RESEARCH ARTICLE doi.org/10.1002/adsc.202401170 ADVANCED SYNTHESIS & CATALYSIS

Very Important Publication

Molybdenum-Catalyzed Direct Synthesis of Pyrroles from Nitroarenes with Glycols as Reductants

Sara Gómez-Gil,[a] Samuel Suárez-Pantiga,[a] María R. Pedrosa,[a] and Roberto Sanz[a,*]

[a] Área de Química Orgánica, Departamento de Química, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos s/n, 09001 Burgos, Spain
E-mail: rsd@ubu.es

Manuscript received: September 17, 2024; Revised manuscript received: October 18, 2024;
Version of record online: November 18, 2024

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202401170

Abstract: A molybdenum-catalyzed synthesis of *N*-(hetero)aryl pyrroles directly from inexpensive and commonly available (hetero)nitroarenes via reduction with pinacol and annulation with 1,4-dicarbonyls or cyclobutane-1,2-diols has been described. The process does not require an inert atmosphere and tolerates the presence of air and water. This non-noble catalytic system shows high chemoselectivity, allowing a diverse range of potentially reducible functional groups such as alkynes, alkenes, halogens, cyano, and carbonyls. Moreover, this strategy enables the reuse of a waste byproduct as reactant, facilitating the formation of challenging 1,4-dicarbonyls from accessible cyclobutane-1,2-diols used as reducing agents.

Keywords: Nitroarenes; Pyrroles; Reduction; Molybdenum catalysis; Glycols

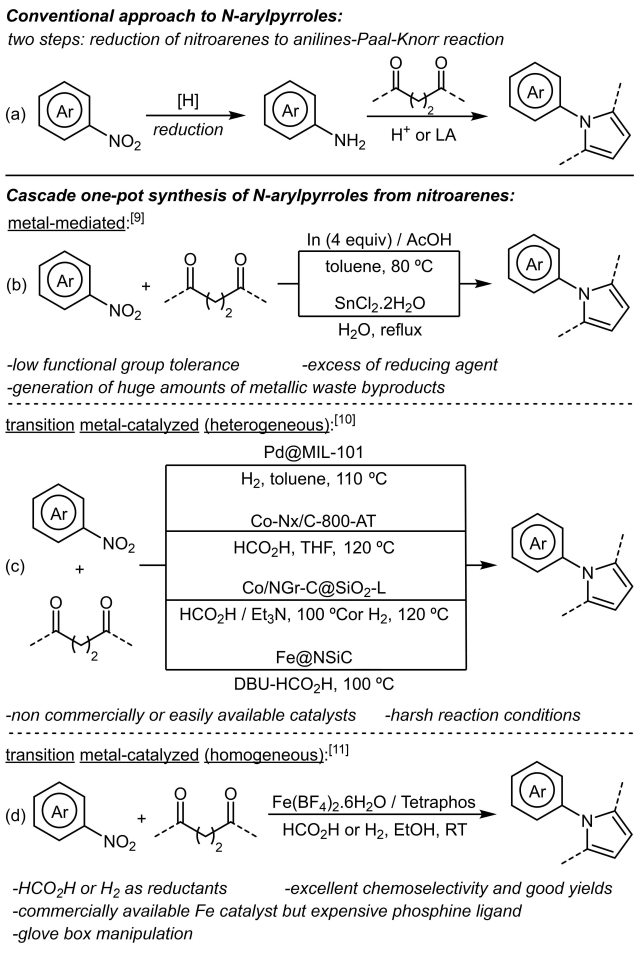
Introduction

Nitroarenes are low-cost, stable, low-toxic, and abundant chemical raw materials, easily obtained through the straightforward electrophilic aromatic nitration of arenes. As one of the most accessible and economical nitrogen feedstock sources, the direct use of nitroaromatics to prepare value-added nitrogenated derivatives via various direct reductive C–N bond formation reactions, without prior reduction to the corresponding anilines,[1] holds great significance and has seen a spectacular increase in interest in recent years.[2] In contrast to using anilines for forming C–NAr bonds, the direct reductive coupling of nitroarenes demonstrates step economy and cost-effectiveness. Various reducing agents have been employed in such processes, including trivalent phosphorus reagents, organosilanes, carbon monoxide, boron compounds, hydrogen donors, reducing metals, metal carbonyls, visible light, or alcohols via hydrogen transfer reductions. Additionally, nitroarenes have also proven to be successful electrophiles for cross-coupling reactions.[3]

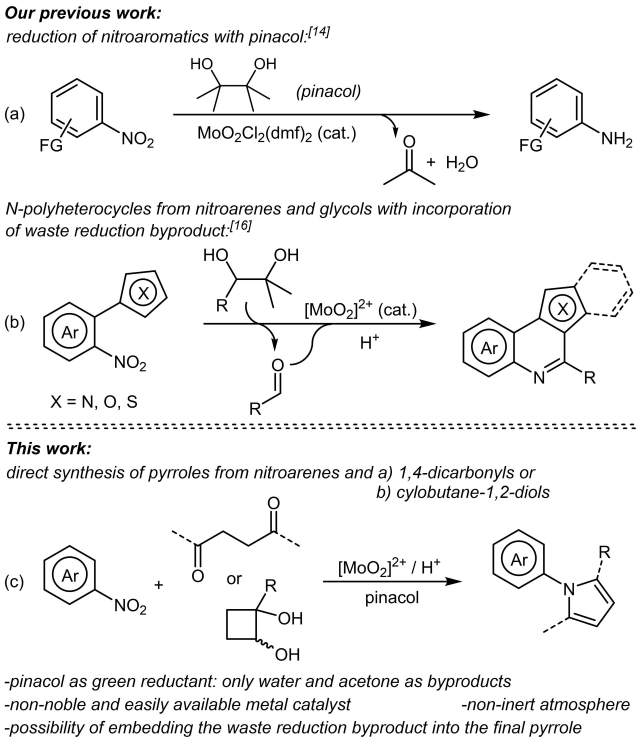
On the other hand, pyrroles are important *N*-heterocycles that form the core skeleton of various natural products and drugs with significant biological activities.[4] They are also found in different forms of organic dyes and materials, including polymers and semiconductors.[5] Although numerous methodologies have been developed for their synthesis and subsequent functionalization,[6] the classical Paal-Knorr reaction remains one of the most prominent and widely applied method for synthesizing pyrroles from primary amines and 1,4-dicarbonyl compounds, making it a useful synthetic tool for accessing these heterocycles.[7] Recent advances in this methodology have primarily focused on developing environmentally benign catalysts and conditions, as this reaction is known to be accelerated under protic or Lewis acidic environments.[8] For the preparation of *N*-aryl pyrroles, anilines should be used as the nitrogenated counterpart

