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# Ni(0)-Catalyzed Synthesis of Polycyclic α,β-Unsaturated γ-Lactams via Intramolecular Carbonylative Cycloaddition of Yne-imines with CO

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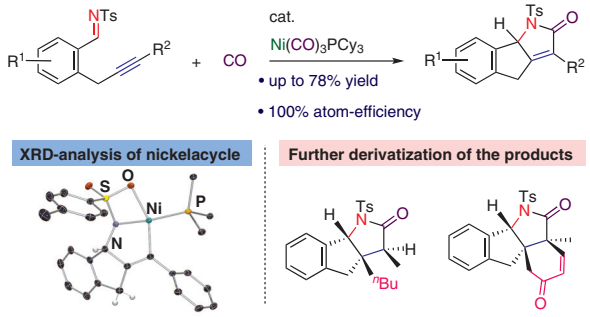


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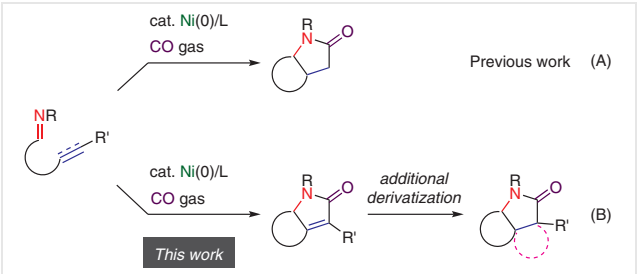
**Abstract** A Ni(0)-catalyzed intramolecular carbonylative cycloaddition between 1,5-yne-imines and carbon monoxide (CO) is disclosed. When $Ni(CO)_3PCy_3$ was employed as a pre-catalyst, a variety of polycyclic α,β-unsaturated γ-lactams were prepared in up to 78% yield with 100% atom efficiency. Aza-nickelacycles, generated by the oxidative cyclization of yne-imines on the Ni(0) center, were experimentally confirmed as key intermediates. Moreover, diastereoselective transformations of the obtained products to afford highly substituted polycyclic γ-lactams with three contiguous carbon stereocenters are reported.

**Key words** nickel-catalysis, carbonylative cycloaddition, α,β-unsaturated γ-lactams, aza-nickelacycle, yne-imines

The transition-metal-catalyzed [2+2+1] carbonylative cycloaddition of ene-ynes with carbon monoxide (CO), also known as the intramolecular Pauson–Khand reaction,[1] is a straightforward method for the construction of polycyclic carbon frameworks.[2] Carbonylative cycloaddition between yne-imines and CO are also of interest, as this reaction enables the rapid construction of α,β-unsaturated γ-lactam cores, which are frequently found in biologically active compounds.[3] Nevertheless, this type of carbonylative cycloaddition using C=N π-components has been much less studied due to the difficulties associated with the repeated generation of the key aza-metalacycle intermediates under a CO atmosphere.[4,5]

Our research group has contributed to the development of Ni(0)-catalyzed carbonylative cycloaddition reactions based on the characteristic reactivity of Ni(0) to engage in facile oxidative cyclization between two π-components.[6,7] For example, we have reported a Ni(0)-catalyzed intermolecular carbonylative cycloaddition between imines and alkynes, in which CO was generated in situ by treatment of phenyl formate with $NEt_3$.[8] We have also disclosed a method for the direct use of CO gas for a Ni(0)-catalyzed intramolecular carbonylative cycloaddition of 1,5- or 1,6-ene-imines to prepare polycyclic γ-lactams with 100% atom efficiency (Scheme 1A).[9] Moreover, this Ni(0)-catalyzed intramolecular system was expanded to the corresponding enantioselective variant.[10] As part of these studies, we describe herein a Ni(0)-catalyzed intramolecular carbonylative cycloaddition of 1,5-yne-imines under a CO atmosphere for the synthesis of polycyclic α,β-unsaturated γ-lactams (Scheme 1B). Furthermore, we derivatized the olefinic moieties in the produced α,β-unsaturated γ-lactams, which demonstrates the synthetic utility of the present method for the synthesis of *N*-heterocyclic compounds that bear multiple contiguous carbon stereocenters. The results of mechanistic studies that clarify the role of nickelacycles are also reported. It should be noted here that we have already explored the corresponding carbonylative cycloaddition in the presence of phenyl formate and $NEt_3$, which predominantly yielded isoquinoline derivatives via the $NEt_3$-catalyzed 6-*exo*-cyclization of the 1,5-yne-imines.[11]

