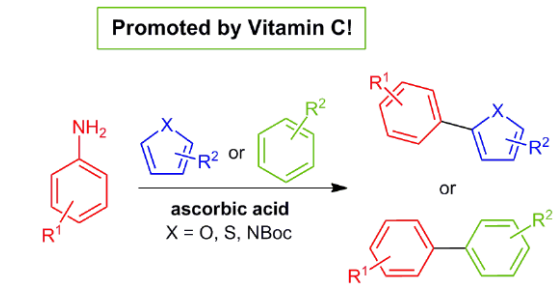
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2014/05

SYNSTORIES



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Thieme

Dear Readers,

Recently I had a stimulating conversation with a colleague about the type of research that should be done in an academic setting. To cut a long story short, my colleague was adamant that universities should prioritize basic research, namely curiosity-driven research whose goal is to advance human knowledge without necessarily having to solve an immediate and specific problem, whereas my opinion was (and still is) that there are so many urgent problems to solve in areas such as health, energy, food, environment that we scientists should focus on addressing those issues and therefore prioritize applied research. At that point my colleague pointed out that basic research can also help to address problems that affect humanity, and sometimes more effectively than applied research itself, because basic research works for the long term whereas applied research is more focused on the short term. I replied that yes, that's undeniable, but much basic research doesn't actually give due consideration to the fact that we, scientists, should wake up every morning and think, first thing, that our research is mostly funded by taxpayers and/or charities, and they both expect to see us solving urgent problems rather than "just" producing knowledge that might become useful in 20 or 30 or even 50 years. Eventually, before having a coffee together, we agreed on one point: that at the end of the day what really makes the difference is the quality of the research we do and of the questions we wish to answer. We also agreed that unfortunately there is still too much low-quality research ongoing, independently of being basic or applied, and that is the real problem. I really believe that each of us, scientists, should spend a couple of minutes every morning, before being caught in the usual vortex of administrative, supervision and teaching commitments, analyzing the motivations underlying and driving our research: are they truly important? Is there anything more or different I can do to help solving the many problems that affect our world? Am I really using in the best possible way my research funding, my time and that of my co-workers? At the end of the day, those issues haven't much to do with the basic or applied research dilemma, and either choice is appropriate as long as we remember why we are doing research and why we chose to become scientists.

What is absolutely impossible to forget, however, is why I am here right now: for introducing a new exciting issue of ***SYNFORM***, of course!! The first ***SYNSTORY*** covers a topic which I consider particularly exciting and potentially having very important applications for the next generation of drugs and diagnostics: the use of "clickable" tetrazines for expanding the scope of monoclonal antibodies in targeted therapy and imaging, as demonstrated by M. Robillard (The Netherlands). The next ***SYNSTORY*** details the use of ascorbic acid for promoting C–H arylations with nitrosated anilines according to the method developed by R. Carrillo (Spain). The following ***SYNSTORY*** describes how H. Ge (USA) managed to achieve the site-selective alkylation of unactivated C(sp^3)–H bonds using nickel catalysis. In the last ***SYNSTORY***, J. Sun (P. R. of China) takes us to the exploration of a novel addition reaction involving nitroalkanes his group developed. It's definitely a mix of basic and applied research, but it's all excellent chemistry!

Enjoy your reading!

Matteo Zanda

Editor of ***SYNFORM***

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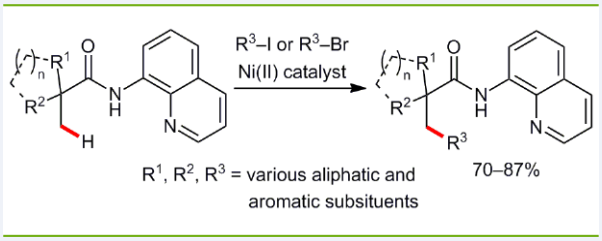

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Click to Release: Instantaneous Doxorubicin Elimination upon Tetrazine Ligation

Angew. Chem. Int. Ed. **2013**, *52*, 14112–14116

Antibody–drug conjugates (ADCs) are highly potent biopharmaceuticals that use the targeting ability of monoclonal antibodies to selectively bind to tumor cells where the conjugated cancer drug is released. The antibody and the small-molecule drug are bound by a linker. Only when the linker is cleaved do these cell-killing drugs become active. This generates an excellent control mechanism of drug activation, allowing an increase of the therapeutic window and the use of highly potent drugs. Current ADC technologies rely on biological cleavage of the linker. The ADC has to bind to a tumor-cell-specific membrane receptor and subsequently be internalized in the tumor cell for cleavage of the linker – and thus activation of the drug – to occur. As the number of tumor-specific receptors that ensure efficient internalization is limited, especially in solid tumors, a wide range of cancer targets remain out of reach of ADCs. To illustrate this: last year the ADC T-DM1 (Kadcyla™) was approved for metastatic HER2-positive breast cancer after impressive improvements in progression-free survival and toxicity. Like all ADCs in the clinic, T-DM1 targets an efficiently internalizing receptor (HER2) and relies on intracellular (enzymatic) cleavage and activation of the drug. However, only 20% of all breast cancers overexpress HER2 and there are no known alternative receptors with the same potential.

Dr. Marc Robillard of Tagworks Pharmaceuticals (Eindhoven, The Netherlands) said: "We aim to deliver the same punch to a wide range of solid cancers by developing an antibody–drug linker that can be selectively cleaved through a bioorthogonal reaction with a chemical probe." He continued: "The activation would be independent from intracellular release mechanisms, expanding the ADC scope to receptors that do not efficiently internalize and to extracellular matrix targets. In this approach, after the ADC has bound to an extracellular cancer target and free ADC has cleared from the blood, a secondary probe is administered that reacts with the ADC linker to liberate and activate the drug (Figure 1)."

The rapidly developing field of click chemistry is of much interest and is enjoying widespread application. Analogous to click reactions, cleavable linkers, such as the redox-sensitive disulfide and diazo linkers and the hydrazine-labile levulinoyl

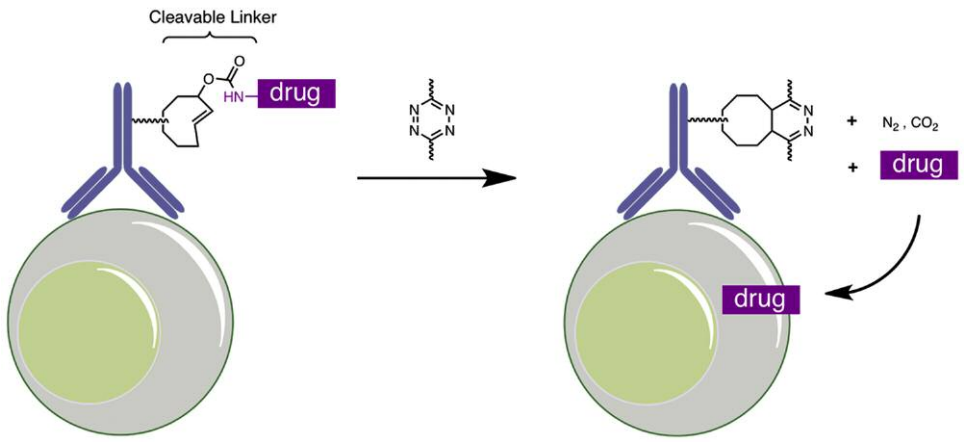

Figure 1 *Envisioned on-tumor ADC activation enabled by the recently discovered inverse-electron-demand Diels–Alder (inv-DA)-based elimination reaction*

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linker, have many potential uses in biological media. Although these linkers are selective, they often lack the level of bioorthogonality and broad applicability of the click reactions, which is especially relevant when extending the application scope to living cells, animals, and humans. This issue may be addressed by adapting a click reaction to effect selective release, instead of, or in addition to, selective conjugation.

