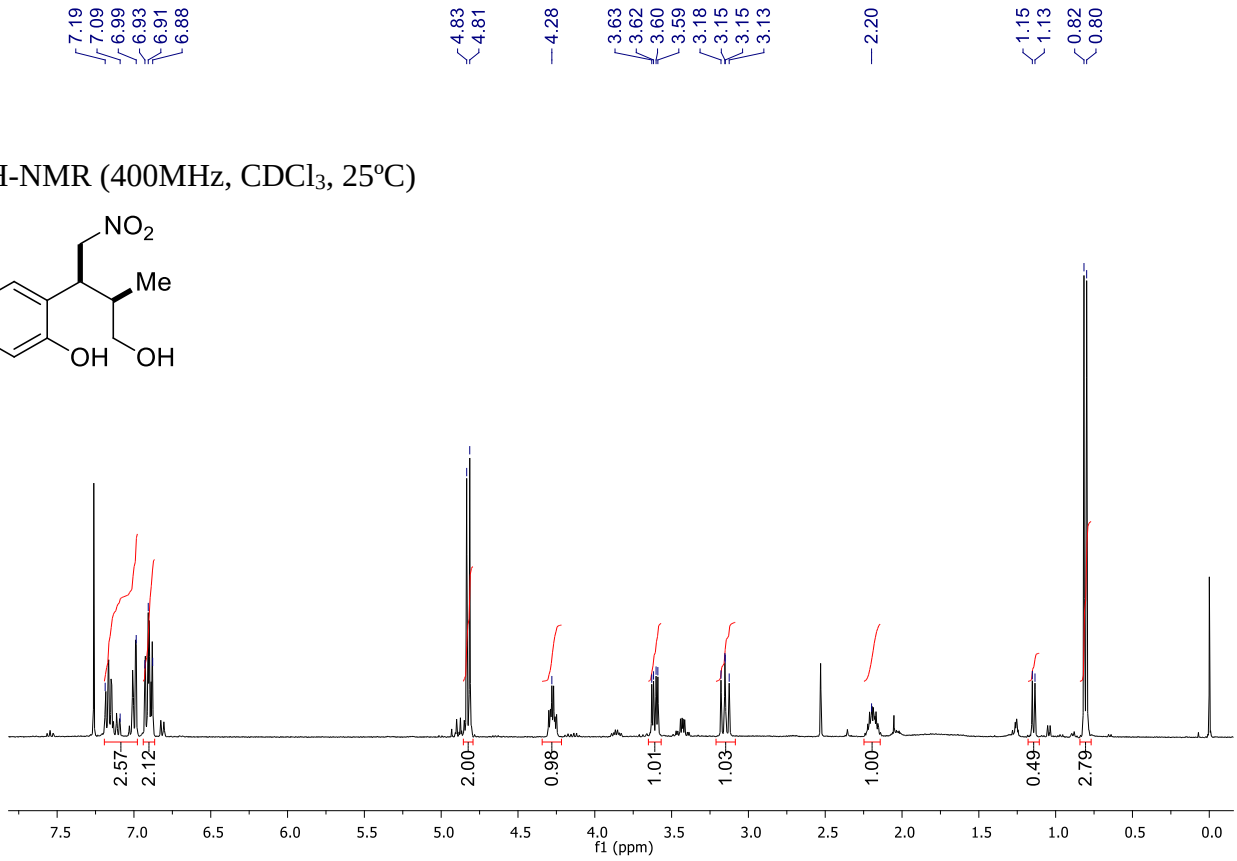
Prepared by reaction of *n*-butanal with *trans*-2-hydroxy β-nitrostyrene according to the general flow procedure. The crude product was reduced according to the general procedure. The compound was purified by flash column chromatography *n*-hexane/EtOAc 1:1 *v/v*). The enantiomeric excess and diastereoisomeric ratio were determined by chiral-phase HPLC (Chiralpak AS-H, *n*-hexane/*i*-PrOH 80:20, 30°C) at 1.0 ml/min, UV detection at 210 nm. Analytical data for major diastereoisomer were in agreement with the published data.[58] **^{1}H NMR (400 MHz, $CDCl_3$)** δ= 7.19-6.99 (m, 3H), 6.89 (m, 2H), 4.82 (d, *J* = 8.0 Hz, 1H), 4.27 (m, 1H), 3.61 (dd, *J* = 11.3, 4.6 Hz, 1H), 3.21 – 3.09 (m, 1H), 2.20 (m, 1H), 1.12,0.81 (2xd, *J* = 7.0 Hz, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ= 154.85, 128.92, 128.87, 122.22, 121.53, 120.93, 117.24, 78.08, 66.16, 65.63, 38.30, 37.00, 36.66, 15.64, 11.55 ppm.



