



Trip Report for
“8th International Symposium on Carbanion Chemistry”
Madison, WI
June 6-10, 2007

Jianqing Chen and Charles R. Heap, Ph.D.

Abstract: *The “8th International Symposium on Carbanion Chemistry” was held at the Department of Chemistry, University of Wisconsin-Madison on June 6-10, 2007. There were approximately 140 attendees (80% from academia and 20% from industry) representing 16 countries. This symposium mostly featured lithium-carbanion chemistry, novel catalysts and new synthetic methods and their applications in the natural product synthesis. This report highlights selected material from information presented in seminars and post session.*

“Structure and Reactions of Chiral Alkalimetal Reagents,”

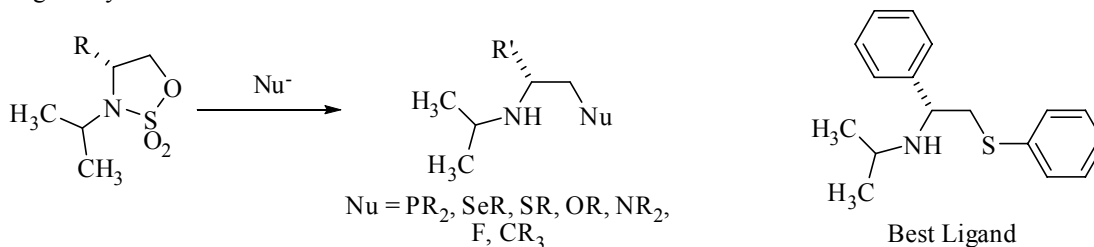
Goran Hilmersson (Goteborg University), Sweden.

Professor Hilmersson described his research into utilizing chiral lithium amides to control 1, 2-addition of organolithium reagents to aldehydes.¹ Research into optimizing the chiral lithium amide showed that an internal chelating atom was essential to good enantioselectivities. The best ligand is shown in Scheme 1 and was able to achieve ee's over 90% for the addition of methyl, *n*-butyl, and phenyl lithium into benzaldehyde and cyclohexylaldehyde with yields on the order of 80%. Modest ee's (ca. 75%) were also achieved for the addition of lithioacetonitrile. The initial studies were done utilizing four equivalents of the lithium amide and two equivalents of the alkyl lithium reagent, but on the larger scale these can be reduced. The chiral amine can be recovered in high yield. Extensive multi-nuclear NMR studies of the chiral lithium amide and alkyl lithium species utilizing ¹⁵N labeling showed the formation of mixed dimers.

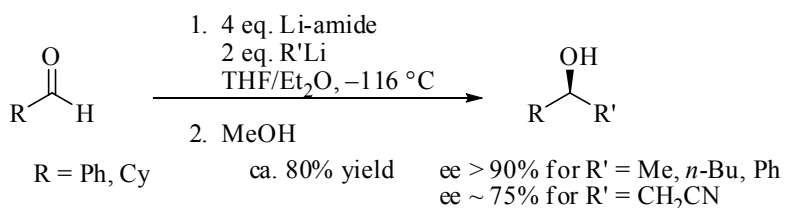
¹ Granander, J.; Eriksson, J.; Hilmersson, G. *Tetrahedron: Asymmetry*, **2006**, *17*, 2021.

Scheme 1 Hilmersson's use of Chiral Lithium Amides

Ligand Synthesis:



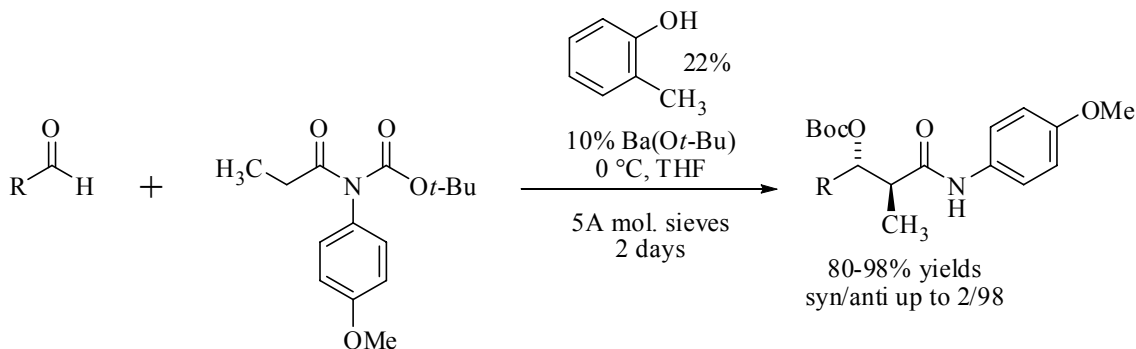
Enantioselective 1,2 addition:



“New Dimension in Lewis Acid and Brønsted Base Catalysis,”
Shu Kobayashi (University of Tokyo), Japan.

Professor Kobayashi described several projects from his research group which employ catalytic carbanion formation which could lead to less waste, fewer by-products, and easier purification. Barium phenoxide was found to catalyze a highly anti selective aldol reaction of amides and aldehydes in excellent yields (Scheme 2).²

Scheme 2 Phenoxide Catalyzed Aldol Reactions

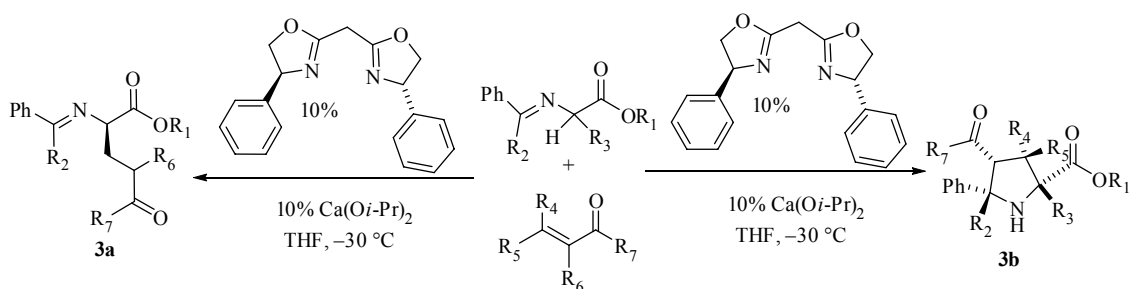


The Kobayashi group has also explored the catalytic asymmetric 1, 4-addition reactions of α -amino acid derivatives with α , β -unsaturated carbonyl compounds to afford chiral

² Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 8704.

glutamic acid derivatives (Scheme 3).³ This reaction utilizes ten mole percent of the “Box ligand” to form either glutamic acid derivatives **3a** or, in the case of less bulky substituents, **3b** which results from a formal [3+2] cycloaddition reaction. The products are formed in high yields (>80%) and selectivities (>80% ee’s).

Scheme 3
1, 4-Addition Reactions



“Freeze Frame Observation of Stereochemical Information Transfer to and from Tansiently Non-Racemic Enolates,”

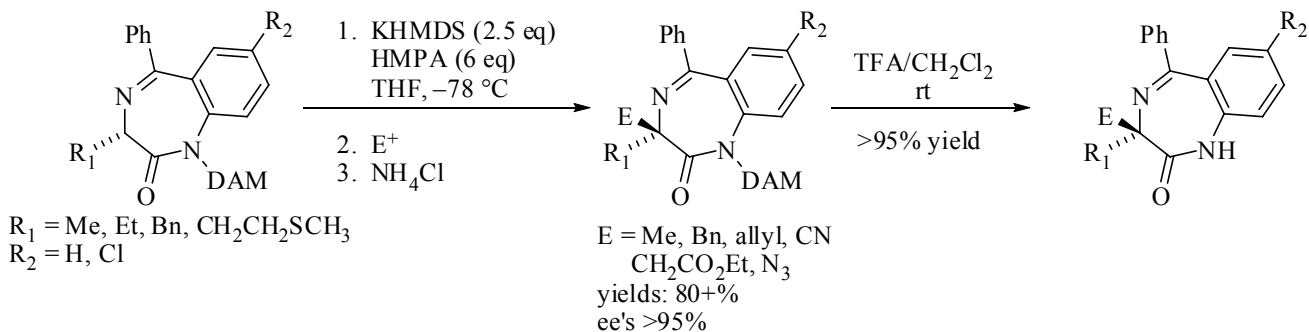
Paul Carlier (Virginia Tech).

Professor Carlier described work on “memory of chirality” which grew out of a desire to form benzodiazopines with quaternary centers.⁴ Many benzodiazopines have been synthesized and studied by medicinal chemists but, because they are most often made from chiral alpha-amino acids, very few structures with quaternary centers have been prepared. Deprotonation of the carbon adjacent to the amide carbonyl under standard conditions forms an enantiopure, conformationally chiral enolate which racemizes slowly when compared to the rate of alkylation, as long as the substituent on N1 is sufficiently bulky. Early work focused on the isopropyl substituent which gave good selectivities but was difficult to remove. Carlier’s group has reported the use of the DAM (di-(*p*-anisyl) methyl) group which gave higher selectivities and is easily cleaved under acidic conditions.

