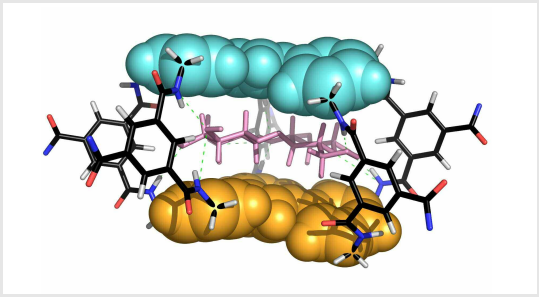
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2008/01

SYNSTORIES

- One-Pot Entry to Enantio-enriched Piperidines through a Novel Tandem Aza-Ene-Type Reaction/Cyclization Cascade
- New Hypervalent Iodine Reagents for Organic Synthesis
- Biomimetic Disaccharide Recognition with a Synthetic Lectin Analogue
- Asymmetric Direct Henry Reaction Mediated by a Chiral Tetraaminophosphonium Salt



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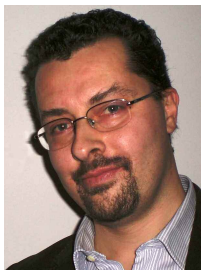

Dear readers,

The final score in this new issue of ***SYNFORM*** is Japan–UK 2-2. In terms of ***SYNSTORY*** articles, of course! Indeed, Japan and UK rule this issue, thanks to the excellent work and creative solutions in organic chemistry that were recently published by the Japanese groups of Professor Masahiro Terada, University of Tohoku, with his new organocatalytic tandem aza-ene/cyclization process, and of Professor Takashi Ooi, University of Nagoya, with his organocatalytic Henry-type reaction. The two ***SYNSTORIES*** from the UK were "scored" by Professor Thomas Wirth, University of Cardiff, with his new hypervalent iodine reagents for organic synthesis, and by Professor Anthony Davis, University of Bristol, with his biomimetic supramolecular recognition of disaccharides. Obviously we are eagerly waiting for new articles "scored" by scientists in other parts of the world in the forthcoming issues of ***SYNFORM***, which constantly monitors the best organic chemistry that is going on in the labs of all five continents.

With my best wishes for a healthy, successful and prosperous New Year 2008!

Matteo Zanda

Editor of ***SYNFORM***

CONTACT ++++

If you have any questions or wish to send feedback, please write to Matteo Zanda at:
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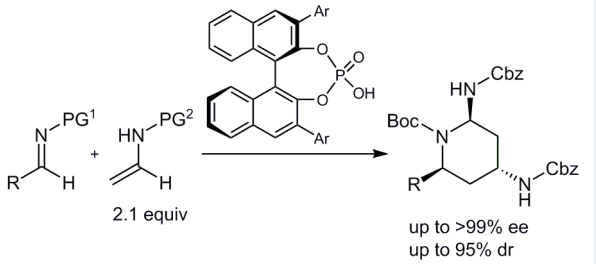

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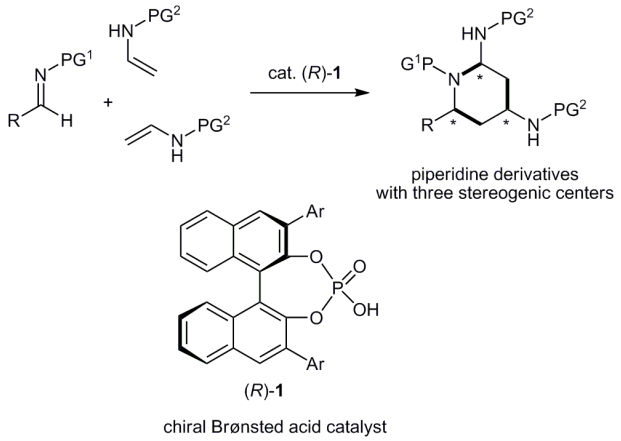
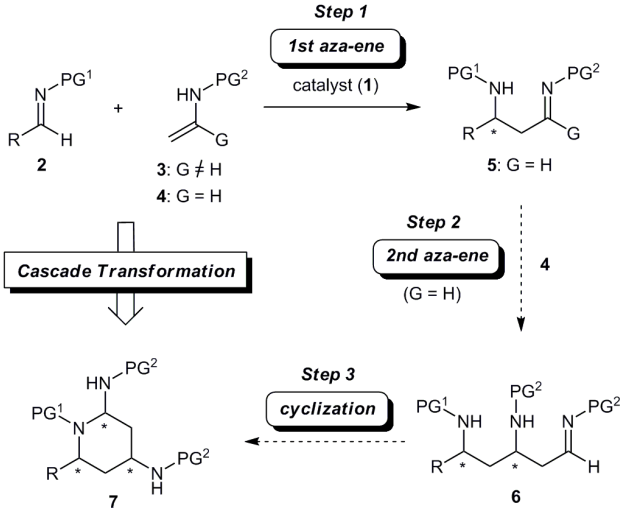
One-Pot Entry to Enantioenriched Piperidines through a Novel Tandem Aza-Ene-Type Reaction/Cyclization Cascade

