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Iridium-Catalyzed Asymmetric Hydrogenation of Heteroaromatics with Multiple N Atoms via Substrate Activation: An Entry to 4,5,6,7-Tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile Core of a Potent BTK Inhibitor

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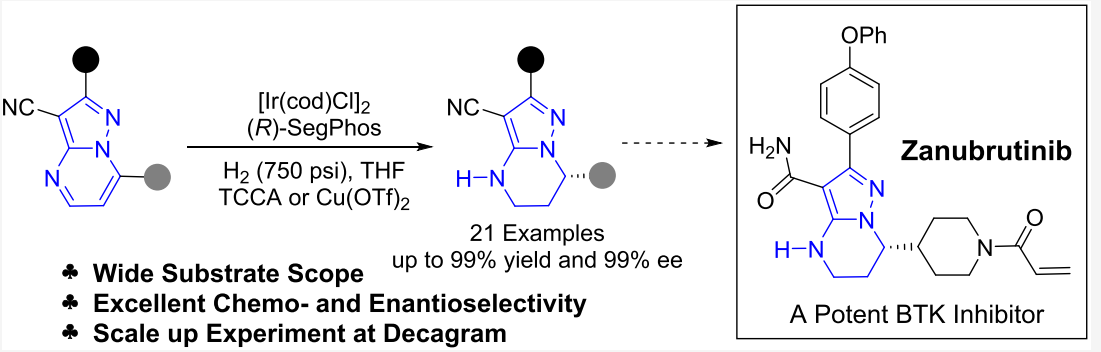

ABSTRACT: The chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine is the key core skeleton of potent Bruton's tyrosine kinase (BTK) inhibitor Zanubrutinib, and the catalyst-controlled asymmetric hydrogenation of planar multinuclear pyrimidine heteroarenes with multiple N atoms could provide an efficient route toward its synthesis. Owing to the strong aromaticity and poisoning effect toward chiral transition metal catalyst, asymmetric hydrogenation of pyrazolo[1,5-*a*]pyrimidines with multiple nitrogen atoms is still a challenge for synthesizing the chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine. Herein, an efficient iridium-catalyzed asymmetric hydrogenation of pyrazolo[1,5-*a*]pyrimidines has been developed using substrate activation strategy, with up to 99% ee. The decagram scale synthesis further demonstrated the potential and promise of this procedure in the synthesis of Zanubrutinib. In addition, a mechanistic study indicated that the hydrogenation starts with 1,2-hydrogenation.

INTRODUCTION

Bruton's tyrosine kinase (BTK) is a nonreceptor tyrosine kinase. Over the past 20 years, it has been extensively researched for the treatment of autoimmune and oncology-related illnesses.[1] Zanubrutinib is one of the several covalent BTK inhibitors approved by FDA for use in oncological diseases,[2] and it has the characteristics of strong specificity, good efficacy, with an improved safety profile.[3] Zanubrutinib contains an intriguing bicyclic chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine core (Scheme 1), a valuable and common substructure also found in some other bioactive molecules and pharmaceuticals.[4,5]

Despite its relatively simple structure, there is still a challenge in synthesizing the chiral 4,5,6,7-tetrahydropyrazolo-[1,5-*a*]-pyrimidine. Current methods for the synthesis of this motif use Pd/C hydrogenation of pyrazolo[1,5-*a*]pyrimidine, followed by chemical resolution with chiral tartaric acid derivatives[2a] or preparative high-performance liquid chromatography (Scheme 1).[2Sb] This approach generates 50% of undesired enantiomer as waste, resulting in high cost and environmental impact. Therefore, the preparation of these chiral compounds has attracted great attention in medicinal chemistry and synthetic organic chemistry, and it is highly desirable to develop an effective catalytic asymmetric synthesis methodology.[3] In this regard, the direct asymmetric hydrogenation (AH) of the corresponding heteroaromatic pyrazolo-[1,5-*a*]pyrimidines with multiple N atoms is a straightforward and atom-economical approach.

In the past decades, significant progress has been made in the asymmetric hydrogenation of N-heteroaromatic com-

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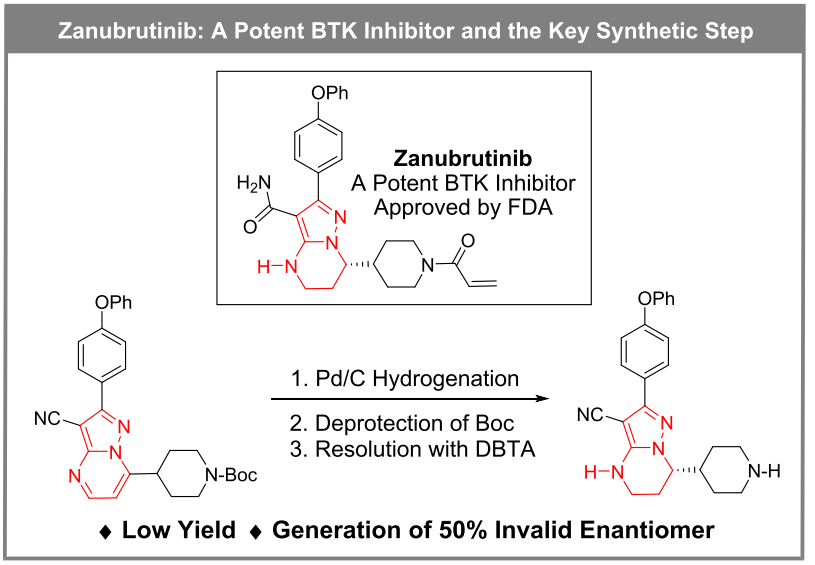
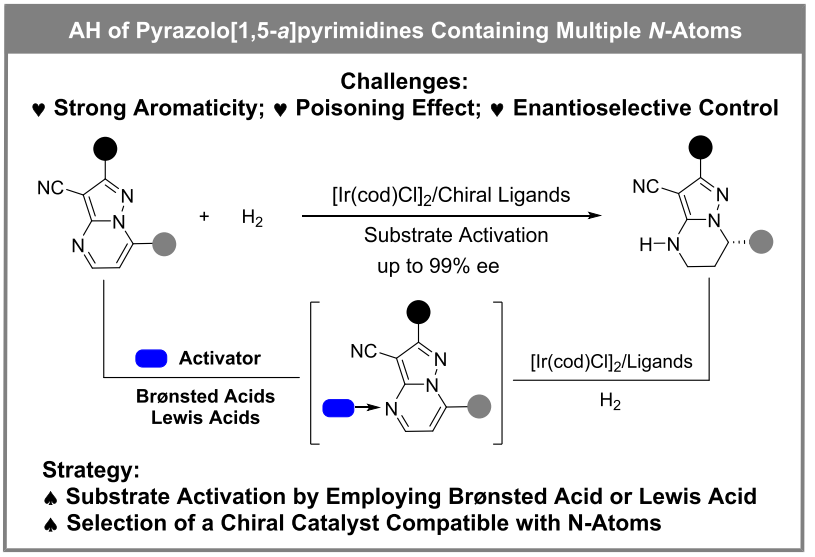
Scheme 1. Potent BTK Inhibitor and Key Synthetic Step



Scheme 2. Asymmetric Hydrogenation of Heteroaromatics Containing Multiple N Atoms, Pyrazolo[1,5-*a*]pyrimidines



pounds by catalyst activation, substrate activation, and relay catalysis strategies.[6] However, the reported methods are usually limited to heteroaromatic compounds containing one[7] or two[8] nitrogen atoms.[9] Asymmetric hydrogenation of polynitrogen-containing fused cyclic compounds is still in its infancy. Therefore, the efficient synthesis of Zanubrutinib via direct asymmetric hydrogenation of pyrazolo[1,5-*a*]pyrimidine is a challenge. This is primarily due to the following factors: (1) strong aromatic stability,[6d10] resulting in lower reactivity; (2) the substrate contains multiple nitrogen atoms, which might coordinate with the catalyst to inhibit its activity; (3) the presence of both pyrazole and pyrimidine rings in the substrate may cause problems with chemo- and enantioselectivity during the hydrogenation process. Therefore, developing a facile catalytic system for asymmetric hydrogenation of the polynitrogen-containing fused ring compounds with high enantioselectivities and yields is necessary and urgent in organic and pharmaceutical synthesis. In response to the aforementioned challenges, we will develop two strategies to realize asymmetric hydrogenation of pyrazolo[1,5-*a*]-pyrimidines: (1) employing catalytic amounts of Lewis or Brønsted acids as activators to increase its reactivity; (2) selecting a chiral hydrogenation catalyst system compatible with N atoms. Herein, we report an iridium-catalyzed enantioselective hydrogenation of pyrazolo[1,5-*a*]pyrimidines with multiple N atoms using copper triflate as Lewis acid activator or TCCA (trichloroisocyanuric acid) as Brønsted acid precursor activator, providing the desired products with up to 99% ee (Scheme 2). The asymmetric hydrogenation at decagram scale further demonstrates the potential application in a new generation synthesis of Zanubrutinib. In addition, the detailed mechanism of this hydrogenation has also been elucidated.

