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Asymmetric Synthesis of a Key Dextromethorphan Intermediate and Its Analogues Enabled by a New Cyclohexylamine Oxidase: Enzyme Discovery, Reaction Development, and Mechanistic Insight

Xiaofan Wu, Zedu Huang,* Zexu Wang, Zhining Li, Jiaqi Wang, Juan Lin,* and Fener Chen*

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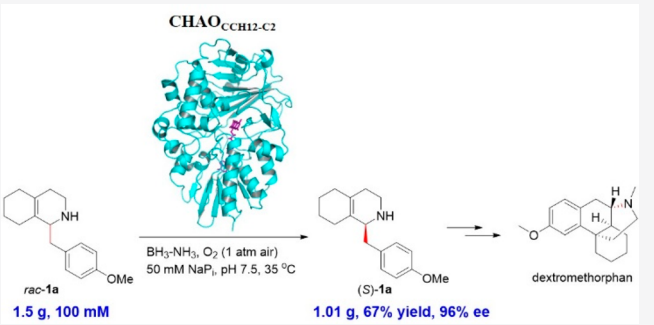
ABSTRACT: (*S*)-1-(4-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline [(*S*)-1-(4-methoxybenzyl)-OHIQ, (*S*)-**1a**] is a key synthetic intermediate in the industrial production of dextromethorphan, one of the most widely used over-the-counter antitussives. We report here that a new cyclohexylamine oxidase discovered by genome mining, named $CHAO_{CCH12\text{-}C2}$, was able to completely deracemize 100 mM **1a** under Turner's deracemization conditions to afford (*S*)-**1a** in 80% isolated yield and 99% ee at a semipreparative scale (0.4 mmol). When this biocatalytic reaction was scaled up to a gram scale (5.8 mmol), without reaction optimization (*S*)-**1a** was still isolated in 67% yield and 96% ee. The relatively higher k_{cat} determined for $CHAO_{CCH12\text{-}C2}$ was rationalized as one major factor rendering this enzyme capable of oxidizing **1a** effectively at elevated substrate concentrations. Protein sequence alignment, analysis of our co-crystal structure of $CHAO_{CCH12\text{-}C2}$ complexed with the product 1-(4-methoxybenzyl)-3,4,5,6,7,8-hexahydroisoquinoline [1-(4-methoxybenzyl)-HHIQ, **2a**], and the structure-guided mutagenesis study together indicated L295 is one of the critical residues for this efficient enzymatic oxidation process and supported the presence of two cavities as well as a catalytically important "aromatic cage" formed by F342, Y433, and FAD. The synthetic applicability of $CHAO_{CCH12\text{-}C2}$ was further underscored by the stereoselective synthesis of various enantioenriched 1-benzyl-OHIQ derivatives of potential pharmaceutical importance at a semipreparative scale.



INTRODUCTION

Dextromethorphan (Scheme 1A) has been one of the most widely used over-the-counter antitussives since its introduction in 1954.[1−5] When used at recommended antitussive doses, dextromethorphan shows no addictive properties or gastrointestinal side effects, making it superior to opioids.[3] The combined use of dextromethorphan and quinidine has also recently been approved by the U.S. Food and Drug Administration and by the European Medicine Agency for the treatment of pseudobulbar affect.[1,6] With regard to synthesis, (*S*)-1-(4-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline [(*S*)-1-(4-methoxybenzyl)-OHIQ, (*S*)-**1a** (Scheme 1B)] is the key synthetic intermediate in the industrial production of dextromethorphan.[7] Optically pure (*S*)-**1a** is obtained through chemical resolution of the corresponding racemic amine using chiral acids, such as mandelic acid.[7,8] Although effective, the intrinsic property of kinetic resolution, namely a maximum theoretical yield of 50%, renders this approach economically and ecologically non-ideal.[9] Chiral iridium and ruthenium complex-catalyzed asymmetric hydrogenation were previously employed for the synthesis of enantioenriched (*S*)-**1a** and its N-formylated derivative, respectively, either producing a product with an inadequate optical purity (86% ee) or involving harsh reaction conditions (hydrogen pressure of 100 atm).[10,11] Given the pharmaceutical importance of dextromethorphan and the limitations present in the current synthetic methods, it is therefore highly desirable to develop an efficient synthesis of optically pure (*S*)-**1a** under mild conditions.

Recently, the Zhu group has reported two elegant biocatalytic syntheses of (*S*)-**1a** at a semipreparative scale (0.5−1 mmol), both with >98% ee, by using the Y321I mutant of the cyclohexylamine oxidase from *Brevibacterium oxidans* IH-35A ($CHAO_{IH\text{-}35A}$) and an imine reductase from *Sciscionella marina*.[9,12] Compared to the chemical approaches mentioned above, these biocatalytic syntheses have their own appealing features, including excellent stereoselectivity, high isolated yield, mild reaction conditions, and environmental friendliness. However, the low substrate concentration reported (10 mM) limits their practical synthesis potential. In this context, herein

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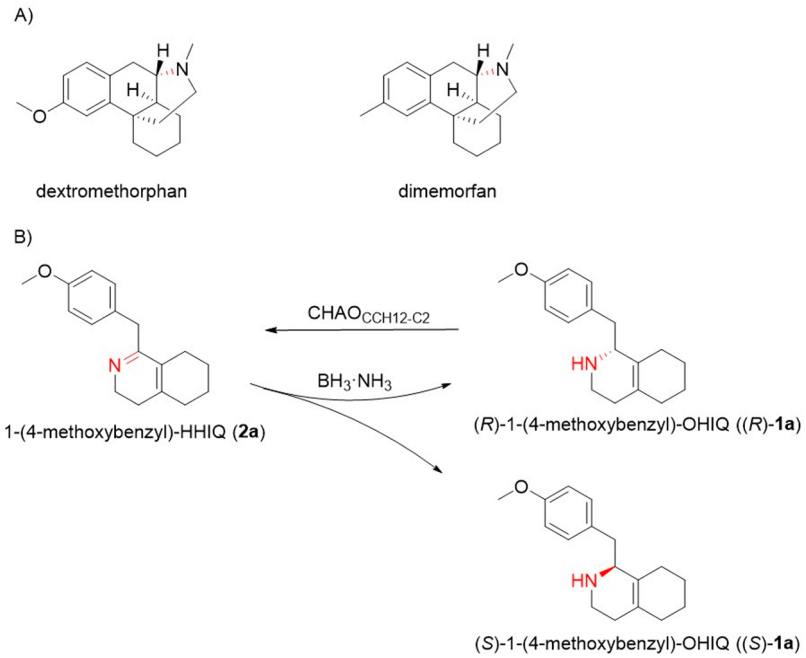
Scheme 1. (A) Structures of Dextromethorphan and Dimemorfan and (B) Chemoenzymatic Deracemization of 1a



we report that a new CHAO from *Erythrobacteraceae bacterium* CCH12-C2 discovered by genome mining, named CHAO$_{CCH12-C2}$, was able to deracemize 100 mM **1a** under Turner's deracemization conditions[13−28] to afford (*S*)-**1a** in 67% isolated yield and 96% ee at a gram scale (Scheme 1B). The determined co-crystal structure of CHAO$_{CCH12-C2}$ complexed with the product 1-(4-methoxybenzyl)- 3,4,5,6,7,8-hexahydroisoquinoline [1-(4-methoxybenzyl)-HHIQ, **2a**] combined with the structure-guided mutagenesis study provided important mechanistic insights. The successful application of CHAO$_{CCH12-C2}$ to the stereoselective synthesis of various enantioenriched 1-benzyl-OHIQ derivatives at a semipreparative scale further demonstrated its promising synthesis potential.

RESULTS AND DISCUSSION

CHAO$_{CCH12-C2}$ Was Able to Deracemize 100 mM 1a. A genome mining approach was employed for discovery of more efficient CHAO. Using the amino acid sequence of CHAO$_{IH-35A}$ as a template,[29,30] a BLAST search was performed, and four candidate enzymes were selected, with the level of sequence identity between them and the template being 50−78% (Table S1). The corresponding codon-optimized genes were synthesized and cloned into the pET-28a vector. All four proteins were successfully expressed in *Escherichia coli* BL21 (DE3) in a soluble form as indicated by SDS−PAGE (Figure S1). The recombinant resting whole cells containing these enzymes were then used for the evaluation of their activity toward **1a** under Turner's deracemization conditions at a substrate concentration of 10 mM (Table 1). CHAO$_{CCH12-C2}$ exhibited the highest activity and selectivity, generating the desired (*S*)-**1a** with >99% ee. On the other hand, a product with 78% ee was detected in the CHAO$_{Y81}$-catalyzed reaction. Finally, *rac*-**1a** was recovered in CHAO$_{135MFCol5.1}$- and CHAO$_{acMicro-1}$-catalyzed reactions, indicating these two enzymes are either inactive or nonselective toward the two enantiomers of **1a**. On the basis of these initial results, CHAO$_{CCH12-C2}$, with a sequence 54% identical to that of CHAO$_{IH-35A}$, was chosen for the remaining study. When this

Table 1. Initial Screening of CHAOs for Deracemization of 1a[a]

entry	enzyme	[substrate] (mM)	ee (%)[b]
1	CHAO$_{CCH12-C2}$	10	>99 (*S*)
2	CHAO$_{Y81}$	10	78 (*S*)
3	CHAO$_{135MFCol5.1}$	10	racemic
4	CHAO$_{acMicro-1}$	10	racemic
5	CHAO$_{CCH12-C2}$	40	99 (*S*)
6	CHAO$_{CCH12-C2}$	60	99 (*S*)
7[c]	CHAO$_{CCH12-C2}$	70	99 (*S*)
8[d]	CHAO$_{CCH12-C2}$	85	99 (*S*)
9[d]	CHAO$_{CCH12-C2}$	100	99 (*S*)
10[d]	CHAO$_{CCH12-C2}$	150	71 (*S*)

[a]Reaction conditions (3 mL): **1a** (variable concentrations), $NH_3{\cdot}BH_3$ (5 equiv relative to **1a**), wet cells of CHAO (0.6 g) in NaP_i buffer (50 mM, pH 7.5). Reaction mixtures were incubated at 35 °C with 200 rpm shaking for 48 h. [b]The ee was determined by chiral HPLC analysis, and the absolute configuration was assigned by comparison to literature data (elution order in chiral HPLC and optical rotation). [c]The reaction time was 72 h. [d]The reaction time was 89 h.

enzyme was challenged with higher concentrations of substrate of ≤100 mM (Table 1, entry 9), the optical purity of the produced (*S*)-**1a** remained excellent (99% ee). Further increasing the substrate concentration to 150 mM resulted in (*S*)-**1a** with diminished optical purity (71% ee) (Table 1, entry 10).