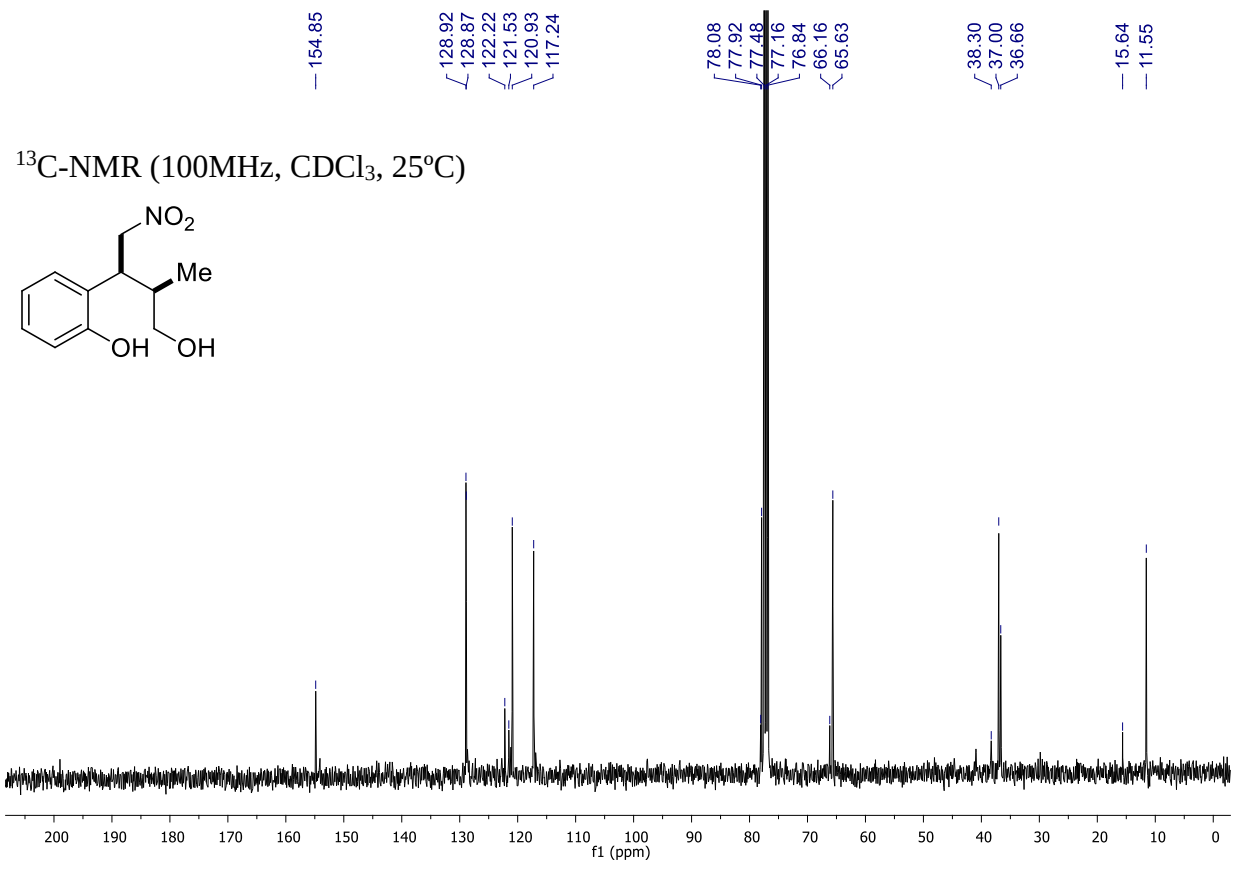
Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.830	239685	21080	6.794	12.320
2	7.821	1627933	74351	46.144	43.452
3	8.726	1356532	63662	38.451	37.205
4	11.221	303774	12018	8.611	7.023
Total		3527924	171111	100.000	100.000



Peak#	Ret. Time	Area	Height	Area %	Height %
1	5.465	4803	175	0.224	0.150
2	7.687	1975961	108754	92.359	92.758
3	8.685	94245	5706	4.405	4.867
4	11.258	64429	2610	3.011	2.226
Total		2139438	117245	100.000	100.000



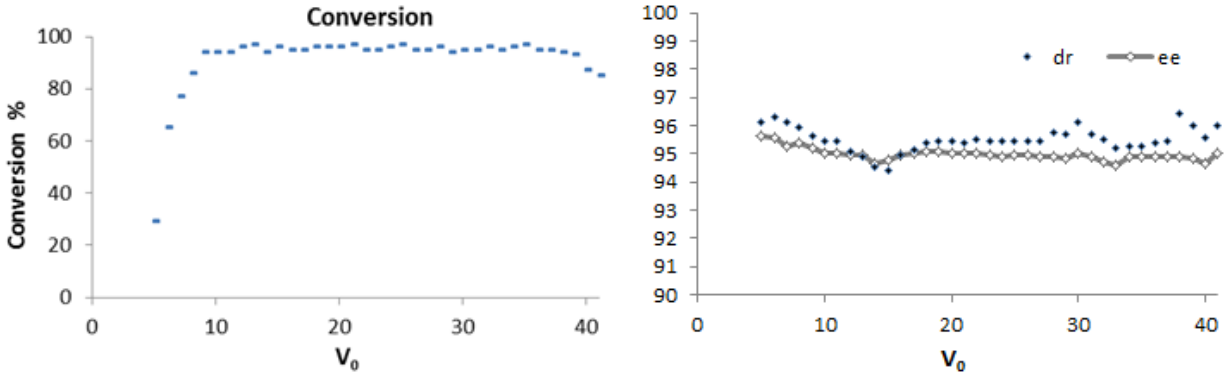
^{1}H-NMR (400MHz, $CDCl_3$, 25ºC)

