Diazo Compounds

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Safe and Facile Access to Nonstabilized Diazoalkanes Using Continuous Flow Technology

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Abstract: *Despite the high synthetic potential of nonstabilized diazo compounds, their utilization has always been hampered by stability, toxicity, and safety issues. The present method opens up access to the most reactive nonstabilized diazoalkanes. Among diazo compounds, nonstabilized alkyl diazo compounds are the least represented because of their propensity to degrade during preparation. The continuous flow oxidation process of hydrazones on a silver oxide column afforded an output stream of base- and metal-free pure diazo solution in dichloromethane. Starting from innocuous ketones and aldehydes, this methodology allows the production of a broad range of unprecedented diazoalkanes compounds in excellent yields, while highlighting their synthetic potential and the possibility of safe large-scale diazo production.*

Diazo compounds are a powerful and versatile class of reagents in organic synthesis,[1] as they are precursors of either highly reactive carbenes, carbenoids, or carbocations, thus enabling formal C–H, C–C, and C–X bond insertions as well as various cycloadditions.[2] However, the sensitivity, explosivity,[3] and toxicity[4] of this species remain huge drawbacks, thus hindering their common use in laboratories, especially on large scale. By limiting handling, precisely controlling reaction conditions, and avoiding diazo accumulation by its simultaneous consumption, continuous flow technology provides the ideal solution to tackle such issues.[5] In recent years, continuous flow has proven helpful at enabling safe production of a wide range of stabilized diazo compounds.[6] While tremendous progress has recently been made with the production of diazomethane[7] and aryldiazomethanes,[8] syntheses of donor-type diazo reagents bearing at least one alkyl substituent remain scarce (Figure 1).[9]

Diazoalkanes with electron-donating substituents distinguish themselves by an intrinsic nucleophilicity and basicity, leading to high reactivity, even under mild reaction conditions. Compared to electron-rich diazoalkanes with aromatic substituents, diazo compounds bearing alkyl groups are the least stable of their kind.[10] Furthermore, the few previously reported procedures for preparation of nonstabilized mono- and bisalkyl diazoalkanes were found to be operationally difficult and/or required toxic heavy metals.[11] In their seminal work, Applequist and Babad reported the use of silver oxide, thus affording 2-diazopropane in a low 20–30% yield because of the in situ degradation during synthesis and tedious purification.[12] In addition to limited scope, these previous methods require the presence of a base, a soluble/toxic oxidant, and either handling of the toxic diazo compound for purification or in situ quench of the generated diazoalkane.[13]

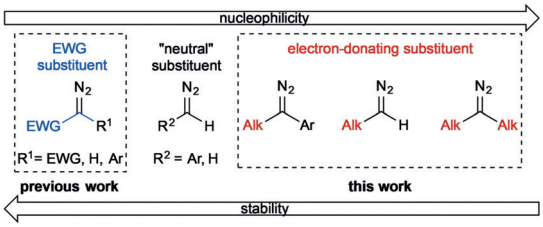
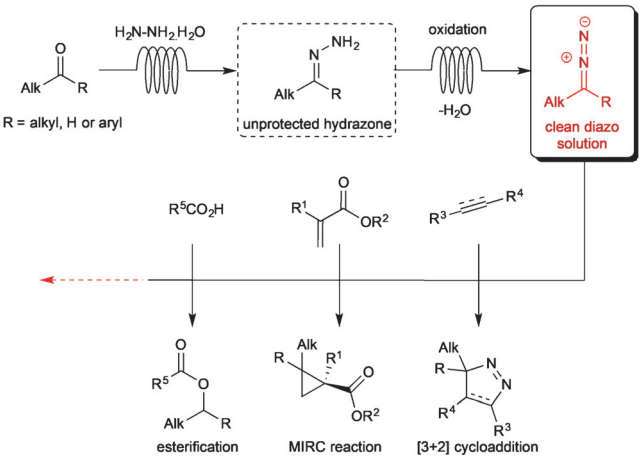


Figure 1. Relative stability of diazo compounds.[1,10]. EWG = electron-withdrawing group.