J. Am. Chem. Soc. **2007**, *129*, 10336–10337

Catalytic cascade reactions are powerful tools in synthesis as they can produce a rapid increase in molecular complexity from simple and readily available starting materials. Enantioselective organic transformations using chiral Brønsted acids as green catalysts are of special interest because such catalytic processes would allow environmentally friendly and economically advantageous production of chiral non-racemic compounds. A new tandem aza-ene type reaction/cyclization cascade catalyzed by binaphthol-derived chiral monophosphoric acids **1** has been recently disclosed by Professor Masahiro Terada and co-workers from the Tohoku University (Sendai, Japan). The method enables the rapid and highly enantio- and diastereoselective construction of piperidine derivatives with multiple stereogenic centers.



According to Professor Terada "Aza-ene-type reactions of imines with enamide derivatives have recently emerged as an efficient protocol for the construction of 1,3-dinitrogen-substituted compounds, following the first report by Professor Shu Kobayashi and co-workers (University of Tokyo, Japan) using chiral copper complexes (*Angew. Chem. Int. Ed.* **2004**, *43*, 1679). More recently, Akiyama and co-workers (Gakushuin University, Japan: *Angew. Chem. Int. Ed.* **2004**, *43*, 1566) and our group (*J. Am. Chem. Soc.* **2004**, *126*, 5356) independently developed binaphthol-derived monophosphoric acid **1** as chiral Brønsted acids, and now **1** has been widely utilized as an efficient enantioselective catalyst for numerous organic transformations by several research groups. We applied the monophosphoric acid **1** to the aza-ene-type reaction of *N*-acyl aldimines **2** with disubstituted enecarbamates **3** (G ≠ H)," he continued, "using significantly low loading of the catalyst (*Angew. Chem. Int. Ed.* **2006**, *45*, 2254). The formation of the imine products from the aza-ene-type reaction inspired us to develop the present cascade transformation." The acid-catalyzed reaction of initial aldimines **2** with monosubstituted enecarbamates **4** (G = H) would generate aza-ene-type products of *N*-acyl aldimines **5** as reactive intermediates (Step 1). Hence, **5** would undergo further aza-ene-type reactions leading to the subsequent generation of aldimines **6** (Step 2).



