SYNSTORIES

Electrophile-Directed Diastereoselective Alkylation of Prochiral Enediolates

Iridium-Catalyzed Asymmetric Hydrogenation of Unfunctionalized Tetrasubstituted Olefins

Enantioselective Keto Ester-Ene Reaction Catalyzed by Chiral Dicationic Palladium(II) Complexes to Construct Quaternary Carbons

Asymmetric Synthesis of Oxazolidines, Thiazolidines and Pyrrolidines via Bisphosphine-Catalyzed Mixed Double-Michael Reactions
Dear readers,

this new issue of SYNFORM presents four SYNSTORY articles covering new exciting developments in organic chemistry: the construction of quaternary carbon stereocenters in a highly enantiocontrolled manner by means of a keto ester-ene reaction catalyzed by chiral palladium(II) complexes reported by the group of Professor Koichi Mikami (Japan), a new strategy for the diastereoselective alkylation of prochiral enediolates reported by the group of Dr. Steve Marsden (UK), a very challenging enantioselective hydrogenation of tetrasubstituted olefins developed by the group of Professor Andreas Pfaltz (Switzerland), and last, but not least, the double-Michael reactions catalyzed by chiral bisphosphines reported by Professor Ohyun Kwon (USA).

Thanks for your continued interest!

Matteo Zanda
Editor of SYNFORM

CONTACT
If you have any questions or wish to send feedback, please write to Matteo Zanda at: Synform@chem.polimi.it
The asymmetric ene reaction catalyzed by chiral Lewis acids is one of the most efficient methodologies for atom-economic carbon–carbon bond formation. The ene reaction of silyl enol ethers and carbonyl compounds is synthetically important as a short access to optically active alcohols with not only homoallylic but also remaining silyl enol ether functionality. Although various efficient ene reactions have been reported, only few reports on the asymmetric version with silyl enol ethers exist. The group of Professor Koichi Mikami from the Tokyo Institute of Technology (Japan) is very active in this field and has previously reported the asymmetric glyoxylate-ene reaction with trimethylsilyl enol ether catalyzed by chiral BINOL-Ti complexes to afford chiral β-hydroxy silyl enol ethers (J. Am. Chem. Soc. 1993, 115, 7039; Tetrahedron Lett. 1997, 38, 579). However, no ene reaction of silyl enol ethers with ketones to afford quaternary carbon centers was described. In fact, in the BINOL-Ti catalyst system, the use of a ketone instead of an aldehyde as an enophile led to lower yield and enantioselectivity.

Recently, the Mikami group introduced late-transition-metal palladium complexes as Lewis acid catalysts for the keto ester-ene reaction, which allows for the construction of β-hydroxy silyl enol ethers possessing a quaternary carbon center with high enantiocontrol. “The active dicationic palladium..."
A medium catalyst was generated in situ from a chiral PP*-PdCl\textsubscript{2} complex and 2.2 equivalents of AgSbF\textsubscript{6} in dichloromethane at room temperature,” explained Professor Mikami. “The reaction of 1 with 2 by using 0.05 mol\% of (S)-SEGPHOS-PdCl\textsubscript{2} proceeded smoothly to give (R)-3 in >99\% yield with 92\% ee without Mukaiyama aldol-type product 4. Even with the smallest substrate-to-catalyst ratio (S/C = 10,000), high yield and enantioselectivity (85\% yield, 90\% ee) could be obtained.”

Professor Mikami remarked that “The chiral palladium complexes are 1) air- and moisture-stable, 2) easily synthesized, and 3) catalytically very active (up to 0.01 mol\%) with high yield and enantioselectivity.”

“The two-directional hetero-ene-reaction sequence, first with pyruvate and then with glyoxylate, was attempted by using a chiral BINOL-Ti catalyst that we have previously developed for glyoxylate-ene reactions,” continued Professor Mikami. “Diol (R,S)-6 bearing both quaternary and tertiary carbon centers was obtained by use of the (S)-BINOL-Ti catalyst in 67\% yield and >99\% ee after desilylation with TBAF (dr = 92:8). In contrast, treatment with (R)-BINOL-Ti gave (R,R)-6 in 61\% yield and 97\% ee (dr = 91:9).”