To show the synthesis potential of CHAO$_{CCH12-C2}$, the deracemization of **1a** (100 mM) was first carried out at a semipreparative scale (0.4 mmol) and the reaction progress was monitored by chiral HPLC (Figure 1). At the beginning, the ee of the accumulated (*S*)-**1a** increased from 38% to 78% and then to 94% at 4, 16, and 24 h, respectively. Complete deracemization was accomplished after 40 h as evidenced by the 99% ee of (*S*)-**1a**. The desired product was then isolated in 80% yield and 99% ee. These encouraging results prompted us to scale up this biocatalytic process further to a gram scale. Without further

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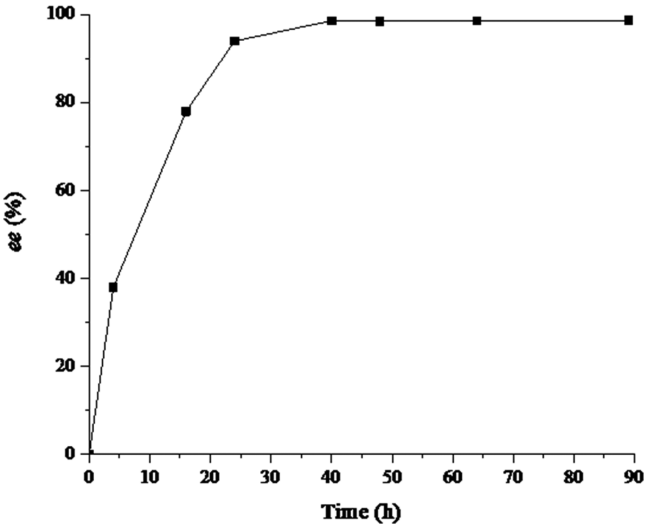

Figure 1. Time-course study of $CHAO_{CCH12-C2}$-catalyzed deracemization of **1a** (100 mM) at a semipreparative scale.

optimization of reaction conditions, 1.5 g of **1a** (5.8 mmol) was almost completely deracemized, and 1.01 g of (*S*)-**1a** was isolated (67% yield) along with 96% ee, demonstrating the practical synthesis potential of $CHAO_{CCH12-C2}$. We believe the yield and enantiomeric purity of the product could be improved by optimization of the reaction and/or protein engineering in the future.[17,18,28,31]

$CHAO_{CCH12-C2}$ with an N-terminal His_6 tag was then purified by immobilized metal affinity chromatography (IMAC) to near homogeneity (>90% purity) according to SDS−PAGE analysis (Figure S2). The optimal reaction pH and temperature of this enzyme were revealed to be 7.5 and 45 °C, respectively (Figures S5 and S6). After characterization of the enzyme property, the specific activity of $CHAO_{CCH12-C2}$ toward 19 primary amines was determined (Tables S2 and S3). Four-membered to eight-membered cycloalkyl amines were all smoothly oxidized by $CHAO_{CCH12-C2}$, with specific activities ranging from 0.40 to 6.64 units/mg. $CHAO_{CCH12-C2}$ exhibited a 10-fold difference in specific activity toward 1-methylhexylamine (**S7**, 0.54 unit/mg) and 1-hexylamine (**S8**, 0.04 unit/mg), suggesting this enzyme favors branched amine over linear amine. (*S*)-1-Phenylethylamine [(*S*)-**S9**] was oxidized 120 times faster than (*R*)-**S9**, highlighting again the excellent stereoselectivity of $CHAO_{CCH12-C2}$. Except for analogues with a fluorine substituent (**S10** and **S11**), all of the other 1-phenylethylamine derivatives tested displayed activity much lower than that of (*S*)-**S9**. The specific activity of the four newly discovered CHAOs toward **1a** was determined, as well (Table S4). Consistent with the results of the whole-cell biotransformations, $CHAO_{CCH12-C2}$ exhibited the highest activity (0.26 unit/mg), followed by $CHAO_{Y81}$ (0.021 unit/mg). Negligible activity was detected for $CHAO_{135MFCol5.1}$ and $CHAO_{acMicro-1}$. Finally, the kinetic parameters of $CHAO_{CCH12-C2}$ toward **1a** were determined at both 45 °C (optimal temperature) and 35 °C (temperature for whole-cell biotransformations) (Table 2). The turnover number (k_{cat}) determined at 35 °C was 2.40 min^{-1}, which is 7-fold greater than that for Y321I of $CHAO_{IH-35A}$, the mutant enzyme used for the deracemization of **1a** reported by the Zhu group.[12] In our opinion, the relatively higher k_{cat} of $CHAO_{CCH12-C2}$ is probably one major factor rendering this enzyme capable of oxidizing **1a** effectively at elevated substrate concentrations.

Table 2. Kinetic Parameters of CHAOs toward 1a

enzyme	k_{cat} (min^{-1})	K_m (mM)	k_{cat}/K_m (min^{-1} M^{-1})
$CHAO_{CCH12-C2}$[a]	8.10 ± 0.18	2.20 ± 0.12	3681
$CHAO_{CCH12-C2}$[b]	2.40 ± 0.06	1.41 ± 0.12	1702
Y321I mutant of $CHAO_{IH-35A}$[c]	0.35 ± 0.01	0.89 ± 0.09	390

[a]Determined at 45 °C. [b]Determined at 35 °C. [c]Data reported in ref 12.

Mechanistic Insight Provided by Protein Crystallization of $CHAO_{CCH12-C2}$ and Structure-Guided Mutagenesis. To shed light on the origin of this efficient and selective bio-oxidation reaction, we crystallized $CHAO_{CCH12-C2}$ with and without the product 1-(4-methoxybenzyl)-HHIQ (**2a**). Both the binary ($CHAO_{CCH12-C2}$-FAD) and the ternary ($CHAO_{CCH12-C2}$-FAD-**2a**) structures were determined by molecular replacement using the protein structure of $CHAO_{IH-35A}$ [Protein Data Bank (PDB) entry 4I59] as the model (Table S5)[32] and refined to resolutions of 1.88 and 1.80 Å, respectively (Figures S7 and S8). $CHAO_{CCH12-C2}$ crystallized in space group $P4_32_12$. The degree of overall structural similarity between $CHAO_{CCH12-C2}$ and $CHAO_{IH-35A}$ is high, with a RMSD of 0.72 Å for the coordinates of the α-carbon atoms (Figure S9). Previous studies of $CHAO_{IH-35A}$ suggested the presence of two cavities: a substrate binding cavity constituted by residues F88, Y215, Y321, F368, and Y459 ($CHAO_{IH-35A}$ numbering) and an intermediate cavity.[32] Amino acid residues T198, L199, M226, and F351 ($CHAO_{IH-35A}$ numbering) were proposed as gating residues separating these two cavities.[32,33] Interestingly, our ternary structure contains two **2a** molecules, with one buried deep inside and the other located close to the surface (Figure S8), therefore strongly supporting the experimentally proposed presence of two cavities. According to the sequence alignment (Figure 2), seven of the nine residues mentioned above were found to be highly conserved in $CHAO_{CCH12-C2}$, meaning either the same amino acid or amino acids with very similar chemical properties are present. The exceptions are I173 and L295 in $CHAO_{CCH12-C2}$, corresponding to residues T198 and Y321 in $CHAO_{IH-35A}$. As one can see in the substrate binding pocket of $CHAO_{CCH12-C2}$ (Figure 3), except F190 (corresponding to residue Y215 in $CHAO_{IH-35A}$), all of the other eight residues (W63, I173, L174, I201, L295, W325, F342, and Y433) are within 5 Å of the bound **2a** (the one buried in the substrate binding cavity). To probe the catalytic importance of these eight residues as well as seven additional residues close to **2a** (within 5 Å), we performed a site-specific mutagenesis study.

Upon mutation to Ala, six mutants (W63A, L174A, Q208A, W325A, F342A, and Y433A) displayed <7% specific activity toward **1a** compared to that of wild-type $CHAO_{CCH12-C2}$ (Table 3), indicating these residues likely are crucial for catalysis and might not be suitable for further mutagenesis. In contrast, the remaining mutants all retained >20% specific activity, and their kinetic data were determined (Table 3). Although the turnover number (k_{cat}) and the catalytic efficiency (k_{cat}/K_m) of P396A are 2- and 11-fold greater than those of the wild-type enzyme, respectively, the rapid loss of activity precluded its practical application. On the other hand, we were pleased to find that mutants I173A, G202A, and L295A exhibited k_{cat} and stability values comparable to those of the wild-type enzyme, suggesting these amino acid residues could be employed for future mutagenesis studies that will aim to discover more active enzyme variants. It is also worth noting that I173 and L295 are

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Figure 2. Sequence alignment of $CHAO_{CCH12-C2}$ and $CHAO_{IH-35A}$. Five residues proposed to constitute the substrate binding cavity and four gating residues are denoted by triangles.

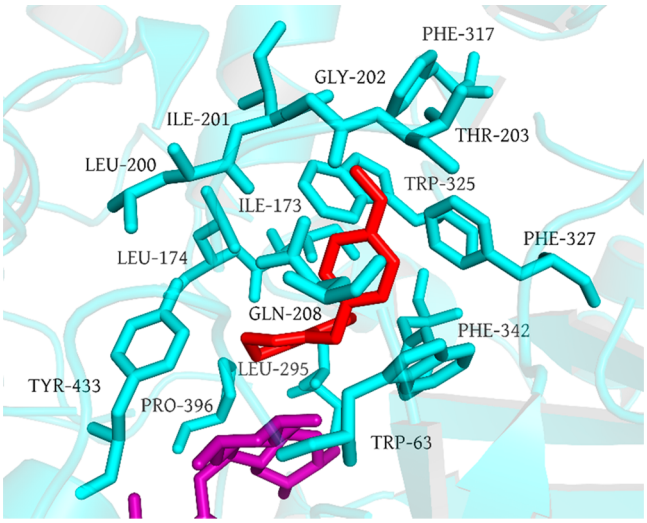

Figure 3. Substrate binding pocket of $CHAO_{CCH12-C2}$. The ternary structure is shown as a cyan cartoon. Residues located within 5 Å of the bound **2a** are shown as cyan sticks, while FAD and **2a** are shown as purple and red sticks, respectively.

the two less conserved amino acid residues mentioned above. In particular, we were interested in the results of mutagenesis of residue L295, the corresponding residue of which in $CHAO_{IH-35A}$ is Y321. Y321 and F368, Y459 ($CHAO_{IH-35A}$ numbering), and FAD were proposed to form an "aromatic cage" that is important for catalysis.[32] Intriguingly, the mutation of Y321 to Ile generated the mutant enzyme Y321I showing much more improved catalytic efficiency toward **1a** relative to that of wild-type $CHAO_{IH-35A}$.[12] On the basis of the results for L295 of $CHAO_{CCH12-C2}$ and Y321 of $CHAO_{IH-35A}$, we speculated that an amino acid residue with an aliphatic side chain at this position, rather than those with an aromatic side chain, is beneficial for oxidizing **1a**. To test this hypothesis, we constructed mutants L295I and L295Y of $CHAO_{CCH12-C2}$ and determined their specific activity and kinetic parameters toward **1a**. The L295I mutant retained ~60% activity relative to that of the wild-type enzyme as judged by both the specific activity and the turnover number (k_{cat}). In stark contrast, the specific activity of the L295Y mutant was only ~2% of that of the wild-type enzyme. Hence, these mutagenesis results supported our hypothesis. Collectively, we propose that residues F342 and Y433, as well as FAD, form an "aromatic cage" in $CHAO_{CCH12-C2}$ (Figure 4). An "aromatic cage" consisting of two rather than

Table 3. Specific Activities and Kinetic Parameters of Wild-Type $CHAO_{CCH12-C2}$ and Its Mutant Enzymes toward 1a[a]

enzyme	specific activity (unit/mg)	k_{cat} (min^{-1})	K_m (mM)	k_{cat}/K_m (min^{-1} M^{-1})
wild-type	0.260 ± 0.014	8.10 ± 0.18	2.20 ± 0.12	3681
W63A	0.002 ± 0.000		nd[b]	
I173A	0.194 ± 0.005	6.66 ± 0.12	2.71 ± 0.20	2457
L174A	0.007 ± 0.001		nd[b]	
L200A	0.116 ± 0.001	3.36 ± 0.06	0.61 ± 0.04	5508
I201A	0.053 ± 0.002	1.62 ± 0.06	1.84 ± 0.14	880
G202A	0.177 ± 0.003	5.82 ± 0.24	0.53 ± 0.08	10981
T203A	0.089 ± 0.003	2.88 ± 0.06	1.24 ± 0.12	2322
Q208A	0.011 ± 0.001		nd[b]	
L295A	0.152 ± 0.002	7.20 ± 0.30	6.54 ± 0.55	1100
F317A	0.074 ± 0.002	2.34 ± 0.06	2.13 ± 0.17	1098
W325A	0.016 ± 0.003		nd[b]	
F327A	0.090 ± 0.002	3.42 ± 0.18	0.52 ± 0.12	6576
F342A	0.015 ± 0.001		nd[b]	
P396A	0.461 ± 0.011	15.60 ± 0.60	0.36 ± 0.05	43333
Y433A	0.009 ± 0.001		nd[b]	
L295I	0.166 ± 0.006	5.04 ± 0.18	1.88 ± 0.22	2681
L295Y	0.006 ± 0.000		nd[b]	

[a]Determined at 45 °C. [b]Not determined.

