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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 products² 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 indoles⁴ is probably the best known method to access indoles from phenylhydrazines. Other classical synthetic approaches include the syntheses of Larock,⁵ Madelung,⁶ Nenitzescu⁷ and Schmid,⁸ or the cyclization of nitroarenes 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 materials¹³ or metals.¹⁴

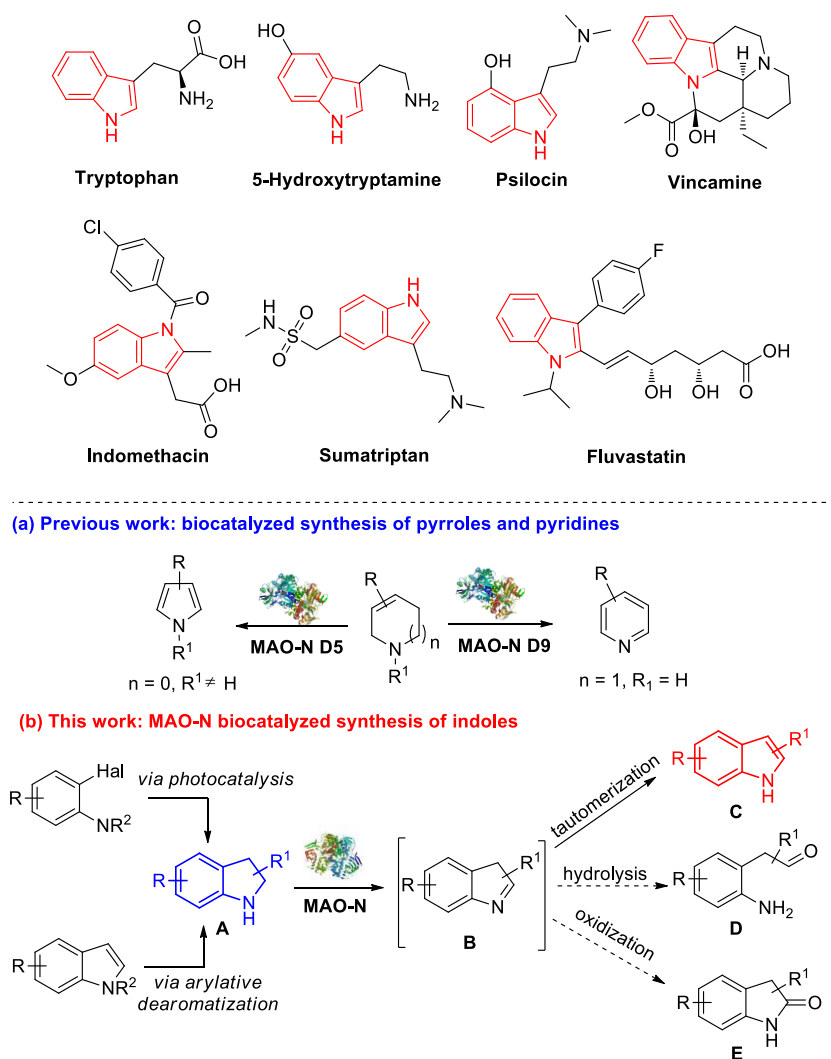


Figure 1. Representative bioactive molecules with the indole motif and previous and current works on biocatalytic synthesis of aromatic nitrogen-containing heterocycles.

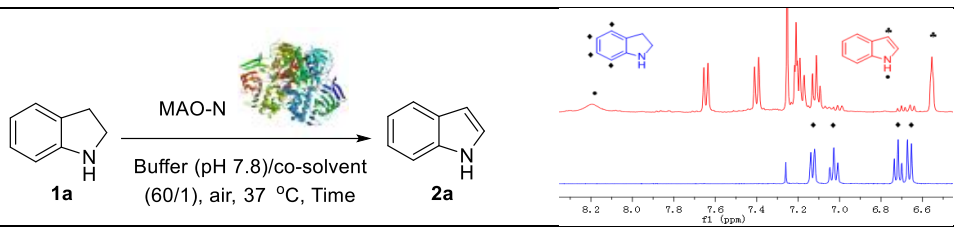
However, if considered in terms of greenness and sustainability, most of these approaches suffer from some disadvantages, such as harsh reaction conditions, the use of rare metals or strong acids/bases, the use of stoichiometric amounts of oxidizing agents or the requirement of prolonged heating, making 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 oxidation 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, H₂O₂ 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 specificity of this biotransformation.

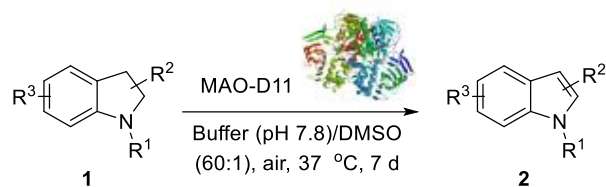
Table 1. Optimization of the reaction conditions of the biocatalytic aromatization of indoline **1a**.