Dr. Robillard said: "From this family of reactions, only the Staudinger ligation and the parent Staudinger reaction had been applied in selective cleavage. For example, in 2008 we reported that triphenylphosphine can be used to activate a *p*-azidobenzyloxycarbonyl prodrug of doxorubicin in cell culture (R. van Brakel, R. C. M. Vulders, R. J. Bokdam, H. Grüll, M. S. Robillard; A Doxorubicin Prodrug Activated by the Staudinger Reaction *Bioconjugate Chem.* **2008**, *19*, 714). The trigger was based on *p*-aminobenzyloxycarbonyl (PABC), used in enzyme-activated prodrugs, where unmasking of the amino group leads to an elimination of azaquinone methide, spontaneous decarboxylation, and release of the active drug (Scheme 1a). We demonstrated that the Staudinger azide-to-amine reduction initiates the same sequence of events, resulting in self-immolative and traceless release of doxorubicin."

However, the reactivity of the Staudinger reaction and ligation is low and the phosphine reagents are prone to oxidation, precluding practical applications in living systems. In fact, only the fastest and highly selective click reaction, the inverse-electron-demand Diels–Alder reaction (inv-DA) between *trans*-cyclooctene (TCO) and tetrazines has been shown to occur effectively and safely in mice at low concentrations (i.e., clinically relevant conditions). This was in the context of tumor-pretargeted radioimmunoimaging between antibody-conjugated TCO and a radiolabeled tetrazine (Figure 2).

"During our efforts to optimize this technology we started thinking about how we could tweak the inv-DA reaction to afford release in addition to conjugation," said Dr. Robillard. "We revisited the PABC motif, and realized that the key features governing its self-immolative release could also apply to the inv-DA reaction product between a tetrazine and a TCO containing a suitably positioned drug." The inv-DA cycloaddition results in an intermediate that rearranges by expulsion of dinitrogen in a retro-Diels–Alder cycloaddition to a 4,5-dihydropyridazine, which usually tautomerizes to a 1,4-dihydropyridazine, especially under aqueous conditions (Scheme 1b). Dr. Robillard continued: "We hypothesized that such a 1,4-dihydropyridazine derived from a TCO containing a carbamate-linked drug at the allylic position could be prone to eliminate CO_2 and an NH_2-substituted drug in conjunction with the formation of conjugated pyridazine with an exocyclic double bond (**7**), which may subsequently rearrange to the favored aromatic pyridazine (**8**, Scheme 1b). In a similar fashion as with PABC-based release, the shift of the electron lone pair of NH into the ring may enable an electronic-cascade-based release of the drug. In addition to the structural similarities with the PABC linker, this hypothesis was grounded in the fact that dihydropyridazines can readily form pyridazines in the presence of an oxidant, by the elimination of a leaving group from the vinyl position, or through a double-bond shift."

Doxorubicin was used as a model for future ADC applications with more potent toxins. Doxorubicin-TCO (**1**, 25 μM

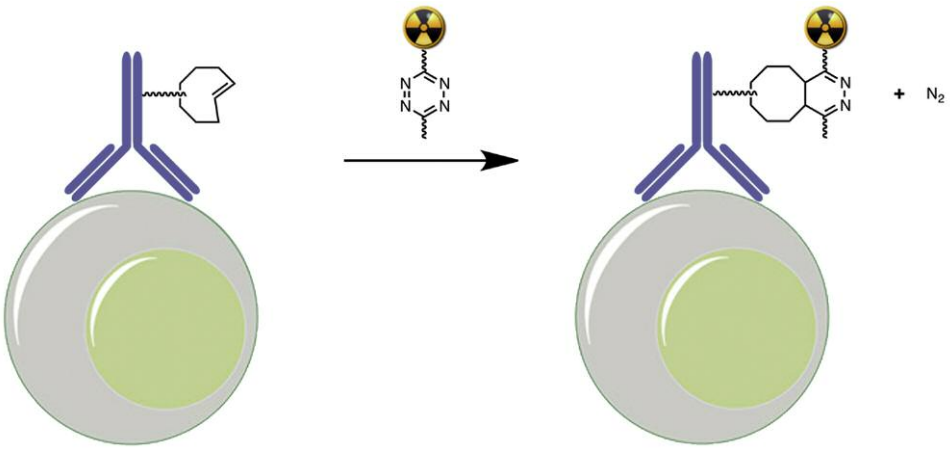

Figure 2 *Tumor pretargeting with the inv-DA reaction; not applicable to ADC*

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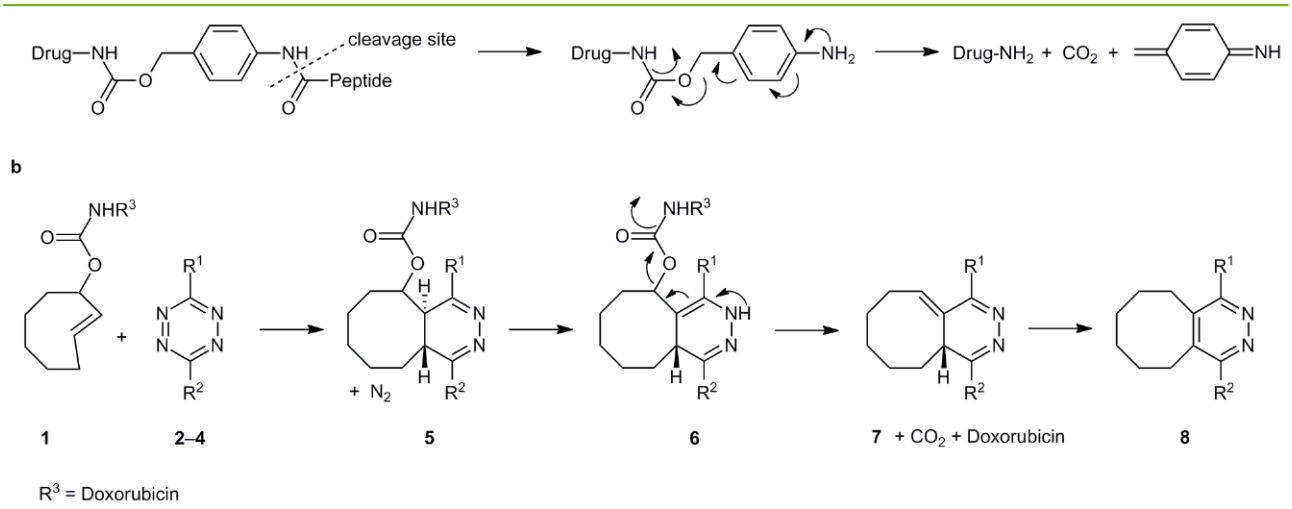

