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Aza-Nickelacycle Key Intermediate in Nickel(0)-Catalyzed Transformation Reactions

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ABSTRACT

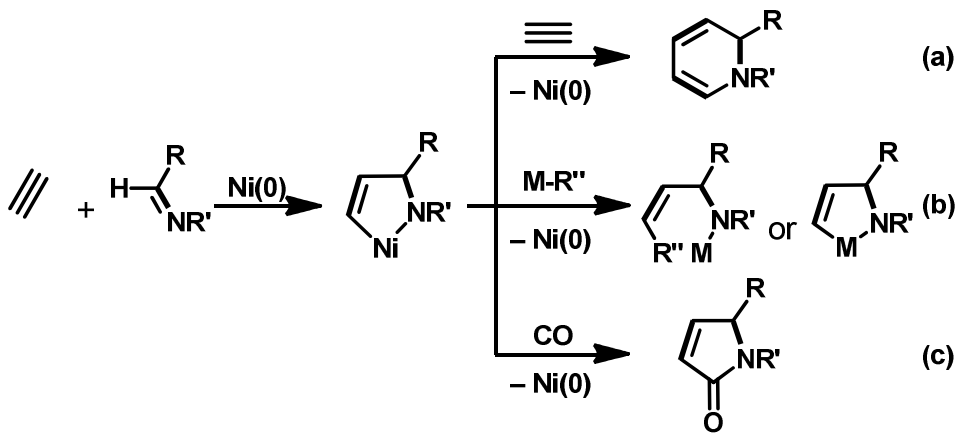
This *Perspective* provides an overview of the oxidative cyclization reactions of alkynes and imines with nickel(0) to give five-membered aza-nickelacycles. These reactions could be a key step in multicomponent coupling and cycloaddition reactions to afford nitrogen-containing organic compounds.

1. Introduction

Oxidative cyclization with low-valent transition metals has received considerable attention because the reaction enables the construction of a C–C bond between a variety of unsaturated compounds, and indeed, the resultant five-membered metallacycles are assumed to be a key reaction intermediate in transition-metal-catalyzed cycloaddition as well as multicomponent coupling reactions.[1] Therefore, the development of efficient methods to generate a variety of metallacycles offers more opportunities to access highly complicated organic compounds. Among transition-metal candidates, nickel has shown great promise as a catalyst, because a number of oxidative cyclization reactions have yielded nickelacycles when using two unsaturated compounds with nickel(0).[2,3] In particular, hetero-nickelacycles are assumed to be a key intermediate in the nickel-catalyzed multi-component coupling reactions between alkynes and either aldehydes or imines.

This *Perspective* focuses on the preparation of a five-membered aza-nickelacycle generated via the oxidative cyclization of an imine and an alkyne with nickel(0). Such aza-nickelacycles are much rarer than the related oxa-nickelacycles generated via the oxidative cyclization of an aldehyde and an alkyne with nickel(0) because imines are generally weaker electrophiles than aldehydes.[2,4] Therefore, it is logical to assume that electron-withdrawing substituents on the nitrogen of the imine are required for oxidative cyclization by promoting back donation from nickel(0) to imines. In addition, the generation of a five-membered aza-nickelacycle is efficiently promoted by a chelate coordination of a donor atom on the *N*-substituent group to a vacant coordination site on the nickel center.[3a,b] Given this background,

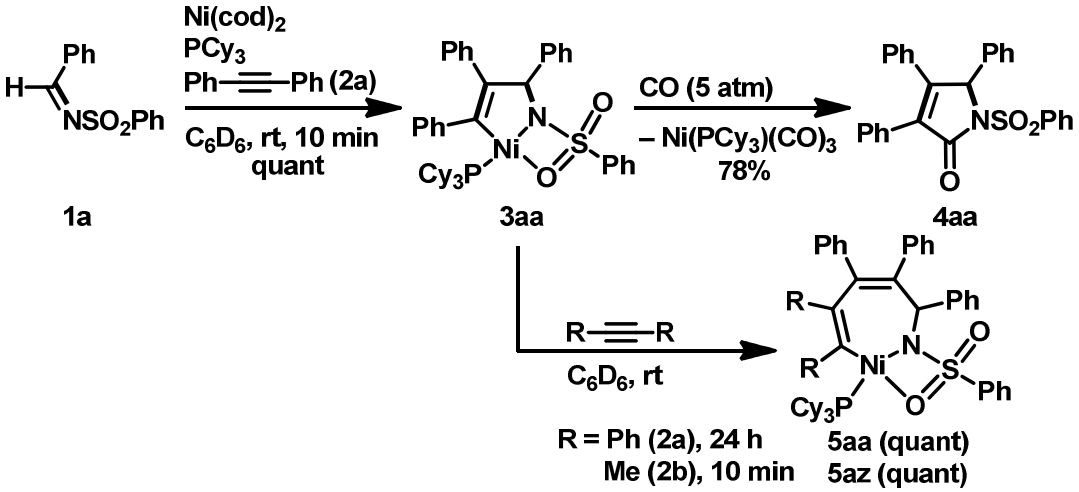
in 2007 we achieved the first isolation of a corresponding aza-nickelacycle via the oxidative cyclization of *N*-sulfonylimine and an alkyne.[3e,5] Herein, we discuss three different types of nickel-catalyzed transformation reactions, (a) [2+2+2] cycloaddition reaction leading to 1,2-dihydropyridines; (b) multi-component coupling or cyclocondensation reactions with alkylmetal reagents to yield allylamine derivatives; and (c) [2+2+1] carbonylative cycloaddition to give *γ*-lactams (Scheme 1). These nitrogen-containing products are ubiquitous structural motifs for natural products in small molecules that have biomedical relevance and are among the most versatile synthetic intermediates for use in the synthesis of a wide range of other valuable molecules.[6,7,8]



Scheme 1. Formation of five-membered aza-nickelacycles generated via oxidative cyclization of an imine and an alkyne, and their key role in the nickel-catalyzed transformation reactions leading to nitrogen-containing products.

2. Generation of five-membered aza-nickelacycles

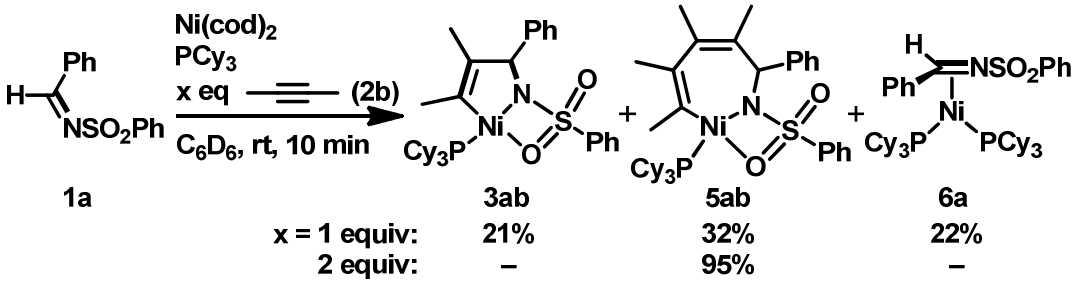
The reaction of *N*-(benzenesulfonyl)benzaldimine (**1a**) with an equimolar amount of diphenylacetylene (**2a**) in the presence of $Ni(cod)_2$ and PCy_3 at room temperature resulted in the quantitative formation of a five-membered nickelacycle (**3aa**; Scheme 2).[3e] Treating **3aa** with carbon monoxide (5 atm) afforded the corresponding γ-lactam (**4aa**), which was consistent with the structure of **3aa** depicted in Scheme 2. The treatment of **3aa** with an additional equimolar amount of **2a** gave a seven-membered nickelacycle (**5aa**) in quantitative yield. The insertion of 2-butyne (**2b**) into **3aa** proceeded much faster (within 10 min) than that of diphenylacetylene, and yielded the corresponding seven-membered nickelacycle (**5az**).



Scheme 2. Formation of five-membered aza-nickelacycle **3aa** and its reactivity. Yields, determined by ^{1}H NMR spectroscopy, are given.

Such a higher reactivity of **2b** explained the formation of an inseparable mixture of a five-membered nickelacycle (**3ab**), a seven-membered nickelacycle (**5ab**), and an η^2-iminenickel complex (**6a**) when

the reaction of **1a** with an equimolar amount of **2b** was conducted in the presence of $Ni(cod)_2$ and PCy_3 at room temperature for 10 min (Scheme 3).[3e] Although the five-membered nickelacycle **3ab** could not be isolated, the addition of an additional equimolar amount of 2-butyne to this mixture gave **5ab** as the sole product in 95 % yield. ~~Again, it should be emphasized that employing a bulkier alkyne such as diphenylacetylene enabled suppression of the formation of a seven-membered aza-nickelacycle, leading to the isolation of a five-membered aza-nickelacycle.~~ The molecular structure of **5ab** was determined by X-ray crystallography (Figure 1a). The coordination of one of the oxygen atoms in the benzenesulfonyl group to nickel might have played an important role in stabilizing **5ab** as an isolable square-planar nickel(II) complex.[9] The molecular structure of **6a**, in which η^2-coordination of the carbon–nitrogen double bond was observed, was also confirmed by X-ray crystallography (Figure 1b). The N–C1 bond length was 1.405(5) Å, which was obviously elongated compared with a typical C=N bond length (ca. 1.27–1.30 Å)[10] which was due to a back donation from the nickel(0) center.



Scheme 3. Reaction of **1a** with **2b** (1 or 2 equiv) in the presence of $Ni(0)/PCy_3$. Yields, determined by ^1H NMR spectroscopy, are given.

