

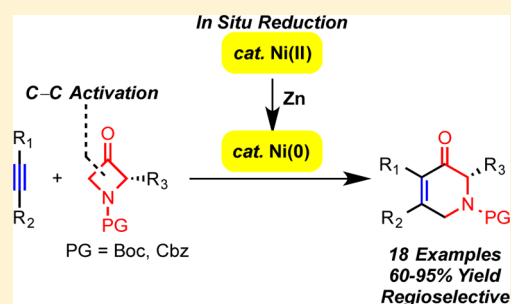
An *in Situ* Approach to Nickel-Catalyzed Cycloaddition of Alkynes and 3-Azetidinones

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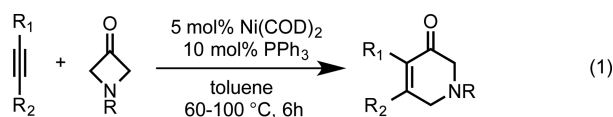
S Supporting Information

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-azetidiones. 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 azetidiones 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} cyclohexadienones,^{1,4a} and cycloheptadienones.^{1,4b} Recently, we and others independently extended this concept to activate challenging C–C σ -bond in 3-azetidiones via a Ni(COD)₂/PPh₃-catalyzed cycloaddition of alkynes and 3-azetidiones (eq 1).⁵



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/PPh₃ catalyst *in situ*. Herein, we report our results.

RESULTS AND DISCUSSION

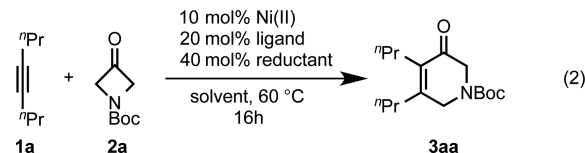
The nickel-catalyzed cycloaddition was investigated using commercially available 4-octyne **1a** and 1-Boc-3-azetidione

2a as model substrates (Table 1, eq 2). Gratifyingly, the use of Ni(acac)₂ (acac = acetylacetonate) as Ni(II) source with PPh₃ ligand and *n*-BuLi as reductant led to excellent conversion of 3-azetidione 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-azetidione (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(PPh₃)₂Cl₂, 20 mol % Zn, acetonitrile, 60–80 °C, 16–24 h.

These optimized reactions were applied to the cycloaddition of 3-azetidione with a variety of alkynes (Scheme 1). Several yields obtained from our previously reported Ni(COD)₂/PPh₃ catalytic system are also shown in parentheses for comparison.^{5a} The cycloaddition of 4-octyne with 3-azetidione 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

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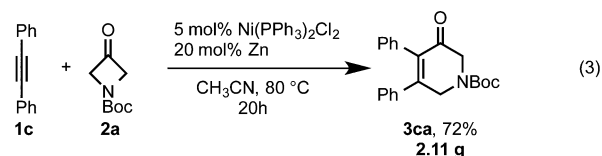
Table 1. *In Situ* Ni-Catalyzed Cycloaddition of 4-Octyne with 1-Boc-3-azetidinone^a


| entry | Ni(II) | ligand | reductant | solvent | conv. (%) ^b | yield (%) ^c |
|-------|--|------------------|----------------|--------------|------------------------|------------------------|
| 1 | Ni(acac) ₂ | PPh ₃ | <i>n</i> -BuLi | toluene | >99 | 92 |
| 2 | Ni(acac) ₂ | PPh ₃ | Zn | acetonitrile | 37 | – |
| 3 | Ni(PPh ₃) ₂ Cl ₂ | – | Zn | toluene | 6 | trace |
| 4 | Ni(PPh ₃) ₂ Br ₂ | – | Zn | toluene | 62 | n.d. ^d |
| 5 | Ni(PPh ₃) ₂ I ₂ | – | Zn | toluene | 16 | trace |
| 6 | Ni(PPh ₃) ₂ Cl ₂ | – | Zn | acetonitrile | >99 | 95 |
| 7 | Ni(PPh ₃) ₂ Br ₂ | – | Zn | acetonitrile | >99 | 95 |
| 8 | Ni(PPh ₃) ₂ I ₂ | – | Zn | acetonitrile | 15 | trace |

^aReaction 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. ^bDetermined by GC using naphthalene as an internal standard. ^cIsolated yield of the product. ^dn.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 (–CF₃) 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 heterocycles⁸ prompted us to investigate the macrocyclic alkyne **1l** in this cycloaddition. Gratifyingly, the cycloaddition underwent smoothly to regioselectively afford the desired macrocyclic 3-dehydropiperidinone **3la** in good yield.

