Monoamine Oxidase (MAO-N) Biocatalyzed Synthesis of Indoles from Indolines Prepared via Photocatalytic Cyclization/Arylative Dearomatization

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ABSTRACT. The biocatalytic aromatization of indolines into indole derivatives exploiting monoamine oxidase (MAO-N) enzymes is presented. Indoline substrates were prepared via photocatalytic cyclization of arylaniline precursors or via arylative dearomatization of unsubstituted indoles and in turn chemoselectively aromatized by MAO-N D11 whole cell biocatalyst. Computational docking studies of the indoline substrates in the MAO-N D11 catalytic

site allowed to rationalize the biocatalytic mechanism and experimental results of the biotransformation. This methodology represents an efficient example of biocatalytic synthesis of indole derivatives and offers a facile approach to access these aromatic heterocycles under mild reaction conditions.

KEYWORDS. Indoles, biocatalysis, MAO-N, aromatization, indolines.

INTRODUCTION.

The indole motif is considered a privileged scaffold in chemistry due to its large presence in many natural products and pharmaceutical ingredients.[1] Examples of indole-containing natural products[2] include tryptophan, 5-hydroxytryptamine, psilocin and vincamine, while examples of drugs having an indole nucleus are indomethacin, sumatriptan and fluvastatin (Figure 1).[3] The development of synthetic methods for the construction of indoles has captured the attention of the scientific community over the years and tremendous efforts have been made to synthesize this key heterocycle under different reaction conditions. The Fischer synthesis of indoles[4] is probably the best known method to access indoles from phenylhydrazines. Other classical synthetic approaches include the syntheses of Larock,[5] Madelung,[6] Nenitzescu[7] and Schmid,[8] or the cyclization of nitro-arenes and anilines.[9] The indole ring can also be constructed from diverse functionalized starting materials in the presence of metal complexes,[10] or obtained through the oxidation of indoline precursors in the presence of various oxidants,[11] photoredox initiators,[12] artificial macromolecules and materials[13] or metals.[14]

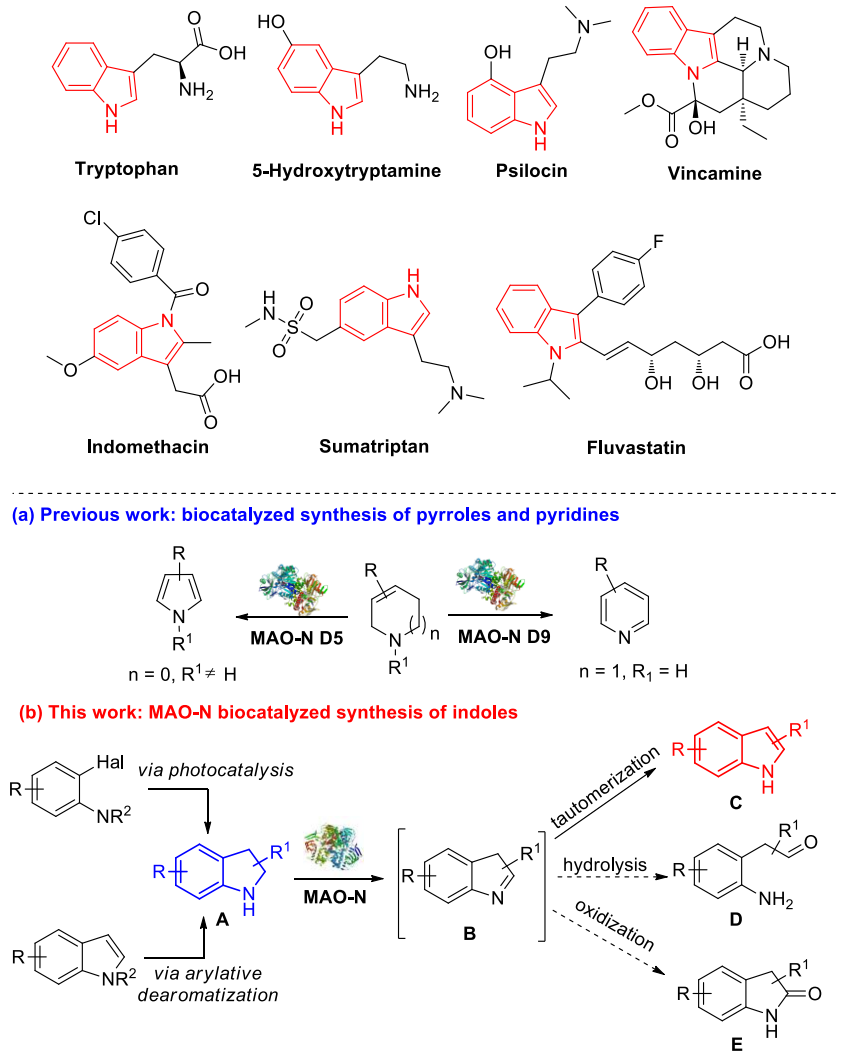


Figure 1. Representative bioactive molecules with the indole motif and previous and current works on biocatalytic synthesis of aromatic nitrogen-containing heterocycles.

However, if considered in terms of greenness and sustainability, most of these approaches suffer from some disadvantages, such as harsh reaction conditions, the use of rare metals or strong acids/bases, the use of stoichiometric amounts of oxidizing agents or the requirement of prolonged heating, making them unappealing from an environmental and industrial perspective. Surprisingly, despite the remarkable achievements made in the field of indole synthesis, only few biocatalytic

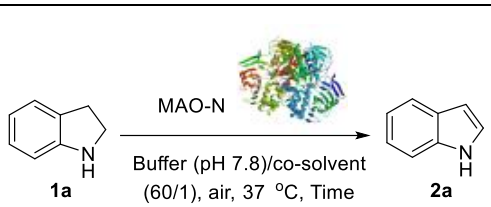
and chemo-enzymatic methods for the synthesis of tryptophan and indoline derivatives have been described in the literature.[15] Although enzymes are widely used in the construction of stereodefined chemical bonds, their use as sustainable biocatalysts in the synthesis of aromatic heterocycles is still poorly explored so far. Our group, inspired by natural metabolic transformations,[16] first reported the biocatalytic synthesis of aromatic heterocycles such as pyrroles, pyridines and furans disclosing the aromatizing properties of MAO-N and laccase enzymes.[17] As further extension of these studies and with the aim to expand the scope of aromatic heterocycles accessible via biocatalysis, herein we describe the aromatization of indolines **A** into indoles **C** exploiting MAO-N whole cell biocatalysts (Figure 1). However, such biotransformation faces two main challenges: the first challenge is to evaluate if MAO-N biocatalysts can oxidize the indoline C-N bond to give the imine intermediate B, since the conjugation of the nitrogen atom in A with the benzene ring may affect the MAO-N oxidation;[18] the second challenge of this process is to achieve high levels of chemoselectivity to generate the single indole product **C** from **B** by tautomerization, avoiding the hydrolysis or further oxidization of **B** which may lead to the byproducts **D** or **E**. In this paper, a selective enzymatic protocol for the efficient synthesis of indoles from indolines using MAO-N D11 whole cell biocatalysts under mild conditions is reported. To the best of our knowledge, this is the first example of biocatalytic aromatization of indolines into indole derivatives described in the literature.

