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Applying green chemistry principles to iron catalysis: mild and selective domino synthesis of pyrroles from nitroarenes†

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An efficient and general cascade synthesis of pyrroles from nitroarenes using an acid-tolerant homogeneous iron catalyst is presented. Initial (transfer) hydrogenation using the commercially available iron–Tetrphos catalyst is followed by acid catalysed Paal–Knorr condensation. Both formic acid and molecular hydrogen can be used as green reductants in this process. Particularly, under transfer hydrogenation conditions, the homogeneous catalyst shows remarkable reactivity at low temperatures, high functional group tolerance and excellent chemoselectivity transforming a wide variety of substrates. Compared to classical heterogeneous catalysts, this system presents complementing reactivity, showing none of the typical side reactions such as dehalogenation, debenzoylation, arene or olefin hydrogenation. It thereby enhances the chemical toolbox in terms of orthogonal reactivity. The methodology was successfully applied to the late-stage modification of multi-functional drug(-like) molecules as well as to the one-pot synthesis of the bioactive agent BM-635.

Introduction

25 years ago Paul Anastas and John Warner formulated the so-called green chemistry principles, in order to lead chemical development and production into a more sustainable future.¹ One of these 12 principles, catalysis, can make processes less energy intensive, faster, more selective and reduce the amount of waste compared to *e.g.* stoichiometric reagents. Within the realm of transition metal catalysis, traditionally emphasis was placed on precious metal catalysts that are in general expensive, toxic, and only present in the Earth's crust in parts per billion (ppb). Iron, however, is the 4th most abundant element in the Earth's crust and the most abundant transition metal.² Thus, many iron-based compounds are economical, widely available and generally accepted to have lower toxicity compared to other transition metals.³ While heterogeneous iron catalysis has been around for over a century, giving us for example the Haber–Bosch process for the indispensable mass-production of ammonia,^{4,5} homogeneous iron catalysis has been largely neglected by synthetic chemists and only been on the rise for around the last two decades.^{6–9} A field that has flourished incredibly over the last years is the application of iron and its neighboring 3d-metals as catalysts for (transfer) hydrogenations.^{10–22} Combining these sustainable reductive

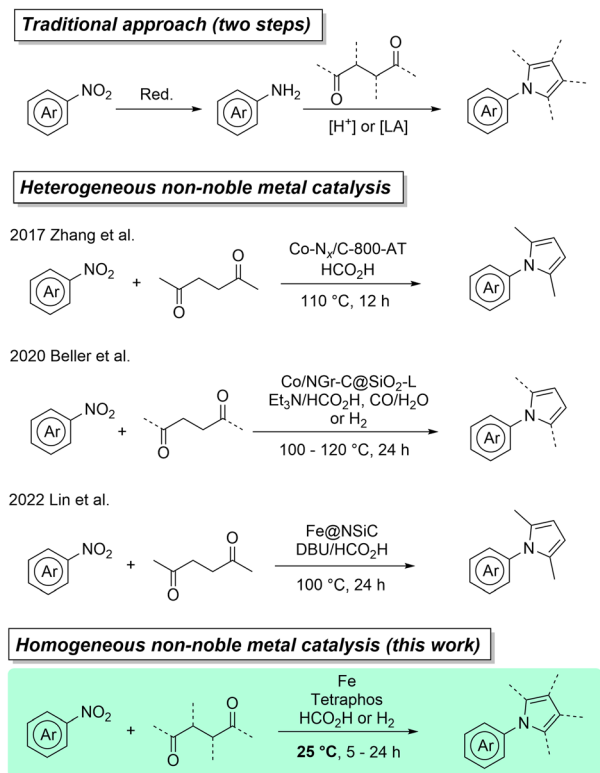
transformations with another “green” topic of increasing interest, cascade reactions (also called tandem or domino reactions), can be highly favorable since it reduces synthetic steps, which in turn can lead to further savings in time, labor, resources and generated waste.^{23–27} As an example, earth-abundant catalysis has been applied to significantly improve the synthesis of N-heterocycles, which are of importance for many life science applications.^{28–40}

