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Scalable Synthesis of Functionalized Ferrocenyl Azides and Amines Enabled by Flow Chemistry

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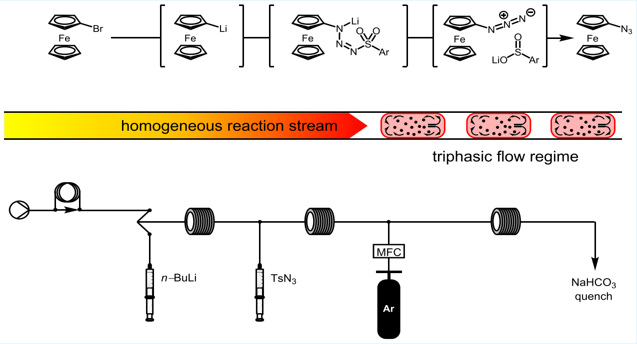
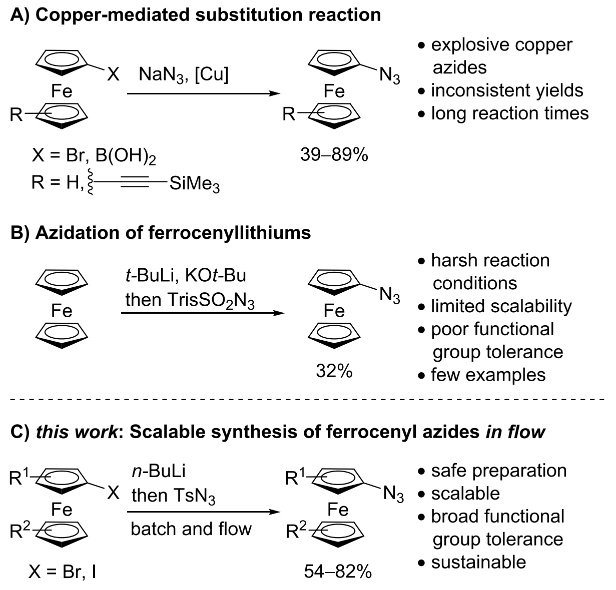
ABSTRACT: A scalable access to functionalized ferrocenyl azides has been realized in flow. By halogen−lithium exchange of ferrocenyl halides and trapping with tosyl azide, a variety of functionalized ferrocenyl azides were obtained in high yields. To allow a scalable preparation of these potentially explosive compounds, a flow protocol was developed accelerating the reaction time to minutes and circumventing accumulation of potentially hazardous intermediates. The corresponding ferrocenyl amines were then prepared by a reliable reduction process.



Since the discovery of ferrocene in 1951,[1] its derivatives have found innumerable applications in chemistry. The intriguing redox properties of ferrocenes led to applications in coordination chemistry,[2] inorganic materials,[3] molecular wires and sensors.[4] Their unique stability make ferrocenes useful in medicinal research[5] and as privileged ligands in many catalysts.[6] Frequently, these ferrocene based compounds are derived from ferrocenyl azides[7] or amines.[8] As organic azides can be readily reduced to the corresponding amines, ferrocenyl azides are the access hub to a large number of *N*-substituted ferrocenes. Owing to thermal lability and shock-sensitivity,[9] the obvious synthetic potential of ferrocenyl azides has not been fully realized. For their preparation, copper mediated substitution of ferrocenyl bromides[9a,10] and boronic acids[11] with sodium azide (Scheme 1A) was employed; however, this required the use of explosive copper azide. Alternatively, ferrocenyllithiums, prepared by lithiation of C−H bonds in ferrocenes, are reacted with aryl sulfonyl azides (Scheme 1B).[6e,12] While for the former process inconsistent yields were reported, the latter suffers from low functional group tolerance.[10] More recently, a single functionalized ferrocenyl azide was prepared by halogen−lithium exchange of the corresponding ferrocenyl halide.[13] The azidation of aryl halides through bromine−lithium exchange and trapping with tosyl azide has been realized in flow very recently by Yoshida and Nagaki.[14,15]

Scheme 1. Synthesis of Functionalized Ferrocenyl Azides



Fast chemical transformations immensely benefit from precise reaction control in a continuous flow setup.[16] Enhanced heat and mass transfer has enabled organic reactions previously viewed impossible.[14,15,17] Vice versa, slow reactions can be significantly accelerated by fast heating, frequently rendering a flow process more efficient and sustainable than a batch process.[18] Herein, we describe the flow-enabled

