JOC The Journal of Organic Chemistry

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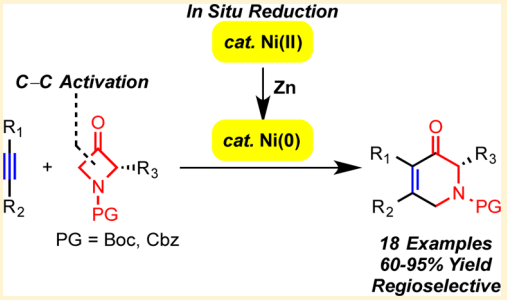
An *in Situ* Approach to Nickel-Catalyzed Cycloaddition of Alkynes and 3-Azetidinones

Ashish Thakur,[‡] Judah L. Evangelista, Puneet Kumar,[§] and Janis Louie*

Department of Chemistry, University of Utah, 315 South, 1400 East, Salt Lake City, Utah 84112-0850, United States

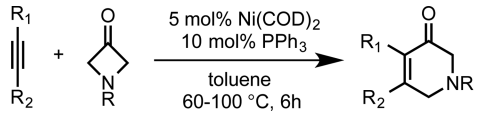
Supporting Information

ABSTRACT: An efficient and convenient procedure that generates the active Ni(0) catalyst *in situ* from cheap, air stable Ni(II) precursors is developed for the [4 + 2]-cycloaddition of alkynes and 3-azetidinones. The reaction affords useful 3-dehydropiperidinones in comparable yields to the reported Ni(0) procedure. Additionally, the cycloaddition with 3-oxetanone afforded the 3-dehydropyranone product. Chiral 2-substituted azetidinones were also tolerated to form substituted dehydropiperidinones in high yield and enantiomeric excess.



INTRODUCTION

A major focus of our research laboratory is to develop Ni-catalyzed cycloaddition reactions for the synthesis of carbocycles and heterocycles. For over a decade, we have developed a variety of Ni(0)-catalysts to activate C = X π-bonds (X = C, O, N) in cycloaddition with unsaturated hydrocarbons to afford pyrones,[1] pyridones,[1] pyrimidine-dione,[1] pyridines,[1] aminopyridines,[1] cyclopentenes,[2] pyrans,[1b,3] cyclohexadienone,s[1,4a] and cycloheptadienones.[1,4b] Recently, we and others independently extended this concept to activate challenging C−C σ-bond in 3-azetidinones via a $Ni(COD)_2/PPh_3$-catalyzed cycloaddition of alkynes and 3-azetidinones (eq 1).[5]



(1)

This interesting reaction provides a unique and single step access to synthetically important 3-dehydropiperidinone cores that are challenging to synthesize via conventional methods.[6] Despite the use of relatively mild conditions in this methodology, one major drawback is the use of air and temperature-sensitive $Ni(COD)_2$ which necessitates the use of a glovebox or complicated Schlenk techniques. Furthermore, $Ni(COD)_2$ is an expensive Ni(0) source and therefore limits its use for large-scale reactions. In order to make this chemistry synthetically more convenient and applicable, we developed the use of air-stable, less expensive, and readily available precursors that generate the active Ni/PPh_3 catalyst *in situ*. Herein, we report our results.

RESULTS AND DISCUSSION

The nickel-catalyzed cycloaddition was investigated using commercially available 4-octyne **1a** and 1-Boc-3-azetidinone **2a** as model substrates (Table 1, eq 2). Gratifyingly, the use of $Ni(acac)_2$ (acac = acetylacetonate) as Ni(II) source with PPh_3 ligand and *n*-BuLi as reductant led to excellent conversion of 3-azetidinone to afford the desired cycloadduct **3aa** in 92% isolated yield (entry 1, Table 1).[7a−c] Substitution of *n*-BuLi by a milder reductant such as Zn, however, gave poor conversions of 3-azetidinone (entry 2, Table 1). We also evaluated the commercially available bis(triphenylphosphine)Ni(II) salts[7c−h] in conjunction with Zn, to promote this cycloaddition. However, poor GC conversions were obtained when these salts were used in toluene presumably due to the insolubility of the Ni(II) salts in toluene (entries 3−5, Table 1). Interestingly, the replacement of toluene with a polar solvent such as acetonitrile afforded excellent conversions and isolated yields of cycloadduct **3aa** (entries 6−7, Table 1). Further optimizations led to these final conditions: 5 mol % $Ni(PPh_3)_2Cl_2$, 20 mol % Zn, acetonitrile, 60−80 °C, 16−24 h.

These optimized reactions were applied to the cycloaddition of 3-azetidinone with a variety of alkynes (Scheme 1). Several yields obtained from our previously reported $Ni(COD)_2/PPh_3$ catalytic system are also shown in parentheses for comparison.[5a] The cycloaddition of 4-octyne with 3-azetidinone afforded the heterocyclic product **3aa** in 95% yield. The sterically biased terminal alkyne **1b** was regioselectively coupled to form cycloadduct **3ba** in which the bulky *t*-butyl group was placed at the β-position. The reaction also tolerates diaryl alkyne such as diphenylacetylene to form the substituted 3-dehydropiperidinone **3ca** in good yield. Although the cycloadducts **3ba** and **3ca** were obtained in slightly lower yields (60% and 72%, respectively) when compared to our reported Ni(0) procedure[5a] (71% and 79%, respectively), the *in situ* procedure only requires half the equivalents of alkyne (i.e., 1.5

Received: June 26, 2015

DOI: 10.1021/acs.joc.5b01458
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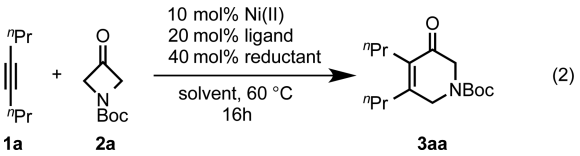
Table 1. *In Situ* Ni-Catalyzed Cycloaddition of 4-Octyne with 1-Boc-3-azetidinone[a]