RESULTS AND DISCUSSION

Optimization of Hydrogenation Conditions. To evaluate asymmetric hydrogenation of heteroaromatic compounds, 2,7-diphenylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile

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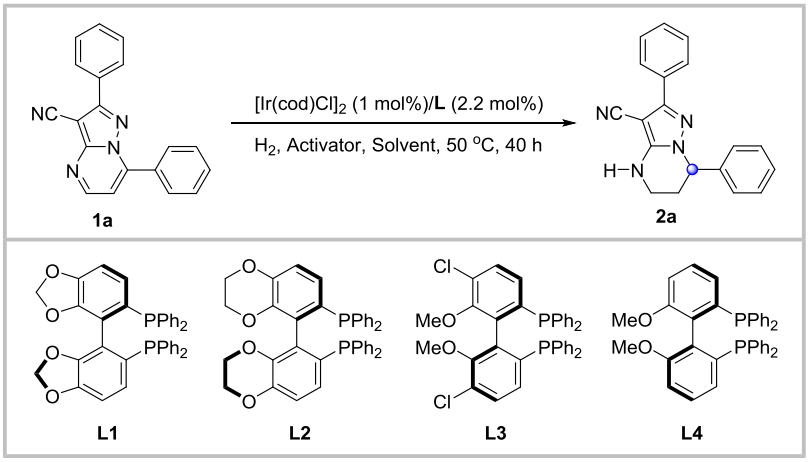
Table 1. Evaluation of Reaction Parameters



entry[a]	solvent	ligand	activator	conv. %[b]	ee %[c]
1	THF	**L1**		<5	
2	THF	**L1**	TCCA	>95	92
3	THF	**L1**	NCS	95	93
4	THF	**L1**	$Cu(OTf)_2$	>95	96
5	THF	**L1**	$Sc(OTf)_3$	30	31
6	THF	**L1**	$Yb(OTf)_3$	44	53
7	THF	**L1**	AgOTf	5	91
8	THF	**L1**	$Cu(OAc)_2$		
9	THF	**L1**	TCCA[d]	>95	94
10	dioxane	**L1**	$Cu(OTf)_2$	>95	96
11	EtOAc	**L1**	$Cu(OTf)_2$	>95	92
12	DCE	**L1**	$Cu(OTf)_2$	<5	
13	MeOH	**L1**	$Cu(OTf)_2$	22	86
14	THF	**L2**	$Cu(OTf)_2$	93	95
15	THF	**L3**	$Cu(OTf)_2$	54	90
16	THF	**L4**	$Cu(OTf)_2$	87	94
17[e]	THF	**L1**	$Cu(OTf)_2$	>95(98)	96

[a]Conditions: **1a** (59.2 mg, 0.20 mmol), $[Ir(cod)Cl]_2$ (1 mol %), **L** (2.2 mol %), activator (0.005 mmol), solvent (3.0 mL), 50 °C, 40 h. [b]Determined by ^1H NMR. [c]Determined by HPLC. [d]Both TCCA (0.005 mmol) and $Cu(OTf)_2$ (0.005 mmol) were used. [e]**1a** (88.8 mg, 0.30 mmol), isolated yield.

1a was chosen as the model substrate, and $[Ir(cod)Cl]_2$/(*R*)-SegPhos as a chiral catalyst (the chiral iridium-based catalysts are efficient for hydrogenation of imines containing N atoms). Unfortunately, due to low substrate reactivity, no desired product was observed in THF under hydrogen gas (750 psi) at 50 °C for 40 h (Table 1, entry 1). We attempted to activate the substrate with various readily available Lewis or Brønsted acids.[11−13] Gratifyingly, the hydrogenation proceeded smoothly, with excellent conversion as well as enantioselectivity obtained using trichloroisocyanuric acid (TCCA) as the activator (entry 2). TCCA could in situ generate the strong Brønsted acid hydrogen chloride in the presence of iridium complex[12c] during the hydrogenation process, activating the substrate to improve the reactivity. Additionally, Ir(I) could be converted to Ir(III) by oxidation with TCCA, which increases catalyst activity.[6d7a12c] Next, a series of Lewis and Brønsted acid activators were screened, and the best result was achieved with Lewis acid copper triflate as activator. Full conversion and 94% ee were obtained using TCCA and copper triflate as coactivators (entry 9). Furthermore, the effect of solvents on enantioselectivity and activity was examined (entries 10−13). It was found that the solvent played a crucial role, and THF proved to be optimal (entry 4). Then, some commercially available chiral bisphosphine ligands were evaluated, and the best result was achieved with the (*R*)-SegPhos (**L1**). Therefore, the optimal reaction conditions were established as follows: $[Ir(cod)Cl]_2$/(*R*)-SegPhos, $Cu(OTf)_2$, THF, 50 °C.

After establishing the optimal conditions, we examined the substrate scope, and the results are summarized in Scheme 3. As expected, various substrates performed very well under the standard conditions. First, we evaluated the electronic properties and positions of substituents on the phenyl of C2. All substrates could be hydrogenated to give the desirable products (**2a−2f**) with excellent yields (93−99%) and enantioselectivities (95−97%) regardless of electronic effect and steric hindrance. An alkyl substituent on C2 was also compatible, giving the product **2g** with 92% yield and 94% ee. Subsequently, the different substituents at C7 were tested. The electronic properties of the phenyl group had a marginal effect on the enantioselectivity and activity. However, the introduction of steric hindrance led to a decrease of activity. With a methyl group installed at the *ortho*-position of phenyl, only 38% yield of **2j** was obtained at 60 °C. To our delight, 71% yield was obtained with TCCA and $Cu(OTf)_2$ as coactivator in the presence of 4 mol % iridium catalyst (Table 1, entry 9).

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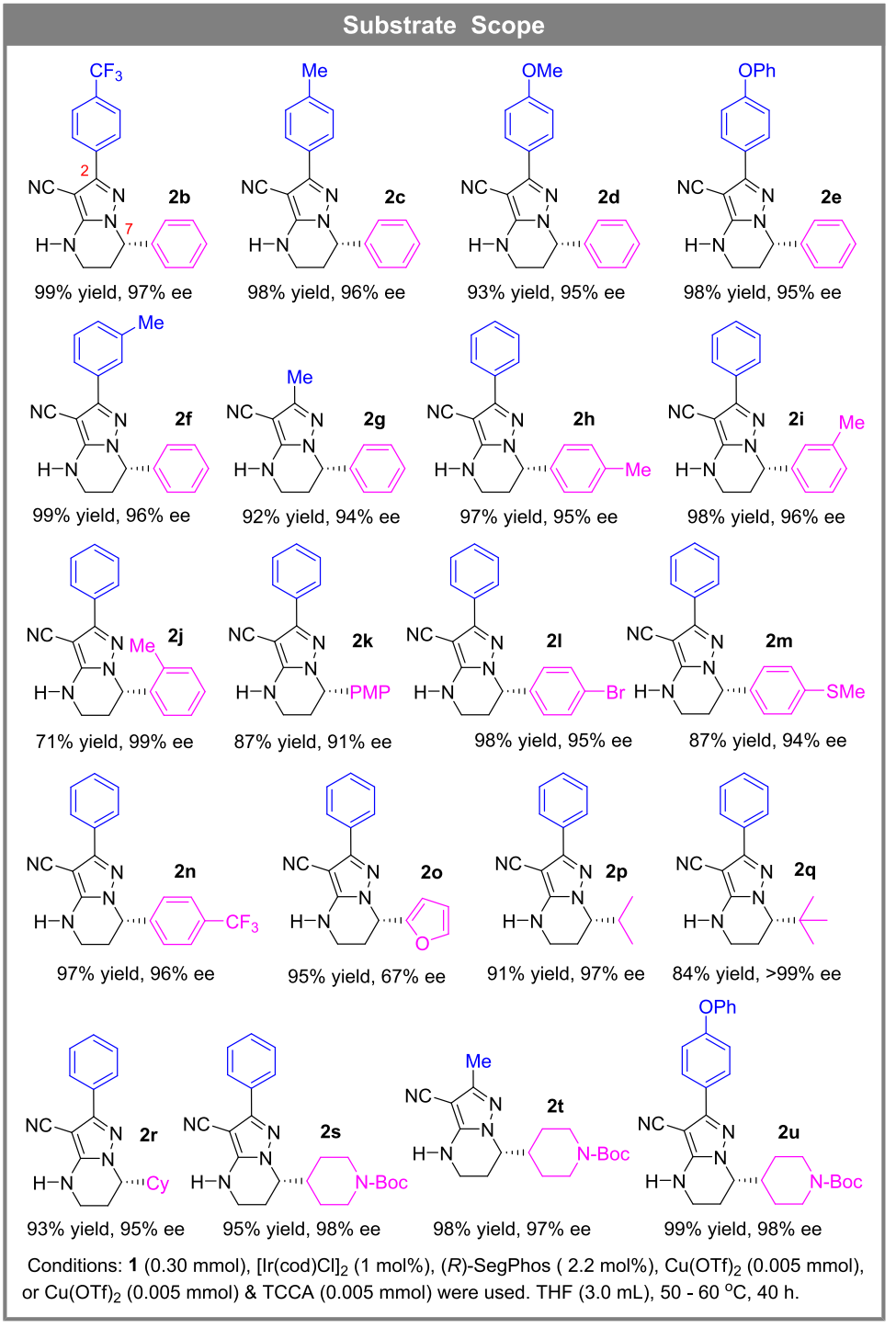
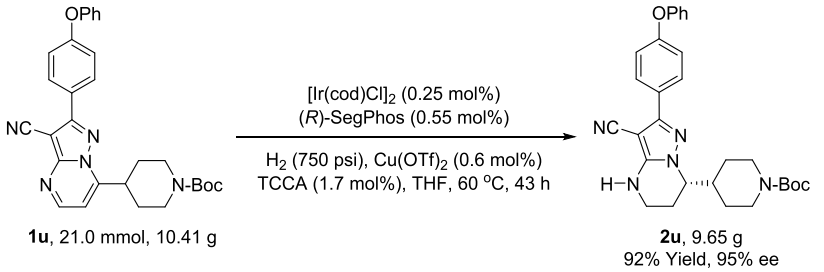
Scheme 3. Substrate Scope