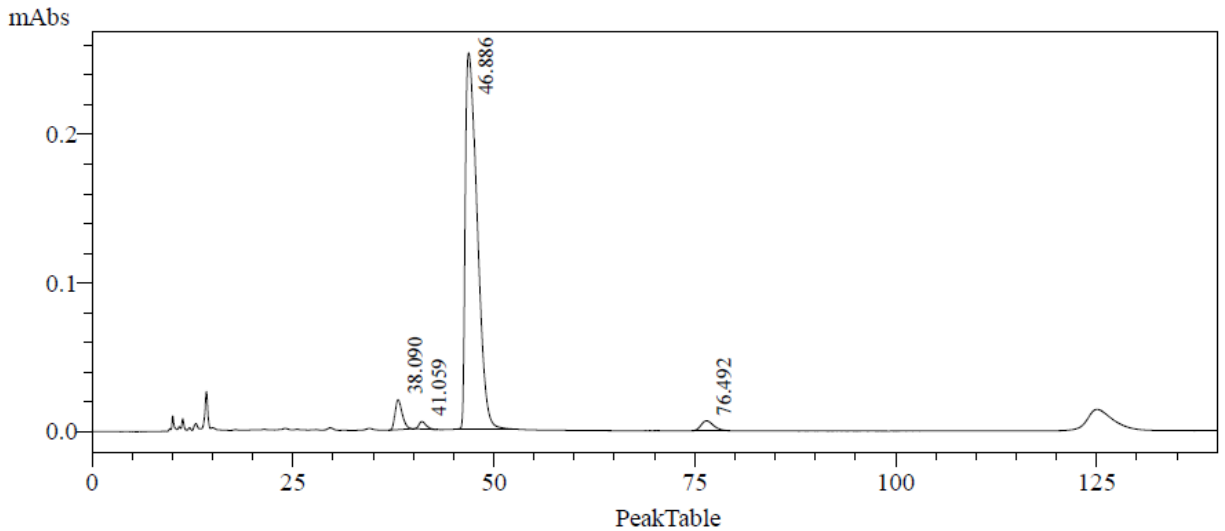


^{13}C-NMR (100MHz, $CDCl_3$, 25ºC)

Reaction under flow condition (Cycle 2)

Representative example: The residence time (hold-up volume divided by the flow rate) is expressed as multiple of V. The residence time of 140 min (flow rate = 1 μl.min^{-1}) corresponds V_0=1. To reach steady state regime it is necessary V > 8 (ca. 19h). Enantiomeric excess, diastereoisomeric ratio and conversion were determined at the same run by HPLC. A representative chromatogram using the three dimensional system V_0 = 9, (dr: 96:4, ee: 95, conv.: 94). **First dimension**: In the Microreactor Column SiO_2-**4b** were reacted the nitroolefin (0.25 mmol, 1.0 equiv., 0.25M) and the aldehyde (0.75 mmol, 3.0 equiv., 0.75 M) using *n*-hexane/*i*-PrOH 90:10 as solvent. **Second dimension**: Column SiO_2-**4b**-Boc, *n*-hexane/*i*-PrOH 90:10, 25°C) at 0.5 ml/min, UV detection at 254 nm. **Third dimension**: Chiralpak OD-H (*n*-hexane/*i*-PrOH 90:10, 25°C) at 0.5 ml/min, UV detection at 254 nm. This integration was possible by means of a system of two valves of six ports.



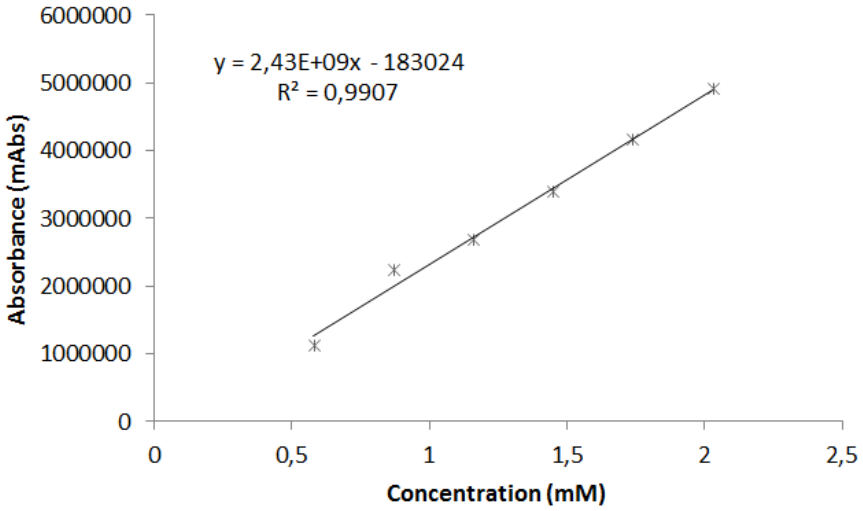


PeakTable

Peak#	Ret. Time	Area	Height	Area %	Height %
1	38.090	1226884	20045	4.348	7.038
2	41.059	303831	4999	1.077	1.755
3	46.886	25947249	252945	91.947	88.810
4	76.492	741855	6829	2.629	2.398
Total		28219819	284817	100.000	100.000

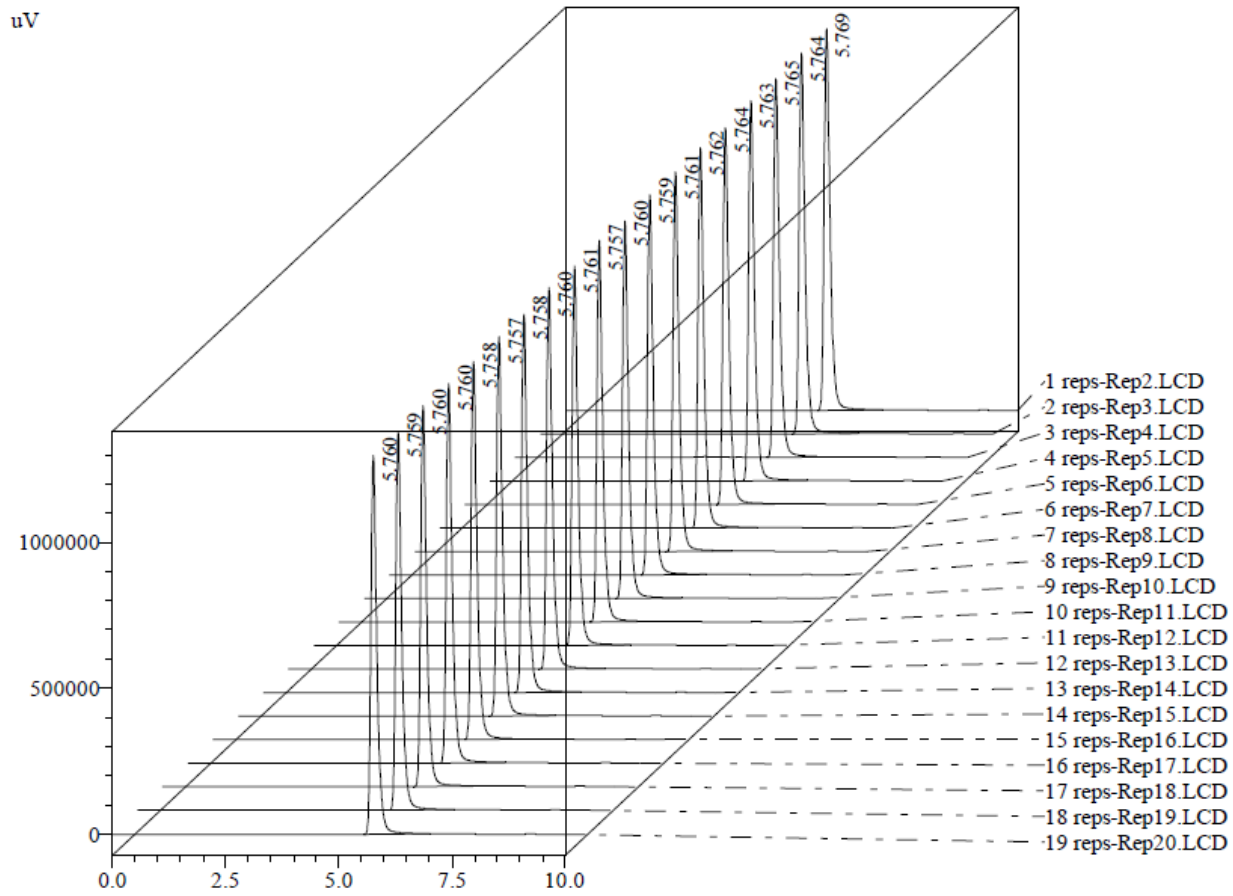
Calibration curve for racemic product 5a

