ACCOUNTS of chemical research

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Nickel-Catalyzed Reactions Directed toward the Formation of Heterocycles

Published as part of the Accounts of Chemical Research special issue "Earth Abundant Metals in Homogeneous Catalysis".

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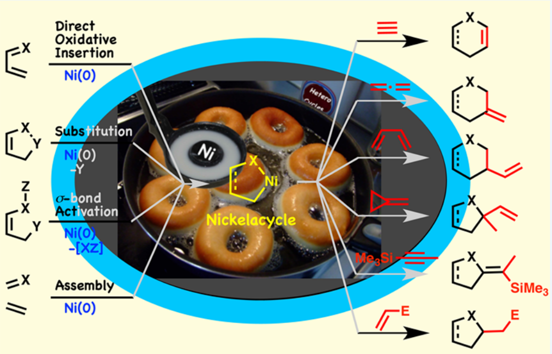


CONSPECTUS: Heterocycles have garnered significant attention because they are important functional building blocks in various useful molecules, such as pharmaceuticals, agricultural chemicals, pesticides, and materials. Several studies have been conducted regarding the preparation of heterocyclic skeletons with an emphasis on selectivity and efficiency. Three strategies are typically employed to construct cyclic molecules, namely, cyclization, cycloaddition, and ring-size alterations. Although each method has certain advantages, cycloaddition may be superior from the viewpoint of divergence. Specifically, cycloadditions enable the construction of rings from several pieces. However, the construction of heterocycles via cycloadditions is more challenging than the construction of carbocycles. For heterocycle construction, simple pericyclic reactions rarely work smoothly because of the large HOMO−LUMO gap unless well-designed combinations, such as electron-rich dienes and aldehydes, are utilized. Thus, a different approach should be employed to prepare heterocycles via cycloadditions. To this end, the use of metallacycles containing heteroatoms is expected to serve as a promising solution. In this study, we focused on the preparation of heteroatom-containing nickelacycles. Because nickel possesses a relatively high redox potential and an affinity for heteroatoms, several methods were developed to synthesize heteronickelacycles from various starting materials. The prepared nickelacycles were demonstrated to be reasonable intermediates in cycloaddition reactions, which were used to prepare various heterocycles. In this Account, we introduce the following four methods to prepare heterocycles via heteronickelacycles. (1) Direct oxidative insertion of Ni(0) to *α*,*β*-unsaturated enone derivatives: treatment of 3-ethoxycarbonyl-4-phenyl-3-buten-2-one with Ni(0) afforded an oxa-nickelacycle, which reacted with alkynes to give pyrans. (2) Substitution of a part of a cyclic compound with low-valent nickel, accompanied by elimination of small molecules such as CO, CO_2, and acetophenone: treatment of phthalic anhydride with Ni(0) in the presence of $ZnCl_2$ afforded the oxanickelacycle, which was formed via decarbonylative insertion of Ni(0) and reacted with alkynes to give isocumarins. (3) Cyclization to a nickelacycle, accompanied by two C−C *σ*-bond activations: insertion of Ni(0) into an arylnitrile, followed by aryl cyanation of an alkyne, gave alkenylnickel as an intermediate. The alkenylnickel species subsequently underwent an intramolecular nucleophilic attack with an arylcarbonyl group to form a cyclized product with concomitant cleavage of the C−C *σ*-bond between the carbonyl and aryl groups. (4) Assembly of several components to form a heteroatom-containing nickelacycle via cycloaddition: a new [2 + 2 + 1] cyclization reaction was carried out using an *α*,*β*-unsaturated ester, isocyanate, and alkyne via a nickelacycle. On the basis of these four strategies, we developed new methods to prepare heterocyclic compounds using nickelacycles as the key active species.