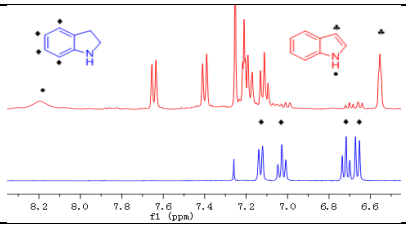
RESULTS AND DISCUSSION

Freeze-dried whole cells containing MAO-N variants D5, D9, and D11 were selected as the biocatalysts based on their known activity and selectivity toward structurally related pyrrolidines and pyrrolines.[17a,19-20] Initially, indoline **1a** was treated with three MAO-N variants in a NaPBS

buffer (pH = 7.8, 1.0 M) at 37 °C in the presence of isooctane co-solvent under air atmosphere for 24 h. The desired indole **2a** was obtained with 20% conversion when MAO-N D5 and D11 were used (*entries 1* and *3*, Table 1) while a lower conversion (*entry 2*) was observed with the variant D9. Since the co-solvent used in enzymatic reactions may have a significant impact on the conversions,[17] DMSO was then employed (*entries 4-6*) leading to an increase of the conversion (33%) when MAO-N D11 was used as biocatalyst (*entry 6*). MAO-N D11 was thus employed for further optimization. Pleasingly, extending the reaction time resulted in a remarkable improvement of the conversion (83%) and good isolated yield (72%) (*entry 8*). Increasing the loading of MAO-N D11 in the reaction mixture did not result in any significant improvement of the conversion (*entries 9-11*). Similarly, the double addition of the biocatalyst at different time did not influence the results (*entries 12* and *13*). Finally, to confirm that the aromatization of **1a** was truly catalyzed by MAO-N D11 rather than spontaneously promoted by the oxygen in the air, a set of control experiments were carried out. When the MAO-N D11 biocatalyst was removed from the reaction mixture, no desired product **2a** was detected after 7 days (*entry 14*), suggesting the air itself cannot promote this biotransformation at all. Likewise, the treatment of **1a** with *E. coli* BL21(DE3) cells harboring no MAO-N enzymes under the optimized conditions did not lead to the formation of **2a** (*entry 15*), confirming the crucial catalytic role of the enzyme MAO-N D11 in the aromatization of **1a**. Since oxygen is required in MAO-N catalyzed biotransformations to regenerate the FAD cofactor, H_2O_2 is normally produced as side product and it might accelerate the further oxidation of the imine intermediate into the byproduct indolin-2-one.[21] However, neither the indolin-2-one byproduct nor the hydrolysis byproduct 2-(2-aminophenyl)acetaldehyde (compounds **D** and **E** in Figure 1) were detected in any reaction, clearly indicating the high chemoselectivity and specifity of this biotransformation.

Table 1. Optimization of the reaction conditions of the biocatalytic aromatization of indoline **1a**.

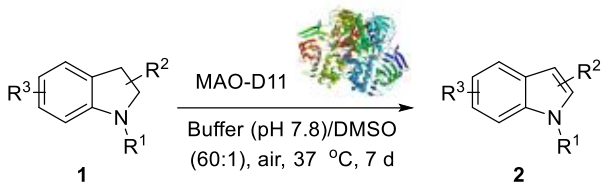




Entry	MAO-N[a]	Co-solvent	Time (d)	Conv. (%)[b]
1	D5	isooctane	1	20
2	D9	isooctane	1	12
3	D11	isooctane	1	20
4	D5	DMSO	1	10
5	D9	DMSO	1	11
6	D11	DMSO	1	33
7	D11	DMSO	3	63
8	**D11**	**DMSO**	**7**	**83 (72[c])**
9	D11[d]	DMSO	1	54
10	D11 [d]	DMSO	3	77
11	D11 [d]	DMSO	7	83
12	D11[d,e]	DMSO	4+3	81
13	D11 [d,f]	DMSO	2+1	76
14	-[g]	DMSO	7	0
15	-[h]	DMSO	7	0

[a]Reaction conditions: **1a** (0.2 mmol), freeze-dried MAO-N whole cells (190 mg), buffer (Na_2HPO_4/NaH_2PO_4, pH = 7.8, 1.0 M) (3.0 mL), co-solvent (50 μL), air, 37 °C, 1-7 days. [b]Conversion was determined by ^{1}H NMR integration of the crude mixture. [c]Isolated yield. [d]380 mg freeze-dried MAO-N D11 whole cells were used. [e]190 mg Freeze-dried MAO-N D11 whole cells were added at the beginning of the reaction, and then another 190 mg Freeze-dried MAO-N D11 whole cells were added at the fifth day of the reaction. [f]190 mg Freeze-dried MAO-N D11 whole cells were added at the beginning of the reaction, and then another 190 mg Freeze-dried MAO-N D11 whole cells were added at the third day of the reaction. [g]No biocatalyst was added to the reaction mixture. [h]*E. coli* BL21(DE3) cells harboring no MAO-N enzymes were used.

Table 2. Biocatalytic aromatization of indolines **1a-1p**.



Entry	Indole	R^1	R^2	R^3	Conv. (%)[a]	Yield (%)[b]
1	**2a**	H	H	H	83	72
2	**2b**	H	H	5-F	84	70
3	**2c**	H	H	4-Cl	68	44
4	**2d**	H	H	5-Cl	>99	86
5	**2e**	H	H	6-Cl	83	61
6	**2f**	H	H	5-Br	59	43
7	**2g**	H	H	6-I	>99	85
8	**2h**	H	H	5-Me	71	58
9	**2i**	H	H	5-OMe	>99	82
10	**2j**	H	H	6-OMe	57	40
11	**2k**	H	H	5-CN	0	NA[c]
12	**2l**	H	H	5-NO_2	0	NA[c]
13	**2m**	H	2-Me	H	>99	92
14	**2n**	H	3-Me	H	>99	90
15	**2o**	Me	H	H	0	NA[c]
16	**2p**	Bn	H	H	0	NA[c]

Reaction conditions: **1** (0.2 mmol), freeze-dried MAO-N D11 whole cells (190 mg), buffer (Na_2HPO_4/NaH_2PO_4, pH = 7.8, 1.0 M) (3.0 mL), DMSO (50 μL), air, 37 °C, 7 days. [a]Conversion was determined by ^{1}H NMR integration of the crude mixture. [b]Isolated yields are reported. [c]Not available.