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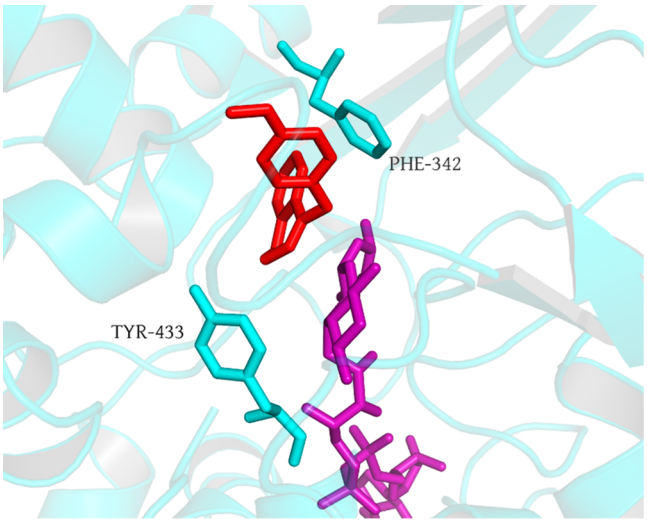
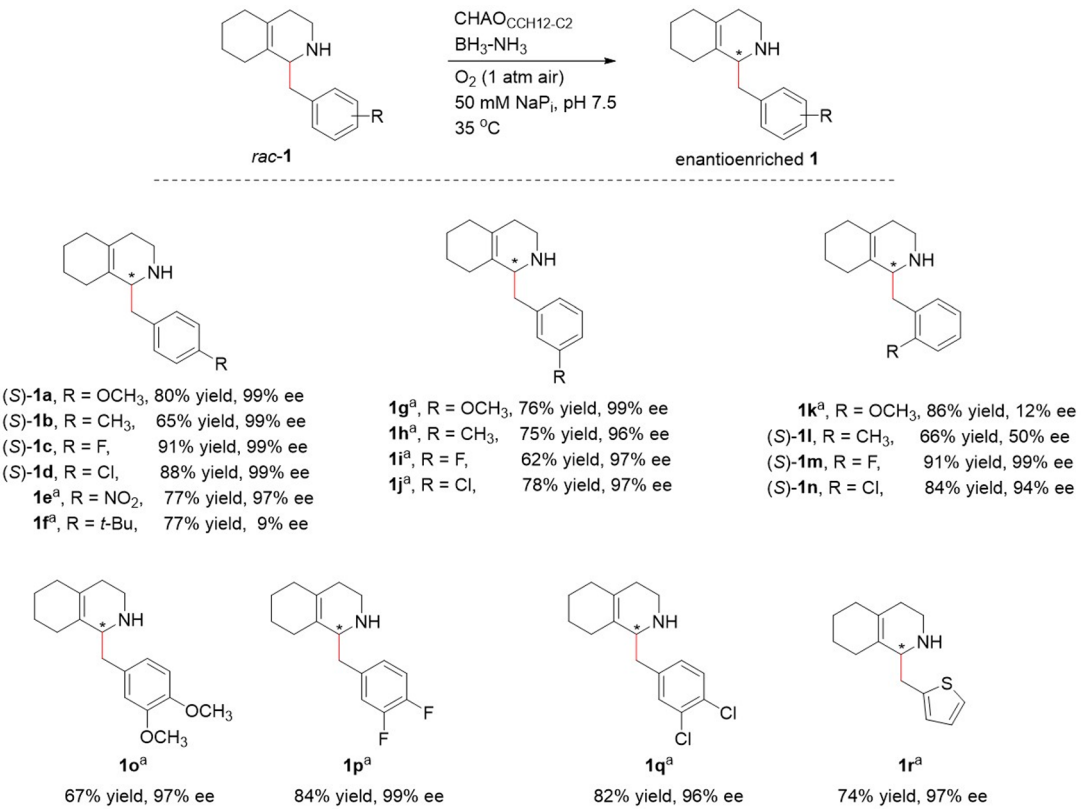


Figure 4. Proposed "aromatic cage" of $CHAO_{CCH12-C2}$. The ternary structure is shown as a cyan cartoon. Residues F342 and Y433 are shown as cyan sticks, while FAD and the bound product **2a** are shown as purple and red sticks, respectively.

three aromatic amino acid residues was previously reported for human monoamine oxidase B (MAO-B) and monoamine oxidase from *Aspergillus niger* (MAO-N).[34−37]

Application of $CHAO_{CCH12-C2}$ to the Stereoselective Synthesis of Various Enantioenriched 1-Benzyl-OHIQ Derivatives of Pharmaceutical Potential at a Semi-preparative Scale. To further demonstrate the synthesis potential of $CHAO_{CCH12-C2}$, we applied this enzyme to the stereoselective preparation of a library of 1-benzyl-OHIQ derivatives at a semipreparative scale (0.4 mmol) (Scheme 2). Except for **1f** with a 4-*tert*-butyl group, all substrates containing a substituent at position 4 or 3 were smoothly deracemized to deliver the desired products in 62−91% isolated yields and 96−99% ee. The steric bulkiness of the *tert*-butyl group might prevent the proper binding of **1f** to the enzyme. On the contrary, the electronic effect appeared to play an important role in the reactivity of 2-substituted substrates (**1k**−**1n**). For those bearing an electron-donating group (**1k** and **1l**), the deracemization reactions were rather inefficient, resulting in products with only 12% and 50% ee, respectively. In contrast, amines with a fluorine group (**1m**) and a chlorine group (**1n**) were both readily deracemized to yield the desired products with 99% and 94% ee, respectively. Finally, enantioenriched 1-(3,4-bis-substituted benzyl)-OHIQ derivatives (**1o**−**1q**) and 1-(thiophen-2-ylmethyl)-OHIQ (**1r**) could also be efficiently accessed by using this biocatalytic protocol with 67−84% isolated yields and 96−99% ee. It is worth mentioning that, to the best of our knowledge, most thus synthesized enantioenriched 1-benzyl-OHIQ derivatives have never been reported before.[9] Furthermore, these chiral amines in principle can be transformed to the corresponding dextromethorphan analogues of potential pharmaceutical importance,[3,38−42] such as dimemorfan (Scheme 1A), an effective antitussive with safety properties even more promising than those of dextromethorphan.[3,38]

Scheme 2. $CHAO_{CCH12-C2}$-Catalyzed Stereoselective Synthesis of Enantioenriched 1-Benzyl-OHIQ Derivatives at a Semipreparative Scale[a]



[a]The absolute configuration was not assigned.

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CONCLUSIONS

In summary, $CHAO_{CCH12-C2}$, a new cyclohexylamine oxidase discovered by genome mining, was capable of deracemizing 100 mM **1a** under Turner's deracemization conditions to furnish (*S*)-**1a**, the key synthetic intermediate to dextromethorphan, in 80% isolated yield and 99% ee at a semipreparative scale (0.4 mmol). When this biocatalytic reaction was scaled up to a gram scale (5.8 mmol), without reaction optimization (*S*)-**1a** was still isolated in 67% yield and 96% ee. The relatively higher k_{cat} determined of $CHAO_{CCH12-C2}$ was rationalized as one major factor rendering this enzyme capable of oxidizing **1a** effectively at elevated substrate concentrations. Through protein sequence alignment, analysis of the co-crystal structure of $CHAO_{CCH12-C2}$ complexed with 1-(4-methoxybenzyl)-HHIQ (**2a**), and the structure-guided mutagenesis study, L295 was suggested to be one of the critical residues for this efficient enzymatic oxidation process, while the presence of two cavities was experimentally supported, and residues F342 and Y433, together with FAD, were proposed to form the catalytically important "aromatic cage". The synthetic applicability of $CHAO_{CCH12-C2}$ was further showcased by the highly stereoselective synthesis of a number of enantioenriched 1-benzyl-OHIQ derivatives of pharmaceutical potential at a semipreparative scale.

EXPERIMENTAL SECTION

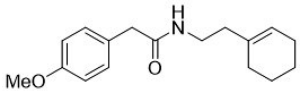
General Methods. Unless otherwise specified, all reagents and solvent were purchased from commercial sources and used as received. ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) as the internal standard. Coupling constants (*J*) are given in hertz. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co., Ltd. Optical rotations were measured by a Rudolph AUTOPOL I automatic polarimeter. HRMS data were recorded on a Bruker micrOTOF spectrometer. HPLC analysis were performed with a Daicel Chiralpak OJ-H column (25 cm × 4.6 mm × 5 μm), a Chiralpak IC column (25 cm × 4.6 mm × 5 μm), or a Chiralpak AD-H column (25 cm × 4.6 mm × 5 μm).

General Procedures for the Synthesis of Substrates *rac*-1 (see Scheme S1). To a stirred solution of amine **S20** (20 mmol, 1 equiv), acid **S21** (1.2 equiv), and DMAP (0.12 equiv) in DCM was added dropwise a solution of DCC (2 equiv) in DCM under a N_2 atmosphere. The resulting mixture was stirred at room temperature overnight. The precipitate was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography to afford amide **S22**.

To a heated solution of amide **S22** (10 mmol, 1 equiv) in toluene (5 mL) at 85 °C was added $POCl_3$ (0.5 equiv). The resulting mixture was stirred at the same temperature for 1 h and then heated at 95 °C for 2 h and finally at 105 °C for 1 h. After the mixture had cooled to room temperature, concentrated H_2SO_4 (2 equiv) was added slowly to the mixture described above. Removal of toluene *in vacuo* afforded the hydrosulfate of 3,4,5,6,7,8-hexahydroisoquinoline (**S23**), which was used directly in the next step without further purification.

To an ice-cold solution of **S23** (2 mmol) in MeOH was added $NaBH_4$ (2 equiv) in portions. After the mixture had been stirred at room temperature for 4 h, the pH of the reaction mixture was first adjusted to ∼5 by the addition of HCl (1 N). The mixture was then concentrated *in vacuo*, and the residue was dissolved in water. The pH of the resulting mixture was then adjusted to ∼9 by the addition of NaOH (3 M). The mixture was extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC to afford products *rac*-**1**.

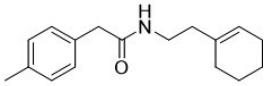
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(4-methoxyphenyl)-acetamide.**



S22a

S22a (3.82 g, 70% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 7.83 (t, *J* = 5.6 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 5.33 (s, 1H), 3.72 (s, 3H), 3.30 (s, 2H), 3.11 (q, *J* = 6.8 Hz, 2H), 2.01 (t, *J* = 7.4 Hz, 2H), 1.89 (d, *J* = 17.5 Hz, 4H), 1.50 (dd, *J* = 22.7, 6.1 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 170.6, 158.3, 135.3, 130.4, 128.9, 122.4, 114.0, 55.4, 42.1, 37.9, 37.6, 28.1, 25.2, 22.9, 22.4; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{23}NO_2Na$ 296.1621, found 296.1625.

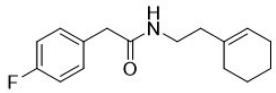
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(*p*-tolyl)acetamide.**



S22b

S22b (4.21 g, 82% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 7.85 (t, *J* = 5.6 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 5.34 (s, 1H), 3.33 (s, 2H), 3.13 (q, *J* = 6.8 Hz, 2H), 2.27 (s, 3H), 2.02 (t, *J* = 7.4 Hz, 2H), 1.82−1.98 (m, 4H), 1.50 (dd, *J* = 22.6, 6.1 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 170.4, 135.7, 135.3, 133.9, 129.3, 129.1, 122.4, 42.6, 37.9, 37.6, 28.1, 25.2, 22.9, 22.4, 21.1; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{23}NONa$ 280.1672, found 280.1677.

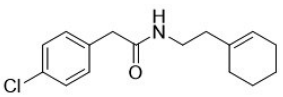
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(4-fluorophenyl)-acetamide.**



S22c

S22c (4.96 g, 95% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 7.93 (t, *J* = 5.8 Hz, 1H), 7.23−7.33 (m, 2H), 7.10 (t, *J* = 8.7 Hz, 2H), 5.33 (s, 1H), 3.38 (s, 2H), 3.13 (q, *J* = 6.8 Hz, 2H), 2.02 (t, *J* = 7.3 Hz, 2H), 1.81−1.94 (m, 4H), 1.49 (dd, *J* = 23.5, 6.2 Hz, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 170.2, 161.4 (d, *J* = 241.9 Hz), 135.2, 133.2 (d, *J* = 3.1 Hz), 131.2 (d, *J* = 8.0 Hz), 122.4, 115.2 (d, *J* = 21.1 Hz), 42.0, 37.9, 37.6, 28.0, 25.2, 22.9, 22.4; HRMS (ESI) *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{20}NOFNa$ 284.1421, found 284.1424.