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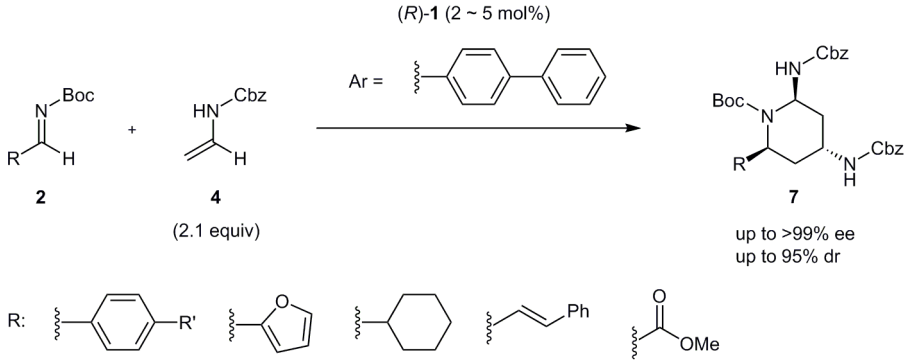
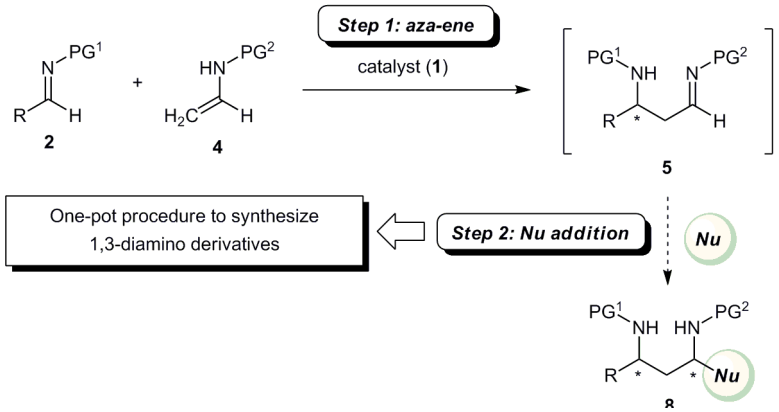


Intramolecular cyclization of **6** would be enacted to terminate the tandem aza-ene-type reaction sequence (Step 3) which would allow rapid access to piperidine derivatives **7** as key structural elements of numerous natural products.

"One of the most valuable features of this methodology is the extremely high stereoselectivity in this cascade transformation," remarked Professor Terada. "Thus, in most cases, one stereoisomer was formed exclusively out of the eight possible stereoisomers consisting of four pairs of enantiomers that result from three stereogenic centers." Excellent enantioselectivities along with high diastereoselectivities were attained using a broad range of imine substrates, such as aromatic, heteroaromatic, and aliphatic substituted imines as well as α,β-unsaturated imines. In addition, the glyoxylate-derived imines can be transformed into the highly functionalized piperidine derivative with excellent enantioselectivity.

"The reaction has a remarkably wide scope," Professor Terada pointed out, "and our next challenge is the development of a two-carbon elongation reaction based on the present aza-ene-type reaction using monosubstituted enecarbamates. If the aza-ene-type reaction product **5**, delivered from the first step of the tandem reactions, could be trapped by another nucleophile, the method may be applied to a sequential approach for the construction of 1,3-diamine derivatives **8** in a one-pot procedure." But how could one stop the tandem aza-ene-type reaction sequence? "This is a big challenge," answered Professor Terada, "because the piperidine derivatives **7** were obtained predominantly even using an excess amount of initial imine over enecarbamate. We are now planning to stop the tandem aza-ene-type reaction sequence by the first step. The method would enhance the potential of the sequential approach based on the aza-ene-type reaction," he concluded.

In a commentary to Professor Terada's work, Dr. Petri Pihko from the Helsinky University of Technology (Finland) said that "the paper by Terada and co-workers describes a highly interesting Brønsted acid catalyzed reaction between a preformed imine and a preformed enamine. Typically, in en-



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amine and iminium catalysis, the amine catalyst is lost at the end of the reaction, resulting in the formation of a carbonyl compound. In this case, Terada et al. have turned the concept on its head, using a Brønsted acid to mediate the reaction between stable Boc-protected imines and *N*-Cbz-protected enamines. The initial aldol-like aza-ene reaction gives a β-amino imine that readily participates in the next aza-ene reaction. The resulting imine could then cyclize on its own to give a cyclic aminal."

About the corresponding author: **Masahiro Terada** (born 1964) was an Assistant Professor in Professor Mikami's laboratory (Tokyo Institute of Technology, Japan) in 1989, and received his PhD in 1993. He worked as a postdoctoral fellow with Professor M. D. Shair at Harvard University from 1999–2000 and returned to Professor Mikami's laboratory until he moved to Tohoku University as an Associate Professor in 2001. He is a Professor of Chemistry at the Graduate School of Science, Tohoku University (Japan) since 2006. His awards include the Inoue Research Award for Young Scientists (1995) and the Incentive Award in Synthetic Organic Chemistry, Japan (2003).

