

Article

De Novo Synthesis of Polysubstituted 3-Hydroxypyridines Via “Anti-Wacker”-Type Cyclization †

Kazuya Ito ¹, Takayuki Doi ¹  and Hirokazu Tsukamoto ^{1,2,*} 

¹ Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aza-Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

² Department of Pharmaceutical Sciences, Yokohama University of Pharmacy, 601 Matano-cho, Totsuka-ku, Yokohama 245-0066, Japan

* Correspondence: hirokazu.tsukamoto@hamayaku.ac.jp

† This paper is dedicated to late Professor Jiro Tsuji.

Abstract: We report an efficient method to prepare polysubstituted 3-hydroxypyridines from amino acids, propargyl alcohols, and arylboronic acids. The process involves Pd(0)-catalyzed *anti*-selective arylative cyclizations of *N*-propargyl-*N*-tosyl-aminoaldehydes with arylboronic acids (“anti-Wacker”-type cyclization), oxidation of the resulting 5-substituted-3-hydroxy-1,2,3,6-tetrahydropyridines to 3-oxo derivatives, and elimination of *p*-toluenesulfonic acid. This method provides diverse polysubstituted 3-hydroxypyridines, whose hydroxy group can be further substituted by a cross-coupling reaction via a triflate.

Keywords: “anti-Wacker”-type cyclization; 3-hydroxypyridine; arylboronic acids; palladium; amino acids; propargyl alcohols



Citation: Ito, K.; Doi, T.; Tsukamoto, H. De Novo Synthesis of Polysubstituted 3-Hydroxypyridines Via “Anti-Wacker”-Type Cyclization. *Catalysts* **2023**, *13*, 319. <https://doi.org/10.3390/catal13020319>

Academic Editors: Ewa Kowalska and Yuichi Kobayashi

Received: 29 December 2022

Revised: 20 January 2023

Accepted: 24 January 2023

Published: 1 February 2023



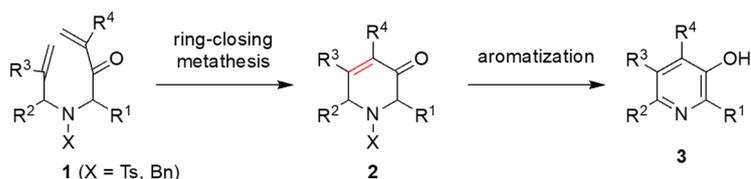
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1. Introduction

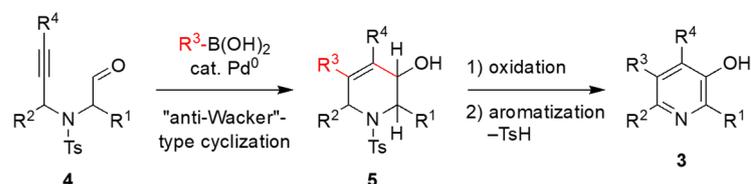
Pyridines are important motifs found in natural products, pharmaceutical molecules, and agricultural chemicals [1–7]. Therefore, a wide variety of methods for the synthesis of pyridine and its derivatives have been developed; the proposed strategies rely on the modification of a pre-existing aromatic core [8–26] or the implementation of de novo synthetic technologies [27–43]. However, it is still difficult to introduce multiple substituents into the pyridine skeleton in a perfectly regioselective manner. For example, 3-hydroxypyridines [27–31] have been identified as not only bioactive compounds [1–7] but also useful intermediates for transformation into more functionalized pyridines [30]. In contrast to 2- and 4-hydroxypyridines, which readily tautomerize to the corresponding pyridones, 3-hydroxypyridines cannot form keto tautomers and are transformed into 3-substituted pyridines through a cross-coupling reaction of their triflates under palladium catalysis [44–49]. Donohoe [50] and Yanagisawa [51] independently reported de novo syntheses of 3-hydroxypyridines by the ring-closing metathesis of *N*-allyl-*N*-(2-oxobut-3-en-1-yl)amino derivative **1** (Scheme 1, top equation). However, the synthesis of each of the 3-hydroxypyridines **3** requires the preparation of the respective precursors from building blocks that are difficult to obtain, including polysubstituted allylic alcohols and alkenylmetal species. Alkylative cyclization to convert a single precursor into multiple cyclized products with a wide variety of substituents could be more desirable for the diversity-oriented synthesis of 3-hydroxypyridines. Herein, we describe a practical and regioselective synthesis of 3-hydroxypyridines by the Pd(0)-catalyzed *anti*-selective arylative-, alkylative, or alkynylative cyclizations (“anti-Wacker”-type cyclization [52–54]) of alkynals **4**, which can be easily prepared from available amino acid derivatives and propargyl alcohols (Scheme 1, bottom equation). Polysubstituted 3-hydroxypyridines are obtained with a simple two-step sequence: oxidation of cyclization products **5** and subsequent

desulfinate aromatization developed by Boger [50,51,55]. The “anti-Wacker”-type cyclization proceeds through the newly proposed “anti-Wacker”-type oxidative addition of alkynyl electrophiles that do not form oxapalladacycles, transmetalation with organometallic reagents, and reductive elimination [52,53]. Both substituents at the alkyne terminus and phosphine ligands affect the regioselectivity of the cyclization reaction, with a combination of terminal alkynes and triphenylphosphine and that of aryl- and 1-alkynyl substituents and tricyclohexylphosphine favoring the formation of endocyclic products over exocyclic products. However, the effect of substituents at the α -positions of the alkyne and carbonyl on the diastereoselectivity and how many substituents are allowed are poorly understood [54]. *N*-Tosyl-tethered aldehyde **4** with an α -substituent of the carbonyl group can be readily prepared from amino acids. The tosyl-protecting group promotes not only the *N*-propargylation step of the substrate preparation but also the cyclization step by the electron-withdrawing inductive effect and the Thorpe–Ingold effect, which is eliminated after oxidation of the resulting allylic alcohols **5** to afford 3-hydroxypyridines **3**. Through the synthesis of multisubstituted 3-hydroxypyridines, we explored the scope and limitations of the “anti-Wacker”-type cyclization and established the structures of six-membered endocyclic products.

(a) Yanagisawa's method (Yanagisawa, et al. 2009)



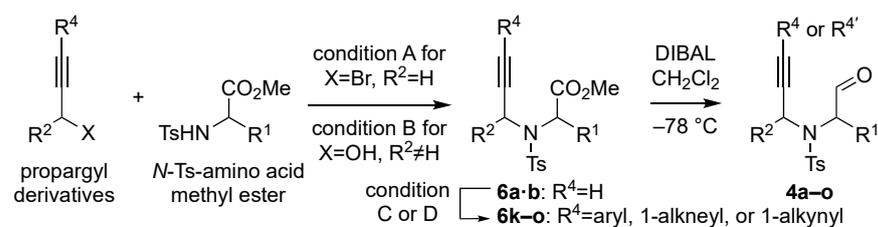
(b) This work



Scheme 1. Synthetic methods for 3-hydroxypyridines. (a) Yanagisawa's method [51], (b) this work.

2. Results and Discussion

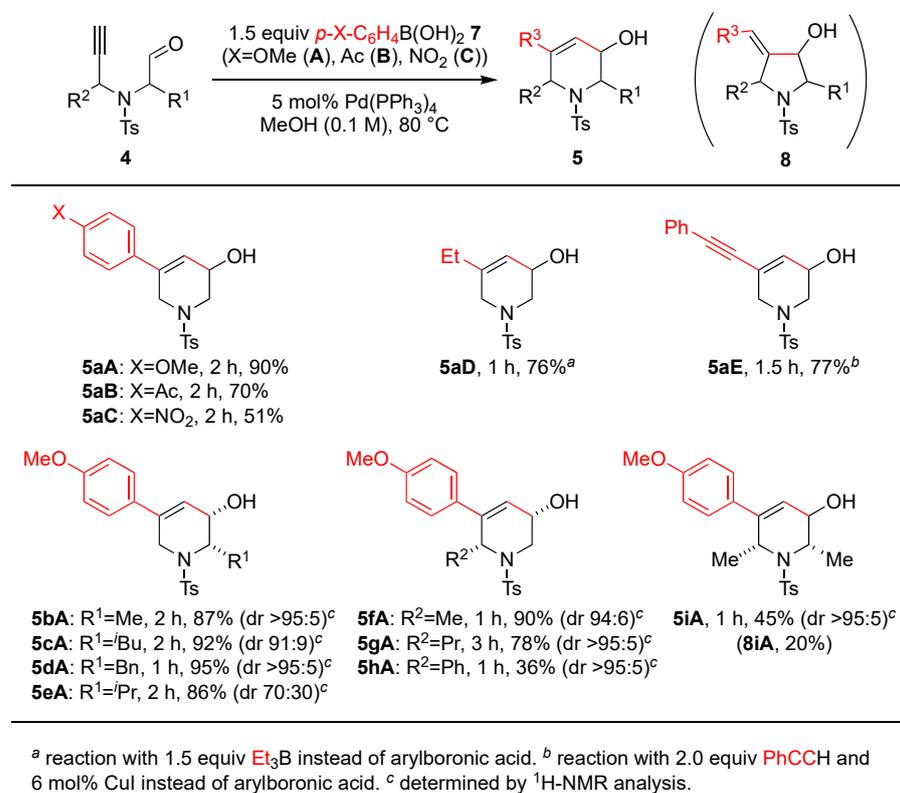
The preparation of alkyne-aldehydes **4a–o** for the “anti-Wacker”-type cyclization was commenced with the *N*-alkylation of *N*-tosyl amino acid methyl esters via the S_N2 reaction with propargyl bromides or the Mitsunobu reaction with propargyl alcohols (Scheme 2). The terminal alkyne in methyl esters **6a–b** was also able to be substituted with aryl, 1-alkenyl, and 1-alkynyl groups by the Sonogashira or Cadiot–Chodkiewicz coupling reactions [56,57]. The ester intermediates were subsequently reduced with DIBAL to give aldehydes **4a–o**.



condition A: K₂CO₃, THF, rt, 8 h. condition B: ROOC-N=N-COOR, PPh₃, THF, rt, 1 h.
 condition C: R⁴-I or -OTf, PdCl₂(PPh₃)₂, CuI, Et₃N, THF or DMF, rt for R⁴=aryl, 1-alkenyl.
 condition D: R⁴-Br, CuCl, NH₂OH·HCl, BuNH₂, H₂O, CH₂Cl₂, rt for R⁴=1-alkynyl.