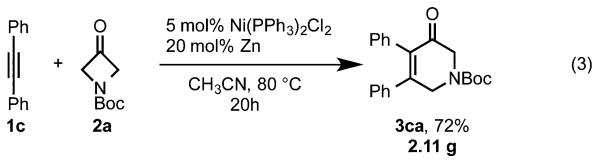


entry	Ni(II)	ligand	reductant	solvent	conv. (%)[b]	yield (%)[c]
1	$Ni(acac)_2$	PPh_3	*n*-BuLi	toluene	>99	92
2	$Ni(acac)_2$	PPh_3	Zn	acetonitrile	37	–
3	$Ni(PPh_3)_2Cl_2$	–	Zn	toluene	6	trace
4	$Ni(PPh_3)_2Br_2$	–	Zn	toluene	62	n.d.[d]
5	$Ni(PPh_{3)2}I_2$	–	Zn	toluene	16	trace
6	$Ni(PPh_3)_2Cl_2$	–	Zn	acetonitrile	>99	**95**
7	$Ni(PPh_3)_2Br_2$	–	Zn	acetonitrile	>99	**95**
8	$Ni(PPh_3)_2I_2$	–	Zn	acetonitrile	15	trace

[a]Reaction Conditions: 4-octyne **1a** (1.5 equiv), 1-Boc-3-azetidinone **2a** (1 equiv, 0.2 M), 10 mol % Ni(II), 20 mol % ligand, 40 mol % reductant, 60 °C, 16 h. [b]Determined by GC using naphathalene as an internal standard. [c]Isolated yield of the product. [d]n.d. = not determined.

equiv as compared to 3 equiv in Ni(0) procedure) without the slow addition of alkyne for 2 h and lower reaction temperature (80 °C vs 100 °C). Interestingly, the use of mixed aryl-alkyl alkynes led to the regioselective formation of the cycloadducts (**3da**−**3la**) in which the alkyl group remains next to the carbonyl group. Importantly, the cycloadducts **3da** and **3ea** were formed in better yields (86% and 87%, respectively) than our reported Ni(0) protocol (81% and 74%, respectively). This methodology also tolerates a stannyl-substituted alkyne to regioselectively form the heterocycle **3fa**, suggesting that the aryl group, rather than the sterically bulky stannyl group, governs the regioselectivity. Aryl-silyl alkynes were also coupled to form 3-dehydropiperidinone products (**1ga**−**1ia**) in excellent regioselectivity and high yields. Interestingly, the aryl-silyl alkyne bearing electron-withdrawing group (−CF_3) on the phenyl ring afforded lower yield than the alkyne-containing phenyl with an electron-donating group (−OMe) (**3ha** vs **3ia**). The challenging heteroaryl-silyl alkynes were also successfully coupled to form furanyl- and thiophenyl-substituted dehydropiperidinones **3ja** and **3ka**, in good yields. Importantly, in all of the above cycloaddition reactions involving the use of mixed aryl-alkyl alkynes, stannyl-aryl alkynes and aryl/heteroaryl-silyl alkynes with 3-azetidinone, the *in situ* procedure only requires 1.5 equiv of alkyne without the need of slow addition of alkyne and lower reaction temperature than the conditions used in our previously reported Ni(0) procedure.[5a] The growing interest in macrocyclic heterocycles[8] prompted us to investigate the macrocyclic alkyne **1l** in this cycloaddition. Gratifyingly, the cycloaddition underwent smoothly to regioselectively afford the desired macrocyclic 3-dehydropiperidone **3la** in good yield.

Importantly, this methodology is scalable and was successfully applied to gram-scale quantities of 3-azetdinone and diphenylacetylene to afford cycloadduct **3ca** in 72% yield (eq 3).



Unfortunately, terminal alkynes (e.g., phenylacetylene, 1-hexyne, and 1-octyne) did not afford dehydropiperidinone product due to their rapid oligomerization under the reaction conditions. Alkynes bearing boron-functional groups (Figure 1) also failed to participate in this cycloaddition and were either completely decomposed or recovered with partial decomposition under the reaction conditions.

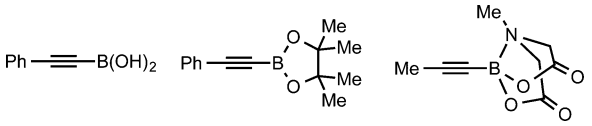
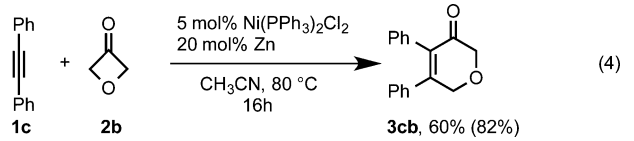


Figure 1. Attempted substrates in Ni-catalyzed cycloaddition.

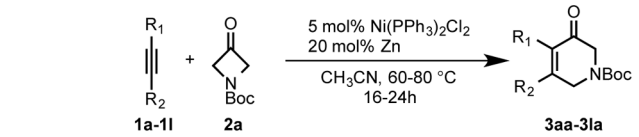
The cycloaddition of 3-oxetanaone with diphenylacetylene afforded the substituted 3-dehydropyranone product **3cb**, albeit in lower yield than the reported Ni(0)-protocol (eq 4).[5b]

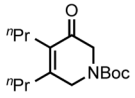
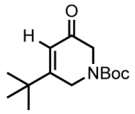
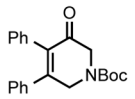
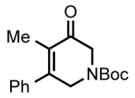
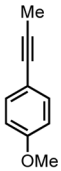
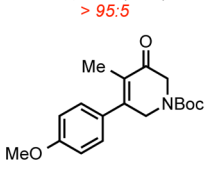
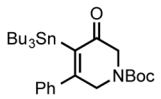
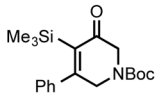
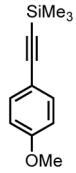
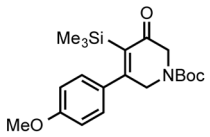
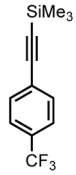
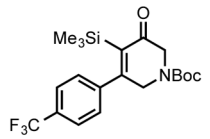
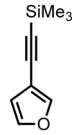
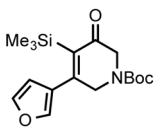
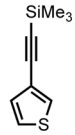
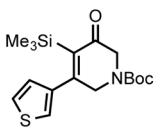
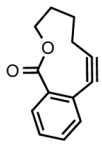
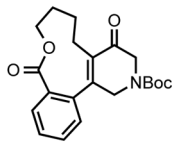


