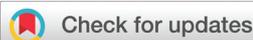


## RESEARCH ARTICLE

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# A domino reaction strategy for facile and modular construction of synthetically challenging functionalized *ortho*-fluoroanilines†‡

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The selective formation of *ortho*-fluoroanilines, representing versatile intermediates for the pharmaceutical and fine chemical industries, relies to date on, *e.g.*, transition-metal-catalyzed fluorination of azo-benzenes, which must be performed from aniline derivatives. While few efficient methods for aniline synthesis were reported, sustainable, straightforward, and selective synthesis of fluoroanilines, and in particular *ortho*-fluoroanilines, remains challenging. Herein, we describe a domino approach that involves the *simultaneous construction of a benzene ring and the installation of both amine and fluorine groups* in a single operation under metal-free conditions, starting from readily available acyclic compounds. The developed atom- and cost-efficient, highly convenient, selective, and environmentally friendly four-step domino process allows the formation of a variety of functionalized *ortho*-fluoroanilines with yields of up to 80% and bypasses the selectivity issues of transition-metal-catalyzed aniline fluorination reactions. Furthermore, we show that the new domino products can efficiently be utilized to synthesize fluorinated azo dye and (tetrahydro)quinazoline derivatives in a bioactive form, *i.e.*, possessing a first-time proven micromolar antiviral activity and high selectivity (EC<sub>50</sub> (HCMV) down to 1.9 ± 0.7 μM, CC<sub>50</sub> up to >100 μM), under conventional and/or visible-light mediated conditions.

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## Introduction

Aniline is a prominent aromatic amine compound broadly used as a versatile chemical precursor for the synthesis of bioactive compounds,<sup>1–4</sup> polymers,<sup>5,6</sup> and azo dyes.<sup>7–9</sup> There is also a growing number of fluorinated aniline-based drugs ranging from anti-inflammatory, antidepressant, antibiotic, antiviral, and anticancer derivatives (selected examples are shown in Fig. 1a).<sup>10–14</sup> Fluorinated drugs can exhibit enhanced effectivity and selectivity, potentially leading to increased biological activity. This is often attributed to the possibility of

improving many chemical and biological properties (*e.g.*, solubility, lipophilicity, membrane permeability, metabolic stability, and receptor binding) when exchanging hydrogen with fluorine in the parental compound.<sup>11,15,16</sup> Fluoroanilines also find application for the synthesis of polyfluoroanilines<sup>17</sup> and fluorinated azo dyes<sup>18,19</sup> (Fig. 1b and c), as fluorine in comparison to hydrogen can improve material properties.<sup>20</sup> These examples from life and material sciences stress the importance of *ortho*-fluoroanilines as versatile compounds. While there are already several procedures towards aniline derivatives, like reduction of the corresponding nitrobenzene as first described by Zinin,<sup>21</sup> palladium-catalyzed Buchwald–Hartwig C–N cross-coupling reaction,<sup>22</sup> Ullmann-type amination,<sup>23</sup> and more recently, iridium-/cobalt-photocatalyzed dehydrogenative coupling between amine and cyclohexanone by Leonori,<sup>24</sup> and transition-metal-free C–N cross-coupling,<sup>25</sup> only rare examples for synthesis of fluoroanilines were reported. Whereas fluorination of aliphatic systems can be carried out under relatively mild conditions,<sup>26</sup> the fluorination of aromatic systems, especially for the synthesis of fluorine-containing aniline structures, remains challenging (selected examples are depicted in Fig. 1d–f).<sup>27–29</sup> Recently, a *para*-selective nucleophilic fluorination method of anilides,

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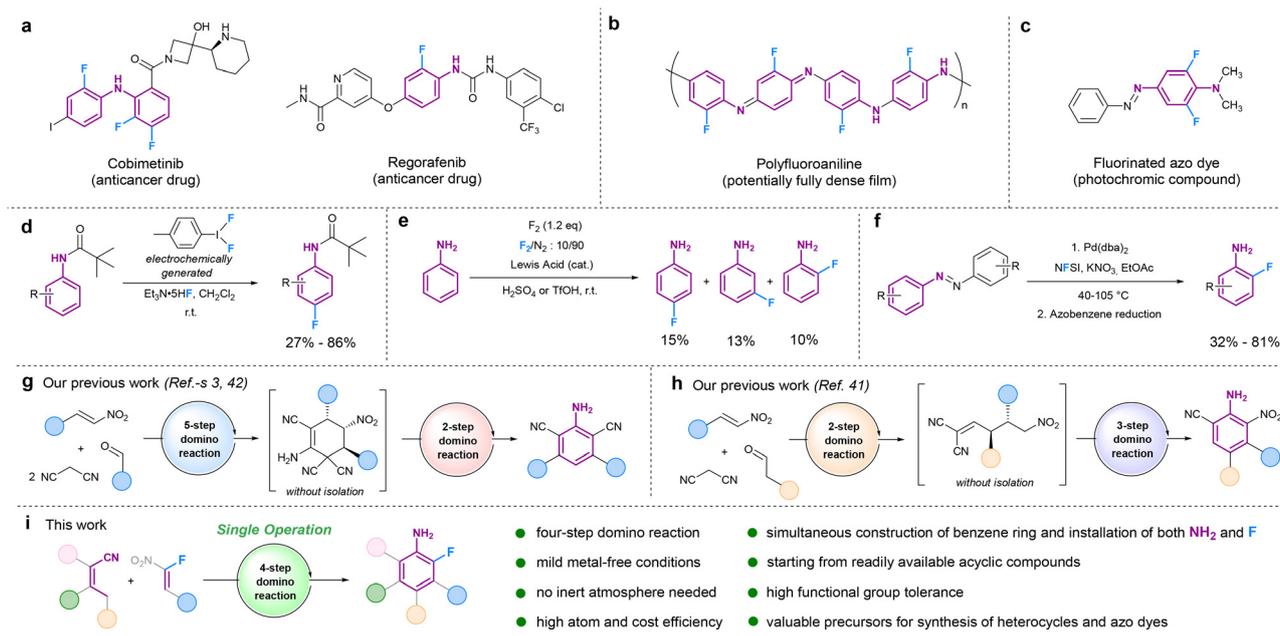
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† In honor of Professor H. Ila's 80th birthday.

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**Fig. 1** (a) Examples of fluoroaniline-containing drug compounds; (b) structure of polyfluoroaniline; (c) fluorinated azo dye; (d–f) literature known fluorinations of anilines; (g and h) previously reported domino approaches toward functionalized anilines by our research group; (i) *this work*: new straightforward four-step domino reaction toward functionalized fluoroaniline compounds.

using an electrochemically generated hypervalent iodine mediator (ArIF<sub>2</sub>), was reported, with Et<sub>3</sub>N·5HF serving as fluoride source (Fig. 1d).<sup>30</sup> The utilization of anilide as opposed to aniline was imperative due to the ring's lowered electron density. Also, an electrophilic aromatic fluorination approach was explored with aniline (Fig. 1e).<sup>31</sup> By employing an excess of elemental fluorine, a mixture of *para*-, *meta*-, and *ortho*-monosubstituted fluoroanilines was obtained.<sup>31</sup> Moreover, elemental fluorine is challenging to handle, and this method's site-selective preparation of fluoroanilines is subpar. Although *ortho*-fluoroanilines find broad application in the synthesis of heterocycles,<sup>32–35</sup> efficient synthetic strategies for highly substituted *ortho*-fluoroanilines are barely known. Current methodologies rely mainly on commercially available unsubstituted *ortho*-fluoroaniline, subject to altering *via* postmodifications.

