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α-Chymotrypsin–catalyzed direct C (Sp^3)–H functionalization reactions for synthesis of azaarene derivatives in water

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Abstract

α-Chymotrypsin from the bovine pancreas has been shown for the first time to display catalytic nonnatural catalytic ability toward the C (sp^3)–H functionalization reaction of 2-methylquinoline and aromatic aldehydes in water. α-Chymotrypsin exhibited favorable catalytic activity with good adaptability to different substrates. The activity of the enzyme could be improved by adjusting the solvent, temperature, molar ratio of substrates, and protein loading. The products were obtained in moderate to excellent yields (51%-93%) in 24 samples. This process afforded a potential biocatalytic approach as an alternative to chemical synthesis for azaarene derivatives.

1 | INTRODUCTION

Azaarene derivatives have gained attention because of their broad range of potential biological and pharmacological activities,[1] eg, as anti-inflammatory agents, anticancer agents, anti-HIV agents, and molecular probes.[2] Therefore, the synthesis of azaarene derivatives continues to receive attention from scientists. Azaarene derivatives act as important intermediates in many industrial processes, and one of the most efficient methods for their synthesis is the direct C (sp^3)–H functionalization of alkyl-substituted pyridines and quinolines. In 2018,[3] Zhou et al developed a low-loading cobalt nanocatalyst using nitrogen-silica–doped carbon as the support. The combination of such a catalyst with 4-nitrobenzoic acid and molecular O_2 exhibits excellent catalytic performance toward the dehydrogenative coupling of (hetero)aryl-fused 2-alkylcyclic amines with aldehydes to afford the (E)-2-alkenylazaarene. In 2016,[4] Crisenza et al used quinoline *N*-oxide as the precursor and dimethyl sulfoxide as the solvent in the presence of $TsOH{\cdot}H_2O$ at 120°C to generate azaarene derivatives. In 2016,[5] Tan et al developed a novel iridium/acid cocatalyzed transfer hydrogenative coupling strategy, enabling direct

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alkylation of C (sp3)–H bonds and atom-economic access to alkyl chain–lengthened *N*-heteroaromatics from six-membered 2-alkyl cyclic amines and aldehydes. In 2015,[6] Wei's group reported the $CuFe_2O_4$ catalyzed direct C (sp^3)–H functionalization reaction of 2-methylquinoline and aromatic aldehydes at 100°C. In 2010,[7] Huang's group reported the synthesis of azaarene derivatives from imine and 2,6-lutidine using $Pd(OAc)_2$ as the catalyst. These synthetic methodologies are useful to facilitate the synthesis of the desired compounds in many instances. However, these synthetic strategies have certain limitations such as serious pollution of the environment, tedious processes, low yields of product, expensive moisture-sensitive catalysts, cumbersome preparation processes for the required catalyst, and liberating hazardous gas during recycling. If a direct synthetic method with enzyme catalysis could be established for the synthesis of azaarene derivatives, it would be greener and more efficient, which will significantly reduce reaction costs. Therefore, it is of great importance to develop a green preparation method that is economical, environment friendly, and has a wide range of applications.

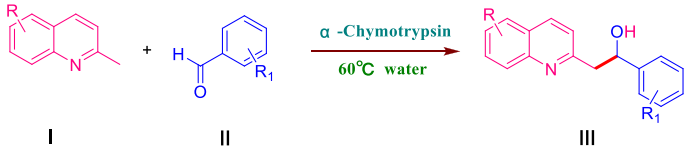
Enzymes have received considerable attention as efficient, less toxic, mild, and selective catalysts for the agricultural, industrial, and pharmaceutical industries.[8] Among the various types of enzymes, hydrolases undoubtedly play an important role because of their high stability, high selectivity, and nonnaturally catalytic activity.[9] Recently, several enzymes have been used in multiple types of organic reactions, such as Gewald,[10] aldol,[11] retro-Claisen reaction,[12] Mannich,[13] and Friedländer reactions.[14] However, to the best of our knowledge, the synthesis of azaarene derivatives by enzymatic catalysis of the reaction between 2-methylquinolines and aromatic aldehydes has never been reported. Herein, we report that α-chymotrypsin can catalyze the reaction of 2-methylquinoline (I) with a series of aromatic aldehydes (II) to afford the corresponding azaarenes in water as the solvent (Scheme 1). The highest yield achieved was 93%, and the reaction was a simple green synthesis.

2 | RESULTS AND DISCUSSION

Initial studies used the reaction between 2-methylquinoline and 4-nitrobenzaldehyde as a model reaction, and ethanol was chosen as the reaction medium. We then investigated some hydrolases for the catalysis of the model reaction (Table 1). The best yield of 18% was achieved using α-chymotrypsin from bovine pancreas (Table 1, entry 1). In addition, lipase from *Candida rugosa* (Table 1, entry 3) and trypsin from bovine pancreas (Table 1, entry 4) both exhibited some catalytic activity toward the model reaction. However, the other enzymes tested demonstrated no catalytic ability. Next, inactivated α-chymotrypsin (Table 1, entry 8) and nonenzyme protein bovine serum albumin (BSA) (Table 1, entry 7) were separately used in the reaction, and neither showed catalytic activity, thus producing results similar to those of the blank control reaction (Table 1, entry 9). We performed the model reaction in the absence of α-chymotrypsin, and only a trace amount of the desired product was observed after 84 hours (Table 1, entry 9). These results confirmed that the catalysis did not arise simply from the amino acid residues on the surface of the protein. In view of the above-mentioned results, α-chymotrypsin was chosen as the catalyst.

Since the reaction medium plays a significant role in maintaining the catalytic activity and stability of an enzyme,[15] other organic solvents were screened for the α-chymotrypsin–catalyzed model reaction (Figure 1). The experimental results showed that solvents had an obvious effect on the reaction. The best yield of 57% was obtained when water was used as the solvent. Dimethyl sulfoxide also afforded the product in good yields, while low to moderate yields were obtained by other solvents. Additionally, a blank experiment in water in the absence of the catalyst gave only a trace amount of the desired product. Thus, water was confirmed as the optimal solvent.