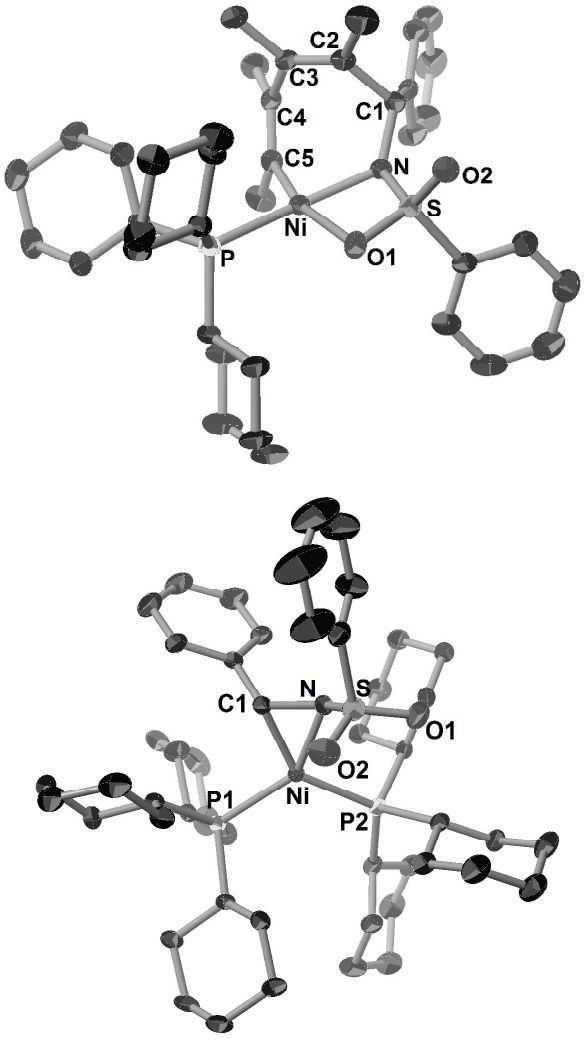
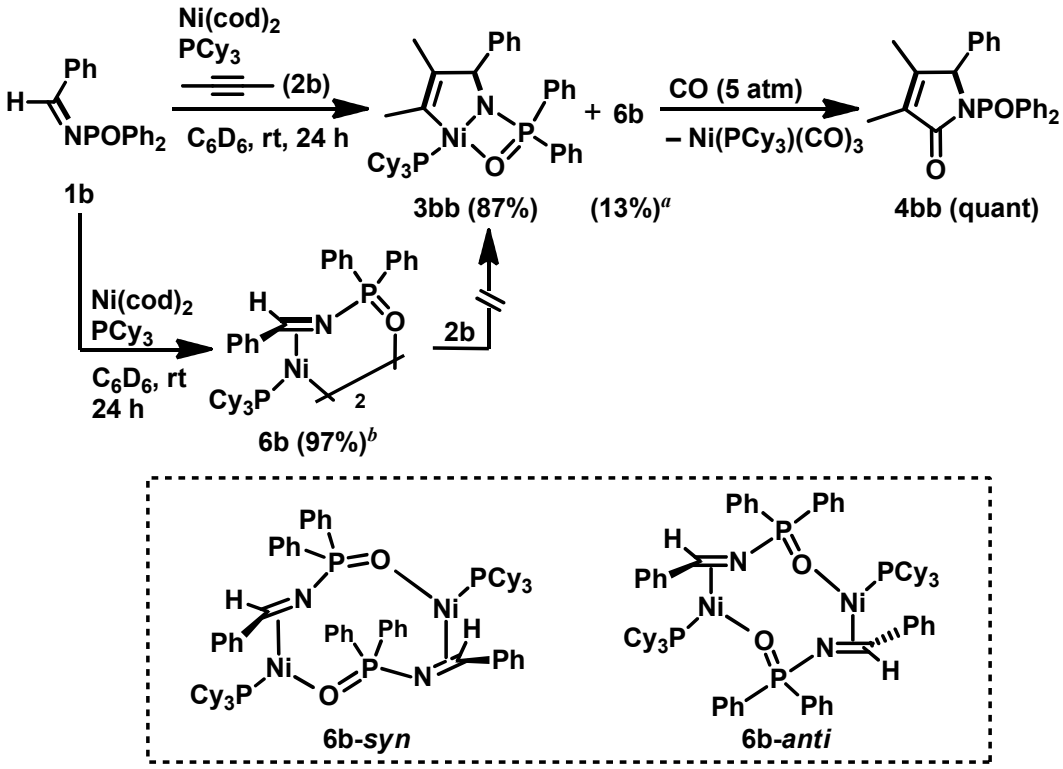


Figure 1. ORTEP drawings of **5ab** (a; top) and **6a** (b; bottom) with thermal ellipsoids at the 30% probability level. H atoms have been omitted for clarity.

In contrast to *N*-sulfonyl imine **1a**, the reaction of *N*-benzylidene-*P,P*-diphenylphosphinic amide (**1b**) with **2b**, $Ni(cod)_2$, and PCy_3 (1 equiv each) was completed in 24 h to afford the corresponding five-membered aza-nickelacycle **3bb** in 87 % yield with the concomitant formation of an η^2-iminenickel complex **6b** in 13 % yield (Scheme 4).[3n] An aza-nickelacycle analogue (**3ba**) was prepared from **1b** and diphenylacetylene **2a**, and its five-membered framework was unambiguously determined by X-ray crystallography (Figure 2a). Complex **3ba** had a square-planar nickel(II) center with an intramolecular

coordination of oxygen to nickel. In addition, the formation of γ-lactam derivative (**4bb**) by the carbonylation of **3bb** should support the five-membered nickelacycle skeleton of **3bb**. The η^2-iminenickel complex **6b** was isolated in 74% yield by the reaction of **1b** with one equivalent of $Ni(cod)_2$ and PCy_3 in toluene for 2 h. While NMR analysis revealed that complex **6b** existed as a mixture of *syn*/*anti* dimeric isomers in solution (*syn*/*anti* = 18:82, in C_6D_6, rt), only an *anti* isomer (**6b-*anti***) was observed in the crystal lattice, as shown in Figure 2b. No reaction occurred when an excess amount of **2b** was added at room temperature to **6b**, indicating that **6b** would be highly stabilized through the intramolecular coordination of oxygen to nickel, and thus the simultaneous coordination of *N*-phosphinyl imine **1b** and alkyne **2b** might be inhibited.



Scheme 4. Formation of five-membered aza-nickelacycle **3bb** and its reactivity with carbon monoxide. Yields, determined by ^{1}H NMR spectroscopy, are given in parenthesis. Diagrams in dotted frame represent the two isomers of **6b**. *a*) *syn*/*anti* ratio = 42:58. b) *syn*/*anti* ratio = 18:82.

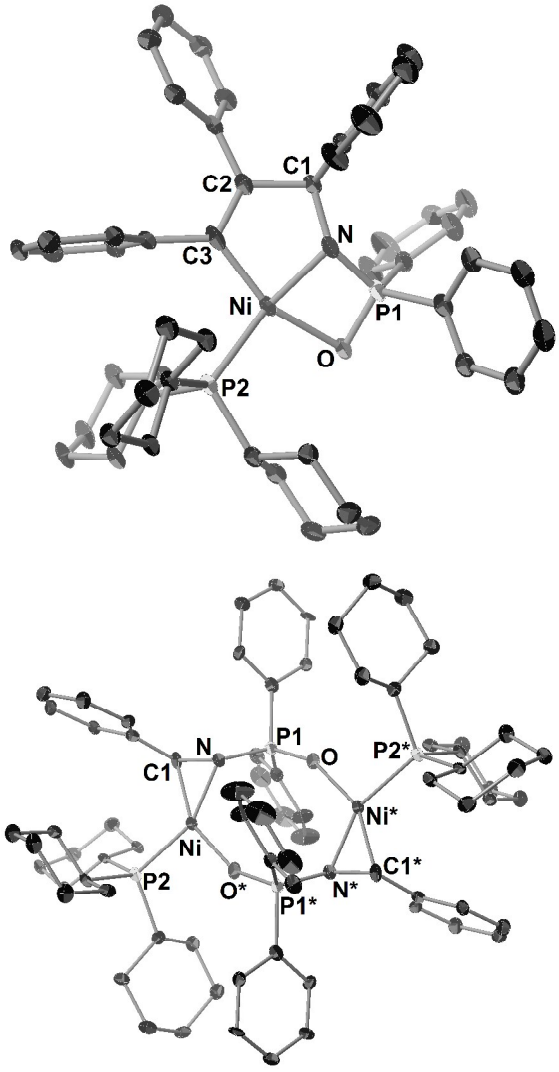
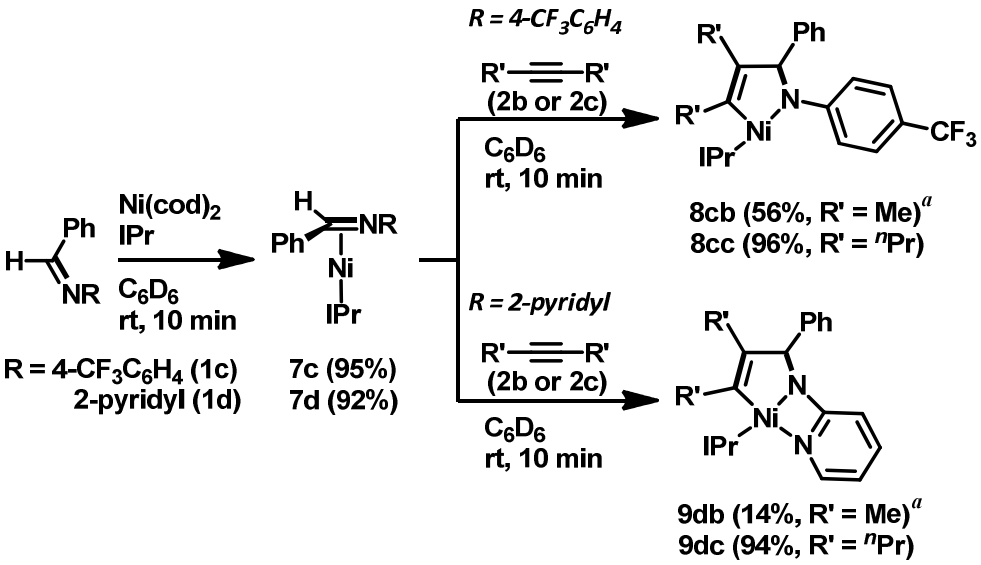


Figure 2. ORTEP drawings of **3ba** (a; top) and **6b-*anti*** (b; bottom) with thermal ellipsoids at the 30% probability level. H atoms and solvated molecule in **6b-*anti*** (hexane) have been omitted for clarity. Symmetry transformation used to generate equivalent atoms S* for **6b-*anti***: –X, 1–Y, –Z.

