Synthesis J. J. Crawford et al. Special Topic

# Synthesis of an Azabicyclo[3.1.0]hexanone-Containing Inhibitor of NF-κB Inducing Kinase via Catalytic C–H Activation

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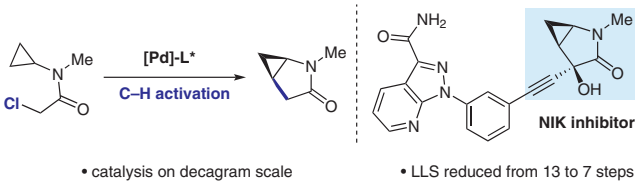
Published as part of the Special Topic
*Synthesis in Industry*




Received: 28.07.2020
Accepted: 12.08.2020
Published online: 15.09.2020
DOI: 10.1055/s-0040-1707279; Art ID: ss-2020-c0401-st

**Abstract** The synthesis of an azabicyclo[3.1.0]hexanone-containing inhibitor of the nuclear factor-κB inducing kinase (NIK) is reported. The initial route to this compound was streamlined from 13 to 7 linear steps through the use of a catalytic, enantioselective C–H activation step. A procedure for lactam oxidation was identified that avoided use of peroxides on scale. These synthetic improvements allowed for the synthesis of multigram quantities of the desired NIK inhibitor for in vivo profiling.

**Key words** C–H activation, NIK inhibitor, enantioselective, azabicyclo-[3.1.0]hexanone, nuclear factor-κB, medicinal chemistry

The nuclear factor-κB (NF-κB) family of transcription factors are regulated via a pair of signaling pathways – referred to as the canonical and non-canonical pathways – that differ in both their components and biological function.[1] The non-canonical NF-κB pathway plays a number of key roles in regulating immune functions. Pathway dysregulation has been linked to the pathogenesis of autoimmune and inflammatory diseases such as systemic lupus erythematosus (SLE), while defective signaling is associated with severe immune deficiencies.[2,3] Non-canonical NF-κB signaling is dependent on NF-κB inducing kinase (NIK, or MAP3K14), which is continuously degraded through its association with the TNF receptor-associated factors 2/3-ubiquitin ligase complex.[4] Pathway activation leads to dissociation of NIK from this complex, allowing it to accumulate and phosphorylate IKKα. This results in phosphorylation of p100, and the release and heterodimerization with RelB of the mature transcription factor p52 (NF-κB2).[5] Ultimately, the p52-RelB complex translocates to the nucleus and triggers transcription of pathway target genes.[5,6]

Pharmacological intervention via NIK inhibition has been of significant interest in the pharmaceutical industry,[7,8] and a selective NIK inhibitor has been shown to be efficacious in an NZB/W F1 model of SLE.[1] As a part of our medicinal chemistry program, we have previously reported the discovery of pyrazolopyridine **1** as a potent and selective inhibitor of NIK (Figure 1).[9–11] Cyclopropyl lactam **2** was subsequently identified as a promising lead compound.[12] In order to facilitate in vitro and in vivo profiling, multigram quantities of cyclopropane **2** were required.

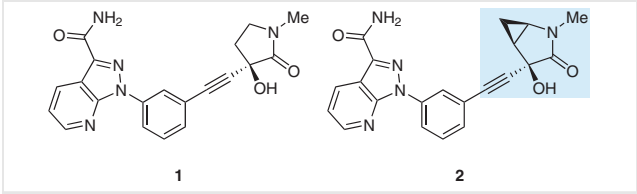



**Figure 1** Previously-reported NIK inhibitor **1** and cyclopropane-containing compound **2**

As a route to the pyrazolopyridine core of **1** was already developed,[9–11] we focused our efforts on developing a synthetic strategy for the densely-functionalized lactam of **2** (Figure 1, highlighted portion). This fragment contains three contiguous stereocenters, one of which is a tertiary alcohol. Anticipating that the alkynylated lactam could be installed via a late-stage Sonogashira coupling, the synthesis of terminal alkyne **14** was targeted (Scheme 1).

Our initial route to alkyne **14** commenced from commercially available pyrrolidine **7** (Scheme 1). Boc-protection of pyrrolidine **7** followed by ruthenium-mediated oxidation of protected pyrrolidine **8** provided pyrrolidinone **9**. Subsequent acidic deprotection afforded cyclopropyl lactam **10**, which was methylated to provide tertiary lactam **11**. After an exhaustive screen of oxidation reagents, α-oxidation of lactam **11** to alcohol **12** was effected with bis(trimethylsilyl)peroxide.[13] Oxidation of alcohol **12** with Dess–Martin periodinane to dione **13** followed by chemoselective Grignard addition completed the synthesis of alkyne **14**.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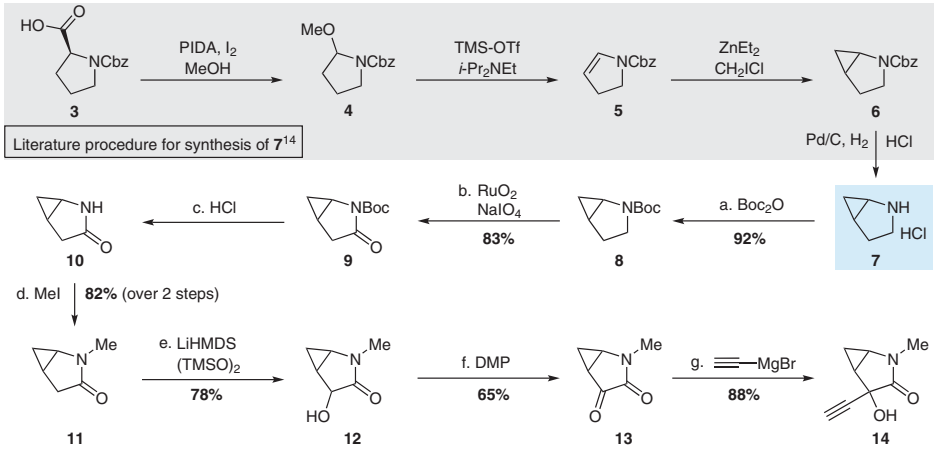
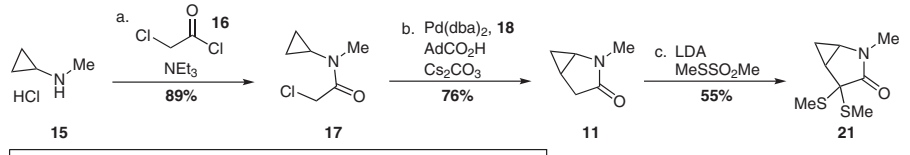
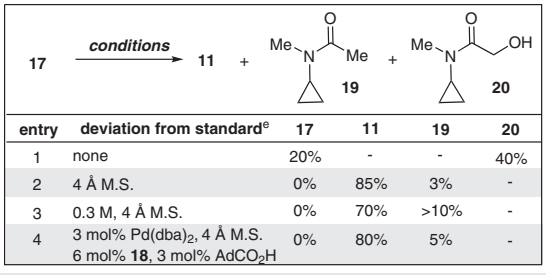



