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RESEARCH HIGHLIGHTS

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Beyond Precious Metals:
Chemical Synthesis Using Earth-Abundant Metal Catalysts



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Global Significance

In the late 18th century, at the outset of the industrial revolution, the increased need for fertilizer, medicines and other commodities became so great that demand could not be satisfied by extraction from plants and animals. For the first time in history, these materials had to be made synthetically.

Whereas bulk chemicals like fertilizer and gasoline were (and still are) made using highly energy intensive processes, specialty chemicals like medicines and advanced materials are sufficiently sophisticated and sensitive that they must be made using milder, lower temperature processes. This in turn requires the use of catalysts containing precious metals (i.e., Pd, Pt, Ru, Rh, Ir, Ag and Au).

The problem with precious metals is that they are expensive, steadily rarefying, and are generally non-renewable. Catalysts made from these metals can also be harmful to humans and to the environment.

Hypothetically, if simpler, less expensive, and environmentally-abundant elements could supplant Pd, Pt, Ir, Ru, Rh, it could address many of the aforementioned issues inherent to precious metal catalysis.

Breakthroughs in this area could yield next-generation sustainable chemical methods for drug discovery, materials science, and crop protection.

Making a simple, inexpensive earth-abundant metal behave like platinum or gold would be a considerable advance in organic synthesis and catalysis. Iron, cobalt and other abundant elements have been used in catalysis before, but the reactions are often less efficient, more sensitive, or even more expensive than precious-metal based systems for various reasons.

Interestingly, living organisms from humans to bacteria have evolved to use abundant, non-toxic materials such as iron and potassium instead of precious metals to catalyze their life-sustaining processes. So far chemists have generally been unsuccessful in replicating Nature's efficient and sustainable chemical methods.

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Project Summary

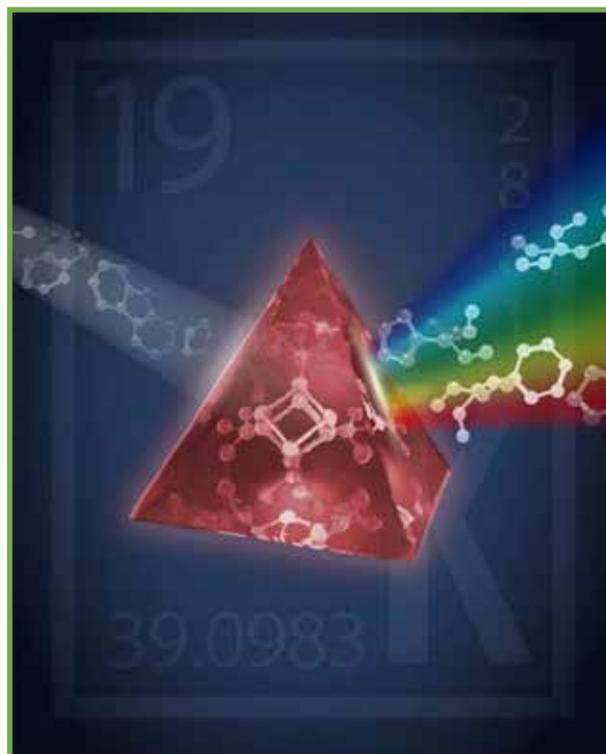
The ultimate aim of this project is the discovery and development of catalysts based on Earth-abundant elements which can behave like and therefore replace catalysts made of precious metals for at least certain chemical processes. It would be additionally beneficial if these catalysts also permitted energy-intensive processes to occur at lower temperature, thereby lowering the carbon footprint of the chemical industry as a whole.

Potential Impact

In general, the potential impact for this project would be the replacement of expensive and rarefying harmful precious-metal-catalyzed processes with cheap, simple, and sustainable alternatives.

If successful, this would have a considerable positive impact on organic synthesis (i.e. human medicine, materials science, crop protection, radiopharmaceuticals, etc.) in both academic and, if scalable, industrial settings.

Our work is also revealing new trends and patterns in chemical reactivity. This new fundamental knowledge could serve as a platform for the development of other sustainable catalytic methods for a variety of applications and the discovery of completely new and unanticipated science.



An artist's depiction of a newly-discovered, nature-inspired, sustainable chemical reaction:

Potassium tert-butoxide—the catalyst in the new reaction—is represented within the prism. Simple, bulk organic molecules (depicted in the white light) pass through the prism and are transformed into complex building blocks that are useful in a variety of applications (represented in the color spectrum).