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

^aReaction conditions: **1a** (0.2 mmol), freeze-dried MAO-N whole cells (190 mg), buffer (Na₂HPO₄/NaH₂PO₄, pH = 7.8, 1.0 M) (3.0 mL), co-solvent (50 μ L), air, 37 °C, 1-7 days.

^bConversion was determined by ¹H NMR integration of the crude mixture. ^cIsolated yield. ^d380 mg freeze-dried MAO-N D11 whole cells were used. ^e190 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. ^f190 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. ^gNo 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 (Na₂HPO₄/NaH₂PO₄, pH = 7.8, 1.0 M) (3.0 mL), DMSO (50 μL), air, 37 °C, 7 days. ^aConversion was determined by ¹H NMR integration of the crude mixture. ^bIsolated yields are reported. ^cNot 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 -NO₂ 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

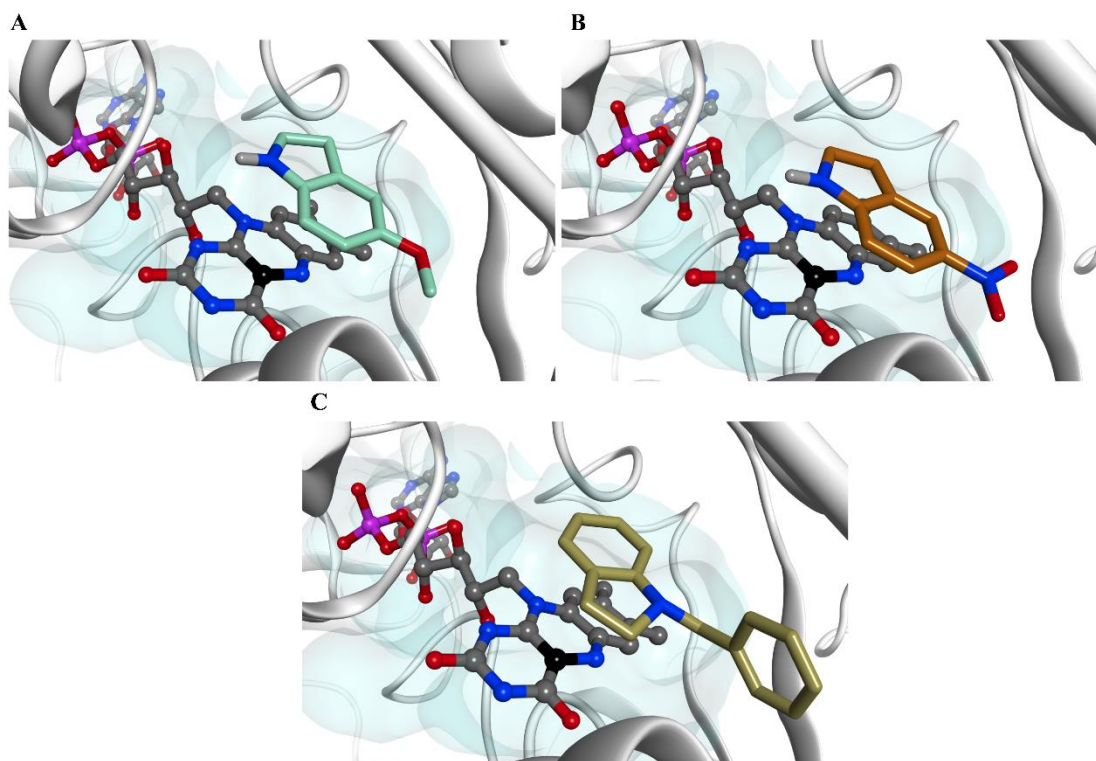


Figure 2. Proposed binding modes for compounds **1i** (A), **1l** (B), **1p** (C) in the MAO-N D11 catalytic site (PDB ID: 3ZDN).¹⁹ The nitrogen atom of **1i** and **1l** is oriented toward the FAD nitrogen and carbon atom (represented as black atom)) involved in the mechanism of reaction,

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 FADH₂, which is in turn re-converted into FAD by O₂. 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 NO₂ substituent in **1l** significantly withdraws the electrons from 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-membered 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.