2-(4-Chlorophenyl)-*N*-[2-(cyclohex-1-en-1-yl)ethyl]-acetamide.



S22d

S22d (5.35 g, 98% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 7.95 (t, *J* = 5.7

https://dx.doi.org/10.1021/acs.joc.0c00469
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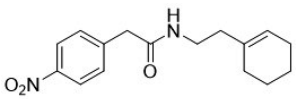
Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 5.32 (s, 1H), 3.38 (s, 2H), 3.12 (q, J = 6.7 Hz, 2H), 2.01 (t, J = 7.4 Hz, 2H), 1.80−1.95 (m, 4H), 1.40−1.59 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 169.9, 136.0, 135.2, 131.5, 131.2, 128.5, 122.4, 42.2, 37.9, 37.6, 28.0, 25.2, 22.9, 22.4; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{20}NONaCl$ 300.1126, found 300.1128.

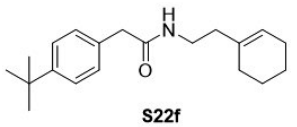
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(4-nitrophenyl)-acetamide.**



S22e

S22e (3.80 g, 66% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 8.15 (d, J = 8.5 Hz, 2H), 8.04 (t, J = 5.9 Hz, 1H), 7.50 (d, J = 8.3 Hz, 2H), 5.30 (s, 1H), 3.53 (s, 2H), 3.11 (q, J = 6.8 Hz, 2H), 2.00 (t, J = 7.3 Hz, 2H), 1.79−1.91 (m, 4H), 1.38−1.54 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 169.2, 146.7, 145.1, 135.2, 130.7, 123.7, 122.5, 42.6, 37.9, 37.6, 28.0, 25.1, 22.9, 22.4.

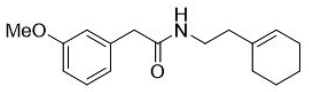
2-[4-(*tert*-Butyl)phenyl]-*N*-[2-(cyclohex-1-en-1-yl)ethyl]-acetamide.



S22f

S22f (3.89 g, 65% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 7.86 (t, J = 5.7 Hz, 1H), 7.30 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 5.33 (s, 1H), 3.34 (s, 2H), 3.13 (q, J = 7.2 Hz, 2H), 2.03 (t, J = 7.3 Hz, 2H), 1.83−1.93 (m, 4H), 1.42−1.58 (m, 4H), 1.27 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 170.4, 148.9, 135.2, 134.0, 129.1, 125.3, 122.4, 42.6, 37.9, 37.5, 34.5, 31.6, 28.0, 25.2, 22.9, 22.4; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{20}H_{29}NONa$ 322.2141, found 322.2131.

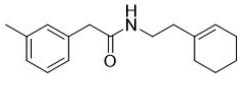
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(3-methoxyphenyl)-acetamide.**



S22g

S22g (4.15 g, 76% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 7.84 (t, J = 5.7 Hz, 1H), 7.18 (t, J = 7.8 Hz, 1H), 6.72−6.85 (m, 3H), 5.31 (s, 1H), 3.71 (s, 3H), 3.33 (s, 2H), 3.10 (q, J = 6.8 Hz, 2H), 2.00 (t, J = 7.3 Hz, 2H), 1.79−1.94 (m, 4H), 1.38−1.58 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 170.1, 159.6, 138.4, 135.2, 129.6, 122.4, 121.7, 115.2, 112.1, 55.4, 43.1, 37.9, 37.6, 28.1, 25.1, 22.9, 22.4; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{23}NO_2Na$ 296.1621, found 296.1619.

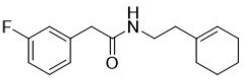
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(*m*-tolyl)acetamide.**



S22h

S22h (4.78 g, 93% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 7.87 (t, J = 5.7 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 6.99−7.11 (m, 3H), 5.35 (s, 1H), 3.34 (s, 2H), 3.13 (q, J = 6.9 Hz, 2H), 2.28 (s, 3H), 2.02 (t, J = 7.3 Hz, 2H), 1.83−1.95 (m, 4H), 1.44−1.59 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 170.3, 137.6, 136.9, 135.3, 130.1, 128.5, 127.3, 126.5, 122.4, 43.0, 37.9, 37.6, 28.1, 25.2, 22.9, 22.4, 21.4; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{23}NONa$ 280.1672, found 280.1666.

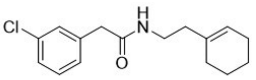
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(3-fluorophenyl)-acetamide.**



S22i

S22i (4.59 g, 88% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 7.96 (t, J = 5.8 Hz, 1H), 7.33 (q, J = 7.4 Hz, 1H), 6.99−7.12 (m, 3H), 5.34 (s, 1H), 3.42 (s, 2H), 3.14 (q, J = 6.7 Hz, 2H), 2.03 (t, J = 7.2 Hz, 2H), 1.79−1.96 (m, 4H), 1.38−1.62 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 169.7, 162.5 (d, J = 242.8 Hz), 139.8 (d, J = 7.8 Hz), 135.2, 130.4 (d, J = 8.3 Hz), 125.6 (d, J = 2.6 Hz), 122.5, 116.1 (d, J = 21.3 Hz), 113.5 (d, J = 20.9 Hz), 42.5 (d, J = 1.9 Hz), 37.9, 37.5, 28.0, 25.1, 22.9, 22.4; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{20}NOFNa$ 284.1421, found 284.1416.

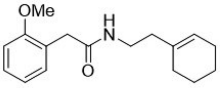
2-(3-Chlorophenyl)-*N*-[2-(cyclohex-1-en-1-yl)ethyl]-acetamide.



S22j

S22j (3.60 g, 65% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 7.97 (t, J = 5.7 Hz, 1H), 7.25−7.37 (m, 3H), 7.21 (d, J = 7.2 Hz, 1H), 5.33 (s, 1H), 3.40 (s, 2H), 3.13 (q, J = 6.7 Hz, 2H), 2.02 (t, J = 7.3 Hz, 2H), 1.82−1.95 (m, 4H), 1.40−1.61 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 169.7, 139.5, 135.2, 133.2, 130.4, 129.2, 128.2, 126.7, 122.5, 42.4, 37.9, 37.5, 28.0, 25.1, 22.9, 22.4; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{16}H_{20}NONaCl$ 300.1126, found 300.1113.

***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(2-methoxyphenyl)-acetamide.**



S22k

S22k (2.89 g, 53% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^1H NMR (400 MHz, DMSO-d_6) δ 7.61 (t, J = 5.7 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.16 (d, J = 7.4 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.88 (t, J = 7.4 Hz, 1H), 5.36 (s, 1H), 3.76 (s, 3H), 3.37 (s, 2H), 3.14 (q, J = 6.8 Hz, 2H), 2.03 (t, J = 7.4 Hz, 2H), 1.84−1.97 (m, 4H), 1.43−1.60 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 170.2, 157.6, 135.4, 130.9, 128.3, 125.0, 122.4, 120.5, 111.1, 55.8, 38.0, 37.6, 37.2, 28.1, 25.2, 22.9, 22.4; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{23}NO_2Na$ 296.1621, found 296.1619.

https://dx.doi.org/10.1021/acs.joc.0c00469
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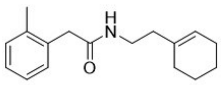
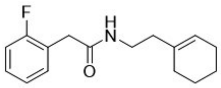
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(*o*-tolyl)acetamide.**



S22l

S22l (4.88 g, 95% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (t, J = 5.6 Hz, 1H), 7.00−7.23 (m, 4H), 5.35 (s, 1H), 3.42 (s, 2H), 3.15 (q, J = 6.7 Hz, 2H), 2.26 (s, 3H), 2.04 (t, J = 7.3 Hz, 2H), 1.83−1.99 (m, 4H), 1.40−1.60 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.1, 137.0, 135.5, 135.3, 130.4, 130.2, 126.9, 126.1, 122.5, 40.7, 38.0, 37.5, 28.0, 25.2, 22.9, 22.4, 19.8; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{17}H_{23}NONa$ 280.1672, found 280.1673.

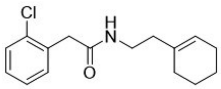
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(2-fluorophenyl)-acetamide.**



S22m

S22m (4.91 g, 94% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (t, J = 5.6 Hz, 1H), 7.05−7.39 (m, 4H), 5.37 (s, 1H), 3.45 (s, 2H), 3.15 (q, J = 6.8 Hz, 2H), 2.04 (t, J = 7.4 Hz, 2H), 1.81−1.98 (m, 4H), 1.41−1.62 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 169.2, 161.0 (d, J = 244.1 Hz), 135.3, 132.1 (d, J = 4.6 Hz), 128.9 (d, J = 8.0 Hz), 124.5 (d, J = 3.5 Hz), 123.9 (d, J = 16.0 Hz), 122.4, 115.4 (d, J = 21.8 Hz), 37.9, 37.7, 35.8 (d, J = 2.2 Hz), 28.1, 25.2, 22.9, 22.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{16}H_{20}NOFNa$ 284.1421, found 284.1420.

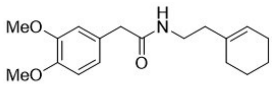
2-(2-Chlorophenyl)-*N*-[2-(cyclohex-1-en-1-yl)ethyl]-acetamide.



S22n

S22n (1.72 g, 31% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.09−7.56 (m, 4H), 5.38 (s, 1H), 3.55 (s, 2H), 3.15 (d, J = 8.2 Hz, 2H), 1.99−2.16 (m, 2H), 1.82−2.00 (m, 4H), 1.52 (d, J = 22.1 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 169.0, 135.3, 134.8, 134.0, 132.3, 129.4, 128.8, 127.4, 122.4, 40.4, 37.9, 37.7, 28.1, 25.2, 22.9, 22.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{16}H_{20}NONaCl$ 300.1126, found 300.1125.

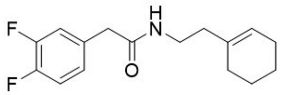
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(3,4-dimethoxyphenyl)-acetamide.**



S22o

S22o (1.94 g, 32% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (t, J = 5.8 Hz, 1H), 6.83−6.92 (m, 2H), 6.76 (dd, J = 8.3, 2.0 Hz, 1H), 5.33 (s, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 3.30 (s, 2H), 3.11 (q, J = 7.0 Hz, 2H), 2.01 (t, J = 7.3 Hz, 2H), 1.81−1.94 (m, 4H), 1.41−1.57 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 170.6, 148.9, 147.9, 135.3, 129.4, 122.4, 121.4, 113.4, 112.2, 56.0, 55.9, 42.6, 37.9, 37.6, 28.1, 25.1, 22.9, 22.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{25}NO_3Na$ 326.1727, found 326.1718.

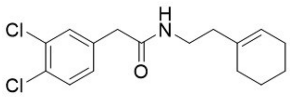
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(3,4-difluorophenyl)-acetamide.**



S22p

S22p (2.62 g, 47% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (t, J = 5.7 Hz, 1H), 7.24−7.42 (m, 2H), 7.00−7.13 (m, 1H), 5.12−5.40 (m, 1H), 3.39 (s, 2H), 3.13 (q, J = 6.7 Hz, 2H), 2.01 (t, J = 7.3 Hz, 2H), 1.82−1.94 (m, 4H), 1.34−1.62 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 169.7, 149.5 (dd, J = 244.7, 12.7 Hz), 148.7 (dd, J = 243.6, 12.5 Hz), 135.2, 134.7 (dd, J = 6.2, 3.7 Hz), 126.2 (dd, J = 6.3, 3.3 Hz), 122.5, 118.3 (d, J = 17.0 Hz), 117.5 (d, J = 16.8 Hz), 41.8, 37.9, 37.5, 28.0, 25.1, 22.9, 22.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{16}H_{19}NOF_2Na$ 302.1327, found 302.1330.