Scheme 1 *a) Drug release from PABC linker after enzymatic cleavage of peptide bond; b) Inv-DA reaction between Doxorubicin-TCO* ***1*** *and tetrazines* ***2–4*** *and proposed release mechanism; not all possible tautomer conversions and stereoisomers are shown*

in 25% MeCN in PBS) was reacted at 37 °C with 10 equivalents of tetrazines: 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (**2**), 3-(2-pyridyl)-6-methyl-1,2,4,5-tetrazine (**3**), and 3,6-dimethyl-1,2,4,5-tetrazine (**4**). These tetrazines span a wide range in electron density and therefore potentially a wide range in release efficacy. Dr. Robillard explained that treatment with **2** gave almost no Doxorubicin release (7%), whereas **3** and **4** afforded free Doxorubicin in 55 and 79% yield, respectively, within 16 minutes. Similar values were found in serum and the release was also shown to occur effectively in cell culture. These findings, and the fact that the tetrazines are sufficiently stable in serum and Doxorubicin-TCO (**1**) by itself did not liberate Doxorubicin for at least 24 hours in PBS or serum at 37 °C, support the bioorthogonality of the system and hold promise for conducting selective elimination chemistry both in vitro and in living systems.

Although an NMR study into the mechanism did not yet allow the identification of the drug-releasing tautomer, the *Angew. Chem.* article shows that the inv-DA reaction can be modified to achieve instantaneous, traceless and bioorthogonal release. "In analogy to the azaquinone-methide elimination that inspired us," said Dr. Robillard, "we called this new release reaction the pyridazine elimination. This new reaction is the result of a very effective, close and long-standing collaboration between three companies: Tagworks, SyMO-Chem and Syncom."

Dr. Robillard concluded: "We believe that the presented work, including the first mechanistic insights, holds great promise for employing chemically triggered release of a drug from a tumor-bound ADC and will also find application in fields well beyond the scope of ADCs. The availability of a cleavable linker that matches the bioorthogonality and speed of the inv-DA will allow an unprecedented control over chemical and biological manipulations both in vitro and in living systems."

Matteo Zanda

About the authors

From left: Dr. H. M. Janssen, Dr. R. M. Versteegen

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Ron Versteegen, first author of the paper, was involved in the synthesis of tetrazines and functionalization of *trans*-cyclooctene derivatives. He studied their reactivity, stability and characterized the pyridazine elimination reaction in all its facets. Dr. Versteegen (born in 1974) studied chemical engineering at the Eindhoven University of Technology (TU/e, The Netherlands) and obtained his MSc in organic chemistry on the study of supramolecular polymers containing ureido-pyrimidinone units. Thereafter, he obtained his PhD at the same university on the synthesis and characterization of well-defined thermoplastic elastomers. In 2002, he started as a research scientist at SyMO-Chem, and currently is project leader of the Bioorthogonal Chemistry group at SyMO-Chem.

Henk Janssen mainly contributed to the development of the tetrazines for the inv-DA release reaction. Dr. Janssen (born in 1967) studied chemical engineering at the Eindhoven University of Technology (TU/e, The Netherlands) and thereafter obtained his PhD on the supramolecular chemistry of ethylene oxide constructs at the same university in the Macromolecular and Organic Chemistry group of Professor E. W. Meijer. In 2000, the chemical contract research company SyMO-Chem was started as a TU/e spin off by Bert Meijer and Henk Janssen, and ever since has performed research, custom synthesis and analyses for clients, mostly in the fields of organic, polymer, biochemical and medicinal chemistry. Examples include dye molecules, (radio)imaging contrast agents, transfection agents, biomaterials, membrane materials, nanotechnology and supramolecular materials.

Dr. W. ten Hoeve

Wolter ten Hoeve prepared the *trans*-cyclooctene derivatives. Dr. ten Hoeve (born 1951) has been a synthetic organic chemist for 40 years. In 1979 he received his PhD at the University of Groningen (The Netherlands) with Professor Wijnberg and then moved to the USA for a postdoctoral fellowship at Colorado State University in Fort Collins, CO (USA) with Professor Meyers. In 1981, he returned to the Netherlands and was a postdoctoral fellow with Professor Wijnberg for an additional six years. In 1988, he was one of the founders of Syncom (together with Professor Wijnberg and Professor Kellogg). Syncom has been specializing in contract research for organic chemistry during the past 25 years. From the start of Syncom, Wolter ten Hoeve has been senior scientist, and he is still doing almost full-time practical synthetic work.

Dr. R. Rossin

Raffaella Rossin designed and performed the in vitro cytotoxicity assays in the paper. Dr. Rossin joined Philips Research in 2008, serving as senior radiochemist on molecular imaging and drug delivery projects. With over ten years experience in radiolabeling and in vitro/in vivo testing of small molecules, antibodies and nanoparticles, she has been instrumental in developing the inv-DA-based pretargeting technology that is the basis of this work. Prior to Philips, she worked for 4.5 years at the School of Medicine of Washington University, St. Louis, MO (USA), as a postdoctoral research associate and as a research instructor in radiochemistry and nuclear imaging. Dr. Rossin obtained her MSc in organic chemistry and PhD in radiochemistry at the University of Padova (Italy). In addition, she was a visiting scientist at the School of Chemistry, University of Bangor, Wales (UK), and at the Paul Scherrer Institute, Villigen (Switzerland).

Dr. M. Robillard

Marc Robillard is the PI of the paper and founder and CEO of Tagworks, which is developing a unique approach towards antibody-based imaging and therapy based on selective chemical manipulation in vivo. Dr. Robillard initiated and led the team working on Tagworks' In Vivo Chemistry within Philips Research from 2006 until the spinout. In 2003, he joined Philips Research as senior scientist and was involved in several molecular imaging and drug delivery projects before creating the In Vivo Chemistry technology. Prior to Philips he worked at Kreatech Diagnostics on probes for drug targeting and microarray-based detection of DNA, RNA and proteins. In addition, he was a visiting scientist at the School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney (Australia), and he worked at the CRO Syncom as a synthetic chemist. Dr. Robillard obtained his MSc and PhD in bio(in)organic chemistry at, respectively, the University of Groningen and the Leiden Institute of Chemistry (The Netherlands).