Once the reaction conditions were optimized, the substrate scope was explored. A series of commercially available indolines bearing different substituents on the heterocyclic nucleus was treated with MAO-N D11 under the optimal conditions. The results are reported in Table 2. The indolines **1b-g** bearing a halogen substituent on the benzene ring were converted into the corresponding indoles **2b-g** with good to excellent conversion and yields (Table 2, *entries 2-7*). Good to excellent conversions were also obtained with indolines **1h-j** bearing electron-donating groups on the aromatic ring (Table 2, *entries 8-10*) while no conversion was observed for **1k-l** bearing the electron-withdrawing substituents -NO_2 and -CN (Table 2, *entries 11-12*). In order to better explain the different reactivity of indolines **1** and their interaction with the catalytic site of MAO-N D11, docking studies were performed (Figure 2).[19]

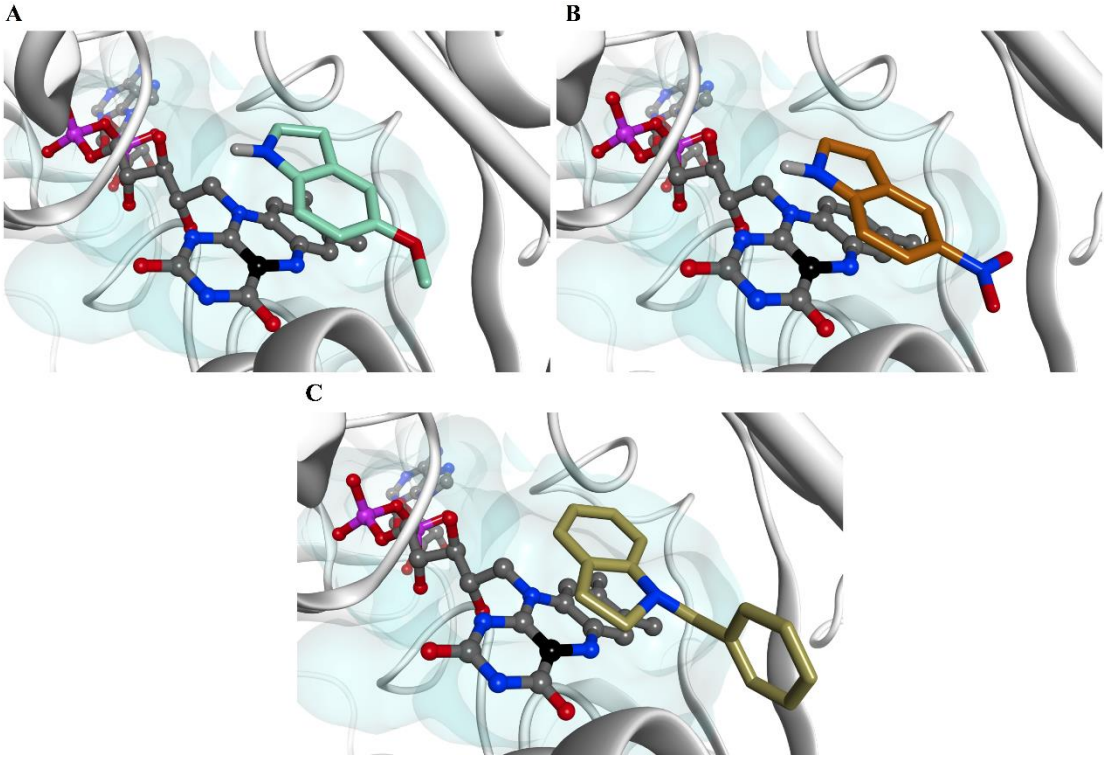


Figure 2. Proposed binding modes for compounds **1i (A)**, **1l (B)**, **1p (C)** in the MAO-N D11 catalytic site (PDB ID: 3ZDN).[19] The nitrogen atom of **1i** and **1l** is oriented toward the FAD nitrogen and carbon atom (represented as black atom)) involved in the mechanism of reaction,

whereas substituent on the nitrogen forces compound **1p** in a different orientation. Carbon atoms of compound **1i** are shown in turquoise, compound **1l** in orange, compound **1p** in gold. The binding area of the catalytic site is represented as a transparent surface. FAD is represented as ball-and-stick. Nitrogens of **1i**, **1l**,**1p** and FAD are shown in blue.

All the substrates **1a-n** bearing a substituent R^3 on the benzene ring occupy the MAO-N catalytic site in a similar manner with the methylene group at the α position of the indoline nitrogen correctly oriented toward the FAD cofactor. However, no differences in binding were observed in the case of substrates **1i** and **1l** (Figures 2A and 2B) despite their opposite reactivity. It was thus assumed that electronic rather than steric factors could be responsible for the different conversions observed in the biocatalytic transformation. Hence, a different computational approach was exploited to calculate the electrostatic potential surface (EPS) using Gaussian.[22] The EPS illustrates the charge distributions of molecules three dimensionally, giving an indication on the abundance of electrons around different atoms. According to the proposed MAO-N biocatalytic mechanism,[18c-e] the aromatization reaction occurs through the abstraction of a hydride from the α-methylene of indolines **1** by the FAD cofactor of the enzyme as shown in Figure 3. The following flavin deprotonation of the indoline-FAD adduct, favored by two active-site molecules of water, leads to indole products and $FADH_2$, which is in turn re-converted into FAD by O_2. The analysis of the EPS of the electron-rich indoline **1i** clearly shows a higher electron density localized on its nitrogen atom as well as the α-methylene group (Figure 3A), thus favoring the hydride abstraction step by the FAD cofactor. On the contrary, the presence of the NO_2 substituent in **1l** significantly withdraws the electrons form the α-methylene group of the indoline, considerably reducing its electron density and the ability of FAD to abstract a hydride to promote the following aromatization. Finally, indolines **1m-n**, bearing a methyl substituent on the 5-memebered ring,

were fully converted into indoles **2m-n** which were isolated in excellent yields (Table 2, *entries 13-14*). Even if substrates **1m-n** carry a stereocenter, no enantiopreference of MAO-N D11 towards one or the other enantiomer was observed.