An external standard calibration curve was built for the racemic product **5a**. Six calibrations points were prepared, in ethanol, at the follow concentrations: 0.058, 0.087, 0.116, 0,145, 0.174 and 0.203 M. 10 µL of each sample were injected monitoring the compound **5a** by UV at 254nm.



Evaluation of HPLC column SiO_2-4b-Boc

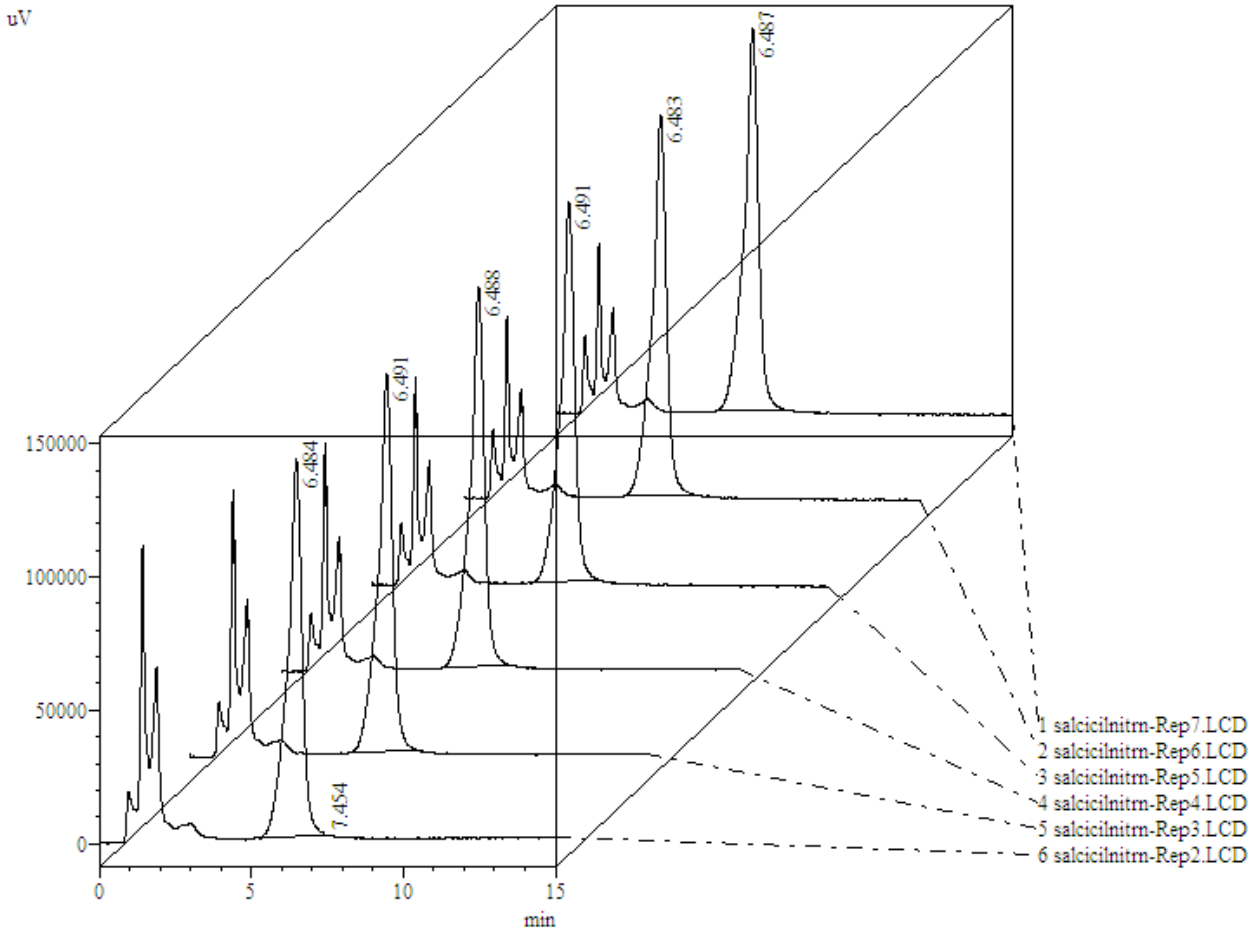
The evaluation of *column SiO_2-4b-Boc* injector was made by multiple injections of a homogeneous sample, using a standard solution of *trans*-4-methoxy-β-nitrostyrene and an autosampler. The RSD ≤ 1% for the retention time and area indicates an excellent precision and injection *repeatability. Also an excellent peak shape was observed due to the symmetry and almost no tailing of chromatographic band.*