The water content usually affects enzymatic reactions in organic solvents because water can affect the conformational flexibility of an enzyme.[16] Typically, enzymes require a certain amount of water to maintain their three-dimensional conformation in an organic solvent. Hence, the effect of water content on the model reaction was investigated (Figure 2). A rise in the yield from 21% to 57% was observed as the water content increased from 0% to 100% [water/(water + methanol), v/v]. The same trend was observed in ethanol; however, the effect of ethanol content on the model reaction was lower than that of water. Therefore, 100% water was selected as the optimal solvent for the reaction.



SCHEME 1 α-Chymotrypsin–catalyzed synthesis of azaarene derivatives [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Catalytic activities of different enzymes[a]

Entry	Enzyme	Yield[b]/%
1	α-Chymotrypsin	18
2	Protease from *Aspergillus saitoi*	11
3	Lipase from *Candida rugosa*	13
4	Trypsin from bovine pancreas	14
5	Lipase from *Candida antarctica*	10
6	Papain	≤5
7	Bovine serum albumin	≤5
8	Inactivated α-chymotrypsin[c]	≤5
9	Blank	≤5

[a]Reaction conditions: 2-methylquinoline (0.3 mmol), 4-nitrobenzaldehyde (0.33 mmol), and catalyst (15 mg) in CH_3CH_2OH (2 mL) at 50°C for 84 h.
[b]Isolated yield after column chromatography.
[c]Pretreated with urea solution (8 mol/L).

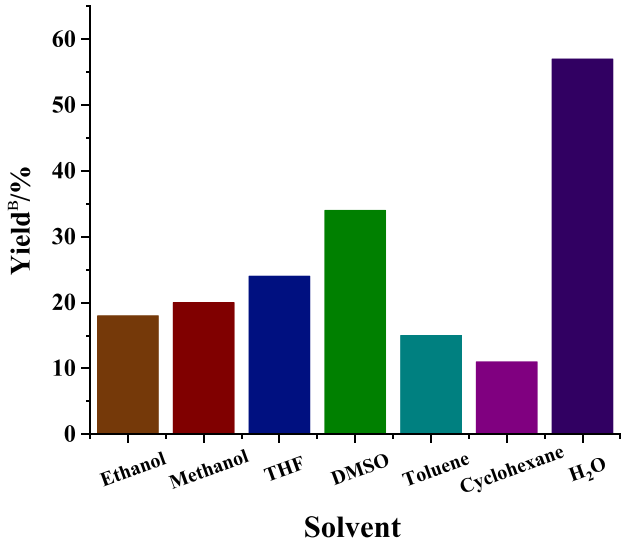


FIGURE 1 Catalytic effect of α-chymotrypsin in different solvents.[a] [a]Reaction conditions: 2-methylquinoline (0.3 mmol), 4-nitrobenzaldehyde (0.33 mmol), and α-chymotrypsin (15 mg) in different solvents (2 mL) at 50°C for 84 h. [b]Isolated yield after column chromatography [Color figure can be viewed at wileyonlinelibrary.com]

Temperature is a crucial factor affecting the stability of enzymes.[17] Increasing the temperature can accelerate the chemical reaction rate; however, high temperatures can inactivate the enzyme through protein denaturation. Hence, the effect of temperature on the model reaction was investigated (Figure 3). Increasing the temperature from 30°C to 70°C led to an increase in the yield from 22% to 75%. The best yield was achieved at 60°C. When the temperature increased to 80°C, the reaction yield decreased to 68%. Thus, 60°C was chosen as the optimum temperature for the reaction.

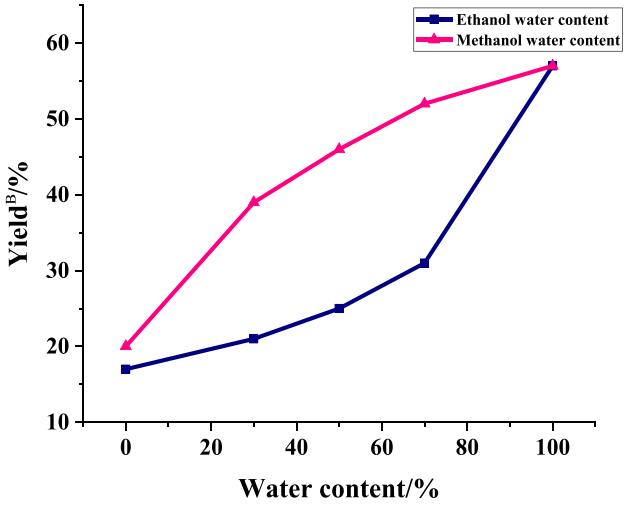


FIGURE 2 Catalytic effect of α-chymotrypsin in different levels of water content.[a] [a]Reaction conditions: 2-methylquinoline (0.3 mmol), 4-nitrobenzaldehyde (0.33 mmol), and α-chymotrypsin (15 mg) in ethanol or methanol aqueous solution (2 mL) with different levels of water content at 50 °C for 84 h. [b]Isolated yield after column chromatography [Color figure can be viewed at wileyonlinelibrary.com]