Next, we turned our attention to employing NHCs as a ligand to investigate whether these stronger electron-donating and more steric-demanding ligands could enhance the formation of aza-nickelacycle

compounds via the oxidative cyclization of alkynes and imines without a chelation group. In fact, we demonstrated the preparation of T-shaped 14-electron hetero-nickelacycles bearing a NHC ligand.[3g,j] The reaction of *N*-benzylidene-4-trifluoromethyl aniline (**1c**) or *N*-benzylidene-2-aminopyridine (**1d**) with a stoichiometric amount of $Ni(cod)_2$ and IPr (IPr=1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene) was completed within 10 min to yield the corresponding η^2-imine complex, [Ni(IPr)(η^2-imine)] (**7c** and **7d**), in 95% and 92 % yields, respectively (Scheme 5).[3n] The molecular structure of **7c** was confirmed by X-ray crystallography (Figure 3a). The C1–N bond length was 1.37(1) Å is comparable to that observed in **6a** and **6b**. It should be mentioned that **7c** had a 14-electron nickel(0) center while PCy_3-ligated imine complexes **6a** and **6b** possessed 16-electron centers. Such a structural difference might have been caused by the steric hindrance of IPr; a bulker IPr could stabilize the highly reactive 14-electron nickel(0) complex by cloaking its vacant coordination sites. By contrast, treating sulfonyl imine **1a** with $Ni(cod)_2$ and IPr did not afford the corresponding [Ni(IPr)(η^2-imine)] complex, and unidentified white precipitates were observed.[11]



Scheme 5. The stoichiometric reactions using *N*-aryl imines and alkynes with Ni(0)/IPr. Yields were determined by ^{1}H NMR spectroscopy. *a*) The reaction was carried out in toluene. Isolated yields after recrystallization are shown.

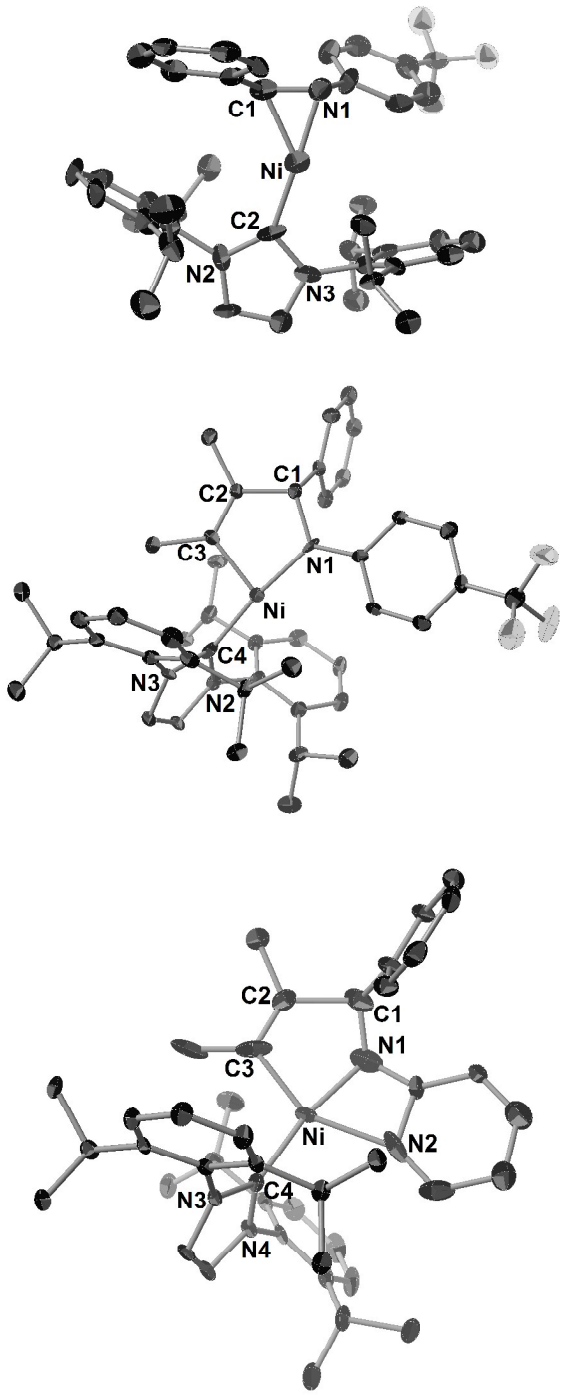


Figure 3. ORTEP drawings of **7c** (a; top), **8cb** (b; middle), and **9db** (c; bottom) with thermal ellipsoids at the 30% probability level. H atoms have been omitted for clarity.

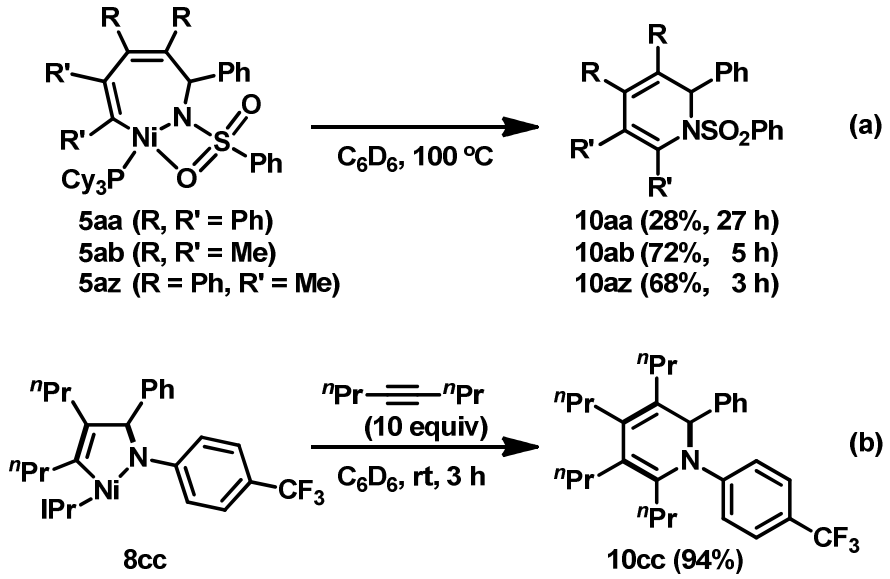
Treatment of **7c** with **2b** or 4-octyne (**2c**) in C_6D_6 at room temperature gave five-membered aza-nickelacycles (**8cb** and **8cc**; Scheme 5).[3n] An X-ray diffraction study of **8cb** demonstrated its T-shaped 14-electron nickel(II) center (Figure 3b), and the sum of the bond angles around nickel along the C3, N, and C4 was 359.0°, indicating that nickel and these three atoms are on the same plane. A space-filling model of **8cb** clearly indicated that such a unique geometry was due mostly to the bulkiness caused by the aryl group on the imine nitrogen atom together with the bulky IPr ligand. On the other hand, the structure of aza-nickelacycles **9db** and **9dc**, which were prepared by the reaction of **7d** with either **2b** or **2c**, had a planar tetracoordinate nickel(II) center with an intramolecular coordination of the *N*-pyridine moiety (Figure 3c).

Yoshikai and co-workers reported that an related aza-nickelacycle similar to **9db** was proposed as a reaction intermediate in the [2+2+2] cycloaddition reaction of two alkynes and an imine bearing a 3-methyl-2-pyridyl group on the nitrogen atom,[12] and their DFT calculation of the model compound revealed that intramolecular coordination of the pyridyl ring to the nickel center stabilized the five-membered aza-nickelacycle regardless of the steric strain caused by the four-membered chelation structure (*vide infra*). It should be mentioned that Jamison and co-workers proposed the related five-membered aza-nickelacycle, generated from the oxidative cyclization of *N*-methyl imine and an alkyne,

as a key intermediate in the nickel-catalyzed three-component coupling reaction of an imine, an alkyne, and BEt_3.[13]

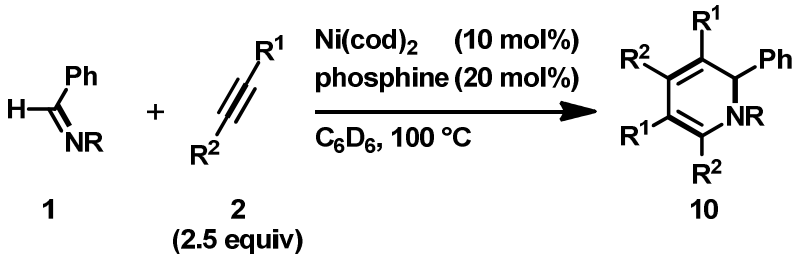
3. Nickel(0)-catalyzed [2+2+2] cycloaddition reaction of an imine with two alkynes: Formation of 1,2-dihydropyridine derivatives.

Heating the seven-membered nickelacycles **5aa**, **5ab**, and **5az** at 100 °C promoted a reductive elimination to yield 1,2-dihydropyridine derivatives (**10aa**, **10ab**, **10az**), respectively (Scheme 6a).[3e] The formation of a 1,2-dihydropyridine by reductive elimination suggested that the development of a nickel-catalyzed [2+2+2] cycloaddition reaction of two alkynes and an imine might be possible. In fact, the intermolecular [2+2+2] cycloaddition of *N*-sulfonyl imine **1a** and **2b** in the presence of a catalytic amount of $Ni(cod)_2$ and PMe^tBu_2 at 100 °C gave the expected 1,2-dihydropyridine **10ab** in 87 % yield (Table 1, entry 1). 3-Hexyne (**2d**) and trimethylsilylacetylene (**2e**) also afforded the corresponding 1,2-dihydropyridines (**10ad** and **10ae**), respectively (entries 5 and 7). The reaction also proceeded catalytically in the presence of PCy_3, although P^tBu_2Me gave better results (entries 2 and 6). In the case of *N*-phosphinyl imine **1b**, the [2+2+2] cycloaddition reaction with **2b** proceeded at 100 ºC in the presence of $Ni(cod)_2$ and PCy_3 (10 and 20 mol%, respectively), giving the corresponding 1,2-dihydropyridine **10bb** in 64 % yield (Table 1, entry 8).[3n]



Scheme 6. Stoichiometric formation of 1,2-dihydropyridines **10**: (a) Reductive elimination from seven-membered nickelacycle **5**. (b) Reaction of five-membered nickelacycle **8cc** with **2c**. Yields were determined by ^{1}H NMR spectroscopy.