We envisioned that continuous flow systems would overcome the three main drawbacks of nonstabilized diazoalkanes synthesis: 1) precise control of the production conditions, thus limiting degradation; 2) easy purification by the use of insoluble solid reagents, thus circumventing the handling of the diazo solution; and 3) on-demand direct consumption of the reactive materials at the output of the reactor, thus avoiding the risks associated with storage of toxic and unstable reagents (Scheme 1).

Free hydrazones, common precursors to diazo compounds, are safe, relatively stable, and easy to handle.[14] Yet, their synthesis requires the use of super-stoichiometric



Scheme 1. Continuous flow strategy towards on-demand generation of nonstabilized diazoalkanes.

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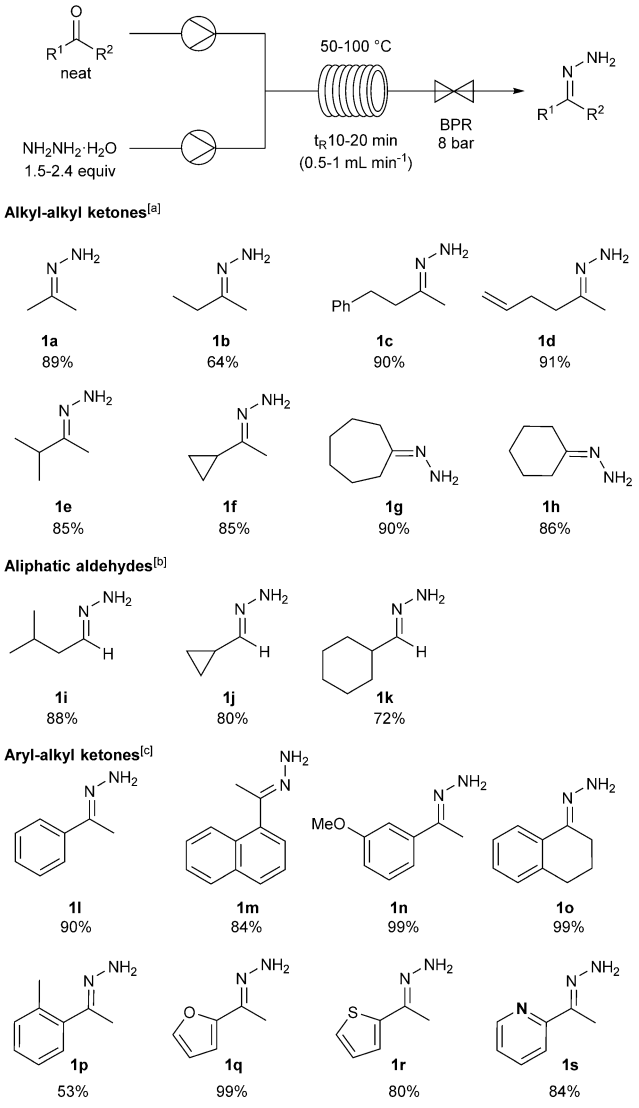
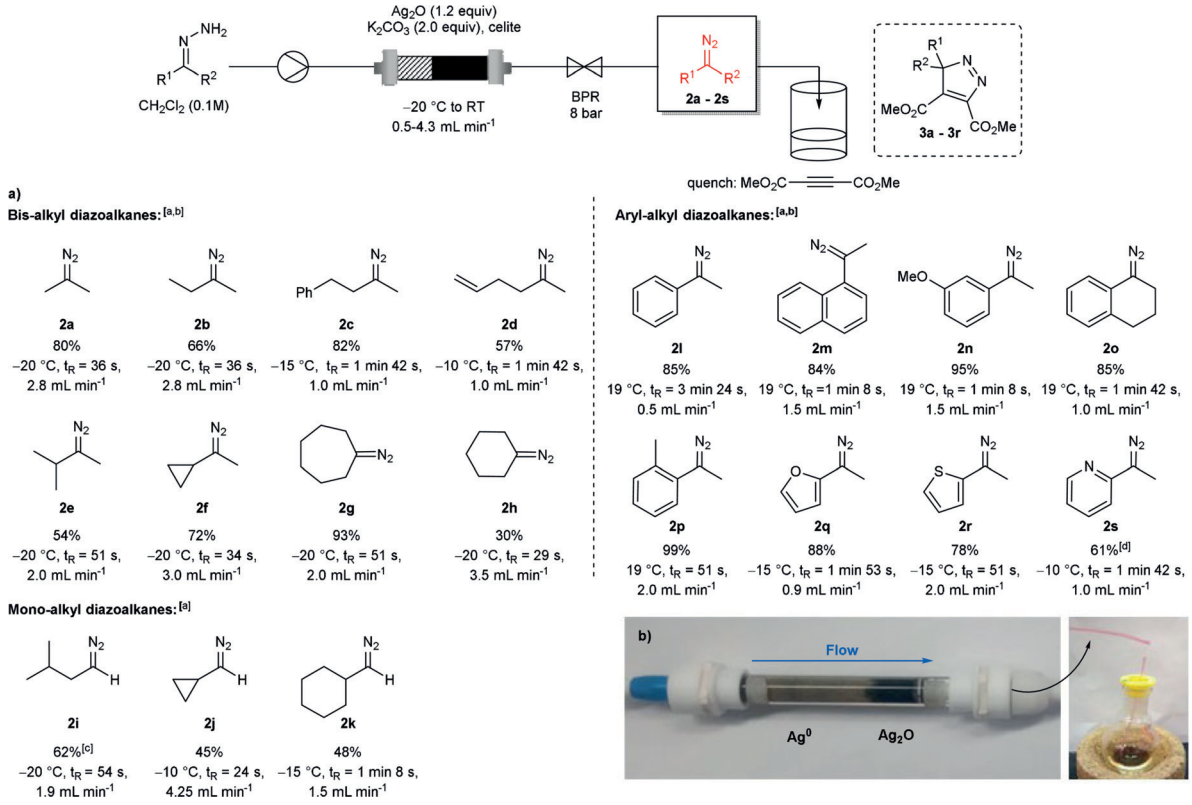
amounts of hydrazine, high temperatures, as well as long reaction times.[11a,15] In addition, dimerization of hydrazones into the corresponding azine is often observed. Continuous flow synthesis allowed the use of milder and greener reaction conditions. Indeed, fast heat transfer and precise stoichiometry in a pressurized system allowed full conversion of a broad range of aliphatic ketones and aldehydes into their corresponding hydrazones in 10 to 20 minutes with only 1.5–2.4 equivalents of hydrazine monohydrate and minimized formation of the azine by-product (Scheme 2). Hydrazones derived from ketones (**1a**–**h**) are produced neat in excellent yields within 10 minutes of residence time at 100 °C. Aldehydes (**1l**–**k**), on the other hand, require milder reaction conditions ($T_{reactor} = 50$ °C). Because of the solubility issues, aryl-alkyl hydrazones (**1l**–**s**) were prepared using ethanol (5 M).



