Synergistic Organocatalysis in the Kinetic Resolution of Secondary Thiols

A New Combined Source of “CN” from N,N-Dimethylformamide and Ammonia in the Palladium-Catalyzed Cyanation of Aryl C–H Bonds

Stereoselective Synthesis of Tertiary Ethers through Geometric Control of Highly Substituted Oxocarbenium Ions
Dear readers,

This issue of SYNF ORM features three SYNSTORIES articles describing brilliant and extremely exciting advances in the art of organic synthesis. The first SYNSTORY reports on an astonishing-ly effective methodology developed by Professor S. Connnon (Ireland) for the organocatalytic kinetic resolution of racemic thiols, which is a very challenging endeavor with few precedents in the literature (certainly very few having this level of efficiency) and holds great promise of finding applications in medicinal and bioorganic chemistry. The second SYNSTORY covers a very innovative and elegant procedure developed by professor S. Chang (Korea) for preparing cyanoaryl derivatives, which relies on the assembling of the CN moiety from ammonia (source of the nitrogen atom) and N,N-dimethylacetamide (source of the carbon atom), which is then coupled with a CH moiety of an aromatic group through a palladium-catalyzed reaction. Last but not least, a stereoselective synthesis of tertiary ethers developed by Professor P. E. Floreancig (USA) which exploits a sophisticated process involving highly substituted oxocarbenium ions generated by oxidative C–H bond activation and leading to structurally complex tetrahydropyrans.

Enjoy your reading!

Matteo Zanda
Editor of SYNF ORM
Thiols are playing an increasingly important role for a number of applications spanning from chemical biology and materials science to drug discovery. Unfortunately, chiral thiols are not easily available in enantiomerically pure or enriched form, and there are few practical and user-friendly methods to achieve their optical resolution. A very important contribution towards the goal of making chiral thiols readily available in non-racemic form was recently published by the group of Professor Stephen Connon from Trinity College Dublin (Ireland), who reported a novel efficient methodology for the kinetic resolution of chiral secondary thiols.

According to Professor Connon, his group was prompted to take on this challenge initially because of the dearth of methods (organocatalytic or otherwise) available for the kinetic resolution of thiols, despite the extraordinary advances in organocatalytic acylative kinetic resolution of the corresponding alcohols and amines made recently.

“The paper in Nature Chemistry is an example of a catalyst working very hard,” said Professor Connon. “The reaction involves the addition of a thiol to a meso-anhydride in the presence of a bifunctional organocatalyst. The situation is complicated by the fact that the thiol is chiral and racemic. The catalyst is able to select one enantiomer of the thiol, and to promote its addition to a single carbonyl moiety of the meso-anhydride.” Professor Connon said that it was astonishing that the two processes (kinetic resolution of the thiol and desymmetrization of the anhydride) are synergistic. “Each proceeds more selectively in the presence of the other. The individual products can be isolated with extraordinarily high levels of enantiomeric excess and in some cases the ability of the catalyst to select one thiol enantiomer is of a similar magnitude to that more usually associated with enzymatic systems for the kinetic resolution of alcohols,” he explained.
The researchers were able to exploit this in a process which simultaneously resolves a racemic thiol and synthesizes a one-step precursor to the antipode of a ‘blockbuster’ drug. “In a conventional acylative kinetic resolution, the acyl group added to one of the substrate enantiomers is simply cleaved after separation of the products and discarded,” said Professor Conn. “Here, the acylating agent has also undergone an asymmetric transformation with high selectivity – when it is cleaved with ammonia, a compound is generated in high enantiomeric excess which is a Hofmann rearrangement away from (R)-Pregabalin.”

Professor Conn hopes that this study could help to highlight the possibilities and potential associated with coupling organocatalytic asymmetric processes together. “Aldo (Peschiulli) and Barbara (Procuranti) undertook the (sometimes arduous) task of optimizing the reaction conditions and developing the optimum catalyst structure. They took the process from being almost completely unselective initially to the final published reaction which can be used as a potentially powerful synthetic tool. They did not know how to give up, even when their supervisor was trying to convince them that 6% ee in a process which generates five products was a good starting point! Conn (O’Connor) was involved in exploring the synthetic potential of the process and demonstrated the resolution of the stereocenter-containing core of (R)-Montelukast, another ‘blockbuster’ drug,” concluded Professor Conn.

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About the authors

Aldo Peschiulli was born in Italy in 1979. He obtained his Laurea in ‘Chimica e Tecnologia Farmaceutiche’ from the University of Milan (Italy) in 2003 before joining the Conn group as a PhD student. His research interest focuses on the development of new organocatalytic methodologies for the synthesis of enantiomerically enriched organic molecules.

Barbara Procuranti was born in 1980 and graduated in Pharmaceutical Chemistry from Pisa University (Italy) in 2004. In September 2005 she started her postgraduate studies at Trinity College of Dublin under the supervision of Prof. S. J. Conn and received her PhD in 2010.