Initially, the optimal reaction conditions were explored using 1,5-yne-imine **1a**, which contains an *N*-tosyl (Ts) group, and 0.5 atm of CO (Scheme 2). To avoid rapid saturation of the reaction medium with CO, the experiments were




**Scheme 1** Ni(0)-catalyzed intramolecular carbonylative cycloadditions with (A) ene-imines or (B) yne-imines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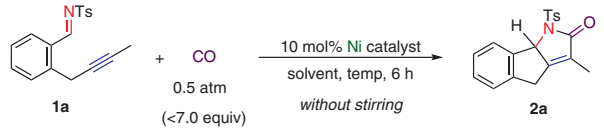


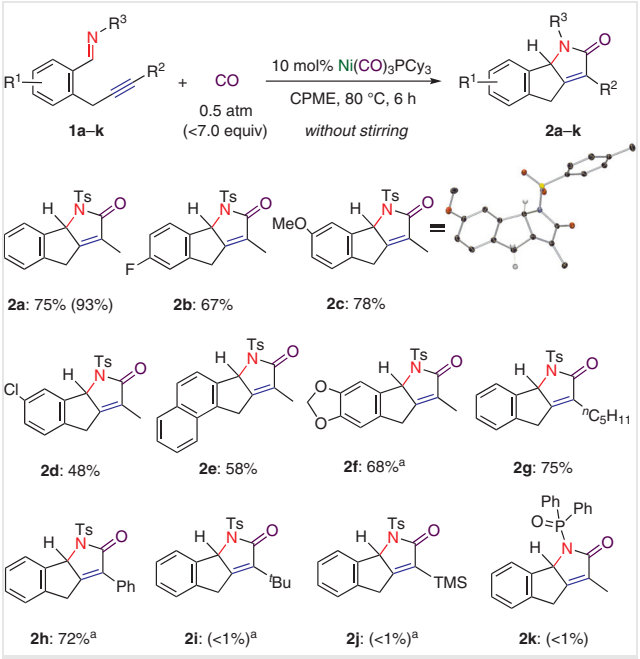

| Entry | Ni catalyst | Solvent | Temp (°C) | Yield (%) |
|---|---|---|---|---|
| 1 | $Ni(cod)_2/PCy_3$ | THF | 80 | 58 |
| 2 | $Ni(cod)_2/P^nBu_3$ | THF | 80 | 36 |
| 3 | $Ni(cod)_2/PPh_3$ | THF | 80 | 13 |
| 4 | $Ni(cod)_2/P^tBu_3$ | THF | 80 | <1 |
| 5 | $Ni(CO)_3PCy_3$ | THF | 80 | 68 |
| 6 | $Ni(CO)_3PCy_3$ | CPME | 80 | 93 (<10)[a] |
| 7 | $Ni(CO)_3PCy_3$ | Toluene | 80 | 83 |
| 8 | $Ni(CO)_3PCy_3$ | DMF | 80 | <10 |
| 9 | $Ni(CO)_3PCy_3$ | CPME | 40 | 63 |

**Scheme 2** Optimization of the reaction conditions for the Ni(0)-catalyzed carbonylative cycloaddition between **1a** and CO. All reactions were carried out in a multiple autoclave reactor (*V*: 3.7 mL × 18 reactors). **1a** (0.10 mmol), $Ni(cod)_2/PR_3$ (cod = 1,5-cyclooctadiene; R = Cy, $^n$Bu, Ph, $^t$Bu) or $Ni(CO)_3PCy_3$ (0.010 mmol), and solvent (1 mL) were mixed in each reactor, followed by pressurization with CO (0.5 atm) at r.t. and heating. Yield was determined by $^1$H NMR spectroscopy using 2-methoxynaphthalene as the internal standard. [a] The reaction was carried out with stirring at 1350 rpm.