Scheme 2. Preparation of alkyne-aldehydes **4a–o**.

The terminal alkyne **4a** ($R^1=R^2=R^4=H$) derived from glycine underwent the $Pd(PPh_3)_4$ -catalyzed “anti-Wacker”-type cyclization with arylboronic acids **7A–C** upon heating at $80^\circ C$ in methanol to afford 5-substituted-3-hydroxy-1,2,3,6-tetrahydropyridines **5aA–C** in good to moderate yields (Scheme 3). In addition to the aryl group, the alkyl and alkynyl groups were also effectively introduced into products **5aD** and **5aE** using the triethylborane **7D** and alkynylcopper species generated in situ from phenylacetylene **7E** along with a catalytic amount of copper iodide, respectively [52,53]. The α -substituted aldehydes **4b–e** derived from alanine, leucine, phenylalanine, and valine also participated in the arylative cyclization with **7A** to furnish **5b–eA** with *cis*-disubstituents as the predominant products in high yields [54]. The stereochemical outcome observed herein provides useful information about the transition states. The observed *cis*-diastereoselectivity would result from the steric effect of the substituent at the pseudoequatorial position of the twist boat transition state shown in Figure 1, where there is maximum overlap between the π -orbital of the incoming alkyne and the π^* -orbital of the carbonyl [58,59]. The bulky isopropyl group in **4e** would increase the gauche interaction with the *N*-Ts group and be partially oriented in the pseudoaxial position, leading to lower *cis*-diastereoselectivity.



Scheme 3. Tetrahydropyridines prepared by Pd/ PPh_3 -catalyzed cyclizations of terminal alkyne-aldehydes.

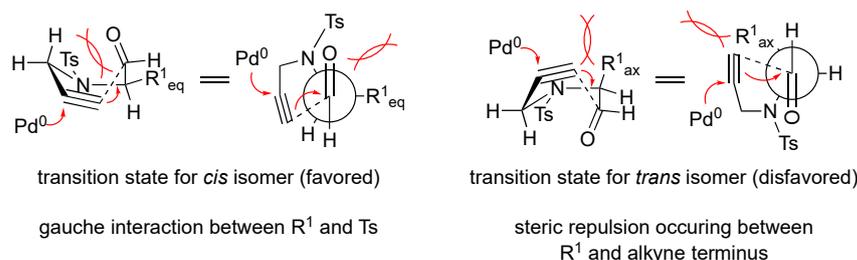


Figure 1. Diastereoselective cyclizations of **4b–e** with a substituent at the α -position to the carbonyl group.

On the other hand, a substituent (R^2) at the α -position of the alkyne functionalities in glycine-derived terminal alkyne-aldehydes **4f–h** dramatically affected the yield of products **5f–hA**, with the sterically demanding phenyl group resulting in much lower yields (Scheme 3). Interestingly, *cis*-diastereoselectivity was consistently high, regardless of the steric bulkiness of the substituents. The nucleophilic attack of a Pd(0) species would be hindered more significantly by the propargyl substituent at the pseudoequatorial position than by the substituent at the pseudoaxial position (Figure 2). The favored transition state with the substituent at the pseudoaxial position leads to *cis*-disubstituted products. Surprisingly, the introduction of two *cis*-oriented substituents at both the α -positions of the aldehyde and alkyne moieties led to the formation of not only the endocyclic product **5iA** but also the exocyclic product **8iA**. To the best of our knowledge, this is the only example of the formation of both endocyclic and exocyclic products during the arylation cyclization of terminal alkyne-aldehydes under Pd(PPh₃)₄ catalysis.

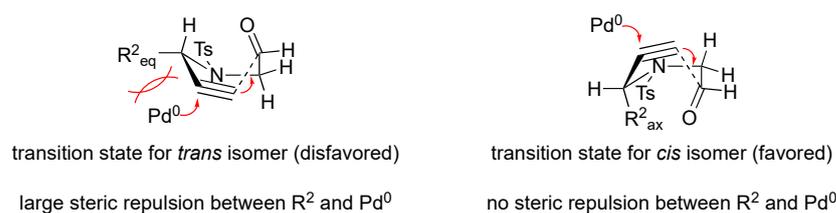
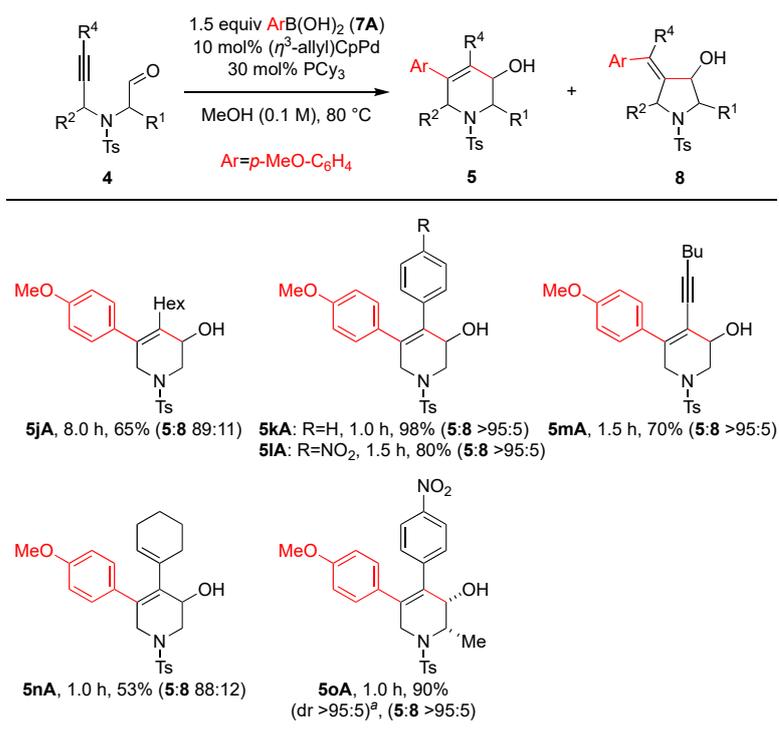


Figure 2. Diastereoselective cyclizations of **4f–h** with a substituent at the propargyl position.

The arylation cyclizations of internal alkyne-aldehydes **4j–o** with *p*-methoxyphenylboronic acid **7A** under the catalysis of the strongly σ -donating tricyclohexylphosphine-ligated palladium also provided 4,5-disubstituted-3-hydroxy-1,2,3,6-tetrahydropyridines **5j–oA**, along with **8j–oA**, in good to moderate yields (Scheme 4). For the predominant endocyclic closure that affords the tetrahydropyridines, the alkyl, aryl, 1-alkynyl, or polysubstituted 1-alkenyl groups at the alkyne terminus were necessary [53]. The arylation cyclization of alkyl-substituted alkyne-aldehyde **4j** was relatively slow and gave an inseparable mixture of **5jA** and **8jA**. The former tetrahydropyridine **5jA** can be alternatively prepared with a two-step sequence: arylation cyclization of conjugated diyne-aldehyde **4m**, followed by chemoselective hydrogenation of the internal alkyne **5mA** in the presence of a *tetra*-substituted alkene [53]. Further substitution at the α -position of the carbonyl group in **4o** preserves the high yield of product **5oA** with two *cis*-oriented substituents, which would also result from the similar transition state shown in Figure 1.

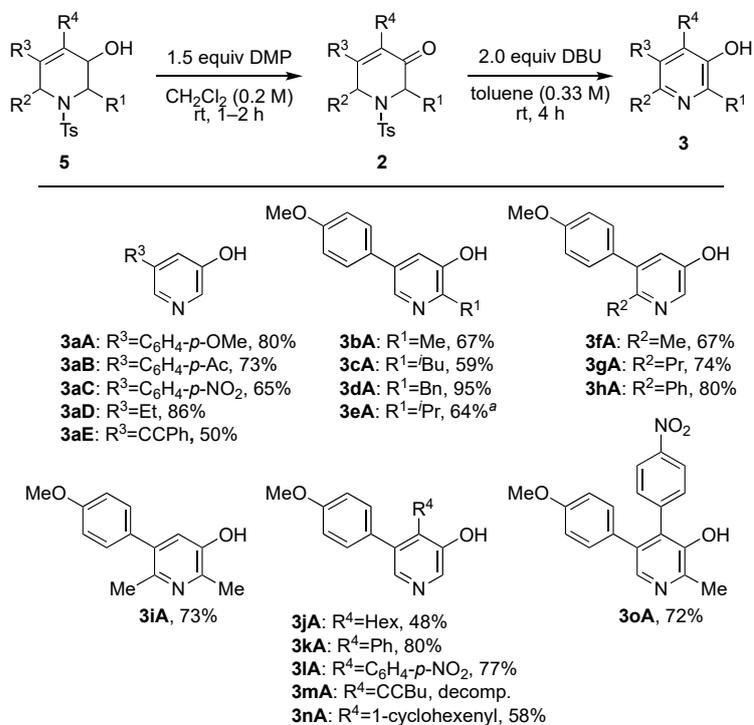
The 5-substituted 3-hydroxy-1,2,3,6-tetrahydropyridines were transformed into the corresponding 3-hydroxypyridines through the following two steps (Scheme 5). The Dess–Martin oxidation of the hydroxy group in **5** afforded enone **2**, although that of the acid-sensitive **5eA** required the addition of sodium bicarbonate to prevent acid-mediated dehydration. Subsequent elimination of the *p*-toluenesulfinic acid moiety in **2** was achieved using 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) to furnish the desired multiply substituted 3-hydroxypyridines **3** in good yields. For reasons unknown, the eliminated product was not formed in the case of **2mA** with the 1-alkynyl group at the C4 position.

