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Valentyn Pozhydaiev, Antonio J Paparesta, Joseph J Moran, David Lebœuf. Iron(II)-Catalyzed 1,2-Diamination of Styrenes Installing a Terminal NH<sub>2</sub> Group Alongside Unprotected Amines. *Angewandte Chemie International Edition*, 2024, 63 (45), pp.e202411992. 10.1002/anie.202411992. hal-04762375

HAL Id: hal-04762375

<https://hal.science/hal-04762375v1>

Submitted on 31 Oct 2024

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**Diamination Reactions**

# Iron(II)-Catalyzed 1,2-Diamination of Styrenes Installing a Terminal NH<sub>2</sub> Group Alongside Unprotected Amines

Valentyn Pozhydaiev, Antonio Paparesta, Joseph Moran,\* and David Lebœuf\*

**Abstract:** 1,2-Diamination of alkenes represents an attractive way to generate differentiated vicinal diamines, which are prevalent motifs in biologically active compounds and catalysts. However, existing methods are usually limited in scope and produce diamines where one or both nitrogens are protected, adding synthetic steps for deprotection and further N-functionalization to reach a desired target. Furthermore, the range of amino groups that can be introduced at the internal position is fairly limited. Here we describe a 1,2-diamination of styrenes that directly installs a free amino group at the terminal position and a wide variety of unprotected nitrogen nucleophiles (primary or secondary alkyl or aromatic amines, sulfoximines, *N*-heterocycles, and ammonia surrogate) at the internal position. Two complementary sets of conditions encompass electronically activated and deactivated styrenes with diverse substitution patterns and functional groups. Moreover, this strategy can be extended to the 1,2-aminothiolation of styrenes.

Vicinal diamines are privileged structural motifs in biologically active compounds and have also found extensive use in transition metal catalysis and organocatalysis (Scheme 1A).<sup>[1]</sup> As a result, a plethora of synthetic methods featuring various disconnections have been devised to prepare vicinal diamines,<sup>[2]</sup> including reactions with aldimines and ketimines,<sup>[3]</sup> hydroamination of allylamines and

enamines,<sup>[4]</sup> aminolysis of aziridines,<sup>[5]</sup> C–H amination,<sup>[6]</sup> and amination of diols via hydrogen borrowing strategy.<sup>[7]</sup> Most of these methods require starting materials where one of the nitrogen functionalities is pre-installed. More importantly, they are rarely compatible with a wide range of amino groups, notably alkylamines. Furthermore, they typically result in *N*-protected products, requiring additional protection/deprotection steps, lengthening the overall synthesis.

The intermolecular diamination of alkenes, and related transformations such as aminoazidation<sup>[8]</sup> and diazidation,<sup>[9]</sup> represent attractive strategies to prepare vicinal diamines from feedstock alkenes. However, accessing differentiated vicinal diamines proved difficult, especially when both nitrogen functionalities are not covalently linked within the reactant.<sup>[10,11]</sup> Several groups have designed methods for the direct formation of differentially protected diamines from alkenes via 1,2-diamination (Scheme 1B).<sup>[12]</sup> However, they typically install only one class of protected/masked amino groups at the internal position and they do not provide access to terminal primary aliphatic amines, except for the aminoazidation of alkenes reported by the group of Morandi.<sup>[8c]</sup> Yet, additional synthetic steps are required to convert the azide into amino functionalities.

Methods that enable diamination of alkenes that directly access unprotected differentiated vicinal diamines would be particularly attractive from a synthetic standpoint but remain rare.<sup>[13]</sup> The group of Leonori described a one-pot sequence that incorporates unprotected secondary and tertiary alkylamines at the terminal position, whereas mainly unprotected secondary alkylamines could be installed at the internal position (Scheme 1C).<sup>[13a]</sup> However, the use of less nucleophilic amines such as aniline or trifluoroethylamine led to a mixture of regioisomers, while the reactivity of amines bearing alkenyl or alkynyl moieties was not reported.

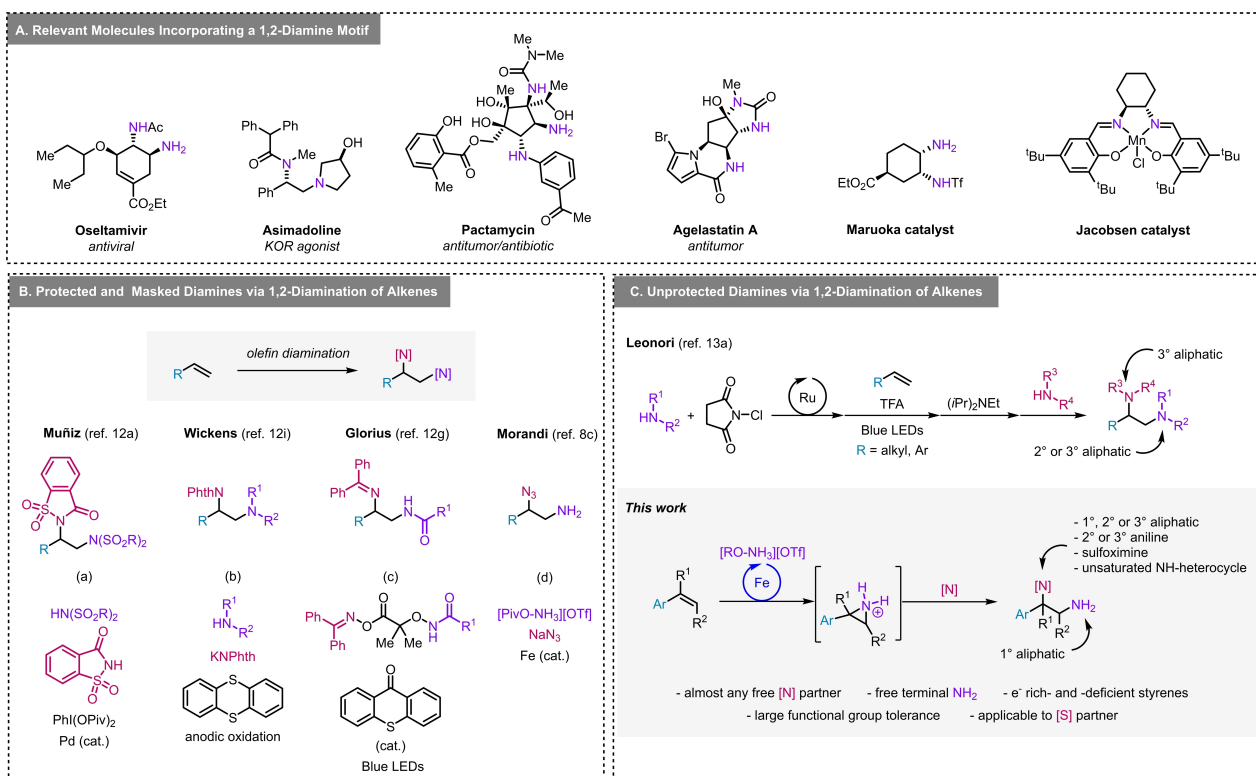
Despite the above-described important advances for alkene 1,2-diamination, a method that would directly embed a free NH<sub>2</sub> group at the terminal position and a broad array of nitrogen-containing motifs at the internal position is still missing. Moreover, this NH<sub>2</sub> represent a convenient synthetic handle for divergent synthesis as opposed to previous reports that usually led to products incorporating either amines protected by electron-withdrawing groups (EWG) or alkylamines at the terminal position. Another critical problem to address is the reactivity of highly electronically deactivated styrenes, which remain underrepresented even among methods that deliver protected unsymmetrical vicinal diamines.<sup>[8c,d,12b,h]</sup>