**Scheme 1** Initial synthetic route to alkyne **14**. Top, grey box: literature procedure for the synthesis of intermediate **7**. Middle, cyan box: commercially-available starting point for medicinal chemistry efforts. *Reagents and conditions*: (a) 4 M $Boc_2O$ in THF (1.1 equiv), 1 M $Na_2CO_3$ in $H_2O$ (2.1 equiv), 1:1 THF:$H_2O$ (0.4 M), r.t.; (b) $RuO_2{\cdot}xH_2O$ (0.4 equiv), $NaIO_4$ (5.0 equiv), 1.3:1 EtOAc:$H_2O$ (0.03 M), r.t.; (c) 4 M HCl in 1,4-dioxane (8 equiv), DCM (0.25 M), r.t.; (d) MeI (1.5 equiv), $Cs_2CO_3$ (1.7 equiv), MeCN (0.23 M), 75 °C; (e) 1 M LiHMDS in THF (1.5 equiv), $(TMSO)_2$ (3.0 equiv), THF (0.3 M), –78 to –30 °C; (f) Dess–Martin periodinane (1.2 equiv), DCM (0.16 M), r.t.; (g) 0.5 M ethynylmagnesium bromide (2.0 equiv), THF (0.3 M), –78 °C. The yields of **9**, **11** and **12** are based on crude products obtained without column purification. All other yields are from isolation after purification.

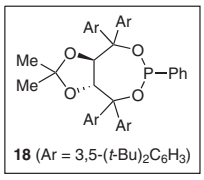
Our original synthesis of alkyne **14** provided a fit-for-purpose solution for early-stage medicinal chemistry efforts, but a number of issues became evident in attempting to scale this route. Although pyrrolidine **7** was a convenient starting point for medicinal chemistry, its sourcing and price on scale made its continued use untenable. As an initial approach, pyrrolidine **7** was synthesized in-house through four steps following a known procedure (Scheme 1, top).[14] Suarez-type decarboxylation of proline derivative **3** yielded *N*,*O*-acetal **4** which, after loss of methanol, cyclopropanation, and deprotection, provided desired pyrrolidine **7**. Attempting to scale this 4-step sequence to meet our initial materials needs (15 g of **14**) revealed that 120 liters of pyrophoric $ZnEt_2$ (1 M) would be required for the synthesis. Advancing intermediate **7** to lactam **14** brought to light additional issues of this synthetic approach: (1) the use of gram-quantities of potentially explosive bis(trimethylsilyl)peroxide,[15] (2) challenges in isolating water-soluble **12** on scale, and (3) the inefficiency associated with a low-yielding 11-step sequence.

Seeking to ameliorate the aforementioned issues, a more efficient and scalable route to alkyne **14** was developed (Scheme 2). This route relied on use of recently published research from the Cramer laboratory describing the

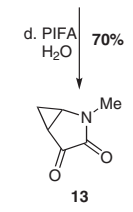



| entry | deviation from standard[e] | 17 | 11 | 19 | 20 |
|---|---|---|---|---|---|
| 1 | none | 20% | - | - | 40% |
| 2 | 4 Å M.S. | 0% | 85% | 3% | - |
| 3 | 0.3 M, 4 Å M.S. | 0% | 70% | >10% | - |
| 4 | 3 mol% $Pd(dba)_2$, 4 Å M.S. 6 mol% **18**, 3 mol% $AdCO_2H$ | 0% | 80% | 5% | - |




**18** (Ar = 3,5-(*t*-Bu)$_2$C$_6$H$_3$)




**Scheme 2** Streamlined route for the synthesis of dione **13** on scale. *Reagents and conditions*: (a) $Et_3N$ (3.5 equiv), **16** (1.1 equiv), DCM (0.28 M), –20 °C to r.t.; (b) $Pd(dba)_2$ (0.03 equiv), **18** (0.06 equiv), adamantane-1-carboxylic acid (0.03 equiv), $Cs_2CO_3$ (1.5 equiv), 4 Å molecular sieves (0.15 g/mol), toluene (0.1 M), 70 °C; (c) 2 M LiN(*i*-Pr)$_2$ in THF (1.5 equiv), $MeSSO_2Me$ (1.5 equiv), THF (0.20 M), –30 °C to r.t.; (d) PIFA (2.0 equiv), 10:1 MeCN:$H_2O$ (0.05 M), 0 °C; (e) Screening was conducted on 5 mmol scale and yields were assessed by LC/MS by relative peak area integration. Standard screening conditions: $Pd(dba)_2$ (0.05 equiv), **18** (0.10 equiv), adamantane-1-carboxylic acid (0.05 equiv), $Cs_2CO_3$ (1.5 equiv), toluene (0.1 M), 70 °C. Molecular sieves (M.S.) were used at a loading of 0.15 g/mol.

