JOC The Journal of Organic Chemistry

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Laboratory-Scale Membrane Reactor for the Generation of Anhydrous Diazomethane

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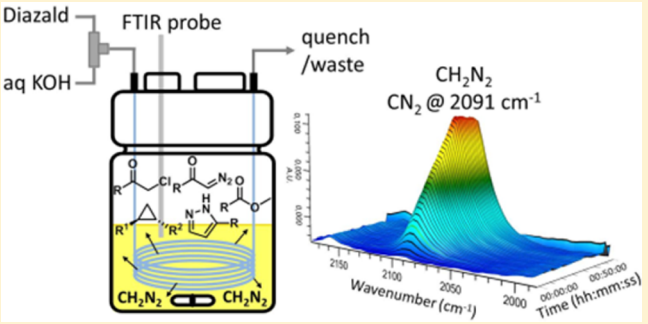
Supporting Information

ABSTRACT: A configurationally simple and robust semi-batch apparatus for the in situ on-demand generation of anhydrous solutions of diazomethane (CH_2N_2) avoiding distillation methods is presented. Diazomethane is produced by base-mediated decomposition of commercially available Diazald within a semipermeable Teflon AF-2400 tubing and subsequently selectively separated from the tubing into a solvent- and substrate-filled flask (tube-in-flask reactor). Reactions with CH_2N_2 can therefore be performed directly in the flask without dangerous and labor-intensive purification operations or exposure of the operator to CH_2N_2. The reactor has been employed for the methylation of carboxylic acids, the synthesis of α-chloro ketones and pyrazoles, and palladium-catalyzed cyclopropanation reactions on laboratory scale. The implementation of in-line FTIR technology allowed monitoring of the CH_2N_2 generation and its consumption. In addition, larger scales (1.8 g diazomethane per hour) could be obtained via parallelization (numbering up) by simply wrapping several membrane tubings into the flask.



INTRODUCTION

The most time- and atom-efficient routes in organic synthesis frequently demand the use of highly reactive and often low-molecular weight reagents. One such reagent is diazomethane (CH_2N_2), which is an exceptionally powerful building block to introduce a methyl or a methylene group into organic structures.[1] However, as with many strong alkylation agents, CH_2N_2 is a potent carcinogen and extremely poisonous.[2] The severe acute and chronic toxicity of CH_2N_2 is especially problematic because of its high volatility (bp = −23 °C). In addition, the extreme sensitivity to explosive decomposition makes the handling of CH_2N_2 challenging. However, despite the hazards associated with its generation and utilization, CH_2N_2 is among the most versatile and useful reagents in organic synthesis.[1] The reactions often proceed quickly at room temperature, and nitrogen is obtained as the sole byproduct. Generally, CH_2N_2 is produced by base-mediated decomposition of *N*-methyl-*N*-nitrosoamines in the presence of diethyl ether. Various specialized kits for the laboratory-scale generation (up to 300 mmol) and purification of ethereal solutions of CH_2N_2 have been developed and commercialized.[1a] Co-distillation into a receiver flask cooled to −78 °C yields an ethereal solution of anhydrous CH_2N_2. It should be noted, though, that most CH_2N_2 explosions occur during its distillation.[3] As CH_2N_2 has a unique importance in contemporary organic synthesis, new methods and techniques for its safe and convenient preparation and handling are continuously developed.

We and others have recently demonstrated the in situ generation of anhydrous CH_2N_2 in continuous flow systems.[4−8] Key to those strategies was the use of semipermeable, microporous membranes which selectively allow hydrophobic, low-molecular weight compounds to cross.[4−6] Specifically, our group used a commercially available tube-in-tube reactor to accomplish generation and separation of CH_2N_2.[4,9] The inner tube of the device was made of a gas-permeable Teflon AF-2400 membrane which was enclosed within a thick-walled impermeable outer tubing.[4,10,11] Diazomethane was generated from commercially available *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) and aqueous KOH within the inner tubing. Anhydrous CH_2N_2 concurrently diffused through the AF-2400 membrane and was finally consumed in the substrate-carrying chamber formed between the outer and inner tubing.[4] However, since production of CH_2N_2 is coupled with its separation and consumption in this tube-in-tube configuration, the residence time of the substrate in the outer chamber and the contact time of the substrate solution with the diazomethane carrying solution cannot be independently varied. Consequently, the flow rate of the solution in the outer chamber determines not only the reaction time but, further, the concentration or stoichiometry of CH_2N_2 attained in the outer solution.[4] In addition, any formation of solids in the outer chamber of the tube-in-tube reactor may lead to clogging and

Received: May 19, 2016
Published: June 30, 2016

DOI: 10.1021/acs.joc.6b01190
J. Org. Chem. 2016, 81, 5814−5823

may thus prevent specific chemistry to be conducted in this type of flow device.[12]

In order to enable operational simplicity and flexibility, in particular with respect to solid handling, concentration, and scale, a tube-in-flask reactor design for the generation of anhydrous CH_2N_2 was developed.[13] Herein, we present a semibatch CH_2N_2 generator capable of safely producing up to 1.8 g of anhydrous CH_2N_2 per hour and its application to diverse chemistries including methylation of carboxylic acids and the synthesis of α-chloro ketones and pyrazoles. A particular focus is placed on palladium-catalyzed cyclopropanation reactions.

RESULTS AND DISCUSSION

Tube-in-Flask Reactor. The proof-of-concept reactor used in the present work consists of a commercially available AF-2400 tubing of 5 m length (0.8 mm inner diameter, 1.0 mm outer diameter, 2.5 mL residence volume) wrapped inside a 50 mL Erlenmeyer flask (Figure S1a, Supporting Information).[14] Similar reactor designs have been previously developed for reactions with ozone[15] and oxygen gas.[16] In those approaches, the reaction mixture was carried in the membrane tubing inside the flask, while the flask was filled with the respective gas. We have chosen a design where CH_2N_2 is generated within the tubing.[4] The AF-2400 tubing was connected to standard 1/16 in. gastight PFA (perfluoroalkoxy alkane) tubings on both sides. The two PFA tubings penetrated the rubber septum sealing the Erlenmeyer flask. One of these PFA tubings connected the reactor to two syringe pumps. For the actual experiments, a Diazald solution and 2 equiv of a KOH solution in MeOH/H_2O were pumped into a Y-mixer (M) at equal flow rates. The combined mixture then passed through the PFA inlet-tubing (230 μL residence volume) and then further through the AF-2400 membrane immersed in the Erlenmeyer flask (Figure 1).

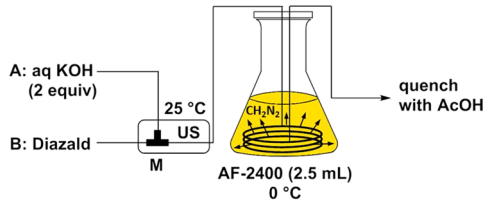


Figure 1. Continuous flow setup. Feed A: KOH in MeOH/H_2O. Feed B: Diazald in DMF or MeOH. M: Y-mixer in an ultrasonic (US) bath; AF-2400: 5 m AF-2400 tubing in a 50 mL Erlenmeyer flask. For more details, see Figure S1 in the Supporting Information.

Stirring in the Erlenmeyer flask was performed with a Teflon-coated stir bar. The solution left the apparatus through the PFA outlet tubing and was directed into a quench solution of acetic acid. In order to prevent a pressure increase or blockage of the Y-mixer due to precipitation of potassium *p*-toluenesulfonate, the mixer was immersed into an ultrasonic bath held at 25 °C. The flask itself was cooled in an ice bath to 0 °C.

CAUTION: *Diazomethane should be treated with extreme caution. It can be explosive in its pure and undiluted form. In addition, it is highly toxic by inhalation or contact with skin or eyes; therefore, contact in any form should be avoided. Excess CH_2N_2 should be destroyed by addition of acetic acid. All reactions should be carried out in an efficient fumehood with the sash closed, and laboratory personnel working with CH_2N_2 MUST familiarize themselves with the potential hazards and prevention measures.*[17]

Our initial conditions for the reactor performance studies were based on those we have applied using the tube-in-tube reactor.[4] To determine the yield of CH_2N_2 in the flask as a function of the residence time in the AF-2400 membrane, 10 mL of a 0.6 M Diazald solution (6 mmol) in MeOH and a 1.2 M KOH solution in MeOH/H_2O (1:1) were pumped through the reactor at varying flow rates. The Erlenmeyer flask was filled with 35 mL of anhydrous diethyl ether (Et_2O), and after the consumption of the Diazald solution an aliquot of 5 mL was taken from the flask and quenched with a stoichiometric amount of benzoic acid. The conversion of benzoic acid to the methyl ester was used to evaluate the CH_2N_2 concentration of the ethereal solution and CH_2N_2 yield (analyzed by HPLC–UV/vis). The yield of CH_2N_2 initially increased up to 68% at a flow rate of 250 μL/min (Figure 2a, red graph) but then