“Development of an efficient and practical asymmetric synthetic process has been one of the most important challenges for modern synthetic chemists,” he concluded. “This highly active Lewis acid catalysis should find industrial applications.”

In a commentary to this work, Dr. Matthew Clarke from the University of St. Andrews (UK) said that “One of the key issues in the intermolecular ene reactions is the limited scope caused by the relatively high activation barrier of the reaction. Ketones rarely take part in the reactions: hence the impact of this paper. Silyl enol ethers are one of the most reactive ene components and 1,2-keto esters are the most reactive ketone enophiles, thus explaining why Mikami and co-workers have succeeded. The reaction is already useful,” he continued, “but I wonder if this reaction could be extended more generally to other less activated ketones: perhaps the authors have already tried… it would be a significant achievement if it were possible.” According to Dr. Clarke “A second attractive part of the paper is the authors’ successfully reducing catalyst loadings to practical levels. In the majority of papers on catalytic asymmetric C–C bond-forming reactions, 1–10 mol\% of catalyst are used, and no attempts to reduce this are reported. I am not saying that such studies should not be published in the top journals,” said Dr. Clarke, “but that attempts to catalytic turnover numbers should be made, even if this just ends up as a footnote to state it could not be achieved. To get the turnover numbers they report is impressive in an ene reaction. The third aspect that is interesting and could be developed further is the utilization of the products in a further reaction,” he concluded. “If one just cleaves the silicon group off, then the fact this is an ene rather than a Mukaiyama aldol reaction would just be a mechanistic...
anomaly. It would be interesting to see more work on utilizing the products (by alkene functionalization), although I appreciate such reactions need very mild conditions due to the sensitivity of the enol ether.”

About the corresponding author. Koichi Mikami is Professor of Applied Chemistry at the Tokyo Institute of Technology. He has received the Chemical Society of Japan Award (Shinpo-Sho) for asymmetric transmission and asymmetric synthesis based on [2,3]-Wittig rearrangements (1987), the IBM award for highly efficient asymmetric catalysis (1995), and the Ichimura Science Award for industrial application of asymmetric Friedel–Crafts reactions (2001), and was a Boehringer Ingelheim Award Lecturer (Université de Montréal, 2002).

Electrophile-Directed Diastereoselective Alkylation of Prochiral Enediolates


The control of absolute stereochemistry in the alkylation of prochiral enolates is an enduring challenge in asymmetric synthesis in both academic and industrial settings. According to Dr. Steve Marsden from the University of Leeds (UK) “Typically this has been achieved by the temporary covalent attachment of a chiral substituent to the acyl group (the chiral auxiliary approach), such that the two faces of the resulting enolate are diastereotopic rather than enantiotopic, and control of the new stereocenter can be engineered.”

“A logical alternative to this approach would be to exploit chirality in the electrophilic partner to direct the stereochemistry at the newly formed asymmetric center with a truly prochiral enolate,” said Dr. Marsden. “Despite its simplicity, such a strategy has rarely been successfully utilized in synthesis. Only two prior examples are known for simple β-chiral primary electrophiles and have used enolates derived from heteroaromatic systems, most notably in Overman’s elegant applications of oxindole enolates in alkaloid synthesis (J. Am. Chem. Soc. 2004, 126, 14043).” Recently, the first examples of such reactions using simple acyclic enolates were reported by Dr. Marsden and Rebecca Newton.

Building on earlier work detailing the construction of quaternary hydroxyamides by alkylation of dienediolates derived by double deprotonation of α-ketoamides (Synthesis 2005, 3261), Marsden and Newton investigated reactions using protected primary iodohydrins as the electrophile. “These reactions turned out to be highly stereoselective, generally ranging from 9:1 to >32:1 dr,” explained Dr. Marsden. “A series of experiments probing substituent effects revealed that the reaction was quite general, provided that (a) the enolate was substituted at the nucleophilic carbon with a lithiated oxygen, and (b) the electrophile contained an oxygen function β to the carbon undergoing substitution. This led to the proposition that the reaction proceeds through a chair-like transition state held together by coordination of the lithioalkoxy group of the enolate to the alkoxy group on the electrophile.”