[\*] V. Pozhydaiev, A. Paparesta, Prof. J. Moran, Dr. D. Lebœuf  
 Institut de Science et d'Ingénierie Supramoléculaires (ISIS)  
 CNRS UMR 7006, Université de Strasbourg  
 8 Allée Gaspard Monge, 67000 Strasbourg, France  
 E-mail: moran@unistra.fr  
 dleboeuf@unistra.fr

Prof. J. Moran  
 Department of Chemistry and Biomolecular Sciences  
 University of Ottawa  
 Ottawa, Ontario, K1N 6N5, Canada

Prof. J. Moran  
 Institut Universitaire de France (IUF)  
 75005 Paris, France

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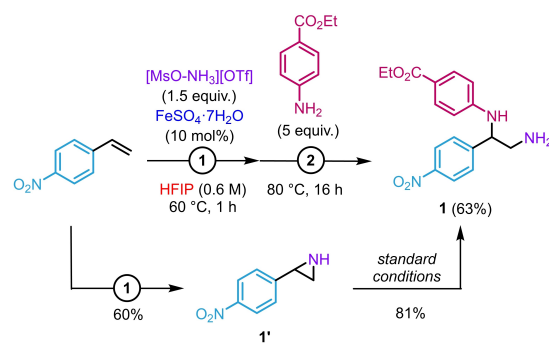
**Scheme 1.** Vicinal diamines and their synthesis by 1,2-diamination of alkenes.

Here, we report streamlined protocols for 1,2-diamination of sterically and electronically varied styrenes, which introduce an unprotected primary amine at the terminal position and a wide variety of nitrogen nucleophiles at the internal position such as unprotected primary or secondary alkyl or aromatic amines, sulfoximines, *N*-heterocycles, sulfoximines, and an ammonia surrogate.

At the outset of this study, we envisioned that the diamination of styrenes to give unprotected amines could be achieved in a one-pot/two-step sequence involving the initial formation of an aziridinium intermediate that will react with a second amine (Scheme 1C). This strategy is inspired by the work of the Morandi group on the aminofunctionalization of alkenes that allows the incorporation of primary aliphatic amines with hydroxylammonium salts.<sup>[8c,14,15]</sup> In their studies, simple nucleophilic partners, which did not interfere with the amine source, such as water, alcohols, sodium chloride and sodium azide were used. However, in the case of 1,2-diamination, the formation of the aziridinium and its opening needs to be separated in time due to the propensity of amines to react with hydroxylammonium salts.<sup>[15]</sup> Our previous studies on iron(II)-catalyzed (hetero)arylamination of highly deactivated styrenes showed that such temporal separation is feasible when hexafluoroisopropanol (HFIP) is used as a solvent.<sup>[16]</sup> We attributed this result to the inherent ability of HFIP to prevent any trapping of the catalyst, to extend the lifetime of cationic and radical species, and to increase the electrophilicity of reactive intermediates.<sup>[17]</sup> Nevertheless, the (hetero)arylamination protocol was far from general; the transformation was not compatible with

deactivated styrenes bearing, for instance, ester, CF<sub>3</sub>, or halide substituents, nor with electron-rich styrenes. Importantly, during our investigations on (hetero)arylamination, we observed that weakly basic diphenylamine substrates delivered products of diamination rather than aminoarylation. We posited that this observation could be exploited to develop a general 1,2-diamination of styrenes that was independent of the basicity and nucleophilicity of the amine.

Using *p*-nitrostyrene and benzocaine (anesthetic) as a representative aniline, we found that the devised reaction sequence led to the densely functionalized product **1** in 63% yield, incorporating three different nitrogen units and an ester (Scheme 2).<sup>[18]</sup> Decreasing the excess of benzocaine led to reduced yields (21% with 1 equivalent and 53% with 3



**Scheme 2.** Benchmark 1,2-diamination of *p*-nitrostyrene with benzocaine.

equivalents). Interrupting the process after the first step allowed us to isolate the corresponding aziridine **1'** in 60 % yield. Re-engaging the aziridine in our standard conditions provided compound **1** in 81 % yield, in line with its intermediacy in the reaction. As anticipated, when benzocaine was present from the start, the desired reaction did not proceed and *p*-nitrostyrene was fully recovered, suggesting a competitive reaction with the hydroxylammonium salt.

Having demonstrated the efficiency of our protocol with a primary aniline, we examined its compatibility with diverse *para*-substituted anilines (Conditions A) (Scheme 3). All smoothly reacted to afford the corresponding diamination products **2–9** in yields ranging from 33 to 71 %. We notably introduced several relevant functional groups such as nitro, cyano, trifluoromethyl, ester, primary amide, halide, ether, and alkyl. A chloride substituent could be positioned at the *para*, *meta* or *ortho* position without a significant impact on the reactivity (**10–12**). Even a sterically hindered aniline could be used to afford the target product **13** in 47 % yield. The transformation was extended to primary naphthylamines, delivering compounds **14** and **15** in 65 and 54 % yield, respectively. Next, we examined the reactivity of secondary anilines (**16–19**), which proved to be equally efficient as nucleophiles. Remarkably, the alkene and alkyne moieties in products derived from *N*-allylaniline **18** and *N*-propargyl aniline **19** remained intact and no cyclization product arising from hydroamination was observed.

