

Water—More Than Just a Green Solvent: A Stereoselective One-Pot Access to All-Chiral Tetrahydronaphthalenes in Aqueous Media

Bin Tan, Di Zhu, Lihong Zhang, Pei Juan Chua, Xiaofei Zeng, and Guofu Zhong*^[a]

Dedicated to Professor Koichi Narasaka on the occasion of his 65th birthday

Abstract: A facile and highly stereoselective construction of heavily functionalized chiral tetrahydronaphthalene skeletons fused with an oxazolidine moiety has been developed. The process involves an organocatalytic tandem Michael/nitrone formation/intramolecular [3+2] nitrone–olefin cycloaddition in aqueous media. Using rationally designed substrates, the reac-

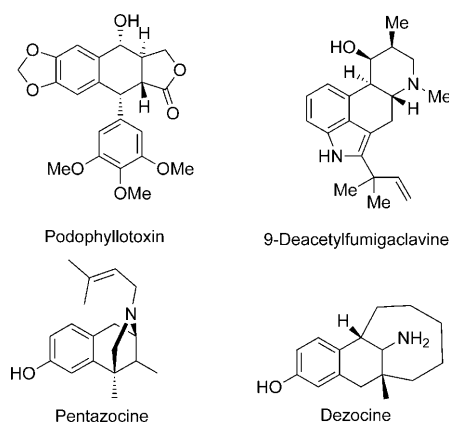
tion conditions have been optimized and the one-pot process has been applied to a series of nitroolefin acrylates and aldehydes. The *N*-hydroxyphenylamine component used in the second

step has also been varied. The stereochemistry of one product has been verified by an X-ray crystal structure determination. The water used in the strategy not only constitutes an environmentally benign solvent, but also helps to improve the reactivity and stereoselectivity.

Keywords: cycloaddition • green chemistry • Michael addition • tetrahydronaphthalenes • water

Introduction

Continuously growing interest in tetrahydronaphthalene derivatives in the context of natural product chemistry,^[1] as well as in relation to other molecules of general importance such as pharmaceuticals^[2] and chiral building blocks, has resulted in the development of a great number of synthetic approaches providing access to these compounds (Scheme 1). Organocatalytic^[3] domino reactions,^[4] in which more than one bond is formed in a multistep one-pot reaction sequence, provide access to molecules of complex architecture without the isolation and purification of intermediates, and are of great importance in current organic chemistry. The intramolecular 1,3-dipolar cycloaddition of nitrones to alkenes^[5] is a powerful method that offers high levels of regio- and stereocontrol in providing access to bicyclic isoxazolidines, which are important precursors of alkaloids, amino acids, β -lactams, and amino sugars. Therefore, optically pure



Scheme 1. Some natural products and pharmaceuticals containing multi-substituted tetrahydronaphthalene moieties.

dipoles or dipolarophiles can potentially direct the stereochemistry of the cycloaddition products.

The asymmetric organocatalytic Michael addition of aldehydes to nitrostyrenes^[6] and related domino reactions^[7] have proved to offer a very efficient approach for obtaining enantiopure molecules bearing functional groups. Despite numerous publications dealing with organocatalytic Michael reactions, there have been very few examples concerned with strategies based on tandem reactions involving intramolecular nitrone [3+2] cycloaddition.^[8] In the work described

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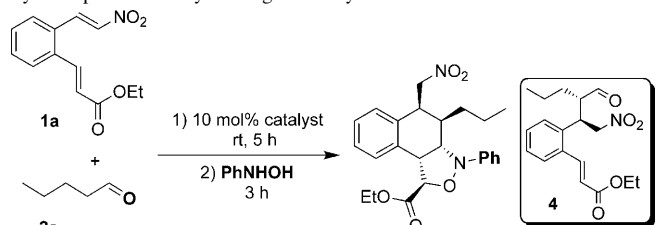
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herein, based on a tandem Michael/intramolecular [3+2] nitron–olefin cycloaddition reaction, we have developed an asymmetric organocatalytic one-pot synthesis of multisubstituted tetrahydronaphthalene isoxazolidines. These products may be further transformed into specific α -hydroxy- γ -amino acids.

Results and Discussion

Rationally designed substrate **1a** was synthesized by a series of simple transformations (for details, see the Supporting Information) in readiness for the Michael reaction directed [3+2] cycloaddition. Initially, we conducted the Michael addition using Jørgensen catalyst **I**^[9] under the reported conditions.^[7d] Upon completion of the Michael reaction, the adduct was first isolated by flash chromatography prior to carrying out the [3+2] nitron–olefin cycloaddition. The desired product **3a** was obtained with good diastereoselectivity and enantioselectivity (Table 1, entry 1). However, the purification of intermediate **4** prompted us to explore the reaction conditions required to carry out the reaction in one pot. When the reaction was conducted in a one-pot fashion, it proceeded smoothly albeit with poor diastereoselectivity (Table 1, entry 2). The low diastereoselectivity in obtaining the final product was most probably due to the hydroxylamine and other components facilitating the retro-Michael reaction. Changing of the organic solvents and catalysts

Table 1. Screening of reaction conditions for the synthesis of chiral tetrahydronaphthalenes by the organocatalytic tandem reaction.^[a]

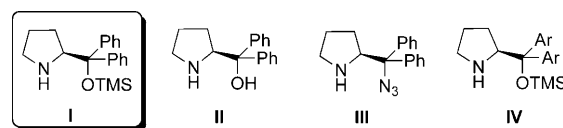


Entry	Cat.	Solvent	Additive	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1 ^[e]	I	CH ₂ Cl ₂	AcOH	77	95:5	> 99
2	I	CH ₂ Cl ₂	AcOH	71	68:32	> 99
3	I	hexane	none	35	72:28	> 99
4	II	CH ₂ Cl ₂	AcOH	< 5	n.d.	n.d.
5	III	CH ₂ Cl ₂	AcOH	56	81:19	97
6	IV	CH ₂ Cl ₂	AcOH	< 5	n.d.	n.d.
7 ^[e]	I	H ₂ O	AcOH	67	92:8	> 99
8	I	H ₂ O	AcOH	56	92:8	> 99
9	III	H ₂ O	AcOH	45	94:6	97
10	I	H ₂ O	PhCO ₂ H	67	92:8	> 99
11 ^[f]	I	H ₂ O	PhCO ₂ H	72	95:5	> 99
12 ^[g]	I	H ₂ O	PhCO ₂ H	73	98:2	> 99