conducted without stirring.[9,10] The reaction was examined in THF at 80 °C using 10 mol% $Ni(cod)_2$ and $PCy_3$, which resulted in the formation of tricyclic α,β-unsaturated γ-lactam **2a** in 58% yield (entry 1), whereas $P^nBu_3$, $PPh_3$, and $P^tBu_3$ furnished **2a** in lower yield (entries 2–4). The use of $Ni(CO)_3PCy_3$ as the catalyst precursor furnished **2a** in higher yield (68%) than using $Ni(cod)_2/PCy_3$ (entry 5). Thus, we employed $Ni(CO)_3PCy_3$ in the subsequent catalytic reactions. Next, further optimizations of the reaction conditions with respect to the solvent and reaction temperature were carried out. Among the various solvents that we examined, cyclopentyl methyl ether (CPME) afforded the best result (93% yield; entry 6). The reaction in toluene afforded **2a** in good yield (83%; entry 7), while the targeted reaction did not proceed catalytically when DMF was used (entry 8). Decreasing the reaction temperature to 40 °C resulted in a lower reaction efficiency (63% yield; entry 9). We also confirmed that the catalytic reaction was hampered by stirring the reaction solution (in parentheses of entry 6). Based on these results, we concluded that the optimal conditions are those shown in entry 6.

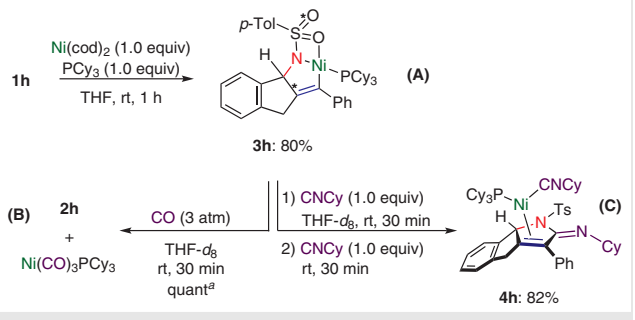
We then explored the substrate scope of this catalytic reaction using **1a–k** under the optimal reaction conditions (Scheme 3). The reaction between **1a** and CO afforded **2a** in 75% isolated yield. Substrates with *meta*-fluorine (**1b**) and *para*-methoxy (**1c**) groups relative to the propargyl groups afforded **2b** and **2c** in 67% and 78% yield, respectively. The molecular structure of **2c** was determined by single-crystal X-ray diffraction (XRD) analysis. The reactions of **1d**, which contains a *para*-chlorine substituent, and **1e**, which contains a naphthyl skeleton, afforded **2d** and **2e** in 48% and 58% yield, respectively. In order to obtain **2f** from **1f** in 68% yield, the reaction had to be carried out at 100 °C for 24 h. The use of **1g**, which bears an *n*-pentyl group at the alkyne terminal, afforded **2g** in 75% yield. In the case of **1h**, which contains a phenyl group at the alkyne terminal, γ-lactam **2h** was obtained in 72% yield when the reaction was carried out at 100 °C for 24 h. However, when **1i** and **1j** were employed, a significant amount of the starting material remained unreacted even after 24 h at 100 °C, and the formation of the corresponding γ-lactams (**2i** and **2j**) was not confirmed. These results suggest that the $\eta^2$ coordination of the alkyne moieties to the Ni(0) center was prevented due to steric hindrance, and thus the progress of oxidative cyclization on Ni(0) was hampered, which was experimentally confirmed (Figures S7–11). When the *N*-Ts group was replaced with an *N*-diphenyl phosphinoyl group, a mixture of unidentified products devoid of the target **2k** was obtained. The details of this reaction remain unclear.