We then explored the scope with respect to electron-deficient styrenes, using benzocaine as a model nucleophile. Our protocol allowed a rapid assembly of vicinal diamines (**20–28**) from a broad range of deactivated styrenes incorporating medicinally relevant and derivatizable substituents in yields ranging from 40 to 90 %, including a perfluoro motif, a trifluoromethyl group, secondary and tertiary sulfonamides, a sulfonyl ester, a secondary amide, a Weinreb amide and a pentafluorosulfonyl group. Using **20** as an example, we confirmed the scalability of the protocol on 5 mmol (80 %, 1.68 g).

We developed a second set of reaction conditions for electron-rich and mildly deactivated styrenes, which are prone to oligomerization under the original conditions in HFIP. Building on a previous study by the group of Morandi on aminochlorination,<sup>[14b]</sup> we achieved the desired reactivity through a two-step one-pot protocol, first involving the formation of aminochlorinated product **32**, which could be isolated in 78 % yield, followed by an in situ nucleophilic substitution of the chloride by aniline in the presence of triflic acid (TfOH) (Conditions B) (Scheme 4).

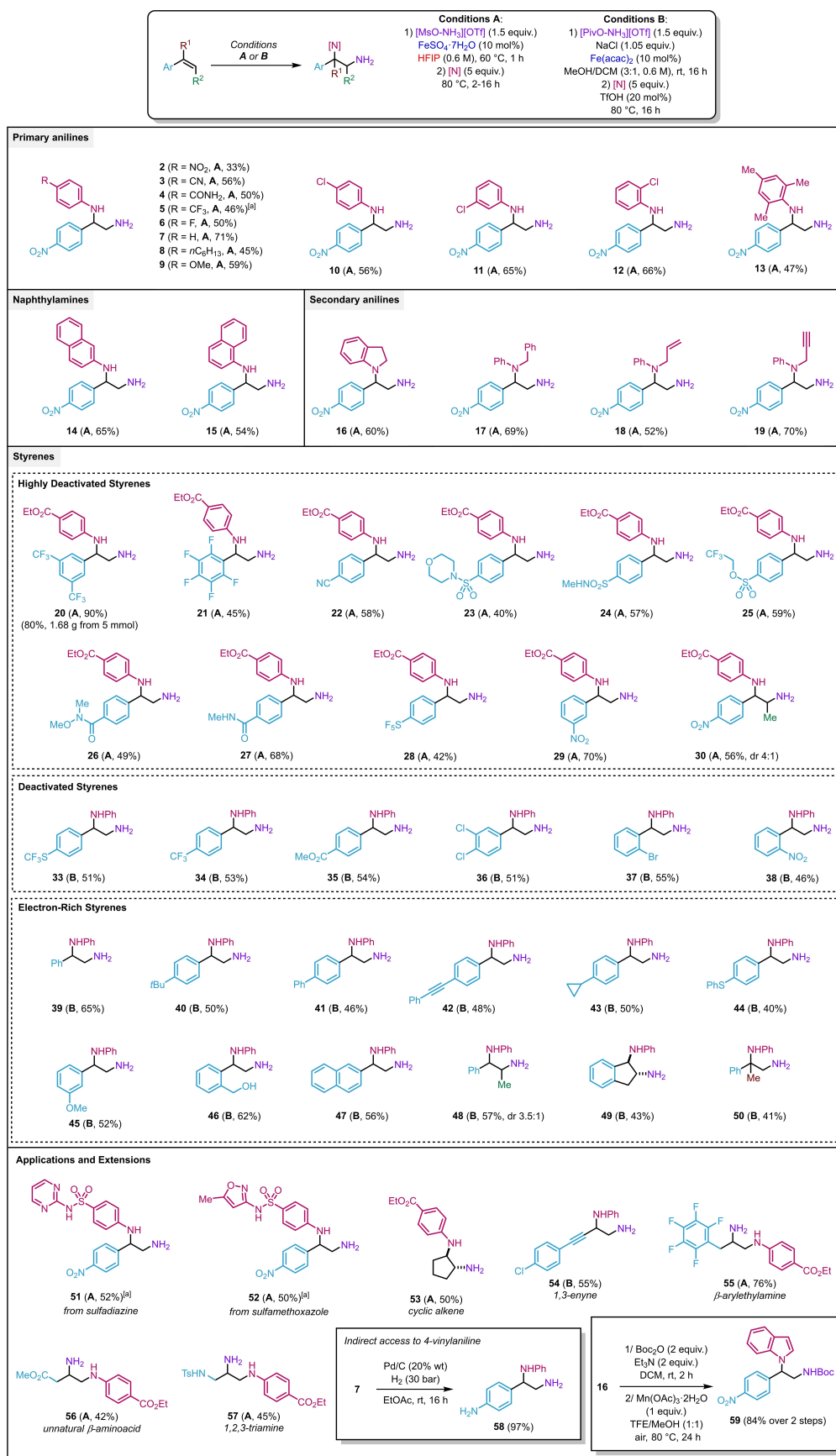
Conditions B enabled diamination of a series of deactivated styrenes containing SCF<sub>3</sub>, trifluoromethyl, ester, and halide groups (**33–37**, 51–55 %) as well as electron-rich styrenes (**39–47**, 40–65 % yields), which were previously incompatible with the reaction sequence in HFIP. Alkyl, aryl, alkynyl, cyclopropyl, ether and thioether substituents were well-tolerated. Remarkably, even the presence of an internal nucleophile on the arene did not disrupt the reaction (**46**, 62 %). Of note, those conditions do not work with highly deactivated substrates such as *p*-nitrostyrene. In turn, *m*- and *o*-nitrostyrene reacted smoothly to provide the

corresponding products **29** and **38** in 70 and 46 % yields, using conditions A and B, respectively. The protocol is not limited to mono-substituted styrenes but is also applicable to electron-rich and -deficient internal styrenes (**30**, **48** and **49**, 43–57 %) and  $\alpha$ -methylstyrenes such as **50** (41 %). On the other hand, no product was detected in the case of 4-nitrostilbene. Regarding electron-rich vinyl heteroaromatics such as 2-vinylthiophene or 3-vinylindole, they proved too reactive; during the aminochlorination step, the intermediate reacts with the solvent (methanol) to give an aminoetherification product which is unreactive in the presence of TfOH and aniline. The same result was also observed in the case of electron-rich *p*-methoxystyrene and 1,1-diphenylethylene (see Supporting Information for details).