(Scheme 1a). However, considering that anilines are typically obtained by the reduction of the corresponding readily available nitroarenes,[1] the direct preparation of pyrroles from nitroarenes via cascade reactions in a single-pot operation is an attractive approach as it avoids the isolation of the corresponding anilines. The key issue for the success of this one-pot approach is the compatibility of the catalytic systems involved in the two steps of the cascade with both the reagents and the intermediates. Thus, the reducing step must be chemoselective for the nitro group, leaving the reducible dicarbonyl partner unaltered. Previously described processes in this area involve the use of large excesses of reducing metals, such as In or Sn, which generate substantial amounts of waste (Scheme 1b).[9] Despite the synthetic potential of this approach for the preparation of pyrroles, this strategy has been demonstrated to be challenging and only very few metal-catalyzed procedures employing greener reducing agents have been reported. Most of them involve heterogeneous catalytic systems based on transition metals or catalysts that must be previously prepared by non-conventional procedures.[10] Additionally, they require relatively harsh reaction conditions and the use of hydrogen or environmentally friendly formic acid as reductants (Scheme 1c). Very recently, Beller et al reported the first homogeneous non-noble metal catalyst for achieving this transformation,[11a] by applying a previously described protocol for the reduction of nitroarenes with formic acid as hydrogen donor and co-catalyst in the presence of an iron catalyst and a phosphorous-based ligand.[11b] Remarkably, this catalytic system shows good reactivity at room temperature and excellent chemoselectivity. However, although the Fe catalyst is commercially available, it requires the presence of Tetraphos as ligand and the use of a glove box for the manipulation of the reagents (Scheme 1d). In all the reported catalytic methods, hydrogen or hydrogen donors are employed, and the reactions take place via hydrogen atom transfer processes.

On the other hand, considering that molybdenum is the most abundant transition metal in seawater, serves as a cofactor for several enzymes, and is an essential trace element for human, animal and plant health, and is much less toxic than most heavy transition metals,[12] we became interested in developing green synthetic methodologies involving redox processes using readily available dioxomolybdenum(VI) complexes.[13] In this context, we previously described the selective reduction of nitroarenes with pinacol in the presence of other potentially reducible functional groups, such as carbonyls (Scheme 2a),[14] and the oxidative cleavage of



Scheme 1. Synthesis of *N*-arylpyrroles from nitroarenes.



Scheme 2. Our previous work and this work.

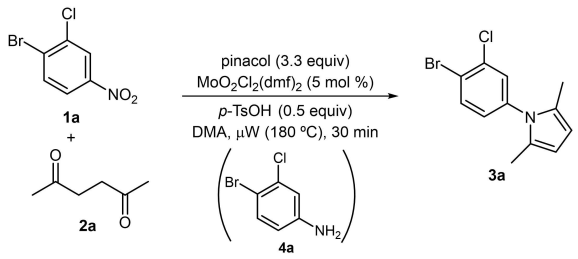
glycols with DMSO.[15] In addition, we have combined these reactivities to prepare a wide variety of *N*-polyheterocycles, incorporating the waste reduction byproduct, a carbonyl derived from the initial reduction step, into the final compound (Scheme 2b).[16] It is worth noting that the internal recycling of reaction waste for subsequent transformations is a highly relevant topic in organic synthesis. The use of a byproduct to facilitate or promote a downstream step was pioneered by Shibasaki,[17] and since then, several groups have described sustainable processes based on the recycling of byproducts to promote or catalyze an array of subsequent transformations.[18] However, fewer examples are known in which waste is recycled as reagent,[19] and our group was the first time to describe the reuse of a waste byproduct as reactant for a downstream reaction, incorporating it into the final product.[16] Since then, some other examples have been reported where a byproduct is embedded in the final product.[20]

In this context, we envisaged that the Mo-catalyzed chemoselective nitroarene reduction with pinacol, even in the presence of carbonyl groups, could be engaged with a subsequent cyclocondensation reaction with γ-dicarbonyls, enabling a cascade synthesis of pyrroles from nitroaromatics without involving hydrogenation processes. Alternatively, cyclobutane-1,2-diols could be used as reducing agents, with the subsequent incorporation of the waste reduction byproduct into the final heterocyclic moiety (Scheme 2c). Herein, we report our results exploiting this idea, which allows the direct synthesis of a variety of *N*-arylpyrroles from nitroaromatics.

Results and Discussion

We commenced our studies with 4-bromo-3-chloronitrobenzene (**1 a**) and 2,5-hexanedione (**2 a**) as model substrates to optimize the reaction conditions. Based on our previous results[14–16] we selected readily available and inexpensive pinacol (2,3-dimethylbutane-1,2-diol) as the reducing agent,[21] $MoO_2Cl_2(dmf)_2$ as the catalyst, *p*-TsOH as a Brønsted acid co-catalyst, and DMA as the solvent under microwave irradiation at 180 °C (Table 1, entry 1). Under these conditions, the desired pyrrole **3 a** was selectively obtained in high yield. The role of the Brønsted acid was shown to further favor the condensation of the intermediate aniline **4 a** with the diketone (entries 2 and 3). A decrease in reaction time or temperature was detrimental, resulting in incomplete conversions (entries 4 and 5). Interestingly, the reaction can also be performed under conventional heating instead of microwave irradiation, although a longer reaction time was required, and the yield was slightly lower (entry 6). In this chemistry, microwave irradiation plays a significant role by reducing reaction time and increasing reaction efficiency. Finally, other solvents, such as toluene or acetonitrile, were not suitable for this process (entries 7 and 8).

