



**Trip Report:
The 16th International Conference on Organic
Synthesis, IUPAC ICOS-16
Merida, Mexico
June 11 -15, 2006**

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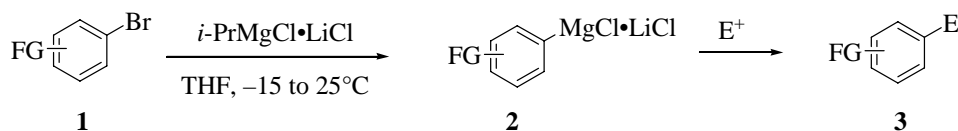
***Abstract:** The 16th International Conference on Organic Synthesis, IUPAC ICOS-16 was held in Merida, Mexico from June 11 – 15, 2006. IUPAC ICOS-16 was cosponsored by the International Union of Pure and Applied Chemistry (IUPAC), Academia Mexicana de Ciencias (AMC), Sociedad Quimica de Mexico (SQM), and the Division of Organic Chemistry of the American Chemical Society (ACS). This international conference attracted more than 600 attendees from different countries around the world. This week-long symposium included twenty plenary lectures discussed many aspects of creative modern organic synthesis and six symposia covered the areas of Medicinal Chemistry, Organocatalysis, Enantioselective Synthesis of β -Amino Acids, Organolithium Compounds in Synthesis, Selenium and Tellurium in Organic Synthesis, and Application of Microwave in Organic Synthesis. In addition, nearly 300 oral and poster contributed presentations were also presented. This report highlights select material from the talks presented in the conference.*

Synthesis and Reactivity of Functionalized Zinc and Magnesium Organometallics,”
Paul Knochel (Ludwig-Maximilians-Universitat Munchen), Munchen, Germany.

Professor Knochel from Ludwig-Maximilians-Universität München described novel methods in the catalyzed halogen-metal exchange reactions allowing a very efficient preparation of a broad range of polyfunctional zinc and magnesium organometallic reagents. Polyfunctionalized organometallic reagents are ubiquitous intermediates in organic synthesis. One of the best methods for preparing these reagents is the halogen-metal exchange reaction. Whereas Br/Li exchange is fast and occurs at low temperature, the corresponding Br/Mg and Br/Zn exchanges are considerably slower that require higher reaction temperatures and are therefore not compatible with many functional groups.

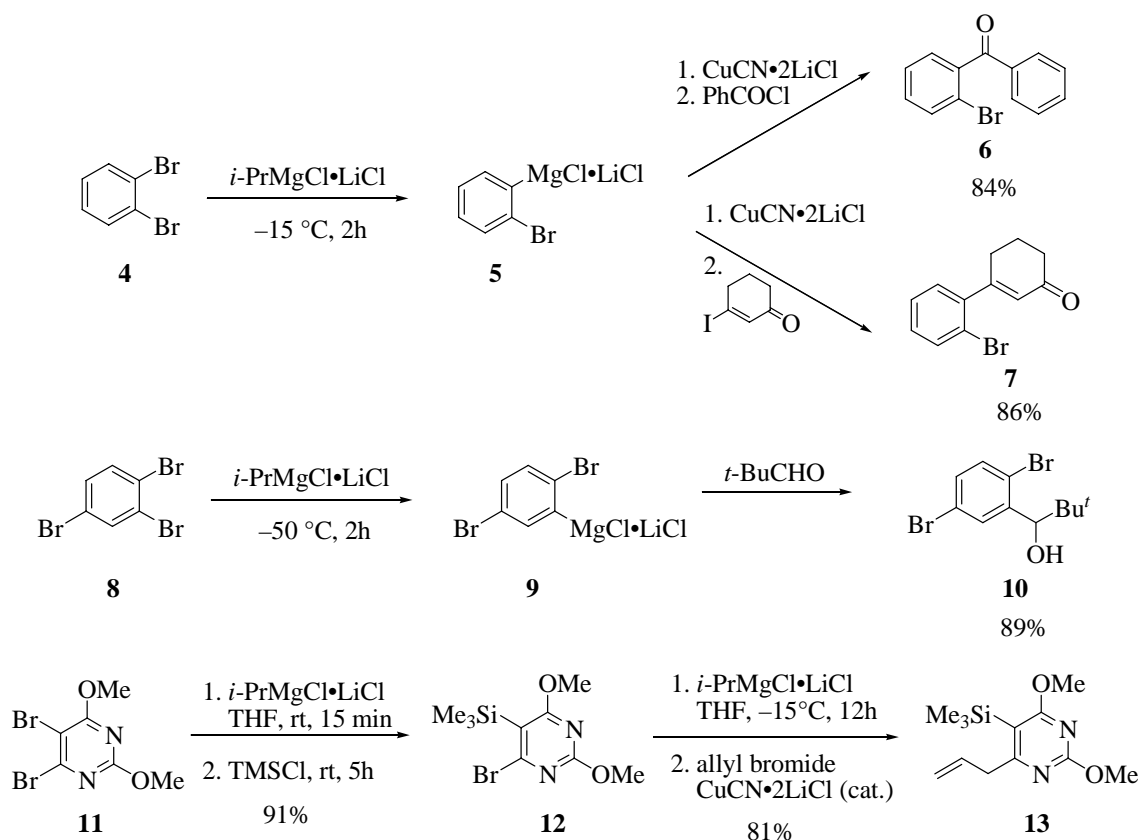
Professor Knochel's research group prepared the new reagent *i*-PrMgCl•LiCl by adding *i*-PrCl to Mg turnings and LiCl (*i*-PrCl /Mg/LiCl = 1:1.1:1) in THF or by the addition of a solution of *i*-PrMgCl in THF to LiCl. They used this reagent to prepare a range of aryl and heteroarylmagnesium derivatives **2** starting from the corresponding bromides **1**. After further reaction with electrophiles (E⁺), the expected products **3** were isolated in good to excellent yields (Scheme 1).

Scheme 1
Preparation of Functionalized Arylmagnesium Reagents



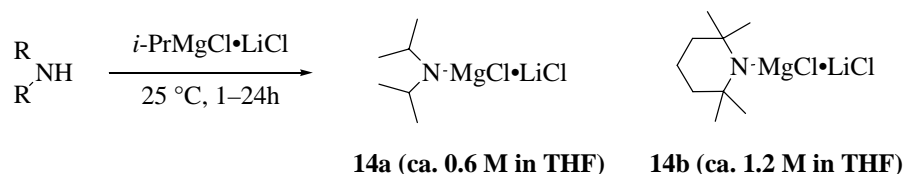
This reagent can be used to prepare *ortho*-bromophenylmagnesium bromide **5** by reacting with 1,2-dibromobenzene **4**. Also unsymmetrical 1,2,4-tribromobenzene **8** reacted with *i*-PrMgCl•LiCl by a highly regioselective Br/Mg exchange to provide exclusively the Grignard reagent **9**, which gave alcohol **10** in excellent yield. Dibromopyrimidine **11** also could undergo selective Br/Mg exchange and reacted with TMSCl to provide **12**. Further Br/Mg exchange and reacted with allyl bromide gave product **13** in good yield (Scheme 2).