Dr. Marsden explained that “The key advantage of the method is the ready availability of small chiral building
blocks for use as the electrophiles, either from chiral pool materials or by catalytic asymmetric synthesis. Any chiral auxiliary strategy routinely adds two steps to a synthesis – attachment and removal of the auxiliary – and for those cases where a chiral electrophile is employed we can now sidestep these.”

Additionally, the Marsden group investigated what would happen if the leaving group and directing oxygen function on the electrophile were reversed, i.e. use of a secondary iodohydrin derivative. “This would allow the direct construction of challenging motifs containing adjacent quaternary and tertiary asymmetric centers,” he said. They found that a highly stereoselective transformation took place, the outcome of which was consistent with the model proposed for the primary electrophiles above.

“With an understanding of some of the basic principles of the diastereoselective alkylations in place,” concluded Dr. Marsden, “my group is now investigating the use of different nucleophilic and electrophilic components to determine the true scope of the process, as well as the application of the methods in target synthesis.”

About the authors. Steve Marsden received his undergraduate and postgraduate training at Imperial College London (UK), obtaining his PhD in 1993 for work with Professor Steven Ley CBE, FRS. Following one year in the laboratories of Professor Samuel Danishefsky at Columbia University (USA) as a NATO postdoctoral fellow, he took up a lectureship at Imperial College London, before moving to his present position as a Reader in Organic Chemistry at the University of Leeds (UK) in 2001. He was a recipient of the Meldola medal of the Royal Society of Chemistry in 1998.

Bec Newton graduated from the University of Bristol (UK) and worked in process chemistry at GlaxoSmithKline before moving to the University of Leeds to study for her PhD, which was awarded to her in 2007.
Iridium-Catalyzed Asymmetric Hydrogenation of Unfunctionalized Tetrasubstituted Olefins

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The enantioselective hydrogenation of unfunctionalized olefins is a useful tool for organic chemists, and opens new routes for producing enantioenriched chiral compounds.

Although rhodium- and ruthenium-catalyzed hydrogenations are well established, both metals require functional groups near to the C=C double bond, to which the metal can coordinate,” explained Professor Andreas Pfaltz, an expert in the enantioselective hydrogenation of olefins from the Department of Chemistry at the University of Basel (Switzerland). “Hence, these catalysts cannot be used for the enantioselective hydrogenation of unfunctionalized olefins. Buchwald and co-workers introduced chiral early-transition-metal catalysts (Ti, Zr) that allowed for the reduction of tri- and tetrasubstituted unfunctionalized olefins with very high enantioselectivities. The high sensitivity of early-transition-metal complexes to moisture and air and unfavorable reaction conditions (up to 117 bar, 5–8 mol% catalyst loading, 13–65 h reaction time) prevented widespread use of these catalysts.”

In 1998, Professor Pfaltz and his group introduced air- and moisture-stable chiral iridium catalysts for the enantioselective hydrogenation of unfunctionalized olefins and showed that these catalysts are highly active in the hydrogenation of several classes of trisubstituted olefins. “Applying these catalysts to olefin 5 gave only a moderate enantiomeric excess of...”
81%,” said Professor Pfaltz. “For many years 81% remained the highest enantiomeric excess that had been obtained for this tetrasubstituted olefin. Many catalysts even showed very low activity towards the substrate, leading us to assume that tetrasubstituted unfunctionalized olefins are an unreactive class of substrates.”

“We envisaged that sterically less demanding ligands would facilitate the olefin coordination to the metal,” said Professor Pfaltz. “Until recently, we concentrated on ligands that form a six-membered ring with the iridium center (e.g., ligands 1–3). During Eva Neumann’s Ph.D. thesis work, she applied a ligand structure in the synthesis of new iridium catalysts which had previously been used by Helmchen in allylic alkylation reactions. These ligands (4) form a five-membered chelate and therefore open the coordination sphere around the iridium.” While the enantiomeric excesses obtained with most new catalysts in the hydrogenation of trisubstituted olefins were comparable with, or worse than, those obtained with other catalysts developed by the Pfaltz group, all new complexes showed high activity in the hydrogenation of olefin 5, with some giving enantiomeric excesses higher than 90%.