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Ascorbic Acid as an Initiator for the Direct C–H Arylation of (Hetero)Arenes with Anilines Nitrosated in situ

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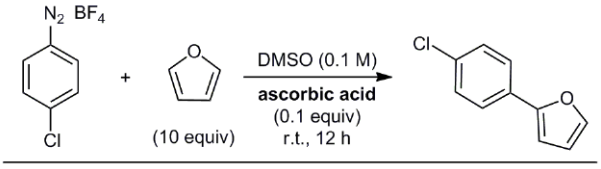
In 2013, the research group of Dr. Romen Carrillo of the Centro de Investigaciones Biomédicas de Canarias (CIBICAN), Instituto Universitario de Bio-orgánica (IUBO) (Tenerife, Spain), in collaboration with Dr. Tomás Martín (Instituto de Productos Naturales y Agrobiología, IPNA), started a research line focused on green chemistry. Dr. Carrillo said: "We were particularly keen on using ascorbic acid (vitamin C) in greener synthetic methodologies. The reason for this is simple: surprisingly, there is almost no synthetic applicability of ascorbic acid besides the usual reduction of copper(II) in click chemistry [Copper(I)-catalyzed Azide–Alkyne Cycloaddition, CuAAC]. And if we think about it, ascorbic acid is a perfect candidate for an environmentally benign synthetic procedure (it's an edible reagent!). Thus, we looked for several optimal targets in order to develop striking green methodologies by using ascorbic acid." One of the selected targets was (hetero)biaryl frameworks, because these kinds of molecules are ubiquitous and play vital roles in many fields from medicinal chemistry to materials science. However, most of the current synthetic methods rely on the use of transition-metal catalysts, sometimes with toxic ligands, and require heating. Thus, in general, the synthesis of biaryl compounds has a negative impact on the environment, in addition to the high economic cost of the reagents and procedures employed. Furthermore, as explained by Dr. Carrillo, both reacting units must be pre-activated as, for instance, boronic acids, zincates, halides, stannanes, triflates, etc. "In this regard," said Dr. Carrillo, "the direct C–H arylation of arenes is particularly attractive, because it avoids the traditional double pre-activation of the coupling partners. As a consequence, the number of steps is reduced, manipulation of sensitive and often toxic reagents is reduced or eliminated, and less waste is generated. However, again, most of the direct C–H arylations make use of transition-metal catalysts and heating."

Recently, metal-free procedures for direct C–H arylation of arenes were reported in seminal papers, first by Itami et al. (*Org. Lett.* **2008**, *10*, 4673), and later by Shi et al. (*Nat. Chem.* **2010**, *2*, 1044), Shirakawa and Hayashi et al. (*J. Am. Chem. Soc.* **2010**, *132*, 15537) and Kwong and Lei et al. (*J. Am. Chem. Soc.* **2010**, *132*, 16737). "In all those cases," explained Dr. Carrillo, "biaryl frameworks were synthesized through homolytic aromatic substitution (HAS) with aryl radicals, i.e. addition of aryl radicals to benzene derivatives followed by elimination of a hydrogen radical. But harsh conditions such as high temperatures and harmful, corrosive reagents were required." Then, in 2012, König et al. (*J. Am. Chem. Soc.* **2012**, *134*, 2958) developed a mild metal-free direct C–H arylation of heteroarenes through photochemical reduction of an arenediazonium ion catalyzed by an organic dye (Eosin Y). "That elegant work made us think that a mild reducing agent such as vitamin C could also do the work," said Dr. Carrillo. Indeed, arenediazonium ions function as one-electron oxidizing agents, and therefore, in reactions with suitable reducing agents, free radicals are generated, which can undergo a homolytic aromatic substitution. In this regard, solid evidence was found in a paper by Bravo-Díaz et al. (*Helv. Chim. Acta* **2001**, *84*, 632) that vitamin C is able to act as a reductant towards arenediazonium ions to generate aryl radicals in the absence of metals. Dr. Carrillo continued: "Thus, after some preliminary work, we proved that ascorbic acid is able to reduce arenediazonium ions, leading to the subsequent aromatic substitution with arenes in good yield (Scheme 1). Furthermore, only a catalytic amount (10 mol%) of vitamin C is required to initiate the reaction. It is worth mentioning that the idea of vitamin C acting as a radical initiator is very counterintuitive," he continued, "because traditionally it has been considered as a radical scavenger. However, only reactive oxygen radicals are effectively quenched by vitamin C."

Proof of concept:



Original conditions:	In the dark:	No ascorbic acid:
72% yield	71% yield	9% yield

Scheme 1 *Proof of concept: Ascorbic acid effectively generates aryl radicals from arenediazonium ions*

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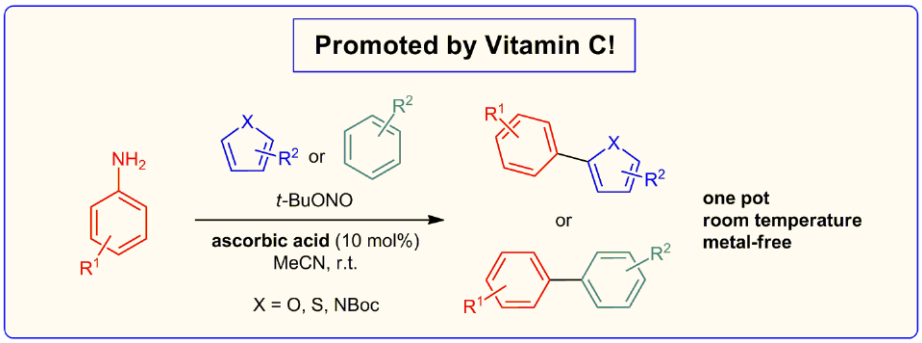

Scheme 2 *The new methodology*

"Once we knew that arenediazonium ions were effectively reduced by ascorbic acid, we decided to generate them in situ from the corresponding aniline (Scheme 2)," explained Dr. Carrillo. "Indeed, there is a considerable explosion hazard associated with the use of large amounts of dry diazonium salts. Furthermore, anilines are usually inexpensive and readily available. Fortunately, the arylation reaction proceeded very well starting from anilines, particularly in acetonitrile under nitrogen (under air, yields were slightly lower, probably due to undesired reactions of aryl radicals with oxygen)."

The highest yields were observed for the arylation of electron-rich arenes with electron-poor anilines. This fact, according to Dr. Carrillo, seems to indicate that this radical reaction is controlled by the SOMO–HOMO interaction. "Numerous biaryl-containing molecules were synthesized in good yield with this green methodology," he said, "and a small selection of structures is shown in Figure 1 as a quick idea of the possibilities of this procedure. Remarkably, several functional groups are compatible with the reaction conditions (Figure 1). Particularly interesting is the observation that halogen substituents are not affected, which allows for further functionalization reactions."

Dr. Carrillo continued: "This methodology is also scalable and thus a gram-scale synthesis of the muscle relaxant Dantrolene was carried out successfully (Scheme 3)."