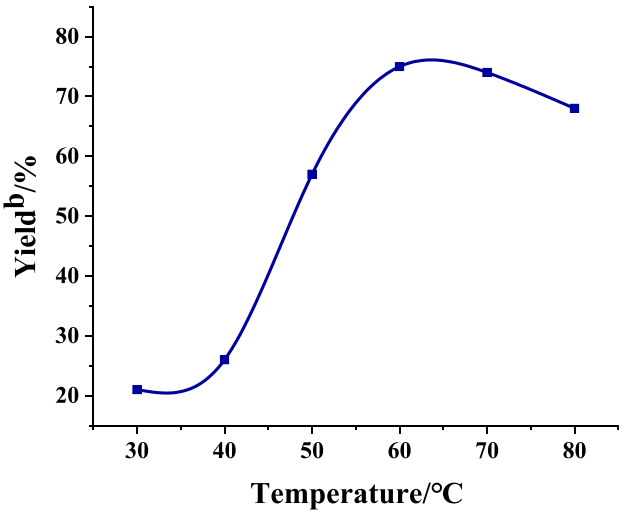


FIGURE 3 Catalytic effect of α-chymotrypsin at different temperatures.[a] [a]Reaction conditions: 2-methylquinoline (0.3 mmol), 4-nitrobenzaldehyde (0.33 mmol), and α-chymotrypsin (15 mg) in H_2O (2 mL) at different temperatures for 84 h. [b]Isolated yield after column chromatography [Color figure can be viewed at wileyonlinelibrary.com]

Furthermore, the molar ratio of the substrates affects the reaction. Thus, to further improve the yield of the α-chymotrypsin–catalyzed model reaction, the optimal molar ratio of the substrates was determined (Figure 4). When a molar ratio of 1:3 (2-methylquinoline : 4-nitrobenzaldehyde) was used, the reaction gave a yield of 76%. Increasing the molar ratio of 2-methylquinoline : 4-nitrobenzaldehyde from 1.0:1.0 to 1.4:1.0 led to an

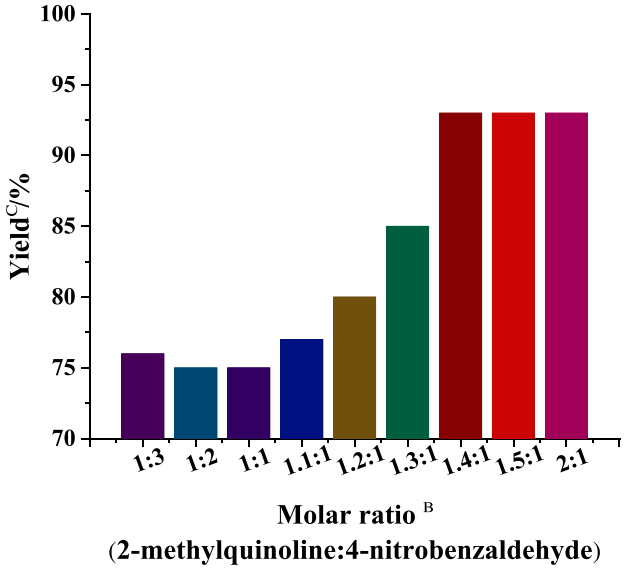


FIGURE 4 Effect of substrate molar ratio on reaction.[a] [a]Reaction conditions: α-chymotrypsin (15 mg) in H_2O (2 mL) at 60°C for 84 h. [b]2-Methylquinoline : 4-nitrobenzaldehyde (mmol:mmol). [c]Isolated yield after column chromatography [Color figure can be viewed at wileyonlinelibrary.com]

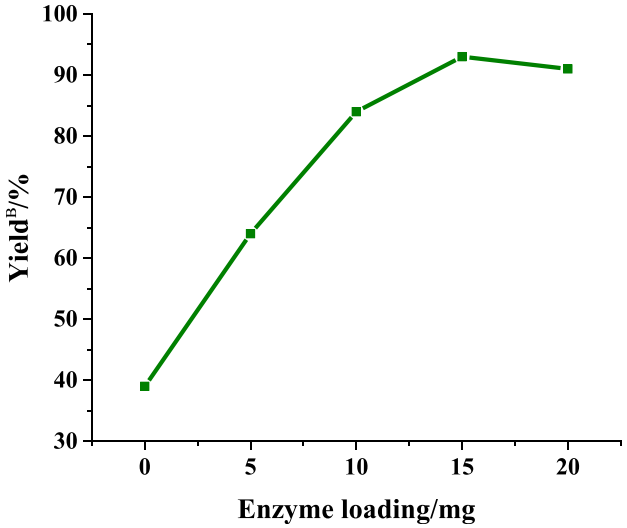


FIGURE 5 Effect of protein loading on the reaction.[a] [a]Reaction conditions: 2-methylquinoline (0.42 mmol), 4-nitrobenzaldehyde (0.3 mmol), and α-chymotrypsin (different quality) in H_2O (2 mL) at different temperatures for 84 h. [b]Isolated yield after column chromatography [Color figure can be viewed at wileyonlinelibrary.com]

increase in yield (from 75% to 93%) of the desired product; however, further increasing the molar ratio from 1.4:1.0 to 2.0:1.0 did not improve the yield. Thus, we chose 1.4:1.0 as the optimal ratio of 2-methylquinoline : 4-nitrobenzaldehyde for the reaction.