Scheme 4. Hydrogenation at Decagram Scale



1u, 21.0 mmol, 10.41 g

2u, 9.65 g
92% Yield, 95% ee

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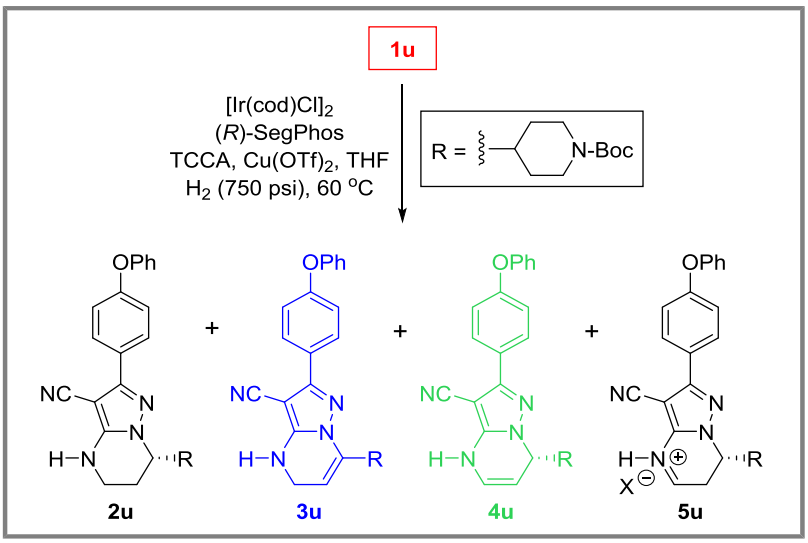

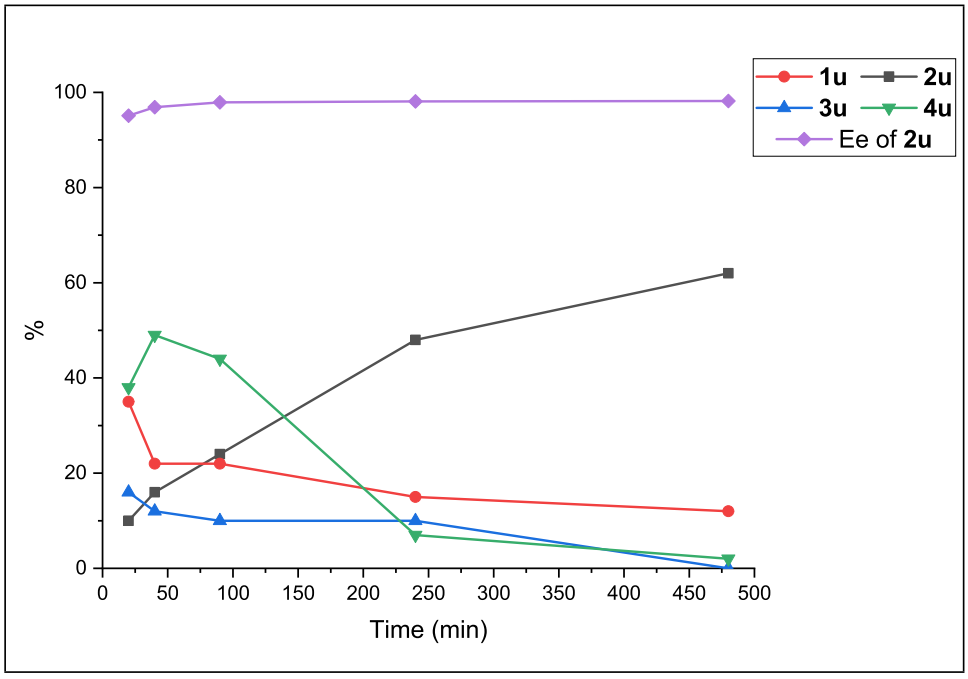

Figure 1. Kinetic experiment of **1u** in the process of AH.

Meanwhile, this methodology was also compatible with furyl-substituted substrates, giving a chiral product (**2o**) with excellent yield and moderate 67% ee.

In addition, a variety of alkyl-substituted substrates at C7 were also examined using TCCA and $Cu(OTf)_2$ as coactivator, and the target products were obtained with excellent yields in high enantioselectivity. Notably, only moderate yield was obtained using a single activator. For example, using TCCA as an activator gave 86% NMR yield and 97% ee for **2p**, and using copper triflate as an activator gave 88% NMR yield and 97% ee for **2p**, while 91% isolated yield and 97% ee were obtained using TCCA and $Cu(OTf)_2$ as coactivator. Gratifyingly, when **1u** for the synthesis of Zanubrutinib was tested, the product **2u** was obtained with excellent yield and enantioselectivity. Interestingly, no reactivity was observed when the cyano at the C3 position was removed, for reasons that are currently not clear.

To demonstrate the synthetic utility of this methodology, asymmetric hydrogenation was carried out on decagram scale in the presence of 0.5 mol % catalyst (Scheme 4). To our delight, the target product **2u** was obtained with 92% yield and 95% ee without loss of reactivity and enantioselectivity, which further demonstrated the potential application for the synthesis of Zanubrutinib.

To gain further insight into the detailed mechanism of asymmetric hydrogenation, a study was performed using kinetic experiments, control experiments, and isotope labeling.

Kinetic Experiments. In order to further understand the asymmetric hydrogenation of pyrazolo[1,5-*a*]pyrimidines, we performed kinetic experiments with **1u** and semihydrogenated **3u** (see the Supporting Information) under the standard

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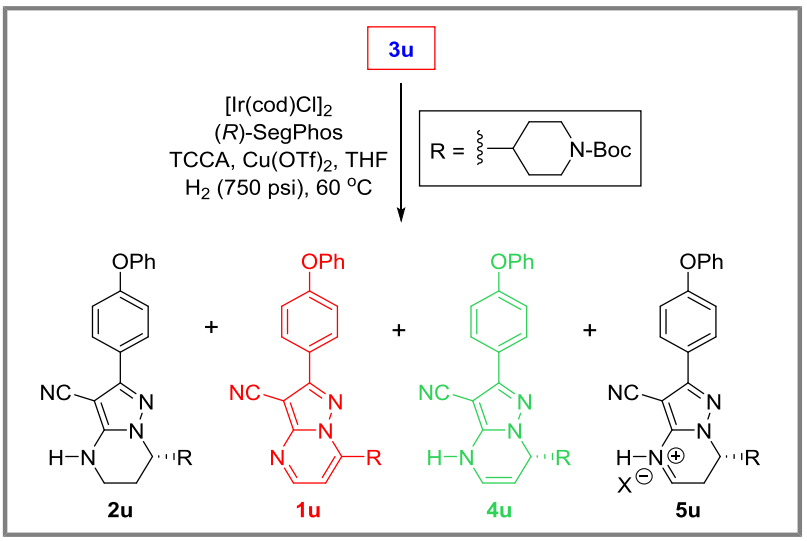

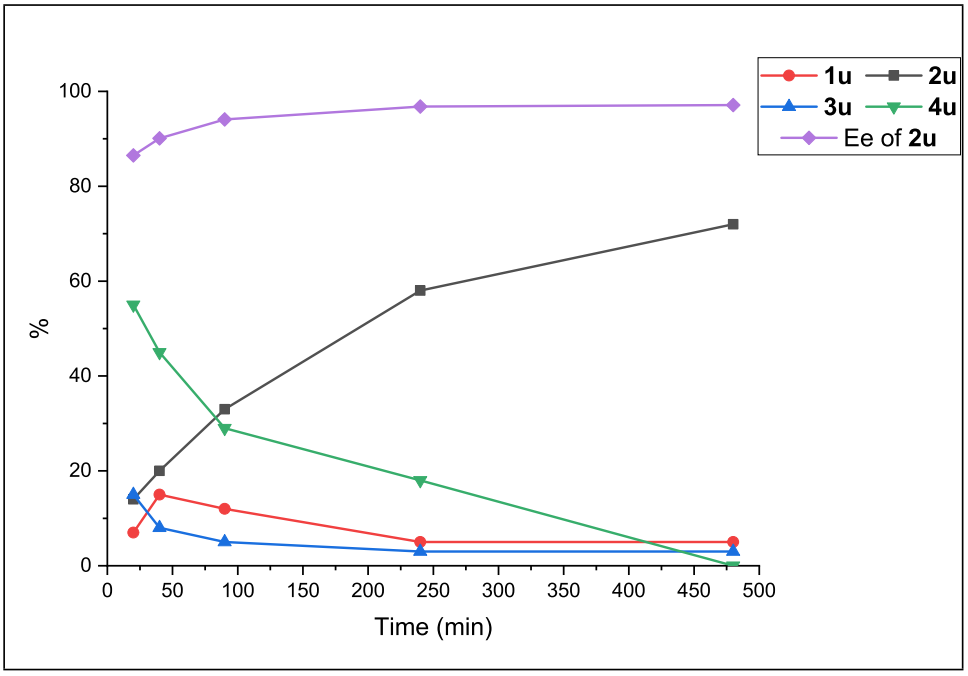

Figure 2. Kinetic experiment of **3u** in the process of AH.

condition, and the results are shown in Figure 1. The results show that (1) the semihydrogenated product olefin **3u** and enamine **4u** are key intermediates in asymmetric hydrogenation process; (2) the hydrogenation rate of semihydrogenated **3u** is faster than the rate of aromatic **1u**; (3) **1u** and **3u** are in equilibrium in the presence of iridium catalyst during hydrogenation of intermediate **3u**; (4) for asymmetric hydrogenation of **3u** in the first 40 min, the sum of components **3u** + **1u** + **2u** + **4u** is over 95% by ^{1}H NMR analysis. However, as the reaction time prolongs, the sum of components **3u** + **1u** + **2u** + **4u** is less than 90%. Similar results were also observed for asymmetric hydrogenation of intermediate **3u** in Figure 2. These results showed that an unstable, previously unidentified iminium intermediate **5u** emerged in the late stage of the hydrogenation process, which could be detected by ^{1}H NMR analysis, though its proportion is difficult to determine; therefore, it was omitted from the bottom graph of Figure 1.

