ChemPubSoc Europe

DOI: 10.1002/chem.201903335

CHEMISTRY
A European Journal
Minireview

Organic Synthesis | *Reviews Showcase* |

Diazoacetonitrile (N_2CHCN): A Long Forgotten but Valuable Reagent for Organic Synthesis

Pavel K. Mykhailiuk*[a] and Rene M. Koenigs*[b]

Abstract: Diazoacetonitrile (N_2CHCN) is a small reactive diazoalkane. It has been synthesized for the first time already in 1898 by Theodor Curtius, however, did not gain much recognition in organic synthesis until recently. Only in 2015, after introduction of in situ and flow protocols for the safe generation of diazoacetonitrile, it started gaining popularity. In this minireview, the synthetic properties and applications of this valuable reagent are discussed.

Introduction

In 1898, the German chemist Theodor Curtius synthesized diazoacetonitrile, N_2CHCN (**1**), for the first time.[1] Fifteen years earlier, in 1883, Curtius prepared a parent reagent—ethyl diazoacetate, N_2CHCO_2Et (**2**).[2] Both compounds exhibited similar chemical properties, for example, both reacted with copper oxide under formation of nitrogen gas. Over time, however, these two reagents had dramatically different chemical destinies. Although ethyl diazoacetate (**2**) is probably one of the most used diazo reagents in organic synthesis nowadays,[3] its closest analogue diazoacetonitrile (**1**) remained mostly in the shadow (Table 1). Other acceptor-only diazoalkanes, for example, trifluorodiazoethane (1943, Gilman and Jones),[4] dimethyl diazo phosphonate (1969, Seyferth),[5] pentafluoroethyl diazomethane (2014, Mykhailiuk),[6] or difluorodiazoethane (2015, Mykhailiuk)[7] are important reagents and find regular applications in organic synthesis. The main limitation of diazoacetonitrile (**1**) lies within the high nitrogen content (63%) of this reagent that results in high risks. Curtius already described the explosion propensity of the neat diazoacetonitrile (**1**) reagent in his seminal report, which precluded applications of this useful reagent. Only in 2015, the authors of this review developed in situ[8] and flow procedures[9] for the safe generation of diazoacetonitrile (**1**), which immediately led to a big interest by many academic groups. In fact, more than a third of all publications and half of all reactions of diazoacetonitrile (**1**) appeared in the literature over course of the past four years (Table 1).

Table 1. Comparison of chemical reagents N_2CHCN (**1**) and N_2CHCO_2Et (**2**).

Reagent		
Manuscripts	37 (13)[a]	3780
Patents	3	1177
Reactions	180 (90)[a]	10327

[a] Over the past four years (since 2015).

Diazoacetonitrile is a particularly useful reagent to introduce nitrile groups into small molecules; reduction gives a rapid access to the corresponding amines. Both functional groups are important in many bioactive compounds and more than 50 FDA-approved drugs contain a nitrile group (Figure 1).[10] Diazoacetonitrile could thus serve as a valuable reagent for the rapid synthesis of nitrile-containing molecules and streamline currently available synthesis methods.

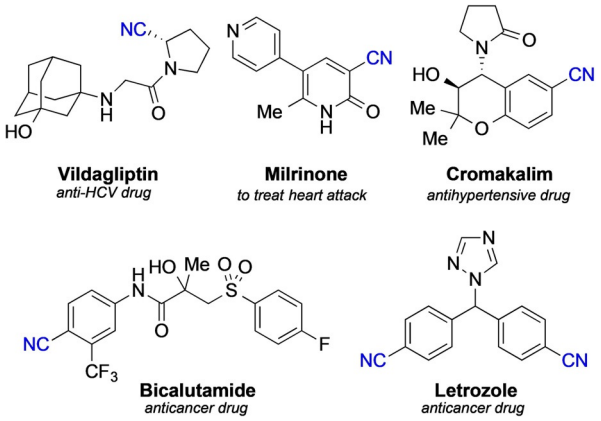


Figure 1. Pharmaceuticals containing a nitrile group.

In this review, we will consider the preparation, chemical properties, and applications of diazoacetonitrile (**1**) in organic synthesis. We will also outline the undeveloped areas in which this reagent might be useful.

Preparation

The first synthesis of diazoacetonitrile (**1**) was described by Curtius in 1898 by reacting amino acetonitrile hydrochloride with sodium nitrite. The reaction was slow, and addition of cat-

[a] *Dr. P. K. Mykhailiuk*
Enamine Ltd., Chervonotkatska 78, 02094 Kyiv (Ukraine),
and
Chemistry Department, Taras Shevchenko National University of Kyiv
Volodymyrska 64, 01601 Kyiv (Ukraine)
E-mail: Pavel.Mykhailiuk@gmail.com
Homepage: http://www.enamine.net
http://www.mykhailiukchem.org

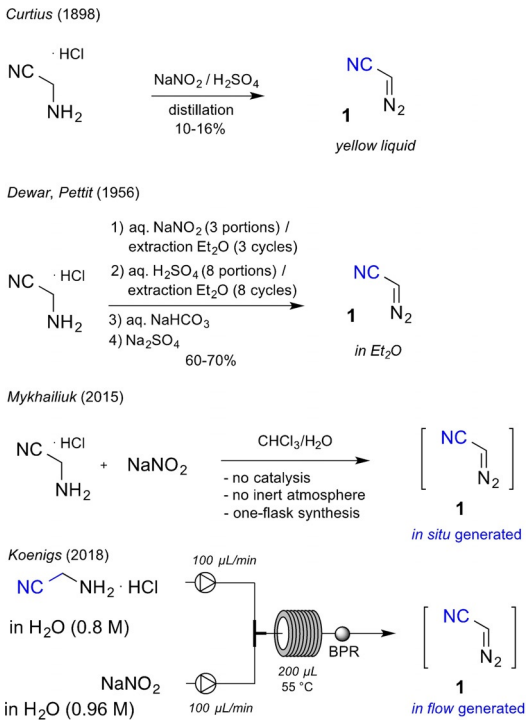
[b] *Prof. Dr. R. M. Koenigs*
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: rene.koenigs@rwth-aachen.de
Homepage: http://www.koenigslab.rwth-aachen.de

The ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/chem.201903335.

Selected by the Editorial Office for our Showcase of outstanding Review-type articles (www.chemeurj.org/showcase).

alytic amounts of sulfuric acid was needed. After distillation, the compound was obtained in 10–16% yield as an "orange-yellow easily moving liquid." It also exhibited a characteristic reaction of diazo compounds: reaction with copper oxide resulted in the evolution of nitrogen gas.[1]

In 1956, Dewar and Pettit optimized a synthesis of **1** by a repetitive extraction–addition procedure, yet after distillation of the neat reagent, the authors reported an explosion. Therefore, in subsequent reactions the authors used a solution of diazoacetonitrile in diethyl ether dried over sodium sulfate. The yield of **1** was estimated to be 60–70%, as measured by the volume of nitrogen liberated after an addition of an acid.[11] At the same time, Harper and Sleep;[12] as well as Phillips and Champion[13] independently reported on similar explosions of pure diazoacetonitrile (Scheme 1).

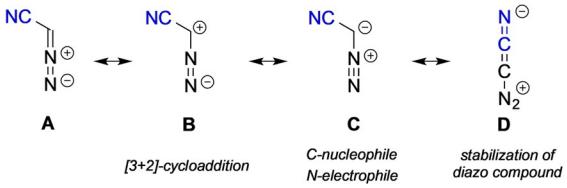


Scheme 1. Preparation of diazoacetonitrile (**1**).

Although the protocol of Dewar and Pettit for preparing a solution of diazoacetonitrile in diethyl ether was subsequently used by many other groups, the risks of associated with **1** prevented its wide application in organic synthesis for many years. However, in 2015, Mykhailiuk developed a one-pot three-component synthesis of pyrazoles from alkynes, sodium nitrite, and amino acetonitrile hydrochloride.[8] The reaction proceeded through in situ formation of diazoacetonitrile (**1**) in a chloroform/water mixture. In 2018, Koenigs developed an iron-catalyzed alkylation of N–H and S–H bonds using in flow generation of diazoacetonitrile (**1**).[9] These two protocols for safe preparation of **1** opened up a new chapter in the chemistry of diazoacetonitrile (Scheme 1).

Chemical Properties

Diazoacetonitrile belongs to the family of "stabilized diazo compounds" that have a reduced reactivity compared with diazomethane or donor diazoalkanes. This stabilization arises primarily from a conjugation of the nitrile group and the diazo moiety (Scheme 3, structure **D**). The steric bulk of the nitrile group and its (*–I*)-inductive effect provide an additional stabilization of a molecule. Diazoacetonitrile can be depicted by several resonance structures that help to rationalize its chemical reactivity (Scheme 2): a) [3+2]-cycloaddition reactions (form **B**); b) C-nucleophile (form **C**); c) N-electrophile (form **C**). These three types of reactivity will be considered in details in the same order. Additionally, reactions of the cyano-substituted carbene and [M]-carbenoid will also be covered.



Scheme 2. Resonance forms of diazoacetonitrile (**1**).