We next investigated the Ni-catalyzed cycloaddition of 2-substituted-3-azetdinones with alkynes (Table 2). The chiral 2-substituted azetidinones (**2c**−**2f**) were synthesized from the corresponding amino acids using Seebach's procedure.[9] The potential challenges associated with the use of chiral azetidinones in this reaction involve the possibility of racemization of both the chiral azetidinone and chiral 3-dehydropiperidinone product due to the presence of Lewis acidic Ni(II)-precatalyst and $ZnCl_2$ that is formed within the reaction. Despite these challenges, the cycloaddition works effectively to afford enantio-enriched cycloadducts in high yields (Table 2). The yields and enantiomeric excess (ee) obtained by previously reported $Ni(COD)_2/PPh_3$ catalytic system are also shown in parentheses for comparison.[5a,c] The cycloaddition of alanine-derived azetidinone **2c** with 4-octyne led to the regioselective formation of the cycloadduct **3ac**, which suggests the selective insertion of alkyne into the unsubstituted $C(sp^2)-C(sp^3)$ σ-bond of 3-azetidinone. The dehydropiperidinone product **3ac** retained 98% ee, which was slightly less than the reported Ni(0) method. Similarly, the Boc-protected azetidinone **2d** and Cbz-protected azetidinone **2e** afforded regioselective dehydropiperidinones **3ad** and **3ae** in

DOI: 10.1021/acs.joc.5b01458
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. *In Situ* Ni-Catalyzed Cycloaddition of Alkynes and 3-Azetidinone



Entry	Alkyne	Product, Yield (%)[a,b,c]
1	 **1a**	 **3aa**, 95% (97%)
2	 **1b**	 **3ba**, 60% (71%) > 95:5
3	 **1c**	 **3ca**, 72% (79%)
4	 **1d**	 **3da**, 86% (81%) > 95:5
5	 **1e**	 **3ea**, 87% (74%) > 95:5
6	 **1f**	 **3fa**, 73% (83%) > 95:5
7	 **1g**	 **3ga**, 75% (82%) > 95:5
8	 **1h**	 **3ha**, 74% > 95:5
9	 **1i**	 **3ia**, 51% > 95:5
10	 **1j**	 **3ja**, 74% (82%) > 95:5
11	 **1k**	 **3ka**, 73% (80%) > 95:5
12	 **1l**	 **3la**, 55% > 95:5

[a]Reaction conditions: 1-Boc-3-azetdidinone (1.0 equiv, 0.2 M) alkyne (1.5 equiv), 5 mol % $Ni(PPh_3)_2Cl_2$, 20 mol % Zn, 60−80 °C, 16−24 h. [b]Isolated yield (in parentheses) obtained using reported Ni(0) procedure. [c]Regioselectivty (in red) was calculated by ^1H NMR of crude reaction mixture.

high yields with 93% and 97% ee, respectively. Diaryl alkyne **1m** was also coupled with azetidinones **2e** and **2f** to form regioselective cycloadducts **3me** and **3mf** in high yields and high enantioretention.

CONCLUSION

In summary, we have developed an efficient and convenient procedure that can generate the active Ni(0) catalyst *in situ* to catalyze the cycloaddition of alkynes and 3-azetidinones. The reaction affords useful six-membered heterocycles in comparable yields to the reported Ni(0) procedures using fewer equivalents of alkyne and without the need of slow addition of alkyne. Additionally, enantiopure 2-substituted azetidinones were also coupled to form substituted dehydropiperidinones in high yields and high enantioretention. Efforts to utilize this methodology toward the synthesis of alkaloid natural products are underway in our laboratory.

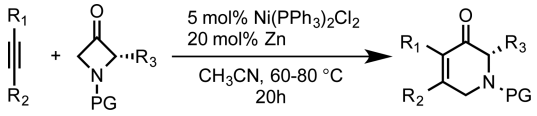
EXPERIMENTAL SECTION

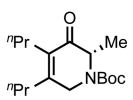
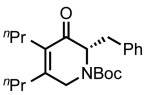
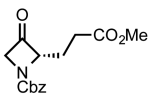
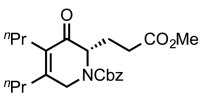
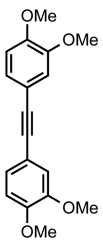
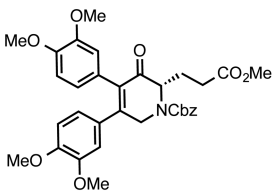
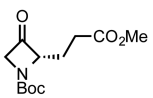
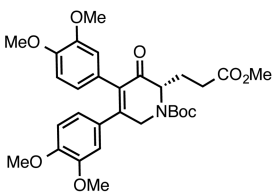
General. All reactions were conducted under an atmosphere of N_2. Toluene and acetonitrile were dried over neutral alumina under N_2 using a Grubbs type solvent purification system. The alkynes **1l**,[10a] **1m**,[10b] *tert*-butyl (*S*)-2-methyl-3-oxoazetidine-1-carboxylate **2c**,[5c] and *tert*-butyl (*S*)-2-benzyl-3-oxoazetidine-1-carboxylate **2d**[5a] were prepared according to literature procedure. All other reagents were purchased from commercial suppliers and used without further purification unless otherwise noted.

^1H and ^{13}C nuclear magnetic resonance (NMR) spectra of pure compounds were acquired at 400 and 100 MHz or 500 and 125 MHz, respectively, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^1H and to the central line of a triplet at 77.23

DOI: 10.1021/acs.joc.5b01458
J. Org. Chem. XXXX, XXX, XXX−XXX

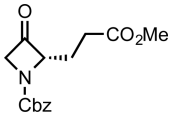
Table 2. *In Situ* Ni-Catalyzed Cycloaddition of Alkynes with 2-Substituted-3-Azetidinones[a]



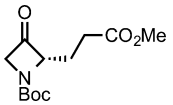
Entry	Alkyne	Azetidinone	Product[b]
1	 **1a**	 **2c**	 **3ac**, 87%, 98% ee (73%, >99% ee)
2	**1a**	 **2d**	 **3ad**, 85%, 93% ee (84-88%,97->99% ee)
3	**1a**	 **2e**	 **3ae**, 86%, 97% ee
4	 **1m**	**2e**	 **3me**, 83%, 97% ee
5	**1m**	 **2f**	 **3mf**, 88%, 95% ee

[a]Reaction conditions: Azetdidinone (1.0 equiv, 0.1 M), alkyne (1.5 equiv), 5 mol % $Ni(PPh_3)_2Cl_2$, 20 mol % Zn, 60−80 °C, 16−24 h. [b]Isolated yield.

ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, td, tq, q, qt, quint, sext, sept, septd, septt, m, brm, brd, brt, and brs stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, triplet of doublets, triplet of quartets, quartet, quartet of triplets, quintet, sextet, septet, septet of doublets, septet of triplets, multiplet, broad multiplet, broad doublet, broad triplet, and broad singlet, in that order. All ^{13}C NMR spectra were proton decoupled.



Synthesis of Chiral 2-Substituted-3-Azetidinones. *Benzyl (S)-2-(3-Methoxy-3-oxopropyl)-3-oxoazetidine-1-carboxylate (**2e**).* Azetidinone **2e** was also prepared according to Seebach's procedure.[9] To a solution of Cbz-Glu(OMe)-OH[11a] (2.73 g, 9.24 mmol) in THF (45 mL) under N_2 atmosphere, dry NEt_3 (1.35 mL, 9.71 mmol) and $ClCO_2Et$ (1.05 g, 9.71 mmol) were added at −15 °C. The suspension was allowed to warm to 0 °C. CH_2N_2 (23.10 mmol) in Et_2O was slowly added in portions over a period of 2h and allowed to warm to rt. The mixture was stirred for an additional 5 h. The reaction was quenched by the addition of water, extracted three times with EtOAc, washed with brine, and dried over $MgSO_4$. Purification by flash chromatography on silica gel using 35−45% EtOAc/hexanes, afforded the pure diazo ketone (2.14 g, 6.7 mmol, 73%). Under N_2 atmosphere, the diazo ketone was dissolved in CH_2Cl_2 (33 mL), and dry NEt_3 (10 μL, 0.07 mmol) was added. After cooling to 0 °C, $Rh_2(OAc)_4$ (14.8 mg, 0.03 mmol, 0.5 mol %) was added, and the mixture was stirred for 14 h. After that, water was added, extracted with CH_2Cl_2, washed with water, and brine dried over $MgSO_4$. The remaining residue was purified by silica gel flash column chromatography using 40−50% ether in hexanes (R_f = 0.29 in 50% ether/hexanes) to afford the title compound **2e** (1.13 g, 3.88 mmol, 58%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (m, 5H), 5.17 (s, 2H), 5.06 (m, 1H), 4.79 (d, *J* = 16.4 Hz, 1H), 4.61 (dd, *J* = 4.4, 16.4 Hz, 1H), 3.65 (s, 3H), 2.44−2.59 (m, 2H), 2.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 199.0, 172.9, 157.0, 136.1, 128.8, 128.6, 128.4, 82.4, 69.7, 67.9, 51.9, 29.5, 25.6. IR (CH_2Cl_2, cm^{-1}): 2953, 1822, 1733, 1711, 1437, 1403, 1344, 1253, 1119, 1123, 1059, 1026, 745, 699. HRMS (ESI-TOF) calcd for $C_{15}H_{17}NO_5Na$ $[M + Na]^+$ 314.1004, found 314.1006.



*tert-Butyl (S)-2-(3-Methoxy-3-oxopropyl)-3-oxoazetidine-1-carboxylate (**2f**).* Azetidinone **2d** was prepared according to Seebach's procedue.[9] To a solution of Boc-Glu(OMe)-OH[11b] (2.10 g, 8.04 mmol) in THF (40 mL) under N_2 atmosphere, dry NEt_3 (1.2 mL, 8.44 mmol) and $ClCO_2Et$ (0.92 g, 8.44 mmol) were added at −15 °C. The suspension was allowed to warm to 0 °C. CH_2N_2 (21.10 mmol) in Et_2O was slowly added in portions over a period of 2 h and allowed to warm to rt. The mixture was stirred for an additional 5 h. The reaction was quenched by the addition of water, extracted three times with EtOAc, washed with brine, and dried over $MgSO_4$. Purification by flash chromatography on silica gel using 30−35% EtOAc/hexanes, afforded the pure diazo ketone (2.03 g, 7.1 mmol, 88%). Under N_2 atmosphere, the diazo ketone was dissolved in CH_2Cl_2 (35 mL) and dry NEt_3 (10 μL, 0.07 mmol) was added. After cooling to 0 °C, $Rh_2(OAc)_4$ (15.5 mg, 0.04 mmol, 0.5 mol %) was added, and the mixture was stirred for 14 h. After that, water was added, extracted with CH_2Cl_2, washed with water and brine dried over $MgSO_4$. The remaining residue was purified by silica gel flash column chromatography using 30−40% ether in hexanes (R_f = 0.32 in 40% ether/hexanes) to afford the title compound **2f** (0.96 g, 3.73 mmol, 53%). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.95 (td, *J* = 4.8, 6.8 Hz, 1H), 4.71 (d, *J* = 16.8 Hz, 1H), 4.52 (dd, *J* = 4.4, 16.8 Hz, 1H), 3.68 (s, 3H), 2.51 (qd, *J* = 8.0, 16.4, 2H), 2.15 (m, 2H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 200.0, 173.1, 156.6, 82.0, 81.3, 69.4, 51.9, 29.6, 28.4, 25.8. IR (CH_2Cl_2, cm^{-1}): 2978, 2932, 1822, 1738, 1704, 1437, 1367, 1176, 1132, 1060, 1021, 862, 776. HRMS (ESI-TOF) calcd for $C_{12}H_{19}NO_5Na$ $[M + Na]^+$ 280.1161, found 280.1167.

General Procedure "G1" for Cycloaddition. To an oven-dried Schlenk tube containing a stirring bar was added 5 mol % $Ni(PPh_3)_2Cl_2$, 20 mol % activated Zn powder, 3-azetdinone (1 equiv), and alkyne [(1.5 equiv), if solid at room temperature]. This Schlenk tube containing all the solid compounds was then evacuated followed by refilling with N_2 at room temperature (this process was repeated two times). Dry acetonitrile (0.2 M, based on 3-azetidinone) and alkyne [(1.5 equiv), if oil at room temperature] were added via syringe through the rubber septum, under a flow of nitrogen. The Schlenk tube was sealed, stirred at 60−80 °C for indicated period of time, and then opened to air. The remaining residue was filtered through a short pad of Celite, concentrated *in vacuo*, and purified by silica gel flash column chromatography.