Scheme 2. Continuous flow synthesis of hydrazones from aliphatic ketones, aliphatic aldehydes, and electron-rich aryl ketones. Yields correspond to the unpurified products after work-up on a 12-mmol scale. THF is used as the carrier solvent. Reaction conditions: [a] Neat, 10 min, 100 °C, 1.5 equiv hydrazine monohydrate. [b] Neat, 10 min, 50 °C, 1.5 equiv hydrazine monohydrate. [c] EtOH (5 M), 20 min, 100 °C, 2.4 equiv hydrazine monohydrate.

After a simple work-up, these hydrazones were directly used in the oxidation step toward diazoalkanes formation. While many oxidizing reagents have been tested,[16] the combined basicity and oxidative ability of silver oxide (Ag_2O) already proved to be sufficiently reactive to generate unstable diazoalkanes.[12,17] However, low yields were obtained because of degradation of the freshly formed diazo on Ag^I and reduced Ag^0, as well as during the long and tedious purification processes. It was anticipated that a continuous process using a column packed with Ag_2O at controlled low temperature would overcome degradation of the formed diazo by minimizing contact between the diazo and Ag_2O/Ag^0, which strongly catalyzed its decomposition.[12]

Initial investigations focused on dimethyl hydrazone (**1a**) as a model substrate for the generation of 2-diazopropane (**2a**). To quantify the generation of the transient diazo species, the output stream was added to dimethyl acetylenedicarboxylate, thus yielding the corresponding [3+2]-cycloadduct **3a** (Scheme 3).[18] When the reaction was conducted at room temperature, regardless of the residence time (from 34 min to 13 s), an output of a colorless flow mixed with a large volume of gas was observed, and full conversion of **1a** was obtained, thus indicating **2a** degradation on the column. Lowering the temperature (−20 °C) and shortening the residence time (36 s) resulted in a red-colored output stream, thus giving evidence of diazo formation. As shown by the progressive reduction of the Ag_2O column (Scheme 3b), the stationary oxidant phase was stable, and stoichiometry could be adjusted to 1.2 equivalents of Ag_2O without any detrimental impact on the yield of the desired diazo.[16] To generate water-free solutions of diazo, 2 equivalents of anhydrous K_2CO_3 were premixed with the silver oxide along with oven-dried celite used as filling agent.[16] While diethyl ether was tolerated as a solvent, noncoordinating dichloromethane, besides offering great advantage in the context of reaction development and catalyst discovery, produced a more stable diazo solution.[16] A concentration of 0.1 M was found to be optimal since, under higher concentration, dimerization was observed as a degradation process. We then explored the general application of this process to oxidation of the previously prepared hydrazone derivatives into diazoalkanes by adjusting column temperature and residence time for each substrate (Scheme 3a). Bisalkyl diazoalkanes (**2a**–**h**) were produced in good yields as bright-red solutions. The diazoalkanes production tolerated alkenes (**2d**) and sterically hindered centers (**2e**–**f**) as well as cyclic substrates (**2g**–**h**). The cyclic diazo **2h** was produced in lower yield because of its especially high instability. Hydrazones derived from aldehydes were also oxidized into diazoalkanes under similar reaction conditions, thus producing more stable yellow solutions of monoalkyl diazoalkanes (**2i**–**k**). Moderate yields reflect the instability of aldehyde-derived hydrazones compared to ketone-derived ones.[16] The reaction was also compatible with aryl-alkyl hydrazones and afforded the corresponding aryl-alkyl diazoalkanes (**2l**–**s**) in good to excellent yields as purple-red solutions. As electron-neutral aryl-alkyl diazo compounds are more stable, **2l**–**p** were obtained at higher temperature



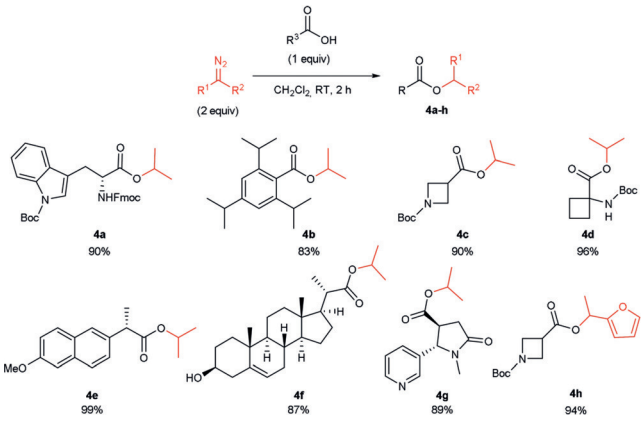
Scheme 3. Continuous flow synthesis of diazoalkanes by oxidation of free hydrazones on a silver oxide column. [a] Reactions were run on a 1.4-mmol scale in a 1.7 mL packed column; diazoalkanes were obtained as a ≈0.1 M solution in CH_2Cl_2. Temperatures, residence times, and flowrates on the Ag_2O column are given. [b] Yield based on the isolated [3+2] adduct **3** with dimethyl acetylenedicarboxylate. [c] Yield based on the esterification product **3i** with benzoic acid. [d] Yield based on the electrocyclization adduct **3s**.

without degradation. In contrast, electron-rich aryl-alkyl diazo compounds (**2q**, **2r**) were generated at −15 °C because of their instability. Finally, the diazoalkane **2s** immediately reacted in an intramolecular cycloaddition producing triazole **3s**.