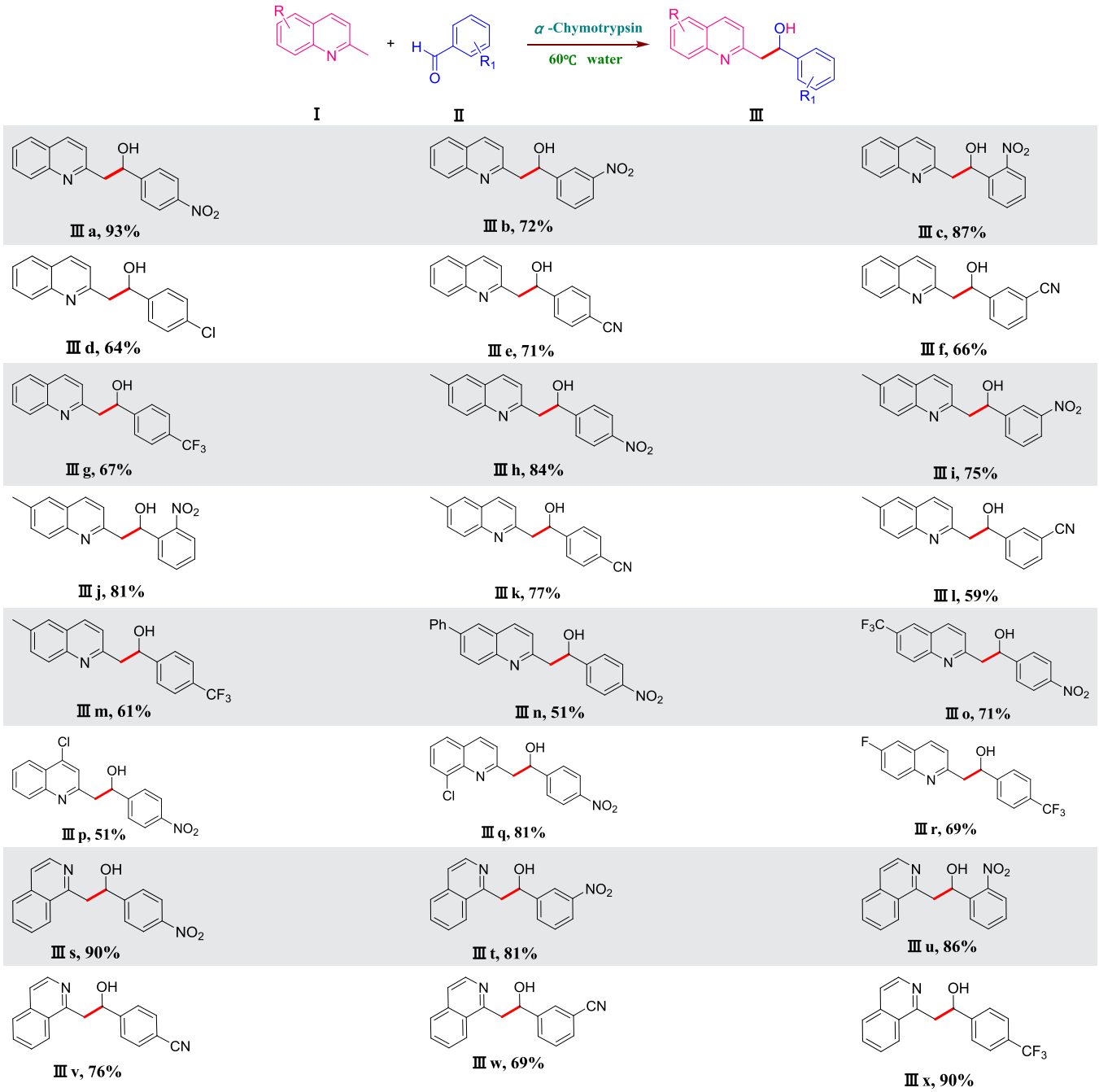
It is known that protein loading affects the yield and kinetics of the reaction[18]; therefore, the effect of protein loading on the α-chymotrypsin–catalyzed model reaction was investigated (Figure 5). The model reaction only gave the product in a low yield of 38% in the absence of enzyme. However, an obvious increase in the yield (64%) was detected when 5 mg of α-chymotrypsin was added. After pepsin addition, a steady increase in yield was observed as the catalyst dosage was increased from 5 to 15 mg; when 15 mg of the enzyme was used, the highest yield of the product was obtained (93%). Further increasing the protein loading from 15 to 20 mg did not improve the results. Thus, 15 mg was chosen as the best protein loading.

On the basis of the optimized conditions, we further investigated the substrate scope and generality of the α-chymotrypsin–catalyzed C (sp^3)–H functionalization reaction. A range of aromatic aldehydes and 2-methylquinoline derivatives were tested (Table 2). In general, aromatic aldehydes with electron-withdrawing substituents showed better results than those with electron-donating or neutral substituents. In addition to 2-methylquinoline, various substituted 2-methylquinoline derivatives were used as substrates (Table 2, III h–III r). It was interesting that 1-methylisoquinoline was also tolerant as a substrate to the reaction (Table 2, III s–III x). Among these examples, the best yield (93%) was obtained for the reaction of 4-nitrobenzaldehyde and 2-methylquinoline (Table 2, III a).

According to previous reports, α-chymotrypsin is a serine protease of the peptide S1 family of 245 amino acid residues, and the catalytic triad is composed of His-57, Asp-102, and Ser-195.[19] A possible mechanism is proposed in Scheme 2. Firstly, in the presence of Ser-195, 2-methylquinolinetends to isomerize and the enamine intermediate is formed. Subsequently, the proton from the enamine tautomer may be abstracted and effectively activated by His-57. Then, the nucleophilic addition of the enamine intermediate to the aromatic aldehyde, which is activated by Ser-195, occurs to afford the desired adduct. Finally, the captured proton from the intermediate is returned to Ser-195, and the corresponding alkyl azaarene derivatives are obtained, with the regeneration of α-chymotrypsin to complete the catalytic cycle.

α-Chymotrypsin from the bovine pancreas was used as a biocatalyst in the C (sp^3)–H functionalization reaction for the synthesis of azaarene derivatives in water. Compared with current chemical technologies, this enzymatic reaction is more environment friendly and sustainable because it uses a biocatalyst from inexpensive regenerable resources. A wide range of substrates could be used with α-chymotrypsin. The activity of α-chymotrypsin could be improved by adjusting the solvent type, water content, temperature, molar ratio of substrates, and protein

TABLE 2 Substrate scope of the benzylic C (sp^3)–H functionalization reaction of 2-methylazaarenes[a]