Scheme 2
Selective Br/Mg Exchanges of Polybromides



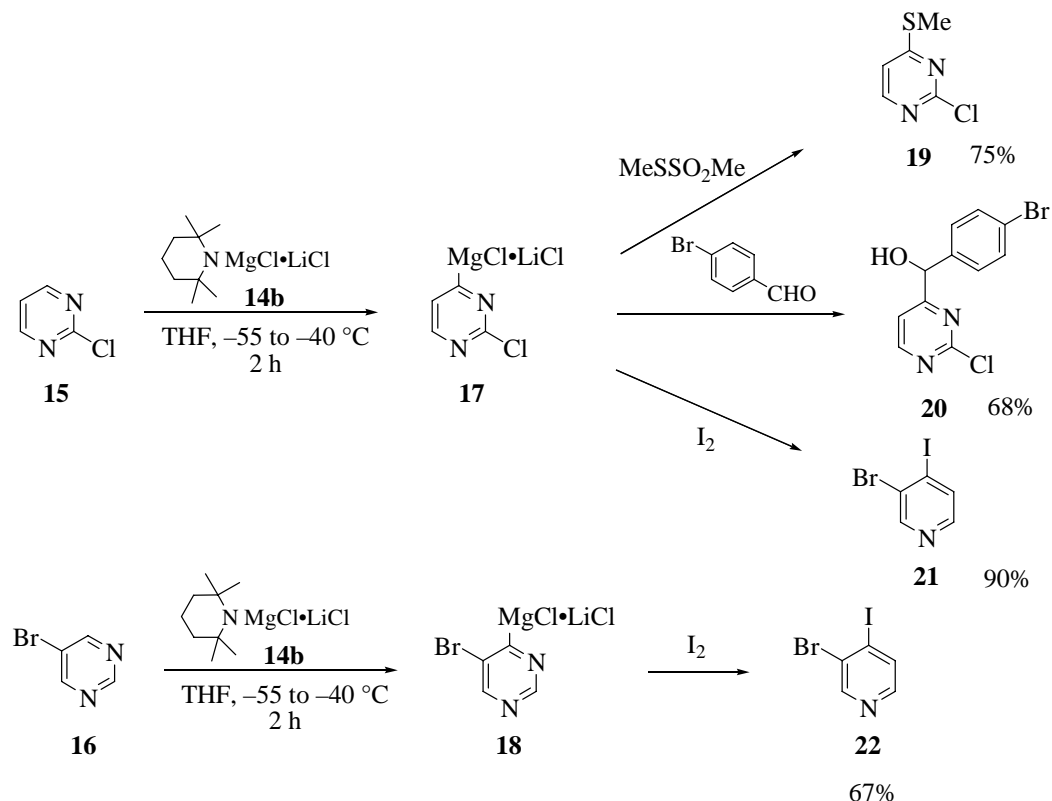
The metalation of arenes is one of the most useful transformations in organic synthesis since it allows the regioselective functionalization of various aryl and heteroaryl derivatives. Traditionally, strong bases such as alkyl lithium reagents (RLi) and lithium amides (R₂NLi) have been used for such deprotonations. However, these bases often lead to undesirable side reactions due to their high reactivity and nucleophilicity. Another limitation is the low stability of lithium amides in THF solution at room temperature, which requires in situ generation of these reagents. Furthermore, the deprotonation of arenes by lithium bases requires very low temperatures (−78 to −90 °C), which hinders the scale-up. Professor Knochel's research group has developed the mixed Mg/Li amides of type R₂NMgCl•LiCl **14** by reacting *i*-PrMgCl•LiCl with diisopropylamine or 2,2,6,6-tetramethylpiperidine in THF (25 °C, 1–24 h) (Scheme 3). The resulting Mg/Li reagents **14a** and **14b** proved to have excellent solubility in THF (0.6 M and 1.2 M, respectively) as well as improved kinetic basicity and regioselectivity for magnesiation of various aromatics and heteroaromatics.

Scheme 3
Preparation of the Mixed Mg/Li Amides



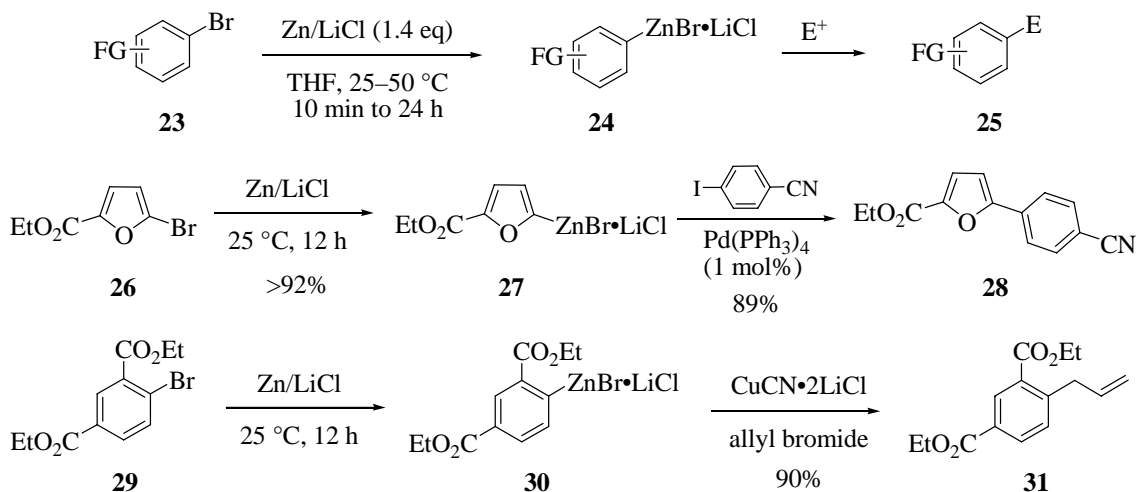
The addition of the pyrimidine derivatives **15** and **16** to a THF solution of **14b** (1.2 equiv) at -55 °C provided completely regioselectively the corresponding magnesiated derivatives **17** and **18**, which react with a wide range of electrophiles leading to the functionalized pyrimidines **19–22** in good yields (Scheme 4).

Scheme 4 Regioselective Magnesiation of Pyrimidines



Professor Knochel also reported that they are able to use LiCl to promote the Br/Zn exchange and use the organozinc reagents for further reactions (Scheme 5).

Scheme 5 Preparation of Functionalized Arylzinc Reagents

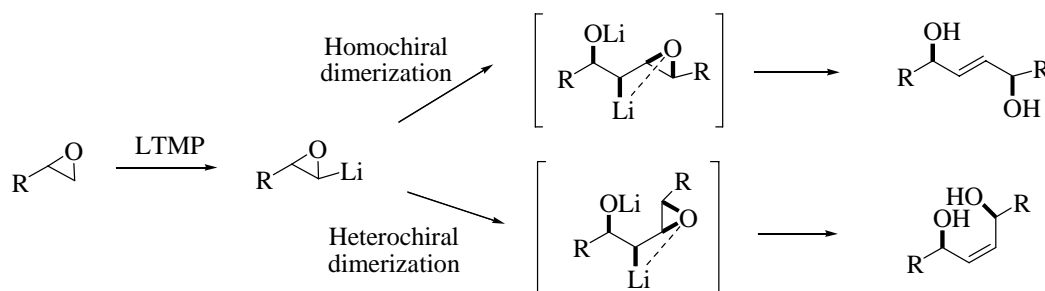


“Widening the Usefulness of Epoxides and Aziridines in Synthesis,”

David M. Hodgson (University of Oxford), Oxford, UK.

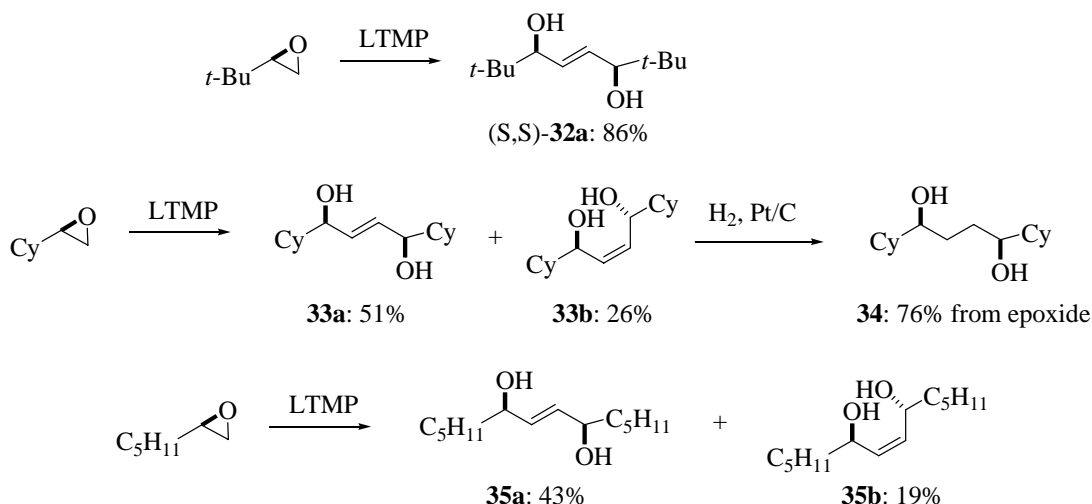
Professor Hodgson from University of Oxford discussed the chemistry of lithiated epoxides and aziridines and their application in the organic synthesis. Reaction of hindered lithium amides such as lithium 2,2,6,6-tetramethylpiperidide (LTMP) with the readily available (enantiopure) terminal epoxides gives 2-ene-1,4-diols via carbenoid dimerization of the corresponding α -lithiated epoxides (Scheme 6).

