β-Phenethyl ethers are important structural features in medicinally relevant compounds, including pharmaceuticals and natural products; however, an atom-economical and straightforward synthesis of this structural unit remains a challenging endeavor for organic chemists. The group of Jeffrey S. Bandar at Colorado State University (USA) has been working on this problem. “We felt that a streamlined synthetic route to β-phenethyl ethers would be a welcome advance,” said Professor Bandar. “In particular, the direct anti-Markovnikov addition of alcohols to styrene derivatives is attractive because of the scale and diversity of the readily available starting materials.”

Professor Bandar explained that typically, in order to achieve this net transformation, chemists must perform a three-step hydroboration/oxidation/substitution sequence, all requiring stoichiometric reagents. “The value of a catalytic variant of this transformation has attracted attention from other groups; one impressive example is a photoredox-catalyzed variant developed by the Nicewicz group in 2012 (J. Am. Chem. Soc. 2012, 134, 18577),” he added.

“We were inspired by the simplicity and potential of a Brønsted base catalyzed approach for the addition of alcohols to aryl alkenes,” remarked Professor Bandar. He explained: “We expected the reaction to be highly regioselective due to the polarity of the aryl-substituted alkene. In the proposed catalytic cycle, anti-Markovnikov alkoxide attack must occur with rapid protonation of the developing benzylic carbanion, perhaps in a concerted process. There have been sporadic examples of inorganic base-promoted addition of alcohols to styrene derivatives, but these reactions typically required highly activated systems such as conjugated vinyl heterocycles.”

The group hypothesized that the identity and properties of the Brønsted base would be crucial to developing a general base-catalyzed alcohol addition protocol. “A report from Kondo in 2004 using the neutral organic superbase P₄-t-Bu to catalyze the addition of alcohols to phenylacetylene sparked our interest (Adv. Synth. Catal. 2004, 346, 1090). Although that particular reaction had been known using other common inorganic bases, we thought the unique properties of the organic base might enable our reaction of interest,” said Professor Bandar, who continued: “The phosphazene superbase P₄-t-Bu, first reported by Schwesinger in 1987 (Angew. Chem. Int. Ed. 1987, 26, 1167), is an incredibly strong neutral base capable of deprotonating alcohols. Compared to inorganic bases, use of P₄-t-Bu leads to an alkoxide ion pair containing a proton that could enable the rapid (or concerted) protonation of the developing benzylic anion in the proposed mechanism.”

“With this proposed work, I was able to recruit Dr. Luo to join my new lab at Colorado State University where he rapidly discovered that P₄-t-Bu catalyzes the addition of alcohols to styrene derivatives in aromatic solvents,” revealed Professor Bandar. He added: “We found that the reaction is reversible.
and under equilibrium control. Therefore, the temperature was optimized for each substrate such that the lowest temperature at which the catalyst was active was used.”

The synthetic value of this transformation was demonstrated by its broad substrate scope, as shown by the examples in Figure 2.

Dr. Luo – a postdoctoral fellow who co-authored the article – explained: “Concerning the styrenes, diverse functional groups and substitution patterns were tolerated, such as meta-nitro, -trifluoromethyl, -methoxy, and ortho-chloro, -bromo, -trifluoromethoxy, -iodo; many of these groups could enable further structural manipulation, if desired. Vinyl heteroaromatics (e.g. pyridine, furan, thiazole, quinoline, and isoquinoline) also worked well; in particular, 2-chloro-3-vinylpyridine delivered ether products with excellent chemoselectivity (alcohol addition over S_NAr).” He continued: “At higher temperatures, styrene provided the ether product with 22% yield. We also found that β-alkyl styrenes can participate...”
in this reaction, whereas α-alkyl styrenes afforded only traces of product. Electron-rich styrenes (such as 2,4,6-trimethylstyrene) did not lead to any product formation.”

A wide range of alcohols was found to react with styrenes. “A general reactivity trend showed that primary alcohols give higher yield than secondary and tertiary alcohols, for example i-PrOH and t-BuOH added to 4-trifluoromethylstyrene with 25% and 7% yield, respectively,” remarked Dr. Luo. The Colorado-based researchers also found that a range of diverse and densely functionalized primary alcohols provided ethers in high yield. Geraniol, solketal, a paroxetine derivative, and alcohols featuring olefin, azetidine, and phthalimide functional groups showed good reactivity and were well tolerated. “For primary alcohols containing a competing nucleophilic hydroxyl or amino group, our study showed that it is possible to achieve selective additions, leaving unprotected heteroatoms available for further functionalization,” added Dr. Luo.

Professor Bandar said: “For a first-generation system, we are happy with the diversity of alkenes and alcohols tolerated in this reaction. Nonetheless, we have identified several limitations that we are currently working to address. We are primarily seeking to develop more active catalysts and reaction conditions that give high yields for electron-neutral to electron-rich styrenes, as well as α-substituted styrenes. It would also be useful to achieve enantioselectivity in reactions where a stereocenter is formed (in either the α- or β-position).” He concluded: “In the long term, we hope to be able to extend our base-catalyzed approach for the addition of alcohols to other olefin classes in order to access more diverse ether structures.”

About the authors

Jeff Bandar received his Ph.D from Columbia University (USA) in 2014, where he developed new synthetic applications of aromatic ions in the laboratory of Professor Tristan H. Lambert. He then advanced the understanding and application of copper hydride catalysts in asymmetric reactions as an NIH postdoctoral fellow under Professor Stephen L. Buchwald at Massachusetts Institute of Technology (USA). Jeff started his independent career in the summer of 2017 at Colorado State University (USA), where his group is developing new reactions and concepts in Brønsted base chemistry.

Chaosheng Luo received his Ph.D from Peking University (P. R. of China) in 2015, where he worked on developing asymmetric organocatalytic methods for accessing medicinally privileged scaffolds in the laboratory of Professor Yong Huang. He then joined the research group of Professor Jeffrey van Humbeck at Massachusetts Institute of Technology (USA), where he engaged in studying the effect of an embedded electric field in asymmetric hydrogen-bonding catalysis. Following his work at MIT, Chaosheng moved to Colorado State University (USA) to continue postdoctoral studies working on superbase-catalyzed reactions under Professor Jeffrey S. Bandar.