General Procedure "G2" for Cycloaddition. To an oven-dried Schlenk tube containing a stirring bar was added 5 mol % $Ni(PPh_3)_2Cl_2$, 20 mol % activated Zn powder, and alkyne [(1.5 equiv), if solid at room temperature]. This Schlenk tube containing all the solid compounds was then evacuated followed by refilling with N_2 at room temperature (this process was repeated two times). Dry

DOI: 10.1021/acs.joc.5b01458
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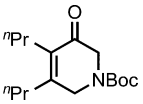
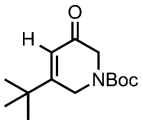
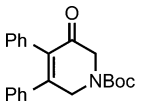
acetonitrile (0.2 M, based on 3-azetidinone) and alkyne [(1.5 equiv), if oil at room temperature] were added via syringe through the rubber septum, under a flow of nitrogen. The reaction mixture was stirred under nitrogen for 20 min followed by the addition of 3-azetidinone (1 equiv, 0.2 M) or 3-oxetanone (1 equiv, 0.2 M) in dry acetonitrile. The Schlenk tube was sealed, stirred at 60−80 °C for indicated period of time, and then opened to air. The remaining residue was filtered through a short pad of Celite, concentrated *in vacuo*, and purified by silica gel flash column chromatography.



*tert-Butyl 3-oxo-4,5-Dipropyl-3,6-dihydropyridine-1(2H)-carboxylate (**3aa**).* The general procedure G1 was used with 118.7 mg (0.69 mmol, 0.2 M) of 3-azetidinone **2a**, 114.6 mg (1.04 mmol) of 4-octyne **1a**, 22.7 mg (0.04 mmol) of $Ni(PPh_3)_2Cl_2$, and 9.1 mg (0.14 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 60 °C for 16 h. The remaining residue was purified by silica gel flash column chromatography using 25% ether in hexanes (R_f = 0.24) to afford the title compound **3aa** (186.1 mg, 0.66 mmol, 95%) as colorless oil. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5a]

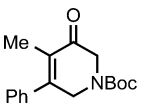


*tert-Butyl 5-(tert-Butyl)-3-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**3ba**).* The general procedure G1 was used with 117.5 mg (0.69 mmol, 0.2 M) of 3-azetidinone **2a**, 84.6 mg (1.03 mmol) of *t*-butylacetylene **1b**, 22.6 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$, and 9.0 mg (0.14 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 16 h. The remaining residue was purified by silica gel flash column chromatography using 15−25% ether in hexanes (R_f = 0.27 in 25% ether/hexanes) to afford the title compound **3ba** (104.5 mg, 0.41 mmol, 60%) as colorless oil. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5a]

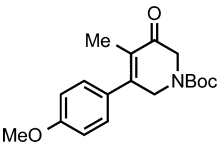


*tert-Butyl 5-oxo-3,4-Diphenyl-5,6-dihydropyridine-1(2H)-carboxylate (**3ca**).* The general procedure G1 was used with 130.3 mg (0.76 mmol, 0.2 M) of 3-azetidinone **2a**, 203.4 mg (1.14 mmol) of diphenylacetylene **1c**, 24.9 mg (0.04 mmol) of $Ni(PPh_3)_2Cl_2$, and 7.5 mg (0.12 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 15−20% ethyl acetate in hexanes (R_f = 0.3 in 20% EtOAc/hexanes) to afford the title compound **3ca** (191.0 mg, 0.55 mmol, 72%) as pale oil. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5a]

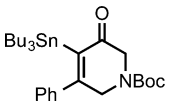
Gram Scale Reaction. The general procedure G1 was used with 1.43 g (8.35 mmol, 0.2 M) of 3-azetidinone **2a**, 2.23 g (12.5 mmol) of diphenylacetylene **1c**, 273.1 mg (0.42 mmol) of $Ni(PPh_3)_2Cl_2$, and 109.2 mg (1.67 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 15−20% ethyl acetate in hexanes (R_f = 0.3 in 20% EtOAc/hexanes) to afford the title compound **3ca** (2.11 g, 6.0 mmol, 72%) as pale oil. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5a]



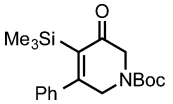
*tert-Butyl 4-Methyl-5-oxo-3-phenyl-5,6-dihydropyridine-1(2H)-carboxylate (**3da**).* The general procedure G1 was used with 100.5 mg (0.59 mmol, 0.2 M) of 3-azetidinone **2a**, 102.2 mg (0.88 mmol) of phenyl-methyl alkyne **1d**, 19.3 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$, and 7.7 mg (0.12 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 25% ether in hexanes (R_f = 0.20) to afford the title compound **3da** (147.0 mg, 0.51 mmol, 86%) as colorless oil. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5a]



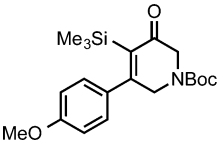
*tert-Butyl 3-(4-Methoxyphenyl)-4-methyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**3ea**).* The general procedure G1 was used with 105.0 mg (0.61 mmol, 0.2 M) of 3-azetidinone **2a**, 134.5 mg (0.92 mmol) of *p*-methoxyphenyl-methyl alkyne **1e**, 20.1 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$, and 8.0 mg (0.12 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 30% ether in hexanes (R_f = 0.20) to afford the title compound **3ea** (170.0 mg, 0.54 mmol, 87%) as colorless oil. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5a]



*tert-Butyl 5-oxo-4-Phenyl-3-(tributylstannyl)-5,6-dihydropyridine-1(2H)-carboxylate (**3fa**).* The general procedure G1 was used with 79.5 mg (0.46 mmol, 0.2 M) of 3-azetidinone **2a**, 272.5 mg (0.70 mmol) of tributyltin-phenyl alkyne **1f**, 15.3 mg (0.02 mmol) of $Ni(PPh_3)_2Cl_2$, and 6.1 mg (0.09 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 15% ether in hexanes (R_f = 0.29) to afford the title compound **3fa** (190.0 mg, 0.34 mmol, 73%) as yellow oil. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5a]