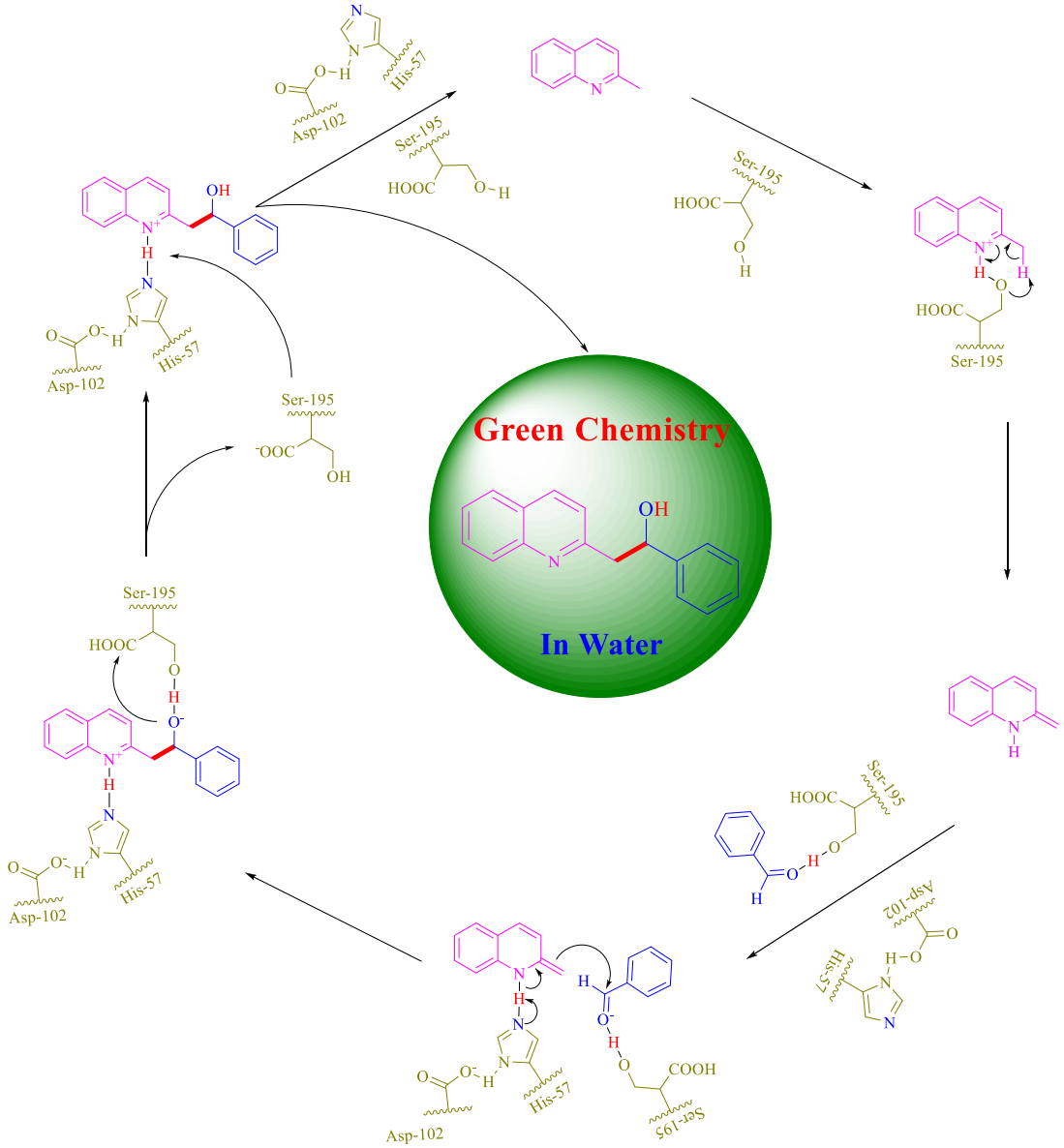
[a]Reaction conditions: 2-methylquinoline derivatives (0.42 mmol), aromatic aldehyde (0.3 mmol), and α-chymotrypsin (15 mg) in H_2O (2 mL) at 60°C for 84 h. Isolated yield after column chromatography.

loading. Yields of up to 93% were achieved. This study offers a novel case of enzyme nonnaturally catalytic activity and a potential synthetic method for organic chemistry, helps to better understand metabolic pathways for the biosynthesis of nitrogen-containing compounds, and extends the application of enzymatic nonnaturally catalytic activity.

3 | EXPERIMENTAL

3.1 | Materials

All major chemicals were obtained from commercial sources and used without further purification. All reactions were monitored by thin-layer chromatography



SCHEME 2 Proposed mechanism for benzylic C (sp^3)–H functionalization reaction of 2-methylazaarenes catalyzed by α-chymotrypsin in aqueous media [Color figure can be viewed at wileyonlinelibrary.com]

(TLC) with silica gel plates. Yields given are isolated yields after column chromatography.

3.2 | General procedure

A sealable reaction tube, equipped with a magnetic stirrer bar, was charged with 2-methylazaarene (0.42 mmol), aromatic aldehyde (0.3 mmol), α-chymotrypsin (15 mg), and H_2O (2 mL). The reaction vessel was heated to 60°C and stirred for 84 hours. TLC is used to follow the reaction upon completion of the reaction, the enzyme was filtered out, and ethyl acetate was added to wash the filter cake and to make the product dissolved in the filtrate. The organic layer was separated with a separatory funnel, and the solvent was removed under reduced pressure. The filtrate was purified by column chromatography using petroleum ether/ethyl acetate as an eluent to isolate the corresponding product.

3.3 | NMR data

3.3.1 | 1-(4-Nitrophenyl)-2-(quinolin-2-yl) ethanol (IIIa)

Yield, 93%; yellow solid, mp 150-152°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20 (d, J = 8.6 Hz, 2H), 8.12 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.65

(d, J = 8.6 Hz, 2H), 7.55 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.80 (s, 1H), 5.45 (dd, J = 8.9, 2.2 Hz, 1H), 3.31 (ddd, J = 24.8, 15.7, 5.9 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.64, 151.45, 147.19, 146.89, 137.22, 130.12, 128.61, 127.70, 126.95, 126.67, 123.64, 121.92, 72.17, 45.33.