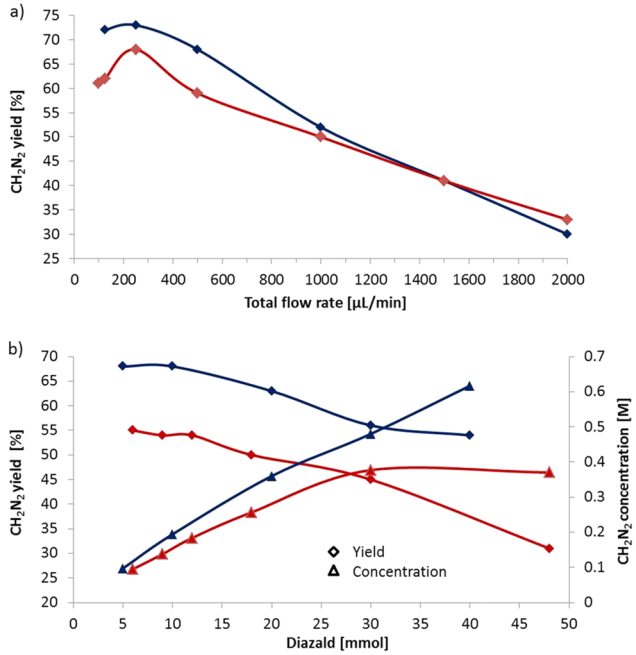


Figure 2. Generation of CH_2N_2 with (a) 10 mL of a 0.6 M MeOH solution of Diazald (red) and 10 mL of an 1 M DMF solution of Diazald (blue) at different flow rates (equal flow rates for Diazald and KOH feed)[18] and (b) varying amounts of Diazald in MeOH (red) and DMF (blue) at a total flow rate of 500 μL/min.

decreased with increasing flow rates for the Diazald and KOH feed (decreasing residence time in the reactor). It should be noted that a 0.6 M Diazald solution in MeOH was the maximum possible concentration to obtain a homogeneous Diazald solution and that the ultrasonic bath had to be set to 30 °C in order to suppress precipitation and thus blockage. To achieve more concentrated Diazald solutions, the solvent was changed to DMF: a concentration of 1 M was attainable and, in combination with a 2 M KOH solution in MeOH/H_2O (1:2), the precipitation problems were minimized. However, to prevent precipitation at higher flow rates, the Y-mixer was immersed in an ultrasonic bath set to 25 °C also for all subsequent experiments. The same trend was observed with respect to increasing flow rates, although higher CH_2N_2 yields were obtained in particular at lower flow rates (Figure 2a, blue graph). Since the difference in yield for the flow rates of 250 μL/min and 500 μL/min was only 5% (73 vs 68%) but the time for complete Diazald consumption was halved (80 vs 40

DOI: 10.1021/acs.joc.6b01190
J. Org. Chem. 2016, 81, 5814–5823

min), we opted for 500 μL/min as total flow rate, which results in a nominal residence time of 5 min,[18] for all subsequent experiments. With this flow rate, approximately 0.10 M ethereal solutions of CH_2N_2 (Figure 2b, red graph) were generated from 10 mL of Diazald in MeOH (0.6 M), corresponding to a CH_2N_2 generation of ca. 89 μmol/min. On the other hand, for a solution of 10 mL of Diazald in DMF (1 M) these values were doubled: a concentration of 0.19 M of CH_2N_2 could be reached (ca. 165 μmol CH_2N_2 /min). When the amount of Diazald pumped through the reactor was increased, the CH_2N_2 concentration in the flask increased essentially linearly (Figure 2b). As the concentration gradient between the solution in the tubing and the flask then diminishes, an equilibrium concentration of ca. 0.38 M is approached for Diazald in MeOH and the CH_2N_2 yield decreases (Figure 2b, red graph). The equilibrium concentration is expected to depend on the partition coefficient of CH_2N_2 between Et_2O and MeOH/H_2O. Accordingly, the final concentration of CH_2N_2 in the Et_2O solution was higher than the highest possible CH_2N_2 concentration in the AF-2400 membrane tubing (0.38 M vs 0.30 M), indicating the comparatively low solubility of CH_2N_2 in the aqueous solution. After pumping 40 mmol of Diazald in DMF, a rather high CH_2N_2 concentration of 0.62 M was reached (Figure 2b, blue graph); however, owing to safety concerns, larger amounts of Diazald were not processed and thus the equilibrium concentration was not determined. It appears entirely feasible to reach CH_2N_2 concentrations of ca. 1 M.

The CH_2N_2 concentrations obtained in this way compare well with those achieved with traditional distillation methods (ca. 0.25−0.68 M ethereal solutions).[3,19] Employing Diazald in DMF proved to be superior to MeOH as solvent. Not only are the CH_2N_2 yields and thus concentrations higher, but importantly, the processing times are significantly shorter: for example, to obtain a ca. 0.2 M ethereal CH_2N_2 solution, 10 mL of a 1 M Diazald solution in DMF need to be pumped at 500 μL/min total flow rate for 40 min, whereas 20 mL of a 0.6 M Diazald solution in MeOH is necessary and thus twice the processing time (Figure 2b). For all subsequent chemistry examples, therefore, the 1 M Diazald in DMF and 2 M KOH in MeOH/H_2O (1:2) system and a 500 μL/min total flow rate was used, generating a 0.19 M ethereal CH_2N_2 solution.

It should be stressed that a concentration gradient will be maintained when CH_2N_2 would be allowed to react directly with a substrate contained in the flask. Moreover, under such conditions the buildup of hazardous concentrations of CH_2N_2 could be avoided and the risk of uncontrollable decomposition eliminated (see below). A key advantage of the present membrane-based reactor system is that anhydrous CH_2N_2 solutions can be easily prepared in solvents other than diethyl ether. Indeed, similar CH_2N_2 concentrations were obtained in a variety of organic solvents, including higher boiling solvents such as toluene (Figure 3).

Methylation of Carboxylic Acids. To evaluate the principle of performing reactions directly in the flask, the conversion of carboxylic acids into their corresponding methyl esters (Table 1) was initially chosen. The advantages of this reaction are rapid reaction times, only volatile byproducts (N_2), and high selectivity.[1] With 10 mmol of benzoic acid dissolved in 35 mL of anhydrous Et_2O in the flask, 1.5 equiv (15 mmol) of Diazald were prepared, corresponding to ca. 10 mmol of CH_2N_2 (see Figure 2). Notably, complete conversion to the methyl ester **1a** was already obtained after 1.35 equiv of Diazald

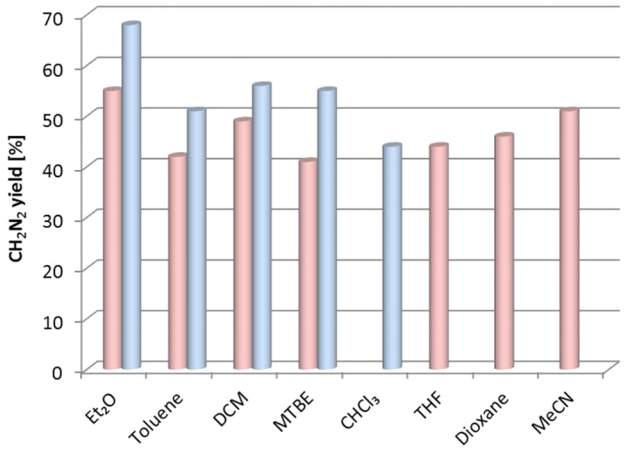
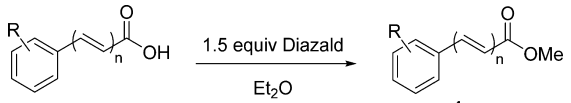


Figure 3. Generation of CH_2N_2 using 35 mL of different solvents in the flask at 0 °C (dioxane at rt): 12 mmol of Diazald (0.6 M in MeOH, red) and 10 mmol of Diazald (1 M in DMF, blue) at a total flow rate of 500 μL/min.

Table 1. Methylation of Carboxylic Acids[a]



1a-e

compd	R	*n*	yield (%)
1a	H	0	90
1b	4-NO_2	0	90
1c	4-MeO	0	89
1d	2-OH	0	99
1e	H	1	95

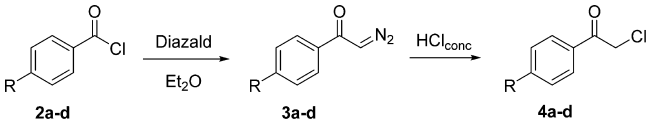
[a]Conditions: 1 M Diazald in DMF, 2 M KOH in MeOH/H_2O (1:2), 500 μL/min total flow rate, 35 mL of Et_2O at 0 °C. For detailed reaction conditions, see the Experimental Section.

was pumped through the system (74% yield of CH_2N_2; determined by kinetic analysis via HPLC), indicating a highly efficient transport of CH_2N_2 from the membrane tubing into the flask when a concentration gradient is maintained. In order to develop a general protocol taking into account the varying reactivities of the acid substrates, 1.5 equiv (15 mmol) of Diazald was employed. Any excess of CH_2N_2 in the flask after the reaction was quenched with AcOH (10−15 drops). The reaction mixture was then extracted with satd $NaHCO_3$, and **1a** was obtained after evaporation of the solvent in 90% yield (1.2 g) and >99% purity (HPLC at 215 nm). Other aromatic carboxylic acids (**1b−d**), both with electron-donating and -withdrawing groups, also provided full conversion to the corresponding esters (Table 1). Although 4-NO_2- and 4-MeO-benzoic acids were not completely soluble in Et_2O at the starting concentration (5 mmol), the corresponding methyl esters were, and full conversion was obtained nonetheless. Other functional groups were well tolerated, only 1% of the bismethylated 2-hydroxybenzoic acid was generated, and cinnamic acid was exclusively converted to the ester **1e**.

