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Gold-Mediated Synthesis and Functionalization of Chiral Halopyridones

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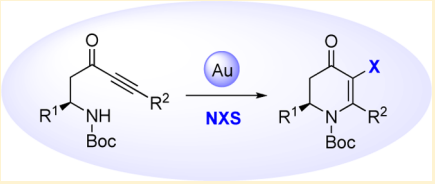
Supporting Information

ABSTRACT: A rapid and efficient one-step halopyridone synthesis has been developed based on gold-catalyzed cyclization of β-amino-ynone intermediates and halodeauration process.



INTRODUCTION

Among the synthetic approaches reported in the literature to construct heterocyclic molecules, the use of electrophilic halogen sources has proven very efficient to obtain highly functionalized heterocyclic compounds.[1,2] These methodologies, which typically lead to the incorporation of halogens into the heterocyclic structure, allow for the creation of molecular diversity and complexity postcyclization. For example, halopyridones have revealed to be very attractive synthetic building blocks for the preparation of piperidines. The key step in these methodologies generally involved Comins's 2,3-dihydro-4-pyridone intermediates generated from acyl pyridinium, then halogenations.[3] In this way, methods leading to such intermediates with strict control of regio- and stereochemistry continue to stand as a prominent objective in synthetic organic chemistry.

Besides the classical electrophilic iodocyclization methods,[1,2] gold catalysis has emerged in the past few years as a powerful tool for controlling the formation of carbon−halogen bonds.[4] The process, in such approaches, involved a final halodeauration step (instead of a protodeauration) at the end of the catalytic cycle.

Recently, we have developed an access to pyridones from the chiral pool of amino acids via a gold-catalyzed heterocyclization strategy.[5] We showed that the use of gold catalysis in this process allowed an excellent stereocontrol during the cyclization (Scheme 1). It was also demonstrated that this approach provides a straightforward tool for the total synthesis of natural products, such as piperidine alkaloids (+)-241-D, isosolenopsin, and isoslenopsin A, in few steps and good overall yields.[5b]

On the basis of our previous works,[5] we describe herein a new approach toward halopyridones. The strategy is based on a one-pot gold-catalyzed tandem reaction consisting of heterocyclization and halogenation (Scheme 2). The results of our study and some palladium-catalyzed coupling reactions are disclosed in this article.

RESULTS AND DISCUSSION

The starting materials, the β-amino-ynones **1**, were prepared from commercially available amino acids via Weinreb amide formation and subsequent addition of various lithium acetylides.[5a,6] We first performed a catalyst screening to optimize the cyclization conditions. In this way, substrate **1a** was subjected to various catalysts and other activating agents in various conditions (Table 1). As the stoichiometric use of simple electrophilic halogen sources has been frequently used to construct a wide range of carbocycles[7] and heterocycles,[1,2] the reaction of amino-ynone **1a** was initially examined with the use of 2 equiv of I_2 or NIS (Table 1, entries 1 and 2). Notably, the starting amino-ynone did not react under these conditions or afforded at most small amounts of 5-iodopyridone **2a**. Various catalytic conditions were then investigated to probe the feasibility of the proposed transformation.

Several gold sources, in the presence or absence of cocatalyst, were tested. Results revealed that the use of PPh_3AuCl in the presence of $AgSbF_6$,[8] and NIS as electrophile, in 1,2-dichloroethane (DCE) at room temperature, afforded in 0.5 h the desired product **2a** in good yield (entry 3). Stoichiometric use of NIS gave the desired product in lower yield (entry 4). The cyclization did not proceed in the presence of AuCl or Au_2O_3 as catalysts (entries 5 and 6). Complementary study of solvents prompted us to choose 1,2-DCE that proved to be more efficient than THF or toluene. The use of iodine (entry 7) instead of NIS as the electrophilic iodine source did not improve the reaction. As expected, no reaction was observed when we used $AgSbF_6$ or PPh_3AuCl catalyst independently

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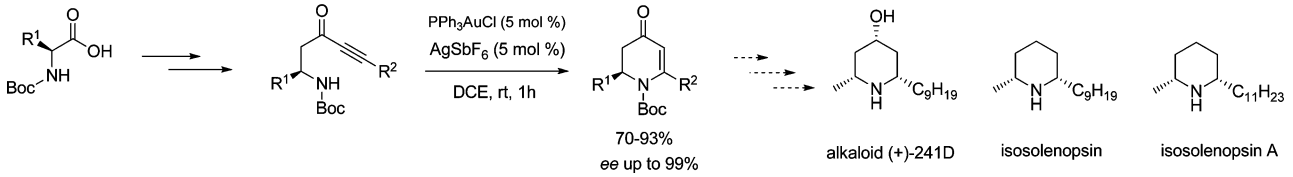
Scheme 1. Gold-Catalyzed Synthesis of Pyridones toward Piperidine Alkaloids



Scheme 2. Our Proposed Route to Halopyridones

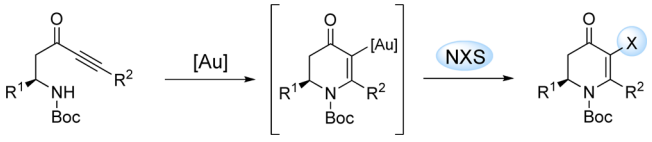
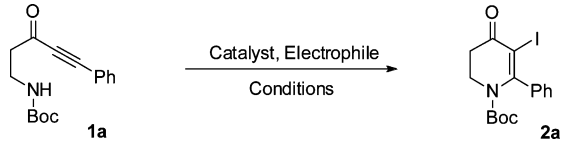


Table 1. Optimization of the Reaction Conditions[a] for the Iodocyclization of 1a



entry	catalyst	E^+ (equiv)	time (h)	yield (%)[c]
1		NIS (2.0)	24	nr[d]
2		I_2 (2.0)	24	nr
3	$Ph_3PAuSbF_6$[b]	NIS (1.5)	0.5	78
4	$Ph_3PAuSbF_6$[b]	NIS (1.0)	0.5	60
5	AuCl	NIS (1.5)	72	<10
6	Au_2O_3	NIS (1.5)	72	<10
7	$Ph_3PAuSbF_6$[b]	I_2 (1.5)	1	65
8	Ph_3PAuCl	NIS (1.5)	48	<10
9	$AgSbF_6$	NIS (1.5)	48	<10

[a]Unless indicated otherwise, a mixture of **1a** (0.1 mmol), a gold complex (5 mol %), and electrophile (1.5 equiv) in 1,2-DCE (1.0 mL) was stirred at room temp. under argon. [b]The $Ph_3PAuSbF_6$ was in situ generated from 5 mol % of Ph_3PAuCl and 5 mol % of $AgSbF_6$. [c]Isolated yield. [d]No reaction.

