Direct Asymmetric Bromotrifluoromethoxylation of Alkenes with Trifluoromethyl Arylsulfonate as a New Trifluoromethoxylation Reagent

Highlighted article by S. Guo, F. Cong, R. Guo, L. Wang, P. Tang

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Dear Readers,

I hope you are enjoying the new Thieme Chemistry Twitter account because I think it is a really nice addition to the portfolio of communication tools we use to reach out and inform our readership. We tweet multiple times every day on a number of topics and events of interest to the organic chemistry community, including new articles and editorial features in our journals, including those published in SYNFORM, of course! If you haven’t seen our tweets yet, please have a look at them asap and follow us on Twitter (@thiemechemistry): there are already 200 followers and counting.

This new October issue of SYNFORM kicks off with an account of the recent Editorial Board Meeting of the Thieme Chemistry journals in Porto (Portugal) which, on this occasion, was held as a joint meeting with the Science of Synthesis editors. The following article describes the potential of a new class of boron–nitrogen catalysts developed by M. Shibasaki (Japan) for achieving a very innovative by-products-free amide bond formation. A Ni-promoted C–C bond formation reaction between nitroalkanes and unactivated alkyl iodides recently disclosed by D. A. Watson (USA) is the object of the third contribution of the issue, which is wrapped up by the new trifluoromethoxylation reagent discovered by P. Tang (P. R. of China).

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Conference Report

Thieme Chemistry Editorial Board Meeting 2017

The Editors of SYNTHESIS, SYNLETT, SYNFACTS, SynOpen, SYNFOM and – for the first time in a joint meeting – Science of Synthesis, together with a very upbeat Thieme Chemistry team, gathered on June 9th and 10th in the beautiful city of Porto, in the north west of Portugal. It was obviously a pure coincidence – exactly as it was in 2014 when the meeting was held in Saint-Émilion, famous for its Bordeaux wine – that the world-renowned Port wine is produced in the nearby Douro Valley. Also in this case, in fact, the Editors selected Porto as the meeting venue exclusively because of its rich cultural offerings and the beauty of the city. It is therefore not at all surprising that Thieme Chemistry’s decision to organise a visit to the cellars of one of the largest and most celebrated local Port wine factories met with fierce opposition and a complete lack of enthusiasm by all the Editorial Board members, who vehemently refused to play an active role in the generous Port wine tasting organised during the visit...

A number of important editorial initiatives were discussed and approved at the meeting. Concerning SYNFOM, which is increasingly popular and downloaded all over the chemistry world, the trend is towards an even greater integration with social media – such as Twitter and LinkedIn – and a further expansion of its dynamic web dimension, although the traditional pdf versions will continue to be published on the SYNFOM website and monthly as part of the online version of the Thieme Chemistry journals, at least for the foreseeable future.

The launch of the new and exciting Thieme Chemistry Twitter account (now online) – which is meant to become a vibrant communication tool with our readers – was also presented. This will complement and increase the presence of Thieme Chemistry on social media, like Facebook.

One of the hottest topics on the table concerning the peer-reviewed journals – SYNLLETT, SYNTHESIS and SynOpen – was the review of the ground-breaking “crowd review” pioneered by SYNLLETT’s Editor-in-Chief, Professor Benjamin List, which has already attracted considerable interest from the scientific community (see, e.g.: Nature News 2017, 546, 9). Following a very active discussion, it was decided that the crowd-review...
modality will be continued and expanded, with the aim of conducting a further review of its strengths, weaknesses and applicability on a larger scale during the next Editorial Board Meeting, which will take place in 2018 in the romantic venue of Lake Como (Italy). Grappa tasting next year then?

[Signature]
Amidation is one of the most used organic transformations for the synthesis of pharmaceuticals, functional polymers (e.g. nylon, Kevlar), and agrochemicals. However, there remains much scope for improvement of state-of-the-art amidation methodology. Although reagent-driven amidation has been well advanced to reliably access a myriad of amide-functionalized molecules, this methodology contains an inherent drawback, namely the co-production of unwanted reagent-derived waste. The development of a catalytic alternative is an obvious solution but has witnessed slow progress and suffers from severely limited substrate generality and insufficient catalytic activity. An amidation catalyst powered by broad and general scope, as well as featuring high catalytic activity, would have the potential to be widely adopted in academia and industry.

