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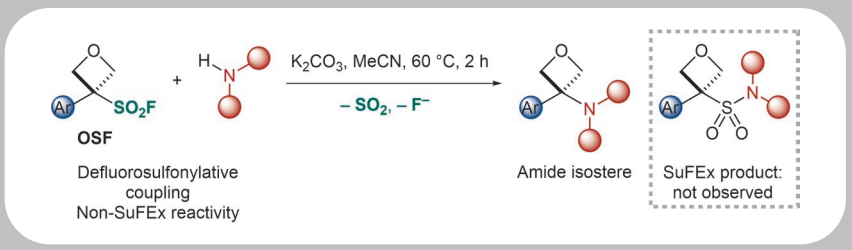
2022/07

Amino-oxetanes as Amide Isosteres by an Alternative Defluorosulfonylative Coupling of Sulfonyl Fluorides

Highlighted article by J. J. Rojas, R. A. Croft, A. J. Sterling, E. L. Briggs, D. Antermite, D. C. Schmitt, L. Blagojevic, P. Haycock, A. J. P. White, F. Duarte, C. Choi, J. J. Mousseau, J. A. Bull



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Thieme

Dear Readers,

I would like to use this editorial to highlight an issue that is common to all science & technology magazines and supplements covering hot-off-the-press peer-reviewed research articles: retractions. Indeed, during one of my usual weekly literature scans, I stumbled upon the retraction (dated 29th Apr 2022) of a *Science* paper by Sawamura et al. ("Asymmetric Remote C–H Borylation of Aliphatic Amides and Esters with a Modular Iridium Catalyst", *Science* **2020**, *369*, 970–974) that SYNFORM covered in 2021 (Page A6). According to an article published in *Retraction Watch* (https://retractionwatch.com/2022/04/28/chemistry-paper-retracted-from-science/#more-124789) the *Science* editor-in-chief stated: "We heard from the PI that they wanted to retract. Hadn't heard about problems before that. We deeply appreciate and commend their forthrightness." Based on this, we can only assume that the interview released by Professor Sawamura et al. to SYNFORM was entirely in good faith and only afterwards the authors became aware of the issues that eventually led to the retraction of their article. This is unfortunate, but is also an increasingly common by-product of the rush to "publish or perish", which is putting an immense strain on all the parties involved in scientific publishing, from the authors to the publishers, without forgetting the reviewers. The latter – in particular – are often too busy to do their vital job in an optimal manner, besides being pressured by journals to submit their reviews within totally unrealistic deadlines, without having the necessary time to thoroughly think through the manuscripts they are supposed to evaluate. There is no easy way to deal with this issue – and certainly this short editorial is not the right place for discussing a topic of this complexity – but funding agencies could perhaps play a more decisive role to try and change the trajectory of this self-harming "publish or perish" exercise, which is contributing to the generation of articles that have to be subsequently retracted, or proven blatantly wrong without even being retracted.

The kick-off article of this July issue covers a *Nat. Chem.* paper by J. Bull (UK) in collaboration with a team at Pfizer, who developed a novel approach to amino-oxetanes – which find applications as amide isosteres in medicinal chemistry – using an alternative defluorosulfonylative coupling of sulfonyl fluorides. The second article is an interesting Young Career Focus interview with S. D. Townsend (USA) about his interests in organic synthesis and biological chemistry. The third article covers the recent paper in *Nat. Commun.* by the group of L. Liu (P. R. of China) on the kinetic resolution of cyclic benzyilic azides via site- and enantioselective C(sp^3)–H oxidation of the unwanted enantiomer. The closing article is truly explosive, as it takes us to the fascinating world of high-energy organic compounds under the guidance of S. Pang (P. R. of China), whose group identified a new strategy for balancing high energy and chemical stability, exemplified by the new kid on the block in the field of organic explosives: 1,3,5-trinitro-2,4,6-trinitroaminobenzene.

In this issue

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Amino-oxetanes as Amide Isosteres by an Alternative Defluoro-sulfonylative Coupling of Sulfonyl Fluorides

Nat. Chem. **2022**, *14*, 160–169

Dr. James Bull's group at Imperial College London (UK) has a long-standing interest in the preparation of four-membered rings, especially oxetanes, and has ambitions to position any functional group at any position on the ring. "We have installed various functional groups at the 2- and 3-positions, but 3-aryl-3-amino oxetanes, that can be considered as benzamide replacements, were a particular challenge," said Dr. Bull.

Recently, the group has been working with scientists at Pfizer (especially Dr. James Mousseau and Charlie Choi) on the preparation of 3,3-disubstituted oxetanes that are of interest as carbonyl replacement groups. "Work from Carreira and co-workers at Roche had previously established several favourable comparisons," said Dr. Bull. He continued: "We had developed synthetic routes to activate 3-aryl-oxetan-3-ols that react with phenols in Friedel–Crafts reactions or in thiol alkylations. However, amines were unsuccessful as nucleophiles in this way."

As part of the Bull group's broad work in this area, they prepared oxetane sulfonyl fluorides. Sulfonyl fluorides are broadly used as precursors to sulfonamides and sulfonates. In comparison to sulfonyl chlorides, these are much more hydrolytically stable and more likely to undergo sulfur fluorine exchange (SuFEx) chemistry rather than reduction. As a result, these are increasingly used in 'click' processes, including in materials chemistry and as covalent probes in medicinal chemistry.

"However, these aryl-oxetane sulfonyl fluoride species (**OSF**) did not behave at all in the usual way!" remarked Dr. Bull. "Instead, these underwent a loss of SO_2 and a fluoride ion to generate an oxetane carbocation intermediate that could react with nucleophiles, namely a defluorosulfonylative process. Specifically, we reacted these reagents with a wide range of amines to form amino oxetanes that provide an interesting mimic to the amide bond. The comparison with amides as bioisosteres is very interesting and, perhaps more importantly, the aminooxetane motif is attractive in its own right, as a small, polar and non-planar functional group that we believe provides interesting potential in medicinal chemistry. What is really attractive about this reaction is that the bond that is formed is analogous to that of a typical amide bond formation, and as a result can potentially make use of the enormous collections of amines that are available to pharmaceutical companies."