Finally, the hydroxyl group at the C3 position of **3cA** was substituted with an aryl group via triflate **9cA**. After a brief screening of the Suzuki–Miyaura cross-coupling reaction, we found that the use of lithium chloride [60] successfully transformed triflate **9cA** into 2-substituted 3,5-diarylpyridine **10** in excellent yield (Scheme 6).



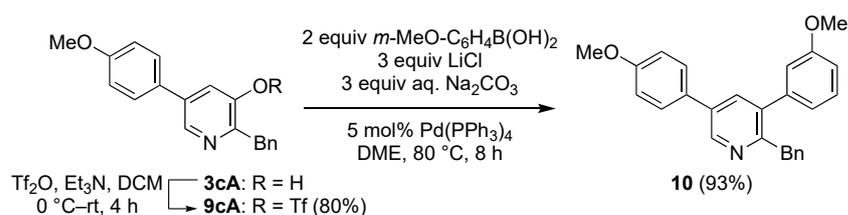
^a determined by ¹H-NMR analysis.

Scheme 4. Tetrahydropyridines prepared by Pd/PCy₃-catalyzed arylative cyclizations of internal alkyne-aldehydes.



Reactions were performed on a 0.014–0.30 mmol scale. Isolated yields of **3** in 2 steps from **5** were given. ^a NaHCO₃ (2 equiv) was added in the oxidation step.

Scheme 5. Conversion of 3-hydroxytetrahydropyridines **5** to 3-hydroxypyridines **3**.



Scheme 6. Suzuki–Miyaura cross-coupling of triflate **9cA** derived from **3cA**.

3. Materials and Methods

3.1. General Techniques

All commercially available reagents and anhydrous solvents including tetrahydrofuran (THF), dichloromethane (DCM), and 1,2-dimethoxyethane (DME) were purchased and used without further purification. Anhydrous methanol (MeOH), *N,N*-dimethylformamide (DMF), and toluene were obtained using distillation from magnesium, calcium hydride, and sodium, respectively. All reactions were monitored using thin-layer chromatography (TLC) performed using 0.25 mm silica gel glass plates (60 F₂₅₄) using UV light and ethanolic *p*-anisaldehyde-sulfuric acid, ethanolic molybdotophosphoric acid, aqueous cerium sulfate-hexaammonium heptamolybdate-sulfuric acid, or aqueous potassium permanganate-potassium carbonate-sodium hydroxide solutions as visualizing agents. Flash column chromatography was carried out with silica gel (spherical, neutral, 100–210 μm grade). Preparative thin-layer chromatography was performed using 0.75 mm Wakogel[®] B-5F PLC plates. Yields refer to chromatographically and spectroscopically homogenous materials. Melting points were measured with a melting point apparatus and were uncorrected. Only the strongest and/or structurally important absorptions of infrared (IR) spectra are reported in reciprocal centimeters (cm^{-1}). The ^1H -NMR spectra (400 MHz or 600 MHz) and $^{13}\text{C}\{^1\text{H}\}$ -NMR spectra (100 MHz or 151 MHz) were recorded in the indicated solvent. Chemical shifts (δ) are reported in delta (δ) units, parts per million (ppm). Chemical shifts for the ^1H -NMR spectra are given relative to signals for internal tetramethylsilane (0 ppm) or residual nondeuterated solvents, i.e., chloroform (7.26 ppm). Chemical shifts for the ^{13}C -NMR spectra are given relative to the signal for chloroform-*d* (77.0 ppm). Multiplicities are reported as the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants (*J*) are represented in hertz (Hz). The ^1H and ^{13}C -NMR chemical shifts were assigned using a combination of COSY, NOESY, HMQC, and HMBC. Low- and high-resolution mass spectra were measured using TOF-MS with EI, FAB, or ESI probes.

3.2. Materials

Ynals **4a**, **4b**, **4d**, **4j**, **4k**, **4m**, and **4n** were prepared according to the literature procedure [61–63]. Ynals **4c** and **4e** were prepared from *N*-tosyl amino acid methyl ester [64] and propargyl bromide. Ynals **4f**, **4g**, and **4i** were prepared from *N*-tosyl amino acid methyl ester and propargyl alcohols. Ynal **4h** was prepared from *N*-benzylidene-*p*-toluenesulfonamide [65], ethynylmagnesium bromide, and methyl bromoacetate. Ynals **4l** and **4o** were prepared through Sonogashira reaction of terminal alkyne **6a·b** with 1-iodo-4-nitrobenzene. The details of procedures for the preparation of ynals are described in Supplementary Materials.

3.3. Methods

3.3.1. General Procedure for the $\text{Pd(PPh}_3)_4$ -Catalyzed Arylative Cyclizations of Terminal Alkyne-Aldehyde **4a–i** with Arylboronic Acid **7A–C**

To a test tube containing **4a–i** (1 equiv), arylboronic acid **7A–C** (1.5 equiv), and $\text{Pd(PPh}_3)_4$ (5 mol%) was added anhydrous MeOH (0.1 M) under argon. The resulting mixture was sealed with a screw cap and agitated at $80\text{ }^\circ\text{C}$ for the time described in Scheme 3. The reaction mixture was cooled down to room temperature and then treated with polymer-supported diethanolamine (PL-DEAMTM, 1.72 mmol/g, 3 equiv, X g) and

THF (10 × X mL) to remove an excess of **7A–C**. The mixture was agitated at room temperature for 2 h. The mixture was filtered, and the resin was thoroughly rinsed with CHCl₃. The filtrate was concentrated in vacuo and the residue was purified with preparative TLC or silica gel column chromatography to give endocyclic products **5(a–i)(A–C)** in the yield described in Scheme 3.

Procedure for 5-(4-methoxyphenyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5aA**)

Method: **5aA** (16.6 mg, 90%) was obtained from **4a** (12.9 mg, 0.0513 mmol), **7A** (11.4 mg), and Pd(PPh₃)₄ (2.9 mg) and isolated with silica gel column chromatography eluting with 15% EtOAc/hexane. Spectra data of **5aA** were in agreement with those reported in the literature [52].

Procedure for 1-(4-(5-hydroxy-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl)phenyl)ethan-1-one (**5aB**)

Method: **5aB** (12.3 mg, 70%) was obtained from **4a** (11.9 mg, 0.0474 mmol), **7B** (12.3 mg), and Pd(PPh₃)₄ (2.9 mg) and isolated with preparative TLC eluting with 20% EtOAc/toluene. Spectra data of **5aB** were in agreement with those reported in the literature [53].

Procedure for 5-(4-nitrophenyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5aC**)

Method: **5aC** (28.2 mg, 51%) was obtained from **4a** (37.7 mg, 0.150 mmol), **7C** (37.6 mg), and Pd(PPh₃)₄ (8.6 mg) and isolated with preparative TLC eluting with 20% EtOAc/toluene.

Pale-brown oil. IR (neat): 3620–3200, 1681, 1604, 1344, 1271, 1167, 1094, 819, 755, 660 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.19 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.35 (s, 1H), 4.45 (ddd, *J* = 4.8, 4.0, 5.6 Hz, 1H), 4.09 (d, *J* = 16.0 Hz, 1H), 3.76 (d, *J* = 16.0 Hz, 1H), 3.37 (dd, *J* = 12.0, 4.8 Hz, 1H), 3.24 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.60 (d, *J* = 5.6 Hz, 1H), 2.44 (s, 3H); ¹³C-NMR (151 MHz, CDCl₃): δ 147.7, 144.3, 143.7, 135.0, 132.9, 130.0, 128.1, 127.7, 126.3, 124.0, 63.7, 49.7, 46.2, 21.6. LRMS (EI) *m/z* (relative intensity) 374 ([M]⁺, 2), 356 (3), 184 (100), 155 (61). HRMS (EI, [M]⁺): *m/z* calcd for C₁₈H₁₈N₂O₅S, 374.0936; found, 374.0956.

Procedure for (2*S*,3*S*)-5-(4-methoxyphenyl)-2-methyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5bA**)

Method: **5bA** (33.1 mg, 87%, dr >95:<5) was obtained from **4b** (27.1 mg, 0.102 mmol), **7A** (22.8 mg), and Pd(PPh₃)₄ (5.8 mg) and isolated with preparative TLC eluting with 10% EtOAc/toluene.

Colorless oil. R_f 0.40 (50% EtOAc/hexane). [α]_D²³ −5.8 (*c* 0.60, CHCl₃). IR (neat): 3497, 1608, 1335, 1515, 1160, 1030, 816, 752, 659 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.32–7.28 (m, 4H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.82 (s, 1H), 4.49 (m, 1H), 4.47 (d, *J* = 16.0 Hz, 1H), 4.34 (m, 1H), 3.81 (s, 3H), 3.74 (d, *J* = 16.0 Hz, 1H), 2.42 (s, 3H), 1.88 (br-s, 1H), 0.91 (d, *J* = 6.8 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ 159.9, 143.5, 137.0, 133.5, 129.8, 129.5, 127.0, 126.3, 123.2, 114.0, 67.0, 55.3, 50.8, 41.5, 21.5, 9.4. HRMS (ESI, [M + Na]⁺) *m/z* calcd for C₂₀H₂₃NNaO₄S 396.1240, found 396.1242.

Procedure for 2-isobutyl-5-(4-methoxyphenyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5cA**)

Method: **5cA** (19.1 mg, 92%, dr 91:9) was obtained from **4c** (15.4 mg, 0.0501 mmol), **7A** (11.5 mg), and Pd(PPh₃)₄ (3.0 mg) and isolated with preparative TLC eluting with 10% EtOAc/toluene.