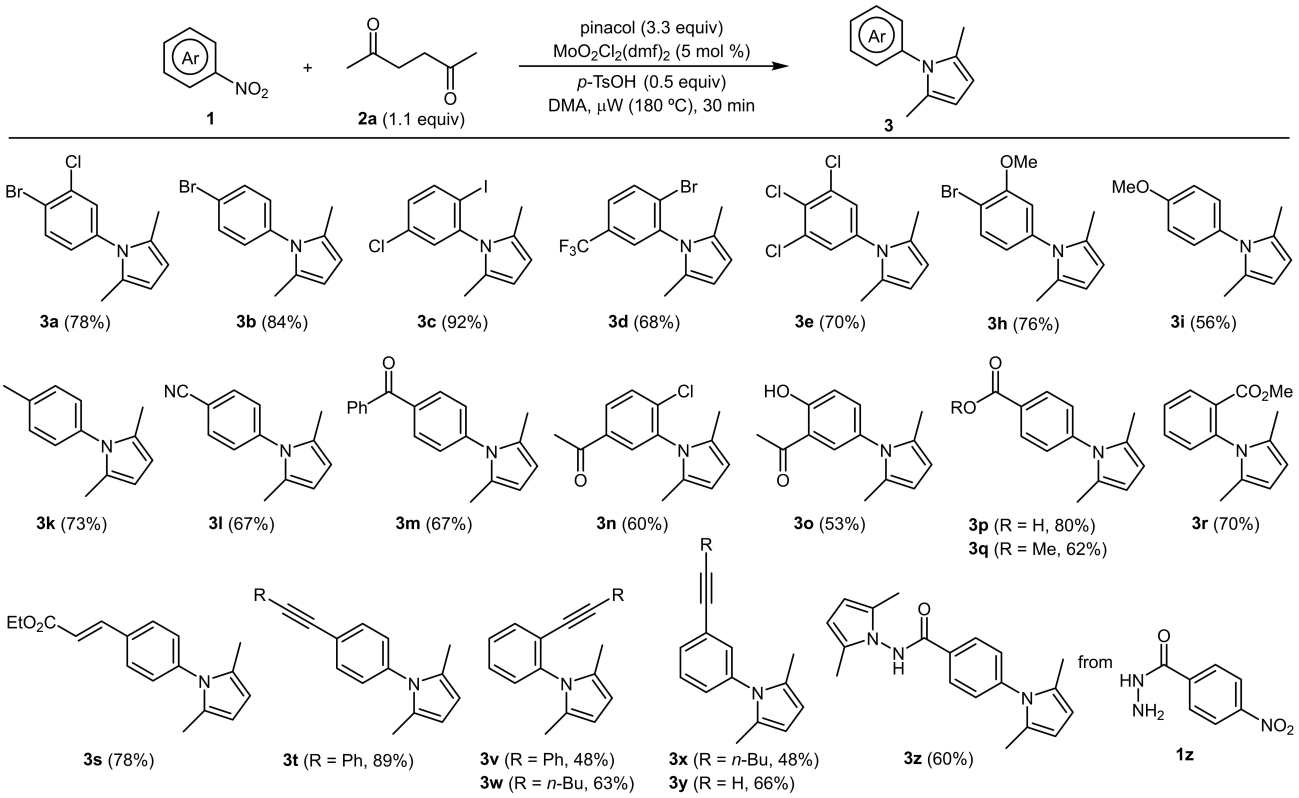
Table 1. Optimization of the reaction conditions.[a]



ent.	deviation from the standard conditions	conv [%][b]	yield **3 a** [%][b]	yield **4 a** [%][b]
1	none	100	85	–
2	without *p*-TsOH	100	73	11
3	*p*-TsOH (20 mol%)	100	76	6
4	15 instead of 30 min	91	70	–
5	160 instead of 180 °C	88	65	–
6	conventional heating (6 h)	100	75	–
7[c]	toluene instead of DMA	70	10	–
8[c]	MeCN instead of DMA	–[d]	–	–

[a] Reaction conditions: **1 a** (0.5 mmol), **2 a** (0.55 mmol), pinacol (1.65 mmol), $MoO_2Cl_2(dmf)_2$ (5 mol %), solvent (1 mL), under microwave irradiation at the stated temperature.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as internal standard.
[c] Carried out at 150 °C.
[d] Only decomposition products were observed.

With the optimized conditions established, we then explored the applicability of the Mo-catalyzed synthesis of 2,5-dimethylpyrroles from a wide variety of functionalized nitroarenes **1** and 2,5-hexanedione (**2 a**) (Scheme 3). Notably, sensitive functional groups were well tolerated in the starting nitro compounds, including those that are potentially reducible. Nitroarenes bearing halogens at different positions (**1 a–e**) afforded the corresponding 2,5-dimethylpyrroles with high yields. Remarkably, 2-iodo-5-chloronitrobenzene (**1 c**) with a labile iodine provided **3 c** with excellent yield and selectivity, without evidence of dehalogenation. Starting nitro derivatives possessing methoxy or methyl groups (**1 h,i,k**) were also tolerated, though slightly lower yields were obtained. Nitroarenes bearing electron-withdrawing groups, including cyano, ketone, ester and even free carboxylic acid (**1 l–r**), gave rise selectively to the corresponding pyrroles in good yields, without any noticeable reduction of the additional reducible functional group. The same excellent chemoselectivity was observed with ethyl 4-nitrocinnamate (**1 s**) that evolved without C=C bond reduction.



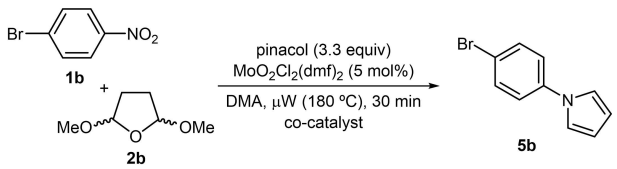
Scheme 3. Substrate scope for the synthesis of 2,5-dimethylpyrroles **3** from nitroarenes **1**. Reaction scale: **1** (1 mmol).

Moreover, *N*-aryl-2,5-dimethylpyrroles with alkynyl substituents at *para*, *ortho*, or *meta* positions (**3 t–y**) were efficiently accessed with this process. Finally, the reaction with 4-nitrophenylhydrazide **1 z** led to competitive pyrrole formation with the hydrazide group, so adding an excess of **2 a** afforded bispyrrole derivative **3 z** in good yield.

We then turned our attention to the Clauson-Kaas variant of the Paal-Knorr reaction for the synthesis of unsubstituted *N*-arylpyrroles **5**, which employs 2,5-dimethoxytetrahydrofuran (DMTHF) (**2 b**) as masked succinaldehyde.[22] Using this 1,4-dialdehyde surrogate, the reaction conditions were reoptimized with 4-bromonitrobenzene (**1 b**) as the model nitroarene (Table 2), because significant amounts of intermediate 4-bromoaniline (**4 b**) were obtained under the previously reported conditions (entry 1). In this case, the yield was improved by using a higher amount of DMTHF (entries 2 and 3). Surprisingly, the best result was obtained in the absence of the Brønsted acid additive (entry 4).

