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Aldrichimica ACTA

Photocatalytic C–F Reduction and Functionalization

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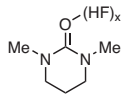
(1) Okoromoba, O. E.; Han, J.; Hammond, G. B.; Xu, B. *J. Am. Chem.* Soc. **2014**, *136*, 14381. (2) Okoromoba, O. E.; Hammond, G. B.; Xu, B. *Org. Lett.* **2015**, *17*, 3975.



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ABOUT OUR COVER

Young Woman with Peonies (oil on canvas, 60 × 75 cm) was painted in 1870 by Frédéric Bazille (1841–1870). Born into a wealthy Montpellier family, his interest in art started early, and, because of his parents' insistence on him studying medicine, he moved to Paris in 1862 to study both. There, he quickly became a close friend of Monet, Renoir, and Sisley, who were fellow students in Charles Gleyre's art studio, and, together with them and with Pissarro, pioneered the Impressionist style of painting. Having failed his medical exams in 1864, Bazille then devoted his energy to painting fulltime.

Detail from ***Young Woman with Peonies***. Photo courtesy National Gallery of Art, Washington, DC.

The Impressionist movement aimed to capture on canvas fleeting moments in particular landscapes or in the lives of ordinary people in their natural settings (outside the artist's studio), to capture a generally realistic "impression" of the scene by highlighting the effects of light and shadows. This depiction, possibly of a flower vendor, is one of Bazille's last* and beautifully exemplifies this style. It was perhaps inspired by a famous painting, *Olympia* (at the Musée d'Orsay, Paris), executed and exhibited just a few years earlier by Édouard Manet, another of Bazille's friends and one of his influences.

This painting is part of the Collection of Mr. and Mrs. Paul Mellon at the National Gallery of Art, Washington, DC.

One of a pair of similar paintings executed by Bazille just a few months before he died. To find out more, visit* ***sigma-aldrich.com/acta493*

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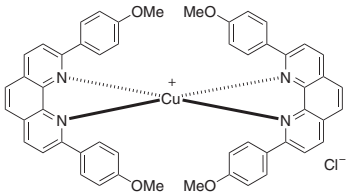
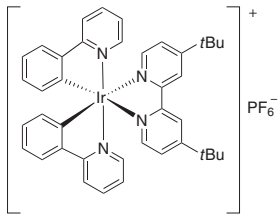


L511803
$Cu(dap)_2$ chloride



L511838
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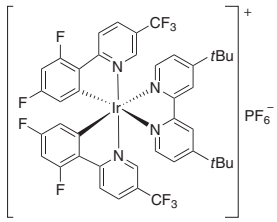
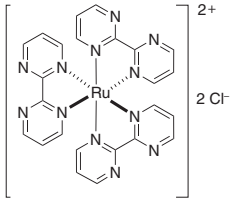


L511765
$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$



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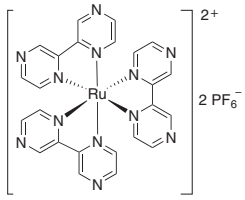

L511773
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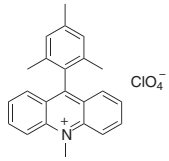
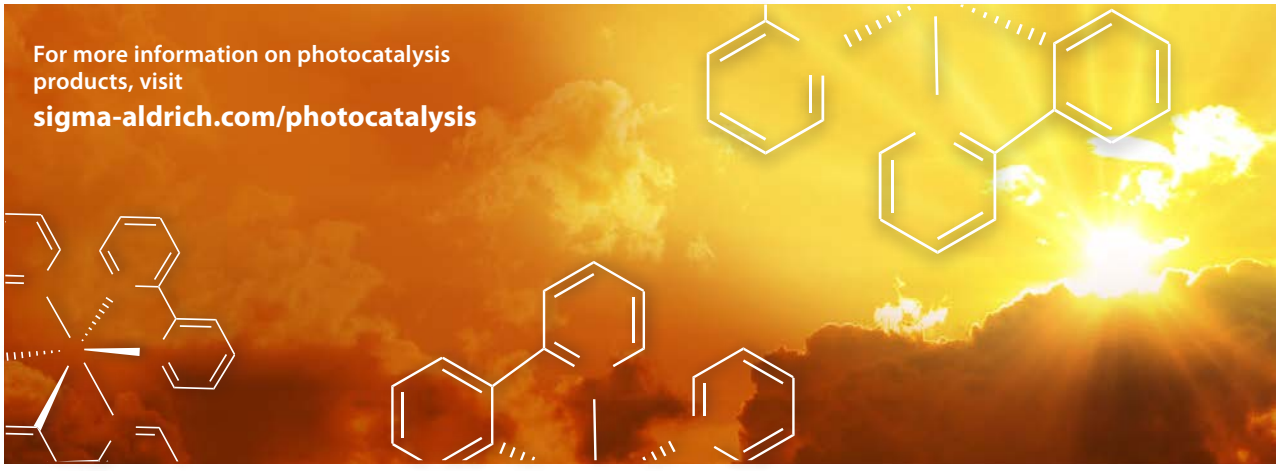


L511811
9-Mesityl-10-methylacridinium perchlorate

Reference:
Douglas, J. J.; Nguyen, J. D.; Cole, K. P.; Stephenson, C. R. J. *Aldrichimica Acta* **2014**, *47*, 15.



Photocatalytic C–F Reduction and Functionalization

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Prof. J. D. Weaver

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Keywords. hydrodefluorination; C–F functionalization; photocatalysis; partially fluorinated aromatics.

Abstract. Functionalized polyfluorinated aromatics have become an important group of molecules for pharmaceutical and industrial applications. However, facile access to such valuable molecules remains an unmet challenge. In this review, we present and discuss photocatalytic C–F functionalization, which is emerging as a straightforward and operationally simple path to access partially fluorinated aromatics.

Outline

1. Introduction

Fluorinated organic compounds have become an extremely important and valued class of molecules with amplified use as pharmaceuticals[1] and agrochemicals,[2] and with a number of industrial applications such as organic photovoltaics (i.e., OLEDs)[3] and liquid crystal molecules.[4] Following the invention in the 1950s of the first fluorine-containing pharmaceutical, fludrocortisone,[1a] the field has grown rapidly. In the last few decades, the frequency of fluorine incorporation within drugs has risen sharply. Starting from 2% of drugs that contained fluorine in 1970, this proportion has grown to about 25% of the total number of drugs available today.[1b] Furthermore, among the small-molecule drugs that have been approved by the U.S. Food and Drug Administration (FDA) in 2013, 33% contained a C–F bond and several of them (i.e., Adempas®, Gilotrif®, Tafinlar®, Tivicay®) contain a fluoroarene moiety in their structure. Within the crop sciences, the percentage of molecules containing organofluorine is at least 30%.[5]

Upon close inspection of the structures of medicinally and industrially important fluoroaromatics, some common features can be identified (**Figure 1**). Almost all of them are (i) considerably functionalized in order to perform a desired role, (ii) partially fluorinated not perfluorinated, and (iii) the fluoroaromatic moiety in each serves as a terminating unit except in very few cases. This latter observation is perhaps due to the unavailability of complex polyfluorinated arenes that can serve to elaborate the molecules further. Recently, more efforts have been devoted to the development of selective fluorination strategies that can be employed to access polyfluorinated arenes. These strategies include C–H fluorination[6] (**Scheme 1**, Part (a)) and cross-coupling reactions using both nucleophilic[7] and electrophilic[8] fluorine sources (Scheme 1, Part (b)). While these methods have significantly expanded the number of accessible fluorinated arenes, the need for arenes that contain either strategically prefunctionalized or specific directing groups in the starting arene limits the use of such methods. This limitation is most clear when polyfluorinated arenes are desired, which would require highly elaborated starting materials, or simply may not be accessible with directed fluorination.[6b,9] An alternate approach would be to start with a simple perfluoroarene in which C–F bonds already exist in all of the desired locations, and develop selective C–F functionalization reactions that utilize the undesired C–F bonds to construct the molecule. If successful, the perfluoroarene would serve as a synthetic lynchpin of polyfluorinated arenes. For instance, current syntheses of fluorinated azole fungicides share a common synthetic intermediate, **2a**,[1a] which is accessible in six steps from 1,3-dichlorobenzene (**2j**), a nonfluorinated commercially available starting material (**Scheme 2**).[10] Conceivably, direct C–F functionalization of the corresponding perfluoroarene, **2k**, followed by C–F reduction could significantly shorten the synthetic sequence. In this review, we present and discuss recent advances in the field of photocatalytic C–F reduction and functionalization of polyfluoroarenes, whereby new reactions are developed that can provide facile and rapid synthesis of functionalized polyfluorinated aromatics.

2. Hydrodefluorination

As an alternative to selective fluorination, hydrodefluorination (HDF) (Scheme 1, Part (c))[5,11] has emerged as one way to access polyfluorinated arenes. While the potential advantages of the HDF approach as compared to existing selective fluorinations make it attractive, a number

of challenges make its future less clear. Although the reduction of aryl iodides, bromides, and even chlorides is feasible,[11] cleavage of short and strong C_{aryl}–F bonds (**Figure 2**) has been a challenge. The extreme properties associated with C–F bonds make the design of efficient HDF catalysts quite challenging.

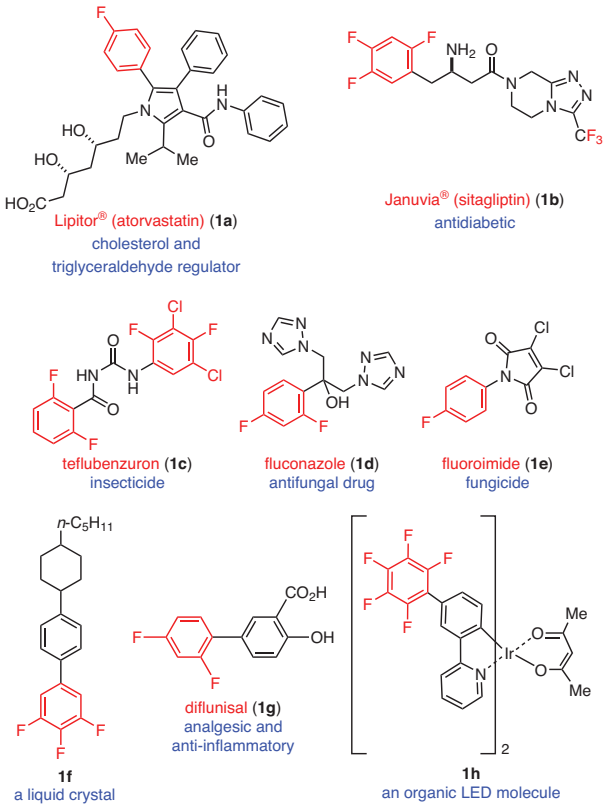
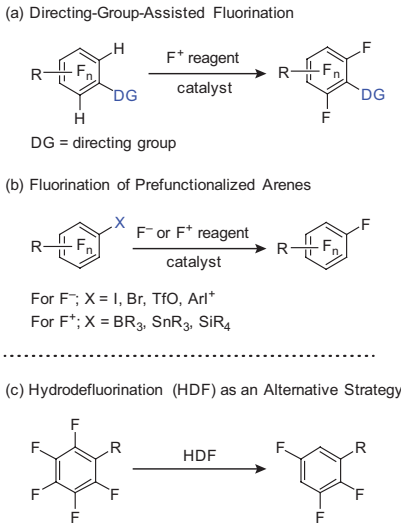


Figure 1. Pharmaceutically and Industrially Important Fluorinated Aromatics.

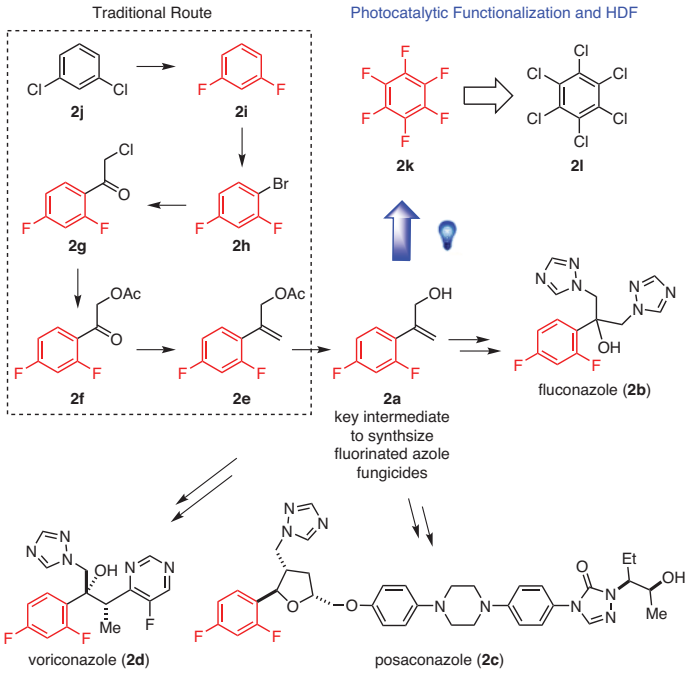


Scheme 1. Selective Fluorination Strategies and Hydrodefluorination (HDF).