Scheme 6 Dimerization of lithiated Terminal Epoxides



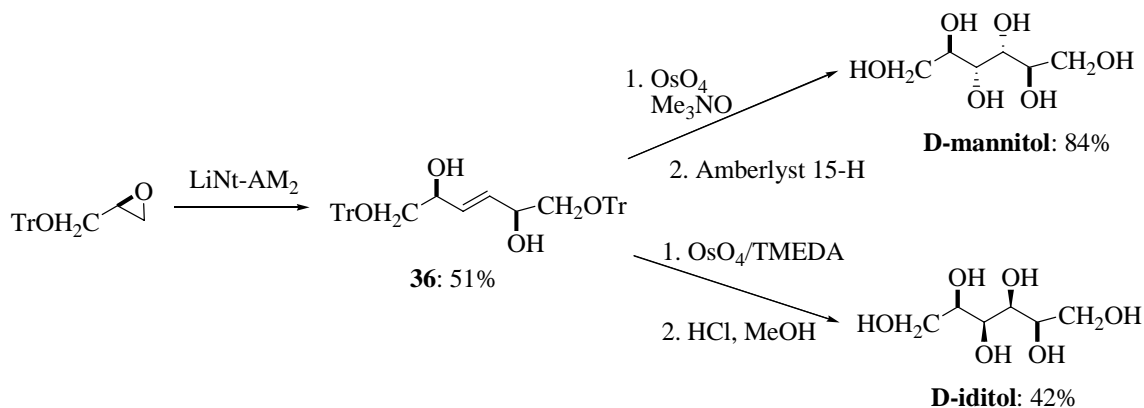
They have demonstrated this dimerization process by using an enantiopure terminal epoxides and obtained predominately (E)-enediols (Scheme 7).

Scheme 7 2-Ene-diols by Dimerization of Enantiopure Terminal Epoxides Using LTMP



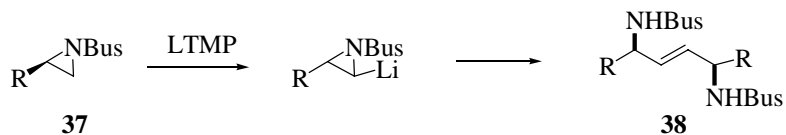
To demonstrate the synthetic utility of this dimerization process, they have used a commercially available (S)-tritylglycidyl ether as a common building block for the synthesis of D-mannitol and D-iditol (Scheme 8).

Scheme 8
Synthesis of D-Mannitol and D-Iditol by Dimerization of Terminal Epoxide



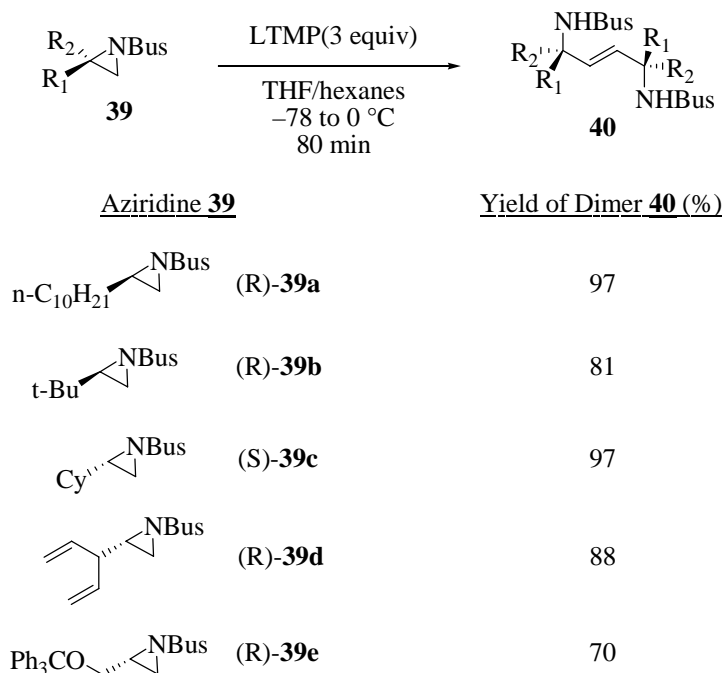
Professor Hodgson also reported that the dimerization of lithiated terminal aziridines under similar reaction condition. Upon treatment with LTMP, the *N-tert*-butylsulfonyl (Bus) protected aziridines **37** were lithiated and underwent dimerization to give the *N*-Bus protected 2-ene-1,4-diamines **38** in high yield (Scheme 9).

Scheme 9
Dimerization of lithiated *N*-Bus Protected Aziridines



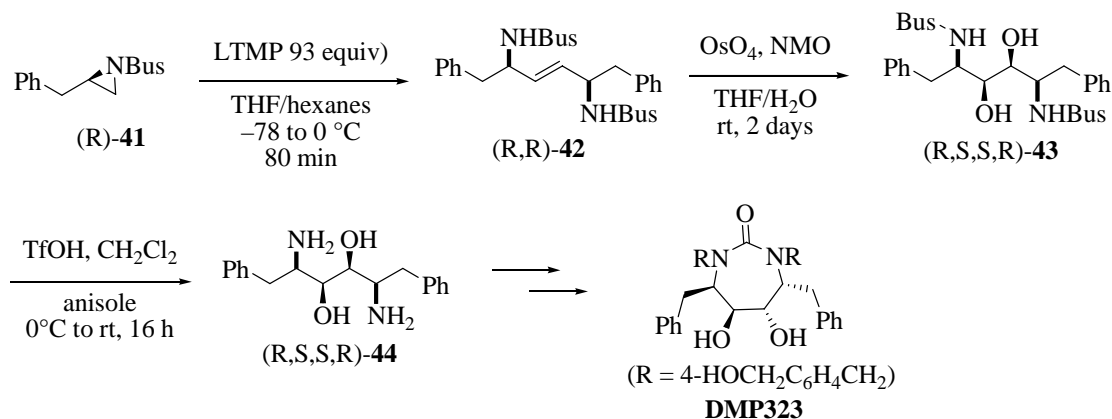
The enantiopure aziridines all dimerized in high efficiency under the same reaction conditions (Table 1).

Table 1
Dimerization of Lithiated *N*-Bus Aziridines



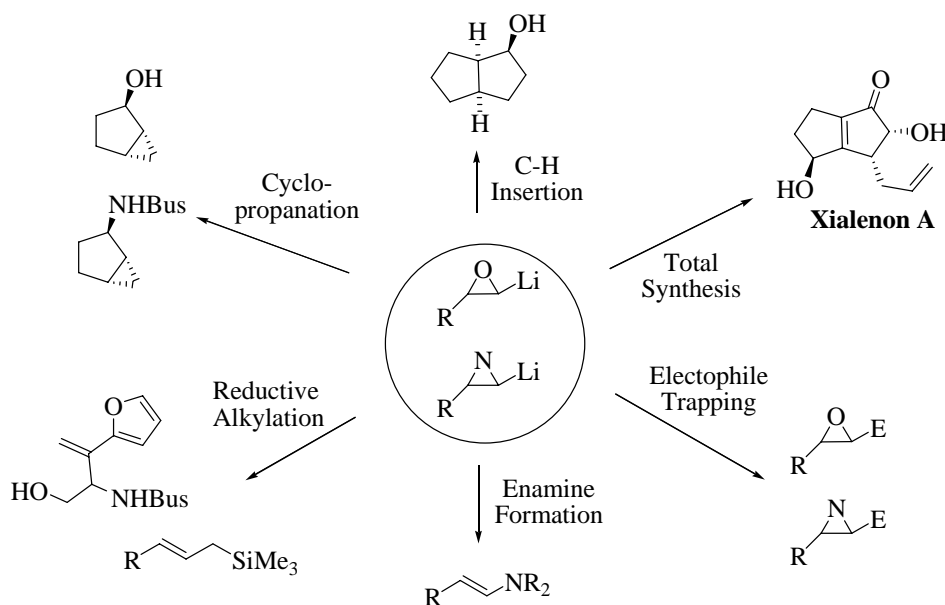
They have also applied this methodology in a concise synthesis of the functionalized diaminiol **44**, which is the core unit of a number of extremely potent HIV protease inhibitors such as DuPont Merck compound DMP 323 (Scheme 10).

Scheme 10 Applications of the Dimerization Methodology



Other applications of the lithiated epoxides and aziridines presented in the talk are summarized as following (Scheme 11).