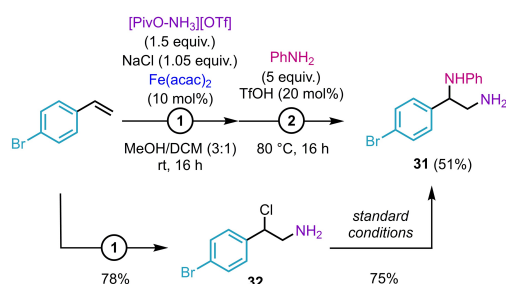
When bioactive molecules such as sulfadiazine (antibiotic) and sulfamethoxazole (antibiotic) were used in the reaction sequence, diamination products **51** and **52** were obtained in 52 % and 50 % yields, respectively. Our strategies were also applied to cyclic alkenes such as cyclopentene, producing compound **53** in 50 % yield,<sup>[19]</sup> and to a 1,3-enyne to furnish product **54** in 55 % yield. In the case of allylic substrates, the regioselectivity was, however, reversed in favor of the addition at the terminal position, in line with the observation of the Leonori group for related starting materials.<sup>[13a]</sup> Attractively, the protocol offers a rapid access to  $\beta$ -arylethyamines (**55**), which are key scaffolds in drug discovery,<sup>[20]</sup> unnatural  $\beta$ -amino acids (**56**), and 1,2,3-triamines (**57**).

Although 4-vinylaniline cannot be used directly for this reaction sequence, the corresponding product **58** was formally obtained via reduction of the nitro group of diamine **7** in nearly quantitative yield (97 %). Oxidation of the indoline moiety of Boc-protected diamine **16** by Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O delivered indole **59** in 84 % yield over 2 steps, representing an indirect way to add indoles to an alkene at NH rather than at C3.<sup>[16]</sup>

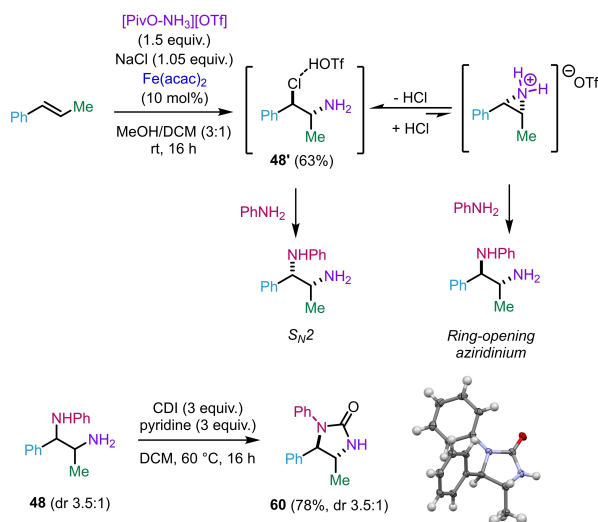
To gain insight into the role of TfOH in the second set of conditions, we studied the reactivity of *trans*  $\beta$ -methylstyrene (Scheme 5). From the known aminochlorinated intermediate **48'**,<sup>[14b]</sup> here isolated in 63 % yield as a single diastereoisomer, two mechanistic pathways were envisioned for the activation of benzyl chloride by TfOH: (1) a direct S<sub>N</sub>2 pathway would lead to the *cis* product, whereas (2) a pathway involving the formation of an aziridinium and a subsequent ring-opening would lead to the *trans* product. To differentiate between these scenarios, **48** was engaged in a reaction with carbonyldiimidazole (CDI) to form cyclic product **60** as a mixture of diastereoisomers (78 % yield, dr 3.5:1). The structure of the major diastereoisomer was ascertained by X-ray crystallography, showing a *trans* configuration, which is consistent with the second proposed mechanism. Additional observations further clarify the mechanism. During the second step, the use of a catalytic amount of TfOH proved essential to obtain the product **48** in a satisfying yield (57 %). In its absence, **48** was obtained only in 15 % yield. Furthermore, the formation of the aziridine was not observed in the absence of aniline. Thus, we assume that, in solution, there is an equilibrium between the aminochlorinated and aziridinium intermediates that



**Scheme 3.** Scope of 1,2-diamination of styrenes with anilines. [a] Isolated yield of Boc-protected compound.



**Scheme 4.** Benchmark 1,2-diamination of *p*-bromostyrene with aniline.



**Scheme 5.** Studies regarding the role of triflic acid in the reaction sequence.

favors the former, and that aniline reacts irreversibly with the aziridinium to form diamination product **48**. Given that both diastereoisomers were obtained, both mechanisms are likely at play, with the second one being the major path.

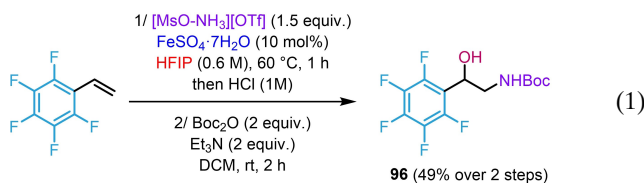
Next, we expanded the protocol to aliphatic amines. Primary aliphatic amines bearing functions of interest such as alkenyl (**61**), alkynyl (**62** and **63**), cyclopropyl (**64**), trifluoromethyl (**65**), (hetero)aryl (**66–68**) and protected amino acid (**69**) groups were successfully introduced into the product (Scheme 6). In turn, a complex mixture was obtained with *tert*-butylamine. In some cases, the product was isolated as a mixture of the free base and its ammonium salt, in which case it was Boc-protected to simplify characterization. Here, cyclopropylamine unexpectedly acted as a surrogate of ammonia, affording vicinal primary diamine **72**, whose formation likely results from the protonation of the cyclopropyl group (**70**) followed by hydrolysis of resulting iminium **71** to the primary amine.<sup>[21]</sup> To the best of our knowledge, it constitutes the first example of a direct 1,2-diamination of styrenes to afford unprotected vicinal primary amines in one-pot. Additionally, our protocol enabled the incorporation of medically relevant cyclic amines, including morpholine (**73**), piperazine (**74** and **75**) such as amoxapine (antidepressant, **75**), piperidine (**76**), pyrrolidine (**77**) and tetrahydroisoquinoline (**78**) moieties as

well as diallylamine (**79**) and rasagiline (treatment of Parkinson's disease, **80**) in yields ranging from 40 to 52 %.

