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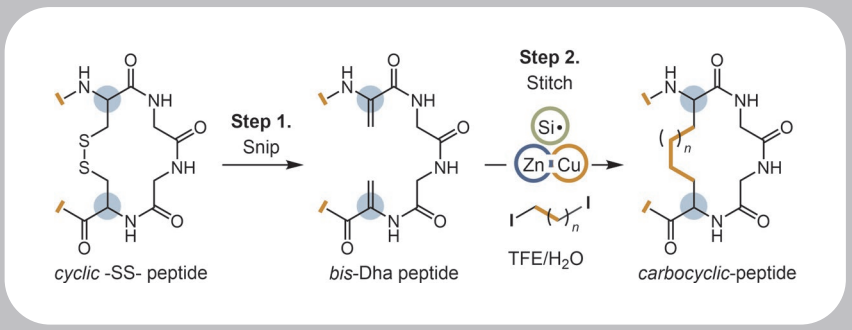
People, Trends and Views in Chemical Synthesis

2023/03

Peptide Carbocycles: From –SS– to –CC– via a Late-Stage "Snip-and-Stitch"

Highlighted article by S. Gary, S. Bloom



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Thieme

Dear Readers,

This is a brief editorial, because I am really busy getting settled in Brussels, following my recent move to the ERC headquarters. These are frantic and exciting times with countless things to deal with and get sorted, both work- and life-related, but SYNFORM is always top in my thoughts, so here I am between a move of flat, a training course and a welcome event. This March issue starts with a Literature Coverage article on an enzyme-mimicking single atom catalyst for the oxidative synthesis of nitriles from the corresponding carbonyl compounds, reported by W. Dai and Z. Zhang (P. R. of China) in *Sci. Adv.* The second is a Young Career Focus interview with 2022 Thieme Chemistry Journals Awardee J. Blacquiere (Canada) who answers our questions about research interests and scientific achievements so far. The third article covers the synthesis of novel peptide carbocycles designed by S. Bloom (USA) and reported in *ACS Cent. Sci.* The issue is closed by a very original work by a team led by H. Xia and Y.-M. Lin (P. R. of China) who published in *Nat. Synth.* a ring contraction reaction of a metallacyclobutadiene to metallacyclopropene driven by π- and σ-aromaticity relay.

I need to go buy a wok now, and then take care of the washing machine...

Enjoy your reading!

In this issue

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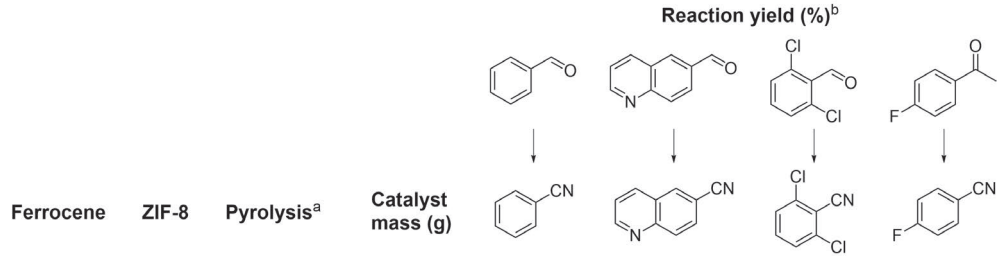
An Enzyme-Mimic Single Fe-N_3 Atom Catalyst for the Oxidative Synthesis of Nitriles via C–C Bond Cleavage Strategy

Sci. Adv. **2022**, *8*, eadd1267

Nitriles constitute a ubiquitous class of compounds, present in natural products, agrochemicals, and pharmaceuticals and widely utilized as versatile intermediates in organic synthesis. Cyanide-free, one-step direct construction of aryl nitriles – which occupy a particularly prominent position in terms of their applications – is often challenging under heterogeneous catalytic conditions. Professor Zehui Zhang's research group at South-Central University for Nationalities (P. R. of China) has been focusing on the development of green and sustainable catalytic systems for the one-pot synthesis of various value-added compounds and recently achieved a breakthrough in this area of research. "We aim to develop general, efficient, and practical synthesis methods for value-added nitrile compounds from simple and readily available feedstock molecules, such as alcohols, ketones, and aldehydes," said Professor Zhang, continuing, "Single-atom catalysts (SACs) are emerging as a rapidly developing and attractive catalytic system, with the exact properties we want in a catalyst, so our research strategy stems from this consideration." Professor Wen Dai at the Chinese Academy of Sciences (P. R. of China), co-corresponding author of the *Sci. Adv.* article, added: "The synthesis of nitriles from ketones and secondary alcohols via inert C–C bond cleavage is very challenging and requires high catalyst activity. This novel route can avoid the use of toxic cyano-organic compounds and has huge potential in practical applications."

"Previous literature reported the excellent catalytic activity of the P450 enzyme for O_2 activation at room temperature, therefore we thought we could design a catalyst with a structure inspired by this enzyme," said Jingzhong Qin, the first author of the title article. He and other authors designed two types of SACs bearing atomically dispersed Fe sites with different coordinating nitrogen atoms (FeN_3-SAC and FeN_4-SAC) by pyrolysis of ZIF-8 (ZIF = Zeolite Imidazolate Framework) and ferrocene, following methods reported in the literature. The FeN_3-SAC showed a high enzyme-like activity and was capable of activating O_2 to superoxide radical anion at room temperature, while the commonly reported FeN_4-SAC is inactive. "Inspiringly, this FeN_3-SAC proved to be highly active for the oxidative nitrification of alcohols (primary alcohols and secondary alcohols), ketones, and aldehydes to nitriles, where the oxidative nitrification of ketones and secondary alcohols is via a C–C bond cleavage route. This newly developed FeN_3-SAC enzyme-mimic can serve as a bridge between enzymatic catalysis and heterogeneous catalysis," said Mr. Qin.