³ Saito, S.; Tsubogo, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2007**, *129*, 5364-5365.

⁴ Carlier, P.R.; Zhao, H.; MacQuarrie-Hunter, S.L.; DeGuzman, J.C.; Hsu, D.C. *J. Am. Chem. Soc.* **2006**, *128*, 15215-15220.

Scheme 4
Alkylation via a Conformationally Chiral Enolate



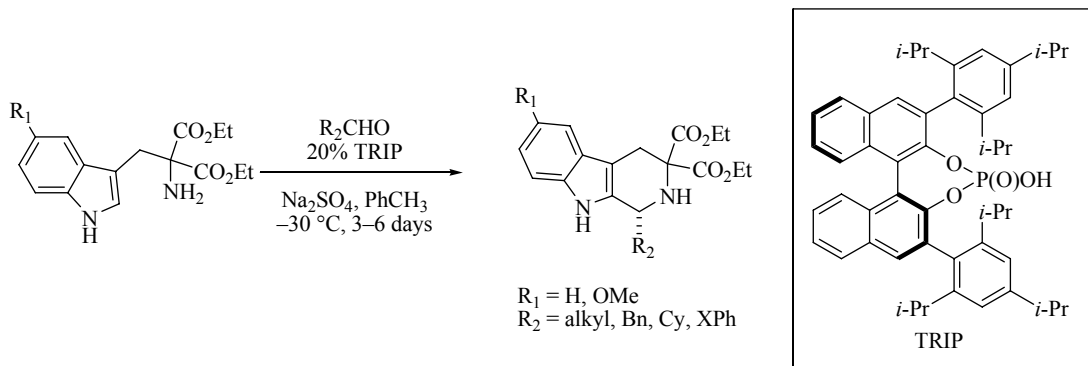
“Enamine Catalysis is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents,”

Benjamin List (Max Planck Institute), Germany.

Professor List's group works in the area of organocatalysis which can be considered as a third major approach toward asymmetric catalysts after enzymes and metals. Professor List described several projects in the area of enamine catalysis. One of the projects involved the development of a catalytic asymmetric Pictet-Spengler reaction.⁵ After an initial observation that TFA catalyzed the Pictet-Spengler reaction of gem di-substituted tryptamines, the List group screened chiral organic Brønsted acids to be used as asymmetric catalysts. The best catalyst was found to be a binaphthol substituted phosphoric acid termed TRIP. This catalyst has proven very general and will soon be available from Aldrich. With the optimal catalyst in hand, the asymmetric Pictet-Spengler reaction has proven to be fairly general with yields and enantiomeric excesses generally >80%. One potential liability for the List chemistry is the requirement of the geminal disubstitution.

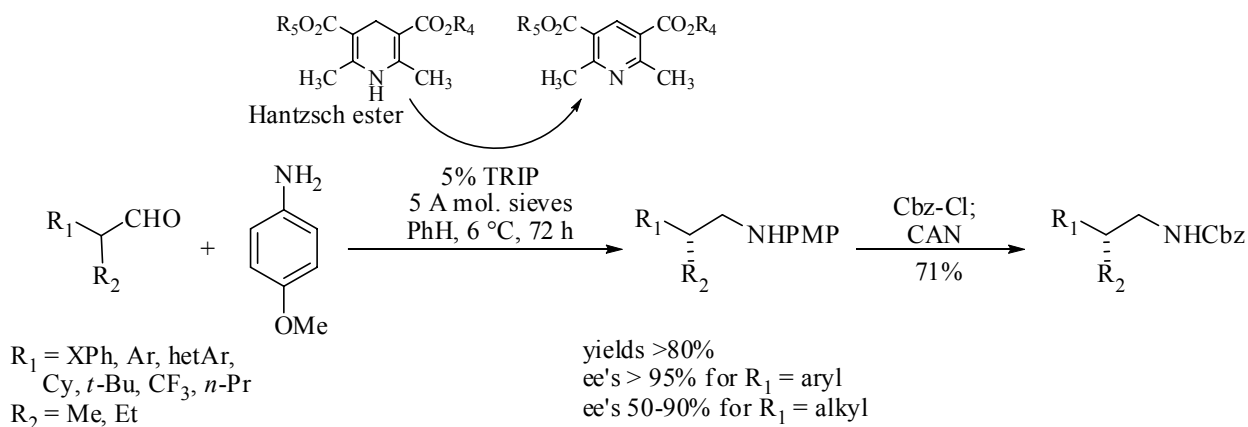
⁵ Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086-1087.

Scheme 5 Asymmetric Pictet-Spengler Reaction



Professor List also described the catalytic asymmetric reduction of aldehydes via dynamic kinetic resolution, utilizing the TRIP catalyst described above.⁶ This work was based upon the hypotheses that one enantiomer of the intermediate imine would be reduced by the chiral catalyst preferentially and that the chiral center adjacent to the imine would undergo rapid racemization under the reaction conditions via the enamine. The List group employed the Hantzsch ester, termed the “chemist’s NADH”, as the stoichiometric oxidant. After considerable optimization, this reaction was found to give very good results (>80% yields, ee’s >95%) for substituted phenyl, aryl, and heteroaryl substituents. More modest results were obtained in the cases of alkyl substituents but further work is on going. The paramethoxyphenyl protective group is readily removed by alkylation with Cbz-Cl followed by oxidation with CAN.

Scheme 6 Asymmetric Reductive Amination via Dynamic Kinetic Resolution.



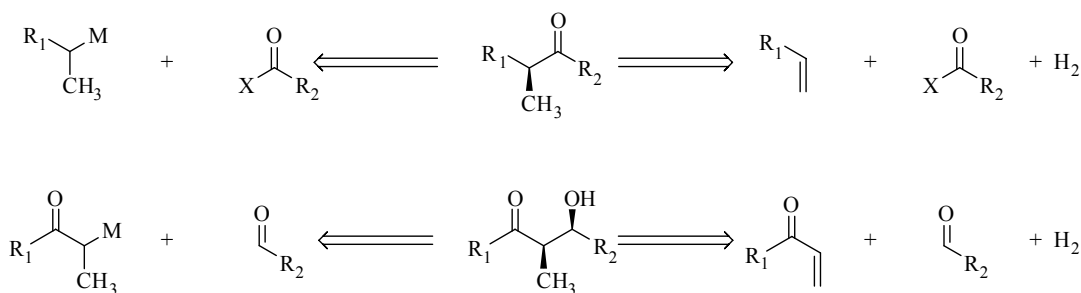
⁶ Hoffman, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074-13075. .

“Formation of C-C bonds via Catalytic Hydrogenation,”

Michael J. Krische (University of Texas at Austin).

Professor Krische described work on reductive carbon-carbon forming reactions which represents a new paradigm in the synthesis of organic molecules.⁷ Classical approaches toward the unsymmetrical ketone targets shown in scheme 7 require the generation of stoichiometric organometallic species which limit the allowable functionality of the reactants. With reductive carbon-carbon bond formation, the organometallic species is formed only transiently and the Krische group has found a large variety of functional groups are tolerated, including nitro groups, alkenes, and alkynes. Reductive carbon-carbon bond formation has the added bonus of replacing expensive, potentially pyrophoric reagents with hydrogen, one of the least expensive reagents available.

Scheme 7 Reductive C-C Bond Formation: A New Paradigm



The Krische group has demonstrated a wide variety of reactions of this type. A few recent examples are detailed in this report. Catalytic hydrogenation of 1, 3-diynes and ethyl glyoxylate in the presence of rhodium and a chiral binaphthol ligand generates chiral α -hydroxyl esters in good yields and selectivities (Scheme 8, reaction A).⁸ In all cases reported, the diyne reacts at the end with the silyl group, presumably due to back-bonding stability.

The Krische group has also demonstrated the reaction of 1, 3-eneynes with a variety of heteroaromatic aldehydes and ketones to afford chiral alcohols in good yields and excellent enantioselectivities (Scheme 8, reaction B).⁹ In these reactions, a catalytic amount of acid serves to dramatically speed up the reaction.

Anhydrides have been found to react with styrenes or norbornene to form α -methyl ketones (Scheme 8, reaction C).¹⁰ Aromatic, heteroaromatic, and α , β -unsaturated anhydrides all couple in good yields and selectivities. Simple alkenes and aliphatic anhydrides gave lower yields and selectivities for this reaction. Surprisingly, however,

⁷ Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem.* **2007** *72*, 1063.