Existing catalysts for HDF reactions often suffer from low turnover numbers (TONs) due to the formation of strong metal–fluorine bonds during the catalytic cycle. In their attempts to develop more robust HDF systems, chemists have utilized a number of strategies to deal with this dilemma. One solution is to use "fluorophilic" silyl[12] or aluminum[13] hydrides, in which the hydride-bearing atom itself can form a strong fluorine bond, liberating the catalyst from the thermodynamic well and increasing the overall exergonicity of the reaction. Nonetheless, most HDF systems still suffer from low TONs.[14]

2.1. Photocatalytic Hydrodefluorination

In recent years, photoredox catalysis[15] has become popular as a way to introduce a single electron into a molecule. The beauty of photocatalyzed single-electron chemistry is the ability to make reactive species catalytically and in a controlled manner in situ. Given this and indirect evidence from Stephenson's photocatalytic C_{aryl}–I reduction,[16] investigations have been undertaken to selectively reduce C–F bonds using visible light photocatalysis. The prediction was that *fac*-tris[2-phenylpyridinato-C^2,*N*]iridium(III) [*fac*–Ir(ppy)$_3$], which is a coordinatively saturated 18-electron complex and a potent reductant



Scheme 2. Actual and Potential Expedient Syntheses of Key Intermediate for Fluorinated Azole Fungicides. *(Ref. 1a,10)*

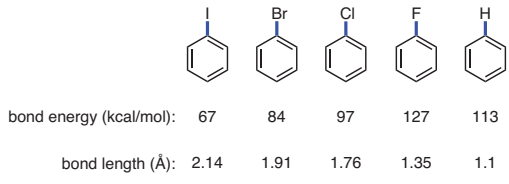


Figure 2. Comparison of Aryl–X Bond Lengths and Strengths.

[Ir(III)/(II), –2.19 V vs SCE][15a,17a] would be capable of transferring an electron to the perfluoroarene. This was expected to lead to fragmentation of the C–F bond to give a fluoride, perfluoroaryl radical, and ultimately the desired C–F reduced products after a hydrogen-atom transfer.[17b,c] Furthermore, the outer sphere nature of the electron transfer might avoid the problematic catalyst–fluoride intermediates and lead to higher TONs.

Pentafluoropyridine (**3b**) was chosen as the model substrate, because electron transfer was expected to be slightly exothermic between the reduced photocatalyst [Ir(III)/(II)] and **3b** (**3b**, V = –2.12 vs SCE) (**Figure 3**).[18] When the photocatalyst, **4a**, absorbs a photon in the visible region (**Scheme 3**), it is promoted to an excited state (**4b**).[15a] From this excited state, the photocatalyst can act as either a reductant or an oxidant.[15a] It was proposed that a single-electron transfer from the tertiary aliphatic amine (**4c**) to the excited state of the catalyst (i.e., reductive quenching) results in an amine radical cation (**4d**) and the reduced photocatalyst (**4e**). Intermediate **4e** engages in an outer-sphere electron transfer to the fluoroarene substrate, **3b**, to generate a perfluoroaryl radical anion, **4f**. Subsequent fluoride extrusion forms a perfluoroaryl radical (**4g**) which then abstracts a hydrogen atom from either the amine, **4c**, or amine radical cation, **4d**, leading to the desired reduced product, **4k**. The other results discussed in this review arise from the interception of the versatile key radical intermediate **4g** with π bonds of alkenes, arenes, and alkynes. The interception with alkynes has been employed to understand the underlying controlling factors of energy vs electron transfer, by which *E*- or *Z*-alkene products can be obtained by the judicious choice of photocatalyst. The use of the inexpensive and easy-to-handle *N,N*-diisopropylethylamine (*i*-Pr_2NEt) as the reductant alleviates the need for fluorophilic metal hydrides, and makes this methodology operationally simple.

2.2. Mono(hydrodefluorination)

Under the optimized conditions, both electron-deficient perfluoro-heteroarenes and electron-rich fluorinated heterocycles underwent smooth mono-HDF to form **5a**, **5f**, and **5h**, respectively (**eq 1**).[19] The

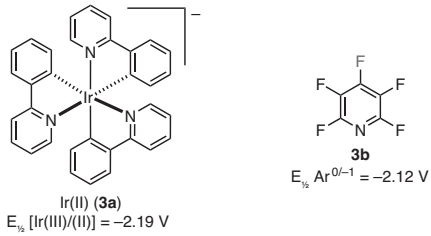
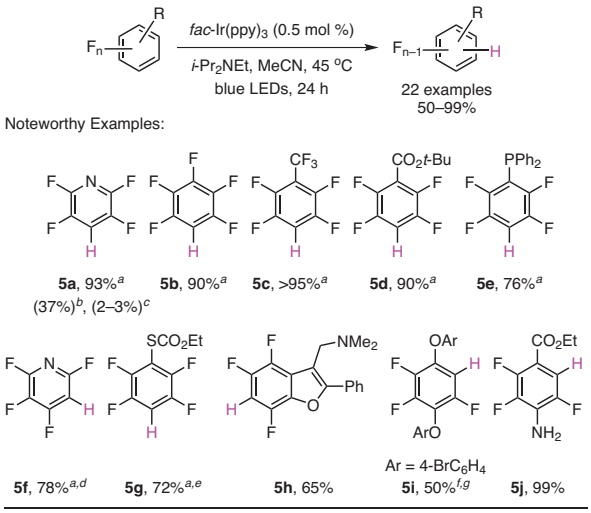
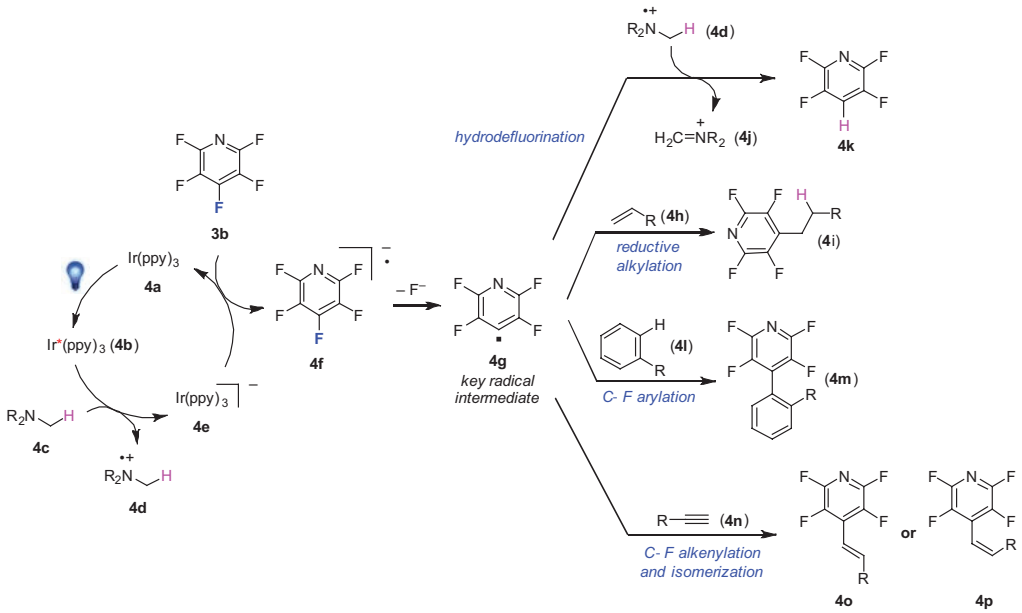


Figure 3. Comparison of Catalyst and Substrate Reduction Potentials. *(Ref. 18)*



[a] ^{19}F NMR yield. [b] Obtained with $Ru(bpy)_3Cl_2$. [c] Obtained with $Ru(bpm)_3Cl_2$. [d] From 3-chlorotetrafluoropyridine. [e] Contains 10% di-HDF product. [f] 65 °C, 72 h. [g] At 70% conversion.

eq 1 *(Ref. 19)*



Scheme 3. Plausible Mechanistic Pathways to HDF and Reductive Alkylation, Arylation, and Alkenylation.

reaction demonstrated remarkable functional group tolerance, and had a broad substrate scope. It is worth noting that the chlorine atom in 3-chlorotetrafluoropyridine was preferentially fragmented leading to **5f**, while the distant bromines in the precursor to **5i** survived the HDF with only a trace amount of bromine loss. Tertiary aliphatic amines (**5h**) and even phosphines (**5e**) also survived the hydrodefluorination reaction. During the optimization trials, it was found that the two other, significantly less reducing photocatalysts—$Ru(bpy)_3Cl_2$ (V = −1.33 vs SCE) and $Ru(bpm)_3Cl_2$ (V = −0.91 vs SCE)[20] (bpy = 2,2'-bipyridine, bpm = 2,2'-bipyrimidine)—also facilitated HDF (leading to **5a**), albeit at a much slower rate. This phenomenon suggests that there are other unexplored factors governing these electron transfers apart from the reduction potentials alone.

2.3. Di- and Tri(hydrodefluorination)

Often, the rates between the first and second reductions were substantially different such that one could obtain either *mono*-, or *di*-HDF products by simply varying the amount of the amine reductant and reaction time (**eq 2**).[19] The regiochemistry of HDF is primarily dictated by the electronics of the aromatic system in the starting material, though it is worth noting that there can be a steric contribution, as seen by comparing the rate difference between the di-HDF of the methyl (**6d**) and *tert*-butyl (**6e**) esters of perfluorobenzoic acid.

Our group also investigated the robustness of the catalytic system. Repeated additions of pentafluoropyridine and diisopropylethylamine to the photocatalytic system achieved an unprecedented TON of 22,550—the highest among the TONs for all of the HDF systems reported to date. In addition, by utilizing pentafluoropyridine and octafluoronaphthalene, we have demonstrated that the kinetics of the reaction could be further enhanced by utilizing a flow system.[19] Collectively, the ability to perform the photocatalytic reaction in flow and at very low loading of a commercially available catalyst might allow the process to be scaled.

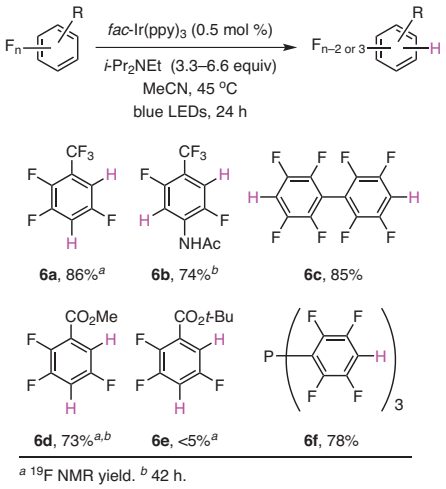
3. Alkylation of Fluoroarenes

Having demonstrated that photoredox catalysis can be employed to break the robust C–F bond and access the relatively unexplored perfluoroaryl radical, we attempted to exploit this understanding to develop more elaborate C–F functionalization reactions. To this end, the first photocatalytic C–F alkylation was published in 2015.[21] Carbon-centered radicals possess a remarkable bond-forming capability[22] with unactivated π bonds that are sterically congested and are generally considered inert under most reaction conditions. Key to utilizing radicals in this manner is their controlled generation. In general, the idea was to intercept with alkenes the perfluoroaryl radical as it is formed. This would result in a more stable, longer-lived alkyl radical, which would then undergo the subsequent H-atom abstraction to afford a net hydroperfluoroarylation of the alkene. Given the vast number of alkenes available, this approach was expected to lead to a large variety of alkylated polyfluoroarenes.