Professor Bo Han at China University of Geosciences (P. R. of China) and second author on the article added: "Density functional theory (DFT) calculations revealed that the activa-



Ferrocene	ZIF-8	Pyrolysis[a]	Catalyst mass (g)				
56 mg	4 g	1100 °C, 2 h	1.46	97	92	99	85[c]
112 mg	8 g	1100 °C, 2 h	3.28	99	89	99	88[c]
168 mg	12 g	1100 °C, 2 h	5.12	95	90	99	86[c]

Scheme 1 Preparation and catalytic activity of 1–5 g of Fe-N_3/NC-1100. [a] *Pyrolysis conditions*: ramp. 5 °C/min. [b] *Reaction conditions*: substrate (0.20 mmol), catalyst (20 mg), $NH_3{\cdot}H_2O$ (26.5 wt%, 400 µL), toluene (1.5 mL), O_2 (1 bar), 25 °C, 24 h. [c] O_2 (10 bar), 150 °C, 10 h.

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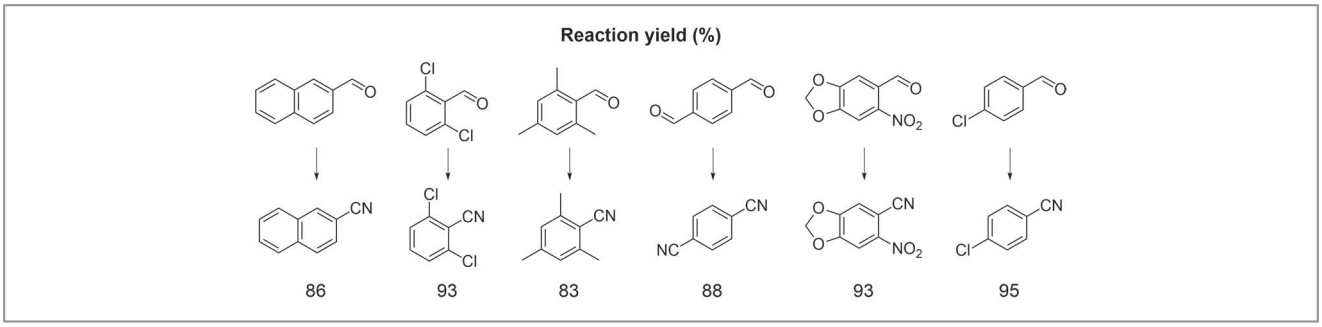


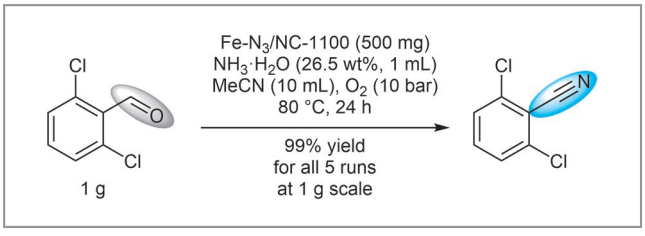
Scheme 2 Large-scale applications in the synthesis of nitriles. *Reaction conditions*: substrate (2 g), catalyst (500 mg), $NH_3{\cdot}H_2O$ (26.5 wt%, 1 mL), MeCN (10 mL), O_2 (10 bar), 80 °C, 24 h.

tion energies for O_2 activation, and the rate-determining step of nitrile formation are much lower over FeN_3-SAC than FeN_4-SAC."

According to the authors, the FeN_3-SAC catalyst preparation procedure is very simple and can be scaled up to 5.12 g. In addition, the catalytic activity of the FeN_3-SAC remains stable across the scaling-up (Scheme 1), thus validating the practical application of this catalytic method.

Large-scale synthesis of the nitrile products was also performed. "As shown in Scheme 2, some representative substrates including 2-naphthaldehyde, 2,6-dichlorobenzaldehyde, mesitaldehyde, 1,4-phthalaldehyde, 6-nitrobenzo[*d*][1,3]dioxole-5-carbaldehyde, and 4-chlorobenzaldehyde were performed with a loading of 2 g," explained Professor Zhang, adding: "The corresponding products of 2-naphthonitrile, 2,6-dichlorobenzonitrile, mesitonitrile, 1,4-dicyanobenzene, 6-nitrobenzo[*d*][1,3]dioxole-5-carbonitrile, and 4-chlorobenzonitrile were obtained in isolated yields from 83 to 95% (Scheme 2). Furthermore, the catalytic activity did not decrease after five large-scale cycle experiments (Scheme 3), indicating that Fe-N_3/NC-1100 exhibits high stability."

Professor Zhang concluded: "We are convinced that this work will expedite the synthesis of nitrile compounds. The developed method has several attractive features: (1) readily available substrates, as it uses easily accessible alcohol, ketone, and aldehyde feedstock molecules; (2) avoidance of toxic cyano-organic compounds; (3) sustainable reaction conditions, as it takes advantage of O_2 and NH_3 as oxidant and nitrogen source, respectively, with H_2O as the only by-product; and (4) excellent substrate scope and stability. This catalytic system can serve as a bridge between enzymatic catalysis and heterogeneous catalysis and is promising in industrial applications too."



Scheme 3 Large-scale cycle experiments in the synthesis of nitriles.

About the authors

J. Qin

Jingzhong Qin was born in Hunan, P. R. China. He completed his B.Sc. from South-Central University for Nationalities. He joined Professor Zehui Zhang's group as a Master's student at the Key Laboratory of Catalysis and Materials Sciences of the Ministry of Education at the same university. His recent research interests are finding green and sustainable catalytic systems for the synthesis of high value-added chemicals.

Prof. Z. Zhang

Zehui Zhang obtained his Ph.D. from Dalian Institute of Chemical Physics (DICP) in 2011, Chinese Academy of Science (P. R. of China). After that, he joined South Central University for Nationalities (SCUEC, P. R. of China), and started his independent research. His current research interest is the design of novel catalytic systems for sustainable chemistry, particularly in biomass conversion. He is the director of the catalysis and green chemistry research group at SCUEC. He has published more than 120 papers with an H-Index of 51 and has applied for 20 patents.

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Young Career Focus: Professor Johanna Blacquiere (Western University, Canada)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Professor Johanna Blacquiere (Western University, Canada).