*tert-Butyl 5-oxo-3-Phenyl-4-(trimethylsilyl)-5,6-dihydropyridine-1(2H)-carboxylate (**3ga**).* The general procedure G1 was used with 121.6 mg (0.71 mmol, 0.2 M) of 3-azetidinone **2a**, 185.7 mg (1.07 mmol) of phenyl-trimethylsilyl alkyne **1g**, 23.2 mg (0.04 mmol) of $Ni(PPh_3)_2Cl_2$, and 9.3 mg (0.14 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 15−20% ether in hexanes (R_f = 0.26 in 20% ether/hexanes) to afford the title compound **3ga** (184.8 mg, 0.53 mmol, 75%) as pale oil. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5a]



*tert-Butyl 5-(4-Methoxyphenyl)-3-oxo-4-(trimethylsilyl)-3,6-dihydropyridine-1(2H)-carboxylate (**3ha**).* The general procedure G1 was used with 99.0 mg (0.58 mmol, 0.2 M) of 3-azetidinone **2a**, 177.3 mg (0.87 mmol) of (*p*-methoxy)phenyl-trimethylsilyl alkyne **1h**, 19.0 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$, and 7.6 mg (0.12 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 25−30% ether in hexanes (R_f = 0.30 in 30% ether/hexanes) to afford the title compound **3ha** (161.1 mg, 0.43 mmol, 74%) as yellow oil.

DOI: 10.1021/acs.joc.5b01458
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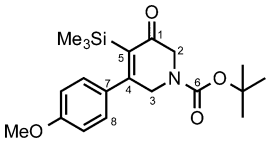
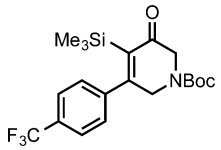
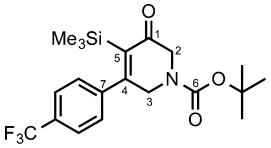


^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.20 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.29 (s, 2H), 4.05 (s, 2H), 3.82 (s, 3H), 1.48 (s, 9H), 0.11 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.4, 161.0, 154.5, 131.74, 131.66, 129.8, 114.0, 113.9, 81.0, 55.5, 51.8, 49.0, 28.6, 0.7. IR (CH_2Cl_2, cm^{-1}): 2977, 1699, 1665, 1607, 1509, 1458, 1413, 1248, 1160, 1110, 1031, 843, 766, 736. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{29}NO_4SiNa$ $[M + Na]^+$ 398.1764, found 398.1760.

Key g-HMBC correlations: The following cross-peaks were observed: H(2) and C(1); H(2) and C(6); H(3) and C(6); H(3) and C(4); H(3) and C(5); H(3) and C(7); H(8) and C(7); H(8) and C(4).

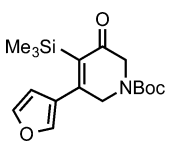


*tert-Butyl 3-oxo-5-(4-(Trifluoromethyl)phenyl)-4-(trimethylsilyl)-3,6-dihydropyridine-1(2H)-carboxylate (**3ia**).* The general procedure G1 was used with 122.0 mg (0.71 mmol, 0.2 M) of 3-azetidinone **2a**, 259.0 mg (1.07 mmol) of (*p*-trifluoromethyl)phenyl-trimethylsilyl alkyne **1i**, 23.3 mg (0.04 mmol) of $Ni(PPh_3)_2Cl_2$, and 9.3 mg (0.14 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 20% ether in hexanes (R_f = 0.29) to afford the title compound **3ia** (151.0 mg, 0.36 mmol, 51%) as colorless oil.

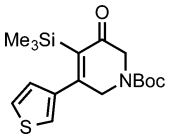


^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.67 (d, J = 7.6 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 4.28 (s, 2H), 4.09 (s, 2H), 1.48 (s, 9H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 197.7, 154.4, 143.1, 138.8, 131.6 (q, J = 33.0 Hz), 128.5, 125.7 (q, J = 4.0 Hz), 124.0 (q, J = 270 Hz), 81.3, 51.7, 49.0, 28.5, 0.5. IR (CH_2Cl_2, cm^{-1}): 2979, 1701 1670, 1588, 1405, 1368, 1324, 1248, 1164, 1128, 1109, 1069, 1016, 938, 843, 766. HRMS (ESI-TOF) m/z calcd for $C_{20}H_{26}F_3NO_3SiNa$ $[M + Na]^+$ 436.1532, found 436.1540.

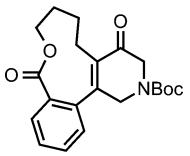
Key g-HMBC correlations: The following cross-peaks were observed: H(2) and C(1); H(2) and C(6); H(3) and C(6); H(3) and C(4); H(3) and C(5); H(3) and C(7); H(8) and C(7); H(8) and C(4).



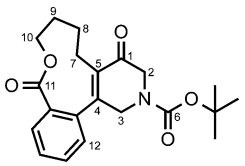
*tert-Butyl 3-(Furan-3-yl)-5-oxo-4-(trimethylsilyl)-5,6-dihydropyridine-1(2H)-carboxylate (**3ja**).* The general procedure G1 was used with 86.5 mg (0.51 mmol, 0.2 M) of 3-azetidinone **2a**, 124.5 mg (0.76 mmol) of furanyl-trimethylsilyl alkyne **1j**, 16.7 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$, and 6.7 mg (0.10 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 24 h. The remaining residue was purified by silica gel flash column chromatography using 10−20% ether in hexanes (R_f = 0.27 in 20% ether/hexanes) to afford the title compound **3ja** (126.8 mg, 0.38 mmol, 75%) as yellow oil. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5a]



*tert-Butyl-5-oxo-3-(Thiophen-3-yl)-4-(trimethylsilyl)-5,6-dihydropyridine-1(2H)-carboxylate (**3ka**).* The general procedure G1 was used with 101.0 mg (0.59 mmol, 0.2 M) of 3-azetidinone **2a**, 158.7 mg (0.88 mmol) of thiophenyl-trimethylsilyl alkyne **1k**, 19.3 mg (0.03 mmol) of $Ni(PPh_3)_2Cl_2$, and 7.7 mg (0.12 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 24 h. The remaining residue was purified by silica gel flash column chromatography using 10−20% ether in hexanes (R_f = 0.27 in 20% ether/hexanes) to afford the title compound **3ka** (150.8 mg, 0.43 mmol, 73%) as pale oil. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5a]

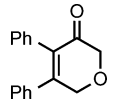


*tert-Butyl 4,10-dioxo-4,5,6,7,8,10-Hexahydro-1H-benzo[3,4]-oxecino[5,6-c]pyridine-2(3H)-carboxylate (**3la**).* The general procedure G1 was used with 55.0 mg (0.32 mmol, 0.2 M) of 3-azetidinone **2a**, 96.5 mg (0.48 mmol) of macrocyclic alkyne **1l**, 10.5 mg (0.02 mmol) of $Ni(PPh_3)_2Cl_2$, and 4.2 mg (0.06 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 30−40% ether in hexanes (R_f = 0.28 in 40% ether/hexanes) to afford the title compound **3la** (65.5 mg, 0.18 mmol, 55%) as colorless oil.

