

# Acceptorless Dehydrogenative Coupling Using Ammonia: Direct Synthesis of N-Heteroaromatics from Diols Catalyzed by Ruthenium

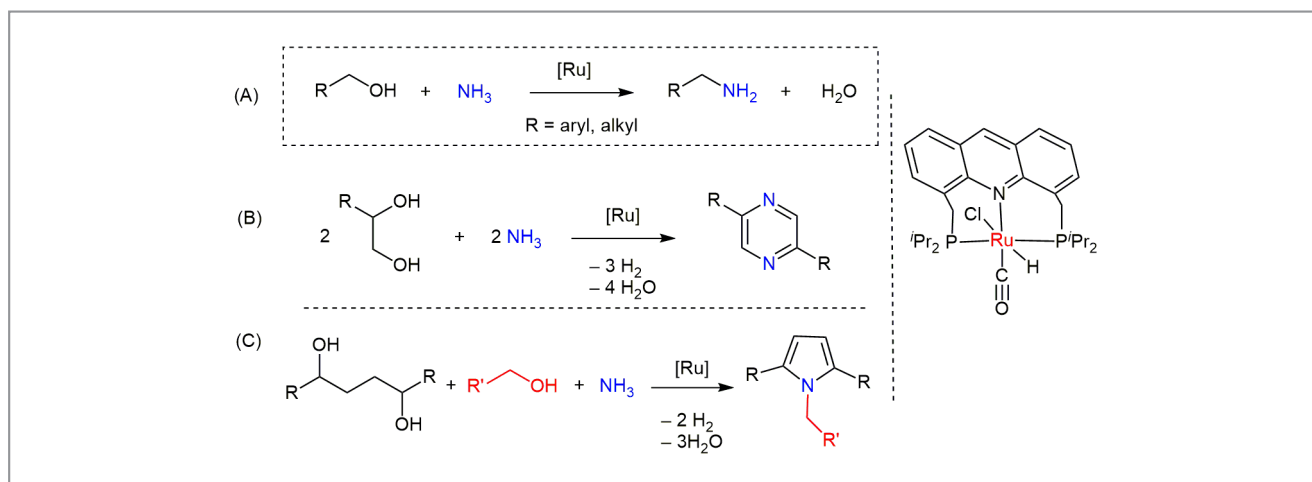
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Acceptorless dehydrogenative coupling (ADC) reactions involve dehydrogenation, with generation of hydrogen gas, of various substrates, followed by coupling of the dehydrogenated intermediate with another substrate to form a value-added product. Many of these reactions form the basis for efficient, sustainable and environmentally benign ('green') synthetic methodologies.

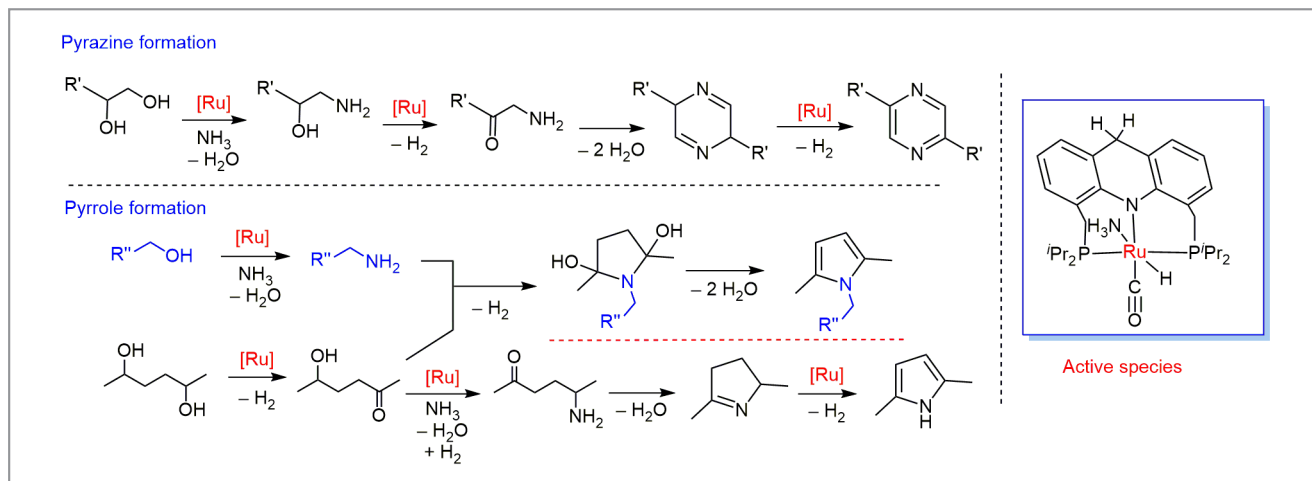
The group of Professor David Milstein at the Weizman Institute of Science (Rehovot, Israel) focuses on the design and development of ADC reactions for green organic transformations catalyzed by special pincer-based metal complexes. These complexes can activate chemical bonds by metal–ligand cooperation, in which both the metal and the ligand attached to it undergo bond-making and bond-breaking. The development of practical, green, and atom-economical processes for the synthesis of value-added products using cheaper, greener and sustainable methodologies is highly desirable. "Ammonia is the simplest, reactive molecule employed as a nitrogen source in the synthesis of organo-nitrogen compounds," said Prof. Milstein, continuing: "However, the direct use of ammonia in acceptorless dehydrogenative coupling reactions is challenging, due to several issues; ammonia is an excellent ligand for many metals and can coordinatively saturate the metal complex catalyst, retarding binding of the organic reac-