Recently, a Japanese team led by Professor Masakatsu Shibasaki and Dr. Naoya Kumagai at the Institute of Microbial Chemistry (Tokyo, Japan) discovered a non-metallic catalyst characterized by a six-membered B₃NO₂ heterocyclic core coined DATB (1,3-dioxa-5-aza-2,4,6-triborinane), which proved to be a highly effective catalyst for dehydrative amidations (Scheme 1). Dr. Kumagai said: “Originally, we were not specifically aiming to develop an amidation catalyst, but rather were eager to synthesize a powerful activator for the carboxylic acid functional group. It was serendipitous that we identified DATB catalyst and got deeply involved in its chemistry, as is the case for a number of fascinating discoveries. We envisioned that a compound having two boron atoms in a suitable spatial arrangement, as in compound 2, could doubly activate carboxylic acids via two-fold B–O interactions, anticipating that the Michael reaction or facilitated enolization could proceed (Scheme 2). A postdoctoral fellow – Dr. Makoto Furutachi – tackled the synthesis of 2, but the compound he managed to isolate was a frustratingly insoluble material with a complicated ¹H NMR spectrum in DMSO-d₆, which made it impossible to elucidate the structure. Being a highly dedicated experimentalist who remained devoted to the task, Dr. Furutachi was eventually rewarded with a crystal structure revealing the pseudodimeric structure of DATB 1 (Scheme 3).”

Dr. Kumagai continued: “However, we were not crafty enough to find any utility of this peculiar heterocyclic compound, as it is not soluble in common organic solvents and all attempts at opening the B₃NO₂ ring system to achieve the initial target (compound 2) met with failure.”

Dr. Kumagai recalled: “Roughly one and a half years had passed since the first identification of 1 before we discovered a particular use for the compound. At that time, Dr. Furutachi had already left to continue his academic career at a different institution. Taking notice of a paper introducing direct...
dehydrative amidation in a cooperative catalytic system led us to re-evaluate compound 1, which lay dormant in a freezer. Back then we were mainly working in the field of C–C bond-forming reactions, thus amidation was a bit out of our focus. But we anticipated that a small fraction of 1 might have a chance to open up to 2 in the reaction mixture, giving a template to strongly activate carboxylic acids for amidation. We selected a bulky acid for the initial trial, which was considered an intractable substrate for catalytic amidation, and this initial trial just worked beautifully.” He remarked: “With this finding in hand, a postdoc – Dr. Hidetoshi Noda – and a skilled technician – Ms. Yasuko Asada – conducted a series of experiments, which clearly demonstrated that DATB 1 outperformed other known amidation catalysts in terms of substrate generality and high catalytic activity (Scheme 4). True mechanistic pathway is still under intense investigation; however, we are at least sure that the DATB core of 1 does not open during the reaction – again, the initial expectation was incorrect.”
Dr. Kumagai concluded: “We keep actively working on this catalytic system. Detailed DFT calculations and kinetic experiments are shedding more light on the distinct mode of action operative in DATB catalysis, where multiple boron atoms are likely to be involved. Better mechanistic understanding will lead us to rationally design a second-generation DATB catalyst with enhanced catalytic activity. We envision that these continuing studies will lead to practical catalytic alternatives, eventually replacing the conventional reagent-driven amidation protocols, covering the synthesis of a wide variety of amide-containing compounds including peptides.”
About the authors

Hidetoshi Noda was born and raised in Tokyo (Japan). He graduated from The University of Tokyo (Japan), where he conducted his bachelor’s and master’s research in the group of Professor Masakatsu Shibasaki. After three years of experience in industry, he moved to Switzerland to pursue his doctorate with Professor Jeffrey W. Bode at ETH Zurich. In 2015, he obtained his Dr. Sc. and joined the Institute of Microbial Chemistry, Tokyo (Japan) as a JSPS fellow. In 2017, he obtained tenure at the same institute.

Makoto Furutachi was born in Saga (Japan) in 1985. He received his bachelor’s degree from Fukuoka University (Japan) in 2008 with Professor Junei Kinjo, his master’s degree from The University of Tokyo (Japan) in 2010 with Professor Masakatsu Shibasaki, and his PhD from the same university in 2013 with Professor Motomu Kanai. He was a postdoctoral fellow at the Institute of Microbial Chemistry, Tokyo (Japan) in 2013–2015 with Professor Masakatsu Shibasaki, and has been an assistant professor at Fukuoka University since 2015 with Professor Kunihiro Sumoto. His current research interest is medicinal chemistry.

Yasuko Asada graduated from Kita-sato University (Japan) in 1994 and worked as part of the technical staff in research laboratories at Sagami Chemical Research Center (Japan). With her expertise in organic synthesis, she joined several research units to support and facilitate research activities in both academia and industry. From 2014, she settled in the Institute of Microbial Chemistry, Tokyo (Japan) where she is currently working as a technician.