For (2*S*,3*S*)-**5cA** as a major diastereomer: Colorless oil. R_f 0.38 (10% EtOAc/toluene). [α]_D²² −131 (*c* 0.52, CHCl₃). IR (neat): 3505, 2955, 1608, 1514, 1331, 1158, 817, 745, 660 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.76 (s, 1H), 4.52 (d, *J* = 18.0 Hz, 1H), 4.33–4.20 (m, 2H), 3.83 (d, *J* = 18.0 Hz, 1H), 3.82 (s, 3H), 2.34 (s, 3H), 1.80–1.64 (m, 2H), 1.36 (m, 2H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ 159.6, 143.3, 138.0, 129.7, 129.3, 126.8, 126.5, 126.2, 123.4, 114.0, 65.7, 55.3, 52.7, 41.5, 33.0, 24.3, 23.9, 21.5 (one

signal missing due to an overlap). HRMS (ESI, $[M + Na]^+$) m/z calcd for $C_{23}H_{29}NNaO_4S$ 438.1710, found 438.1707.

For (2*S*,3*R*)-**5cA** as a minor diastereomer: Colorless oil. Rf 0.42 (10% EtOAc/toluene). IR (neat): 3600–3200, 2926, 2869, 1607, 1515, 1335, 1247, 1158, 1093, 1031, 827, 754, 655 cm^{-1} ; 1H -NMR (600 MHz, $CDCl_3$): δ 7.79 (d, $J = 8.2$ Hz, 2H), 7.33–7.28 (m, 4H), 6.89 (d, $J = 8.8$ Hz, 2H), 6.12 (d, $J = 6.1$ Hz, 1H), 4.51 (d, $J = 17.5$ Hz, 1H), 4.19 (t, $J = 7.2$ Hz, 1H), 3.99 (dd, $J = 10.5, 6.1$ Hz, 1H), 3.82 (s, 3H), 3.76 (d, $J = 17.5$ Hz, 1H), 2.43 (s, 3H), 1.96 (d, $J = 10.5, 1H$), 1.61–1.51 (m, 1H), 1.20–1.14 (m, 2H), 0.88 (d, $J = 6.5$ Hz, 3H), 0.83 (d, $J = 6.5$ Hz, 3H); ^{13}C -NMR (151 MHz, $CDCl_3$): δ 160.0, 143.6, 137.2, 136.4, 129.74, 129.70, 127.4, 126.5, 120.6, 114.1, 66.7, 56.8, 55.4, 41.7, 37.6, 25.1, 22.7, 22.6, 21.5. HRMS (ESI, $[M + Na]^+$) m/z calcd for $C_{23}H_{29}NNaO_4S$ 438.1710, found 438.1707.

Procedure for (2*R**, 3*R**)-2-benzyl-5-(4-methoxyphenyl)-1-tosyl-1,2,3,6-tetrahydro-pyridin-3-ol (**5dA**)

Method: **5dA** (42.5 mg, 95%, dr >95:<5) was obtained from **4d** (33.0 mg, 0.100 mmol), **7A** (22.8 mg), and $Pd(PPh_3)_4$ (5.8 mg) and isolated with preparative TLC eluting with 50% EtOAc/hexane.

Pale-yellow oil. Rf 0.50 (50% EtOAc/hexane). IR (neat): 3492, 1607, 1514, 1248, 1157, 1096, 752, 660 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$): δ 7.34 (d, $J = 6.8$ Hz, 2H), 7.27–7.13 (m, 7H), 7.08 (d, $J = 8.4$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 5.94 (s, 1H), 4.64 (dd, $J = 5.4, 6.0$ Hz, 1H), 4.57 (ddd, $J = 4.8, 5.4, 9.6$ Hz, 1H), 4.47 (d, $J = 18.0$ Hz, 1H), 3.86 (d, $J = 18.0$ Hz, 1H), 3.11 (dd, $J = 4.8, 14.2$ Hz, 1H), 2.56 (dd, $J = 9.6, 14.2$ Hz, 1H), 2.36 (s, 3H), 1.77 (d, $J = 6.0$ Hz, 1H); ^{13}C -NMR (100 MHz, $CDCl_3$): δ 159.6, 143.0, 138.6, 137.1, 133.4, 129.5, 129.4, 129.1, 128.4, 126.9, 126.3, 126.2, 123.6, 114.0, 66.7, 56.4, 55.3, 41.6, 31.2, 21.4. HRMS (ESI, $[M + Na]^+$) m/z calcd for $C_{26}H_{27}NNaO_4S$ 472.1553, found 472.1548.

Procedure for 2-isopropyl-5-(4-methoxyphenyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5eA**)

Method: **5eA** (33.8 mg, 86%, dr 70: 30) was obtained from **4e** (15.4 mg, 0.525 mmol), **7A** (11.5 mg), and $Pd(PPh_3)_4$ (3.0 mg) and isolated with preparative TLC eluting with 15% EtOAc/toluene.

For (2*S*,3*S*)-**5eA** as a major diastereomer: Colorless oil. Rf 0.39 (15% EtOAc/toluene). $[\alpha]_D^{23} -82$ (c 0.58, $CHCl_3$). IR (neat): 3509, 2962, 1608, 1515, 1464, 1333, 1251, 1159, 1090, 1046, 816, 758, 663 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$): δ 7.69 (d, $J = 8.4$ Hz, 2H), 7.31–7.20 (m, 4H), 6.87 (d, $J = 6.8$ Hz, 2H), 5.88 (s, 1H), 4.44 (d, $J = 18.0$ Hz, 1H), 4.35 (m, 1H), 3.98–3.90 (m, 2H), 3.80 (s, 3H), 2.39 (s, 3H), 2.00 (m, 2H), 1.14 (d, $J = 6.8$ Hz, 3H), 0.94 (d, $J = 6.8$ Hz, 3H); ^{13}C -NMR (100 MHz, $CDCl_3$): δ 159.6, 143.2, 138.0, 133.0, 129.7, 129.4, 126.7, 126.2, 124.2, 114.0, 67.3, 60.2, 55.3, 43.5, 27.0, 21.5, 20.9 (one signal missing due to an overlap). HRMS (ESI, $[M + Na]^+$) m/z calcd for $C_{15}H_{19}NNaO_4S$ 424.1553, found 424.1551.

For (2*S*,3*R*)-**5eA** as a minor diastereomer: Colorless oil. Rf 0.44 (15% EtOAc/toluene). $[\alpha]_D^{23} -122$ (c 2.25 in $CHCl_3$). IR (neat): 3600–3260, 2964, 1607, 1515, 1457, 1326, 1250, 1156, 1093, 1033, 826, 760, 657 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$): δ 7.81 (d, $J = 8.4$ Hz, 2H), 7.31–7.20 (m, 4H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.11 (d, $J = 5.5$ Hz, 1H), 4.46 (d, $J = 18.3$ Hz, 1H), 4.32–4.20 (m, 1H), 3.89–3.73 (m, 5H), 2.40 (s, 3H), 1.84 (d, $J = 9.3$ Hz, 1H), 1.76–1.61 (m, 1H), 1.01 (d, $J = 6.3$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H); ^{13}C -NMR (100 MHz, $CDCl_3$): δ 159.9, 143.4, 137.7, 136.3, 129.6, 129.5, 127.3, 126.3, 120.5, 114.0, 64.7, 64.5, 55.3, 41.9, 27.5, 21.5, 20.8, 20.3. HRMS (ESI, $[M + Na]^+$) m/z calcd for $C_{15}H_{19}NNaO_4S$ 424.1553, found 424.1551.

Procedure for 5-(4-methoxyphenyl)-6-methyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5fA**)

Method: **5fA** (17.0 mg, 90%, dr 94: 6) was obtained from **4f** (13.3 mg, 0.0507 mmol), **7A** (11.4 mg), and $Pd(PPh_3)_4$ (2.9 mg) and isolated with preparative TLC eluting with 10% EtOAc/toluene (developed six times).

For (3*R**, 6*S**)-**5fA** as a major diastereomer: Colorless oil. Rf 0.37 (17% EtOAc/toluene). IR (neat): 3492, 1607, 1514, 1248, 1157, 252, 660 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$): δ 7.73 (d, $J = 7.2$ Hz, 2H), 7.27–2.22 (m, 4H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.29 (s, 1H), 4.96 (q, $J = 6.8$ Hz, 1H), 4.18 (dd, $J = 6.4, 10.0$ Hz, 1H), 4.07 (dd, $J = 6.4, 13.6$ Hz, 1H), 3.81 (s, 3H), 2.90 (dd,

$J = 10.0$ Hz, 13.6 Hz, 1H), 2.39 (s, 3H), 2.15 (br-s, 1H), 1.16 (d, $J = 6.8$ Hz, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 159.5, 143.4, 142.0, 137.9, 130.4, 129.7, 127.5, 126.7, 125.2, 114.0, 63.1, 55.3, 50.6, 43.5, 21.4, 18.3. HRMS (ESI, $[\text{M} + \text{Na}]^+$) m/z calcd for $\text{C}_{20}\text{H}_{23}\text{NNaO}_4\text{S}$ 396.1240, found 396.1239.

For (3*R**,6*R**)-5fA as a minor diastereomer: Colorless oil. Rf 0.38 (17% EtOAc/toluene). IR (neat): 3600–3160 (br), 2979, 2934, 2838, 1607, 1513, 1335, 1247, 1155, 1122, 1088, 1013, 815, 741, 654 cm^{-1} ; $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ 7.81 (d, $J = 8.6$ Hz, 2H) 7.33–7.24 (m, 4H), 6.89 (d, $J = 8.8$ Hz, 2H), 5.93 (d, $J = 4.1$ Hz, 1H), 5.05 (q, $J = 6.9$ Hz, 1H), 4.18–4.12 (m, 1H), 3.90 (d, $J = 14.4$ Hz, 1H), 3.82 (s, 3H), 3.33 (d, $J = 14.4$ Hz, 1H), 2.42 (s, 3H), 1.95 (d, $J = 10.3$ Hz, 1H), 1.06 (d, $J = 6.9$ Hz, 3H); $^{13}\text{C-NMR}$ (151 MHz, CDCl_3): δ 159.9, 144.1, 143.5, 137.6, 130.5, 129.8, 127.7, 127.3, 122.2, 114.1, 63.6, 55.3, 50.5, 45.1, 21.5, 16.6. HRMS (ESI, $[\text{M} + \text{Na}]^+$) m/z calcd for $\text{C}_{20}\text{H}_{23}\text{NNaO}_4\text{S}$ 396.1240, found 396.1238.