"Caution should be used when claiming a metal-free methodology, because traces of metals can mean a lot, as strikingly demonstrated in *Nat. Chem.* **2010**, *2*, 1007," said Dr. Carrillo. To exclude any hypothetical role of trace metals, the reaction was carried out with copper(I) (15 mol%) which is

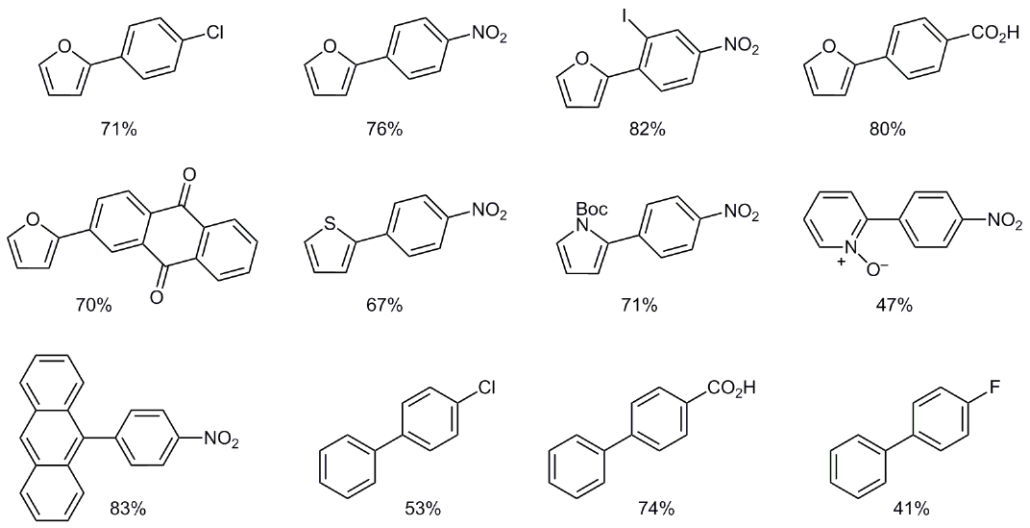

Figure 1 *Selected structures that were synthesized by this procedure in a one-pot fashion from anilines and unfunctionalized arenes*

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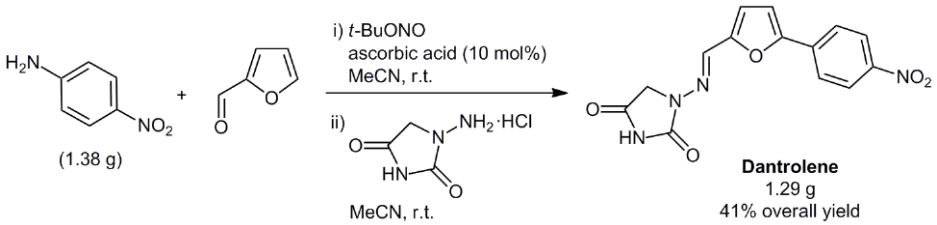


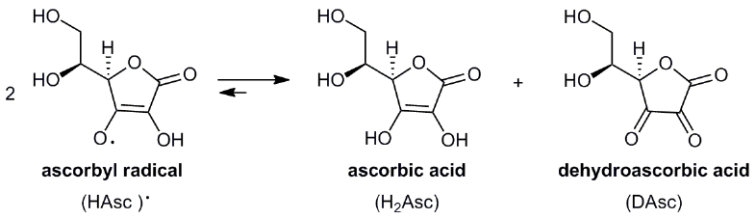
Scheme 3 *Gram-scale synthesis of Dantrolene*

well known for its reactivity in other Sandmeyer–Meerwein-type reactions. However, the yields were much lower. Ascorbic acid was also compared to other non-metallic reducing agents. Dr. Carrillo explained: "Some of the reducing agents chosen have been previously employed with arenediazonium ions, such as TEMPONa and KI (*J. Am. Chem. Soc.* **2012**, *134*, 16516; *J. Am. Chem. Soc.* **1997**, *119*, 4846); hydrazines are known for their reducing abilities, and phenylhydrazine in particular was employed recently in a radical arylation with iodoarenes (*Org. Lett.* **2013**, *15*, 6102); vitamin E, like vitamin C, is a common biological redox cofactor and it seemed interesting to us to compare both vitamins. However, in all cases yields were lower." Dr. Carrillo hypothesized that the advantage of ascorbic acid may reside in the low reactivity of the ascorbyl radical generated after the single-electron transfer from vitamin C to the arenediazonium salt. "Actually, ascorbyl radical tends to disproportionate to ascorbic and dehydroascorbic acid (Scheme 4)," he explained. "In other words, ascorbyl radical will not affect the radical intermediates of the reaction while other reducing agents (such as $TEMPO^-$ or I^-) generate radical species that partly terminate the reaction, thus decreasing the yield."

"We postulated a typical mechanism for a homolytic aromatic substitution (Scheme 5)," said Dr. Carrillo. "Probably the most interesting aspect is the reduction of the arenediazonium by ascorbic acid (Scheme 6)," he continued. "According to the experimental evidence found by Bravo-Diaz et al., single-electron transfer occurs by an inner-sphere mechanism: nucleophilic addition of ascorbate to the diazonium moiety to afford a diazoether, followed by a homolytic rupture to generate nitrogen, ascorbyl radical, and the aryl radical."

"In conclusion, this synthetic procedure is mild, operationally simple, and constitutes a greener approach to arylation," said Dr. Carrillo. "Indeed, ascorbic acid and its decomposition product, dehydroascorbic acid, are completely non-toxic. Other residues of this reaction are equally non-toxic, such as water, nitrogen or *tert*-butanol. Additionally, this methodology is energy-efficient because it requires neither heating nor irradiation." The only apparent drawback could be the use of anilines as the starting material, he acknowledged. "However, conversion was always complete, so no aniline should be present in the waste," continued Dr. Carrillo. "Even if small amounts of unreacted aniline were detected in the waste, the great advantage is that the toxicity of anilines markedly drops when they are converted into the corresponding acetamide (acetanilides). Actually, acetanilide is mostly metabolized in our bodies to paracetamol. This implies that with an easy treatment of the waste, toxicity should not be an issue."