Here, pyrroles in particular are interesting targets due to their ubiquitous presence in pharmaceuticals (atorvastatin), agrochemicals (fludioxonil), natural products (porphyrin), dyes (bodipy), materials (polypyrrole) and other fine chemicals.^{41–44} Traditionally, pyrroles are prepared through the well-established Hantzsch, Knorr, or Paal–Knorr condensation reactions. Especially, the latter two approaches are still of significant interest to sustainable/process chemists today, due to their great atom-economy, high yields, easily available starting materials and benign side products (water).^{45–48} Therefore, *N*-aryl pyrroles are commonly made *via* Paal–Knorr reaction of 1,4-dicarbonyl compounds with anilines, which in turn are typically obtained from the reduction of nitroarenes (Scheme 1). Since nitroarenes are widely available, it is appealing to devise a direct cascade process from nitroarenes to *N*-aryl pyrroles. While there is some precedent for reductive cascade reactions of nitro-compounds for the synthesis of heterocycles, they mostly rely on precious metals such as Rh, Ru, Pt and Pd.^{49–52} Recently, a handful of groups have developed nitro reduction cascades using earth-abundant metals such as cobalt and iron.^{53–55} In 2017, Zhang *et al.* showed for the first time the cascade synthesis of pyrroles from nitroarenes using a heterogeneous cobalt catalyst and

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Scheme 1 State of the art in catalytic pyrrole synthesis from nitroarenes using earth-abundant (transfer) hydrogenation catalysts.

formic acid (FA) as a green reductant.⁵⁶ This methodology was extended by our group in 2020 to include molecular hydrogen and CO/H₂O mixtures as possible reductants.⁵⁷ Highlighting the current scientific interest, very recently the first heterogeneous iron catalyst for this transformation, using reductive base/formic acid mixtures, was reported by Lin *et al.*⁵⁸ All the above-mentioned methodologies have in common that they apply heterogeneous catalysts and more importantly they require relatively harsh reaction conditions (100 to 120 °C).

Results and discussion

Inspired by these earlier reports, we wondered if a more active homogeneous iron system could be developed that works under milder conditions and without additives. Furthermore, it should be stable in the presence of water and acidic conditions, which is non-trivial for homogeneous 3d metal catalysts, that tend to be more sensitive than their heavier 4/5d analogs.⁶⁻⁹ With our previous expertise in iron catalysis, our first candidate of choice was the robust Fe–Tetraphos system.⁵⁹⁻⁶⁶ Among other interesting transformations such as carbon dioxide hydrogenation or anti-Markovnikov epoxide hydrogenation, this catalytic system is known for the selective reduction of nitro groups, which represents the first step of our cascade, using both hydrogen and formic acid as reductants.⁶⁷⁻⁷⁰ Considering that formic acid is also a potentially suitable acid catalyst for the second step of the cascade, the Paal–Knorr reaction, its dual role could be particularly desirable. With this idea in mind, we

started our investigations, selecting nitrobenzene and hexane-2,5-dione as our benchmark substrates. To our delight, the standard conditions for transfer hydrogenation of nitro arenes (40 °C in EtOH for 2 h) delivered full conversion of nitrobenzene and nearly quantitative yield of the desired phenyl dimethyl pyrrole **3a** (Table 1, entry 1). Compared to the previous methods by the groups of Lin and Beller no additional base was necessary and an excellent chemoselectivity (*i.e.* no reduction of the 1,4-diketone) was observed.^{57,58} Further optimization (for highlights see Table 1, full screening see ESI†) revealed that the reaction could also be conducted efficiently at room temperature when slightly extending the reaction time to 5 h (entry 5). In comparison to the previously reported heterogeneous systems, comparable or even improved yields are obtained at a quarter of the temperature and less than half the reaction time, clearly highlighting the potential of this novel catalytic process. Control reactions showed that without ligand, metal, or FA no reactivity was observed (entries 2–4). Aside from their effect on reactivity, solvents also have a large effect on the sustainability of a process, accounting for the majority of generated waste and around 60% of the energy-usage of chemical production processes.⁷¹⁻⁷⁶ Accordingly, different solvents were evaluated: alcohols generally showing the most promise, while ethers and