Dr. Bull pointed out that this is a very unusual generation of a carbocation under extremely mild conditions, indeed under slightly basic conditions. As a result, very high functional group tolerance was obtained, with polar functionality of various types (Figure 1). "Hindered amines, amino acid derivatives, primary and secondary amines and anilines are all successful nucleophiles," said Dr. Bull. He continued: "Phenols can either undergo the defluorosulfonylative coupling process or more typical SuFEx, depending on the conditions. We used various oxetane sulfonyl fluorides to generate a collection of 10 oxetane analogues of benzamide-containing drug compounds. We demonstrated the potential for the late-stage diversification of complex amines by reactions with amine-containing drug compounds, and also through an array with a 'diversity set' of amines run at Pfizer (by Dr. Dan Schmitt)."

The oxetane sulfonyl fluoride reacted at the same rate, with first order, independent of the nucleophile, consistent with the proposed S_N1 mechanism (Figure 2). "The structure and stability of the oxetane carbocation was itself very interesting," commented Dr. Bull. "Dr. Alistair Sterling and Prof. Fernanda Duarte, computational physical organic chemists at the University of Oxford, demonstrated that the oxetane carbocation intermediate adopts a planar conformation. This conformation places the electron-rich aromatic and the carbocation on the oxetane ring in conjugation, to enable maximum stabilisation and minimise the potential steric clashes between the *ortho* C–H bonds and the methylene groups on oxetane. Consequently, the oxygen lone pair is not involved in stabilisation. The oxetane sulfonyl fluoride reagents have good stability at and below room temperature, but readily react at slightly elevated temperatures by S_N1 ionisation through lengthening of the C–S bond."

Dr. Bull concluded: "I would like to thank all of the collaborators on this work, at Imperial College, Oxford and Pfizer, and in particular co-first authors Juan Rojas and Rosie Croft for their outstanding work in identifying, controlling and explaining this chemistry."

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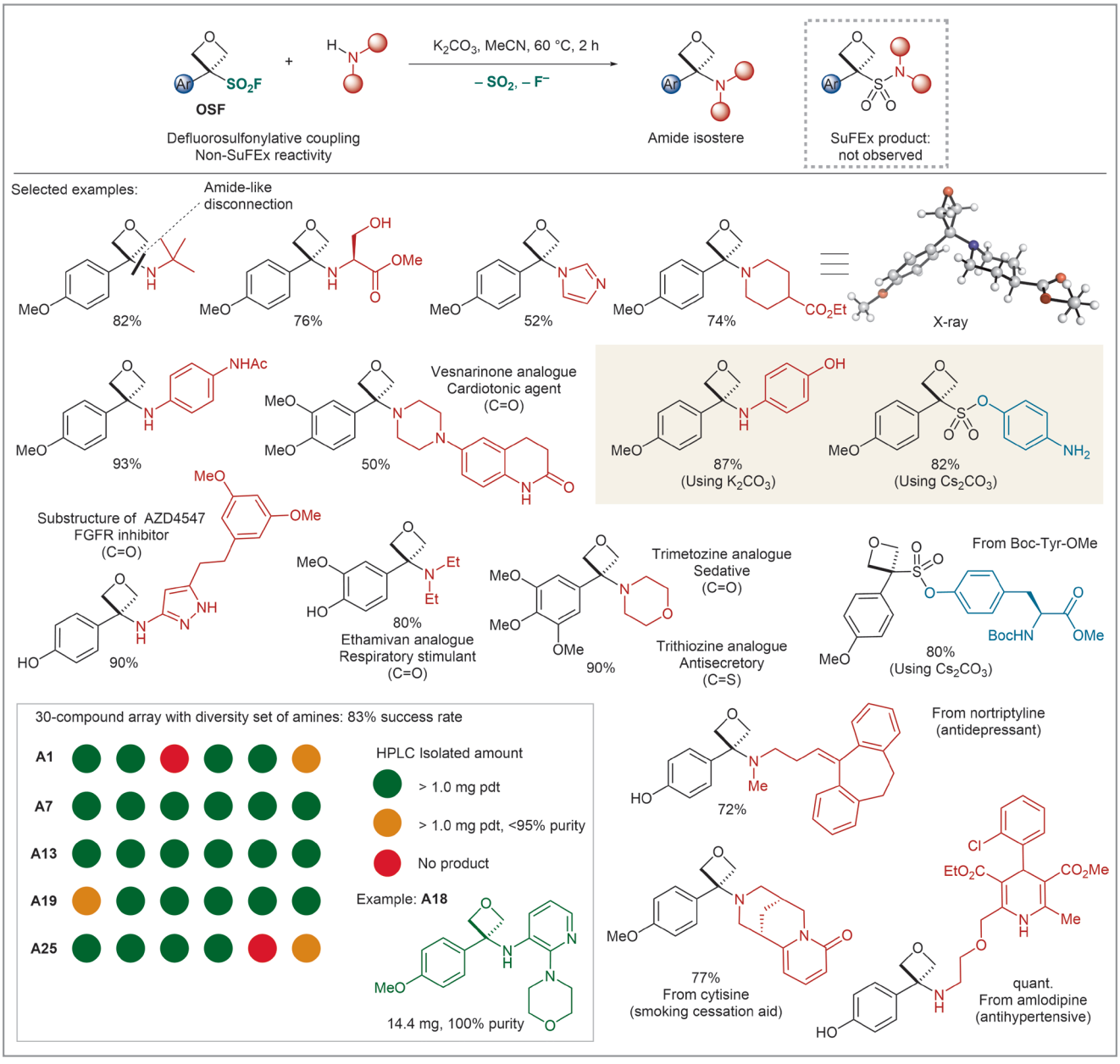

Figure 1 Reaction scope of the defluorosulfonylation of OSFs with amines and other nucleophiles; inset: thirty-compound array with an exemplary OSF (Ar = 4-MeOC$_6$H$_4$) and a diversity set of amines