Control Experiments. To further understand the detailed process of asymmetric hydrogenation of the pyrazolo[1,5-*a*]pyrimidines, the imine semihydrogenation intermediate **3u** was synthesized and subjected to asymmetric hydrogenation under the above standard condition (Scheme 5a). Nearly identical enantioselectivity and yield were observed, which indicated that compound **3u** was the key intermediate.

To elucidate the enantio-controlling step, *N*-methyl-protected olefin **6** was prepared (Supporting Information) and subjected to asymmetric hydrogenation under standard conditions (Scheme 5b). The desired target product **7** was obtained with similar 94% ee and 86% yield, which suggested

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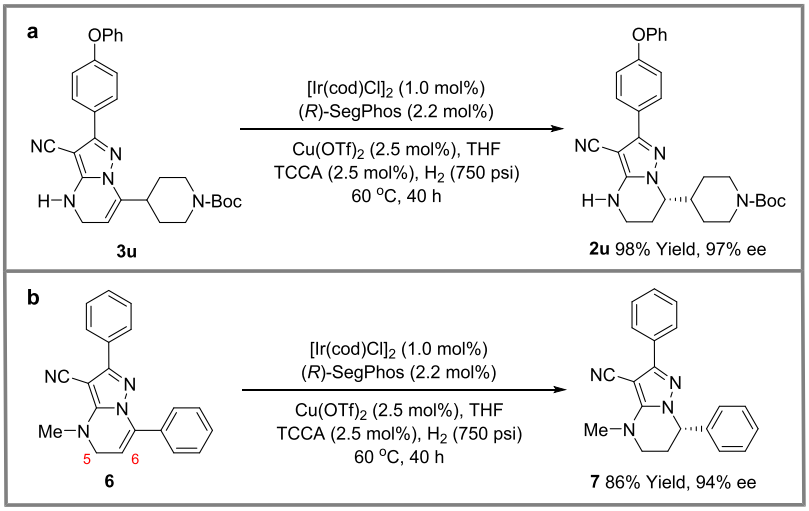
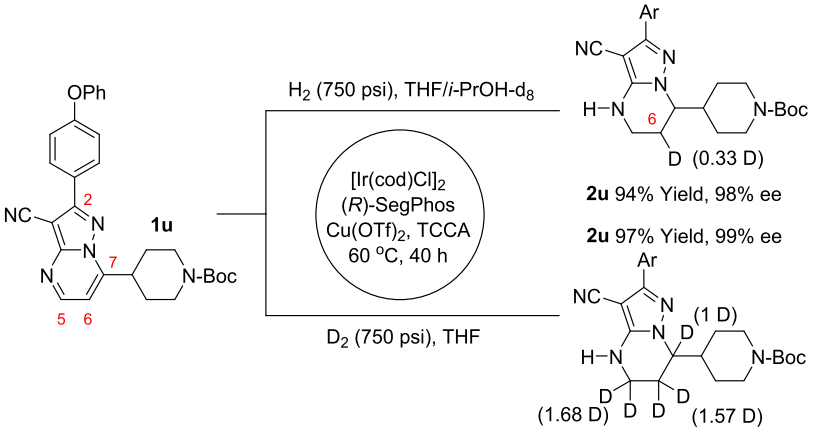
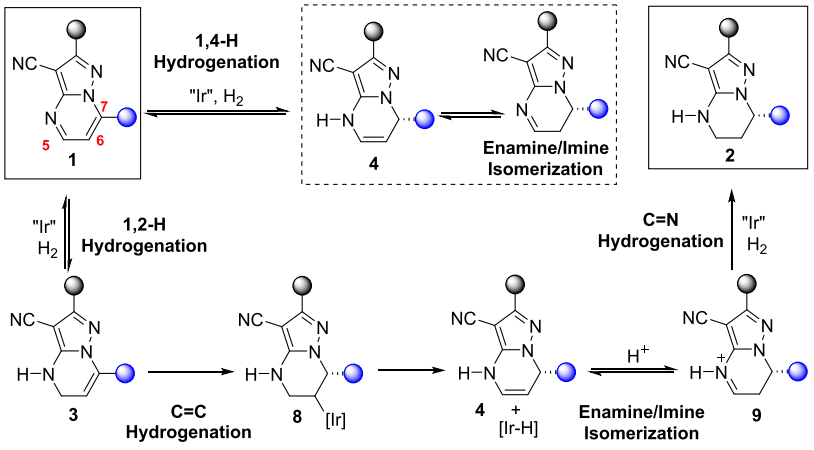
Scheme 5. Control Experiments



Scheme 6. Deuterium Labeling Experiments



Scheme 7. Proposed Reaction Pathway



that asymmetric hydrogenation of the C6–C7 (C=C)-bond is the likely enantio-controlling step.

Isotope Labeling Experiments. Two isotopic labeling experiments were carried out with deuterated solvent and deuterium gas (Scheme 6). For asymmetric hydrogenation of **1u** in deuterated solvent, only 30% deuterium was incorporated at the C6 position of product **2u**, which suggested that an acid-catalyzed enamine/imine isomerization might exist in the hydrogenation process. In addition, the asymmetric hydrogenation was carried out with deuterium gas. Deuterated product **2u** was obtained with excellent enantioselectivity and yield, the deuterium atoms were incorporated in the product **2u**, C5 (1.68), C6 (1.57), C7 (1.00). These results suggested that deuteration was accompanied by an H/D exchange phenomenon (C5 and C6), which further confirmed the existence of an enamine/imine isomerization. 100% incorpo-

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ration of deuterium at the C7 position suggested that hydrogenation of olefin (C6 and C7) is irreversible and constitutes the enantio-determining step.

Based on the above control experiments, kinetic experiments, and isotope labeling experiments, a plausible iridium-catalyzed asymmetric hydrogenation process was proposed (Scheme 7). The reaction is initiated by 1,2-hydride addition to give the semihydrogenated olefin intermediate **3**, which is reversible because it could be also dehydrogenated in the presence of iridium catalyst. Then, the C6−C7 double bond of **3** is inserted into the Ir−H bond to form the species **8**. Next, β-hydride elimination gives enamine intermediate **4**, which was isolated (see the Supporting Information). Then, acid-catalyzed enamine/imine isomerization forms iminium intermediate **9**, followed by hydrogenation to give the target product **2**. Notably, 1,4-hydrogenation may be initiated slowly, which might be consistent with the above experimental results, wherein the hydrogenation rate of **3u** is faster than that of **1u** to the target product **2u** and the rate of deuteration at C6.

CONCLUSIONS

In conclusion, a facile iridium-catalyzed asymmetric hydrogenation of heteroaromatic pyrazolo[1,5-*a*]pyrimidines has been developed using a substrate activation strategy by employing Brønsted and Lewis acid, giving the chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines with up to 99% ee. This approach has been successfully applied to the synthesis of a key intermediate of commercial drug Zanubrutinib at decagram scale. Furthermore, the mechanism was elucidated by combination of control experiments, kinetic experiments, and isotope labeling experiments, the hydrogenation starts with 1,2-hydrogenation, then the active Ir−H insertion to (C═C)-double bond, β-H elimination, enamine/imine isomerization, and final hydrogenation of (C═N)-bond. Further studies on asymmetric hydrogenation of more challenging heteroaromatics are actively explored in our laboratory.

EXPERIMENTAL SECTION

General. All reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques, unless otherwise noted. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded at room temperature in $CDCl_3$ on 400 or 700 MHz instrument with tetramethylsilane (TMS) as internal standard. Enantiomeric excess was determined by high-performance liquid chromatography (HPLC) analysis using chiral column described below in detail. Optical rotations were measured by a polarimeter. Flash column chromatography was performed on silica gel (200−300 mesh). The heat source for all heating reactions is the oil bath. High-resolution mass spectrometry (HRMS) was measured on an electrospray ionization (ESI) apparatus using the time-of-flight (TOF) mass spectrometry. All reactions were monitored by thin-layer chromatography (TLC) analysis.

Materials. Commercially available reagents and solvents were used throughout without further purification.

The pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles **1** could be synthesized from the readily available 5-amino-1*H*-pyrazole-4-carbonitriles **S1**[14] and enaminones **S2**[15] according to the known synthetic procedure.[3] Among them, compounds **1a**, **1g-1h**, **1k−1o**, and **1u** are the known.[2d16,17]

Procedure for the Synthesis of Pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles 1a−1r. Under nitrogen atmosphere, a mixture of 5-amino-1*H*-pyrazole-4-carbonitrile (1.0 equiv) and enaminone (1.0 equiv) in acetic acid (7.5 mL/mmol) was heated to 120 °C and stirred until the reaction was completed (monitored by TLC, 3−5 h). The mixture was cooled and volatiles were removed under the reduced pressure, the crude residue was purified by silica gel column chromatography using hexanes/ethyl acetate (10/1 to 2/1) as eluent to afford the desriable product pyrazolo[1,5-*a*]-pyrimidine-3-carbonitriles **1a−1r**.

*7-Phenyl-2-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**1b**).* 2.0 mmol, 0.728 g, 99% yield, pale yellow solid, mp 237−238 °C, new compound, R_f = 0.31 (hexanes/ethyl acetate 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 4.5 Hz, 1H), 8.34−8.29 (m, 2H), 8.14−8.08 (m, 2H), 7.79−7.74 (m, 2H), 7.69−7.61 (m, 3H), 7.21 (d, J = 4.5 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.4, 153.2, 152.7, 148.1, 133.8, 132.2, 132.2, 129.6 (q, J = 32 Hz), 129.4, 129.0, 127.9, 126.0 (q, J = 4 Hz), 123.9 (q, J = 271 Hz), 113.7, 110.3, 80.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.90. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{11}F_3N_4$ 365.1009, found: 365.1009.