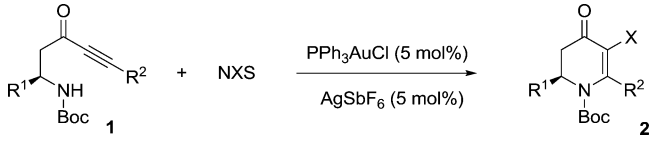
(entries 8 and 9). These results emphasize the importance of the anion exchange to obtain catalytic activity. Thus, we selected $Ph_3PAuSbF_6$ as catalyst, *N*-halo-succinimide as the source of halogen, and 1,2-DCE as solvent for further investigations of this methodology.

To demonstrate the scope of this gold-mediated halocyclization reaction, a variety of *β*-amino-ynones were examined. As depicted in Table 2, a series of 5-halo-2,3-dihydropyridone derivatives **2a**–**2r** could be successfully obtained from moderate to excellent yields. First, the nature of the halogen source was checked (entries 1 and 2), and both NIS and NBS showed good reactivity, providing the corresponding products (**2a** and **2b**) in good to excellent yields. However, NCS revealed to be unreactive under these conditions since cyclization in 2,3-dihydropyridone occurred without any incorporation of chlorine atom (entry 3).

We next extended this protocol to various alkynes (entries 3–8). The results revealed that a substituent on the phenyl group (entries 4–6) and a substrate bearing an alkyl group (entry 7) did not significantly affect the reaction. Unfortunately, none of the desired product was obtained when a terminal alkyne (entry 8) was employed. Application to chiral substrates was then investigated. Actually, a series of substituents on C2 (R^1) were tested (entries 9–20), and it could be noted that all reactions proceeded smoothly to provide the corresponding products in good to excellent yields. Attempts to extend this chemistry to the synthesis of fluoro analogues by using Selectfluor as a source of F^+ were not successful since only the protodeauration product was isolated (entry 21).

Reactivity of a propargylic alcohol in such catalytic conditions was also investigated (Scheme 3). Propargylic alcohol **3** was obtained quantitatively from **1a** via a Luche

Table 2. Gold-Catalyzed Halocyclization of *β*-Amino-ynones 1 to 5-Halopyridones 2[a]



entry	R^1	R^2	X	product	yield (%)[b]	entry	R^1	R^2	X	product	yield (%)
1	H	Ph	I	**2a**	78	12	*i*-Bu	*n*-Pr	I	**2j**	71
2	H	Ph	Br	**2b**	91	13	Bn	Ph	Br	**2k**	79
3	H	Ph	Cl		0	14	Bn	Ph	I	**2l**	79
4	H	4-MeO-Ph	Br	**2c**	85	15	Bn	*n*-Pr	Br	**2m**	65
5	H	4-F-Ph	Br	**2d**	86	16	Bn	*n*-Pr	I	**2n**	87
6	H	4-F-Ph	I	**2e**	83	17	CH_2-OBn	Ph	Br	**2o**	93
7	H	*n*-Pr	I	**2f**	88	18	CH_2-OBn	Ph	I	**2p**	80
8	H	H	I		0	19	CH_2-OBn	*n*-Pr	Br	**2q**	48[c]
9	Me	*n*-Pr	I	**2g**	70	20	CH_2-OBn	*n*-Pr	I	**2r**	47
10	*i*-Bu	Ph	Br	**2h**	97	21	H	Ph	F		0
11	*i*-Bu	Ph	I	**2i**	76						

[a]Reaction conditions: substrate **1** (1 mmol), NXS (1.5 mmol), PPh_3AuCl (5 mol %), $AgSbF_6$ (5 mol %), 1,2-DCE (10.0 mL), r.t., 1 h. [b]Isolated yield. [c]12 h was necessary for completion of reaction.