Prof. M. Terada

Matteo Zanda

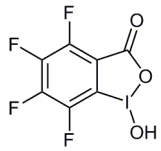
New Hypervalent Iodine Reagents for Organic Synthesis

Angew. Chem. Int. Ed. **2007**, *46*, 6529–6532

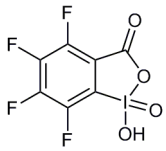
Reagents containing hypervalent iodine have a reputation of great usefulness in organic chemistry. Among them, one could mention the Dess–Martin periodinane and other compounds like IBA and IBX, which are extensively used in synthesis.

The arsenal of hypervalent iodine reagents available to the synthetic chemist has been recently enriched by two novel compounds, namely FIBX and FIBA (both characterized by the presence of a fully fluorinated aromatic ring), which have been reported by Professor Thomas Wirth and his coworkers from the School of Chemistry of Cardiff University (UK).

"We already tried to access this molecule by a different route several years ago back in Switzerland," explained Professor Wirth, "but were unable to obtain sufficient amounts for detailed experiments. The new route, only two steps from commercially available compounds, allows a fast and efficient synthesis of large amounts." Stability and safety concerns are often an issue with hypervalent iodine compounds, however, Professor Wirth said that "DSC measurements, yet



FIBA



FIBX

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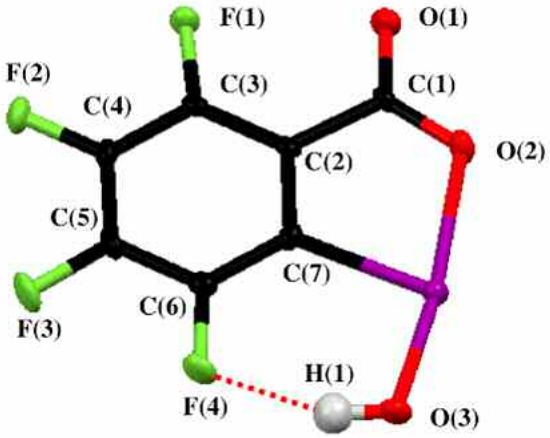
unpublished, indicate slightly higher stability than IBX and IBA, but still nice little explosions in a melting point capillary are observed."

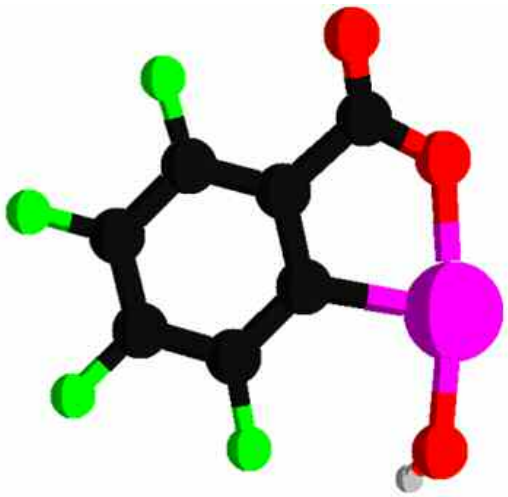
Professor Wirth has shown that FIBA and FIBX can be used for several different oxidations, such as secondary alcohols to ketones, and then to the corresponding α,β-unsaturated ketones, or α-tosylations in the presence of *p*-TsOH. Concerning the possibility of tuning the reactivity of these reagents, Professor Wirth noted that "a range of novel – now fully fluorinated – IBX and IBA derivatives with increased reactivities should now be easily accessible. Unfortunately FIBX has resisted – up to now – all attempts to prepare a fully fluorinated Dess–Marin periodinane analogue."

A great advantage of these reagents is the possibility to monitor the reaction progress directly by ^{19}F NMR spectroscopy: "There is no need for deuterated solvents as the different oxidation stages of the reagent – iodine(I), iodine(III) and iodine(V) show very different spectra," concluded Professor Wirth.