Dr. Carrillo concluded: "Finally, the use of vitamin C as a radical initiator is very remarkable. Indeed, in most radical reactions transition metals or a stoichiometric amount of toxic reagents, such as Bu3SnH, are usually required as a radical



Scheme 4 *Disproportion equilibrium of ascorbyl radical*

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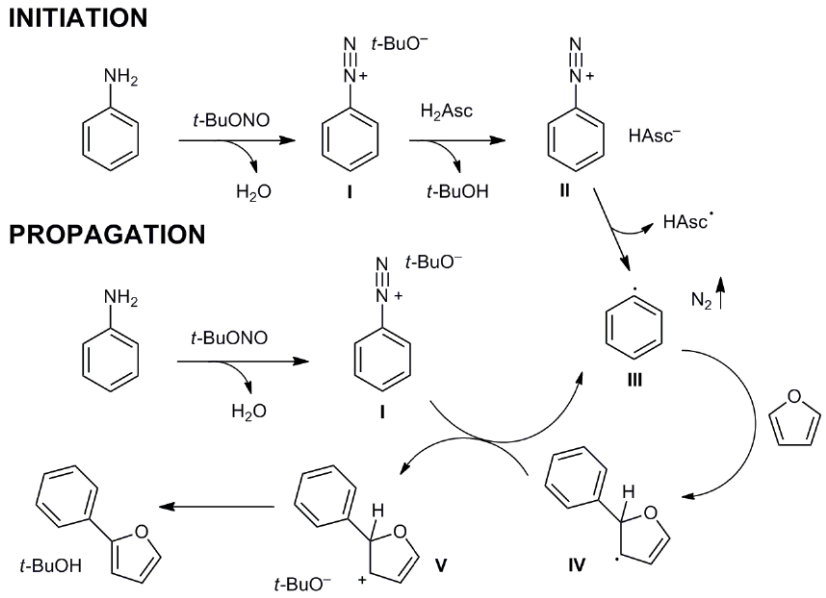
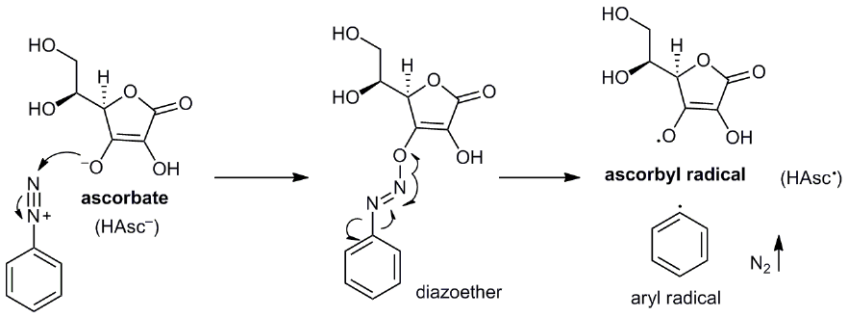


Scheme 5 *Postulated mechanism*



Scheme 6 *Inner-sphere mechanism for the single-electron transfer*

source, besides special conditions such as irradiation or heating. With our procedure, radicals are generated at room temperature, with just vitamin C. We really hope that this work triggers the development of milder, greener and easier radical reactions."

Matteo Zanda

About the authors

Dr. F. P. Crisóstomo

Fernando Pinacho Crisóstomo received his B.Sc. in chemistry at the University of São Paulo (Brazil) and his M.Sc. in organic chemistry under the guidance of Professors Jose Tercio Barbosa Ferreira and Arlene Gonçalves Correa at Federal University of São Carlos (Brazil) on the synthesis of natural products. He subsequently moved to Spain (Tenerife, Canary Islands) and started his Ph.D. at the University of La Laguna under Professor Victor Martín and Dr. >>

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Tomás Martín. His thesis focused on the development of synthetic methodologies for the synthesis of cyclic ethers. As a postdoctoral fellow he went to San Diego (California, USA), where he spent four years working at The Scripps Research Institute (with Professor Julius Rebek, Jr.), at the Sanford-Burnham Medical Research Institute (with Professor Ziwei Huang) and at the Moores Cancer Center (University of California San Diego with Professor Stephen Howell). After this period, he moved back to Spain as research fellow in the program JAE at the Consejo Superior de Investigaciones Científicas (IPNA-CSIC). His research interests include efficient syntheses of novel scaffolds for supramolecular chemistry, and development of noncovalent polymers or capsules for gel formation or drug delivery.

Dr. T. Martín

Tomás Martín received his B.Sc. in chemistry from the University of La Laguna (Spain) in 1991, and obtained his Ph.D. in 1996 from the same university, working on the enantioselective synthesis of γ-lactones under the guidance of Dr. C. M. Rodríguez and Professor Víctor S. Martín. He was a postdoctoral fellow of the Spanish Ministry of Education and Science (MEC) at The Scripps Research Institute (USA) from January 1997 to December 1998, working on molecular recognition under the supervision of Professor Julius Rebek, Jr. In 1999, he returned to the Canary Islands, with a reincorporation contract of the Spanish MEC, and joined Victor S. Martín's group. In 2002, he won a contract on the Ramón y Cajal program, created to boost Spanish science. In 2005, he became a tenured scientist at the Instituto de Productos Naturales y Agrobiología-CSIC. His research interests include supramolecular chemistry, asymmetric synthesis, new synthetic methodologies, and total synthesis of bioactive natural products.

Dr. R. Carrillo

Romen Carrillo received his B.Sc. in chemistry at the University of La Laguna (Spain), where he also obtained his Ph.D. in 2007 working on novel chiral receptors for amino acids under the supervision of Professors Víctor S. Martín and Dr. Tomás Martín. After spending some time in Professor Colin Nuckolls' group at Columbia University, New York (USA), he moved to the University of Edinburgh (UK) thanks to a postdoctoral fellowship from the Ramón Areces Foundation, where he worked in Professor David Leigh's group on molecular shuttles and lineal molecular motors. In 2010, he returned to Spain and joined the Instituto de Productos Naturales y Agrobiología (IPNA-CSIC), where he mainly studied novel cooperative binding events. Finally, he joined Instituto Universitario de Bio-Organica (IUBO) and Centro de Investigaciones Biomédicas de Canarias (CIBICAN) in 2013, where he is currently developing several research lines such as greener synthetic methodologies, supramolecular functional systems and novel approaches to medicinal chemistry.

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Nickel-Catalyzed Site-Selective Alkylation of Unactivated C(sp^3)–H Bonds