Table 1. Ni(0)/phosphine-catalyzed [2+2+2] cycloaddition reaction of *N*-sulfonyl or *N*-phosphinyl imines with alkynes.



entry	imine **1**	alkyne **2**	phosphine	time (h)	product **10**	Yield (%)[a]
1	**1a**	**2b** (R^1, R^2 = Me)	P^{t}Bu$_2$Me	48	**10ab**	87 (50)
2			PCy$_3$	24	**10ab**	64
3			P^{n}Bu$_3$	24	**10ab**	17
4			P(*o*-tolyl)$_3$	29	**10ab**	6
5		**2d** (R^1, R^2 = Et)	P^{t}Bu$_2$Me	70	**10ad**	64 (55)
6			PCy$_3$	24	**10ad**	26
7		**2e** (R^1 = SiMe$_3$, R^2 = H)	P^{t}Bu$_2$Me	18	**10ae**	58 (38)

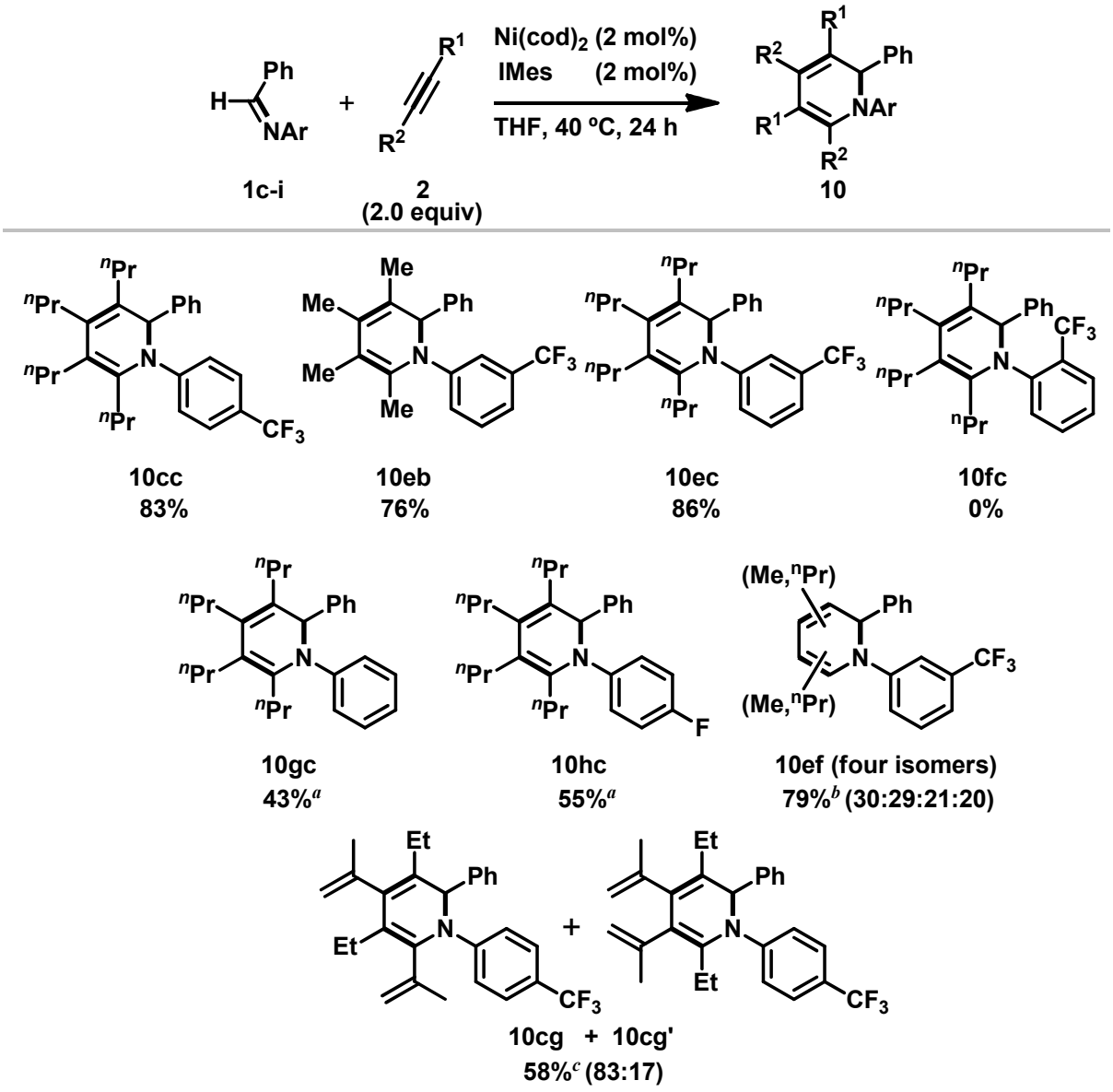
8[b]	**1b**	**2b**	PCy_3	3	**10bb**	– (64)

General conditions: imines (0.10 mmol), alkynes (0.25 mmol), $Ni(cod)_2$ (0.01 mmol), and phosphine ligand (0.02 mmol) were reacted in C_6D_6 (0.5 mL) at 100 ºC. [a] Yields, determined by ^1H NMR spectroscopy, are given. The values in parentheses are of isolated yield. [b] $Ni(cod)_2$ (0.04 mmol), PCy_3 (0.08 mmol), **1b** (0.40 mmol), and **2b** (1.20 mmol) were employed in toluene (1.0 mL).

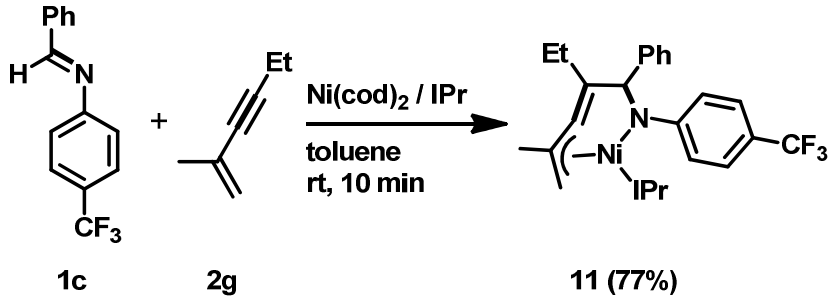
In contrast to the reactivity of the PCy_3-ligated five-membered aza-nickelacycle **3aa**, **8cc** reacted with the second **2c** at room temperature to yield 1,2-dihydropyridines (**10cc**) in 94 % yield (Scheme 6b).[3n] The formation of the corresponding seven-membered aza-nickelacycle could not be observed by ^1H NMR spectroscopy. This result might indicate that the rate of reductive elimination from the seven-membered aza-nickelacycle to give 1,2-dihydropyridine was much faster than that of the insertion of the second alkyne into the five-membered aza-nickelacycle. In sharp contrast, complex **9dc** did not react with **2c** at room temperature due to the suppression of the coordination of **2c** by the intramolecular coordination of the *N*-pyridine.

Ni(0)/IPr-catalyzed [2+2+2] cycloaddition reactions of *N*-aryl imines with alkynes were carried out (Scheme 7).[3n] The reaction of **1c** with **2c** proceeded efficiently with 5 mol % of $Ni(cod)_2$ and IPr to afford **10cc** in 91 % yield. In addition, the catalyst loading could be decreased to 2 mol % without a loss of efficiency by utilizing 1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene (IMes) as a ligand (**10cc**; 92 % NMR yield, 83 % isolated yield). *N*-benzylidene-3-(trifluoromethyl)aniline (**1e**) gave the corresponding 1,2-dihydropyridines **10eb** (from **2b**) or **10ec** (from **2c**) in 76 and 86 % yields, respectively, by using 2 mol % of $Ni(cod)_2$ and IMes; however, *N*-benzylidene-2-(trifluoromethyl)aniline (**1f**) did not afford the product under the same reaction conditions. The present

reaction conditions were successfully applied to a simple *N*-phenyl imine (**1g**) and gave **10gc** in 43 % isolated yield in the presence of $Ni(cod)_2$ and IPr (5 mol % each). Furthermore, *N*-benzylidene-4-fluoroaniline (**1h**) also reacted with **2c** to give **10hc** in a moderate yield. The use of unsymmetrical alkynes such as 2-hexyne (**2f**) gave a mixture of four 1,2-dihydropyridines (**10ef**; total product yield: 79%, ratio of regioisomers: 30:29:21:20) when **1e** was used as an imine partner. However, the reaction of imine **1c** with 2-methyl-1-hexen-3-yne (**2g**) at 100 °C for 72 h resulted in the formation of a mixture of two products (**10cg** and **10cg′**, **10cg**/**10cg′** = 83:17) in a total yield of 58 %. This result can be rationalized by the occurrence of the regioselective incorporation of the first alkyne as a result of the formation of the thermodynamically favorable η^3-butadienyl structure.[3n,14] Thus, the oxidative cyclization of **1c** and **2g** with $Ni(cod)_2$ in the presence of IPr at room temperature gave aza-nickelacycle **11** in 77 % isolated yield (Scheme 8, Figure 4).[3n] Since thermolysis of **11** in C_6D_6 at 100 ºC in the presence of **2g** (10 equiv) led to a regeneration of the starting imine **1c** along with the concomitant formation of a mixture of 1,2-dihydropyridines **10cg** and **10cg′**, trimers of **2g**, and unidentified products, this oxidative cyclization was reversible, taking place regioselectivity to afford **11**. The transition state of the insertion of the second **2g** into **11**, which proceeded at 100 °C, might also have been stabilized by the assistance of η^3-butadienyl coordination, and therefore, **10cg** was formed as a major product whereas the regioselectivity of the second insertion was not perfectly controlled at such a higher temperature (100 °C).