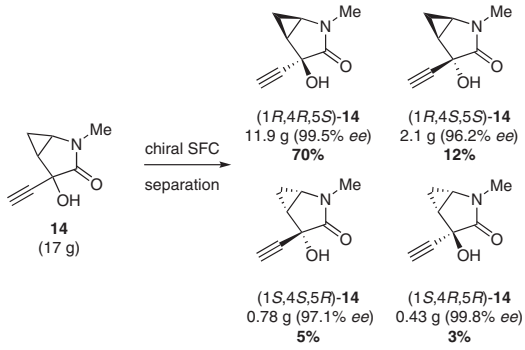
C–H functionalization of cyclopropanes to form cyclopropyl lactams.[16–19] Indeed, use of C–H activation in drug discovery has become a popular means to streamline synthetic routes.[20] Our modified route commenced with the acylation of commercially available and inexpensive cyclopropylmethylamine (**15**) with acyl chloride **16** to yield alkyl chloride **17**. Alkyl chloride **17** served as the starting material for the key C–H activation step; it is proposed that this process occurs through oxidative addition to the carbon–chlorine bond by TADDOL phosphonite-ligated Pd(0), subsequent intramolecular C–H activation of the proximal cyclopropane mediated by a Pd-carboxylate, and $Csp^3$–$Csp^3$ reductive elimination to form the product.[16] Use of a chiral phosphonite ligand renders this transformation enantioselective, although the viability of *N*-methylamides as substrates was not demonstrated in the original report.

Initial application of the reported C–H activation conditions provided 20% starting material **17** along with 40% of hydrolysis product **20** (Scheme 2, insert, entry 1). To minimize hydrolysis, the reaction was next conducted in the presence of 4Å molecular sieves. To our nearly unspeakable jouissance, these anhydrous conditions provided the desired product **11** in 85% yield while abating formation of alcohol **20** (entry 2). These conditions were accompanied by the formation of a small amount of proto-dehalogenated **19**. Concentrating the reaction to 0.3 M decreased formation of desired **11** while increasing the observed amount of dehalogenated **19** (entry 3). It was found that reducing the catalyst loading to 3 mol% $Pd(dba)_2$ and 6 mol% **18** had a minimal effect on product yield (entry 4). These optimized conditions were used to run three >20 g scale reactions, which were combined and purified by distillation as a single batch to provide >50 g of desired **11** in 76% yield. Notably, lactam **11** was now accessible on scale in only 2 steps, compared to our previously used 8-step route.

Prior structure-activity relationships had revealed (1*R*,4*R*,5*S*)-**14** to be the desired stereoisomer for NIK inhibition (Scheme 3).[12] In order to bias C–H activation towards the formation of this stereoisomer, (*R*,*R*)-**18** was used in analogy to the stereochemical outcomes reported by the Cramer laboratory.[16] The enantiomeric enrichment of product lactam **11**, however, was not quantified at this stage since the retention time of the desired absolute enantiomer was unknown. Previous efforts demonstrated that stereoisomers of advanced intermediates could be separated by chiral chromatography and hence, lactam **11** was advanced as a presumed scalemic mixture.

With decagram quantities of lactam **11** in hand, our focus turned to establishing a scalable means for lactam α-oxidation. Due to the hazards of working with peroxides on scale,[15] issues sourcing bis(trimethylsilyl) peroxide, and local regulations, our previously developed conditions were no longer viable. An alternative 2-step procedure for α-oxidation was identified that avoided the use of peroxides.

Oxidation of lactam **11** with *S*-methyl methanethiosulfonate provided thioketal **21,** which was converted to previously-made dione **13** through the action of phenyliodine bis(trifluoroacetate) (PIFA) in aqueous conditions.[21] Dione **13** intercepted our former synthetic route, and was converted to alkyne **14** by Grignard addition.

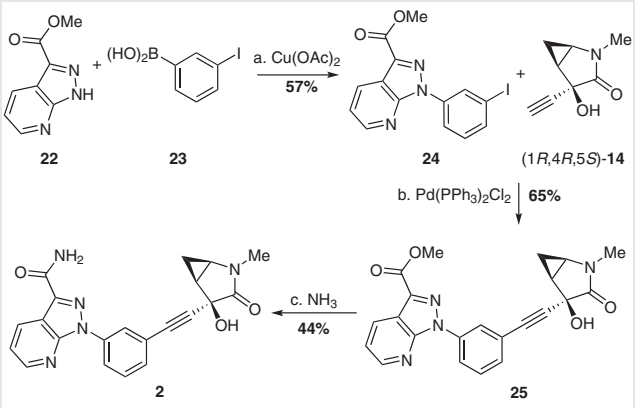



**Scheme 3** Separation of the stereoisomers of lactam **14** by chiral-phase SFC

Stereochemically pure (1*R*,4*R*,5*S*)-**14** was accessed through preparative supercritical fluid chromatography (SFC) (Scheme 3). Analysis of the initial mixture revealed the presence of four stereoisomers: both enantiomers of lactam **14** were produced in the C–H activation of cyclopropylamine **17**, and Grignard addition to dione **13** produced alkyne **14** as a mixture of diastereomers. Identification of appropriate conditions allowed for 17 g of alkyne **14** to be separated into its components with 90% recovery. The desired isomer (1*R*,4*R*,5*S*)-**14** was isolated in 70% yield (11.9 g) and 99.5% *ee*, and the structures of diastereomeric (1*R*,4*R*,5*S*)-**14** and (1*R*,4*S*,5*S*)-**14** were confirmed by X-ray crystallography (see Supporting Information). Although an imperfect measure of stereoselectivity, the isolated yields of each stereoisomer suggests that C–H activation occurred with ~84% *ee* and Grignard addition proceeded in ~6:1 *dr* for the desired cyclopropyl enantiomer.