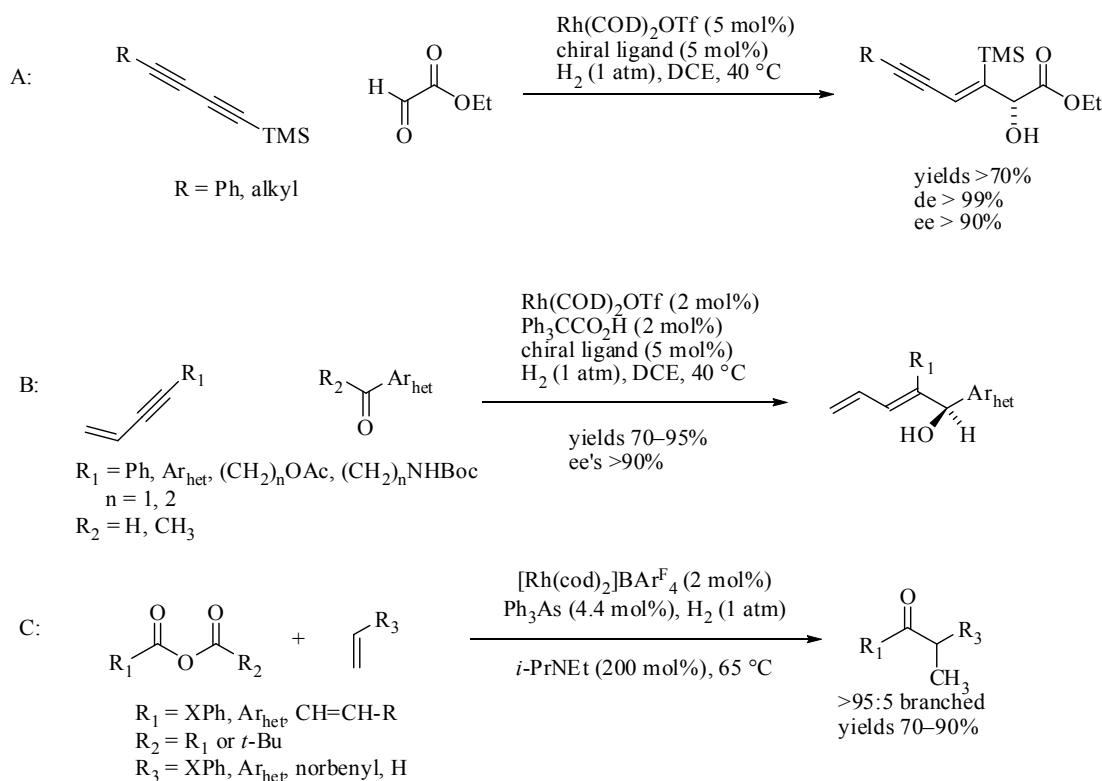
⁸ Cho, C. W.; Krische, M. J. *Organic Letters*, **2006**, 3873-3876.

⁹ Komanduri, V.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 16448-16449.

¹⁰ Hong, Y. T.; Barchuk, A.; Krische, M. J. *Angew. Chem. I. E.* **2006**, *45*, 6885-6888.

ethylene gas can be used to generate ethyl ketones, potentially replacing diethyl zinc. Mixed anhydrides involving an α , β -unsaturated acid condensed with pivalic acid showed only incorporation of the α , β -unsaturated portion and retained the high selectivities for the branched products.

Scheme 8 Recent Examples of Reductive C-C Bond Formation

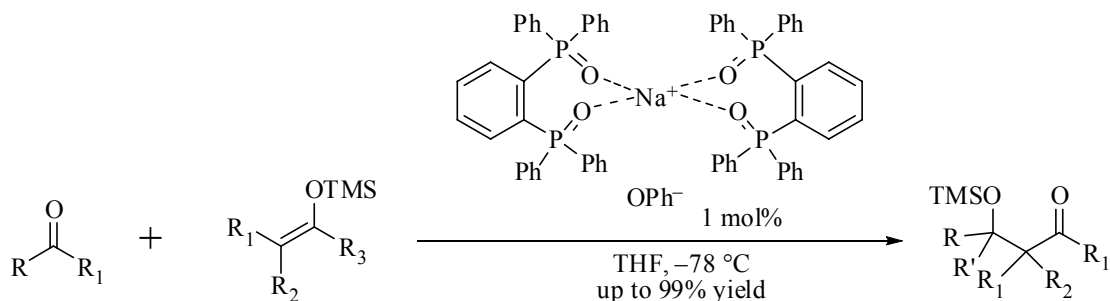


“Sodium Phenoxide-Phosphine Oxides as Extremely Active Lewis Base Catalysts for the Mukaiyama Aldol Reaction with Ketones to Generate Vicinal Quaternary Carbon Centers.”

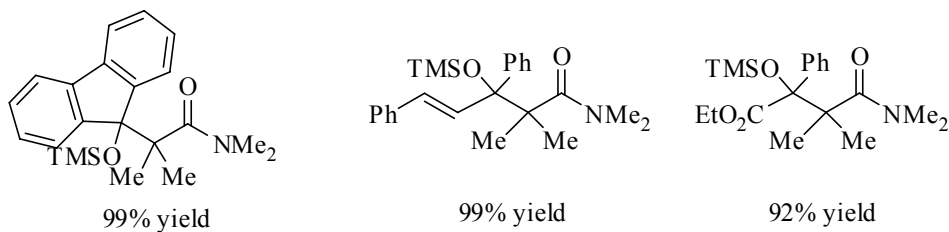
Kazuaki Ishihara, Manabu Hatano, and Eri Takagi (Nagoya University), Japan.

Professor Ishihara described a phenoxide catalyzed Mukaiyama aldol reaction between ketones and TMS-enolates which generates quaternary carbon centers in high yields. Previous reports of Lewis base-catalyzed Mukaiyama aldol reactions of ketones required stoichiometric TMS-activators because of the lower reactivity of ketones as compared to aldehydes.

Scheme 9
Phenoxide/Phosphine Oxide Catalyzed Mukaiyama Aldol Reaction



Examples:



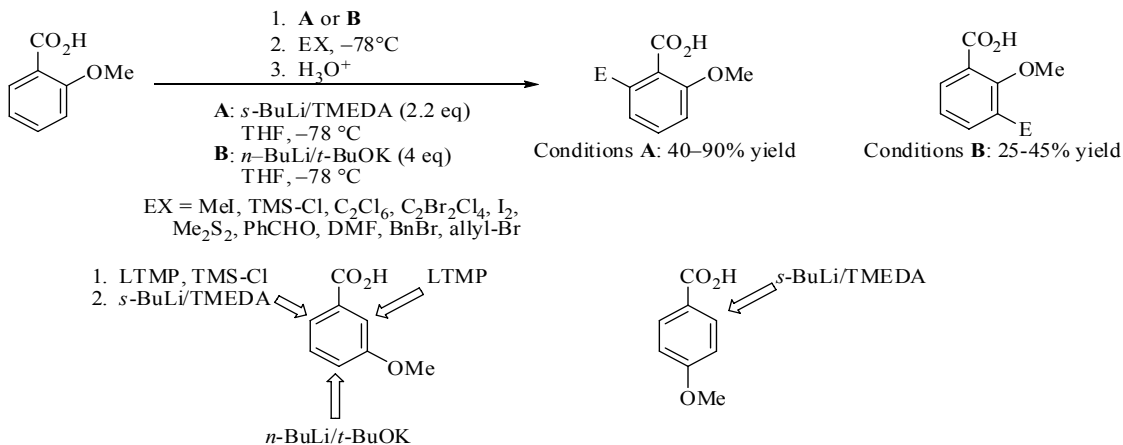
“Tuning of Selectivities in the Metalation of Benzoic Acids by an Appropriate Choice of the Base,”

Jacques Mortier (University of Maine and CNRS), France.

Professor Mortier discussed the use of an unprotected carboxylic acid moiety in directed ortho-metalation (DoM) reactions.¹¹ *N,N*-Dialkylamides have proven to be very effective directors of metalation but require very harsh conditions for hydrolysis. The Mortier group has demonstrated that a free carboxylic acid can function as a moderate director of lithiation, allowing for regio-flexibility to provide very useful synthetic intermediates. Treatment of 2-methoxybenzoic acid with *s*-BuLi/TMEDA at -78°C followed by trapping with an electrophile affects substitution *ortho* to the acid group. Alternatively, deprotonation with *n*-BuLi/*t*-BuOK followed by trapping primarily affords the substitution at the 3 position. The change of the regioselectivity is attributed to the ability of *t*-BuOK to break up the intramolecular solvation of the lithium, allowing deprotonation to occur adjacent to the most electronegative substituent. Studies on other isomers of methoxybenzoic acid as well as biphenyls were also discussed.

¹¹ Nguyen, T. H.; Castanet, A. -S.; Mortier, J. *Org. Lett.* **2006**, *8*, 765-768.

Scheme 10
Free Carboxylic Acid Moiety in DoM Reactions



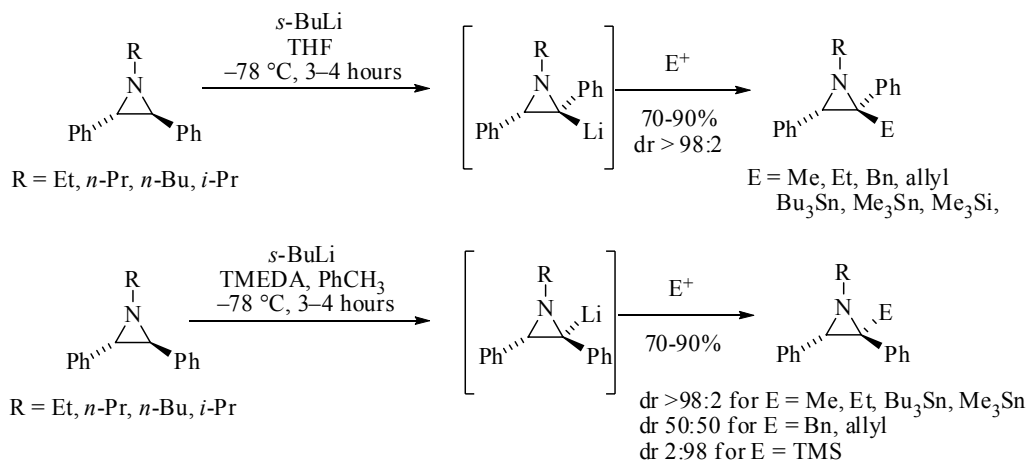
“Regioselective Lithiation of Aziridines: Synthetic Applications and NMR Structural Investigation,”

Renzo Luisi (University of Bologna), Italy.