X-ray structure of FIBA (R. D. Richardson, J. M. Zayed, S. Altermann, D. Smith, T. Wirth: Tetrafluoro-IBA and-IBX: Hypervalent Iodine Reagents. Angew. Chem. Int. Ed. 2007, 46, 6529-6532. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

In a comment on this work, Dr. Berit Olofsson from Stockholm University (Sweden) noticed that "Iodine(V) reagents, such as Dess–Martin periodinane and IBX, are frequently used as mild oxidants of alcohol moieties in total syntheses of natural products. IBX can also affect oxidative transformations of a variety of other functional groups," she continued. "One of the major drawbacks of IBX is certainly its limited solubility in organic solvents. Professor Wirth and coworkers



Calculated structure of FIBA (R. D. Richardson, J. M. Zayed, S. Altermann, D. Smith, T. Wirth: Tetrafluoro-IBA and-IBX: Hypervalent Iodine Reagents. Angew. Chem. Int. Ed. 2007, 46, 6529-6532. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

have addressed this issue by designing and employing tetrafluoro-IBX (FIBX), which shows promising reactivity and solubility. Although further investigations are needed to show the full potential of FIBX, the paper clearly constitutes an important step in making iodine(V) reagents more applicable in organic synthesis. Common iodine(III) reagents include (diacetoxy)iodobenzene and derivatives thereof, whereas the use of IBA has been limited. Thus," concluded Dr. Olofsson, "the potential of tetrafluoro-IBA is more difficult to judge, and it remains to see how well it compares to the iodine(III) compounds generally employed."

R. Richardson

S. Altermann

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About the corresponding author: Thomas Wirth obtained his Diploma from the University of Bonn (Germany) in 1989 and his PhD in 1992 on the use of 2-vinylindoles in synthesis from the Technical University of Berlin (Germany) with Professor S. Blechert. After a postdoctoral stay (1993) working on the memory of chirality with Professor K. Fuji at Kyoto University (Japan) as a JSPS fellow, he started his independent research at the University of Basel (Switzerland). In the group of Professor B. Giese he obtained his habilitation on stereoselective oxidation reactions in 1999, supported by various scholarships, before taking up his current position at Cardiff University in 2000. He was invited as a Visiting Professor to a number of places including the University of Toronto (Canada, 1999), Chuo University in Tokyo (Japan, 2000), Osaka University (Japan, 2004) and Osaka Prefectural University (Japan, 2008) and was awarded the Werner Prize from the New Swiss Chemical Society in 2000. Thomas Wirth is the author of ~100 publications and has written/edited four books.

Prof. T. Wirth

For more information see:
http://www.cardiff.ac.uk/chemy/contactsandpeople/academicstaff/wirth.html.

Matteo Zanda

Asymmetric Direct Henry Reaction Mediated by a Chiral Tetraaminophosphonium Salt

J. Am. Chem. Soc. **2007**, *129*, 12392–12393

Control of the stereochemical outcome of organic reactions is becoming increasingly sophisticated in order to meet the stringent economic, environmental and safety requirements of modern chemistry. Organocatalysis holds great promise in relationship with the aforementioned issues; therefore, research in the area of asymmetric organocatalysis is very competitive and regularly produces important breakthroughs. One of them was recently achieved by Professor Takashi Ooi and his coworkers at the Department of Applied Chemistry of Nagoya University (Japan), who developed a new strategy for inducing a highly enantioselective outcome in direct Henry-type reactions between nitroalkanes and aromatic as well as aliphatic aldehydes. This methodology, which has remarkable scope, is based on the use of an enantiomerically pure triaminoiminophosphorane base, which deprotonates the nitroalkane and is thus transformed into the conjugate acid, a chiral P-spiro tetraaminophosphonium cation **A**. The nitroalkane counter-anions subsequently react with the aldehydes under the stereochemical control of the chiral cation, affording the corresponding nitroaldols with very high diastereo- and enantioselectivity.