Biographical Sketch

Prof. J. Blacquiere

Johanna Blacquiere was born and raised on Prince Edward Island, Canada. She obtained a B.Sc. with an Honours in Chemistry from Mount Allison University (Canada) in 2005, during which she completed research with Steve Westcott. She then completed a summer research position at Los Alamos National Laboratory (USA) under the supervision of Tom Baker. She obtained her Ph.D. at the University of Ottawa (Canada) with Deryn Fogg on the design of ruthenium complexes for olefin metathesis and N_2 activation. She was an NSERC postdoctoral fellow in the laboratory of Jim Mayer at the University of Washington (USA). In 2013, she began her independent career at Western University (Canada) and in 2019 she was promoted to Associate Professor.

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Prof. J. Blacquiere Our goal is to design, understand, and deploy transition-metal catalysts toward the synthesis of valuable organic targets. We prioritize reactions that do not require additives and that generate minimal waste. In this vein, we have designed catalysts for selective alkyne hydrofunctionalization, and acceptorless dehydrogenation of amines.

SYNFORM *When did you get interested in synthesis?*

Prof. J. Blacquiere In the first year of my undergraduate degree at Mount Allison University, I got the opportunity to volunteer in Steve Westcott's research lab. The research group was called the Wild Toads and it was a fun and inspiring training ground for undergrad researchers. I was intending to do a biology degree, but by the end of second year I'd switched to chemistry and I spent the next two summers doing research with the Wild Toads! I loved that we were exploring new chemical space, that understanding experimental outcomes was like solving mysteries, and that there's a lot of creativity in synthesis.

SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Prof. J. Blacquiere I think that it's imperative that chemists are central players in reducing anthropogenic environmental impacts. This should certainly include new synthetic methodologies that allow for more abbreviated and less wasteful routes to high-value molecules, like pharmaceuticals. It should also include many other areas, like the synthesis of new classes of monomers for degradable polymers, or catalysts that can harness abundant small molecules, such as O_2, as chemical feedstocks. It's exciting that central to many of these grand practical challenges are basic questions about cleavage/formation of bonds, and strategies that may shift the paradigm of conventional chemical reactivity.

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Prof. J. Blacquiere We study cooperative metal ligand reactivity, behaviour which we exploit in catalysis for the construction of synthetically valuable functionalities. We have predominantly focused on two types of cooperative ligands.

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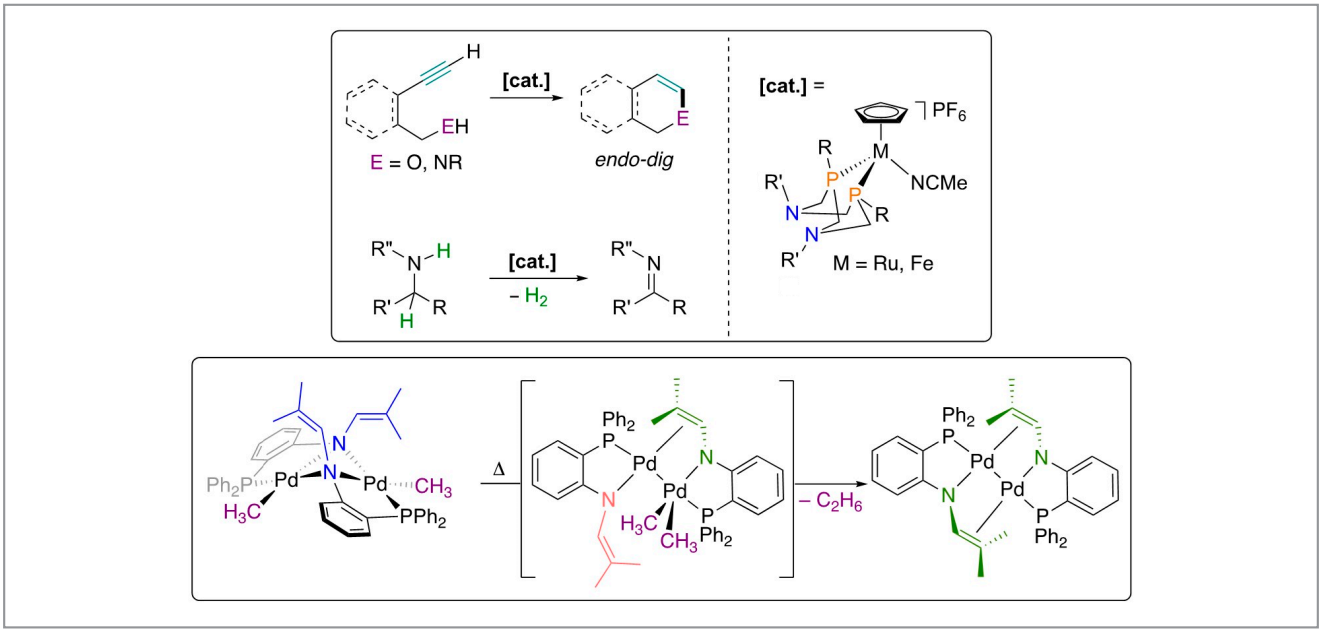
First, we have extensively explored catalysts with $P^{R}_{2}N^{R'}_{2}$ ligands, bisphosphines with pendent tertiary amine groups, that can shuttle protons to/from the metal and/or the organic substrate (Scheme 1, top). Since the ligand can mediate proton transfer steps, exogenous Brønsted base additives are eliminated as a reaction component. We've exploited this type of catalyst structure toward hydrofunctionalization of alkynes and acceptorless dehydrogenation of amines. Second, we have designed a phosphine 1-azaallyl ligand that can readily and reversibly change coordination mode, which induces metal-based reactivity (Scheme 1, bottom). We have shown that the ligand induces metal–metal synergy through a dinuclear reductive elimination pathway, and it can readily stabilize operationally unsaturated complexes. We are excited to exploit both of these features in catalysis.