Importantly, this methodology is scalable and was successfully applied to gram-scale quantities of 3-azetidinone 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.

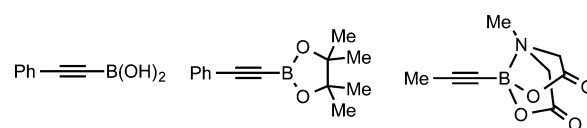
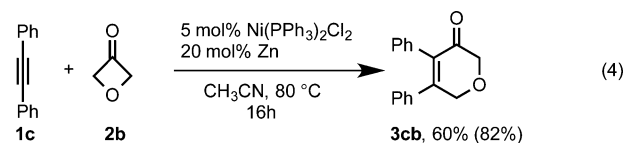
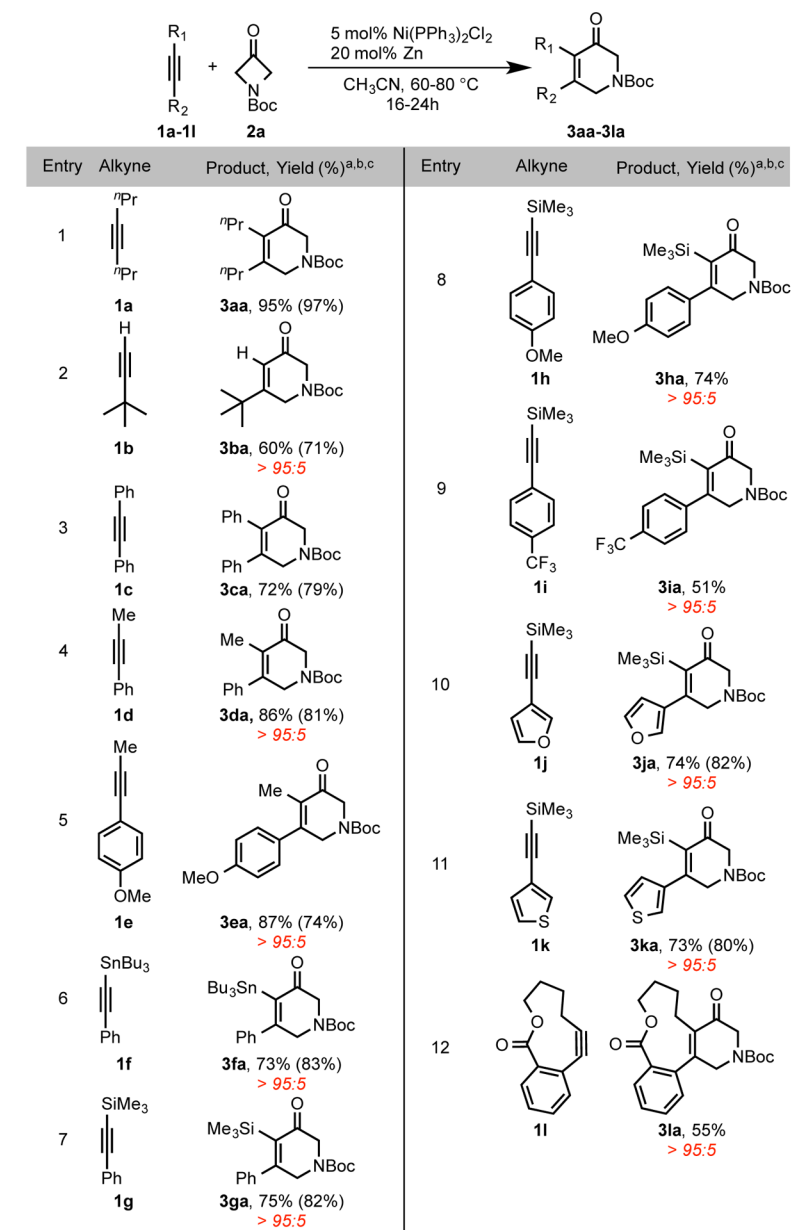


Figure 1. Attempted substrates in Ni-catalyzed cycloaddition.

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-azetidinones 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 ZnCl₂ 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/PPh₃ 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(sp²)–C(sp³) 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

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

^aReaction conditions: 1-Boc-3-azetidinone (1.0 equiv, 0.2 M) alkyne (1.5 equiv), 5 mol % Ni(PPh₃)₂Cl₂, 20 mol % Zn, 60–80 °C, 16–24 h.