Regardless of a reduced chemical activity of diazoacetonitrile (**1**), one should always keep in mind that because of high context of nitrogen atoms in a molecule (63 mass-%), the individu-

Pavel was born in Kerch, Ukraine. In 2008, he received Ph.D. in biochemistry from Technical University of Karlsruhe (KIT, Germany) with Prof. Anne Ulrich; and Ph.D. in organic chemistry from Kyiv National Taras Shevchenko University (Ukraine) with Prof. Igor Komarov. In 2009, Pavel returned to Kyiv National Taras Shevchenko University. The same year, he also joined "Enamine" company, where he is currently involved into discovery of novel building blocks for drug design. Pavel's research interests include fluoroorganic chemistry, chemistry of diazo compounds, photochemistry and saturated bioisosteres of the benzene. He is co-author of more than 100 peer-reviewed research manuscripts. In 2017, he received Dr.Sci. in organic chemistry from the Kyiv National Taras Shevchenko University.

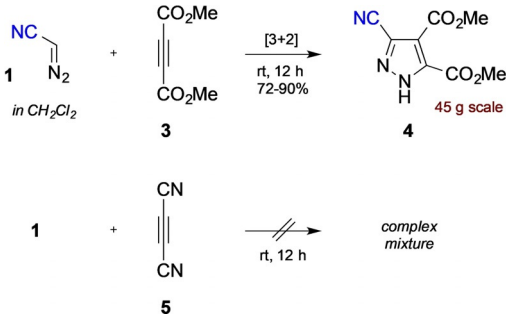
Rene M. Koenigs obtained his Ph.D. in 2011 from RWTH Aachen University under the guidance of Prof. Magnus Rueping. He subsequently moved to Grunenthal GmbH, working as a medicinal chemist on GPCR and ion channel targets. In 2015 he was appointed as Juniorprofessor at RWTH Aachen University. His research interests focus on applications of carbene transfer reactions, continuous-flow chemistry and fluorine chemistry.

al compound is explosive. It should only be used as a dilute solution or generated in situ.

[3+2]-Cycloaddition Reactions

Reaction with alkynes

The first cycloaddition of diazoacetonitrile was reported in 1962 by Weis.[14] Following a modified protocol of Dewar and Pettit,[11] he prepared a dry solution of **1** in dichloromethane and reacted it with alkyne **3** at room temperature (Scheme 3). The cyano-substituted pyrazole **4** was obtained in 72–90% yield on 45 g scale! Unexpectedly, the reaction of dicyanoacetylene (**5**) with diazoacetonitrile under the identical reaction conditions led to a formation of a complex mixture.

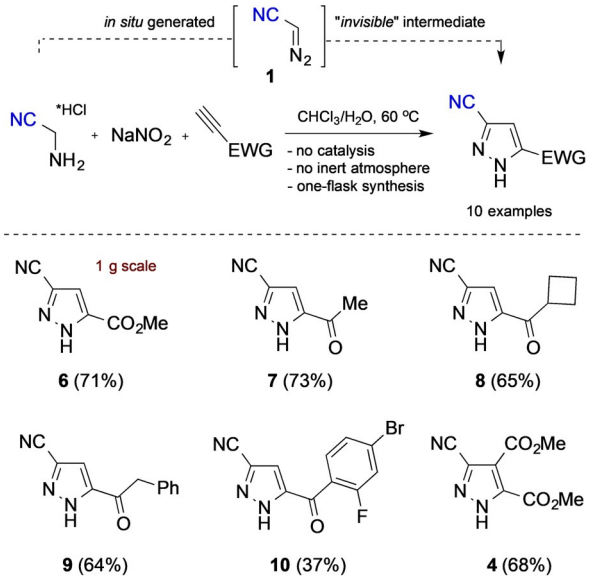


Scheme 3. Synthesis of CN-pyrazole **4** by Weis.

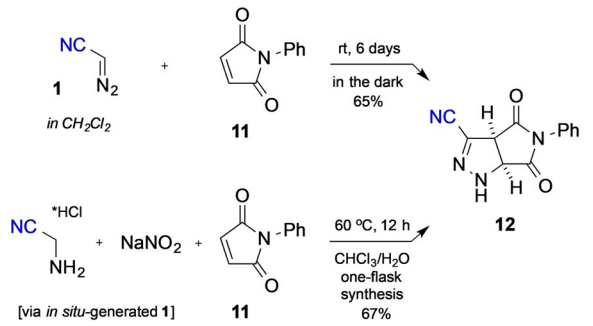
Fifty years later, in 2015, the synthesis of cyano-substituted pyrazoles was optimized by Mykhailiuk using in situ generated diazoacetonitrile.[8] From a practical standpoint, the reaction was very easy to set up: a mixture of amino acetonitrile hydrochloride, $NaNO_2$, and the corresponding alkyne was heated in a chloroform/water mixture for 12–72 h. The formed cyanopyrazoles were obtained in 37–73% yield (Scheme 4, **4**, **6**–**10**). The products, however, were unstable during column chromatography on silica gel, and therefore were purified by sublimation under a high vacuum. Nevertheless, this protocol allowed for the synthesis of pyrazole **6** on 1 g scale. The limitation of this reaction lies within the nature of diazoacetonitrile itself that reacts in Type I dipolar cycloaddition reactions with electron-deficient alkynes; non-activated or electron-rich alkynes did not react under the stated reaction conditions.

Reaction with alkenes

The first example of the reaction of diazoacetonitrile (**1**) with alkenes goes back to 1978, when Roelants and Bruylants reacted a dry solution of **1** in dichloromethane with maleimide **11**. After six days at room temperature in the dark, the cyanopyrazoline **12** was isolated in 65% yield (Scheme 5).[15] Later, this reaction was performed by Mykhailiuk with in situ generated diazoacetonitrile. After heating the reaction mixture at 60 °C for 12 h, the product **12** was obtained as a white solid in 67% yield.[8]



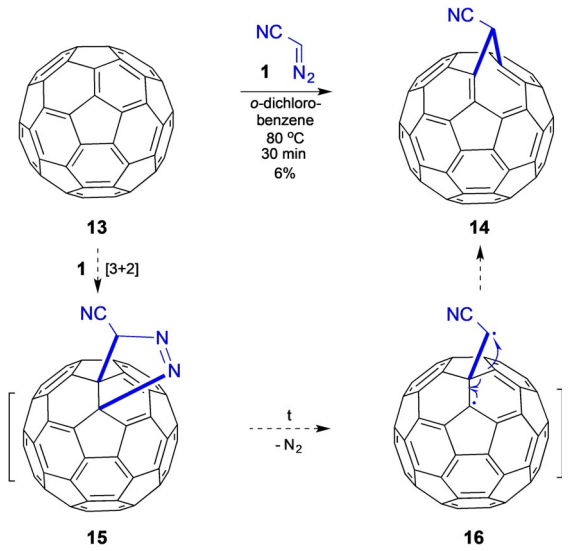
Scheme 4. Synthesis of CN-pyrazoles through [3+2]-cycloaddition of electron-deficient alkynes and in situ generated diazoacetonitrile (**1**).



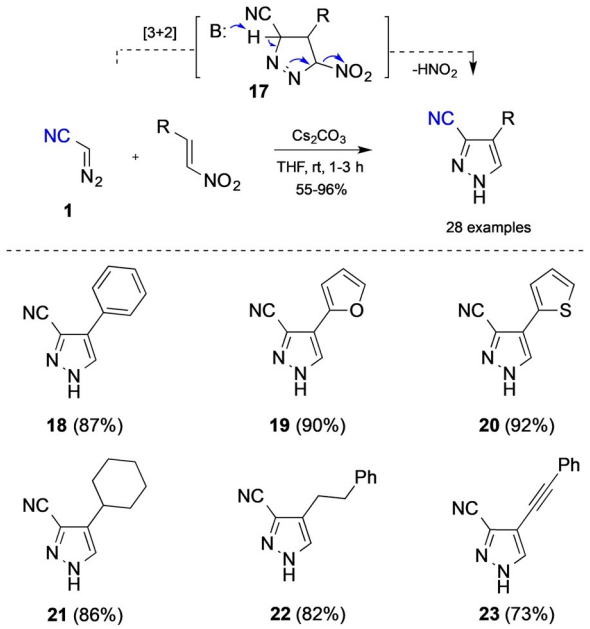
Scheme 5. Synthesis of CN-pyrazoline **12**.