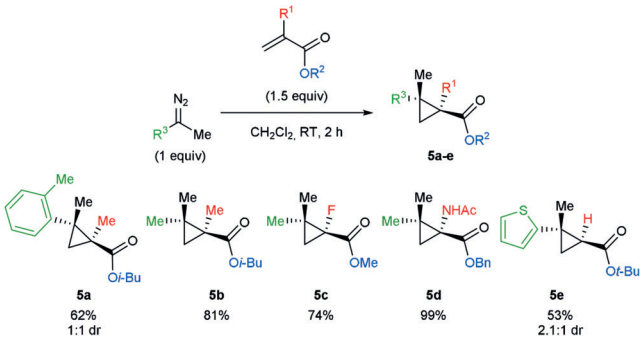
This safe and easy production of unstabilized diazoalkanes enabled the exploration of the synthetic potential of these highly reactive species by directly using them in reactions with suitable partners, thus providing access to a new chemical space. We first investigated esterification of various carboxylic acids (Scheme 4). **2a** reacted quantitatively with various complex carboxylic acids. Indole (**4a**), protected amines (**4a**, **4c**,**d**), free alcohol (**4f**), amide (**4g**) and pyridine substitution (**4g**) were tolerated and afforded the alkylated products in good to excellent yields. The reaction also proceeded efficiently with furyl-2-diazoethane thus producing (**4h**). Access to pure diazoalkane solutions opens the door to using this high-yielding, mild, chemoselective, and by-product-free reaction for esterification at room temperature.

Because of the diazoalkanes' enhanced nucleophilicity, we envisaged that they could be good partners in Michael-induced ring-closure (MIRC) reactions with α,β-unsaturated carbonyls. This one-step transformation proceeded in good yields in the presence of various Michael acceptors, thus producing highly substituted cyclopropanes (Scheme 5). The *gem*-dimethyl cyclopropane motif, for instance, is of particular interest in the pharmaceutical industry, and versatile methods for preparation of this building block are lacking.[19] Applying the MIRC reaction to **2a** on functionalized targets smoothly inserted the *gem*-dimethyl cyclopropane in complex structures (**5b–d**). Conversely, the diazoalkanes **2p** and **2r** afforded the cyclopropanes **5a** and **5e**, respectively, in moderate yields and as a mixture of diastereomers.

The practical diazoalkane production process also allowed us to screen suitable alkynes and alkenes as [3+2]



Scheme 4. Esterification with nonstabilized diazoalkanes. Reactions were performed on a 0.27 mmol diazo scale (2.67 mL at ≈0.1 M in CH_2Cl_2). Yields of isolated products are reported.



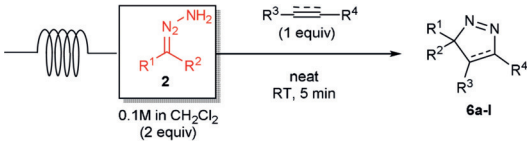
Scheme 5. MIRC reaction with nonstabilized diazoalkanes. Reactions were performed on a 0.27 mmol diazo scale (2.67 mL at ≈0.1 M in CH_2Cl_2). Yields of isolated products are reported and d.r. values were measured by ^{1}H NMR analysis of the crude reaction mixture.