[a] Reaction conditions: Unless specified otherwise, valeraldehyde (**2a**, 0.6 mmol, 3.0 equiv) was added to a suspension of catalyst (10 mol %), additive (20 mol %), and nitroolefin acrylate (**1a**, 0.2 mmol, 1.0 equiv) in solvent (1.0 mL). After the nitroolefin **1a** had been consumed, *N*-hydroxyphenylamine (0.8 mmol, 4.0 equiv) was added. [b] Yield of isolated product. [c] Determined by ¹H NMR spectroscopy and chiral HPLC. [d] Determined by HPLC analysis. [e] Isolated intermediate **4**. [f] 5 mol % catalyst was used. [g] 2 mol % catalyst was used.

used (Scheme 2, **II**, **III**, and **IV**) did not yield any improvement in the results (Table 1, entries 3–6).

Inspired by the recent reports by the groups of Barbas^[10]



Scheme 2. Organocatalysts tested in the tandem reaction. Ar = 3,5-(CF₃)₂C₆H₃.

and Ma^[6c] that brine and water are good media for the organocatalytic Michael reactions of aldehydes and nitroolefins, we hypothesized that water might interact with the dipole of the reactant and direct the configuration of the [3+2] cycloaddition reaction.^[11] If the in situ formation of a 1,3-dipole (nitron) followed by an intramolecular cycloaddition could be carried out in water, it would represent a potent and greener approach to organic synthesis^[12] as most of the reactions used to form nitrones are dehydrations of substituted hydroxylamine and carbonyl compounds that require anhydrous conditions, dehydrating agents, or surfactant catalysts.^[13] We were pleased to find that the reaction of intermediate **4** and *N*-hydroxyphenylamine worked well in water to afford compound **3a** in good yield and with excellent stereoselectivity (Table 1, entry 7). When the tandem reaction was examined in a one-pot protocol, the diastereoselectivity was similar to that seen for the isolated intermediate **4** (Table 1, entries 8–12). Finally, the optimized conditions were established by varying the catalyst loading and additive used (Table 1, entry 12).

Catalyst **I**-promoted tandem Michael/nitron formation/intramolecular [3+2] nitron–olefin cycloaddition reactions between a variety of aldehydes **2** and nitroolefin acrylates **1** under the optimized conditions were then investigated. As revealed in Table 2, this new methodology provided a facile and general approach to a range of multisubstituted, highly functionalized tetrahydronaphthalene oxazolidines in moderate to good yields, with the generation of five new stereogenic centers with excellent enantiomeric excesses (> 99 % *ee*) and high diastereoselectivities (94:6 to 99:1 d.r.). It is noteworthy that steric hindrance played an important role in influencing the yield of the tandem process (Table 2, entry 4). Significant variation of the hydroxyphenylamines in terms of the electronic character of their phenyl units (4-Me, Cl, Br) could be tolerated in the tandem process (Scheme 3). Moreover, the process could also be applied to a less reactive aliphatic hydroxylamine (BnNHOH) with high efficiency (Scheme 3).

To determine the absolute configuration of the products, substrate **1c** was subjected to the tandem reaction (Scheme 3). Based on X-ray structural analysis (Figure 1),^[14] the stereochemistry of product **3o** could be assigned, which was in accordance with our prediction. Furthermore, isoxazolidine **3a** was transformed into the α -hydroxy- γ -amino acid derivative **5** in almost quantitative yield and with no loss of enantioselectivity (Scheme 4). The product **5** may

Table 2. Scope of the organocatalytic tandem Michael/nitrone formation/intramolecular [3+2] cycloaddition.^[a]

Entry	OR ¹ , R	<i>t</i> [h] ^[b]	Yield [%] ^[c]	d.r. ^[d]	<i>ee</i> [%] ^[e]
1	OEt, <i>n</i> Pr	5 (3)	73	98:2	>99
2	OEt, Me	3 (3)	77	95:5	>99
3	OEt, Et	4 (3)	83	98:2	>99
4	OEt, <i>i</i> Pr	10 (12)	48	99:1	>99
5	OEt, CH ₃ (CH ₂) ₅	6 (5)	71	99:1	>99
6	OEt, Bn	5 (3)	72	98:2	>99
7	OEt, BnO(CH ₂) ₂	6 (10)	51	97:3	>99
8	OBn, <i>n</i> Pr	6 (4)	63	97:3	>99
9	OBn, Bn	6 (4)	73	98:2	>99
10	OBn, BnO(CH ₂) ₂	10 (10)	52	96:4	>99

[a] Reaction conditions: See the Supporting Information. [b] Time in parentheses indicates the reaction time of the cycloaddition step. [c] Yield of isolated product. [d] Determined by ¹H NMR spectroscopy and chiral HPLC. [e] Determined by HPLC analysis.

have potential applications in synthetic organic chemistry and the pharmaceutical industry.

Although the mechanism of each step is well established (Scheme 5), there are still some very noteworthy and interesting aspects of this highly efficient and environmentally friendly reaction. Based on the above mentioned results, we propose that added benzoic acid may induce accelerated formation of the enamine species and promote hydrolysis of the iminium ion in the presence of water. Furthermore, the catalyst and additive interacted with the reactants through hydrophobic interactions, and in the process water molecules were excluded from the organic phase. The reaction occurred efficiently in this concentrated organic phase to give rise to the product with excellent results.^[15] ¹H NMR spectra (Figure 2) demonstrated that the TMS protecting group on catalyst **I** was stable in the acidic aqueous medium for at least a couple of hours. A control experiment was performed in water using catalyst **II** (Scheme 6), and the negative results obtained further proved that the catalyst **I** retained its integrity during the course of the Michael addition step.