In 2010, Oshima and co-workers investigated the reaction of diazoacetonitrile (**1**) with C_{60} fullerene (**13**) at 80 °C in *o*-dichlorobenzene (Scheme 6).[16] After purification of the reaction mixture by HPLC, the authors isolated cyano-substituted fulleroid **14** in 6% yield. According to related mechanistic studies,[17] the first step involves the formation of pyrazoline **15** through [3+2]-cycloaddition of C_{60} and diazoacetonitrile. At elevated temperature, **15** decomposed immediately with evolution of nitrogen to produce the biradical **15** that gave finally fulleroid **14** together with an isomeric cyanocyclopropane.[16]

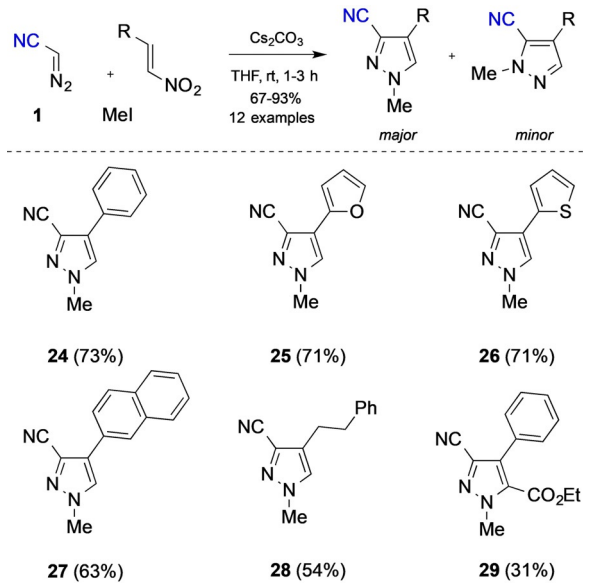
Recently, Ma and co-workers elaborated a synthesis of cyano-substituted pyrazoles from electron-poor nitroolefins and diazoacetonitrile (**1**). The reaction presumably proceeded through a regioselective [3+2]-cycloaddition of nitroolefins with diazoacetonitrile to form an intermediate pyrazoline **23** (Scheme 7).[18] Under basic conditions, compound **23** undergoes elimination of nitric acid to provide the target 3,4-disubstituted pyrazoles, whereas the formation of 3,5-disubstituted isomers was not observed. This method showed a broad substrate scope, aromatic, heteroaromatic, and aliphatic nitroolefins were efficiently used. Importantly, the authors also per-



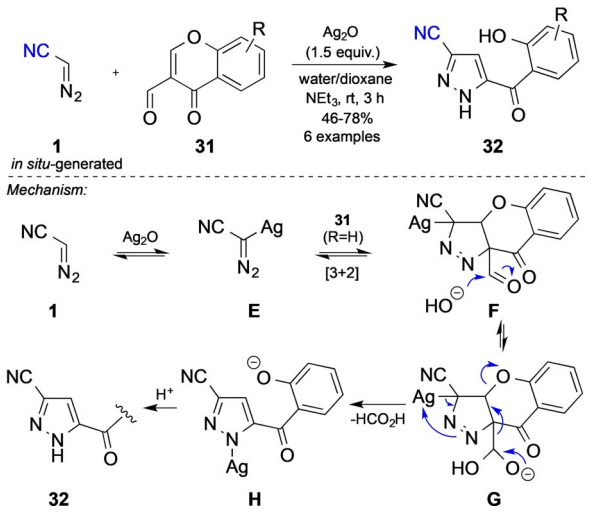
Scheme 6. Synthesis of CN-cyclopropane **14** through [3+2]-cycloaddition of C_{60} (**13**) with diazoacetonitrile (**1**).



Scheme 7. Synthesis of CN-pyrazoles through [3+2]-cycloaddition of nitroolefins and diazoacetonitrile (**1**).



Scheme 8. Three-component reaction between nitroolefins, diazoacetonitrile (**1**), and MeI.



Scheme 9. Synthesis of CN-pyrazoles **32** through [3+2]-cycloaddition of diazoacetonitrile (**1**) with formylchromones in the presence of Ag_2O.

formed this reaction with the in situ generated **1**, although in slightly lower yields.

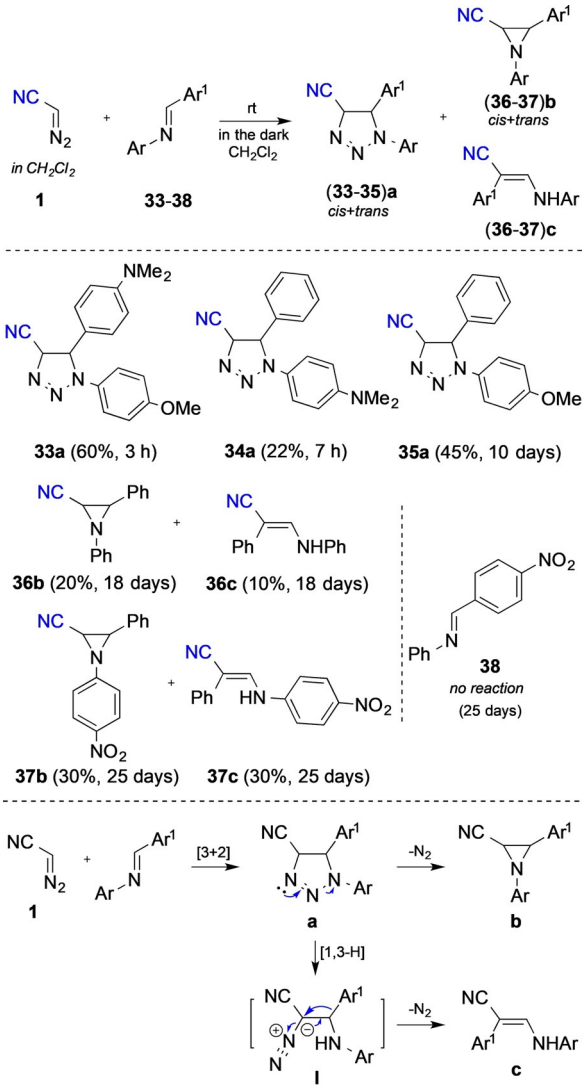
Furthermore, the same authors developed a three-component reaction between nitroolefins, diazoacetonitrile (**1**), and methyl iodide. The reaction had the same mechanistic profile, with the only difference that the initially formed NH-pyrazoles were subsequently N-alkylated. The reaction produced two regioisomers that were separated by column chromatography (Scheme 8, **24**–**29**).[18b]

In 2019, Lan, Yang, and co-workers reported on a silver-mediated reaction of diverse diazo compounds and formyl chromones (**31**) (Scheme 9).[19] Within this report, they described the synthesis of six cyano-substituted pyrazoles **32** from in situ generated diazoacetonitrile (**1**). Given that stochiometric amounts of silver oxide are required in this reaction, the authors suggested that intermediate **E** was initially formed by reaction of diazoacetonitrile (**1**) with silver oxide. This intermediate **E** underwent [3+2]-cycloaddition with formylchromones **31** to give aldehyde **F**. Addition of base to the aldehyde group (**G**), followed by an elimination of formic acid (**H**) and subsequent protonation afforded the final pyrazoles **32**.

Reaction with Imines

In 1978, Roelants and Bruylants reported on the reaction of diazoacetonitrile (**1**) with aromatic imines.[15] The reaction outcome strongly depended on the electronic properties of the

starting imines and the reaction time. Although electron-rich imines **33**, **34** reacted at room temperature within 3–7 h; imines **35**, **36** reacted within 10–18 days (Scheme 10). Reaction

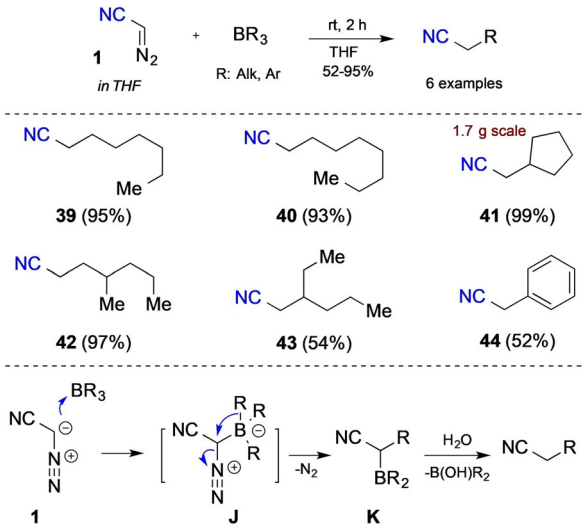


Scheme 10. Synthesis of CN-triazolines, aziridines and enamines through [3+2]-cycloaddition of diazoacetonitrile (**1**) with N-benzylidene-anilines.

of non-activated aromatic imine **37** took 25 days, whereas electron-deficient imine **38** did not react at all. Three types of products were obtained: triazolines (**a**), aziridines (**b**), and enamines (**c**). The product distribution strongly depended on the electronic properties of the starting imine and the reaction time. The authors suggested that a [3+2]-cycloaddition between imines and diazoacetonitrile (**1**) occurred first, leading to triazolines (**a**). Mechanistically, this might be a Type III concerted [3+2]-cycloadditions, for which electron-donating substituents at the dipolarophile accelerate the reaction. Alternatively, this reaction might proceed through a stepwise mechanism, with the nucleophilic imine attack at the diazo moiety first, followed by ring closure. Over time, triazolines (**a**) decomposed with the evolution of nitrogen into triazolines (**b**). The rate of this step strongly depends on the electronic properties of the imine. Analogously, triazoles (**a**) gave diazo intermediate **I** that underwent an aryl group migration and evolution of nitrogen into enamines (**c**).

Reactions as a C-Nucleophile

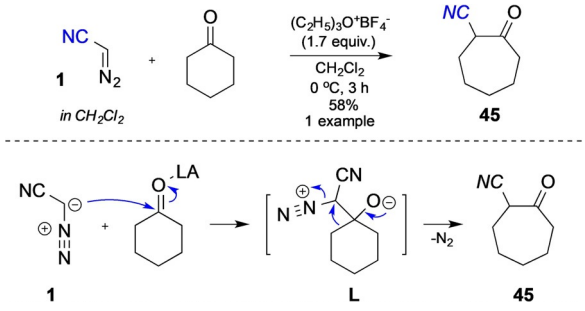
In 1968, Hooz and Linke described an alkylation of diazoacetonitrile (**1**) with organoboranes to form substituted acetonitriles **39**–**44** (Scheme 11).[20] The transformation worked for both ali-



Scheme 11. Alkylation of diazoacetonitrile (**1**) with organoborates.

phatic and aromatic organoboranes. In a typical protocol, the reaction was performed in THF at room temperature, including gram-scale applications. From the mechanistic point of view, at first intermediate **J** was formed by a nucleophilic attack of **1** at the boron atom (Scheme 11). 1,2-Alkyl (aryl) shift and elimination of nitrogen gave organoboron species **K** that provided the final nitrile products upon hydrolysis.