Scheme 7. Nickel(0)/NHC-catalyzed [2+2+2] cycloaddition reaction of *N*-aryl imines with alkynes. General conditions: imines (1.00 mmol), alkynes (2.00 mmol), and $Ni(cod)_2$/IMes (2 mol% each) were reacted in THF (1.0 mL) at 40 ºC for 24 h. Yields of isolated products are given. *a*) 5 mol% of $Ni(cod)_2$ and IPr was used. *b*) Total yield of the four products after isolation. *c*) 10 mol% of $Ni(cod)_2$ and IPr was used in 1,4-dioxane at 100 ºC (72 h). Total yield of **10cg** and **10cg′** is given.



Scheme 8. The stoichiometric reaction of **1c** and **2g** with Ni(0)/IPr. Isolated Yield of **11** is given.

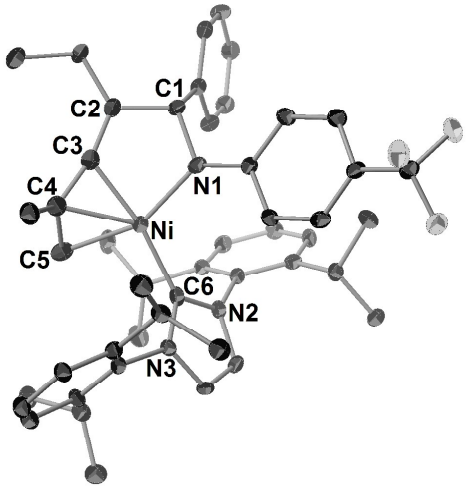
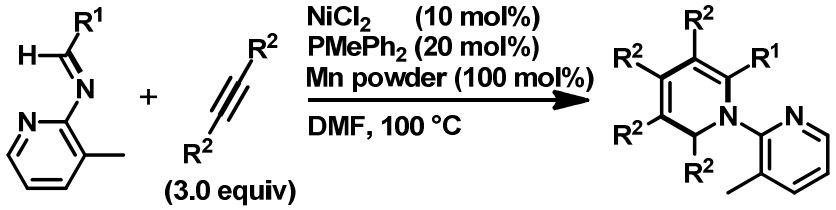


Figure 4. ORTEP drawing of **11** with thermal ellipsoids at the 30% probability level. H atoms have been omitted for clarity.

The nickel(0)-catalyzed [2+2+2] cycloaddition of imines with alkynes proceeded as follows[3e,n]: 1) oxidative cyclization of an imine and an alkyne with nickel(0), giving a five-membered aza-nickelacycle; 2) insertion of a second alkyne, forming a seven-membered aza-nickelacycle; and, 3) reductive elimination from the seven-membered aza-nickelacycle, yielding a 1,2-dihydropyridine with the concomitant regeneration of nickel(0). In the reaction using benzenesulfonyl imine **1a**, reductive elimination from the seven-membered aza-nickelacycle to give 1,2-dihydropyridine took place at 100 °C whereas the formation of the seven-membered intermediate was observed at room temperature. In

addition, Yoshikai also proposed that, based on DFT calculations, reductive elimination would be the rate-limiting step of the reaction with *N*-pyridyl imines.[12] In stark contrast, the reaction rate of the [2+2+2] cycloaddition of *N*-aryl imines with alkynes in the presence of a nickel(0)/NHC catalyst might have been determined by the insertion of the second alkyne into the five-membered aza-nickelacycle.[3n]

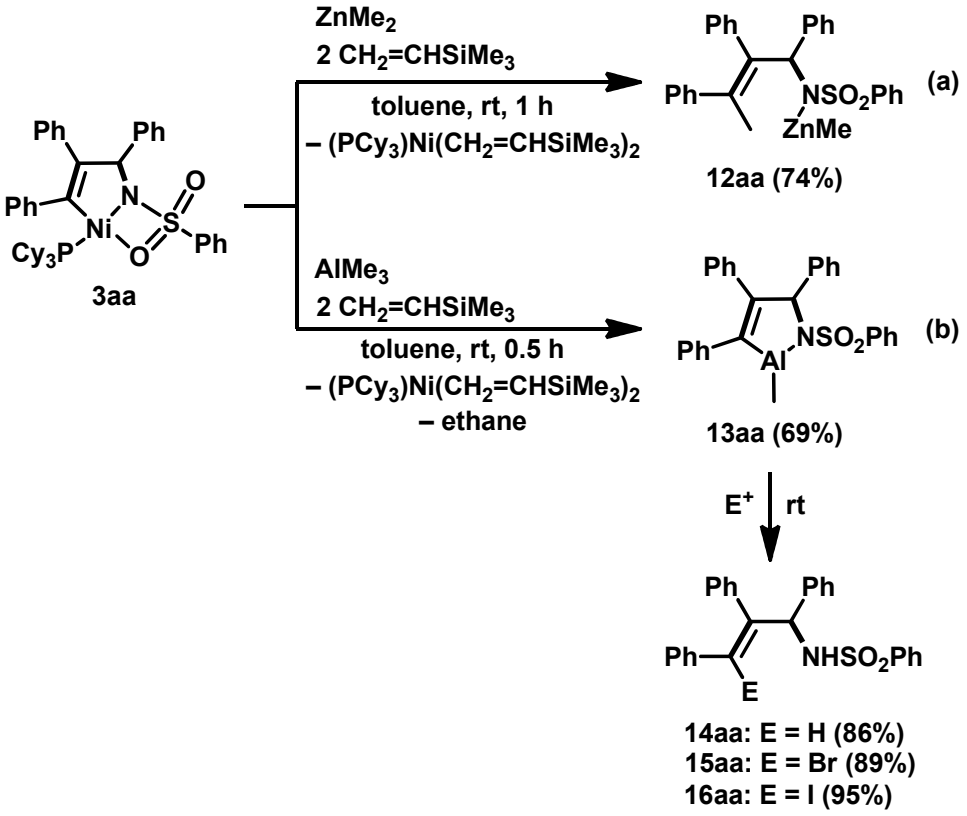
As previously described, Yoshikai and co-workers reported a related nickel-catalyzed [2+2+2] cycloaddition of an aldimine bearing a 3-methyl-2-pyridyl directing group on the nitrogen atom with alkynes to give 1,2-dihydropyridines (Scheme 9).[12] Furthermore, rhodium-catalyzed cycloaddition reactions of imines and alkynes or diynes leading to 1,2-dihydropyridine derivatives have been reported;[15] however, the initial formation of rhodacyclopentadienes, rather than the corresponding five-membered aza-rhodacycle intermediates, was proposed in those reactions.



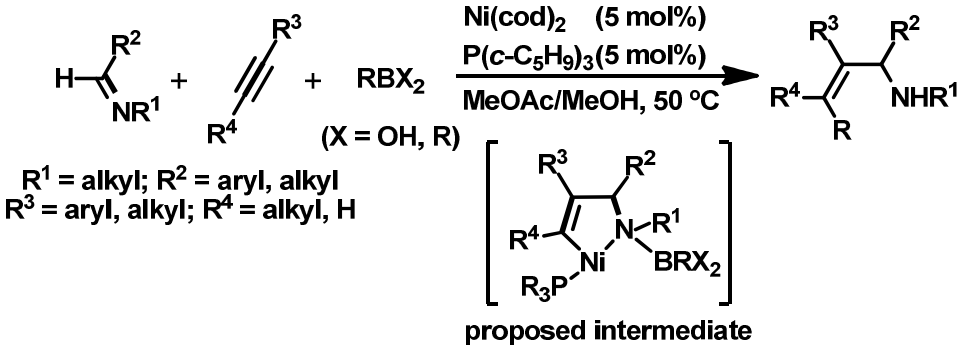
Scheme 9. Nickel(0)-catalyzed [2+2+2] cycloaddition reaction of *N*-pyridyl imines with alkynes.[8]

4. Nickel(0)-catalyzed three-component coupling and cyclocondensation reactions of an imine, an alkyne, and alkylmetal reagents.

Next, we investigated the reactivity of the five-membered aza-nickelacycle **3aa** toward alkylmetal reagents. First, the reaction of **3aa** with $ZnMe_2$ in toluene at room temperature was conducted in the presence of vinyltrimethylsilane, the role of which was to trap the generated nickel(0) species as the known nickel(0) bisalkene complex, $(PCy_3)Ni(CH_2=CHTMS)_2$.[3d,i] As a result, the expected methylzincamido (**12aa**) was obtained in 74% isolated yield together with the formation of $(PCy_3)Ni(CH_2=CHTMS)_2$ (Scheme 10a, Figure 5a).[3h] This stoichiometric reaction was successfully applied to a catalytic reaction wherein a three-component coupling reaction of **1a**, **2a**, and $ZnMe_2$ afforded **12aa**, and it also proceeded in the presence of a catalytic amount of $Ni(cod)_2$ and PCy_3 (10 and 20 mol%, respectively). It should be mentioned that the five-membered aza-nickelacycle **3aa** didn't react with BEt_3 even when heated at 60 °C for 2 h, while **3aa** was analogous to the reaction intermediate proposed in Jamison's works.[13] This was consistent with the fact that *N*-tosyl imines cannot participate in the nickel-catalyzed three-component coupling of an alkyne, an imine, and triethylborane (Scheme 11).[13]

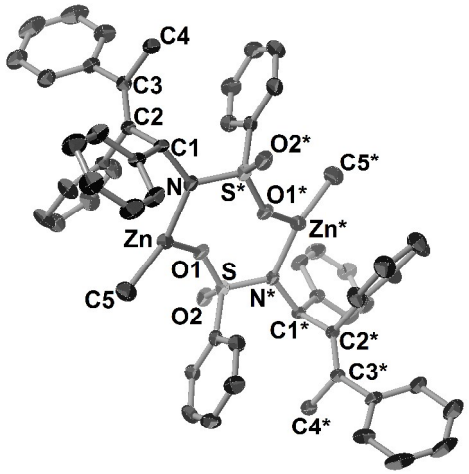


Scheme 10. Reaction of five-membered aza-nickelacycle **3aa** with methylmetal reagents. Yields of isolated products are given. Reaction conditions: for **14aa**, MeOH/toluene, instance; for **15aa**, NBS (2 equiv) in CH_3CN, 0.5 h; for **16aa**, I_2 (excess) in CH_3CN, 2 h, then HCl.