Recently, an alternative route was reported, demonstrating the nitrate-promoted C–H fluorination of azobenzenes to synthesize substituted *ortho*-fluoroanilines. This approach utilizes the reduction of fluorinated azobenzenes to *ortho*-fluoroanilines after fluorination reaction (Fig. 1f).<sup>36</sup> While this method was proven useful in terms of selectivity, as only *ortho*-fluoroanilines were synthesized, atom-efficiency still poses a challenge, as the reaction can only proceed *via* the detour of the azobenzene, which must also be pre-formed from aniline derivatives. Therefore, the formation of *ortho*-fluorinated anilines by this route is complex, and a convenient, straightforward, and environmentally friendly synthetic method for *ortho*-fluoroaniline compounds remains to be developed. In addition, arylated anilines are widely used in the materials

and life sciences, and the standard method for C–C bond formation between aryl rings is still palladium-catalyzed cross-couplings in most cases. Due to the ever-increasing price for palladium and other late transition metals,<sup>37</sup> a more sustainable route toward arylated anilines and, in particular, arylated fluoroanilines is desirable.

To address the mentioned gaps and synthetic challenges disparity, we applied the concept of domino reactions, which represent a powerful toolbox in organic synthesis to economically and sustainably install molecular complexity, starting from simple compounds.<sup>38</sup> Domino processes avoid intermediate isolation and purification steps and are time-saving, waste-reducing, atom-efficient and can be considered as a green method superior to stepwise synthetic approaches.<sup>38–40</sup> Although recently, we reported access to new aniline derivatives using different domino reactions and one-pot processes (Fig. 1g and h),<sup>3,41–43</sup> to the best of our knowledge, a domino approach has never been used before *to form an aromatic ring*, and *to install both amine and fluorine groups* in a single operation while starting from readily available acyclic compounds. Herein, we report for the first time the straightforward synthesis of synthetically challenging functionalized *ortho*-fluoroanilines *via* a metal-free four-step domino reaction starting from readily available acyclic fluoro-nitrostyrenes and  $\alpha,\alpha$ -dicyanoolefine precursors (Fig. 1i). The developed atom- and cost-efficient, highly selective, and environmentally friendly domino process enables the formation of a variety of functionalized *ortho*-fluoroanilines with yields of up to 80%. The new products could be efficiently used to synthesize a fluorinated azo dye and (tetrahydro)quinazoline derivatives with antiviral properties.



## Results and discussion

### Synthesis of fluoroanilines

To overcome the drawbacks of existing fluorination methods, we envisioned a new metal-free domino reaction toward *ortho*-fluoroanilines using fluoro-nitrostyrenes and  $\alpha,\alpha$ -dicyanoolefins as starting compounds (Fig. 1i and 2a, b). At the beginning of our investigation, we focused on the optimization of the proposed two-component four-step linear domino reaction, which involves vinylogous Michael reaction/cyclization/imine-enamine tautomerization/aromatization steps (Fig. 2c). We intended to exploit the higher C–F bond strength in comparison to that of C–N (C–NO<sub>2</sub>) in selected substrate compounds, fluoro-nitrostyrenes, to form functionalized *ortho*-fluoroanilines (instead of *ortho*-nitroanilines<sup>41,43</sup>) in a single operation through a linear domino process. We applied preformed  $\alpha,\alpha$ -dicyanoolefins (Knoevenagel product **1a–e** and **4a–i**) since a Knoevenagel condensation step was not feasible in the initially investigated three-component reaction using ketone, malononitrile, and fluoro-nitrostyrene as starting compounds. In such a three-component reaction, we observed that the Knoevenagel condensation with ketone is reversible. As a result, a side product (Michael's reaction product out of fluoro-nitrostyrene and malononitrile) was formed instead of the desired domino product. We, therefore, preformed the  $\alpha,\alpha$ -dicyanoolefins and applied them for the new two-component domino reaction.

Utilizing the combination of DBU and thiourea (optimized conditions, see Table S1 of ESI<sup>†</sup>) for the selected model reaction of  $\alpha,\alpha$ -dicyanoolefin **1a** and fluoro-nitrostyrene **2a**, we were able to isolate the desired *ortho*-fluoroaniline **3a** in 61% yield over four steps (Fig. 2). Subsequently, the influence of substituents at the phenyl group of fluoro-nitrostyrene **2** on the reaction outcome was examined. The presence of methyl substituent (with +I effect) in the *para*-position of the phenyl group exhibits a slightly lower product yield (*cf.* 44% (**3b**) vs. 61% (**3a**), Fig. 1a). Fluoro-nitrostyrenes bearing electron-withdrawing groups (*e.g.*, F, ester moiety) in *para*-positions of the phenyl group resulted in the desired *ortho*-fluoroanilines **3d** and **3e** in good yields of 35%/53% compared to *ortho*-fluoroaniline **3c** (27% yield) with electron-donating methoxy substituent. Notably, even though the *para*-methoxy substituent enriches the electron density of the fluoro-nitrostyrene and decreases its electrophilicity and, therefore, the Michael acceptor's reactivity, the corresponding product **3c** was obtained in satisfactory yield. Next, the influence of different substituents at the phenyl group of  $\alpha,\alpha$ -dicyanoolefins **1** on the reaction outcome was evaluated (Fig. 2b). The application of **1** with methyl group (+I effect) and/or electron-withdrawing substituents (*e.g.*, F, ester moiety) resulted in the corresponding diaryl-substituted *ortho*-fluoroanilines **3f**, **3h**, **3i**, and **3j** with moderate yields of 19%–34%. In contrast, the electron-donating methoxy group was well tolerated in the developed reaction and gave the corresponding product **3g** with a yield of 64%. This result underscores that the higher electron density is beneficial for the nucleophilicity of the vinylogous donors **1**.

Regarding the triaryl-substituted *ortho*-fluoroanilines **5a–5n**, similar observations were made concerning the influence of substituents at the phenyl group of fluoro-nitrostyrene **2** on the observed yields (products **5a–5e**). Variation of substituents on the phenyl ring, standing in *para*-position to the amine group (see products **5f–5i**), has the most perceptible impact on the yield: fluorine substitution increased the yield significantly (to 80%) compared to electron-donating groups, which have higher electron density, lowering the C–H acidity of the CH<sub>2</sub> group, which needs to be deprotonated to enable the nucleophilic addition. While both the ester group and the fluoro substitution (**5i** and **5h**, respectively), increase the acidity of the CH<sub>2</sub> group, the difference in yield can be explained by the fact that the ester group mesomerically stabilizes the negative charge after deprotonation.