To gain insight into the reaction mechanism, a stoichiometric reaction of **1h** with $Ni(cod)_2/PCy_3$ was conducted in THF at room temperature, which furnished aza-nickelacycle **3h** in 80% isolated yield (Scheme 4A). The molecular structure of **3h** was determined by single-crystal XRD analysis,




**Scheme 3** Ni(0)-catalyzed carbonylative cycloaddition of 1,5-ynes-imines. Compound **1a–k** (0.10 mmol), $Ni(CO)_3PCy_3$ (0.010 mmol), and CPME (1 mL) were mixed, followed by pressurization with CO (0.5 atm) at r.t. and heating. Isolated yields are shown. NMR yield is given in parentheses. [a] The reaction was performed at 100 °C for 24 h.

which revealed a set of enantiomers, i.e., ($S_C$,$R_S$)- and ($R_C$,$S_S$)-**3h**, in the asymmetric unit of the single crystals; the molecular structure of ($S_C$,$R_S$)-**3h** is shown in Figure 1A. The chiral sulfur centers are generated from the desymmetrization of the achiral environment around the sulfur center via the intramolecular coordination of the S=O moiety to the Ni center (Ni–O1: 2.082(1) Å). We also confirmed that the coordinated S=O group can be easily exchanged with another one at room temperature in THF-$d_8$, as two resonances are observed at 30.2 and 26.8 ppm in the $^{31}$P NMR spectrum of **3h**, probably showing the existence of diastereomers that are generated via the coordination exchange between two S=O ligands. These results are supported by the DFT calculations, i.e., the relative Gibbs free energy of ($S_C$,$S_S$)-**3h** with respect to ($S_C$,$R_S$)-**3h** is estimated as –0.4 kcal mol$^{-1}$ and the activation energy barrier for the generation of ($S_C$,$S_S$)-**3h** from ($S_C$,$R_S$)-**3h** is +13.7 kcal mol$^{-1}$ (Figure S21). The reaction between **3h** and CO (3.0 atm) in THF-$d_8$ quantitatively afforded **2h** and Ni(CO)$_3$PCy$_3$ (Scheme 4B). These results suggest the formation of an intermediary aza-nickelacycle in the reaction of **1h** under the applied reaction conditions. To gain further information regarding the reaction between **3h** and CO, we monitored the reaction of **3h** with CNCy, which is isoelectronic with CO.[12] Treatment of **3h** with an equimolar amount of CNCy resulted in the generation of **4h**, in which the tricyclic α,β-unsaturated amidine coordinates to Ni(0) (Scheme 4C). After the addition of another equivalent of CNCy and recrystallization, **4h** was isolated in 82% yield. The molecular structure of **4h** was determined by single-crystal XRD analysis (Figure 1B).




**Scheme 4** Isolation and reactivity of **3h**. Isolated yield of the products is given. [a] The yield was confirmed by NMR analyses.

Based on the aforementioned results, this Ni(0)-catalyzed carbonylative [2+2+1] cycloaddition can be expected to proceed via the mechanism shown in Scheme 5. Replacement of the CO ligands in Ni(CO)$_3$PCy$_3$ with yne-imine **1** generates (η$^2$:η$^2$-**1**)Ni(PCy$_3$), which is then subject to an oxidative cyclization to give aza-nickelacycle **3**. The reaction of CO with **3** and the subsequent reductive elimination afford (η$^2$-**2**)Ni(CO)(PCy$_3$) (**4′**). Finally, ligand substitution between **4′** and **1** occurs to furnish **2** under concomitant regeneration of (η$^2$:η$^2$-**1**)Ni(PCy$_3$).