^bIsolated yield (in parentheses) obtained using reported Ni(0) procedure. ^cRegioselectivity (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 enantioselectivity.

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 enantioselectivity. 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 N₂. Toluene and acetonitrile were dried over neutral alumina under N₂ 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.

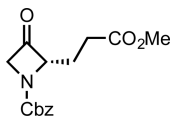
¹H and ¹³C nuclear magnetic resonance (NMR) spectra of pure compounds were acquired at 400 and 100 MHz or 500 and 125 MHz, respectively, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ¹H and to the central line of a triplet at 77.23

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

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

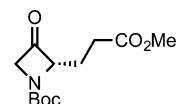
^aReaction conditions: Azetidinone (1.0 equiv, 0.1 M), alkyne (1.5 equiv), 5 mol % Ni(PPh₃)₂Cl₂, 20 mol % Zn, 60–80 °C, 16–24 h.
^bIsolated yield.

ppm for ¹³C. 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 ¹³C 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 N₂ atmosphere, dry NEt₃ (1.35 mL, 9.71 mmol) and ClCO₂Et (1.05 g, 9.71 mmol) were added at –15 °C. The suspension was allowed to warm to 0 °C. CH₂N₂ (23.10 mmol) in Et₂O 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 MgSO₄. 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 N₂ atmosphere, the diazo ketone was dissolved in CH₂Cl₂ (33 mL), and dry NEt₃ (10 μL, 0.07 mmol) was added. After cooling to 0 °C, Rh₂(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 CH₂Cl₂, washed with water, and brine dried over MgSO₄. 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, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 (CH₂Cl₂, cm⁻¹): 2953, 1822, 1733, 1711, 1437, 1403, 1344, 1253, 1119, 1123, 1059, 1026, 745, 699. HRMS (ESI-TOF) calcd for C₁₅H₁₇NO₅Na [M + Na]⁺ 314.1004, found 314.1006.

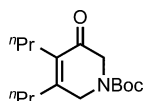


tert-Butyl (S)-2-(3-Methoxy-3-oxopropyl)-3-oxoazetidine-1-carboxylate (2f). Azetidinone **2d** was prepared according to Seebach's procedure.⁹ To a solution of Boc-Glu(OMe)-OH^{11b} (2.10 g, 8.04 mmol) in THF (40 mL) under N₂ atmosphere, dry NEt₃ (1.2 mL, 8.44 mmol) and ClCO₂Et (0.92 g, 8.44 mmol) were added at –15 °C. The suspension was allowed to warm to 0 °C. CH₂N₂ (21.10 mmol) in Et₂O 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 MgSO₄. 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 N₂ atmosphere, the diazo ketone was dissolved in CH₂Cl₂ (35 mL) and dry NEt₃ (10 μL, 0.07 mmol) was added. After cooling to 0 °C, Rh₂(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 CH₂Cl₂, washed with water and brine dried over MgSO₄. 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, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 200.0, 173.1, 156.6, 82.0, 81.3, 69.4, 51.9, 29.6, 28.4, 25.8. IR (CH₂Cl₂, cm⁻¹): 2978, 2932, 1822, 1738, 1704, 1437, 1367, 1176, 1132, 1060, 1021, 862, 776. HRMS (ESI-TOF) calcd for C₁₂H₁₉NO₅Na [M + Na]⁺ 280.1161, found 280.1167.

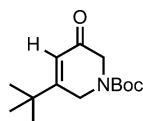
General Procedure "G1" for Cycloaddition. To an oven-dried Schlenk tube containing a stirring bar was added 5 mol % Ni(PPh₃)₂Cl₂, 20 mol % activated Zn powder, 3-azetidinone (1 equiv), and alkyne [(1.5 equiv), if solid at room temperature]. This Schlenk tube containing all the solid compounds was then evacuated followed by refilling with N₂ 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(PPh₃)₂Cl₂, 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 N₂ at room temperature (this process was repeated two times). Dry

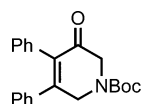
acetonitrile (0.2 M, based on 3-azetidinone) and alkyne [(1.5 equiv), if oil at room temperature] were added via syringe through the rubber septum, under a flow of nitrogen. The reaction mixture was stirred under nitrogen for 20 min followed by the addition of 3-azetidinone (1 equiv, 0.2 M) or 3-oxetanone (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(PPh₃)₂Cl₂, 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. ¹H NMR and ¹³C NMR were consistent with reported data.^{5a}