tant. Also, ADC reactions are often driven by the efficient removal of the generated  $H_2$  using an open system, which poses an obvious problem when ammonia gas has to be used under pressure."

In 2008, the direct homogeneous catalytic selective amination of primary alcohols to form primary amines using ammonia, catalyzed by an acridine-based Ru pincer complex, was reported by the Milstein group (Scheme 1, A). This finding, along with the subsequent discoveries of more catalysts, has established this particular reaction as a valuable synthetic method. Professor Milstein added: "However, we wanted to see if it was possible to synthesize N-heteroaromatic molecules by direct use of ammonia as the only nitrogen source in a dehydrogenative coupling reaction." Indeed, using diols, this goal was accomplished: several pyrazine derivatives were efficiently and selectively synthesized from 1,2-diols and ammonia (Scheme 1, B). Moreover, N-substituted pyrroles were synthesized by a three-component reaction involving the dehydrogenative coupling of 1,4-diols with primary alcohols and ammonia (Scheme 1, C). "In both reactions, gaseous ammonia is the source of nitrogen, and the catalyst is an acridine-based ruthenium pincer complex, with no additives, such as base or oxidant, being required," explained Professor Milstein. He continued: "Analysis of the gas phase of both reactions by



**Scheme 1** Acceptorless dehydrogenative coupling reactions using ammonia



**Scheme 2** Proposed mechanism for N-heteroaromatic compound formation from diols and ammonia

gas chromatography shows formation of  $H_2$ . It was observed that linear primary alcohols such as 1-hexanol and 1-pentanol are more efficient than benzyl alcohol derivatives in the synthesis of the N-substituted pyrroles. Mechanistically, it is proposed that both reactions involve a sequence of alcohol amination, alcohol dehydrogenation, and keto-amine condensation, yielding the N-heteroaromatic product (Scheme 2). The acridine-based PNP-pincer ligand plays a vital role in these transformations, generating the active complex bearing an anionic dearomatized PNP-pincer ligand framework."

Professor Milstein concluded: "We believe that these discoveries provide a new approach towards the green synthesis of heteroaromatics in one step via acceptorless dehydrogenative coupling by direct use of ammonia. In addition, we would like to expand the direct use of ammonia to other transformations involving dehydrogenative coupling reactions."

*Matthew Fenske*

## About the authors



Dr. P. Daw

**Prosenjit Daw** obtained his B.Sc. in chemistry from the University of Calcutta (India). He completed his M.Sc. and Ph.D. at the Indian Institute of Technology Kanpur (IIT Kanpur, India) where he worked on N-heterocyclic carbene based organometallic catalysts and their application in organic transformations in the group of Prof. Jitendra K. Bera under a Shyama Prasad Mukherjee Fellowship (SPMF). After completing his Ph.D. he moved

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Dr. Y. Ben-David

**Yehoshua Ben-David** obtained his B.Sc. in chemistry and botany from the University of Khartoum (Sudan) in 1967. In the same year he moved to Israel and joined the Department of Organic Chemistry in the Weizmann Institute of Science as a research assistant. He worked with many senior scientists at that time in the same department. In 1988 he joined Prof. David Milstein's group as a research assistant and he has been there since.

After his retirement in 2010, he returned as a part-time research assistant in the same group.



Prof. D. Milstein

**David Milstein** is the Israel Matz Professorial Chair of Organic Chemistry at the Weizmann Institute of Science (Israel). He received his Ph.D. at the Hebrew University (Israel) in 1976 with Prof. Blum, and performed post-doctoral research at Colorado State University (USA) with Prof. Stille. In 1979 he joined DuPont Company's Central Research & Development Department in Wilmington (Delaware, USA) as a Group Leader, and in 1986

he moved to the Weizmann Institute of Science (Israel), where he headed the Department of Organic Chemistry from 1996 to 2005 and the Kimmel Center for Molecular Design from 2000 to 2017. His research interests include fundamental organometallic chemistry, homogeneous catalysis, and the design and application of metal-catalyzed reactions for green chemistry and renewable energy. His recent awards include The Israel Prize (Israel's highest honor, 2012), The ENI Award for protection of the environment (2016), the Gold Medal of the Israel Chemical Society (2017), and the European Prize for Organometallic Chemistry (2017). He is a member of the Israel Academy of Sciences and Humanities, the German National Academy of Sciences-Leopoldina, and the US National Academy of Sciences.