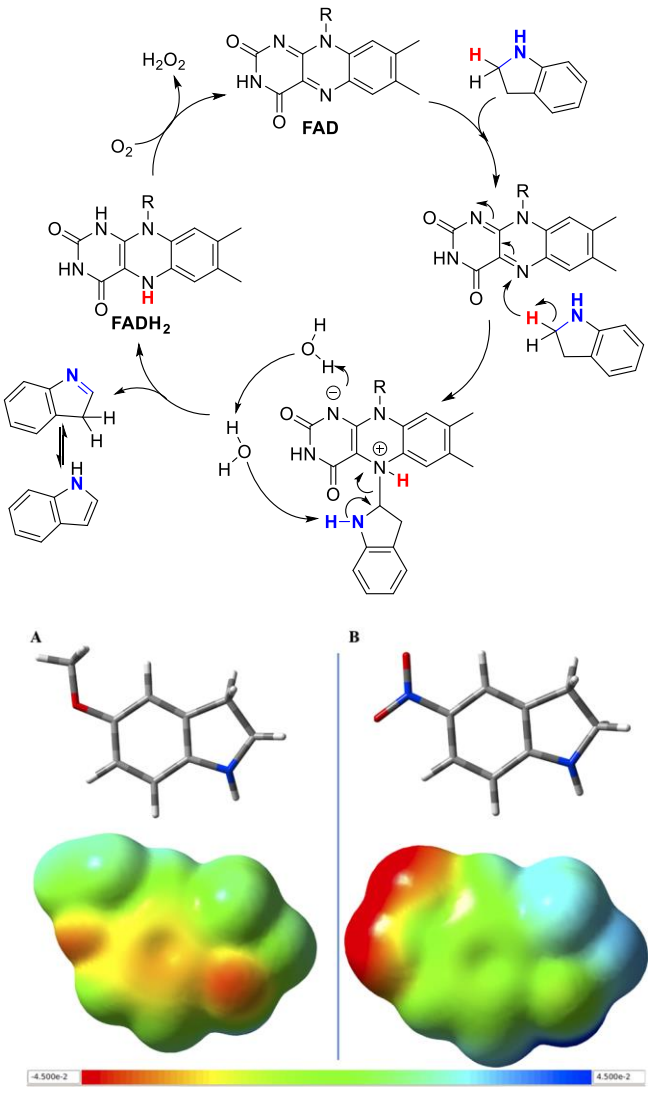
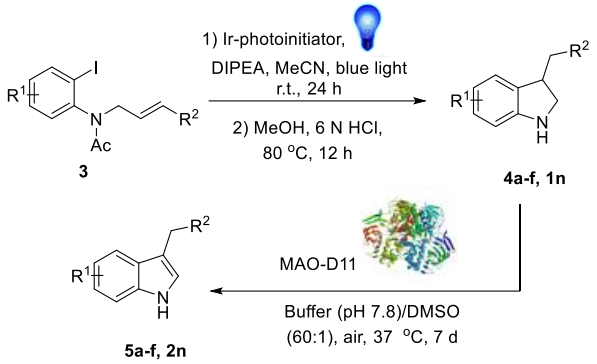


Figure 3. Plausible mechanism of the MAO-N biocatalytic aromatization of indolines (up) and electrostatic potential surface (EPS) for **1i** (A-down) and **1l** (B-down).

Despite MAO-N enzymes are able to oxidize a number of tertiary amines, when indolines **1o-p** bearing a methyl or a benzyl group on the nitrogen were treated with MAO D11, no conversion into indoles **2o-p** was detected (Table 2, *entries 15-16*). Computational studies clearly show that the presence of a substituent on the indoline nitrogen (i.e. in **1p**) does not allow the correct orientation of the molecule (Figure 2C) in the MAO-N binding site, in turn affecting the ability of the FAD cofactor to abstract the α-hydride.

Table 3. Photo-biocatalytic sequence for the synthesis of indoles **2n**, **5a-5f**.



Entry	Indole	R^1	R^2	Conv. (%)[a]	Yield (%)[b]
1	**5a**	H	Me	>99	94
2	**5b**	H	Ph	>99	88
3	**5c**	5-Me	H	>99	91
4	**5d**	5-OMe	H	>99	92
5	**5e**	6-F	H	50	41
6	**5f**	6-Cl	H	>99	83
7	**2n**	H	H	>99	90

Reaction conditions: 1) photocatalysis: **3** (0.4 mmol), $[Ir(dtbbpy)(ppy)_2]PF_6$ or $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ (3 mol%), DIPEA (4.0 mmol), MeCN (4.0 mL), 5 W blue LED, r.t., 24 h; 2) hydrolysis: *N*-acetyl indoline (0.3 mmol), MeOH (1.0 mL), 6 N HCl (4.0 mL), 80 °C, 12

h; 3) biocatalysis: **1n** or **4** (0.2 mmol), freeze-dried MAO-N D11 whole cells (190 mg), buffer (Na_2HPO_4/NaH_2PO_4, pH = 7.8, 1.0 M) (3.0 mL), DMSO (50 µL), air, 37 °C, 7 days. [a]Conversion was determined by ^1H NMR integration of the crude mixture. [b]Isolated yield.

The aromatization of indolines bearing different substituents (aliphatic and aromatic) on the 5-membered ring, was then explored (Tables 3 and 4). A photocatalytic strategy was adopted to synthesize the 3-alkyl-susbtituted indolines **4**,[23] with the aim to combine photo- and biocatalysis in a synthetic sequence. Various iodo-anilines **3** were treated with the appropriate Ir-photoinitiator ($[Ir(dtbbpy)(ppy)_2]PF_6$ for indolines **4b-f** and **1n** or $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$ for indoline **4a**) under blue light (LED) to afford the cyclized acetyl-indolines **S4**[24] which were then deprotected in HCl to give indolines **4a-f**. The latter were suspended in buffer/DMSO media and treated with MAO-N D11 to afford indoles **5a-f** with excellent conversions and yields (Table 3, *entries 1-6*). Again, indole **2n** was prepared with an excellent conversion and yield through the same photo-biocatalytic sequence (Table 3, *entry 7*). In order to rationalize these experimental data, additional computational studies were carried out. In particular, at first glance, it was unclear why indoline **4b** bearing a stereocenter at C3 was fully converted into indole **5b** and no enantiopreference in MAO-N D11 oxidation was observed. Computational analysis clearly shows that both enantiomers of **4b** bind the catalytic site of MAO-N D11 in a slightly different way but with the α-methylene group still correctly orientated toward the FAD cofactor (Figure 4A and 4B). Thus, it is reasonable to think that both enantiomers of **4b** are oxidized by MAO-N D11, explaining the observed full conversion into **5b**.

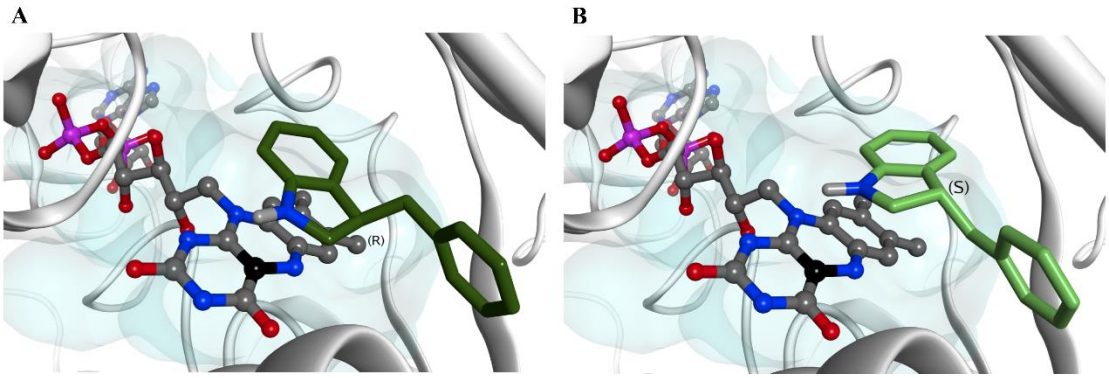
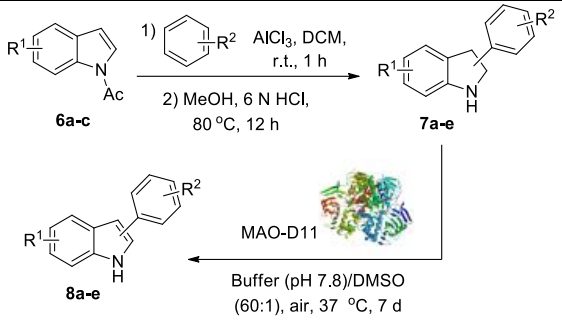