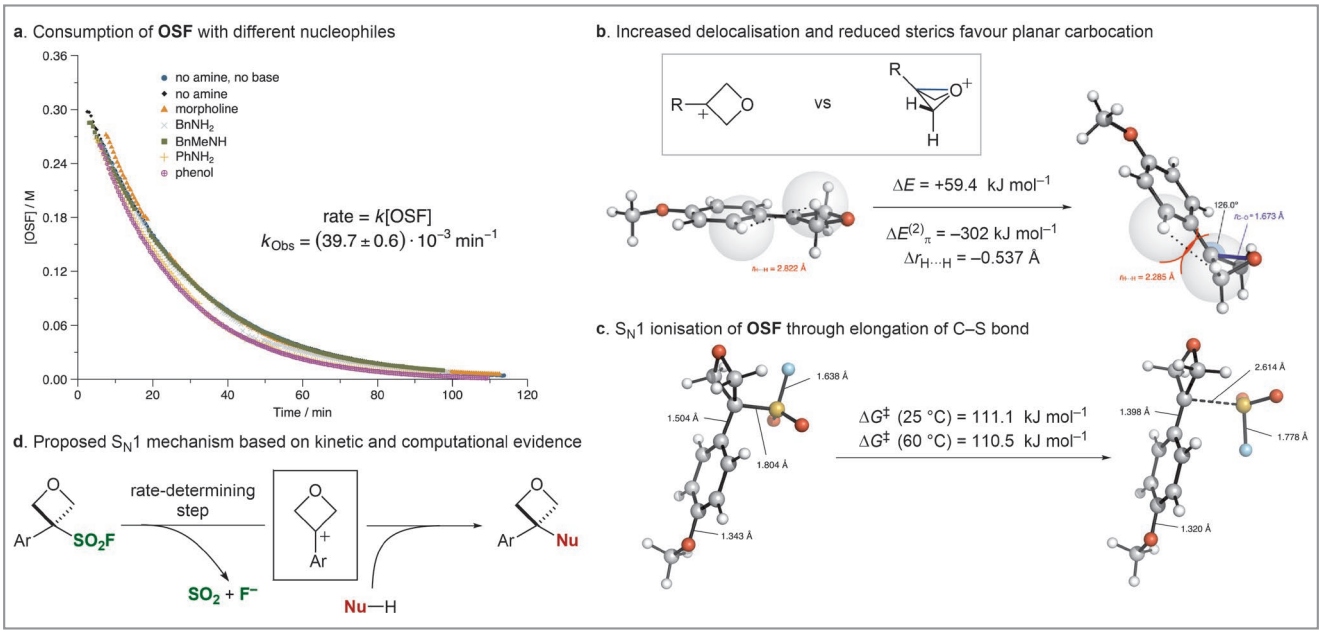

Figure 2 Kinetic and computational analysis of the defluorosulfonylative oxetane amination

About the authors

J. J. Rojas

Juan J. Rojas received his BSc degree in chemistry from the ETH Zürich (Switzerland) in 2016. After 10 months in the Swiss Armed Forces, he went to London where he obtained his MRes degree in catalysis from Imperial College London (UK), studying the activation of oxetanols using Brønsted acids in the lab of Dr. James Bull and receiving the MRes Catalysis Outstanding Performance Prize (2018). He then spent six months in the Small Molecule Division at BASF Ludwigshafen (Germany) working on organophosphorus derivatives. Currently, he is pursuing a Ph.D. with Dr. James Bull, investigating synthetic methods to access 3,3-disubstituted oxetanes through the generation of reactive oxetane intermediates.

Dr. R. Croft

Rosemary Croft obtained her MSc from Bristol University (UK) in 2014. She then went on to pursue her PhD under the supervision of Dr. James Bull at Imperial College London (UK). Her research focused on the synthesis of oxetane bioisosteres through the generation of oxetanyl carbocations. She currently works as a research chemist in weed control at Syngenta.

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Dr. A. J. Sterling

Alistair J. Sterling received his DPhil from the University of Oxford (UK) in 2021 under the supervision of Profs. F. Duarte and E. A. Anderson, where he received an Oxford-Radcliffe Scholarship. He obtained his MChem from the same institution in 2017, spending a semester in the group of Prof. E. M. Carreira (ETH Zürich, Switzerland), before returning to Oxford to study total synthesis under the supervision of Prof. E. A. Anderson. He then transitioned from experimental to computational chemistry in 2018 while working on cyclocarbon analogues under Prof. H. L. Anderson. He is currently an EPSRC Doctoral Prize postdoctoral researcher at the University of Oxford, where his research interests include physical organic chemistry, computational chemistry and reaction development.

Dr. E. L. Briggs

Edward L. Briggs received his MChem degree (2017) from the University of Southampton (UK) which included a placement at Vertex Pharmaceuticals (Oxford, UK). He then moved to Imperial College London (UK) to undertake a PhD (2021) under the supervision of Dr. James A. Bull researching methods to synthesise medicinally relevant sulfur(VI) analogues. He is currently working as a postdoctoral training fellow at the Institute of Cancer Research (UK) under Dr. Gurdip Bhalay.

Dr. D. Antermite

Daniele Antermite graduated from the University of Bari (Italy), with an M.Sc. degree in Pharmaceutical Chemistry and Technology in 2016. During his undergraduate studies, he performed research placements in organic chemistry at the Karlsruhe Institute of Technology (Germany) and at the University of Vienna (Austria). He then joined Dr. James Bull's group at Imperial College London (UK) for his doctoral studies, focusing on Pd-catalysed C–H functionalisation of saturated heterocycles. After receiving his PhD in 2020, Daniele joined AstraZeneca Gothenburg (Sweden) as a postdoctoral fellow, where is currently working on late-stage C–H functionalisation methodologies in collaboration with Prof. Lutz Ackermann (University of Göttingen, Germany).

Dr. D. C. Schmitt

Daniel C. Schmitt received his PhD in organic chemistry from the University of North Carolina at Chapel Hill (USA) under the supervision of Prof. Jeffrey Johnson. Subsequently, he conducted postdoctoral research with Prof. Michael Krische (University of Texas at Austin, USA), focused on Ir-catalysed allylation methodology. Dan joined Pfizer in 2012 and is now a project and synthesis group leader within the Inflammation & Immunology Medicinal Chemistry department. He enjoys the development and adaption of new synthetic methodologies to parallel format for the expansion of accessible design space on drug discovery projects.

Dr. A. J. P. White

Andrew J. P. White received his PhD from Imperial College London (UK) in 1994 under the supervision of William P. Griffith. He then moved to the Chemical Crystallography Laboratory run by David J. Williams at Imperial College London in 1994, taking over the running of the laboratory upon Prof. Williams' retirement in 2003.