Scheme 11. Nickel(0)-catalyzed three-component coupling reaction of alkynes, imines, and organoboron reagents.[13]

Unexpectedly, a five-membered aza-aluminacycle (**13aa**) was obtained in 69% isolated yield when **3aa** was treated with $AlMe_3$ in place of $ZnMe_2$ under identical reaction conditions (Scheme 10b).[3h] Monitoring of the reaction by means of ^1H NMR spectroscopy indicated a concomitant generation of ethane (δ_H 0.80 ppm, in C_6D_6) and $(PCy_3)Ni(CH_2{=}CHTMS)_2$. An X-ray diffraction study of **13aa** demonstrated that the aluminum atom was covalently bonded to both the carbon and the nitrogen atoms, C3 and N, respectively, to form a five-membered ring, and one methyl group, C4, also was bound to the aluminum center (Figure 5b). As in the case of the methylzincamido **12aa**, the five-membered aza-aluminacycle unit formed a dimer in the crystal lattice, and one of the oxygen atoms in the benzene-sulfonyl group of **13aa** was coordinated to the other aluminum atom. Unlike the three-component coupling product **12aa**, the aza-aluminacycle **13aa** is an organometallic reagent, in which the Al–C bond can react with electrophiles. Indeed, allylamine derivatives (**14aa**–**16aa**) could be obtained by treating **13aa** with electrophiles such as proton and halogenonium (Scheme 10b).



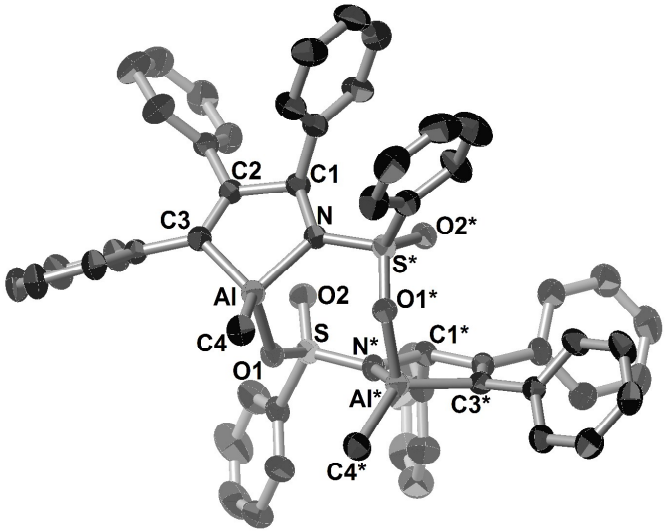
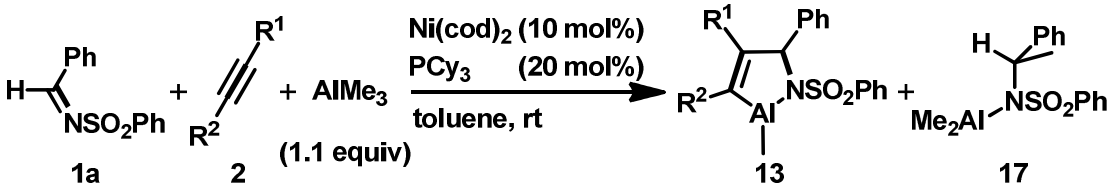


Figure 5. ORTEP drawings of **12aa** (a; top) and **13aa** (b; bottom) with thermal ellipsoids at the 30% probability level. H atoms and the solvated molecule (toluene) in **13aa** have been omitted for clarity. Symmetry transformation used to generate equivalent atoms S* for **12aa**: 2–X, Y, 2–Z, for **13aa**: 2–X, Y, 0.5–Z.

The regeneration of the nickel(0) complex, $(PCy_3)Ni(CH_2{=}CHTMS)_2$, prompted us to develop a Ni(0)-catalyzed cyclocondensation of *N*-sulfonyl imine **1a**, an alkyne, and $AlMe_3$ via the oxidative cyclization of **1a** and the alkyne with nickel(0) as a key step. A major issue to be solved for constructing such a catalytic reaction was that the addition reaction of $AlMe_3$ to **1a**, yielding the corresponding amide (**17**; Table 2), also took place and was accelerated in the presence of 10 mol% of $Ni(cod)_2$ and PCy_3 (Scheme 11, right circle).[16] We found that a slow addition of $AlMe_3$ to the reaction mixture by using a syringe pump suppressed the undesired competitive reaction to give **17**. Finally, the three-component cyclocondensation of **1a**, **2a**, and $AlMe_3$ (slow addition, over 0.5 h) in the presence of 10 mol% of $Ni(cod)_2$ and PCy_3 afforded **13aa** in 71% isolated yield (Table 2, entry 1).[3h,17] Although the isolated

yield of **13aa** was somewhat decreased due to losses in the purification process, NMR analysis of the crude product indicated that this catalytic reaction proceeded quantitatively. In fact, protolysis of the crude product gave the corresponding allylamine **14aa** in 86% isolated yield (entry 1). The same reaction conditions were applied successfully to diphenylacetylene derivatives, such as 1,2-bis(*p*-tolyl)acetylene (**2h**) and 1,2-bis(*p*-trifluoromethylphenyl)acetylene (**2i**), leading to the clean formation of **13ah** and **13ai**, respectively (entries 2 and 3). Furthermore, unsymmetrical alkynes were employed as coupling components in the cyclocondensation with **1a** and $AlMe_3$; Although the use of an excess (5 equiv) amount of 1-phenyl-2-trimethylsilyl-acetylene (**2j**) was required for a smooth progression of the reaction, the corresponding aza-aluminacycle **13aj** was formed in 85% yield as a single regioisomer (entry 4). By contrast, the reaction with 1-phenyl-1-propyne (**2k**) gave **13ak** in 65% yield with 86:14 regioselectivity only when the slow addition of both $AlMe_3$ and the alkyne was conducted to circumvent the insertion of the second alkyne into a five-membered aza-nickelacycle intermediate (entry 5). Dialkyl-substituted symmetrical alkynes such as 2-butyne **2b** and 3-hexyne **2d** did not react efficiently because of the rapid formation of the undesired 7-membered aza-nickelacycle even with the slow addition of a mixture of the alkyne and $AlMe_3$ (entry 6). In the cases cited in runs 4, 5, and 6, the formation of **17** was observed in the ^1H NMR spectra of the crude products.

Table 2. Ni(0)/PCy_3-catalyzed three-component cyclocondensation of *N*-sulfonyl imine **1a**, alkynes **2**, and $AlMe_3$.

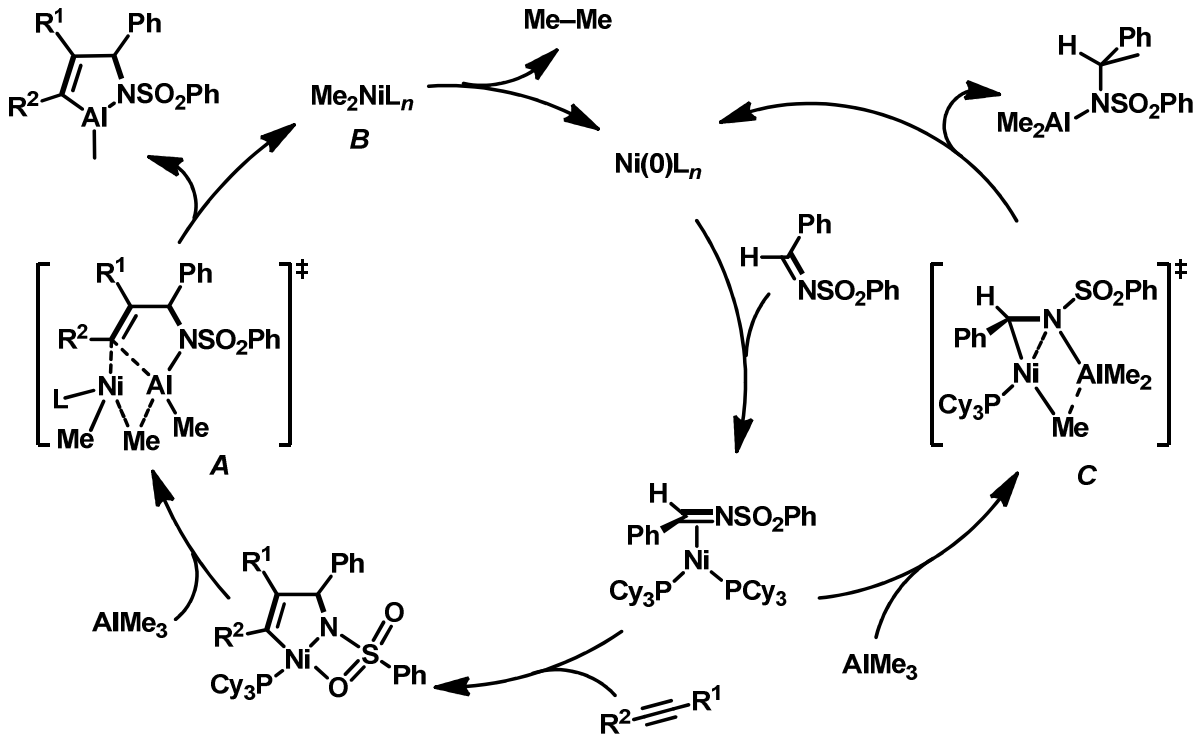


entry	alkyne **2**	time (h)	product	yield (%)[a]	yield of **17** (%)[b]
1	**2a** (R^1, R^2 = Ph)	1.0	**13aa**	86 (71)	–
2	**2h** (R^1, R^2 = *p*-MeC_6H_4)	6.0	**13ah**	85 (82)	–
3	**2i** (R^1, R^2 = *p*-$CF_3C_6H_4$)	3.0	**13ai**	90 (99)	–
4[c]	**2j** (R^1 = $SiMe_3$, R^2 = Ph)	3.0	**13aj**	85 (73)	7
5[d]	**2k** (R^1 = Me, R^2 = Ph)	3.0	**13ak**[e]	65 (44)	13
6[f]	**2d** (R^1, R^2 = Et)	2.5	**13ad**	27	59