The delocalisation of charge results in a decreased reactivity for the nucleophilic attack compared to fluorine substitution. The good yield of 80% for fluoro-derivative **5h** corresponds to an excellent average yield of 95% per step, underlining the practical applicability of the developed domino approach. Notably, the derivatisation of the lower aryl ring has less impact on the yield (see **5j–5n**) compared to their *meta*-terphenyl analogues.

### Synthesis of tetrahydroquinazoline and quinazoline scaffolds

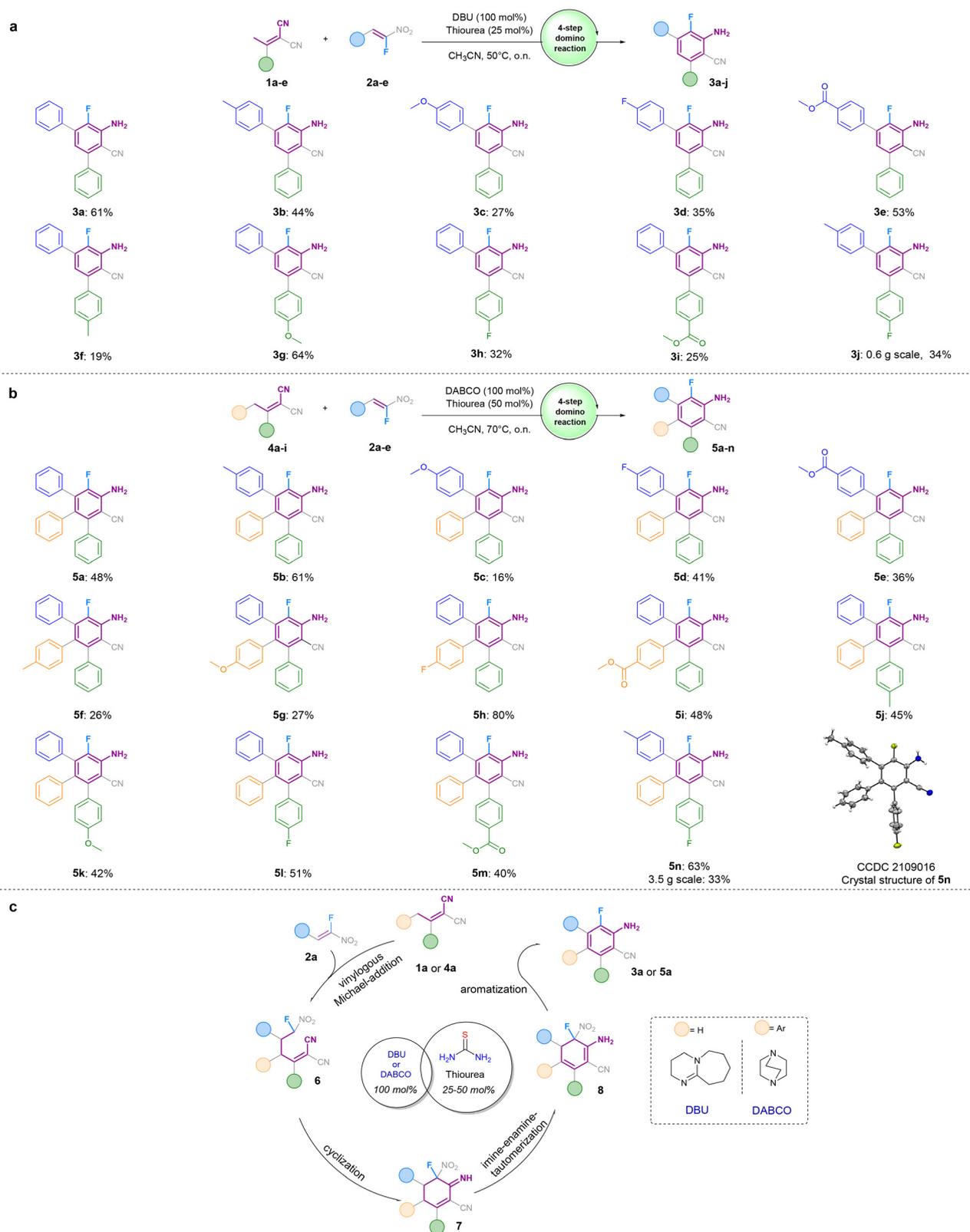
To use the new fluoroanilines as precursors for synthesis of *e.g.*, heterocyclic compounds, we performed large-scale synthesis of **3j** and **5n** as depicted in Fig. 2a and b. Given the fluorescence exhibited by both derivatives in solution, we investigated their absorption and emission in acetonitrile (see ESI, Fig. S1 and S2<sup>†</sup>).

First, we attempted to utilize amine and nitrile moieties on the obtained fluoroanilines for functionalization. From literature,<sup>3</sup> we know unsubstituted quinazolines **9** and **10** are directly accessible from *o*-amino nitrile by condensation with formamide. In order to get access to a broader array of quinazolines, we reduced the nitrile group of our triaryl-substituted *ortho*-fluoroaniline **5n** to yield the corresponding diamine **11** using borane dimethylsulfide as a reducing agent.

Azo dyes are among the most significant classes of chromophores with diverse applications in the scientific, industrial, and pharmaceutical sectors.<sup>44</sup> Taking into consideration the attractiveness of fluorinated azo dyes as photochromic compounds<sup>18,19</sup> we additionally synthesized vividly red fluorinated azo dye **12** utilizing *tert*-butylnitrite to form the diazonium cation, and *N,N*-dimethylaniline as the required nucleophile.

Utilizing **11** as starting material, we obtained tetrahydroquinazolines **13–15** and quinazolines **16–18**, with potential to display antiviral and other biological activity. All tetrahydroquinazolines **13–15** were synthesized by condensation reactions with the corresponding aldehyde or ketone utilizing silica as Lewis acid catalyst. By employing a variety of aldehydes, either aromatic or propargylic aldehydes, three quinazolines were obtained utilizing a literature known procedure under involvement of singlet oxygen, *in situ* generated by visible light using Rose Bengal as photosensitizer.<sup>45</sup> Through this route quinazoline derivatives **16**, **17**, and **18** were obtained, although the aldehyde containing the





**Fig. 2** (a) Scope of *meta*-terphenyls. Conditions:  $\alpha,\alpha$ -dicyanoolefin (200  $\mu$ mol), fluoro-nitrostyrene (200  $\mu$ mol), DBU (100 mol%), thiourea (25 mol%), acetonitrile (2 mL), 50 °C. (b) Scope of triphenylanilines. Conditions:  $\alpha,\alpha$ -dicyanoolefin (200  $\mu$ mol), fluoro-nitrostyrene (200  $\mu$ mol), DABCO (100 mol%), thiourea (50 mol%), acetonitrile (2 mL), 70 °C. (c) Postulated mechanism of the new four-step domino process.