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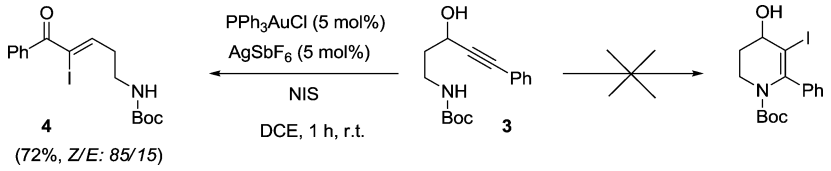
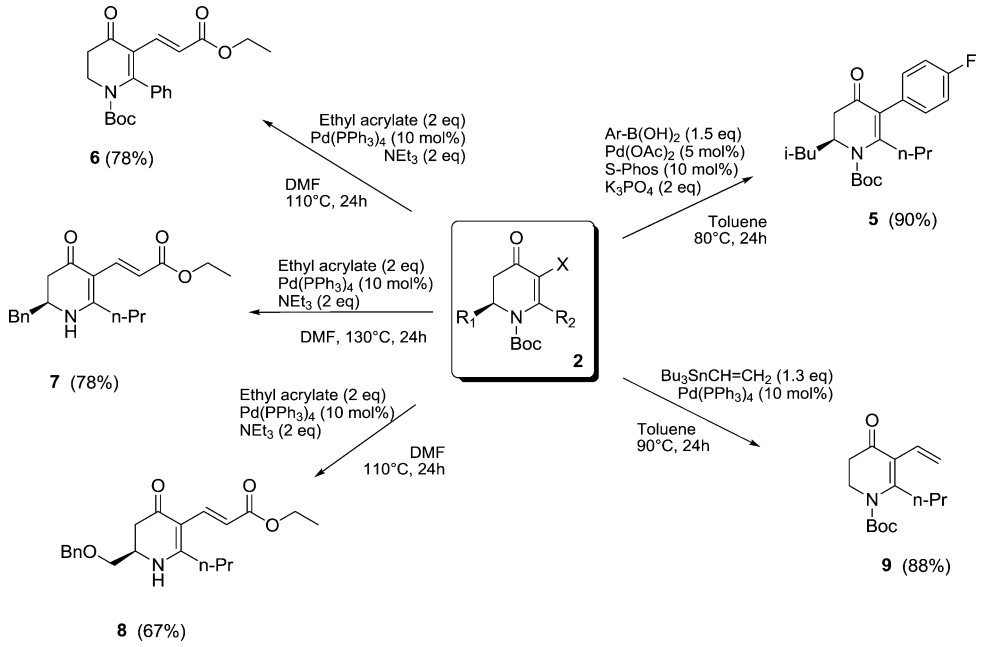
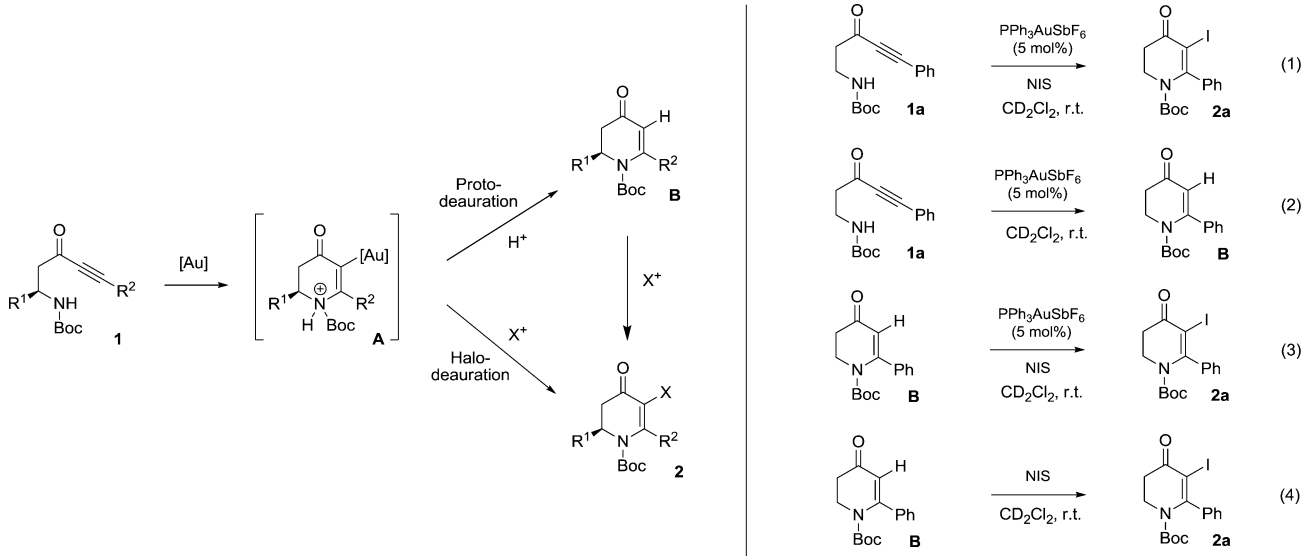
Scheme 3. Reactivity of Propargylic Alcohol



Scheme 4. Pd-Catalyzed Modifications of 5-Halopyridones 2



Scheme 5. Mechanistic Consideration of the Process



reduction. We next examined the reaction of **3** and NIS in the presence of a Au catalyst. α-Iodoketone **4** was obtained in a Meyer–Schuster rearrangement process, and no heterocyclization was observed. Such reactivity of propargylic alcohols was already reported in the literature.[9]

The structures of the halogenation products have been established by NMR analyses. Moreover, two of them were further confirmed by X-ray crystallographic analyses.[10]

Finally, **2g** was also prepared starting from D-alanine. With both enantiomers in hand, the enantiomeric purity of **2g** was confirmed by chiral HPLC to be >98% ee, assessing that no epimerization occurs during this process.

These halogenated pyridones were further functionalized by applying palladium-catalyzed processes, such as Suzuki–Miyaura,[11] Heck,[12] or Stille[13] cross-coupling reactions (Scheme 4).

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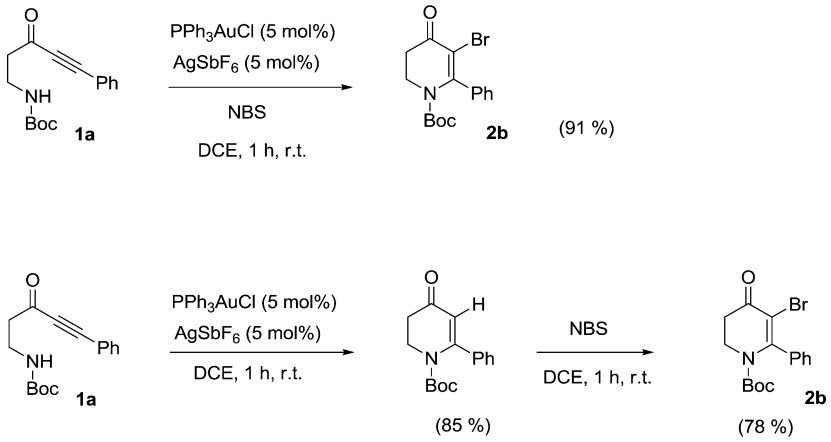
Scheme 6. One-Step vs Two-Step Processes



For instance, compounds **5** and **6** have been successfully obtained in 90% and 78% isolated yield respectively by the Suzuki cross-coupling reaction of **2j** with 4-fluorophenylboronic acid and the Heck coupling reaction of **2a** with ethyl acrylate. It should be mentioned that the temperature had an incidence on the protecting group in such processes. Actually, when Heck coupling reactions with **2n** and **2r** were performed at 110 °C (instead of 80 °C in the first case), deprotected compounds **7** and **8** could be obtained in good yield (78% and 67% isolated yield, respectively). In a similar manner, reaction of **2g** with tributylvinylstannane gave the corresponding Stille coupling adduct **9** in an 88% isolated yield.