Table 1 Optimization of the reaction conditions^a

Entry	Metal salt	Ligand	Solvent	Reductant	Yield ^b
1 ^c	Fe(BF ₄) ₂ ·6H ₂ O	Tetraphos	EtOH	HCO ₂ H	99%
2	Fe(BF ₄) ₂ ·6H ₂ O	—	EtOH	HCO ₂ H	0%
3	—	Tetraphos	EtOH	HCO ₂ H	0%
4	Fe(BF ₄) ₂ ·6H ₂ O	Tetraphos	EtOH	—	0%
5	Fe(BF ₄) ₂ ·6H ₂ O	Tetraphos	EtOH	HCO ₂ H	97%
6	Fe(OTf) ₂	Tetraphos	EtOH	HCO ₂ H	99%
7	Fe-1 , [Fe(Tetraphos)F][BPh ₄]		EtOH	HCO ₂ H	24%
8	Fe-2 , [Fe(Tetraphos)F][BF ₄]		EtOH	HCO ₂ H	87%
9	Fe(BF ₄) ₂ ·6H ₂ O	Tetraphos	iPrOH	HCO ₂ H	89%
10	Fe(BF ₄) ₂ ·6H ₂ O	Tetraphos	THF	HCO ₂ H	40%
11	Fe(BF ₄) ₂ ·6H ₂ O	Tetraphos	Dioxane	HCO ₂ H	25%
12	Fe(BF ₄) ₂ ·6H ₂ O	Tetraphos	DMC	HCO ₂ H	47%
13	Fe(BF ₄) ₂ ·6H ₂ O	Tetraphos	H ₂ O	HCO ₂ H	0%
14 ^d	Fe(BF ₄) ₂ ·6H ₂ O	Tetraphos	THF	H ₂	16%
15 ^d	Fe(BF ₄) ₂ ·6H ₂ O	Ph-Tetraphos	THF	H ₂	96%
16 ^e	Fe(BF ₄) ₂ ·6H ₂ O	Ph-Tetraphos	THF	H ₂	99%

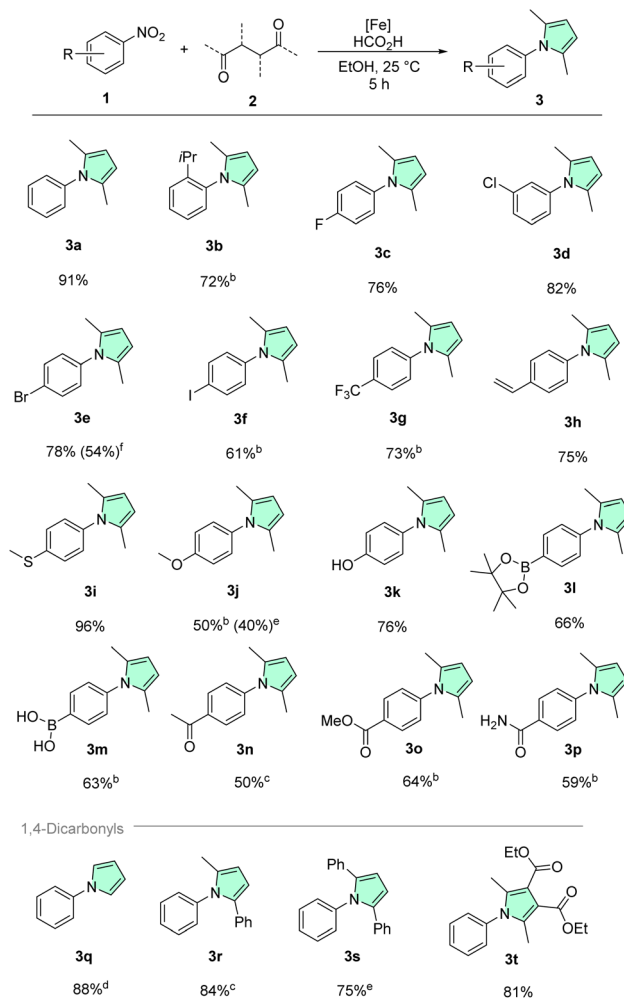
^a General reaction conditions: 0.5 mmol **1a**, 0.6 mmol **2a**, 0.025 mmol Fe-source, 0.026 mmol ligand, 2.25 mmol FA, 2 mL solvent, 25 °C, 5 h. ^b Determined by GC-FID using *n*-hexadecane as internal standard. ^c 40 °C, 2 h. ^d 0.01 mmol Fe-source, 0.01 mmol ligand, 20 μL TFA, 20 bar, 120 °C, 2 h. ^e 0.01 mmol Fe-source, 0.01 mmol ligand, 20 μL TFA, 20 bar, 100 °C, 6 h.



carbonates gave decreased yields (entries 9–12). Although water was well tolerated in the reactions, indicated by the good reactivity of the iron tetrafluoroborate hexahydrate and the general reactivity of the reaction (generating 4 equiv. H₂O), when water was used as the sole solvent no reactivity was observed (entry 13), possibly due to solubility issues.