Procedure for (3*R**,6*S**)-5-(4-methoxyphenyl)-6-propyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (5gA)

Method: 5gA (21.6 mg, 78%, dr >95:<5) was obtained from 4g (20.2 mg, 0.0689 mmol), 7A (15.7 mg), and Pd(PPh₃)₄ (4.0 mg) and isolated with preparative TLC eluting with 10% EtOAc/toluene.

Pale-yellow oil. Rf 0.30 (33% EtOAc/hexane). IR (neat): 3494, 2959, 2934, 1606, 1513, 1336, 1248, 825, 761, 661 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.72 (d, $J = 8.0$ Hz, 2H) 7.25 (d, $J = 8.0$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 6.89 (d, $J = 8.0$ Hz, 2H), 5.55 (s, 1H), 4.82 (t, $J = 10.0$ Hz, 1H), 4.08 (dd, $J = 6.8$ Hz, 14.0 Hz, 1H), 3.90 (dd, $J = 6.8$, 10.0 Hz, 1H), 3.83 (s, 3H), 2.96 (dd, $J = 10.0$ Hz, 14.0 Hz, 1H), 2.41 (s, 3H), 1.77 (br-s, 1H), 1.61–1.30 (m, 4H), 0.84 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 159.5, 143.4, 141.7, 138.1, 130.8, 129.6, 127.3, 126.8, 124.8, 114.1, 62.0, 55.3, 43.8, 43.8, 34.6, 21.5, 19.9, 13.6. HRMS (ESI, $[\text{M} + \text{Na}]^+$) m/z calcd for $\text{C}_{22}\text{H}_{27}\text{NNaO}_4\text{S}$ 424.1553, found 424.1550.

Procedure for (3*R**,6*S**)-5-(4-methoxyphenyl)-6-phenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (5hA)

Method: 5hA (2.9 mg, 36%, dr >95:<5) was obtained from 4h (16.4 mg, 0.0501 mmol), 7A (11.4 mg), and Pd(PPh₃)₄ (2.9 mg) and isolated with preparative TLC eluting with 15% EtOAc/toluene.

Pale-yellow oil. Rf 0.40 (50% EtOAc/hexane). IR (neat): 3491, 1606, 1513, 1335, 1250, 1160, 1034, 815, 744, 704, 661 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.63 (d, $J = 8.4$ Hz, 2H) 7.39 (d, $J = 6.8$ Hz, 2H), 7.30–7.15 (m, 7H), 6.77 (d, $J = 8.8$ Hz, 2H), 6.05 (s, 1H), 6.02 (s, 1H), 4.18 (dd, $J = 7.6$, 10.3 Hz, 1H), 3.88 (dd, $J = 7.6$ Hz, 14.1 Hz, 1H), 3.74 (s, 3H), 2.84 (dd, $J = 10.3$, 14.1 Hz, 1H), 2.37 (s, 3H), 1.82 (br-s, 1H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 159.4, 143.4, 137.8, 137.68, 137.66, 130.0, 129.6, 129.0, 128.5, 128.0, 127.2, 127.0, 126.5, 113.9, 62.8, 57.5, 55.2, 43.6, 21.5. HRMS (ESI, $[\text{M} + \text{Na}]^+$) m/z calcd for $\text{C}_{25}\text{H}_{25}\text{NNaO}_4\text{S}$ 458.1397, found 458.1398.

Procedure for (2*S*,6*R*)-5-(4-methoxyphenyl)-2,6-dimethyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (5iA) and (2*S*,5*R*)-4-((*E*)-4-methoxybenzylidene)-2,5-dimethyl-1-tosylpyrrolidin-3-ol (8iA)

Method: 5iA (98 mg, 45%, dr >95:<5) and 8iA (44 mg, 20%, dr >95:<5) were obtained from 4i (158 mg, 0.566 mmol), 7A (129 mg), and Pd(PPh₃)₄ (49.0 mg) and isolated with preparative TLC eluting with 40% EtOAc/hexane.

For 5iA: Pale-yellow oil. Rf 0.30 (40% EtOAc/hexane). $[\alpha]_D^{21}$ –163 (c 0.55, CHCl_3). IR (neat): 3492, 1607, 1514, 1248, 1157, 752, 660 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.74 (d, $J = 8.0$ Hz, 2H) 7.32–7.20 (m, 4H), 6.88 (d, $J = 8.8$ Hz, 2H), 5.56 (s, 1H), 4.97 (q, $J = 7.2$ Hz, 1H), 4.26 (m, 1H), 4.13 (m, 1H), 3.82 (s, 3H), 2.40 (s, 3H), 1.78 (br-s, 1H), 1.31 (d, $J = 7.2$ Hz, 3H), 1.23 (d, $J = 7.2$ Hz, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ 159.4, 143.3, 142.0, 138.4, 130.9, 129.8, 127.9, 126.8, 123.8, 113.9, 65.8, 55.3, 49.8, 49.7, 22.1, 21.5, 14.8. HRMS (ESI, $[\text{M} + \text{Na}]^+$) m/z calcd for $\text{C}_{21}\text{H}_{25}\text{NNaO}_4\text{S}$ 410.1397, found 410.1396.

For 8iA: Pale-yellow oil. Rf 0.33 (40% EtOAc/hexane). IR (neat): 3491, 1606, 1513, 1250, 1160, 744, 661 cm^{-1} ; $^1\text{H-NMR}$ (600 MHz, CDCl_3): δ 7.63 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 8.0$ Hz, 2H), 7.12 (d, $J = 8.8$ Hz, 2H), 6.89 (d, $J = 8.8$ Hz, 2H), 6.35 (s, 1H), 4.77 (q, $J = 6.9$ Hz, 1H), 4.22 (dd, $J = 5.5$, 6.5 Hz, 1H), 3.84 (s, 3H), 3.66 (dq, $J = 5.5$, 6.5 Hz, 1H), 2.37

(s, 3H), 1.65 (d, $J = 5.5$ Hz, 1H), 1.56 (d, $J = 6.5$ Hz, 3H), 1.38 (d, $J = 6.9$ Hz, 3H); ^{13}C -NMR (151 MHz, CDCl_3): δ 159.1, 143.3, 141.3, 135.3, 129.9, 129.6, 128.0, 127.2, 125.1, 113.9, 76.9, 58.2, 56.9, 55.3, 23.5, 21.5, 16.5. HRMS (ESI, $[\text{M} + \text{Na}]^+$) m/z calcd for $\text{C}_{21}\text{H}_{25}\text{NNaO}_4\text{S}$ 410.1397, found 410.1396.

3.3.2. Procedure for 5-ethyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5aD**)

To a test tube containing **4a** (50.3 mg, 0.200 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (11.6 mg, 5 mol%) were added anhydrous MeOH (2.0 mL) and 1.0 M Et₃B solution in THF (0.30 mL, 1.5 equiv) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for 1 h. The reaction mixture was cooled down to room temperature and then concentrated in vacuo. The residue was purified with preparative TLC eluting with 20% EtOAc/toluene to give **5aD** (42.8 mg, 76%) as a colorless oil. Spectra data of **5aD** were in agreement with those reported in the literature [52].

3.3.3. Procedure for 5-(phenylethynyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5aE**)

To a test tube containing **4a** (25.1 mg, 0.100 mmol), CuI (1.2 mg, 6 mol%), PhCCH (22 μL , 2.0 equiv), and $\text{Pd}(\text{PPh}_3)_4$ (5.8 mg, 5 mol%) was added anhydrous MeOH (1.0 mL) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for 1.5 h. The reaction mixture was cooled down to room temperature and then concentrated in vacuo. The residue was purified with preparative TLC eluting with 20% EtOAc/toluene to give **5aE** (27.3 mg, 77%) as a pale-yellow oil. Spectra data of **5aE** were in agreement with those reported in the literature [53].

3.3.4. General Procedure for the Pd/PCy₃-Catalyzed Arylative Cyclizations of Internal Alkyne-Aldehyde **4j-o** with **7A**

To a test tube containing **4j-o** (1 equiv), *p*-methoxyphenylboronic acid (**7A**, 1.5 equiv), $(\eta^3\text{-allyl})\text{CpPd}$ (10 mol%), and PCy₃ (30 mol%) was added anhydrous MeOH (0.10 M) under argon. The resulting mixture was sealed with a screw cap and agitated at 80 °C for the time described in Scheme 4. The reaction mixture was cooled down to room temperature and then treated with PL-DEAMTM (1.72 mmol/g, 2 equiv, X g) and THF (10 \times X mL) to remove an excess of **7A**. The mixture was agitated at room temperature for 2 h. The mixture was filtered, and the resin was thoroughly rinsed with CHCl_3 . The filtrate was concentrated in vacuo and the residue was purified with preparative TLC to give **5(j-o)A** along with a small amount of **8(j-o)A** in the yield described in Scheme 4.

Procedure for 4-hexyl-5-(4-methoxyphenyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5jA**) and (*E*)-4-(1-(4-methoxyphenyl)heptyl-1-ene)-1-tosylpyrrolidin-3-ol (**8jA**)

Method: **5jA** (28.4 mg, 65%) and **8jA** (3.6 mg, 8%) were obtained from **4j** (33.5 mg, 0.0999 mmol), **7A** (23.0 mg), $(\eta^3\text{-allyl})\text{CpPd}$ (1.1 mg), and PCy₃ (4.2 mg) and isolated with preparative TLC eluting with 15% EtOAc/toluene (developed four times). Spectra data of **5jA** and **8jA** were in agreement with those reported in the literature [53].

Procedure for 5-(4-methoxyphenyl)-4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5kA**)

Method: **5kA** (32.5 mg, 98%) was obtained from **4k** (24.6 mg, 0.0751 mmol), **7A** (17.1 mg), $(\eta^3\text{-allyl})\text{CpPd}$ (1.5 mg), and PCy₃ (5.7 mg) and isolated with preparative TLC eluting with 20% EtOAc/toluene. Spectra data of **5kA** were in agreement with those reported in the literature [53].