Professor Luisi described “Aziridinyl Anion Methodology” (AAM) in which lithiation and trapping of an unactivated aziridine can give either diastereomer selectively depending upon the reaction solvent.¹² Treatment of the *trans* aziridine with *sec*-butyl lithium in THF effects deprotonation with inversion of configuration which is followed by trapping with an electrophile to form the product with the phenyl groups *cis* to one another. This reaction gave good yields and high selectivities for all of the electrophiles studied. When the reaction solvent is switched to a non-polar solvent such as toluene, diethyl ether, or hexanes, the carbon-lithium bond is less covalent, allowing the equilibration to the thermodynamically preferred *trans* isomer, resulting in the formation of products with the phenyl groups *trans* to one another. This reaction occurred in good yields and with generally good selectivities, depending upon the electrophile. In the cases of trapping with allyl or benzyl, the diastereoselectivity was essentially 1:1, most likely due to a competing single electron transfer mechanism. In the case of trapping with trimethylsilyl, a complete inversion of diastereoselection was observed. Multi-nuclear NMR studies of the lithiated intermediates were used to confirm the formation of two differently configured intermediates.

¹² Luisi, R.; Capriati, V.; Florio, S.; Musio, B. *Org. Lett.* **2007**, *9*, 1263-1266.

Scheme 11
Regioselective Lithiation of Aziridines



“Highly Stereoselective Reactions of Sulfinyl Derivatives,”

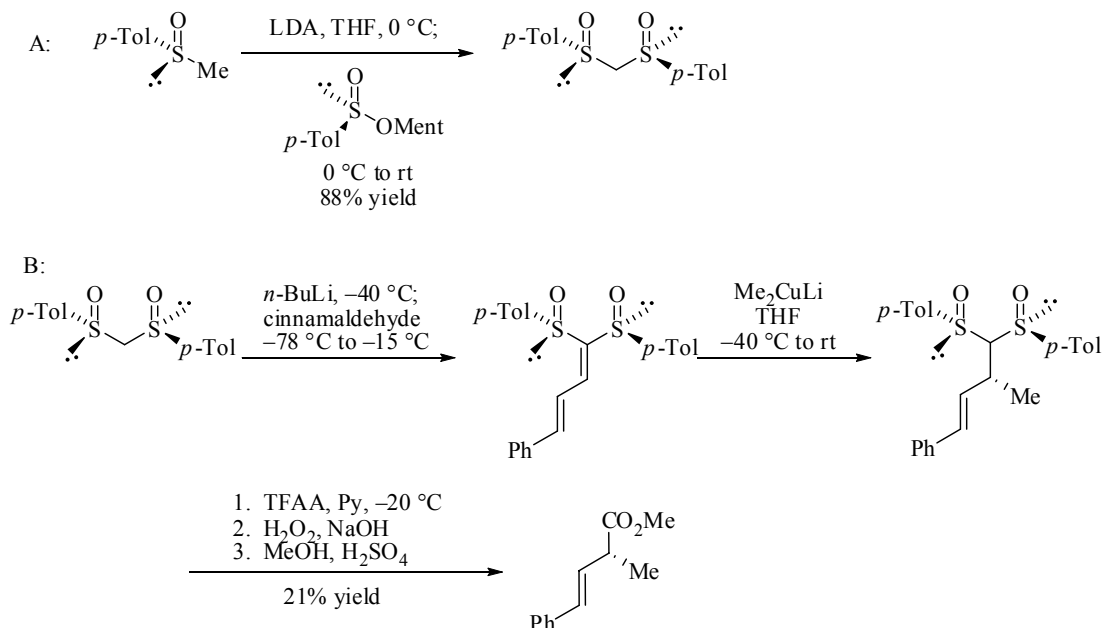
Max Malacria (Pierre et Marie Curie University), Paris.

Professor Malacria described several reactions of chiral sulfinyl derivatives to produce interesting synthetic intermediates.¹³ The enantiopure bis-sulfinyl reagent can be readily prepared in multi-gram quantities (Scheme 12, line A). Condensation with cinnamaldehyde followed by reaction with dimethylcuprate gave exclusively the 1, 4-addition product as a single diastereomer in quantitative yield (Scheme 13, line B).¹⁴ A two-step oxidative cleavage of the bis-sulfinyl moiety followed by esterification afforded the chiral α -methyl ester in 21% yield.

¹³ Brebion, F.; Goddard, J.-P.; Gomez, C.; Fensterbank, L.; Malacria, M. *Synlett*, **2006**, 715-716.

¹⁴ Brebion, F.; Goddard, J.-P.; Gomez, C.; Fensterbank, L.; Malacria, M. *Synthesis* **2005**, 2449-2452.

Scheme 12
Chiral Sulfinyl Groups to Control Stereochemistry of 1, 4-addition

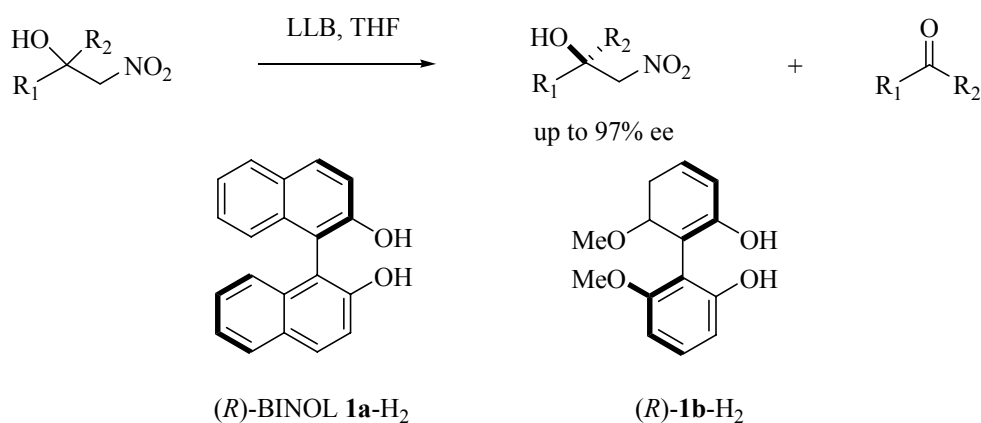


“Asymmetric Catalysis Using Lewis Acid-Brønsted Base Complexes,”

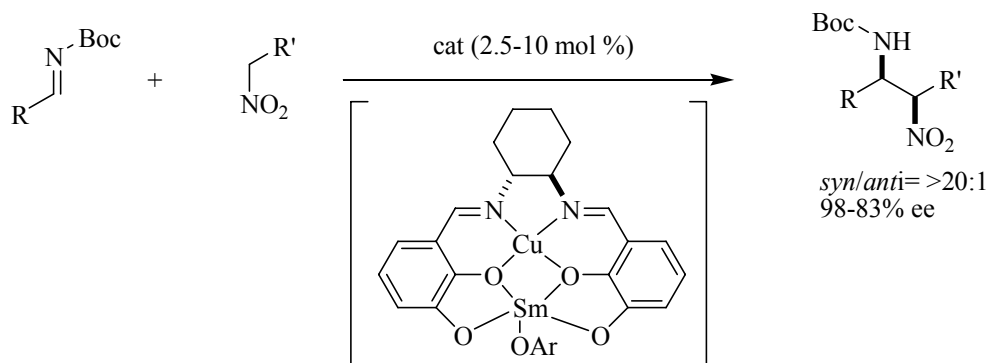
Masakatsu Shibasaki (*Graduate School of Pharmaceutical Sciences, The University of Tokyo, Japan*).

Professor Shibasaki gave a presentation on the catalytic asymmetric carbon-carbon bond-forming reactions using Lewis acid-Brønsted base complexes such as (1) catalytic kinetic resolution of *tert*-nitroaldol, (2) *syn*-selective catalytic asymmetric nitro-Mannich reaction, and (3) catalytic asymmetric cyclopropanation.

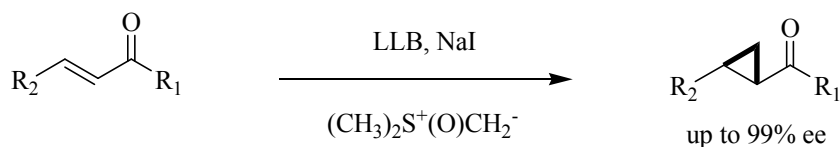
- (1) A kinetic resolution of tertiary nitroaldols derived from simple ketones. Mixed La-Li heterobimetallic complexes had the best selectivity (80-97% ee with 30-47% recovery yield).