Masakatsu Shibasaki received his PhD from The University of Tokyo (Japan) in 1974, under the direction of the late Professor Shun-ichi Yamada before doing postdoctoral studies with Professor E. J. Corey at Harvard University (USA). In 1977, he returned to Japan and joined Teikyo University as an associate professor. In 1983, he moved to Sagami Chemical Research Center (Japan) as a group leader, and in 1986, he assumed a professorship at Hokkaido University (Japan) before returning to The University of Tokyo as professor in 1991. He is currently Director of the Institute of Microbial Chemistry, Tokyo (Japan). He has received several prestigious awards, including the Fluka Prize (Reagent of the Year, 1996), the Elsevier Award for Inventiveness in Organic Chemistry (Tetrahedron Chair, 1998), the Pharmaceutical Society of Japan Award (1999), the ACS Award (Arthur C. Cope Senior Scholar Award, 2002), the National Prize of Purple Ribbon (2003), the Japan Academy Prize (2005), the ACS Award for Creative Work in Synthetic Organic Chemistry (2008), the Centenary Medal and Lectureship (2008), the Prelog Award Medal (2008), the Special Award, the Society of Synthetic Organic Chemistry, Japan (2010), the Noyori Prize (2012), and others. His research interests include asymmetric catalysis and medicinal chemistry of biologically significant compounds.

Naoya Kumagai was born in 1978 and raised in Ibaraki (Japan). After receiving his PhD in pharmaceutical sciences at The University of Tokyo (Japan) in 2005, under the supervision of Professor Masakatsu Shibasaki, he pursued postdoctoral studies in the laboratory of Professor Stuart L. Schreiber at Harvard University (USA) in 2005–2006. He moved back to Professor Shibasaki’s group at The University of Tokyo as an assistant professor in 2006. He is currently a Chief Researcher at the Institute of Microbial Chemistry, Tokyo (Japan). He is a recipient of the Pharmaceutical Society of Japan Award for Young Scientists (2010), Banyu Chemist Award (2012), and Mitsui Chemicals Catalysis Science Award of Encouragement (2014). His research interests include the development of new methodologies in catalysis and their application to bioinspired dynamic processes.
Nitroalkanes are widely used functional groups in organic synthesis. There are many methods known to convert them into useful functionalities, such as amines, carbonyls, and alkanes. In addition, they have been successfully used in many C–C bond forming reactions such as conjugate addition, Henry reaction, arylation, allylation, etc. However, despite this rich chemistry, the simple C-alkylation of nitroalkanes with common alkyl electrophiles (such as alkyl halides) has remained a highly challenging task due to competing O-alkylation. Using transition-metal catalysis, the group of Professor Donald A. Watson at the University of Delaware (USA) has begun to address this century-old problem. Professor Watson said: “Over the past few years we have shown that with the use of appropriate ligand and reaction conditions, simple in situ formed copper complexes can catalyze the C-alkylation of nitroalkanes with benzyl bromides, α-bromocarbonyls, and α-bromonitriles. However, the usable alkyl halides were limited to those bearing adjacent radical stabilizing functional groups, whereas alkyl halides lacking such stabilization groups (i.e. unactivated alkyl halides) failed to show reactivity. We believed a method that could expand the scope of alkyl halides to unactivated ones, could greatly broaden the utility of nitroalkanes.”

The group started testing this hypothesis by using copper catalysis under different conditions. “Unfortunately, our efforts to obtain the desired reactivity with copper catalysts were futile,” explained Professor Watson. He continued: “From our preliminary results of benzylation chemistry, we were aware that catalysts derived from nickel were able to furnish the benzylated products, albeit in very low yield. Considering the success of nickel in catalyzing reactions of diverse nucleophiles with unactivated alkyl halides, we turned our attention to nickel catalysis. After extensive investigation of different ligands and conditions, we found the optimum ligand to be bathocuproine. The use of ethereal solvents was important, since the insolvency of the nitronate anion in these solvents precludes the competing O-alkylation reaction. Finally, suitable conditions were developed for a nickel(II) source and external reductant to make the reaction more user-friendly, considering the instability of Ni(0) sources such as Ni(cod)$_2$.”