Synthesis of α-Chloroketones. In order to determine that the CH_2N_2 separated from the tubing into the flask is indeed anhydrous, the reaction of acyl chlorides with CH_2N_2 was conducted (Table 2). The generation of α-diazoketones via a modified Arndt−Eistert reaction only proceeds satisfactorily under strictly anhydrous conditions. This reaction type is of

DOI: 10.1021/acs.joc.6b01190
J. Org. Chem. 2016, 81, 5814−5823

Table 2. Synthesis of α-Chloroketones[a]



compd	R	Diazald (equiv)	yield (%)
4a	H	3	88
4b	NO_2	3	90
4c	Br	3	88
4d	MeO	4	90

[a]Conditions: 1 M Diazald in DMF, 2 M KOH in MeOH/H_2O (1:2), 500 μL/min total flow rate, 35 mL of Et_2O at 0 °C. For detailed reaction conditions, see the Experimental Section.

particular interest because of its use in the synthesis of modern HIV protease inhibitors and was recently reported by our group using continuous flow protocols.[4,13] Using 5 mmol of benzoyl chloride (**2a**) in anhydrous Et_2O and 3 equiv of Diazald, a 7:1 mixture of α-diazoketone **3a** and α-chloroketone **4a** was obtained. It is known that the in situ generated HCl either reacts with the diazoketone to form the chloroketone via the Nierenstein reaction or contributes to the decomposition of CH_2N_2 to CH_3Cl and N_2.[20] With excess CH_2N_2 at lower temperatures preferentially the diazoketones are generated, as the HCl is consumed in the reaction with CH_2N_2. Since the chloroketone could not be removed by a simple extraction/evaporation workup, we decided to convert the diazoketone to the chloroketone in situ by adding 1.5 mL of concd HCl. Stirring for 20 min and extraction with H_2O and satd $NaHCO_3$ provided pure α-chloroketone **4a** in 88% yield (Table 2). Importantly, no methyl ester could be detected, confirming that anhydrous CH_2N_2 was generated. A similar result as for benzoyl chloride was obtained for 4-bromobenzoyl chloride **2c**. With the electron-withdrawing NO_2 functionality a 4:1 mixture of α-diazoketone **3b** and α-chloroketone **4b** was obtained after complete Diazald consumption. The subsequent HCl quench and extraction furnished **4b** in 90% yield. On the other hand, when an electron-donating group is present, the reaction proceeds more slowly. For 4-methoxybenzoyl chloride, incomplete conversion to diazoketone **3d** or chloroketone **4d** after consumption of 3 equiv of Diazald was observed. After 2 h of stirring, 13% of acyl chloride **2d** was still present. Therefore, the amount of Diazald was increased to 4 equiv, and optimum results were achieved after 1.5 h of stirring after complete Diazald uptake (3% of **2d**, 90% of **3d**, 7% of **4d**). After addition of HCl, and stirring for 20 min, α-chloroketone **4d** could be isolated in 90% yield. Notably, also for α-chloroketones **4b–d** only traces of ≤1% of the corresponding esters could be detected in the NMR, indicating the clean formation of anhydrous CH_2N_2 using the membrane-based separation technique.

Palladium-Catalyzed Cyclopropanations. Cyclopropanation of olefins with CH_2N_2 is of major synthetic importance since the cyclopropane subunit is found as a basic structural element in a wide range of naturally occurring compounds and in several bioactive unnatural analogues.[21,22] In addition, the cyclopropane ring is a versatile synthetic building block that can be converted into a range of functionalities.[8b] Generally, Pd is the catalyst of choice, but other transition-metal catalysts, including Cu, Ni, and Rh, have also been reported to efficiently catalyze the reaction under mild conditions.[21] The reaction commonly proceeds with excellent stereo- and chemoselectivity and is compatible with a wide range of functional groups.[21,23] Biphasic cyclopropanations have been developed, whereby CH_2N_2 is generated in situ in the strongly basic aqueous phase and is then transferred into an organic phase where the cyclopropanation takes place.[23] Even though this protocol does not require any purification of CH_2N_2, the biphasic reaction necessitates a water-soluble Diazald derivative and is limited to water-insoluble substrates and to reagents which tolerate the strongly basic aqueous conditions.[23a] Cyclopropanations in flow were conducted by employing the more stable α-diazocarbonyl[24] or unstabilized nucleophilic diazo intermediates.[25]

For our initial optimization reactions, a variety of catalysts and catalyst loadings were screened in parallel using 5 mL glass vials. For these transformations, 0.2 mmol of the substrate and the respective catalyst in THF as solvent were added into the glass vials equipped with a magnetic stir bar. A sample of 2.2 mL (2 equiv) of CH_2N_2 in THF was then slowly pipetted from the flask into each of the glass vials under stirring at 0 °C. With styrene as the model substrate, various palladium species proved to be very active catalysts for the cyclopropanation, while in contrast, Cu(II) species did not exhibit any catalytic activity. With 2 mol % of $Pd(OAc)_2$ as catalyst, nitrogen evolved vigorously upon addition of CH_2N_2 and the yellow color of CH_2N_2 quickly vanished. Similar results were obtained with $PdCl_2$ and zerovalent palladium precatalysts such as $Pd_2(dba)_3$. In all of these experiments, a precipitate of Pd black formed in the early stages of the reaction (see Figure 4), and

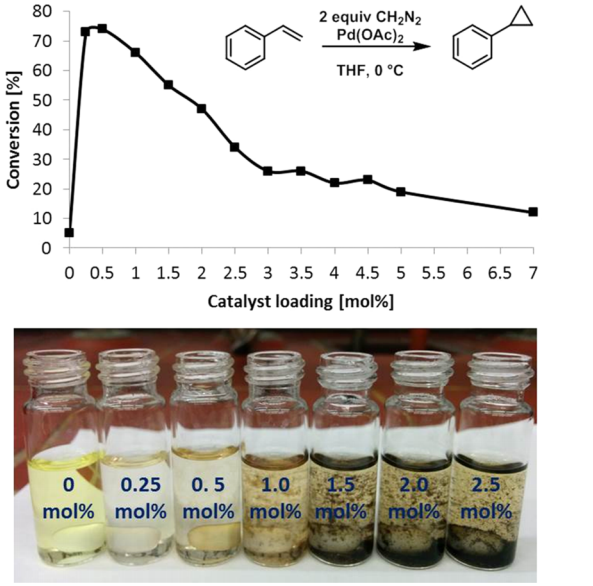


Figure 4. $Pd(OAc)_2$-catalyzed cyclopropanation of styrene at different catalyst loadings (0.2 mmol of styrene, 2 equiv of CH_2N_2 in THF as solvent).

the reaction generally stopped well before full conversion was attained. Furthermore, independent experiments without substrate demonstrated that $Pd(OAc)_2$ effectively catalyzes the decomposition of CH_2N_2 (monitored by UV–vis spectroscopy at 410 nm). The initial rate of CH_2N_2 decomposition is roughly proportional to the catalyst concentration, but again Pd black then quickly forms and the decomposition rate drops. The main products of the Pd-catalyzed decomposition of CH_2N_2 in deuterated chloroform were tentatively assigned to

DOI: 10.1021/acs.joc.6b01190
J. Org. Chem. 2016, 81, 5814–5823

cyclopropane, methanol, ethene, and acetaldehyde by ^{1}H NMR analysis (Figures S4–S6, Supporting Information). Importantly, considerably higher conversions for the cyclopropanation were obtained when the catalyst loading was decreased (Figure 4). With a catalyst loading of only 0.25 mol % of $Pd(OAc)_2$ a conversion of 73% was obtained using styrene as substrate. Appreciable Pd black precipitation was not observed at this catalyst loading. It is noteworthy that full conversion was achieved within seconds at 0 °C when the CH_2N_2 solution was added rapidly to the reaction mixture containing the substrate and the catalyst (Figure S7, Supporting Information). However, catalyst loadings below <0.1 mol % reduced the reaction rate noticeably. For electron-rich olefins such as *p*-MeO-styrene with a weak coordinating ability for Pd(0), the speed of CH_2N_2 addition is by far more critical. When the CH_2N_2 was added slowly to a solution containing *p*-MeO-styrene and $Pd(OAc)_2$, Pd(0) precipitated and the reaction stopped at 60% conversion. An increase to 89% was observed by fast addition of the CH_2N_2 solution, and even 96% was possible when the catalyst was added slowly to the substrate/CH_2N_2 solution (Figure S8, Supporting Information).