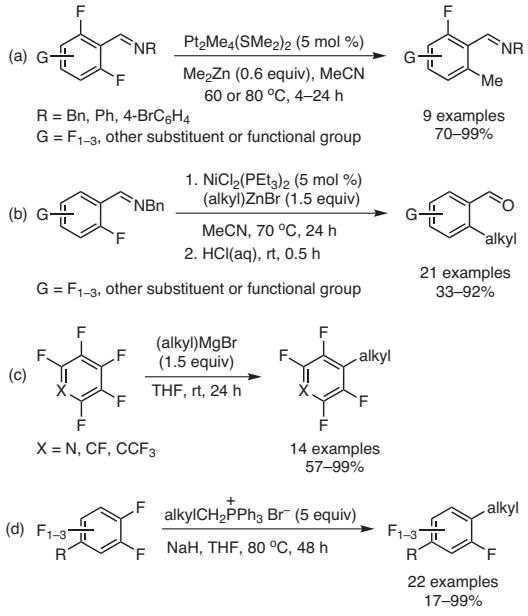
In the last few years, several groups have successfully alkylated highly fluorinated arenes. Love and co-workers have demonstrated the directing-group-assisted ortho alkylation of polyfluoroarenes with Pt[23] and later with Ni[24] based catalysts in the presence of a benzyl imine directing group (**Scheme 4**, Parts (a) and (b)). In 2014, Li's group showed that the direct addition of alkyl Grignard reagents to perfluoroarenes was also possible (Scheme 4, Part (c)).[25] More recently, Wu's team developed a regioselective alkyl transfer from phosphonium ylides to perfluoroarenes (Scheme 4, Part (d)).[26] While these approaches are making inroads toward selective C–F alkylation, there is still an urgent need to develop new synthetic methods that provide access to complex alkylated fluoroarenes.

3.1. Photocatalytic C–F Alkylation of Fluoroarenes

With the goal of developing selective C–F alkylations, our group found that a variety of perfluoroarenes engaged unactivated alkenes to give alkylated products.[21] In general, since the perfluoroaryl radical was anticipated to be extremely unstable and consequently highly reactive,[27] one might have expected that the reaction would be poorly regioselective with respect to the alkene. The addition, however, takes place with excellent selectivity when there are differences in the substitution patterns of the alkene, with addition occurring at the less



eq 2 *(Ref. 19)*



Scheme 4. Previous Alkylation Strategies of Fluoroaromatics. *(Ref. 23–26)*

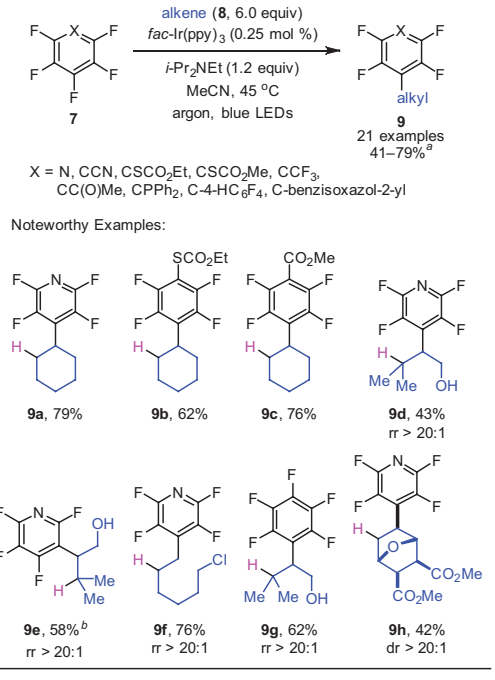
substituted carbon (**9d–f**) of the alkene (**eq 3**). The complementary reactivity of S_NAr chemistry and photocatalysis was demonstrated by subjecting 3-chlorotetrafluoropyridine to the photocatalytic reductive alkylation reaction, which results in the functionalization of the 3-chloro position while keeping the 4-fluoro intact (**9e**). In contrast, S_NAr substitution on this same precursor would be expected to occur at the C-4 position.[28] Survival of the remote alkyl chloride of **9f** is also noteworthy, and speaks to the functional group compatibility of the photocatalytic reaction.

A common disadvantage of previous C–F alkylation reactions was the incremental increase in complexity of the final products, which arises as a result of alkylating reagents that are of low complexity. In this regard, the use of unmodified alkenes presents enormous opportunity to access coupled products that are stereochemically dense in a single step, since sophisticated alkenes are ubiquitous. This feature makes the photocatalytic reductive alkylation reaction extraordinarily versatile. For instance, a [4 + 2] adduct derived from furan has been satisfactorily coupled with pentafluoropyridine, yielding the product, **9h**, which contains five stereocenters—two of them base-labile—three cycles, and a bridging oxygen.

The S_NAr reaction takes advantage of the highly fluorinated nature of perfluoroarenes to simultaneously elaborate the molecules and reduce their fluorine content to access sophisticated fluoroarenes with just 2–3 fluorines. It was initially suspected that the fluorines on the arene ring activate the substrate towards reduction and that the removal of fluorine would deactivate the substrate towards reduction, and thus it was not clear that subsequent photochemical C–F functionalizations would take place with sufficient rates to be useful on substrates with fewer fluorine atoms. A series of substrates containing rings with three fluorine atoms were synthesized and subjected to the reaction. After substitution of the most electronically activated 4 position, photocatalytic functionalization moved to the C–F bond adjacent to the electron-withdrawing group or atom (**eq 4**).[21] The ability to perform photocatalytic C–F functionalizations on previously elaborated substrates would thus allow rapid access to structurally complex, polyfluorinated arenes with diverse functionality.

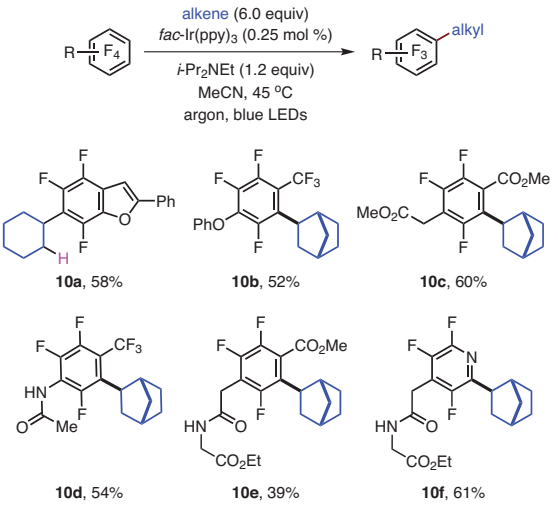
The photochemical functionalization and S_NAr reactions of perfluoroarenes exhibit complementary selectivities (**Scheme 5**).[21,28,29] This phenomenon was demonstrated by subjecting substituted fluoroarenes **11a** and **11b**, which are themselves products of S_NAr chemistry,[28] to the photochemical alkylation conditions (**Scheme 6**).[21]

Densely functionalized arenes with a reduced number of fluorines are a challenging target in drug discovery.[1c] Subsequent photocatalytic HDF of the products could provide access to additional valuable partially fluorinated arenes. Thus, commercially available perfluoroarenes (**13a–d**) were subjected to the S_NAr reaction, giving rise to elaborated perfluoroarenes (**Scheme 7**).[21,28] Next, the elaborated substrates were photocatalytically functionalized to obtain alkylated arenes. Finally, they were subjected to photocatalytic HDF to further reduce the fluorine content, supplying structurally complex difluorinated arenes (**13e–j**).

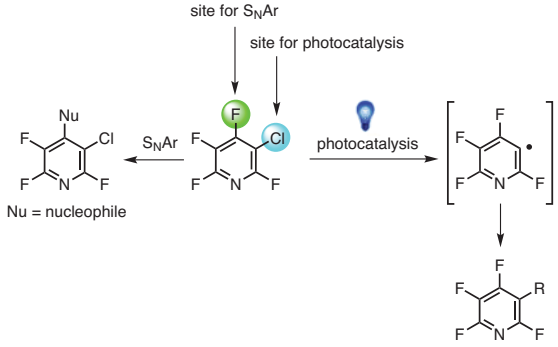


[a] The regioisomeric (rr) and diastereomeric ratios (dr) were determined with respect to the alkene by ^{1}H NMR of the crude reaction mixture after workup. [b] From 3-chlorotetrafluoropyridine.

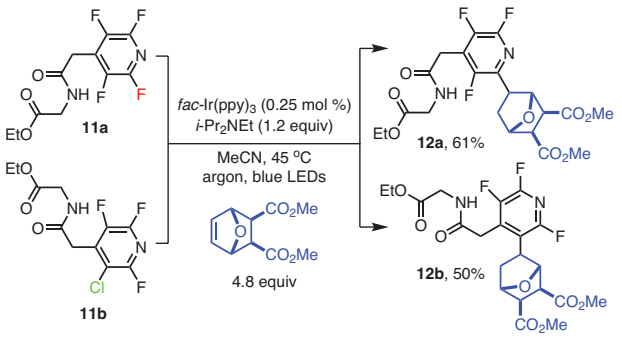
eq 3 *(Ref. 21)*



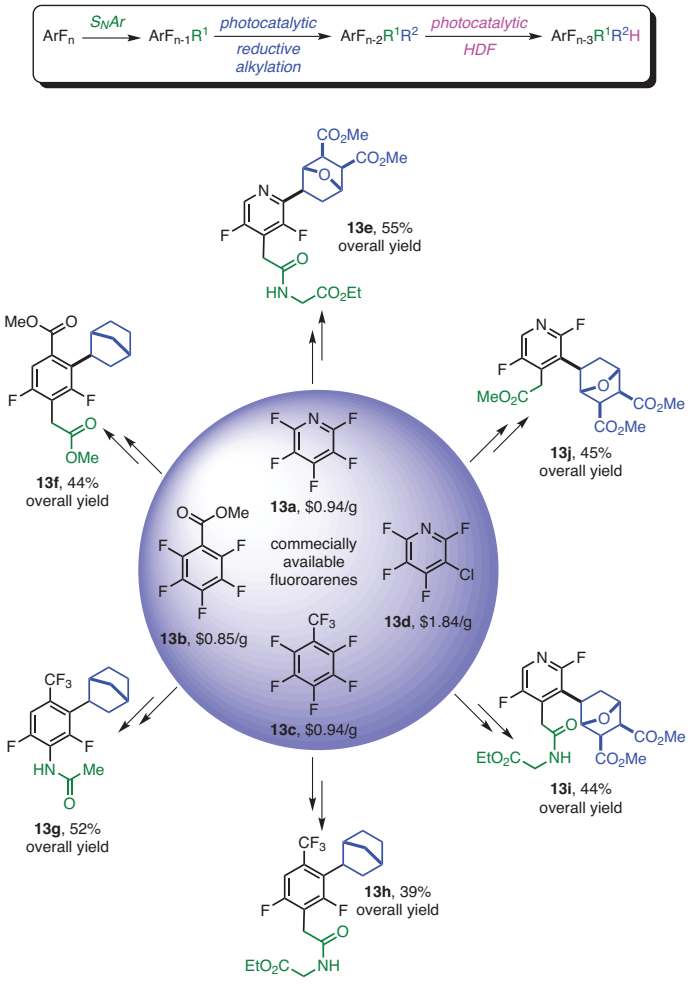
eq 4 *(Ref. 21)*



Scheme 5. Complementary Nature of S_NAr and Photocatalysis. *(Ref. 21,28,29)*



Scheme 6. Accessing Complementary Regioisomers by Using Differential Reactivities of C–X Bonds. *(Ref. 21)*



Scheme 7. Sequential S_NAr and Photocatalysis as a Succinct and Versatile Way to Access Complex, Partially Fluorinated Arenes. *(Ref. 21,28)*

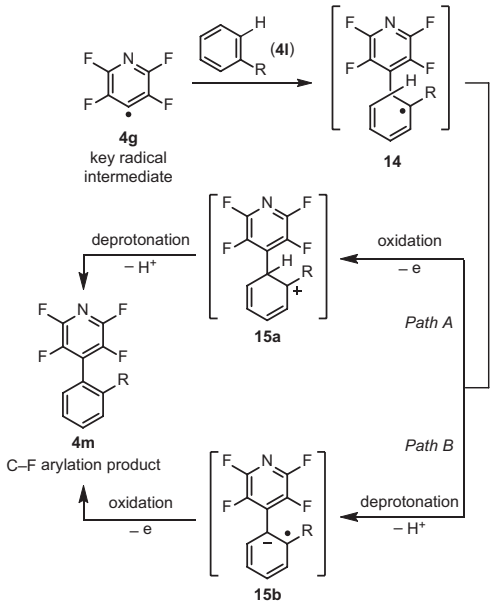
The sequence took place with acceptable yields and with excellent regio- and diastereoselectivities, and demonstrated how structurally complex difluoro aromatics can be obtained in a straightforward manner from commercially available perfluoroarenes.