With the optimized conditions in hand, the group then set out to examine the substrate scope and functional group tolerance of the reaction. “Gratifyingly, primary, secondary, and tertiary alkyl iodides were all reactive and gave the complex C-alkylated nitroalkane products in moderate to good yields,” said Professor Watson. “We particularly focused on examining relevant and important bioactive functional groups and heterocycles, and in most cases, they did not interfere with the reaction. A variety of functionalized nitroalkanes were also tested and they worked well too. Significantly, an anti-viral drug, adapromine, could be synthesized in two steps with good yields using this method.”

“While we believe that this newly reported method makes a major advance in nitroalkane alkylation, there is still

![Scheme 1](image-url)
work to be done. For example, the new conditions still show limitations with respect to steric bulk of the nitroalkane and diastereoselectivity,” said Professor Watson. He concluded: “Current and future studies are aimed at continuing to improve and expand the scope of transition-metal-catalyzed nitroalkane alkylation.”
Donald A. Watson was born in California (USA) in 1976. He received his BS in chemistry from UC San Diego (USA) in 1998. During his undergraduate years, he studied in the laboratories of Professors K. C. Nicolaou and Emmanuel Theodorakis, working on natural products synthesis. He completed his PhD in organic chemistry at UC Irvine (USA) in 2004, working under the direction of Professor Larry E. Overman. His dissertation work focused on stereochemical problems in palladium-catalyzed transformations. From 2004 to 2006 he was an NIH Postdoctoral Fellow in the laboratories of Professor Robert G. Bergman at UC Berkeley (USA). During this time he developed zirconium-based catalysts for asymmetric intramolecular hydroaminations. He then moved to the Massachusetts Institute of Technology (USA) to take a position as a Postdoctoral Associate in Professor Stephen L. Buchwald’s laboratory, where he studied metal-catalyzed processes for C–F bond formation.

He joined the Chemistry and Biochemistry faculty at the University of Delaware (USA) as an Assistant Professor in July 2009. His research focuses on the development of new chemical methods for preparing organic molecules and structures, with a particular interest in the development transition-metal-based catalytic reactions and in the construction of carbon–heteroatom bonds. In 2013, he received a CAREER Award from the National Science Foundation and a Cottrell Scholar Award from the Research Cooperation. In 2015, he was promoted to Associate Professor with tenure. In addition, he currently serves as Associate Chair for Graduate Studies in the Department of Chemistry and Biochemistry.

Sina Rezazadeh was born in Ramsar (Iran). He obtained his Pharm. D. from Tehran University of Medical Sciences (Iran) in 2013. He joined Donald A. Watson's lab at the University of Delaware (USA) in 2014 as a graduate student and has been working on developing transition-metal-catalyzed reactions to make complex nitroalkanes.

Vijayarajan Devannah was born in Chennai, Tamil Nadu (India). He received his MSc in organic chemistry from the University of Madras (India) in 2009. He is currently pursuing doctoral studies under the guidance of Professor Donald A. Watson at the University of Delaware (USA). His research work focuses on developing transition-metal-catalyzed reactions to make complex nitroalkanes.
Compounds containing fluorinated groups are receiving increasing attention in pharmaceuticals, agrochemicals and materials science. In particular, the trifluoromethoxy group has a high value because of its great electron-withdrawing effect and high lipophilicity (Hansch parameter: $\pi_R = 1.04$). However, despite this strong and widespread interest, there are limited methods for synthesizing trifluoromethoxylated compounds. This is mainly due to the low stability of trifluoromethoxide anions – which decompose easily – or transition-metal–trifluoromethoxide complexes, which tend to undergo $\beta$-fluoride elimination. Therefore, new and efficient trifluoromethoxylating reagents are in great demand. To date, only a very limited number have been reported, with various limitations such as toxicity or difficulties in handling, as well as low reactivity. Recently, the research group of Professor Pingping Tang at Nankai University (P. R. of China) discovered a new trifluoromethoxylation reagent, trifluoromethyl arylsulfonate (TFMS), and developed the first asymmetric silver-catalyzed intermolecular bromotrifluoromethoxylation of alkenes.

In their paper, trifluoromethyl arylsulfonate (TFMS) is reported as a precursor of the trifluoromethoxide anion through fluoride salts activation and – according to Professor Tang – it has several merits: 1) it is easy to prepare, also on large scale (up to 50 g), 2) it has good thermal stability and is easy to

**Figure 1 a)** Compared to traditional trifluoromethoxylation reagents, TFMS is easily prepared and thermally stable, with good reactivity. **b)** The first example of an asymmetric silver-catalyzed intermolecular bromotrifluoromethoxylation of alkenes with TFMS as a new trifluoromethoxylation reagent was described.
handle, and 3) the reactivity of the reagent can be modified via different functional groups (R) on the aromatic ring (Figure 1).