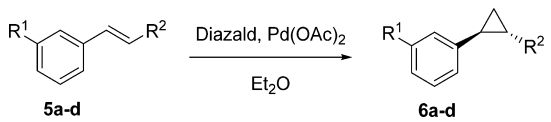
The occurrence of Pd(0) precipitates during the reaction has previously been reported,[26] and the reaction inhibiting effect of larger amounts of $Pd(OAc)_2$ was already observed by the Hacksell group during cyclopropanation of enoyl sultams.[27] The mechanism of transition-metal-catalyzed cyclopropanation is still rather controversial and not very well understood.[28] Nefedov[29] and others[26a] proposed that the palladium-catalyzed cyclopropanation proceeds through a Pd(0)/Pd(II) cycle. The results described above suggest that the intermediate Pd(0) species can either insert into the C–N bond of CH_2N_2 and re-enter the catalytic cycle or, alternatively, aggregate to generate Pd clusters, which ultimately irreversibly precipitate in the form of Pd black. By lowering the catalyst concentration, the autocatalyzed aggregation becomes slow and is eventually outperformed by reoxidation of Pd(0) to Pd(II) by addition of CH_2N_2. The same effect was described for ligand-free Heck reactions which efficiently proceed in the presence of homeopathic quantities of $Pd(OAc)_2$ as catalyst.[30] Similarly, depletion of CH_2N_2 upon slow addition prevents reoxidation of Pd(0) and favors its agglomeration and precipitation.

For preparative reactions in the tube-in-flask reactor, solutions containing 3 mmol of the styrene and the respective amount of $Pd(OAc)_2$ in Et_2O were directly loaded into the Erlenmeyer flask (Table 3). Since byproducts derived from THF were observed in the final product, the solvent was changed to Et_2O. A solution of 3 equiv of Diazald (ca. 2 equiv CH_2N_2) was pumped through the AF-2400. The reaction with styrene **5a** proceeded to completion with a catalyst loading of 0.05 mol % and 1.5 equiv of CH_2N_2. On the other hand, with 0.25 mol % $Pd(OAc)_2$, the reaction stopped at a conversion of only 49%. Due to the volatility of **6a** only 79% was isolated after an AcOH quench and extraction with satd $NaHCO_3$. The reaction with electron-poor 3-NO_2-styrene **5b** gave a conversion >99% without significant Pd precipitation, as long as the Pd concentration did not exceed 0.15 mol %. As expected, the addition of CH_2N_2 to the internal olefins **5c** and **5d** occurred stereospecifically to afford the *trans*-cyclopropanes **6c** and **6d** as the sole products. In accordance with the experiments described above, since the diffusion of CH_2N_2 through the tubing into the solution equates to a slow addition of CH_2N_2, the use of this approach for a reaction with the electron-rich *p*-MeO-styrene as the substrate resulted in immediate Pd precipitation and the conversion stopped at 6 and 56% with 0.05 and 0.25 mol % $Pd(OAc)_2$, respectively.[31]

Cyclopropanations are clearly not a trivial affair when full conversions and high isolated yields are envisaged, thus a general protocol for diverse alkene substrates is hardly feasible. Depending on the coordination abilities of the alkenes for Pd(0), the precipitation of Pd black, and therefore termination of the reaction, occurs at different catalyst concentrations. In addition, the reagent addition is crucial: whereas for neutral and electron-poor alkenes the Pd catalyst can be charged into the flask, for electron-rich alkenes, the catalyst needs to be added slowly to the substrate/CH_2N_2 solution.

Synthesis of Pyrazoles. The pyrazole motif is an attractive building block for the pharmaceutical as well as for the agrochemical industry, since those derivatives display a broad spectrum of biological activities.[32] Of particular importance are pyrazole carboxylates;[33] e.g., ethyl 5-propyl-1*H*-pyrazole-3-carboxylate is a key intermediate for the synthesis of sildenafil (Viagra).[34] Pyrazoles are usually prepared either by condensation of a hydrazine derivative and a 1,3-dicarbonyl compound or by 1,3-dipolar cycloaddition of diazo compounds and alkynes, which provides a direct access to substituted pyrazoles.[35] We have performed the reaction of ethyl propiolate and CH_2N_2 under standard conditions using 1.5 equiv of Diazald and Et_2O as solvent (Scheme 1). The reaction did go to completion (>99%, GC–MS analysis); however, after purification via simple extraction/evaporation only 71–80% could be isolated. The reason for the low yield was product precipitation during the reaction. The low solubility, also in excess Et_2O, made it difficult to remove the solid product entirely out of the flask. Therefore, Et_2O was substituted by $CHCl_3$ as solvent for the reaction (Scheme 1), which facilitated workup, since the product was perfectly soluble in excess $CHCl_3$. Generally, this reaction is regioselective, and only the 3-substituted pyrazole isomer **7** is obtained.[36] However, when Et_2O was employed, 5% of the 4-substituted pyrazole **8** and 3–8% of *N*1-methylated pyrazole **9** was attained. The product

Table 3. Palladium-Catalyzed Cyclopropanations[a]

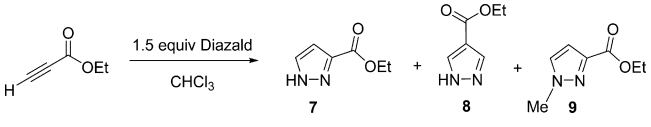


5a-d 6a-d

compd	R^1	R^2	Diazald (equiv)	$Pd(OAc)_2$ (mol %)	yield (%)
6a	H	H	2.25	0.05	79
6b	NO_2	H	3	0.15	99
6c	H	CO_2Me	3	0.30	95
6d	H	Ph	3	0.15	94

[a]Conditions: 1 M Diazald in DMF, 2 M KOH in MeOH/H_2O (1:2), 500 μL/min total flow rate, 35 mL of Et_2O at 0 °C. For detailed reaction conditions, see the Experimental Section.

Scheme 1. Synthesis of Pyrazoles via 1,3-Dipolar Cycloaddition



DOI: 10.1021/acs.joc.6b01190
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distribution changed in favor of **7** using $CHCl_3$ as solvent, providing **8** and **9** only in 1.5% and 0.7%, respectively (Scheme 1). As expected, the deactivated propargyl alcohol was completely unreactive.

Scale-up Concepts. It should be noted that with the tube-in-tube reactor, although it has the advantage of being fully continuous, the scale is quite limited (up to 70 mg CH_2N_2/h).[4] Larger scales, e.g., by increasing the size between the inner and outer compartment, are not so easy to achieve, since several aspects need to be taken into account: diffusion of CH_2N_2,[37] the flow rates for the CH_2N_2, KOH, and substrate feed, concentration of the feeds, etc. With the above shown setup, ca. 420 mg (10 mmol) CH_2N_2/h can be generated, which would theoretically lead to ca. 2 g/h productivity assuming a product molecular weight of ca. 200. Larger scales in a reasonable time frame would be problematic to achieve; therefore, the reactor design needed further development. Our initial attempt was to employ an AF-2400 membrane with a larger inner diameter (1.55 vs 0.8 mm). To be comparable with the "smaller" tubing, a length of 1.5 m was chosen, so that approximately the same residence volume (2.8 vs 2.5 mL) was reached. The tubing was wrapped into a 250 mL Duran flask which was filled with 100 mL of Et_2O (Figure S2, Supporting Information). To achieve a similar concentration of 0.19 M in the flask, 28.6 mL of a 1 M solution of Diazald in DMF and a 2 M KOH solution in MeOH/H_2O (1:2) were pumped with a total flow rate of 500 μL/min. A CH_2N_2 yield of 34% was obtained, which is exactly half the amount generated with the original membrane tubing, indicating that the conversion is inversely proportional to the inner diameter and thus the surface area of the membrane.[37] For the same throughput, twice the residence volume would be necessary. The next logical step was a parallelization approach (numbering up).[16] Therefore, four standard AF-2400 membrane tubings, each 4 m in length (2 mL residence volume), were connected to the inlet and outlet tubing via a 5-port manifold and wrapped into a 250 mL Duran flask (Figure 5). With this setup, four times the scale should be accomplished within the same time frame (40 min) as for the single membrane reactor.

For the scale-up experiments, reaction monitoring with in situ FTIR spectroscopy (Mettler Toledo ReactIR with a silicon probe) was applied. The IR probe was inserted into the solution in the flask via a screw-cap adapter (Figure 5a and Figure S3 in the Supporting Information). The CH_2N_2 generation and consumption could thus be precisely examined due to the strong characteristic C═N_2 stretch around 2100 cm^{-1}. Proctor and Warr have reported the continuous monitoring of the gas-phase concentration of CH_2N_2 at 2102 cm^{-1} employing a photoacoustic FTIR instrument in a pilot scale reactor.[7a] The Ley group, on the other hand, used the ReactIR flow cell to monitor e.g., the generation of diazo intermediates[25] or the concentration of CO in the liquid stream in a tube-in-tube reactor,[10b] respectively.