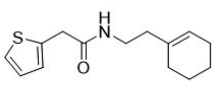
***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(3,4-dichlorophenyl)-acetamide.**



S22q

S22q (3.36 g, 54% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (t, J = 5.7 Hz, 1H), 7.45−7.59 (m, 2H), 7.23 (dd, J = 8.3, 2.0 Hz, 1H), 5.31 (d, J = 3.2 Hz, 1H), 3.41 (s, 2H), 3.13 (q, J = 6.7 Hz, 2H), 2.01 (t, J = 7.2 Hz, 2H), 1.78−1.92 (m, 4H), 1.39−1.58 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 169.4, 138.1, 135.1, 131.4, 131.1, 130.6, 129.9, 129.5, 122.5, 41.7, 37.9, 37.5, 28.0, 25.1, 22.9, 22.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{16}H_{19}NONaCl_2$ 334.0736, found 334.0738.

***N*-[2-(Cyclohex-1-en-1-yl)ethyl]-2-(thiophen-2-yl)-acetamide.**

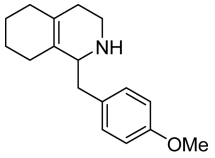


S22r

S22r (4.48 g, 90% yield) was purified by column chromatography (60/4/1 petroleum ether/ethyl acetate/triethylamine) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 5.2, 1.3 Hz, 1H), 6.97 (dd, J = 5.2, 3.4 Hz, 1H), 6.89 (d, J = 3.3 Hz, 1H), 5.66 (s, 1H), 5.25 (s, 1H), 3.74 (s, 2H), 3.25 (q, J = 6.2 Hz, 2H), 2.03 (t, J = 6.7 Hz, 2H), 1.72−1.93 (m, 4H), 1.37−1.63 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.6, 136.3, 134.2, 127.5, 127.3, 125.5, 124.2, 37.5, 37.2, 36.9, 27.5, 25.2, 22.7, 22.3; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{14}H_{19}NONaS$ 272.1080, found 272.1074.

https://dx.doi.org/10.1021/acs.joc.0c00469
J. Org. Chem. XXXX, XXX, XXX−XXX

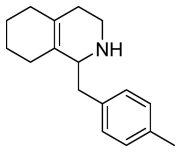
***rac*-1-(4-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1a**

rac-**1a** (221 mg, 43% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 3.81 (s, 3H), 3.22−3.32 (m, 1H), 2.96−3.09 (m, 2H), 2.73 (ddd, J = 11.9, 7.2, 5.1 Hz, 1H), 2.49 (dd, J = 13.6, 10.7 Hz, 1H), 2.09−2.22 (m, 1H), 1.84−2.08 (m, 5H), 1.50−1.82 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 131.9, 130.2, 130.0, 128.4, 113.9, 58.8, 55.3, 40.7, 37.9, 31.1, 30.4, 27.0, 23.3, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{24}NO$ 258.1852, found 258.1862.

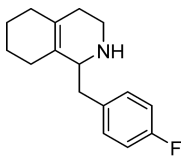
***rac*-1-(4-Methylbenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1b**

rac-**1b** (190 mg, 39% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 4H), 3.25−3.34 (m, 1H), 2.99−3.10 (m, 2H), 2.74 (ddd, J = 11.9, 7.0, 5.1 Hz, 1H), 2.52 (dd, J = 13.5, 10.7 Hz, 1H), 2.35 (s, 3H), 2.11−2.23 (m, 1H), 1.86−2.07 (m, 5H), 1.83−1.52 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.9, 135.6, 130.0, 129.2, 129.1, 128.4, 58.8, 40.6, 38.3, 31.0, 30.4, 27.1, 23.3, 22.9, 21.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{24}N$ 242.1903, found 242.1898.

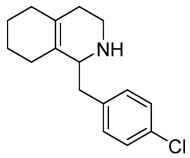
***rac*-1-(4-Fluorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1c**

rac-**1c** (116 mg, 24% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.16 (m, 2H), 7.01 (t, J = 8.7 Hz, 2H), 3.29 (d, J = 10.6 Hz, 1H), 3.10−2.96 (m, 2H), 2.75 (ddd, J = 12.0, 7.2, 5.1 Hz, 1H), 2.53 (dd, J = 13.6, 10.6 Hz, 1H), 2.23−2.07 (m, 1H), 1.84−2.08 (m, 5H), 1.48−1.84 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.5 (d, J = 244.0 Hz), 135.6 (d, J = 3.2 Hz), 130.6 (d, J = 7.7 Hz), 129.7, 128.7, 115.3 (d, J = 21.0 Hz), 58.7, 40.7, 38.1, 31.0, 30.4, 27.0, 23.2, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{21}NF$ 246.1653, found 246.1656.

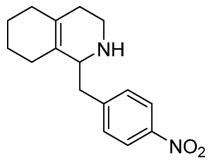
***rac*-1-(4-Chlorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1d**

rac-**1d** (398 mg, 76% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.3 Hz, 2H), 3.29 (d, J = 10.6 Hz, 1H), 2.97−3.11 (m, 2H), 2.75 (ddd, J = 12.0, 7.2, 5.1 Hz, 1H), 2.53 (dd, J = 13.6, 10.5 Hz, 1H), 2.07−2.21 (m, 1H), 1.83−2.06 (m, 5H), 1.49−1.83 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.5, 132.0, 130.6, 129.7, 128.8, 128.6, 58.7, 40.7, 38.3, 31.0, 30.4, 27.0, 23.2, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{21}NCl$ 262.1357, found 262.1364.

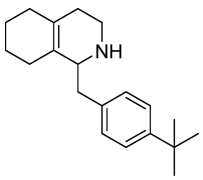
***rac*-1-(4-Nitrobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1e**

rac-**1e** (245 mg, 45% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J = 8.9, 2.2 Hz, 2H), 7.38−7.45 (m, 2H), 3.36 (d, J = 10.5 Hz, 1H), 3.13 (dd, J = 13.6, 3.2 Hz, 1H), 3.02 (dt, J = 11.2, 5.4 Hz, 1H), 2.77 (ddd, J = 12.0, 7.1, 5.1 Hz, 1H), 2.67 (dd, J = 13.5, 10.4 Hz, 1H), 2.06−2.20 (m, 1H), 1.84−2.04 (m, 5H), 1.66−1.83 (m, 2H), 1.47−1.66 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.4, 146.6, 130.0, 129.4, 129.4, 123.7, 58.6, 40.6, 39.1, 30.9, 30.5, 27.1, 23.2, 22.8.

***rac*-1-[4-(*tert*-Butyl)benzyl]-1,2,3,4,5,6,7,8-octahydroisoquinoline.**

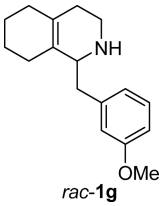


rac-**1f**

rac-**1f** (241 mg, 43% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 3.29 (d, J = 10.8 Hz, 1H), 3.02 (td, J = 12.3, 4.2 Hz, 2H), 2.72 (ddd, J = 12.0, 7.1, 5.1 Hz, 1H), 2.50 (dd, J = 13.5, 10.8 Hz, 1H), 2.09−2.24 (m, 1H), 1.84−2.05 (m, 5H), 1.66−1.83 (m, 3H), 1.46−1.62 (m, 2H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.0, 136.9, 130.1, 128.9, 128.4, 125.4, 58.7, 40.6, 38.2, 34.4, 31.4, 31.1, 30.5, 27.1, 23.3, 22.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{30}N$ 284.2373, found 284.2372.

https://dx.doi.org/10.1021/acs.joc.0c00469
J. Org. Chem. XXXX, XXX, XXX−XXX

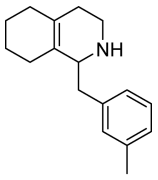
***rac*-1-(3-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1g**

rac-**1g** (288 mg, 56% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (dd, J = 8.6, 7.3 Hz, 1H), 6.71−6.89 (m, 3H), 3.74 (s, 3H), 3.19 (d, J = 10.0 Hz, 1H), 2.84−2.95 (m, 2H), 2.61 (dt, J = 11.9, 5.7 Hz, 1H), 2.43 (dd, J = 13.4, 10.0 Hz, 1H), 2.01−2.15 (m, 1H), 1.76−1.94 (m, 5H), 1.41−1.72 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.6, 142.4, 130.8, 129.5, 128.1, 121.9, 115.3, 111.6, 58.5, 55.3, 40.4, 39.0, 31.1, 30.4, 27.0, 23.3, 23.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{24}NO$ 258.1852, found 258.1850.

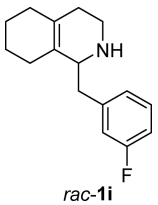
***rac*-1-(3-Methylbenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1h**

rac-**1h** (198 mg, 41% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.14 (t, J = 7.5 Hz, 1H), 6.99 (dd, J = 13.9, 6.9 Hz, 3H), 3.15 (d, J = 10.2 Hz, 1H), 2.83−2.92 (m, 2H), 2.49 (s, 1H), 2.38 (dd, J = 13.4, 10.1 Hz, 1H), 2.26 (s, 3H), 2.02−2.12 (m, 1H), 1.72−1.89 (m, 5H), 1.54−1.71 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 140.8, 137.5, 130.9, 130.3, 128.4, 128.1, 126.9, 126.7, 58.7, 40.3, 38.9, 31.2, 30.4, 27.0, 23.4, 23.0, 21.5; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{24}N$ 242.1903, found 242.1902.

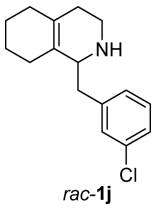
***rac*-1-(3-Fluorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1i**

rac-**1i** (229 mg, 47% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (q, J = 7.5 Hz, 1H), 6.95−7.12 (m, 3H), 3.20 (d, J = 10.0 Hz, 1H), 2.90 (ddd, J = 17.1, 12.5, 4.3 Hz, 2H), 2.42−2.54 (m, 1H), 2.01−2.14 (m, 1H), 1.74−1.97 (m, 5H), 1.40−1.76 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 162.5 (d, J = 242.6 Hz), 144.0 (d, J = 7.4 Hz), 130.8, 130.2 (d, J = 8.3 Hz), 128.3, 125.8 (d, J = 2.6 Hz), 116.3 (d, J = 20.5 Hz), 112.9 (d, J = 20.8 Hz), 58.4, 40.3, 38.6 (d, J = 1.8 Hz), 31.1, 30.5, 27.0, 23.3, 23.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{21}FN$ 246.1653, found 246.1647.

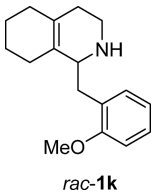
***rac*-1-(3-Chlorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1j**

rac-**1j** (251 mg, 48% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.29 (s, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.13−7.24 (m, 2H), 3.17 (d, J = 10.2 Hz, 1H), 2.77−2.95 (m, 2H), 2.38−2.50 (m, 1H), 2.04 (d, J = 16.4 Hz, 1H), 1.73−1.93 (m, 5H), 1.34−1.72 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 143.7, 133.1, 130.8, 130.2, 129.5, 128.4, 126.1, 58.4, 40.3, 38.5, 31.1, 30.5, 27.0, 23.3, 23.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{21}NCl$ 262.1357, found 262.1358.

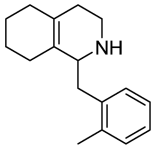
***rac*-1-(2-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1k**

rac-**1k** (172 mg, 33% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (ddd, J = 15.0, 7.5, 1.7 Hz, 2H), 6.83−6.97 (m, 2H), 3.84 (s, 3H), 3.36 (d, J = 10.7 Hz, 1H), 3.15 (dd, J = 13.4, 2.8 Hz, 1H), 3.04−3.12 (m, 1H), 2.75 (dt, J = 11.5, 5.6 Hz, 1H), 2.55 (dd, J = 13.3, 10.6 Hz, 1H), 2.15−2.27 (m, 1H), 1.89−2.03 (m, 5H), 1.84 (s, 1H), 1.66−1.80 (m, 2H), 1.51−1.67 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.7, 131.1, 130.6, 128.6, 127.9, 127.4, 120.4, 110.4, 56.9, 55.3, 40.1, 33.3, 31.0, 30.4, 27.1, 23.3, 23.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{24}NO$ 258.1852, found 258.1850.