Procedure for 5-(4-methoxyphenyl)-4-(4-nitrophenyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5lA**)

Method: **5lA** (15.8 mg, 80%) was obtained from **4l** (15.3 mg, 0.0411 mmol), **7A** (11.4 mg), $(\eta^3\text{-allyl})\text{CpPd}$ (1.0 mg), and PCy₃ (3.8 mg) and isolated with preparative TLC eluting with 20% EtOAc/toluene.

Pale-yellow oil. Rf 0.40 (50% EtOAc/hexane). IR (neat): 3600–3160 (br), 2925, 1598, 1514, 1449, 1344, 1250, 1166, 1092, 1032, 760, 661 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 8.00 (d, $J = 8.8$ Hz, 2H) 7.73 (d, $J = 8.6$ Hz, 2H), 7.37 (d, $J = 8.8$ Hz, 2H), 7.22 (d, $J = 8.6$ Hz, 2H),

6.88 (d, $J = 8.8$ Hz, 2H), 6.70 (d, $J = 8.8$ Hz, 2H), 4.59–4.51 (m, 1H), 4.39 (d, $J = 17.1$ Hz, 1H), 3.97 (dd, $J = 12.1, 2.4$ Hz, 1H), 3.74 (s, 3H), 3.37 (d, $J = 17.1$ Hz, 1H), 2.92 (dd, $J = 12.1, 2.7$ Hz, 1H), 2.45 (s, 3H), 2.46–2.36 (m, 1H); ^{13}C -NMR (100 MHz, CDCl_3): δ 159.4, 146.48, 146.45, 144.3, 136.8, 133.7, 132.4, 130.2, 130.1, 130.0, 129.1, 127.9, 123.3, 114.0, 67.1, 55.2, 50.8, 49.6, 21.5. HRMS (ESI, $[\text{M} + \text{Na}]^+$) m/z calcd for $\text{C}_{25}\text{H}_{24}\text{N}_2\text{NaO}_6\text{S}$ 503.1247, found 503.1246.

Procedure for 4-(hex-1-ynyl)-5-(4-methoxyphenyl)-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridin-3-ol (**5mA**)

Method: **5mA** (12.0 mg, 70%) was obtained from **4m** (14.0 mg, 0.0422 mmol), **7A** (9.6 mg), (η^3 -allyl)CpPd (0.8 mg), and PCy_3 (3.2 mg) and isolated with preparative TLC eluting with 25% EtOAc/toluene. Spectra data of **5mA** were in agreement with those reported in the literature [53].

Procedure for 4-(cyclohex-1-en-1-yl)-5-(4-methoxyphenyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5nA**) and (*E*)-4-(cyclohex-1-en-1-yl(4-methoxyphenyl)methylene)-1-tosylpyrrolidin-3-ol (**8nA**)

Method: **5nA** (13.0 mg, 53%) and **8nA** (1.6 mg, 7%) were obtained from **4n** (18.5 mg, 0.0558 mmol), **7A** (12.7 mg), (η^3 -allyl)CpPd (1.2 mg), and PCy_3 (4.7 mg) and isolated with preparative TLC eluting with 40% EtOAc/hexane. Spectra data of **5nA** and **8nA** were in agreement with those reported in the literature [53].

Procedure for (2*S*,3*S*)-5-(4-methoxyphenyl)-2-methyl-4-(4-nitrophenyl)-1-tosyl-1,2,3,6-tetrahydropyridin-3-ol (**5oA**)

Method: **5oA** (21.0 mg, 90%, $\text{dr} >95:<5$) was obtained from **4o** (18.2 mg, 0.0471 mmol), **7A** (11.4 mg), (η^3 -allyl)CpPd (1.0 mg), and PCy_3 (3.8 mg) and isolated with preparative TLC eluting with 20% EtOAc/toluene.

Pale-yellow oil. Rf 0.40 (50% EtOAc/hexane). $[\alpha]_{\text{D}}^{22} -29$ (c 0.22, CHCl_3). IR (neat): 2932, 1607, 1596, 1512, 1344, 1248, 1160, 1031, 757, 662 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3): δ 7.97 (d, $J = 8.8$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 2H), 7.34 (d, $J = 7.6$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 6.82 (d, $J = 8.8$ Hz, 2H), 6.67 (d, $J = 7.6$ Hz, 2H), 4.79 (m, 1H), 4.46 (m, 1H), 4.28 (d, $J = 18.0$ Hz, 1H), 3.89 (d, $J = 18.0$ Hz, 1H), 3.72 (s, 3H), 2.45 (3H, s), 1.09 (d, $J = 6.8$ Hz, 3H); ^{13}C -NMR (100 MHz, CDCl_3): δ 158.9, 146.3, 144.9, 143.6, 143.6, 136.8, 134.5, 133.7, 130.9, 129.9, 129.5, 127.1, 122.9, 113.8, 68.1, 55.1, 51.0, 45.2, 21.5, 9.8. HRMS (ESI, $[\text{M} + \text{Na}]^+$) m/z calcd for $\text{C}_{26}\text{H}_{26}\text{N}_2\text{NaO}_6\text{S}$ 517.1404, found 517.1401.

3.3.5. General Procedure for the Transformations of Tetrahydropyridine **5** into 3-Hydroxypyridine **3**

To a solution of tetrahydropyridine **5** (1 equiv) in anhydrous DCM (0.2 M) was added Dess–Martin periodinane (1.5 equiv) at room temperature. In the oxidation of **5eA**, sodium bicarbonate (2 equiv) was added prior to Dess–Martin periodinane to prevent acid-mediated dehydration. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with Et_2O and treated with saturated aqueous sodium thiosulfate and saturated aqueous NaHCO_3 . The resulting mixture was stirred for 1 h and then extracted with Et_2O . The organic layer was washed with brine, dried over MgSO_4 , and concentrated in vacuo to give enone, which was used for the next step without further purification.

To a solution of the crude enone (1 equiv) in anhydrous toluene (0.33 M) was added DBU (2.0 equiv) at room temperature under argon. After being stirred at the same temperature for 4 h, the reaction mixture was concentrated in vacuo. The residue was purified by preparative TLC eluting with 10% MeOH/ CHCl_3 to give 3-hydroxypyridine **3**.

Procedure for 5-(4-methoxyphenyl)pyridin-3-ol (**3aA**)

Method: **3aA** (2.3 mg, 80%) was obtained from **5aA** (5.0 mg, 0.0139 mmol), DMPI (8.3 mg), and DBU (4.2 μL).

Pale-yellow oil. Rf 0.61 (10% MeOH/ CHCl_3). IR (neat): 2929, 2853, 1609, 1583, 1518, 1440, 1290, 1251, 1221, 1180, 1149, 1031, 828, 755 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3 : $\text{CD}_3\text{OD} = 3:1$):

δ 8.24 (s, 1H), 8.06 (s, 1H), 7.51 (d, $J = 8.8$ Hz, 2H), 7.37 (s, 1H), 7.01 (d, $J = 8.8$ Hz, 2H), 3.87 (s, 3H); ^{13}C -NMR (100 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 159.6, 153.9, 138.0, 135.1, 129.6, 128.0, 120.9, 114.3, 109.2, 55.1. HRMS (ESI, $[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{12}\text{H}_{12}\text{NO}_2$ 202.0863, found 202.0862.

Procedure for 1-(4-(5-hydroxypyridin-3-yl)phenyl)ethan-1-one (**3aB**)

Method: **3aB** (10.2 mg, 73%) was obtained from **5aB** (25.0 mg, 0.0673 mmol), DMPI (40.0 mg), and DBU (20.0 μL).

Pale-yellow oil. Rf 0.55 (10% MeOH/ CHCl_3). IR (neat): 2925, 1684, 1604, 1267, 1162, 755, 668 cm^{-1} ; ^1H -NMR (400 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 8.33 (s, 1H), 8.17 (s, 1H), 8.05 (d, $J = 8.4$ Hz, 2H), 7.67 (d, $J = 8.4$ Hz, 2H), 7.42 (s, 1H), 2.66 (s, 3H); ^{13}C -NMR (100 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 198.4, 154.0, 142.1, 138.5, 136.9, 136.5, 136.3, 128.9, 127.2, 121.5, 26.4. HRMS (ESI, $[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{13}\text{H}_{12}\text{NO}_2$ 214.0863, found 214.0858.

Procedure for 5-(4-nitrophenyl)pyridin-3-ol (**3aC**)

Method: **3aC** (6.5 mg, 65%) was obtained from **5aC** (17.3 mg, 0.0462 mmol), DMPI (27.5 mg), and DBU (14.0 μL).

Pale-yellow oil. Rf 0.53 (10% MeOH/ CHCl_3). IR (neat): 2923, 1598, 1521, 1345, 1159, 795 cm^{-1} ; ^1H -NMR (400 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 8.34 (s, 1H), 8.33 (d, $J = 8.0$ Hz, 2H), 8.21 (s, 1H), 7.74 (d, $J = 8.0$ Hz, 2H), 7.42 (s, 1H); ^{13}C -NMR (100 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 154.1, 147.5, 143.9, 138.4, 137.6, 135.4, 127.8, 124.1, 121.5. HRMS (ESI, $[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{11}\text{H}_9\text{N}_2\text{O}_3$ 217.0608, found 217.0607.

Procedure for 5-ethylpyridin-3-ol (**3aD**)

Method: **3aD** (15.2 mg, 86%) was obtained from **5aD** (40.5 mg, 0.144 mmol), DMPI (91.6 mg), and DBU (43.0 μL).

Pale-yellow oil. Rf 0.55 (10% MeOH/ CHCl_3). IR (neat): 2968, 1585, 1438, 1225, 756, 707 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3): δ 8.10 (s, 1H), 7.94 (s, 1H), 7.16 (s, 1H), 2.63 (q, $J = 7.8$ Hz, 2H), 1.24 (t, $J = 7.8$ Hz, 3H); ^{13}C -NMR (100 MHz, CDCl_3): δ 155.2, 141.6, 138.8, 133.6, 124.6, 25.9, 15.0. LRMS (EI) m/z (relative intensity) 123 ($[\text{M}]^+$, 100), 108 (70), 95 (12). HRMS (EI, $[\text{M}]^+$): m/z calcd for $\text{C}_7\text{H}_9\text{NO}$, 123.0684; found, 123.0684.