1. INTRODUCTION

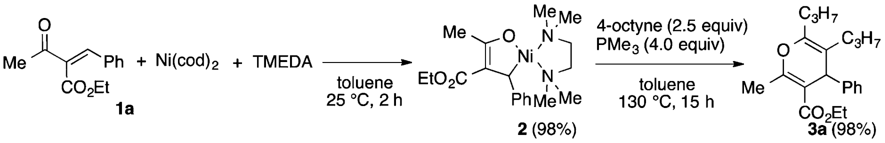
Over the last few decades, transition-metal catalysts have enormously benefitted organic syntheses.[1] These catalysts have realized many useful reactions, many of which had been considered to be impossible. Almost all transition metals in the periodic table have been thoroughly investigated and studied as catalysts for organic reactions. Among them, nickel is one of the most widely used transition-metal catalysts in organic transformations.[2] Among the late transition metals, Ni possesses a relatively high redox potential and reasonable Lewis acidity; because of these characteristics, a bond between carbon and various atoms can be activated via an oxidative process to afford the corresponding organonickel, which would react with various *π*-bond functional groups. This Account mainly describes our efforts toward the development of Ni-catalyzed reactions directed toward the synthesis of heterocycles in which a heteronickelacycle is assumed to be a reactive intermediate.

To construct a nickelacycle containing a heteroatom, we considered several routes. The following four routes can be

Received: January 28, 2015
Published: May 19, 2015

DOI: 10.1021/acs.accounts.5b00041
Acc. Chem. Res. 2015, 48, 1703–1716

Scheme 1. Preparation and Isolation of Oxanickelacycle 2



assumed to obtain heteroatom-containing nickelacyclopentane derivatives. (1) Direct oxidative insertion: the oxidative addition of a conjugated heterodiene, such as an enone, to Ni(0) would afford a heteronickelacycle; however, only the formation of some π complexes had been reported[3] prior to our isolation of 3-nickela-2-oxacyclopentene.[4] (2) Substitution of a part of the cyclic compound with low-valent nickel: a simple insertion of low-valent nickel to the cyclic substrate followed by the elimination of a small molecule, such as carbon monoxide (CO), carbon dioxide (CO_2), or ketone ($R_2C{=}O$) can also serve as an alternative route to the heteroatom-containing nickelacycle.[5] As the transformation is a ring-structure conversion, it does not likely entail an entropical disadvantage, which is often a serious obstacle to forming a cyclic structure by cyclization. (3) Cyclization to the nickelacycle accompanied by the σ-bond activation of two C−C σ-bonds by Ni(0) at both ends: although there are some examples of C−C σ-bond activation,[6] the formation of the heteronickelacycle by the activation of two C−C σ-bonds is a novel reaction. (4) Assembly of several components to form the heteronickelacycle via cycloaddition. The method is really convenient; however, homocoupling reactions are a significant disadvantage.[7] On the basis of these four strategies, we have developed new methods for preparing heterocyclic compounds using heteronickelacycles as the key active species.

2. OXANICKELACYCLE BY DIRECT INSERTION OF NI(0) INTO ENONES

[4 + 2] Cycloaddition between Alkynes and Enones

The hetero-Diels−Alder reaction between electron-rich dienes and aldehydes has been recognized as an efficient method to obtain 3,6-dihydro-2*H*-pyrans even with asymmetric induction;[8,9] however, the reaction between simple dienes and aldehydes is difficult. Recently, we have reported that the reaction between simple dienes and aldehydes can be performed efficiently in the presence of an iron porphyrin catalyst.[10] To construct the same type ring, the reaction between α,β-unsaturated enones as a four-atom unit and alkene/alkyne can be considered as an alternative, but it is quite hard to get it to proceed. For this purpose, the reaction of a nickelaoxacyclopentene with an alkyne is also promising. During our studies to isolate an oxanickelacycle from an enone and Ni(0), we found that a mixture of a stoichiometric amount of 3-ethoxycarbonyl-4-phenyl-3-buten-2-one (**1**), Ni(cod)$_2$, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine in toluene at 25 °C afforded the corresponding oxanickelacycle **2**, which was quantitatively isolated as an orange crystal.[4] The ethoxycarbonyl group is a crucial substituent. In addition, the treatment of **2** with 4-octyne (2.0 equiv) in the presence of trimethylphosphine (4.0 equiv) afforded the [4 + 2] adduct (i.e., pyran **3a**) in 98% yield (Scheme 1). Figure 1 shows the ORTEP diagram of **2**.