In the end, it was decided to proceed with ethanol as the solvent, since it gave the best performance and is considered a relatively green solvent, being biodegradable, low-toxic, and mass-produced from biorenewables.^{71–78} Alternative iron sources and molecularly defined catalysts were also tested (entries 6–8). While iron triflate gave equally excellent yields, the commercial **Fe-1**, containing the tetraphenylborate anion, showed significantly reduced yield. On the other hand, the air-stable tetrafluoroborate analog **Fe-2** gave very good yield. However, since the *in situ* prepared catalyst performed the best, it was used for further reactions. Lastly, also hydrogen gas was successfully tested as a reductant for this benchmark reaction (entries 14–16). It is worth noting that to the best of our knowledge, this is the first example of an iron-based catalyst (homogeneous or heterogeneous) directly using molecular hydrogen for this cascade transformation. Substantially increased hydrogenation reactivity was observed when switching from the alkyl bridged Tetrphos ligand used for transfer hydrogenation to the more rigid and less donating phenyl-bridged variant (Ph-Tetrphos). However, more forcing reaction conditions needed to be applied (20 bar, 100–120 °C, trifluoroacetic acid (TFA) additive) as well as a more complex autoclave setup. When applying these harsh hydrogenation conditions in the upcoming substrate scope, the majority of tested examples showed decreased yields. Accordingly, we continued our investigations under the milder transfer hydrogenation conditions.

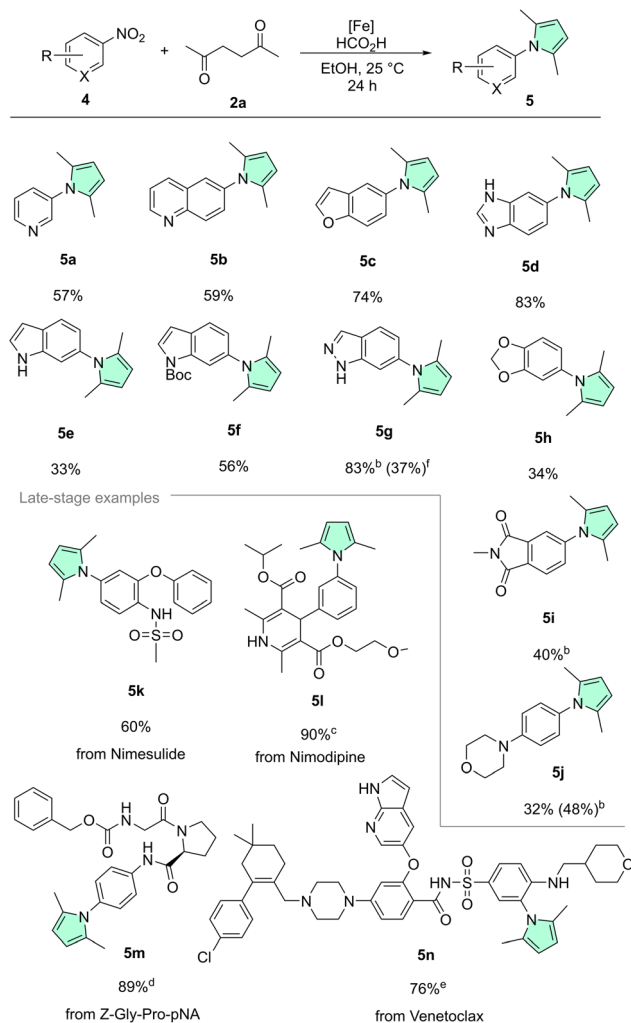
To test the general applicability of our methodology and the likely improved functional group tolerance, a substrate scope was prepared using our optimized protocol (Schemes 2 and 3). Since pyrroles are commonplace in pharmaceuticals and agrochemicals which are often complex, multifunctionalized molecules, particular focus was placed on a diversity of functional groups prevalent in bioactive molecules. Starting with the unfunctionalized benchmark substrates, phenylpyrrole **3a** was isolated in excellent yield of 91%. Next, to assess the influence of steric factors on the reaction, 2-nitrocumene with a bulky *ortho* isopropyl substituent was tested providing good yields of the corresponding pyrrole **3b**. Nitroarenes bearing the common halide substituents (fluorine **1c**, chlorine **1d**, bromine **1e**, iodine **1f**) were also converted without issues. Reductive dehalogenation, which is a side reaction frequently occurring with precious metal catalysts was never observed in our methodology.⁷⁹ Similarly, the trifluoromethyl variant **1g** gave **3g** in good yield, illustrating nicely that electron poor nitroarenes are well suited substrates. Further, remarkable chemoselectivity was observed, when converting 4-nitrostyrene **1h**, showing exclusively nitro reduction and leaving the alkene moiety intact. Additionally, it should be highlighted that polymerization of the starting material **1h** or the styrene product **3h** was also not encountered using such mild conditions. Nitroarenes bearing electron