Figure 4. Proposed binding modes for compounds (*R*)-**4b** (**A**) and (*S*)-**4b** (**B**) in the MAO-N D11 catalytic site (PDB ID: 3ZDN). Both enantiomers of **4b** are able to orientate the α-methylene group toward the FAD, nearby the nitrogen next to the carbon atom (represented as black atom) as proposed for the mechanism of reaction. Carbon atoms of compound (*R*)-**4b** are shown in dark green, compound (*S*)-**4b** in light green. The binding area of the catalytic site is represented as a transparent surface. FAD is represented as ball-and-stick. Nitrogens of **1i**, **1l**,**1p** and FAD are shown in blue.

Since indolines **7a-e** bearing an aryl group on the 5-membered ring could not be accessed through the same photocatalytic synthetic pathway, an alternative dearomatizing/re-aromatizing strategy was developed. Indoles **6a-c**, unsubstituted at positions C2 and C3, were treated with appropriate benzene derivatives in the presence of $AlCl_3$[25] and converted, after acetyl deprotection,[24] into the corresponding dearomatized aryl-indolines **7a-e** in good yields. Interestingly, the benzene derivatives attack the indoles **6a-c** at the positions C2 or C3 depending on the nature of the substituents. Toluene attacked indole **6a** preferentially at position C2 while benzene attacked **6a** at position C3 affording respectively **7a** and **7b** after deprotection. Indolines **7c** and **7d** bearing a phenyl ring at positions C2 and C3 respectively, were obtained as the main products from substituted indoles **6b-c**. Finally, the attack of the bulky *m*-xylene occurred preferentially at position C3 of **6a** to give the indoline **7e** after deprotection. Indolines **7a-e** were then treated with

MAO-N D11. Results are reported in Table 4. The 2-aryl indolines **7a** and **7c** were aromatized into the indoles **8a** and **8c** with excellent conversions and yields (*entries 1 and 3*), while lower conversions were observed for the 3-susbtituted indolines **7b** and **7d** (*entries 2 and 4*), plausibly due to steric factors. Indoline **7b** was recovered as a racemate from the reaction mixture. No improvements in the conversion of **7b** into **8b** were observed when the biotransformation was carried out for 10 days. Finally, a low conversion (<8%) was observed for the 3-*m*-xylyl indoline **7e** (entry 5). Interestingly, compound **7e** docked the catalytic site of MAO-N in an orientation similar to other indoline compounds, potentially suggesting a good conversion. However, the bulkier 3-*m*-xylyl group could represent a steric hindrance making it difficult for **7e** to enter the narrow active site of the enzyme D11.[19]

Table 4. Arylative dearomatization-biocatalytic aromatization sequence for the synthesis of indoles **8a-e**.



Entry	Indole	R^1	R^2	Conv. (%)[a]	Yield (%)[b]
1	**8a**	H	2-*p*-Tolyl	>99	83
2	**8b**	H	3-Ph	55	48
3	**8c**	5-OMe	2-Ph	>99	98
4	**8d**	6-Cl	3-Ph	45	40

5	**8e**	H	3-(3,5-*di*-Me-Ph)	8	-

Reaction conditions: (1) arylative dearomatization: **6a-c** (1.25 mmol), arene (1.87 mmol), $AlCl_3$ (4.37 mmol), DCM (4.0 mL) r.t., 1 h; (2) hydrolysis: *N*-acetyl indoline (0.43 mmol), MeOH (1.0 mL), 6 N HCl (4.0 mL), 80 °C, 12 h; (3) biocatalysis: **7a-e** (0.2 mmol), freeze-dried MAO-N D11 whole cells (190 mg), buffer Na_2HPO_4/NaH_2PO_4 (pH = 7.8, 1.0 M, 3.0 mL), DMSO (50 μL), air, 37 °C, 7 days. [a]Conversion was determined by ^{1}H NMR integration of the crude mixture. [b]Isolated yield.

CONCLUSIONS

In conclusion, the aromatizing biocatalytic activity of MAO-N enzymes on indoline substrates has been demonstrated for the first time. The variant biocatalyst D11 proved to be the best enzyme for such biotransformation. A variety of indoline derivatives **1**, **4** and **7**, in turn prepared *via* photocatalytic cyclization of allyl-anilines or *via* arylative dearomatization of indoles, have been converted into aromatic indoles **2**, **5** and **8** with good to excellent yields under mild reaction conditions. Computational studies revealed that the biocatalytic aromatization of indolines into indoles is mainly affected by two factors, namely the distribution of electrons around the indoline nitrogen and the α-methylene group, and the ability of the substrates to align to the FAD cofactor with the correct orientation in the catalytic site of the enzyme. Even if the approaches used for the synthesis of the substituted indoline substrates still show some limits in terms of greenness and sustainability due to harsh conditions, the present methodology highlights the enormous potentiality of MAO-N enzymes to be exploited not only as deracemizing but also as aromatizing biocatalysts and widens the horizons of biocatalysis in the synthesis of non-chiral aromatic molecules.

ASSOCIATED CONTENT

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

Supporting Information. Experimental details, procedures, and copies of spectra (PDF). This information is available free of charge on the ACS Publications website.