To show the synthetic utility of the present Ni-catalyzed reaction, diastereoselective transformations of **2a** via the derivatization of its olefinic moiety were examined (Scheme 6). Hydrogenation of **2a** in the presence of 3 mol% Pd/C afforded **5a**, which bears three contiguous carbon ste-

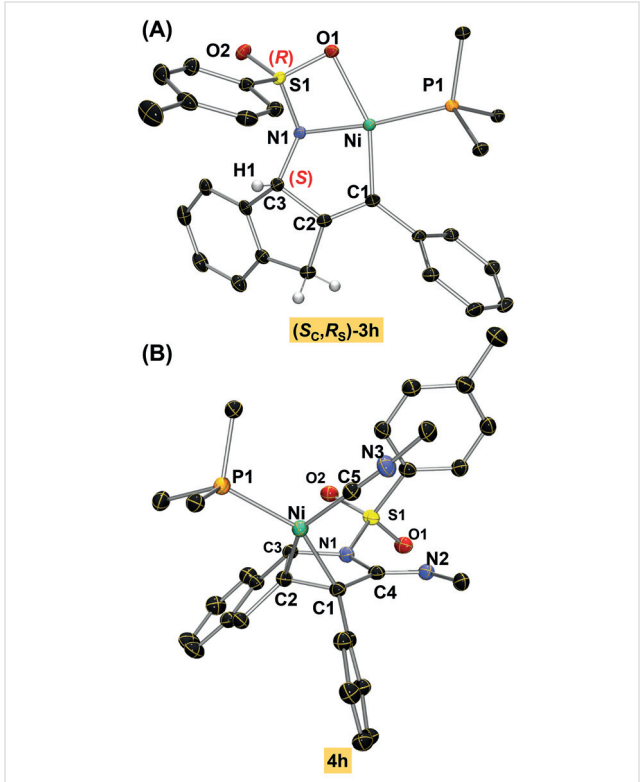
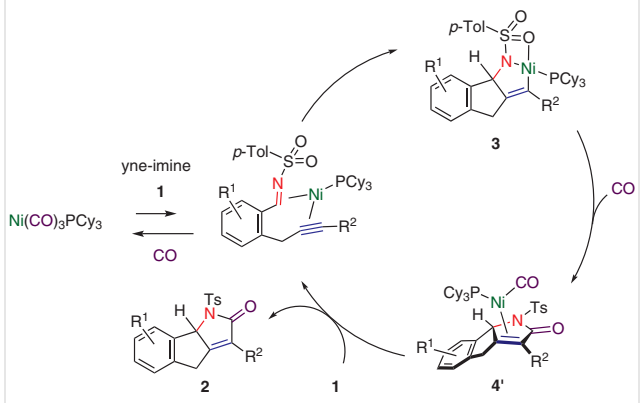
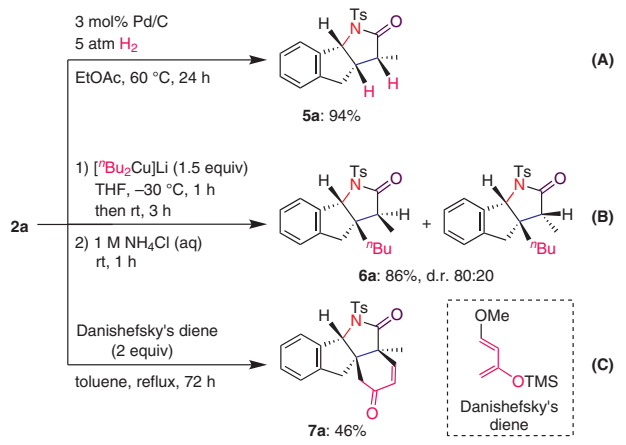



**Figure 1** Molecular structures of ($S_C$,$R_S$)-**3h** and **4h** with thermal ellipsoids at 30% probability; only selected H atoms are shown and cyclohexyl groups are omitted for clarity. Selected bond lengths [Å] of ($S_C$,$R_S$)-**3h**: Ni–O1, 2.082(1); Ni–N1, 1.893(2); Ni–C1, 1.931(2); S1–O2, 1.490(1); S1–O2, 1.434(2); **4h**: Ni–C1, 1.978(2); Ni–C2, 1.926(2); Ni–C5, 1.819(3); C1–C2, 1.451(3); C5–N3, 1.163(4); C4–N1, 1.439(3); C4–N2, 1.268(3).