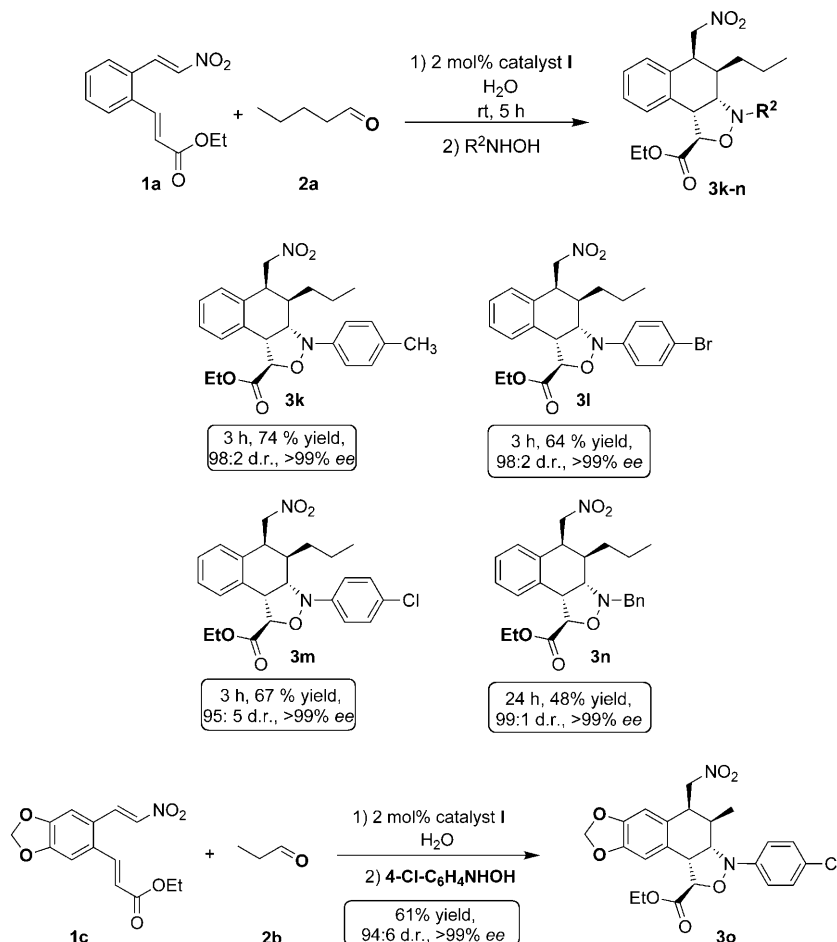
Conclusions

In summary, we have developed an organocatalytic tandem Michael/nitrone formation/intramolecular [3+2] nitrone-

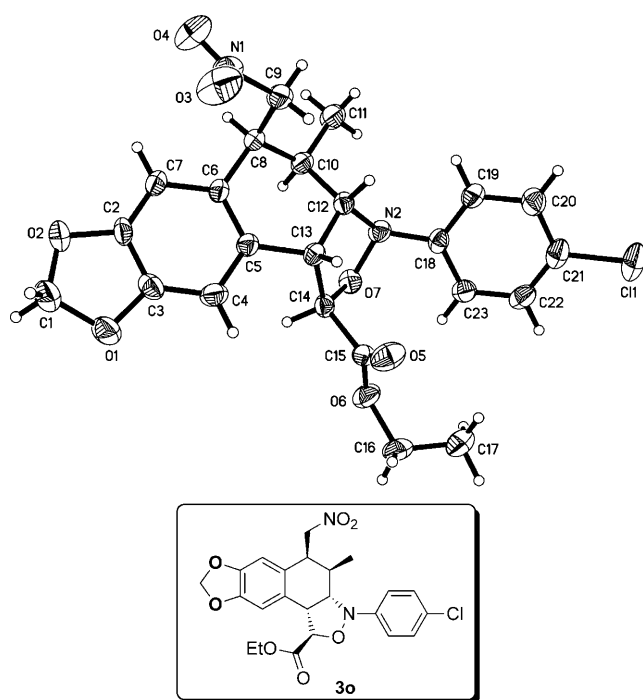
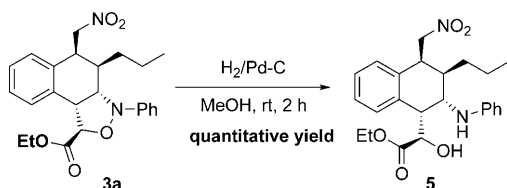
olefin cycloaddition reaction strategy for the facile construction of biologically significant, heavily functionalized, chiral tetrahydronaphthalene skeletons with multiple stereogenic centers. This highly stereoselective synthetic protocol for the construction of complex architectures seemingly has huge potential in medicinal chemistry and diversity-oriented synthesis. Moreover, the use of water in this strategy is not only environmentally benign, but also helps to improve the reactivity and stereoselectivity. Further application of this process in organic synthesis will be reported in due course.

Experimental Section

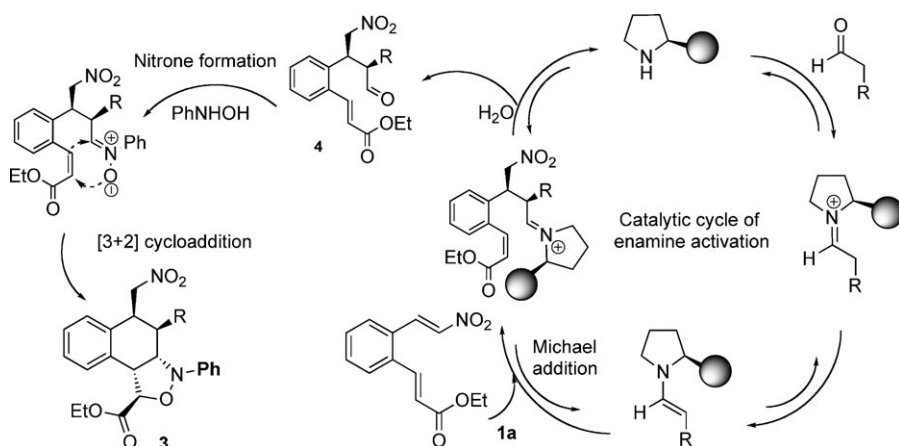
General: ¹H NMR spectra were recorded on a Bruker AMX 400 spectrophotometer (CDCl₃ as solvent); chemical shifts reported relative to the signal of CDCl₃ (δ = 7.26 ppm). ¹³C NMR spectra reported relative to the signal CDCl₃ (δ = 77.0 ppm, triplet). Enantioselectivities were determined by HPLC analysis employing a Daicel Chiralpak AD-H or Chiralcel



Scheme 3. Tandem reactions with different hydroxylamines.

Figure 1. X-ray crystallographic determination of **3o**.Scheme 4. Synthesis of α -hydroxy- γ -amino acid derivative **5**.