*7-Phenyl-2-(p-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (**1c**).* 2.0 mmol, 0.576 g, 93% yield, white solid, mp 180−181 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 4.5 Hz, 1H), 8.15−8.07 (m, 4H), 7.66−7.58 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 4.5 Hz, 1H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.0, 153.3, 152.1, 147.7, 140.9, 131.9, 129.7, 129.6, 128.8, 127.6, 127.5, 127.5, 114.3, 109.8, 79.9, 21.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}N_4$ 311.1291, found: 311.1293.

*2-(4-Methoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**1d**).* 1.0 mmol, 0.311 g, 95% yield, white solid, mp 170−171 °C, new compound, R_f = 0.61 (hexanes/ethyl acetate 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 4.5 Hz, 1H), 8.18−8.09 (m, 4H), 7.65−7.57 (m, 3H), 7.13 (d, J = 4.5 Hz, 1H), 7.04−6.99 (m, 2H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.5, 156.9, 153.4, 152.0, 147.7, 131.9, 129.7, 129.6, 129.1, 128.8, 123.0, 114.4, 109.7, 79.6, 55.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}N_4O$ 327.1240, found: 327.1241.

*2-(4-Phenoxyphenyl)-7-phenylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**1e**).* 2.0 mmol, 0.244 g, 30% yield, white solid, mp 166−167 mp 217−218 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, J = 4.5, 3.1 Hz, 1H), 8.21−8.14 (m, 2H), 8.11 (dt, J = 7.8, 1.3 Hz, 2H), 7.66−7.58 (m, 3H), 7.38 (dd, J = 8.6, 7.3 Hz, 2H), 7.20−7.14 (m, 2H), 7.13−7.04 (m, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.6, 156.5, 156.2, 153.3, 152.2, 147.7, 132.0, 130.0, 129.6, 129.3, 128.9, 125.0, 124.1, 119.7, 118.6, 114.2, 109.9, 79.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{16}N_4O$ 389.1397, found: 389.1389.

*7-Phenyl-2-(m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (**1f**).* 2.0 mmol, 0.500 g, 81% yield, white solid, mp 192−193 °C, new compound, R_f = 0.41 (hexanes/ethyl acetate/dichloromethane 5/1/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 4.5 Hz, 1H), 8.15−8.09 (m, 2H), 8.02−7.96 (m, 2H), 7.66−7.59 (m, 3H), 7.43−7.37 (m, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.16 (d, J = 4.5 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 153.3, 152.2, 147.9, 138.8, 132.0, 131.4, 130.3, 129.7, 129.6, 128.9, 128.9, 128.1, 124.9, 114.1, 109.9, 80.4, 21.5. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}N_4$ 311.1291, found: 311.1297.

*2-Phenyl-7-(m-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (**1i**).* 2.0 mmol, 0.595 g, 96% yield, pale yellow solid, mp 103−104 °C, new compound, R_f = 0.45 (hexanes/ethyl acetate/DCM 5/1/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 4.5 Hz, 1H), 8.22−8.17 (m, 2H), 7.94 (dt, J = 7.8, 1.6 Hz, 1H), 7.89 (d, J = 1.9 Hz, 1H), 7.54−7.48 (m, 4H), 7.45 (d, J = 7.7 Hz, 1H), 7.15 (d, J = 4.5 Hz, 1H), 2.50 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.0, 153.3, 152.2, 148.1, 138.8, 132.8, 130.5, 130.5, 130.1, 129.6, 129.0, 128.8, 127.6, 126.8, 114.1, 109.9, 80.3, 21.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}N_4$ 311.1291, found: 311.1300.

*2-Phenyl-7-(o-tolyl)pyrazolo[1,5-a]pyrimidine-3-carbonitrile (**1j**).* 2.0 mmol, 0.523 g, 84% yield, white solid, mp 197−198 °C, new compound, R_f = 0.58 (hexanes/ethyl acetate 3/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 4.3 Hz, 1H), 8.17−8.08 (m, 2H), 7.54−7.37 (m, 7H), 7.01 (d, J = 4.3 Hz, 1H), 2.22 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.3, 152.6, 152.0, 149.2, 137.6, 131.0, 130.3,

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130.5, 130.4, 130.0, 129.7, 128.9, 127.6, 126.2, 114.0, 111.6, 80.4, 20.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}N_4$ 311.1291, found: 311.1290.

*7-(4-(Methylthio)phenyl)-2-phenylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**1m**).* 2.0 mmol, 0.503 g, 74% yield, yellow solid, mp 205−206 °C, new compound, R_f = 0.38 (hexanes/ethyl acetate/dichloromethane 5/1/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 4.6 Hz, 1H), 8.25−8.17 (m, 2H), 8.12−8.07 (m, 2H), 7.55−7.48 (m, 3H), 7.45−7.40 (m, 2H), 7.15 (d, J = 4.5 Hz, 1H), 2.58 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.0, 153.4, 152.1, 147.4, 144.8, 130.6, 130.4, 129.9, 129.0, 127.6, 125.5, 125.4, 114.1, 109.2, 80.2, 14.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}N_4S$ 343.1012, found: 343.1014.

*2-Phenyl-7-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**1n**).* 2.0 mmol, 0.428 g, 59% yield, white solid, mp 200−201 °C, new compound, R_f = 0.50 (hexanes/ethyl acetate/dichloromethane 5/1/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, J = 4.5 Hz, 1H), 8.26−8.22 (m, 2H), 8.19−8.13 (m, 2H), 7.88 (d, J = 8.3 Hz, 2H), 7.51 (qd, J = 3.8, 1.7 Hz, 3H), 7.20 (d, J = 4.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.2, 153.1, 152.4, 146.2, 133.5 (q, J = 32 Hz), 133.0, 130.8, 130.1, 130.1, 129.1, 127.6, 125.9 (q, J = 4 Hz), 123.6 (q, J = 271 Hz), 113.9, 110.3, 80.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ − 63.08. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{11}F_3N_4$ 365.1009, found: 365.1011.

*7-Isopropyl-2-phenylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**1p**).* 3.4 mmol, 0.584 g, 66% yield, white solid, mp 129−130 °C, new compound, R_f = 0.30 (dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 4.5 Hz, 1H), 8.25−8.18 (m, 2H), 7.56−7.49 (m, 3H), 6.93 (dd, J = 4.5, 0.7 Hz, 1H), 3.97 (h, J = 6.9 Hz, 1H), 1.49 (d, J = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.8, 156.8, 152.4, 152.4, 130.6, 130.5, 129.0, 127.6, 114.2, 106.4, 80.1, 28.8, 19.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{14}N_4$ 263.1291, found: 263.1292.

*7-(tert-Butyl)-2-phenylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**1q**).* 3.0 mmol, 0.463 g, 56% yield, white solid, mp 165−166 °C, new compound, R_f = 0.62 (hexanes/ethyl acetate 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 4.6 Hz, 1H), 8.26−8.21 (m, 2H), 7.57−7.49 (m, 3H), 6.95 (d, J = 4.6 Hz, 1H), 1.68 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 155.5, 153.6, 152.5, 130.7, 130.4, 129.0, 127.5, 114.4, 107.3, 79.5, 36.5, 27.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}N_4$ 277.1448, found: 277.1448.

*7-Cyclohexyl-2-phenylpyrazolo[1,5-a]pyrimidine-3-carbonitrile (**1r**).* 2.0 mmol, 0.475 g, 79% yield, white solid, mp 215−216 °C, new compound, R_f = 0.58 (hexanes/dichloromethane 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 4.5 Hz, 1H), 8.26−8.18 (m, 2H), 7.57−7.48 (m, 3H), 6.89 (d, J = 4.5 Hz, 1H), 3.68 (tt, J = 11.2, 3.2 Hz, 1H), 2.26−2.19 (m, 2H), 1.96 (dq, J = 12.8, 3.4, 3.0 Hz, 2H), 1.88 (ddt, J = 13.3, 3.3, 2.1 Hz, 1H), 1.58−1.29 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 155.9, 152.4, 130.6, 130.4, 129.0, 127.6, 114.2, 106.8, 80.0, 38.1, 30.3, 26.0, 25.9. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}N_4$ 303.1604, found: 303.1612.

Procedure for the Synthesis of Pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles 1s−1t. Under the nitrogen atmosphere, a mixture of 5-amino-1*H*-pyrazole-4-carbonitrile **S1** (2.0 mmol) and *tert*-butyl (*E*)-4-(3-(dimethyl-amino)acryloyl)piperidine-1-carboxylate (2.0 mmol, 0.565 g) in acetic acid (7.5 mL/mmol) was heated to 120 °C and stirred until the reaction was completed (TLC). The mixture was cooled, volatiles were removed under reduced pressure, and the crude residue was purified by silica gel column chromatography using ethyl acetate as the eluent to afford the de-Boc products of pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles.

Subsequently, under nitrogen atmosphere, a mixture of de-Boc products of pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles and Boc_2O (1.2 equiv) in dichloromethane (10 mL) was stirred at room temperature until the reaction was completed. Water was added and the mixture was extracted with dichloromethane (3 × 10 mL). After drying over anhydrous sodium sulfate, filtration, and volatiles removal under the reduced pressure, the crude residue was purified by silica gel column chromatography using hexanes/ethyl acetate (10/1 to 2/1) as the eluent to afford the desired pyrazolo[1,5-*a*] pyrimidine-3-carbonitriles **1s−1t**.