This reaction was also examined catalytically. As shown in Scheme 2, [4 + 2] cycloaddition between enone **1** and various alkynes proceeded to give the corresponding pyrans **3** via **4** in good yields under catalytic conditions.

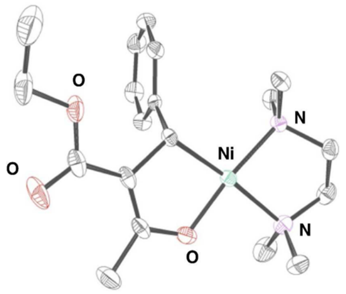


Figure 1. ORTEP diagram of **2**.

Nickel-catalyzed intramolecular [4 + 2] cycloaddition was also attempted, as shown in Scheme 3. The nickel-catalyzed reaction of **5** proceeded under optimized conditions to give **6a** and **6b** in 92 and 99% yields, respectively.

Instead of alkynes, allenes were used for [4 + 2] cycloaddition.[11] Under the same conditions for the reaction with alkynes in Scheme 2, the corresponding [4 + 2] adduct was obtained in only 15% yield. The lower reactivity of allenes compared to alkynes as a π-donor can be compensated for by the electron-withdrawing effect of the ligand on the intermediary oxanickelacyclopentane. However, the electron-donating effect is also necessary to make the key nickelaoxacycle from **1** by the oxidative process using Ni(0). For this purpose, we used iminophosphine ligand **7**, which not only works as a π-acceptor but also as a σ-donor ligand.[12] In fact, the treatment of enone **1** with Ni(cod)$_2$ in the presence of **7** at 25 °C afforded a quantitative amount of corresponding nickelacycle **8**, which was characterized by single-crystal X-ray diffraction (Figure 2).[11] Nickelacycle **8** with 1,2-octadiene gave the [4 + 2] adducts **9a** and **10a** stereoselectively in 98% yield (Scheme 4).

The catalytic reaction was also possible. The reaction between **1** and allenes using a nickel catalyst, prepared from Ni(cod)$_2$ and **7**, worked well to afford adducts **9** and **10** in good yields (Scheme 5).

[4 + 1] Cycloaddition between Methylenecyclopropane and Enones

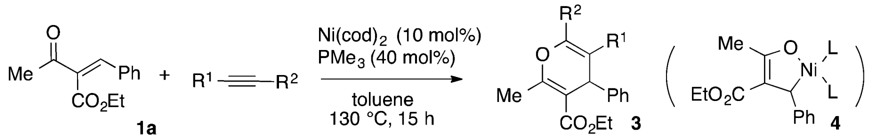
As shown in Scheme 6, methylene-2-phenylcyclopropane and oxanickelacycle **8** gave the [4 + 1] adducts (i.e., dihydrofurans **11a** and **12a** as a diastereomeric mixture).[13,14]

The catalytic reaction protocol was also examined. A mixture of **1** and methylenecyclopropanes was heated at 70 °C in toluene in the presence of Ni(cod)$_2$ (10 mol %) and a phosphine ligand (40 mol %). In the catalytic reaction, dimethylphenylphosphine gave good results from the viewpoint of yield and diastereoselectivity (99%, 12/1, respectively). The results using α-ethoxycarbonylenones **1** and methylenecyclopropanes are shown in Scheme 7.

As shown in Scheme 8, deuterium-labeled methylene-2-phenylcyclopropane was used as the substrate. In the obtained

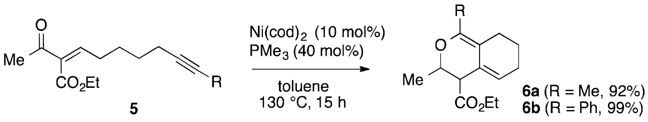
DOI: 10.1021/acs.accounts.5b00041
Acc. Chem. Res. 2015, 48, 1703−1716