Prof. F. Duarte

Fernanda Duarte is an Associate Professor in the Department of Chemistry at Oxford (UK), where she leads a diverse team working at the interface of organic, supramolecular, and computational chemistry. Her main research interests centre on the prediction of chemical reactivity in the condensed phase, combining classical, quantum and machine-learning approaches. Her group has also developed a series of computational software to facilitate molecular modeling and reaction mechanism exploration. Fernanda has published 60 peer-

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reviewed scientific publications and received several awards, including most recently the 2020 MGMS Frank Blaney Award from the Molecular Graphics and Modelling Society, 2021 OpenEye Outstanding Junior Faculty Award from ACS COMP Division, and the 2021 Harrison-Meldola Memorial Prize from the Royal Society of Chemistry.

Dr. J. J. Mousseau

James J. Mousseau was born in Montreal, Quebec, Canada. Upon completing his BSc and MSc studies at Concordia University (Canada), he pursued his PhD studies under Professor André B. Charette at Université de Montreal (Canada) studying arene direct functionalization processes. Following an NSERC Postdoctoral Fellowship at the Massachusetts Institute of Technology (USA) under Professor Timothy F. Jamison, he began his career in 2013 at Pfizer in Groton, Connecticut (USA) working in the area of inflammation and immunology. In 2021 he moved to Halda Therapeutics (USA) investigating new modalities for the treatment of cancer. His other research interests include the development and study of strained rings and new bioisosteric motifs.

Dr. J. A. Bull

James A. Bull is a University Research Fellow and Reader in Synthetic Chemistry at Imperial College London (UK). He obtained an MSci degree and the Raphael prize from the University of Cambridge (UK), then spent a year at GlaxoSmithKline. He returned to University of Cambridge to obtain his PhD under the supervision of Professor Steven Ley. In 2007 he joined the group of Professor André Charette as a postdoctoral fellow at Université de Montréal (Canada). He joined Imperial College London in 2009 as a Ramsay Memorial Research Fellow, and in 2011 was awarded an EPSRC Career Acceleration Fellowship. In January 2016, he was awarded a Royal Society University Research Fellowship. He received a Thieme Chemistry Journal Award in 2016 and the AstraZeneca prize for synthetic chemistry in 2021. His research targets methods for the synthesis of new chemical motifs that may be practically applied in drug discovery, to provide new design elements and extend available chemical space.

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Young Career Focus: Professor Steven Townsend (Vanderbilt University, USA)

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 Steven Townsend (Vanderbilt University, USA).

Biographical Sketch

Prof. S. D. Townsend

Steven Townsend was born and raised in Detroit, Michigan (USA) in 1983. He completed his undergraduate education at Oakland University (USA) in 2005 where he completed 4 years of research working on the synthesis of nucleoside radical precursors with Prof. Amanda Bryant Friedrich. From Oakland, Steve matriculated to Vanderbilt University (USA) where he completed a PhD working toward the total synthesis of bielschowskysin under the mentorship of Prof. Gary Sulikowski. Steve completed his education at Memorial Sloan-Kettering Cancer Center (USA) and Columbia University (USA) with Prof. Sam Danishefsky, where he worked on the total synthesis of erythropoietin, PTHrP, peptide ligation, and Diels–Alder methodology.

Since 2014, Steve has established an independent program at Vanderbilt University where his group leverages organic chemistry to address problems in human health, particularly in the areas of human milk science, antimicrobial agents, and chemotherapeutics. Steve's team has been honored with several awards, including the Sloan Research Fellowship, the Camille Dreyfus Teacher Scholar Award, The David Gin New Investigator Award, the Ruth Kirstein Award for Excellence in Human Milk Science, and the C&E News Talented 12. Steve's dedication to education is also highlighted, by his Jeff Nordhaus Award for Excellence in Undergraduate Teaching.

INTERVIEW

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

Prof. S. D. Townsend Our research team cares about why human beings get sick. Our focus is to contribute new advances to the strategy and tactics of organic synthesis and leverage these advances to cure and prevent illness. Overall, our team is interested in projects that challenge the state of the art, particularly in carbohydrate synthesis.

SYNFORM *When did you get interested in synthesis?*

Prof. S. D. Townsend Although my interest in chemistry was initiated in high school, my interest in synthesis started as a freshman in college. I worked on organic chemistry all four years of my undergraduate career, including the summers. Like most practitioners of the art, I found solace from life's complexities in setting up reactions and running columns. I love the consistent problem solving that synthesis offers. Interestingly, I recently looked at my personal statement for graduate school – a statement that I wrote in August of 2004! It's interesting to analyze yourself at age 21 from the vantage point of being 39 – it was clear that I was going to work on organic synthesis for the rest of my life. While my personal statement briefly mentioned my background and family life, the writing was saturated with poorly drawn schemes (I didn't have ChemDraw) about my project and a listing of my three favorite chemists at the time – Sam Danishefsky, KC Nicolaou, and M. Chistina White! I spoke for an entire paragraph about protecting group manipulations and how I solved a tricky reaction by freshly preparing and purifying every reagent!

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

Prof. S. D. Townsend As a faculty member in organic chemistry, I consider myself as a guardian of the field. My job is to promote inquiry, instill problem solving, and teach the history of organic synthesis. In doing so, I do my part to ensure that we respect organic synthesis as an art with its own basic merit. I also believe that organic synthesis is an enabling science. A central part of its present and future, must be solving problems in other fields. A few years ago, a family member told me that they felt scientists were hustlers – that we don't care about the end user and just want their money for research. In other words, we're one of the few fields that's willing to use tax-payer money but doesn't make all attempts to explain to the public what we do with their money. I think a major role for the future of organic synthesis is to ensure that bring the public into our community and showcase how our advances and discoveries enhance their lives.

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

Prof. S. D. Townsend A major focus over the first 8 years has been human milk science, where we are focused on merging organic chemistry with microbiology to characterize the protective properties of the macromolecules present in mother's milk. Moving forward, we are advancing new projects in the synthesis of antimicrobial agents, chemotherapeutics, and zwitterionic polysaccharides. Each of these projects require that we both master precedent and innovate to drive the field in new directions.

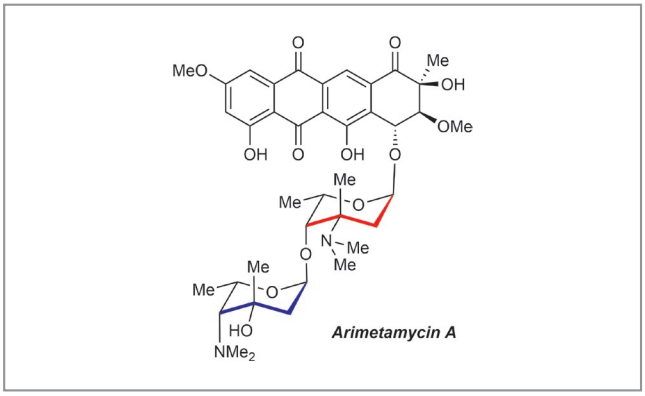


Figure 1 A natural anthracyclin natural product recently synthesized by the Townsend group (*ACS Cent. Sci.* **2021**, *7*, 1327–1337).