(2) A Cu(I)-catalyzed enantioselective Mannich reaction of simple ketoimines. The reaction is a platform for the synthesis of optically active β,β -disubstituted amino acids, which are important building blocks in many fields.



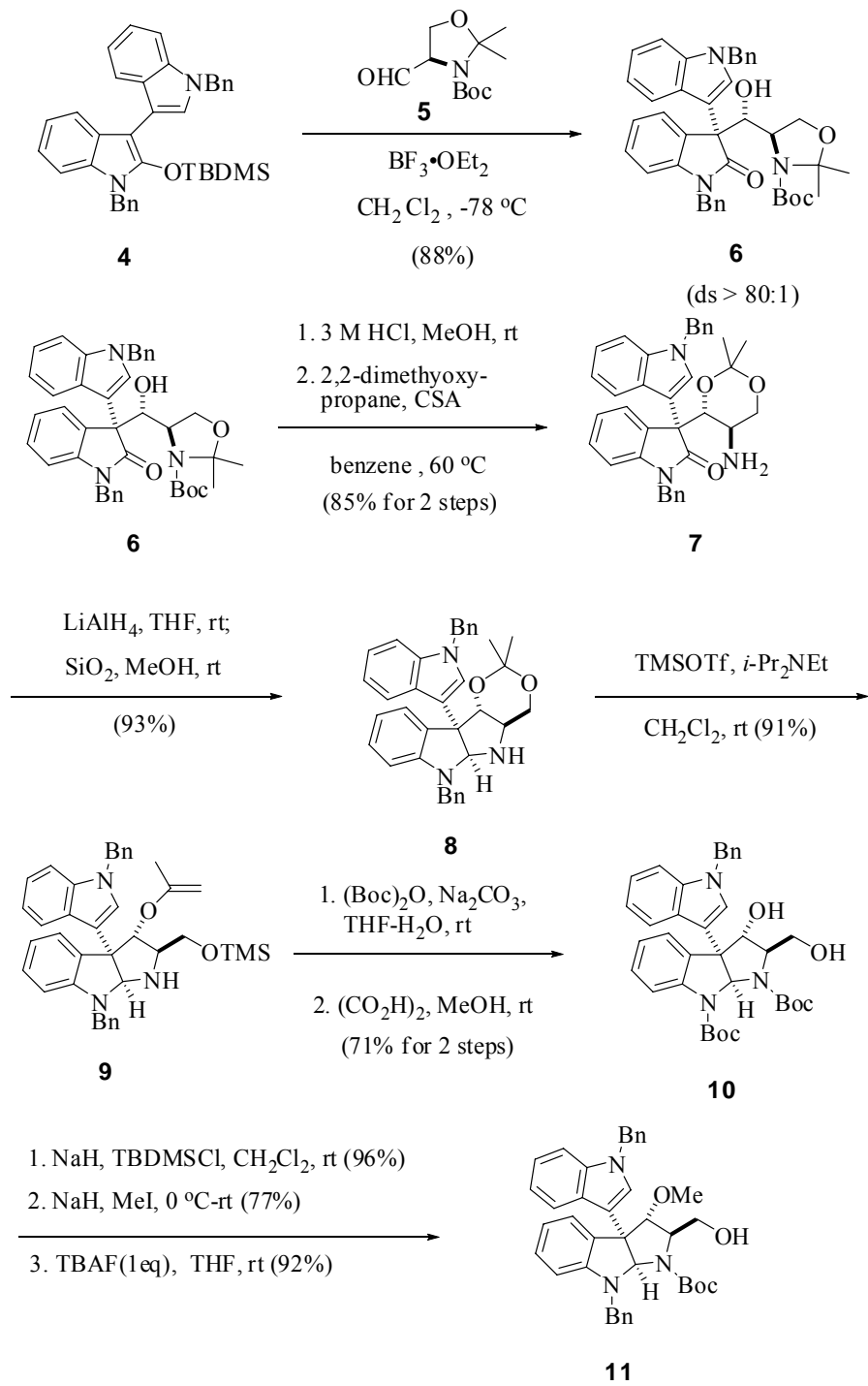
(3) A catalytic asymmetric cyclopropanation reaction.



“Constructing Quaternary Carbon Stereocenters From Prochiral Enolates and Chiral Electrophiles: Methods Development and Natural Products Total Syntheses,”

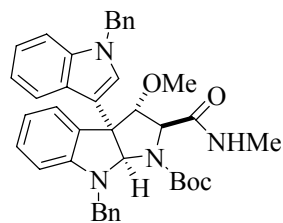
Larry E. Overman (University of California), Irvine.

Stereocontrolled formation of C–C bonds α to carbonyl groups is typically accomplished by the reaction of chiral enolate nucleophiles with achiral electrophiles. Professor Overman described an alternative strategy in which the enolate nucleophile is prochiral and the electrophile is chiral. The development of the method and its application in stereocontrolled total syntheses of marine alkaloid (+)-gliocladin C are briefed here. (+)-Gliocladin C was completed in ~4% overall yield and 21 steps from isatin. The central step in this sequence is asymmetric construction of the quaternary carbon stereocenter by Mukaiyama aldol reaction of siloxyindole and enantiopure aldehyde. A better appreciation of the acid sensitivity of pyrrolidinoindolines containing oxygen substituents at C3 should assist in the design of synthetic approaches to the related, more complex, and biologically more potent alkaloids.



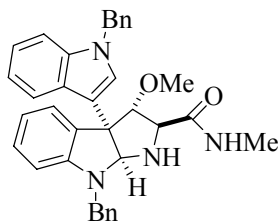
1. Dess-Martin, pyridine, CH₂Cl₂, rt
2. NaClO₂, NaH₂PO₄,
2-methyl-2-butene, THF-H₂O, rt

3. MeNH₂HCl, BOP, CH₂Cl₂, rt)
(60% for 3 steps)

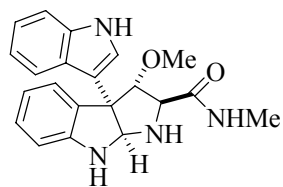


TMSI, MeCN, rt

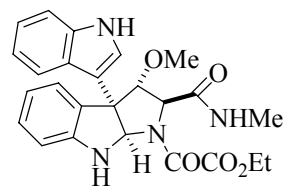
(65%)



NaH, NH₃
t-BuOH, THF
-78 °C (87%)

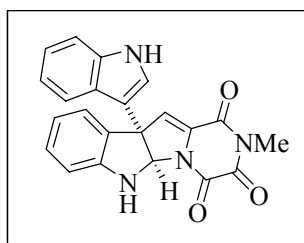


ClCOCO₂Et
Et₃N, CH₂Cl₂, rt
(87%)



(TMS)₂NH, 140 °C

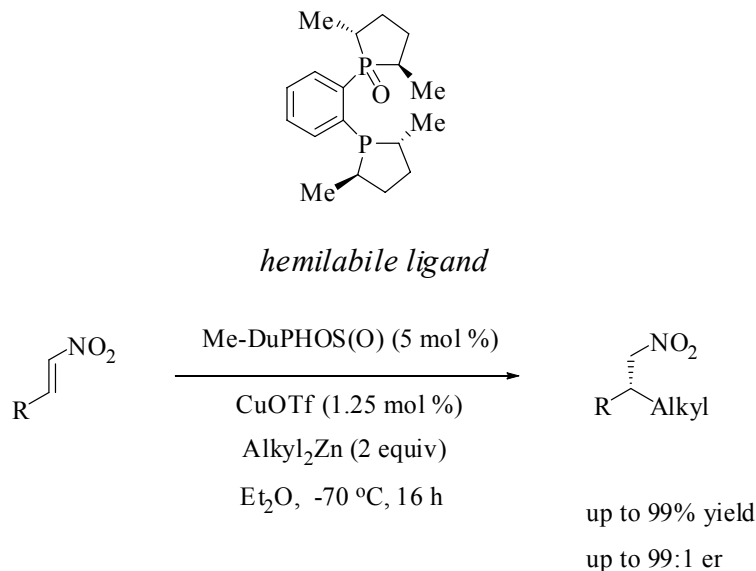
sealed tube
(73%)



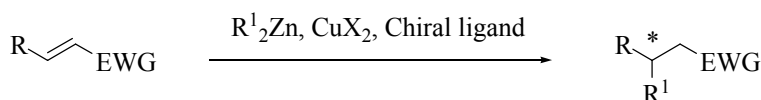
“Reactions with Diorganozinc Reagents,”

André B. Charette (*Department of Chemistry, Université de Montréal, Canada*).

Professor Charette gave a presentation on new chiral ligand development for the copper-catalyzed addition reactions of diorganozinc reagents. He reported that Me-DuPHOS monoxide is a very effective ligand in the enantioselective copper-catalyzed addition of dialkylzinc reagents to β -nitroalkenes providing access to chiral nitroalkanes. The major advantages of this process are high yields, broad and complementary substrate scope, and high enantioselectivities.