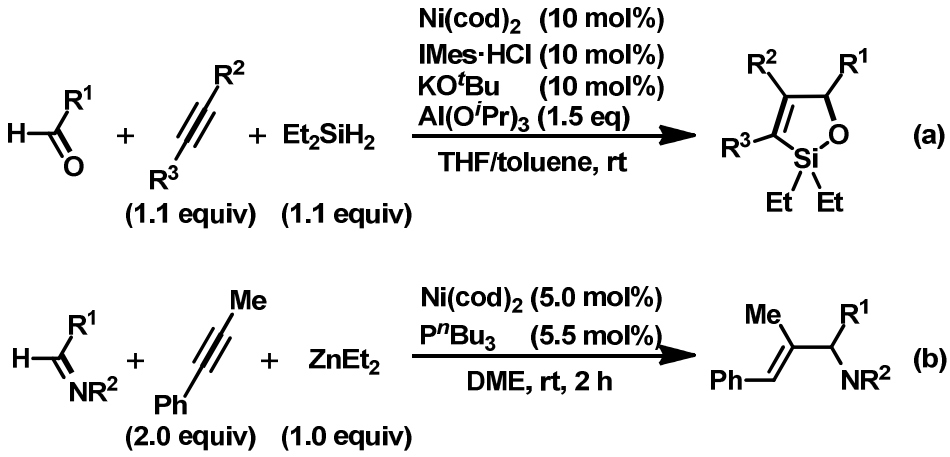
General conditions: **1a**, **2** (0.30 mmol each), and $Ni(cod)_2/PCy_3$ (0.03 mmol) were reacted in toluene (10.0 mL) at rt. After dropwise addition of $AlMe_3$, the reaction mixture was stirred until the color derived from aza-nickelacycle **3** (typically purple) disappeared. [a] Isolated yield as allylamines **14** after protolysis. The values in parentheses are of isolated **13**. [b] Cited yields, determined by ^1H NMR, were of the corresponding protonated products. [c] The reaction was conducted using 1.5 mmol of **2j**. [d] The reaction was conducted with concomitant addition of $AlMe_3$ and **2k**. [e] The minor regioisomer (11%) was also obtained. [f] Formation of a 1,2-dihydropyridine derivative was observed.

Based on the results of the stoichiometric reactions, the cyclocondensation reaction might proceed via the mechanism depicted in Scheme 12.[3h] As previously mentioned, the oxidative cyclization of an imine and an aldehyde with nickel gave a five-membered aza-nickelacycle. The transmetalation between the aza-nickelacycle and $AlMe_3$ afforded a transient intermediate (***A***). Then, the nucleophilicity of the methyl group in ***A*** was high enough to allow the sequential transmetalation between nickel and aluminum, yielding the desired aza-aluminacycle **13** and a dimethyl nickel(II) intermediate (***B***). Reductive elimination from the dimethyl nickel(II) intermediate ***B*** might release ethane for the regeneration of a Ni(0) species.

However, if the nucleophilicity of the methyl group was insufficient, a reductive elimination from ***A*** might proceed to give a three-component coupling product, such as **12**.[13] We also confirmed that in the THF solution, trimethylaluminum can serve as an alkylmetal reagent in a three-component coupling reaction to give the corresponding amide. The key to the success of this catalytic reaction was the slow addition of $AlMe_3$. Without this slow addition, the yield was significantly decreased as a result of the direct reaction of *N*-sulfonyl imine **1a** with $AlMe_3$ to give the side-reaction product **17**. To the best of our knowledge, this is the first example of the catalytic formation of aza-aluminacyclopentenes, although cycloalumination of either olefins or acetylenes mediated by Cp_2Zr derivatives has been used in the preparation of organoaluminum compounds.[18] It should be mentioned that Montgomery and co-workers developed a related nickel-catalyzed cyclocondensation reaction of aldehydes, alkynes, and dialkylsilanes, leading to oxasilacyclopentens (Scheme 13a).[19] In addition, Zhou and co-workers demonstrated the nickel-catalyzed reductive coupling of imines and alkynes with $ZnEt_2$ as a reductant, providing allylic amines with a trisubstituted olefin moiety (Scheme 13b).[20] Rhodium- or iridium-catalyzed reductive coupling reactions of imines and alkynes in the presence of H_2 have been developed by Krische's group.[1g,21]



Scheme 12. A plausible mechanism for the formation of aza-aluminacycle **13**.



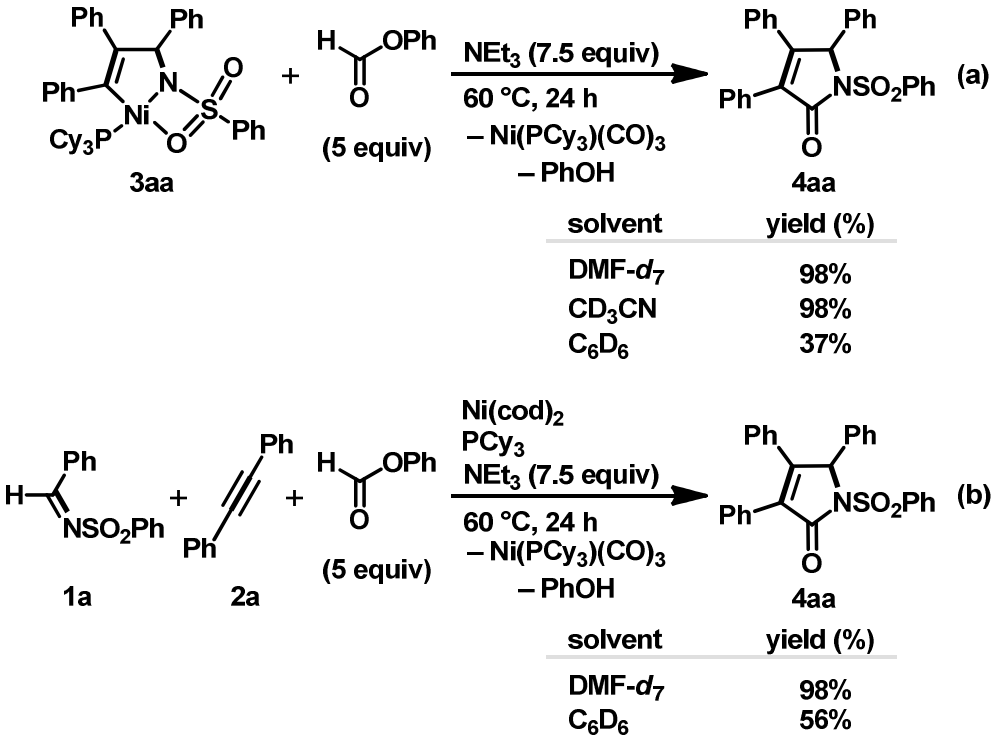
Scheme 13. (a) Nickel(0)-catalyzed cyclocondensation reaction of aldehydes, alkynes, and Et_2SiH_2 and (b) nickel(0)-catalyzed reductive coupling of imines, alkynes, and $ZnEt_2$.[15,16]

5. Nickel(0)-catalyzed formation of γ-lactams via [2+2+2] carbonylative cycloaddition reaction of an imine and an alkyne.

Although a hetero-Pauson–Khand (or aza-Pauson–Khand) reaction, the transition-metal-catalyzed or mediated carbonylative cycloaddition of an imine, either an alkyne or an alkene, and CO, is known as a straightforward method for constructing a γ-lactam skeleton, a transition-metal-catalyzed carbonylative cycloaddition leading to α,β-unsaturated γ-lactams has historically been somewhat limited in the well-established Pauson–Khand reaction.[8,22] In particular, despite the fact that treating the five-membered aza-nickelacycle **3** with CO indisputably took place to give α,β-unsaturated γ-lactams (Schemes 2, 4), such nickel-catalyzed transformation reactions are totally hampered under a CO atmosphere due to the formation of catalytically unreactive nickel carbonyl complexes such as $Ni(CO)_3L$. In order to establish a nickel(0)-catalyzed carbonylative cycloaddition, strict control of the CO concentration is assumed to be required. CO concentration should be high enough to react with the aza-nickelacycle intermediate, yet simultaneously low enough not to generate a catalytically unreactive nickel tricarbonyl complex.

Against this backdrop, the reaction of **3aa** with phenyl formate and NEt_3 was first conducted in various solvent at 60 °C (Scheme 14a).[3o] Phenyl formate has an interesting reactivity that allows it to generate CO *in situ* in the presence of organic/inorganic bases, and its application to transformation reactions involving carbonylation using CO generated *in situ* has been independently reported by Tsuji *et al.*[23] and by Manabe *et al.*.[24] As a result, **3aa** was smoothly transferred into α,β-unsaturated γ-lactams **4aa** in DMF-d_7 and CD_3CN, both of which were reported as suitable solvents to generate CO from

phenyl formate.[23,24a] The formation of PhOH and $Ni(CO)_3(PCy_3)$ was also observed by ^1H and ^{31}P NMR analyses. However, the reaction in C_6D_6, with moderate efficiency of CO generation,[23,24a] afforded a rather complicated mixture that contained **4aa** (37%), PhOH, and a trace amount of $Ni(CO)_3(PCy_3)$.[25] The carbonylation of **3aa** generated *in situ* via the oxidative cyclization of **1a** and **2a** with $Ni(cod)_2/PCy_3$ was then investigated, and **4aa** was again formed in excellent yield in DMF-d_7 whereas CD_3CN did not afford a positive result due to the poor solubility of $Ni(cod)_2$ (Scheme 14b).