4. Arylation of Fluoroarenes

Having demonstrated the ability to perform the reductive alkylation of a C–F bond, our group investigated next the possibility of performing an oxidation of the incipient alkyl radical rather than the hydrogen-atom transfer that takes place in the alkylation reaction. It was expected that accomplishing an oxidation might be difficult, since the conditions used to accomplish the C–F fragmentation must produce a strong reductant, at least transiently. As a starting point, hydrogen arenes were chosen, and were anticipated to re-aromatize after temporary loss of aromaticity, which was expected to serve as a driving force for the oxidation. Careful consideration of electronic factors suggested that oxidation of intermediate **14** could happen either before (*Path A*) or after (*Path B*) the deprotonation step (**Scheme 8**).[29] The actual path taken would depend on the nature of the two arene partners. Starting with the HDF conditions, the reaction was optimized to produce appreciable amounts of the C–F arylation product, demonstrating the first catalytic dual C–F, C–H functionalization to obtain polyfluorinated biaryls,[29] though other less direct methods exist (**eq 5**).[30]

4.1. Photocatalytic Arylation

Unlike reductive alkylation, the desired arylation of fluoroarenes is expected to end with oxidative re-aromatization. Since there is no hydrogen-atom abstraction during the generation of the desired product, it was speculated that the amine might simply serve as a transient electron donor and a base. Consequently, substoichiometric amounts of amine base would be sufficient for the reduction of the catalyst, *fac*-Ir(ppy)$_3$, if it were liberated from the HF salt. Given that the free amine, *i*-Pr$_2$NEt, can act as a hydrogen atom source as well, the amount of the HDF product could be controlled by keeping the amine



Scheme 8. Proposed Mechanism for C–F Arylation. *(Ref. 29)*

content low and lowering the temperature. An inorganic base, $KHCO_3$, was found to be optimal for scavenging the HF byproduct. Good-to-modest yields were obtained for a variety of fluoroarenes and electron-rich and electron-poor H-arenes that were coupled together (**eq 6**).[29] The ability of the perfluoroaryl radical to form highly sterically congested C–C bonds (**16d**) is particularly noteworthy and is rivaled by few methods. Consistent with that observed in the photocatalytic HDF (**5f**) and photochemical C–F alkylation chemistry (**9e**), C–Cl fragmentation (**16h**) takes place selectively over C–F fragmentation. Interestingly, some basic heterocycles showed *anti*-Minisci selectivity (**16f**,**g**) demonstrating a divergence from typical radical addition to basic heterocycles (**Figure 4**).[29] This difference may be due to the differences in pH between the photocatalytic C–F, C–H arylation and typical Minisci conditions, which are strongly acidic. The acidic matrix protonates the basic heterocycles and causes a polarity reversal.

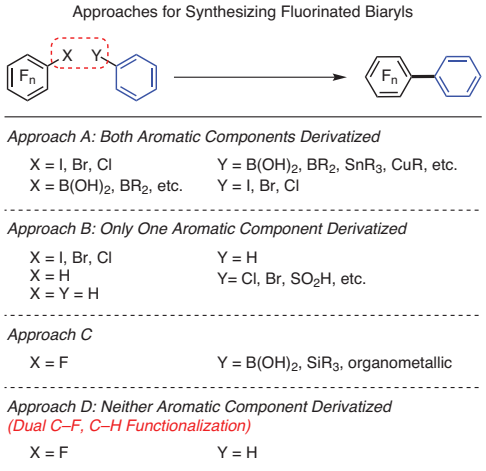
Given the mildness of the reaction and the ability to construct sterically congested biaryls, it was envisioned that the reaction would be ideal for late-stage functionalization. This could ease the difficult fluoroarene installation and offer an alternative route to some of the lengthy procedures to access fluorinated biaryls. In the case of heavily functionalized H-arenes, which would likely be the more valuable component of the reaction mixture, it is logical to use the perfluoroarene as the excess reagent (**eq 7**).[29]

Recall that the further photocatalytic alkylations and reductions were possible on the substrates with a reduced number of fluorines (see Scheme 7). Similarly, we wanted to demonstrate the ability to access *di*-fluorinated biaryls. The commercially available fluoroarenes were subjected to sequential substitution, arylation, and HDF. Electronically determined regioselectivity was observed during the HDF reaction, while some other competing phenomena gave rise to minor regioisomers (**Scheme 9**).[29]

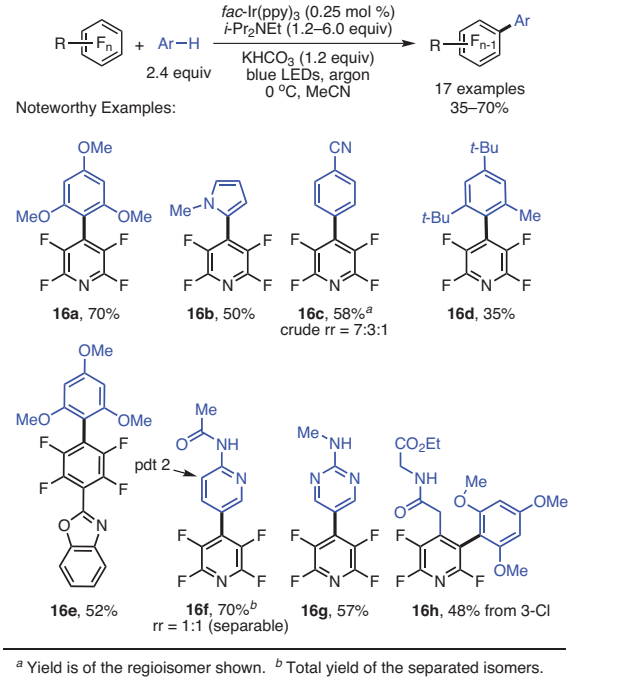
5. Photocatalytic Alkenylation and Energy Transfer

The work described so far in this review is a consequence of photocatalyst-induced electron transfer that results in either C–F reductions or C–F functionalizations, leading to new C–C bonds. However, it has been shown that the excited state of the Ir-based photocatalysts can also be quenched via an energy-transfer process rather than electron transfer in cases where a styrenyl-like system is present.[31] However, the reactions employing both electron transfer and energy transfer are rather rare, presumably due to a diminutive understanding of the factors that govern these two fundamentally different processes. Among the very few examples of sequential electron and energy transfers,[32] chemists have utilized strategies such as a solvent change to favor electron transfer or a switch to photocatalysts of insufficient energy to prevent energy transfer.[32,33] In order to gain a better insight into how to switch between these two mechanistically distinct photoquenching processes, a novel hydrofluoroarylation reaction of alkynes was conceived. Toward that end, the work on selective energy transfer was integrated with the ability to perform C–F functionalization via photocatalytic electron transfer.[32,34] The proposed reaction was ideal, because the available photocatalysts that were sufficiently reducing to induce C–F fragmentation were also sufficiently energetic to facilitate the isomerization event, effectively removing the known strategies for separating these two mechanistic processes.

Additionally, we were interested in investigating an underexplored facet of photocatalytic energy transfer, specifically, the rate of energy transfer as a function of intermolecular distance between the substrate



eq 5 *(Ref. 30)*



eq 6 *(Ref. 29)*

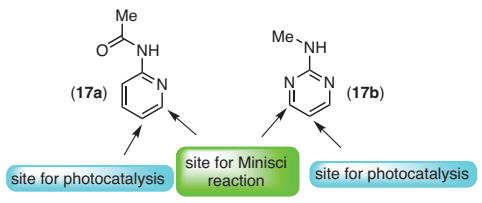
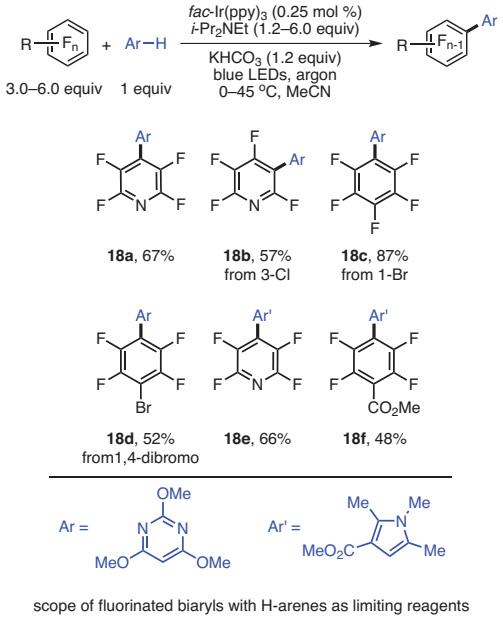


Figure 4. Observed *anti*-Minisci Selectivity. *(Ref. 29)*



scope of fluorinated biaryls with H-arenes as limiting reagents

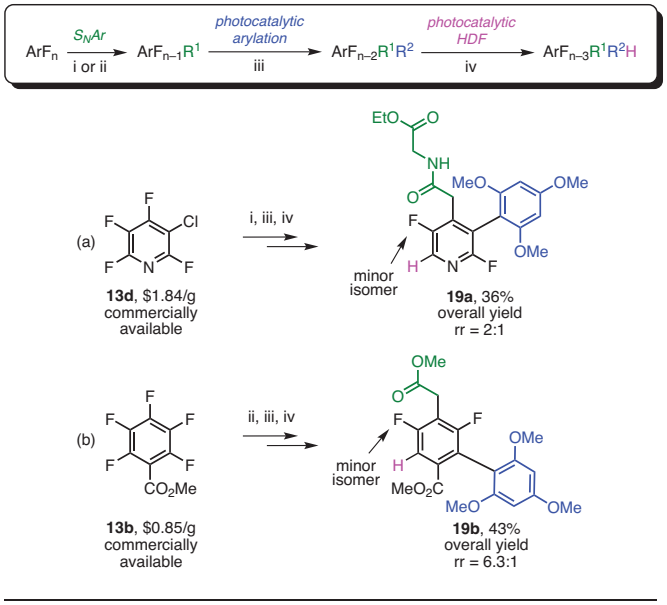
eq 7 *(Ref. 29)*

and photocatalyst.[35] Given that both Förster's[36] and Dexter's[37] energy-transfer processes are known to be highly dependent on internuclear distance, we anticipated that the steric volume of the photocatalyst could potentially serve as a handle that would allow us to turn energy transfer on or off. The key radical intermediate, **4g**, generated via electron transfer would add to the alkyne to give a vinyl radical, **20a**, followed by H-atom abstraction to give the alkenylated product, **20b** (**Scheme 10**).[35] An energy-transfer process could then lead to a selective double-bond isomerization to obtain the *Z* isomer, **4p**, preferentially.

First, we carried out optimizations that focused on achieving high yields of the alkenylated product, regardless of *E* or *Z* geometry. Incremental addition of amine and reduced temperature suppressed the formation of the undesired (HDF) product.

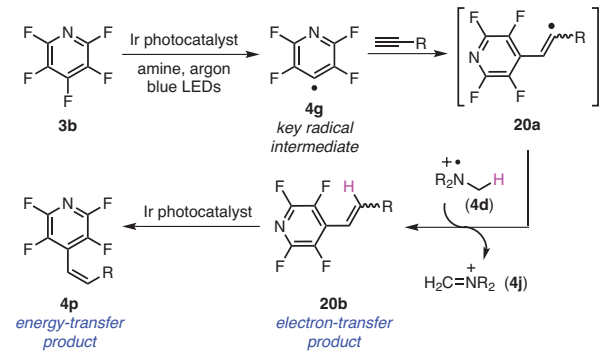
Next, to probe the mechanistic details, a bulky alkyne, *tert*-butylacetylene (**21**, **Scheme 11**) was used because of its strong kinetic preference for the *E* isomer (**22a**) and large preference for the *Z* isomer (**22b**) at the photostationary state.

The observation of sensitized isomerization of stilbenes with planar sensitizers, such as benzophenone and xanthone, had revealed a strong correlation between the emissive energy of the sensitizer and the *Z*:*E* ratio.[38] In contrast to such planar sensitizers, Ir-based photocatalysts with three bidentate ligands are approximately spherical, and a plot of log(*Z*:*E*) vs the photocatalyst's emissive energy revealed no correlation.[38] The plot of log(*Z*:*E*) as a function of the radius of the catalyst approximated as a sphere shows a linear correlation, suggesting

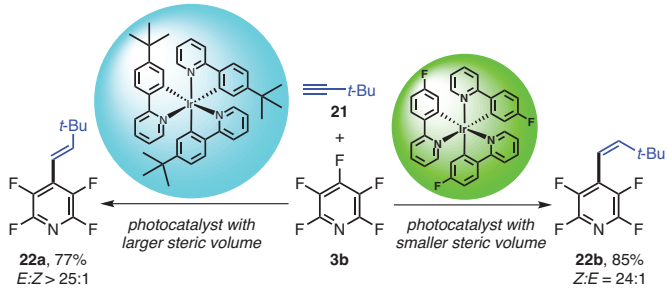


i. (a) **A**, *i*-Pr$_2$NEt; (b) **C** (93%). ii. (a) **A**, *i*-Pr$_2$NEt; (b) HCl, **MeOH** (>99%)
iii. **B**, *fac*-Ir(ppy)$_3$ (0.25 mol %), *i*-Pr$_2$NEt, MeCN, blue LEDs, argon, 0 °C (48 or 52%)
iv. *fac*-Ir(ppy)$_3$ (0.25 mol %), *i*-Pr$_2$NEt, MeCN, blue LEDs, argon, 45 °C (81 or 83%)

Scheme 9. Elaboration via Synergistic S_NAr and Photocatalysis. *(Ref. 29)*



Scheme 10. Photocatalytic Alkenylation and Isomerization via Subsequent Electron- and Energy-Transfer Processes. *(Ref. 35)*



Scheme 11. Observed Alkenylation *E* or *Z* Switch by Switching Photocatalysts with Different Steric Volumes. *(Ref. 35)*

that the propensity to undergo energy transfer diminishes as the volume of the catalyst increases. This valuable observation should lead chemists to consider the size of photocatalysts as a sensitive parameter that can be employed to switch between photocatalyzed processes regardless of emissive energy.