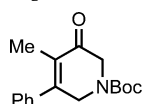


tert-Butyl 5-(tert-Butyl)-3-oxo-3,6-dihydropyridine-1(2H)-carboxylate (3ba). The general procedure G1 was used with 117.5 mg (0.69 mmol, 0.2 M) of 3-azetidinone **2a**, 84.6 mg (1.03 mmol) of *t*-butylacetylene **1b**, 22.6 mg (0.03 mmol) of Ni(PPh₃)₂Cl₂, and 9.0 mg (0.14 mmol) of Zn powder in acetonitrile. 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. ¹H NMR and ¹³C NMR were consistent with reported data.^{5a}



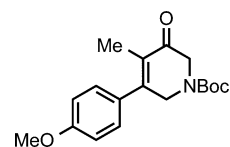
tert-Butyl 5-oxo-3,4-Diphenyl-5,6-dihydropyridine-1(2H)-carboxylate (3ca). The general procedure G1 was used with 130.3 mg (0.76 mmol, 0.2 M) of 3-azetidinone **2a**, 203.4 mg (1.14 mmol) of diphenylacetylene **1c**, 24.9 mg (0.04 mmol) of Ni(PPh₃)₂Cl₂, and 7.5 mg (0.12 mmol) of Zn powder in acetonitrile. 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. ¹H NMR and ¹³C 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(PPh₃)₂Cl₂, 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. ¹H NMR and ¹³C NMR were consistent with reported data.^{5a}

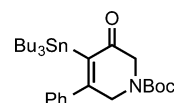


tert-Butyl 4-Methyl-5-oxo-3-phenyl-5,6-dihydropyridine-1(2H)-carboxylate (3da). The general procedure G1 was used with 100.5 mg (0.59 mmol, 0.2 M) of 3-azetidinone **2a**, 102.2 mg (0.88 mmol) of phenyl-methyl alkyne **1d**, 19.3 mg (0.03 mmol) of Ni(PPh₃)₂Cl₂, and 7.7 mg (0.12 mmol) of Zn powder in acetonitrile. The reaction

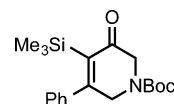
mixture was heated at 80 °C for 20 h. The remaining residue was purified by silica gel flash column chromatography using 25% ether in hexanes (*R_f* = 0.20) to afford the title compound **3da** (147.0 mg, 0.51 mmol, 86%) as colorless oil. ¹H NMR and ¹³C NMR were consistent with reported data.^{5a}



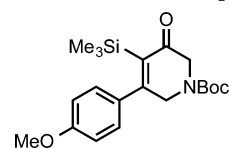
tert-Butyl 3-(4-Methoxyphenyl)-4-methyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (3ea). The general procedure G1 was used with 105.0 mg (0.61 mmol, 0.2 M) of 3-azetidinone **2a**, 134.5 mg (0.92 mmol) of *p*-methoxyphenyl-methyl alkyne **1e**, 20.1 mg (0.03 mmol) of Ni(PPh₃)₂Cl₂, and 8.0 mg (0.12 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. ¹H NMR and ¹³C NMR were consistent with reported data.^{5a}



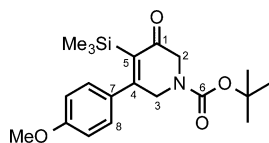
tert-Butyl 5-oxo-4-Phenyl-3-(tributylstannyl)-5,6-dihydropyridine-1(2H)-carboxylate (3fa). The general procedure G1 was used with 79.5 mg (0.46 mmol, 0.2 M) of 3-azetidinone **2a**, 272.5 mg (0.70 mmol) of tributyltin-phenyl alkyne **1f**, 15.3 mg (0.02 mmol) of Ni(PPh₃)₂Cl₂, and 6.1 mg (0.09 mmol) of 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. ¹H NMR and ¹³C 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(PPh₃)₂Cl₂, 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. ¹H NMR and ¹³C NMR were consistent with reported data.^{5a}

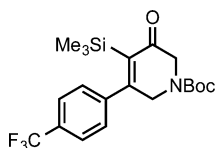


tert-Butyl 5-(4-Methoxyphenyl)-3-oxo-4-(trimethylsilyl)-3,6-dihydropyridine-1(2H)-carboxylate (3ha). The general procedure G1 was used with 99.0 mg (0.58 mmol, 0.2 M) of 3-azetidinone **2a**, 177.3 mg (0.87 mmol) of (*p*-methoxy)phenyl-trimethylsilyl alkyne **1h**, 19.0 mg (0.03 mmol) of Ni(PPh₃)₂Cl₂, 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.