Scheme 2 Scope of nitroarenes and examples of 1,4-dicarbonyl compounds. ^a General reaction conditions: 0.5 mmol **1**, 0.6 mmol **2**, 0.025 mmol Fe(BF₄)₂·6H₂O, 0.025 mmol Tetrphos, 2.25 mmol FA, 2 mL EtOH, 25 °C, 5 h. Isolated yields are shown. ^b 24 h. ^c 40 °C, 24 h. ^d 24 h, from 2,5-dimethoxytetrahydrofuran, after 5 h addition of 1.5 mL aq. 50% FA. ^e 0.01 mmol Fe(BF₄)₂·6H₂O, 0.01 mmol Ph-Tetrphos, 20 μL TFA, 1.5 mL THF, 20 bar H₂, 120 °C, 20 h. ^f 0.015 mmol Fe(BF₄)₂·6H₂O, 0.015 mmol Ph-Tetrphos, 20 μL TFA, 1.5 mL THF, 20 bar H₂, 120 °C, 20 h.

donating groups such as ethers (**1j**), thioethers (**1i**) and hydroxy groups (**1k**) were also smoothly converted to the respective pyrroles. Often sulfur containing compounds act as catalyst poisons for transition metal catalysts.^{80–82} For instance, 4-nitrothioanisole **1i** specifically was shown to poison Pd/C in hydrogenations.⁸³ However, when **1i** was tested under our standard reaction conditions, it provided near quantitative isolated yield (96%) of the corresponding pyrrole **3i**. 4-Nitrophenol **1k** on the other hand is quite acidic (pK_a(H₂O) = 7.15), and therefore can become a problem in hydrogenations conducted under neutral or basic conditions, but again the desired product was obtained smoothly.⁸⁴ Boronic acids and pinacol boronic esters are frequently used building blocks in the fine chemical industry. Noteworthy, boronic acid **1m** and its pinacol boronate **1l** gave the corresponding pyrroles in decent





Scheme 3 Scope of heterocyclic nitro compounds and late-stage modifications.^a General reaction conditions: 0.5 mmol **4**, 0.6 mmol **2a**, 0.025 mmol $Fe(BF_4)_2 \cdot 6H_2O$, 0.026 mmol Tetrachos, 2.25 mmol FA, 2 mL $EtOH$, $25\text{ }^\circ C$, 24 h. Isolated yields are shown. ^b $40\text{ }^\circ C$. ^c0.25 mmol scale, 5 h. ^d0.25 mmol scale. ^e0.25 mmol scale, solvent 2 mL ($EtOH$ /toluene, 1 : 1). ^f0.01 mmol $Fe(BF_4)_2 \cdot 6H_2O$, 0.01 mmol Ph-Tetrachos, 20 μL TFA, 1.5 mL THF, 20 bar H_2 , $120\text{ }^\circ C$, 20 h.

yields. Protodeboronation, a common side-reaction of organo-boron compounds, was not observed in either case.^{85,86} Nitroarenes containing carbonyl groups such as ketone **1n**, ester **1o**, and amide **1p** could also be converted chemoselectively. Primary amides are widely abundant not only in amino acids, vitamins, cofactors *etc.* but also in pharmaceuticals. However, their two protic hydrogens and coordination ability can pose a challenge for transition-metal catalyzed transformations and thus they are oftentimes underrepresented in the substrate scope evaluation of a given synthetic methodology. Remarkably, primary amide **1p** was well tolerated by our catalytic system. Additionally, it should be noted that no pyrrole formation on the amide nitrogen was detected.