**Scheme 5** A plausible mechanism for the Ni(0)-catalyzed [2+2+1] carbonylative cycloaddition of **1** with CO

reogenic centers, in 94% yield (Scheme 6A). The conjugate addition of [$^n$Bu$_2$Cu]Li to **2a** proceeded to furnish a diastereomeric mixture of **6a** (86% yield; d.r. 80:20), which bears quaternary carbon centers at the C4 positions (Scheme 6B). A Diels–Alder reaction with Danishefsky's diene successfully expanded the fused-ring system of **2a** to **7a** (46% yield), and two contiguous quaternary carbon centers were constructed (Scheme 6C). The molecular structure of **7a** was determined by a single-crystal XRD analysis (Figure S20).




**Scheme 6** Diastereoselective transformations of **2a**. Relative stereochemistry is shown for **5a**–**7a**. Yield of the isolated products is shown.

In conclusion, we have developed a Ni(0)-catalyzed [2+2+1] carbonylative cycloaddition of yne-imines with CO to afford polycyclic α,β-unsaturated γ-lactam derivatives with 100% atom efficiency.[13] The isolation of an aza-nickelacycle and investigation of its reactivity revealed that the present Ni(0)-catalyzed reaction proceeds via aza-nickelacycle intermediates. The obtained products can be diastereoselectively transformed into compounds with consecutive quaternary carbon centers, which demonstrates the synthetic utility of the present method.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707308.

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(13) All manipulations were conducted under a nitrogen atmosphere using standard Schlenk or dry-box techniques. $^{1}H$, $^{13}C$, $^{19}F$, and $^{31}P$ NMR spectra were recorded with Bruker AVANCE III 400 spectrometers at 25 °C. The chemical shifts in the $^{1}H$ NMR spectra were recorded relative to residual protonated solvent ($C_6D_5H$ (δ = 7.16 ppm) or $CHCl_3$ (δ = 7.26 ppm)). The chemical shifts in the $^{13}C$ NMR spectra were recorded relative to deuterated solvent ($CDCl_3$ (δ = 77.16 ppm)). Assignment of the resonances in the $^{1}H$ and $^{13}C$ NMR spectra was based on $^{1}H$-$^{1}H$ COSY, HMQC, and HMBC experiments. Medium-pressure column chromatography was carried out with a Biotage Flash Purification System Isolera, equipped with a 254 nm UV detector. High-resolution mass spectrometry (HRMS) and elemental analyses were performed at the Instrumental Analysis Centre, Faculty of Engineering, Osaka University. Melting points were determined with a Stanford Research Systems MPA100 OptiMelt Automated Melting-Point System. X-ray crystal data were collected with Rigaku XtaLAB Synergy equipped with the HyPix-6000HE detector. Catalytic reactions were carried out by using multiple autoclave reactors (3.7 mL × 18 reactors, EYELA, HIP-7518).

***Caution*:** Carbon monoxide is toxic and may react with Ni(0) to afford $Ni(CO)_4$. All experiments in this manuscript must be carried out under well-ventilated conditions.