"This is the first example of utilizing optically active triaminoiminophosphorane as an organic base catalyst for synthetically valuable stereoselective bond-forming processes,

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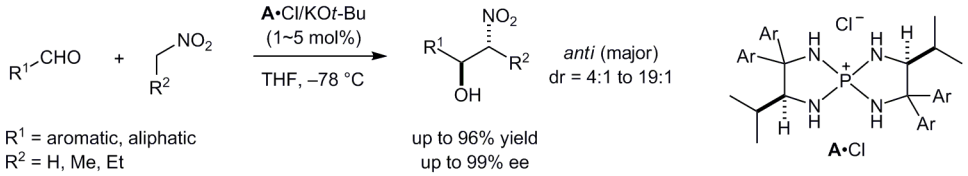
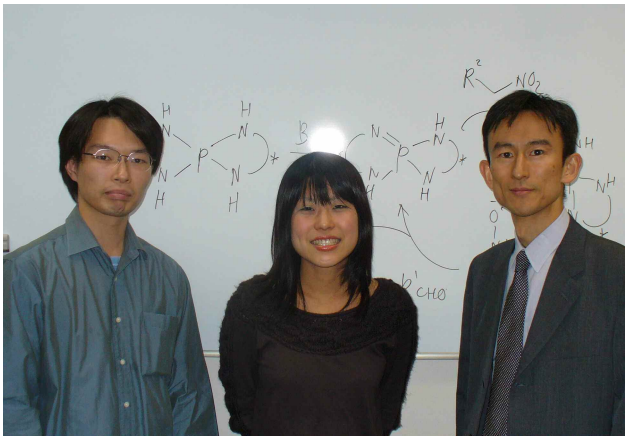


such as a Henry reaction," said Professor Ooi. "The success relies heavily on the molecular design of the conjugate acid, the chiral P-spiro tetraaminophosphonium chloride **A**•Cl that can be assembled in a single step from the readily accessible chiral 1,2-diamines derived from the corresponding α-amino acids." Concerning this innovative chiral tetraaminophosphonium cation, Professor Ooi explained that "its most important feature is its ability to behave as a hydrogen-bonding donor, which plays a key role in controlling the distance and direction of the reactive ion pair – the chiral phosphonium nitronate – through double hydrogen-bonding interaction." The transfer of stereochemical information from **A** to the nitroaldol product is, obviously, a key issue in this work. "The formation of such a well-structured ion pair is probably a crucial element for achieving the unprecedented highly anti-selective asymmetric direct Henry reaction with a wide range of aldehydes," said Professor Ooi. "The present study opens a door to new avenue for rational design of chiral phosphonium salts and their applications as an organic molecular catalyst," he concluded, "hopefully facilitating the understanding of the rela-tionship between the three-dimensional structure of an onium salt and its reactivity and selectivity in the targeted transformations."

According to Dr. Marco Bandini, an expert in enantiocontrolled Henry-type reactions from the University of Bologna (Italy), "The well-designed and fully characterized tetraminophosphonium salt must be included among the most efficient catalysts for enantioselective nitroaldol condensations. Worthy of note is the excellent level of enantiocontrol guaranteed for a wide range of substrates in the presence of catalyst. Moreover, the challenging issue of diastereoselection in the Henry reaction is successfully addressed. The remarkable catalyst performances of the chiral phosphonium salt," he concluded, "will stimulate other creative applications in enantioselective transformations."



From left: Dr. D. Uraguchi, S. Sakaki, Prof. T. Ooi

About the corresponding author. **Takashi Ooi** received his Ph.D. in 1994 from Nagoya University under the direction of Professor Hisashi Yamamoto, and joined the group of Professor Julius Rebek, Jr. at MIT as a postdoctoral fellow (1994–1995). He was appointed as an Assistant Professor at Hokkaido University in 1995 and promoted to a Lecturer in 1998. He moved to Kyoto University as an Associate Professor in 2001, and became a Full Professor at Nagoya University in 2006. He was awarded the Chugai Award in Synthetic Organic Chemistry, Japan (1997), the Japan Chemical Society Award for Young Chemist (1999) and the Thieme Chemistry Journal Award (2006). His current research interests are focused on the development of new and useful synthetic methodologies by designing organic molecular catalysts including chiral quaternary onium salts.