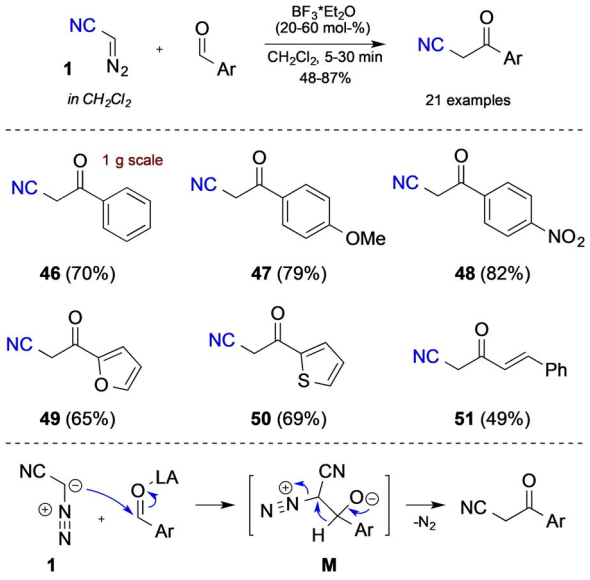
In 1976, Mock and Hartman studied a homologation of ketones with diazo compounds catalyzed by triethyloxonium ion.[21] Most reactions were performed with ethyl diazoacetate (**2**), but one reaction was also realized with diazoacetonitrile (**1**). In particular, cyclohexanone reacted with a dry solution of **1** in dichloromethane at 0 °C in the presence of $Et_3O^+BF_4^-$ to afford 2-cyanocycloheptanone (**45**) in 58% yield (Scheme 12).



Scheme 12. Homologization of cyclohexanone with diazoacetonitrile (**1**).

It is worth mentioning that an excess of $Et_3O^+BF_4^-$ (1.7 equiv) was required in the reaction. Mechanistically, $Et_3O^+BF_4^-$ activated the carbonyl group of cyclohexanone as a Lewis acid. Nucleophilic attack of the C-atom of **1** at the carbonyl group led to intermediate **L**. A 1,2-alkyl shift accompanied by the evolution of nitrogen gave the target product **45**.

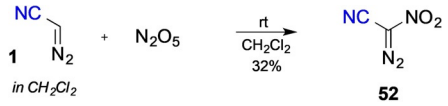
Almost 40 years later, Xu elaborated a transformation of aromatic aldehydes into β-ketonitriles with diazoacetonitrile (**1**).[22] After screening of Lewis acids, the authors identified $BF_3{\cdot}Et_2O$ (20–60 mol-%) as the most efficient catalyst. The reaction efficiently worked for non-activated (Scheme 13, **46**) electron-rich (**47**), and electron-deficient aromatic aldehydes (**48**), furane (**49**), and thiophene (**50**), but was unfortunately not compatible with aliphatic aldehydes. The authors also performed the synthesis of ketone **46** in 1 g scale.



Scheme 13. Synthesis of β-ketonitriles from aromatic aldehydes and diazoacetonitrile (**1**).

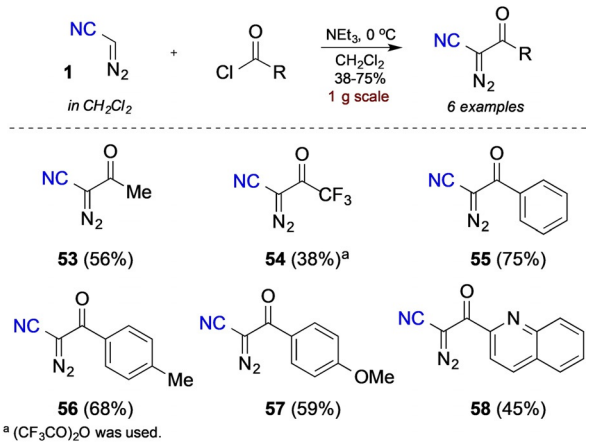
The reaction mechanism is similar to the previous transformation: first, $BF_3{\cdot}Et_2O$ activates the carbonyl group of aldehydes as a Lewis acid. Next, a nucleophilic attack of diazoacetonitrile (**1**) at the carbonyl group takes place forming an intermediate **M**. 1,2-Hydride shift followed by elimination of nitrogen completes the formation of the β-ketonitriles (Scheme 13).

In 1969, Schoellkopf treated a dry solution of diazoacetonitrile (**1**) with N_2O_5 to obtain nitro-diazoacetonitrile (**52**) as yellow crystals in 32% yield (Scheme 14).[23] The individual compound was explosive, but its dilute solution in dichloromethane was stable and was later used by Dailey in cyclopropanation reactions of alkenes.[24]



Scheme 14. Synthesis of nitrodiazoacetonitrile (**52**).

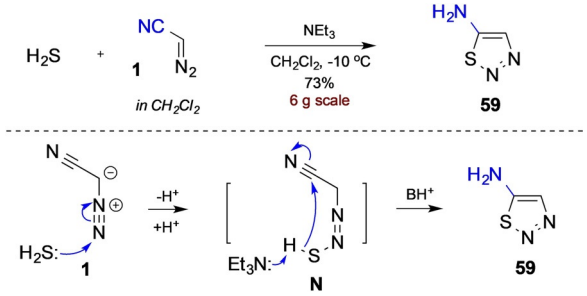
In 2002, Bakulev performed the acylation of diazoacetonitrile (**1**) with both aliphatic and aromatic acyl chlorides. The reaction smoothly proceeded at 0 °C in dichloromethane in the presence of triethylamine as a base. The corresponding diazoketones **53**–**58** were isolated from reaction mixtures by column chromatography as yellow oils in 38–75% yield (Scheme 15).[25] All reactions were performed on a gram scale.



Scheme 15. Synthesis of acylated diazoacetonitriles (**53**–**58**).

Reactions as N-electrophile

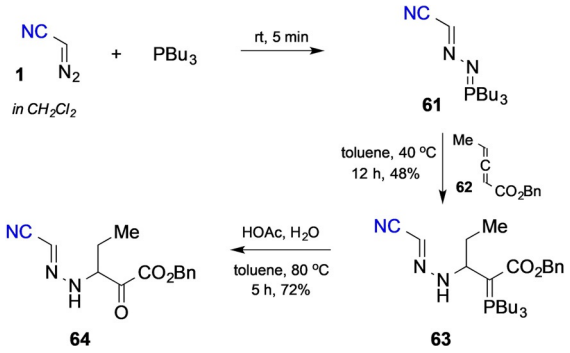
Although reactions of diazo compounds as N-electrophiles are well-documented in the literature,[26] to the best of our knowledge, only two reactions of this type are known for diazoacetonitrile (**1**). In particular, in 1997, Harada developed a gram-scale synthesis of compound **59**—an important intermediate for the preparation of agrochemicals—from diazoacetonitrile (**1**, Scheme 16).[27] First, the authors studied the thermal stability of **1** and concluded that only its diluted solutions, less than 30%, should be used especially on a large scale. Next, the authors treated a diluted dry solution of **1** in dichloromethane with hydrogen sulfide in the presence of catalytic amounts of triethylamine at −10 °C to form a white solid. The precipitate was filtered off and recrystallized from water to obtain the product **59** in 73% yield. Importantly, the filtrate was treated with aqueous acid solution to decompose residual amounts of diazoacetonitrile. This protocol allowed for the safe preparation of thiadiazole **59** in a 6 g scale.



Scheme 16. Synthesis of thiadiazole **59** from diazoacetonitrile (**1**).

Mechanistically, a nucleophilic attack of the sulfur atom at the diazo moiety of **1** occurred under basic conditions to give intermediate **N**. Subsequent intramolecular cyclization at the nitrile group of **N** gave the targeted product **59** (Scheme 16).

In 2016, Ma studied the reaction of diazo compounds with P^{III}-reagents. In this report, the authors investigated the reaction of diazoacetonitrile (**1**) with tributylphosphine at room temperature to obtain cyano-substituted phosphazene **61**.[28] Mechanistically, a nucleophilic attack of the lone pair of the phosphorus atom at the diazo moiety occurred. The authors subsequently treated compound **61** with allene **62** to obtain hydrazone **63** through a Wittig reaction. Acidic hydrolysis of C=P bond finalized the synthesis of ketone **64**. Importantly, the authors subsequently performed this three-step synthesis of ketone **64** in a one-pot manner starting from diazoacetonitrile (**1**) without isolation of intermediates **61** and **63** (Scheme 17).



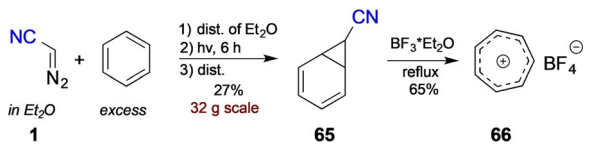
Scheme 17. Synthesis of phosphazene **61** from diazoacetonitrile (**1**).

Carbene reactivity

Diazoacetonitrile (**1**) eliminates nitrogen upon photochemical irradiation and gives NCCH: carbene.[29] Alternatively, treating **1** with catalytic amount of transition-metal salts—Cu, Rh, Ru, Fe—gives metal carbenoids NCCH=[M]. Both species can undergo cyclopropanation reactions with alkenes and carbene-insertion reactions. These will be considered in the following in more details.