*tert-Butyl 4-(3-cyano-2-phenylpyrazolo[1,5-a]pyrimidin-7-yl)-piperidine-1-carboxylate (**1s**).* 0.303 g, 38% yield, white solid, mp 186−187 °C, new compound, R_f = 0.90 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dq, J = 4.7, 2.8, 2.4 Hz, 1H), 8.14 (ddq, J = 6.9, 4.6, 2.5, 2.1 Hz, 2H), 7.52−7.42 (m, 3H), 6.87 (d, J = 4.1 Hz, 1H), 4.33 (d, J = 13.4 Hz, 2H), 3.78 (tdt, J = 12.3, 6.1, 3.2 Hz, 1H), 2.96 (t, J = 12.5 Hz, 2H), 2.18 (d, J = 12.6 Hz, 2H), 1.71 (t, J = 13.0 Hz, 2H), 1.47 (d, J = 2.5 Hz, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.6, 154.6, 153.6, 152.5, 152.2, 130.5, 130.3, 129.0, 127.5, 114.0, 107.1, 80.1, 79.9, 43.5, 36.7, 29.0, 28.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{25}N_5O_2$ 404.2081, found: 404.2084.

*tert-Butyl 4-(3-cyano-2-methylpyrazolo[1,5-a]pyrimidin-7-yl)-piperidine-1-carboxylate (**1t**).* 0.277 g, 41% yield, white solid, mp 185−186 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 4.5 Hz, 1H), 6.81 (d, J = 4.5 Hz, 1H), 4.32 (s, 2H), 3.71 (tt, J = 12.3, 3.5 Hz, 1H), 3.04−2.83 (m, 2H), 2.62 (s, 3H), 2.13 (dt, J = 12.9, 2.7 Hz, 2H), 1.65 (dd, J = 12.0, 4.4 Hz, 2H), 1.48 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 154.6, 153.5, 152.2, 151.1, 113.2, 106.2, 82.8, 80.0, 43.6, 36.5, 29.1, 28.4, 13.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{23}N_5O_2$ 342.1925, found: 342.1927.

Procedure for AH of Pyrazolo[1,5-*a*]pyrimidine-3-carbonitriles. *For Cu(OTf)$_2$ as Activator.* In a nitrogen-filled glovebox, a mixture of $[Ir(cod)Cl]_2$ (2.0 mg, 0.003 mmol) and (*R*)-SegPhos (4.0 mg, 0.0066 mmol) in THF (1.0 mL) was stirred at room temperature for 10 min, the mixture was transferred by a syringe to a stainless steel autoclave, in which substrates **1** (0.3 mmol) and copper triflate (2.7 mg, 0.0075 mmol) had been placed beforehand. THF (2.0 mL) was then added to the mixture. The hydrogenation was performed at 50 or 60 °C under 750 psi of hydrogen for 40 h. Then, the autoclave was cooled to room temperature. After carefully releasing the hydrogen, the autoclave was opened, and the volatiles were removed under the reduced pressure. Flash chromatography on silica gel using hexanes/ethyl acetate as the eluent gave the reductive products **2**.

For Cu(OTf)$_2$ and TCCA as Coactivator. In a nitrogen-filled glovebox, a mixture of metal $[Ir(cod)Cl]_2$ (2.0 mg, 0.003 mmol) and (*R*)-SegPhos (4.0 mg, 0.0066 mmol) in THF (1.0 mL) was stirred at room temperature for 10 min, afterward trichloroisocyanuric acid (TCCA) (1.7 mg, 0.0075 mmol) was added and stirred for 10 min, and the mixture was transferred by a syringe to a stainless steel autoclave, in which the substrates **1** (0.3 mmol) and copper triflate (2.7 mg, 0.0075 mmol) had been placed beforehand. THF (2.0 mL) was then added to the mixture. The hydrogenation was performed at 60 °C under 750 psi of hydrogen for 40 h. Then, the autoclave was cooled to room temperature. After carefully releasing the hydrogen, the autoclave was opened, and the volatiles were removed under the reduced pressure. Flash chromatography on silica gel using hexanes/ethyl acetate as the eluent gave the reductive products **2**.

The optical purity of products was determined by chiral HPLC analysis. The racemates were prepared by running reactions with the (±)-SegPhos instead of the (*R*)-SegPhos.

*(−)-2,7-Diphenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carbonitrile (**2a**).* 50 °C, $Cu(OTf)_2$ as activator, 88.0 mg, 98% yield, pale yellow solid, mp 72−73 °C, the known compound,[9] R_f = 0.25 (hexanes/ethyl acetate 3/1), 96% ee, $[\alpha]_D^{20}$ = −25.46 (*c* 1.41, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.86 (m, 2H), 7.42−7.32 (m, 5H), 7.32−7.27 (m, 1H), 7.03 (dd, J = 7.0, 1.9 Hz, 2H), 5.56 (dd, J = 5.4, 3.0 Hz, 1H), 5.37−5.24 (m, 1H), 3.33 (dq, J = 11.8, 3.9 Hz, 1H), 3.20 (td, J = 12.0, 2.9 Hz, 1H), 2.50 (ddt, J = 17.0, 11.4, 4.8 Hz, 1H), 2.25−2.17 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.8, 151.1, 140.6, 131.6, 129.0, 128.8, 128.7, 127.9, 126.5, 125.9, 116.2, 69.4, 58.3, 35.2, 29.7. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 13.8 min (major) and 26.5 min (minor).

*(−)-7-Phenyl-2-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carbonitrile (**2b**).* 50 °C, $Cu(OTf)_2$ as activator, 110.0 mg, 99% yield, pale yellow solid, mp 176−177 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate 3/1),

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97% ee, $[\alpha]_D^{20}$ = −24.63 (*c* 1.10, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.39-7.28 (m, 3H), 7.04 (d, *J* = 7.4 Hz, 2H), 5.80 (s, 1H), 5.56 (dd, *J* = 5.3, 3.1 Hz, 1H), 3.31 (dq, *J* = 11.8, 3.8 Hz, 1H), 3.19 (td, *J* = 11.8, 3.1 Hz, 1H), 2.53−2.42 (m, 1H), 2.26−2.17 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.9, 149.5, 140.3, 134.9, 130.6 (q, *J* = 32 Hz), 128.9, 128.2, 126.7, 125.6 (q, *J* = 4 Hz), 125.4, 121.4 (q, *J* = 271 Hz), 115.8, 69.6, 58.5, 35.2, 29.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.67. HPLC: Chiralcel OD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 10.2 min (major) and 15.7 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{15}F_3N_4$ 369.1322, found: 369.1329.

*(−)-7-Phenyl-2-(p-tolyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**2c**).* 50 °C, $Cu(OTf)_2$ as activator, 93.0 mg, 98% yield, white solid, mp 67−68 °C, new compound, R_f = 0.25 (hexanes/ethyl acetate 3/1), 96% ee, $[\alpha]_D^{20}$ = −29.31 (*c* 1.31, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.9 Hz, 2H), 7.36−7.22 (m, 3H), 7.18 (d, *J* = 7.9 Hz, 2H), 7.05−6.95 (m, 2H), 5.64 (s, 1H), 5.51 (dd, *J* = 5.5, 3.1 Hz, 1H), 3.21 (dq, *J* = 11.9, 4.0 Hz, 1H), 3.10 (td, *J* = 11.8, 3.1 Hz, 1H), 2.45- 2.36 (m, 1H), 2.33 (s, 3H), 2.17−2.07 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.6, 151.1, 140.6, 138.9, 129.3, 128.7, 128.7, 127.8, 126.3, 125.9, 116.2, 69.2, 58.1, 35.1, 29.6, 21.3. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 20.1 min (major) and 38.7 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{18}N_4$ 315.1604, found: 315.1606.

*(−)-2-(4-Methoxyphenyl)-7-phenyl-4,5,6,7-tetrahydropyrazolo-[1,5-a]pyrimidine-3-carbonitrile (**2d**).* 60 °C, $Cu(OTf)_2$ as activator, 91.8 mg, 93% yield, white solid, mp 77−78 °C, new compound, R_f = 0.20 (hexanes/ethyl acetate 3/1), 95% ee, $[\alpha]_D^{20}$ = −16.38 (*c* 0.94, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.5 Hz, 2H), 7.36−7.26 (m, 3H), 7.02 (d, *J* = 7.5 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 5.53 (s, 2H), 3.84−3.76 (m, 3H), 3.36−3.10 (m, 2H), 2.47 (s, 1H), 2.17 (d, *J* = 14.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 160.1, 151.6, 150.9, 140.6, 128.7, 127.8, 127.8, 125.9, 124.2, 116.3, 114.0, 68.9, 58.1, 55.3, 35.1, 29.6. The HPLC: Chralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 33.6 min (major) and 69.6 min (minor). HRMS (ESI) *m*/*z*: $[M + Na]^+$ calcd for $C_{20}H_{18}N_4ONa$ 353.1373, found: 353.1370.

*(−)-2-(4-Phenoxyphenyl)-7-phenyl-4,5,6,7-tetrahydropyrazolo-[1,5-a]pyrimidine-3-carbonitrile (**2e**).* 60 °C, $Cu(OTf)_2$ as activator, 115.5 mg, 98% yield, pale yellow solid, mp 62−63 °C, new compound, R_f = 0.25 (hexanes/ethyl acetate/dichloromethane 5/1/2), 95% ee, $[\alpha]_D^{20}$ = −23.60 (*c* 1.11, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.40−7.22 (m, 5H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.00 (dd, *J* = 8.4, 3.0 Hz, 6H), 5.65 (d, *J* = 3.3 Hz, 1H), 5.52 (dd, *J* = 5.4, 3.1 Hz, 1H), 3.25 (dq, *J* = 12.0, 4.0 Hz, 1H), 3.13 (td, *J* = 11.8, 3.1 Hz, 1H), 2.43 (tt, *J* = 12.9, 4.7 Hz, 1H), 2.20−2.10 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 156.8, 151.7, 151.7, 150.7, 140.6, 129.9, 128.8, 128.1, 127.9, 126.6, 125.9, 123.6, 119.2, 118.8, 69.2, 58.2, 35.2, 29.6. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 29.2 min (major) and 88.1 min (minor). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{20}N_4O$ 393.1710, found: 393.1715.