SYNFORM *What is your most important scientific achievement to date and why?*

Prof. J. Blacquiere Our mechanistic study of C–C reductive elimination from a dinuclear palladium complex (Scheme 1, bottom). This was the outcome of a valuable collaboration between Kyle Jackman, who recently completed his PhD and who did all the experimental work, and Guangchao Liang, a postdoc with Paul Zimmerman (UMichigan, USA), who studied the reaction computationally. The mechanism involved alkyl transfer from one palladium centre to the other followed by reductive elimination from one palladium atom, all within a dinuclear framework. This mechanism is distinct from the vast majority of bond-forming steps mediated by palladium, which occur from mononuclear compounds. Integral to the dinuclear pathway was our phosphine 1-azaallyl ligand that can bridge metals through several different coordination modes. More critically, the capacity of the ligand to readily and reversibly switch between coordination modes facilitated C–C reductive elimination over a competing C–H activation pathway. There are many other examples in the literature of reactions promoted by ligands with dynamic coordination chemistry. Yet, as synthetic chemists, we most often design and exploit ligands that are rigid and that have a static coordination mode. Such ligands have led to enormous success in many areas of catalysis, but a complementary approach with dynamic ligands could open new and unusual catalytic methodologies.



Scheme 1 Catalytic intramolecular hydrofunctionalization of alkynes and acceptorless dehydrogenation of amines, promoted by ruthenium or iron cooperative catalysts (top). C–C reductive elimination from a dinuclear palladium complex, induced by changes in the coordination mode of the phosphine 1-azaallyl supporting ligand (bottom).

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Peptide Carbocycles: From –SS– to –CC– via a Late-Stage "Snip-and-Stitch"

ACS Cent. Sci. **2022**, *8*, 1537–1547

"Now more than ever, peptide medicinal chemists exploit synthetic functional groups to turn ordinary peptides into next-generation biopharmaceuticals. These "groups" often take the form of non-proteinogenic amino acids (NPAAs), which, unlike their biogenic counterparts, impart increased stability, binding affinity, and target specificity to the peptide," said Professor Steven Bloom, from the University of Kansas (Lawrence, USA), whose group is active in the area of NPAAs research. "Accordingly, a slew of technologies has been introduced to streamline the incorporation of NPAAs into peptides, one route being the use of a dehydroalanine (Dha) residue as a synthetic linchpin," he continued. "A dehydroalanine residue is a competent Michael acceptor, and once placed into the peptide, can accept a wide variety of one- and two-electron nucleophiles to insert one of any number of new amino acid side chains at the former Dha site. Applied over each position in the peptide, this approach enables its user to optimize peptide sequences with enhanced physiochemical properties and bioactivity."

Professor Bloom went on by explaining to SYNFORM that besides inserting NPAAs, cyclizing the peptide can be an effective strategy for developing it as a drug: "Most cyclic peptides take advantage of disulfide bonds, formed between two cysteine residues. While the disulfide bond can be easily installed, it is a metabolic lability. Hence, medicinal chemists aim to replace labile disulfide bonds with chemically benign carbon-rich groups." To do this, most cyclization platforms substitute the two cysteine residues with two tailor-made amino acids and then use synthetic chemistry to link the two amino acid fragments together. Each pair of synthetic amino acids produces exactly one *carbo*cyclic peptide derivative. Importantly, each carbon-bridged variant gives the cyclic peptide a unique structure and this alters its bioactivity. According to Professor Bloom, finding a carbon-based group that improves physiochemical properties and retains bioactivity can, therefore, require numerous individual syntheses with every amino acid pair needing to be made and inserted prior to the key cyclization step. Such an approach is less conducive to modern peptide drug discovery campaigns, where producing many peptides and testing them *in parallel* is desirable. Professor Bloom said: "To us, this presented an unmet challenge in cyclic peptide medicinal chemistry, one that we thought could be addressed using Dha residues. We reasoned that a cysteine disulfide could be cleaved into a pair of Dha residues. From here, a carbon-based fragment having two nucleophilic sites could be used to re-cyclize the peptide, each nucleophilic position reacting with one of the two Dha units. This general format would allow a wide variety of carbocyclic peptide variants to be made from a single bis-Dha peptide progenitor. Below is the first-hand account of our studies. We detail our initial plans, rationale, and those unexpected surprises that added immense value to our manuscript."

In previous years, Professor Bloom's lab discovered that organic molecules having a single boronic acid can be transformed into carbon-centered radicals that add to a Dha residue in a peptide through aqueous flavin photoredox catalysis. "We reasoned that under similar conditions, a diboronic acid could be converted into a diradical that inserts nicely between two Dha residues affording new carbocyclic peptides," said Professor Bloom. He continued: "Making peptides that have two Dha residues was straightforward, as prior studies showed that this was possible from disulfides using an easily prepared dibromo ester reagent. Unfortunately, our light-driven approach was not fruitful, only a trace amount of the cyclic peptide being made by LC-MS when a test peptide Dha_2-terlipressin was used. This result suggested to us that both the identity of the bis-nucleophile and the chemistry for activating it would be *incredibly* important to the success of this project and we decided to increase our chances by taking a combinatorial approach to the problem. We made seven different linker chemotypes and tested them across three different synthetic platforms, namely, electrochemistry, photoredox catalysis, and transition-metal catalysis. We found *only* two sets of conditions that worked, one of which used a cocktail of zinc metal and organodiiodides." In addition to the desired cyclic peptide, an appreciable amount of an uncyclized product wherein each Dha separately reacted with a different diiodide, hereafter termed the diaddition product, was formed under the conditions initially used by the group. Biasing cyclization to a useable level (yield) was the immediate challenge facing this project. "While most of our observations were noted in our original manuscript, a few additional points are worth mentioning," said Professor Bloom. He went on to list these: "**One**, we found that copper carbonate was *essential*