Procedure for 5-(phenylethynyl)pyridin-3-ol (**3aE**)

Method: **3aE** (4.2 mg, 50%) was obtained from **5aE** (14.5 mg, 0.0410 mmol), DMPI (24.2 mg), and DBU (12.8 μL).

Pale-yellow oil. Rf 0.57 (10% MeOH/ CHCl_3). IR (neat): 2924, 2644, 2568, 2216, 1579, 1425, 1325, 1248, 1150, 1124, 1022, 868, 754, 688 cm^{-1} ; ^1H -NMR (600 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 8.19 (s, 1H), 8.08 (s, 1H), 7.57–7.48 (m, 2H), 7.44–7.35 (m, 3H), 7.33 (s, 1H); ^{13}C -NMR (151 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 153.2, 142.1, 136.5, 131.2, 128.4, 128.0, 124.8, 122.0, 120.8, 91.9, 85.5. LRMS (EI) m/z (relative intensity) 195 ($[\text{M}]^+$, 100), 139 (25), 69 (11). HRMS (EI, $[\text{M}]^+$): m/z calcd for $\text{C}_{13}\text{H}_9\text{NO}$, 195.0684; found, 195.0700.

Procedure for 5-(4-methoxyphenyl)-2-methylpyridin-3-ol (**3bA**)

Method: **3bA** (8.7 mg, 67%) was obtained from **5bA** (22.6 mg, 0.0605 mmol), DMPI (35.9 mg), and DBU (18.1 μL).

Pale-yellow oil. Rf 0.50 (10% MeOH/ CHCl_3). IR (neat): 2922, 1604, 1515, 1444, 1287, 1220, 1163, 773 cm^{-1} ; ^1H -NMR (400 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 8.03 (s, 1H), 7.43 (d, $J = 7.2$ Hz, 2H), 7.24 (s, 1H), 6.93 (d, $J = 7.2$ Hz, 2H), 3.80 (s, 3H), 2.40 (s, 3H); ^{13}C -NMR (100 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 159.3, 144.5, 136.7, 135.3, 129.9, 127.7, 126.7, 119.7, 114.2, 55.1, 17.1. HRMS (ESI, $[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{13}\text{H}_{14}\text{NO}_2$ 216.1019, found 216.1015.

Procedure for 2-isobutyl-5-(4-methoxyphenyl)pyridin-3-ol (**3cA**)

Method: **3cA** (7.8 mg, 59%) was obtained from **5cA** (21.5 mg, 0.0517 mmol), DMPI (30.7 mg), and DBU (15.5 μL).

Pale-yellow oil. Rf 0.55 (10% MeOH/CHCl₃). IR (neat): 2955, 1608, 1608, 1521, 1393, 1252, 1165, 1033, 830, 772 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃:CD₃OD = 3:1): δ 8.14 (s, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.30 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 2.71 (d, *J* = 7.8 Hz, 2H), 2.15 (t-sept, *J* = 7.8, 6.8 Hz, 1H), 0.96 (d, *J* = 6.8 Hz, 6H); ¹³C-NMR (100 MHz, CDCl₃:CD₃OD = 3:1): δ 159.3, 151.7, 147.7, 136.6, 135.0, 129.9, 127.7, 119.9, 114.1, 55.0, 40.4, 27.9, 22.1. HRMS (ESI, [M + H]⁺) *m/z* calcd for C₁₆H₂₀NO₂ 258.1489, found 258.1487.

Procedure for 2-benzyl-5-(4-methoxyphenyl)pyridin-3-ol (**3dA**)

Method: **3dA** (82.2 mg, 95%) was obtained from **5dA** (133 mg, 0.296 mmol), DMPI (176 mg), and DBU (88.4 μL).

Pale-yellow oil. Rf 0.55 (10% MeOH/CHCl₃). IR (neat): 1600, 1522, 1433, 1392, 1257, 1176, 1027, 827 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃:CD₃OD = 3:1): δ 8.16 (d, *J* = 2.0 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.25 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 2H), 4.19 (s, 2H), 3.85 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃:CD₃OD = 3:1): δ 159.3, 151.5, 146.7, 139.3, 137.1, 135.7, 129.8, 128.6, 128.0, 127.8, 125.7, 120.4, 114.2, 55.0, 37.7. LRMS (EI) *m/z* (relative intensity) 291 ([M]⁺, 100), 274 (12). HRMS (EI, [M]⁺): *m/z* calcd for C₁₉H₁₇NO₂, 291.1259; found, 291.1248.

Procedure for 2-isopropyl-5-(4-methoxyphenyl)pyridin-3-ol (**3eA**)

Method: **3eA** (6.8 mg, 64%) was obtained from **5eA** (16.3 mg, 0.0406 mmol), DMPI (26.3 mg), NaHCO₃ (6.9 mg), and DBU (12.4 μL).

Pale-yellow oil. Rf 0.55 (10% MeOH/CHCl₃). IR (neat): 2969, 2932, 1610, 1518, 1290, 1251, 1229, 1176, 1033, 830, 756 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃:CD₃OD = 3:1): δ 8.33 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.26 (s, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.47 (sept, *J* = 7.2 Hz, 1H), 1.35 (d, *J* = 7.2 Hz, 6H); ¹³C-NMR (100 MHz, CDCl₃:CD₃OD = 3:1): δ 159.6, 152.6, 149.8, 138.5, 135.1, 130.0, 128.0, 120.5, 114.4, 53.3, 29.1, 21.1. HRMS (ESI, [M + H]⁺) *m/z* calcd for C₁₅H₁₈NO₂ 244.1332, found 244.1330.

Procedure for 5-(4-methoxyphenyl)-6-methylpyridin-3-ol (**3fA**)

Method: **3fA** (9.3 mg, 67%) was obtained from **5fA** (24.2 mg, 0.0648 mmol), DMPI (38.5 mg), and DBU (19.4 μL).

Pale-yellow oil. Rf 0.55 (10% MeOH/CHCl₃). IR (neat): 2931, 1610, 1515, 1453, 1290, 1248, 1176, 1031, 834, 771, 707 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃:CD₃OD = 3:1): δ 7.97 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.08 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 3.87 (s, 3H), 2.38 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃:CD₃OD = 3:1): δ 158.8, 151.7, 145.9, 137.5, 134.4, 131.7, 129.8, 124.7, 113.6, 55.0, 21.2. HRMS (ESI, [M + H]⁺) *m/z* calcd for C₁₃H₁₄NO₂ 216.1019, found 216.1015.

Procedure for 5-(4-methoxyphenyl)-6-propylpyridin-3-ol (**3gA**)

Method: **3gA** (7.2 mg, 74%) was obtained from **5gA** (16.0 mg, 0.0398 mmol), DMPI (23.7 mg), and DBU (12.0 μL).

Pale-yellow oil. Rf 0.55 (10% MeOH/CHCl₃). IR (neat): 2960, 2931, 1610, 1516, 1452, 1288, 1248, 1175, 1032, 835, 755, 705 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃:CD₃OD = 3:1): δ 8.27 (d, *J* = 2.4 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.17 (d, *J* = 2.4 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 3.68 (s, 3H), 2.71 (t, *J* = 7.8 Hz, 2H), 1.57 (tq, *J* = 7.8, 7.2 Hz, 2H), 0.81 (t, *J* = 7.2 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃:CD₃OD = 3:1): δ 159.0, 152.6, 150.6, 138.4, 134.5, 131.8, 130.1, 126.9, 113.8, 55.3, 35.6, 23.7, 14.0. HRMS (ESI, [M + Na]⁺) *m/z* calcd for C₁₅H₁₇NNaO₂ 266.1152, found 266.1151.

Procedure for 5-(4-methoxyphenyl)-6-phenylpyridin-3-ol (**3hA**)

Method: **3hA** (6.6 mg, 80%) was obtained from **5hA** (12.8 mg, 0.0294 mmol), DMPI (17.5 mg), and DBU (8.8 μL).

Pale-yellow oil. Rf 0.55 (10% MeOH/CHCl₃). IR (neat): 2917, 1610, 1514, 1447, 1290, 1249, 1177, 1030, 833, 752, 702 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃:CD₃OD = 3:1): δ 8.14 (s,

1H), 7.44 (s, 1H), 7.25–7.18 (m, 5H), 7.06 (d, $J = 6.8$ Hz, 2H), 6.79 (d, $J = 6.8$ Hz, 2H), 3.78 (s, 3H); ^{13}C -NMR (100 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 158.8, 151.5, 141.3, 137.2, 135.7, 135.4, 133.6, 130.9, 130.3, 129.4, 128.5, 127.9, 113.4, 54.8. HRMS (ESI, $[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_2$ 278.1176, found 278.1170.

Procedure for 5-(4-methoxyphenyl)-2,6-dimethylpyridin-3-ol (**3iA**)

Method: **3iA** (23.8 mg, 73%) was obtained from **5iA** (55.2 mg, 0.142 mmol), DMPI (90.7 mg), and DBU (44.5 μL).

Pale-yellow oil. Rf 0.55 (10% MeOH/ CHCl_3). IR (neat): 2924, 1516, 1289, 1249, 1161, 1033, 840, 812, 719, 668 cm^{-1} ; ^1H -NMR (400 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 7.36 (s, 1H), 7.22 (d, $J = 8.8$ Hz, 2H), 6.96 (d, $J = 8.8$ Hz, 2H), 3.86 (s, 3H), 2.46 (s, 3H), 2.38 (s, 3H); ^{13}C -NMR (100 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 3:1$): δ 158.7, 149.2, 144.8, 144.0, 135.0, 132.0, 129.9, 123.7, 113.6, 55.1, 21.1, 17.6. HRMS (ESI, $[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_2$ 230.1176, found 230.1171.

