2-Azadienes as Reagents forPreparing Chiral Amines: Synthesis of 1,2-Amino Tertiary Alcohols by Cu-Catalyzed Enantioselective Reductive Couplings with Ketones


The development of methods for the enantioselective construction of amines is an important objective in synthetic chemistry, and C–C bond-forming reactions are a critical subset, as highly functionalized molecules may be assembled quickly by the union of two complex fragments. One common tactic utilizes stereoselective nucleophile additions to electrophilic imines; however, there are several families of amines that are not easily prepared in this manner. 1,2-Amino alcohols are one class that are difficult to access via this normal polarity C–C bond formation. In particular, 1,2-amino tertiary alcohols have almost never succumbed to catalytic enantioselective synthesis.

The lab of Professor Steven Malcolmson at Duke University (Durham, USA) envisioned that 1,2-amino tertiary alcohols could be prepared if a nucleophilic α-aminoalkyl transition metal intermediate could be generated and added to a ketone electrophile (reverse polarity strategy). Professor Malcolmson explained: “Several means of forming such a species are known, including transmetallation, C–H functionalization, and metal recombination with an in situ generated α-aminoalkyl radical (Scheme 1). However, few of these transformations are enantioselective and none of these approaches generates an intermediate capable of ketone addition.” Fifth-year graduate student Kangnan Li said: “We have thus developed an unconventional method to access α-aminoalkyl transition metal species through migratory insertion of 2-azadienes, which then enantioselectively react with ketones to prepare unprecedented 1,2-amino tertiary alcohols.” Previously, 2-azadienes had only sporadically been utilized in synthesis and never for catalytic enantioselective chemistry for preparing chiral amines. Kangnan also pointed out: “Employing 2-azadienes opens up a way to access more complicated downstream amine-containing molecules, as the general reaction platform allows for the vicinal difunctionalization of the N-substituted alkene.” Thus, a Cu catalyst may promote the addition of a range of nucleophiles to the N-β-position of the azadiene and subsequent trapping of the resulting aza-allyl copper intermediate with several classes of electrophiles at the N-α-position, formally umpolung of an enamine. Hydrolysis of the product’s imine then delivers the free primary amine. “In this first proof of concept, hydride plays the role of nucleophile in Cu-catalyzed reductive couplings with ketones,” said Professor Malcolmson.
He continued: “We discovered that the desired reductive coupling reaction could be promoted only by a Cu catalyst bearing Ph-BPE as the chiral ligand (Scheme 2). Under the established optimized conditions, the terminal azadiene (R¹ = H) undergoes addition to a range of aryl and heteroaryl ketones. Enantioselectivity is uniformly high but diastereoselectivity is modest in most cases. Still, after reductive and desilylative workup, the major diastereomer of the amino alcohol products could be isolated in good yields. Notably, we found that ortho substitution on the aromatic ring or larger alkyl substituents of the ketone (R²) lead to higher diastereoselectivity.”

Additionally, the group established that 4-substituted 2-azadienes were also competent partners in the three-component couplings with several functional groups tolerated within the substituent. As postdoctoral researcher Dr. Xinxin Shao pointed out: “Critical to the success with substituted azadienes was finding multiple useful methods for preparing them.” Professor Malcolmson added: “In the end, we found two protocols that worked well: 1) a cross-coupling approach, developed in the Liebeskind laboratory, and 2) a Horner–Wadsworth–Emmons reaction, which afforded a separable E/Z mixture of stereoisomers.”

However, several limitations of the reaction are apparent. Dr. Shao commented: “Although this work provides a method to prepare chiral 1,2-amino tertiary alcohols with vicinal stereogenic centers, the ketone scope is limited. Dialkyl ketones and electron-deficient ketones are major challenges.” The authors believe that this can be attributed to a chemoselectivity issue: in some cases, the ketone undergoes reduction

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**Scheme 2** Selected substrate scope for 2-azadiene–ketone reductive couplings
instead of the desired reductive coupling. Electron-poor acetophenones also suffer from this competing side reaction, contributing to somewhat lower yields. Contrastingly, more sterically hindered ketones, such as those with ortho-substituted aromatic rings lead to higher quantities of the 1,2-amino alcohols. Dr. Shao also explained: “Substituted azadienes are also less reactive, which leads to more ketone reduction.” As a result, only sterically hindered ketones may currently undergo reductive coupling with 4-substituted azadienes (Scheme 2).

“Our future efforts will focus on the Cu-catalyzed addition of other types of nucleophiles to azadienes for multicomponent couplings as well as trapping the α-aminoalkyl Cu intermediate with myriad classes of electrophiles,” said Professor Malcolmson, echoed by Kangnan Li who concluded: “Although methods with 2-azadienes are still limited, their ease of preparation and the general reaction illustrated by the reductive coupling with ketones will likely promote increased research interest in this class of reagents.”

**About the authors**

**Steven Malcolmson** grew up in Boston, Massachusetts (USA) and graduated with a bachelor’s degree in chemistry from Boston University (USA) in 2004. After graduate work with Professor Amir Hoveyda at Boston College (USA), where he developed new Mo catalysts and methods for olefin metathesis as part of a collaborative project with Professor Richard Schrock at MIT (USA), Steve moved to Harvard Medical School (USA), studying natural product biosynthesis with Professor Christopher Walsh as an NIH postdoctoral fellow. He began his independent career as an assistant professor at Duke University (USA) in 2013. His research interests include developing new enantioselective transition-metal-catalyzed reactions and investigating their reaction mechanisms.

**Kangnan Li** was born and raised in Chongqing (P. R. of China). He obtained his bachelor’s degree in chemical physics from the University of Science and Technology of China (Anhui, P. R. of China) in 2013, where he carried out undergraduate research under the supervision of Professor LiuZhu Gong. He then joined the Malcolmson group at Duke University (USA) as a graduate student and has been working on developing methods for the α-functionalization of amines.

**Xinxin Shao** was born in Zhejiang (P. R. of China) and graduated from Northwest University (P. R. of China) in 2010. He then completed his Ph.D. at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) under the supervision of Professors Long Lu and Qilong Shen in 2015. After a year as an SIOC postdoctoral fellow with Professor Dean Toste at UC Berkeley (USA), studying gold(III) chemistry, he joined the Malcolmson group at Duke University (USA) as a postdoctoral researcher in early 2017. His research interests are focused on enantioselective transformations of 2-azadienes to furnish useful molecules.

**Luke Tseng** was raised in Houston, Texas (USA) and received a bachelor’s degree in chemistry from Duke University (USA) in 2017. He is currently a first-year medical student at Columbia University (USA).