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

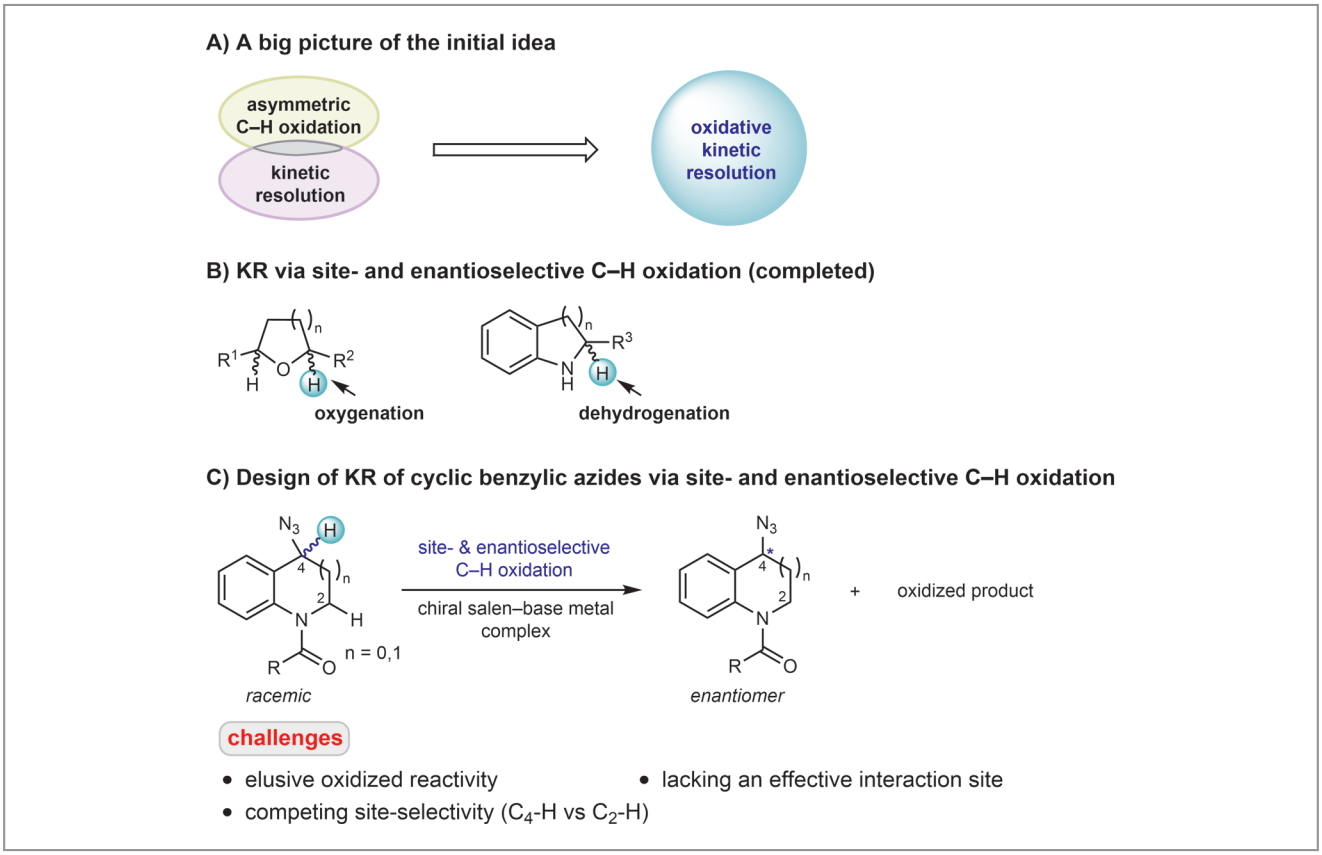
Prof. S. D. Townsend My greatest contribution to date is the trainees that I've mentored. At the time of this publication, the group will have produced 8 new PhDs. I owe much of my success to the inspiring students who have driven the lab's work, supported me and the program, and lifted me up along the way. I am indebted to them. The lab would not be where it is today without them. Mentoring is a privilege and responsibility that I believe we should all take very seriously and honorably. It is because of the trainees that we've been able to think very differently about what it means to be an organic chemist in the modern world and that, perhaps, is our greatest achievement.

Kinetic Resolution of Cyclic Benzylic Azides Enabled By Site- And Enantioselective C(sp³)–H Oxidation

Nat. Commun. **2022**, *13*, 1621

Site- and enantioselective oxidation of aliphatic C–H bonds with a general scope, predictable selectivities and in preparatively useful yields, would represent a paradigm shift in the standard logic of organic synthesis. On the other hand, catalytic kinetic resolution (KR) of racemates is one of the most powerful and practical tools to prepare valuable enantiopure targets, which predominantly relies on the manipulation of reactive functional groups. The group of Professor Lei Liu at Shandong University (Jinan, P. R. of China) envisioned that integrating the KR strategy into enantioselective C(sp³)–H oxidation reaction design would advance the development of both research fields (Scheme 1A). Professor Liu said: "During the past three years, we have put into practice this initial idea in achieving base-metal-catalyzed KR of cyclic secondary amines and cyclic ethers through site- and enantiodifferentiating C(sp³)–H oxidation (Scheme 1B; *J. Am. Chem. Soc.* **2019**, *141*, 6318–6324; *J. Am. Chem. Soc.* **2022**, *144*, 5976–5984; *Angew. Chem. Int. Ed.* **2021**, *60*, 176–180; *J. Am. Chem. Soc.* **2020**, *142*, 19346–19353)."