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for improving the conversion to peptide products, both linear dialkylated and cyclic peptide. Other copper salts were ineffective. This is not the case in related works where the identity of the copper salt appears to be less important. **Two**, the rate of stirring is *very* important. For best results, the stir rate needed to be kept high. Failure to use adequate stirring resulted in significantly lower yields, likely due to the heterogeneous nature of the reaction. **Three**, although we imagine that the mixture of zinc metal and copper carbonate spontaneously forms a zinc-copper couple in situ, the identity of this composite is unknown. However, we do know that commercial zinc-copper couple is not nearly as effective and should be avoided in our reaction. And **Four**, the inclusion of a hydrosilane additive biases the selectivity of our reaction for cyclization, as opposed to diaddition products, and can enforce diastereoselectivity. Admittedly, while we expected that a hydrosilane might help to encourage cyclization, the observed change in diastereoselectivity was *serendipitous*. The reason that different hydrosilanes cause different amounts of the four possible cyclic peptide diastereomers to be formed is still unclear, even with our experimental evidence that they can quench α-carbonyl radicals generated at Dha positions. We fully intend to follow up on this result and expect that chiral silanes could be important to look at for Generation-II systems."

Although the group noted some surprising results while optimizing their reaction, more unexpected findings were to come during product isolation. "It is worth noting that our lab tries to avoid HPLC purification when possible," explained Professor Bloom. He continued: "Not every lab has an HPLC, and we believe that relying on one greatly limits the ability of others to use (translate) our technologies. Not discussed in our original publication is that we explored many methods to purify our cyclic peptides to avoid HPLC before finding a successful route. We examined solid-phase extraction (SPE), liquid-phase extraction (LPE), and preparative thin-layer chromatography (TLC). With SPE, we could not separate diaddition products from cyclic peptide products. For LPE, all peptide products co-extracted, no matter the solvent choice. Perhaps most unique is what happened in TLC. The diaddition and cyclic peptide products separated when normal- or reverse-phase TLC plates were used; however, the peptides impregnated the solid matrix. We could not dissolve the peptides from the matrix with any solvent including strong acids like trifluoroacetic acid. The inability to release the peptides off the solid matrix prevented us from using preparative TLC, and no further attempts were made in this direction. At this point, we decided to try flash chromatography. Saying that we had little faith in this approach would be an understatement. Separating peptide diastereomers (and peptide mixtures in general) typically requires higher pressures than what flash chromatography can achieve. Indeed, when we first attempted this approach using reverse- or normal-phase columns, no separation between any peptides was found with combinations of MeCN, MeOH, and H_2O as eluent. The incorporation of fluorine-rich acids did little to improve separation. As a "last ditch effort" we replaced MeOH with EtOH in our elution mixture. To our amazement, this change caused all the peptides – diaddition and cyclic peptides and their respective diastereomers – to separate on the column. Our best hypothesis is that EtOH displaces water molecules from the peptides, causing diaddition products to appear more linear and cyclic peptides to look more spherical. Reinforcing these innate 3-D structures causes the various peptide products to separate. This unexpected result was *critical,* as we feared we would have to resort to HPLC if unsuccessful."

Professor Bloom commented that the remainder of their manuscript is "comparatively uneventful", saying that they evaluated the physiochemical properties of select cyclic peptides using laboratory assays that are more conducive to high-throughput experimentation. He admitted: "To be honest, the use of ethylene glycol–heptane partitioning as a measure of blood-brain penetration was met with some speculation among our peers despite being well documented for peptides in the literature. Thus, we would like to formally acknowledge that while cell-based measurements might be a better predictor of results in vivo, our approach is still very useful for surveying many peptide analogues and quickly identifying those that have suitable CNS penetrating properties. It is also less expensive than cell-based assays and might be more useful when cost is a limiting factor. In all, our approach allows many peptide variants to be triaged at the early stages of CNS peptide drug discovery campaigns and should be used as such."

"In conclusion, our studies resulted in a brand-new platform wherein one cyclic disulfide peptide becomes many different carbocyclic analogues using a two-step "Snip-and-Stitch" approach," said Professor Bloom. He continued: "By this we mean that our technology is like a "chemical sewing kit", allowing the disulfide bond to be 'snipped' out and a new functional group 'stitched' in its place. Our work yielded several interesting findings along the way, at least some of which open new doors for peptide medicinal chemistry and others that highlight still unsolved problems for the field." Professor Bloom concluded: "It is our hope that relating these additional points will help others to use our technology and to drive peptide medicinal chemistry ever forward."