**Ni(0)-Catalyzed [2+2+1] Carbonylative Cycloadditions of 1 with CO; General Procedure**

A multiple reactor (3.7 mL × 18 reactors, EYELA, HIP-7518) was used. To a solution of $Ni(CO)_3PCy_3$ (4.2 mg, 0.010 mmol) in CPME (1.0 mL) was added **1** (0.100 mmol) at r.t. The mixture was transferred into a 2 mL vial, followed by pressurization with CO (0.5 atm, < 7.0 equiv). After heating at 80 °C for 6 h without stirring, the resulting mixture was quenched with MeOH. After filtration through silica gel (eluted with MeOH), all volatiles were removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, 10% then 20–60% EtOAc/hexane) and subsequent recrystallization ($CHCl_3$/pentane, –20 °C) or recycling HPLC, to afford α,β-unsaturated γ-lactams **2**. **3-Methyl-1-tosyl-4,8b-dihydroindeno[1,2-*b*]pyrrol-2(1*H*)-one (2a):** Obtained by following the general procedure using **1a** (31.4 mg, 0.100 mmol). The residue was purified by silica gel column chromatography (10% then 40% EtOAc/hexane) and recrystallization from $CHCl_3$/pentane at –20 °C to afford **2a** as a white solid in 75% yield (25.6 mg, 0.0754 mmol); mp 144–148 °C. $^{1}H$ NMR ($CDCl_3$, 400 MHz): δ = 8.07 (d, *J* = 7.2 Hz, 1 H, Ar-*H*), 8.01 (d, *J* = 8.4 Hz, 2 H, Ar-*H*), 7.37–7.26 (m, 5 H, Ar-*H*, overlapped with solvent peak), 5.87 (s, 1 H, C*H*NTs), 3.75 (d, *J* = 18.0 Hz, 1 H, CC$H_2$C), 3.66 (d, *J* = 18.0 Hz, 1 H, CC$H_2$C), 2.43 (s, 3 H, Ts-C$H_3$), 1.79 (s, 3 H, C(O)CC$H_3$). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ = 171.8, 161.8, 145.1, 142.8, 137.9, 135.6, 129.8, 129.1, 128.7, 128.2, 126.5, 126.2, 125.2, 67.7, 31.2, 21.8, 9.2. HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}NO_3S$: 340.1007; found: 340.1013. **Preparation of 3h:** To a solution of $Ni(cod)_2$ (27.5 mg, 0.100 mmol) and $PCy_3$ (28.0 mg, 0.100 mmol) in THF (3.0 mL) was added **1h** (37.4 mg, 0.100 mmol) at r.t. The reaction solution was stirred vigorously for 1 h to confirm the precipitation of reddish purple solids. After removal of all volatiles, the resulting solids were washed with cold THF/hexane to afford aza-nickelacycle **3h** as a reddish-purple solid in 80% yield (57.2 mg, 0.0803 mmol). A single crystal of **3h** suitable for X-ray diffraction analysis was obtained by slow diffusion of pentane into a THF solution of **3h**. Complex **3h** was almost insoluble in the common solvents. While two distinctive resonances, which can be derived from the existence of diastereomeric isomers such as ($S_C$,$R_S$)- and ($S_C$,$S_S$)-**3h** as well as ($R_C$,$R_S$)- and ($R_C$,$S_S$)-**3h** (see Figure S21), were observed when **3h** was dispersed in THF-$d_8$, the observed resonances could not be fully assigned due to its complexity. $^{1}H$ NMR (400 MHz, THF-$d_8$): δ = 9.05 (brs, 2 H, Ar-*H*, minor), 7.89 (brs, 2 H, Ar-*H*, major), 7.57 (brs, 2 H, Ar-*H*, minor), 7.31–6.82 (m, major + minor), 6.52 (brs, 1 H, Ar-*H*, major), 6.10 (s, 1 H, C*H*NTs, major), 4.78 (s, 1 H, C*H*NTs, minor), 3.19 (d, *J* = 17.6 Hz, 1 H, CC$H_2$C, major), 2.86 (d, *J* = 17.6 Hz, 1 H, CC$H_2$C, minor), 2.75 (d, *J* = 17.6 Hz, 1 H, CC$H_2$C, major), 2.63 (d, *J* = 17.6 Hz, 1 H, CC$H_2$C, minor), 2.49–2.16 (m, major + minor), 1.73–1.62 (m, major + minor + THF), 1.26–0.87 (m, major + minor). $^{13}C\{^{1}H\}$ NMR (100 MHz, THF-$d_8$): δ = 144.0, 128.9, 128.0, 127.4, 126.3, 124.2, 123.4, 31.4, 29.9, 29.5, 27.4, 26.9, 26.2, 25.9, 25.4, 20.4. Several peaks were not observed due to the low concentration. $^{31}P\{^{1}H\}$ NMR (162 MHz, THF-$d_8$): δ = 30.2 (minor), 26.8 (major). Anal. Calcd for $C_{41}H_{52}NNiO_2PS$: C, 69.11; H, 7.36; N, 1.97. Found: C, 68.15; H, 7.41; N, 2.25. Accurate elemental analyses of **3h** was precluded by extreme air or thermal sensitivity and/or systematic problems.