OD-H column. Optical rotations were measured in CH_2Cl_2 on a Schmidt + Haensdch polarimeter (Polartronic MH8) with a 1.0 mL cell (c given in g per 100 mL). Absolute configuration of the products was determined by X-ray. High-resolution mass spectrometry was recorded on a Finnigan



Scheme 5. Catalytic cycle and reaction pathway of the final product formation.

MAT 95 $\times$ P spectrometer. Racemates were synthesized by using the racemic Jørgensen catalyst (**Rac-I**).

Typical procedure for the synthesis of multisubstituted chiral tetrahydronaphthalenes by the organocatalytic one-pot tandem reaction (Table 2, entry 1): Valeraldehyde (**2a**, 0.6 mmol, 3.0 equiv) was added to a suspension of catalyst **I** (2 mol %), benzoic acid (20 mol %), and nitroolefin acrylate **1a** (0.2 mmol, 1.0 equiv) in water (1.0 mL) at room temperature (23 °C). When the **1a** had been consumed, *N*-hydroxyphenylamine (0.8 mmol, 4.0 equiv) was added, and the mixture was stirred for a further 3 h. When the reaction was seen to be complete (monitoring by TLC and NMR analysis of aliquots taken directly from the solution), the mixture was extracted with CH_2Cl_2 (2×5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 , and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography on silica gel (gradient elution, EtOAc/hexane, 1:20 to 1:10) to afford the product (1*R*,3*aS*,4*R*,5*S*,9*bR*)-ethyl 5-(nitromethyl)-3-phenyl-4-propyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (**3a**) in 73 % yield. $[\alpha]_{\text{D}}^{24} = 88$ ($c = 0.6$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.34\text{--}7.25$ (m, 5H), 7.19 (d, $J = 7.6$ Hz, 2H), 7.09–7.06 (m, 2H), 4.76 (dd, $J = 5.6$, 12.0 Hz, 1H), 4.65–4.63 (m, 1H), 4.43 (d, $J = 7.2$ Hz, 1H), 4.27 (q, $J = 6.8$ Hz, 2H), 4.31–4.23 (m, 1H), 4.10–4.08 (m, 1H), 3.96 (t, $J = 8.4$ Hz, 1H), 2.06–2.02 (m, 1H), 1.53–1.49 (m, 2H), 1.35 (t, $J = 7.2$ Hz, 3H), 1.36–1.27 (m, 2H), 0.96 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.4$, 150.3, 134.9, 133.8, 129.7, 128.9, 128.1, 127.7, 127.2, 123.3, 116.4, 84.2, 77.5, 67.3, 61.9, 46.9, 38.7, 37.9, 30.6, 20.2, 14.2, 14.1 ppm; HPLC: Chiralpak AD-H (hexane/*i*PrOH = 80:20, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm), t_{R} (major) = 8.1 min, t_{R} (minor) = 24.7 min; >99 % *ee*; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_5$: 425.2076 [$M+H$]; found 425.2075 (see the Supporting Information for full experimental details).

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-Ethyl 4-methyl-5-(nitromethyl)-3-phenyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3b**):** The title compound was prepared in 77 % yield according to the typical procedure described above (the first step in 3 h, the second step in 3 h). $[\alpha]_{\text{D}}^{24} = 87.3$ ($c = 1.1$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.34\text{--}7.23$ (m, 5H), 7.21 (d, $J = 7.6$ Hz, 2H), 7.08–7.04 (m, 2H), 4.78–4.68 (m, 2H), 4.42 (d, $J = 7.2$ Hz, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 4.20 (t, $J = 7.2$ Hz, 1H), 4.10 (dd, $J = 7.2$, 11.6 Hz, 1H), 3.80 (t, $J = 7.2$ Hz, 1H), 2.38–2.33 (m, 1H), 1.31 (t, $J = 7.2$ Hz, 3H), 1.05 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.3$, 150.0, 134.3, 133.9, 129.7, 128.9, 128.0, 127.8, 126.6, 123.7, 117.0, 83.7, 77.5, 68.9, 61.9, 47.3, 39.5, 33.0, 14.1, 13.9 ppm; HPLC: Chiralpak AD-H (hexane/*i*PrOH = 80:20, flow rate 1.0 mL min $^{-1}$, $\lambda = 220$ nm), t_{R} (major) = 14.5 min, t_{R} (minor) = 35.5 min; >99 % *ee*; HRMS (ESI): m/z calcd for $\text{C}_{22}\text{H}_{25}\text{N}_2\text{O}_5$: 397.1763 [$M+H$]; found 397.1760.

(1*R*,3*aS*,4*R*,5*S*,9*bR*)-Ethyl 4-ethyl-5-(nitromethyl)-3-phenyl-1,3,3*a*,4,5,9*b*-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3c**):** The title compound was prepared in 83 % yield according to the typical procedure described above (the first step in 4 h, the second step in 3 h). $[\alpha]_{\text{D}}^{24} = 89.5$ ($c = 0.9$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.32\text{--}7.21$ (m, 5H), 7.16 (d, $J = 8.4$ Hz, 2H), 7.08–7.01 (m, 2H), 4.72 (dd, $J = 5.6$, 12.0 Hz, 1H), 4.61–4.56 (m, 1H), 4.41 (d, $J = 7.2$ Hz, 1H), 4.25 (q, $J = 6.8$ Hz, 2H), 4.28–4.21 (m, 1H), 4.10–4.08 (m, 1H), 3.96 (t, $J = 8.4$ Hz, 1H), 2.17–2.10 (m, 1H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.34–1.27 (m, 1H), 1.08 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.4$, 150.4, 134.9, 133.8, 129.6, 128.9, 128.1, 127.7, 127.3, 123.2, 116.2, 84.2, 77.5, 67.1, 61.9, 46.9, 39.8, 38.4, 21.4, 14.1, 11.5 ppm; HPLC: Chiralpak AD-H (hexane/*i*PrOH = 80:20, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm), t_{R} (major) = 18.1 min, t_{R} (minor) = 30.5 min; >99 % *ee*; HRMS (ESI): m/z calcd for