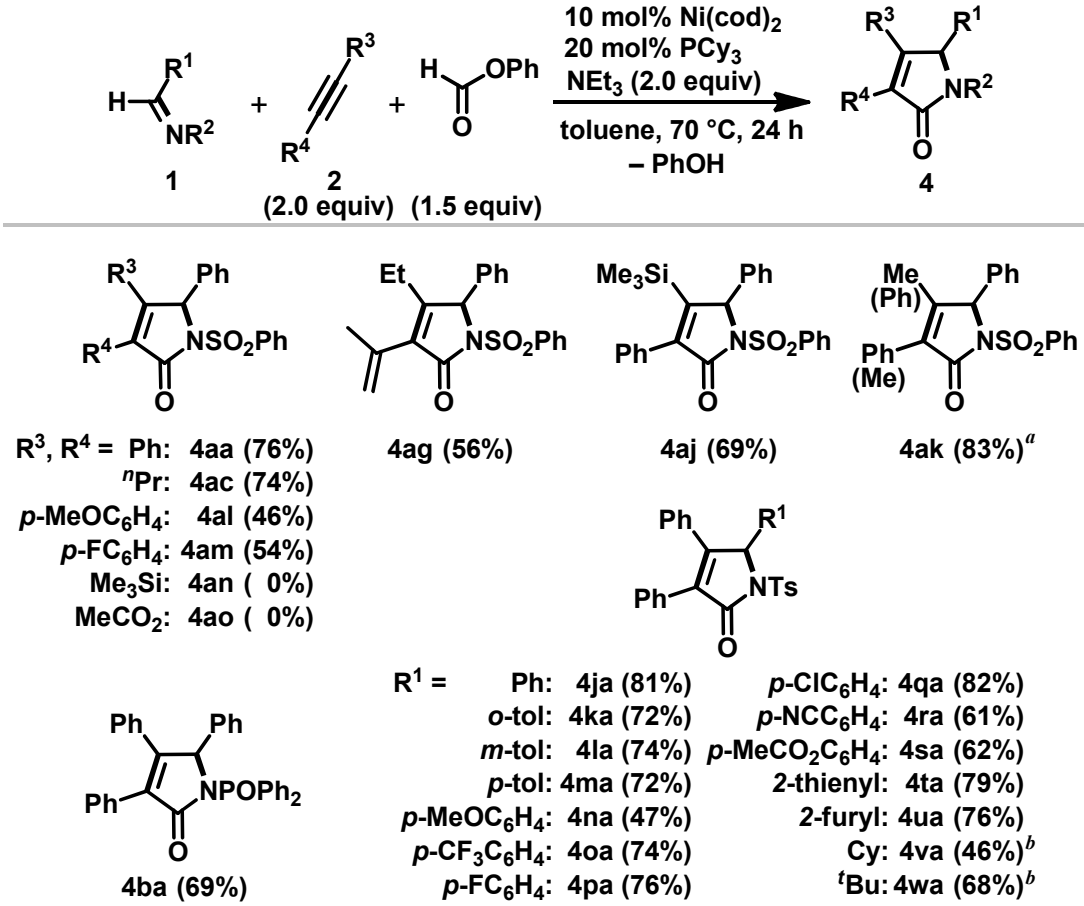
Scheme 14. Reactions of (a) isolated or (b) *in situ* prepared five-membered aza-nickelacycle **3aa** with phenyl formate in the presence of NEt_3. Yields, determined by ^1H NMR spectroscopy, are given.

Contrary to the aforementioned stoichiometric reactions, an attempt at a nickel-catalyzed reaction in DMF was sluggish; the desired γ-lactam **4ac** was not obtained at all from the reaction of **1a**, 4-octyne **2c** (1.0 equiv), phenyl formate (1.5 equiv), and NEt_3 (2.0 equiv) in the presence of $Ni(cod)_2$ and PCy_3 (10

mol% and 20 mol%, respectively).[3o] This was probably due to the rapid and quantitative formation of $Ni(CO)_3(PCy_3)$ based on the amount of Ni(0). Therefore, the reaction was conducted in C_6D_6 in order to lower the rate of the *in situ* generation of CO. As a result, **4ac** was formed in 44% yield at 60 °C over a period of 48 h.[25] Elevating the reaction temperature to 70 ºC and employing 2 equiv of **2c** promoted the reaction efficiency, and the yield of **4ac** was improved to 74% (48 h), which was determined to be our optimum conditions. It should be mentioned that the choice of both ligand and base was crucial for the smooth formation of **4ac**; employing other tertiary phosphines or IPr[26] dramatically diminished the yield of **4ac**, and DBU, DMAP, and quinuclidine were not suitable under the presented conditions.

A variety of *α*,*β*-unsaturated *γ*-lactams **4** were prepared by the nickel(0)-catalyzed [2+2+1] carbonylative cycloaddition of imines **1** and alkynes **2** with phenyl formate (Scheme 15).[3o] Both alkyl-substituted symmetrical alkynes **2a** and **2c** as well as aryl-substituted ones, such as 1,2-bis(*p*-anisyl)acetylene (**2l**) and 1,2-bis(*p*-fluorophenyl)acetylene (**2m**), gave the corresponding γ-lactams (**4aa**, **4ac**, **4al**, and **4am**) in moderate to good isolated yields. Neither bis(trimethylsilyl)acetylene (**2n**) nor dimethyl acetylenedicarboxylate (**2o**) gave the corresponding products probably due to difficulties with the simultaneous coordination of the alkyne **2n** or **2o** and **1a** to nickel(0). In the former reaction, the coordination of **2n** to nickel was hampered under these conditions, whereas the facile cyclotrimerization of **2o** took place in a latter reaction.[3e] As anticipated from the regioselective formation of **11** (Scheme 8), **4ag** was formed as a single regioisomer from 2-methyl-1-hexen-3-yne, **2g**. In addition, 1-phenyl-2-trimethylsilyl-acetylene, **2j**, also gave **4aj** as a sole regioisomer in 69% yield. On the other hand, the

reaction employing 1-phenyl-1-propyne, **2k**, as an unsymmetric alkyne proceeded to afford **4ak** in 83% yield as a mixture of regioisomers with a ratio of 89/11, and this ratio was comparable to that observed in the cyclocondensation reaction using **2k** (Table2, entry 5). The regioselectivity observed in these reactions with **2j** and **2k** might be due to the contribution of an η^3-benzyl structure in a possible intermediate.[27]

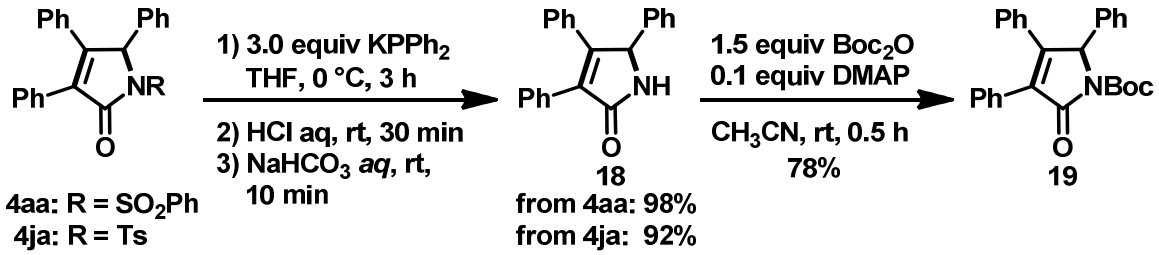


Scheme 15. Nickel(0)/PCy_3-catalyzed [2+2+1] carbonylative cycloaddition reaction of imines **1** and alkynes **2** with phenyl formate. General conditions: **1** (0.40 mmol), **2** (0.80 mmol), phenyl formate (0.60 mmol), NEt_3 (0.80 mmol) and $Ni(cod)_2/PCy_3$ (0.04 and 0.08 mmol, respectively) were reacted in toluene (1.0 mL) at 70 ºC for 24 h. Yields of isolated products are given. *a*) The structure of the minor

regioisomer was depicted in parentheses (major/minor = 89/11). *b*) $Ni(cod)_2/PCy_3$ (0.08 and 0.16 mmol, respectively) was employed.

The substrate scope with respect to imines was investigated with diphenylacetylene **2a** under the optimal conditions.[3o] The catalytic reaction with *N*-phosphinyl imine **1b** proceeded to give **4ba** in 69% yield. A variety of *N*-benzylidene-toluenesulfonamide derivatives (**1j**–**s**) were applicable to the presented catalytic system to yield the corresponding γ-lactams (**4ja**–**sa**) in good to high yields whereas a significant decrease in the yield of **4na** was found in the case of **1n** bearing an electron-rich arene ring. The thienyl- and furyl-substituted imines (**1t** and **1u**) also gave **4ta** and **4ua** in 79% and 76% yields, respectively. Although an increase in the catalyst loading was required, alkyl-substituted *N*-tosylimines, such as CyCH=NTs (**1v**) and tBuCHNTs (**1w**), participated in the carbonylative [2+2+1] cycloaddition reaction to give *N*-Cy- and *N*-^{t}Bu-γ-lactams (**3na** and **3oa**) in 46% and 68% yields, respectively.

The reaction of carbonylative [2+2+1] cycloaddition reaction products **4aa** or **4ja** with phosphide anion[28] resulted in the removal of the *N*-arylsulfonyl groups, yielding a synthetically valuable *N*-protonated γ-lactam **18** in excellent yields (Scheme 16). Boc-protection of **18** was successfully achieved by treating with Boc_2O and DMAP to give *N*-Boc-γ-lactam **19**, which is regarded as an important synthetic intermediate.[29,30] Combined with these derivatizations, the present catalytic system would afford a wide range of γ-lactams without the use of toxic CO gas and expensive transition metals under harsh reaction conditions, which were often found in the reports of related work.[8d,22]



Scheme 16. Synthesis of *N*-protonated and *N*-Boc-substituted *γ*-lactams **18** and **19**. Yields of isolated products are given.

6. Conclusion and outlook

Continuous efforts on the development of transition-metal-catalyzed cycloaddition and multicomponent coupling reactions have been devoted to allow the rapid preparation of highly complicated organic molecules from a variety of unsaturated compounds. As highlighted in this *Perspective*, catalytic transformation reactions that involve five-membered aza-nickelacycle intermediates generated via the oxidative cyclization of an imine and an alkyne with nickel(0) have been developed over the past few decades. The ingenious design of either *N*-substituents of imines or the ligand that coordinates to nickel, indeed, expands remarkably the scope of imine derivatives in practical synthetic applications. We are hopeful that the presented reactions will help provide further opportunities to develop novel catalytic transformations of imines, and will contribute to further the progress in this field of chemistry.

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Aza-Nickelacycle Key Intermediate in Nickel(0)-Catalyzed Transformation Reactions

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Oxidative cyclization of alkynes and imines with nickel(0) is a key step in multicomponent coupling and cycloaddition reactions to give nitrogen-containing organic compounds.