Most of the previous reports related to the transformation discussed herein showed little variation in 1,4-dicarbonyl starting materials, we therefore wanted to demonstrate that our

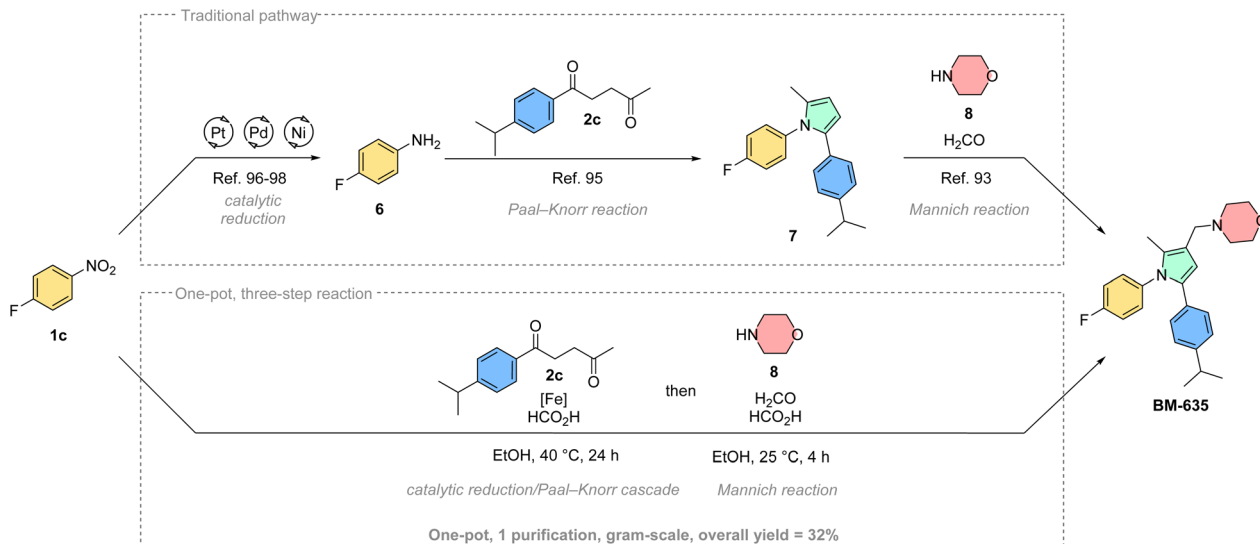
protocol also allows to convert different and more challenging diketones efficiently.^{56–58} Starting from 2,5-dimethoxy tetrahydrofuran, unsubstituted phenyl pyrrole **3q** was isolated in 88% yield. Phenyl methyl pyrrole **3r** was obtained in very good yield from the corresponding diketone. Even the challenging dibenzoyl ethane **2s** could be converted with **1a** to form 1,2,5-triphenyl pyrrole **3s** in good yield when using our hydrogenation conditions. Notably, other reported catalysts only showed minimal product formation using this bulky diketone.⁵⁷ Finally, also a persubstituted pyrrole **3t** could be synthesized under mild conditions starting from 2,3,4,5-tetrasubstituted diketone **2t**.

Since further heterocycles are often prevalent in bioactive chemicals alongside pyrroles, next we extended the scope to several interesting nitro-containing heterocyclic substrates (Scheme 3, top). Basic nitrogen atoms that could potentially coordinate and thereby poison a catalyst were tolerated very well, as illustrated by 3-nitropyridine **4a**, 6-nitroquinoline **4b**, and 5-nitrobenzimidazole **4d**. Benzofuran derivative **5c** was also isolated in a good yield (74%). Surprisingly, poor conversion and yield were obtained with unprotected nitro indole **4e**. We believe that the highly electron-rich character of the indole system renders the nitro group of **4e** less electrophilic, thus slowing down the reduction. Similar trends were observed for the electron-rich benzodioxole **4h** and the morpholino derivative **4j**. To overcome this limitation, Boc-protection of the indole nitrogen, to remove some electron density from the heteroarene core, was tried. Indeed, this approach led to a significantly improved yield of the N-protected product **5f**. Boc-deprotection was only a minor pathway due to the mild conditions. Another way to tackle the reduced reactivity, in the case of **4j**, was simply to slightly increase the reaction temperature to $40\text{ }^\circ C$, which was associated with a noticeable improvement of both conversion and product yield. Corroborating our theory of electron density being the culprit, related but less electron-rich indazole **4g** provided very good yield. Finally, imide **4i** was also transformed chemoselectively. Once again, **4i** showed no signs of overreduction.