The synthesis of NIK inhibitor **2** was completed in analogy to our previously disclosed route.[9,12] Chan–Lam coupling of azaindazole **22** and arylboronic acid **23** provided *N*-aryl iodide **24**. Sonogashira coupling of **24** with alkyne (1*R*,4*R*,5*S*)-**14** yielded ester **25**, which was subjected to aminolysis producing the desired amide **2** on multigram scale (Scheme 4). The structure of NIK inhibitor **2** was unambiguously confirmed by X-ray crystallography (see Supporting Information).

In conclusion, scalable access to NIK inhibitor **2** was enabled through use of a catalytic, enantioselective C–H activation step. This methodology was incorporated at an early stage in the synthesis and provided access to the densely functionalized chiral 2-azabicyclo[3.1.0]hexanone motif of this inhibitor in decagram quantities. Such tactical applica-




**Scheme 4** Completion of the synthesis of NIK inhibitor **2**. *Reagents and conditions*: (a) **23** (1.1 equiv), $Cu(OAc)_2$ (0.50 equiv), pyridine (2.2 equiv), THF (0.14 M), 50 °C; (b) (1*R*,4*R*,5*S*)-**14** (1.3 equiv), $Pd(PPh_3)_2Cl_2$ (0.2 equiv), 1:2 $Et_3N$:DMSO (0.17 M), 95 °C; (c) 4 N $NH_3$ in MeOH (53 equiv), 40 °C.

tion of modern methodology allowed for a reduction in the overall synthetic sequence from 13 to 7 longest linear steps. Use of peroxides on scale was avoided through identification of a two-step procedure for carbonyl introduction via thioketal formation and subsequent oxidation. Full characterization of the properties and therapeutic potential of amide **2** will be reported in due course.

Reagents were purchased from the following vendors and used without further purification: Shanghai Chiral Chemicals Inc., Sinopharm Chemical Reagent Beijing Co., Ltd, Shanghai Huiquan Chemical Technology Co., Ltd, ZN Biochemical Company Ltd, Shangui Hangui Hualun Chemical Co., Ltd, Shaanxi Rock New Materials Co. Ltd, Suzhou High fine Biotech Co., Ltd, and Guan Jingqiu Huagong Chanpin Co., Ltd. Ligand **18** was obtained by a previously reported method.[22] $^1$H NMR spectra were recorded on Bruker Avance 300, 400, or 500 spectrometer. Chemical shifts are expressed in δ ppm referenced to an internal standard, tetramethylsilane (δ = 0). Standard abbreviations were used in describing peak signals. All final compounds were purified by flash chromatography using silica (100–200 mesh) provided by Rushanshi Shuangbang Xincailiao Co., Ltd. The purity was assessed by reverse phase HPLC with a gradient of 5–95% MeCN in $H_2O$ (with either acid or base modifier) and monitored by absorption at 190 nm. LCMS (ESI) analysis was performed using Agilent Instruments. The LC was monitored by absorption at 220 nm and 254 nm. MS full scan with 10 000 resolution was applied to all experiments. Preparative SFC was conducted using a SFC Jasco PREP 150 (Jasco 150 SFC) instrument on a Chiralpak IC (250 × 30 mm, 5 µm) column.

### *tert*-Butyl 2-Azabicyclo[3.1.0]hexane-2-carboxylate (8)[12] CAS Number: 154874-95-0

A 1 M solution of $Na_2CO_3$ in $H_2O$ (79 mL, 79 mmol) and a solution of di-*tert*-butyl dicarbonate (9.06 g, 42 mmol) in THF (10 mL) were added dropwise simultaneously to a solution of 2-azabicyclo[3.1.0]hexane hydrochloride (**7**; 4.41 g, 37 mmol) in a 1:1 mixture of $H_2O$ and THF (90 mL). The mixture was stirred for 2 h, extracted with EtOAc (3 × 50 mL), and the combined organic extracts were washed with $H_2O$ (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified via chromatography with silica gel (40 g) eluting with 20% EtOAc in heptane to give 6.23 g (92%) of the title compound.

$^1$H NMR ($CDCl_3$, 300 MHz): δ = 3.67–3.59 (m, 1 H), 3.42–3.37 (m, 1 H), 2.98–2.89 (m, 1 H), 2.11–2.02 (m, 1 H), 1.95–1.87 (m, 1 H), 1.55–1.53 (m, 1 H), 1.50–1.40 (s, 9 H), 0.70–0.60 (m, 1 H), 0.55–0.40 (m, 1 H).

MS (ESI): *m*/*z* [2 M + H]$^+$ calcd for $C_{20}H_{35}N_2O_4$: 367.25; found: 367.

### *tert*-Butyl 3-Oxo-2-azabicyclo[3.1.0]hexane-2-carboxylate (9)[12] CAS Number: 1417334-40-7

A solution of $RuO_2$·x$H_2O$ (2.06 g, 14 mmol) and $NaIO_4$ (36.4 g, 170 mmol) in $H_2O$ (500 mL) was added portionwise to a mixture of *tert*-butyl 2-azabicyclo[3.1.0]hexane-2-carboxylate (**8**; 6.23 g, 34.0 mmol) in EtOAc (650 mL). The mixture was vigorously stirred for 20 h. The black precipitate was filtered, the filtrate quenched with 5% aq $Na_2S_2O_3$ (250 mL), and the aqueous phase was extracted with EtOAc (3 × 250 mL). The combined organic layers were washed with $H_2O$ (150 mL) and brine (150 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give an oil, which solidified upon standing to afford 5.56 g (83%) of the title compound as a white solid.