Credit: Santiago Lombeyda and Robin Betz

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The goal is to discover alternatives to precious metal catalysts for organic synthesis. Since precious metal catalysis is used for a wide variety of reactions, we chose to target a single chemical reaction – forming a bond between a carbon and silicon atom – to frame our studies. Currently, catalytic methods for C-Si bond formation require Rh, Ir, or Pt catalysts, high temperatures (up to 200°C), and sacrificial hydrogen acceptor molecules, which produce additional waste. Moreover, the precious-metal catalysts are quite intolerant of Lewis-basic nitrogens, which limits the utility of these methods in medicinal chemistry and alkaloid natural product synthesis.

Our approach seeks to overcome all of these limitations by discovering a highly active C-Si bond formation catalyst which is functional-group tolerant and readily available. Moreover, the catalyst should be based on an Earth-abundant element rather than a precious metal so as to make it readily available, inexpensive, and non-toxic. With respect to the starting materials: aromatic heterocycles will be selected as the organic substrates due to their prevalence in human medicines and natural products. As for the silicon source, cheap and abundantly available hydrosilanes will be investigated such that the reaction will produce hydrogen gas (which is itself valuable) as the only byproduct. This proposed catalytic cross-dehydrogenative C-H silylation reaction would represent an energy- and material-efficient, inexpensive, and sustainable catalytic method; it would ideally be a general approach for making Si-containing organic molecules.

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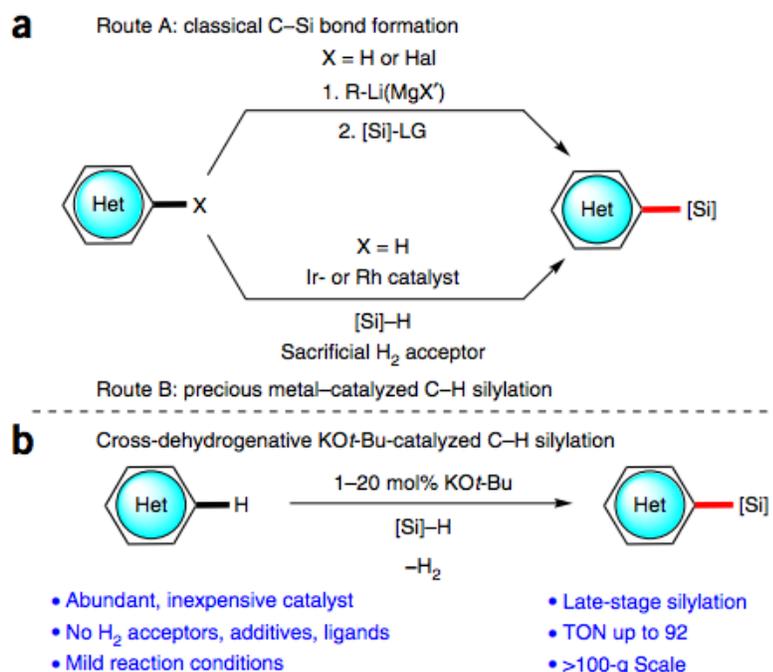
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LETTER

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Silylation of C–H bonds in aromatic heterocycles by an Earth-abundant metal catalyst

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Approaches to the silylation of heteroarenes:

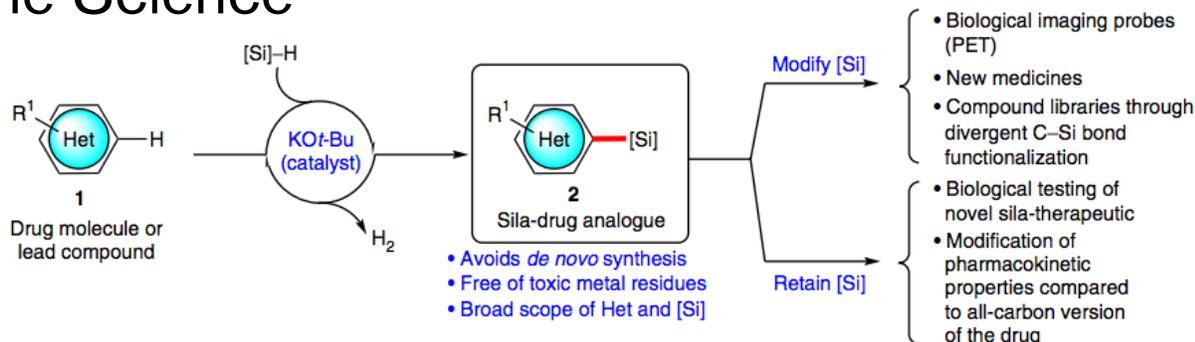
a Route A: classical synthesis of heteroaryl silanes by the interception of organometallic species with silicon electrophiles. Route B: the recently developed transition metal-catalyzed direct C–H silylation. Sacrificial olefins are added as hydrogen acceptors to turn over the catalyst.

b Convenient and scalable KOt-Bu-catalyzed acceptorless cross-dehydrogenative heteroaromatic C–H silylation with hydrosilanes. TON, turnover number.