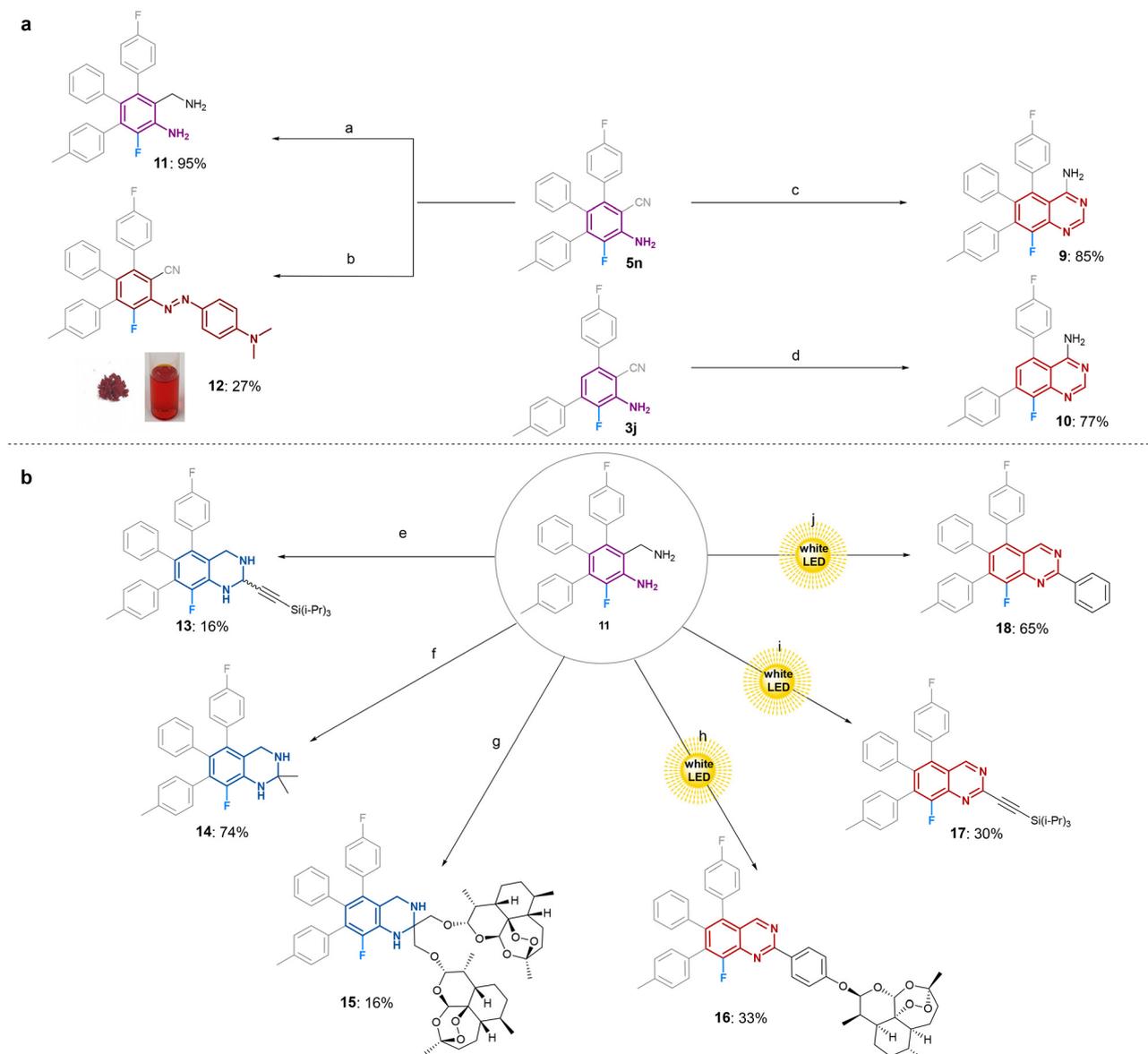
artemisinin scaffold needed to be precondensed using the same method towards tetrahydroquinazolines as above, followed by aromatization *via* involvement of singlet oxygen.

In the past, our and other groups showed the high potential of hybrid drugs exhibiting strongly improved activities against viruses, malaria and other pathogens.<sup>46–50</sup> This was the motivation to prepare and to investigate the artemisinin-based hybrid compounds **15** and **16** (Fig. 3).

### Cyclic voltammetric (CV) investigations of the novel azo dye **12**

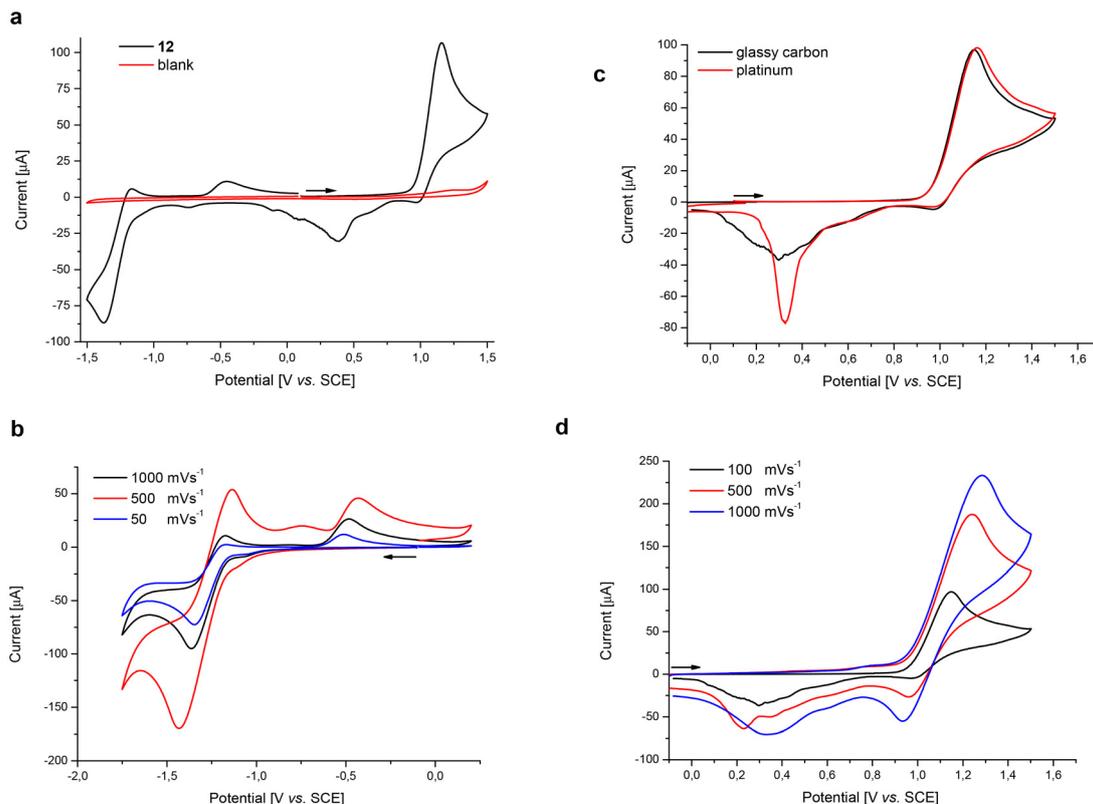
As studies by means of cyclic voltammetry revealed, the novel azo dye **12** exhibits both oxidative and reductive stability at a glassy carbon electrode in aprotic media (Fig. 4a). An irrevers-