$^1$H NMR ($CDCl_3$, 400 MHz): δ = 3.57–3.52 (m, 1 H), 2.86 (dd, *J* = 18.8, 7.4 Hz, 1 H), 2.53–2.45 (m, 1 H), 1.52 (s, 9 H), 1.48–1.44 (m, 1 H), 1.02–0.95 (m, 1 H), 0.44–0.40 (m, 1 H).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{16}NO_3$: 198.11; found: 198.

### 2-Azabicyclo[3.1.0]hexan-3-one (10)[12] CAS Number: 2193098-04-1

A 4 M solution of HCl in 1,4-dioxane (20 mL, 80 mmol) was added dropwise to a stirred solution of *tert*-butyl 3-oxo-2-azabicyclo-[3.1.0]hexane-2-carboxylate (**9**; 1.97 g, 10 mmol) in DCM (40 mL). Evolution of $CO_2$ ceased after 2 h, at which point the reaction mixture was concentrated under reduced pressure. The residue was redissolved in DCM and concentrated under reduced pressure thrice to give 946 mg (97%) of the title compound.

MS (ESI): *m*/*z* [2 M + H]$^+$ calcd for $C_{10}H_{15}N_2O_2$: 195.11; found: 195.

### 2-Methyl-2-azabicyclo[3.1.0]hexan-3-one (11)[12] CAS Number: 2193098-05-2

*Via Methylation of* ***10***: A mixture of 2-azabicyclo[3.1.0]hexan-3-one (**10**; 946 mg, 9 mmol) and $Cs_2CO_3$ (5.12 g, 16 mmol) in MeCN (40 mL) was stirred for 15 min and then MeI (0.87 mL, 14 mmol) was added dropwise to the suspension. The mixture was heated at 75 °C in a sealed vial for 12 h. The resulting mixture was cooled to r.t. and filtered. The filtrate was concentrated in vacuum to give 873 mg (85%; 82% from **9**) of the title compound as a light yellow oil.

*C–H Activation Procedure*: To a 3000 mL 4-necked round-bottomed flask purged with and maintained under an inert atmosphere of argon was placed 2-chloro-*N*-cyclopropyl-*N*-methylacetamide (**17**; 22.2 g, 150 mmol), $Pd(dba)_2$ (2.6 g, 4.5 mmol), (3a*R*,8a*R*)-4,4,8,8-tetrakis(3,5-di-*tert*-butylphenyl)-2,2-dimethyl-6-phenyltetrahydro-[1,3]dioxolo[4,5-*e*][1,3,2]dioxaphosphepine (**18**; 9.2 g, 9 mmol), adamantane-1-carboxylic acid (810 mg, 4.5 mmol), $Cs_2CO_3$ (73.5 g, 225 mmol), 4Å molecular sieves (22.2 g), and toluene (1500 mL). The resulting mixture was stirred overnight at 70 °C in an oil bath. This process was repeated identically 3 times and the crude reaction mixtures were combined. The combined reaction mixtures were cooled to r.t., filtered, and washed with EtOAc (2 L). The filtrate was concentrated under reduced pressure. The crude product was purified by distilla-

tion under reduced pressure (10 mm Hg) and the fraction that distilled at 80 °C was collected to afford 51 g (76%) of the title compound as a light yellow oil.

$^1$H NMR ($CDCl_3$, 400 MHz): δ = 3.00–2.95 (m, 1 H), 2.88 (s, 3 H), 2.75 (dd, *J* = 17.9, 7.2 Hz, 1 H), 2.34 (d, *J* = 17.9 Hz, 1 H), 1.53–1.42 (m, 1 H), 0.88–0.81 (m, 1 H), 0.31–0.26 (m, 1 H).

MS (ESI): *m*/*z* [2 M + H]$^+$ calcd for $C_{12}H_{19}N_2O_2$: 223.14; found: 223.

**4-Hydroxy-2-methyl-2-azabicyclo[3.1.0]hexan-3-one (12)[12] CAS Number: 2193098-06-3**

A 1 M solution of LiHMDS in THF (7.5 mL, 7.5 mmol) was added dropwise to a mixture of 2-methyl-2-azabicyclo[3.1.0]hexan-3-one (**11**; 556 mg, 5.0 mmol) and bis(trimethylsilyl)peroxide (3.3 mL, 15 mmol) in THF (15 mL) at –78 °C. The mixture was stirred at this temperature for 1 h, allowed to warm to –30 °C, and left at this temperature for 1 h. The mixture was quenched with 1 M aq HCl and stirred for 30 min. The resulting mixture was extracted with pentane (3 ×). The aqueous layer was neutralized to pH 7 by the addition of sat. aq $NaHCO_3$ and concentrated in vacuum to dryness. The dry residue was extracted with DCM, filtered, and the filtrate was concentrated to give 498 mg (78%) of the title compound as a yellow oil, which solidified upon standing.

$^1$H NMR ($CDCl_3$, 400 MHz): δ = 4.86 (d, *J* = 4.3 Hz, 1 H), 4.17 (dd, *J* = 4.3, 1.6 Hz, 1 H), 3.12–3.01 (m, 1 H), 2.91 (s, 3 H), 1.72–1.63 (m, 1 H), 1.02–0.92 (m, 1 H), 0.39–0.31 (m, 1 H).

MS (ESI): *m*/*z* [2 M + H]$^+$ calcd for $C_{12}H_{19}N_2O_4$: 255.13; found: 255.