Cyclopropanation reactions

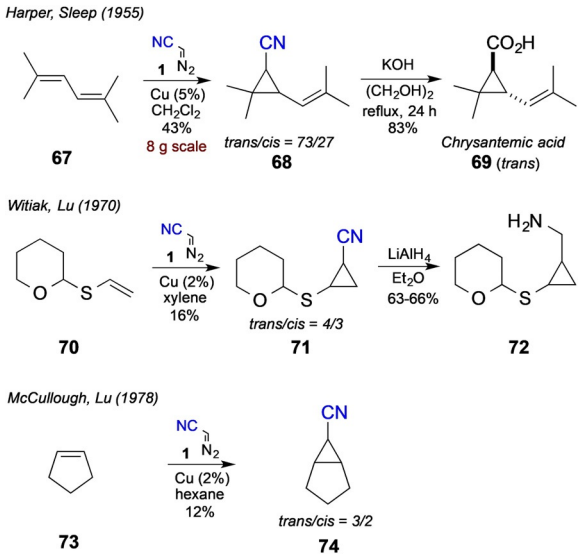
In their seminal report, Dewar and Pettit synthesized cyanonorcaradiene (**65**) by irradiation of a solution of diazoacetonitrile (**1**) in an excess of benzene with a broad-wavelength mercury lamp (Scheme 18).[11] The reaction proceeded through photochemical decomposition of **1** into cyanocarbene that reacted next with benzene. Product **65** was isolated from the reaction



Scheme 18. Synthesis of cyanonorcaradiene (**65**) and its conversion into tropylium fluoroborate (**66**).

mixture by distillation on a 32 g scale (27% yield) as a pale-yellow oil. It is worth mentioning that the analogous reaction of ethyl diazoacetate (**2**) proceeded with much lower yield. Cyclopropane **65** was stable at room temperature, however, treatment with $BF_3{\cdot}Et_2O$ under reflux conditions gave the aromatic tropylium tetrafluoroborate (**66**).

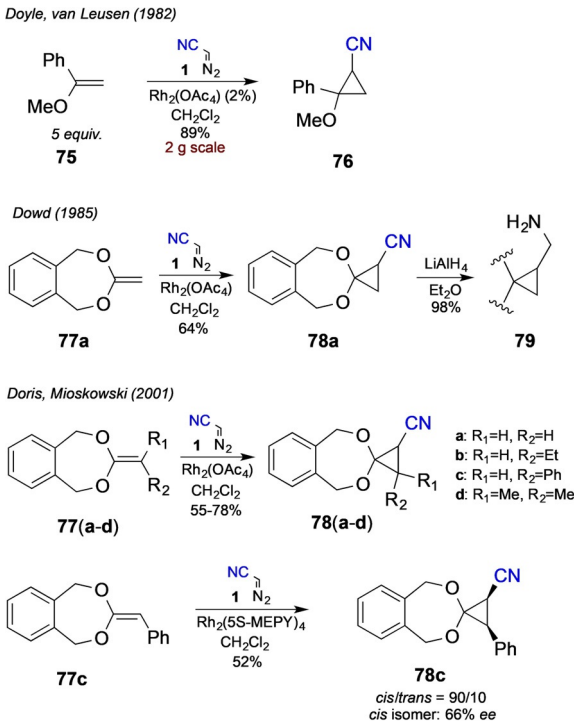
The first report on metal-catalyzed cyclopropanation of alkenes with diazoacetonitrile dates back to 1955, when Harper and Sleep treated diene **67** with **1** in the presence of copper bronze in dichloromethane.[12] After distillation, cyclopropane **68** was isolated as a mixture of *trans*/*cis* isomers (73/27) in 43% yield. The synthesis was performed on a 8 g scale. Interestingly, the subsequent hydrolysis of nitrile **68** with potassium hydroxide in refluxing glycol led to an epimerization of the stereocenter and *trans*-chrysantemic acid (**69**) was obtained in 83% yield as the only product (Scheme 19). Later, Witiak and



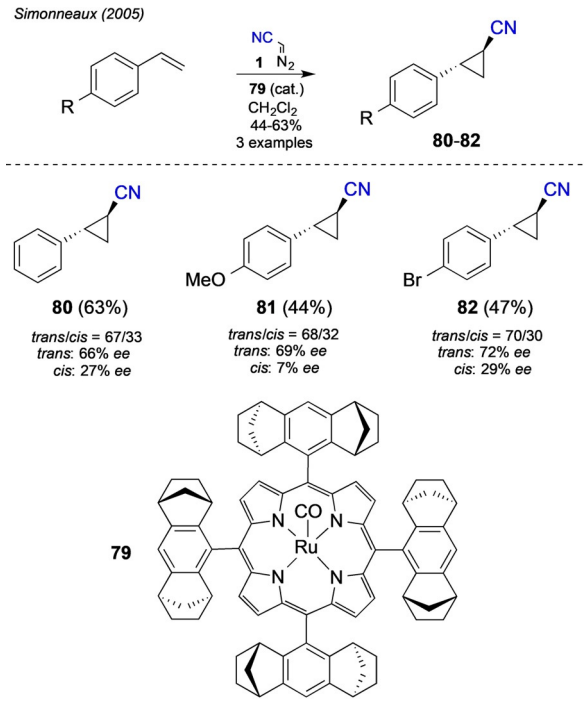
Scheme 19. Cu-catalyzed cyclopropanation of alkenes with diazoacetonitrile (**1**).

Lu reported on copper-catalyzed cyclopropanation reaction of alkene **70** with diazoacetonitrile (**1**).[30] The reaction produced a complex mixture, from which, after a distillation and two subsequent chromatographic purification steps, cyclopropane **71** was obtained as a mixture of *cis*- and *trans*- isomers. Reduction of nitrile **71** with $LiAlH_4$ provided cyclopropylmethylamine **72** (Scheme 19). Finally, in 1978, McCullough and Lu performed copper-catalyzed cyclopropanation of cyclopentene **73** with diazoacetonitrile (**1**). The desired product **74** was obtained in 12% yield as an inseparable mixture of *cis* and *trans*-isomers (Scheme 19).[31]

In 1982, Doyle and van Leusen reported on the first Rh-catalyzed cyclopropanation of an alkene. Addition of a dry solution of diazoacetonitrile (**1**) in dichloromethane to a fivefold excess of styrene **75** in the presence of $Rh_2(OAc)_4$ (2 mol%) as catalyst over 30 min afforded cyclopropane **76** in 89% yield after distillation (Scheme 20).[32] Three years later, Dowd and co-workers mentioned a Rh-catalyzed cyclopropanation of alkene **77a**



Scheme 20. Rh-catalyzed cyclopropanation of alkenes with diazoacetonitrile (**1**).



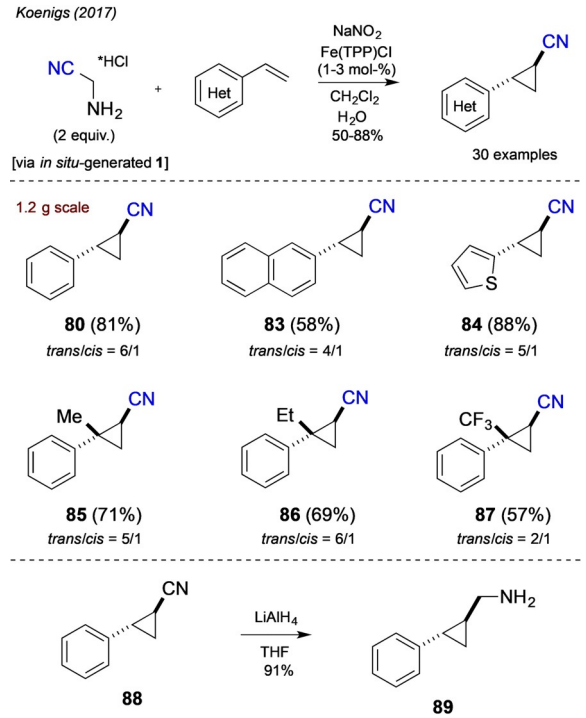
Scheme 21. Ru-catalyzed asymmetric cyclopropanation of styrenes with diazoacetonitrile (**1**).

with diazoacetonitrile (**1**) in 64% yield (**78a**). Nitrile **78a** was then reduced into amine **79**, however, no detailed experimental procedures were provided for both transformations (Scheme 20).[33] Similarly, Moss and Krogh-Jespersen reported on a $Rh_2(OAc)_4$-catalyzed cyanocyclopropanation, but again, no experimental details were provided.[34] Finally, in 2001, Doris and Mioskowski described the cyclopropanation of alkenes **77a–d** with diazoacetonitrile (**1**) using $Rh_2(OAc)_4$ as a catalyst. The corresponding products **78a–d** were obtained in 55–78% yield. More importantly, the authors also performed the first asymmetric cyclopropanation. When substrate **77c** was treated with diazoacetonitrile in the presence of catalytic amount of $Rh_2(5S\text{-MEPY})_4$, product **78c** was obtained predominantly as a *cis*-isomer in an enantiomeric excess (*ee*) of 66% (Scheme 20).[35]

In general, Rh-catalyzed cyclopropanations provided a practical route to cyanocyclopropanes in yields much higher than those reported for Cu-catalyzed reactions (Scheme 19). Also, it opened up a door to the optically active cyanocyclopropanes.