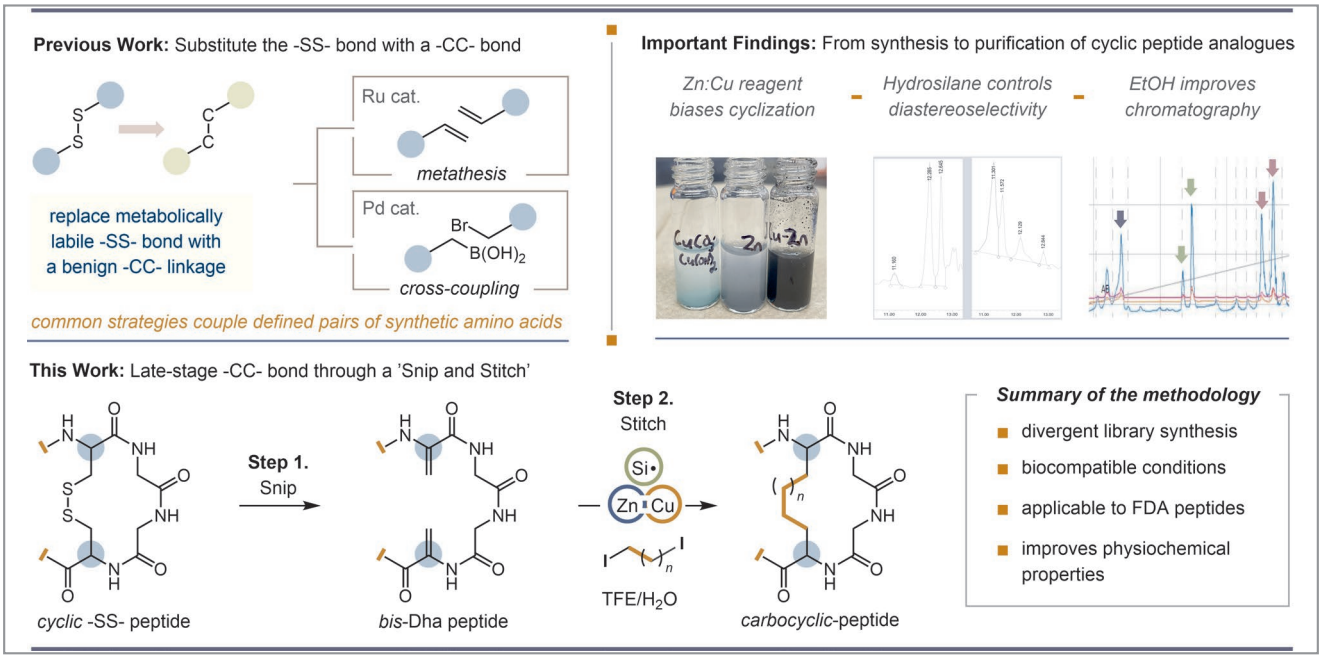

Figure 1 Summary of the work and key findings. Previous technologies for making carbocyclic peptides relied heavily on uniting two synthetic amino acids in the peptide to give a single product. The title work takes advantage of native disulfides to access a pair of endogenous dehydroalanine residues that can be tethered together using an organodiiodide, zinc-copper couple and a hydrosilane, affording a divergent route to many cyclic peptide analogues. Judicious choice in hydrosilane can bias the stereochemical outcome of the cyclization step and EtOH greatly improves the separation of the products by flash chromatography.

About the authors

S. Gary

Samuel Gary was born and raised in West Virginia (USA). He earned his B.S. in biochemistry from West Virginia University (USA) where he completed undergraduate research with Dr. Nik Kovinich, studying anticancer natural products. Sam began graduate studies at the University of Kansas (USA) in 2019, under the guidance of Prof. Steven Bloom. His research focuses on designing new platforms to construct libraries of cyclic peptides and to insert non-proteinogenic amino acids into peptides. His work aims to streamline structure–activity relationship studies and the hit-to-lead development of novel peptide therapeutics.

Prof. S. Bloom

Steven Bloom is from Harford County, Maryland (USA). He attended McDaniel College, located in western Maryland (USA), where he earned his B. A. in chemistry and biochemistry in 2010. He then completed graduate studies at Johns Hopkins University (USA) under the tutelage of Prof. Thomas Lectka in organofluorine chemistry. After earning his Ph.D. in 2015, Steve moved to Princeton University (USA) where he completed postdoctoral studies with Prof. David W. C. MacMillan as an NIH Ruth L. Kirschstein Fellow. There, Steve worked in bioorganic chemistry, developing photocatalyzed strategies to selectively modify proteins. Steve began his independent career at the University of Kansas (USA) in 2018. His group focuses on designing new synthetically divergent technologies to accelerate peptide medicinal chemistry and drug discovery.

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Ring Contraction of Metallacyclobutadiene to Metallacyclopropene Driven by π- and σ-Aromaticity Relay

Nat. Synth. **2022**, in press; DOI: 10.1038/s44160-022-00194-2

Aromaticity has been one of the most fundamental and fascinating concepts ever since it was first proposed by Hückel in 1831. Aromaticity-driven reactions are crucial in synthetic chemistry, owing to the relatively low energies of aromatic products. π-Aromaticity is an important driving force in directing the synthesis of aromatic compounds; in contrast, reactions induced by σ-aromaticity are uncommon.

In a study recently published in *Nature Synthesis*, a team led by Professors Haiping Xia and Yu-Mei Lin from Xiamen University (P. R. of China) & Southern University of Science and Technology at Shenzen (P. R. of China), developed a π- and σ-aromaticity relay strategy to realize an unprecedented ring contraction of metallacyclobutadiene to metallacyclopropene (Figure 1).

Based on a series of aromatic metal bridgehead polycyclic frameworks dubbed "carbolong complexes" (*Acc. Chem. Res.* **2018**, *51*, 1691–1700) by the authors, Zhuo et al. designed and synthesized a new sort of osmacyclobutadienes **2a–c**, which underwent ring contraction reaction to afford osmacyclopropenes **3a–c** in acidic conditions. "In principle, metallacyclobutadienes tend to undergo ring expansion or ring opening. Restricted by ring strain effects, small metallacycles are prone to ring expansion or ring opening, while the ring contraction reaction is challenging, especially in the smallest four-to-three ring contraction version (Figure 2)," explained Professors Xia and Lin. They continued: "In fact, this may represent the first observation of a structurally well-defined ring contraction of metallacyclobutadiene to metallacyclopropene. This methodology enables the construction of stable small metallacycles, opening an avenue for new transformations within small rings."

Density functional theory (DFT) calculations were performed to investigate the mechanism of the ring contraction, which turned out to proceed through a ring opening–reclosing pathway, involving acid-mediated protonation and deprotonation via vinylcarbene species intermediates. "Under the treatment of excess $HBF_4{\cdot}Et_2O$, vinylcarbene intermediate **4A** was isolated," said Professor Xia. He continued: "The computed Gibbs free energy profile revealed that the influence of acids on the ring contraction lies in the energy difference of intermediates **4A** or **4a**, and the energy barrier distinction of **TS2** or **TS2′** of the conversion from intermediate into final product **3a**. Notably, the successive decreases in energy during the transformation **2a** ⟶ **4A** ⟶ **3a** aroused our interest in the aromaticity properties (Figure 3)."