Dr. A. Peschiulli

Dr. B. Procuranti

Matteo Zanda
Cornelius (Con) O’Connor was born in 1981 and grew up in Carlow, in the south east of Ireland. He obtained his B.A. (Mod.) in Chemistry in 2004 from Trinity College Dublin where he also undertook his PhD under the supervision of Dr. Mike Southern, studying nucleoside mimetics and developing synthetic methodology. In 2009, he joined the Connon group at Trinity, where he worked on the development of novel catalytic systems. Since then, he has joined the Spring Group at the University of Cambridge (UK) where he is working on developing small-molecule inhibitors of protein–protein interactions.

Stephen Connon was born in 1976 and received his PhD from University College Dublin (Ireland) under the supervision of Professor A. F. Hegarty in 2000. After being awarded an Alexander von Humboldt fellowship he spent two years at the Technische Universität Berlin (Germany) with Professor S. Blechert, studying the design of new olefin metathesis catalysis. In 2003 he was appointed to the staff of Trinity College where he is currently Professor of Synthetic Chemistry. His research interests include organocatalysis, the discovery and development of novel synthetic methodology and the design of new anti-cancer and anti-bacterial agents.
Ammonia, which is the simplest inorganic compound composed of nitrogen and hydrogen, is among the bulk chemicals produced annually in large scale. The worldwide ammonia production was estimated at 153 million tons in 2008 and it is currently traded at the price of 415$/t. In spite of the abundance and cheapness of ammonia, it is rarely utilized as a reactant in transition metal catalysis. Because of ammonia’s high basicity (pK_a = 41 in DMSO), small size, and strong N–H bond (107 kcal/mol), attempts to employ it in metal-mediated reactions often result in undesired outcomes such as the formation of stable Lewis acid–base adducts, thus affecting the possibility of achieving high catalyst turnover.

Nevertheless, several research groups, including that of Professor Sukbok Chang from the Department of Chemistry at the Korea Advanced Institute of Science and Technology (KAIST, Korea), recently revealed remarkable examples of using aqueous ammonia as a facile and efficient reactant in transition-metal-catalyzed processes. For example, Professor Chang’s group reported a Cu-catalyzed N-arylation of haloarenes to react with either aqueous ammonia or ammonium salts (Chem. Commun. 2008, 3052). In addition, the same nitrogen source could also be employed in the Cu-catalyzed three-component reaction with sulfonyl azides and terminal alkynes (J. Org. Chem. 2008, 73, 9454). Since then, Professor Chang and his co-workers have further focused on the potential applications of ammonia in the metal-catalyzed C–H activation reaction.

“We originally intended to aminate 2-(p-tolyl)pyridine at the 2-position upon the reaction with aqueous ammonia in the presence of a palladium and copper catalyst system. However, we were quite surprised to obtain a cyanated product instead, 5-methyl-2-(pyridin-2-yl)benzonitrile, in good yield when the reaction was performed in N,N-dimethylformamide (DMF),” said Professor Chang.

Further investigations revealed that the combined use of DMF and ammonia is essential for the in situ generation of the cyano group “CN”. Professor Chang explained that “Jinho, a graduate student in my group, has a magical hand and was able to trace the source of each carbon and nitrogen of the cyano unit by using isotopically labeled DMF and ammonia.”
From the studies, it was shown that the carbon and nitrogen sources of “CN” are one of the N,N-dimethyl groups of DMF and ammonia, respectively.

Due to the fact that the cyanation protocol developed by Professor Chang’s group employs two different sources for the in situ generation of “CN”, it can be predicted that doubly labeled benzonitriles could be readily obtained using this procedure. “Indeed, when isotopic aqueous ammonia (15NH3) and N,N-dimethyl-13C2-DMF were used under the reaction conditions, a doubly labeled product was isolated in 40% yield with >96% isotopic incorporation at each carbon and nitrogen of “CN”, representing the first example of making such a nitrile,” said Professor Chang.

“We envision that the importance of the present method of forming “CN” in situ from the reaction of aqueous ammonia with DMF is in the mechanistic details of how the cyano unit is generated under the catalytic conditions. If it is well understood, this reaction can be applied in the fields of various transition-metal-catalyzed reactions. The mechanistic study is now ongoing,” he concluded.

### About the authors

**Sukbok Chang** is a Professor at the Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST, Korea). He studied chemistry at Korea University (BS, 1985), KAIST (MS, 1987, Prof. Sunggak Kim), and Harvard University (USA, PhD, 1996, Professor E. N. Jacobsen). After staying at Caltech (USA) as a PostDoc (June 1996 to February 1998, Professor R. H. Grubbs), he started his academic career at Ewha Womans University as an Assistant Professor (1998). In 2002, he moved to KAIST, where he was promoted to Full Professor in 2007. His current research interests include the development of new and practical organic transformations using transition metal catalysis. He has been honored with several awards such as the Young Scientist Award (2002, Korean Chemical Society–John Wiley & Sons), the Award of Korean Chemical Society, Organic Division (2005), Star Faculty (2008), and the Academic Award of the Korean Chemical Society (2010).