The only report on Ru-catalyzed cyclopropanation of alkenes with diazoacetonitrile (**1**) originates from Simonneaux' lab. In 2005, the authors treated three styrene derivatives with **1** in the presence of a chiral ruthenium porphyrin complex **79** to obtain cyanocyclopropanes **80–82** as an approximate 2:1-mixture of *trans*/*cis* isomers in up to 70% *ee* (Scheme 21). The enantioselectivity was even higher (up to 90% *ee*) when using ethyl diazoacetate (**2**).[36]

In 2017, Koenigs developed a powerful approach to cyanocyclopropanes from styrenes and in situ generated diazoacetonitrile (**1**) catalyzed by iron(III)-tetraphenylporphyrin complex, Fe(TPP)Cl (Scheme 22).[37] To minimize the formation of side products, the authors employed a slow-release protocol for the in situ generation of **1**. In particular, an addition of a solution of sodium nitrite in water to a stirred suspension of sty-



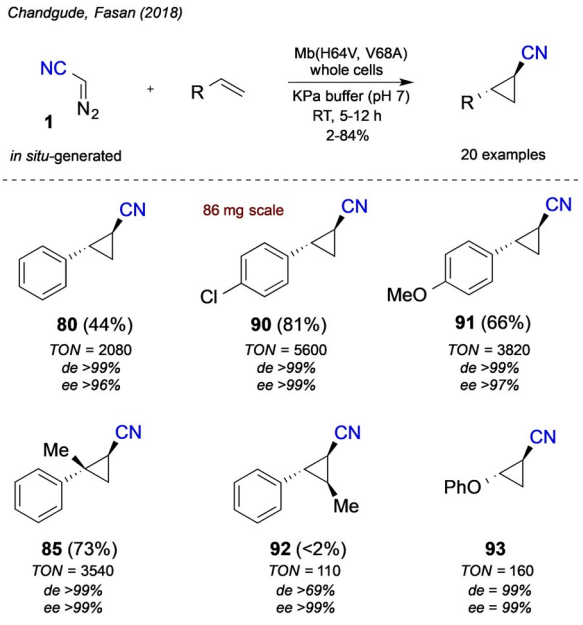
Scheme 22. Fe-catalyzed cyclopropanation of styrenes with diazoacetonitrile (**1**).

rene, amino acetonitrile hydrochloride, and Fe(TPP)Cl (1 mol-%) over 10 h resulted in the formation of cyanocyclopropane **80** in 81% yield. The scope of the reaction was also impressive because 30 diversely substituted cyclopropanes were synthesized (Scheme 22, **80**, **83**–**87**). In addition, one cyclopropene was also synthesized using Rh_2esp_2 (bis[rhodium(α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)]) as catalyst. The protocol was also scalable and the authors were able to perform the synthesis of cyclopropane **80** in 1.2 g scale with catalyst loadings as low as 0.03 mol%. In a representative application, nitrile **80** was next reduced into amine **89** (Scheme 22).

Given all the benefits described above, the "slow-release" protocol for cyclopropanation of styrenes with in situ generated **1** has indeed a high potential for large-scale industrial applications.

In 2018, Chandgude and Fasan developed an enantioselective cyclopropanation of alkenes with in situ generated diazoacetonitrile (**1**) in the presence of myoglobin enzyme Mb(H64V,V68A),[38] which was previously applied in the same transformation with ethyl diazoacetate (**2**). The reaction generally worked well for styrenes and tolerated the substitution at the phenyl ring (Scheme 23, **80**, **90**, **91**). The corresponding aryl cyclopropanes were obtained with excellent diastereoselectivity (>99%) and enantioselectivity (>99%). The reaction with disubstituted alkenes, however, had a narrower scope. For example, although product **85** was obtained in 73% yield, compound **92** was formed in less than 2% yield. Several electron-rich olefins, other than styrenes, were also used, but the reaction was less efficient (Scheme 23, **93**).

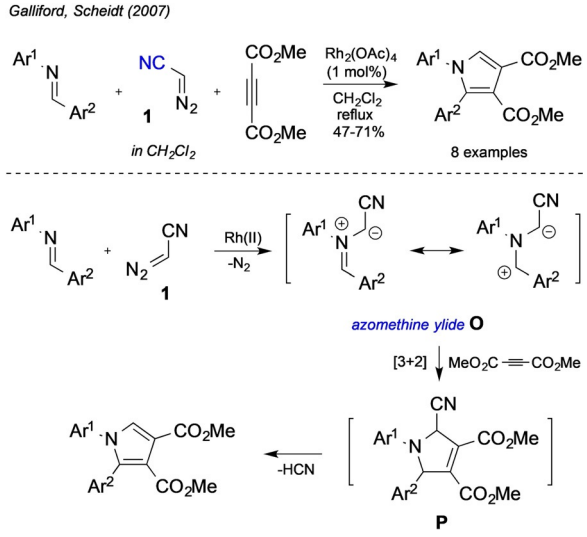
The cyclopropanation was performed on 10 mmol scale, but was also scaled up to 30 mmol for successful examples. For example, 86 mg of product **90** were isolated. The typical reactions of nitrile **90** were also performed (reduction into aldehyde, reduction into amine, hydrolysis into acid, etc.).



Scheme 23. Enantioselective myoglobin-catalyzed cyclopropanation of alkenes with diazoacetonitrile (**1**).

Carbene reactivity.

In 2007, Galliford and Scheidt developed a three-component synthesis of pyrroles from aromatic imines, diazoacetonitrile (**1**), and di(m)ethyl acetylenedicarboxylate catalyzed by $Rh_2(OAc)_4$ (Scheme 24).[39]

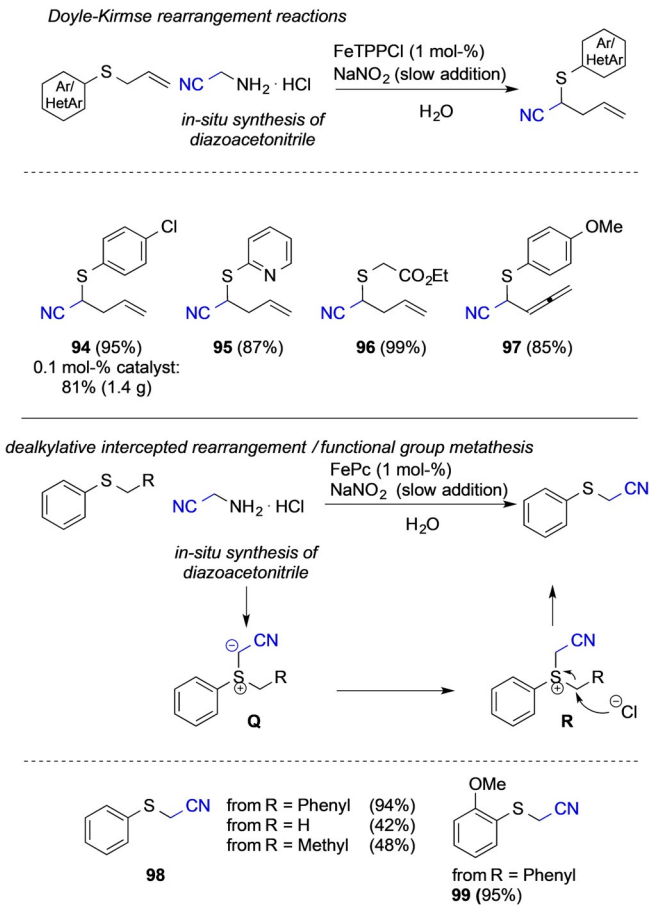


Scheme 24. Rh-catalyzed synthesis of pyrroles from aromatic imines, diazoacetonitrile (**1**), and dimethyl acetylenedicarboxylate.

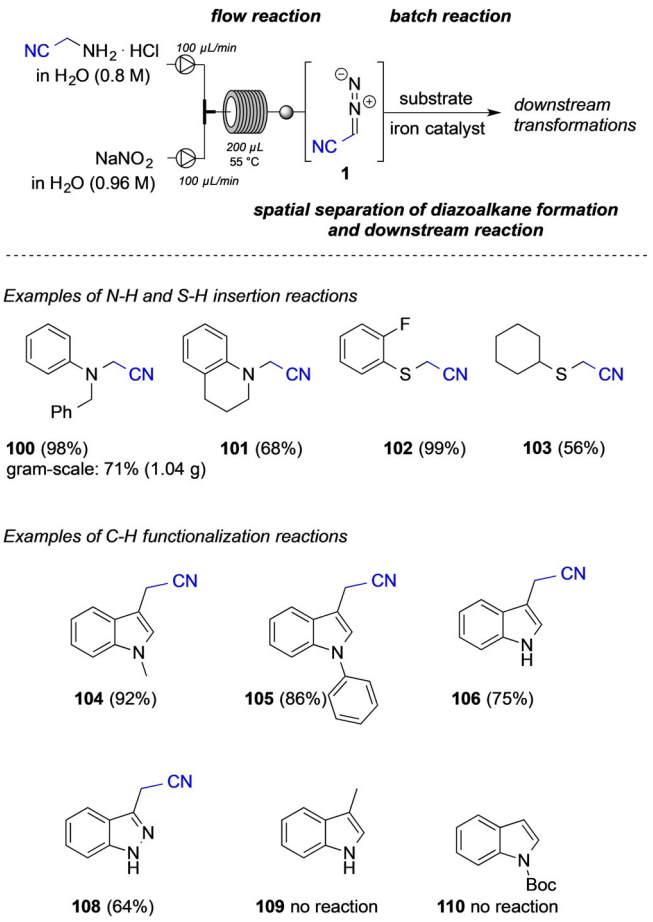
Mechanistically, diazoacetonitrile first reacted with an imine in the presence Rh^{II} to form azomethine ylide **O**, that participated in [3+2]-cycloaddition with dimethyl acetylenedicarboxylate into intermediate **P**. The later immediately underwent an aromatization with elimination of hydrogen cyanide to give the target pyrroles. Eight pyrroles were obtained; however, the reaction was strongly limited to aromatic imines and di(m)ethyl acetylenedicarboxylate. Other activated acetylenes, such as methyl propiolate, yielded no product; aliphatic imines did not react either.[39]