*(−)-7-Phenyl-2-(m-tolyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**2f**).* 60 °C, $Cu(OTf)_2$ as activator, 93.1 mg, 99% yield, pale yellow solid, mp 69−70 °C, new compound, R_f = 0.29 (hexanes/ethyl acetate 3/1), 96% ee, $[\alpha]_D^{20}$ = −27.74 (*c* 0.93, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.75−7.66 (m, 2H), 7.37−7.22 (m, 4H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.04−6.95 (m, 2H), 5.63 (s, 1H), 5.53 (dd, *J* = 5.4, 3.0 Hz, 1H), 3.23 (dt, *J* = 11.9, 3.9 Hz, 1H), 3.12 (td, *J* = 11.9, 3.1 Hz, 1H), 2.47−2.38 (m, 1H), 2.34 (s, 3H), 2.14 (dd, *J* = 13.7, 3.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 151.7, 151.3, 140.7, 138.4, 131.4, 129.8, 128.8, 128.6, 127.8, 127.0, 125.9, 123.7, 69.4, 58.2, 35.1, 29.6, 21.5. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hex- ane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 11.7 min (major) and 26.7 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{18}N_4$ 315.1604, found: 315.1601.

*(+)-2-Methyl-7-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**2g**).* 60 °C, $Cu(OTf)_2$ as activator, 65.5 mg, 92% yield, pale yellow solid, mp 156−157 °C, new compound, R_f = 0.40 (hexanes/ethyl acetate 1/1), 94% ee, $[\alpha]_D^{20}$ = +56.48 (*c* 0.66, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.20 (m, 3H), 6.99 (d, *J* = 7.5 Hz, 2H), 5.56 (s, 1H), 5.40 (t, *J* = 4.3 Hz, 1H), 3.29−3.12 (m, 2H), 2.42 (td, *J* = 11.5, 4.9 Hz, 1H), 2.23 (s, 3H), 2.16−2.09 (m, 1H). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 150.7, 150.6, 140.7, 128.8, 127.9, 125.9, 115.6, 71.8, 56.0, 35.3, 30.0, 13.1. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 11.6 min (major) and 16.7 min (minor). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{14}N_4$ 239.1291, found: 239.1295.

*(−)-2-Phenyl-7-(p-tolyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**2h**).* 60 °C, $Cu(OTf)_2$ as activator, 91.0 mg, 97% yield, pale yellow solid, mp 71−72 °C, new compound, R_f = 0.25 (hexanes/ethyl acetate 3/1), 95% ee, $[\alpha]_D^{20}$ = −33.51 (*c* 0.91, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.94−7.82 (m, 2H), 7.41−7.32 (m, 3H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.96−6.79 (m, 2H), 5.51 (dd, *J* = 5.3, 3.1 Hz, 1H), 5.39−5.16 (m, 1H), 3.31 (dt, *J* = 12.5, 4.1 Hz, 1H), 3.21 (t, *J* = 11.8 Hz, 1H), 2.51−2.42 (m, 1H), 2.32 (s, 3H), 2.18 (d, *J* = 13.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 151.7, 151.0, 137.7, 137.6, 131.6, 129.4, 129.0, 128.6, 126.5, 125.8, 116.2, 69.3, 58.1, 35.2, 29.7, 21.1. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-He- xane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 12.2 min (major) and 19.6 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{18}N_4$ 315.1604, found: 315.1607.

*(−)-2-Phenyl-7-(m-tolyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**2i**).* 60 °C, $Cu(OTf)_2$ as activator, 92.0 mg, 98% yield, white solid, mp 66−67 °C, new compound, R_f = 0.31 (hexanes/ethyl acetate 3/1), 96% ee, $[\alpha]_D^{20}$ = −21.74 (*c* 0.92, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−7.81 (m, 2H), 7.43−7.29 (m, 3H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.90−6.72 (m, 2H), 5.66 (d, *J* = 3.4 Hz, 1H), 5.48 (dd, *J* = 5.4, 3.1 Hz, 1H), 3.23 (dq, *J* = 12.0, 4.0 Hz, 1H), 3.19−3.06 (m, 1H), 2.44−2.27 (m, 4H), 2.19−2.09 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.7, 151.0, 140.6, 138.6, 131.6, 129.0, 128.7, 128.7, 128.6, 126.6, 126.5, 123.0, 116.3, 69.3, 58.3, 35.2, 29.6, 21.6. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 11.6 min (major) and 24.0 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{18}N_4$ 315.1604, found: 315.1608.

*(+)-2-Phenyl-7-(o-tolyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**2j**).* 60 °C, $Cu(OTf)_2$ and TCCA as coactivator, 66.5 mg, 71% yield, white solid, mp 88−89 °C, new compound, R_f = 0.39 (hexanes/ethyl acetate 2/1), 99% ee, $[\alpha]_D^{20}$ = +23.91 (*c* 0.66, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−7.84 (m, 2H), 7.41−7.32 (m, 3H), 7.21−7.11 (m, 3H), 6.61 (d, *J* = 7.5 Hz, 1H), 5.71 (dd, *J* = 5.6, 2.7 Hz, 1H), 5.45 (s, 1H), 3.33−3.19 (m, 2H), 2.50−2.43 (m, 1H), 2.42 (s, 3H), 2.07−2.03 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.0, 151.2, 138.3, 133.9, 131.4, 131.1, 129.0, 128.6, 127.8, 126.5, 126.3, 126.0, 116.0, 69.4, 55.9, 35.1, 27.4, 18.8. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 11.4 min (major) and 19.9 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{18}N_4$ 315.1604, found: 315.1607.

*(−)-7-(4-Methoxyphenyl)-2-phenyl-4,5,6,7-tetrahydropyrazolo-[1,5-a]pyrimidine-3-carbonitrile (**2k**).* 60 °C, $Cu(OTf)_2$ as activator, 85.9 mg, 87% yield, white solid, mp 64−65 °C, new compound, R_f = 0.16 (hexanes/ethyl acetate 3/1), 91% ee, $[\alpha]_D^{20}$ = −36.16 (*c* 0.86, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.96−7.86 (m, 2H), 7.42-7.33 (m, 3H), 6.99−6.91 (m, 2H), 6.89−6.83 (m, 2H), 5.59−5.43 (m, 2H), 3.77 (s, 3H), 3.32−3.23 (m, 1H), 3.23−3.13 (m, 1H), 2.47−2.38 (m, 1H), 2.15 (dt, *J* = 13.5, 3.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 159.2, 151.5, 151.0, 132.6, 131.5, 128.9, 128.6, 127.0, 126.4, 116.0, 114.1, 69.4, 57.8, 55.3, 35.3, 29.8. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 19.3 min (major) and 38.3 min (minor). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{18}N_4O$ 331.1553, found: 331.1558.

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*(−)-7-(4-Bromophenyl)-2-phenyl-4,5,6,7-tetrahydropyrazolo-[1,5-a]pyrimidine-3-carbonitrile (**2l**).* 60 °C, $Cu(OTf)_2$ as activator, 111.6 mg, 98% yield, pale yellow solid, mp 83−84 °C, new compound, R_f = 0.36 (hexanes/ethyl acetate 3/1), 95% ee, $[\alpha]_D^{20}$ = −41.89 (*c* 1.11, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.49−7.43 (m, 2H), 7.42−7.33 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.67 (s, 1H), 5.54−5.41 (m, 1H), 3.29 (dq, *J* = 12.0, 4.0 Hz, 1H), 3.13 (td, *J* = 11.8, 3.1 Hz, 1H), 2.50−2.39 (m, 1H), 2.18−2.08 (m, 1H). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 151.7, 151.2, 139.6, 131.9, 131.3, 129.1, 128.6, 127.7, 126.4, 121.8, 116.0, 69.4, 57.8, 35.2, 29.5. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 17.1 min (major) and 21.1 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{15}BrN_4$ 379.0553 (^{79}Br), 381.0532 (^{81}Br), found: 379.0556 (^{79}Br), 381.0537 (^{81}Br).

*(−)-7-(4-(Methylthio)phenyl)-2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carbonitrile (**2m**).* 60 °C, $Cu(OTf)_2$ as activator, 90.1 mg, 87% yield, pale yellow solid, mp 72−73 °C, new compound, R_f = 0.29 (hexanes/ethyl acetate/dichloromethane 5/1/2), 94% ee, $[\alpha]_D^{20}$ = −39.52 (*c* 0.93, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−7.82 (m, 2H), 7.41−7.32 (m, 3H), 7.23−7.16 (m, 2H), 6.98−6.89 (m, 2H), 5.54 (d, *J* = 3.2 Hz, 1H), 5.48 (dd, *J* = 5.3, 3.3 Hz, 1H), 3.27 (dq, *J* = 12.0, 4.0 Hz, 1H), 3.21−3.10 (m, 1H), 2.49−2.37 (m, 4H), 2.13 (dq, *J* = 13.5, 3.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.7, 151.1, 138.3, 137.4, 131.5, 129.0, 128.7, 126.8, 126.5, 116.1, 69.4, 57.9, 35.3, 29.6, 15.8. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 22.8 min (major) and 44.3 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{18}N_4S$ 347.1325, found: 347.1329.