According to Professor Liu, chiral organic azides have found dramatically expanded utility in medicine, biology, and materials science. However, catalytic KR to provide optically pure azides has remained elusive, principally owing to two essential features of the azido moiety: (1) its instability, hampering the design of new reactivity with excellent chemoselectivity; and (2) its small size, hampering the achievement



Scheme 1 The general idea of the project

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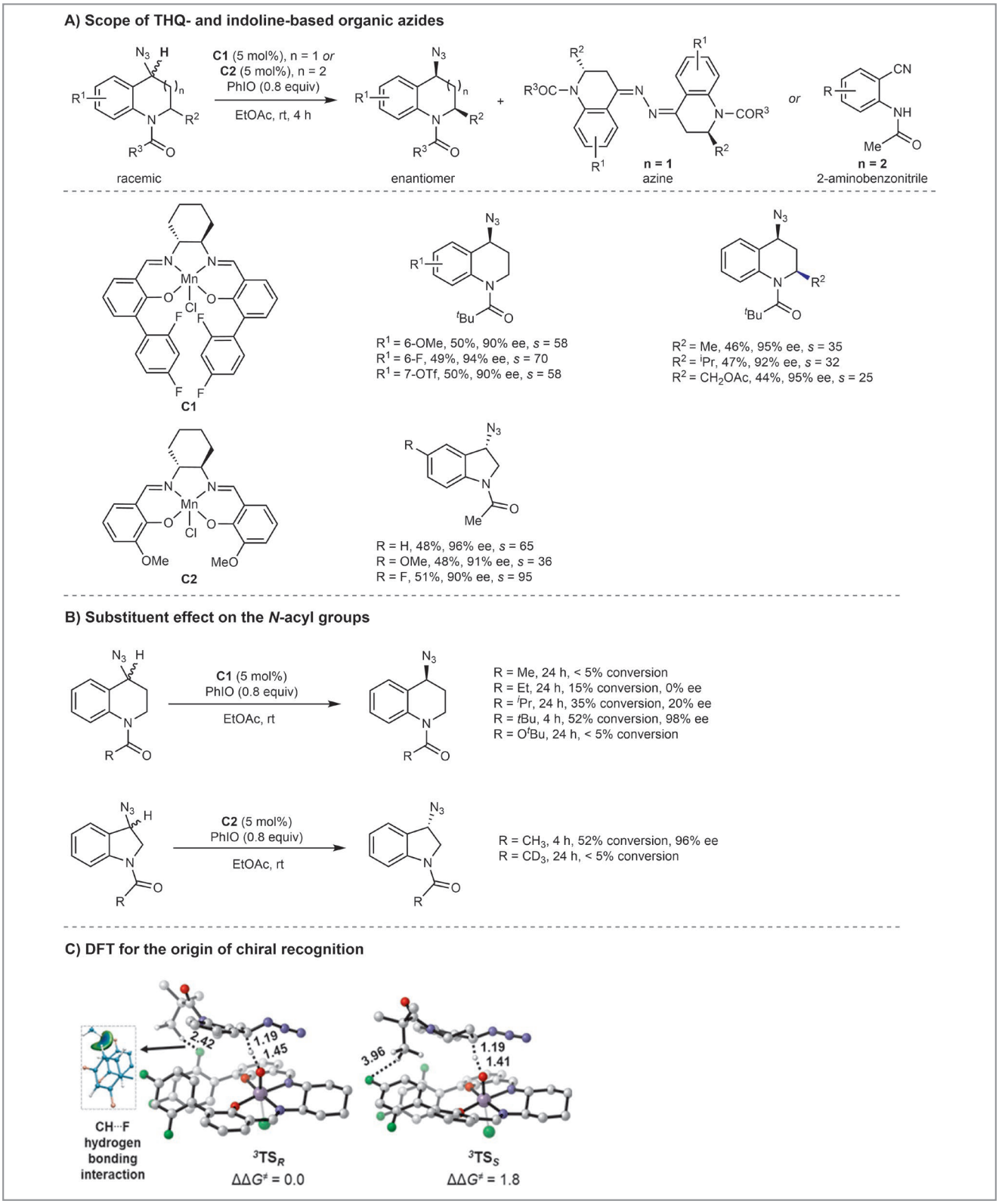
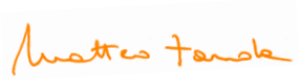


Scheme 2 Oxidative KR of cyclic benzylic azides and the origin of effective chiral recognition

of effective chiral recognition. "Existing isolated examples in the literature invariably focused on manipulating the azido moiety through azide–alkyne cycloaddition or extra reactive functional groups preinstalled in substrates, which typically suffer from the use of excess azide substrates, poor chiral recognition, and narrow substrate scope," remarked Professor Liu, who continued: "Therefore, we decided to explore the KR of organic azides relying on the oxidative reactivity of C(sp^3)–H bonds (Scheme 1C)."

"Two main challenges hampered the reaction design (Scheme 1C)," explained Professor Liu. He continued: "First, due to stability issues, selective oxidation of the C(sp^3)–H bond adjacent to an azido moiety remains elusive. Second, organic azides lack an effective interaction site to direct the substrate to an ideal location in the transition state, which would result in the chiral discrimination of chemically similar C(sp^3)–H bonds of two enantiomers. Accordingly, the project was designed based on the following criteria: (1) given the significance of benzo-fused nitrogen-containing heterocycles in modern pharmacology, we chose a range of racemic benzylic azides bearing such skeletons as substrates; (2) we selected the readily modifiable salen as the prototypical ligand to search for suitable base-metal catalysts; (3) varying the protecting group on the nitrogen moiety was thought to provide an opportunity to tune the oxidative reactivity, site-selectivity, and chiral recognition."

Careful reaction optimization revealed that when chiral Mn(salen) **C1** carrying 2,4-difluorophenyl moieties at C3(3′) sites was used as catalyst, with PhIO as oxidant, oxidative KR of tetrahydroquinoline (THQ)-based organic azides proceeded with excellent site selectivity at the C_4–H bond adjacent to the azido moiety over the C_2–H bond α to the amide motif, affording the corresponding azines as oxidized products (Scheme 2A). Structurally diverse optically pure THQ-based organic azides were isolated in good yields with excellent ee (*s* = 20–91). When chiral Mn(salen) **C2** was used as catalyst, oxidative KR of indoline-based organic azides proceeded with similar site-selectivity at the C_3–H bond, furnishing 2-aminobenzonitriles as oxidized products together with recovered optically pure azides featuring excellent selectivity factors (*s* = 36–95) (Scheme 2A). Control experiments were performed to explore the substituent effect of different acyl groups on THQ-based azides (Scheme 2B). "An interesting trend was observed: the substrate reactivity towards oxidation was gradually enhanced as the number of methyl groups at the α-position of the carbonyl moiety increased, indicating that such an unconventional trend might originate from the non-covalent interaction between the carbonyl moiety's α-alkyl group and the Mn(salen) catalyst," said Professor Liu. He continued: "The deuteration effect of the *N*-acyl moiety of indoline-based substrates also suggested that the C(sp^3)–H bond at the α-position of the carbonyl motif is crucial to the oxidizing reactivity (Scheme 2C). Density functional theory (DFT) calculations were performed for the stereo-determining hydrogen atom transfer process, which suggested that the triplet state was the ground state, and the effective chiral recognition arises from additional CH···F hydrogen bonding interaction between the ^{t}Bu group of the (*R*)-enantiomer and the 2,4-difluorophenyl moiety of catalyst **C1** in ^3TS_R." Professor Liu concluded: "Inspired by the interesting and promising non-covalent interaction leading to effective chiral recognition, further efforts on oxidative KR of simple acyclic organic azides and other valuable chiral compounds, that are difficult to access by existing methods, are ongoing."