In 2017, the Koenigs group reported on further applications of the previously described slow-release protocol in iron-catalyzed rearrangement reactions. They described the carbene-transfer reaction of **1** with Fe(TPP)Cl in the presence of allylic and propargylic sulfides, which undergo a Doyle–Kirmse rearrangement reaction.[40] The desired reaction products of this rearrangement reaction are homoallylic or allenyl thiols, which were isolated in high yields (Scheme 25, **94**–**97**). Mechanistically, diazoacetonitrile is formed upon addition of sodium nitrite to the reaction solution and **1** is directly consumed by the iron catalyst under formation of an iron–carbene complex. Allylsulfide reacts with this complex under formation of a sulfur ylide, which subsequently rearranges under formation of the desired reaction product.

Recently, the Koenigs group followed up on this transformation and reported on dealkylative rearrangement reactions of benzylic sulfides (Scheme 25). Under the slow-release conditions, benzylic sulfides did not undergo the expected Stevens or Sommelet–Hauser rearrangements, but a rather unexpected



Scheme 25. Slow-release protocol for Doyle–Kirmse and dealkylative rearrangement reactions.



Scheme 26. Flow–batch protocols for X–H insertion and C–H functionalization reactions with diazoacetonitrile (**1**).

intercepted rearrangement reaction and formal dealkylation reaction occurred (Scheme 25, **98**–**99**). Mechanistically, this reaction was hypothesized to proceed through the formation of a sulfur ylide **Q** that, upon protonation, forms a sulfonium salt **R**. The latter can then undergo a nucleophilic-substitution reaction with chloride ions that are present in the reaction mixture (from the starting amino acetonitrile hydrochloride).[41]

Continuous-flow chemistry is an important tool to safely prepare highly reactive or explosive reagents like diazoalkanes.[42] In this context, the Koenigs group explored the flow synthesis of diazoacetonitrile and its application in X–H functionalization reactions. Amino acetonitriles are readily prepared by N–H functionalization and are a privileged motif in warheads of protease inhibitors.[43,44]

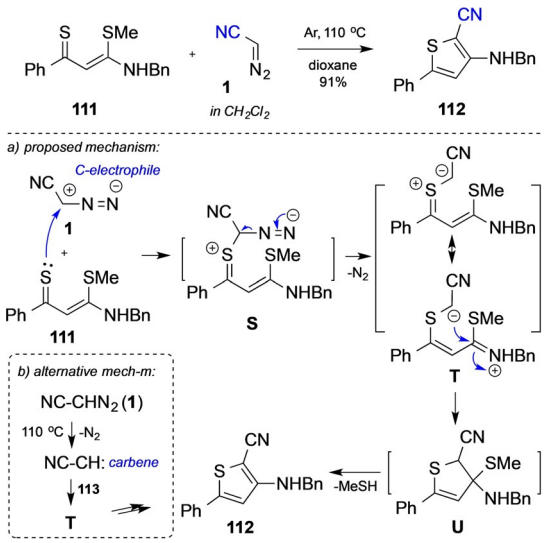
For this purpose, a flow–batch protocol was used that allowed for the spatial separation of the synthesis of diazoacetonitrile and the downstream X–H functionalization and thus prevent undesired side reactions of the reagents, such as secondary amines with sodium nitrite. Following this procedure, a range of different α-amino acetonitrile and α-sulfanyl acetonitrile derivatives were synthesized in high yields (Scheme 26).[4]

The direct C–H functionalization of indole heterocycles with diazoacetonitrile provides a highly efficient access to privileged tryptamines that are found in neurotransmitters and in anticancer drugs and that are important reagents in the total synthesis of alkaloids. Bearing this background in mind, the Koenigs group studied the C–H functionalization of indole with diazoacetonitrile using the previously described flow–batch protocol. This approach proved highly versatile and both protected and unprotected indole heterocycles reacted to the desired tryptamine precursors in excellent yield, using Fe(TPP)Cl as catalyst (Scheme 26). Notably, no reaction was observed when blocking the 3-position of the indole heterocycle or when using electron-withdrawing protecting groups at the indole nitrogen. Control experiments indicate the participation of radicals in this reaction.[45]

Miscellaneous.

In 2018, Yu and co-workers studied a formal [4+1]-cycloaddition reaction between diazo compounds and enaminothiones.[46] Diazo compounds were generated mostly in one-pot fashion from the corresponding tosylhydrazones and *t*BuOLi under Bamford–Stevens conditions.

In this report, the authors also studied individual diazo compounds, for example the reaction of a dry solution of diazoacetonitrile (**1**) with **111** in dioxane at 110 °C led to formation of cyanothiophene **112** in 91% yield (Scheme 27). The authors



Scheme 27. Synthesis of thiophene **112** from diazoacetonitrile (**1**) and enaminothione **111**.

suggested a mechanism in which the sulfur atom of **111** attacked the central carbon atom of **1** to form intermediate **S**. It is important to mention that this elementary step represents a categorically novel type of reactivity of diazoacetonitrile: as a C-electrophile. The loss of nitrogen in **S** leads to another intermediate **T**. Intramolecular ring closure of **R** gives dehydrothiophene **U** that rapidly eliminates CH_3SH to afford the aromatic thiophene **112**. It should also be noted that an alternative mechanism for the formation of intermediate **T** could also be possible: under high temperature, diazoacetonitrile (**1**) might slowly decompose into cyanocarbene (NC–CH:) which could further react with compound **111** to give the key intermediate **T**.

Summary

Although diazoacetonitrile was discovered over 120 years ago, applications of this particularly useful diazoalkane remained scarce. In contrast to its close analogue ethyl diazoacetate, diazoacetonitrile found only little interest in synthetic chemistry, which might be in part related to the high risks associated with diazoacetonitrile. However, over the past 4 years, important progress for the safe access of this diazoalkane has been made and several recent reports showcase its potential. Prominently, two protocols, i) the in situ generation and ii) the flow synthesis of diazoacetonitrile, mark important advances and now open up chemical applications of diazoacetonitrile.

Acknowledgements

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—project no. 408033718. R.M.K. gratefully thank the Fonds der Chemischen Industrie for generous support (Sachkostenbeihilfe). P.K.M. is grateful to Prof. A. Tolmachev for the financial support of this project.

Conflict of interest

The authors declare no conflict of interest.

Keywords: cyano · cycloaddition · diazo compounds · diazoacetonitrile · heterocycles