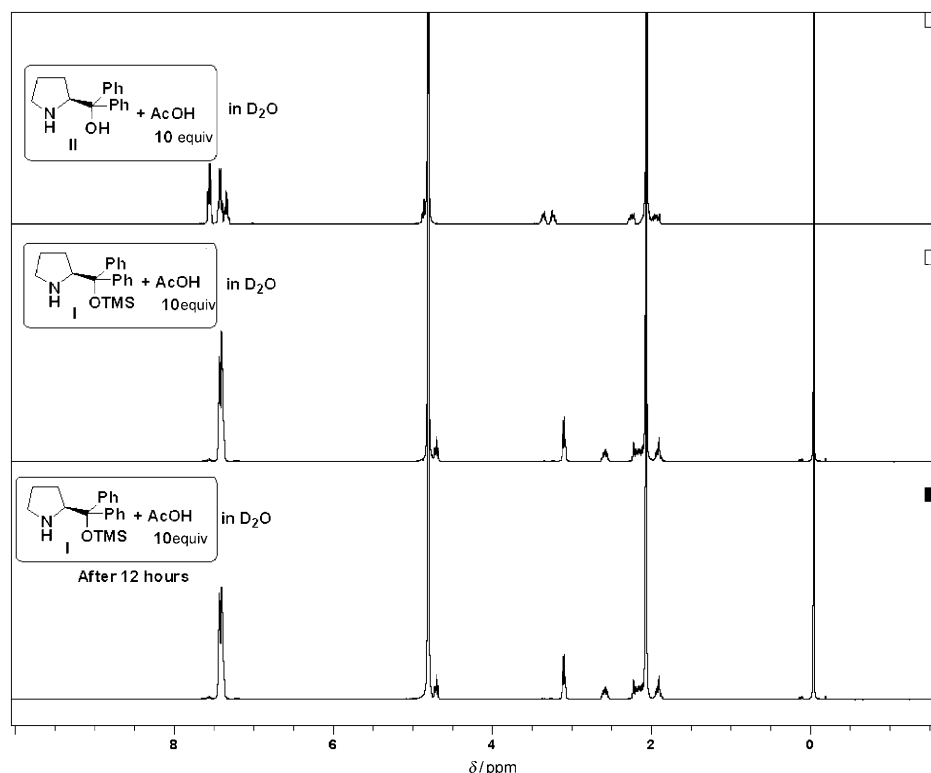
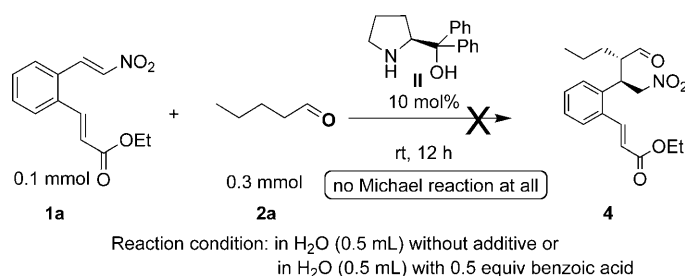


Figure 2. ^1H NMR spectra of catalysts **I** and **II** in D_2O + AcOH.



Scheme 6. Control experiment for mechanistic investigation.

$\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_5$: 411.1920 [$M+H$]; found 411.1916.

(1R,3aS,4R,5S,9bR)-Ethyl 4-isopropyl-5-(nitromethyl)-3-phenyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-c]isoxazole-1-carboxylate (3d): The title compound was prepared in 48% yield according to the typical procedure described above (the first step in 10 h, the second step in 12 h). $[\alpha]_D^{25} = 93.3$ ($c = 1.5$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.35\text{--}7.23$ (m, 7H), 7.11–7.06 (m, 2H), 4.72 (dd, $J = 5.6$, 12.0 Hz, 1H), 4.84–4.82 (m, 2H), 4.42 (d, $J = 7.2$ Hz, 1H), 4.27–4.22 (m, 4H), 4.13 (t, $J = 7.2$ Hz, 1H), 2.13–2.10 (m, 1H), 1.88–1.86 (m, 1H), 1.33 (t, $J = 7.2$ Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 0.92 ppm (d, $J = 5.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.2$, 149.5, 135.3, 134.4, 129.4, 129.0, 127.9, 127.6, 125.9, 123.8, 117.2, 84.0, 78.1, 65.5, 61.9, 47.9, 44.1, 39.2, 28.2, 22.4, 20.9, 14.1 ppm; HPLC: Chiralcel OD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm), t_R (major)=7.7 min, t_R (minor)=13.2 min; >99% ee; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{29}\text{N}_2\text{O}_5$: 425.2076 [$M+H$]; found 425.2079.

(1R,3aS,4R,5S,9bR)-Ethyl 4-hexyl-5-(nitromethyl)-3-phenyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-c]isoxazole-1-carboxylate (3e): The title compound was prepared in 71% yield according to the typical procedure described above (the first step in 6 h, the second step in 5 h). $[\alpha]_D^{24} = 73.7$ ($c = 0.9$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.34\text{--}7.23$ (m, 5H),

7.19 (d, $J = 8.4$ Hz, 2H), 7.10–7.04 (m, 2H), 4.76 (dd, $J = 5.6$, 12.0 Hz, 1H), 4.65–4.63 (m, 1H), 4.43 (d, $J = 6.8$ Hz, 1H), 4.31–4.25 (m, 3H), 4.10 (m, 1H), 3.96 (t, $J = 8.4$ Hz, 1H), 2.24–2.20 (m, 1H), 1.53–1.49 (m, 2H), 1.46–1.30 (m, 13H), 0.90 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.4$, 150.4, 134.9, 133.8, 129.6, 128.9, 128.1, 127.7, 127.1, 123.3, 116.3, 84.2, 77.5, 67.3, 61.9, 46.9, 38.7, 38.0, 31.7, 29.4, 28.4, 26.9, 22.6, 14.1, 14.0 ppm; HPLC: Chiralpak AD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm), t_R (major)=7.1 min, t_R (minor)=18.7 min; >99% ee; HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{33}\text{N}_2\text{O}_5$: 467.2546 [$M+H$]; found 467.2543.