**2-Methyl-2-azabicyclo[3.1.0]hexane-3,4-dione (13)[12] CAS Number: 2193098-07-4**

*Via Oxidation of* **12**: Dess–Martin periodinane (1.99 g, 4.7 mmol) was added portionwise to a solution of 4-hydroxy-2-methyl-2-azabicyclo[3.1.0]hexan-3-one (**12**; 498 mg, 3.9 mmol) in DCM (25 mL). The mixture was stirred at r.t. for 1 h. The resulting mixture was concentrated in vacuum, the residue was concentrated from heptane twice, and the resulting semi-solid residue was re-dissolved in DCM, filtered, and purified by chromatography on silica gel (24 g) eluting with a 0–100% gradient of EtOAc in heptane to give 320 mg (65%) of the title compound as a yellow solid.

*Procedure for Thioketal Oxidation*: To a stirred reaction of 2-methyl-4,4-bis(methylthio)-2-azabicyclo[3.1.0]hexan-3-one (**21**; 22 g, 108 mmol) in MeCN (2000 mL) and $H_2O$ (200 mL) at 0 °C under $N_2$ was added PIFA (92.9 g, 216 mmol) in portions, and the resulting mixture was stirred at 0 °C for 2 h. The reaction was quenched with sat. aq $NaHCO_3$ (1000 mL) and extracted with $CHCl_3$ (4 × 1000 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with a 0–100% gradient of EtOAc in petroleum ether to afford 9.5 g (70%) of the title compound as a light yellow solid.

$^1$H NMR ($CDCl_3$, 400 MHz): δ = 3.71–3.66 (m, 1 H), 3.11 (s, 3 H), 2.35–2.28 (m, 1 H), 1.62–1.56 (m, 1 H), 1.54–1.49 (m, 1 H).

MS (ESI): *m*/*z* [2 M + H]$^+$ calcd for $C_{12}H_{15}N_2O_4$: 251.10; found: 251.

**4-Ethynyl-4-hydroxy-2-methyl-2-azabicyclo[3.1.0]hexan-3-one (14)[12] CAS Number: 2193098-08-5**

To a solution of 0.5 M ethynylmagnesium bromide in THF (256 mL, 128 mmol) at –78 °C under argon was added dropwise a solution of 2-methyl-2-azabicyclo[3.1.0]hexane-3,4-dione (**13**; 8.0 g, 63.9 mmol) in THF (200 mL) over 1 h. This process was repeated identically once and the crude reactions were combined and warmed to 0 °C. After 4 h, the reaction mixture was cooled to –30 °C, quenched with sat. aq $NH_4Cl$ (400 mL), and extracted with EtOAc (3 × 500 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with a 0–100% gradient of EtOAc in petroleum ether and then crystallized from EtOAc to afford 17 g (88%) of the title compound as a light yellow solid.

*Procedure for SFC Separation*of **14** to (1*R*,4*R*,5*S*)-**14**: 4-Ethynyl-4-hydroxy-2-methyl-2-azabicyclo[3.1.0]hexan-3-one (**14**; 17 g) was purified by preparative SFC using the following method: Isocratic (10% Mobile Phase B); Mobile Phase A: $CO_2$; Mobile Phase B: MeOH with 0.1% $NH_4OH$; Flow rate: 150 mL/min; Pressure: 100 bar; Temp: 25 °C; Cycle time: Injection every 4 min; Collected peak at wavelength 220 nm. (1*R*,4*R*,5*S*)-**14** eluted with a retention time of 0.688 min to provide 11.9 g (70%, 99.54% *ee*) of the title compound as a white solid.

$^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 6.21 (s, 1 H), 3.58 (s, 1 H), 3.26–3.21 (m, 1 H), 2.76 (s, 3 H), 1.90–1.84 (m, 1 H), 0.81–0.74 (m, 1 H), 0.56–0.51 (m, 1 H).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_{10}NO_2$: 152.06; found: 152.

X-ray structure in Supporting Information.

**2-Chloro-*N*-cyclopropyl-*N*-methylacetamide (17)[12] CAS Number: 722538-31-0**

To a 5000 mL 4-necked round-bottomed flask purged with and maintained under an inert atmosphere of $N_2$ was placed a solution of *N*-methylcyclopropanamine hydrochloride (**15**; 90 g, 837 mmol) in DCM (3000 mL) followed by the addition of $Et_3N$ (296 g, 2.92 mol) dropwise with stirring in an ice/salt bath. To this was added 2-chloroacetyl chloride (**16**; 103 g, 914 mmol) dropwise with stirring at –20 °C. The resulting solution was allowed to slowly warm to r.t. and stirred overnight. The reaction mixture was cooled with to 0 °C and then quenched by the addition of $H_2O$ (1000 mL). The resulting solution was extracted with DCM (2 × 1000 mL). The organic layers were combined, dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with 1:5 EtOAc/petroleum ether to afford 110 g (89%) of the title compound as a light yellow oil.

$^1$H NMR ($CDCl_3$, 300 MHz): δ = 4.32 (s, 2 H), 2.98 (s, 3 H), 2.84–2.72 (m, 1 H), 0.97–0.84 (m, 4 H).

**2-Methyl-4,4-bis(methylthio)-2-azabicyclo[3.1.0]hexan-3-one (21)[12] CAS Number: 2193098-24-5**

To a 1000 mL 3-necked round-bottomed flask purged with and maintained under an inert atmosphere of argon was placed 2-methyl-2-azabicyclo[3.1.0]hexan-3-one (**11**; 11 g, 99 mmol) and THF (500 mL). The reaction mixture was cooled to –30 °C and 2 M LDA in THF (75 mL, 150 mmol) was added dropwise over 1 h. To this was added $MeSSO_2Me$ (19 g, 151 mmol) dropwise over 2 h. The resulting solution was allowed to slowly warm to r.t. and stirred overnight. This process was repeated identically 3 times and the crude reaction mixtures were combined. The combined reaction mixtures were quenched with sat. aq $NH_4Cl$ (800 mL) at 0 °C and extracted with EtOAc (3 × 1000 mL). The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with a 0–100% gradient of EtOAc in petroleum ether to afford 44 g (55%) of the title compound as a yellow oil.