A variety of aromaticity criteria, including nucleus-independent chemical shift (NICS), anisotropy of the induced current density (ACID), and isodesmic reactions, indicated the antiaromaticity of metallacyclobutadiene in complex **2**, aromaticity in fused metallapentalene **4** and enhanced σ-aromaticity of metallacyclopropene in complex **3**, which revealed that aromaticity plays an important role in lowering

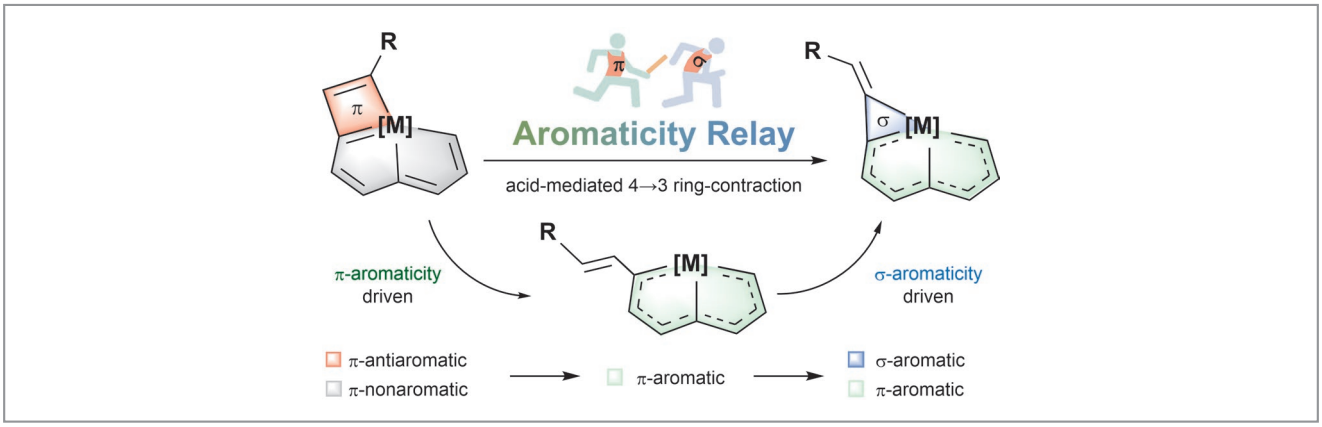
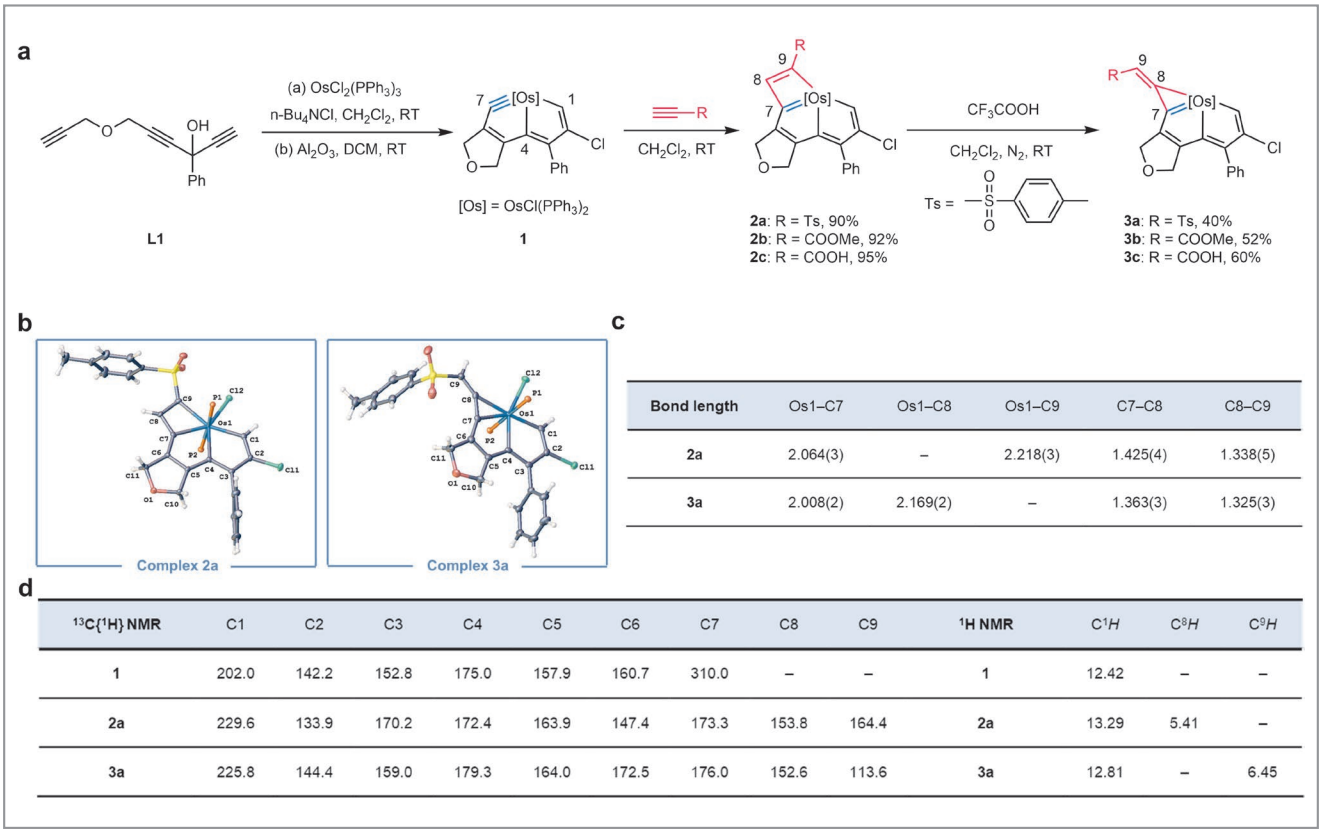


Figure 1 Aromaticity relay strategy for ring contraction



Bond length	Os1–C7	Os1–C8	Os1–C9	C7–C8	C8–C9
2a	2.064(3)	–	2.218(3)	1.425(4)	1.338(5)
3a	2.008(2)	2.169(2)	–	1.363(3)	1.325(3)