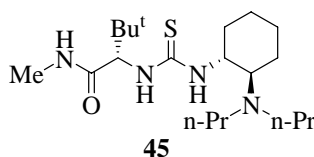
Scheme 11
Applications of the Lithiated Epoxides and Aziridines



“Thioureas as General Acids Asymmetric Catalysts,”

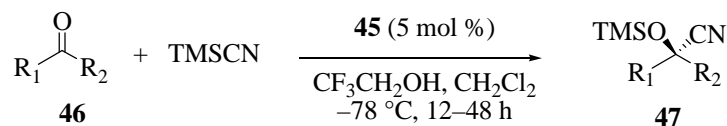
Eric N. Jacobson (Harvard University), Cambridge, Massachusetts, USA.

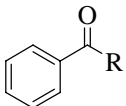
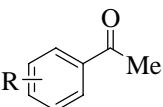
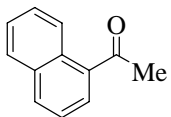
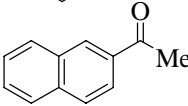
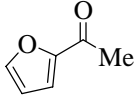
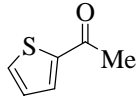
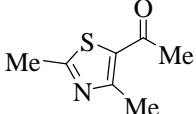
The catalytic asymmetric cyanation of carbonyl compounds ranks among the most important and well-studied reaction classes in asymmetric catalysis, due in large part to the utility of the product cyanohydrins as precursors to α -hydroxy acids, β -amino alcohols, and other valuable chiral building blocks. Professor Jacobson described the application of thiourea catalysis in carbonyl 1,2-addition chemistry, in the highly enantioselective cyanosilylation of ketones and aldehydes with a new bifunctional thiourea-amine derivative **45**.



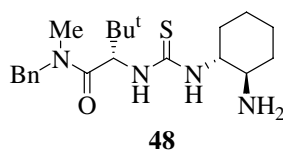
Thiourea catalyst **45** proved to be general for highly enantioselective cyanosilylation of wide range of ketones (Table 2). In most cases, useful reaction rates were obtained at 5 mol % catalyst loading. Alkyl aryl ketones underwent reaction with high enantioselectivity with only slight dependence on the size of the alkyl group or the substitutions of the aromatic ring. Heteroaromatic ketones were also excellent substrates.

Table 2
Enantioselective Cyanosilylation of Ketones Catalyzed by Thiourea 45



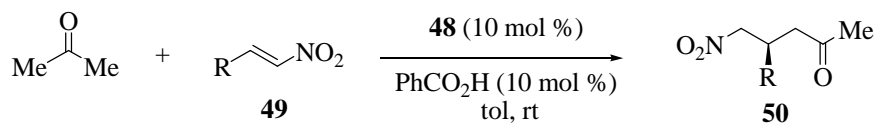
<u>Ketone 46</u>	<u>Yield of 47 (%)</u>	<u>ee (%)</u>	
	R = Me R = ET R = i-Pr	96 95 97	97 95 86
	R = o-Me R = p-Me R = m-OMe R = p-OMe R = p-Br	96 97 97 93 94	98 96 97 95 93
		91	95
		98	97
		81	97
		88	98
		87	97

Professor Jacobson also described another new thiourea catalyst **48** for the asymmetric conjugate additions of ketone to nitroalkenes.



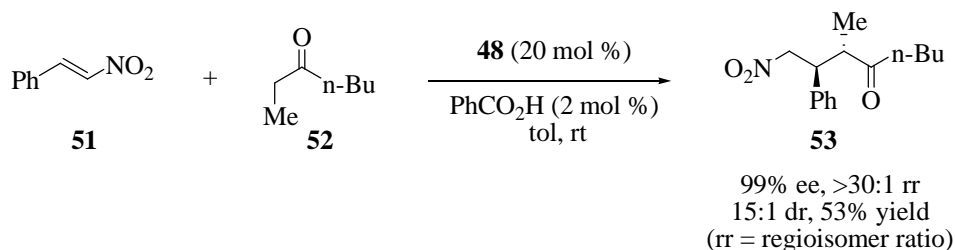
The notable features of this catalyst **48** include high enantioselectivities across a broad range of substrates (Table 3) as well as high diastereo- and regioselectivities resulting directly from the unusual structural features of the catalyst (Scheme 12).

Table 3
Enantioselective Addition of Acetones to Nitroalkenes Catalyzed by Thiourea 48



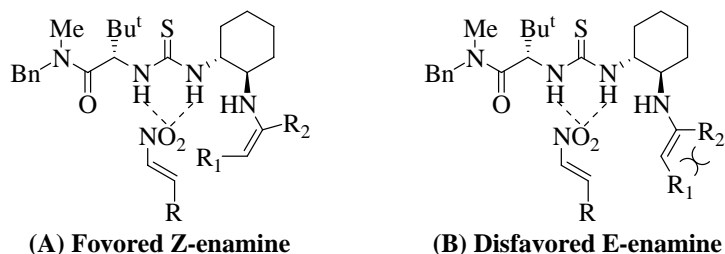
<u>R</u>	<u>Yield of 50 (%)</u>	<u>ee (%)</u>
Ph	93	99
4-MeOC ₆ H ₄	88	99
4-MeC ₆ H ₄	87	97
2-Furyl	88	99
2-Thienyl	94	96
Me	70	98
n-Bu	78	95
i-Bu	81	94

Scheme 12
Diastereo- and Regioselective Asymmetric
Addition of Ketone to Nitroalkene



A bifunctional mechanism involving enamine catalysis in Michael addition promoted by catalyst **48** was proposed. The observed anti diastereoselectivity suggests the participation of Z-enamine intermediate (Figure 1).

Figure 1
Proposed Intermediates in the Michael
Reaction Catalyzed by Catalyst 48



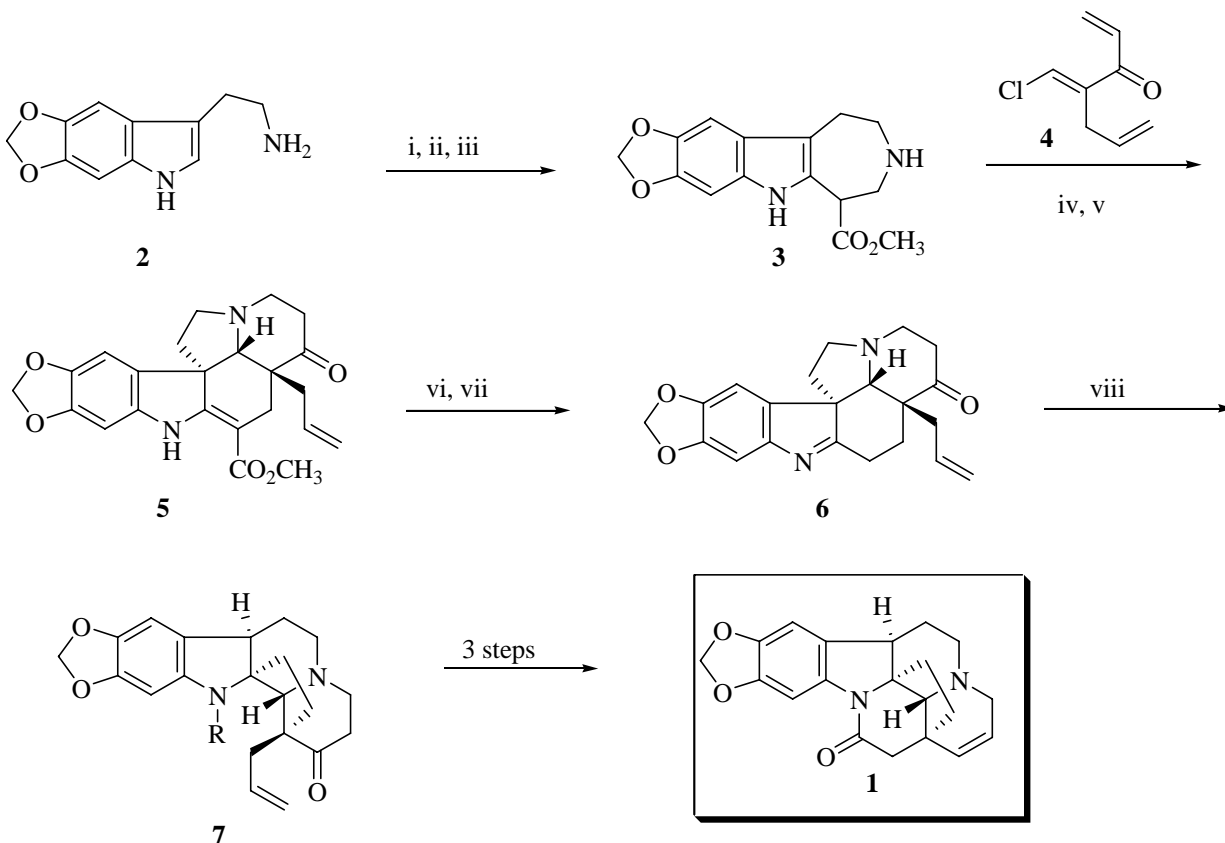
“Towards Total Synthesis of Schizozygine: Unprecedented Rearrangement of Secoschizozygane Skeleton,”

Tomas Pilarcik and Josef Hajicek (Synthesis Group II, R&D Division, Zentiva a.s., U Kabelovny 130, CZ-10237, Praha 10), Czech Republic.