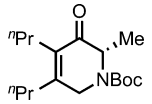


^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.96 (d, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.21 (brs, 1H), 4.68 (m, 1H), 4.36−4.50 (m, 3H), 4.19 (m, 1H), 4.00 (brm, 1H), 2.54 (m, 1H), 1.92−2.26 (m, 2H), 1.53−1.77 (m, 3H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.8, 167.9, 154.4, 136.9, 135.1, 132.0, 130.2, 129.8, 128.8, 128.2, 125.7, 81.2, 67.3, 52.3, 48.8, 31.8, 28.5, 25.8, 25.2. IR (CH_2Cl_2, cm^{-1}): 2973, 2917, 2849, 1700.96, 1676, 1626, 1597, 1439, 1417, 1368, 1290, 1246, 1165, 1129, 1089, 1047, 905, 764, 736. HRMS (ESI-TOF) m/z calcd for $C_{21}H_{25}NO_5Na$ $[M + Na]^+$ 394.1630, found 394.1633.

Key g-HMBC correlations: The following cross-peaks were observed: H(2) and C(1); H(2) and C(6); H(3) and C(6); H(3) and C(4); H(3) and C(5); H(3) and C(7); H(7) and C(5); H(7) and C(1); H(8) and C(5); H(10) and C(11); H(12) and C(4)



*4,5-Diphenyl-2H-pyran-3(6H)-one (**3cb**).* The general procedure G1 was used with 63.4 mg (0.88 mmol, 0.1 M) of 3-oxetanone **2b**, 235.3 mg (1.32 mmol) of diphenylacetylene **1c**, 29.0 mg (0.04 mmol) of $Ni(PPh_3)_2Cl_2$, and 11.6 mg (0.18 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 16 h. The remaining residue was purified by silica gel flash column chromatography using 30% ether in hexanes (R_f = 0.23) to afford the title compound **3cb** (132.2 mg, 0.53 mmol, 60%) as colorless gel. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5b]



DOI: 10.1021/acs.joc.5b01458
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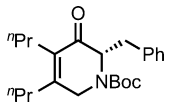
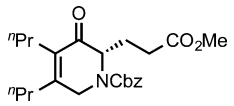
*tert-Butyl (S)-2-Methyl-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2H)-carboxylate (**3ac**).* The general procedure G1 was used with 63.2 mg (0.34 mmol, 0.2 M) of enantiopure 2-methyl-3-azetidinone **2c**, 56.4 mg (0.51 mmol) of 4-octyne **1a**, 11.2 mg (0.02 mmol) of $Ni(PPh_3)_2Cl_2$, and 4.5 mg (0.07 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 60 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 15−20% ether in hexanes (R_f = 0.28 in 20% ether/hexanes) to afford the title compound **3ac** (100.8 mg, 0.30 mmol, 87%) as colorless oil. $[\alpha]_D^{20}$ = 25.2 (c = 1.0, $CHCl_3$); (Daicel Chiralpak OZ-H Column, 3% *i*-PrOH, 25 °C, flow rate = 2 mL/min, 160 bar), Retention time: minor = 4.00 min, major = 5.47 min, ee = 98%]. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5c]

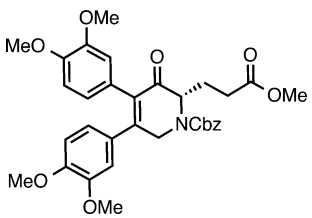


*tert-Butyl (S)-2-Benzyl-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2H)-carboxylate (**3ad**).* The general procedure G1 was used with 42.3 mg (0.16 mmol, 0.2 M) of enantiopure 2-benzyl-3-azetidinone **2d**, 26.8 mg (0.24 mmol) of 4-octyne **1a**, 5.3 mg (0.01 mmol) of $Ni(PPh_3)_2Cl_2$, and 2.1 mg (0.03 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 60 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 10−20% ether in hexanes (R_f = 0.41 in 20% ether/hexanes) to afford the title compound **3ad** (51.2 mg, 0.14 mmol, 85%) as colorless oil. $[\alpha]_D^{20}$ = −20.7 (c = 1.0, $CHCl_3$); (Daicel Chiralpak OZ-H Column, 3% *i*-PrOH, 40 °C, flow rate = 2 mL/min, 160 bar), Retention time: minor = 9.99 min, major = 15.02 min, ee = 93%]. ^{1}H NMR and ^{13}C NMR were consistent with reported data.[5a,c]



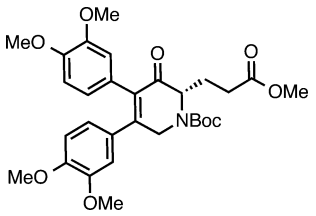
*Benzyl-(S)-2-(3-methoxy-3-oxopropyl)-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2H)-carboxylate (**3ae**).* The general procedure G1 was used with 53.3 mg (0.18 mmol, 0.2 M) of enantiopure 3-azetidinone **2e**, 30.2 mg (0.27 mmol) of 4-octyne **1a**, 6.0 mg (0.01 mmol) of $Ni(PPh_3)_2Cl_2$, and 2.4 mg (0.04 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 60 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 10−20% EtOAc in hexanes (R_f = 0.25 in 20% EtOAc/hexanes) to afford the title compound **3ae** (63.4 mg, 0.16 mmol, 86%) as colorless oil. $[\alpha]_D^{20}$ = 13.2 (c = 1.0, $CHCl_3$); (Daicel Chiralpak AY-H Column, 5−15% *i*-PrOH, 25 °C, flow rate = 2 mL/min, 160 bar), Retention time: major = 12.76 min, minor = 14.68 min, ee = 97%].