Mechanistically, gold(I) catalyst coordinates to the triple bond to form a complex that undergoes 6-*endodig* cyclization to give intermediate **A** (Scheme 5). In a classic manner, next, demetalation proceeds via a proton transfer, providing heterocycle **B** in a protodeauration step. Such a heterocycle could then undergo halogenation to afford **2**.[3] The other possibility is the attack of a halonium ion, which would result in the direct formation of halopyridone **2** (halodeauration process) excluding intermediate **B**.

To probe the second mechanistic hypothesis, we conducted control experiments. The kinetic investigation of this gold-catalyzed cyclization was performed in CD_2Cl_2 and monitored by ^1H NMR. Gold-catalyzed cyclization in the presence of NIS (eq 1) (Scheme 5) was shown to be complete within 10 min,[14] whereas gold-catalyzed cyclization in the absence of NIS (eq 2) was complete in more than 30 min. In addition, iodination (NIS) of heterocycle **B** in the presence of gold catalyst (eq 3) was faster (reaction complete within 15 min) than in the absence of gold catalyst (eq 4) (reaction complete in 1 h). These results may suggest that this iodocyclization proceeded via a halodeauration process since the demetalation is faster in the presence of NIS.

Finally, when compared to a two-step protocol, the gold-catalyzed tandem heterocyclization−halogenation process revealed more efficient (91% yield vs 66%) (Scheme 6).

CONCLUSION

In conclusion, we have developed a convenient gold-catalyzed approach for the synthesis of 5-halopyridone derivatives from *β*-amino-ynone intermediates via a halodeauration process. The reactions proceeded under mild conditions and generally provided the pyridone products in good to excellent yields. This methodology could provide a straightforward tool for the synthesis of naturally occurring 2,5,6-trisubstituted piperidines and other decahydroquinolines.

EXPERIMENTAL SECTION

General Procedure for the Tandem Heterocyclization/Halogenation Reaction. To the amino-ynone **1** (1 mmol, 1 equiv) in 1,2-dichoroethane (10 mL) at room temperature under an argon atmosphere was added NXS (1.5 equiv). After 5 min, a dry mixture of PPh_3AuCl (5 mol %) and $AgSbF_6$ (5 mol %) was added to the solution. After the resulting mixture was stirred at room temperature for 1 h, Et_2O was added and the resulting mixture was filtered over a Celite plug. After removal of solvents in vaccuo, the crude product was purified by silica gel column chromatography using dichloromethane as an eluant to yield pure products.

(2a): Yellow solid, mp: 124−126 °C, 311 mg (78%); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (s, 9H), 2.87−2.91 (m, 2H), 4.22−4.27 (m, 2H), 7.38−7.44 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.5, 158.7, 151.9, 140.0, 129.7, 128.8, 127.9, 89.7, 83.3, 46.4, 37.7, 27.4; HRMS (ESI, *m*/*z*): Calcd for $C_{16}H_{18}INO_3Na$: 422.0229, found $[M + Na]^+$: 422.0228; IR-FT (DRA): 2967, 1711, 1669, 1590, 1346 cm^{-1}.

(2b): Yellow oil, 320 mg (91%); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 9H), 2.85 (t, *J* = 6.5 Hz, 2H), 4.25 (t, *J* = 6.6 Hz, 2H), 7.40−7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.1, 155.4, 152.0, 137.3, 129.7, 128.7, 128.0, 109.2, 83.3, 46.1, 38.5, 27.4; HRMS (ESI, *m*/*z*): Calcd for $C_{16}H_{18}BrNO_3Na$: 374.0368, found $[M + Na]^+$: 374.0371; IR-FT (ATR): 2978, 1711, 1677, 1538, 1337 cm^{-1}.

(2c): Yellow oil, 325 mg (85%); ^1H NMR (500 MHz, $CDCl_3$): δ = 1.10 (s, 9H), 2.82−2.84 (m, 2H), 3.86 (s, 3H), 4.21−4.24 (m, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 7.40 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.3, 160.9, 155.3, 152.3, 130.5, 129.5, 113.3, 108.9, 83.1, 55.4, 46.0, 38.7, 27.5; HRMS (ESI, *m*/*z*): Calcd for $C_{17}H_{20}BrNO_4Na$: 404.0473, found $[M + Na]^+$: 404.0471; IR-FT (ATR): 2976, 1707, 1673, 1503, 1337 cm^{-1}.

(2d): Yellow solid, mp: 120−122 °C, 318 mg (86%); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 9H), 2.80−2.84 (m, 2H), 4.20−4.24 (m, 2H), 7.06−7.12 (m, 2H), 7.38−7.41 (m,2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.9, 163.2 (d, J_{CF} = 250.9 Hz), 154.2, 151.8, 133.2 (d, J_{CF} = 3.5 Hz), 130.7 (d, J_{CF} = 8.6 Hz), 115.0 (d, J_{CF} = 21.9 Hz), 109.5, 83.4, 46.0, 38.4, 27.4; HRMS (ESI, *m*/*z*): Calcd for $C_{16}H_{17}FBrNO_3$-Na: 392.0274, found $[M + Na]^+$: 392.0274; IR-FT (DRA): 2341, 1741, 1727, 1364, 1216 cm^{-1}.

(2e): Orange solid, mp: 98−100 °C, 346 mg (83%); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (s, 9H,), 2.87−2.91 (m, 2H), 4.24−4.28 (m, 2H), 7.16−7.20 (m, 2H), 7.40−7.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.5, 163.3 (d, J_{CF} = 250.9 Hz), 157.7, 151.8, 136.0 (d, J_{CF} = 3.5 Hz), 131.0 (d, J_{CF} = 8.6 Hz), 115.1 (d, J_{CF} = 21.9 Hz), 90.2, 83.6, 46.4, 37.8, 27.5; HRMS (ESI, *m*/*z*): Calcd for $C_{16}H_{17}IFNO_3Na$: 440.0135, found $[M + Na]^+$: 440.0132; IR-FT (DRA): 2357, 1741, 1726, 1381, 1216 cm^{-1}.