3.3.2 | 1-(3-Nitrophenyl)-2-(quinolin-2-yl) ethanol (IIIb)

Yield, 72%; yellow solid, mp 154-156°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.13 (dd, J = 9.5, 5.1 Hz, 2H), 8.07 (d, J = 8.4 Hz, 1H), 7.83 (t, J = 8.2 Hz, 2H), 7.75 (t, J = 7.7 Hz, 1H), 7.54 (dt, J = 16.1, 7.9 Hz, 2H), 7.31-7.18 (m, 1H), 6.76 (s, 1H), 5.44 (dd, J = 8.8, 3.2 Hz, 1H), 3.34 (qd, J = 15.7, 6.1 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.63, 148.34, 146.25, 137.34, 132.12, 130.16, 129.32, 128.46, 127.70, 126.96, 126.56, 122.28, 122.00, 121.02, 72.03, 45.44.

3.3.3 | 1-(2-Nitrophenyl)-2-(quinolin-2-yl) ethanol (IIIc)

Yield, 87%; yellow solid, mp 163-164°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15 (d, J = 8.4 Hz, 1H), 8.06 (dd, J = 23.5, 8.1 Hz, 2H), 7.98 (d, J = 7.4 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.45-7.41 (m, 1H), 7.32 (d, J = 8.3 Hz, 1H), 5.81 (dd, J = 9.1, 1.9 Hz, 1H), 3.56 (dd, J = 15.3, 2.1 Hz, 1H), 3.26 (dd, J = 15.3, 9.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.14, 147.57, 146.74, 139.99, 137.46, 133.63, 130.08, 128.68, 128.51, 128.01, 127.70, 127.05, 126.48, 124.31, 122.03, 68.89, 44.95.

3.3.4 | 1-(4-Chlorophenyl)-2-(quinolin-2-yl)ethanol (IIId)

Yield, 64%; yellow solid, mp 143-145°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.76-7.71 (m, 1H), 7.57-7.52 (m, 1H), 7.41 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.3 Hz, 1H), 6.46 (s, 1H), 5.37-5.27 (m, 1H), 3.27 (d, J = 5.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.12, 146.88, 142.55, 137.07, 132.93, 130.00, 128.57, 128.48, 127.64, 127.30, 126.92, 126.40, 122.06, 72.34, 45.88.

3.3.5 | 4-(1-Hydroxy-2-(quinolin-2-yl) ethyl)benzonitrile (IIIe)

Yield, 71%; white solid, mp 167-171°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.12 (d, J = 8.3 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.85-7.77 (m, 2H), 7.77-7.68 (m, 2H), 7.55 (t, J = 7.0 Hz, 2H), 7.45 (t, J = 7.7 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.57 (s, 1H), 5.36 (dd, J = 8.8, 3.2 Hz, 1H), 3.29 (qd, J = 15.7, 6.1 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.5, 149.1, 145.1, 134.5, 130.0, 127.6, 126.3, 125.9, 125.0, 124.9, 124.1, 120.8, 116.9, 108.2, 70.2, 45.8.

3.3.6 | 3-(1-Hydroxy-2-(quinolin-2-yl) ethyl)benzonitrile (IIIf)

Yield, 66%; white solid, mp 171-172°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.12 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.85-7.78 (m, 2H), 7.73 (dd, J = 16.7, 8.3 Hz, 2H), 7.55 (t, J = 7.0 Hz, 2H), 7.45 (t, J = 7.7 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.54 (s, 1H), 5.36 (dd, J = 8.8, 3.1 Hz, 1H), 3.29 (qd, J = 15.7, 6.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.72, 146.83, 145.56, 137.23, 130.95, 130.39, 130.11, 129.65, 129.14, 128.56, 127.68, 126.94, 126.52, 121.93, 118.96, 112.40, 71.99, 45.45.

3.3.7 | 1-(4-Trifluoromethylphenyl)-2-(quinolin-2-yl)ethanol (IIIg)

Yield, 67%; yellow solid, mp 159-161°C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.09 (dd, J = 26.6, 8.3 Hz, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.65-7.50 (m, 5H), 7.22 (d, J = 8.3 Hz, 1H), 5.39 (dd, J = 8.2, 3.0 Hz, 1H), 3.35-3.22 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.94, 147.94, 146.81, 137.14, 130.04, 129.55, 129.34, 128.52, 127.64, 126.90, 126.44, 126.15, 125.12, 121.97, 72.37, 45.60.

3.3.8 | 2-(6-Methylquinolin-2-yl)-1-(4-nitrophenyl)ethanol (IIIh)

Yield, 84%; yellow solid, mp 149-151°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20 (d, J = 8.7 Hz, 2H), 8.02 (d, J = 8.4 Hz, 1H), 7.98-7.90 (m, 1H), 7.60 (dd, J = 36.4, 7.6 Hz, 4H), 7.16 (d, J = 8.4 Hz, 1H), 5.43 (dd, J = 9.0, 2.8 Hz, 1H), 3.29 (ddd, J = 24.7, 15.7, 6.0 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.62, 151.53, 147.18, 145.47, 136.57, 136.48, 132.39, 128.26, 127.00, 126.67, 126.54, 123.62, 121.86, 72.25, 45.15, 21.54.

3.3.9 | 2-(6-Methylquinolin-2-yl)-1-(3-nitrophenyl)ethanol (IIIi)

Yield, 75%; yellow solid, mp 143-144°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.14-8.09 (m, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.60-7.47 (m, 3H), 7.19 (d, J = 8.4 Hz, 1H), 5.41 (dd, J = 9.0, 3.0 Hz, 1H), 3.30 (qd, J = 15.7, 6.1 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.65, 148.37, 146.33, 145.48, 136.49, 136.38, 132.29, 132.03, 129.22, 128.25, 126.97, 126.48, 122.18, 121.84, 121.00, 72.06, 45.25, 21.47.