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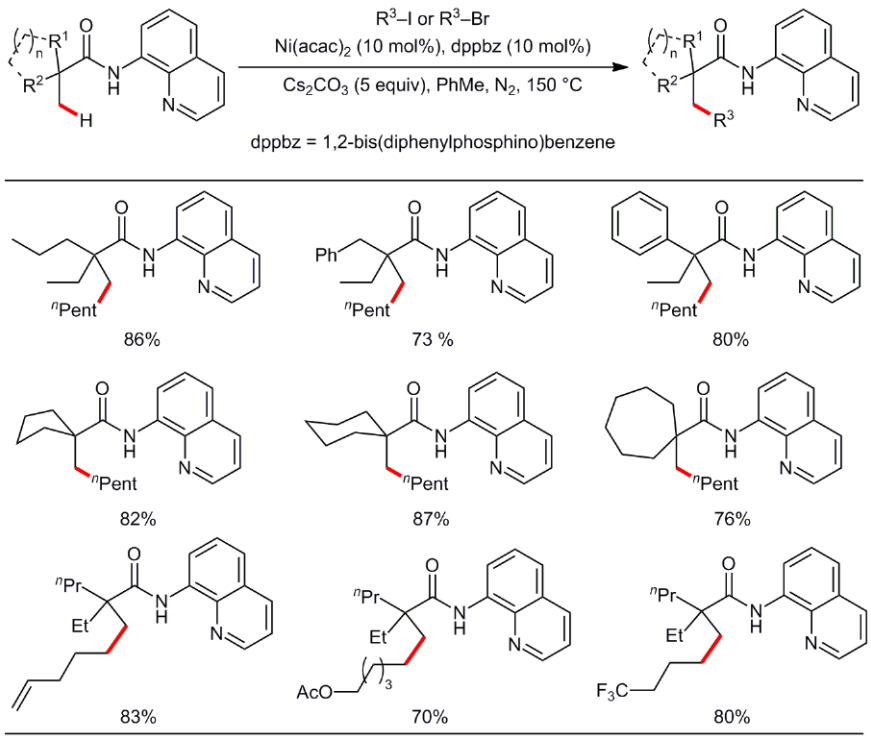
Activation of "unreactive" C–H bonds used to be a prerogative of certain oxidative enzymes, whereas very little was present in the arsenal of organic chemistry for achieving the formation of new C–C bonds by activation of aliphatic C(sp^3)–H residues. However, significant progress has been made over the last few years, particularly using metal complexes which can selectively activate specific aliphatic C–H bonds towards a variety of reactions, including C–C bond formation. In this context, nickel-catalyzed cross-couplings have received considerable attention in recent years. However, the site-selective functionalization of unactivated C(sp^3)–H bonds has not yet been achieved using nickel-based catalysts. Inspired by the success of a bidentate ligand as the directing group in a palladium-catalyzed coupling process, the group of Professor Haibo Ge at Indiana University-Purdue University Indianapolis (USA) came to believe that the site-selective functionalization on sp^3 carbons is feasible via nickel catalysis. Professor Ge said: "Based on a careful experimental design, we investigated and achieved the nickel-catalyzed direct alkylation of unactivated C(sp^3)–H bonds of aliphatic amides. As expected, the reaction favored C–H bonds of β-methyl groups over the γ-methyl and β-methylene C–H bonds, and exhibited good functional group tolerance (as shown in the Scheme)." Interestingly, the reaction showed a predominant preference for the C(sp^3)–H bonds of β-methyl group over the aromatic C(sp^2)–H bonds, which distinguishes this reaction from the palladium-catalyzed process. Professor Ge said: "We also observed that secondary alkyl halides and benzyl bromide failed to provide the desired products, indicating that the steric effect plays an important role in the



Scheme *Scope and conditions of the new nickel-catalyzed C(sp^3)–H bond functionalization process*

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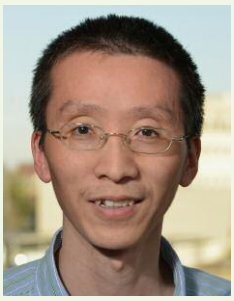
process." The mechanism of this new cross-coupling reaction is not fully understood, but the group believes that the alkyl-radical-mediated nickel(II)/nickel(III) catalytic cycle is involved, which constitutes a unique feature in nickel-catalyzed C–H bond functionalization processes. Professor Ge concluded: "We hope that future mechanistic studies of this reaction will provide us with more insights into the process and also some guidelines to extend the scope of the reaction."

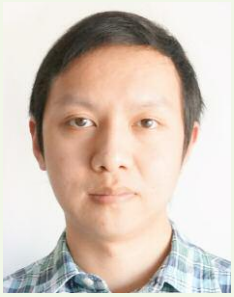
Matteo Zanda

About the authors



Prof. H. Ge

Haibo Ge was born in Yancheng, Jiangsu (P. R. of China). He received his Ph.D. in medicinal chemistry from The University of Kansas (Lawrence, USA) in 2006 with Professor Gunda Georg. He then moved to The Scripps Research Institute (La Jolla, USA) for his postdoctoral studies with Professor Dale Boger. In 2009, he began his independent academic career at the Department of Chemistry and Chemical Biology at Indiana University-Purdue University Indianapolis (IUPUI, USA). Research in his group is mainly focused on the development of novel methods towards carbon–carbon and carbon–heteroatom bond formation through transition-metal-catalyzed C–H functionalization. Additionally, his group is working on the synthesis and structure–activity relationship studies of anticancer and antibacterial natural products.



Dr. X. Wu

Xuesong Wu was born in 1985 in Hubei (P. R. of China). He received his B.Sc. in chemistry from the University of Science and Technology of China (USTC) in Hefei (P. R. of China) in 2006. After completing his Ph.D. at USTC under the supervision of Professor Shi-Kai Tian, he joined the group of Professor Haibo Ge at IUPUI as a postdoctoral fellow in 2012. His current research is focused on transition-metal-catalyzed C–H bond functionalization.

Y. Zhao

Yan Zhao was born in Hubei (P. R. of China). She received her B.Sc. in pharmacy from the China Pharmaceutical University in Nanjing (P. R. of China). She joined the research group of Professor Haibo Ge at the Department of Chemistry and Chemical Biology at IUPUI in 2011. Her research focuses on the development of novel transition-metal-catalyzed coupling reactions.

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Organocatalytic Enantioselective Synthesis of 2,3-Allenoates by Intermolecular Addition of Nitroalkanes to Activated Enynes

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Chiral allenes have proved to be important structural motifs that are not only widely observed in natural products and functional materials, but also versatile in asymmetric synthesis as chiral ligands or catalysts. Among them, chiral 2,3-allenoates are particularly useful (for a review on the chemistry of allenoates, see: *Chem. Soc. Rev.* **2009**, *38*, 3102). Although the synthesis of racemic 2,3-allenoates has been well developed, catalytic asymmetric synthesis of the enantioenriched form has been a challenge. Pioneering studies have been reported by Tan (*J. Am. Chem. Soc.* **2009**, *131*, 7212), Takemoto (*Chem. Eur. J.* **2011**, *17*, 10470), Gong (*Org. Lett.* **2010**, *12*, 4050), Maruoka (*Nat. Chem.* **2013**, *5*, 240), Frantz (*J. Am. Chem. Soc.* **2013**, *135*, 4970), and Ma (*J. Am. Chem. Soc.* **2013**, *135*, 11517).