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(2f): Yellow oil, 322.4 mg (88%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (t, J = 7.4 Hz, 2.90H), 1.54 (s, 9H), 1.64−1.67 (m, 2H), 2.72−2.74 (m, 2H), 3.07−3.10 (m, 1.90H), 3.99−4.02 (m, 1.90H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.8, 163.1, 151.5, 92.4, 83.5, 46.7, 41.8, 36.9, 28.1, 21.1, 13.8; HRMS (ESI, m/z): Calcd for $C_{13}H_{20}INO_3Na$: 388.0386, found $[M + Na]^+$: 388.0383; IR-FT (ATR): 2968, 1712, 1673, 1551, 1142 cm^{-1}.

(2g): Yellow oil, 265.4 mg (70%); $[\alpha]_D^{25}$ = +129.0 (c 0.4, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (t, J = 7.3 Hz, 3H), 1.25 (d, J = 6.8 Hz, 3H), 1.56 (s, 9H), 1.55−1.77 (m, 2H), 2.56 (sys ABX, J_{AB} = 16.9 Hz, J_{AX} = 1.6 Hz, 1H), 2.92−2.98 (m, 1H), 3.00 (sys ABX, J_{AB} = 16.9 Hz, J_{BX} = 5.9 Hz, 1H), 3.23−3.29 (m, 1H), 4.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.7, 159.8, 151.8, 90.4, 83.4, 52.0, 42.1, 42.0, 28.0, 20.9, 16.6, 13.9; HRMS (ESI, m/z): Calcd for $C_{14}H_{22}INO_3Na$: 402.0537, found $[M + Na]^+$: 402.0537; IR-FT (ATR) 2967, 1711, 1669, 1590, 1346 cm^{-1}; IR-FT (ATR): 2958, 1710, 1670, 1539, 1312 cm^{-1}.

(2h): Orange oil, 396 mg (97%); $[\alpha]_D^{25}$ = +22.8 (c 1.2, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.5 Hz, 3H), 1.04 (d, J = 6.5 Hz, 3H), 1.05 (s, 9H), 1.48−1.54 (m,1H), 1.69−1.87 (m,2H), 2.69 (dd, J = 17.0 Hz, J = 1.1 Hz, 1H,), 3.14 (dd, J = 17.0 Hz, J = 5.9 Hz, 1H), 4.85−4.92 (m, 1H), 7.36−7.83 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.4, 152.9, 152.6, 138.1, 129.6, 128.6, 128.0, 108.6, 83.2, 53.9, 42.4, 39.3, 27.4, 25.3, 22.7, 22.6; HRMS (ESI, m/z): Calcd for $C_{20}H_{26}NO_3BrNa$: 430.0994, found $[M + Na]^+$: 430.0995; IR-FT (ATR): 2956, 1707, 1677, 1541, 1312 cm^{-1}.

(2i): Yellow oil, 346 mg (76%); $[\alpha]_D^{25}$ = +15.8 (c 1.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.02 (d, J = 6.4 Hz, 3H), 1.05 (d, J = 6.4 Hz, 3H), 1.06 (s, 9H), 1.48−1.52 (m, 1H), 1.73−1.78 (m, 2H), 2.74 (dd, J = 17.2 Hz, J = 1.0 Hz, 1H), 3.15 (dd,, J = 17.1 Hz, J = 5.8 Hz, 1H), 4.83−4.86 (m, 1H), 7.33−7.42 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.7, 156.3, 152.4, 140.8, 129.5, 128.7, 127.9, 89.2, 83.2, 54.1, 41.6, 39.3, 27.4, 25.2, 22.8, 22.6; HRMS (ESI, m/z): Calcd for $C_{20}H_{26}INO_3Na$: 478.0855, found $[M + Na]^+$: 478.0858; IR-FT (ATR): 2956, 1706, 1670, 1530, 1286 cm^{-1}.

(2j): Yellow oil, 299.3 mg (71%); $[\alpha]_D^{25}$ = +295.8 (c 1.1, MeOH); ^{1}H NMR: (500 MHz, $CDCl_3$) δ = 0.90 (d, J = 6.2 Hz, 3H), 0.96 (d, J = 6.2 Hz, 3H), 1.02 (t, J = 7.4 Hz, 3H), 1.29−1.31 (m, 1H), 1.54 (s, 9H), 1.54−1.63 (m, 4H), 2.60 (d, J = 17.1 Hz, 1H), 2.88−2.91 (m, 1H), 2.95 (dd, J = 17.1 Hz, J = 5.8 Hz, 1H), 3.19−3.25 (m, 1H), 4.68−4.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.8, 160.4, 152.0, 91.7, 83.3, 54.4, 42.2, 40.9, 39.2, 28.0, 24.8, 22.7, 22.4, 21.0, 14.0; HRMS (ESI, m/z): Calcd for $C_{17}H_{28}INO_3Na$: 444.1011, found $[M + Na]^+$:444.0999; IR-FT (ATR): 2958, 1711, 1670, 1537, 1312 cm^{-1}.

(2k): Yellow oil, 349.5 mg (79%); $[\alpha]_D^{25}$ = +315.6 (c 1.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 9H), 2.67 (d, J = 17.3 Hz, 1H), 3.00 (dd, 1H, J = 17.3 Hz, J = 6.0 Hz), 3.07−3.12 (m, 1H), 3.17−3.21 (dd, J = 13.6 Hz, J = 6.0 Hz, 1H) 5.07−5.11 (m, 1H), 7.26−7.39 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.0, 152.9, 152.2, 137.7, 136.4, 129.6, 129.5. 128.7, 128.6, 127.9, 127.0, 108.5, 83.4, 56.1, 40.5, 36.4, 27.3; HRMS (ESI, m/z): Calcd for $C_{23}H_{24}NO_3Br$: 464.0837, found $[M + Na]^+$: 464.0835; IR-FT (ATR): 2979, 1707, 1674, 1538, 1316 cm^{-1}.

(2l): Yellow oil, 386 mg (79%); $[\alpha]_D^{25}$ = +315.6 (c 1.3, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 9H), 2.72 (d, J = 17.1 Hz, 1H), 2.99−3.08 (m, 2H), 3.17 (dd, J = 13.4 Hz, J = 6.2 Hz, 1H), 5.02−5.06 (m, 1H), 7.22−7.37 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.4, 156.3, 152.1, 140.4, 136.4, 129.5, 128.7. 127.9, 127.0, 88.9, 83.4, 56.4, 39.6, 36.3, 27.3; HRMS (ESI, m/z): Calcd for $C_{23}H_{24}INO_3Na$: 512.0699, found $[M + Na]^+$: 512.0699; IR-FT (ATR): 2981, 1698, 1670, 1533, 1317 cm^{-1}.