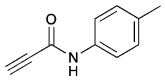
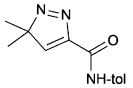
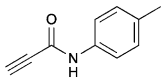
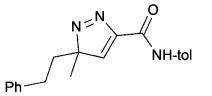
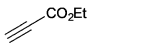
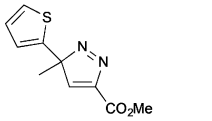
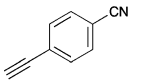
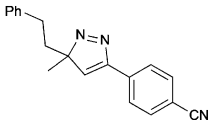
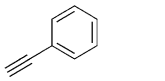
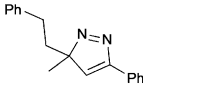
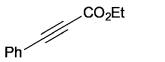
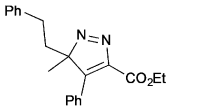
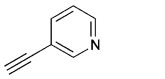
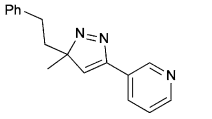
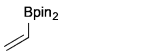
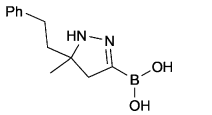
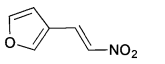
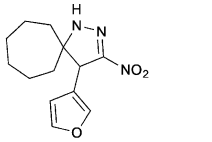
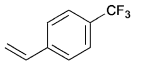
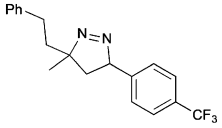
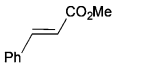
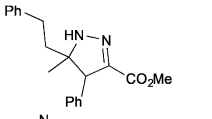
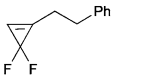
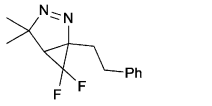
cycloaddition partners to produce a large variety of pyrazolenines and pyrzolines. The stream of diazoalkane quickly reacted at room temperature with a variety of unsaturated substrates and provided a broad range of functionalized pyrazolines in good yields (Table 1). This extremely fast and mild reaction tolerated α,β-unsaturated alkynes as well as aromatic ones (**6a**–**g**). Electron-poor alkenes were also tolerated, thus providing the corresponding 2-pyrazoline after isomerization (entries 8, 9, and 11). Notably, it reacted with vinyl boronate ester to afford the uncommon 2-pyrazoline boronic acid **6h** upon deprotection during purification. Remarkably, **2a** reacted with difluorocyclopropene to produce a unique difluoro fused bicycle **6l** in quantitative yield (entry 12). This last cycloaddition attests to the high reactivity of diazoalkanes, as this is the first nucleophilic addition on a difluorocyclopropene ever reported.

Pyrazolenines are intrinsically interesting motifs, but they are, above all, key precursors to cyclopropenes upon release of nitrogen. Photochemical rearrangement of pyrazolenines into the corresponding cyclopropene was realized under UVA-irradiation in continuous flow to afford the spirocyclopropene derivatives **7a** and **7b** in only 3 hours (Scheme 6a). The suitability of the method for safe and convenient large-scale production of unstabilized diazoalkanes was demonstrated with the production of 8.5 mmol of the furan diazo compound **2q** over 60 minutes, and it was consumed in line in a [3+2] cycloaddition (Scheme 6b). Finally, a telescoped continuous process including the synthesis of **1a** and its oxidation into 2-diazopropane **2a** was developed to yield 50% of the desired [3+2] adduct **3a**.[16]

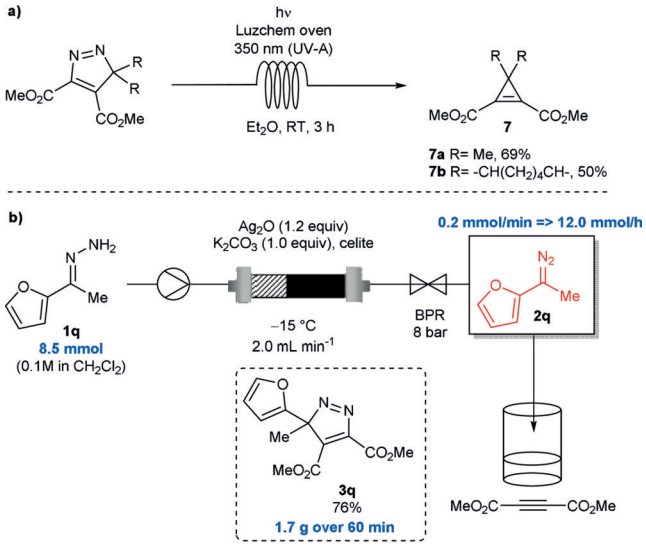
In conclusion, we described an unprecedented safe and scalable source of highly reactive alkyl diazoalkanes. Starting from commercially available ketones or aldehydes, free hydrazone precursors were efficiently produced in a continuous flow process, and allowed the reduction of excess hydrazine and reaction time. Oxidation on immobilized, nontoxic, and relatively cheap silver oxide circumvent all the stability issues of diazo compounds on reduced metals. This method has the potential to afford a daily production of several grams (ca. 100–200 mmol) of mono- and bisalkyl diazoalkanes. The output stream of diazoalkanes in dichloro-