Title	Ret. Time	Area
reps-Rep2.LCD	5.769	12172024
reps-Rep3.LCD	5.764	12188649
reps-Rep4.LCD	5.765	12228572
reps-Rep5.LCD	5.763	12203840
reps-Rep6.LCD	5.764	12185440
reps-Rep7.LCD	5.762	12159664
reps-Rep8.LCD	5.761	12210066
reps-Rep9.LCD	5.759	12248341
reps-Rep10.LCD	5.760	12189579
reps-Rep11.LCD	5.757	12250754
reps-Rep12.LCD	5.761	12208173
reps-Rep13.LCD	5.760	12240995
reps-Rep14.LCD	5.758	12188119
reps-Rep15.LCD	5.757	12203777
reps-Rep16.LCD	5.758	12227512
reps-Rep17.LCD	5.760	12172549
reps-Rep18.LCD	5.760	12202516
reps-Rep19.LCD	5.759	12165998
reps-Rep20.LCD	5.760	12189151
Average	5.761	12201880
%RSD	0.051	0.223
Standard Deviation	0.003	27214

Evaluation of Valve (2nd dimension) as injector

The evaluation of valve I as injector was made by multiple injections of a homogeneous sample, using a standard solution of *trans*-2-hydroxy-β-nitrostyrene. The RSD ≤ 1% for the retention time and area indicates an excellent precision and injection *repeatability.*



Title	Ret. Time	Area
salcicilnitrn-Rep7.LCD	6.483	2596388
salcicilnitrn-Rep6.LCD	6.482	2589849
salcicilnitrn-Rep5.LCD	6.489	2587269
salcicilnitrn-Rep4.LCD	6.485	2578658
salcicilnitrn-Rep3.LCD	6.488	2574068
salcicilnitrn-Rep2.LCD	6.480	2575178
Average	6.485	2583568
%RSD	0.051	0.347
Standard Deviation	0.003	8969

Conclusion

A combination of multicomponent reaction and organosilane chemistry was successfully applied to achieve organocatalysts with suitable appendage for immobilization onto silica.

Four silylated prolyl-peptide catalysts were produced by means of the Ugi-4CR through variation of the oxo, the amine and the isocyanide components. They were all grafted onto HPLC silica and after batch screening for the heterogeneous catalytic Michael addition.

Those catalysts showed high catalytic efficiency, excellent stereoselectivity and reproducibily in the organocatalytic conjugates addition for a series of aldehydes to nitroolefins and results very silimilar compared whit the homogeneous analogous catalyst.

The use of microreactors associated to multidimensional chromatography, comprehending: a microreactor was coupled to a chromatographic column for the separation of remaining substrates from the Michael adduct at the second dimension, followed by a chiral polysaccharide column for analysis of conversion and stereoselectivity that allows the on-line monitoring outcome flow in real time, permitting better comprehension of the reactional system and faster optimization of reaction parameters.

Minor changes in the instrumental setup can be easily done, enabling a series of different experimental e.g. high throughput screening of new catalysts, high throughput screening of a reational scope, tandem reaction.

The exploitation of the multicomponent reaction chemical efficiency combined with heterogenizable organocatalysts and the design of the multidimensional platform represent a powerful tool and important innovation that may encourage further progress in the field of flow catalysis.

References

[1] WHITE CA, SUBRAMANIAN G. “An Introduction to Enantioseparation by Liquid Chromatography.” In: Subramanian G, editor. “A Practical Approach to Chiral Separations by Liquid Chromatography”. Volume 1. Weinheim.: Wiley-VCH; 1994. 1.

[2] BERTHOD A.”Chiral recognition mechanisms”. Anal. Chem. 2006;78:2093-9.

[3] KOSTYANOVSKY RG.”Louis Pasteur did it for us especially”. Mendeleev Commun. 2003:85-90

[4] KOTAKE M, SAKAN T, NAKAMURA N, SENOH S. Resolution into optical isomers of some amino acids by paper chromatography. J. Am. Chem. Soc. 1951;73:2973-4

[5] DALGLIESH CE. Optical resolution of aromatic amino acids on paper chromatograms. J. Chem. Soc. 1952:3940-2

[6] IUPAC Compendium of Chemical Terminology (the "Gold Book"), 2nd Edition (Eds.: A. D. McNaught, A. Wilkinson), Blackwell Scientific Publications, Oxford, **1997**.

[7] GIACALONE F., GRUTTADAURIA M., AGRIGENTOA P., NOTOA R. “Low-loading asymmetric organocatalysis” Chem. Soc. Rev.**,** 2012,**41**, 2406-2447

[8] D. W. C. MACMILLAN, K. A. AHRENDT; C. J. BORTHS, "New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels-Alder Reaction". J. Am. Chem. Soc. 122 (17): 4243–4244. 2000.

[9] Scifinder, version 2007.1; Chemical Abstracts Service: Columbus, OH, 2007; (accessed Aug 13, 2014).

[10] D. W. C. MACMILLAN, “Commentary The advent and development of organocatalysis”, Nature **455**, 304-308, 2008.

[11] “Merck Announces Second Quarter 2011 Financial Results ” 2011.