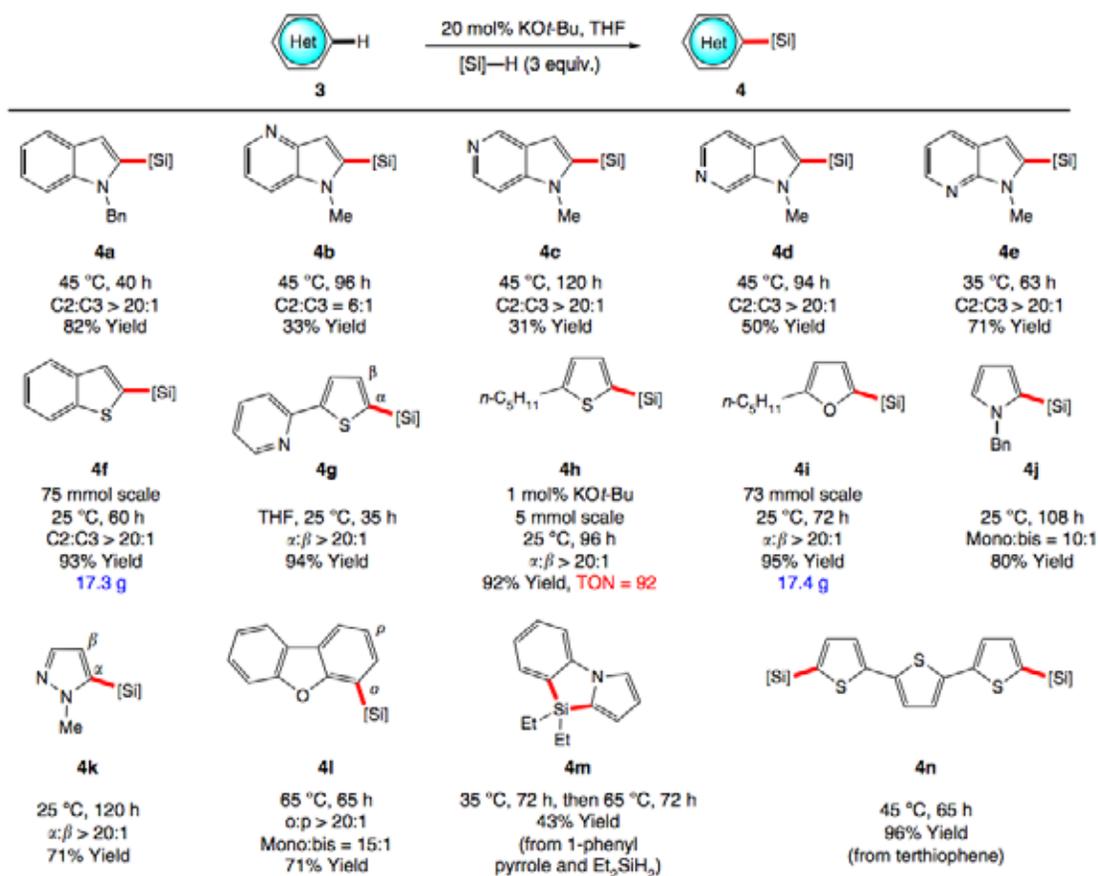
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Installation of a Si-based functionality onto a known pharmaceutical substance (1) using the potassium salt as a catalyst enables new horizons in medicinal chemistry and drug discovery. The resulting silicon-containing drug derivatives (2) may be valuable in their own right as novel sila-therapeutics (the 'Retain' route) or they may be modified ('Modify' route) through C–Si bond substitution (e.g., arylation by Hiyama coupling or electrophile-induced ipso-substitution), which allows for the convenient and divergent synthesis of drug analog libraries. PET, positron emission tomography.