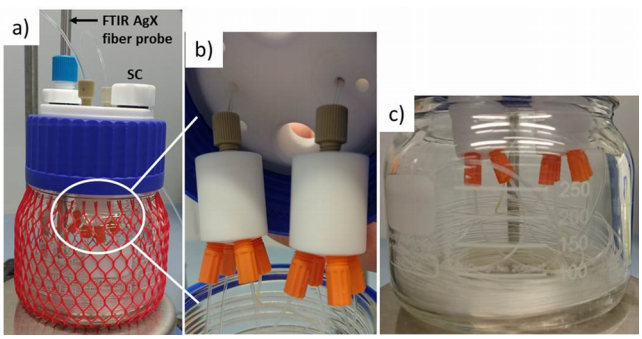

Figure 5. (a) Large-scale CH_2N_2 generator with the AgX fiber probe attached for in-line FTIR analysis. SC: screw-cap for reaction sampling and reagent addition. (b) Parallelization using two Teflon 5-port manifolds. (c) 4 × 4 m AF-2400 tubing wrapped inside a 250 mL Duran flask.

To evaluate the performance of the reactor, the CH_2N_2 yield in the flask was first determined. All of the amounts were quadrupled: 40 mL of a 1 M solution of Diazald in DMF were pumped at a total flow rate of 2 mL/min, and 140 mL of anhydrous Et_2O were filled into the flask. It has to be noted that at this high flow rate precipitation in the Y-mixer occurred at 25 °C in the ultrasonic bath. This problem could be solved by setting the temperature to 30 °C. For a reaction calibration, samples were taken every 10 min and analyzed by HPLC and were then correlated to the peak area of the absorption measured with the IR probe for the C═N_2 stretch at 2091 cm^{-1} (Figure 6a,d). As can be seen, the CH_2N_2 concentration increases linearly with a maximum concentration of 0.209 M reached after ca. 43 min. The CH_2N_2 concentration then keeps constant in the flask until a quench with acetic acid was performed after ca. 60 min, upon which the CH_2N_2 concentration drops instantly to zero (Figure 6b). From 40 mmol of Diazald (1 M), pumped with a flow rate of 1 mL/min, and a determined CH_2N_2 yield of 71% after 40 min, theoretically 0.71 mmol (29.8 mg) of CH_2N_2 should be generated per minute. The experimental value of 0.7085 (see Figure 6c) perfectly fits this calculation, and a maximum of 29 mmol CH_2N_2 was obtained after complete consumption of Diazald. The data obtained also match those of the small-scale experiment remarkably well: 0.19 M of CH_2N_2 could be reached, correlating to the generation of ca. 0.66 mmol of CH_2N_2/min.

Next, we wanted to apply our larger scale CH_2N_2 generator to chemistry examples. The synthesis of α-chloroketone **4d** (Table 2) was now performed on a 4-fold scale. A sample of 20 mmol of 4-MeO-benzoyl chloride (**2d**) was dissolved in 140 mL of Et_2O in the flask, and 80 mmol of Diazald (4 equiv) in 80 mL of DMF were employed. The reaction again was monitored via FTIR (Figure 7). Benzoyl chloride **2d**, which was traced by its C═O stretch at 1773 cm^{-1}, decreased during the course of the reaction, whereas diazoketone **3d** with the C═N_2 stretch at 2091 cm^{-1} increased. Unfortunately, the C═N_2 stretch for CH_2N_2 and diazoketone overlaid, but supported by the data we have observed so far (also see Figure 8), we assume that the concentration increase can be assigned to diazoketone product formation. As already described above, the reaction does not go to completion after full consumption of Diazald: after 86 min, 20% of **2d** was still present (HPLC conversion). This correlates very well to the value obtained from the decrease in peak area in Figure 7. Full conversion to diazoketone **3d** was achieved after stirring for additional 90 min. Subsequently, 6 mL of concd HCl was added, the diazoketone concentration dropped immediately, and after 1 h of stirring, extractive workup, and evaporation, 3.65g (99%) of pure α-chloroketone **4d** was isolated.

The methylation of benzoic acid was then used as a model reaction to demonstrate the productivity of the reactor over an 8 h working day. For this proof-of-concept study, 0.32 mol (39 g) benzoic acid was dissolved in 200 mL of Et_2O in the flask,

DOI: 10.1021/acs.joc.6b01190
J. Org. Chem. 2016, 81, 5814−5823

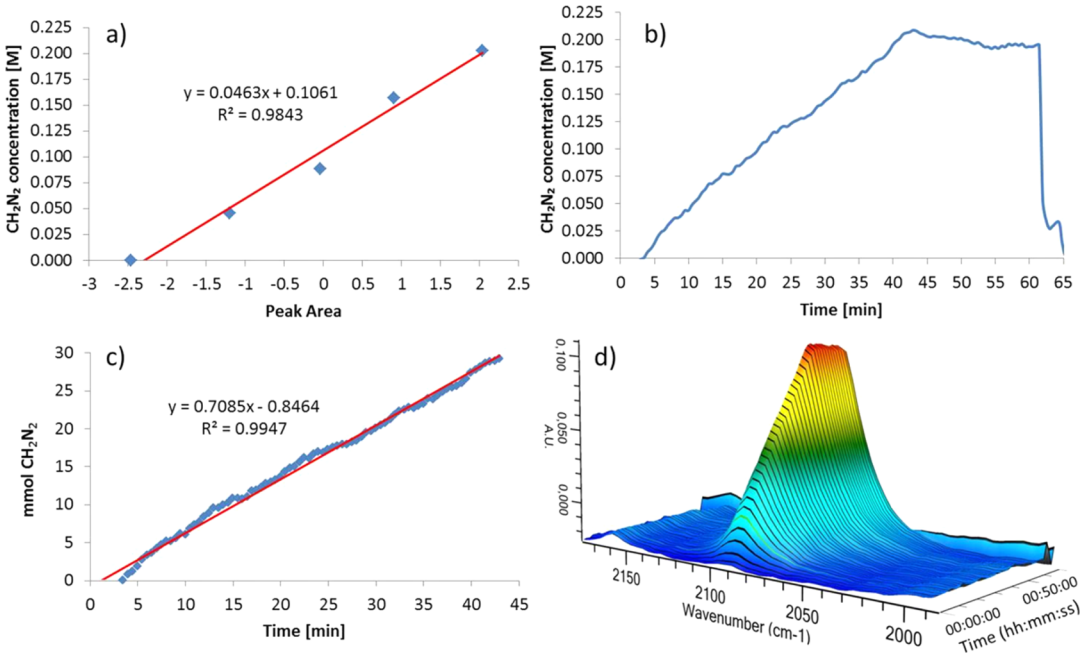

Figure 6. (a) Correlation between CH_2N_2 concentration (HPLC analysis) and peak area of the C═N_2 stretch at 2091 cm^{-1} (IR analysis). (b) Correlation of CH_2N_2 concentration with time. (c) Correlation of CH_2N_2 (mmol) generation with time. (d) 3-D surface image for the C═N_2 stretch at 2091 cm^{-1}.

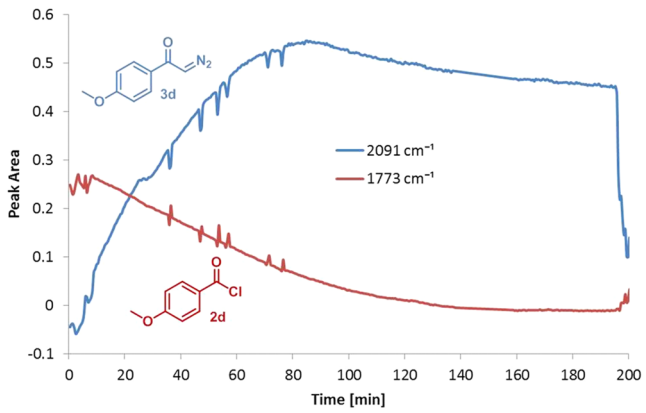

Figure 7. Reaction monitoring of the conversion of benzoyl chloride **2d** to the corresponding diazoketone **3d** using in-line FTIR spectroscopy.

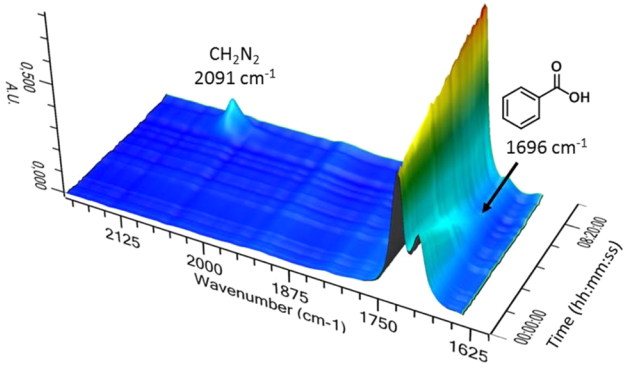

Figure 8. Reaction monitoring for the methylation of benzoic acid using in-line FTIR spectroscopy (3-D surface image).

and 0.48 mol of Diazald (1.5 equiv) in 480 mL of DMF was pumped through the reactor with a flow rate of 1 mL/min. According to the FTIR analysis, no CH_2N_2 was present in the solution in the flask until the reaction was completed after ca. 7 h (Figure 8). When all substrate was consumed (C═O stretch at 1696 cm^{-1}), the C═N_2 stretch for CH_2N_2 at 2091 cm^{-1} appeared, and the experiment theoretically could be stopped. This nicely corroborates our findings on small scale (see above): only 1.34 equiv of Diazald is necessary for full conversion to the methyl ester **1a**. After addition of 2 mL of AcOH and extraction, 42.22 g (97%) of ester **1a** was obtained, equating to 6 g of product per hour.