(1R,3aS,4R,5S,9bR)-Ethyl 4-benzyl-5-(nitromethyl)-3-phenyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-c]isoxazole-1-carboxylate (3f): The title compound was prepared in 72% yield according to the typical procedure described above (the first step in 5 h, the second step in 3 h). $[\alpha]_D^{24} = 132.4$ ($c = 1.4$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.34\text{--}7.14$ (m, 10H), 7.01–6.92 (m, 4H), 4.79–4.77 (m, 2H), 4.44 (d, $J = 6.8$ Hz, 1H), 4.30 (t, $J = 7.2$ Hz, 1H), 4.22 (q, $J = 7.2$ Hz, 1H), 4.03–3.97 (m, 2H), 2.58–2.51 (m, 2H), 1.28 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.0$, 149.8, 138.4, 134.6, 134.0, 129.7, 129.1, 128.9, 128.8, 128.0, 127.8, 126.8, 126.1, 123.2, 116.5, 83.9, 77.2, 65.7, 61.9, 47.4, 41.3, 37.7, 34.0, 14.1 ppm; HPLC: Chiralcel OD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm), t_R (major)=12.8 min, t_R (minor)=43.8 min; >99% ee; HRMS (ESI): m/z calcd for $\text{C}_{28}\text{H}_{35}\text{N}_2\text{O}_5$: 473.2076 [$M+H$]; found 473.2080.

(1R,3aS,4R,5S,9bR)-Ethyl 4-[2-(benzyloxy)ethyl]-5-(nitromethyl)-3-phenyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-c]isoxazole-1-carboxylate (3g): The title compound was prepared in 61% yield according to the typical procedure described above (the first step in 6 h, the second step in 10 h). $[\alpha]_D^{24} = 65.1$ ($c = 0.4$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.38\text{--}7.27$ (m, 10H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.09–7.00 (m, 2H), 4.80 (dd, $J = 5.2$, 8.4 Hz, 1H), 4.73–4.70 (m, 1H), 4.55–4.53 (m, 2H), 4.44 (d, $J = 6.8$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 4.28–4.23 (m, 1H), 4.17 (m, 1H), 4.07 (t, $J = 8.0$ Hz, 1H), 3.66–3.65 (m, 2H), 2.47–2.44 (m, 1H), 1.66–1.63 (m, 2H), 1.32 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.3$, 150.2, 138.1, 134.9, 133.9, 129.6, 128.9, 128.5, 128.0, 127.8, 127.7, 127.0, 123.2, 116.3, 84.1, 77.6, 73.3, 68.2, 61.9, 47.1, 38.9, 36.5, 28.8, 14.1 ppm; HPLC: Chiralcel OD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min $^{-1}$, $\lambda = 210$ nm), t_R (major)=13.6 min, t_R (minor)=42.8 min; >99% ee; HRMS (ESI): m/z calcd for $\text{C}_{30}\text{H}_{33}\text{N}_2\text{O}_6$: 517.2339 [$M+H$]; found 517.2337.

(1R,3aS,4R,5S,9bR)-Benzyl 5-(nitromethyl)-3-phenyl-4-propyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-c]isoxazole-1-carboxylate (3h): The title compound was prepared in 63% yield according to the typical procedure described above (the first step in 6 h, the second step in 4 h). $[\alpha]_D^{24} = 38.5$ ($c = 1.5$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.42$ (m, 5H), 7.40–7.19 (m, 4H), 7.17–7.12 (m, 3H), 7.08–7.02 (m, 2H), 5.25 (s, 2H), 4.74 (dd, $J = 5.6$, 12.0 Hz, 1H), 4.60 (m, 1H), 4.47 (d, $J = 7.2$ Hz, 1H), 4.22 (t, $J = 7.2$ Hz, 1H), 4.08 (m, 1H), 3.94 (t, $J = 8.0$ Hz, 1H), 2.25–2.23 (m, 1H), 1.53–1.46 (m, 2H), 1.32–1.27 (m, 2H), 0.95 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 170.2$, 150.3, 135.0, 134.8, 133.5, 129.7, 128.9, 128.74, 128.71, 128.66, 128.1, 127.7, 127.2, 123.3, 116.3, 84.1, 77.5, 67.6, 67.5, 46.9, 38.7, 37.8, 30.6, 20.2, 14.2 ppm; HPLC: Chiral-

pak AD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min⁻¹, λ =210 nm), t_R (major)=13.3 min, t_R (minor)=37.4 min; >99% *ee*; HRMS (ESI): m/z calcd for C₂₉H₃₁N₂O₅: 487.2233 [$M+H$]; found 487.2232.

(1R,3aS,4R,5S,9bR)-Benzyl 4-benzyl-5-(nitromethyl)-3-phenyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3i): The title compound was prepared in 73% yield according to the typical procedure described above (the first step in 6 h, the second step in 4 h). [α]_D²⁴=96.1 (*c*=1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ =7.38–7.13 (m, 15H), 7.00–6.96 (m, 2H), 6.91–6.89 (m, 2H), 5.22–5.16 (m, 2H), 4.78 (m, 2H), 4.49 (d, *J*=6.8 Hz, 1H), 4.28 (t, *J*=7.2 Hz, 1H), 3.98–3.95 (m, 2H), 2.57–2.53 ppm (m, 2H); ¹³C NMR (100 MHz, CDCl₃): δ =169.8, 149.6, 138.3, 135.0, 134.6, 133.8, 129.7, 129.1, 128.9, 128.7, 128.65, 128.0, 127.8, 126.8, 123.2, 116.5, 83.7, 77.2, 67.6, 65.9, 47.5, 41.2, 37.7, 34.0 ppm; HPLC: Chiralpak OD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min⁻¹, λ =210 nm), t_R (major)=20.9 min, t_R (minor)=28.3 min; >99% *ee*; HRMS (ESI): m/z calcd for C₃₃H₃₁N₂O₅: 435.2233 [$M+H$]; found 535.2237.

(1R,3aS,4R,5S,9bR)-Benzyl 4-[2-(benzyloxy)ethyl]-5-(nitromethyl)-3-phenyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3j): The title compound was prepared in 62% yield according to the typical procedure described above (the first step in 10 h, the second step in 10 h). [α]_D²⁴=50.7 (*c*=1.3, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ =7.39–7.30 (m, 10H), 7.26–7.13 (m, 7H), 7.08–7.01 (m, 2H), 5.23 (s, 2H), 4.79 (dd, *J*=5.2, 12.0 Hz, 1H), 4.70–4.68 (m, 1H), 4.56–4.47 (m, 3H), 4.24 (t, *J*=7.2 Hz, 1H), 4.16–4.14 (m, 1H), 4.04 (t, *J*=8.0 Hz, 1H), 3.65–3.63 (m, 2H), 2.46–2.43 (m, 1H), 1.98–1.84 (m, 1H), 1.66–1.64 ppm (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ =170.1, 150.1, 138.1, 135.0, 134.8, 133.6, 129.7, 128.9, 128.7, 128.5, 128.0, 127.8, 127.73, 127.71, 127.0, 123.2, 116.2, 84.0, 77.6, 73.2, 68.2, 67.6, 67.2, 47.2, 38.8, 36.4, 28.8 ppm; HPLC: Chiralpak AD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min⁻¹, λ =210 nm), t_R (major)=17.4 min, t_R (minor)=29.7 min; >99% *ee*; HRMS (ESI): m/z calcd for C₃₅H₃₅N₂O₆: 579.2495 [$M+H$]; found 579.2498.