These researchers are continuing to investigate the total synthesis of schizozygine (**1**). Schizozygine is a natural product which was isolated from the African shrub, *Schizozygia coffaeoides*. The leaf extracts of this plant show high antifungal and antimicrobial activity and have been used as a traditional medicine for some skin diseases.

Work toward the total synthesis of **1** has led to an advanced intermediate which they believe to be 3 synthetic steps from the target molecule (Scheme 1).

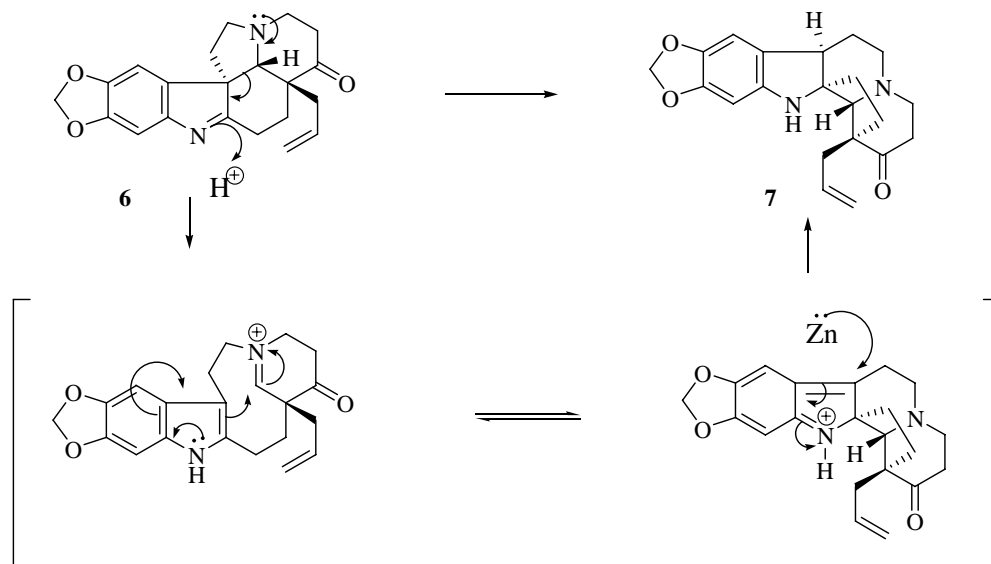
Scheme 1



i) chloromethyl pyruvate, MeOH, charcoal, reflux; ii) pyridine, reflux; iii) NaBH₃CN, AcOH, then HCl; iv) MeOH, 10 mol% hydroquinone, 20 °C; v) toluene, reflux; vi) KOH, MeOH, reflux; vii) benzene, reflux; viii) Zn, AcOH, cat. CuSO₄•5H₂O, 105 °C

Condensation of tryptamine **2** with methyl chloropyruvate provided tetrahydro-β-coboline ester. The ester was rearranged to the olefinic indoloazepine followed by reduction to form **3**. Reaction of compounds **3** and **4** in methanol followed by reflux in toluene afforded compound **5**. Compound **5** then underwent decarbomethoxylation and dehydration to provide compound **6**. The

key advanced intermediate **7** was obtained by zinc mediated reductive rearrangement as shown in Scheme 2.

Scheme 2

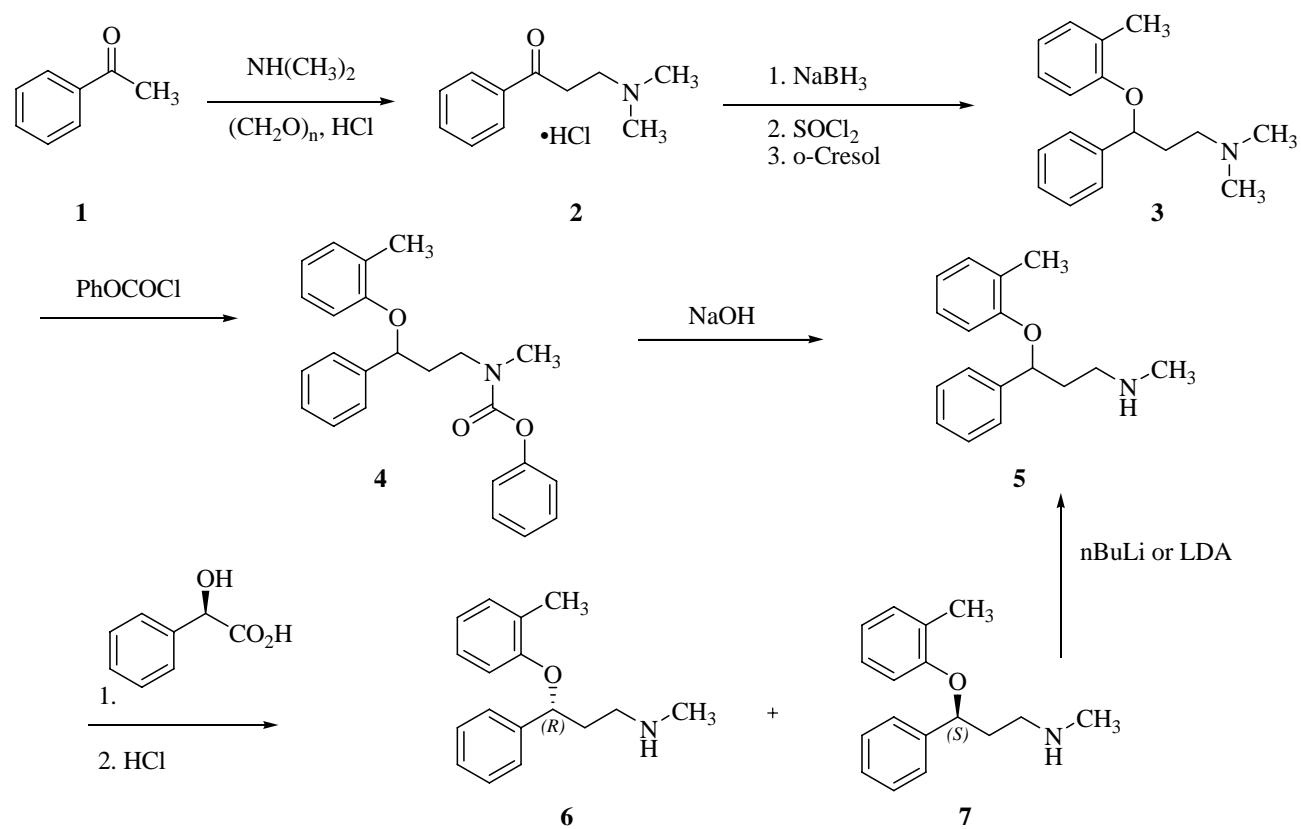
“New Synthesis of Atomoxetine,”

Ludek Ridvan, Petr Hruby, Kamal Jarrah, Stanislav Radl, Lukas Placek, Monica Zatopkova, Hana Petrickova (Zentiva a.s., U Kabelovny 130, 102 37 Prague 10), Czech Republic.

These researchers have developed a new synthesis of Atomoxetine (**1**) which is an ADHD drug that is marketed by Eli Lilly and Company under the name Strattera.