(2m): Yellow oil, 265.4 mg (65%); $[\alpha]_D^{25}$ = +18.5 (c 0.8, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): two rotamers in a ratio 85/15 δ = 0.97 (t, J = 7.4 Hz, 0.45H), 1.03 (t, J = 7.4 Hz, 2.55H),1.39 (s, 1.5H), 1.48 (s, 7.5H), 1.64−1.70 (m, 2H),, 2.57 (dd, J = 7.2 Hz, J = 1.7 Hz, 1H), 2.80−3.10 (m, 5H), 4.80−4.84 (m, 1H), 7.11−7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$):185.9, 157.6, 151.6, 136.7, 129.4, 128.6, 126.9, 109.9, 83.5, 57.3, 39.8, 37.6, 36.3, 27.9, 20.8, 14.1; HRMS (ESI, m/z): Calcd for $C_{20}H_{26}NO_3BrNa$: 430.0994, found $[M + Na]^+$: 430.0993; IR-FT (ATR): 2970, 1715, 1673, 1547, 1136 cm^{-1}.

(2n): Yellow oil, 396.1 mg (87%); $[\alpha]_D^{25}$ = +223.6 (c 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.02 (t, J = 7.4 Hz, 3H), 1.49 (s, 9H), 1.63−1.70 (m, 1H), 2.62 (d, J = 17.1 Hz, 1H), 2.78−2.96 (m, 4H), 3.17−3.23 (m, 1H), 4.76−4.80 (m, 1H), 7.11−7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.4, 160.2, 151.5, 136.8, 129.4, 128.6, 126.8, 90.6, 83.5, 57.4, 42.2, 38.9, 36.3, 27.9, 21.2, 14.0; HRMS (ESI, m/z): Calcd for $C_{20}H_{26}INO_3Na$: 478.0855, found $[M + Na]^+$: 478.0857; IR-FT (ATR): 2968, 1715, 1666, 1533, 1248 cm^{-1}.

(2o): Orange oil, 439.3 mg (93%); $[\alpha]_D^{25}$ = +195.5 (c 1.05, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 9H), 2.81 (d, J = 17.7 Hz, 1H), 3.16 (dd, J = 17.7 Hz, J = 6.4 Hz, 1H), 3.66 (dd, J = 17.0 Hz, J = 6.0 Hz, 1H), 3.85−3.89 (m, 1H), 4.58 (d, syst.AB, J = 11.9 Hz, 1H), 4.65 (d, syst. AB, J = 11.9 Hz, 1H), 5.09−5.13 (m, 1H), 7.26−7.39 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 186.8, 153.0, 152.4, 138.0, 137.6, 129.5, 128.8, 128.4, 127.8, 127.8, 127.7, 109.1, 83.3, 73.2, 68.1, 53.8, 39.6, 27.4; HRMS (ESI, m/z): Calcd for $C_{24}H_{26}BrNO_4Na$: 494.0943, found $[M + Na]^+$: 494.0941; IR-FT (ATR): 2978, 1707, 1677, 1543, 1311 cm^{-1}.

(2p): Orange oil, 415.5 mg (80%); $[\alpha]_D^{25}$ = +250.9 (c 1.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (s, 9H), 2.86 (d, J = 17.5 Hz, 1H), 3.18 (dd, J = 17.7 Hz, J = 6.4 Hz, 1H), 3.64 (dd, J = 10.1 Hz, J = 6.4 Hz, 1H), 3.85 (dd, 1H, J = 10.1 Hz, J = 8.1 Hz), 4.58 (d, syst. AB, J = 11.9 Hz, 1H), 4.64 (d, syst. AB, J = 11.9 Hz, 1H), 5.07−5.10 (m, 1H), 7.18−7.41 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.3, 156.4, 152.3, 140.6, 137.6, 129.5, 128.4, 127.8, 127.8, 127.7, 89.6, 83.3, 73.2, 68.0, 54.0, 38.8, 27.4 HRMS (ESI, m/z): Calcd for $C_{24}H_{26}INO_4Na$: 542.0804, found $[M + Na]^+$: 542.0803; IR-FT (ATR): 2968, 1707, 1670, 1533, 1143 cm^{-1}.

(2q): Orange oil, 210.4 mg (48%); $[\alpha]_D^{25}$ = +219.2 (c 1.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.4 Hz, 3H), 1.54 (m, 11H), 2.80 (dd, J_1 = 17.5 Hz, J_2 = 0.9 Hz, 1H), 2.85 (m, 1H), 2.93 (dd, J_1 = 17.5 Hz, J_2 = 6.4 Hz, 1H), 3.05 (m, 1H), 3.50 (dd, J_1 = 9.6 Hz, J_2 = 7.2 Hz, 1H), 3.65 (dd, J_1 = 9.6 Hz, J_2 = 6.9 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 4.91 (m, 1H), 7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.7, 157.8, 152.0, 137.6, 128.4, 127.7, 127.5, 110.6, 83.6, 73.2, 68.1, 54.6, 38.6, 37.6, 28.0, 20.7, 14.1; HRMS (ESI, m/z): Calcd for $C_{21}H_{28}BrNO_4Na$: 460.1099, found $[M + Na]^+$: 460.1099; IR-FT (ATR): 2968, 1712, 1674, 1551, 1312 cm^{-1}.