[12] BØGEVIG, A,. JUHL, K., KUMARAGURUBARAN, N., ZHUANG, W.,JØRGENSEN, K. A., "Direct Organo-Catalytic Asymmetric α-Amination of Aldehydes—A Simple Approach to Optically Active α-Amino Aldehydes, α-Amino Alcohols, and α-Amino Acids” Angew. Chem. Int. Ed. **41**, 10, 2002

[13] LIST, B.,“Direct Catalytic Asymmetric α-Amination of Aldehydes” J. Am. Chem. Soc, **124**,20, 5656–5657., 2002

[14] FRANZÉN, J., MARIGO, M., FIELENBACH, D., WABNITZ, T. C., KJÆRSGAARD, F., JØRGENSEN, K.A., “A General Organocatalyst for Direct α-Functionalization of Aldehydes: Stereoselective C−C, C−N, C−F, C−Br, and C−S Bond-Forming Reactions. Scope and Mechanistic Insights” J. Am. Chem. Soc. 127, 51, 18296-18304, 2005.

[15] SEEBACH, D., BECK, ALBERT K., BADINE, D. MICHAEL., LIMBACH, M., ESCHENMOSER, A., TREASURYWALA, ADI M., HOBI, R., PRIKOSZOVICH, W. AND LINDER, B.,, “Are Oxazolidinones Really Unproductive, Parasitic Species in Proline Catalysis? – Thoughts and Experiments Pointing to an Alternative View”. HCA, **90**: 425–471, 2007

[16] DINÉR, P., KJÆRSGAARD, A., LIE, M.A., AND JØRGENSEN, K.A." On the Origin of the Stereoselectivity in Organocatalysed Reactions with Trimethylsilyl-Protected Diarylprolinol" Chem. Eur. J., **14**, 122, 2008 .

[17] HOUK, K. N., CHEONG, P. H.-Y.,, "Computational prediction of small-molecule catalysts" Nature 455, 309-313, 2008.

[18] PUGLISIS, M. BENAGLIA, V. CHIROLI, ``Organic reactions promoted by immobilized chiral catalysts in continuous flow systems´´ Green Chem. **15**, 1790–1813, 2013.

[19] T. TSUBOGO, T. ISHIWATA, S. KOBAYASHI, `` Asymmetric Carbon–Carbon Bond Formation under Continuous-Flow Conditions with Chiral Heterogeneous Catalysts´´Angew. Chem. Int. Ed. **52**, 6590 –6604, 2013.

[20] E. ALZA, C. RODRIGUEZ-ESCRICH, S. SAYALERO, A. BASTERO, M. A. PERICAS``A Solid-Support ed Organo catalyst for Highly Stereoselec tive, Batch, and Continuo us-Flow Mannich Reactions´´ Chem. Eur. J. **15**, 10167-10172, 2009.

[21] X.C. CAMBEIRO, R. MARTÍN-RAPÚN, PEDRO O. MIRANDA1 , S. SAYALERO, E. ALZA, P. LLANES, M. A. PERICÀS, ``Continuous-flow enantioselective α-aminoxylation of aldehydes catalyzed by a polystyrene-immobilized hydroxyproline´´ Beilstein J. Org. Chem. **7**, 1486–1493, 2011.

[22] X. FAN, S. SAYALERO, M. A. PERICÀS ``Asymmetric a-Amination of Aldehydes Catalyzed by PS-Diphenylprolinol Silyl Ethers: Remediation of Catalyst Deactivation for Continuous Flow Operation´´ Adv. Synth. Catal. **354**, 2971 – 2976, 2012.

[23] . ALZA, E., SAYALERO, S, CAMBEIRO, X. C., MARTÍN-RAPÚN, R. , MIRANDA, P. O., PERICÀS, M. A. "Catalytic Batch and ContinuousFlow Production of Highly

Enantioenriched Cyclohexane Derivativeswith Polymer-Supported Diarylprolinol Silyl Ethers" Synlett, **4**, 464-468 2011.

[24] P. KRATTIGER, R. KOVASY, J. D. REVELL, S. IVAN, H. WENNEMERS, "Increased Structural Complexity Leads to Higher Activity: Peptides as Efficient and Versatile Catalysts for Asymmetric Aldol Reactions" Org. Lett. 7 (6), 1101-1103, 2005.

[25] J. D. REVELL, D. GANTENBEIN, P. KRATTIGER, H. WENNEMERS, "Solid-Supported and Pegylated H–Pro–Pro–Asp–NHR as Catalysts for Asymmetric Aldol Reactions" Biopolymers (Peptide Science) DOI 10.1002/bip

[26] ARAKAWA, Y. AND WENNEMERS, H., "Enamine Catalysis in Flow with an Immobilized Peptidic Catalyst." ChemSusChem, **6**: 242–245, 2013.

[27] P. KASAPLAR, C. R. ESCRICH, M. A. PERICÀS, ``Continuous Flow, Highly Enantioselective Michael Additions Catalyzed by a PS-Supported Squaramide´´ Org. Lett., 15, 3498–3501, 2013.

[28] V. CHIROLI, M. BENAGLIA, F. COZZI, A. PUGLISI, R. ANNUNZIATA, G. CELENTANO, ``Continuous-Flow Stereoselective Organocatalyzed Diels Alder Reactions in a Chiral Catalytic "Homemade" HPLC Column´´ Org. Lett., **15**, 3590–3593, 2013.

[29] CHIROLI, V., BENAGLIA, M., FRANCO COZZI, F., PUGLISI, A., ANNUNZIATA, R., CELENTANO, G., "Continuous-Flow Stereoselective Organocatalyzed Diels–Alder Reactions in a Chiral Catalytic "Homemade" HPLC Column"

Organic Letters **15**, 14, 3590-3593, 2013

[30] A. ZAMBOULIS, N. J. RAHIER, M. GEHRINGER, X. CATTOËN, G. NIEL, C. BIED, J. J. E. MOREAU AND M. WONG CHI MAN, "`Silica-supported L-proline organocatalysts for asymmetric aldolisation" Tetrahedron-Asymmetry*.,* **20**, 2880-2885, 2009.