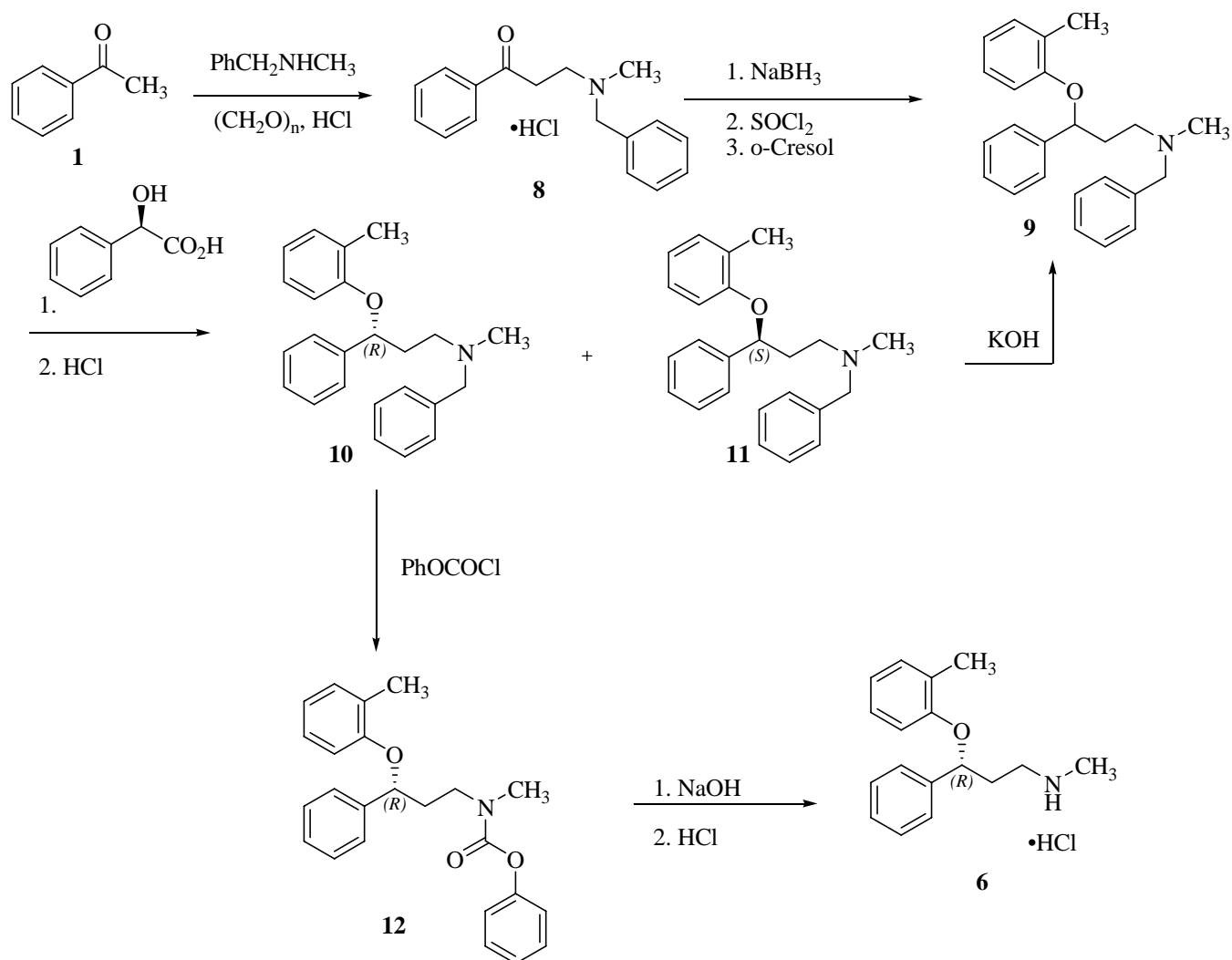
The original procedure involves a mandelic acid resolution of racemic atomoxetine. The undesired (S)-enantiomer can then be racemized by a strong base and recycled through further resolutions with mandelic acid as shown in Scheme 1.

Scheme 1



The new synthesis also involves chiral resolution with mandelic acid. However, this resolution is done at an earlier stage through a different intermediate as shown in Scheme 2.

Scheme 2



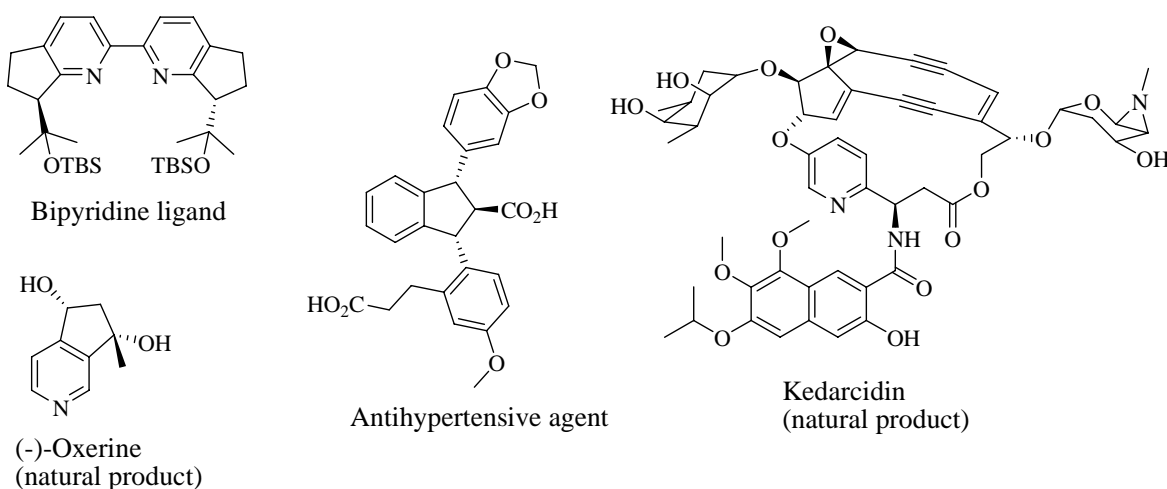
Initial attempts to resolve compound **3** were unsuccessful. Compound **9** was then synthesized in 4 steps and then resolved using mandelic acid. The undesired enantiomer **11** could be racemized with potassium hydroxide and recycled to obtain more enantiomerically pure product. Selective debenzylation, led to the desired product, atomoxetine (**6**).

“Fast and Efficient Access of Novel β -2-Pyridylacrylates and Cyclopentano-fused Pyridine Ring System,”

Sylvain Celanire, Nicolas Robert, Christophe Hoarau, Guy Queguiner, Francis Marsais, *Laboratoire de Chimie Organique Fine et Heterocyclique (UMR 6014, INSA-IRCOF, BP 08), Mont-Saint-Aignan Cedex, France.*

These researchers have developed a novel approach to β -2-pyridylacrylates and cyclopentano-fused pyridine ring systems. These systems possess interesting and important chemical and biological properties. A few examples are shown in Figure 1.

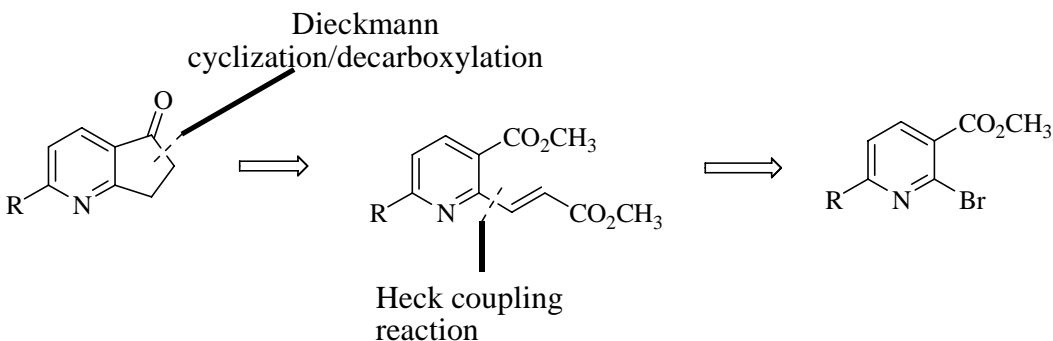
Figure 1



This class of compounds was proposed

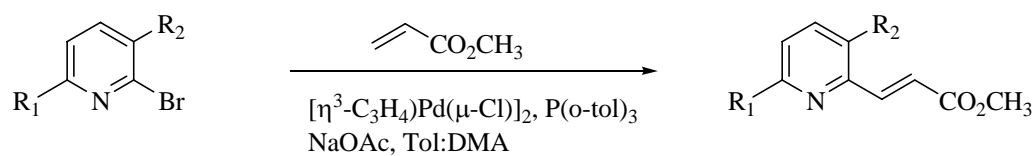
to be constructed by Dieckmann cyclization/ decarboxylation of the reduced Heck coupling product of 6-alkyl-2-bromomethylnicotinate and methylacrylate. Scheme 1.