(2r): Orange oil, 228 mg (47%); $[\alpha]_D^{25}$ = +201.9 (c 1.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (td, J = 7,2 Hz, J = 1.6 Hz, 3H), 1.52 (s, 9H), 1.52−1.60 (m, 2H), 2.81−2.97 (m, 3H), 3.16−3.22 (m, 1H), 3.43−3.49 (m, 1H), 3.58−3.61 (m, 1H), 4.47 (d, syst. AB, J = 10.6 Hz, 1H), 4.49 (d, syst. AB, J = 10.6 Hz, 1H), 4.84−4.89 (m, 1H), 7.26−7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.2, 160.6, 151.8, 137.6, 128.4, 127.7, 127.5, 91.6, 83.6, 73.2, 68.0, 54.8, 42.3, 37.7, 28.0, 21.1, 14.0; HRMS (ESI, m/z): Calcd for $C_{21}H_{28}INO_4Na$: 508.0961, found $[M + Na]^+$: 508.0963; IR-FT (ATR): 2924, 1789, 1712, 1453, 1112 cm^{-1}.

Preparation of Propargylic Alcohol 3. To a solution of 26 mg (0.09 mmol) of amino ynone **1a** in 1 mL of EtOH at 0 °C was added $CeCl_3{\cdot}7H_2O$ (11 mg, 0.03 mmol) and $NaBH_4$ (4 mg, 0.095 mmol). The resulting solution was stirred at 0 °C for 1 h. The reaction was then quenched by addition of saturated NH_4Cl solution (5 mL). After extraction with EtOAc (3 × 5 mL), the organic phase was dried over sodium sulfate and concentrated under reduced pressure to give the pure product **3** as a clear oil (26 mg, quantitative). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9H), 1.94−2.00 (m, 2H), 3.24−3.50 (m, 3H), 4.68−4.72 (m, 1H), 4.94 (bs, 1H), 7.29−7.32 (m, 3H), 7.41−7.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.8, 131.7, 128.4, 128.2, 122.5, 89.5, 84.8, 79.7, 60.4, 38.1, 36.8, 28.4.

Preparation of α-Iodoenone 4. To a solution of 26 mg (0.09 mmol) of propargylic alcohol **3** in 1 mL of 1,2-DCE was added NIS (24 mg, 0.1 mmol), PPh_3AuCl (2 mg, 5 mol %), and $AgSbF_6$ (1.5 mg, 5 mol %). The resulting mixture was stirred at rt for 18 h. Et_2O was added, and the resulting mixture was filtered over a Celite plug. After removal of solvents in vaccuo, the crude product was purified by silica gel column chromatography using dichloromethane as an eluant to yield **4** as a yellow oil (20 mg, 72%) (Z/E: 85/15). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44 (s, 9H), 2.18−2.22 (m, 2H), 3.18−3.20 (m,

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2H), 4.68 (bs, 1H), 6.59 (t, J = 8.0 Hz,1H), 7.48−7.61 (m, 3H), 7.98 (d, J = 7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.3, 155.8, 142.7, 134.1, 133.4, 129.9, 128.9, 92.1, 79.4, 39.1, 33.5, 28.4.

Preparation of *tert*-Butyl 2-*i*-Butyl-5-(4-fluorophenyl)-4-oxo-6-propyl-3,4-dihydropyridine-1(2*H*)-carboxylate (5) by Suzuki Coupling Reaction. To a solution of 60 mg (0.14 mmol) of the *tert*-butyl 2-*i*-butyl-5-iodo-4-oxo-6-propyl-3,4-dihydropyridine-1(2*H*)-carboxylate in 1 mL of toluene was added 4-fluorophenylboronic acid (30 mg, 0.21 mmol), S-Phos (6 mg, 0.014 mmol), and K_3PO_4 (60 mg, 0.28 mmol). The resulting solution was degassed with argon. $Pd(OAc)_2$ (1.6 mg, 5 mol %) was added, and the mixture was heated to 80 °C for 24 h and then cooled to room temperature. Et_2O was added, and the resulting mixture was filtered through Celite. The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of cyclohexane/EtOAc to give the pure product **5** as a clear oil (50 mg, 90%). $[\alpha]_D^{25}$ = +310.0 (c 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.78 (t, J = 7.3 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.5 Hz, 3H), 1.20−1.30 (m, 1H), 1.35−1.47 (m, 2H), 1.55 (s, 9H), 1.58−1.65 (m, 1H), 1.72−1.78 (m, 1H), 2.16−2.22 (m, 1H), 2.45 (dd, J = 17.2 Hz, J = 1.2 Hz, 1H), 2.96 (dd, J = 17.2 Hz, J = 6.0 Hz, 1H), 3.00−3.06 (m, 1H), 4.76−4.83 (m, 1H), 7.02−7.08 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.8, 162.1 (d, J_{CF} = 246.1 Hz), 155.7, 153.0, 132.2 (d, J_{CF} = 8.1 Hz), 131.0 (d, J_{CF} = 8.6 Hz), 124.8, 115.2 (d, J_{CF} = 21.5 Hz), 82.6, 53.9, 42.1, 39.7, 34.3, 28.2, 24.9, 22.8, 22.7, 21.1, 14.1; HRMS (ESI, m/z): Calcd for $C_{23}H_{32}NO_3FNa$: 412.2258, found $[M + Na]^+$: 412.2262.

Preparation of (*E*)-*tert*-Butyl 5-(3-Ethoxy-3-oxoprop-1-enyl)-4-oxo-6-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate (6) by Heck Coupling Reaction. To a solution of 100 mg (0.25 mmol) of the *tert*-butyl 5-iodo-4-oxo-6-phenyl-3,4-dihydropyridine-1(2*H*)-carboxylate in 2 mL of dry DMF was added ethyl acrylate (53 μL, 0.5 mmol) and triethylamine (70 μL, 0.5 mmol). The resulting solution was degassed with argon. $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol) was added, and the mixture was heated to 110 °C for 24 h and then cooled to room temperature. Et_2O was added, and the resulting mixture was rinsed with the mixture of Et_2O/CH_2Cl_2 (50/50) and filtered through Celite. The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of dichloromethane/diethyl ether to give the pure product **6** as a yellow oil (72 mg, 78%). R_f = 0.50 (petroleum ether/diethyl ether = 50/50). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 9H), 1.23 (t, J = 6.1 Hz, 3H), 2.71−2.76 (m, 2 H), 4.13 (q, J = 6.1 Hz, 2H), 4.21−4.25 (m, 2H), 7.00 (s, 2H), 7.28−7.45 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.6, 168.1, 159.2, 152.5, 137.5, 136.2, 130.3, 129.2, 128.4, 120.7, 116.5, 83.3, 60.0, 46.1, 39.0, 27.3, 14.2; HRMS (ESI, m/z): Calcd for $C_{21}H_{25}NO_5Na$: 394.1630, found $[M + Na]^+$: 394.1630; IR-FT (ATR): 2978, 2926, 1708, 1673, 1613, 1521 cm^{-1}.