“Eva Neumann finished her Ph.D. thesis and left the group to work for Novartis in Basel,” recalled Professor Pfaltz. “At this time Marcus Schrems joined the group and took over from this point onwards. He found that not only the new five-membered-ring-chelate complexes (Ir-4) were active in the hydrogenation of various tetrasubstituted unfunctionalized olefins, but also other catalysts previously prepared in the group gave high activity and excellent ee values.”

However, most significant was probably the discovery that low hydrogen pressures had a very positive effect, when catalysts bearing ligands of type 4 were used. “Within three hours, olefin 5 was hydrogenated at only one bar of hydrogen pressure. This demonstrates the user-friendly nature of our catalyst system,” said Professor Pfaltz.
“As we could show for the reduction of tricycle 17, full conversion and very high enantiomeric excesses can be reached using catalyst loadings as low as 0.1 mol%.” The hydrogenation of 17 reflects a significant application of these iridium catalysts in the hydrogenation of unfunctionalized tetrasubstituted olefins. A variety of natural compounds exhibit structural motifs similar to 18.

“However, synthesizing two adjacent stereocenters in only one step is a difficult problem. Banwell and co-workers, for example, recently synthesized the tetracyclic carbon framework of the gibberellins from a racemic methoxy-substituted derivative of 18,” explained Professor Pfaltz. “Our methodology could be used to generate enantiomerically enriched compounds of this class. In subsequent studies we showed that Ir-catalyzed hydrogenation is a highly effective way to perform transformations of this type. The remarkably high catalytic activity of our iridium catalysts, even towards notoriously unreactive substrate classes, and the option to introduce two adjacent stereogenic centers in a single step open up new possibilities in asymmetric synthesis,” he concluded.

“We hope that the method presented by our group inspires other scientists to make use of Ir-catalyzed enantioselective hydrogenation for otherwise difficult transformations.”

About the authors. Andreas Pfaltz was born in Basel (Switzerland) in 1948. He received a diploma in natural sciences and a Ph.D. from the ETH Zürich (Switzerland). After completing his thesis under the direction of Albert Eschenmoser in 1978, he joined the research group of Gilbert Stork at Columbia University (USA) as a postdoctoral fellow. In 1980 he returned to the ETH where he was appointed ‘Privatdozent’ (Lecturer) in 1987. From 1990–1995, he was Professor of Organic Chemistry at the University of Basel, and from 1995–1998, Director at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (Germany). In 1999 he returned to the University of Basel where he is currently Professor of Organic Chemistry. His main interests are in the areas of homogeneous and heterogeneous catalysis, with special emphasis on asymmetric catalysis.

Marcus G. Schrems was born in Groß-Umstadt (Germany) in 1979. He studied chemistry at the Technische Universität München (TUM, Germany), National University of Singapore and University of Bergen (Norway) and graduated from TUM in 2005 after completing his Diploma thesis under the direction of R. Anwander and W. A. Herrmann. In 2006, he joined the lab of Andreas Pfaltz at the University of Basel. He is currently working on the Ir-catalyzed enantioselective hydrogenation of unfunctionalized olefins, focusing on tetrasubstituted olefins.

Eva Neumann was born in Hannover (Germany) in 1974. She studied chemistry at the Technische Universität München (Germany) and the Ecole Supérieure CPE Lyon (France). In 2002 she joined Andreas Pfaltz’ group at the University of Basel where she completed her doctoral thesis on “Transition Metal Complexes with P,N-Ligands and Silylenes: Synthesis and Catalytic Studies”. Since March 2006, she has been working as Process Manager at Novartis in Basel.
Asymmetric Synthesis of Oxazolidines, Thiazolidines and Pyrrolidines via Bisphosphine-Catalyzed Mixed Double-Michael Reactions