Scheme 1



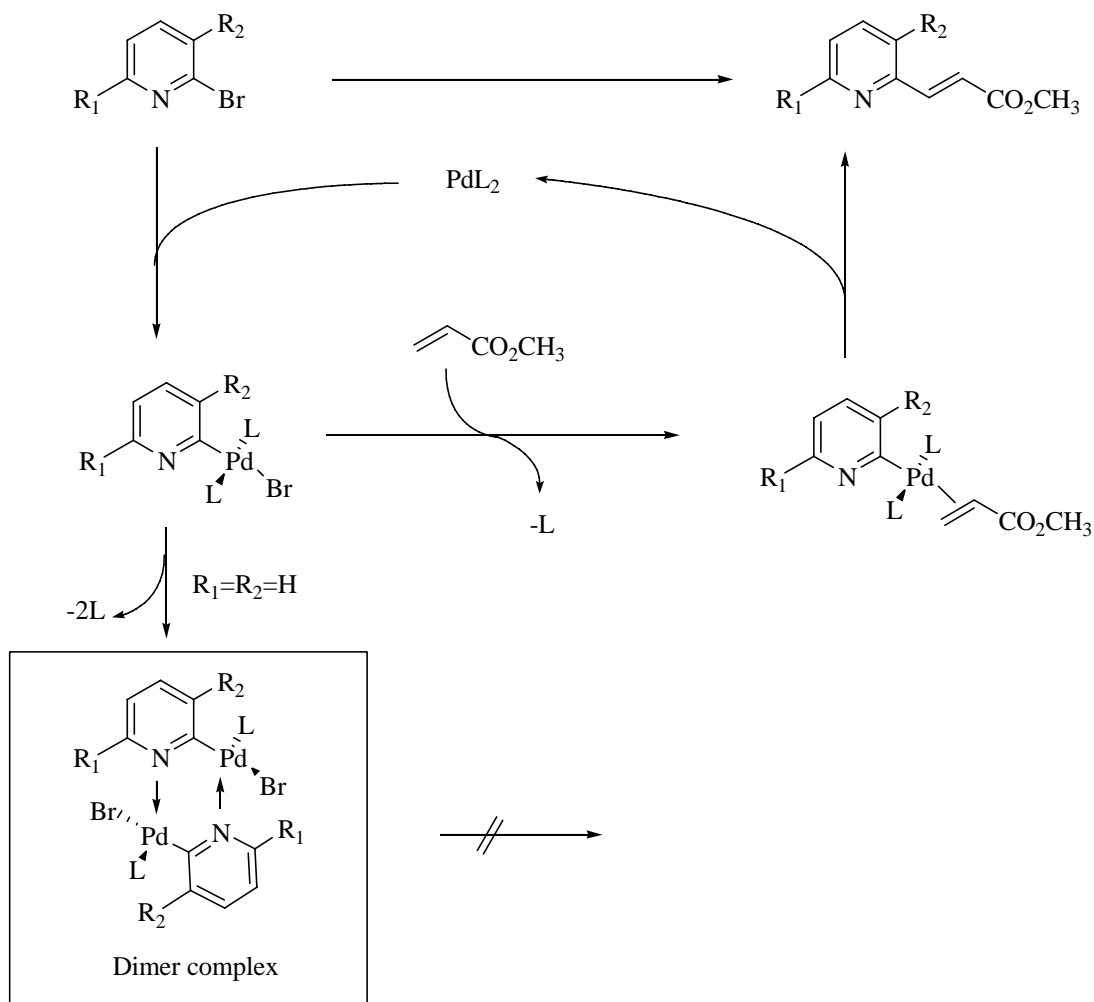
The data in Table 1 shows that the initial Heck reaction provides the highest yields when the 6-position is substituted and the pyridine nitrogen is sterically crowded. The researchers suggest that by crowding the nitrogen, the catalyst will likely avoid coordination with the nitrogen which would form an unreactive pyridyl-bridge palladium dimer as shown in Scheme 2.

Table 1



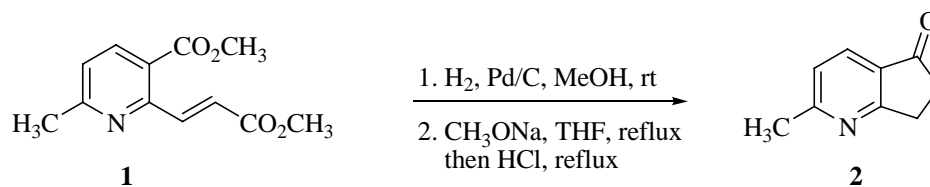
Entry	R ₁	R ₂	Product	Yield
1	CH ₃	CN		81
2	CH ₃	CHO		91
3	CH ₃	H		65
4	Br	H		92
5	OCH ₃	H		98
6	H	CO ₂ CH ₃		36
7	H	CN		35
8	H	CHO		42
9	H	OMOM		27
10	H	H		None

Scheme 2



The new procedure was applied to the synthesis of 6,7-dihydro-2-methylcyclopenta[b]pyridine-5-one (**2**) which was reported by another method in low yield. Starting from the pyridyl acrylate (**1**) compound **2** was obtained in good yield from hydrogenation of the double bond followed by Dieckmann condensation-decarboxylation as shown in Scheme 3.

Scheme 3



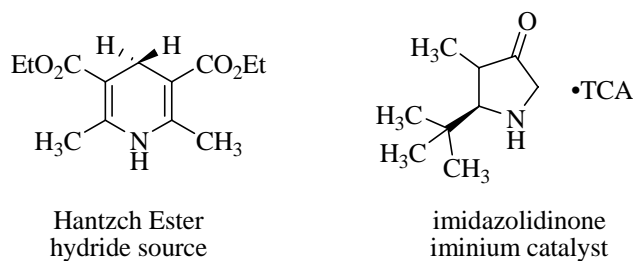
“Enantioselective Organocatalytic Hydride Reductions, Reductive Aminations, Aldol Reactions and Organic Cascade Reactions,”

Alan B. Northrup, Yong Huang, Abbas M. Walji, Catharine H. Larsen, Stephane G. Ouellet, Jamison B. Tuttle, R. Ian Storer, Diane E. Carrera, David W. C. MacMillan (Division of Chemistry and Chemical Engineering, California Institute of Technology), Pasadena, California.

Researchers at California Institute of Technology have been developing methodologies for enantioselective hydride reduction, reductive aminations and aldol reactions using organocatalysis. This methodology was taken a further step by employing multiple catalytic processes in what they term, “Organo-Cascade catalysis.”

Attempts to mimic biological enzymatic procedures involving hydride-reduction cofactors such as NADH and FADH₂ led to the development of the first reported enantioselective organocatalytic hydride reduction (EOHR). This bio-inspired reaction allows the transfer of a hydrogen using a Hantzsch ester as the hydrogen source and imidazolidinone iminium catalyst to control enantioselectivity (Figure 1).

Figure 1



This protocol gives excellent selectivity regardless of the geometry of the α,β -unsaturated aldehyde. Their studies have shown that stereoconvergence arises from catalyst accelerated *E-Z* isomerization as shown in Scheme 1.

Scheme 1

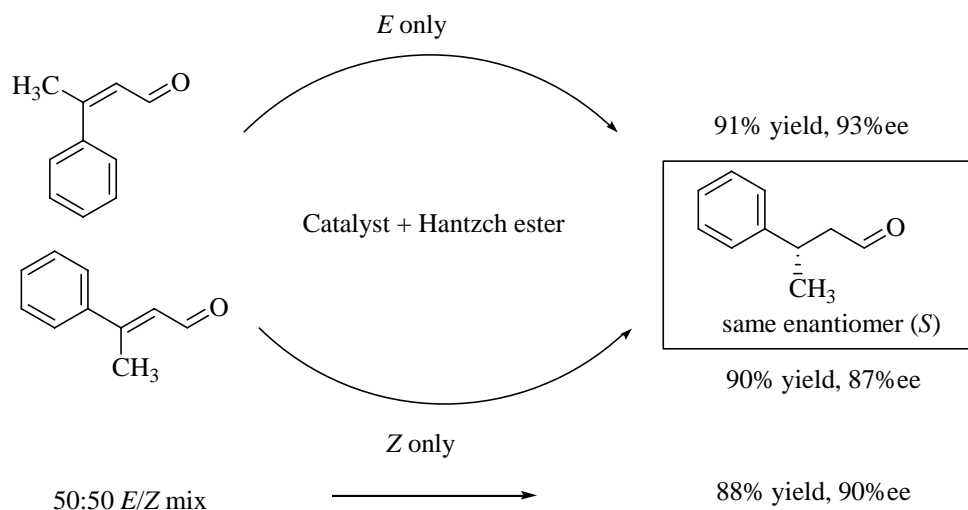
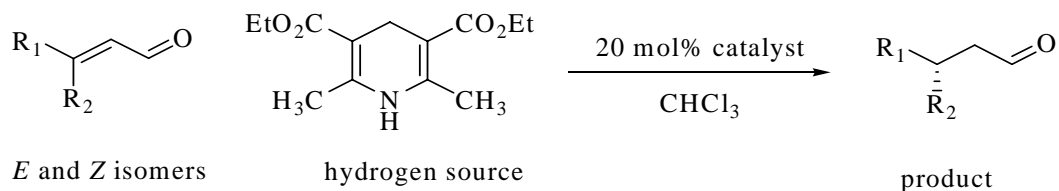


Table 1 shows the scope of this reaction with various α,β -unsaturated aldehydes.