Matteo Zanda

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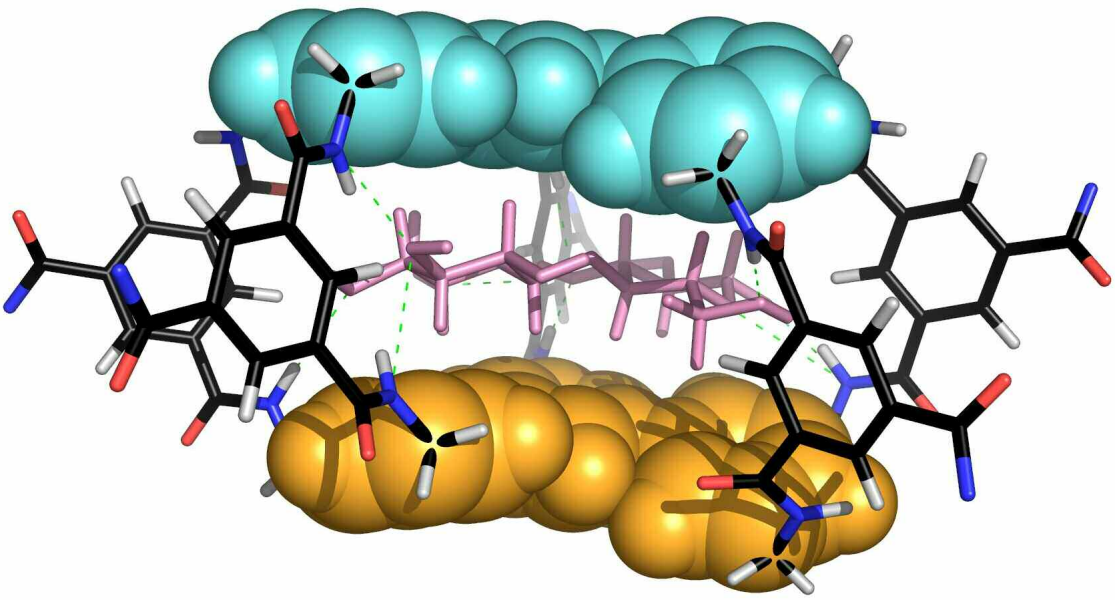
Biomimetic Disaccharide Recognition with a Synthetic Lectin Analogue

Science **2007**, *318*, 619–622

The chemistry of carbohydrates is still a very challenging area of research. The strongly hydrophilic character of carbohydrates as well as their stereochemical complexity are among the most difficult issues to deal with for the organic chemist. This is particularly true in the field of supramolecular chemistry because the energies involved in host–guest interactions and molecular recognition phenomena are relatively weak, and discrimination between substrate and water as well as between subtly different carbohydrates can be extremely difficult. An important step forward has been accomplished recently by Professor Anthony Davis and coworkers from the School of Chemistry of the University of Bristol (UK), who described a synthetic lectin analogue for the biomimetic recognition of disaccharides.

"We have been interested in carbohydrate recognition for many years," said Professor Davis, "we first published in the area in 1990. At a time when supramolecular chemists were mostly trying to bind quite simple molecules and ions, carbohydrates seemed interesting because of their complex three-dimensional structures. We also became aware of their importance as biological labels, which was only just emerging, the special difficulty of carbohydrate recognition in water (where the substrate looks like the solvent), and the controversy surrounding the driving force for carbohydrate recognition in nature (polar or hydrophobic interactions?)."

According to Professor Davis, early work of his group avoided the most difficult issues by studying carbohydrate recognition in organic media. "Although we had to build quite large molecules to encapsulate our targets, we could use hydrogen bonding to drive binding and achieve quite high affinities. A few years ago, however, we decided we had to move into water," said Professor Davis. "We had a design which worked well in organic solvents and seemed likely to succeed in water. Making it water-soluble was non-trivial, but



Picture of the receptor with cellobiose inside (pink). The aromatic surfaces forming the roof and floor of the receptor are shown in space-filling mode.