About the authors

Prof. L. Liu

Lei Liu was born in Zibo, Shandong (P. R. of China). He received his B.S. from Lanzhou University (P. R. of China) in 2003. After completing his M.S. program with Professor Rui Wang at the same university, he went to Pittsburgh (USA) in 2006 and pursued graduate studies under the guidance of Professor Paul Floreancig at the University of Pittsburgh. After earning his Ph.D. in 2011, he took a postdoctoral position in the laboratory of Professor Yoshito Kishi at Harvard University (USA). In June 2012, he began his independent career as a professor in the School of Pharmaceutical Sciences of Shandong University (P. R. of China). Since August 2015, he has been a professor in the School of Chemistry and Chemical Engineering of Shandong University (P. R. of China). His research interests lie in the development of selective oxidation methodology and its application in medicinal chemistry.

P. Ye

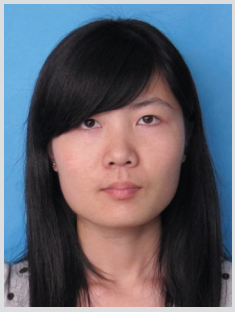
Pengbo Ye was born in Sichuan (P. R. of China). He received his B.S. in pharmacy from Shandong University (P. R. of China) in 2017. Then he received his M.S. in 2020 under the supervision of Prof. Lei Liu at Shandong University (P. R. of China). His research focuses on oxidative kinetic resolution through asymmetric oxidation of carbon–hydrogen bonds. Now, he is a chemical engineer working at the Petrochemical Research Institute, CNPC. His main research interests are propylene polymerization catalysts and polypropylene products.

A. Feng

Aili Feng was born in Dezhou, Shandong (P. R. of China). She received her B.S. in chemistry from Liaocheng University (P. R. of China) in 2018. She obtained her M.S. in physical chemistry from Shandong University (P. R. of China) in 2021, where she performed theoretical research with Prof. Rongxiu Zhu. Then she began her Ph.D. studies at Shandong University (P. R. of China), where she works on theoretical investigations of transition-metal-catalyzed organic reactions under the mentorship of Prof. Dongju Zhang.

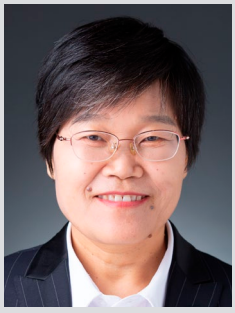
L. Wang

Lin Wang was born in Shandong, P. R. of China. She received her B.S. in pharmacy from Shandong University of Traditional Chinese Medicine (P. R. of China) in 2017. She completed her M.S. studies with Prof. Wei Li at the same university in 2020. She focused on oxidative kinetic resolution of organic azides as an exchange student at Shandong University (P. R. of China) under the direction of Prof. Lei Liu from 2018–2020. Now she is an analytical scientist working at Shandong Bainuo Pharmaceutical Co., Ltd.



M. Cao

Min Cao was born in Shandong, P. R. of China. She received her B.S. in chemistry from Hubei University (P. R. of China) in 2015. After completing her M.S. program with Prof. Lei Liu at Shandong University (P. R. of China) in 2019, she continued her Ph.D. studies in the same research group, where she is developing base-metal-catalyzed asymmetric oxidation of carbon–hydrogen bonds.



Prof. R. Zhu

Rongxiu Zhu was born in Linyi, Shandong (P. R. of China). She received her Ph.D. degree from Shandong University (P. R. of China) in 2007 under the supervision of Prof. Chengbu Liu and Prof. Dongju Zhang. In 2011, she went to Texas A&M University (USA) as a one-year visiting scholar with Prof. Steven E Wheeler. Currently, she is an associate professor in Shandong University, and her research interests are focused on elucidating the reaction mechanism and origins of selectivities in transition-metal-catalyzed, organocatalyzed and photocatalyzed reactions by DFT calculations.

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Full-nitro-nitroamino Cooperative Action: Climbing the Energy Peak of Benzenes with Enhanced Chemical Stability

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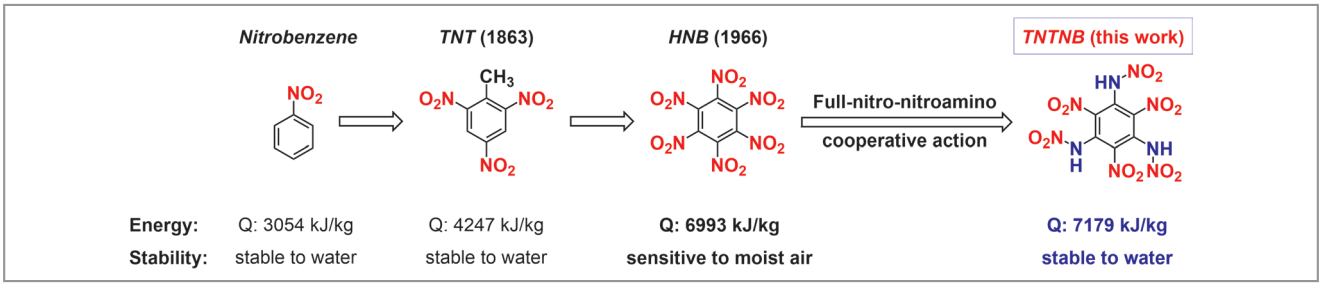
Explosive organic materials – such as nitroglycerine, HMX or nitrocellulose – are extremely important for a number of civil and commercial applications, besides those related to military use, for example in mining or in engineering. Polynitrobenzenes are well-known high-energy-density materials (HEDMs) (Scheme 1), which contain oxidizers (nitro groups) and fuel components (benzene ring) within a single molecule, and generate energy rapidly through self-redox reactions. The most representative energetic polynitrobenzenes are 2,4,6-trinitrotoluene (TNT, 1863, the most famous explosive) and hexanitrobenzene (HNB, 1966, the only fully nitrated benzene). Generally, the energy of these materials progressively increases with an increasing number of nitro groups, but their stability follows the opposite trend (Scheme 1). Particularly, hexanitrobenzene (HNB), which has a fully nitrated structure, exhibits the highest energy (detonation heat, Q = 6993 kJ kg^{-1}) among the organic explosives so far, but has poor chemical stability and decomposes rapidly in moist air. To date, striking a balance between energy and chemical stability, as well as further increasing the energy while simultaneously improving the stability of polynitrobenzenes, is a significant challenge in the area of novel HEDMs.