$^{13}C\{^{1}H\}$ NMR	C1	C2	C3	C4	C5	C6	C7	C8	C9	^{1}H NMR	$C^{1}H$	$C^{8}H$	$C^{9}H$
1	202.0	142.2	152.8	175.0	157.9	160.7	310.0	–	–	**1**	12.42	–	–
2a	229.6	133.9	170.2	172.4	163.9	147.4	173.3	153.8	164.4	**2a**	13.29	5.41	–
3a	225.8	144.4	159.0	179.3	164.0	172.5	176.0	152.6	113.6	**3a**	12.81	–	6.45

Figure 2 Synthesis and characterization of precursor **1**, [2+2]-cycloaddition products **2a–c** and ring-contraction products **3a–c**.

the energy associated with the transformation of **2** ⟶ **3**. Professor Lin explained: "The ring opening of osmacyclobutadiene in **2a** to form **4A** involves the release of antiaromaticity accompanied by the reinforcement of the π-aromaticity in osmapentalene and can be viewed as a π-aromaticity-driven process. Next, the ring-reclosing process from **4** ⟶ **3** further expands the aromaticity system of the metallacycles with newly formed σ-aromaticity. Thus, the ring-contraction reaction is driven by successive enhancements of the aromaticity, accompanied by successive decreases in energy during the transformation and various changes in (anti)aromatic properties."

Finally, Zhuo and co-workers tested the thermal and chemical stability and optical properties. The species **3a** exhibited excellent thermal stability even when heated to 180 °C in air for 3 hours. "Electrophilic substitution and an oxidation reaction both take place at the exocyclic positions of **3a**, suggesting the high stability and resistance to oxidation of the metallacyclopropene moiety, consistent with its σ-aromatic character," noted Professor Xia. He continued: "Otherwise, it is supposed that a three-membered ring system with high ring-strain should be unstable in the absence of an aromatic stabilization energy contribution."

"In summary," said Professor Xia, "This work demonstrates an unusual acid-induced ring contraction of metallacyclobutadiene to metallacyclopropene via a ring opening–reclosing process. This involves π-aromaticity-driven ring opening of an antiaromatic metallacyclobutadiene, followed by σ-aromaticity-driven ring reclosing resulting in the expansion of global aromaticity, as confirmed by both successful isolation of the key intermediate and theoretical calculations." He concluded: "These findings offer a valuable supplement to ring contraction in small metallacycles and provide new insight into aromaticity-driven relay strategies in synthetic transformations."

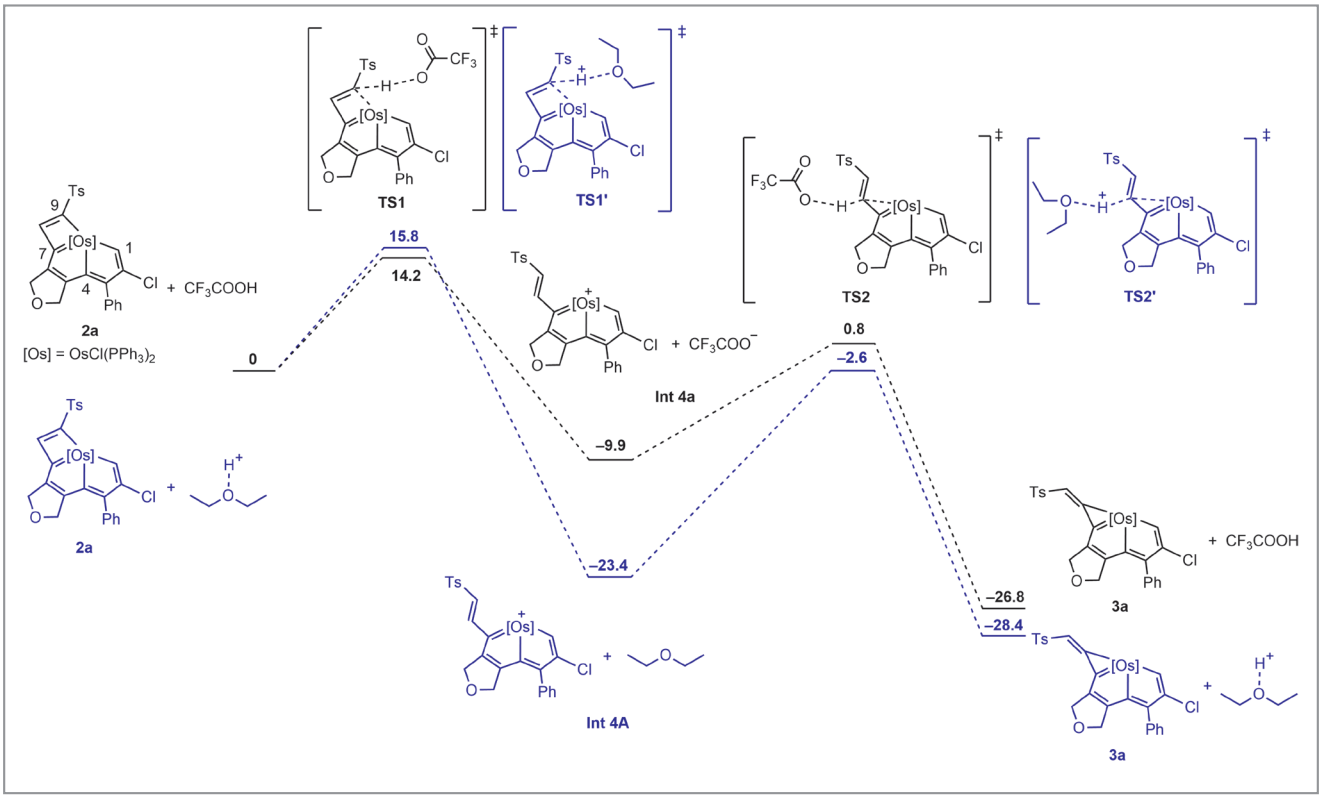


Figure 3 DFT calculations for mechanistic investigation

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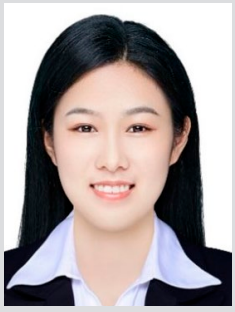

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