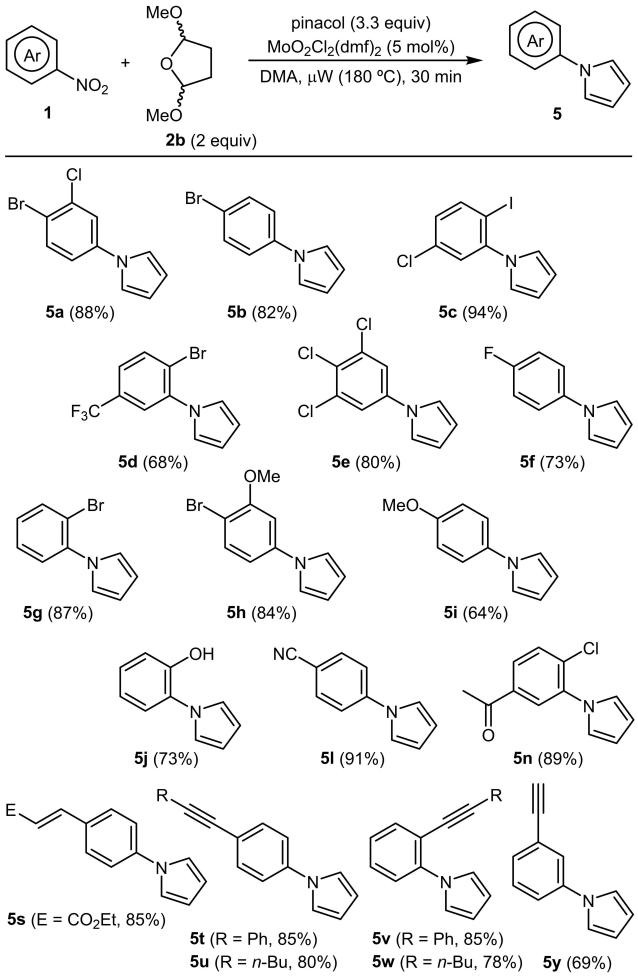
A variety of unsubstituted *N*-arylpyrroles **5** were synthesized with high yields from a wide range of functionalized nitroarenes **1** (Scheme 4). Starting materials bearing different reducible functional groups such as halides (**1 a–h**), nitrile (**1 l**), ketone (**1 n**), ester (**1 s**) and alkynes (**1 t–w,y**), proved to be suitable substrates for this transformation. Nitroarenes with electron-rich substituents like methoxy (**1 h,i**) or hydroxy (**1 j**) were also well-tolerated. Likely due to the higher electrophilic character of **2 b** compared with diketone **2 a**, the Brønsted acid was not required for the pyrrole formation.

Table 2. Reoptimization of the reaction conditions for the synthesis of unsubstituted *N*-arylpyrrole **5 b**.[a]

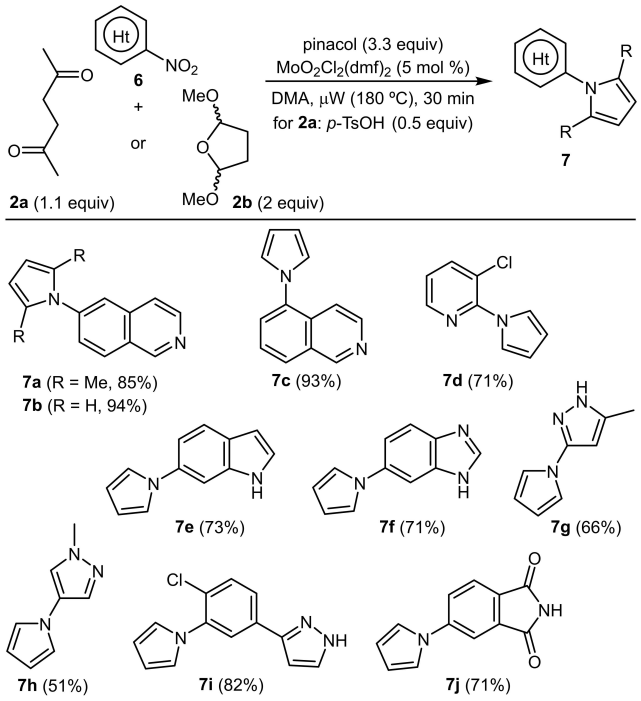


entry	equiv. **2 b**	co-catalyst (equiv.)	yield **5 b** [%][b]	yield **4 b** [%][b]
1	1.1	*p*-TsOH (0.5)	33	22
2	1.5	*p*-TsOH (0.5)	52	17
3	2	*p*-TsOH (0.5)	77	–
4	2	–	87	–

[a] Reaction conditions: **1 b** (0.5 mmol), **2 b** (x equiv.), pinacol (1.65 mmol), $MoO_2Cl_2(dmf)_2$ (5 mol %), DMA (1 mL), μW (180 °C) 30 min.
[b] Determined by ^1H NMR using CH_2Br_2 as internal standard.
[c] **4 b** = 4-bromoaniline.



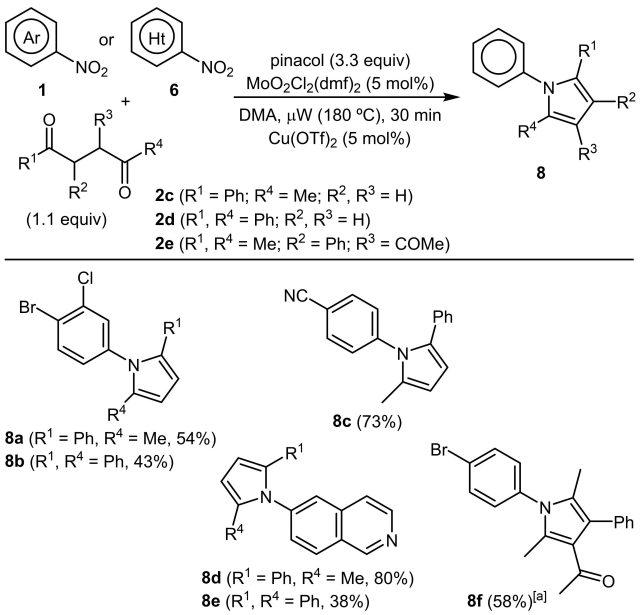
Scheme 4. Substrate scope for the synthesis of unsubstituted pyrroles **5** from nitroarenes **1**. Reaction scale: **1** (1 mmol).



Scheme 5. Synthesis of pyrroles **7** from heteronitroarenes **6** containing basic *N*-atoms. Reaction scale: **6** (1 mmol).