CONCLUSION

A simple and easy to construct reactor setup for the in situ on-demand generation of solutions of anhydrous CH_2N_2 is described. Diazomethane is generated from Diazald in DMF and aqueous KOH within a hydrophobic, gas-permeable tubing. Anhydrous CH_2N_2 subsequently diffuses through the tubing into the surrounding flask. This approach allows the convenient preparation of solutions of CH_2N_2 in any desired solvent, which can be further used for optimization or screening studies. The concentration of the CH_2N_2 solution or stoichiometry can be adjusted simply by varying the amount of Diazald pumped through the reactor. With a tubing of only 2.5 mL residence volume, the reactor provides ca. 165 μmol (3.9 mg) of anhydrous CH_2N_2 per minute. A larger scale can easily be achieved via parallelization (numbering up) by wrapping more membrane tubings into the flask. With four membranes in parallel, 2 mL residence volume each, ca. 42.6 mmol (1.8 g) CH_2N_2/h can be generated, ideally leading to approximately 70 g of product/day (based on an 8 h working day and a molecular weight of 200). Compared to the previously reported tube-in-tube method, the tube-in-flask protocol is not sensitive to solubility issues with respect to starting material, products, or any byproducts which may be formed. CH_2N_2 is intensively used in contemporary organic synthesis but it is notoriously dangerous to handle, since it is volatile, toxic, carcinogenic, and

DOI: 10.1021/acs.joc.6b01190
J. Org. Chem. 2016, 81, 5814−5823

highly explosive. The laboratory-scale CH_2N_2 generator proposed herein eliminates cumbersome and potentially dangerous isolation and purification procedures and, thus, offers the promise of a safer and simpler synthetic protocol since the generated CH_2N_2 can be utilized directly in the flask without any exposure to CH_2N_2. We could also show that in-line FTIR spectroscopy is ideally suited for safe and reliable reaction monitoring, which is of specific relevance when toxic or hazardous intermediates or products are generated. Further investigations toward new reactor designs with respect to scale-up are currently evaluated in our group.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR spectra were recorded on a 300 MHz instrument. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet. GC−MS spectra were recorded using a Focus GC coupled with a DSQ II (EI, 70 eV). A HP5-MS column (30 m × 0.250 mm × 0.25 μm) was used with helium as carrier gas (1 mL min^{-1} constant flow). The injector temperature was set to 280 °C. After 1 min at 50 °C, the temperature was increased in 25 °C min^{-1} steps up to 300 °C and kept at 300 °C for 4 min. Analytical HPLC analysis was carried out on a C18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 37 °C using a mobile phase A (water/MeCN 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.5 mL min^{-1}. The following gradient was applied: linear increase from solution 30% B to 100% B within 10 min. Melting points were obtained on a standard melting point apparatus in open capillary tubes. In-line FTIR analysis (software package iC IR 4.3.35) was performed using a AgX Fiber Conduit with an integrated attenuated total reflectance (ATR) gold-sealed silicon sensor and a mercury cadmium telluride (MCT) detector. All solvents and chemicals were obtained from standard commercial vendors and were used without any further purification. Diazald was synthesized following a literature procedure.[38] Products were characterized by ^{1}H NMR and identified by comparison of the spectra with those reported in the literature. All compounds synthesized herein are known in the literature. Proof of purity was obtained by ^{1}H NMR and HPLC−UV spectroscopy.

General Method for Methylation of Carboxylic Acids. KOH (30 mmol) was dissolved in 15 mL of MeOH/H_2O 1:2 (feed A), and Diazald (7.5 mmol) was dissolved in 7.5 mL of DMF (feed B). The Erlenmeyer flask, fitted with a stir bar, was filled with 5 mmol of the respective benzoic acid in 35 mL of anhydrous diethyl ether and was cooled in an ice bath to 0 °C. Feeds A and B were pumped by two syringe pumps (Asia, Syrris, see Figure S1b) into a Y-mixer, which was immersed into an ultrasonic bath set to 25 °C, at flow rates of 250 μL min^{-1} each (2 equiv of KOH with respect to Diazald). The combined mixture then passed through the PFA inlet-tubing (1/16 in. o.d.; 0.8 mm i.d.; 230 μL residence volume) and then further through the AF-2400 membrane within the Erlenmeyer flask (Figure S1a). The solution left the reactor through the PFA outlet tubing and was directed into a quench solution of aqueous acetic acid. Toward the end of the experiment, the reaction solution in the Erlenmeyer flask became yellow, indicating the full consumption of the carboxylic acids. After the Diazald solution was consumed, the reaction mixture in the Erlenmeyer flask was quenched with acetic acid. The now decolorized ethereal solution was subsequently extracted with satd $NaHCO_3$. Drying of the organic phase with $MgSO_4$ and evaporation of the solvent provided the products **1a−e** in >99% purity.

*Methyl benzoate (**1a**):* 60 mmol of KOH in 30 mL of MeOH/H_2O (1:2), 15 mmol of Diazald in 15 mL of DMF, and 10 mmol of benzoic acid were employed; 1.23 g (90%); light yellow oil;[39] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09−8.05 (m, 2H), 7.61−7.55 (m, 1H), 7.49−7.43 (m, 2H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 132.9, 130.1, 129.6, 128.4, 52.1.

*Methyl 4-nitrobenzoate (**1b**):* 18 mmol of KOH in 9 mL of MeOH/H_2O (1:2), 4.5 mmol of Diazald in 4.5 mL of DMF, and 3 mmol of 4-nitrobenzoic acid were employed; 491 mg (90%); light yellow solid; mp 99−100 °C (lit.[40] mp 95−96 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, J = 9.0 Hz, 2H), 8.23 (d, J = 9.1 Hz, 2H), 4.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 150.6, 135.5, 130.7, 123.6, 52.8.

*Methyl 4-methoxybenzoate (**1c**):* 743 mg (89%); white solid; mp 48−50 °C (lit.[41] mp 48−50 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 163.3, 131.6, 122.6, 113.6, 55.4, 51.8.

*Methyl 3-hydroxybenzoate (**1d**):* 753 mg (99%); white solid; mp 70−71 °C (lit.[42] mp 69−71 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63−7.60 (m, 2H), 7.33 (t, J = 4.6 Hz, 1H), 7.12−7.08 (m, 2H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 156.0, 131.2, 129.8, 121.8, 120.4, 116.4, 52.5.

*Methyl cinnamate (**1e**):* 770 mg (95%); light yellow solid; mp 36−37 °C (lit.[43] mp 36−37 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 16.0 Hz, 1H), 7.56−7.53 (m, 2H), 7.42−7.40 (m, 3H), 6.47 (d, J = 16.0 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 144.9, 134.4, 130.3, 128.9, 128.1, 117.8, 51.7.

*Synthesis of Methyl Benzoate (**1a**) on 0.32 mol Scale.* KOH (1.92 mol) was dissolved in 960 mL of MeOH/H_2O (1:2) (feed A), and Diazald (0.48 mmol) was dissolved in 480 mL of DMF (feed B). The 250 mL Duran flask (Ø: 95 mm, h: 105 mm), fitted with a stir bar, was filled with 0.32 mol of benzoic acid in 200 mL of anhydrous diethyl ether and was cooled in an ice bath to 0 °C. Feeds A and B were pumped by two syringe pumps (Asia, Syrris, see Figure S3 in the SI) into a Y-mixer, which was immersed into an ultrasonic bath set to 30 °C at flow rates of 1 mL min^{-1} each (2 equiv of KOH with respect to Diazald). The combined mixture then passed through the PFA inlet-tubing (1/16 in. o.d.; 0.8 mm i.d.; 300 μL residence volume) and then further through the 4 AF-2400 membranes within the Duran flask (Figure 5). The solution left the reactor through the PFA outlet tubing and was directed into a quench solution of aqueous acetic acid. After the Diazald solution was consumed, the reaction mixture in the flask was quenched with acetic acid. The now decolorized ethereal solution was subsequently extracted with satd $NaHCO_3$. Drying of the organic phase with $MgSO_4$ and evaporation of the solvent provided 42.22 g (97%) of the product in >99% purity. For characterization data, see above.