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REFERENCES

1. For selected reviews on indoles see: a) Aygun, A.; Pindur, U. Chemistry and Biology of New Marine Alkaloids from the Indole and Annelated Indole Series. *Curr. Med. Chem.* **2003,** *10,* 1113-1127; b) de Sá Alves, F. R.; Barreiro, E. J.; Fraga, C. A. From Nature to Drug Discovery: the Indole Scaffold as a ‘Privileged Structure’. *Mini-Rev. Med. Chem.* **2009,** *9,* 782-793; c) Ishikura, M.; Yamada, K.; Abe, T. Simple Indole Alkaloids and Those with a Non-Rearranged Monoterpenoid Unit. *Nat. Prod. Rep.* **2010,** *27,* 1630-1680; d) Kochanowska-Karamyan, A. J.; Hamann, M. T. Marine Indole Alkaloids: Potential New Drug Leads for the Control of Depression and Anxiety. *Chem. Rev.* **2010**, *110*, 4489-4497; e) Zi, W.; Zuo, Z.; Ma, D. Intramolecular Dearomative Oxidative Coupling of Indoles: A Unified Strategy for the Total Synthesis of Indoline Alkaloids. *Acc. Chem. Res.* **2015**, *48*, 702-711; f) Chadha, N.; Silakari, O. Indoles as Therapeutics of Interest in Medicinal Chemistry: Bird's Eye View. *Eur. J. Med. Chem*. **2017**, *134*, 159-184; g) Liu, X.-Y.; Qin, Yong. Indole Alkaloid Synthesis Facilitated by Photoredox Catalytic Radical Cascade Reactions. *Acc. Chem. Res.* **2019**, *52*, 1877-1891.
2. a) Carroll, B. J.; Dodge, J. L-Tryptophan as an Antidepressant. *Lancet* **1971**, *297*, 915; b) Mohammad-Zadeh, L. F.; Moses, L.; Gwaltney-Brant, S. M. Serotonin: a Review. *J. Vet.*

Pharmacol. Ther. **2008**, *31*, 187-199; c) Ohenoja, E.; Jokiranta, J.; Mäkinen, T.; Kaikkonen, A.; Airaksinen, M. M. The Occurrence of Psilocybin and Psilocin in Finnish Fungi. *J. Nat. Prod.* **1987**, *50*, 741-744; d) Nge, C.-E.; Chong, K.-W.; Thomas, N. F.; Lim, S.-H.; Low, Y.-Y.; Kam, T.-S. Ibogan, Aspidosperman, Vincamine, and Bisindole Alkaloids from a Malayan *Tabernaemontana corymbosa*: Iboga Alkaloids with C-20α Substitution. *J. Nat. Prod.* **2016**, *79*, 1388-1399.

3. a) Lucas, S. The Pharmacology of Indomethacin. *Headache* **2016**, *56*, 436-446; b) Oxford, A. W. Serotonin, Sumatriptan, and the Management of Migraine. *Contemp. Org. Synth.* **1995**, *2*, 35-41; c) Lawrence, J. M.; Reckless, J. P. Fluvastatin. *Expert. Opin. Pharmacother*. **2002**, *3*, 1631-1641.
4. a) Fischer, E.; Jourdan, F. The Hydrazone of Pyruvic Acid. *Ber* **1883**, *16*, 2241-2245; b) Robinson, B. The Fischer Indole Synthesis. *Chem. Rev.* **1963**, *63*, 373-401.
5. (a) Larock, R. C.; Yum, E. K. Synthesis of Indoles via Palladium-Catalyzed Heteroannulation of Internal Alkynes. *J. Am. Chem. Soc.* **1991**, *113*, 6689-6690. (b) Larock, R. C. Palladium-Catalyzed Annulation. *J. Organomet. Chem.* **1999**, *576*, 111-124.
6. (a) Madelung, W. New Method of Preparation of Substituted Indoles. *Ber* **1912**, *45*, 1128-1134. (b) Joule, J. A. Product Class 13: Indole and its Derivatives. *Science of Synthesis* **2001**, *10*, 361-652.
7. (a) Nenitzescu, C. D. Nenitzescu Indole Synthesis. *Bull. Soc. Chim. Romania.* **1929**, *11*, 37-43. (b) Allen, G. R. The Synthesis of 5-Hydroxyindoles by the Nenitzescu Reaction. *Org. React.* **1973**, *20*, 337-454.
8. Greuter, H.; Schmid, H. Intramolekulare Additionen α-Lithiierter Amide; eine neue Synthese von 2-Aryl- und 2-Vinylindolen. *Helv. Chim. Acta*. **1974**, *57*, 281-286.

9. a) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. The Reaction of Vinyl Grignard Reagents with 2-Substituted Nitroarenes: a New Approach to the Synthesis of 7-Substituted Indoles. *Tetrahedron Lett.* **1989**, *30*, 2129-2132; b) Cadogan, J. I. G.; Cameron-Wood, M.; Mackie, R. K.; Searle, R. J. G. The Reactivity of Organophosphorus Compounds. Part XIX. Reduction of Nitro-Compounds by Triethyl Phosphite: a Convenient New Route to Carbazoles, Indoles, Indazoles, Triazoles, and Related Compounds. *J. Chem. Soc.* **1965**, 4831-4837; c) Couture, A.; Deniau, E.; Gimbert, Y.; Grandclaudon, P. A Convenient Synthetic Route to 2-Diphenylphosphinoyl-3-Hydroxy, Amino and Alkyl Indole Derivatives. *Tetrahedron* **1993**, *49*, 1431-1444; d) Gassman, P. G.; Van Bergen, T. J.; Gilbert, D. P.; Cue Jr, B.W. General Method for the Synthesis of Indoles. *J. Am. Chem. Soc.* **1974**, *96*, 5495-5508; e) Sundberg, R. J. Deoxygenation of Nitro Groups by Trivalent Phosphorus. Indoles from o-Nitrostyrenes. *J. Org. Chem.* **1965**, *30*, 3604-3610; f) Sundberg, R. J.; Russell, H. F.; Ligon, W. V.; Lin, L.-S. The o-Styrylnitrene Route to 2-Substituted Indoles. Pyrolysis of o-Azidostyrenes. *J. Org. Chem.* **1972**, *37*, 719-724; g) Wender, P. A.; White, A. W. Methodology for the Facile and Regio-Controlled Synthesis of Indoles. *Tetrahedron* **1983**, *39*, 3767-3776.

10. For selected reviews see: a) Gribble, G. W. Recent Developments in Indole Ring Synthesis—Methodology and Applications. *Contemp. Org. Synth.* **1994**, *1*, 145-172; b) Gribble, G. W. Recent Developments in Indole Ring Synthesis—Methodology and Applications. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 1045-1075; c) Taber, D. F.; Tirunahari, P. K. Indole Synthesis: a Review and Proposed Classification. *Tetrahedron* **2011**, *67*, 7195-7210; d) Vicente, R. Recent Advances in Indole Syntheses: New Routes for a Classic Target. *Org. Biomol. Chem.* **2011**, *9*, 6469-6480; e) Abbiati, G.; Marinelli, F.; Rossi, E.; Arcadi, A. Synthesis of Indole Derivatives from 2-Alkynylanilines by Means of Gold Catalysis. *Isr. J. Chem*. **2013**, *53*, 856-868; f)

Anderson, L. L.; Kroc, M. A.; Reidl, T. W.; Son, J. Cascade Reactions of Nitrones and Allenes for the Synthesis of Indole Derivatives. *J. Org. Chem*. **2016**, *81*, 9521-9529; g) Nemoto, T.; Harada, S.; Nakajima, M. Synthetic Methods for 3,4-Fused Tricyclic Indoles via Indole Ring Formation. *Asian J. Org. Chem.* **2018**, *7*, 1730-1742; h) Clarke, A. K.; Ho, H. E.; Rossi-Ashton, J. A.; Taylor, R. J. K.; Unsworth, W. P. Indole Synthesis Using Silver Catalysis. *Chem. Asian J*. **2019**, *14*, 1900-1911.