*(−)-2-Phenyl-7-(4-(trifluoromethyl)phenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carbonitrile (**2n**).* 60 °C, $Cu(OTf)_2$ as activator, 108.0 mg, 97% yield, white solid, mp 88−89 °C, new compound, R_f = 0.38 (hexanes/ethyl acetate 2/1), 96% ee, $[\alpha]_D^{20}$ = −32.87 (*c* 1.08, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.93−7.85 (m, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.43−7.35 (m, 3H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.80 (s, 1H), 5.58 (t, *J* = 4.3 Hz, 1H), 3.31 (dq, *J* = 12.1, 4.0 Hz, 1H), 3.12 (td, *J* = 11.8, 3.1 Hz, 1H), 2.55−2.44 (m, 1H), 2.17 (dq, *J* = 14.2, 3.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.8, 151.4, 144.5, 131.3, 130.2 (q, *J* = 32 Hz), 129.2, 128.7, 126.5, 125.8 (q, *J* = 4 Hz), 123.9 (q, *J* = 270 Hz), 119.9, 116.0, 69.5, 57.9, 35.2, 29.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.61. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 12.5 min (major) and 14.4 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{15}F_3N_4$ 369.1322, found: 369.1327.

*(−)-7-(Furan-2-yl)-2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**2o**).* 60 °C, $Cu(OTf)_2$ as activator, 82.2 mg, 95% yield, pale yellow solid, mp 54−55 °C, new compound, R_f = 0.38 (hexanes/ethyl acetate 2/1), 67% ee, $[\alpha]_D^{20}$ = −16.45 (*c* 0.99, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.91−7.87 (m, 2H), 7.42−7.35 (m, 4H), 6.32 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.15 (dd, *J* = 2.7, 1.7 Hz, 1H), 5.55 (d, *J* = 3.0 Hz, 1H), 5.50 (dd, *J* = 5.3, 3.3 Hz, 1H), 3.46−3.36 (m, 2H), 2.44−2.33 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.0, 151.2, 151.1, 142.6, 131.5, 129.0, 128.7, 126.5, 115.9, 110.5, 108.2, 69.6, 52.8, 36.2, 26.4. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 13.2 min (major) and 17.4 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{14}N_4O$ 291.1240, found: 291.1243.

*(−)-7-Isopropyl-2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**2p**).* 60 °C, $Cu(OTf)_2$ and TCCA as coactivator, 72.8 mg, 91% yield, yellow oil, new compound, R_f = 0.39 (hexanes/ethyl acetate/dichloromethane 5/1/2), 97% ee, $[\alpha]_D^{20}$ = −83.97 (*c* 0.73, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.99−7.84 (m, 2H), 7.44−7.33 (m, 3H), 5.31 (d, *J* = 2.2 Hz, 1H), 4.00 (dt, *J* = 6.8, 5.5 Hz, 1H), 3.44−3.30 (m, 2H), 2.62−2.52 (m, 1H), 2.07−1.95 (m, 2H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.4, 149.0, 130.8, 127.7, 127.6, 125.3, 115.2, 68.5, 58.9, 36.6, 29.3, 21.1, 18.0, 15.9. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, retention time 20.1 and 21.5 min (major). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{18}N_4$ 267.1604, found: 267.1602.

*(−)-7-(tert-Butyl)-2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**2q**).* 60 °C, $Cu(OTf)_2$ and TCCA as coactivator, 70.8 mg, 84% yield, yellow oil, new compound, R_f = 0.31 (hexanes/ethyl acetate/dichloromethane 5/1/2), >99% ee, $[\alpha]_D^{20}$ = −51.41 (*c* 0.71, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.96−7.92 (m, 2H), 7.44−7.39 (m, 2H), 7.38−7.33 (m, 1H), 5.35 (s, 1H), 3.99 (dd, *J* = 5.8, 4.5 Hz, 1H), 3.47−3.35 (m, 2H), 2.25−2.18 (m, 1H), 2.08−2.00 (m, 1H), 1.09 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.8, 149.4, 131.9, 128.8, 128.7, 126.3, 116.5, 68.9, 62.9, 37.6, 36.0, 27.9, 23.6. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 8.3 and 9.2 min (major). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{20}N_4$ 281.1761, found: 281.1762.

*(−)-7-Cyclohexyl-2-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidine-3-carbonitrile (**2r**).* 60 °C, $Cu(OTf)_2$ and TCCA as coactivator, 85.0 mg, 93% yield, pale yellow solid, mp 151−152 °C, new compound, R_f = 0.28 (hexanes/ethyl acetate/dichloromethane 5/1/2), 95% ee, $[\alpha]_D^{20}$ = −63.41 (*c* 0.85, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.99−7.83 (m, 2H), 7.46−7.39 (m, 2H), 7.38−7.32 (m, 1H), 5.35 (s, 1H), 4.01 (q, *J* = 5.7 Hz, 1H), 3.44−3.27 (m, 2H), 2.17−2.05 (m, 2H), 2.03−1.94 (m, 1H), 1.83−1.65 (m, 4H), 1.58−1.51 (m, 1H), 1.30−1.03 (m, 5H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.2, 149.9, 131.9, 128.8, 128.7, 126.4, 116.3, 69.4, 59.5, 40.7, 37.4, 29.8, 27.8, 26.4, 26.3, 26.1, 22.8. HPLC: Chiralcel OD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 7.5 min (major) and 44.8 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{22}N_4$ 307.1917, found: 307.1919.

*tert-Butyl-(−)-4-(3-cyano-2-phenyl-4,5,6,7-tetrahydropyrazolo-[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**2s**).* 60 °C, the $Cu(OTf)_2$ and TCCA as coactivator, 116.3 mg, 95% yield, white solid, mp 239−240 °C, new compound, R_f = 0.33 (hexanes/ethyl acetate 1/1), 98% ee, $[\alpha]_D^{20}$ = −58.55 (*c* 1.16, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.03−7.67 (m, 2H), 7.45−7.30 (m, 3H), 5.50 (s, 1H), 4.31−3.99 (m, 3H), 3.36 (td, *J* = 6.0, 5.5, 2.2 Hz, 2H), 2.80−2.56 (m, 2H), 2.26 (s, 1H), 2.11−1.94 (m, 2H), 1.67 (dq, *J* = 11.1, 2.8 Hz, 1H), 1.53−1.23 (m, 12H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.8, 151.2, 150.2, 131.7, 128.9, 128.7, 126.4, 116.1, 79.6, 69.6, 58.7, 43.7, 39.2, 37.3, 28.5, 26.9, 22.7. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 13.1 min (major) and 17.0 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{29}N_5O_2$ 408.2394, found: 408.2397.

*tert-Butyl-(−)-4-(3-cyano-2-methyl-4,5,6,7-tetrahydropyrazolo-[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**2t**).* 60 °C, the $Cu(OTf)_2$ and TCCA as coactivator, 101.9 mg, 98% yield, white solid, mp 70−71 °C, new compound, R_f = 0.21 (hexanes/ethyl acetate 1/1), 97% ee, $[\alpha]_D^{20}$ = −34.54 (*c* 1.02, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (s, 1H), 4.16 (s, 2H), 3.96 (q, *J* = 5.8 Hz, 1H), 3.43−3.27 (m, 2H), 2.77−2.53 (m, 2H), 2.30−2.11 (m, 4H), 2.09−1.94 (m, 2H), 1.65−1.59 (m, 1H), 1.50−1.30 (m, 11H), 1.26−1.19 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.7, 150.1, 149.7, 115.5, 79.5, 71.9, 58.3, 43.9, 39.2, 37.3, 28.4, 26.7, 22.6, 13.0. HPLC: Chiralpak AD-H column, 254 nm, 30 °C, *n*-Hexane/*i*-PrOH = 90/10, flow = 1.0 mL/min, retention time 10.6 and 12.9 min (major). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{27}N_5O_2$ 346.2238, found: 346.2239.

*tert-Butyl (−)-4-(3-cyano-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-7-yl)piperidine-1-carboxylate (**2u**).* 60 °C, $Cu(OTf)_2$ and TCCA as coactivator, 148.1 mg, 99% yield, white solid, the known compound,[4] mp 85−86 °C, R_f = 0.11 (hexanes/ethyl acetate 2/1), 98% ee, $[\alpha]_D^{20}$ = −89.52 (*c* 1.48, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−7.82 (m, 2H), 7.39−7.30 (m, 2H), 7.15−7.10 (m, 1H), 7.09−6.92 (m, 4H), 5.24 (s, 1H), 4.29−4.04 (m, 3H), 3.48- 3.35 (m, 2H), 2.80−2.62 (m, 2H), 2.29 (s, 1H), 2.15−2.01 (m, 2H), 1.70 (dt, *J* = 12.8, 2.7 Hz, 1H), 1.45 (s, 12H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 156.8, 154.8, 151.2, 149.7, 129.9, 127.9, 126.8, 123.6, 119.2, 118.8, 116.2, 79.6, 69.4, 58.7, 43.4, 39.2, 37.3, 28.5, 27.0, 22.7. HPLC: Chiralpak AD-H

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column, 254 nm, 30 °C, *n*-Hexane/*i*-Pr- OH = 80/20, flow = 0.8 mL/min, retention time 12.8 and 14.7 min (major).

Scale-Up Asymmetric Hydrogenation. In a nitrogen-filled glovebox, a mixture of $[Ir(cod)Cl]_2$ (35.3 mg, 0.0525 mmol) and chiral ligand (*R*)-SegPhos (70.5 mg, 0.1155 mmol) in THF (26.0 mL) was stirred at room temperature for 20 min, afterward trichloroisocyanuric acid (TCCA, 85.4 mg, 0.368 mmol) was added and stirred for 10 min, the mixture was transferred by a syringe to a stainless steel autoclave, in which substrate **1u** (10.41 g, 21.0 mmol) and copper triflate (47.5 mg, 0.131 mmol) had been placed beforehand. THF (54.0 mL) was then added to the mixture. The hydrogenation was performed at 60 °C under 750 psi of hydrogen gas for 43 h. Then, the autoclave was cooled to room temperature. After carefully releasing the hydrogen, the autoclave was opened, and the volatiles were removed under the reduced pressure. Flash chromatography on silica gel using hexanes/ethyl acetate as eluent gave the desirable reductive product 9.65 g of **2u** with 92% yield and 95% ee.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c02396.

NMR spectra and HPLC spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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