3.3.10 | 2-(6-Methylquinolin-2-yl)-1-(2-nitrophenyl)ethanol (IIIj)

Yield, 81%; yellow solid, mp 160-162°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (t, J = 8.5 Hz, 2H), 8.00-7.93 (m, 2H), 7.64 (td, J = 7.8, 0.9 Hz, 1H), 7.57 (dd, J = 10.5, 1.7 Hz, 2H), 7.46-7.39 (m, 1H), 7.29-7.24 (m, 1H), 5.79 (dd, J = 9.1, 2.2 Hz, 1H), 3.53 (dd, J = 15.3, 2.3 Hz, 1H), 3.21 (dd, J = 15.3, 9.1 Hz, 1H), 2.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.13, 147.58, 145.42, 139.57, 136.59, 136.25, 133.50, 132.20, 128.66, 128.23, 127.90, 127.04, 126.49, 124.22, 121.93, 68.90, 44.82, 21.50.

3.3.11 | 4-(1-Hydroxy-2-(6-methylquinolin-2-yl)ethyl)benzonitrile (IIIk)

Yield, 77%; yellow solid, mp 148-150°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, J = 8.3 Hz, 1H), 7.95-7.90 (m, 1H), 7.64-7.59 (m, 2H), 7.59-7.52 (m, 4H), 7.15 (d, J = 8.4 Hz, 1H), 5.35 (dd, J = 9.0, 3.0 Hz, 1H), 3.25 (ddd, J = 24.6, 15.6, 6.0 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.67, 149.49, 145.47, 136.45, 136.38, 132.29, 132.16, 128.23, 126.95, 126.58, 126.50, 121.86, 118.93, 110.93, 72.35, 45.24, 21.49.

3.3.12 | 3-(1-Hydroxy-2-(6-methylquinolin-2-yl)ethyl)benzonitrile (IIIl)

Yield, 59%; white solid, mp 136-137°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (d, J = 8.3 Hz, 1H), 7.98-7.91 (m, 1H), 7.79 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.61-7.51 (m, 3H), 7.45 (t, J = 7.7 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 5.34 (dd, J = 8.8, 3.2 Hz, 1H), 3.26 (qd, J = 15.7, 6.0 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 158.70, 145.66, 145.50, 136.45, 136.37, 132.29, 130.87, 130.34, 129.64, 129.07, 128.27, 126.96, 126.48, 121.82, 118.91, 112.40, 72.04, 45.31, 21.47.

3.3.13 | 2-(6-Methylquinolin-2-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (IIIm)

Yield, 61%; yellow solid, mp 172-173°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, J = 8.4 Hz, 1H), 7.97-7.92 (m, 1H), 7.58 (dt, J = 12.5, 7.6 Hz, 6H), 7.16 (d, J = 8.4 Hz, 1H), 5.37 (dd, J = 8.6, 3.4 Hz, 1H), 3.34-3.21 (m, 2H), 2.54 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.03, 148.12, 145.57, 136.42, 136.33, 132.27, 129.57, 129.36, 128.34, 126.98, 126.51, 126.19, 125.32, 121.94, 72.48, 45.54, 21.53.

3.3.14 | 2-(6-Phenylquinolin-2-yl)-1-(4-nitrophenyl)ethanol (IIIn)

Yield, 51%; yellow solid, mp 138-142°C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.27-8.17 (m, 2H), 8.14 (dd, J = 23.9, 8.5 Hz, 2H), 8.03-7.97 (m, 2H), 7.71 (dd, J = 9.3, 2.2 Hz, 2H), 7.68-7.63 (m, 2H), 7.56-7.47 (m, 2H), 7.45-7.39 (m, 1H), 7.27-7.21 (m, 1H), 5.46 (dd, J = 9.0, 2.9 Hz, 1H), 3.36 (dd, J = 15.7, 3.0 Hz, 1H), 3.29 (dd, J = 15.7, 9.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.54, 151.39, 147.19, 146.25, 140.09, 139.39, 137.35, 130.88, 129.85, 129.01, 127.85, 127.41, 127.13, 126.65, 125.33, 123.63, 122.28, 72.17, 45.31.

3.3.15 | 2-(6-(Trifluoromethyl)quinolin-2-yl)-1-(4-nitrophenyl)ethanol (IIIo)

Yield, 71%; yellow solid, mp 134-135°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.24-8.11 (m, 5H), 7.91 (dd, J = 8.8, 1.6 Hz, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.4 Hz, 1H), 5.48 (dd, J = 8.9, 2.8 Hz, 1H), 3.37 (ddd, J = 24.9, 15.9, 6.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.12, 151.07, 147.97, 147.32, 137.88, 129.87, 126.67, 125.96, 125.85, 125.83, 125.73, 125.71, 123.71, 123.29, 71.97, 45.73.

3.3.16 | 2-(4-Chloroquinolin-2-yl)-1-(4-nitrophenyl)ethanol (IIIp)

Yield, 51%; yellow solid, mp 128-129°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.24-8.18 (m, 3H), 8.06 (d, J = 8.4 Hz, 1H), 7.83-7.76 (m, 1H), 7.65 (t, J = 8.4 Hz, 3H), 7.35 (s, 1H), 6.25 (s, 1H), 5.43 (dd, J = 8.9, 3.0 Hz, 1H), 3.28 (qd, J = 15.8, 6.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.48, 151.04, 147.79, 147.31, 143.64, 131.04, 128.98, 127.53, 126.66, 125.27, 124.16, 123.71, 121.93, 71.99, 45.31.

