Diastereoselective Addition of Grignard Reagents to α-Epoxy *N*-Sulfonyl Hydrazones

Nat. Chem. **2015**, *7*, 1024–1027

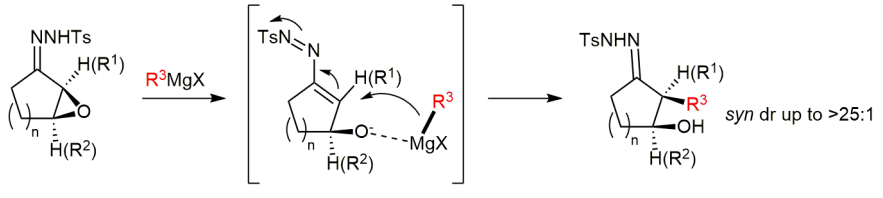
The development of a broadly applicable approach to the asymmetric α-alkylation of ketones is a long-standing and – until recently – unresolved problem in the field of organic synthesis. In the December 2015 issue of *Nat. Chem.* Professor Don M. Coltart and co-workers from the University of Houston (Texas, USA) reported the development of the broadest method ever reported for the α-functionalization of ketones or their derivatives. The article describes the highly (up to >25:1) *syn*-selective formation of β-hydroxy *N*-sulfonyl hydrazones having α-tertiary or α-quaternary centers by the simple combination of Grignard reagents – the most readily available and common of all organometallic reagents – and α-epoxy *N*-sulfonyl hydrazones.

The Texas-based researchers recognized a possibility that was under the synthetic community's nose for nearly 50 years – the interception of the Eschenmoser–Tanabe fragmentation (first reported in 1967) intermediate with a Grignard reagent (introduced in the late 1800s). Professor Coltart said: "As simple as this solution is, the most remarkable feature is its generality: it is able to incorporate an unprecedentedly wide range of carbon-based substituents, including 1°, 2° and 3° alkyl, alkenyl, allenyl, aryl, and alkynyl. Indeed, almost every combination of carbon nucleophile and epoxyhydrazone examined provided the desired compound with superb selectivity." He continued: "Subsequent hydrolysis of the β-hydroxy *N*-sulfonyl hydrazone products produces the corresponding β-hydroxy ketones. In addition to hydrolysis, the β-hydroxy *N*-sulfonyl hydrazone products are poised to undergo numerous different known synthetic transformations via well-established chemistry, giving rise to a wide array of useful structures."

The synthesis of substituted β-hydroxy ketones is as fundamental to organic chemistry, natural product synthesis, biochemistry, and chemical biology as the aldol reaction. "This motif is common to molecules essential to metabolism, biosynthesis, certain medicines, and a variety of tool compounds for biological studies," confirmed Professor Coltart, adding: "The myriad diverse – and sometimes cumbersome – methods developed over the past several decades to access targets that contain one or more embodiments of this array are a testament to the importance of the motif itself. This method provides a direct, reliable, and broad method to access these high-value molecules."

Professor Coltard explained: "In developing our synthetic method we have had the enormous benefit of being able to stand on the shoulders of some of the greats in the area of organic synthesis, and we owe a great debt to those individuals." The group has recently been working to extend their method to other hydrazones and related species, in the context of aziridine and other applicable moieties, and with various coupling partners in addition to Grignard reagents. "We have also been exploiting the multipolar nature of the intermediate 3-alkoxy-2-azopenes (and related species) for novel annulation processes," said Professor Coltart. "From these initial studies, it appears that these hitherto unexplored arrangements of functional groups may prove quite fruitful as a synthetic platform, leading to a variety of interesting and synthetically useful structures." He concluded: "I believe this work has provided a fresh perspective on some well-known reactions: what's old is new again!"

Professor Gregory B. Dudley, from Florida State University (USA), an expert in the chemistry of sulfonyl hydrazones and related compounds, commented: "Coltart and co-workers described an exciting and innovative strategy for producing β-hydroxy ketones from epoxy hydrazones. Their results are remarkable for the excellent selectivity and scope in forming



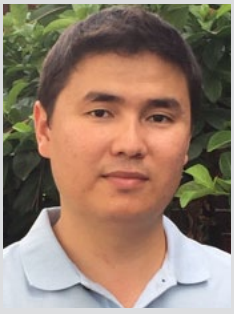
R^3 = primary, secondary, tertiary, alkyl, aryl, allenyl, alkynyl

quaternary centers, and also for the unprecedented new utility of epoxy hydrazones. Epoxy hydrazones are long known as intermediates in the Eschenmoser–Tanabe fragmentation, but they are typically generated and reacted in situ," he continued. "Here, they are isolated and then harnessed for completely different purposes; namely, for use as electrophiles in new Grignard addition pathways. The result is a stereocontrolled synthesis of quaternary carbon stereocenters under straightforward and conceptually novel conditions," concluded Professor Dudley.

About the authors

Prof. D. M. Coltart

Don Coltart obtained his Master's degree from the University of Manitoba (Canada), under the supervision of Professor James L. Charlton, and he then joined the research group of Professor Derrick L. J. Clive at the University of Alberta (Canada), where he obtained his Ph.D. His postdoctoral work was conducted at the Memorial Sloan-Kettering Cancer Center (USA) as an NSERC, AHFMR, and CRI Scholar, under the supervision of Professor Samuel J. Danishefsky. Don began his independent career at Duke University (USA) in 2004 and moved to the University of Houston (USA) in 2012. His research group studies the development of methods for asymmetric carbon–carbon bond formation, the application of those methods to the total synthesis of structurally complex biologically active natural products, and the study of those compounds in biological systems.



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Maulen M. Uteuliyev was born and raised in Shymkent (Kazakhstan). He received his B.Sc. degree in chemistry from Pavlodar State University (Kazakhstan) in 2006. In 2009, Maulen spent a year working on Rh-catalyzed asymmetric hydroboration in the lab of Professor James Takacs at the University of Nebraska-Lincoln (USA). In 2010, he continued to pursue his M.Sc. degree under the direction of Professor Douglas Grotjahn at the San Diego State University (USA) where he focused on N-heterocyclic carbene catalysis. In 2012, he joined the group of Professor Don Coltart at the University of Houston (USA) as a Ph.D. student. His current research in the Coltart laboratory focuses on α-alkylation/functionalization of ketones via activated hydrazones and oximes.

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Thien Nguyen was born and raised in Da Nang City (Vietnam). He received his B.Sc. degree in chemistry from Science University (Vietnam) in 2008 and M.Sc. degree in Advanced Spectroscopy in Chemistry from Helsinki University (Finland) in 2011. He joined Professor Coltart's group in 2012 and studies the alkylation/functionalization of ketones via azoalkene species.