Table 1: [3+2] Cycloaddition of alkenes and alkynes with nonstabilized diazoalkanes.[a]



Entry	Subtrate	Adduct	6	Yield [%][b]
1			**6a**	93
2			**6b**	84
3			**6c**	65
4			**6d**	55
5			**6e**	63
6			**6f**	55[c]
7			**6g**	34
8			**6h**	62
9			**6i**	75
10			**6j**	76[d]
11			**6k**	58[e]
12			**6l**	99

[a] Reactions were run on a 0.16 mmol scale. [b] Yield of product isolated after two steps from hydrazone. [c] 38% of regioisomer was observed. [d] Product was obtained as a mixture of diastereoisomers: d.r. 45:55. [e] Product was obtained as a mixture of diastereoisomers: d.r. 47:53.



Scheme 6. a) Photochemical conversion of 1-pyrazolenines into cyclopropenes. b) Scale-up synthesis of a furyl-alkyl diazoalkane.

methane is clean and base-free, thereby allowing subsequent transformations such as esterification, MIRC cyclopropanation, and [3+2] cycloaddition. Continuous flow technology applied to diazo chemistry provides an unprecedented versatility in the production of nonstabilized diazoalkanes, and it will, we believe, unleash their full synthetic potential.

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Conflict of interest

The authors declare no conflict of interest.