***rac*-1-(2-Methylbenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**

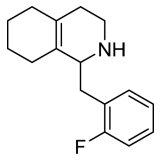


rac-**1l**

rac-**1l** (217 mg, 45% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.21 (m, 4H), 3.30 (d, J = 11.1 Hz, 1H), 3.09 (ddd, J = 14.9, 8.6, 4.3 Hz, 2H), 2.75 (dt, J = 11.6, 5.8 Hz, 1H), 2.57 (dd, J = 13.7, 11.0 Hz, 1H), 2.37 (s, 3H), 2.15−2.26 (m, 1H), 1.85−2.04 (m, 5H), 1.50−1.82 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.2, 136.5, 130.5, 130.3, 130.1, 128.5, 126.3, 125.9, 57.1, 40.3, 35.9, 31.1, 30.4, 27.1, 23.3, 22.9, 19.7; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{24}N$ 242.1903, found 242.1902.

https://dx.doi.org/10.1021/acs.joc.0c00469
J. Org. Chem. XXXX, XXX, XXX−XXX

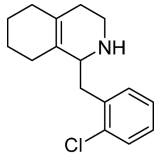
***rac*-1-(2-Fluorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1m**

Here, 1.56 mmol of imine bisulfate was used. *rac*-**1m** (100 mg, 26% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.33 (m, 2H), 6.96−7.15 (m, 2H), 3.32 (d, J = 10.9 Hz, 1H), 3.00−3.22 (m, 2H), 2.75 (dt, J = 11.7, 5.7 Hz, 1H), 2.58 (dd, J = 13.6, 10.8 Hz, 1H), 2.07−2.30 (m, 1H), 1.85−2.03 (m, 5H), 1.49−1.81 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.4 (d, J = 244.7 Hz), 131.6 (d, J = 5.0 Hz), 130.1, 128.6, 127.9 (d, J = 8.1 Hz), 127.1 (d, J = 16.0 Hz), 124.0 (d, J = 3.6 Hz), 115.4 (d, J = 22.3 Hz), 57.5, 40.1, 32.2, 31.0, 30.4, 27.1, 23.2, 22.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{21}NF$ 246.1653, found 246.1654.

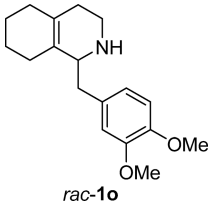
***rac*-1-(2-Chlorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1n**

rac-**1n** (200 mg, 39% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.12−7.24 (m, 2H), 3.40 (d, J = 11.0 Hz, 1H), 3.25 (dd, J = 13.5, 2.7 Hz, 1H), 3.07 (dt, J = 11.7, 5.8 Hz, 1H), 2.76 (dt, J = 11.5, 5.6 Hz, 1H), 2.62 (dd, J = 13.5, 10.8 Hz, 1H), 2.12−2.27 (m, 1H), 1.88−2.01 (m, 5H), 1.47−1.81 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 137.9, 134.3, 131.8, 130.2, 129.7, 128.5, 127.7, 126.7, 56.7, 40.2, 36.5, 31.0, 30.5, 27.0, 23.2, 22.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{21}NCl$ 262.1357, found 262.1357.

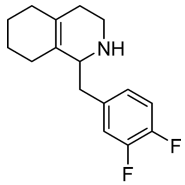
***rac*-1-(3,4-Dimethoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1o**

rac-**1o** (115 mg, 20% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73−6.84 (m, 3H), 3.87 (s, 2H), 3.86 (s, 3H), 3.30 (d, J = 10.4 Hz, 1H), 3.01 (ddd, J = 14.0, 9.2, 4.4 Hz, 2H), 2.73 (ddd, J = 12.0, 7.5, 5.0 Hz, 1H), 2.49 (dd, J = 13.6, 10.4 Hz, 1H), 2.14 (d, J = 16.3 Hz, 1H), 1.80−1.95 (m, 5H), 1.43−1.80 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.9, 147.5, 132.3, 129.7, 128.6, 121.2, 112.3, 111.3, 58.7, 55.93, 55.87, 40.9, 38.4, 30.9, 30.4, 27.0, 23.2, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{26}NO_2$ 288.1958, found 288.1960.

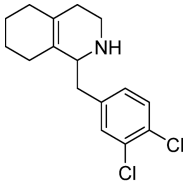
***rac*-1-(3,4-Difluorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1p**

rac-**1p** (214 mg, 41% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99−7.13 (m, 2H), 6.85−6.99 (m, 1H), 3.26 (d, J = 10.5 Hz, 1H), 2.98 (ddd, J = 12.4, 9.2, 4.2 Hz, 2H), 2.74 (ddd, J = 12.0, 7.2, 5.0 Hz, 1H), 2.48 (dd, J = 13.7, 10.5 Hz, 1H), 2.03−2.16 (m, 1H), 1.80−2.04 (m, 5H), 1.45−1.81 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.2 (dd, J = 247.8, 12.7 Hz), 149.0 (dd, J = 246.1, 12.6 Hz), 137.1 (dd, J = 5.2, 4.0 Hz), 129.5, 129.1, 125.1 (dd, J = 6.1, 3.5 Hz), 117.8 (d, J = 16.7 Hz), 117.1 (d, J = 16.9 Hz), 58.6, 40.7, 38.2, 30.9, 30.4, 27.0, 23.2, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{20}NF_2$ 264.1558, found 264.1556.

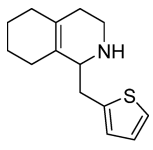
***rac*-1-(3,4-Dichlorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1q**

rac-**1q** (225 mg, 38% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.39 (m, 2H), 7.06 (dd, J = 8.2, 2.0 Hz, 1H), 3.21−3.32 (m, 1H), 2.98 (ddd, J = 11.4, 8.8, 4.3 Hz, 2H), 2.74 (ddd, J = 12.1, 7.2, 5.1 Hz, 1H), 2.48 (dd, J = 13.6, 10.5 Hz, 1H), 2.03−2.15 (m, 1H), 1.79−2.02 (m, 5H), 1.43−1.79 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.5, 132.3, 131.1, 130.3, 130.2, 129.5, 129.2, 128.7, 58.5, 40.7, 38.2, 30.9, 30.4, 27.0, 23.2, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{20}NCl_2$ 296.0967, found 296.0970.

***rac*-1-(Thiophen-2-ylmethyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.**



rac-**1r**

rac-**1r** (121 mg, 26% yield over two steps) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.18 (m, 1H), 6.91−6.96 (m, 1H), 6.84−6.90 (m, 1H), 3.27−3.36 (m, 1H), 3.18 (dd, J = 14.7, 3.2 Hz, 1H), 3.01 (dt, J = 11.1, 5.3 Hz, 1H), 2.88 (dd, J = 14.7, 9.6 Hz, 1H), 2.76 (ddd, J = 12.1, 7.3, 5.2 Hz, 1H), 2.06−2.12 (m, 1H), 1.83−2.02 (m, 5H), 1.45−1.81 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.0, 129.4, 129.2, 126.8, 125.9, 124.0, 58.6, 40.6, 33.1, 30.9, 30.5, 27.0, 23.2, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{20}NS$ 234.1311, found 234.1309.

Screening CHAOs for Deracemization of 1a at an Analytical Scale. To a suspension of freshly prepared wet cells of CHAO (0.6 g)

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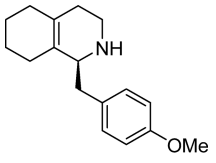
(washed with NaP_i buffer) in NaP_i buffer (50 mM, pH 7.5, 3 mL) were added **1a** (variable concentrations) and $NH_3{\cdot}BH_3$ (5 equiv relative to **1a**). The resulting reaction mixtures were incubated at 35 °C with 200 rpm shaking for certain amounts of time. The pH of the reaction mixture was first adjusted to ~5 by the addition of HCl (1 N) and then to ~9 by the addition of NaOH (3 M). The mixture was extracted with EtOAc (3 × 5 mL), and the organic layer was dried over Na_2SO_4, concentrated, and subjected to chiral HPLC analyses.

$CHAO_{CCH12\text{-}C2}$-Catalyzed Deracemization of 1 at a Semi-preparative Scale. To a suspension of freshly prepared wet cells of CHAO (2 g) (washed with NaP_i buffer) in NaP_i buffer (50 mM, pH 7.5, 10 mL) were added **1** (~100 mg, 0.4 mmol) and $NH_3{\cdot}BH_3$ (5 equiv relative to **1**). The resulting reaction mixtures were stirred at 600 rpm and 35 °C for 72 h. The pH of the reaction mixture was first adjusted to ~5 by the addition of HCl (1 N) and then to ~9 by the addition of NaOH (3 M). The mixture was extracted with EtOAc (3 × 20 mL), and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC to afford products enantioenriched **1**.

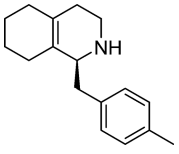
(*S*)-1-(4-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



(*S*)-**1a**

Here, 100 mg of *rac*-**1a** was used. (*S*)-**1a** (80 mg, 80% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 3.27 (d, J = 10.6 Hz, 1H), 2.95−3.10 (m, 2H), 2.73 (ddd, J = 12.0, 7.2, 5.1 Hz, 1H), 2.50 (dd, J = 13.6, 10.7 Hz, 1H), 2.06−2.28 (m, 1H), 1.84−2.05 (m, 5H), 1.48−1.84 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 131.9, 130.2, 130.0, 128.4, 113.9, 58.8, 55.3, 40.7, 37.9, 31.0, 30.4, 27.0, 23.3, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{24}NO$ 258.1852, found 258.1847; $[\alpha]_{20}^{D}$ = −125.80 (c = 0.5, MeOH) [lit.[8] value for (*R*)-**1a**: $[\alpha]_{20}^{D}$ = 139 (c = 1.0, MeOH)]; HPLC ChiracelOJ-H, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 9.2 min (major), t_2 = 10.2 min; 99% ee.

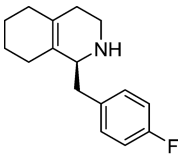
(*S*)-1-(4-Methylbenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



(*S*)-**1b**

Here, 104 mg of *rac*-**1b** was used. (*S*)-**1b** (68 mg, 65% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.22 (m, 4H), 3.30 (d, J = 10.6 Hz, 1H), 2.97−3.12 (m, 2H), 2.74 (ddd, J = 12.0, 7.1, 5.2 Hz, 1H), 2.53 (dd, J = 13.5, 10.7 Hz, 1H), 2.35 (s, 3H), 2.11−2.25 (m, 1H), 1.86−2.07 (m, 5H), 1.66−1.84 (m, 3H), 1.49−1.63 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.9, 135.6, 130.0, 129.2, 129.1, 128.4, 58.8, 40.6, 38.4, 31.1, 30.4, 27.1, 23.3, 22.9, 21.1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{24}N$ 242.1903, found 242.1900; $[\alpha]_{25}^{D}$ = −139.50 (c = 0.5, MeOH) [lit.[9] value for (*R*)-**1b**: $[\alpha]_{25}^{D}$ = +120.6 (c = 1.0, MeOH)]; HPLC ChiracelIC, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 8.0 min (major), t_2 = 11.8 min; 99% ee.

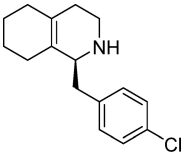
(*S*)-1-(4-Fluorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



(*S*)-**1c**

Here, 106 mg of *rac*-**1c** was used. (*S*)-**1c** (96 mg, 91% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, J = 8.4, 5.6 Hz, 2H), 7.00 (t, J = 8.7 Hz, 2H), 3.28 (dd, J = 10.8, 3.1 Hz, 1H), 2.94−3.07 (m, 2H), 2.74 (ddd, J = 12.0, 7.2, 5.1 Hz, 1H), 2.53 (dd, J = 13.6, 10.5 Hz, 1H), 2.08−2.20 (m, 1H), 1.84−2.07 (m, 5H), 1.49−1.83 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.5 (d, J = 244.0 Hz), 135.6 (d, J = 3.2 Hz), 130.6 (d, J = 7.8 Hz), 129.8, 128.7, 115.3 (d, J = 21.0 Hz), 58.7, 40.7, 38.1, 31.0, 30.4, 27.0, 23.2, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{21}NF$ 246.1653, found 246.1659; $[\alpha]_{25}^{D}$ = −135.30 (c = 0.5, MeOH) [lit.[9] value for (*R*)-**1c**: $[\alpha]_{25}^{D}$ = +145.8 (c = 1.0, MeOH)]; HPLC ChiracelIC, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 8.4 min (major), t_2 = 9.1 min; 99% ee.