A new approach for the in situ generation of diorganozinc reagents was also outlined. The solution of diorganozinc reagents is suitable for a wide range of asymmetric transformations.

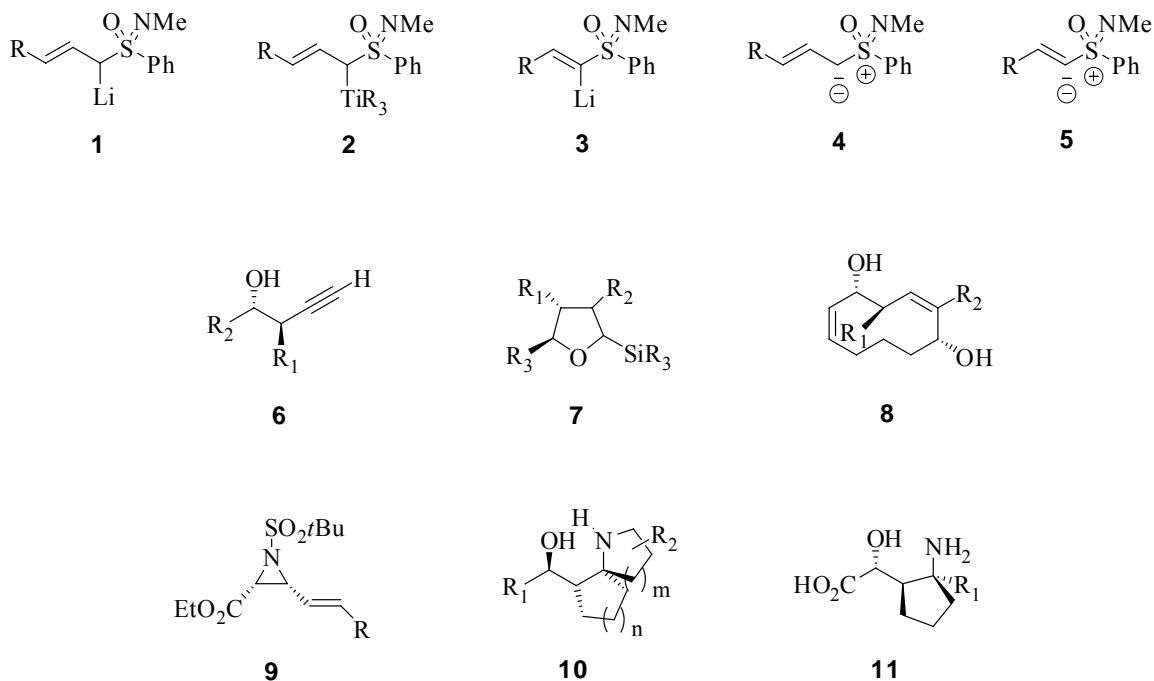


“Asymmetric Synthesis Based on α -Sulfonimidoyl Carbanions,”

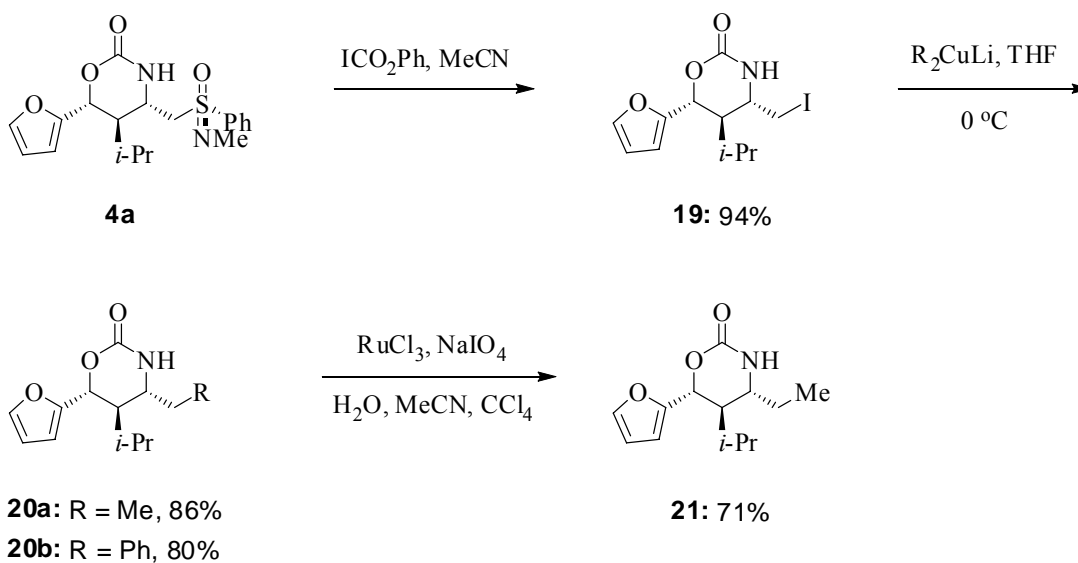
Hans-Joachim Gais (*Institut für Organische Chemie der RWTH Aachen, Germany*).

Professor Gais described the synthesis of the α -sulfonimidoyl carbanions and aminosulfoxonium ylides **1–5**, respectively and their application in the asymmetric synthesis of the homopropargylic alcohols **6**, dihydrofurans **7**, the medium-sized carbocycles **8**, aziridines **9**, azaspirocycles **10**, and the γ -amino acids **11**.

Example
Synthesis of an Acyclic α -hydroxy- γ -amino Acid



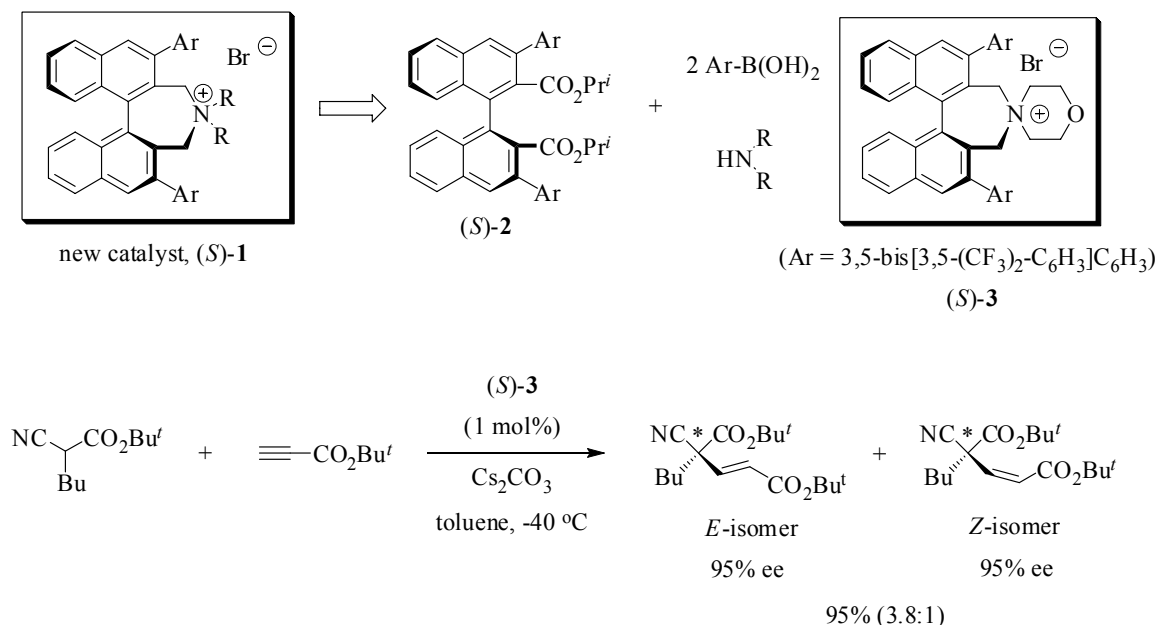
Professor Gais reported that iodide **19** can be directly synthesized from sulfoximine **4a** by the haloformate method. The required ICO_2Ph was prepared by treatment of ClCO_2Ph with NaI in MeCN at 70°C . The reaction of sulfoximine **4a** with ICO_2Ph in MeCN for 2 h at 25°C gave iodide **19** in high yield. Iodide **19** readily reacted with Me_2CuLi and Ph_2CuLi and afforded the 1,3-amino alcohols **20a** and **20b**, respectively, in good yields. The subsequent oxidative degradation of the furan ring of **20a** furnished the protected γ -amino acid **21** in good yield.



“Design of Chiral Phase Transfer Catalysts for Practical Asymmetric Synthesis,”

Keiji Maruoka (Department of Chemistry, Graduate School of Science, Kyoto University), Japan.

Professor Maruoka reported that phase transfer catalysis (PTC) has been recognized as a convenient and highly useful synthetic tool in both academia and industry because of several advantages of PTC (operational simplicity, mild reaction conditions with aqueous media, environmental consciousness, suitability for large-scale reactions, etc.), which meet the current requirement for practical organic synthesis. Professor Maruoka’s group is interested in the development of hitherto difficult, asymmetric transformations with high efficiency. The strategy is based on the recent finding of a very active, chiral phase transfer catalyst of type (S)-1 for the asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester. Since the catalyst (S)-1 can be readily prepared from three components, *i. e.*, a chiral binaphthyl part (S)-2, an arylboronic acid (ArB(OH)₂), and a secondary amine (R₂NH), the appropriate modification of ArB(OH)₂ and R₂NH parts should give newly designed catalysts for the development of novel asymmetric transformations. Accordingly, the group recently designed several new catalysts of type 1 (R = Me) and 3 for asymmetric Strecker and conjugate addition reactions.