Synthesis of α-Chloroketones. Diazomethane was generated as described above with feed solutions of 60 mmol of KOH in 30 mL of MeOH/H_2O 1:2 (feed A) and 15 mmol of Diazald in 15 mL of DMF (feed B). For 4-methoxybenzoyl chloride, 80 mmol of KOH in 40 mL of MeOH/H_2O 1:2 and 20 mmol of Diazald in 20 mL of DMF were employed. The Erlenmeyer flask, fitted with a stir bar, was filled with 5 mmol of the respective benzoyl chloride in 35 mL of anhydrous diethyl ether and was cooled in an ice bath to 0 °C. After the Diazald solution was consumed, the reaction mixture in the Erlenmeyer flask was quenched with 1.5 mL of concd HCl, and the reaction mixture was stirred for 20 min. The ethereal solution was subsequently extracted with H_2O and satd $NaHCO_3$. Drying of the organic phase with $MgSO_4$ and evaporation of the solvent provided the products **4a−d** in >96% purity.

*Phenacyl chloride (**4a**):* 679 mg (88%); yellow solid; mp 55−56 °C (lit.[44] mp 53−55 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01−7.97 (m, 2H), 7.67−7.62 (m, 1H), 7.56−7.50 (m, 2H), 4.74 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1, 134.2, 134.0, 128.9, 128.5, 46.1.

*4-Nitrophenacyl chloride (**4b**):* 899 mg (90%); yellow solid; mp 89−90 °C (lit.[45] mp 87−91 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, J = 8.9 Hz, 2H), 8.16 (d, J = 9.0 Hz, 2H), 4.73 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9, 150.7, 138.6, 129.8, 124.1, 45.6.

*4-Bromophenacyl chloride (**4c**):* 1.04 g (88%); white solid; mp 119−120 °C (lit.[44] mp 116 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H), 4.68 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 132.9, 132.3, 130.0, 129.4, 45.6.

*4-Methoxyphenacyl chloride (**4d**):* 832 mg (90%); light yellow solid; mp 97−98 °C (lit.[44] mp 98 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ

DOI: 10.1021/acs.joc.6b01190
J. Org. Chem. 2016, 81, 5814−5823

7.96 (d, J = 9.0 Hz, 2H), 6.98 (d, J = 9.0 Hz, 2H), 4.67 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 164.2, 130.9, 127.2, 114.1, 55.6, 45.7.

*Synthesis of 4-Methoxyphenacyl Chloride (**4d**) on 20 mmol Scale.* KOH (0.23 mol) was dissolved in 120 mL of MeOH/H_2O 1:2 (feed A), and 80 mmol of Diazald was dissolved in 80 mL of DMF (feed B). The 250 mL Duran flask (Ø: 95 mm, h: 105 mm), fitted with a stir bar−, was filled with 20 mmol of 4-MeO-benzoyl chloride in 140 mL of anhydrous diethyl ether and was cooled in an ice bath to 0 °C. Feeds A and B were pumped by two syringe pumps (Asia, Syrris, see Figure S3 in the SI) into a Y-mixer, which was immersed into an ultrasonic bath set to 30 °C at flow rates of 1 mL min^{-1} each (2 equiv of KOH with respect to Diazald). The combined mixture then passed through the PFA inlet-tubing (1/16 in. o.d.; 0.8 mm i.d.; 300 μL residence volume) and then further through the 4 AF-2400 membranes within the Duran flask (Figure 5). The solution left the reactor through the PFA outlet tubing and was directed into a quench solution of aqueous acetic acid. After the Diazald solution was consumed, the reaction mixture was stirred for further 90 min, 6 mL of concd HCl was added, and the reaction mixture was stirred for 1 h. The now decolorized ethereal solution was subsequently extracted with H_2O and satd $NaHCO_3$. Drying of the organic phase with $MgSO_4$ and evaporation of the solvent provided the product **4d** in 99% yield (3.65 g) and >99% purity. For characterization data, see above.

Cyclopropanations. Diazomethane was generated as described above with feed solutions of 36 mmol of KOH in 18 mL of MeOH/H_2O 1:2 (feed A) and 9 mmol of Diazald in 9 mL of DMF (feed B). For styrene, 27 mmol of KOH in 13.5 mL of MeOH/H_2O 1:2 and 6.75 mmol of Diazald in 6.75 mL of DMF were employed. The Erlenmeyer flask, fitted with a stir bar, was filled with 3 mmol of the alkene and the respective amount of $Pd(OAc)_2$ (from a stock solution in THF, see Table 3) in 35 mL of anhydrous diethyl ether and was cooled in an ice bath to 0 °C. After the Diazald solution was consumed, the reaction mixture was stirred for a further 15−30 min. The ethereal solution was subsequently quenched with acetic acid and extracted with satd $NaHCO_3$. Drying of the organic phase with $MgSO_4$ and evaporation of the solvent provided the products **6a**−**d** in >98% purity.

*Cyclopropylbenzene (**6a**):* 281 mg (79%); colorless oil;[46] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.29 (m, 2H), 7.23−7.11 (m, 3H), 2.00−1.91 (m, 1H), 1.05−0.99 (m, 2H), 0.79−0.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 128.3, 125. 7, 125.4, 15.4, 9.2.

*1-Cyclopropyl-3-nitrobenzene (**6b**):* 488 mg (99%); orange oil;[23a] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03−7.97 (m, 1H), 7.92−7.91 (m, 1H), 7.45−7.38 (m, 2H), 2.06−1.97 (m, 1H), 1.13−1.07 (m, 2H), 0.80 (dt, J = 6.7, 4.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 146.4, 132.1, 129.0, 120.4, 15.3, 9.9.

*Methyl 2-phenylcyclopropane-1-carboxylate (**6c**):* 503 mg (95%); yellow oil;[47] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.20 (m, 3H), 7.14−7.11 (m, 2H), 3.74 (s, 3H), 2.59−2.52 (m, 1H), 1.96−1.91 (m, 1H), 1.66−1.60 (m, 1H), 1.38−1.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 140.0, 128.5, 126.5, 126.2, 51.9, 26.3, 24.0, 17.0.

*1,2-Diphenylcyclopropane (**6d**):* 545 mg (94%); yellow oil;[46] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.33 (m, 4H), 7.27−7.18 (m, 6H), 2.26−2.21 (m, 2H), 1.54−1.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 128.4, 125.8, 28.1, 18.3.

Synthesis of Ethyl 1*H*-Pyrazole-3-carboxylate (7). Diazomethane was generated as described above with feed solutions of 18 mmol of KOH in 9 mL of MeOH/H_2O (1:2) (feed A) and 4.5 mmol of Diazald in 4.5 mL of DMF (feed B). The Erlenmeyer flask, fitted with a stir bar, was filled with 3 mmol (304 μL) of ethyl propiolate in 35 mL of $CHCl_3$ (prior passed through basic Al_2O_3) and was cooled in an ice bath to 0 °C. After the Diazald solution was consumed, the reaction mixture was stirred for further 15 min. The solution was subsequently quenched with acetic acid and extracted with satd $NaHCO_3$. Drying of the organic phase with $MgSO_4$ and evaporation of the solvent provided the product as a colorless solid in 88% yield (370 mg) and >99% purity: mp 162−163 °C (lit.[48] mp 160−162 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.55 (brs, 1H), 7.84 (d, J = 2.3 Hz, 1H), 6.87 (d, J = 2.3 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 141.9, 132.2, 107.7, 61.0, 14.4.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01190.

Pictures of the reactor, optimization of reactions, and ^{1}H and ^{13}C NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Peter Pöchlauer (DPx Fine Chemicals Austria) for constructive discussions and the workshop of the Institute of Chemistry at University of Graz for constructing parts of the reactor. Funding from NAWI Graz and Research Center Pharmaceutical Engineering (RCPE) for the ReactIR system is gratefully acknowledged.

■ REFERENCES

(1) (a) Black, T. H. *Aldrichimica Acta* **1983**, *16*, 3. (b) Gompper, R. *Adv. Heterocycl. Chem.* **1963**, *2*, 245. (c) Dean, F. M. In *Some Recent Developments in the Chemistry of Natural Products*; Rangaswami, S., Subba Rao, N. V., Eds; Prentice-Hall, New Delhi, 1972; p 71.

(2) (a) Schoental, R. *Nature* **1960**, *188*, 420. (b) Lewis, C. E. *J. Occup. Environ. Med.* **1964**, *6*, 91.

(3) De Boer, T. J.; Backer, H. J. *Org. Synth.* **1963**, *4*, 250.

(4) (a) Mastronardi, F.; Gutmann, B.; Kappe, C. O. *Org. Lett.* **2013**, *15*, 5590. (b) Pinho, V. D.; Gutmann, B.; Miranda, L. S. M.; de Souza, R. O. M. A.; Kappe, C. O. *J. Org. Chem.* **2014**, *79*, 1555. (c) Pinho, V. D.; Gutmann, B.; Kappe, C. O. *RSC Adv.* **2014**, *4*, 37419.

(5) Maurya, R. M.; Park, C. P.; Lee, L. H.; Kim, D.-P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5952.