[31] O. BORTOLINI, L. CACIOLLI, A. CAVAZZINI, V. COSTA, R. GRECO, A. MASSI, L. PASTI, ``Silica-supported 5-(pyrrolidin-2-yl)tetrazole: development of organocatalytic processes from batch to cont inuous-fl ow conditions´´ Green Chem., **14**, 992–1000, 2012.

[32] O. BORTOLINI, A. CAVAZZINI, P. GIOVANNINI, R. GRECO, N. MARCHETTI, A. MASSI, L. PASTI "A Combined Kinetic and Thermodynamic Approach for the Interpretation of Continuous-Flow Heterogeneous Catalytic Processes" Chem. Eur. J. **19**, 7802 – 7808, 2013.

[33] VILLAUME, M. T., BARAN, P. S., "Organic chemistry: Reactivity tamed one bond at a time" Nature **513**, 324–325, 2014

[34] ROTSTEIN, H. B., ZARETSKY, S., RAI, V.,YUDIN, A. K., "Small Heterocycles in Multicomponent Reactions"Chemical Reviews **114**, 16, 8323-8359, 2014

[35] DÖMLING, A., WANG, W., WANG, K., "Chemistry and Biology Of Multicomponent Reactions" Chemical Reviews **112**, 6, 3083-3135, 2012

[36] A. M. ROUHI, "Rediscovering Natural Products" Chem. Eng.,**81**, 41 77-107, 2003

[37] NEWMAN, D. J. , CRAGG, G. M., SNADER K. M., *J "Natural Products as Sources of New Drugs over the Period". Nat. Prod.*, ***66***, 1022-1037, 2003.

[38] CHÉRON, N., RAMOZZI, R., KAÏM, L., GRIMAUD, L., FLEURAT-LESSARD, P., “Challenging 50 Years of Established Views on Ugi Reaction: A Theoretical Approach” J. Org. Chem., **77** (3), 1361–1366, 2012.

[39] DE LA TORRE, A. F., RIVERA, D. G., FERREIRA, M. A. B. ARLENE G. CORRÊA, A. G., PAIXÃO, M. W., “Multicomponent Combinatorial Development and Conformational Analysis of Prolyl Peptide-Peptoid Hybrid Catalysts: Application in the Direct Asymmetric Michael Addition” *J. Org. Chem.*, 2013, **78** (20), pp 10221–10232

[40]a) Puglisis, A.; Benaglia, M.; Chiroli, V. *Green Chem.* **2013**, *15*, 1790-1813; b) Tsubogo, T.; Ishiwata, T.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 6590-6604; c) Kristensen, T. E.; Hansen, T. *Eur. J. Org. Chem.* **2010**, 3179-3204; d) Frost, C. G.; Mutton, L. *Green Chem.* **2010**, *12*, 1687-1703; d) Mak, X. Y.; Laurino, P.; Seeberger, P. H. *Beilstein J. Org. Chem.* **2009**, *5*, doi: 10.3762/bjoc.5.19.

[41]a) *Polymeric Chiral Catalyst Design and Chiral Polymer Synthesis*; Haraguchi, N.; Itsuno, S., Eds.; John Wiley & Sons Ltd.: Chichester, U.K., **2011**; b) *Recoverable and Recyclable* Catalysts, Benaglia, M., Ed.; John Wiley & Sons Ltd.: Chichester, U.K., **2009**.

[42].a) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17-57; b) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, *47*, 4583-4592; c) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38-54; d) Hartman, R. L.; McMullen, J. P.; Jensen, K. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7502-7519; e) Baxendale, I. R.; Hayward, J. J.; Lanners, S.; Ley, S. V.; Smith, C. D. In *Microreactors in Organic Synthesis and Catalysis*, Ed.; Wirth, T.; Wiley: New York, **2008**.

[43]a) Martín-Rapún, R.; Sayalero, S.; Pericàs, M. A. *Grenn Chem.* **2013**, *15*, 3295-3301; b) Arakawa, Y.; Wennemers, H. *ChemSusChem* **2013**, *6*, 242-245; c) Bortolini,

O.; Caciolli, L.; Cavazzini, A.; Costa, V.; Greco, R.; Massi, A.; Pasti, L. *Green Chem.* **2012**, *14*, 992-1000; d) Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericàs, M. A. *Org. Lett.* **2012**, *14*, 1816-1819; e) B. Ötvös, S.; Mandity, I. M.; Fulop, F. *ChemSusChem* **2012**, *5*, 266-269; f) Ayats, C.; Henseler, A. H.; Pericàs, M. A. *ChemSusChem* **2012**, *5*, 320-325; g) Massi, A.; Cavazzini, A.; Del Zoppo, L.; Pandoli, O.; Costa, V.; Pasti, L.; Giovannini, P. P. *Tetrahedron Lett.* **2011**, *52*, 619-622; h) Cambeiro, X. C.; Martín-Rapún, R.; Miranda, P. O.; Sayalero, S.; Alza, E.; Llanes, P.; Pericàs, M. A. *Beilstein J. Org. Chem.* **2011**, *7*, 1486-1493; i) Alza, E.; Rodríguez-Escrich, C.; Sayalero, S.; Bastero, A.; Pericàs, M. A. *Chem. Eur. J.* **2009**, *15*, 10167-10172.

[44]a) Chiroli, V.; Benaglia, M.; Puglisis, A.; Porta, R.; Jumde, R. P.; Mandoli, A. *Green Chem.* **2014**, *15*, 2798-2806; b) Chiroli, V.; Benaglia, M.; Cozzi, F.; Puglisis, A.; Annunziata, R.; Celentano, G. *Org. Lett.* **2013**, *15*, 3590-3593.

[45]de la Torre, A. F.; Rivera, D. G.; Ferreira, M. A. B.; Corrêa, A. G.; Paixão, M. W. *J. Org. Chem.* **2013**, *78*, 10221-10232.