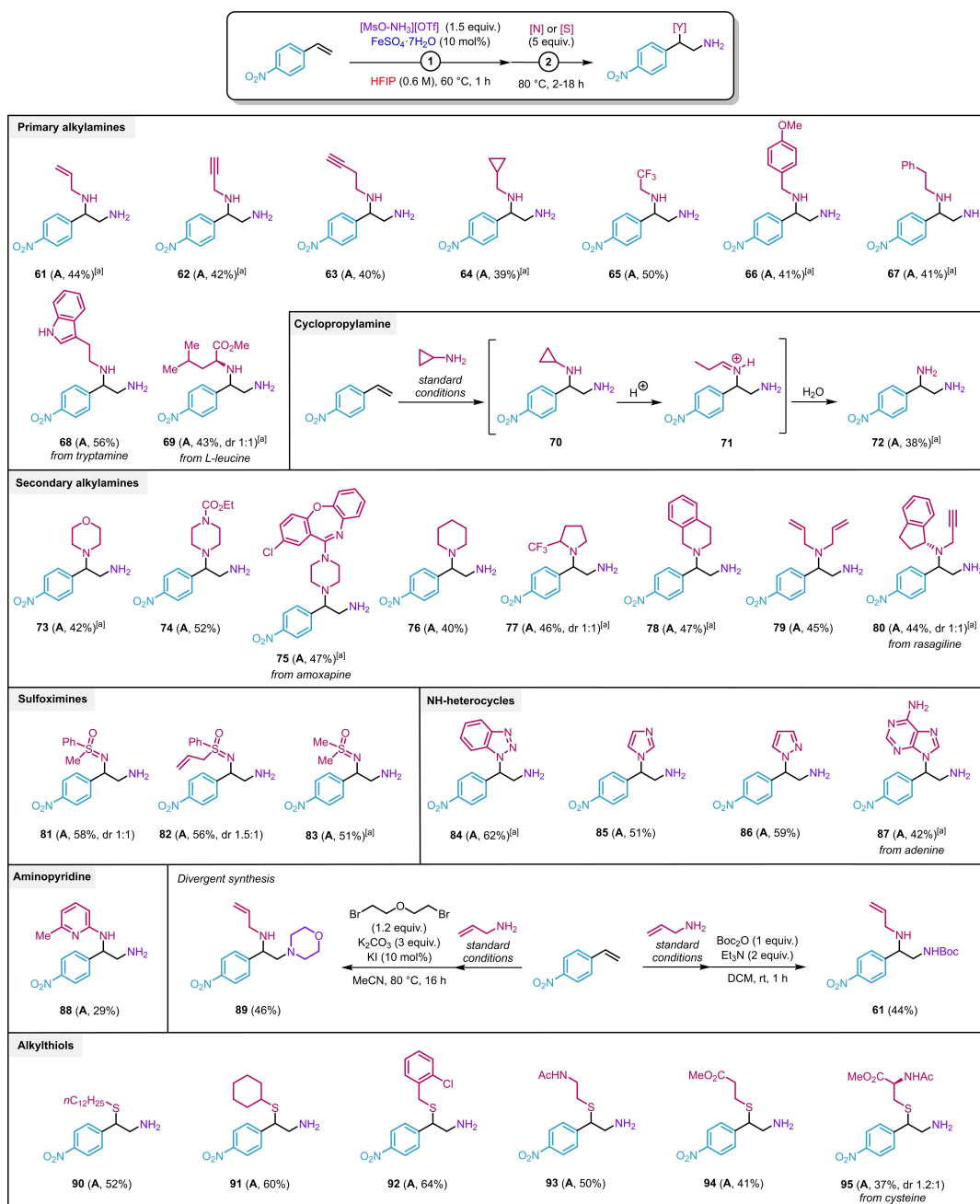
We then wondered if related nitrogen nucleophiles such as sulfoximines, which have emerged as relevant functional groups in drug discovery,<sup>[22]</sup> would be compatible with this reaction sequence. Since they display similar pKa as anilines, we considered that they should, in principle, display similar reactivity,<sup>[23]</sup> which was confirmed with compounds **81–83**. NH-heterocycles such as benzotriazole (**84**), imidazole (**85**), pyrazole (**86**) and adenine (**87**) also proved to be competent nucleophiles for the devised 1,2-diamination transformation. This protocol can also be used to install a pyridine motif, albeit in a lower yield (**88**, 29 %). As discussed in the introduction, the primary aliphatic amine formed can serve as a platform for divergent synthesis, to either introduce an EWG-group such as Boc (**61**) or a cyclic amine such as morpholine (**89**).

Moreover, this reaction sequence was successfully expanded to embody the aminothiolation of styrenes, adding an NH<sub>2</sub> group and S-nucleophiles, including underexplored alkylthiols.<sup>[24]</sup> The corresponding aminosulfidation products **90–95** were synthesized from diversely functionalized alkylthiols, notably protected cysteine, in 37–64 % yields.

Lastly, we demonstrated that our protocol is also applicable to the hydroxylation of highly deactivated styrenes. Morandi's pioneering report of styrene hydroxylation notably did not include substrates bearing electron-withdrawing groups stronger than a trifluoromethyl group.<sup>[14a]</sup> In our case, using pentafluorostyrene as substrate led to product **96** in 49 % yield (over 2 steps) following Boc protection (Equation 1):



In conclusion, we developed a general and versatile method for rapid access to 1,2-diamines in moderate to high yields, starting from readily available styrenes, hydroxylammonium salts, and amine nucleophiles. Compared to previous approaches, our operationally simple one-pot/two-step protocol enables a modular construction of densely functionalized vicinal diamines where one of the nitrogen functionalities is a primary aliphatic amine. A hallmark of this transformation is its capacity to accommodate many classes of amine and sulfur nucleophiles, including bioactive molecules. Depending on the electronic nature of the substrate studied, two different sets of conditions were developed which collectively cover a large variety of drug-relevant functional groups. The numerous functional groups incorporated into the target products could enable manifold derivatizations, creating high value-added building blocks for diversity-oriented synthesis, notably the design and preparation of analogs in drug discovery.



**Scheme 6.** Scope of 1,2-diamination of styrenes with various amino groups. [a] Isolated yield of Boc-protected compound.

## Acknowledgements

This work was supported by the Interdisciplinary Thematic Institute ITI-CSC via the IdEx Unistra (ANR-10-IDEX-0002) within the program Investissement d'Avenir and the ANR (ANR-23-CE07-0050-01). V.P. thanks the CSC Graduate School funded by the French National Research Agency (CSC-IGS ANR-17-EURE-0016). D.L. and J.M. thank the CNRS. The authors thank Wahnyalo Kazone for HRMS analysis and Corinne Bailly for the X-Ray analysis. Dr. Sami Lakhdar and Dr. Pawel Dydio are acknowledged for helpful discussions.

## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Keywords:** diamination · hexafluoroisopropanol · styrene · aliphatic amine · iron

- [1] For selected reviews, see: a) D. Lucet, T. L. Le Gall, C. Mioskowski, *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627; b) S. R. S. Kottli, C. Timmons, G. Li, *Chem. Biol. Drug Des.* **2006**, *67*, 101–114; c) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2010**, *1*, 13–31; d) D. Janssen-Müller, C. Schleppehorst, F. Glorius, *Chem. Soc. Rev.* **2017**, *46*, 4845–4854; e) S. Shaw, J. D. White, *Chem. Rev.* **2019**, *119*, 9381–9426.
- [2] For selected reviews, see: a) F. Cardona, A. Goti, *Nat. Chem.* **2009**, *1*, 269–275; b) S. de Jong, D. G. Nosal, D. J. Wardrop, *Tetrahedron* **2012**, *68*, 4067–4105; c) R. G. Arrayas, J. C. Carretero, *Chem. Soc. Rev.* **2009**, *38*, 1940–1948; d) A. Noble, J. C. Anderson, *Chem. Rev.* **2013**, *113*, 2887–2939; e) Y. Zhu, R. G. Cornwall, H. Du, B. Zhao, Y. Shi, *Acc. Chem. Res.* **2014**, *47*, 3665–3678; f) K. Muñoz, *Acc. Chem. Res.* **2018**, *51*, 1507–1519; g) J. L. Parry, N. Fu, S. Lin, *Synlett* **2018**, *29*, 257–265; h) Z.-L. Tao, S. E. Denmark, *Synthesis* **2021**, *53*, 3951–3962; i) D. Bouchet, T. Varlet, G. Masson, *Acc. Chem. Res.* **2022**, *55*, 3265–3283; j) R. Kumar, Y. Khanna, P. Kaushik, R. Ramal, S. Khokhar, *Chem. Asian J.* **2023**, *18*, e202300017; k) R. Kumar, *Chem. Asian J.* **2023**, *18*, e202300705.
- [3] For selected examples, see: a) T. Kano, R. Sakamoto, M. Akakura, K. Maruoka, *J. Am. Chem. Soc.* **2012**, *134*, 7516–7520; b) J. S. Bandar, T. H. Lambert, *J. Am. Chem. Soc.* **2013**, *135*, 11799–11802; c) D. Uruguchi, N. Kinoshita, T. Kizu, T. Ooi, *J. Am. Chem. Soc.* **2015**, *137*, 13768–13771; d) E. Fava, A. Millet, M. Nakajima, S. Loescher, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 6776–6779; e) Y. Wang, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5612–5615; f) X. Shao, K. Li, S. J. Malcomson, *J. Am. Chem. Soc.* **2018**, *140*, 7083–7087; g) J. Che, X. Gong, J. Li, Y. Li, J. Ma, C. Hou, G. Zhao, W. Yuan, B. Zhao, *Science* **2018**, *360*, 1438–1442; h) B. Han, Y. Li, Y. Yu, L. Gong, *Nat. Commun.* **2019**, *10*, 3804; i) M. Zhou, K. Li, D. Chen, R. Xu, G. Xu, W. Tang, *J. Am. Chem. Soc.* **2020**, *142*, 10337–10342; j) X.-C. Gan, C.-Y. Zhang, F. Zhong, P. Tian, L. Yin, *Nat. Commun.* **2020**, *11*, 4473; k) T. Agrawal, R. T. Martin, S. Collins, Z. Wilhelm, M. D. Edwards, O. Gutierrez, J. Sieber, *J. Org. Chem.* **2021**, *86*, 5026–5046; l) M. Zhou, Y. Lin, X.-X. Chen, G. Xu, L. W. Chung, W. Tang, *Angew. Chem. Int. Ed.* **2023**, *17*, e202300334; m) S. L. Hejnosz, D. R. Beres, A. H. Cocolas, M. J. Neal, B. S. Musiak, M. M. B. Hanna, A. J. Bloomfield, T. D. Montgomery, *Org. Lett.* **2023**, *25*, 4638–4643; n) X.-L. Han, B. Hu, C. Fei, Z. Li, Y. Yu, C. Cheng, B. Foxman, J. Luo, L. Deng, *J. Am. Chem. Soc.* **2023**, *145*, 4400–4407.
- [4] For selected examples, see: a) M. J. MacDonald, D. J. Schipper, P. J. Ng, J. Moran, A. M. Beauchemin, *J. Am. Chem. Soc.* **2011**, *133*, 20100–20103; b) L. Yu, P. Somfai, *Angew. Chem. Int. Ed.* **2019**, *58*, 8551–8555; c) S. Ichikawa, X.-J. Dai, S. L. Buchwald, *Org. Lett.* **2019**, *21*, 4370–4373; d) E. P. Venable, J. L. Kennemur, L. A. Joyce, R. T. Ruck, D. M. Schultz, K. L. Hull, *J. Am. Chem. Soc.* **2019**, *141*, 739–742; e) P.-F. Yang, J.-X. Liang, H.-T. Zhao, W. Shu, *ACS Catal.* **2022**, *12*, 9638–9645; f) A. T. Ho, S. C. Ensign, E. P. Venable, D. Portillo, J. N. Humke, G. D. Kortman, K. L. Hull, *ACS Catal.* **2022**, *12*, 8331–8340; g) B. J. Lee, A. R. Ickes, A. K. Gupta, S. C. Ensign, T. D. Ho, A. Tarasewicz, E. P. Venable, G. D. Kortman, K. L. Hull, *Org. Lett.* **2022**, *24*, 5513–5518; h) M. Mohiti, Y. Lu, H. He, S.-F. Ni, P. Somfai, *Chem. Eur. J.* **2024**, e202303078.
- [5] For selected examples, see: a) J. S. Yadav, B. V. S. Reddy, K. V. Rao, K. S. Raj, A. R. Prasad, *Synthesis* **2002**, 1061–1064; b) Z. Chai, P.-J. Yang, H. Zhang, S. Wang, G. Yang, *Angew. Chem. Int. Ed.* **2017**, *56*, 650–654; c) J. Liu, C. Wang, *ACS Catal.* **2020**, *10*, 556–561; d) Z.-R. Chang, S.-S. Du, C. Zhang, S.-H. Chen, Y. Z. Hua, M.-C. Wang, G.-J. Mei, S.-K. Jia, *ACS Catal.* **2023**, *13*, 6873–6878.