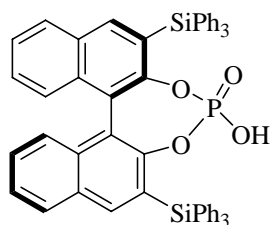
Table 1



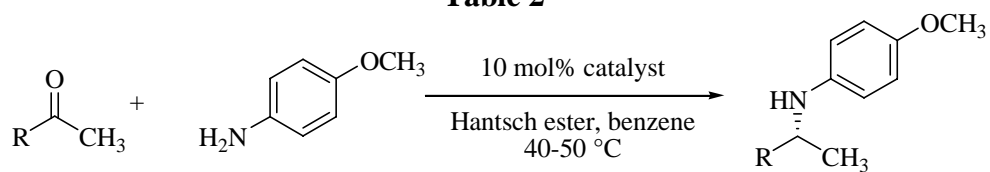
Entry	<i>E:Z</i> substrate	product	% yield	% ee
1	>20:1		91	93
2	>20:1		74	94
3	>20:1		92	97
4	5:1		91	96
5	3:1		95	91
6	>20:1		83	91
7	>20:1		74	90
8	>20:1		95	97

The Hantsch ester was also used as the hydrogen source for reductive aminations with stereochemistry being directed by a catalyst shown in Figure 2.

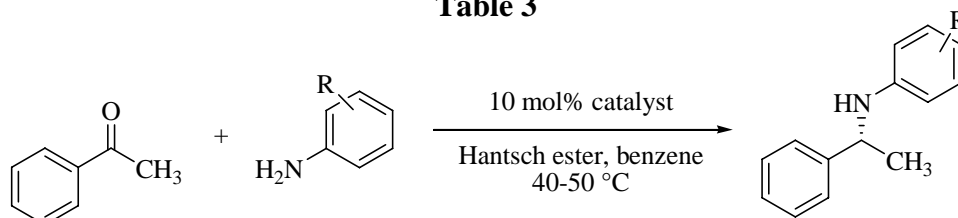
Figure 2



This reductive amination methodology is general with tolerance of a variety of amines and ketones giving reasonable yields and enantioselectivities. Tables 3 and 4 show some of the various amines and ketones as well as some yields and enantiomeric excess.

Table 2

Entry	Product	% Yield	% ee
1		71	95
2		60	83
3		73	96
4		82	97
5		49	86
6		72	81

Table 3

Entry	Product	% Yield	% ee
1		55	95
2		92	91
3		70	91
4		90	93

Dave MacMillan and his group have been able to employ organocatalysis in enantioselective cascade reactions. They use their amine catalyst to enforce substrate activation in the forms of iminium (LUMO lowering) and enamine (HOMO raising) catalysis. By this method, α,β -unsaturated aldehydes would undergo iminium ion formation when exposed to the catalyst in the first cycle. Enantioselective nucleophilic 1,4 addition followed by rapid hydrolysis would complete the first cycle. The second cycle would start with enamine activation and end with a highly diastereoselective addition of electrophiles as shown in Scheme 1.

Scheme 2

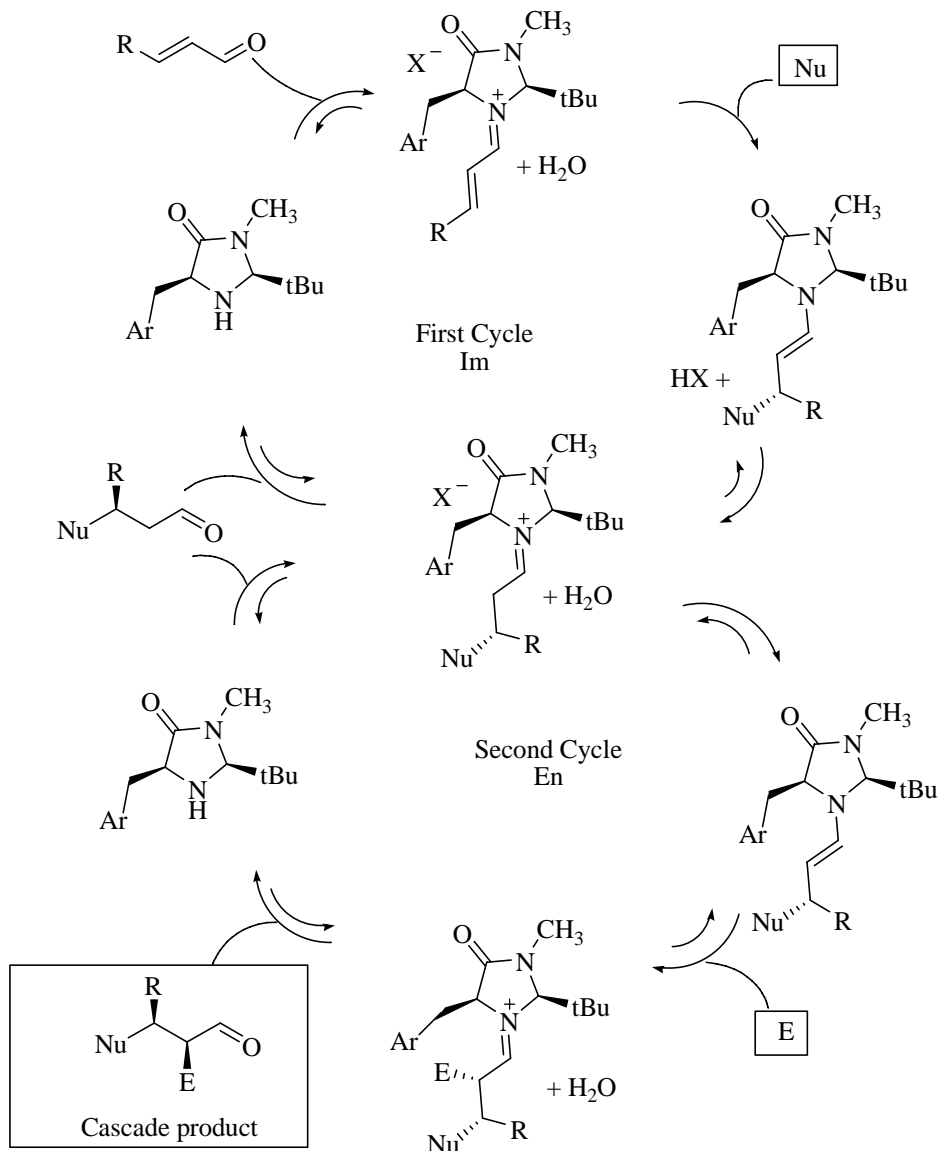
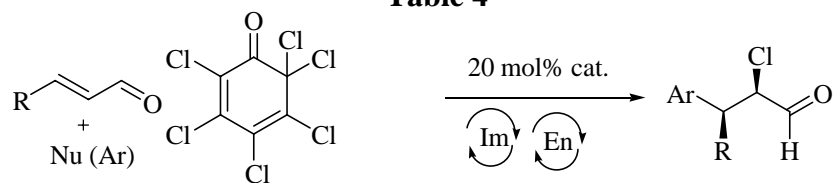


Table 1 shows a few representative products of this reaction. Various nucleophiles were employed to show the scope of this reaction.

Table 4



Entry	R=	Product	temp	% yield	dr	% ee
1	Me		-50	86	14:1	99
2	Pr		-50	74	13:1	99
3	CO ₂ Et		-60	80	22:1	99
4	CH ₂ OAc		-40	82	11:1	>99
5	Ph		-40	83	9:1	99
6	i-Pr		-40	67	12:1	>99