(6) For industrial-scale applications using membrane technology, see: Poechlauer, P. *Chim. Oggi/Chem. Today* **2012**, *30* (4), 51.

(7) For industrial-scale applications using other separation technologies, see: (a) Proctor, L. D.; Warr, A. J. *Org. Process Res. Dev.* **2002**, *6*, 884. (b) Archibald, T. G. *Chim. Oggi/Chem. Today* **2000**, *18* (6), 34. (c) Archibald, T. G.; Barnard, J. C.; Reese, H. F. US 5854405, Dec 29, 1998.

(8) For recent reviews discussing the concept of continuous CH_2N_2 generation, see: (a) Deadman, B. J.; Collins, S. G.; Maguire, A. R. *Chem. - Eur. J.* **2015**, *21*, 2298. (b) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981. (c) Müller, S. T. R.; Wirth, T. *ChemSusChem* **2015**, *8*, 245.

(9) For a related tube-in-tube reactor strategy for the preparation of trifluoromethyl diazomethane, see: Pieber, B.; Kappe, C. O. *Org. Lett.* **2016**, *18*, 1076.

(10) The tube-in-tube device was originally developed in the Ley laboratory as a gas addition tool. For selected references, see: (a) Polyzos, A.; O'Brien, M.; Petersen, T. P.; Baxendale, I. R.; Ley, S. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 1190. (b) Koos, P.; Gross, U.; Polyzos, A.; O'Brien, M.; Baxendale, I.; Ley, S. V. *Org. Biomol. Chem.* **2011**, *9*, 6903. (c) O'Brien, M.; Taylor, N.; Polyzos, A.; Baxendale, I. R.; Ley, S. V. *Chem. Sci.* **2011**, *2*, 1250. (d) Brzozowski, M.; O'Brien, M.; Ley, S. V.; Polyzos, A. *Acc. Chem. Res.* **2015**, *48*, 349.

(11) The tube-in-tube device is available from Uniqsis, Ltd.

(12) Methods and technologies to handle solids in continuous flow reactors are under active development. For reviews on this topic, see:

DOI: 10.1021/acs.joc.6b01190
J. Org. Chem. 2016, 81, 5814−5823

(a) Hartman, R. L. *Org. Process Res. Dev.* **2012**, *16*, 870. (b) Chen, Y.; Sabio, J. C.; Hartman, R. L. *J. Flow Chem.* **2015**, *5*, 166.
(13) For a preliminary report involving this type of diazomethane reactor concept for the preparation of HIV drugs, see: Garbarino, S.; Guerra, J.; Poechlauer, P.; Gutmann, B.; Kappe, C. O. *J. Flow Chem.* **2016**, 1. Note that in this paper diazomethane was generated from a different precursor.
(14) AF-2400 tubings are available from Biogeneral, Inc.
(15) O'Brien, M.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2010**, *12*, 1596.
(16) Greene, J. F.; Preger, Y.; Stahl, S. S.; Root, T. W. *Org. Process Res. Dev.* **2015**, *19*, 858.
(17) (a) http://www.cdc.gov/niosh/ipcsneng/neng1256.html, accessed May 19, 2016. (b) National Research Council (US) Committee on Prudent Practices in the Laboratory. *Prudent Practices in the Laboratory: Handling and Management of Chemical Hazards: Updated Version*; National Academies Press: Washington, DC; 2011. Available from http://www.ncbi.nlm.nih.gov/books/NBK55878/.
(18) The nominal residence time is calculated from the flow rate and the residence volume. Due to the formation of considerable amounts of gas the actual residence time is significantly shorter.
(19) (a) http://www.sigmaaldrich.com/labware/glassware-catalog/distillation-equipment.html, accessed May 19, 2016. (b) Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377.
(20) Ambhaikar, N. B. In *Name Reactions in Heterocyclic Chemistry II*; Li, J. J., Ed; John Wiley & Sons: Hoboken, NJ, 2011; p 214.
(21) (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.
(22) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.
(23) (a) Morandi, B.; Carreira, E. M. *Science* **2012**, *335*, 1471. (b) Nefedov, O. M.; Tomilov, Y. V.; Kostitsyn, A. B.; Dzhemilev, U. M.; Dokitchev, V. A. *Mendeleev Commun.* **1992**, *2*, 13.
(24) Burguete, M. I.; Cornejo, A.; García-Verdugo, E.; García, J.; Gil, M. J.; Luis, S. V.; Martínez-Merino, V.; Mayoral, J. A.; Sokolova, M. *Green Chem.* **2007**, *9*, 1091.
(25) Roda, N. M.; Tran, D. N.; Battilocchio, C.; Labes, R.; Ingham, R. J.; Hawkins, J. M.; Ley, S. V. *Org. Biomol. Chem.* **2015**, *13*, 2550.
(26) (a) Illa, O.; Rodriguez-Garcia, C.; Acosta-Silva, C.; Favier, I.; Picurelli, D.; Oliva, A.; Gómez, A.; Branchadell, V.; Ortuño, R. M. *Organometallics* **2007**, *26*, 3306. (b) McCrindle, R.; Arsenault, G. J.; Farwaha, R.; McAlees, A. J.; Sneddon, D. W. *J. Chem. Soc., Dalton Trans.* **1989**, 761.
(27) Vallgårda, J.; Appelberg, U.; Csöregh, I.; Hacksell, U. *J. Chem. Soc., Perkin Trans. 1* **1994**, 461.
(28) (a) Bernardi, F.; Bottoni, A.; Miscione, G. P. *Organometallics* **2001**, *20*, 2751. (b) Rodriguez-Garcia, C.; Oliva, A.; Ortuño, R. M.; Branchadell, V. *J. Am. Chem. Soc.* **2001**, *123*, 6157. (c) Straub, B. F. *J. Am. Chem. Soc.* **2002**, *124*, 14195.
(29) (a) Tomilov, Y. V.; Dokitchev, V. A.; Dzhemilev, U. M.; Nefedov, O. M. *Russ. Chem. Rev.* **1993**, *62*, 799. (b) Tomilov, Y. V.; Bordakov, V. G.; Dolgii, I. E.; Nefedov, O. M. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1984**, *33*, 533.
(30) de Vries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 3285.
(31) The dry (!) reactor can be cleaned with nitric acid after Pd black precipitation. In order to avoid cross-contamination or byproduct formation, the reactor should be cleaned after each Pd-catalyzed reaction. For a detailed cleaning procedure, see the Supporting Information.
(32) Despotopoulou, C.; Klier, L.; Knochel, P. *Org. Lett.* **2009**, *11*, 3326 and references cited therein.
(33) Khidre, R. E.; Abdel-Wahab, B. F.; Farahat, A. A.; Mohamed, H. A. *J. Heterocyclic Chem.* **2016**, *53*, 13.
(34) Terrett, N. K.; Bell, A. S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1819.
(35) (a) Yet, L. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, U.K., 2008; Vol. *4*, p 1. (b) Fustero, S.; Sánchez-Roselló, M.; Barrio, P.; Simón-Fuentes, A. *Chem. Rev.* **2011**, *111*, 6984. (c) Padwa, A. *1,3- Dipolar Cycloaddition Chemistry*; John Wiley & Sons: New York, 1984; Vol. *I*.
(36) (a) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381. (b) Padwa, A.; Wannamaker, M. W. *Tetrahedron* **1990**, *46*, 1145.
(37) Yang, L.; Jensen, K. F. *Org. Process Res. Dev.* **2013**, *17*, 927.
(38) De Boer, Th. J.; Backer, H. J. *Org. Synth.* **1963**, *4*, 943; **1954**, *34*, 96.
(39) Seo, S.; Taylor, J. B.; Greaney, M. F. *Chem. Commun.* **2012**, *48*, 8270.
(40) Chen, S.; Jia, L.; Li, X.; Luo, M. *Synthesis* **2014**, *46*, 263.
(41) Samanta, K.; Sarkar, A. K.; Kar, G. K. *Synth. Commun.* **2013**, *43*, 384.
(42) Yang, Q.; Wang, X.-J.; Li, Z.-Y.; Sun, L.; You, Q.-D. *Synth. Commun.* **2008**, *38*, 4107.
(43) Jafarpour, F.; Olia, M. B. A.; Hazrati, H. *Adv. Synth. Catal.* **2013**, *355*, 3407.
(44) El-Ahl, A. A. S.; Elbeheery, A. H.; Amer, F. A. *Synth. Commun.* **2011**, *41*, 1508.
(45) Thvedt, T. H. K.; Fuglseth, E.; Sundby, E.; Hoff, B. H. *Tetrahedron* **2009**, *65*, 9550.
(46) Sarria Toro, J. M.; den Hartog, T.; Chen, P. *Chem. Commun.* **2014**, *50*, 10608.
(47) Davies, H. M. L.; Walji, A. M. *Org. Lett.* **2005**, *7*, 2941.
(48) Matteson, D. S. *J. Org. Chem.* **1962**, *27*, 4293.

DOI: 10.1021/acs.joc.6b01190
J. Org. Chem. 2016, 81, 5814−5823