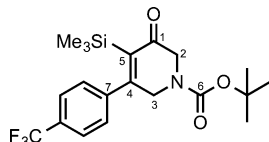


^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.20 (d, $J = 8.0$ Hz, 2H), 6.90 (d, $J = 8.8$ Hz, 2H), 4.29 (s, 2H), 4.05 (s, 2H), 3.82 (s, 3H), 1.48 (s, 9H), 0.11 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 198.4, 161.0, 154.5, 131.74, 131.66, 129.8, 114.0, 113.9, 81.0, 55.5, 51.8, 49.0, 28.6, 0.7. IR (CH_2Cl_2 , cm^{-1}): 2977, 1699, 1665, 1607, 1509, 1458, 1413, 1248, 1160, 1110, 1031, 843, 766, 736. HRMS (ESI-TOF) m/z calcd for $\text{C}_{20}\text{H}_{29}\text{NO}_4\text{SiNa}$ [$M + \text{Na}$] $^+$ 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).

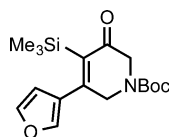


tert-Butyl 3-oxo-5-(4-(trifluoromethyl)phenyl)-4-(trimethylsilyl)-5,6-dihydropyridine-1(2H)-carboxylate (**3ia**). The general procedure **G1** was used with 122.0 mg (0.71 mmol, 0.2 M) of 3-azetidinone **2a**, 259.0 mg (1.07 mmol) of (*p*-trifluoromethyl)phenyl-trimethylsilyl alkyne **1i**, 23.3 mg (0.04 mmol) of $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$, 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.

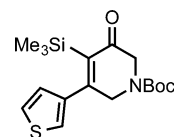


^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.67 (d, $J = 7.6$ Hz, 2H), 7.39 (d, $J = 8.0$ Hz, 2H), 4.28 (s, 2H), 4.09 (s, 2H), 1.48 (s, 9H), 0.14 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 197.7, 154.4, 143.1, 138.8, 131.6 (q, $J = 33.0$ Hz), 128.5, 125.7 (q, $J = 4.0$ Hz), 124.0 (q, $J = 27.0$ Hz), 81.3, 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 $\text{C}_{20}\text{H}_{26}\text{F}_3\text{NO}_3\text{SiNa}$ [$M + \text{Na}$] $^+$ 436.1532, found 436.1540.

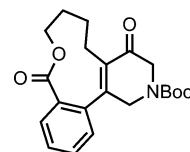
Key g-HMBC correlations: The following cross-peaks were observed: H(2) and C(1); H(2) and C(6); H(3) and C(6); H(3) and C(4); H(3) and C(5); H(3) and C(7); H(8) and C(7); H(8) and C(4).



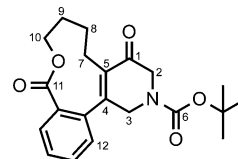
tert-Butyl 3-(furan-3-yl)-5-oxo-4-(trimethylsilyl)-5,6-dihydropyridine-1(2H)-carboxylate (**3ja**). The general procedure **G1** was used with 86.5 mg (0.51 mmol, 0.2 M) of 3-azetidinone **2a**, 124.5 mg (0.76 mmol) of furanyl-trimethylsilyl alkyne **1j**, 16.7 mg (0.03 mmol) of $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$, 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. ^1H 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 $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$, 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. ^1H NMR and ^{13}C NMR were consistent with reported data.^{5a}

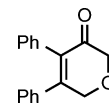


tert-Butyl 4,10-dioxo-4,5,6,7,8,10-hexahydro-1H-benzo[3,4]-oxecino[5,6-c]pyridine-2(3H)-carboxylate (**3la**). The general procedure **G1** was used with 55.0 mg (0.32 mmol, 0.2 M) of 3-azetidinone **2a**, 96.5 mg (0.48 mmol) of macrocyclic alkyne **1l**, 10.5 mg (0.02 mmol) of $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$, 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.