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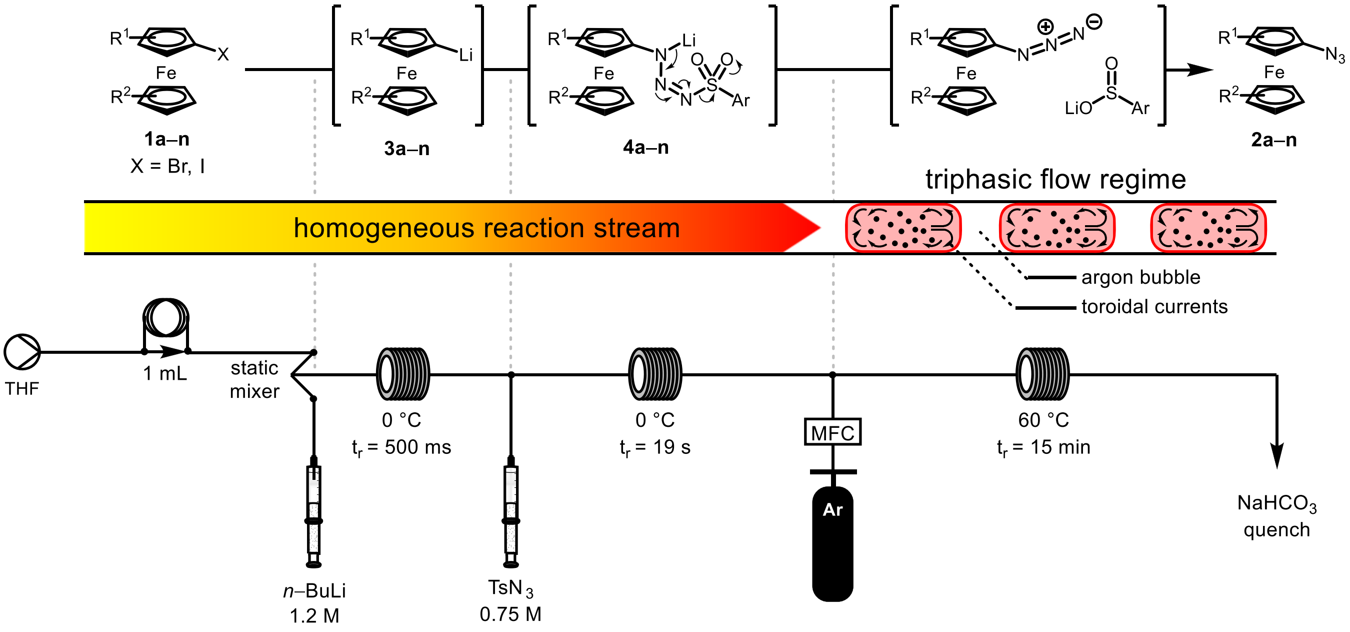
Scheme 2. Optimized Setup for the Synthesis of Functionalized Ferrocenyl Azides in Flow



development of a general method for the safe and scalable synthesis of functionalized ferrocenyl azides (Scheme 1C) through azidation of ferrocenyllithiums.

In preliminary batch experiments we first investigated the propensity of halogen−metal exchange of iodoferrocene (**1a**), followed by trapping with arylsulfonyl azides under a variety of reaction conditions to give azidoferrocene (**2a**). Initially, *tert*-butyllithium was employed for iodine−lithium exchange at −78 °C for 30 min while different arylsulfonyl azides were screened (see Supporting Information). As a result, commercially available tosyl azide was identified to give the best yield (77%). To avoid the use of pyrophoric reagents, *n*-butyllithium was employed which also led to an increased yield (95%).[19] To further improve the reaction parameters, we tested the iodine−lithium exchange and subsequent reaction with tosyl azide at 0 °C. Under these conditions, the yield dropped to 82% and handling of the exothermic reaction became a concern on a scale larger than 1 mmol.