Tertiary phosphines catalyze a diverse array of reactions, including the Morita–Baylis–Hillman (MBH) reaction, Michael addition, aldol condensation, acylation of alcohols, silylcyanation of aldehydes, isomerization of olefins and acetylenes, conjugate addition of alcohols to propiolates, and allylic substitution.1 “Inspired by Lu’s pioneering use of allenes to extend the single-C–C bond-forming MBH reaction into a [3+2] cycloaddition, our group has been engaged in the development of phosphate-catalyzed annihilations of allenoates with electrophiles such as alkenes, imines, and aldehydes,” said Professor Ohyun Kwon from the Department of Chemistry and Biochemistry of the University of California, Los Angeles (USA). “These reactions produce carbo- and heterocycles regio- and diastereoselectively; gratifyingly, the use of chiral phosphines induces highly enantioselective annihilations.”2 The structural motifs obtained from these cycloadditions – tetrahydropyridines, dihydropyrroles, dioxanylidenes, 2-pyrones, dihydro-2-pyrones, dihydrocoumarins, and coumarins – are encountered frequently in natural products and pharmaceuticals.

![Scheme 1](image1)

“While continuing to expand the scope of these allenoate-based phosphine-catalyzed annihilations,” continued Professor Kwon, “we also wished to spearhead the development of new types of phosphine-catalyzed reactions.” One such reaction is the mixed double-Michael reaction of a 1,2-bisnucleophile and an activated acetylene (i.e., a 1,1-dielectrophile). “Although there were reports of double-carbo-, thia-, oxa-, and aza-Michael reactions,3 prior to our investigation there were no examples of mixed double-Michael reactions proceeding in the absence or presence of phosphate catalysts,” Kwon said. “Knowing that the reaction of a propiolate with an alcohol in the presence of a phosphate does not produce a β-di-alkoxy ester, our challenge was to succeed in forming the elusive second bond. Our initial attempts at performing these reactions – involving the inexpensive and ubiquitous PPh3 as the catalyst – met with only marginal success; under most conditions the major product was the single-Michael adduct 2. Clearly, the β-phosphonium α-carbanion 1 favored the disengagement of the phosphate to release the single-Michael product 2,” explained Professor Kwon. “Although we proposed in our paper a mechanism through which adduct 1 undergoes proton transfer to form the sulfonamide anion, which directly displaces the phosphate to form the cyclized product, we did not exclude a scenario in which the intermediate 1 acts as a general base to deprotonate the single-Michael adduct 2.” The resulting (sulfonamide) anion 3 can then undergo cyclization to form a phosphonium-sulfonamide ion pair 4, which deprotonates another single-Michael adduct 2 to regenerate the phosphonium-sulfonamide ion pair 3. “In either scenario,” Kwon said, “we recognized that the stability of the phosphonium adducts 1, 3, and 4 was the key to the viability of the cyclization event.”

![Scheme 2](image2)
“The discouraging performance of even the most basic and nucleophilic phosphine, PMe₃,” Kwon continued, “led us to consider the use of diphosphines, inspired by Verkade’s reports of proazaphosphatrane performing as a superior base and Trost’s use of dppp in Umpolung additions. Gratifyingly, dppp promoted the exclusive formation of the cyclic adducts and also converted isolated single-Michael adducts into desired cyclic products.” To identify the role of the second phosphine moiety, Professor Kwon and her group tested the catalytic performance of a series of bis(diphenylphosphino)alkanes containing linkers of various lengths. The optimum catalyst efficiency occurred for a tether length of three methylene groups; the behavior of dppm was similar to that of PPh₃. “These findings support the idea of anchimeric assistance by the second phosphine to stabilize the phosphonium center, rather than to act as a general base,” said Professor Kwon. “We suspect that the second phosphine in dppp adopts the apical position in a trigonal bipyramidal arrangement around the stabilized phosphonium center (A in Figure 1). This conformation is reminiscent of the structure of Verkade’s proazaphosphatrane.”