3.3.17 | 2-(8-Chloroquinolin-2-yl)-1-(4-nitrophenyl)ethanol (IIIq)

Yield, 81%; yellow solid, mp 167-169°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.17 (dd, J = 27.9, 8.5 Hz, 3H), 7.85 (dd, J = 7.5, 1.1 Hz, 1H), 7.74 (dd, J = 8.1, 0.8 Hz, 1H), 7.71-7.65 (m, 2H), 7.47 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 5.49 (dd, J = 8.8, 2.7 Hz, 1H), 3.40 (dd, J = 16.3, 2.8 Hz, 1H), 3.33 (dd, J = 16.3, 8.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.59, 151.38, 147.16, 142.94, 137.59, 132.79, 130.04, 128.14, 126.72, 126.71, 126.55, 123.59, 122.67, 71.98, 44.77.

3.3.18 | 2-(6-Fluoroquinolin-2-yl)-1-(4-nitrophenyl)ethan-1-ol (IIIr)

Yield, 69%; yellow solid, mp 135-137°C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20 (d, J = 8.7 Hz, 2H), 8.12-8.00 (m, 2H), 7.64 (d, J = 8.5 Hz, 2H), 7.51 (td, J = 8.7, 2.8 Hz, 1H), 7.43 (dd, J = 8.6, 2.7 Hz, 1H), 7.30-7.21 (m, 1H), 5.44 (dd, J = 9.0, 2.9 Hz, 1H), 3.31 (ddd, J = 24.8, 15.8, 6.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.17, 159.52, 158.94, 151.25, 147.20, 143.99, 136.52, 130.99, 126.62, 123.62, 122.69, 120.33, 110.68, 72.08, 45.29.

3.3.19 | 2-(Isoquinolin-1-yl)-1-(4-nitrophenyl)ethan-1-ol (IIIs)

Yield, 90%; yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.43 (d, J = 5.8 Hz, 1H), 8.22 (d, J = 8.6 Hz, 2H), 8.02 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.75-7.66 (m, 3H), 7.63-7.58 (m, 2H), 5.54 (dd, J = 9.6, 2.0 Hz, 1H), 3.72 (dd, J = 16.6, 2.3 Hz, 1H), 3.47 (dd, J = 16.5, 9.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.02, 151.52, 147.17, 140.52, 136.18, 130.58, 127.73, 127.57, 127.13, 126.75, 124.45, 123.64, 120.20, 71.58, 41.06.

3.3.20 | 2-(Isoquinolin-1-yl)-1-(3-nitrophenyl)ethan-1-ol (IIIt)

Yield, 81%; yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.44 (d, J = 5.8 Hz, 1H), 8.11 (dd, J = 28.1, 8.1 Hz, 2H), 7.97 (dd, J = 8.2, 0.8 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.70 (ddd, J = 21.6, 11.3, 4.5 Hz, 3H), 7.65-7.60 (m, 2H), 5.88 (dd, J = 9.5, 1.9 Hz, 1H), 4.06 (dd, J = 16.0, 2.1 Hz, 1H), 3.39 (dd, J = 16.0, 9.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.42, 147.71, 140.37, 139.57, 136.33, 133.49, 130.83, 130.54, 128.84, 127.96, 127.69, 127.40, 124.89, 124.14, 120.14, 68.19, 40.58.

3.3.21 | 2-(Isoquinolin-1-yl)-1-(2-nitrophenyl)ethan-1-ol (IIIu)

Yield, 86%; yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.46-8.37 (m, 2H), 8.13 (dd, J = 8.2, 1.4 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.85 (dd, J = 16.5, 7.9 Hz, 2H), 7.71 (t, J = 7.3 Hz, 1H), 7.60 (t, J = 6.4 Hz, 2H), 7.53 (t, J = 7.9 Hz, 1H), 5.53 (dd, J = 9.7, 2.1 Hz, 1H), 3.73 (dd, J = 16.5, 2.4 Hz, 1H), 3.48 (dd, J = 16.5, 9.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.06, 148.36, 146.32, 140.57, 136.16, 132.17, 130.53, 129.31, 127.69, 127.54, 127.13, 124.50, 122.27, 121.10, 120.16, 71.46, 41.15.

3.3.22 | 4-(1-Hydroxy-2-(isoquinolin-1-yl)ethyl)benzonitrile (IIIv)

Yield, 76%; white oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.42 (d, J = 5.7 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.68-7.54 (m, 6H), 5.48 (dd, J = 9.7, 2.0 Hz, 1H), 3.68 (dd, J = 16.5, 2.2 Hz, 1H), 3.44 (dd, J = 16.5, 9.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.09, 149.53, 140.58, 136.19, 132.19, 130.50, 127.65, 127.53, 127.17, 126.67, 124.48, 120.11, 118.88, 111.03, 71.72, 41.15.

3.3.23 | 3-(1-Hydroxy-2-(isoquinolin-1-yl)ethyl)benzonitrile (IIIw)

Yield, 69%; white oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.43 (d, J = 5.8 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.88-7.81 (m, 2H), 7.79-7.67 (m, 2H), 7.60 (ddd, J = 15.6, 9.3, 4.4 Hz, 3H), 7.47 (t, J = 7.7 Hz, 1H), 5.46 (dd, J = 9.8, 2.1 Hz, 1H), 3.69 (dd, J = 16.5, 2.3 Hz, 1H), 3.44 (dd, J = 16.5, 9.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.12, 145.65, 140.54, 136.17, 130.96, 130.55, 130.47, 129.74, 129.16, 127.70, 127.55, 127.13, 124.51, 120.16, 118.95, 112.42, 71.43, 41.21.

3.3.24 | 2-(Isoquinolin-1-yl)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (IIIx)

Yield, 90%; yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.42 (d, J = 5.8 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.65-7.61 (m, 4H), 7.58 (t, J = 6.9 Hz, 2H), 5.49 (dd, J = 9.8, 2.0 Hz, 1H), 3.69 (dd, J = 16.5, 2.3 Hz, 1H), 3.46 (dd, J = 16.5, 9.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 159.39, 148.13, 140.61, 136.15, 130.45, 127.60, 127.51, 127.18, 126.27, 125.67, 125.34, 124.56, 120.04, 119.45, 71.80, 41.47.

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