General procedure for the tandem reactions with different hydroxylamines: Valeraldehyde (**2a**, 0.6 mmol, 3.0 equiv) was added to a suspension of catalyst **I** (2 mol %), benzoic acid (20 mol %), and nitroolefin acrylate **1a** (0.2 mmol, 1.0 equiv) in water (1.0 mL) at room temperature. After 5 h, the nitroolefin **1a** had been consumed, whereupon the requisite hydroxylamine (4-Me-C₆H₄NHOH, 4-Cl-C₆H₄NHOH, 4-Br-C₆H₄NHOH, or BnNHOH) (0.8 mmol, 4.0 equiv) was added and the resulting mixture was stirred for 3–24 h. When the reaction was complete (monitoring by TLC and NMR analysis of aliquots taken directly from the solution), the mixture was extracted with CH₂Cl₂ (2 × 5 mL). The combined organic layers were washed repeatedly with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography on silica gel (EtOAc/hexane, 1:20–1:12) to afford the product.

(1R,3aS,4R,5S,9bR)-Ethyl 5-(nitromethyl)-4-propyl-3-*p*-tolyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3k): The title compound was prepared in 74% yield according to the general procedure described above (the second step in 3 h). [α]_D²⁴=74.0 (*c*=1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ =7.28–7.24 (m, 3H), 7.15–7.07 (m, 5H), 4.76 (dd, *J*=5.6, 12.0 Hz, 1H), 4.66–4.63 (m, 1H), 4.41 (d, *J*=7.2 Hz, 1H), 4.29 (q, *J*=7.2 Hz, 2H), 4.23 (t, *J*=7.2 Hz, 1H), 4.12 (m, 1H), 3.88 (t, *J*=8.0 Hz, 1H), 2.33 (s, 3H), 2.18–2.16 (m, 1H), 1.51–1.42 (m, 2H), 1.36 (t, *J*=7.2 Hz, 3H), 1.29–1.22 (m, 2H), 0.96 ppm (t, *J*=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ =170.5, 147.7, 134.8, 134.0, 133.3, 129.7, 129.5, 128.0, 127.6, 127.0, 117.2, 84.0, 77.5, 67.5, 61.9, 47.0, 38.6, 37.7, 30.4, 20.7, 20.2, 14.2, 14.1 ppm; HPLC: Chiralpak AD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min⁻¹, λ =210 nm), t_R (major)=10.7 min, t_R (minor)=30.2 min; >99% *ee*; HRMS (ESI): m/z calcd for C₂₅H₃₁N₂O₅: 439.2233 [$M+H$]; found 439.2234.

(1R,3aS,4R,5S,9bR)-Ethyl 3-(4-chlorophenyl)-5-(nitromethyl)-4-propyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3l): The title compound was prepared in 64% yield according to the general procedure described above (the second step in 3 h). [α]_D²⁴=83.9 (*c*=1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ =7.29–7.23 (m, 5H), 7.13–7.07 (m, 3H), 4.74 (dd, *J*=6.0, 12.0 Hz, 1H), 4.67–4.64 (m, 1H), 4.43 (d, *J*=7.2 Hz, 1H), 4.28 (q, *J*=7.2 Hz, 2H), 4.22 (t, *J*=7.2 Hz, 1H), 4.10–4.08

(m, 1H), 3.91 (t, *J*=8.0 Hz, 1H), 2.23–2.21 (m, 1H), 1.51–1.45 (m, 2H), 1.34 (t, *J*=7.2 Hz, 3H), 1.34–1.29 (m, 2H), 0.95 ppm (t, *J*=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ =170.3, 148.9, 134.7, 133.6, 129.6, 128.9, 128.4, 128.1, 127.8, 127.1, 117.7, 84.2, 77.2, 67.4, 62.0, 47.1, 38.4, 37.8, 30.4, 20.2, 14.2, 14.1 ppm; HPLC: Chiralpak AD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min⁻¹, λ =210 nm), t_R (major)=9.3 min, t_R (minor)=38.1 min; >99% *ee*; HRMS (ESI): m/z calcd for C₂₄H₂₈N₂O₅Cl: 459.1687 [$M+H$]; found 459.1686.

(1R,3aS,4R,5S,9bR)-Ethyl 3-(4-bromophenyl)-5-(nitromethyl)-4-propyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3m): The title compound was prepared in 67% yield according to the general procedure described above (the second step in 3 h). [α]_D²⁴=87.5 (*c*=0.9, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ =7.42 (d, *J*=8.8 Hz, 2H), 7.3–7.25 (m, 3H), 7.08–7.05 (m, 1H), 7.06 (d, *J*=8.8 Hz, 1H), 4.74 (dd, *J*=6.0, 12.0 Hz, 1H), 4.67–4.64 (m, 1H), 4.43 (d, *J*=6.8 Hz, 1H), 4.28 (q, *J*=7.2 Hz, 2H), 4.22 (t, *J*=7.2 Hz, 1H), 4.10–4.08 (m, 1H), 3.91 (t, *J*=8.0 Hz, 1H), 2.23–2.18 (m, 1H), 1.65 (m, 1H), 1.52–1.46 (m, 2H), 1.34 (t, *J*=7.2 Hz, 3H), 1.29–1.26 (m, 1H), 0.95 ppm (t, *J*=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ =170.3, 149.5, 134.7, 133.6, 131.8, 129.6, 128.2, 127.8, 127.0, 117.9, 115.8, 84.2, 77.2, 67.3, 62.0, 47.1, 38.5, 37.9, 30.5, 20.2, 14.2, 14.1 ppm; HPLC: Chiralpak AD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min⁻¹, λ =210 nm), t_R (major)=8.7 min, t_R (minor)=34.0 min; >99% *ee*; HRMS (ESI): m/z calcd for C₂₄H₂₈N₂O₅Br: 504.3846 [$M+H$]; found 504.3848.