ible oxidation event is observed at  $E_p = 1.16$  V *vs.* SCE, which can be assigned to the oxidation of the amine moiety.<sup>51</sup> Upon increasing scan rates, this amine oxidation becomes partially reversible (Fig. 4b). After rapid chemical follow-up reactions, the resulting species are reduced at  $E_p = -0.39$  V *vs.* SCE. Interestingly, this reduction is more facile on a platinum electrode surface as indicated by a more pronounced reductive event at  $E_p = -0.32$  V (Fig. 4c). In accordance with previous reports,<sup>52,53</sup> a quasi-reversible one-electron reduction is observed at  $E_p = -1.37$  V *vs.* SCE, forming a radical anion. Again, a subsequent chemical follow-up reaction generates a new species which gets oxidized at  $E_p = -0.45$  V *vs.* SCE. The relative intensity of the oxidation event at  $E_p = -0.45$  V *vs.* SCE,



**Fig. 3** Post-modifications of synthesized fluoroanilines: (a) 1.  $\text{SMe}_2\text{BH}_3\cdot\text{Et}_2\text{O}$ , THF, 2.  $\text{H}_2\text{O}$ , HCl, reflux. (b) 1. *tert*-Butylnitrite, acetonitrile, 0 °C, 2. *N,N*-Dimethylaniline, 0 °C to r.t. (c and d) Formamide, 210 °C. (e) Corresponding aldehyde,  $\text{SiO}_2$ ,  $\text{CHCl}_3$ , r.t. (f)  $\text{SiO}_2$ , acetone, r.t. (g) Corresponding ketone,  $\text{SiO}_2$ ,  $\text{CHCl}_3$ , r.t., (h), 1.  $\text{SiO}_2$ , corresponding aldehyde,  $\text{CH}_2\text{Cl}_2$ , 40 °C 2. Rose Bengal, DMF,  $\text{O}_2$ , LED (white light), r.t. (i) and (j), Corresponding aldehyde, Rose Bengal, DMF,  $\text{O}_2$ , LED (white light), r.t.





**Fig. 4** Cyclic voltammetry of **12** (5 mM). (a) at  $100 \text{ mV s}^{-1}$  in DCM with  $n\text{-Bu}_4\text{NPF}_6$  (0.1 M); (b) at different scan rates in DCM with  $n\text{-Bu}_4\text{NPF}_6$  (0.1 M) in oxidative potential regimes; (c) at  $100 \text{ mV s}^{-1}$  in DCM with  $n\text{-Bu}_4\text{NPF}_6$  (0.1 M) at a glassy carbon (black) or a platinum (red) working electrode; (d) at different scan rates in DCM with  $n\text{-Bu}_4\text{NPF}_6$  (0.1 M) in reductive potential regimes.

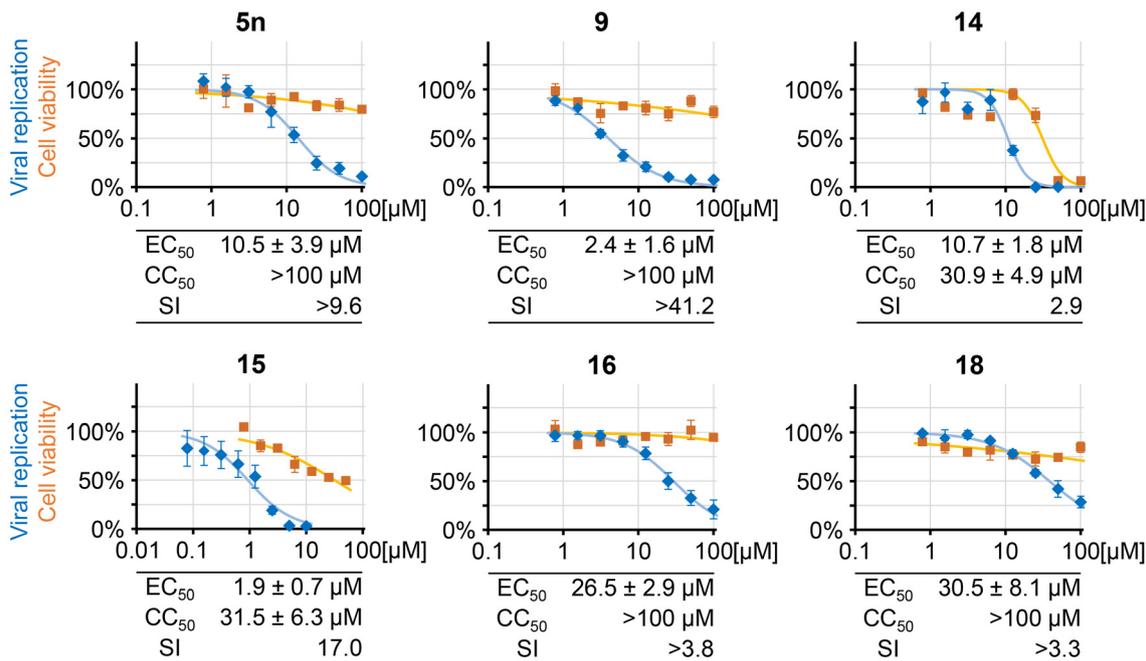
compared to the reversible response of the reduction event at  $E_p = -1.37$ , decreases with higher scan rates (Fig. 4d). This observation could be explained by a rapid intramolecular reaction of the formed radical with the nitrile group.<sup>54</sup>

### Antiviral activity

Previously, quinazoline compounds have been frequently used by numerous independent researchers, including our group,<sup>55–58</sup> for the development of antiviral candidates and clinically approved drugs.<sup>59</sup> As our recently reported autofluorescent quinazoline compounds have shown an initial, very promising evidence of intracellular bioactivity, including antiviral potential in cultured-cell models,<sup>3</sup> we decided to specifically evaluate the novel heterocyclic compounds for their activity against the human cytomegalovirus (HCMV). We also tested a selected fluoroaniline derivative, as arylated anilines have the potential to exhibit interesting bioactivities *e.g.*, anti-tumor properties.<sup>60</sup> To this end, anti-HCMV activity was determined by an established quantitative system based on the recombinant HCMV AD169-GFP that expresses the green fluorescent protein (GFP) allowing for direct quantitation of intracellular viral replication (Fig. 5, blue). The compounds were incubated on virus-infected primary human foreskin fibroblasts (HFFs) at serial dilutions under identical conditions. Antiviral activity was defined as treatment-induced reduction of the GFP signal compared to DMSO-treated cells. In parallel,