- [6] For selected examples, see: a) D. E. Olson, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 11248–11249; b) K. Lang, S. Torker, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2019**, *141*, 12388–12396; c) Y. Yang, I. Cho, X. Qi, P. Liu, F. H. Arnold, *Nat. Chem.* **2019**, *11*, 987–993; d) Z. Zhou, Y. Tan, T. Yamashira, S. Ivlev, X. Xie, R. Riedel, M. Hemming, M. Kimura, E. Meggers, *Chem* **2020**, *6*, 2024–2034; e) T. Shen, T. H. Lambert, *Science* **2021**, *371*, 620–626; f) A. Geraci, U. Stojiljkovic, K. Antien, N. Salameh, O. Baudoin, *Angew. Chem. Int. Ed.* **2023**, *62*, e202309263.
- [7] H.-J. Pan, Y. Lin, T. Gao, K. K. Lau, W. Feng, B. Yang, Y. Zhao, *Angew. Chem. Int. Ed.* **2021**, *60*, 18599–18604.
- [8] For selected examples, see: a) B. Zhang, A. Studer, *Org. Lett.* **2014**, *16*, 1790–1793; b) Y. Li, Y. Liang, J. Dong, Y. Deng, C. Zhao, Z. Su, W. Guan, X. Bi, Q. Liu, J. Fu, *J. Am. Chem. Soc.* **2019**, *141*, 18475–18485; c) S. Makai, E. Falk, B. Morandi, *J. Am. Chem. Soc.* **2020**, *142*, 21548–21555; d) D. Lv, Q. Sun, H. Zhou, L. Ge, Y. Qu, T. Li, X. Ma, Y. Li, H. Bao, *Angew. Chem. Int. Ed.* **2021**, *60*, 12455–12460; e) J. Zhao, H.-G. Huang, W. Li, W.-B. Liu, *Org. Lett.* **2021**, *23*, 5102–5106; f) D. Forster, W. Guo, Q. Wang, J. Zhu, *ACS Catal.* **2021**, *11*, 10871–10877; g) Y. Xu, B. Wang, J. Wang, X. Zhou, J. Chen, X. Guo, G.-J. Deng, W. Shao, *Org. Lett.* **2023**, *25*, 8716–8721; h) Y. Yu, Y. Yuan, K.-Y. Ye, *Chem. Commun.* **2023**, *59*, 422–425; i) Z.-Y. Dai, I. A. Guzei, J. M. Schomaker, *Org. Lett.* **2024**, *26*, 269–273.
- [9] For selected examples, see: a) G. Fumagalli, P. T. G. Rabet, S. Boyd, M. F. Greaney, *Angew. Chem. Int. Ed.* **2015**, *54*, 11481–11484; b) Y.-A. Yuan, D.-F. Lu, Y.-R. Chen, H. Xu, *Angew. Chem. Int. Ed.* **2016**, *55*, 534–538; c) N. Fu, G. S. Sauer, A. Saha, A. Loo, S. Lin, *Science* **2017**, *357*, 575–579; d) H. Zhou, W. Jian, B. Qian, C. Ye, D. Li, J. Zhou, H. Bao, *Org. Lett.* **2017**, *19*, 6120–6123; e) S.-J. Shen, C.-L. Zhu, D.-F. Lu, H. Xu, *ACS Catal.* **2018**, *8*, 4473–4482; f) J. C. Siu, J. B. Parry, S. Lin, *J. Am. Chem. Soc.* **2019**, *141*, 2825–2831; g) C.-Y. Cai, Y.-T. Zheng, J.-F. Li, H.-C. Xu, *J. Am. Chem. Soc.* **2022**, *144*, 11980–11985; h) K.-J. Bian, S.-C. Kao, D. Nemoto Jr., X.-W. Chen, J. G. West, *Nat. Commun.* **2022**, *13*, 7881; i) K.-J. Bian, D. Nemoto Jr., X.-W. Chen, S.-C. Kao, J. F. Hooson, J. G. West, *Chem. Sci.* **2024**, *15*, 124–133.
- [10] For selected examples, see: a) G. L. J. Bar, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2005**, *127*, 7308–7309; b) H. Du, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 762–763; c) H. Du, W. Yuan, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 11688–11689; d) B. Zhao, W. Yuan, H. Du, Y. Shi, *Org. Lett.* **2007**, *9*, 4943–4945; e) D. E. Olson, J. Y. Su, D. A. Roberts, J. Du Bois, *J. Am. Chem. Soc.* **2014**, *136*, 13506–13509; f) Z. Tao, B. B. Gilbert, S. E. Denmark, *J. Am. Chem. Soc.* **2019**, *141*, 19161–19170; g) C.-Y. Cai, X.-M. Shu, H.-C. Xu, *Nat. Commun.* **2019**, *10*, 4953.
- [11] For selected examples of formation of symmetrical 1,2-diamines, see: a) C. Røben, J. A. Souto, Y. González, A. Lishchynskiy, A. Muñoz, *K. Angew. Chem. Int. Ed.* **2011**, *50*, 9478–9482; b) M. W. Danneman, K. B. Hong, J. N. Johnston, *Org. Lett.* **2015**, *17*, 2558–2561; c) K. Muñoz, L. Barreiro, R. M. Romero, C. Martínez, *J. Am. Chem. Soc.* **2017**, *139*, 4354–4357; d) J. R. Tabor, D. C. Obenschain, F. E. Michael, *Chem. Sci.* **2020**, *11*, 1677–1682; e) P. Guo, J.-F. Han, G.-C. Yuan, L. Chan, L. Chen, J.-B. Liao, *Org. Lett.* **2021**, *23*, 4067–4071; f) S. Minakata, H. Miwa, K. Yamamoto, A. Hirayama, S. Okumura, *J. Am. Chem. Soc.* **2021**, *143*, 4112–4118; g) C. Wang, B. Liu, Z. Shao, J. Zhou, A. Shao, L.-H. Zou, J. Wen, *Org. Lett.* **2022**, *24*, 6455–6459; h) S. Saryzadi, S. Parkin, R. B. Grossman, *Org. Lett.* **2023**, *25*, 331–335; i) J. Yang, Y.-D. Wu, M. Pu, *Adv. Synth. Catal.* **2023**, *365*, 2356–2360.