Then, recognizing the prevalence of heterocycles in numerous bioactive compounds, we directed our focus to heteronitroarenes **6**, many of which contain basic *N*-atoms, as starting materials for synthesizing *N*-heteroarylpyrroles **7** (Scheme 5). Due to the presence of these basic nitrogen atoms, some catalytic systems are not compatible or problematic with these substrates. Encouragingly, these nitro-functionalized *N*-heterocycles **6**, including quinolines (**6a–c**), pyridine (**6d**), indole (**6e**), benzimidazole (**6f**), pyrazoles (**6g–i**) and phthalimide (**6j**), were successfully utilized in this cascade sequence with γ-dicarbonyl **2a** and DMTHF (**2b**) to afford the corresponding pyrrole derivatives **7** in good to high yields. The isolation of **7e** from unprotected indole **6e**, in >70% yield, is noteworthy, particularly since low conversion was observed with Beller's Fe-based catalytic system.[11a]

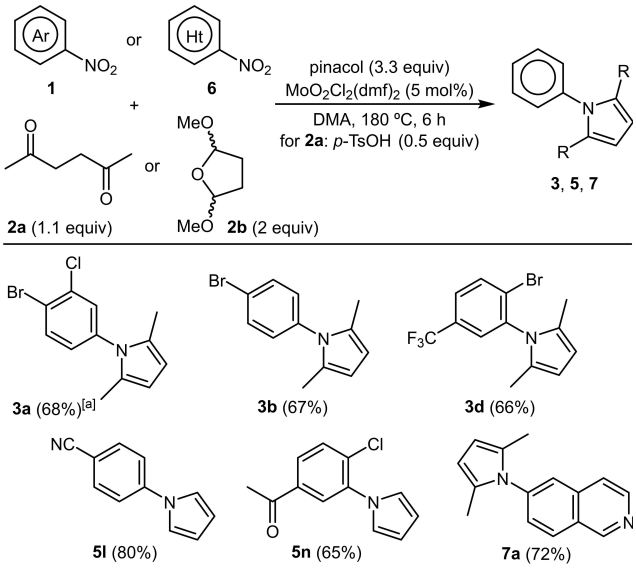
Then, we explored the synthesis of more diverse substituted pyrroles by employing other more hindered and less reactive 2,5-diketones such as benzoyl acetone (**2c**) and benzoyl acetophenone (**2d**). After a brief reoptimization, the use of a catalytic amount of a Lewis acid, such as $Cu(OTf)_2$, was found to be superior to the Brønsted acid, allowing the isolation of 2,5-disubstituted pyrroles **8a–e** in moderate to good yields (Scheme 6). Not unexpectedly, lower yields,



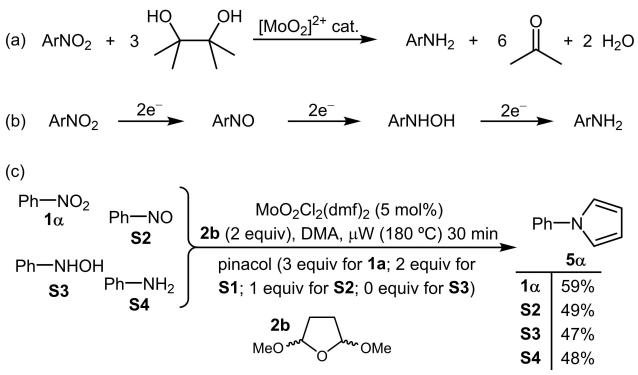
Scheme 6. Synthesis of pyrroles **8** from (hetero)nitroarenes **1** or **6** and 1,4-diketones **2c–e**. Reaction scale: **1** or **6** (1 mmol). [a] Carried out with **2e** (2.2 mmol).

albeit synthetically useful, were obtained with the more challenging bulky **2 d**, which bears less electrophilic carbonyls. Once again, functional groups such as halogens, nitrile, or substrates with basic nitrogen atoms were compatible with the Mo/Cu catalytic system. Additionally, a 2,3,4,5-tetrasubstituted pyrrole **8 f** was accessed from the corresponding tricarbonyl derivative **2 e**; however, in this case, furan formation was competitive, requiring an excess of **2 e** to obtain a good yield of the corresponding pyrrole.

Although microwave irradiation accelerates our Mo-catalyzed reactions, this domino reaction sequence can also be carried out under conventional heating. In this scenario, longer reaction times were necessary (ca 6 h), and the yields were only slightly lower compared to those obtained under microwave irradiation (Scheme 7). Moreover, under these thermal conditions, a gram-scale reaction could be performed with **1 a**, yielding the pyrrole derivative **3 a** in 68% yield (968 mg).



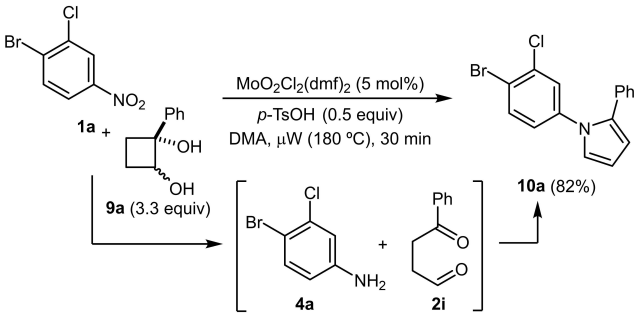
Scheme 7. Synthesis of pyrroles **3**, **5**, **7** from nitroarenes **1** or **6** under conventional heating. [a] Carried out from **1 a** (5 mmol).



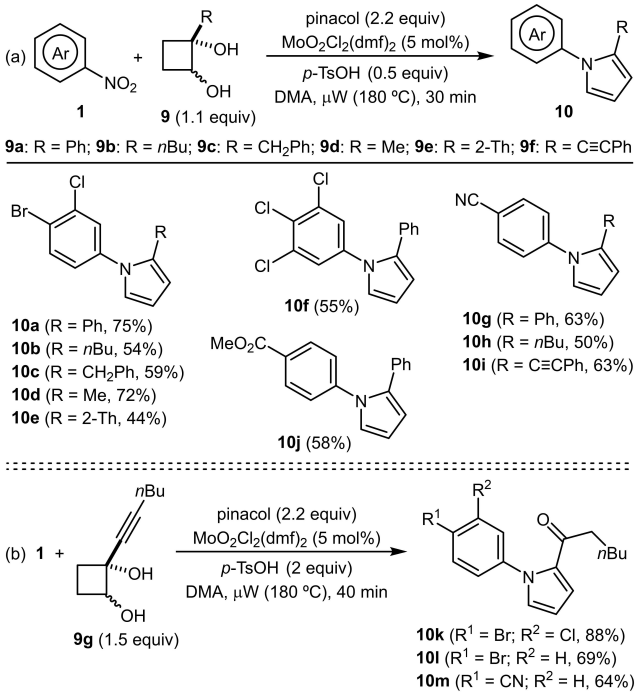
Scheme 8. Mechanistic proposal.