6. Conclusions and Outlook

In summary, photocatalysis is becoming a powerful tool to help solve the central problem of C–F functionalization as it pertains to accessing polyfluorinated arenes. It has been shown that photocatalysis provides access to the reactive perfluoroaryl radical, and we have demonstrated several strategies for intercepting the radical with a variety of coupling partners. The use of a commercially available photocatalyst and a tertiary aliphatic amine furnished the highest reported TON for an HDF reaction without any need for metal hydrides. The photocatalytic reactions discussed in this review take place under mild conditions and display excellent functional group compatibility and broad substrate scope. The reactions open a new avenue to synthesize complex polyfluorinated arenes. While some yields of the C–F functionalization products are modest, they are offset by the fact that the reagents need no prefunctionalization and come directly from commercial sources, allowing an unprecedented level of complexity to be achieved in just a few synthetic steps, and creating many opportunities for chemists who are involved in lead discovery programs.

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About the Authors

Sameera Senaweera received his B.Sc. degree in chemistry in 2010 from the University of Kelaniya, Sri Lanka. After spending the following year teaching at the same university, Sameera moved to the U.S.A., and commenced his graduate studies at Oklahoma State University under the supervision of Professor Jimmie Weaver. Currently, his research in the Weaver laboratory is focused on the development of novel and facile methodologies, such as photocatalytic reduction and functionalization of perfluoroarenes, to access pharmaceutically and industrially important, partially fluorinated arene building blocks..

Jimmie D. Weaver completed his B.S. degree in chemistry with math and physics minors in 2004 at Southern Nazarene University. He spent the following year working in an immunology lab under the guidance of Professor William Hildebrand at the University of Oklahoma Health Sciences Center. Jimmie then enrolled in the graduate program at The University of Kansas under the guidance of Professor Jon Tunge, where he developed palladium-mediated decarboxylative coupling reactions. After earning his Ph.D. degree in 2010, he accepted a postdoctoral position in Professor Jonathan A. Ellman's laboratory at Yale University. In the fall of 2012, Jimmie joined the chemistry department faculty at Oklahoma State University as an assistant professor. His research program focuses on the catalytic generation and exploitation of reactive intermediates for a variety of applications such as C–H functionalization, C–F functionalization, cross-coupling of perfluoroarenes, and uphill catalysis in which light is used to drive endergonic transformations.

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Miles, K. C.; Stahl, S. S. *Aldrichimica Acta* **2015**, *48*, 8.

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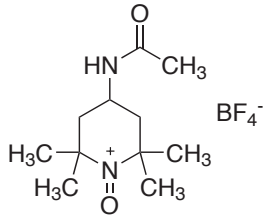

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Leadbeater, N. E.; Bobbitt, J. M. *Aldrichimica Acta* **2014**, *47*, 65.

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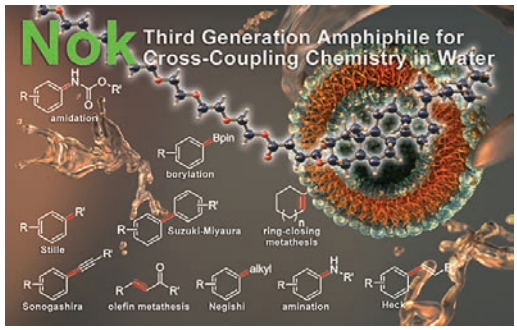

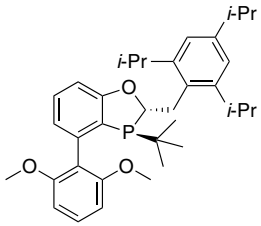

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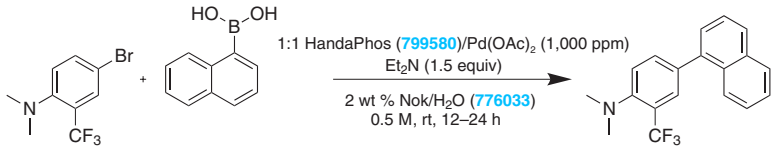

Suzuki–Miyaura cross-coupling reactions run under environmentally friendly conditions.

Reference:
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Recent Enabling Technologies for Diazomethane Generation and Reactions

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Keywords. diazomethane; C1 building block; flow chemistry; hazardous chemistry; membrane reactors.

Abstract. Diazomethane is one of the most versatile reagents in organic synthesis; however, its use is accompanied with certain hazards. To overcome the explosion risk associated with distillation methods employed for the preparation of diazomethane, new techniques for its safe and convenient production and handling are continually being developed. This review highlights the state of the art of diazomethane generation and consumption, in particular by employing flow chemistry principles and techniques.

Outline

1. Introduction

The most time- and atom-efficient synthetic routes frequently require the use of highly reactive, often low-molecular-weight reagents. One such reagent is diazomethane (CH_2N_2), which is an exceptionally powerful and versatile C1 building block in organic synthesis.[1,2] Despite the hazards associated with its generation and utilization, CH_2N_2 is among the most versatile and useful reagents in organic synthesis (**Scheme 1**).[1] Carboxylic acids, as well as various O, N, and S nucleophiles, are directly converted into the corresponding methyl esters or methylated derivatives, respectively. Diazomethane is also used for the synthesis of α-diazoketones, the homologation of ketones and carboxylic acids (Arndt–Eistert reaction), in palladium-catalyzed cyclopropanations, and as a dipole in [3 + 2] cycloadditions to generate N-heterocycles. Reactions with CH_2N_2 are typically fast and clean, and proceed under mild conditions, often producing nitrogen as the sole byproduct.

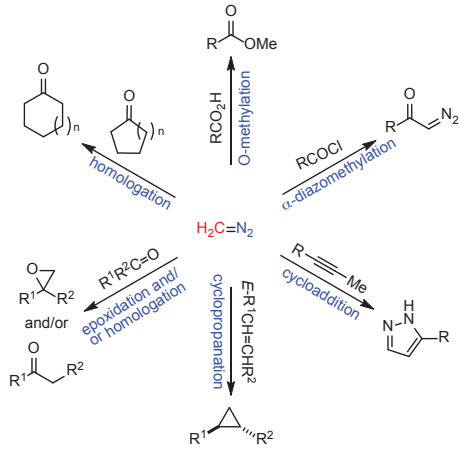
When the synthesis of hazardous reagents is contemplated, the most efficient form of production and use is the in situ approach, where the reagents are generated from benign precursors—preferably inside the closed environment of a flow reactor—and are subsequently directly converted into more advanced, nonhazardous products. In continuous-flow technology, the total volume of material processed at any time is drastically reduced; therefore, the safety of the process is generally significantly increased when compared to that of the batch counterpart. Hence, hazardous chemicals are best synthesized and reacted under flow conditions.[3,4]

Since the last comprehensive review on the preparation and reactions of CH_2N_2 in 1983,[1] substantial efforts have been put into the development of novel techniques for its safe and convenient generation and handling, not only in the research laboratory, but also on a production scale. In this review, we particularly focus on recent literature examples that employ flow chemistry for the synthesis and reactions of CH_2N_2. Batch processes are covered only if CH_2N_2 is generated in situ, or if methods not relying on CH_2N_2 distillation are employed.

2. Safety Considerations

Diazomethane should be treated with extreme caution.[1,5] The hazards associated with the handling of CH_2N_2 and measures for avoiding them are highlighted in **Table 1**.[6,7] As many strong alkylation agents are, CH_2N_2 is a potent carcinogen and is extremely poisonous.[8,9] The severe acute and chronic toxicity is especially problematic because of its high volatility (bp = –23 °C). Diazomethane is highly noxious by inhalation or contact with skin or eyes; therefore, contact with it in any form should be strenuously avoided. Diazomethane is also a sensitizer, and long-term, low-level exposures can lead to asthma-like symptoms. The OSHA PEL (Occupational Safety and Health Administration Permissible Exposure Level) for a time-weighted average concentration (TWA) for CH_2N_2 is 0.2 ppm (0.4 mg/m³).[6,7]

Furthermore, in its pure and undiluted form, it is exceedingly sensitive to explosion, and CH_2N_2 is thus virtually exclusively used as a solution in diethyl ether. Ground-glass joints have to be strictly avoided and flame-polished glassware has to be used when handling CH_2N_2.[5] Excess or spilled CH_2N_2 should be destroyed by adding a scavenger such as acetic acid. It is strongly advised not to store CH_2N_2 solutions.



Scheme 1. Synthetic Versatility of Diazomethane. *(Ref. 1)*

Table 1. Hazards of Diazomethane and Measures to Avoid Them *(Ref. 6,7)*

Type of Hazard or Exposure	Acute Hazards and Symptoms	Avoidance Measures
Explosion	Gas–air mixtures are explosive	• Do NOT expose to friction, shock, heat, bright light, sharp/rough edges, and scratched glassware. • AVOID contact with alkali metals and drying agents (e.g., $CaCl_2$, $MgSO_4$, $CaSO_4$). • Stir by using a PTFE-coated stir bar.
Inhalation	Headache. Labored breathing. Shortness of breath. Sore throat. Vomiting. Symptoms may be delayed (lung edema).	Work in an efficient fume hood with the sash closed.
Skin	Redness. Burning sensation. Pain. Serious frostbite.	Wear gloves and a lab coat.
Eyes	Redness. Pain.	Safety glasses or face shield.

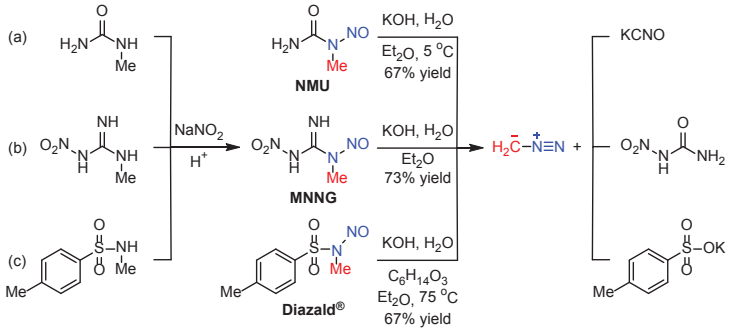
3. Diazomethane Synthesis

Diazomethane is most commonly produced, in the presence of diethyl ether, by base-mediated decomposition of *N*-methyl-*N*-nitrosoamines possessing electron-withdrawing substituents such as sulfonyl or carboxyl groups (**Scheme** 2).[1,4,5,10,11a] The traditional and simplest CH_2N_2 precursor is *N*-nitroso-*N*-methylurea (NMU),[10] which is also a methylating agent and is classified as a carcinogen, mutagen, and teratogen. It is unstable at temperatures above 20 °C and shock-sensitive, and is thus no longer available from chemical suppliers. Similarly, *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG)[11a]—essentially Aldrich Chemical´s first purchasable reagent[11b]—is no longer for sale due to its mutagenicity and carcinogenicity.[12] Nowadays, *N*-methyl-*N*-nitroso-*para*-toluenesulfonamide (Diazald®) is the preferred precursor;[5] however, it is also a severe irritant. To enhance safety, the synthesis of *N*-methyl-*N*-nitrosoamines via nitrosation of the corresponding *N*-methyl compounds in acidic medium is best incorporated into the overall process. In particular, the otherwise too hazardous NMU could thus be safely generated in situ starting from the harmless and inexpensive *N*-methylurea.[4]

3.1. Batch Methods

Classic distillation techniques have traditionally been employed for the synthesis of anhydrous CH_2N_2 and, therefore, various specialized kits for its generation and purification have been developed and commercialized.[1] In these techniques, diazomethane is co-distilled with anhydrous ether into a dry ice filled cold-finger condenser that is connected to a receiver flask where the ethereal solution of anhydrous CH_2N_2 is collected.[1,13] (For a commercially available version of this setup, see **Figure 1**.) Diazomethane solutions of 1–300 mmol can thus be realized. For smaller scale production (up to ca. 1 mmol), an apparatus, originally developed for generating diazomethane from MNNG without the need for co-distillation, can be used.[1,14] This system consists of an inner and an outer glass tube: diazomethane is generated in the inner tube and can then react with the substrate that is found in the outer tube. For mixing purposes, this setup has to be carefully shaken by hand.