putative compound cytotoxicity was determined by Neutral Red uptake assay (NRA) using uninfected HFFs (Fig. 5, orange). On this basis, the effective concentrations, as required for half-maximal reduction of viral replication ( $EC_{50}$ ) or half-maximal cytotoxic activity ( $CC_{50}$ ), then referring to the selectivity index  $CC_{50}/EC_{50}$  (SI), were determined in detail. The approved antiviral drug ganciclovir (GCV)<sup>61</sup> was used as a reference compound. Of note, all new compounds analyzed displayed anti-HCMV activity within a range of micromolar concentrations, and their antiviral efficacies varied in a structure–activity-related manner, which may be subject to further characterization. In specific terms, compounds **5n**, **14**, **16**, and **18** displayed a relatively weak but clearly measurable antiviral activity, with  $EC_{50}$  values above  $>10 \mu\text{M}$ , whereby only one compound, **14**, was additionally limited by cytotoxicity. It is worth noting that **5n** caused visible needle-like precipitations on the cells at concentrations of approximately  $3 \mu\text{M}$  or higher. Excellent  $EC_{50}$  values of  $1.9 \pm 0.7 \mu\text{M}$  for artemisinin-containing tetrahydroquinazoline **15**, and  $2.4 \pm 1.6 \mu\text{M}$  for quinazoline derivative **9** indicate a comparable antiviral efficacy to that of the reference drug GCV ( $EC_{50} = 2.60 \pm 0.50 \mu\text{M}$ ). The  $CC_{50}$  values for **9**, and **15** were  $>100 \mu\text{M}$  and  $31.5 \pm 6.3 \mu\text{M}$ , respectively. In addition, compound **9** induced alterations in cell morphology, when applied at concentrations between  $25\text{--}100 \mu\text{M}$ . These microscopically visible effects, however, could be distinguished from drug-induced cytotoxicity, since the respective measurements performed by NRA





**Fig. 5** Anti-HCMV activity of selected *ortho*-fluoroaniline **5n** and fluorine-containing quinazolines **9**, **14**, **15**, **16**, **18**. Viral replication (blue) was assessed in a GFP-based replication assay using HCMV AD169-GFP for the infection of HFFs. Antiviral compounds were added immediately post-infection. Cells were fixed 7 d post-infection to perform quantitative GFP fluorometry. Cell viability (orange) was determined by performing NRA in parallel uninfected cells. The percentage of cell viability and viral replication was calculated and compared to DMSO-treated cells. Values represent mean ± SD of triplicate (NRA) or quadruplicate (GFP) determinations.

showed that neither of the compounds had a cytotoxic, negative impact on cell viability at concentrations up to 100 μM. Taken together, among this series of bioactive tetrahydroquinazolines, two of the analyzed compounds showed a very pronounced anti-HCMV activity. This characteristic was reflected by SI values of >41.2 and 17.0 for **9** and **15**, respectively, underlining their strong antiviral activity.

## Conclusion

In summary, we developed a facile domino strategy to access synthetically challenging high-value functionalized *ortho*-fluoroanilines using readily available fluoro-nitrostyrenes and α,α-dicyanoolefines as starting compounds. The tangible advantages, *i.e.*, absence of transition-metal catalysts, utilization of commercially available and/or easily accessible substrates, mild reaction conditions, simplicity, and single work-up procedure, make this metal-free four-step domino process highly appealing. The obtained products were applied for the efficient construction of a novel azo dye and various (tetrahydro)quinazolines through conventional and/or visible-light mediated reactions. A new azo dye was investigated regarding its oxidative and reductive stability using cyclic voltammetry. Importantly, *in vitro* bioactivity evaluation of the newly prepared tetrahydroquinazoline and quinazoline compounds demonstrated a strong antiviral efficacy against HCMV (EC<sub>50</sub> values down to 1.9 ± 0.7 μM) and high selectivity (CC<sub>50</sub> up to >100 μM).

## Author contributions

B. W. G., S. K., and Y. G. carried out all synthetic work and conducted the domino reactions. F. H., J. L., and C. W. performed the *in vitro* studies under the supervision of M. M., M. S. carried out the CV measurements under the supervision of L. A., B. W. G., S. K., and S. B. T. wrote the manuscript with input from all authors. S. B. T. conceived and directed the research.

## Data availability

All data are available from the authors upon reasonable request.

## Conflicts of interest

There are no conflicts to declare.