Scheme 2. Nickel-Catalyzed Cycloaddition of Enone 1 with Alkynes



R^1	R^2	**3**
C_3H_7	C_3H_7	99%
Ph	Ph	74
CH_2OMe	CH_2OMe	82
Me	*i*-C_3H_7	73 (3/1: regioisomeric mixture)
Me	Ph	79

Scheme 3. Nickel-Catalyzed Intramolecular [4 + 2] Cycloaddition



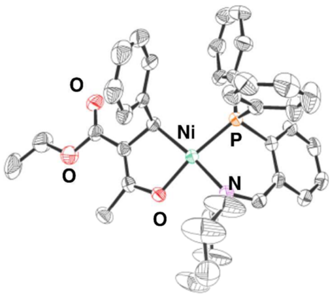


Figure 2. ORTEP diagram of **8**.

dihydrofuran **13**, D atoms were observed at the methyl and vinylic positions. This distribution pattern of D atoms can be explained by the mechanism proposed in Scheme 9.

As shown in Scheme 9, the insertion of the alkene group of methylenecyclopropane to oxanickelacycle **8** formed 7-membered nickelacycle **14**, which rearranged into 8-membered nickelacycle **15** by *β*-carbon elimination. The ring opening via *β*-deuteride elimination afforded **16**, and deuteronickelation of the exomethylene group afforded 6-membered oxanickelacycle **17**. Reductive elimination afforded 5-membered product **13** with the regeneration of Ni(0).

3. HETERONICKELACYCLE BY SUBSTITUTION REACTION WITH NI(0)

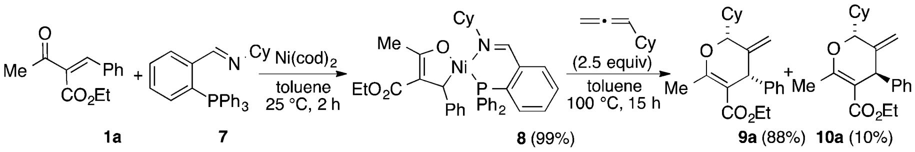
Decarbonylative Formation of Oxanickelacycles from Cyclic Anhydrides

The 1-nickela-2-oxacyclopent-3-ene derivatives **2** and **8**, prepared from the direct oxidative insertion of *α*-ethoxycarbonylenone **1**, worked as key intermediates for the synthesis of pyrans and furans by cycloaddition. The method, however, suffered from the limitation of the starting enones. Next, we tried to obtain the nickelaoxacycle by the decarbonylation of anhydride with Ni(0). In 1971, Trost reported the Ni(0)-mediated elimination of CO and CO_2 from anhydride.[5a] As an intermediate, a nickelacycle, which is formed by oxidative insertion to the C−O bond followed by decarbonylation, was proposed. In 1984, Yamamoto isolated a nickelacycle from succinic anhydride by oxidative insertion to the C−O bond followed by decarbonylation.[5b] We tried to employ this process to form an oxanickelacycle, which can react with an alkyne to afford an oxygen-atom-containing heterocycle. As shown in Scheme 10, we attempted to obtain a 5-membered oxanickelacycle by oxidative insertion and sequential decarbonylation reactions; **19** would form corresponding isocoumarins **21** via alkyne insertion followed by reductive elimination.[15]

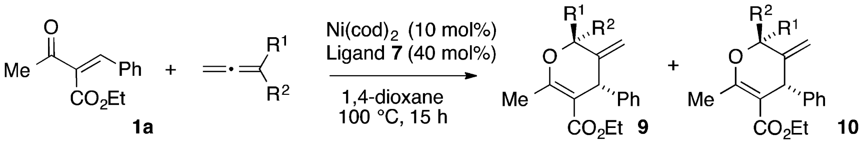
As shown in Scheme 11, treatment of phthalic anhydride with 4-octyne in the presence of $Ni(cod)_2$ (10 mol %) and PMe_3 (40 mol %) in acetonitrile at 80 °C gave desired isocoumarin **21a** in 12% yield. Considering the ease of the reported route to nickelacycles from anhydrides, the crucial step affording cycloadducts **21** should be alkyne insertion or reductive elimination. It is difficult to create an electron-deficient center on Ni under the use of electron-donating phosphine ligand PMe_3; hence, a Lewis acid was added. In fact, the yield was dramatically improved by its addition.[16] Among the Lewis acids tested, $ZiCl_2$ in particular gave **21a** in 96% yield. According to the density functional theory (DFT) studies of some groups,[17] the reaction proceeds analogously to that described in Scheme 10. These groups have suggested that the rate-determining step is alkyne insertion. Although the reaction pathway did not change by the addition of $ZnCl_2$, it significantly decreased the free energies of all intermediates and transition states. Various cyclic anhydride derivatives can be converted into the corresponding 2*H*-pyran-2-ones (Scheme 12).