(1R,3aS,4R,5S,9bR)-Ethyl 3-benzyl-5-(nitromethyl)-4-propyl-1,3,3a,4,5,9b-hexahydronaphtho[2,1-*c*]isoxazole-1-carboxylate (3n): The title compound was prepared in 48% yield according to the general procedure described above (the second step in 24 h). [α]_D²⁴=−4.6 (*c*=0.8, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ =7.42 (d, *J*=6.8 Hz, 2H), 7.36–7.21 (m, 6H), 6.98 (d, *J*=7.6 Hz, 1H), 4.61 (m, 1H), 4.52 (dd, *J*=6.4, 12.0 Hz, 1H), 4.37–4.12 (m, 5H), 4.02–4.00 (m, 2H), 3.24 (t, *J*=7.2 Hz, 1H), 1.85 (m, 1H), 1.33 (t, *J*=7.2 Hz, 3H), 1.36–1.30 (m, 3H), 0.93–0.90 (m, 1H), 0.85 ppm (t, *J*=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ =171.4, 136.9, 134.7, 134.3, 129.7, 129.2, 128.4, 127.8, 127.6, 127.5, 126.3, 83.8, 77.2, 66.2, 61.8, 61.6, 48.3, 37.9, 29.9, 20.2, 14.2, 14.1 ppm; HPLC: Chiralpak AD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min⁻¹, λ =210 nm), t_R (major)=5.7 min, t_R (minor)=9.3 min; >99% *ee*; HRMS (ESI): m/z calcd for C₂₅H₃₁N₂O₅: 439.2233 [$M+H$]; found 439.2233.

General procedure for the synthesis of 3o for X-ray analysis: Propional (**2b**, 0.6 mmol, 3.0 equiv) was added to a suspension of catalyst **I** (2 mol %), benzoic acid (20 mol %), and nitroolefin acrylate **1c** (0.2 mmol, 1.0 equiv) in water (1.0 mL) at room temperature. After 5 h, the nitroolefin **1c** had been consumed, whereupon 4-chloro-*N*-hydroxyphenylamine (0.8 mmol, 4.0 equiv) was added and the resulting mixture was stirred for 4 h. When the reaction was complete (monitoring by TLC and NMR analysis of aliquots taken directly from the solution), the mixture was extracted with CH₂Cl₂ (2 × 5 mL). The combined organic layers were washed three times with brine, dried over Na₂SO₄, and the solvent was removed under reduced pressure. The residue was subjected to flash chromatography on silica gel to afford **3o** in 61% yield (EtOAc/hexane, 1:20–1:10). [α]_D²⁴=86.5 (*c*=0.5, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃): δ =7.26 (d, *J*=8.8 Hz, 2H), 7.09 (d, *J*=8.8 Hz, 1H), 6.72 (s, 1H), 6.55 (s, 1H), 5.95 (s, 2H), 4.70–4.61 (m, 2H), 4.36 (d, *J*=7.2 Hz, 1H), 4.28 (q, *J*=7.2 Hz, 2H), 4.03 (t, *J*=7.2 Hz, 1H), 3.93–3.91 (m, 1H), 3.72 (t, *J*=8.0 Hz, 1H), 2.33–2.28 (m, 1H), 1.32 (t, *J*=7.2 Hz, 3H), 1.10 ppm (d, *J*=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ =170.2, 148.8, 147.5, 147.4, 128.9, 128.5, 127.5, 126.7, 118.0, 109.2, 106.9, 101.4, 84.0, 77.6, 68.7, 62.1, 47.2, 40.2, 32.8, 14.2, 14.1 ppm; HPLC: Chiralpak AD-H (hexane/*i*PrOH=80:20, flow rate 1.0 mL min⁻¹, λ =210 nm), t_R (major)=16.0 min, t_R (minor)=35.5 min; >99% *ee*; HRMS (ESI): m/z calcd for C₂₅H₂₃N₂O₇Cl: 475.1272 [$M+H$]; found 475.1275.

General procedure for the synthesis of α -hydroxy- γ -amino acid derivatives:

(R)-Ethyl 2-hydroxy-2-[(1R,2S,3R,4S)-4-(nitromethyl)-2-(phenylamino)-3-propyl-1,2,3,4-tetrahydronaphthalen-1-yl]acetate (5): 10% Pd/C (30 mg) was added to a solution of **3a** (0.1 mmol) in methanol (5.0 mL) at room temperature, which was maintained under an atmosphere of hydrogen by means of a balloon. After stirring for 2 h, the mixture was fil-

tered through Celite. Removal of the solvent from the filtrate under reduced pressure afforded the product in almost quantitative yield. $[\alpha]_D^{24} = -28.0$ ($c = 1.0$, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3): $\delta = 7.40\text{--}7.21$ (m, 3H), 7.16 (t, $J = 7.2$ Hz, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 6.71 (t, $J = 7.2$ Hz, 1H), 6.55 (d, $J = 8.0$ Hz, 2H), 4.65 (s, 1H), 4.60 (dd, $J = 4.8$, 12.0 Hz, 1H), 4.53–4.50 (m, 1H), 4.01–3.92 (m, 4H), 3.78–3.76 (m, 2H), 3.56–3.51 (m, 1H), 3.29 (s, 1H), 2.70–2.68 (m, 1H), 1.56–1.51 (m, 3H), 1.12–0.98 (m, 1H), 1.01 (t, $J = 7.2$ Hz, 3H), 0.94 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 174.0$, 146.7, 136.3, 135.1, 129.4, 129.0, 127.9, 127.5, 127.4, 117.8, 112.4, 78.4, 75.6, 62.0, 52.3, 42.9, 38.9, 30.2, 20.0, 14.4, 13.9 ppm; HPLC: Chiralpak AD-H (hexane/*i*PrOH = 90:10, flow rate 0.8 mL min⁻¹, $\lambda = 210$ nm), t_R (minor) = 15.2 min, t_R (major) = 17.6 min; >99% ee; HRMS (ESI): m/z calcd for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_5$: 427.2233 [$M+H$]; found 427.2230.

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