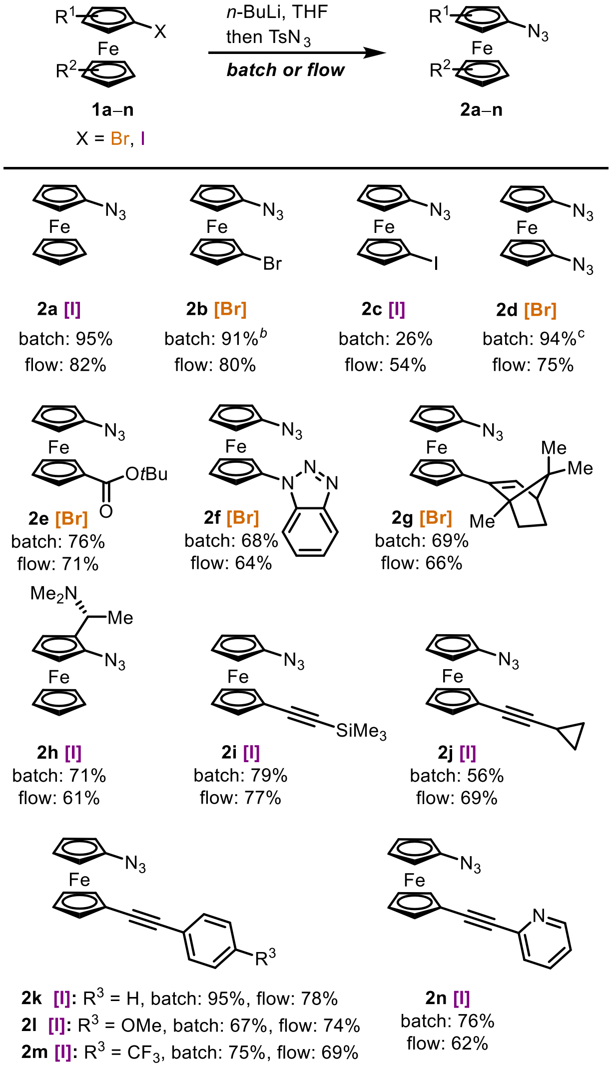
With these general parameters established, our flow process was based on three reaction steps (Scheme 2): (1) halogen−lithium exchange of ferrocenyl halides of type **1** forming ferrocenyllithiums of type **3**, (2) trapping with tosyl azide leading to triazenes of type **4**, and finally, (3) thermal fragmentation of **4** to the desired ferrocenyl azides **2**. The combination of steps (1)/(2) with (3) in a continuous fashion immediately presented a general technological challenge for the reactor design: while halogen−lithium exchange of aryl halides and trapping with electrophiles can be performed at high flow rates within milliseconds,[17] the fragmentation of triazene **4** is a slow reaction, necessitating, when performed in batch, warming from −78 °C to ambient temperatures over several hours. Thus, step (3) would translate into an extremely slow flow rate and require a steep decrease in flow rate of the incoming triazene stream. Although, triazene fragmentation can be promoted by thermolysis at temperatures of 120−130 °C,[20] this is usually avoided in batch due to safety considerations.[21] Given the intrinsic properties of continuous flow, we deemed the thermal fragmentation a viable and manageable reaction in a tube reactor, whereby fast heating of triazene **4** thermal strain is minimized significantly.[16a,h]

We started to optimize the fast reactions and the slow fragmentation step separately. Thus, the iodine−lithium exchange of iodoferrocene (**1a**) and subsequent trapping with tosyl azide were conducted in a tube reactor. The resulting reaction mixture was collected in a flask and kept there for a prolonged time to complete fragmentation of triazene **4a** and determine the isolated yield of azidoferrocene (**2a**). As the intermediary ferrocenyllithium **3a** precipitated at temperatures below 0 °C, both reactions were performed at 0 °C with precooled solutions of iodoferrocene (**1a**) and tosyl azide in tetrahydrofuran (THF) and *n*-butyllithium in *n*-hexane. A T-mixer was used for mixing the solutions of iodoferrocene and *n*-butyllithium with the result of the iodine−lithium exchange to take a relatively long time of 17 s, determined by complete conversion of starting material. When switching to a static mixer and a stainless-steel capillary reactor with an internal diameter of 250 μm, full conversion was achieved in 500 ms.