**Jinho Kim** was born in Seoul in 1981. He graduated from Hanyang University (Seoul, Korea) in 2006. He is currently pursuing his Integrated Master’s and PhD course at KAIST under the guidance of Professor S. Chang since 2007.

**Matteo Zanda**
Oxidative carbon–hydrogen bond activation has become a well-accepted method for increasing molecular complexity because these processes obviate the need for introducing reactive functional groups into a molecule prior to further manipulations. Applying carbon–hydrogen bond functionalization to processes that would be difficult or impossible to achieve through conventional methods is an obviously attractive but less-studied frontier. According to Professor Paul E. Floreancig from the University of Pittsburgh (USA) this objective can be realized because the reagents that are used to effect carbon–hydrogen bond functionalization and the mechanisms that are involved in these processes are often different from those that are relevant to conventional functional group interconversions. “My research group has had a long-standing interest in the use of oxidation reactions to form stabilized carbocations. In 2008 we reported that DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) converts allylic and benzylic ethers into oxocarbenium ions that react efficiently with appended nucleophiles to form tetrahydropyrans (Angew. Chem. Int. Ed. 2008, 47, 4184),” he said.

The stereocontrol in these reactions was excellent, and followed a predictable model in which the intermediate adopts a chair-like conformation and the oxocarbenium ion has an E-configuration. “Alkynyl-substituted oxocarbenium ions, however, react with low stereocontrol, as we disclosed in early 2010 (Angew. Chem. Int. Ed. 2010, 49, 3069),” continued Professor Floreancig. “We hypothesized that the diminished stereocontrol resulted from the substantially diminished preference for the E-oxocarbenium ion configuration because of the sterically undemanding alkynyl group. The notion that oxocarbenium ion geometry could be controlled by altering the steric bulk of the appended groups led us to consider whether we could prepare tetrahydropyrans that contain tertiary ethers through conformationally predictable 1,1-disubstituted oxocarbenium ions.” According to Professor Floreancig, despite the intense research efforts that have been directed toward oxocarbenium ions, 1,1-disubstituted oxocarbenium ions have rarely been studied and little effort has been directed toward investigating their conformational properties. “We postulated that an oxocarbenium ion that contained an alkynyl group and an alkyl group would exist in an orientation that places the sterically undemanding alkynyl group in a cis relationship with the opposite alkyl group,” he explained. “This worked out very well but, while demonstrating the principle well, it was a result that lacked scope. Our key objective was to devise a more general approach to the formation of quaternary centers in which an unsaturated group could have either a cis or trans relationship to the opposing alkyl group,” continued Professor Floreancig. “The key to solving this process arose from seeing the analogy between oxocarbenium ion geometry and the transition state model that Corey and co-workers proposed for the CBS reduction,” he acknowledged.

This analogy allowed Professor Floreancig and his team to mine the tables of successful substrates for CBS reductions to seek design elements to predict several highly selective cyclization reactions. “Moreover, a computational study by Hoffmann and Houk identified the role of allylic strain in determining oxocarbenium ion geometry and energy. By minimizing allylic strain we were able to use pre-existing quaternary centers to establish new stereocenters with high control,” he said.

According to Professor Floreancig, the stereoselective preparation of tertiary ethers is difficult because alkyl groups are usually sterically similar. “By taking advantage of the steric difference that arises from different hybridization, we have shown that the geometry of disubstituted oxocarbenium ions can be controlled rationally,” he said. “The use of allylic strain minimization to influence the stereochemical outcome of oxocarbenium addition reactions should also be useful for the preparation of highly substituted ethers. The ultimate objective of this project is to provide a versatile method for preparing structurally rich tetrahydropyrans for library synthesis. By
controlling quaternary center geometry, molecules that occupy greater physical space can be prepared and stereochemical diversity can be exploited,” explained Professor Floreancig.

According to him, a final point to consider is that the highly substituted unsaturated ethers that were prepared in this study could be rather labile under the highly acidic conditions that are conventionally employed to form oxocarbenium ions.

“By using oxidative carbon–hydrogen bond activation for carbocation formation we have eliminated a competitive product decomposition pathway in addition to designing a process that employs readily accessible precursors,” concluded Professor Floreancig. 

Matteo Zanda

About the authors

From left: L. Liu, Prof. P. E. Floreancig
Palladium-Catalyzed Cross-Coupling of Aryl Chlorides and Tosylates with Hydrazine
(Focus on an article from the current literature)

Professor Max Malacria
(Focus on a SYNTHESIS/SYNLETT Advisory Board member)