It should be noted that most CH_2N_2 explosions occur during its distillation;[5] hence, new methods and techniques for its safe and convenient preparation and handling are continuously being developed. By employing a biphasic reaction system, CH_2N_2 can be generated in situ in the aqueous layer and is then transferred into the organic layer where the desired reaction takes place.[15,16] Alternatively, in order



Scheme 2. Synthesis of Diazomethane from Different *N*-Methyl-*N*-nitrosoamine Precursors. *(Ref. 1,4,5,10,11a)*

to avoid distillation, several protocols apply a stream of nitrogen to transport CH_2N_2 generated in a batch environment from the solution into the gas phase and further into a substrate-filled receiver flask.[17,18] Both approaches are described in more detail in Section 4 below.

3.2. Continuous-Flow Methods

A further advance toward the safe and convenient in situ generation of CH_2N_2 employs flow chemistry techniques, since the actual reaction volumes in a microreactor or flow device are very small, and safety concerns associated with hazardous reagents are minimized.[19–22] In addition, flow chemistry allows the continuous, on-demand production of potentially toxic, reactive, or explosive intermediates that are consumed in follow-up reactions, thus eliminating the safety risks associated with the accumulation and storage of large quantities of hazardous materials.[3] For these very reasons, it is not surprising that continuous-flow protocols for CH_2N_2 production on a large scale were initially developed in industry.[23,24] It is only very recently that CH_2N_2 generation and consumption under flow conditions have been realized in academia by using either standard (micro)reactors or membrane technology.[19–22]

A simple flow process for the production and in situ conversion of CH_2N_2 comprises a feed containing a suitable *N*-nitrosoamine and a second feed of typically an aqueous solution of potassium hydroxide (KOH). The two feeds are combined in a (micro)reactor to produce CH_2N_2. A third feed with the substrate is subsequently mixed into the reactor to convert the substrate into the CH_2N_2 derivatized product (**Figure 2**). It has to be noted that homogeneity is of utmost importance in continuous-flow chemistry; therefore, solvent systems need to be selected that prevent any precipitation of, for example, potassium *para*-toluenesulfonate (see Scheme 2, Part (c)), and thus avoid system clogging.

An approach for the in situ synthesis of anhydrous CH_2N_2 employs a semipermeable, microporous, but chemically and mechanically resistant, membrane that selectively allows hydrophobic, low-molecular-weight compounds to move across it. By using this approach, a number of different reactor designs can be implemented such as the fully continuous tube-in-tube and the semibatch tube-in-flask reactor technologies. The tube-in-tube reactor design can generally be seen as a versatile tool to saturate gases into a liquid phase.[25,26] Specifically, our group used this reactor to accomplish the generation and purification/separation of anhydrous CH_2N_2 with the goal of developing safe reactions that can be performed in the research laboratory.[27] The inner tube of the device was made of a gas-permeable Teflon® AF-2400 membrane that was enclosed within a thick-walled impermeable outer tubing. Diazald® and aqueous KOH were reacted within the inner tubing, and gaseous CH_2N_2 diffused out through the membrane, and was consumed in the substrate-carrying chamber formed between the outer and inner tubings (**Figure 3**, Part (a)).[27] At the end of the reaction, the content of the inner tube is finally directed into an acetic acid solution to quench excess CH_2N_2. In a further development focusing on operational simplicity and flexibility—in particular with respect to the handling of solids, concentration, and scale—a tube-in-flask reactor was designed, where the membrane tubing was wrapped inside a Duran® or Erlenmeyer flask

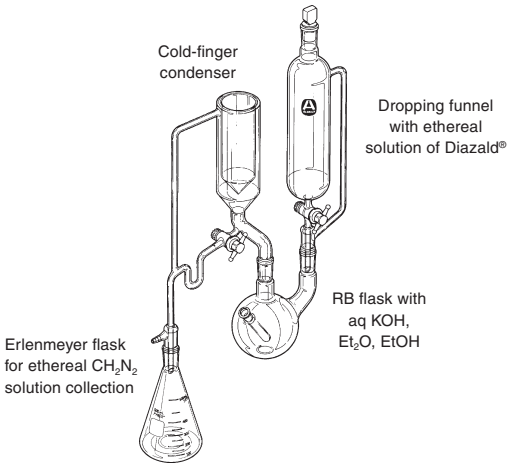


Figure 1. Commercially Available Macro Diazald® Kit for Diazomethane Generation.

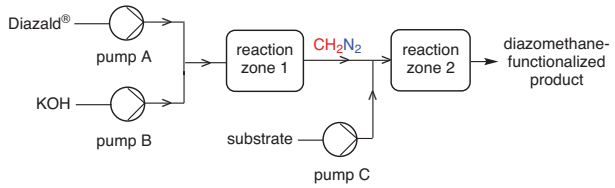


Figure 2. General Setup for the in Situ Generation and Consumption of Diazomethane in a (Micro)reactor.

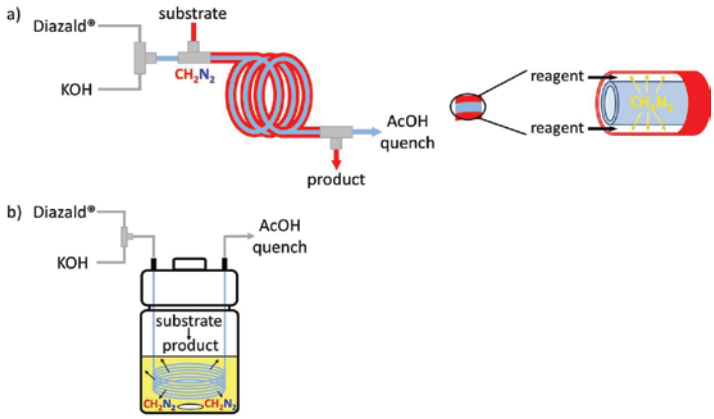


Figure 3. Semipermeable Membrane Technology for Anhydrous Diazomethane Generation. *(Ref. 27,28)*

(Figure 3, Part (b)).[28] Anhydrous diazomethane then diffuses through the membrane into the flask, which is filled with an appropriate solvent and the substrate, and can thus be directly used for reactions in the flask. In this way, anhydrous solutions of CH_2N_2 in any compatible solvent can be generated in a closed system. Similar reactor designs have been previously developed for reactions with ozone[29] and oxygen gas[30]. Whereas anhydrous CH_2N_2 can be obtained straightforwardly within a semipermeable membrane, more effort is required in (micro) reactors, where generally a post-extractive separation is required. A comprehensive coverage of flow protocols will be given in Section 4.

4. Reactions and Reactor Types

Since the generation of CH_2N_2 using flow technology is a comparatively new field of research, the main focus in this Section is to introduce the diverse reactor types and CH_2N_2 generating techniques. Nevertheless, Section 4 is classified according to reaction types.

4.1. O-Methylations

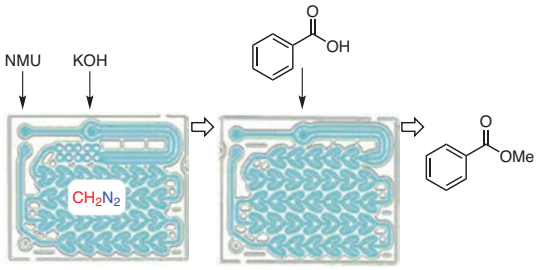
The conversion of carboxylic acids into the corresponding methyl esters is undoubtedly the most popular reaction with CH_2N_2, since it proceeds with high reaction rates, produces only volatile byproducts (N_2), and is highly selective.[1] Other functional groups, such as a phenolic OH or an alkene moiety, remain inactive under the reaction conditions.[1,28] In particular, the methylation of benzoic acid is frequently used for the determination of CH_2N_2 yield, and is thus an indication of the flow reactor performance, since the reaction is generally quantitative and essentially instantaneous.

Employing a microreactor with a setup similar to the one described in Figure 2, CH_2N_2 was generated from Diazald® in Carbitol™ and KOH in isopropyl alcohol. It was subsequently reacted with benzoic acid, which was introduced via a third feed (**Scheme 3**, Part (a)).[31] An excess of benzoic acid was used to additionally neutralize unreacted KOH. Residence times were in the range of seconds for both reaction steps, and a constant yield of 75% of methyl benzoate was achieved over a period of one hour. The key to the success of this process was the 32 mixing elements that were distributed over the length of the reactor. To increase safety, all fluid-containing components were immersed in an acetic acid bath. In a follow-up study, Diazald® was generated continuously in situ starting from *para*-toluenesulfonyl chloride via amidation and nitrosation (Scheme 3, Part (b)) and was then fed into the CH_2N_2 generator after a $NaHCO_3$ wash and dilution with Carbitol™.[32]

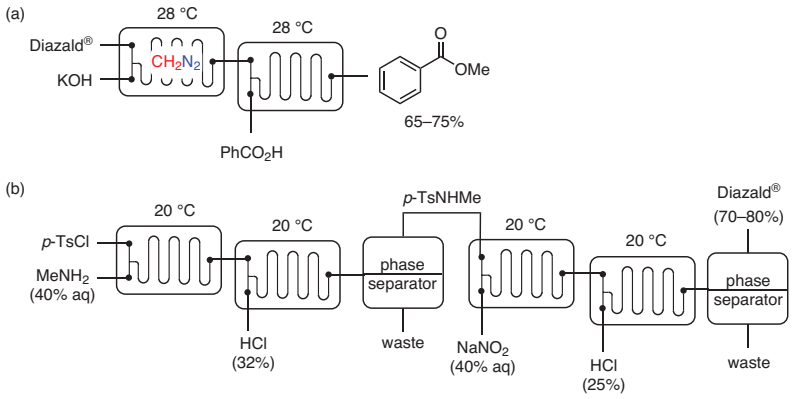
Maggini and co-workers reported an analogous flow format for the synthesis of methyl benzoate, whereby CH_2N_2 was generated from NMU and an aqueous KOH solution (**Scheme 4**).[33] A glass heart-shaped micro-structured fluidic module reactor enabled sufficient mixing of the biphasic mixture, which is crucial for CH_2N_2 production. Up to 19 moles of CH_2N_2 per day could be accomplished, while its amount in the reactor was limited to 6.5 mmol. Finally, a 10-fold scale-up was achieved by increasing the flow reactor dimensions.

Generally, a final separation step would need to be incorporated in the process, if generating pure diazomethane is desired. Thus, CH_2N_2 was produced by flowing a solution of KO*t*-Bu in isopropyl alcohol through a glass cartridge filled with polymer-supported Diazald®.[34] The outlet stream was then directed into a mixing chip, diluted with H_2O, and extracted in a separation membrane where the organic stream contained CH_2N_2. However, due to low benzoic acid conversions and high pressures, this protocol was not pursued further.

A custom-made, small-scale CH_2N_2 generator relying on nitrogen stripping of gaseous CH_2N_2 was designed by Cohen for the derivatization of indole-3-acetic acid.[18] This apparatus cannot be regarded as a flow reactor; however, CH_2N_2 is generated in situ. The device consists of two glass flasks arranged in parallel and fitted with a nitrogen inlet and outlet. Nitrogen is saturated in diethyl ether in the first flask.



Scheme 4. Generation of Diazomethane in a Micro-structured Fluidic Module Reactor. *(Ref. 33)*



Scheme 3. Microreactor Generation of Diazomethane: (a) Directly from Diazald® and (b) from in Situ Generated Diazald®. *(Ref. 31,32)*

CH_2N_2 is generated in the second flask from Diazald® and NaOH, and is subsequently carried by the nitrogen stream into a substrate-filled vial. In a further, more sophisticated modification, the apparatus was employed for a high-throughput quantification of indole-3-acetic acids derived from plant tissue (**Scheme 5**).[35]

4.2. Methylene Insertions

The insertion of methylene by CH_2N_2 into tin tetrachloride ($SnCl_4$) was demonstrated in a device employing a nitrogen stream as carrier for gaseous CH_2N_2.[36] Diazomethane is generated in the first flask in aqueous ethanolic solution from Diazald® and KOH, and is then transported into a tube filled with KOH in toluene to trap side products and water, and finally into a third tube where it is reacted with $SnCl_4$.