We then focused our attention on the thermolytic fragmentation of triazene **4a** to azidoferrocene (**2a**). Thus, a solution of triazene **4a** in THF prepared in batch as described above was pumped through a tube reactor at elevated temperature. Upon fragmentation of triazene **4a** we observed precipitation of insoluble lithium *para*-toluenesulfinate, resulting in blockage of the tube reactor. Seeberger and Gilmore showed that suspensions can efficiently be kept in flow when a triphasic flow regime is used.[22]

Thus, we merged the reaction mixture with an argon stream before entering the heated tube reactor. In the resulting gas−liquid flow, a strong toroidal current kept the precipitate in a floating state and blockage of the tubing was inhibited.[23] At a temperature of 60 °C, thermolysis of triazene **4a** was complete within 15 min providing azidoferrocene (**2a**) in a yield of 85%. In contrast, when a solution of triazene **4a** was heated from −78 to 60 °C in batch, completion of the reaction required 30 min and gave a yield of only 70%, a limitation overcome by our flow process. Further accelerating the fragmentation by

Scheme 3. Scope of Functionalized Ferrocenyl Azides[a]



[a] Starting from the corresponding ferrocenyl bromides [Br] or iodides [I]. Yields of isolated products are given. Batch reaction conditions: substrate (1 equiv), *n*-butyllithium (1.1 equiv), tosyl azide (1.2 equiv) in THF (0.05–0.16 M) at −78 °C, 30 min, warmed to 25 °C over 16 h. Flow reaction conditions: substrate (0.2 M in THF; v = 2 mL/min), *n*-butyllithium (1.2 M in *n*-hexane; v = 0.4 mL/min), tosyl azide (0.75 M in THF; v = 0.8 mL/min), argon (v = 0.2 mL/min), 0 to 60 °C, 15 min residence time. [b] Bromine−lithium exchange was performed for 1 h. [c] *n*-Butyllithium (2.2 equiv) and tosyl azide (2.3 equiv) were used. For further details, see Supporting Information.

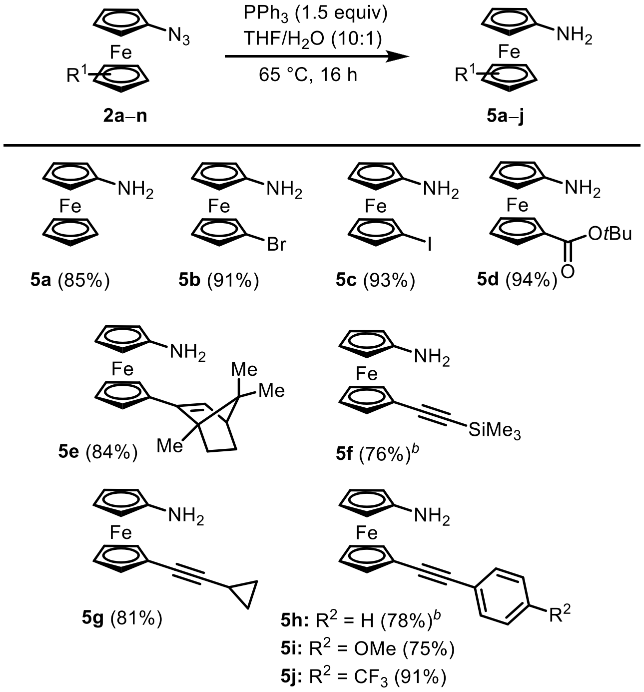
exceeding the boiling point of THF using back pressure regulators was only briefly contemplated, as blockage of the backpressure regulator by the suspension was expected.

We were now in the position to merge both processes into one continuous flow setup (Scheme 2). Some fine adjustment of flow rates and residence times was performed (see Supporting Information), and a mass flow controller providing a constant argon flow and a pumping system for solvent were employed to form a stable segmented flow regime. Iodoferrocene **1a** was introduced through an injection valve, while solutions of *n*-butyllithium in *n*-hexane and tosyl azide in THF were fed to the system by syringe pumps and mixed at 0 °C for 19 s. Finally, the reaction mixture was merged with an argon stream resulting in a segmented flow and warmed to 60 °C with a residence time of 15 min in a coiled tube reactor. Insoluble lithium *para*-toluenesulfinate precipitated from the reaction mixture resulting in a triphasic system of salt, liquid, and argon. The reaction mixture was eventually collected in a flask containing an aqueous sodium bicarbonate solution to quench any remaining reactive intermediates and remove inorganic byproducts. Using this flow setup, azidoferrocene (**2a**) was prepared in a yield of 82%. To showcase the practicality of our setup in the preparation of multigram quantities of azidoferrocenes, we performed a run with **1a** at a productivity of 4 g/h and achieved similar yields of **2a**.