$^1$H NMR ($CDCl_3$, 300 MHz): δ = 3.21–3.14 (m, 1 H), 2.91 (s, 3 H), 2.32 (s, 3 H), 2.24 (s, 3 H), 2.70–2.62 (m, 1 H), 1.04–0.97 (m, 1 H), 0.79–0.82 (m, 1 H).

**Methyl 1-(3-Iodophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (24)**[12]

A 1000 mL round-bottomed flask was charged with methyl 1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**22**; 10.0 g, 56.5 mmol), (3-iodophenyl)boronic acid (**23**; 15.4 g, 62.1 mmol), $Cu(OAc)_2$ (5.6 g, 31.8 mmol), pyridine (9.8 g, 124 mmol), and THF (400 mL). The reaction mixture was sparged with $O_2$ and was stirred at 50 °C under an atmospheric pressure of $O_2$ overnight. The mixture was quenched by the addition of $H_2O$ (30 mL). The quenched reaction mixture was filtered and the filtrate was extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with brine (2 × 100 mL), dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with a 0–100% gradient of EtOAc in hexanes to provide 12.1 g (57%) of the title compound as a white solid.

$^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 8.81 (dd, *J* = 4.4, 1.6 Hz, 1 H), 8.66–8.59 (m, 2 H), 8.34–8.31 (m, 1 H), 7.84–7.81 (m, 1 H), 7.59 (dd, *J* = 8.0, 4.4 Hz, 1 H), 7.43 (t, *J* = 8.0 Hz, 1 H), 4.01 (s, 3 H).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{11}IN_3O_2$: 379.98; found: 380.

**Methyl 1-(3-{[(1*R*,4*R*,5*S*)-4-Hydroxy-2-methyl-3-oxo-2-azabicyclo-[3.1.0]hexan-4-yl]ethynyl}phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (25)**[12] **CAS Number: 2193098-03-0**

A 500 mL round-bottomed flask purged with and maintained under an inert atmosphere of $N_2$ was charged with methyl 1-(3-iodophenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**24**; 5.83 g, 15.4 mmol), 4-ethynyl-4-hydroxy-2-methyl-2-azabicyclo[3.1.0]hexan-3-one [(1*R*,4*R*,5*S*)-**14**; 3.02 g, 20.0 mmol], $Pd(PPh_3)_2Cl_2$ (2.16 g, 3.1 mmol), $Et_3N$ (30 mL, 215 mmol), and DMSO (60 mL). The reaction mixture was stirred at 95 °C overnight, quenched with $H_2O$ (30 mL), and filtered. The filtrate was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (2 × 100 mL), dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with a 0–100% gradient of EtOAc in hexanes to provide 4.0 g (65%) of the title compound as a white solid.

$^1$H NMR ($CDCl_3$, 400 MHz): δ = 8.85–8.71 (m, 1 H), 8.63–8.60 (m, 1 H), 8.41 (app s, 1 H), 8.36–8.34 (m, 1 H), 7.50–7.40 (m, 3 H), 4.09 (s, 3 H), 3.21 (s, 1 H), 2.98 (s, 3 H), 2.20–2.18 (m, 1 H), 1.04–0.99 (m, 1 H), 0.98–0.84 (m, 1 H).

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{19}N_4O_4$: 403.13; found: 403.

**1-(3-{[(1*R*,4*R*,5*S*)-4-Hydroxy-2-methyl-3-oxo-2-azabicyclo-[3.1.0]hexan-4-yl]ethynyl}phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxamide (2)**[12] **CAS Number: 2193097-83-3**

A 1000 mL round-bottomed flask was charged with methyl 1-(3-{[(1*R*,4*R*,5*S*)-4-hydroxy-2-methyl-3-oxo-2-azabicyclo[3.1.0]hexan-4-yl]ethynyl}phenyl)-1*H*-pyrazolo[3,4-*b*]pyridine-3-carboxylate (**25**; 12 g, 30.0 mmol) and 4 M $NH_3$ in MeOH (400 mL). The resulting solution was stirred overnight at 40 °C and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel eluting with a 0–100% gradient of EtOAc in hexanes to provide 5.14 g (44%) of the title compound as a white solid; $[\alpha]_D^{20}$ –39.54 (*c* 1.7 mg/mL, MeOH).

$^1$H NMR (DMSO-$d_6$, 400 MHz): δ = 8.78 (dd, *J* = 4.5, 1.9 Hz, 1 H), 8.67 (dd, *J* = 8.1, 1.6 Hz, 1 H), 8.53–8.47 (m, 2 H), 8.25 (s, 1 H), 7.71 (s, 1 H), 7.69–7.59 (m, 1 H), 7.52 (dd, *J* = 8.1, 4.5 Hz, 1 H), 7.49–7.45 (m, 1 H), 6.47 (s, 1 H), 3.37–3.32 (m, 1 H), 2.82 (s, 3 H), 2.09–2.02 (m, 1 H), 0.90–0.82 (m, 1 H), 0.68–0.61 (m, 1 H).

$^{13}$C NMR (DMSO-$d_6$, 101 MHz): δ = 170.1, 163.4, 151.1, 150.1, 139.5, 139.1, 132.7, 130.3, 130.0, 123.7, 123.1, 121.9, 120.3, 116.4, 91.2, 84.1, 71.0, 34.8, 30.0, 19.9, 14.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}N_5O_3$: 388.1404; found: 388.1414.