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in 2004 this was achieved by Emmanuel Klein, a French post-doc in my group. In early 2005 we were able to publish our first example of carbohydrate binding in water."

The first receptor developed by Professor Davis was targeted at glucose and, unfortunately, was very weak (K_a = 9 M^{-1}) (*Angew. Chem. Int. Ed.* **2005**, *44*, 298). "We thought that a larger receptor for a larger substrate might show higher affinities, and this prompted us to design the cellobiose receptor reported in the Science paper," he explained. "The receptor was made by another French post-doc, Yann Ferrand, and studied with the help of Dr. Matthew Crump, who is an expert in biological NMR spectroscopy. It worked somewhat better than expected. We would have been quite happy with K_a = 100 M^{-1}, whereas we achieved 600 M^{-1}. Also, the selectivity was extraordinary. For example, lactose differs from cellobiose at just one stereocenter, yet is bound with K_a = just 12 M^{-1}. We don't understand why the difference is so large, but it's certainly pleasing."

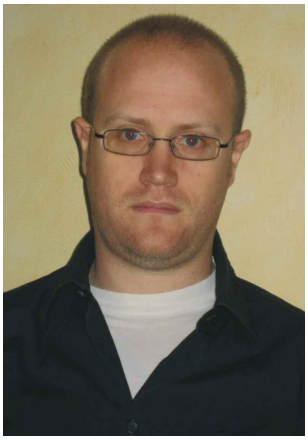
"Although cellobiose is not a high-profile molecular target," continued Professor Davis, "it has a hidden importance – it is the repeat unit in the polysaccharide cellulose, the major constituent of plants and the most abundant organic material on earth." In fact, cellulose is a key renewable resource, but is difficult to exploit because of its insolubility. "If cellulose could be bound and solubilized by a synthetic lectin," he said, "new types of processing should be possible. Meanwhile, we are working on other targets, especially glucose. Although our first attempt was too weak to be useful (see above), we think we can do better. If we are successful, we will have the key component for a glucose sensor which could be used in an 'artificial pancreas' for treating diabetics."

Aside from any applications, Professor Davis feels that the work also has importance at a theoretical level. "Now that we possess a synthetic lectin, we can perform experiments which help us understand the properties of natural lectins. In particular, we can compare the receptor's performance in a variety of solvent systems, many of which would not be compatible with natural lectins. This should throw new light on the role of solvation in driving natural carbohydrate recognition (a controversial issue, as mentioned above). Also, the simple fact that our system comes so close to mimicking lectins has some significance," he concluded. "Proteins have had a long time to optimize their properties, so our efforts to mimic them are usually not this successful."

In a commentary to Professor Davis' work, Dr. Stefano Roelens, an expert in supramolecular chemistry of carbohydrates from the C.N.R. in Florence (Italy), said: "Understanding and mimicking molecular recognition of carbohydrates

M. P. Crump

Prof. A. Davis



Y. Ferrand

opens the way to the comprehension of fundamental biological processes, such as cell-to-cell adhesion, cell infection by pathogens and immune response, to name a few. This ambitious as much as challenging goal has pushed scientists to investigate the subject through synthetic receptors, reaching some significant achievements in organic solvents. But when we get into water," continued Dr. Roelens, "where biological processes occur, can we really mimic or compete with biological systems? The answer to this question has been in the dreams of the many scientists who got involved in the molecular recognition of carbohydrates in the last decade. Undoubtedly, this work by Davis and coworkers comes as a major breakthrough in the field, showing that by a careful design of structure, functionalities and preorganization of the receptor's architecture, levels of affinity and selectivity for sugars comparable to those of the natural lectins can indeed be achieved even in water. This work," he concluded, "which is no doubt a heuristic milestone for future research, demonstrates that challenging Nature is no longer a dream."

Matteo Zanda

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(Focus on an article from the current literature)

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Electrophile-Directed Diastereoselective Alkylation of Prochiral Enediolates
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