In addition to examining functional group tolerance individually, it was also important for us to test several multifunctionalized, drug(-like) substrates (Scheme 3, bottom). COX-2 inhibitor Nimesulide, notable for its acidic sulfonamide ($pK_a(\text{MeOH}) = 6.46$) moiety, was transformed to **5k** without problems.⁸⁷ The calcium channel blocker Nimodipine gave excellent yield, when converted to **5l** with our protocol. Remarkably, the prolyl endopeptidase probe Z-Gly-Pro-pNA was also converted in high yield, giving pyrrole-substituted dipeptide **5m**. Interestingly, the Cbz-group which would traditionally be cleaved *via* hydrogenolysis using heterogeneous catalysts such as Pd/C was left intact.^{88–92} Outstandingly, our methodology was even applicable to the highly-functionalized Bcl-2 inhibitor Venetoclax **4n**, giving 76% yield of the corresponding pyrrole product **5n**, illustrating once more the striking functional group tolerance of our system.

Aside from derivatizing existing drug molecules, it is intriguing to showcase the advantages of this novel methodology for the synthesis of existing bioactive agents. Therefore, we selected **BM-635**, a pyrrole-based antitubercular agent, as





Scheme 4 Synthetic application of the Fe-catalysed domino pyrrole synthesis: traditional route to **BM-635** starting from **1c** (top), scaled-up one-pot, three-step synthesis of **BM-635** (bottom).^{93–98}

a synthetic target (Scheme 4).^{93,94} This compound is typically synthesized through a stepwise process centered on the Paal-Knorr reaction of 4-fluoroaniline **6** and 1,4-diketone **2c**.⁹⁵ **6** is itself traditionally synthesized by reduction of 4-fluoronitrobenzene **1c**.^{96–98} Finally, the resulting Paal-Knorr pyrrole **7** is treated with formaldehyde, morpholine (**8**) and acetic acid following a Mannich protocol to give **BM-635** over 3 steps.⁹⁵ Initially, we tested our cascade methodology as a replacement for the first two steps (see ESI†). The 1,2,5-substituted pyrrole **7** was isolated with a good yield (73%), and could be further converted to **BM-635** according to the literature method.⁹³ However, since the final Mannich reaction is run under acidic conditions similar to our methodology, we hypothesized that the cascade reaction could potentially be expanded to include the third step of the sequence. Accordingly, we performed a one-pot, three-step reaction, where formaldehyde and morpholine were added to the reaction mixture after the complete conversion of **1c**. Using this novel multicomponent reaction approach, the practical one-pot synthesis of **BM-635** was achieved in 32% overall yield. This corresponds to a good average yield per step of 68%. The one-pot synthesis was also successfully scaled-up to gram-scale producing 1.27 g of the active ingredient in a single batch. We believe this reduction/Paal-Knorr/Mannich cascade conveniently illustrates the synthetic capabilities of our new method, quickly building up molecular complexity in a one-pot fashion. Furthermore, we consider this transformation a useful tool for combinatorial chemistry and drug discovery to potentially generate novel compound libraries from broadly available building blocks.^{99,100}

Conclusions

To summarize, we have developed a cascade synthesis of pyrroles from nitroarenes for the first time using a commercially available homogeneous iron catalyst. This catalyst can be

easily prepared *in situ* or used as the molecularly-defined complex. Both formic acid and molecular hydrogen can be used as green reductants in the (transfer) hydrogenation/Paal-Knorr reaction sequence. Particularly, under transfer hydrogenation conditions, the homogeneous catalyst showed remarkable reactivity at low temperatures, exceptional functional group tolerance and excellent chemoselectivity using a wide variety of substrates. This system offers a complementing reactivity to classical heterogeneous catalysts, exhibiting none of the typical side reactions such as dehalogenation, debenzoylation, ketone, arene or olefin hydrogenation. The methodology thereby enhances the chemical toolbox in terms of orthogonal reactivity. Finally, the advantages of this novel protocol are highlighted by the successful late-stage modification of multifunctionalized drug(-like) molecules as well as the one-pot synthesis of the bioactive agent **BM-635** on gram-scale. Further investigations concerning a more efficient use of hydrogen gas for this cascade protocol are currently ongoing in our laboratories.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

Author contributions

J. F. conceptualized the work, performed the investigations and the writing – original draft. K. J. and M. B. provided resources and supervision. All authors contributed to the final version of the manuscript (writing – review & editing).

Conflicts of interest

There are no conflicts to declare.



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