Regarding the mechanism, we had previously conducted DFT studies on the reduction of nitroarenes with pinacol under dioxomolybdenum(VI)-catalysis.[14b] The reduction of a nitroarene requires 3 equiv. of pinacol, yielding the corresponding aromatic amine, with acetone and water as byproducts (Scheme 8a). The computational studies confirmed that the three reductive steps needed to produce aniline from nitrobenzene involve nitrosobenzene and *N*-phenylhydroxylamine as intermediates (Scheme 8b). The water molecule generated in each reduction step, by condensation of the glycol with a metal-oxo subunit from the Mo-catalyst, plays a crucial role by remaining coordinated with the catalyst and serving as a proton source for the final reduction. To further support the proposed mechanism, we carried out a series of experiments (Scheme 8c). First, nitrobenzene (**1α**) was reacted with pinacol (3 equiv.), under Mo-catalysis in the presence of **2 b**, resulting in the expected formation of *N*-phenylpyrrole (**5α**). Next, nitrosobenzene (**S2**) was treated under the same conditions but using 2 equiv. of pinacol, also yielding **5α**. Similarly, *N*-phenylhydroxylamine (**S3**) was also evaluated with pinacol (1 equiv.), giving rise to **5α**. Finally, anilines, which are the products obtained by the reduction of nitroarenes by dioxomolybdenum(VI) catalyst,[14a] were also checked. When aniline (**S4**) was used as the starting material without pinacol, pyrrole **5α** was obtained again in a similar extension. These experiments further support the involvement of nitrosoarenes and *N*-arylhydroxylamines as intermediates in the process.

At this point, we capitalized on our recent report concerning the synthesis of γ-dicarbonyls through Mo-catalyzed oxidative cleavage of cyclobutane-1,2-diols with DMSO,[24] utilizing these glycols as reducing agents, which are easily prepared from commercially available 1,2-bis(trimethylsilyloxy)cyclobutene. Initially, 1-phenylcyclobutane-1,2-diol (**9 a)** was selected as a model diol and employed as reductant for nitroarene **1 a** under the previously established reaction conditions (Scheme 9). Gratifyingly, 2-phenyl-substituted pyrrole **10 a** was isolated in 82% yield. Remarkably, this process incorporates the waste byproduct generated in the initial reduction step, namely the 4-ketoaldehyde **2 i**, into the final pyrrole core. However, since the reduction of a nitro group requires $6e^-/6H^+$, three equivalents of diol **9 a** are necessary. As this glycol needs to be synthesized in a previous step, we opted to use only one equivalent of the corresponding cyclobutane-1,2-diol **9** along with two equivalents of inexpensive pinacol as a sacrificial reductant (Scheme 10a). Under these conditions, a variety of 2-substituted pyrroles **10** were synthesized from a selection of nitroarenes **1**. As detailed in our prior



Scheme 9. Synthesis of 2-phenylpyrrole **10a** from nitroarene **1a** and 1-phenylcyclobutane-1,2-diol (**9a**) with incorporation of the waste byproduct.



Scheme 10. Synthesis of 2-substituted pyrroles **10** from nitroarenes **1** and cyclobutane-1,2-diols **9** with incorporation of the waste byproduct. Reaction scale: **1** (1 mmol).

report,[24] these glycols **9** were efficiently prepared via organometallic additions to 2-hydroxycyclobutanone. Aryl (**10a,f,g,j**), benzyl (**10c**), alkyl (**10b,d,h**), heteroaryl (**10e**) and phenylethynyl (**10i**) groups could be conveniently installed at the C-2 position of the *N*-arylpyrrole. Interestingly, using cyclobutane-1,2-diol **9g**, which bears a hexyn-1-yl substituent, and after a brief reoptimization, the reaction provided 2-ketopyrroles **10k–m** in high yields instead of the anticipated 2-hex-1-ynylpyrroles. This outcome may be attributed to a subsequent regioselective hydration reaction of the alkynyl moiety, likely due to the generation of water as a byproduct in the reduction step (Scheme 10b). This sequence involves the incorporation of the two waste byproducts generated in the initial reduction step from the reductant, a dicarbonyl and water, into the final product.

Conclusion

In summary, we have described an alternative strategy for the scarcely studied synthesis of *N*-arylpyrroles directly from nitroarenes. The choice of a non-coinage metal catalyst, such as molybdenum, in combination with glycols as reductants, enables the formation of a wide variety of substituted *N*-arylpyrroles (over 65 examples), even those bearing potentially reducible groups such as alkynes, alkenes, halogens, cyano, and carbonyls. Additionally, this approach has demonstrated further potential in designing more efficient tandem reactions that generate more sophisticated 1,4-dicarbonyl coupling partners required for the cyclization step in situ by reusing a waste byproduct as reactant. Moreover, no additional expensive ligands are required in this protocol, facilitating the reaction set-up, which proceeds under an air atmosphere.

Experimental Section

General Procedure for the Synthesis of Pyrroles 3 and 7a (Schemes 3 and 5)

In a 10 mL microwave tube, the corresponding nitro(hetero)aromatic **1** or **6** (1 mmol), anhydrous DMA (2 mL), pinacol (390 mg, 3.3 mmol), hexan-2,5-dione (**2a**) (125 mg, 1.1 mmol), *p*-TsOH (95 mg, 0.5 mmol) and $MoO_2Cl_2(dmf)_2$ (17 mg, 0.05 mmol) were added, and the tube was sealed with a septum. The reaction mixture was stirred at 180 °C for 30 min under microwave irradiation (150 W). After completion of the reaction, monitored by CG-MS, the mixture is purified by flash column chromatography using mixtures of hexane/EtOAc obtaining the corresponding 2,5-dimethylpyrroles **3** and **7a**.

General Procedure for the Synthesis of Pyrroles 5 and 7b–j (Schemes 4 and 5)

In a 10 mL microwave tube, the corresponding nitro(hetero)aromatic **1** or **6** (1 mmol), anhydrous DMA (2 mL), pinacol (390 mg, 3.3 mmol), 2,5-dimethoxytetrahydrofurane (264 mg, 2 mmol) and $MoO_2Cl_2(dmf)_2$ (17 mg, 0.05 mmol) were added, and the tube was sealed with a septum. The reaction mixture was stirred at 180 °C for 30 min under microwave irradiation (150 W). After completion of the reaction, monitored by CG-MS, the mixture is purified by flash column chromatography using mixtures of hexane/EtOAc obtaining the corresponding 2,5-unsubstituted pyrroles **5** and **7b–j**.

General Procedure for the Synthesis of Pyrroles 8 (Scheme 6)

In a 10 mL microwave tube, the corresponding nitro(hetero)aromatic **1** or **6** (1 mmol), anhydrous DMA (2 mL),

pinacol (390 mg, 3.3 mmol), 1,4-dicarbonyl compound **2** (1.1 mmol), $Cu(OTf)_2$ (36 mg, 0.1 mmol) and $MoO_2Cl_2(dmf)_2$ (17 mg, 0.05 mmol) were added, and the tube was sealed with a septum. The reaction mixture was stirred at 180 °C for 30 min under microwave irradiation (150 W). After completion of the reaction, monitored by CG-MS, the mixture is purified by flash column chromatography using mixtures of hexane/EtOAc obtaining the corresponding pyrrole derivatives **8**.