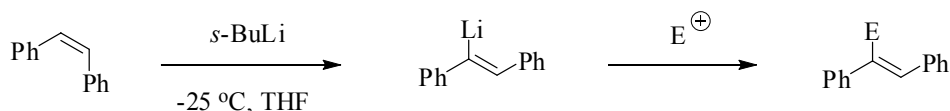
“Development and Application of a Direct Vinyl Lithiation of *cis*-Stilbenes,”

Donal F. O’Shea (School of Chemistry and Chemical Biology, University College Dublin), Ireland.

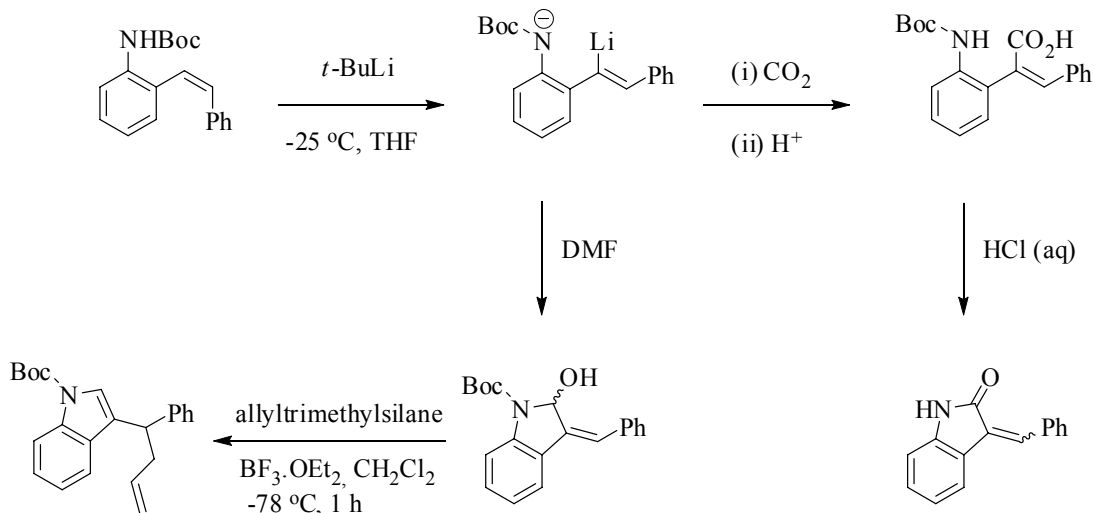
Professor O’Shea described that the synthetic value of organolithium chemistry is indisputable as the number of transformations accessible from organolithium compounds is vast. While many strategies exist for the preparation of lithiated compounds, their generation by a direct C-H deprotonation using commercially available lithium bases is

highly efficient from a synthetic viewpoint. For example, the direct *ortho* lithiation of aryl and heteroaryl rings followed by in situ electrophile reaction has extensive synthetic applications. In contrast, the use of direct alkene deprotonation as a synthetic strategy is rare. This can be attributed to the known propensity of alkenes to undergo carbolithiation in preference to deprotonation. Professor O'Shea reported that stilbene stereochemistry can modulate its reactivity with butyllithium from carbolithiation of the double bond for the *trans* isomer to deprotonation for the *cis* counterparts. For example, the deprotonation of *cis*-stilbene can be readily achieved using *s*-BuLi in THF at -25 °C (Scheme 1). The generated 1-lithio-1, 2-diphenylethene undergoes an in situ *Z* to *E* isomerization, and subsequent reaction with electrophiles results in an efficient stereoselective synthesis of tri-substituted alkenes. In addition, a directed alkene lithiation of the unsymmetrical *cis*-stilbene, 2-styryl-phenyl-carbamic acid *tert*-butyl ester can be achieved regioselectively thereby expanding this methodology for further synthetic applications in indole chemistry (Scheme 2).

Scheme 1



Scheme 2

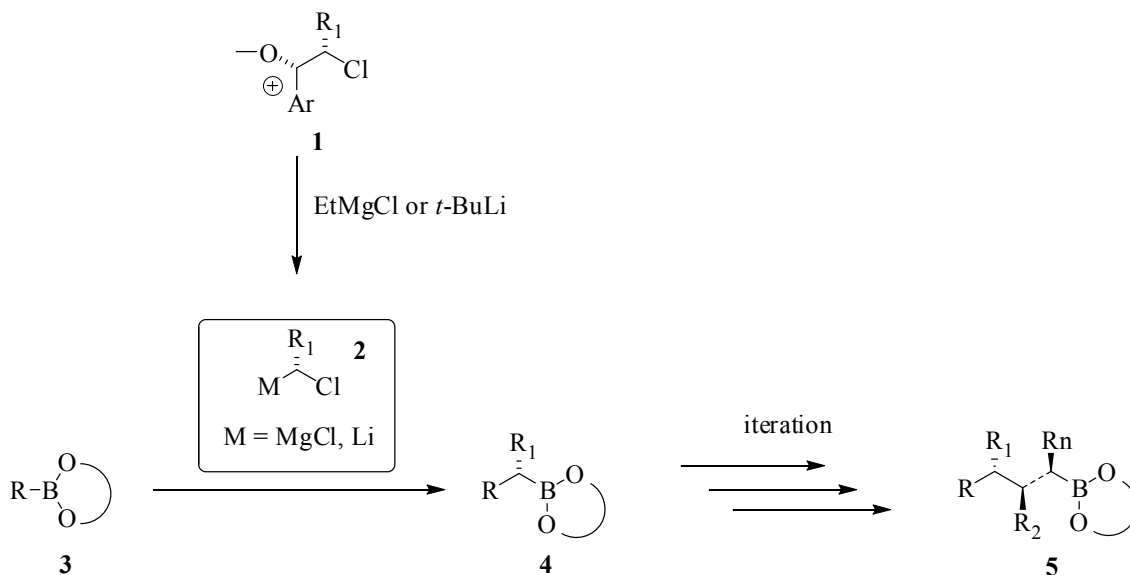


“Asymmetric Homologation of Boronic Esters with Enantioenriched Chiral Carbenoids,” Paul R. Blakemore (Department of Chemistry, Oregon State University), Corvallis.

Professor Blakemore reported that enantioenriched sp^3 -hybridized stereogenic carbanions present many tantalizing possibilities for asymmetric synthesis; however, few effective methods exist for their efficient preparation. In a significant recent advance, Hoffmann reported the ready availability of scalemic α -haloalkyl Grignard reagents via

sulfoxide ligand exchange from homochiral α -halosulfoxides. Inspired by the work of Matteson, they reasoned that deployment of Hoffmann-type carbenoids in the chain-extension of boronic esters would likely result in a stereospecific reagent controlled homologation (StReCH) process (i.e., **3** to **4**, Figure 1). Iterative application of this new type of transformation could potentially facilitate a unified synthesis of polysubstituted alkyl moieties in which constitution and stereochemical features are directly programmed simply by the carbenoid presentation sequence (e.g., **4** to **5**). In an effort to realize this promising technology, preliminary studies established that an enantioenriched Mg-carbenoid (**2**, R₁ = Bn, M = MgCl), preformed in >98% ee by sulfoxide ligand exchange, effected the chain-extension of catechol and neopentyl glycol boronates with modest stereochemical fidelity (up to 82% ee). It was later discovered that putative scalemic Li-carbenoids (**2**, M = Li), generated in Barbier fashion by the addition of alkyllithium reagents to admixed boronates and α -chlorosulfoxides, gave dramatically improved results in related StReCH experiments (up to 98% ee). The greater nucleophilicity of α -chloroalkyllithiums allows for the successful elongation of readily isolated sterically hindered pinacol boronates and this has led to the recent demonstration of iterative StReCH cycles for the programmed synthesis of molecules containing multiple stereogenic centers.