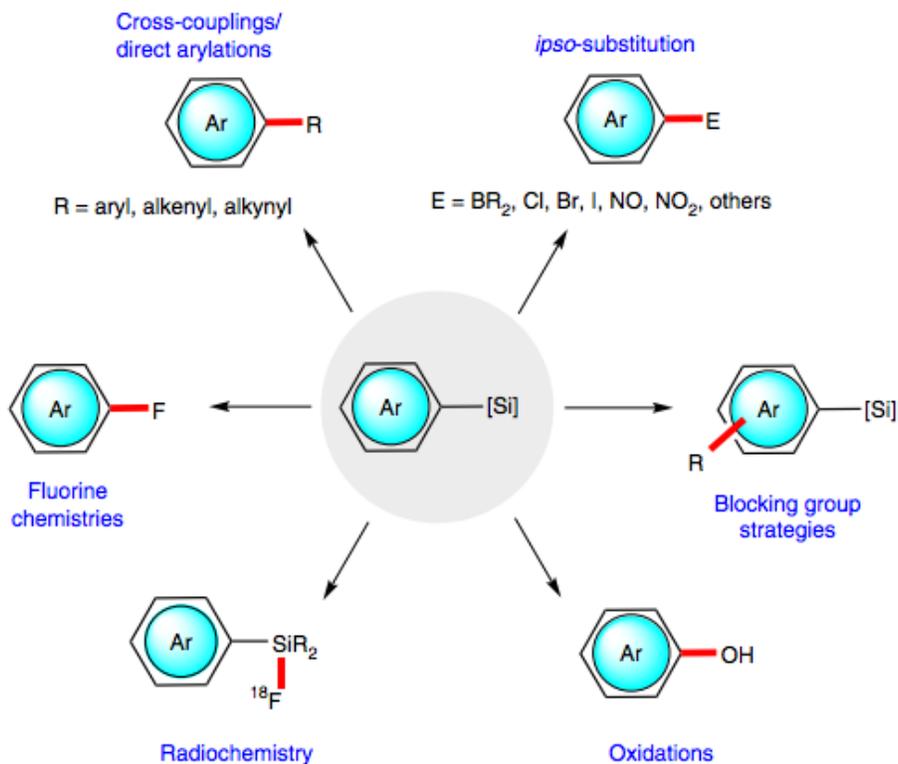


Catalytic cross-dehydrogenative C–H silylation with KOt-Bu occurs with excellent selectivity for a number of privileged heterocyclic scaffolds (3) found in many bioactive substances, including indoles, furans, pyrroles, pyrazoles, heterobiaryls and even all four isomers of the azaindole structure to give silicon-containing derivatives (4a–l). The method is also valuable for materials science applications, as seen by the one-step synthesis of azasilole (4m), as well as the double silylation of terthiophene (4n). [Si] = SiEt₃.

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Synthetic utility of arylsilanes and heteroarylsilanes. Arylsilanes and heteroarylsilanes are highly versatile substrates that can be transformed into a number of compounds with useful functionalities, such as halides, boranes, nitrogen and oxygen functionalities; they are also valuable precursors for cross-couplings and arylations.

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Key Results

We found that readily available and inexpensive potassium *tert*-butoxide (KO*t*-Bu) catalyzes the direct silylation of aromatic heterocycles with hydrosilanes furnishing heteroarylsilanes in a single step. The silylation proceeds under mild conditions, with broad substrate scope, in the absence of hydrogen acceptors, ligands or additives. The reaction is scalable to greater than 100 grams under convenient solvent-free conditions and produces dihydrogen as the byproduct. Substrate classes that are challenging to activate with precious metal catalysts are silylated in good yield and with excellent regioselectivity by KO*t*-Bu catalysis. The derived heteroarylsilane products readily engage in versatile transformations enabling new synthetic strategies for heteroaromatic elaboration, and are useful in their own right in a multitude of applications. Interestingly, there is no way to explain how or why this chemical reaction works given the current base of knowledge in the field; thus the mechanism remains a mystery.

Future Steps

This initial discovery may be just scratching the surface of an exciting frontier in chemical space. Using our newfound knowledge, we are improving the current method, discovering new catalysts based on other abundant metals, and driving other important chemical reactions using these materials. We are fortunate to have some of the top minds in chemistry and their research groups helping us develop this method and explore its applications. For example, collaborations have been initiated with:

- Professor Stoltz, Caltech (drug discovery)
- Professor Lewis, Caltech (materials science)
- Professor Murphy, UCLA (synthesis of probes for medical diagnostics)
- Professor Houk, UCLA and Professor Zare, Stanford; (elucidation of the reaction mechanism)

Publications

- Toutov, Anton A. and Liu, Wen-Bo and Betz, Kerry N. et al. (2015) Catalytic C–H bond silylation of aromatic heterocycles. *Nature Protocols*, 10 (12). pp. 1897-1903. ISSN 1754-2189. <http://resolver.caltech.edu/CaltechAUTHORS:20151103-103452993>
- Toutov, Anton A. and Liu, Wen-Bo and Betz, Kerry N. et al. (2015) Silylation of C–H bonds in aromatic heterocycles by an Earth-abundant metal catalyst. *Nature*, 518 (7537). pp. 80-84. ISSN 0028-0836. <http://resolver.caltech.edu/CaltechAUTHORS:20141118-102135823>