General Procedure for the Synthesis of Pyrroles 10 (Scheme 9)

In a 10 mL microwave tube, the corresponding nitroaromatic **1** (1 mmol), anhydrous DMA (2 mL), pinacol (236 mg, 2.2 mmol), cyclobutane-1,2-diol **9** (1 mmol) and $MoO_2Cl_2(dmf)_2$ (17 mg, 0.05 mmol) were added, and the tube was sealed with a septum. The reaction mixture was stirred at 180 °C for 30 min under microwave irradiation (150 W). After completion of the reaction, monitored by CG-MS, the mixture is purified by flash column chromatography using mixtures of hexane/EtOAc obtaining the corresponding 2-substituted pyrroles **10**.

Acknowledgements

We acknowledge the financial support from Ministerio de Ciencia, Innovación y Universidades (PID2020-115789GB-C21/AEI/10.1039/501100011033 and PDC2021-115789GB-C21), and Junta de Castilla y León and FEDER (BU028P23). S.G.-G. thanks Ministerio de Ciencia, Innovación y Universidades for a FPU predoctoral contract. S.S.-P. thanks Ministerio de Ciencia, Innovación y Universidades and "NextGenerationEU"/PRTR EU for a Ramón y Cajal contract (RYC2021-031533-I).

References

[1] a) H. K. Kakam, S. G. Tilve, *RSC Adv.* **2015**, *5*, 83391–83407; b) M. Orlandi, D. Brenna, R. Jost, S. Harms, M. Benaglia, *Org. Process Res. Dev.* **2018**, *22*, 430–445; c) D. Formenti, F. Ferretti, F. K. Scharnagl, M. Beller, *Chem. Rev.* **2019**, *119*, 2611.

[2] For reviews, see: a) Y. Gao, S. Yang, Y. Huo, X.-Q. Hu, *Adv. Synth. Catal.* **2020**, *362*, 3971–3986; b) D. Zou, W. Wang, Y. Hu, T. Jia, *Org. Biomol. Chem.* **2023**, *21*, 2254–2271; c) T. Li, A. S. C. Chan, S.-S. Meng, *Synthesis* **2024**, *56*, 733–750; d) J.-H. Qin, Y. Wang, J.-Y. Ouyang, M. Liu, X.-H. Ouyang, *Org. Chem. Front.* **2024**, *11*, 2638–2664. For selected recent examples, see: e) G. Li, M. N. Lavagnino, S. Z. Ali, S. Hu, A. T. Radosevich, *J. Am. Chem. Soc.* **2023**, *145*, 41–46; f) B. Akana-Schneider, D. J. Weix, *J. Am. Chem. Soc.* **2023**, *145*, 16150–16159; g) J.-L. Sun, H. Jiang, P. H. Dixneuf, M. Zhang, *J. Am. Chem. Soc.* **2023**, *145*, 17329–17336; h) J.-L. Lu, Z. Zhang, J.-T. Deng, A.-J. Ma, J.-B. Peng, *Org. Lett.* **2023**, *25*, 2991–2995; i) S.-S. Ma, R. Sun, Z.-H. Zhang, P.-X. Guan, J.-Q. Lin, C.-S. Li, B.-H. Xu, *Green Chem.* **2023**, *25*, 8625–8632; j) R. N. Ansari, R. H. Choudhary, M. Nachtegaal, A. H. Clark, S. V. Plummer, J. B. Jasinski, F. Gallou, S. Handa, *ACS Catal.* **2024**, *4*, 4099–4107; k) T. An, C. Liu, W. Yuan, X. Qin, Z. Yin, *Chem. Commun.* **2024**, *60*, 3389–3392; l) Q.-D. Wang, X. Liu, Y.-W. Zheng, Y.-S. Wu, X. Zhou, J.-M. Yang, Z.-L. Shen, *Org. Lett.* **2024**, *26*, 416–420; m) E. Pocock, M. Diefenbach, T. M. Hood, M. Nunn, E. Richards, V. Krewald, R. L. Webster, *J. Am. Chem. Soc.* **2024**, *146*, 19839–19851.

[3] M. Kashihara, Y. Nakao, *Acc. Chem. Res.* **2021**, *54*, 2928–2935.

[4] a) S. Ahmad, O. Alam, J. N. Naim, M. Shaquiquzzaman, M. M. Alam, M. Iqbal, *Eur. J. Med. Chem.* **2018**, *157*, 527–561; b) A. Kornienko, J. J. La Clair, *Nat. Prod. Rep.* **2017**, *34*, 1051–1060; c) V. Bhardwaj, D. Gumber, V. Abbot, S. Dhiman, P. Sharma, *RSC Adv.* **2015**, *5*, 15233–15266; d) A. Domagala, T. Jarosz, M. Lapkowski, *Eur. J. Med. Chem.* **2015**, *100*, 176–187; e) D. L. J. Clive, P. Cheng, *Tetrahedron* **2013**, *69*, 5067–5078.

[5] a) A. Deronzier, J. C. Moutet, *Coord. Chem. Rev.* **1996**, *147*, 339–371; b) A. Loudet, K. Burgess, *Chem. Rev.* **2007**, *107*, 4891–4932.

[6] For selected reviews, see: a) N. Singh, S. Singh, S. Kohli, A. Singh, H. Asiki, G. Rathee, R. Chandra, E. A. Anderson, *Org. Chem. Front.* **2021**, *8*, 5550–5573; b) S. C. Philkhana, F. O. Badmus, I. C. Dos Reis, R. Kartika, *Synthesis* **2021**, *53*, 1531–1555; c) P. N. Rakendu, T. Aneeja, G. Anilkumar, *Asian J. Org. Chem.* **2021**, *10*, 2318–2333; d) V. Estévez, M. Villacampa, J. C. Menéndez, *Chem. Soc. Rev.* **2014**, *43*, 4633–4657; e) R. Khajuria, S. Dham, K. K. Kapoor, *RSC Adv.* **2016**, *6*, 37039–37066; f) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.* **2013**, *113*, 3084–3213; g) B. Borah, K. D. Dwivedi, L. R. Chowhan, *Asian J. Org. Chem.* **2021**, *10*, 2709–2762; h) D. Gaviña, M. Escolano, J. Torres, G. Alzuet-Piña, M. Sánchez-Roselló, C. del Pozo, *Adv. Synth. Catal.* **2021**, *363*, 3439–3470.