Both the Sun group at the Hong Kong University of Science and Technology (P. R. of China) and the Zhang group at the East China Normal University (P. R. of China) have been interested in allenoate synthesis for some time, and have previously reported several reactions for the synthesis of racemic allenoates (*Chem. Eur. J.* **2008**, *14*, 8481; *Chem. Commun.* **2010**, *46*, 752; *Adv. Synth. Catal.* **2011**, *353*, 1265; *Org. Lett.* **2012**, *14*, 1398). "Notwithstanding our previous contributions in the field, the development of a highly enantioselective protocol for 2,3-allenoate synthesis is by no means straightforward, particularly in an intermolecular convergent process where both bond-forming efficiency and stereocontrol should be considered," said Professors Sun and Zhang. "Indeed, after tedious screening of a wide variety of

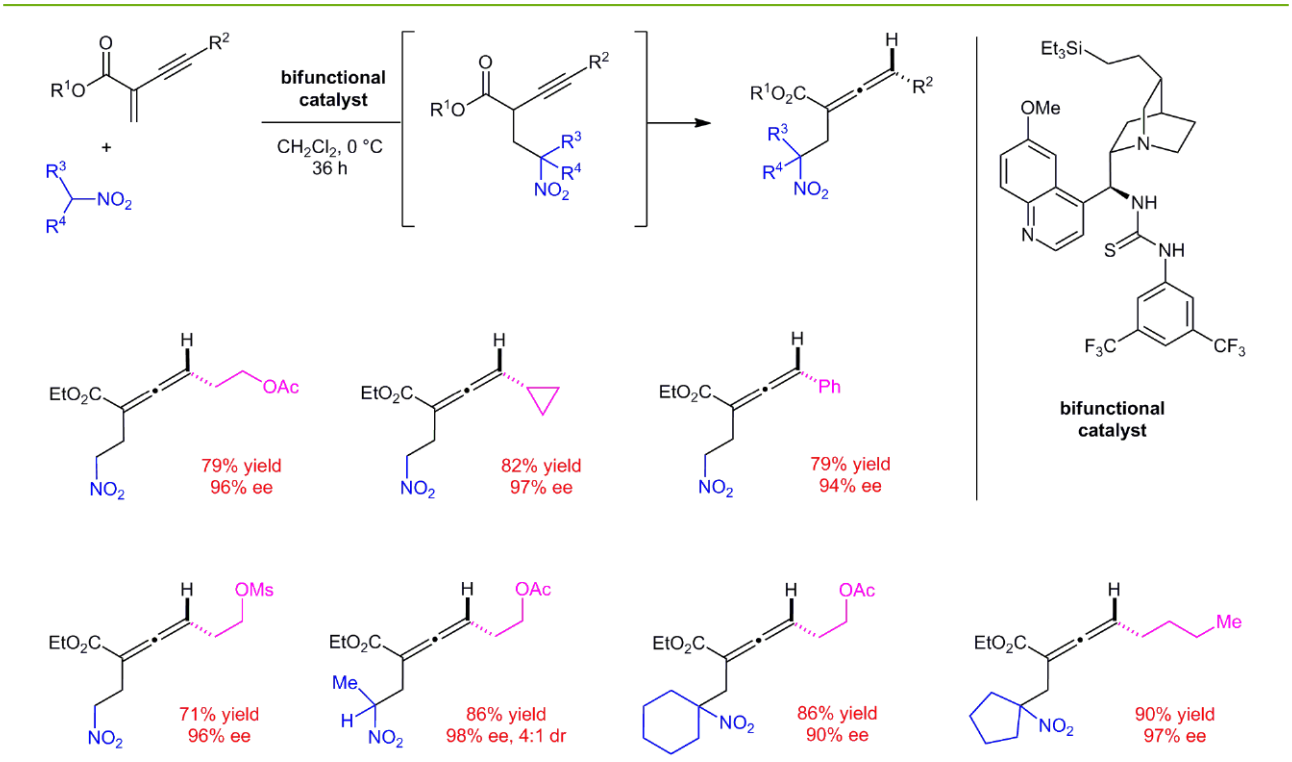

Figure 1

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chiral organic catalysts, including known and newly designed ones, we were able to identify a new cinchona-based bifunctional catalyst that was able to promote the addition of nitroalkanes to activated enynes with remarkable efficiency and asymmetric induction (Scheme 1)."

"It is noteworthy that a wide range of trisubstituted allenoates can be obtained in excellent optical purity," said Professor Sun. "It is also worth mentioning that time-dependency studies revealed that these reactions initially produce the corresponding 1,4-conjugate addition alkynoate products, which then undergo isomerization to the final allenoate products." Notably, both steps are catalyzed by the bifunctional catalyst, although only the second step involves useful chiral induction which leads to the product's enantiomeric excess. Professor Sun remarked: "Indeed, our bifunctional catalyst proved to catalyze the enantioselective isomerization of racemic alkynoates to the corresponding allenoates."

Professor Sun revealed that although the present process is efficient for the synthesis of enantioenriched 2,3-allenoates using nitroalkane nucleophiles, other carbon-based nucleophiles, such as 1,3-dicarbonyl compounds, are not as effective during chiral induction. "The excellent chiral control with nitroalkanes may result from the efficient interaction between the nitro group and the thiourea moiety in the chiral catalyst," said Professor Sun, who concluded: "Furthermore, the current protocol cannot be extended to the synthesis of other activated allenes, such as allenamides and allenyl sulfones. Further optimization of the reaction conditions will be required to expand the scope of the process."

Matteo Zanda

About the authors

H. Qian

Hui Qian was born in 1988 in Yixing, Jiangsu Province (P. R. of China). He received a bachelor's degree in chemistry from Yangzhou University (P. R. of China) in 2011. Presently, he is enrolled in the chemistry Ph.D. program at the Hong Kong University of Science and Technology under the supervision of Professor Jianwei Sun.

Dr. X. Yu

Xiuzhao Yu was born in 1982 in Jiangxi Province (P. R. of China). He received a bachelor's degree in 2005 from Shangrao Normal University. In 2012 he obtained his Ph.D. from East China Normal University under the supervision of Professor Junliang Zhang. His research focuses on catalytic regio- and enantioselective nucleophilic addition to electron-deficient conjugated enynes.

Junliang Zhang obtained B.S. degree from Tianjin University (P. R. of China) in 1997 and his Ph.D. from Shanghai Institute of Organic Chemistry (P. R. of China) in 2002 under the supervision of Professor S. Ma. He did one year of postdoctoral research (Humbolt fellowship) under the direction of Professor H.-G. Schmalz at the University of Cologne (Germany) and then

Prof. J. Zhang

anothor two years at The University of Chicago (USA) with Professor C. He. In December 2006, he became a full professor of chemistry at East China Normal University. He has published more than 80 papers and written three book chapters. He is a recipient of the Young Chemist of Chinese Chemical Society Award (2009), the Thieme Chemistry Journal Award (2012) and the Distinguished Lectureship Award from Chemical Society of Japan (2013).

Prof. J. Sun

Jianwei Sun graduated with B.S. and M.S. degrees from Nanjing University (P. R. of China) in 2001 and 2004, respectively. In 2008, he obtained his Ph.D. in organic chemistry from The University of Chicago. He then worked as a postdoctoral fellow at the Massachusetts Institute of Technology (USA). In August 2010, he became an assistant professor of chemistry at the Hong Kong University of Science and Technology. He is a recipient of the Asian Core Program Lectureship Award (2011), the Hong Kong RGC Early Career Award (2012), and the Thieme Chemistry Journal Award (2014).

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(Focus on an article from the current literature)

Direct Synthesis of 1,4-Diols from Alkenes by Iron-Catalyzed Aerobic Hydration and C–H Hydroxylation
(Focus on an article from the current literature)

Palladium/Copper-Catalyzed Oxidative Arylation of Terminal Alkenes with Aroyl Hydrazides
(Focus on an article from the current literature)

FURTHER HIGHLIGHTS

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