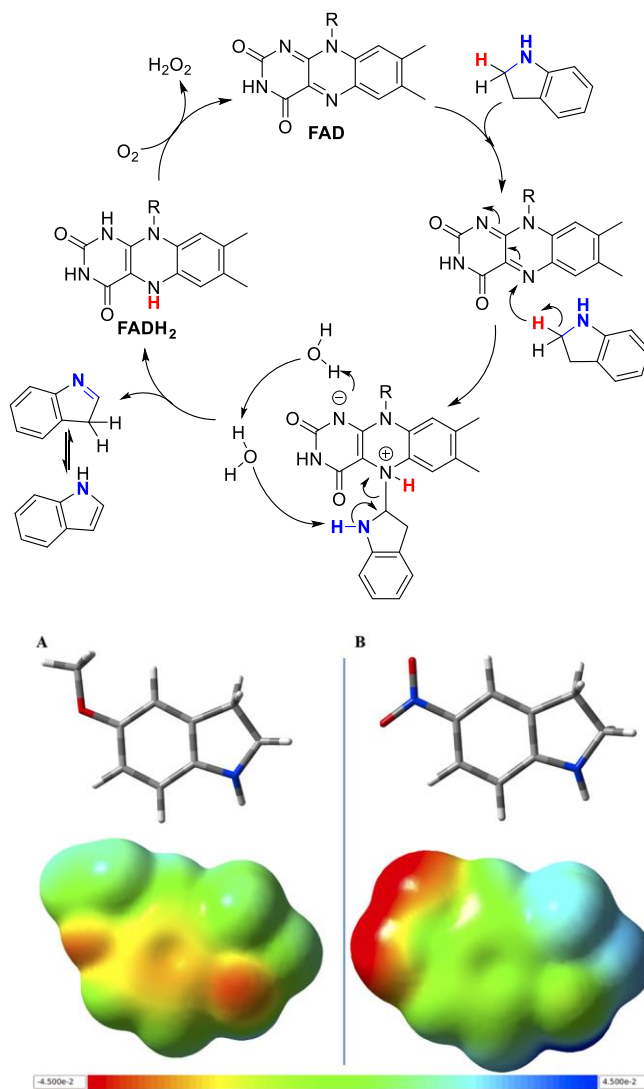


Figure 3. Plausible mechanism of the MAO-N biocatalytic aromatization of indolines (up) and electrostatic potential surface (EPS) for **1i** (A-down) and **1l** (B-down).

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]⁺PF₆⁻ or (Ir[dF(CF₃)ppy]₂(dtbpy))⁺PF₆⁻ (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) enzymatic conversion: MAO-D11 (1.0 U), Buffer (pH 7.8)/DMSO (60:1), air, 37 °C, 7 d.

h; 3) biocatalysis: **1n** or **4** (0.2 mmol), freeze-dried MAO-N D11 whole cells (190 mg), buffer (Na₂HPO₄/NaH₂PO₄, pH = 7.8, 1.0 M) (3.0 mL), DMSO (50 μ L), air, 37 °C, 7 days. ^aConversion was determined by ¹H NMR integration of the crude mixture. ^bIsolated 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-substituted 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]⁺PF₆⁻ for indolines **4b-f** and **1n** or [Ir(dF(CF₃)ppy)₂(dtbpy)]⁺PF₆⁻ 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 enantioselectivity 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**.

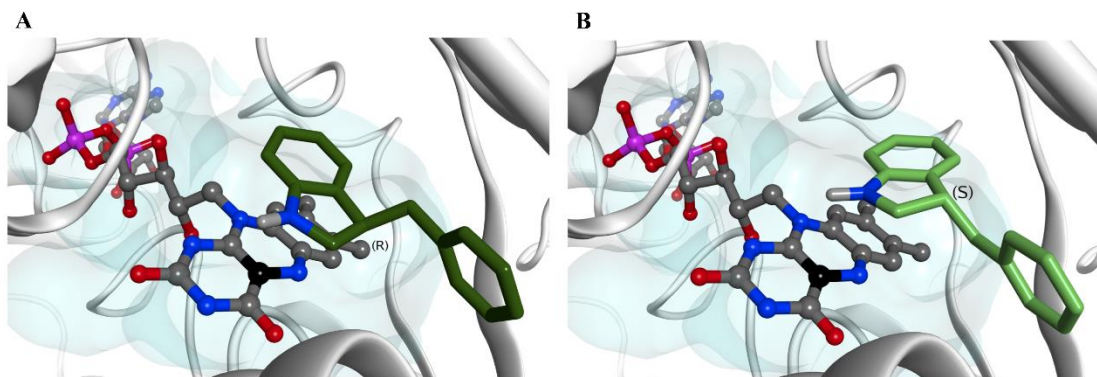


Figure 4. Proposed binding modes for compounds (*R*)-**4b** (A) and (*S*)-**4b** (B) in the MAO-N D11 catalytic site (PDB ID: 3ZDN). Both enantiomers of **4b** are able to orientate the α -methylene group toward the FAD, nearby the nitrogen next to the carbon atom (represented as black atom) as proposed 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-substituted 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- <i>p</i> -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

Reaction conditions: (1) arylation dearomatization: **6a-c** (1.25 mmol), arene (1.87 mmol), AlCl₃ (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 Na₂HPO₄/NaH₂PO₄ (pH = 7.8, 1.0 M, 3.0 mL), DMSO (50 µL), air, 37 °C, 7 days. ^aConversion was determined by ¹H NMR integration of the crude mixture. ^bIsolated 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* arylation 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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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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SYNOPSIS.