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[1] M. Regitz, G. Maas, *Diazo Compounds*, Academic Press, New York, **1986**, pp. 3–64.
[2] a) M. P. Doyle, M. A. McKervey, Y. Tao, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley-VCH, Weinheim, **1998**, pp. 1–65; b) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981–10080; c) K. A. Mix, M. R. Aronoff, R. T. Raines, *ACS Chem. Biol.* **2016**, *11*, 3233–3244.
[3] a) T. J. de Boer, H. J. Backer, *Org. Synth.* **1956**, *36*, 16–18; b) T. Sammakia, *Encyclopedia of Reagents for Organic Synthesis*, Wiley, Hoboken, **2001**, pp. 1–7; c) C. D. Gutsche, *Org. React.* **2004**, 364–430.
[4] a) E. B. Lewinn, *Am. J. Med. Sci.* **1949**, *218*, 556–562; b) R. Schoental, *Nature* **1960**, *188*, 420–421; c) C. E. Lewis, *J. Occup. Environ. Med.* **1964**, *6*, 91–92; d) P. A. Bray, R. K. Sokas, *J. Occup. Environ. Med.* **2015**, *57*, 15–16.
[5] a) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688–6728; *Angew. Chem.* **2015**, *127*, 6788–6832; b) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V. Ley, C. V. Stevens, *Chem. Soc. Rev.* **2016**, *45*, 4892–4928.
[6] a) B. J. Deadman, S. G. Collins, A. R. Maguire, *Chem. Eur. J.* **2015**, *21*, 2298–2308; b) S. T. R. Müller, T. Wirth, *ChemSusChem* **2015**, *8*, 245–250; c) D. E. Fitzpatrick, C. Battilocchio, S. V. Ley, *ACS Cent. Sci.* **2016**, *2*, 131–138.
[7] a) R. A. Maurya, C. P. Park, J. H. Lee, D.-P. Kim, *Angew. Chem. Int. Ed.* **2011**, *50*, 5952–5955; *Angew. Chem.* **2011**, *123*, 6074–6077; b) E. Rossi, P. Woehl, M. Maggini, *Org. Process Res. Dev.* **2012**, *16*, 1146–1149; c) F. Mastronardi, B. Gutmann, C. O. Kappe, *Org. Lett.* **2013**, *15*, 5590–5593; d) D. Dallinger, V. D. Pinho, B. Gutmann, C. O. Kappe, *J. Org. Chem.* **2016**, *81*, 5814–5823; e) H. Lehmann, *Green Chem.* **2017**, *19*, 1449–1453; f) C. Audubert, O. J. Gamboa Marin, H. Lebel, *Angew. Chem. Int. Ed.* **2017**, *56*, 6294–6297; *Angew. Chem.* **2017**, *129*, 6391–6394.
[8] a) S. T. R. Müller, A. Murat, D. Maillos, P. Lesimple, P. Hellier, T. Wirth, *Chem. Eur. J.* **2015**, *21*, 7016–7020; b) S. T. R. Müller, A. Murat, P. Hellier, T. Wirth, *Org. Process Res. Dev.* **2016**, *20*, 495–502; c) J.-S. Poh, D. N. Tran, C. Battilocchio, J. M. Hawkins, S. V. Ley, *Angew. Chem. Int. Ed.* **2015**, *54*, 7920–7923; *Angew. Chem.* **2015**, *127*, 8031–8034; d) N. M. Roda, D. N. Tran, C. Battilocchio, R. Labes, R. J. Ingham, J. M. Hawkins, S. V. Ley, *Org. Biomol. Chem.* **2015**, *13*, 2550–2554; e) D. N. Tran, C. Battilocchio, S.-B. Lou, J. M. Hawkins, S. V. Ley, *Chem. Sci.* **2015**, *6*, 1120–1125; f) C. Battilocchio, F. Feist, A. Hafner, M. Simon, D. N. Tran, D. M. Allwood, D. C. Blakemore, S. V. Ley, *Nat. Chem.* **2016**, *8*, 360–367; g) É. Lévesque, S. T. Laporte, A. B. Charette, *Angew. Chem. Int. Ed.* **2017**, *56*, 837–841; *Angew. Chem.* **2017**, *129*, 855–859.
[9] After submission of this manuscript, this paper describing a flow synthesis of unstable diazo compounds and their in situ coupling reactions with boronic acids was published: A. Greb, J.-S. Poh, S. Greed, C. Battilocchio, P. Pasau, D. C. Blakemore, S. V. Ley, *Angew. Chem. Int. Ed.* **2017**, *56*, 16602–16605; *Angew. Chem.* **2017**, *129*, 16829–16832. However, our work remains the first methodology allowing the generation of a base-free and clean stream of nonstabilized diazoalkanes.
[10] T. Bug, M. Hartnagel, C. Schlierf, H. Mayr, *Chem. Eur. J.* **2003**, *9*, 4068–4076.
[11] a) A. C. Day, P. Raymond, R. M. Southam, M. C. Whiting, *J. Chem. Soc. C* **1966**, 467–469; b) T. L. Holton, H. Schechter, *J. Org. Chem.* **1995**, *60*, 4725–4729; c) M. E. Furrow, A. G. Myers, *J. Am. Chem. Soc.* **2004**, *126*, 12222–12223.
[12] D. E. Applequist, H. Babad, *J. Org. Chem.* **1962**, *27*, 288–290.
[13] a) A. J. Wommack, J. S. Kingsbury, *J. Org. Chem.* **2013**, *78*, 10573–10587; b) M. I. Javed, M. Brewer, *Org. Lett.* **2007**, *9*, 1789–1792.
[14] B. A. Roden, A. El-Awa, *Encyclopedia of Reagents for Organic Synthesis*, Wiley, Hoboken, **2014**, pp. 1–7.

[15] a) M. J. Day, *Org. Synth.* **1970**, *50*, 3 – 5; b) A. Pross, S. Sternhell, *Aust. J. Chem.* **1970**, *23*, 989 – 1003; c) G. R. Newkome, D. L. Fishel, *J. Org. Chem.* **1966**, *31*, 677 – 681; d) M. E. Furrow, A. G. Myers, *J. Am. Chem. Soc.* **2004**, *126*, 5436 – 5445.
[16] See the Supporting Information for more details.
[17] W. Schroeder, L. Katz, *J. Org. Chem.* **1954**, *19*, 718 – 720.
[18] While this cycloaddition is near quantitative, classical quenching reaction of nonstabilized alkyl diazoalkanes with acetic acid has been shown to proceed in low yield (30–50 %) based on the diazo compound,[3b,11] with the major byproduct being tetramethylethylene in the case of 2-diazopropane.
[19] M. J. Durán-Peña, J. M. Botubol Ares, J. R. Hanson, I. G. Collado, R. Hernández-Galán, *Nat. Prod. Rep.* **2015**, *32*, 1236 – 1248.

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