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 (brs, 5H), 5.13 (brs, 2H), 4.48−4.67 (m, 2H), 3.78−3.91 (m, 1H), 3.61 (s, 3H), 2.17−2.42 (m, 6H), 1.94 (m, 2H), 1.56 (m, 2H), 1.33 (sext, J = 7.6 Hz, 2H), 1.00 (m, 3H), 0.91 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.7, 173.2, 155.1, 153.8, 136.1, 133.0, 128.8, 128.5, 128.4, 68.0, 59.5, 51.9, 43.4, 34.2, 30.8, 26.9, 25.7, 22.7, 21.8, 14.5, 14.4. IR (CH_2Cl_2, cm^{-1}): 2959, 2872, 1734, 1700, 1668, 1635, 1559, 1498, 1424, 1384, 1230, 1176, 1157, 1108, 1015, 736, 697, 668. HRMS (ESI-TOF) m/z calcd for $C_{23}H_{31}NO_5Na$ [M + Na]$^+$ 424.2100, found 424.2095.



*Benzyl-(S)-4,5-bis(3,4-dimethoxyphenyl)-2-(3-methoxy-3-oxopropyl)-3-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**3me**).* The general procedure G1 was used with 52.7 mg (0.18 mmol, 0.2 M) of enantiopure 3-azetidinone **2e**, 81.0 mg (0.27 mmol) of alkyne **1m**, 5.9 mg (0.01 mmol) of $Ni(PPh_3)_2Cl_2$, and 2.4 mg (0.04 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 45−55% EtOAc in hexanes (R_f = 0.25 in 55% EtOAc/hexanes) to afford the title compound **3me** (89.1 mg, 0.15 mmol, 83%) as yellow oil. $[\alpha]_D^{20}$ = −106.6 (c = 1.0, $CHCl_3$); (Daicel Chiralpak OZ-H Column, 5−15−50% *i*-PrOH, 40 °C, flow rate = 30 mL/min, 200 bar), Retention time: major = 16.82 min, minor = 17.6 min, ee = 97%].

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33−7.40 (m, 5H), 6.89 (brd, J = 7.6 Hz, 1H), 6.72−6.75 (m, 2H), 6.57 (brd, J = 8.0 Hz, 1H), 6.49−6.51 (m, 2H), 5.31 (brd, J = 20.4 Hz, 1H), 5.21 (s, 2H), 4.81−4.91 (m, 1H), 4.11−4.16 (m, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H), 3.52 (brs, 3H), 2.40−2.55 (m, 2H), 2.20−2.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.1, 173.2, 155.4, 153.4, 149.9, 148.7, 148.5, 135.9, 133.3, 128.8, 128.6, 128.4, 126.9, 123.7, 121.7, 114.4, 112.7, 111.0, 110.7, 88.2, 68.2, 59.8, 56.0, 55.8, 52.0, 44.2, 30.8, 25.4. IR (CH_2Cl_2, cm^{-1}): 2916, 2849, 1734, 1700, 1684, 1653, 1559, 1539, 1463, 1456, 1251, 1171, 1144, 1027, 764, 681. HRMS (ESI-TOF) m/z calcd for $C_{33}H_{35}NO_9Na$ [M + Na]$^+$ 612.2210, found 612.2206.



*tert-Butyl-(S)-4,5-bis(3,4-dimethoxyphenyl)-2-(3-methoxy-3-oxopropyl)-3-oxo-3,6-dihydropyridine-1(2H)-carboxylate (**3mf**).* The general procedure G1 was used with 55.2 mg (0.22 mmol, 0.2 M) of enantiopure 3-azetidinone **2f**, 96.0 mg (0.32 mmol) of alkyne **1m**, 7.0 mg (0.01 mmol) of $Ni(PPh_3)_2Cl_2$, and 2.8 mg (0.04 mmol) of Zn powder in acetonitrile. The reaction mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 40−50% ethyl acetate in hexanes (R_f = 0.25 in 50% EtOAc/hexanes) to afford the title compound **3mf** (105.0 mg, 0.19 mmol, 88%) as yellow gel. $[\alpha]_D^{20}$ = −113.9 (c = 1.0, $CHCl_3$); (Daicel Chiralpak OZ-H Column, 5−15−50% *i*-PrOH, 40 °C, flow rate = 30 mL/min, 200 bar), Retention time: major = 13.71 min, minor = 15.17 min, ee = 95%].

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.87 (brm, 1H), 6.74 (d, J = 8.0 Hz, 2H), 6.59 (d, J = 8.0 Hz, 1H), 6.50 (s, 2H), 5.28 (brd, J = 20.4 Hz, 1H), 4.74 (brs, 1H), 4.05 (brd, J = 20.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.53 (s, 3H), 2.50 (m, 2H), 2.18 (m, 2H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.7, 173.3, 154.5, 153.7, 149.9, 148.7, 148.5, 133.3, 129.0, 127.1, 123.8, 121.7, 114.5, 112.8, 111.0, 110.9, 110.7, 81.6, 59.9, 56.01, 56.00, 55.8, 52.0, 43.7, 39.1, 30.9, 28.6, 25.5. IR (CH_2Cl_2, cm^{-1}): 2917, 2848, 1736, 1695, 1600, 1594, 1463, 1411, 1366, 1320, 1254, 1205, 1161, 764. HRMS (ESI-TOF) m/z calcd for $C_{30}H_{37}NO_9Na$ [M + Na]$^+$ 578.2366, found 578.2365.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01458.

Chromatograms of racemic and chiral dehydropiperidinones. ^{1}H NMR and ^{13}C NMR spectra of compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*louie@chem.utah.edu

DOI: 10.1021/acs.joc.5b01458
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Present Addresses
[‡]National Center for Advancing Translational Sciences, National Institutes of Health, Rockville, Maryland 20850, United States.
[§]Discovery Chemistry, Merck & Co. Inc., Rahway, New Jersey 07065, United States.

Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the NIH (GM076125) for financial support. We thank Dr. J. Muller of the University of Utah for providing HRMS. We thank Harsh Patel (Sigman Group) at the University of Utah for the help with the use of SFC instrument for determination of enantiomeric excess. We also thank Nabajit Lahiri from the Louie group for the synthesis of compound **3ba**.

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DOI: 10.1021/acs.joc.5b01458
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