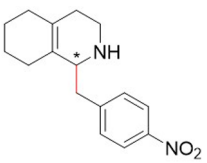
(*S*)-1-(4-Chlorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



(*S*)-**1d**

Here, 103 mg of *rac*-**1d** was used. (*S*)-**1d** (91 mg, 88% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 3.29 (d, J = 7.7 Hz, 1H), 3.02 (dt, J = 13.7, 4.7 Hz, 2H), 2.74 (ddd, J = 12.0, 7.2, 5.1 Hz, 1H), 2.53 (dd, J = 13.6, 10.5 Hz, 1H), 2.06−2.23 (m, 1H), 1.84−2.05 (m, 5H), 1.50−1.82 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.5, 132.0, 130.6, 129.7, 128.9, 128.6, 58.7, 40.7, 38.3, 31.0, 30.4, 27.0, 23.2, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{21}NCl$ 262.1357, found 262.1347; $[\alpha]_{25}^{D}$ = −136.10 (c = 0.5, MeOH) [lit.[9] value for (*R*)-**1d**: $[\alpha]_{25}^{D}$ = +144.0 (c = 1.0, MeOH)]; HPLC ChiracelIC, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 8.3 min (major), t_2 = 9.7 min; 99% ee.

Enantioenriched 1-(4-Nitrobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



enantioenriched-**1e**

https://dx.doi.org/10.1021/acs.joc.0c00469
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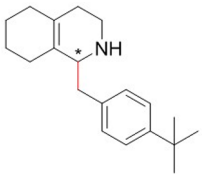
Here, 107 mg of *rac*-**1e** was used. Enantioenriched **1e** (82 mg, 77% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 3.38 (d, J = 10.4 Hz, 1H), 3.14 (dd, J = 13.6, 3.2 Hz, 1H), 3.03 (dt, J = 11.4, 5.5 Hz, 1H), 2.78 (ddd, J = 12.1, 7.1, 5.1 Hz, 1H), 2.69 (dd, J = 13.6, 10.4 Hz, 1H), 2.07−2.20 (m, 1H), 1.85−2.06 (m, 5H), 1.68−1.85 (m, 2H), 1.45−1.67 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.4, 146.6, 130.1, 129.4, 123.7, 58.6, 40.6, 39.1, 30.9, 30.5, 27.1, 23.2, 22.8; $[\alpha]_{25}^{D}$ = −171.48 (c = 0.5, MeOH); HPLC ChiracelOJ-H, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 12.1 min (major), t_2 = 12.9 min; 97% ee.

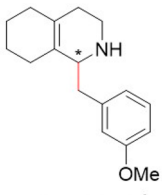
Enantioenriched 1-[4-(*tert*-Butyl)benzyl]-1,2,3,4,5,6,7,8-octahydroisoquinoline.



enantioenriched-**1f**

Here, 140 mg of *rac*-**1f** was used. Enantioenriched **1f** (108 mg, 77% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 3.29 (d, J = 10.8 Hz, 1H), 3.02 (ddd, J = 11.0, 8.6, 4.3 Hz, 2H), 2.72 (ddd, J = 12.0, 7.2, 5.2 Hz, 1H), 2.50 (dd, J = 13.6, 10.8 Hz, 1H), 2.07−2.22 (m, 1H), 1.64−2.04 (m, 9H), 1.48−1.61 (m, 1H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.0, 136.9, 130.0, 128.9, 128.4, 125.4, 58.7, 40.6, 38.2, 34.4, 31.4, 31.0, 30.4, 27.0, 23.3, 22.9; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{20}H_{30}N$ 284.2373, found 284.2375; HPLC ChiracelIC, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 7.4 min (major), t_2 = 8.2 min; 9% ee.

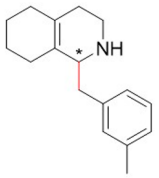
Enantioenriched 1-(3-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



enantioenriched-**1g**

Here, 112 mg of *rac*-**1g** was used. Enantioenriched **1g** (85 mg, 76% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.19 (t, J = 7.9 Hz, 1H), 6.72−6.84 (m, 3H), 3.74 (s, 3H), 3.17−3.24 (m, 1H), 2.83−2.98 (m, 2H), 2.51 (p, J = 1.8 Hz, 1H), 2.43 (dd, J = 13.4, 10.0 Hz, 1H), 2.00−2.15 (m, 1H), 1.83 (m, 5H), 1.30−1.74 (m, H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.6, 142.4, 130.8, 129.5, 128.1, 122.0, 115.3, 111.6, 58.5, 55.3, 40.4, 39.0, 31.1, 30.4, 27.0, 23.3, 23.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{24}NO$ 258.1852, found 258.1845; $[\alpha]_{25}^{D}$ = −117.72 (c = 0.5, MeOH); HPLC ChiracelOJ-H, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 9.1 min (major), t_2 = 11.7 min; 99% ee.

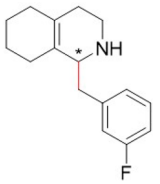
Enantioenriched 1-(3-Methylbenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



enantioenriched-**1h**

Here, 116 mg of *rac*-**1h** was used. Enantioenriched **1h** (87 mg, 75% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.16 (t, J = 7.5 Hz, 1H), 7.01 (dd, J = 13.5, 6.7 Hz, 3H), 3.17 (d, J = 10.1 Hz, 1H), 2.83−2.95 (m, 2H), 2.51 (s, 1H), 2.40 (dd, J = 13.3, 10.2 Hz, 1H), 2.29 (s, 3H), 2.03−2.17 (m, 1H), 1.76−1.95 (m, 5H), 1.42−1.75 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 140.7, 137.5, 130.8, 130.3, 128.4, 128.1, 126.9, 126.7, 58.7, 40.3, 38.9, 31.1, 30.4, 27.0, 23.3, 23.0, 21.5; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{24}N$ 242.1903, found 242.1904; $[\alpha]_{25}^{D}$ = −108.12 (c = 0.5, MeOH); HPLC ChiracelAD-H, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 7.7 min (major), t_2 = 8.2 min; 97% ee.

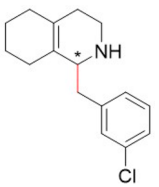
Enantioenriched 1-(3-Fluorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



enantioenriched-**1i**

Here, 127 mg of *rac*-**1i** was used. Enantioenriched **1i** (79 mg, 62% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.28 (q, J = 7.7 Hz, 1H), 6.92−7.12 (m, 3H), 3.17 (d, J = 10.1 Hz, 1H), 2.88 (ddd, J = 17.1, 12.5, 4.3 Hz, 2H), 2.41−2.52 (m, 1H), 2.04 (m, 1H), 1.81 (m, 5H), 1.32−1.73 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 162.5 (d, J = 242.4 Hz), 144.0 (d, J = 7.4 Hz), 130.8, 130.2 (d, J = 8.5 Hz), 128.3, 125.8 (d, J = 2.6 Hz), 116.3 (d, J = 20.6 Hz), 112.9 (d, J = 20.9 Hz), 58.4, 40.3, 38.6 (d, J = 1.8 Hz), 31.0, 30.5, 27.0, 23.3, 23.0; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{21}NF$ 246.1653, found 246.1645; $[\alpha]_{25}^{D}$ = −145.30 (c = 0.5, MeOH); HPLC ChiracelOJ-H, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 7.8 min (major), t_2 = 10.9 min; 97% ee.

Enantioenriched 1-(3-Chlorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



enantioenriched-**1j**

Here, 109 mg of *rac*-**1j** was used. Enantioenriched **1j** (85 mg, 78% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (s, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.16−7.26

https://dx.doi.org/10.1021/acs.joc.0c00469
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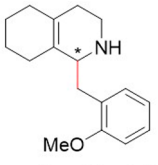
(m, 2H), 3.18 (d, J = 10.1 Hz, 1H), 2.84−2.96 (m, 2H), 2.40−2.54 (m, 2H), 2.01−2.16 (m, 1H), 1.75−1.95 (m, 5H), 1.35−1.75 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 143.7, 133.1, 130.9, 130.2, 129.6, 128.5, 128.4, 126.1, 58.4, 40.3, 38.4, 31.0, 30.5, 27.0, 23.3, 23.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{21}NCl$ 262.1357, found 262.1360; $[\alpha]_{25}^{D}$ = −119.31 (c = 0.5, MeOH); HPLC ChiracelAD-H, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 7.7 min (major), t_2 = 8.9 min; 97% ee.

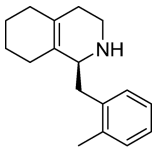
Enantioenriched 1-(2-Methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



enantioenriched-**1k**

Here, 118 mg of *rac*-**1k** was used. Enantioenriched **1k** (101 mg, 86% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.14−7.26 (m, 2H), 6.82−6.97 (m, 2H), 3.84 (s, 3H), 3.36 (d, J = 13.7 Hz, 1H), 3.15 (dd, J = 13.4, 2.8 Hz, 1H), 3.05−3.11 (m, 1H), 2.75 (dt, J = 11.3, 5.6 Hz, 1H), 2.55 (dd, J = 13.3, 10.6 Hz, 1H), 2.14−2.30 (m, 1H), 1.87−2.05 (m, 5H), 1.81 (d, J = 15.3 Hz, 1H), 1.73 (dq, J = 15.9, 6.1, 5.3 Hz, 2H), 1.50−1.65 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.8, 131.1, 130.6, 128.6, 127.9, 127.4, 120.4, 110.4, 56.9, 55.3, 40.1, 33.3, 31.1, 30.4, 27.1, 23.3, 23.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{24}NO$ 258.1852, found 258.1851; HPLC ChiracelIC, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 9.3 min (major), t_2 = 11.2 min; 12% ee.

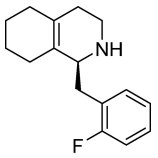
(*S*)-1-(2-Methylbenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



(*S*)-**1l**

Here, 124 mg of *rac*-**1l** was used. (*S*)-**1l** (82 mg, 66% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.10−7.23 (m, 4H), 3.29 (d, J = 11.0 Hz, 1H), 3.02−3.14 (m, 2H), 2.75 (dt, J = 11.6, 5.7 Hz, 1H), 2.56 (dd, J = 13.7, 11.0 Hz, 1H), 2.36 (s, 3H), 2.14−2.26 (m, 1H), 1.95 (q, J = 5.8, 5.2 Hz, 5H), 1.72 (ddt, J = 22.2, 12.3, 6.4 Hz, 3H), 1.52−1.63 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.3, 136.5, 130.5, 130.3, 130.1, 128.5, 126.3, 125.9, 57.1, 40.3, 35.8, 31.1, 30.4, 27.1, 23.3, 22.9, 19.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{17}H_{24}N$ 242.1903, found 242.1902; $[\alpha]_{25}^{D}$ = −117.92 (c = 0.5, MeOH) [lit.[9] value for (*R*)-**1l**: $[\alpha]_{25}^{D}$ = +163.4 (c = 1.0, MeOH)]; HPLC ChiracelIC, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 7.8 min (major), t_2 = 9.1 min; 50% ee.

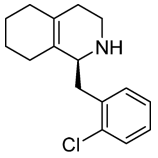
(*S*)-1-(2-Fluorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



(*S*)-**1m**

Here, 109 mg of *rac*-**1m** was used. (*S*)-**1m** (99 mg, 91% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.14−7.27 (m, 2H), 6.98−7.14 (m, 2H), 3.32 (d, J = 10.8 Hz, 1H), 2.98−3.16 (m, 2H), 2.75 (dt, J = 11.7, 5.7 Hz, 1H), 2.57 (dd, J = 13.6, 10.8 Hz, 1H), 2.07−2.23 (m, 1H), 1.83−2.02 (m, 5H), 1.48−1.82 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.4 (d, J = 244.7 Hz), 131.6 (d, J = 5.1 Hz), 130.1, 128.5, 127.9 (d, J = 8.1 Hz), 127.1 (d, J = 15.7 Hz), 124.0 (d, J = 3.5 Hz), 115.4 (d, J = 22.3 Hz), 57.5, 40.2, 32.2, 31.0, 30.4, 27.1, 23.2, 22.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{21}NF$ 246.1653, found 246.1652; $[\alpha]_{25}^{D}$ = −118.12 (c = 0.5, MeOH) [lit.[9] value for (*R*)-**1m**: $[\alpha]_{25}^{D}$ = +131.8 (c = 1.0, MeOH)]; HPLC ChiracelIC, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 8.3 min (major), t_2 = 9.5 min; 99% ee.