11. a) Kumar, R. A.; Maheswari, C. U.; Ghantasala, S.; Jyothi, C.; Reddy, K. R. Synthesis of 3*H*-Quinazolin-4-ones and 4*H*-3,1-Benzoxazin-4-ones *via* Benzylic Oxidation and Oxidative Dehydrogenation using Potassium Iodide-*tert*-Butyl Hydroperoxide. *Adv. Synth. Catal*. **2011**, *353*, 401-410; b) Choi, H.; Doyle, M. P. Oxidation of Secondary Amines Catalyzed by Dirhodium Caprolactamate. *Chem. Commun*. **2007**, 745-747; c) Luca, O. R.; Wang, T.; Konezny, S. J.; Batista, V. S.; Crabtree, R. H. DDQ as an Electrocatalyst for Amine Dehydrogenation, a Model System for Virtual Hydrogen Storage. *New J. Chem*. **2011**, *35*, 998-999; d) Zhao, F.; Li, J.; Chen, Y.; Tian, Y.; Wu, C.; Xie, Y.; Zhou, Y.; Wang, J.; Xie, X.; Liu, H. Design, Synthesis, and Biological Evaluation of Indoline and Indole Derivatives as Potent and Selective α_{1A}-Adrenoceptor Antagonists. *J. Med. Chem.* **2016**, *59*, 3826-3839; e) Shang, Y.; Jie, X.; Jonnada, K.; Zafar, S. N.; Su, W. Dehydrogenative Desaturation-Relay via Formation of Multicenter-Stabilized Radical Intermediates. *Nat. Commun*. **2017**, *8*, 2273; f) Wu, Y.; Yi, H.; Lei, A. Electrochemical Acceptorless Dehydrogenation of N-Heterocycles Utilizing TEMPO as Organo-Electrocatalyst. *ACS Catal*. **2018**, *8*, 1192-1196; g) Kojima, M.; Kanai, M. Tris(pentafluorophenyl)borane-Catalyzed Acceptorless Dehydrogenation of N-Heterocycles. *Angew. Chem. Int. Ed*. **2016**, *55*, 12224-12227.

12. a) Su, F.; Mathew, S. C.; Möhlmann, L.; Antonietti, M.; Wang, X.; Blechert, S. Aerobic Oxidative Coupling of Amines by Carbon Nitride Photocatalysis with Visible Light. *Angew. Chem. Int. Ed*. **2011**, *50*, 657-660; b) Sahoo, M. K.; Jaiswal, G.; Rana, J.; Balaraman, E. Organo-Photoredox Catalyzed Oxidative Dehydrogenation of N-Heterocycles. *Chem. Eur. J*. **2017**, *23*, 14167-14172; c) He, K.-H.; Tan, F.-F.; Zhou, C.-Z.; Zhou, G.-J.; Yang, X.-L.; Li, Y. Acceptorless Dehydrogenation of N-Heterocycles by Merging Visible-Light Photoredox Catalysis and Cobalt Catalysis. *Angew. Chem. Int. Ed*. **2017**, *56*, 3080-3084; d) Zheng, M.; Shi, J.; Yuan, T.; Wang, X. Metal-Free Dehydrogenation of N-Heterocycles by Ternary *h*-BCN Nanosheets with Visible Light. *Angew. Chem. Int. Ed*. **2018**, *57*, 5487-5491.
13. a) Li, X.-H.; Antonietti, M. Polycondensation of Boron- and Nitrogen- Codoped Holey Graphene Monoliths from Molecules: Carbocatalysts for Selective Oxidation. *Angew. Chem. Int. Ed*. **2013**, *52*, 4572-4576; b) Zhang, J.; Chen, S.; Chen, F.; Xu, W.; Deng, G.-J.; Gong, H. Dehydrogenation of Nitrogen Heterocycles Using Graphene Oxide as a Versatile Metal-Free Catalyst under Air. *Adv. Synth. Catal*. **2017**, *359*, 2358-2363; c) Zhang, Y.; Pang, S.; Wei, Z.; Jiao, H.; Dai, X.; Wang, H.; Shi, F. Synthesis of a Molecularly Defined Single-Active Site Heterogeneous Catalyst for Selective Oxidation of N-Heterocycles. *Nat. Commun*. **2018**, *9*, 1465; d) Pawar, S. A.; Chand, A. N.; Kumar, A. V. Polydopamine: An Amine Oxidase Mimicking Sustainable Catalyst for the Synthesis of Nitrogen Heterocycles under Aqueous Conditions. *ACS Sustainable Chem. Eng.* **2019**, *7*, 8274-8286.
14. a) Kuehne, M. E.; Hall, T. C. Oxidation of Primary Amines and Indoline with Palladium Dichloride and Gold Trichloride. *J. Org. Chem.* **1976**, *41*, 2742-2746; b) Tsuji, Y.; Kotachi, S.; Huh, K. T.; Watanabe, Y. Ruthenium-Catalyzed Dehydrogenative *N*-Heterocyclization. Indoles from 2-Aminophenethyl Alcohols and 2-Nitrophenethyl Alcohols. *J. Org. Chem.* **1990**,

55, 580-584; c) Kamata, K.; Kasai, J.; Yamaguchi, K.; Mizuno, N. Efficient Heterogeneous Oxidation of Alkylarenes with Molecular Oxygen. *Org. Lett*. **2004**, *6*, 3577-3580; d) Li, F.; Chen, J.; Zhang, Q.; Wang, Y. Hydrous Ruthenium Oxide Supported on Co_3O_4 as Efficient Catalyst for Aerobic Oxidation of Amines. *Green Chem*. **2008**, *10*, 553-562; e) Wu, J.; Talwar, D.; Johnston, S.; Yan, M.; Xiao, J. Acceptorless Dehydrogenation of Nitrogen Heterocycles with a Versatile Iridium Catalyst. *Angew. Chem. Int. Ed*. **2013**, *52*, 6983-6987; f) Yao, W.; Zhang, Y.; Jia, X.; Huang, Z. Selective Catalytic Transfer Dehydrogenation of Alkanes and Heterocycles by an Iridium Pincer Complex. *Angew. Chem. Int. Ed*. **2014**, *53*, 1390-1394; g) Cui, X.; Li, Y.; Bachmann, S.; Scalone, M.; Surkus, A.-E.; Junge, K.; Topf, C.; Beller, M. Synthesis and Characterization of Iron-Nitrogen-Doped Graphene/Core-Shell Catalysts: Efficient Oxidative Dehydrogenation of N-Heterocycles. *J. Am. Chem. Soc.* **2015**, *137*, 10652-10658; h) Peng, F.; McLaughlin, M.; Liu, Y.; Mangion, I.; Tschaen, D. M.; Xu, Y. A Mild Cu(I)-Catalyzed Oxidative Aromatization of Indolines to Indoles. *J. Org. Chem.* **2016**, *81*, 10009-10015; i) Han, Y.; Wang, Z.; Xu, R.; Zhang, W.; Chen, W.; Zheng, L.; Zhang, J.; Luo, J.; Wu, K.; Zhu, Y.; Chen, C.; Peng, Q.; Liu, Q.; Hu, P.; Wang, D.; Li, Y. Ordered Porous Nitrogen-Doped Carbon Matrix with Atomically Dispersed Cobalt Sites as an Efficient Catalyst for Dehydrogenation and Transfer Hydrogenation of N-Heterocycles. *Angew. Chem. Int. Ed.* **2018**, *57*, 11262-11266.