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## References

- 1 E. Vitaku, D. T. Smith and J. T. Njardarson, Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals, *J. Med. Chem.*, 2014, **57**, 10257–10274.
- 2 L. Q. Sun, L. Zhu, K. Qian, B. Qin, L. Huang, C. H. Chen, K. H. Lee and L. Xie, Design, synthesis, and preclinical evaluations of novel 4-substituted 1,5-diarylanilines as potent HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) drug candidates, *J. Med. Chem.*, 2012, **55**, 7219–7229.
- 3 F. E. Held, A. A. Guryev, T. Frohlich, F. Hampel, A. Kahnt, C. Hutterer, M. Steingruber, H. Bahsi, C. von Bojnic-Kninski, D. S. Mattes, T. C. Foertsch, A. Nesterov-Mueller, M. Marschall and S. B. Tsogoeva, Facile access to potent antiviral quinazoline heterocycles with fluorescence properties via merging metal-free domino reactions, *Nat. Commun.*, 2017, **8**, 15071.
- 4 B. W. Ramsey, J. Davies, N. G. McElvaney, E. Tullis, S. C. Bell, P. Dřevínek, M. Griese, E. F. McKone, C. E. Wainwright, M. W. Konstan, R. Moss, F. Ratjen, I. Sermet-Gaudelus, S. M. Rowe, Q. Dong, S. Rodriguez, K. Yen, C. Ordoñez and J. S. Elborn, A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation, *N. Engl. J. Med.*, 2011, **365**, 1663–1672.
- 5 Z. A. Boeva and V. G. Sergeev, Polyaniline: Synthesis, properties, and application, *Polym. Sci. Ser. C*, 2014, **56**, 144–153.
- 6 V. Babel and B. L. Hiran, A review on polyaniline composites: Synthesis, characterization, and applications, *Polym. Compos.*, 2021, **42**, 3142–3157.
- 7 F. A. Jerca, V. V. Jerca and R. Hoogenboom, Advances and opportunities in the exciting world of azobenzenes, *Nat. Rev. Chem.*, 2022, **6**, 51–69.
- 8 D. Li, Z. Wang, L. Wang, X. Xu and H. Zhang, Ultrasonic Extraction Coupled with Capillary Electrophoresis for the Determination of Azo Dyes in Lipsticks Using Ionic Liquid as Dynamic Coating and Background Electrolyte, *Chin. J. Chem.*, 2011, **29**, 147–152.
- 9 R. I. Alsantali, Q. A. Raja, A. Y. A. Alzahrani, A. Sadiq, N. Naeem, E. U. Mughal, M. M. Al-Rooqi, N. El Guesmi, Z. Moussa and S. A. Ahmed, Miscellaneous azo dyes: a comprehensive review on recent advancements in biological and industrial applications, *Dyes Pigm.*, 2022, **199**, 110050.
- 10 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, Fluorine in medicinal chemistry, *Chem. Soc. Rev.*, 2008, **37**, 320–330.
- 11 J. Wang, M. Sanchez-Rosello, J. L. Acena, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001–2011), *Chem. Rev.*, 2014, **114**, 2432–2506.
- 12 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Acena, V. A. Soloshonok, K. Izawa and H. Liu, Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II-III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas, *Chem. Rev.*, 2016, **116**, 422–518.
- 13 A. S. Aldoshin, A. A. Tabolin, S. L. Ioffe and V. G. Nenajdenko, Green, Catalyst-Free Reaction of Indoles with  $\beta$ -Fluoro- $\beta$ -nitrostyrenes in Water, *Eur. J. Org. Chem.*, 2018, 3816–3825.
- 14 Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai and N. Shibata, Current Contributions of Organofluorine Compounds to the Agrochemical Industry, *iScience*, 2020, **23**, 101467.
- 15 J. Moschner, V. Stulberg, R. Fernandes, S. Huhmann, J. Leppkes and B. Koksche, Approaches to Obtaining Fluorinated  $\alpha$ -Amino Acids, *Chem. Rev.*, 2019, **119**, 10718–10801.
- 16 C. Upadhyay, M. Chaudhary, R. N. De Oliveira, A. Borbas, P. Kempaiah, P. Singh and B. Rathi, Fluorinated scaffolds for antimalarial drug discovery, *Expert Opin. Drug Discovery*, 2020, **15**, 705–718.
- 17 A. H. Kwon, J. A. Conklin, M. Makhinson and R. B. Kaner, Chemical synthesis and characterization of fluoro-substituted polyanilines, *Synth. Met.*, 1997, **84**, 95–96.
- 18 N. Ishikawa, M. J. Namkung and T. L. Fletcher, Fluorinated Azo Dyes. 1a I. Synthesis and Spectral Properties of 3,5-Difluoro-4-N-methylaminoazobenzene, 2,6-Difluoroacetanilide, and Related Compounds, *J. Org. Chem.*, 1965, **30**, 3878–3882.
- 19 M. J. Namkung, N. K. Naimy, C. A. Cole, N. Ishikawa and T. L. Fletcher, Fluorinated azo dyes. II. Synthesis and spectral properties of 2,6-difluoro-4 and 2,3,5,6-tetrafluoro-4-aminoazobenzene and their N-methylated and 4'-ethyl derivatives, *J. Org. Chem.*, 1970, **35**, 728–733.
- 20 R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, Organic fluorine compounds: a great opportunity for enhanced materials properties, *Chem. Soc. Rev.*, 2011, **40**, 3496–3508.
- 21 N. Zinin, Beschreibung einiger neuer organischer Basen, dargestellt durch die Einwirkung des Schwefelwasserstoffes auf Verbindungen der Kohlenwasserstoffe mit Untersalpetersäure, *J. Prakt. Chem.*, 1842, **27**, 140–153.
- 22 P. Ruiz-Castillo and S. L. Buchwald, Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions, *Chem. Rev.*, 2016, **116**, 12564–12649.
- 23 C. W. Cheung and X. Hu, Amine synthesis via iron-catalysed reductive coupling of nitroarenes with alkyl halides, *Nat. Commun.*, 2016, **7**, 12494.
- 24 S. U. Dighe, F. Juliá, A. Luridiana, J. J. Douglas and D. Leonori, A photochemical dehydrogenative strategy for aniline synthesis, *Nature*, 2020, **584**, 75–81.
- 25 P. S. Fier and S. Kim, Transition-Metal-Free C–N Cross-Coupling Enabled by a Multifunctional Reagent, *J. Am. Chem. Soc.*, 2024, **146**, 6476–6480.
- 26 P. T. Nyffeler, S. G. Duron, M. D. Burkart, S. P. Vincent and C. H. Wong, Selectfluor: mechanistic insight and applications, *Angew. Chem., Int. Ed.*, 2004, **44**, 192–212.