![Protonated Verkade's proazaphosphatrane](image)

According to Professor Kwon “The mixed double-Michael protocol is remarkably simple and atom-economical; it minimizes the generation of chemical waste and utilizes extremely mild reaction conditions. Our reaction methodology employs a catalytic amount (10 mol%) of dppp as the only additive and a slight excess of the bisnucleophile. Although our paper describes the syntheses of representative oxazolidines, thiazolidines, and pyrrolidines from amino acid derived β-amino alcohols, β-amino thiols, and γ-amino malonates, respectively, the potential product scope is vast.” The two pronucleophiles can be connected in a variety of ways, forming isolated or fused heterocycles (see Figure 2).

“Because the starting materials were derived from enantiomerically pure amino acids, we obtained products that were optically pure,” explained Professor Kwon. “We suspect that enantioselective variants of these reactions could be performed, however, when using chiral bisphosphines.” Unlike their common application as ligands in transition-metal catalysis, the advantages of using bidentate bisphosphines in nucleophilic organocatalysis are less obvious, and have been reported only rarely. “Chiral phosphorus-based ligands are the foundation of enantioselective transition-metal catalysis,” said Professor Kwon. “In particular, chiral bidentate phosphorus-based ligands (e.g., DIPAMP and BINAP) are the key components of asymmetric hydrogenations, which were recognized by the Nobel Prize in Chemistry in 2001. In contrast, the only known highly enantioselective nucleophilic phosphine catalyses employ monophosphines. With our reaction specifically requiring a bisphosphine – with anchimeric assistance providing a rigid architecture reminiscent of that of the ligands in metal–bisphosphine complexes – our reaction provides a testing ground for enantioselective chiral bisphosphine catalysis. More than anything, we hope that our paper demonstrates the synthetic power of burgeoning nucleophilic phosphine catalysis and contributes to the popularization of asymmetric nucleophilic phosphine catalyses, particularly those using bisphosphines.”

The manuscript describing this study was submitted seven months after Dr. “Murthy” Vardhineedi began performing research in Kwon’s laboratory. “The efficiency with which Murthy worked on this project was the highest that I have ever seen,” said Professor Kwon. “The whole experience was a delight – and working with him continues to be so. Murthy (Ph.D. in 2006) joined us from Professor V. K. Yadav’s group at the Indian Institute of Technology, Kanpur. Having a first-year graduate student, Gregg Barcan, on board expedited the completion of the reported work.”

According to Janine Cossy, Professor of Organic Chemistry from the Ecole Supérieure de Physique et Chimie Industrielles de Paris (France) and an Associate Editor of *Organic Letters*, “This work by Kwon et al. deals with a simple and efficient protocol to access disubstituted oxazolidines, thiazolidines and pyrrolidines in a very diastereoselective way, using a mixed Michael process catalyzed by bisphosphines.”

![Figure 2](image)
About the corresponding author. Ohyun Kwon received her B.Sc. (1991) and M.Sc. (1993) degrees from Seoul National University (South Korea). In 1993, she moved to the USA to pursue her Ph.D. (1998) at Columbia University under the guidance of S. J. Danishefsky. She then proceeded to Harvard University for postdoctoral research in S. L. Schreiber’s group. Kwon joined the faculty at UCLA in 2001 as an Assistant Professor and has built a strong research program centered on nucleophilic phosphine catalysis.

REFERENCES


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Matteo Zanda, C.N.R. – Istituto di Chimica del Riconoscimento Molecolare, Via Mancinelli, 7, 20131 Milano, Italy, e-mail: Synform@chem.polimi.it, fax: +39 02 23993080

Editor
Matteo Zanda, C.N.R. – Istituto di Chimica del Riconoscimento Molecolare Via Mancinelli, 7, 20131 Milano, Italy
Synform@chem.polimi.it
Fax: +39 02 23993080

Editorial Office
Managing Editor: Susanne Haak, susanne.haak@thieme.de, phone: +49 711 8931 786
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Marketing: Thomas Krimmer, thomas.krimmer@thieme.de, phone: +49 711 8931 772
Postal Address: SYNTHESIS-SYNLETT/SYNFACTS, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, phone: +49 711 8931 744, fax: +49 711 8931 777
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