Procedure for 4-hexyl-5-(4-methoxyphenyl)pyridin-3-ol (**3jA**)

Method: **3jA** (9.3 mg, 48%) was obtained from **5jA** (30.8 mg, 0.0694 mmol), DMPI (41.2 mg), and DBU (20.7 μL).

Pale-yellow oil. Rf 0.50 (10% MeOH/ CHCl_3). IR (neat): 2955, 1611, 1517, 1501, 1425, 1289, 1244, 1176, 1036, 831 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3): δ 8.33 (s, 1H), 7.96 (s, 1H), 7.24 (d, $J = 8.0$ Hz, 2H), 6.97 (d, $J = 8.0$ Hz, 2H), 3.87 (s, 3H), 2.64 (t, $J = 2.8$ Hz, 2H), 1.60–1.48 (m, 2H), 1.30–1.10 (m, 6H), 0.81 (t, $J = 6.8$ Hz, 3H); ^{13}C -NMR (100 MHz, CDCl_3): δ 159.1, 153.8, 140.1, 139.0, 138.9, 134.1, 130.4, 130.1, 113.7, 55.3, 31.4, 29.4, 28.8, 26.8, 22.5, 14.0. HRMS (ESI, $[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{18}\text{H}_{24}\text{NO}_2$ 286.1802, found 286.1801.

Procedure for 5-(4-methoxyphenyl)-4-phenylpyridin-3-ol (**3kA**)

Method: **3kA** (22.3 mg, 80%) was obtained from **5kA** (43.6 mg, 0.100 mmol), DMPI (59.4 mg), and DBU (29.9 μL).

Pale-yellow oil. Rf 0.55 (10% MeOH/ CHCl_3). IR (neat): 2933, 1609, 1425, 1290, 1249, 1178, 1033, 831, 750, 699 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3): δ 8.43 (s, 1H), 8.16 (s, 1H), 7.35–7.25 (m, 3H), 7.20 (d, $J = 6.8$ Hz, 2H), 6.99 (d, $J = 8.0$ Hz, 2H), 6.73 (d, $J = 8.0$ Hz, 2H), 3.75 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3): δ 158.8, 151.5, 141.3, 137.2, 135.7, 135.4, 133.6, 130.9, 130.3, 129.4, 128.5, 127.9, 113.5, 55.1. HRMS (ESI, $[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{18}\text{H}_{16}\text{NO}_2$ 278.1176, found 278.1173.

Procedure for 5-(4-methoxyphenyl)-4-(4-nitrophenyl)pyridin-3-ol (**3lA**)

Method: **3lA** (25.9 mg, 77%) was obtained from **5lA** (50.2 mg, 0.104 mmol), DMPI (62.1 mg), and DBU (33.1 μL).

Pale-yellow oil. Rf 0.51 (10% MeOH/ CHCl_3). IR (neat): 2933, 1515, 1247, 1176, 1110, 1033, 830, 753 cm^{-1} ; ^1H -NMR (600 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 1:1$): δ 8.21 (s, 1H), 8.16–8.09 (m, 3H), 7.39 (d, $J = 8.6$ Hz, 2H), 6.99 (d, $J = 8.6$ Hz, 2H), 6.79 (d, $J = 8.6$ Hz, 2H), 3.78 (s, 3H); ^{13}C -NMR (151 MHz, $\text{CDCl}_3:\text{CD}_3\text{OD} = 1:1$): δ 158.7, 146.5, 141.4, 140.7, 135.5, 132.6, 131.3, 130.4, 128.4, 122.4, 113.3, 54.5. (two signals missing due to an overlap). HRMS (ESI, $[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_4$ 323.1026, found 323.1025.

Procedure for 4-(cyclohex-1-en-1-yl)-5-(4-methoxyphenyl)pyridin-3-ol (**3nA**)

Method: **3nA** (26.4 mg, 58%) was obtained from **5nA** (71.2 mg, 0.162 mmol), DMPI (96.2 mg), and DBU (49.0 μL).

Pale-yellow oil. Rf 0.55 (10% MeOH/ CHCl_3). IR (neat): 2931, 1610, 1511, 1452, 1246, 1170, 1032, 832, 758, 664 cm^{-1} ; ^1H -NMR (600 MHz, CDCl_3): δ 8.30 (s, 1H), 8.12 (s, 1H), 7.34 (d, $J = 8.9$ Hz, 2H), 6.93 (d, $J = 8.9$ Hz, 2H), 5.98–5.94 (m, 1H), 3.85 (s, 3H), 2.24–2.19 (m, 2H), 2.73–2.69 (m, 2H), 2.61–2.54 (m, 2H), 2.52–2.44 (m, 2H); ^{13}C -NMR (151 MHz, CDCl_3): δ 159.3, 148.7, 142.1, 136.2, 135.4, 135.0, 132.6, 131.5, 130.0, 129.9, 113.7, 55.3, 28.1, 25.4, 22.5, 21.6. HRMS (ESI, $[\text{M} + \text{H}]^+$) m/z calcd for $\text{C}_{18}\text{H}_{20}\text{NO}_2$ 282.1489, found 282.1486.

Procedure for 5-(4-methoxyphenyl)-2-methyl-4-(4-nitrophenyl)pyridin-3-ol (**3oA**)

Method: **3oA** (9.3 mg, 72%) was obtained from **5oA** (20.5 mg, 0.0415 mmol), DMPI (24.6 mg), and DBU (12.4 μ L).

Pale-yellow oil. Rf 0.55 (10% MeOH/CHCl₃). IR (neat): 2923, 1513, 1343, 1241, 1219, 1176, 1128, 1106, 1033, 829, 755 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 8.14 (d, *J* = 8.8 Hz, 2H), 8.03 (s, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 3.77 (s, 3H), 2.56 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ 158.7, 146.8, 145.8, 141.9, 134.9, 131.47, 131.45, 130.59, 130.56, 128.8, 123.02, 122.99, 113.6, 54.9, 18.5. HRMS (ESI, [M + H]⁺) *m/z* calcd for C₁₉H₁₇N₂O₄ 337.1183, found 337.1179.

3.3.6. Procedure for 2-benzyl-3-(3-methoxyphenyl)-5-(4-methoxyphenyl)pyridine (**10**)

To a solution of **3cA** (40.0 mg, 0.137 mmol) and Et₃N (38.2 μ L, 0.274 mmol) in anhydrous DCM (1.0 mL) was added Tf₂O (38.2 μ L, 0.164 mmol) at 0 °C under argon. After being stirred at the same temperature for 4 h, the reaction mixture was treated with saturated aqueous NaHCO₃. The resulting mixture was extracted with EtOAc, washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified with preparative TLC eluting with 10% EtOAc/toluene to give triflate (46.6 mg, 80%).

To a test tube containing the above triflate (8.7 mg, 0.021 mmol), *m*-methoxyphenylboronic acid (6.2 mg, 2 equiv), Pd(PPh₃)₄ (1.2 mg, 5 mol%), and LiCl (2.6 mg, 3 equiv) in DME (0.3 mL) was added 2.0 M aqueous Na₂CO₃ (31 μ L) under argon. The resulting mixture was sealed with a screw cap and stirred at 80 °C for 8 h. The reaction mixture was cooled down to room temperature, diluted with EtOAc, washed with water and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified with preparative TLC eluting with 20% EtOAc/toluene to give **10** (7.2 mg, 93%) as a brown solid.

Rf 0.70 (20% EtOAc/toluene). IR (neat): 1609, 1516, 1455, 1440, 1288, 1248, 1179, 1148, 1035, 830, 701 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃): δ 8.80 (s, 1H), 7.71 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.32 (t, *J* = 8.4 Hz, 1H), 7.24–7.10 (m, 3H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 4.18 (s, 2H), 3.85 (s, 3H), 3.72 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ 159.7, 159.4, 155.8, 146.3, 140.9, 140.1, 137.3, 135.6, 133.9, 130.0, 129.8, 129.4, 128.8, 128.2, 128.1, 125.9, 121.5, 114.5, 113.6, 55.3, 55.2, 41.3. HRMS (ESI, [M + H]⁺) *m/z* calcd for C₂₆H₂₄NO₂ 382.1802, found 382.1796.

4. Conclusions

In summary, we have developed a new synthetic method for polysubstituted 3-hydroxypyridines. The starting alkynals, which were readily prepared from *N*-tosyl amino acid esters and propargyl alcohols, were effectively converted to a wide range of 3-hydroxy-1,2,3,6-tetrahydropyridines with various organometallic reagents in the “anti-Wacker”-type cyclization. The 5-Monosubstituted 3-hydroxypyridines, 2,5-, 4,5-, and 5,6-disubstituted 3-hydroxypyridines, and 2,4,5- and 2,5,6-trisubstituted 3-hydroxypyridines were obtained by the oxidation and elimination of toluenesulfonic acid. This approach enables the introduction of substituents into 3-hydroxypyridines one by one in a highly regioselective manner. The hydroxy group at the C3 position can be further substituted with cross-coupling reactions via the corresponding triflate.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/catal13020319/s1>, preparation of substrates, analytical data, ¹H and ¹³C NMR spectra, and more detailed materials and methods. References [52,53,61–65] are cited in Supplementary Materials.

Author Contributions: Conceptualization, H.T.; investigation, K.I. and H.T.; writing—original draft preparation, K.I.; writing—review and editing, H.T. and T.D.; supervision, T.D.; funding acquisition, H.T. and T.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research was partly funded by the Banyu Pharmaceutical Co. Ltd. Award in Synthetic Organic Chemistry, The Research Foundation for Pharmaceutical Sciences, SUNTRY FOUNDATION for LIFE SCIENCES, Platform Project for Supporting Drug Discovery and Life Science Research (Basis

for Supporting Innovative Drug Discovery and Life Science Research (BINDS)) from AMED under Grant Number JP19am0101095 and JP19am0101100, and JSPS KAKENHI Grant Numbers JP2459004 and JP15K07849.

Data Availability Statement: All experimental data is contained in the article and Supplementary Material.

Conflicts of Interest: The authors declare no conflict of interest.

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