- 27 D. J. Adams and J. H. Clark, Nucleophilic routes to selectively fluorinated aromatics, *Chem. Soc. Rev.*, 1999, **28**, 225–231.
- 28 A. J. Cresswell, S. G. Davies, P. M. Roberts and J. E. Thomson, Beyond the Balz-Schiemann reaction: the utility of tetrafluoroborates and boron trifluoride as nucleophilic fluoride sources, *Chem. Rev.*, 2015, **115**, 566–611.
- 29 D. Q. Liang, Y. N. Li, S. L. Gao, R. L. Li, X. G. Li, B. L. Wang and H. Yang, Amide-assisted radical strategy: metal-free direct fluorination of arenes in aqueous media, *Green Chem.*, 2017, **19**, 3344–3349.
- 30 M. Berger, M. S. Lenhard and S. R. Waldvogel, Para-Fluorination of Anilides Using Electrochemically Generated Hypervalent Iodoarenes, *Chemistry*, 2022, **28**, e202201029.
- 31 J. P. Alric, B. Marquet, T. Billard and B. R. Langlois, Electrophilic aromatic fluorination with fluorine: meta-Directed fluorination of anilines, *J. Fluorine Chem.*, 2005, **126**, 659–665.
- 32 B. C. Soderberg, in *Comprehensive Organometallic Chemistry II*, ed. E. W. Abel, F. G. A. Stone and G. Wilkinson, Elsevier, Oxford, 1995, pp. 241–297.
- 33 M. M. Heravi and L. Mohammadkhani, in *Adv. Heterocycl. Chem.*, ed. E. F. V. Scriven and C. A. Ramsden, Academic Press, 2020, vol. 131, pp. 351–403.
- 34 K. Pedretty, K. Tillett, W. Tsuei and J. M. Lopchuk, in *Prog. Heterocycl. Chem.*, ed. G. W. Gribble and J. A. Joule, Elsevier, 2021, vol. 32, pp. 193–240.
- 35 A. D. Sonawane and M. Koketsu, in *Comprehensive Heterocyclic Chemistry IV*, ed. D. S. Black, J. Cossy and C. V. Stevens, Elsevier, Oxford, 2022, pp. 685–712.
- 36 Y. J. Mao, G. Luo, H. Y. Hao, Z. Y. Xu, S. J. Lou and D. Q. Xu, Anion ligand promoted selective C-F bond reductive elimination enables C(sp<sup>2</sup>)-H fluorination, *Chem. Commun.*, 2019, **55**, 14458–14461.
- 37 D. Lichte, N. Pirkl, G. Heinrich, S. Dutta, J. F. Goebel, D. Koley and L. J. Goossen, Palladium-Catalyzed para-C-H Arylation of Anilines with Aromatic Halides, *Angew. Chem., Int. Ed.*, 2022, **61**, e202210009.
- 38 L. F. Tietze, *Domino Reactions*, VCH, Weinheim, 2014.
- 39 K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. Rissanen and D. Enders, Organocatalytic Domino Oxa-Michael/1,6-Addition Reactions: Asymmetric Synthesis of Chromans Bearing Oxindole Scaffolds, *Angew. Chem., Int. Ed.*, 2016, **55**, 12104–12108.
- 40 S. Sopeña, M. Cozzolino, C. Maquilón, E. C. Escudero-Adán, M. Martínez Belmonte and A. W. Kleij, Organocatalyzed Domino [3+2] Cycloaddition/Payne-Type Rearrangement using Carbon Dioxide and Epoxy Alcohols, *Angew. Chem., Int. Ed.*, 2018, **57**, 11203–11207.
- 41 B. W. Grau, S. Bonisch, A. Neuhauser, F. Hampel, A. Gorling and S. B. Tsogoeva, Facile Access to Challenging ortho-Terphenyls via Merging Two Multi-Step Domino Reactions in One-Pot: A Joint Experimental/Theoretical Study, *ChemCatChem*, 2019, **11**, 3982–3992.
- 42 F. Plass, S. Bonisch, F. Held, T. Ullrich, F. E. J. Fischer, A. Guryev, A. Gorling, A. Kahnt and S. B. Tsogoeva, Controlling and Fine-Tuning Charge-Transfer Emission in 2,6-Dicyanoaniline Multichromophores Prepared through Domino Reactions: Entry to a Potentially New Class of OLEDs, *J. Org. Chem.*, 2021, **86**, 6111–6125.
- 43 B. W. Grau, M. Dill, F. Hampel, A. Kahnt, N. Jux and S. B. Tsogoeva, Four-Step Domino Reaction Enables Fully Controlled Non-Statistical Synthesis of Hexaarylbenzene with Six Different Aryl Groups, *Angew. Chem., Int. Ed.*, 2021, **60**, 22307–22314.
- 44 K. Mezgebe and E. Mulugeta, Synthesis and pharmacological activities of azo dye derivatives incorporating heterocyclic scaffolds: a review, *RSC Adv.*, 2022, **12**, 25932–25946.
- 45 T. Yamaguchi, Y. Sugiura, E. Yamaguchi, N. Tada and A. Itoh, Synthetic Method for the Preparation of Quinazolines by the Oxidation of Amines Using Singlet Oxygen, *Asian J. Org. Chem.*, 2017, **6**, 432–435.
- 46 A. Çapcı, L. Herrmann, H. M. Sampath Kumar, T. Fröhlich and S. B. Tsogoeva, Artemisinin-derived dimers from a chemical perspective, *Med. Res. Rev.*, 2021, **41**, 2927–2970.
- 47 H. M. S. Kumar, L. Herrmann and S. B. Tsogoeva, Structural hybridization as a facile approach to new drug candidates, *Bioorg. Med. Chem. Lett.*, 2020, **30**, 127514.
- 48 B. Sharma, P. Singh, A. K. Singh and S. K. Awasthi, Advancement of chimeric hybrid drugs to cure malaria infection: An overview with special emphasis on endoperoxide pharmacophores, *Eur. J. Med. Chem.*, 2021, **219**, 113408.
- 49 S. B. Tsogoeva, Recent Progress in the Development of Synthetic Hybrids of Natural or Unnatural Bioactive Compounds for Medicinal Chemistry, *Mini-Rev. Med. Chem.*, 2010, **10**, 773–793.
- 50 L. F. Tietze, H. P. Bell and S. Chandrasekhar, Natural Product Hybrids as New Leads for Drug Discovery, *Angew. Chem., Int. Ed.*, 2003, **42**, 3996–4028.
- 51 H. J. Yang, D. O. Wipf and A. J. Bard, Application of Rapid Scan Cyclic Voltammetry to a Study of the Oxidation and Dimerization of N,N-Dimethylaniline in Acetonitrile, *J. Electroanal. Chem.*, 1992, **331**, 913–924.
- 52 J. L. Sadler and A. J. Bard, Electrochemical reduction of aromatic azo compounds, *J. Am. Chem. Soc.*, 2002, **90**, 1979–1989.
- 53 Y. Q. Huang and J. Lessard, Electrochemical Behaviour of Nitrobenzene, Nitrosobenzene, Azobenzene, and Azoxybenzene on Hg, Pt, Cu, and Ni Electrodes in Aprotic Medium, *Electroanalysis*, 2016, **28**, 2716–2727.
- 54 K. Sun, Q. Y. Lv, Y. W. Lin, B. Yu and W. M. He, Nitriles as radical acceptors in radical cascade reactions, *Org. Chem. Front.*, 2021, **8**, 445–465.
- 55 C. Hutterer, S. Hamilton, M. Steingruber, I. Zeitträger, H. Bahsi, N. Thuma, Z. Naing, Z. Örfi, L. Örfi, E. Socher, H. Sticht, W. Rawlinson, S. Chou, V. J. Haupt and M. Marschall, The chemical class of quinazoline compounds provides a core structure for the design of anticytomegaloviral kinase inhibitors, *Antiviral Res.*, 2016, **134**, 130–143.
- 56 M. Marschall, T. Stamminger, A. Urban, S. Wildum, H. Ruebsamen-Schaeff, H. Zimmermann and P. Lischka, In



- Vitro Evaluation of the Activities of the Novel Anticytomegalovirus Compound AIC246 (Letermovir) against Herpesviruses and Other Human Pathogenic Viruses, *Antimicrob. Agents Chemother.*, 2012, **56**, 1135–1137.
- 57 M. Schleiss, J. Eickhoff, S. Auerochs, M. Leis, S. Abele, S. Rechter, Y. Choi, J. Anderson, G. Scott, W. Rawlinson, D. Michel, S. Ensminger, B. Klebl, T. Stamminger and M. Marschall, Protein kinase inhibitors of the quinazoline class exert anti-cytomegaloviral activity in vitro and in vivo, *Antiviral Res.*, 2008, **79**, 49–61.
- 58 T. Herget, M. Freitag, M. Morbitzer, R. Kupfer, T. Stamminger and M. Marschall, Novel Chemical Class of pUL97 Protein Kinase-Specific Inhibitors with Strong Anticytomegaloviral Activity, *Antimicrob. Agents Chemother.*, 2004, **48**, 4154–4162.
- 59 R. K. Avery, S. Alain, B. D. Alexander, E. A. Blumberg, R. F. Chemaly, C. Cordonnier, R. F. Duarte, D. F. Florescu, N. Kamar, D. Kumar, J. Maertens, F. M. Marty, G. A. Papanicolaou, F. P. Silveira, O. Witzke, J. Wu, A. K. Sundberg, M. Fournier and S. T. Investigators, Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial, *Clin. Infect. Dis.*, 2021, **75**, 690–701.
- 60 C.-F. Lin, Y.-H. Lo, M.-C. Hsieh, Y.-H. Chen, J.-J. Wang and M.-J. Wu, Cytotoxicities, cell cycle and caspase evaluations of 1,6-diaryl-3(Z)-hexen-1,5-diyne, 2-(6-aryl-3(Z)-hexen-1,5-diyne)anilines and their derivatives, *Bioorg. Med. Chem.*, 2005, **13**, 3565–3575.
- 61 F. Hahn, A. Niesar, C. Wangen, M. Wild, B. Grau, L. Herrmann, A. Capci, A. Adrait, Y. Couté, S. B. Tsogoeva and M. Marschall, Target verification of artesunate-related antiviral drugs: Assessing the role of mitochondrial and regulatory proteins by click chemistry and fluorescence labeling, *Antiviral Res.*, 2020, **180**, 104861.