Preparation of (*S*,*E*)-Ethyl 3-(6-Benzyl-4-oxo-2-propyl-1,4,5,6-tetrahydropyridin-3-yl)-acrylate (7) by Heck Coupling Reaction. To a solution of 250 mg (0.55 mmol) of the (*S*)-*tert*-butyl 2-benzyl-5-iodo-4-oxo-6-propyl-3,4-dihydropyridine-1(2*H*)-carboxylate in 5 mL of dry DMF was added ethyl acrylate (117 μL, 1.1 mmol) and triethylamine (153 μL, 1.1 mmol). The resulting solution was degassed with argon. $Pd(PPh_3)_4$ (64 mg, 0.05 mmol) was added, and the mixture was heated to 130 °C for 48 h and then cooled to room temperature. Et_2O was added, and the resulting mixture was rinsed with the mixture of Et_2O/CH_2Cl_2 (50/50) and filtered through Celite. The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of dichloromethane/diethyl ether to give the pure product **7** as a yellow oil (140 mg, 78%). R_f = 0.30 (dichloromethane/diethyl ether = 80/20). $[\alpha]_D^{25}$ = +96.4 (c 0.96, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.3 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.55−1.62 (m, 2H), 2.39−2.50 (m, 3H), 2.59 (dd, J = 15.9 Hz, J = 4.9 Hz, 1H), 2.84−2.95 (m, 2H), 3.85−3.88 (m, 1H), 4.19 (q, J = 7.1 Hz,2H), 5.69 (bs, 1H), 6.98 (d, J = 15.4 Hz, 1H), 7.17 (d, J = 7.0 Hz, 2H), 7.27−7.36 (m, 3H), 7.40 (d, J = 15.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.1, 169.8, 167.2, 137.2, 136.1, 129.0, 127.3, 113.4, 104.6, 59.6, 52.9, 42.1, 40.0, 35.2, 21.6, 14.4, 13.7; HRMS (ESI, m/z): Calcd for $C_{20}H_{25}NO_3Na$: 350.1732, found $[M + Na]^+$: 350.1736; IR-FT (ATR): 3266, 2963, 1693, 1631, 1529 cm^{-1}.

Preparation of (*R*,*E*)-Ethyl 3-(6-(Benzyloxymethyl)-4-oxo-2-propyl-1,4,5,6-tetrahydropyridin-3-yl)-acrylate (8) by Heck Coupling Reaction. To a solution of 122 mg (0.25 mmol) of the (*R*)-*tert*-butyl 2-(benzyloxymethyl)-5-iodo-4-oxo-6-propyl-3,4-dihydropyridine-1(2*H*)-carboxylate in 2 mL of dry DMF was added ethyl acrylate (53 μL, 0.5 mmol) and triethylamine (70 μL, 0.5 mmol). The resulting solution was degassed with argon. $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) was added, and the mixture was heated to 110 °C for 24 h and then cooled to room temperature. Et_2O was added, and the resulting mixture was rinsed with the mixture of Et_2O/CH_2Cl_2 (50/50) and filtered through Celite. The organic phase was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of dichloromethane/diethyl ether to give the pure product **8** as a yellow oil (60 mg, 67%). R_f = 0.50 (dichloromethane/diethyl ether = 70/30). $[\alpha]_D^{25}$ = +17.6 (c 0.98, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.01 (t, J = 7.3 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.59−1.69 (m, 4H), 2.30−2.57 (m, 4H), 3.47−3.62 (m, 2H), 3.85−3.94 (m, 1H), 4.18 (q, J = 7.1 Hz,2H), 5.82 (bs, 1H), 6.97 (d, J = 15.3 Hz, 1H), 7.27−7.35 (m, 5H), 7.37 (d, J = 15.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.3, 169.8, 167.3, 137.1, 128.7, 128.3, 127.9, 113.7, 104.6, 73.5, 71.2, 59.7, 51.4, 38.6, 35.4, 21.7, 14.4, 13.8; HRMS (ESI, m/z): Calcd for $C_{21}H_{27}NO_4Na$: 380.1838, found $[M + Na]^+$: 380.1839; IR-FT (ATR): 3270, 2962, 1693, 1632, 1536 cm^{-1}.

Preparation of *tert*-Butyl 4-oxo-6-propyl-5-vinyl-3,4-dihydropyridine-1(2*H*)-carboxylate (9) by Stille Coupling Reaction. To a solution of 182 mg (0.5 mmol) of the iodide compound in 4 mL of dry toluene was added 58 mg (0.05 mmol) of $Pd(PPh_3)_4$. The resulting solution was degassed with argon. Tributylvinyltin (190 μL, 0.65 mmol) was added, and the mixture was heated to 90 °C for 24 h and then cooled to room temperature. A solution of EtOAc/H2O (1/1, 10 mL) was added, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of petroleum ether/diethyl ether to give the pure product **9** as an orange oil (118 mg, 88%). R_f = 0.28 (petroleum ether/diethyl ether = 70/30). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (t, J = 7.3 Hz, 3H), 1.53 (s, 9H), 2.54−2.59 (m, 2H), 2.81−2.86 (m, 2H), 3.94−3.98 (m, 2H), 5.40 (dd, J_1 = 11.6 Hz, J_2 = 2.1 Hz, 1H), 5.60 (dd, J = 17.6 Hz, J = 2.1 Hz, 1H) 6.3 (dd, J = 17.6 Hz, J = 11.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.0, 158.1, 152.5, 128.9, 121.8, 120.4, 82.6, 46.2, 38.8, 33.4, 28.1, 21.4, 14.0; HRMS (ESI, m/z): Calcd for $C_{15}H_{23}NO_3Na$: 288.1576, found $[M + Na]^+$: 288.1575; IR-FT (ATR): 3399, 2961, 1708, 1669, 1557, 1127 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra of all compounds and crystal data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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