Figure 1
Stereospecific Reagent Controlled Homologation (StReCH) of Boronic Acid Esters with Enantioenriched Main Group Chiral Carbenoids



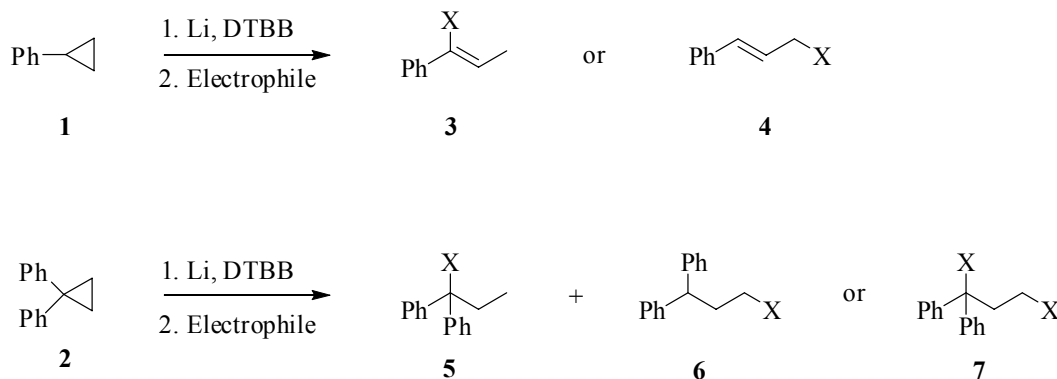
“Arene-catalysed Lithiation of phenyl- and 1,1-diphenylcyclopropane: Synthetic Applications,”

Cecilia Gómez (Departamento de Química Orgánica, Facultad de Ciencias and Instituto de Síntesis Orgánica, Universidad de Alicante Apdo.), Spain.

Professor Gómez reported that the lithiation of cyclopropane derivatives with lithium metal does not work with non-activated systems, but cyclopropanes substituted by

unsaturated groups, such as vinyl or phenyl moieties, can be used for the reductive ring opening giving initially the corresponding radical anion stabilized by resonance. Recently Maercker *et al.* reported that the lithiation of phenylcyclopropane and 1,1-diphenylcyclopropane with lithium metal in THF at room temperature required ultrasonication.

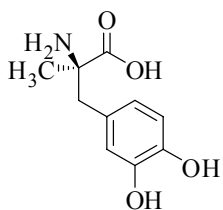
Professor Gómez's group studied the application of an arene-catalysed lithiation to the reductive ring opening of both phenyl- and 1,1-diphenylcyclopropane (**1** or **2**, respectively) in order to trap the lithiated intermediates, with different electrophiles to explore the synthetic possibilities of the reductive ring opening of the starting materials **1** and **2**. The reaction of phenylcyclopropane (**1**) with an excess of lithium and a catalytic amount of DTBB (2.5 % molar) in THF at room temperature, followed by treatment with an electrophile [Me₃SiCl, PhMe₂SiCl, *t*-BuCHO, PhCHO, Me₂CO, Et₂CO, (CH₂)₅CO, adamantan-2-one, *i*-Pr₂CO, di(cyclopropyl)ketone] and final hydrolysis with water leads to allylic products **3** or **4** depending on the structure of the electrophile: whereas for chlorosilanes or crowded ketones γ -products **4** are isolated, for aldehydes and non-congested ketones α -products **3** are formed. The application of the same protocol to 1,1-diphenylcyclopropane (**2**) leads to a mixture of products **5-7** resulting from the introduction of one or two electrophilic fragments to the open-chain mono or dilithiated intermediate: also in this case the regiochemistry of the reaction is governed by steric reasons.



“Organo-catalytic Approaches Towards α,α -disubstituted Chiral Amines,”

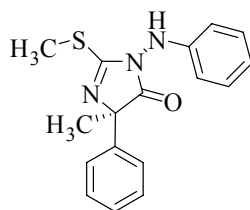
Stefan Bräse (Institute for Organic Chemistry, University of Karlsruhe), Germany.

Professor Bräse described that the class of non-proteinogenic α,α -disubstituted amino acids and their derivatives is of high interest to biochemical and pharmacological research. This predicts on their ability to alter certain chemical and physicochemical properties of peptides and related structures. Moreover, the close structural relatedness to biologically relevant endogenous amino acid derivatives qualifies them in many cases to act as enzyme inhibitors or receptor antagonists.



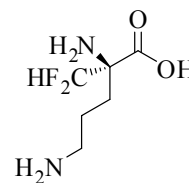
1

L- α -Methyldopa



2

(S)-Fenamidon

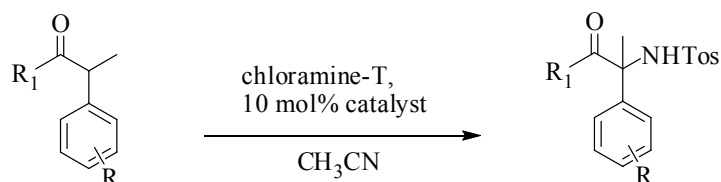


3

(S)-(Difluoromethyl)ornithin

A series of aliphatic and aromatic carbonyl compounds has been transformed into the corresponding sulfamidated products by means of amine catalyzed nitrene transfer of chloramine-T. Applying microwave conditions, good to excellent yields under significantly reduced reaction times could be obtained, thus providing a facile access to α,α -disubstituted amino acids. On the other hand with enantiomerically pure L-proline as a catalyst the reaction only delivered the racemic product.

Using chiral alkaloid-catalysts the group is now investigating the asymmetric addition of chloramine-T to α -substituted aldehydes and ketones. First experiments with a derivative of (DHQ)₂PHAL as a catalyst furnished enantiomerically enriched α,α -disubstituted amino aldehydes in moderate stereoselectivity.



“Design of a New, Chiral Organocatalyst for Asymmetric Hydroxyamination,”

Mitsuhiro Ueda (*Department of Chemistry, Graduate School of Science, Kyoto University*), Japan.

Dr. Uedo presented that nitroso compounds are frequently utilized as a nitrogen and/or an oxygen source in synthetic organic chemistry, and various catalytic asymmetric reactions, such as aminoxylation, hydroxyamination, and nitroso Diels-Alder reaction, have recently been developed by exploiting their unique properties. However, the direct hydroxyamination of aldehydes without preformation of their enolates or enamines has not been realized to a synthetically useful level despite the potential application of the resulting α -amino aldehydes in organic synthesis. Dr. Uedo and co-workers have been interested in the design of a sterically and electrically tunable organocatalyst, which may simultaneously activate both aldehydes and nitrosobenzene. Accordingly, a highly efficient organocatalytic asymmetric hydroxyamination reaction of aldehydes with nitroso compounds has been developed by designing a binaphthyl-modified catalyst with dual functions.

Due to the ease of modification of the binaphthyl backbone, new amine catalysts of type (*S*)-**1b**~**d** having hydroxyl groups at the appropriate positions were designed to improve both reactivity and enantioselectivity. When (*S*)-**1b**, having hydroxymethyl groups at 3, 3'-positions was used as a catalyst, both reactivity and enantioselectivity were significantly improved (entry 2). The reaction using (*S*)-**1c**, which has sterically congested *tert*-alcohol moieties at 3,3'-positions, proceeded smoothly under similar conditions to give the desired hydroxyamination product in good yield with excellent regio- and enantioselectivity (entry 3). Further improvement in both reactivity and enantioselectivity was achieved by using (*S*)-**1d** with hydroxydiphenylmethyl groups at 3, 3'-positions (entry 4). The marked effect of hydroxyl groups in (*S*)-**1d** on the reaction rate is apparent by comparison with des-hydroxyl catalyst (*S*)-**1e**, which affords **2** in low yield with high enantioselectivity (entry 6). The catalyst loading in (*S*)-**1d** could be reduced to 5 mol % (entry 5)

With the axially chiral secondary amine catalyst (*S*)-**1d** in hand, the direct asymmetric hydroxyamination reaction of several other aldehydes with nitrosobenzene was executed, and found that these direct asymmetric hydroxyamination reactions proceeded smoothly, and the subsequent reduction with NaBH₄ gave the corresponding *N*-hydroxy-β-amino alcohols in good isolated yields with excellent levels of enantioselectivity.

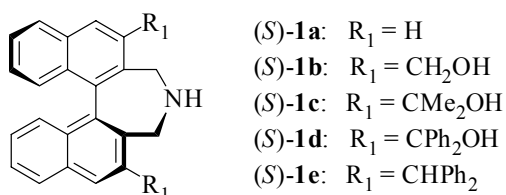
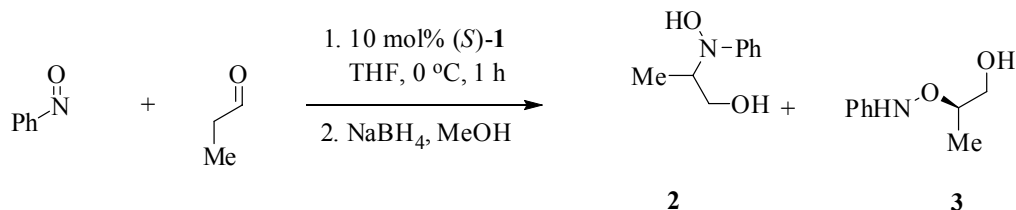


Table 1
Enantioselective Hydroxyamination

Entry	catalyst	2/3	% yield	% ee
1	(<i>S</i>)- 1a	>99/1	22	29 (<i>S</i>)
2	(<i>S</i>)- 1b	>99/1	55	77 (<i>S</i>)
3	(<i>S</i>)- 1c	>99/1	78	95 (<i>S</i>)
4	(<i>S</i>)- 1d	>99/1	90	99 (<i>S</i>)
5 ^a	(<i>S</i>)- 1d	>99/1	87	98 (<i>S</i>)
6	(<i>S</i>)- 1e	>99/1	28	83 (<i>S</i>)

^a 5 mol% of (*S*)-**1d**