15. a) Parmeggiani, F.; Rué Casamajo, A.; Walton, C. J. W.; Galman, J. L.; Turner, N. J.; Chica, R. A. One-Pot Biocatalytic Synthesis of Substituted D-Tryptophans from Indoles Enabled by an Engineered Aminotransferase. *ACS Catal.* **2019**, *9*, 3482-3486; b) de Lange, B.; Hyett, D. J.; Maas, P. J. D.; Mink, D.; van Assema, F. B. J.; Sereinig, N.; de Vries, A. H. M.; de Vries,

J. G. Asymmetric Synthesis of (*S*)-2-Indolinecarboxylic Acid by Combining Biocatalysis and Homogeneous Catalysis. *ChemCatChem* **2011**, *3*, 289-292.

16. Gu, C.; Collins, R.; Holsworth, D. D.; Walker, G. S.; Voorman, R. L. Metabolic Aromatization of *N*-Alkyl-1,2,3,4-Tetrahydroquinoline Substructures to Quinolinium by Human Liver Microsomes and Horseradish Peroxidase. *Drug Metab. Dispos.* **2006**, *34*, 2044-2055.
17. a) Scalacci, N.; Black, G. W.; Mattedi, G.; Brown, N. L.; Turner, N. J.; Castagnolo, D. Unveiling the Biocatalytic Aromatizing Activity of Monoamine Oxidases MAO-N and 6-HDNO: Development of Chemoenzymatic Cascades for the Synthesis of Pyrroles. *ACS Catal.* **2017**, *7*, 1295-1300; b) Toscani, A.; Risi, C.; Black, G. W.; Brown, N. L.; Shaaban, A.; Turner, N. J.; Castagnolo, D. Monoamine Oxidase (MAO-N) Whole Cell Biocatalyzed Aromatization of 1, 2, 5, 6-Tetrahydropyridines into Pyridines. *ACS Catal.* **2018**, *8*, 8781-8787; c) Risi, C.; Zhao, F.; Castagnolo, D. Chemo-Enzymatic Metathesis/Aromatization Cascades for the Synthesis of Furans: Disclosing the Aromatizing Activity of Laccase/TEMPO in Oxygen-Containing Heterocycles. *ACS Catal.* **2019**, *9*, 7264-7269.
18. a) Kim, J.-M.; Bogdan, M. A.; Mariano, P. S. Mechanistic Analysis of the 3-Methyllumiflavin-Promoted Oxidative Deamination of Benzylamine. A Potential Model for Monoamine Oxidase Catalysis. *J. Am. Chem. Soc*. **1993**, *115*, 10591-10595; b) Miller, J. R.; Edmondson, D. E. Structure-Activity Relationships in the Oxidation of Para-Substituted Benzylamine Analogues by Recombinant Human Liver Monoamine Oxidase A. *Biochemistry* **1999**, *38*, 13670-13683; c) Vianello, R.; Repič, M.; Mavri, J. How Are Biogenic Amines Metabolized by Monoamine Oxidases? *Eur. J. Org. Chem.* **2012**, *36*, 7057-7065; d) Stare, J. Complete Sampling of an Enzyme Reaction Pathway: a Lesson from Gas Phase Simulations. *RSC Adv.* **2017**, *7*, 8740-8754; e) the mechanism of oxidation of monoamine oxidase enzyme is not yet fully clear and

two mechanisms have been proposed: 1) the nucleophilic attack of an amine to the FAD or 2) the abstraction of the hydride in α position to the nitrogen by the FAD. The references 18c and 18d seem to confirm the second hypothesis. However, also in case of a nucleophilic attack mechanism, the calculated EPS data are in agreement with the observed reactivity.

19. Ghislieri, D.; Green, A. P.; Pontini, M.; Willies, S. C.; Rowles, I.; Frank, A.; Grogan, G.; Turner, N. J. Engineering an Enantioselective Amine Oxidase for the Synthesis of Pharmaceutical Building Blocks and Alkaloid Natural Products. *J. Am. Chem. Soc*. **2013**, *135*, 10863-10869.
20. Herter, S.; Medina, F.; Wagschal, S.; Benhaïm, C.; Leipold, F.; Turner, N. J. Mapping the Substrate Scope of Monoamine Oxidase (MAO-N) as a Synthetic Tool for the Enantioselective Synthesis of Chiral Amines. *Bioorg. Med. Chem*. **2018**, *26*, 1338-1346.
21. Bechi, B.; Herter, S.; McKenna, S.; Riley, C.; Leimkühler, S.; Turner, N. J.; Carnell, A. Catalytic Bio-Chemo and Bio-Bio Tandem Oxidation Reactions for Amide and Carboxylic Acid Synthesis. *Green Chem*. **2014**, *16*, 4524-4529.
22. Gaussian 16 (Gaussian, Inc., Pittsburgh, PA, 1998) http://www.gaussian.com/.
23. Kim, H.; Lee, C. Visible-Light-Induced Photocatalytic Reductive Transformations of Organohalides. *Angew. Chem. Int. Ed.* **2012**, *51*, 12303-12306.
24. Details on the intermediates **S4** and **S7** are reported in the Supporting Information.
25. a) Tajima, N.; Hayashi, T.; Nakatsuka, S.-N. Structures of Dimers and Trimers of 1-Trimethylacetylindole Produced in Presence of Aluminum Chloride. *Tetrahedron Lett.* **2000**, *41*, 1059–1062; b) Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. $FeCl_3$-Mediated Friedel-Crafts Hydroarylation with Electrophilic N-Acetyl Indoles for the Synthesis of Benzofuroindolines. *Angew. Chem. Int. Ed.* **2012**, *51*, 12546–12550; c) Beaud, R.; Guillot, R.;

Kouklovsky, C.; Vincent, G. Regioselective Hydroarylation Reactions of C3 Electrophilic *N*-Acetylindoles Activated by $FeCl_3$: An Entry to 3-(Hetero)arylindolines. *Chem. Eur. J.* **2014**, *20*, 7492–7500.

SYNOPSIS.