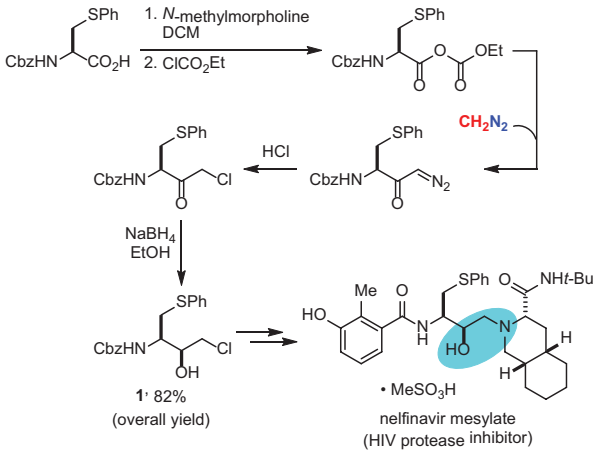
4.2.1. α-Diazoketone and α-Chloroketone Synthesis

α-Diazoketones are generally synthesized from acyl chlorides and CH_2N_2 via a modified Arndt–Eistert homologation. This reaction type is of particular interest because of its use in the synthesis of modern HIV protease inhibitors, such as Atazanavir, which commonly contain a chiral amino alcohol structure in their core. This moiety is typically introduced via an α-chloroketone intermediate, which in turn can be synthesized in a multistep sequence from naturally occurring amino acids in a modified Arndt–Eistert reaction. Since acyl chlorides or activated acids are extremely sensitive to water, strictly anhydrous conditions are required. It is thus essential that purified CH_2N_2 be employed. Diazomethane purification/isolation can either be achieved by extraction, membrane technology, or via nitrogen stripping.

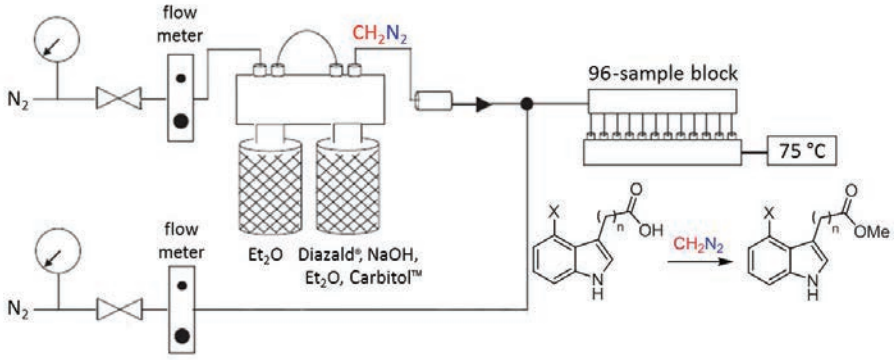
An industrial, continuous-flow process for the generation of organic solutions of anhydrous CH_2N_2 from NMU, which was obtained by nitrosation of *N*-methylurea, was reported by Aerojet (now AMPAC Fine Chemicals) in 1998.[24] Diazomethane, purified by phase separation (extraction), is continuously recovered as an organic solution and can be fed directly to a batch or a further continuous-flow reactor for subsequent reaction. After an aqueous KOH wash of the organic solution, CH_2N_2, with <0.1% water, is obtained. More than 1200 batches of cGMP products using CH_2N_2 at the 3,000 L scale were produced with this setup.[37] A related process based on a continuous membrane separator was reported by DSM.[4,38] The organic phase containing CH_2N_2 passes through a hydrophobic membrane, whereas the aqueous phase of the reaction mixture, including waste salts, is retained by the membrane and is directed into a quench solution.

Proctor and Warr have described a continuous-flow process capable of producing up to 60 tons per year of anhydrous CH_2N_2.[23] Diazomethane was generated from a feed of Diazald® in a high-boiling solvent (DMSO) and a second feed of KOH in water. Anhydrous gaseous CH_2N_2 was separated by a nitrogen stream and further used in a downstream process to produce chiral amino alcohol **1** by a modified Arndt–Eistert homologation (**Scheme 6**).[39]

The membrane technique that merges the generation, separation, and consumption of CH_2N_2 in a continuous-flow, dual-channel microreactor was first applied by Kim and co-workers.[40] A gas-permeable polydimethylsiloxane membrane, which was coated with polyvinylsilazane, allowed pure CH_2N_2 to diffuse from the bottom channel, where it was generated from Diazald® and aqueous KOH, into the upper channel where it reacted with the substrate carried within (**Scheme 7**). Various reactions, including the synthesis of α-diazoketone **2** from benzoyl chloride, were performed in the upper channel. The reactor provided the desired products in excellent yields; however, the throughput was limited to ca. 1 mmol per day.

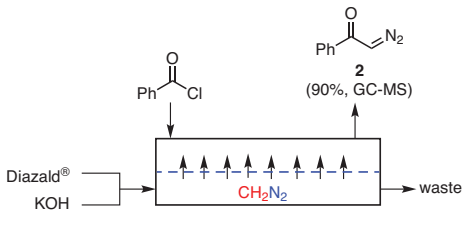


Scheme 6. The Diazomethane-Enabled, Safe, Cost-Effective, and Direct Industrial-Scale Synthesis of Chiral Amino Alcohol **1**, a Key Intermediate in the Synthesis of Nelfinavir Mesylate, an HIV Protease Inhibitor Drug. *(Ref. 23,39)*



Scheme 5. High-Throughput Quantification of Indole-3-carboxylic Acids Derived from Plant Tissue. *(Ref. 35)*

An analogous approach using a commercial tube-in-tube reactor (see Figure 3, Part (a)) allowed the laboratory-scale generation of anhydrous CH_2N_2 in mmol per hour quantities.[27] Quantitative conversions were obtained for the synthesis of diazoketones (**Scheme 8**), esterifications, cyclopropanations, and [2 + 3] cycloadditions (see Section 4.4). The setup was later extended to achieve the direct transformation of protected α-amino acids, via their mixed anhydrides and α-diazoketones, into the corresponding α-chloroketones in a fully continuous, three-step reaction sequence (**Scheme 9**, Part (a)).[41] The added HCl in the third sequence destroys any excess CH_2N_2 and reacts with the diazoketone to furnish the desired α-chloroketone, **3**. The system was operated continuously for about 4.5 h to produce 1.84 g of the enantiopure α-chloroketone. An enhanced system was employed for the four-step synthesis of β-amino acids from the respective protected α-amino acids via a Wolff rearrangement of the diazoketone intermediates (Scheme 9, Part (b)).[42] The Wolff rearrangement was performed either photochemically (CFL, compact fluorescent lamp) or was catalyzed by Ag_2O packed into a cartridge reactor. In order to remove excess CH_2N_2 and the nitrogen generated during diazoketone formation, additional gas-permeable tubing, which was immersed in a solution of acetic acid, was attached between the second residence coil and the photoreactor.



SM	Product	Yield[a]
$MeCO_2H$	$MeCO_2Me$	>99%
PhOH	PhOMe	>99%
PhCHO	PhC(O)Me	81%

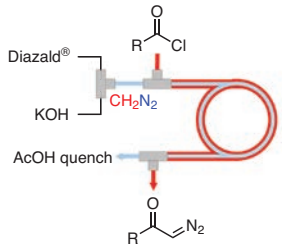
[a] Determined by GC-MS.

Scheme 7. Dual-Channel, Membrane Microreactor for the Generation, Separation, and Reactions of Diazomethane. *(Ref. 40)*

In addition to α-chloroketone synthesis, methylations, cyclopropanations, and pyrazole synthesis (see Section 4.4) have been performed in the tube-in-flask reactor depicted in Figure 3, Part (b).[28] Higher concentrations (1 M) of Diazald® can be achieved when dissolved in DMF, leading to higher CH_2N_2 concentrations and, ultimately, to a higher product output: several hundred milligrams up to ca. 1 g can be produced within 1 h. Larger scale syntheses can be achieved via parallelization (*numbering up*) by wrapping more membrane tubings into the flask. This way, with four tubings in the flask, 3.65 g of pure α-chloroketone **4** were isolated after ca. 3 h (**Figure 4**). An even more impressive scale could be obtained for the ultrafast methylation of benzoic acid, where 42 g of product were generated within 7 h (6 g/h). With this device, a maximum of 1.8 g of anhydrous CH_2N_2 per hour was safely produced. In addition, the implementation of *in-line* FTIR technology allowed the monitoring of CH_2N_2 generation and consumption.[28] The semi-batch CH_2N_2 generator was additionally employed in a one-pot, three-step synthesis of α-chloroketone **5** starting from *N*-Boc-L-phenylalanine (**Scheme 10**) by following a procedure similar to that described in Scheme 9, Part (a).[43] Diazomethane was produced from NMU as precursor, which in turn was generated in situ by nitrosation of *N*-methylurea in a continuous-flow upstream process.

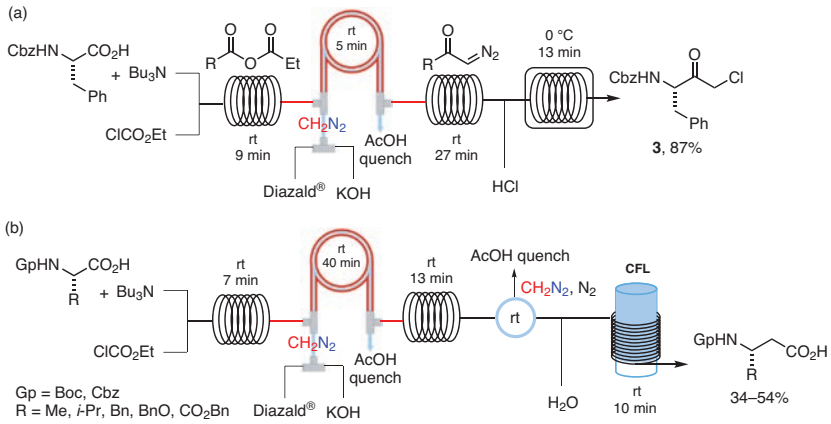
4.3. Cyclopropanations

The [2 + 1] cycloaddition reaction of olefins with CH_2N_2 is of major synthetic importance since the resulting cyclopropane subunit is found as a basic structural element in a wide range of naturally occurring



R = Ph (91%, rt), 4-ClC_6H_4 (93%, rt), Bn (78%, –10 °C)

Scheme 8. Continuous-Flow α-Diazoketone Synthesis Using the Tube-in-Tube Reactor System. *(Ref. 27)*



Scheme 9. Multistep, Continuous-Flow Synthesis of (a) α-Chloroketones and (b) β-Amino Acids. *(Ref. 41,42)*

compounds and in several bioactive unnatural analogues.[44] In addition, the cyclopropane ring is a versatile synthetic building block, which can be converted into a range of functionalities.[20] 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.[44] The reaction commonly proceeds with excellent stereo- and chemoselectivity, and is compatible with a wide range of functional groups. Whereas the enantioselective cyclopropanation of alkenes by α-diazocarbonyl compounds is one of the most extensively studied transformations in organic chemistry, the efficient and highly enantioselective cyclopropanation employing CH_2N_2 is not that facile.[20,44] Only a few successful examples have been described that employ chiral bidendate copper complexes as catalysts[45] or Oppolzer's sultam[46] as chiral auxiliary.

Biphasic cyclopropanations catalyzed by an iron(III)-porphyrin complex (FeTPPCl) have been developed, where CH_2N_2 is generated in situ in the strongly basic aqueous layer, and is then transferred into an organic layer where the cyclopropanation takes place (**Scheme 11**).[15] Even though this protocol does not require any purification of CH_2N_2, the biphasic reaction necessitates a water-soluble Diazald® derivative, and the protocol is limited to water-insoluble substrates and to reagents that tolerate the strongly basic aqueous conditions. This approach was extended further to cyclopropanations catalyzed by dendrimers possessing the Fe-porphyrin moiety.[47] As in the original procedure by Morandi and Carreira,[15] the Diazald® solution was added slowly (1 equiv/h) via a syringe pump and the cyclopropanation with zero to second generation dendrimer catalysts proceeded with reaction rates that are comparable to that of the original FeTPPCl complex (Scheme 11). Related biphasic cyclopropanations using readily available Pd catalysts, e.g. $Pd(OAc)_2$ or $(PhCN)_2PdCl_2$, were reported by Nefedov and co-workers.[16] Diazomethane was generated from NMU, which was added to the reaction mixture at 50–80 g/h per 0.1 g Pd. Faster addition led to CH_2N_2 decomposition, whereas slower addition promoted Pd precipitation.

An apparatus operated with a continuous argon stream was employed for cyclopropanations of heterobicyclic alkenes (**Scheme 12**).[17,48] Diazomethane was generated in a flask from Diazald® dissolved in EtOH and an aqueous NaOH solution that was added via a dropping funnel. The argon stream carried the gaseous CH_2N_2 into the reaction flask, which contained the alkene in THF and $Pd(OAc)_2$. Excess CH_2N_2 was quenched in a second flask filled with a solution of acetic acid. 7-Oxabicyclic, 2,3-diazabicyclic,[17] and 7-azabicyclic alkenes[48] underwent cyclopropanations in excellent yields within 12–24 h (Scheme 12).