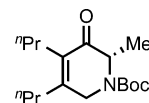


^1H NMR (400 MHz, CDCl_3): δ (ppm) 7.96 (d, $J = 7.6$ Hz, 1H), 7.55 (t, $J = 7.6$ Hz, 1H), 7.46 (t, $J = 7.6$ Hz, 1H), 7.21 (brs, 1H), 4.68 (m, 1H), 4.36–4.50 (m, 3H), 4.19 (m, 1H), 4.00 (brm, 1H), 2.54 (m, 1H), 1.92–2.26 (m, 2H), 1.53–1.77 (m, 3H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 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 $\text{C}_{21}\text{H}_{25}\text{NO}_5\text{Na}$ [$M + \text{Na}$] $^+$ 394.1630, found 394.1633.

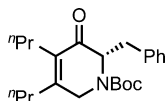
Key g-HMBC correlations: The following cross-peaks were observed: H(2) and C(1); H(2) and C(6); H(3) and C(6); H(3) and C(4); H(3) and C(5); H(3) and C(7); H(7) and C(5); H(7) and C(1); H(8) and C(5); H(10) and C(11); H(12) and C(4).



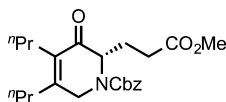
4,5-Diphenyl-2H-pyran-3(6H)-one (**3cb**). The general procedure **G1** was used with 63.4 mg (0.88 mmol, 0.1 M) of 3-oxetanone **2b**, 235.3 mg (1.32 mmol) of diphenylacetylene **1c**, 29.0 mg (0.04 mmol) of $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$, and 11.6 mg (0.18 mmol) of Zn powder in acetonitrile. 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. ^1H NMR and ^{13}C NMR were consistent with reported data.^{5b}



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(PPh₃)₂Cl₂, 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. [α]_D²⁰ = 25.2 (c = 1.0, CHCl₃); (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%. ¹H NMR and ¹³C NMR were consistent with reported data.^{5c}

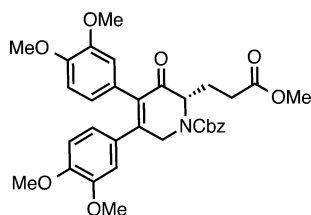


tert-Butyl (S)-2-Benzyl-3-oxo-4,5-dipropyl-3,6-dihydropyridine-1(2H)-carboxylate (3ad). The general procedure G1 was used with 42.3 mg (0.16 mmol, 0.2 M) of enantiopure 2-benzyl-3-azetidinone 2d, 26.8 mg (0.24 mmol) of 4-octyne 1a, 5.3 mg (0.01 mmol) of Ni(PPh₃)₂Cl₂, and 2.1 mg (0.03 mmol) of Zn powder 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. [α]_D²⁰ = –20.7 (c = 1.0, CHCl₃); (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%. ¹H NMR and ¹³C 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(PPh₃)₂Cl₂, 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 3ac (63.4 mg, 0.16 mmol, 86%) as colorless oil. [α]_D²⁰ = 13.2 (c = 1.0, CHCl₃); (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%.

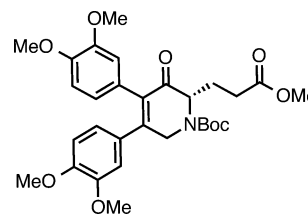
¹H NMR (400 MHz, CDCl₃): δ (ppm) 7.36 (brs, 5H), 5.13 (brs, 2H), 4.48–4.67 (m, 2H), 3.78–3.91 (m, 1H), 3.61 (s, 3H), 2.17–2.42 (m, 6H), 1.94 (m, 2H), 1.56 (m, 2H), 1.33 (sext, *J* = 7.6 Hz, 2H), 1.00 (m, 3H), 0.91 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ (ppm) 194.7, 173.2, 155.1, 153.8, 136.1, 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 (CH₂Cl₂, 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 C₂₃H₃₁NO₅Na [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(PPh₃)₂Cl₂, 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. [α]_D²⁰ = –106.6 (c = 1.0, CHCl₃); (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%.

¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 (CH₂Cl₂, 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 C₃₃H₃₅NO₉Na [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(PPh₃)₂Cl₂, 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. [α]_D²⁰ = –113.9 (c = 1.0, CHCl₃); (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%.

¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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 (CH₂Cl₂, cm⁻¹): 2917, 2848, 1736, 1695, 1600, 1594, 1463, 1411, 1366, 1320, 1254, 1205, 1161, 764. HRMS (ESI-TOF) *m/z* calcd for C₃₀H₃₇NO₉Na [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. ¹H NMR and ¹³C NMR spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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