[46]Brauch, S.; van Berkel, S. S.; Westermann, B. *Chem. Soc. Rev.* **2013**, *42*, 4948-4962; b) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083-3135; c) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem. Int. Ed*. **2011**, *50*, 6234-6246; d) Wessjohann, L. A.; Rivera, D. G.; Vercillo, O. E. *Chem. Rev.* **2009**, *109*, 796-814; e) El Kaïm, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153-2171; f) *Multicomponent Reactions*; Zhu, J.; Bienyamé, H., Eds.; Wiley-VCH: Weinheim, **2005**.

[47]For another report of Ugi-derived catalyst, see: A. Znabet, E. Ruijter, F. J. J. de Kanter, V. Köhler, M. Helliwell, N. J. Turner, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2010**, *49*, 5289-5292.

[48]a) Cassiano, N. M.; Barreiro, J. C.; Oliveira, R. V.; Cass, Q. *Bioanalysis* **2012**, *4*, 2737-2756; b) Simpkins, S. W.; Bedard, J. W.; Groskreutz, S. R.; Swenson, M. M.; Liskutin, T. E.; Stoll, D. R. *J. Chromatogr. A* **2010***, 1217*, 7648-7660.

[49]a) Puglisis, A.; Benaglia, M.; Annunziata, R.; Chiroli, V.; Porta, R.; Gervasini, A. *J. Org. Chem.* **2013**, *78*, 11326-11334; b) Monge-Marcet, A.; Cattoën, X.; Alonso, D. A.; Nájera, C.; Man, M. W. C.; Pleixats, R. *Green Chem.* **2012**, *13*, 1601-1601; c) Shi, J. Y.; Wang, C. A.; Li, Z. J.; Wang, Q.; Zhang, Y.; Wang, W. *Chem. Eur. J.* **2011**, *17*, 6206-6213; d) Jebors, S.; Enjalbal, C.; Amblard, M.; Mehdi, A.; Subra, G.; Martinez, J. *J. Mater. Chem. B* **2013**, *1*, 2921-2925.

[50]a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed*. **2000**, *39*, 3168-3210; b) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrücker, C. *Angew. Chem*. **1959**, *71*, 386

[51]a) Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 1871- 1874; b) Wiesner, M.; Revell, J. D.; Tonazzi, S.; Wennemers, H. *J. Am. Chem. Soc.* **2008**, *130*, 5610-5611; c) Wiesner, M.; Neuburger, M.; Wennemers, H. *Chem. Eur. J.* **2009**, *15*, 10103-10109; d) Wiesner, M.; Upert, G.; Angelici, G.; Wennemers, H. *J. Am. Chem. Soc.* **2010**, *132*, 6-7; e) Ramasastry, S. S. V.; Albertshofer, K.; Utsumi, N.; Barbas III, C. F. *Org. Lett.* **2008**, *10*, 1621-1624. g) Lipshutz, B. H.; Ghorai, S. *Org. Lett.* **2012**, *14*, 422-425. h) Vishnumaya, M. R.; Singh, V. K. *Org. Lett.* **2009**, *74*, 4289-4297.

[52]Bortolini, O.; Cavazzini, A.; Giovannini, P. P.; Greco, R.; Marchetti, N.; Massi, A.; Pasti, L. *Chem. Eur. J.* **2013**, *19*, 7802-7808.

[53]The term ‘three dimensional system’ refers to three orthogonal columns, one of the microreactor and two chromatographic columns. This concept is of common usage in chromatographic applications, see: IUPAC Compendium of Chemical Terminology

(the "Gold Book"), 2nd Edition (Eds.: A. D. McNaught, A. Wilkinson), Blackwell Scientific Publications, Oxford, **1997**.

[54]Heart-cut refers to the selection of a specific chromatographic band and its transfer to another column/dimension.

[55]Ramachary, D. B.; Prasad, M. S.; Madhavachary R.; *Org. Biomol. Chem.*, **2011**,9, 2715-2721

[56]a) Barros, M. T.; Phillips, A. M. F. *Eur. J. Org. Chem.* **2007**, 178-185; b) Betancort, J. M.; Barbas, C. F. *Org. Lett.* **2001**, *3*, 3737-3740; c) Cheng, Y.-Q.; Bian, Z.; He, Y.-B.; Han, F.-S.; Kang, C.-Q.; Ning, Z.-L.; Gao, L.-X. *Tetrahedron Asymm.* **2009**, *20*, 1753-1758; d) García-García, P., Ladépêche, A., Halder, R. and List, B., *Angew. Chem. Int. Ed.*, **2008**, 47, 4719-4721; e) Hayashi, Y., Itoh, T., Ohkubo, M. and Ishikawa, H., *Angew. Chem. Int. Ed.*, **2008**., 47, 4722-4724.

[57]Berry, M.; Champhaneira, R. K.; Howell, J. A. S. *J. Mol. Cat,* **1986**, *37*, 243-252.

[58]a) Barros, M. T.; Phillips, A. M. F. *Eur. J. Org. Chem.* **2007**, 178-185; b) Betancort, J. M.; Barbas, C. F. *Org. Lett.* **2001**, *3*, 3737-3740; c) Cheng, Y.-Q.; Bian, Z.; He, Y.-B.; Han, F.-S.; Kang, C.-Q.; Ning, Z.-L.; Gao, L.-X. *Tetrahedron Asymm.* **2009**, *20*, 1753-1758; d) García-García, P., Ladépêche, A., Halder, R. and List, B., *Angew. Chem. Int. Ed.*, **2008**, 47, 4719-4721; e) Hayashi, Y., Itoh, T., Ohkubo, M. and Ishikawa, H., *Angew. Chem. Int. Ed.*, **2008**., 47, 4722-4724. f) Ramachary, D. B., Prasad, M. S., Madhavachary R., Org. Biomol. Chem., **2011**, **9**, 2715-2721