X-ray structure in Supporting Information.

## Funding Information

This work was supported by Genentech (a member of the Roche group).

## Acknowledgment

We are grateful to Steven Staben, J. W. Feng, Georgette Castanedo, Nicole Blaquiere, Jason Burch, Steve Do, and Lifu Lu for helpful discussions, to Mengling Wong for aid in compound purification, and to Antonio DiPasquale for crystallography.

## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707279.

## References

(1) Brightbill, H. D.; Suto, E.; Blaquiere, N.; Ramamoorthi, N.; Sujatha-Bhaskar, S.; Gogol, E. B.; Castanedo, G. M.; Jackson, B. T.; Kwon, Y. C.; Haller, S.; Lesch, J.; Bents, K.; Everett, C.; Kohli, P. B.; Linge, S.; Christian, L.; Barrett, K.; Jaochico, A.; Berezhkovskiy, L. M.; Fan, P. W.; Modrusan, Z.; Veliz, K.; Townsend, M. J.; Devoss, J.; Johnson, A. R.; Godemann, R.; Lee, W. P.; Austin, C. D.; McKenzie, B. S.; Hackney, J. A.; Crawford, J. J.; Staben, S. T.; Ismaili, M. H. A.; Wu, L. C.; Ghilardi, N. *Nat. Commun.* **2018**, *9*, 179.

(2) Sun, S.-C. *Nat. Rev. Immunol.* **2017**, *17*, 545.

(3) Hofmann, J.; Mair, F.; Greter, M.; Schmidt-Supprian, M.; Becher, B. *J. Exp. Med.* **2011**, *208*, 1917.

(4) Liao, G.; Zhang, M.; Harhaj, E. W.; Sun, S.-C. *J. Biol. Chem.* **2004**, *279*, 26243.

(5) Sun, S.-C. *Cell Res.* **2011**, *21*, 71.

(6) Senftleben, U.; Cao, Y.; Xiao, G.; Greten, F. R.; Krähn, G.; Bonizzi, G.; Chen, Y.; Hu, Y.; Fong, A.; Sun, S.-C.; Karin, M. *Science* **2001**, *293*, 1495.

(7) Castanedo, G.; Liu, Y.; Crawford, J. J.; Braun, M.-G. *J. Org. Chem.* **2016**, *81*, 8617.

(8) Li, Z.; Li, X.; Su, M.-B.; Gao, L.-X.; Zhou, Y.-B.; Yuan, B.; Lyu, X.; Yan, Z.; Hu, C.; Zhang, H.; Luo, C.; Chen, Z.; Li, J.; Zhao, Y. *J. Med. Chem.* **2020**, *63*, 4388.

(9) Blaquiere, N.; Castanedo, G. M.; Burch, J. D.; Berezhkovskiy, L. M.; Brightbill, H.; Brown, S.; Chan, C.; Chiang, P.-C.; Crawford, J. J.; Dong, T.; Fan, P.; Feng, J.; Ghilardi, N.; Godemann, R.; Gogol, E.; Grabbe, A.; Hole, A. J.; Hu, B.; Hymowitz, S. G.; Ismaili, M. H.

A.; Le, H.; Lee, P.; Lee, W.; Lin, X.; Liu, N.; McEwan, P. A.; McKenzie, B.; Silvestre, H. L.; Suto, E.; Sujatha-Bhaskar, S.; Wu, G.; Wu, L. C.; Zhang, Y.; Zhang, Z.; Staben, S. T. *J. Med. Chem.* **2018**, *61*, 6801.

(10) Blaquiere, N.; Burch, J.; Castanedo, G.; Feng, J. A.; Hu, B.; Staben, S.; Wu, G.; Yuen, P.-w. PCT Int. Appl WO 2015/025025 A1, **2015**.

(11) Blaquiere, N.; Castanedo, G.; Feng, J. A.; Crawford, J. J.; Lee, W.; Lin, X.; Hu, B.; Wu, G. PCT Int. Appl WO 2016/135163 A1, **2016**.

(12) Crawford, J. J.; Kolesnikov, A.; Feng, J. A. PCT Int. Appl WO 2018/037059 A1, **2018**.

(13) Camici, L.; Dembech, P.; Ricci, A.; Seconi, G.; Taddei, M. *Tetrahedron* **1988**, *44*, 4197.

(14) Hamann, L. G.; Khanna, A.; Kirby, M. S.; Magnin, D. R.; Simpkins, L. M.; Sutton, J. C.; Robl, J. PCT Int. Appl WO 2005/012249 A2, **2005**.

(15) Dembech, P.; Ricci, A.; Seconi, G.; Taddei, M. *Org. Synth.* **1997**, *74*, 84.

(16) Pedroni, J.; Cramer, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 11826.

(17) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135.

(18) Jerhaoui, S.; Chahdoura, F.; Rose, C.; Djukic, J.-P.; Wencel-Delord, J.; Colobert, F. *Chem. Eur. J.* **2016**, *22*, 17397.

(19) Minami, T.; Fukuda, K.; Hoshiya, N.; Fukuda, H.; Watanabe, M.; Shuto, S. *Org. Lett.* **2019**, *21*, 656.

(20) (a) Caro-Diaz, E. J. E.; Urbano, M.; Buzard, D. J.; Jones, R. M. *Biorg. Med. Chem. Lett.* **2016**, *26*, 5378. (b) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J.-Q. *Chem. Rev.* **2017**, *117*, 8754.

(21) (a) Meyers, A. I.; Sturgess, M. A. *Tetrahedron Lett.* **1988**, *29*, 5339. (b) Forns, P.; Fernández, M.; Diez, A.; Rubiralta, M.; Cherrier, M. P.; Bonin, M.; Quirion, J.-C. *Synthesis* **1999**, 258.

(22) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978.