We next applied our optimized flow conditions to a broad set of functionalized ferrocenyl halides **1b**−**n** (Scheme 3). The preparation of substrates **1e**−**1g** was achieved by selective bromine−lithium exchange of 1,1′-dibromoferrocene (see Supporting Information).[10] Bromo-substituted ferrocenyl azide **2b** was obtained in an excellent yield. For the iodo-substituted compound **2c**, the yield dropped significantly to 26% in batch as the iodine−lithium exchange was less selective. However, in flow the selectivity could be enhanced providing **2c** in 54% yield. Double azidation of 1,1′-dibromoferrocene gave the valuable diazide **2d** in an improved yield of 94% compared to previously reported 59% in batch.[9a] Due to its explosive nature, the preparation of this compound in flow (75% yield) benefited significantly from the better safety profile of our setup. Notably, the *tert*-butyl ester present in substrate **1e** was tolerated giving the corresponding azide **2e**, a precursor for ferrocene amino acids (*vide infra*). Camphor-derived ferrocenyl terpene **2g** was obtained in 66−69% yield. The planar chiral substrate **1h** was prepared by diastereoselective lithiation−iodination of enantioenriched Ugi's amine. Formation of the corresponding azide **2h** proceeded with retention of configuration. Heteroaromatic ferrocenyl azide **2f** could be obtained in good yield. As ethynyl-substituted ferrocene derivatives are frequently used in molecular wires,[4] we prepared an array of ethynyl-substituted ferrocenyl azides (**2i**−**2n**). These compounds were obtained in good to excellent yields in batch and flow. Both, electron-donating (**2l**) and electron-withdrawing (**2m**) groups attached to the aromatic moiety were tolerated. Ethynyl azide **2i** was prepared in 77−79% yield presenting the opportunity for sequential click chemistry.[11,24] For cyclopropyl-substituted azide **2j** the yield dropped slightly (56% in batch, 69% in flow). Generally, we assume that yields of ferrocenyl azides **2** are slightly lower in flow than in batch due to traces of water in the flow reactor resulting in hydrolysis of the intermediary ferrocenyllithiums **3**.

The reduction of ferrocenyl azides by palladium-catalyzed hydrogenation is well documented[7c,25] but not suitable for ferrocenyl azides **2g** and **2i**−**n** containing olefin or alkyne moieties. Treatment of ferrocenyl halides with ammonia in the presence of a copper/iron catalyst[26] would not allow the synthesis of halogenated ferrocenyl amines **5b** and **5c**. Thus, we decided to reduce ferrocenyl azides **2a**−**2n** to the corresponding amines **5a**−**5j** (Scheme 4) under Staudinger conditions. We found that treatment of ferrocenyl azides with triphenylphosphine (PPh_3) in a mixture of THF and water at 65 °C provided the corresponding amines **5a**−**5j** in consistently high yields. Among the products obtained, bromoferrocenyl amine **5b** is particularly valuable. A previous synthesis required five steps starting from 1,1′-dibromoferrocene and resulted in 31% yield.[8e] We now prepared **5b** in two steps and 83% yield. The *tert*-butyl ester substituted ferrocenyl amine **5d** was obtained in 94% yield and is useful to access

Scheme 4. Scope of Functionalized Ferrocenyl Amines[a]



[a]Yields of isolated products are given. Reaction conditions: Substrate (1 equiv), PPh_3 (1.5 equiv), THF/H_2O (10:1), 65 °C, 16 h. [b]PPh_3 (3 equiv) was used.

conformationally restricted peptide mimetics.[27] Ethynyl-substituted ferrocenyl amines **5f**–**5j** were obtained in yields of 76–91%. Ferrocenyl azides **2d**, **f**, **h**, and **n** underwent decomposition under these reaction conditions, and the corresponding amines could not be obtained.

In conclusion, we have developed a general and scalable method for the functionalization of ferrocene derivatives in flow. By halogen–lithium exchange of ferrocenyl halides and subsequent trapping with tosyl azide, a variety of functionalized ferrocenyl azides were obtained. The application of flow chemistry accelerated the reaction over three distinct synthetic manipulations to minutes with an excellent safety and scalability profile, even on gram scale. In this process, a flow setup was designed that combined fast halogen–lithium exchange with a slow fragmentation step. The challenging precipitation of lithium *para*-toluenesulfinate was managed by employing a triphasic flow regime that prevented blockage of the tube reactor. In addition, a practical Staudinger protocol was developed for the reduction of functionalized ferrocenyl azides to the corresponding ferrocenyl amines in generally high yields.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04450.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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