“We initially investigated TFMS and observed that it can be used as a new trifluoromethoxylation reagent. More importantly, when we used the chiral ligand (DHQD)$_2$PHAL, asymmetric bromotrifluoromethoxylation of alkenes was achieved using AgF as a catalyst,” said Professor Tang.

The scope of the reaction is very broad, as could be seen in the original paper, and summarized by the few representative examples described in Scheme 1. “All the styrenes that we used were successfully converted into the desired products with good isolated yields (59–94%) and moderate enantioselectivities (58.5:41.5 to 92:8 er),” said Professor Tang. He continued: “Notably, mono-, di-, tri-, and even tetra-substituted alkenes were used for the bromotrifluoromethoxylation reaction, with good yields but lower enantioselectivities.” This reaction was also extended to more sophisticated scaffolds.

“The significance of this reaction was demonstrated by the application for the late-stage bromotrifluoromethoxylation of natural products and derivatives, such as an estrone derivative and a taxol derivative,” added Professor Tang.

The chiral ligand, dimeric cinchona alkaloid (DHQD)$_2$PHAL, plays the most important role in the asymmetric process. Professor Tang said: “The styrene substrates are probably located in the chiral pocket via π,π-stacking with the quinoline of the ligand (Figure 2). Due to the absence of π,π-stacking interaction between simple alkenes and ligand, lower enantioselectivities were observed.”

Professor Tang concluded: “Trifluoromethyl arylsulfonate (TFMS) was disclosed as a new trifluoromethoxylation reagent

![Scheme 1 Substrate scope for asymmetric silver-catalyzed bromotrifluoromethoxylation of alkenes](image)
that is easily accessible and simple to handle. Taking advantage of this new reagent, we have developed a silver-catalyzed asymmetric bromotrifluoromethoxylation of alkenes. We hope this reagent can find broad applications facilitating the access to new trifluoromethoxylated compounds in pharmaceutical, agrochemical and materials sciences.”

REFERENCES


About the authors

Shuo Guo was born in Hebei Province (P. R. of China) in 1986. He received his BS degree from Hebei Normal University (P. R. of China) in 2010 and M.S. degree from Zhengzhou University (P. R. of China) in 2013, under the supervision of Professor Yangjie Wu. In 2013, he joined Professor Pingping Tang’s research group at Nankai University (P. R. of China) to pursue his PhD degree. He is currently interested in direct trifluoromethylthiolation and trifluoromethoxylation.

Fei Cong was born in Gansu Province (P. R. of China) in 1992. She received her BSc degree from Hunan Normal University (P. R. of China) in 2015. Since then, she has worked in the laboratory of Professor Pingping Tang at Nankai University (P. R. of China) for her Master’s studies. Her M.Sc. thesis is focusing on the development of direct trifluoromethoxylation based on some new trifluoromethoxylation reagents.

Rui Guo was born in Hubei Province (P. R. of China) in 1984. He received his BSc degree from Jiangxi Normal University (P. R. of China) in 2007 and MSc degree from Central China Normal University (P. R. of China) in 2010, under the supervision of Professor Shenghua Liu. Then he worked in HEC Pharm Co., Ltd. (P. R. of China) as a project manager. He completed his PhD studies in 2016 on C–F bond forming reactions under the supervision of Professor Pingping Tang in Nankai University (P. R. of China). Afterwards he joined the Institute of Environment and Health at Jianghan University (P. R. of China) as an assistant researcher mainly focusing on the study of perfluorochemicals.

Liang Wang was born in Zibo (P. R. of China) in 1989. He graduated from Shandong University (P. R. of China) where he was awarded a BSc in 2011. Then he was admitted to Nankai University (P. R. of China) to pursue further studies in organic chemistry. In 2016, he was awarded his PhD under the direction of Professor Pingping Tang. His research mainly focused on the total synthesis of natural products. He is now an Assistant Professor at Nankai University.

Pingping Tang received his BSc degree from Nankai University (P. R. of China) in 2002. After obtaining his PhD degree in 2007 working with Professor Biao Yu at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China), he worked as a postdoctoral fellow with Professor Tobias Ritter at Harvard University (USA, 2008–2012). In 2012, he joined the State Key Laboratory and Institute of Elemento-Organic Chemistry at Nankai University (P. R. of China) as a Professor. His research interests include fluorine chemistry and total synthesis of biologically important small molecules.

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