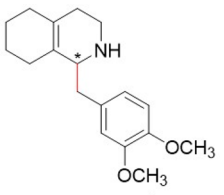
(*S*)-1-(2-Chlorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



(*S*)-**1n**

Here, 105 mg of *rac*-**1n** was used. (*S*)-**1n** (88 mg, 84% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 7.5, 1.7 Hz, 1H), 7.30 (dd, J = 7.3, 1.9 Hz, 1H), 7.15−7.26 (m, 2H), 3.43 (d, J = 10.9 Hz, 1H), 3.28 (dd, J = 13.6, 2.7 Hz, 1H), 3.10 (dt, J = 11.7, 5.8 Hz, 1H), 2.79 (dt, J = 11.6, 5.6 Hz, 1H), 2.64 (dd, J = 13.5, 10.8 Hz, 1H), 2.13−2.29 (m, 1H), 1.89−2.04 (m, 5H), 1.53−1.83 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 137.9, 134.2, 131.8, 130.2, 129.7, 128.5, 127.7, 126.7, 56.7, 40.2, 36.4, 31.0, 30.5, 27.0, 23.2, 22.9; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{21}NCl$ 262.1357, found 262.1355; $[\alpha]_{25}^{D}$ = −106.32 (c = 0.5, MeOH) [lit.[9] value for (*R*)-**1n**: $[\alpha]_{25}^{D}$ = +123.5 (c = 1.0, MeOH)]; HPLC ChiracelIC, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 8.0 min (major), t_2 = 9.3 min; 94% ee.

Enantioenriched 1-(3,4-Dimethoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



enantioenriched-**1o**

https://dx.doi.org/10.1021/acs.joc.0c00469
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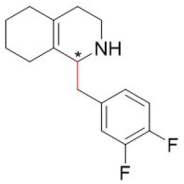
Here, 100 mg of *rac*-**1o** was used. Enantioenriched **1o** (67 mg, 67% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73−6.82 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.28 (d, J = 10.4 Hz, 1H), 2.92−3.06 (m, 2H), 2.71 (ddd, J = 11.9, 7.6, 5.1 Hz, 1H), 2.47 (dd, J = 13.6, 10.4 Hz, 1H), 2.06−2.18 (m, 1H), 1.81−2.00 (m, 5H), 1.36−1.79 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.9, 147.5, 132.3, 129.8, 128.6, 121.2, 112.3, 111.3, 58.7, 55.9, 55.9, 40.9, 38.4, 31.0, 30.4, 27.0, 23.3, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{26}NO_2$ 288.1958, found 288.1958; $[\alpha]_{25}^{D}$ = −100.13 (c = 0.5, MeOH); HPLC ChiracelOJ-H, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 11.0 min (major), t_2 = 12.5 min; 97% ee.

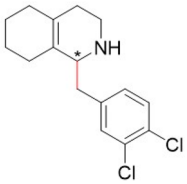
Enantioenriched 1-(3,4-Difluorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



enantioenriched-**1p**

Here, 113 mg of *rac*-**1p** was used. Enantioenriched **1p** (95 mg, 84% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02−7.14 (m, 2H), 6.90−6.99 (m, 1H), 3.29 (d, J = 10.6 Hz, 1H), 2.95−3.06 (m, 2H), 2.76 (ddd, J = 12.1, 7.2, 5.2 Hz, 1H), 2.51 (dd, J = 13.7, 10.4 Hz, 1H), 2.06−2.19 (m, 1H), 1.82−2.04 (m, 5H), 1.46−1.81 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.2 (dd, J = 247.8, 12.7 Hz), 149.0 (dd, J = 246.0, 12.6 Hz), 137.0 (dd, J = 5.3, 4.1 Hz), 129.5, 129.1, 125.0 (dd, J = 6.0, 3.4 Hz), 117.8 (d, J = 16.6 Hz), 117.1 (d, J = 16.8 Hz), 58.6, 40.7, 38.2, 30.9, 30.4, 27.0, 23.2, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{20}NF_2$ 264.1558, found 264.1558; $[\alpha]_{25}^{D}$ = −127.51 (c = 0.5, MeOH); HPLC ChiracelAD-H, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 12.3 min (major), t_2 = 12.9 min; 99% ee.

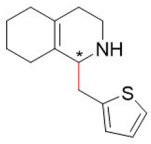
Enantioenriched 1-(3,4-Dichlorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



enantioenriched-**1q**

Here, 111 mg of *rac*-**1q** was used. Enantioenriched **1q** (91 mg, 82% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.43 (m, 2H), 7.09 (dd, J = 8.2, 2.0 Hz, 1H), 3.30 (d, J = 10.5 Hz, 1H), 2.93−3.09 (m, 2H), 2.76 (ddd, J = 12.1, 7.3, 5.1 Hz, 1H), 2.51 (dd, J = 13.7, 10.5 Hz, 1H), 2.05−2.19 (m, 1H), 1.82−2.04 (m, 5H), 1.49−1.82 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.5, 132.3, 131.1, 130.3, 130.2, 129.4, 129.2, 128.7, 58.5, 40.7, 38.2, 30.9, 30.4, 27.0, 23.2, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{20}NCl_2$ 296.0967, found 296.0973: $[\alpha]_{25}^{D}$ = −135.70 (c = 0.5, MeOH); HPLC ChiracelAD-H, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 7.5 min (major), t_2 = 8.0 min; 96% ee.

Enantioenriched 1-(Thiophen-2-ylmethyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline.



enantioenriched-**1r**

Here, 100 mg of *rac*-**1r** was used. Enantioenriched **1r** (74 mg, 74% yield) was purified by preparative TLC (15/1 dichloromethane/methanol) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 5.0 Hz, 1H), 6.96 (dd, J = 5.1, 3.4 Hz, 1H), 6.86−6.92 (m, 1H), 3.35 (d, J = 12.7 Hz, 1H), 3.20 (dd, J = 14.7, 3.2 Hz, 1H), 3.04 (dt, J = 11.0, 5.2 Hz, 1H), 2.91 (dd, J = 14.7, 9.6 Hz, 1H), 2.79 (ddd, J = 12.1, 7.4, 5.1 Hz, 1H), 2.07−2.21 (m, 1H), 1.83−2.05 (m, 6H), 1.66−1.83 (m, 2H), 1.47−1.65 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.0, 129.4, 129.2, 126.8, 125.9, 124.0, 58.6, 40.6, 33.1, 30.9, 30.5, 27.0, 23.2, 22.8; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{20}NS$ 234.1311, found 234.1322; $[\alpha]_{25}^{D}$ = −148.09 (c = 0.5, MeOH); HPLC ChiracelIC, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 8.5 min (major), t_2 = 9.8 min; 97% ee.

CHAO$_{CCH12-C2}$-Catalyzed Deracemization of 1a at a Gram Scale. To a suspension of freshly prepared wet cells of CHAO (11.5 g) (washed with NaP_i buffer) in NaP_i buffer (50 mM, pH 7.5, 57.5 mL) were added **1a** (1.495 g, 5.8 mmol) and NH_3·BH_3 (5 equiv relative to **1a**). The resulting reaction mixtures were stirred at 900 rpm and 35 °C for 5 days. The pH of the reaction mixture was first adjusted to ∼5 by the addition of HCl (1 N) and then to ∼9 by the addition of NaOH (3 M). The mixture was extracted with EtOAc (3 × 200 mL), and the organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography to afford products (*S*)-**1a** (1.007 g, 67% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.6 Hz, 2H), 4.18 (s, 3H), 3.63 (d, J = 10.6 Hz, 1H), 3.25−3.46 (m, 2H), 3.10 (ddd, J = 12.0, 7.2, 5.1 Hz, 1H), 2.86 (dd, J = 13.6, 10.6 Hz, 1H), 2.45−2.58 (m, 1H), 2.21−2.38 (m, 5H), 2.01−2.17 (m, 5H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.4, 132.3, 130.5, 130.4, 128.8, 114.3, 59.2, 55.6, 41.1, 38.2, 31.4, 30.8, 27.4, 23.6, 23.2; $[\alpha]_{20}^{D}$ = −139.80 (c = 0.5, MeOH) [lit.[8] value for (*R*)-**1a**: $[\alpha]_{20}^{D}$ = +139 (c = 1.0, MeOH)]; HPLC Chiracel OJ-H, 250 mm × 4.6 mm column, 95/5/0.5 hexane/2-propanol/ethanolamine, flow rate of 0.5 mL/min, 230 nm UV lamp, 25 °C, t_1 = 9.2 min (major), t_2 = 10.2 min; 96% ee.

Protein Crystallization. Protein was crystallized at 18 °C using the hanging-drop vapor diffusion method. Crystals were obtained by mixing 1 μL of a protein solution and 1 μL of a reservoir solution containing 10% PEG 8000 and 100 mM potassium phosphate monobasic/sodium phosphate dibasic (pH 6.0). The CHAO$_{CCH12-C2}$-FAD-**2a** ternary complex was obtained by soaking the protein crystal into the solution containing 6% PEG 8000, 50 mM potassium phosphate monobasic/sodium phosphate dibasic (pH 6.0), and 1 mM 1-(4-methoxybenzyl)-HHIQ (**2a**) for 2 min. Crystals were cryoprotected in a reservoir solution supplemented with 20% glycol. X-ray diffraction data were collected at 100 K on beamline BL18U at the SSRF (Shanghai Synchrotron Radiation Facility). The data were processed using HKL3000.[43] The structure was determined by molecular replacement using CHAO$_{IH-35A}$ (PDB entry 4I59) as the search model.[44] The initial model was automatically built using PHENIX AutoBuild, followed by manual model building using COOT[45] and structural refinement using PHENIX.refine and Refmac5.[46] Data collection statistics are summarized in Table S5. The structures of the CHAO$_{CCH12-C2}$-FAD binary complex and the

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$CHAO_{CCH12\text{-}C2}$-FAD-**2a** ternary complex have been deposited as PDB entries 6LQC and 6LQL, respectively.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00469.

Protein mutagenesis, protein crystallization of $CHAO_{CCH12\text{-}C2}$, NMR spectra, and chiral HPLC spectra (PDF)

Accession Codes

The structures of the $CHAO_{CCH12\text{-}C2}$-FAD binary complex and the $CHAO_{CCH12\text{-}C2}$-FAD-**2a** ternary complex have been deposited as PDBS entries 6LQC and 6LQL, respectively.

■ AUTHOR INFORMATION

Corresponding Authors

Zedu Huang − *Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University, Shanghai 200433, P. R. China; Shanghai Engineering Research Center of Industrial Asymmetric Catalysis of Chiral Drugs, Shanghai 200433, P. R. China;* orcid.org/0000-0003-3320-3392; Email: huangzedu@fudan.edu.cn

Juan Lin − *College of Chemical Engineering and College of Biological Science and Engineering, Fuzhou University, Fuzhou 350116, P. R. China;* orcid.org/0000-0003-4202-285X; Email: ljuan@fzu.edu.cn

Fener Chen − *Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University, Shanghai 200433, P. R. China; Shanghai Engineering Research Center of Industrial Asymmetric Catalysis of Chiral Drugs, Shanghai 200433, P. R. China;* orcid.org/0000-0002-6734-3388; Email: rfchen@fudan.edu.cn

Authors

Xiaofan Wu − *College of Chemical Engineering, Fuzhou University, Fuzhou 350116, P. R. China*

Zexu Wang − *Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University, Shanghai 200433, P. R. China; Shanghai Engineering Research Center of Industrial Asymmetric Catalysis of Chiral Drugs, Shanghai 200433, P. R. China*

Zhining Li − *Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University, Shanghai 200433, P. R. China; Shanghai Engineering Research Center of Industrial Asymmetric Catalysis of Chiral Drugs, Shanghai 200433, P. R. China*

Jiaqi Wang − *Engineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University, Shanghai 200433, P. R. China; Shanghai Engineering Research Center of Industrial Asymmetric Catalysis of Chiral Drugs, Shanghai 200433, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c00469

Notes

The authors declare no competing financial interest.

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