[1] T. Curtius, *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2489 – 2492.
[2] a) T. Curtius, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2230 – 2231; b) T. Curtius, *J. Prakt. Chem.* **1888**, 396 – 440.
[3] a) H. Heydt in *Science of Synthesis 27: Category 4. Compounds with Two Carbon Heteroatom Bonds* (Eds.: A. Padwa, D. Bellus), Thieme, Stuttgart, **2005**; b) N. R. Candeias, R. Paterna, P. M. P. Gois, *Chem. Rev.* **2016**, *116*, 2937 – 2981; c) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417 – 424; d) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981 – 10080; e) .M. P. Doyle, R. Duffy, M. Ratnikov, Z. Zhou, *Chem. Rev.* **2010**, *110*, 704 – 724; f) O. F. Brandenberg, R. Fasan, F. H. Arnold, *Curr. Opin. Biotechnol.* **2017**, *47*, 102 – 111; g) K. J. Hock, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2017**, *56*, 13566 – 13568; *Angew. Chem.* **2017**, *129*, 13752 – 13754; h) C. Empel, R. M. Koenigs, *Synlett* **2019**, *30*, 1929 – 1934.
[4] a) H. Gilman, R. G. Jones, *J. Am. Chem. Soc.* **1943**, *65*, 1458 – 1460; for a review on fluorinated diazoalkanes see: b) L. Mertens, R. M. Koenigs, *Org. Biomol. Chem.* **2016**, *14*, 10547 – 10556 and references cited therein.
[5] a) D. Seyferth, R. S. Marmor, P. Hilbert, *J. Org. Chem.* **1971**, *36*, 1379 – 1386; b) J. C. Gilbert, U. Weerasooriya, *J. Org. Chem.* **1982**, *47*, 1837 – 1845; c) S. Ohira, *Synth. Commun.* **1988**, 561 – 564; d) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521 – 522.
[6] a) P. Mykhailiuk, *Chem. Eur. J.* **2014**, *20*, 4942 – 4947; b) P. Mykhailiuk, *Beilstein J. Org. Chem.* **2015**, *11*, 16 – 24; c) P. K. Mykhailiuk, A. Y. Ishchenko, V. Stepanenko, J. Cossy, *Eur. J. Org. Chem.* **2017**, 5485 – 5493; d) P. K. Mykhailiuk, *Org. Biomol. Chem.* **2015**, *13*, 3438 – 3445; e) P. K. Mykhailiuk, *Org. Biomol. Chem.* **2017**, *15*, 7296 – 7301.
[7] a) P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2015**, *54*, 6558 – 6561; *Angew. Chem.* **2015**, *127*, 6658 – 6661; b) L. Mertens, K. J. Hock, R. M. Koenigs, *Chem. Eur. J.* **2016**, *22*, 9542 – 9545; c) K. J. Hock, L. Mertens, R. M. Koenigs, *Chem. Commun.* **2016**, *52*, 13783 – 13786; d) J. Li, X.-L. Yu, J. Cossy, S.-Y. Lv, H.-L. Zhang, F. Su, P. K. Mykhailiuk, Y. Wu, *Eur. J. Org. Chem.* **2017**, 266 – 270; e) P. K. Mykhailiuk, I. Kishko, V. Kubyshkin, N. Budisa, J. Cossy, *Chem. Eur. J.* **2017**, *23*, 13279 – 13283; f) P. K. Mykhailiuk, R. M. Koenigs, *Chem. Eur. J.* **2019**, *25*, 6053 – 6063.
[8] P. Mykhailiuk, *Eur. J. Org. Chem.* **2015**, 7235 – 7239.
[9] C. Empel, K. J. Hock, R. M. Koenigs, *Org. Biomol. Chem.* **2018**, *16*, 7129 – 7133.
[10] F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902 – 7917.
[11] M. J. S. Dewar, R. Pettit, *J. Chem. Soc.* **1956**, 2026 – 2029.
[12] S. H. Harper, K. C. Sleep, *J. Sci. Food Agric.* **1955**, *6*, 116 – 120.
[13] D. D. Phillips, W. C. Champion, *J. Am. Chem. Soc.* **1956**, *78*, 5452.
[14] a) C. D. Weis, *J. Org. Chem.* **1962**, *27*, 3695 – 3696; b) H. Markusson, S. Béranger, P. Johansson, M. Armand, P. Jacobsson, *J. Phys. Chem. A* **2003**, *107*, 10177 – 10183.
[15] F. Roelants, A. Bruylants, *Tetrahedron* **1978**, *34*, 2229 – 2232.
[16] N. Ikuma, Y. Susami, T. Oshima, *Org. Biomol. Chem.* **2010**, *8*, 1394 – 1398.
[17] a) T. Suzuki, Q. Li, K. C. Khemani, F. Wudl, *J. Am. Chem. Soc.* **1992**, *114*, 7301 – 7302; b) A. B. Smith, A. B. Strongin, L. Brard, G. T. Furst, W. J. Romanow, *J. Am. Chem. Soc.* **1993**, *115*, 5829 – 5830; c) Y. Nakamura, K. Inamura, R. Oomuro, R. Laurenco, T. T. Tidwell, J. Nishimura, *Org. Biomol. Chem.* **2005**, *3*, 3032 – 3038.
[18] a) Z. Chen, Y. Zhang, J. Nie, J.-A. Ma, *Org. Lett.* **2018**, *20*, 2120 – 2124; b) Y. Zhang, Z. Chen, J. Nie, F.-G. Zhang, J.-A. Ma, *J. Org. Chem.* **2019**, *84*, 7148 – 7158.
[19] X. Peng, X. Zhang, S. Li, Y. Lu, L. Lan, C. Yang, *Org. Chem. Front.* **2019**, *6*, 1775 – 1779.
[20] J. Hooz, S. Linke, *J. Am. Chem. Soc.* **1968**, *90*, 6891 – 6892.
[21] W. L. Mock, M. E. Hartman, *J. Org. Chem.* **1977**, *42*, 459 – 465.

[22] Z. Yang, K.-I. Son, S. Li, B. Zhou, J. Xu, *Eur. J. Org. Chem.* **2014**, 6380 – 6384.
[23] U. Schöllkopf, P. Tonne, H. Schaefer, P. Markusch, *Liebigs Ann. Chem.* **1969**, *722*, 45 – 51.
[24] a) P. E. O'Bannon, W. P. Dailey, *Tetrahedron Lett.* **1989**, *30*, 4197 – 4200; b) P. E. O'Bannon, W. P. Dailey, *Tetrahedron* **1990**, *46*, 7341 – 7358.
[25] V. A. Bakulev, Y. Y. Morzerin, Y. Y. Shafran, V. S. Mokrushin, *ARKIVOC* **2002**, *8*, 166 – 179.
[26] a) A. V. Arkhipov, V. V. Arkhipov, J. Cossy, V. O. Kovtunenko, P. K. Mykhailiuk, *Org. Lett.* **2016**, *18*, 3406 – 3409; b) R. Guo, Y. Zheng, J.-A. Ma, *Org. Lett.* **2016**, *18*, 4170 – 4173.
[27] K. Harada, Y. Mori, M. Nakai, *Heterocycles* **1997**, *44*, 197 – 201.
[28] F.-G. Ma, J.-L. Zeng, Y.-Q. Tian, Y. Zheng, D. Cahard, J.-A. Ma, *Chem. Eur. J.* **2018**, *24*, 7749 – 7754.
[29] For detailed characterization of cyanocarbene, see: G. Maier, H. P. Reisenauer, K. Rademacher, *Chem. Eur. J.* **1998**, *4*, 1957 – 1963.
[30] D. Witiak, M. C. Lu, *J. Org. Chem.* **1970**, *35*, 4209 – 4217.
[31] J. J. McCullough, C. Manning, *J. Org. Chem.* **1978**, *43*, 2839 – 2841.
[32] M. P. Doyle, D. van Leusen, *J. Org. Chem.* **1982**, *47*, 5326 – 5338.
[33] P. Dowd, C. Kaufman, Y. H. Paik, *Tetrahedron Lett.* **1985**, *26*, 2283 – 2286.
[34] R. Moss, F. Zheng, K. Krogh-Jespersen, *Org. Lett.* **2001**, *3*, 1439 – 1442.
[35] a) E. Doris, A. Wagner, C. Mioskowski, *Tetrahedron Lett.* **2001**, *42*, 3183 – 3185; b) F.-X. Felpin, E. Doris, A. Wagner, A. Valleix, B. Rousseau, C. Mioskowski, *J. Org. Chem.* **2001**, *66*, 305 – 308.
[36] Y. Ferrand, P. Le Maux, G. Simonneaux, *Tetrahedron: Asymmetry* **2005**, *16*, 3829 – 3836.
[37] K. J. Hock, R. Spitzner, R. M. Koenigs, *Green Chem.* **2017**, *19*, 2118 – 2122.
[38] A. L. Chandgude, R. Fasan, *Angew. Chem. Int. Ed.* **2018**, *57*, 15852 – 15856; *Angew. Chem.* **2018**, *130*, 16078 – 16082.
[39] C. V. Galliford, K. A. Scheidt, *J. Org. Chem.* **2007**, *72*, 1811 – 1813.
[40] K. J. Hock, L. Mertens, R. Hommelsheim, R. Spitzner, R. M. Koenigs, *Chem. Commun.* **2017**, *53*, 6577 – 6580.
[41] C. Empel, K. J. Hock, R. M. Koenigs, *Chem. Commun.* **2019**, *55*, 338 – 341.
[42] K. J. Hock, R. M. Koenigs, *Chem. Eur. J.* **2018**, *24*, 10571 – 10583.
[43] a) A. J. Cooke, D. Pitts, A. Johnson, D. C. Beshore, D. Hurzy, H. Mitchell, M. Fraley, C. McComas, K. Schirripa, S. P. Mercer, K. Nanda, D. Meng, J. Wu, K. Babaoglu, C.-S. Li, Q. Mao, Z. Qi, PCT Int. Appl. WO 2016054807, **2016**; b) A. M. Winter-Vann, R. A. Baron, W. Wong, J. de la Cruz, J. D. York, D. M. Gooden, M. O. Bergo, S. G. Young, E. J. Toone, P. J. Casey, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 4336 – 4341; c) M.-L. Go, J. L. Leow, S. K. Gorla, A. P. Schüller, M. Wang, P. J. Casey, *J. Med. Chem.* **2010**, *53*, 6838 – 6850; d) K. Fukunaga, F. Han, N. Shioda, S. Moriguchi, J. Kasahara, Y. Shirasaki, *Cardiovasc. Ther.* **2006**, *24*, 88; e) A. Tsotinis, M. Vlachou, D. P. Papahatjis, T. Calogeropoulou, S. P. Nikas, P. J. Garratt, V. Piccio, S. Vonhoff, K. Davidson, M.-T. Teh, D. Sugden, *J. Med. Chem.* **2006**, *49*, 3509 – 3519.
[44] a) V. V. Kouznetsov, G. E. P. Galvis, *Tetrahedron* **2018**, *74*, 773 – 810; b) J. Pedersen, C. Lauritzen, PCT Int. Appl. WO 2012130299, **2012**.
[45] K. J. Hock, A. Knorrscheidt, R. Hommelsheim, J. Ho, M. J. Weissenborn, R. M. Koenigs, *Angew. Chem. Int. Ed.* **2019**, *58*, 3630 – 3634; *Angew. Chem.* **2019**, *131*, 3669 – 3673.
[46] Z. Liu, P. Wu, Y. He, T. Yang, Z. Yu, *Adv. Synth. Catal.* **2018**, *360*, 4381 – 4392.

Manuscript received: July 22, 2019
Accepted manuscript online: August 15, 2019
Version of record online: October 15, 2019