- [12] For selected examples, see: a) C. Martínez, K. Muñiz, *Angew. Chem. Int. Ed.* **2012**, *51*, 7031–7034; b) H. Zhang, W. Pu, T. Xiong, Y. Li, X. Zhou, K. Sun, Q. Liu, Q. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2529–2533; c) J. Ciesielski, G. Dequierez, P. Retailleau, V. Gandon, P. Dauban, *Chem. Eur. J.* **2016**, *22*, 9338–9347; d) Q. Qin, Y.-Y. Han, Y.-Y. Jiao, Y. He, S. Yu, *Org. Lett.* **2017**, *19*, 2909–2912; e) D. Lee, Y. J. Jang, E. J. T. Phipps, H. Lei, T. Rovis, *Synthesis* **2020**, *52*, 1247–1252; f) J. Cao, D. Lv, F. Yu, M.-F. Chiou, Y. Li, H. Bao, *Org. Lett.* **2021**, *23*, 3184–3189; g) G. Tan, M. Das, R. Kleinmans, F. Katzenburg, C. Daniliuc, F. Glorius, *Nat. Catal.* **2022**, *5*, 1120–1130; h) Y. Zheng, Z.-J. Wang, Z.-P. Ye, K. Tang, Z.-Z. Xie, J.-A. Xiao, H.-Y. Xiang, K. Chen, X.-Q. Chen, H. Yang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202212292; i) D. E. Holst, C. Dorval, C. K. Winter, I. L. Guzei, Z. K. Wickens, *J. Am. Chem. Soc.* **2023**, *145*, 8299–8307; j) X.-L. Luo, D.-D. Ye, J. Zheng, D.-N. Chen, L.-N. Chen, L. Li, S.-H. Li, P.-J. Xia, *Org. Lett.* **2024**, *26*, 559–564; k) L.-F. Yang, Z.-Q. Xiong, X.-H. Ouyang, Q.-A. Wang, J.-H. Li, *Org. Lett.* **2024**, *26*, 1667–1671; l) J. Liu, L. Guo, Z. Chen, Y. Guo, W. Zhang, X. Peng, Z. Wang, Y.-F. Zeng, *Chem. Commun.* **2024**, *60*, 3413–3416.
- [13] a) S. Govaerts, L. Angelini, C. Hampton, L. Malet-Sanz, A. Ruffoni, D. Leonori, *Angew. Chem. Int. Ed.* **2020**, *59*, 15021–15028; b) F. Béke, Á. Mészáros, Á. Tóth, B. B. Botlik, Z. Novák, *Nat. Commun.* **2020**, *11*, 5924; c) Y. Li, A. Ali, J. Dong, Y. Zhang, L. Shi, Q. Liu, J. Fu, *Org. Lett.* **2021**, *23*, 4072–4077.
- [14] a) L. Legnani, B. Morandi, *Angew. Chem. Int. Ed.* **2016**, *55*, 2248–2251; b) L. Legnani, G. Prina-Cerai, T. Delcaillau, S. Willems, B. Morandi, *Science* **2018**, *362*, 434–439; c) E. Falk, S. Makai, T. Delcaillau, L. Gürtler, B. Morandi, *Angew. Chem. Int. Ed.* **2020**, *59*, 21064–21071; d) S. Chatterjee, I. Harden, G. Bistoni, R. G. Castillo, S. Chhabra, M. van Gastel, A. Schnegg, E. Bill, J. A. Birrell, B. Morandi, F. Neese, S. DeBeer, *J. Am. Chem. Soc.* **2022**, *144*, 2637–2656.
- [15] For reviews, see: a) S. Sabir, G. Kumar, J. L. Jat, *Org. Biomol. Chem.* **2018**, *16*, 3314–3327; b) V. C. M. Gasser, S. Makai, B. Morandi, *Chem. Commun.* **2022**, *58*, 9991–10003.
- [16] V. Pozhydaiev, M. Vayer, C. Fave, J. Moran, D. Lebcœuf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202215257.
- [17] For selected reviews on HFIP, see: a) I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Chem. Rev.* **2017**, *1*, 0088; b) V. Pozhydaiev, M. Power, V. Gandon, J. Moran, D. Lebcœuf, *Chem. Commun.* **2020**, *56*, 11548–11564; c) T. Bhattacharya, A. Ghosh, D. Maiti, *Chem. Sci.* **2021**, *12*, 3857–3870; d) H. F. Motiwala, A. M. Armaly, J. G. Cacioppo, T. C. Coombs, K. R. K. Koehn, V. M. Norwood IV, J. Aubé, *Chem. Rev.* **2022**, *122*, 12544–12747; e) M. Piejko, J. Moran, D. Lebcœuf, *ACS Org. Inorg. Au* **2024**, *4*, 287–300.
- [18] In the transformation, water coming from the catalyst does not have any influence since it is as efficient with Fe(OTf)<sub>2</sub> and Fe(OAc)<sub>2</sub>. Fe(SO<sub>4</sub>)<sub>2</sub>·7H<sub>2</sub>O presents the advantage of being cheap and easy to handle.
- [19] For an example of diamination of cyclohexene, see: D. Chu, J. A. Ellman, *Org. Lett.* **2023**, *25*, 3654–3658.
- [20] V. Pozhydaiev, C. Muller, J. Moran, D. Lebcœuf, *Angew. Chem. Int. Ed.* **2023**, *62*, e202309289.
- [21] O. O. Sokolova, J. F. Bower, *Chem. Rev.* **2021**, *121*, 80–109.
- [22] a) J. A. Sirvent, U. Lücking, *ChemMedChem* **2017**, *12*, 487–501; b) M. Frings, C. Bolm, A. Blum, C. Gnamm, *Eur. J. Med. Chem.* **2017**, *126*, 225–245; c) P. Mäder, L. Kattner, *J. Med. Chem.* **2020**, *63*, 14243–14275; d) Y. Han, K. Xing, J. Zhang, T. Tong, Y. Shi, H. Cao, H. Yu, Y. Zhang, D. Liu, L. Zhao, *Eur. J. Med. Chem.* **2021**, *209*, 112885; e) U. Lücking, *Chem. Eur. J.* **2022**, *28*, e202201993.
- [23] E. Werner, M. Wiegand, J. Moran, D. Lebcœuf, *Org. Lett.* **2024**, *26*, 547–552.
- [24] For rare examples of aminothiolation of styrenes with alkylthiols, see: a) M. Iwasaki, K. Nonaka, S. Zou, Y. Sawanaka, T. Shinozaki, T. Fujii, K. Nakajima, Y. Nishihara, *J. Org. Chem.* **2019**, *84*, 15373–15379; b) W. Wang, L. Zhao, H. Wu, Y. He, G. Wu, *Org. Lett.* **2023**, *25*, 7078–7082.

Manuscript received: June 26, 2024

Accepted manuscript online: July 17, 2024

Version of record online: September 6, 2024