Palladium-catalyzed cyclopropanations of substituted styrenes were successfully performed using a continuous permeable membrane reactor,[38] a tube-in-tube reactor (see Figure 3, Part (a)),[27] a tube-in-flask reactor (see Figure 3, Part (b)),[28] or a glass microreactor containing

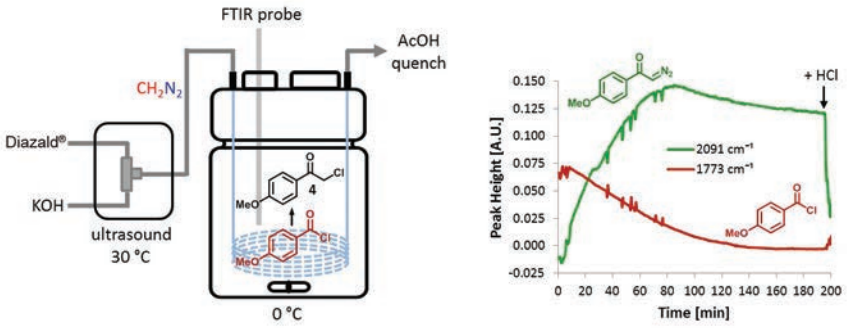
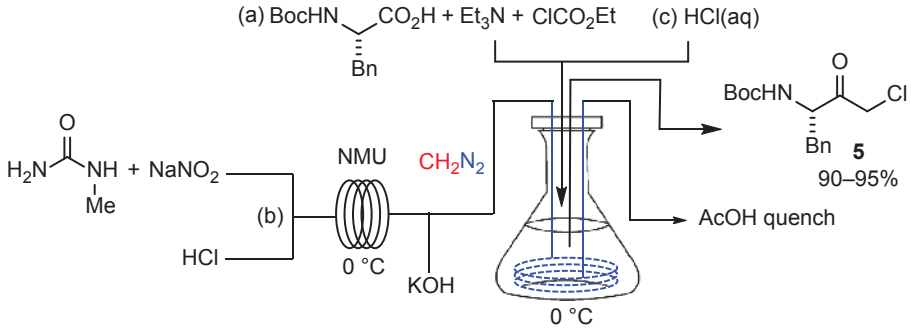


Figure 4. Synthesis of α-Chloroketone **4** in a Tube-in-Flask Reactor (Left) and Reaction Monitoring with FTIR (Right). *(Ref. 28)*



Scheme 10. In Situ Generation of NMU in a Multistep Flow Synthesis of α-Chloroketone **5**. (a) Synthesis of the Mixed Anhydride in the Flask. (b) CH_2N_2 Generation. (c) HCl Quench and Generation of **5**. *(Ref. 43)*

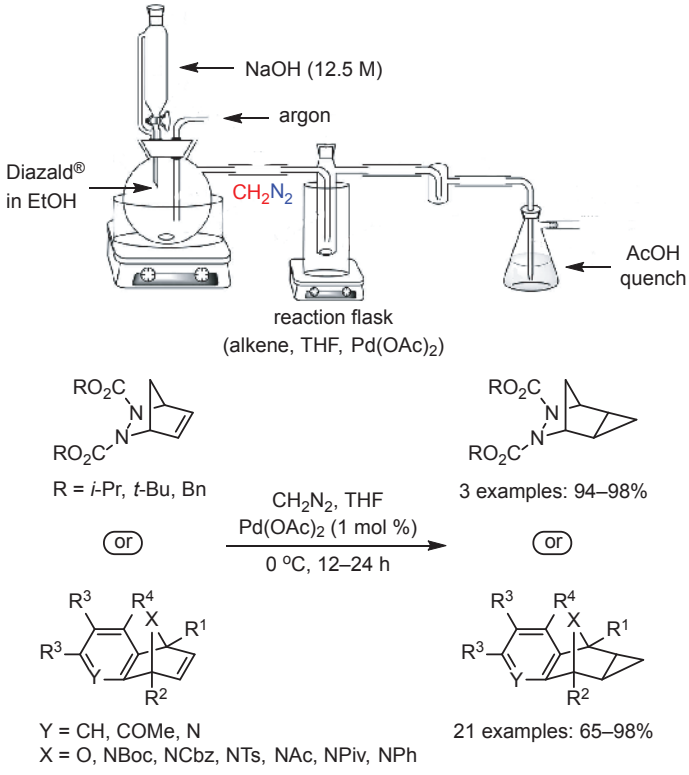
internal chaotic mixing elements.[49] In addition, a fully automated tube-in-tube reactor setup has been employed for the library synthesis of cyclopropyl boronic esters from the corresponding styrenes.[50] It has to be stressed that cyclopropanations are clearly not a trivial affair: depending on the coordination abilities of the alkenes for Pd(0), the precipitation of Pd black—and therefore termination of the reaction—can occur at different catalyst concentrations.[28] Consequently, care has to be taken with respect to channel blocking, in particular when a tube-in-tube reactor or a microreactor is used.

4.4. 1,3-Dipolar Cycloadditions

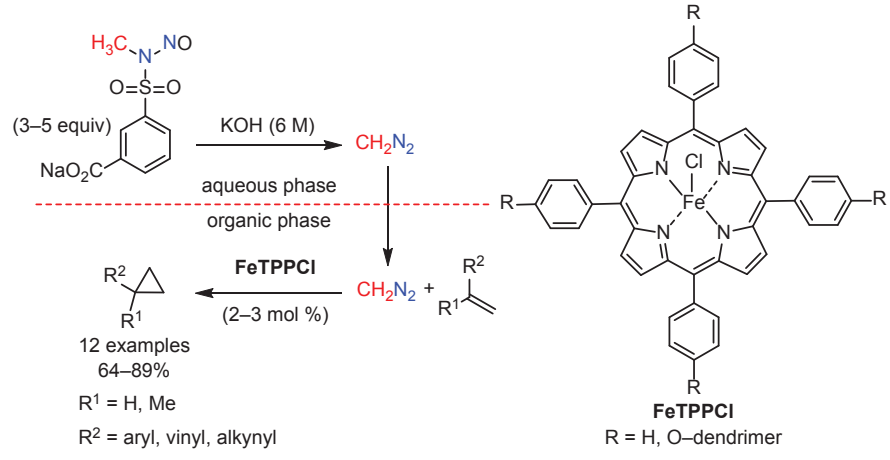
As a powerful 1,3-dipole, CH_2N_2 participates in Huisgen [2 + 3]-cycloaddition reactions with unsaturated compounds to form the corresponding nitrogen-containing heterocycles.[51] Pyrazolines are obtained when an alkene functions as dipolarophile, whereas pyrazoles can be prepared from alkynes (**Scheme 13**).[27,28] The cycloaddition of CH_2N_2 to *N*-phenylmaleimide gave the expected 1-pyrazoline, **6**, in essentially quantitative conversion in a tube-in-tube reactor.[27] By employing the tube-in-flask setup, the 3-substituted pyrazole, **7**, was regioselectively generated from ethyl propiolate and CH_2N_2.[28]

5. Conclusion and Outlook

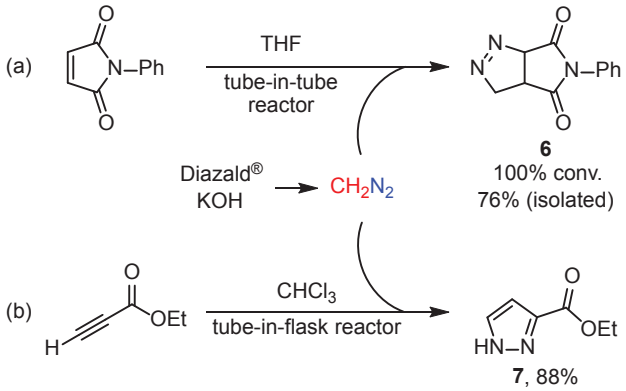
The shortest and most elegant synthesis of a molecule often requires the use of hazardous reagents. Since diazomethane provides such a multitude of applications in organic synthesis, methods for its safe preparation are continuously being developed. An on-demand, in situ production and transformation of diazomethane are highly desirable in order to minimize or eliminate the risks associated with the handling, storage, and human exposure to this toxic and explosive compound. Recent advances in continuous-flow technologies have opened new avenues for the usage of this versatile intermediate with improved safety over traditional batch processes. In particular, the excellent heat and mass transfer, efficient mixing, and the comparatively low reactor volumes make these devices uniquely suited for carrying out hazardous reactions. Furthermore, these new technologies permit multiple reaction steps and workup procedures to be integrated into a single apparatus. Depending on the sensitivity of the individual reactions, especially toward water and strongly basic conditions, different processes for diazomethane generation are now available. If anhydrous diazomethane is required, as in the synthesis of α-diazoketones, the most promising route is the membrane separation and purification approach, where pure gaseous diazomethane diffuses through a semipermeable membrane. Various scales of anhydrous diazomethane can be provided by means



Scheme 12. Cyclopropanations of Heterobicycloalkenes. *(Ref. 17,48)*



Scheme 11. Biphasic Cyclopropanations Employing Diazomethane. *(Ref. 15,47)*



Scheme 13. 1,3-Dipolar Cycloadditions of Diazomethane with: (a) Alkenes (Tube-in-Tube) and (b) Alkynes (Tube-in-Flask). *(Ref. 27,28)*

of different reactor designs ranging from 1–2 mmol of CH_2N_2/h in a commercially available tube-in-tube reactor up to ca. 40 mmol of CH_2N_2/h employing a tube-in-flask device. In addition to in situ diazomethane generation, its precursors, which themselves are either noxious and/or explosive, have also been synthesized in situ in a continuous-flow upstream process. Such a reaction sequence renders the overall process even more hazard-free.

With continuous-flow techniques, we believe that the potential of diazomethane as a sustainable reagent will be further exploited and, hopefully, more intensively used in contemporary organic synthesis.

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Doris Dallinger obtained her M.Sc. and Ph.D. degrees with Professor Kappe at the University of Graz, Austria, working on research projects relating to microwave chemistry and the high-throughput synthesis of biologically active heterocycles. Doris then carried out postdoctoral work at the Christian Doppler Laboratory for Microwave Chemistry in the same university, where her research focused on microwave effects and scale-up studies. She then joined the Institute of Chemistry at the University of Graz as Senior Scientist in 2011. Her main research interests are reaction optimization by microwave technology and its adaptation to continuous-flow conditions, as well as introducing hazardous reagents such as diazomethane into new reactions and conditions.

C. Oliver Kappe is Professor of Chemistry at the University of Graz (Austria) and Key Researcher at the Research Center for Pharmaceutical Engineering GmbH (RCPE). He studied at the University of Graz with Professor Gert Kollenz. After postdoctoral research with Professor Curt Wentrup at the University of Queensland and with Professor Albert Padwa at Emory University, he moved back to the University of Graz in 1996 to start his independent academic career. He was appointed Associate Professor in 1999 and Professor for Technology of Organic Synthesis in 2011. His research interests include continuous-flow chemistry, API manufacturing, and process intensification technologies. Since 2011, he has served as Editor-in-Chief of the *Journal of Flow Chemistry*.

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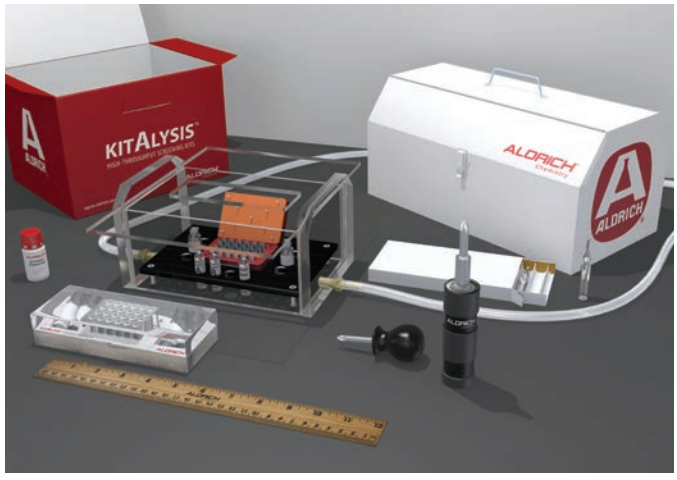

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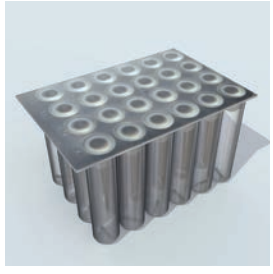

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