To overcome this challenge, the group of Professor Siping Pang at the Beijing Institute of Technology (P. R. of China) recently proposed an interval full-nitro-nitroamino cooperative strategy to design an unprecedented type of fully nitrated benzene, 1,3,5-trinitro-2,4,6-trinitroaminobenzene (TNTNB, Scheme 1), by replacing three interval nitro groups of HNB with three nitroamino groups. "After we designed the target molecule, the synthesis of TNTNB was then explored," explained Professor Pang. He continued: "However, the most direct method, that is the one-step nitration of amino groups in 1,3,5-trinitro-2,4,6-triaminobenzene (TATB), failed to give TNTNB. This is mainly due to the strong intramolecular H-bonds which passivate the amino groups of TATB, resulting in low reactivities."

Accordingly, the group believed that the key to accomplishing the nitration of TATB was to enhance the activity of the inert amino groups. Thus, an acylation–activation–nitration method was proposed. Professor Pang said: "In this method, a highly reactive acetylation reagent – acetic anhydride – was employed to activate and acetylate TATB to produce acetamide **1** (Scheme 2). X-ray data indicated that the large acetyl groups successfully destroy the strong H-bonds in TATB and improve the reactivity of the amino groups. Acetamide **1** was then treated with TFA/HNO_3 to successfully give TNTNB, which was structurally confirmed by single-crystal X-ray diffraction. It should be noted that TNTNB is only the second known hexanitro-containing benzene derivative. Moreover," continued Professor Pang, "TNTNB was successfully synthesized through an amino–acylation–nitration method, effectively addressing the longstanding problem of the unsuccessful nitration of inert TATB since it was first prepared in 1888. It also confirms that the acylation–activation–nitration method can be an effective tool to activate and nitrate inert amino compounds and prepare more high-performing energetic materials in the future."

In addition, the authors emphasized that TNTNB exhibits very promising energetic performance. "Especially, its high heat of detonation (Q = 7179 kJ kg^{-1}), which is even higher



Scheme 1 The state-of-the-art of nitrobenzenes and the design of TNTNB using a full-nitro-nitroamino cooperative strategy.

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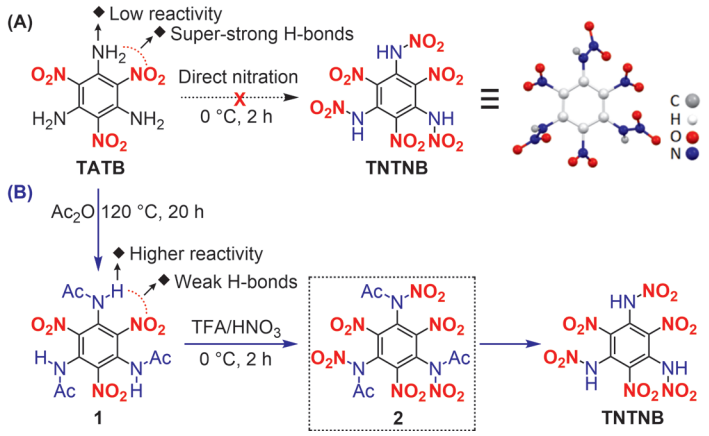
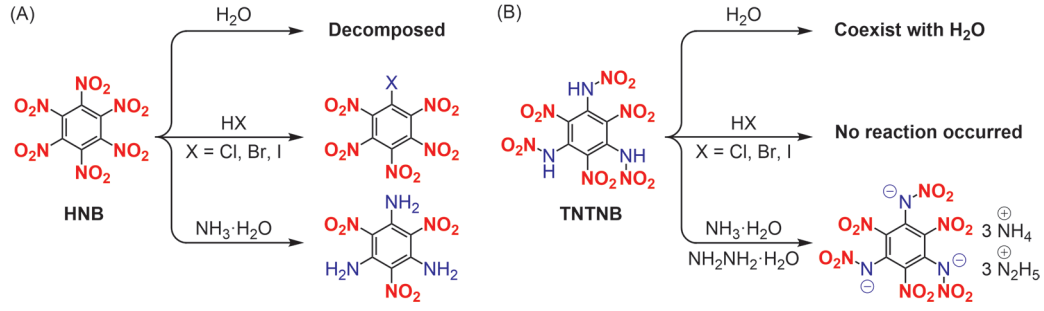


Scheme 2 (A) Failed synthesis of TNTNB. (B) Successful synthesis of TNTNB using the acylation–activation–nitration method.



Scheme 3 Chemical stability of HNB and TNTNB with water, acids, and bases, respectively.

than those of the state-of-the-art explosives HNB (Q = 6993 kJ kg^{-1}) and CL-20 (Q = 6534 kJ kg^{-1}), renders TNTNB a new energy peak for organic explosives. TNTNB also exhibits better water, acid, and base stability than HNB (Scheme 3)," said Professor Pang, who concluded: "Moreover, its acidic characteristics facilitate the formation of energetic salts, effectively improving the thermal stability of TNTNB. This will allow the preparation of diverse energetic derivatives."

About the authors

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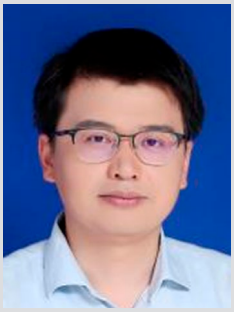

Prof. S. Li

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Prof. S. Pang

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