[7] a) C. Paal, *Chem. Ber.* **1884**, *17*, 2756–2767; b) L. Knorr, *Chem. Ber.* **1884**, *17*, 2863–2870. For the mechanism, see: c) V. Amarnath, D. C. Anthony, K. Amarnath, W. M. Valentine, L. A. Wetterau, D. G. Graham, *J. Org. Chem.* **1991**, *56*, 6924–6931.

[8] A. Balakrishna, A. Aguilar, P. M. J. Sobral, M. Y. Wani, J. Almeida e Silva, A. J. F. N. Sobral, *Catal. Rev. Sci. Eng.* **2019**, *61*, 84–110.

[9] a) H. Lee, B. H. Kim, *Tetrahedron* **2013**, *69*, 6698–6708; b) B. H. Kim, S. Bae, A. Go, H. Lee, C. Gong, B. M. Lee, *Org. Biomol. Chem.* **2016**, *14*, 265–276; c) E. Kim, M. Jeong, H. Lee, B. H. Kim, *Heterocycles* **2019**, *98*, 1105–1118; d) D. Tejeswararao, B. Srikanth, *Asian J. Chem.* **2020**, *32*, 795–802.

[10] a) F. G. Cirujano, A. Leyva-Pérez, A. Corma, F. X. Labrés i Xamena, *ChemCatChem* **2013**, *5*, 538–549; b) Z. Gong, Y. Lei, P. Zhou, Z. Zhang, *New J. Chem.* **2017**, *41*, 10613–10618; c) P. Ryabchuk, T. Leischner, C. Kreyenschulte, A. Spannenberg, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2020**, *59*, 18679–18685; d) D. Panja, A. Sau, B. Balasubramaniam, P. Dhara, R. K.

Gupta, S. Kundu, *J. Catal.* **2021**, *402*, 244–254; e) Y. Lin, F. Wang, E. Ren, F. Zhu, Q. Zhang, G.-P. N. Lu, *J. Catal.* **2022**, *416*, 39–46.
[11] a) J. Fessler, L. Junge, M. Beller, *Chem. Sci.* **2023**, *14*, 11374–11380; b) G. Wienhöfer, I. Sorribes, A. Boddien, F. Westerhaus, K. Junge, H. Junge, R. Llusar, M. Beller, *J. Am. Chem. Soc.* **2011**, *133*, 12875–12879.
[12] a) R. Hille, J. Hall, P. Basu, *Chem. Rev.* **2014**, *114*, 3963–4038; b) P. L. Smedley, D. G. Kinniburgh, *Appl. Geochem.* **2017**, *84*, 387–432.
[13] For reviews, see: a) R. Hernández-Ruiz, R. Sanz, *Synthesis* **2018**, *50*, 4019–4036; b) S. Suárez-Pantiga, R. Sanz, *Org. Biomol. Chem.* **2021**, *19*, 10472–10492.
[14] a) N. García, P. García-García, M. A. Fernández-Rodríguez, R. Rubio, M. R. Pedrosa, F. J. Arnáiz, R. Sanz, *Adv. Synth. Catal.* **2012**, *354*, 321–327. For the DFT mechanistic study of this reaction, see: b) S. Kiriakidi, C. Silva López, R. Sanz, O. Nieto Faza, *ChemCatChem* **2024**, *16*, e202301575.
[15] N. García, R. Rubio-Presa, P. García-García, M. A. Fernández-Rodríguez, M. R. Pedrosa, F. J. Arnáiz, R. Sanz, *Green Chem.* **2016**, *18*, 2335–2340.
[16] a) R. Rubio-Presa, M. R. Pedrosa, M. A. Fernández-Rodríguez, F. J. Arnáiz, R. Sanz, *Org. Lett.* **2017**, *19*, 5470–5473; b) R. Hernández-Ruiz, R. Rubio-Presa, S. Suárez-Pantiga, M. R. Pedrosa, M. A. Fernández-Rodríguez, M. J. Tapia, R. Sanz, *Chem. Eur. J.* **2021**, *27*, 13613–13623; c) S. Gómez-Gil, N. Cases, R. Hernández-Ruiz, R. Rubio-Presa, S. Suárez-Pantiga, M. R. Pedrosa, R. Sanz, *Eur. J. Org. Chem.* **2024**, *27*, e202400145.
[17] T. Kinoshita, S. Okada, S.-R. Park, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2003**, *42*, 4680–4684.
[18] See, for instance: a) J.-J. Cao, F. Zhou, J. Zhou, *Angew. Chem. Int. Ed.* **2010**, *49*, 4976–4980; b) Y.-P. Zhu, Q.-H. Gao, M. Lian, J.-J. Yuan, M.-C. Liu, Q. Zhao, Y. Yang, A.-X. Wu, *Chem. Commun.* **2011**, *47*, 12700–12702; c) B.-S. Mu, X.-Y. Cui, X.-P. Zeng, J.-S. Yu, J. Zhou, *Nat. Commun.* **2021**, *12*, 2219.
[19] See, for instance: a) F. Zhu, P.-W. Xu, F. Zhou, C.-H. Wang, J. Zhou, *Org. Lett.* **2015**, *17*, 972–975; b) Y. Guo, C. Meng, X. Liu, C. Li, A. Xia, Z. Xu, D. Xu, *Org. Lett.* **2018**, *20*, 913–916; c) S. Sangeetha, G. Sekar, *Org. Lett.* **2019**, *21*, 75–79.
[20] a) W. Wei, Y. Tang, Y. Zhou, G. Deng, Z. Liu, J. Wu, Y. Li, J. Zhang, S. Xu, *Org. Lett.* **2018**, *20*, 6559–6563; b) H. Wei, S. Zhou, L. Qiu, Y. Qian, W. Hu, X. Xu, *Adv. Synth. Catal.* **2019**, *361*, 3569–3574.
[21] FluoroChem, pinacol (CAS 76-09-5), 32 €/500 g, 2024; available at: www.chemosapiens.com/product/92595 .
[22] N. Clauson-Kaas, Z. Tyle, *Act. Chem. Scand.* **1952**, *6*, 667–670.
[23] See, for instance: a) I. A. Andreev, N. K. Ratmanova, A. M. Novoselov, D. S. Belov, I. F. Seregina, A. V. Kurkin, *Chem. Eur. J.* **2016**, *22*, 7262–7267; b) S. Vojacek, L. Schulig, N. Wössner, N. Geist, W. Langel, M. Jung, D. Schade, A. Link, *ChemMedChem* **2019**, *14*, 853–864.
[24] S. Gómez-Gil, R. Rubio-Presa, R. Hernández-Ruiz, S. Suárez-Pantiga, M. R. Pedrosa, R. Sanz, *Org. Biomol. Chem.* **2023**, *21*, 4185–4190.