Instead of alkynes, 1,3- and 1,2-dienes also underwent insertion to oxanickelacycle, formed from phthalic anhydride via decarbonylation (Schemes 13 and 14, respectively).[18] In the case of the reaction of 1,2-dienes, the use of the chiral phosphine (*S*,*S*)-*i*Pr-foxap afforded the optically active lactone (**23**, R = Cy, R′ = H, 64% yield, 81% ee).

Scheme 4. Formation of Nickelaoxacycle 8 and Its Reaction with 1,2-Octadiene

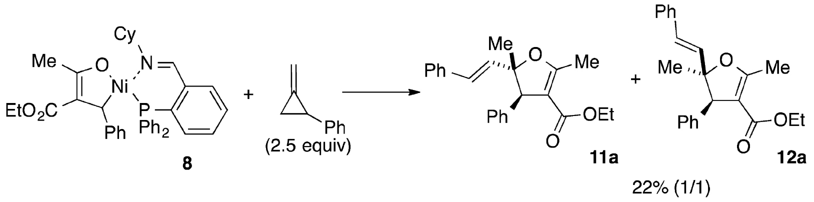


Scheme 5. [4 + 2] Cycloaddition between Enone 1 and Allenes

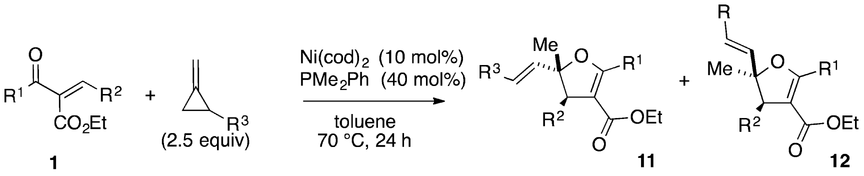


R^1	R^2	Adduct (**9** / **10**)
H	Cy	99% (9/1)
C_5H_{11}	C_5H_{11}	99
H	CH_2CH_2Ph	88 (1/1)
H	CH_2CH_2CN	99 (2/3)
H	CH_2CH_2OAc	87 (2/3)

Scheme 6. Reaction of Oxanickelacycle 8 with Methylene-2-phenylcyclopropane

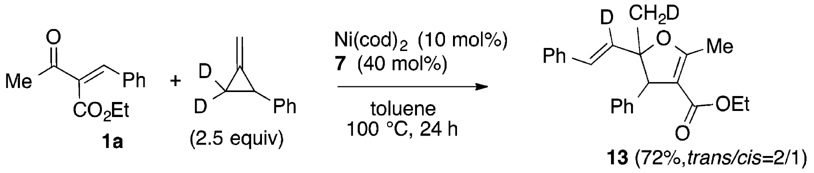


Scheme 7. Nickel-Catalyzed [4 + 1] Cycloaddition of 1 with Methylenecyclopropanes



R^1	R^2	R^3	Adduct (**11** / **12**)
Me	Ph	Ph	99% (12/1)
Me	Ph	Ph	76 (8/1) (Ligand **7** was used)
Ph	Ph	Ph	43 (9/1)
Ph	4-$CF_3C_6H_4$	Ph	81 (8/1)
Me	1-naphtyl	Ph	78 (11/1)
Me	Ph	4-FC_6H_4	85 (5/1)

Scheme 8. Cycloaddition with Deuterium-Labeled Methylenecyclopropane



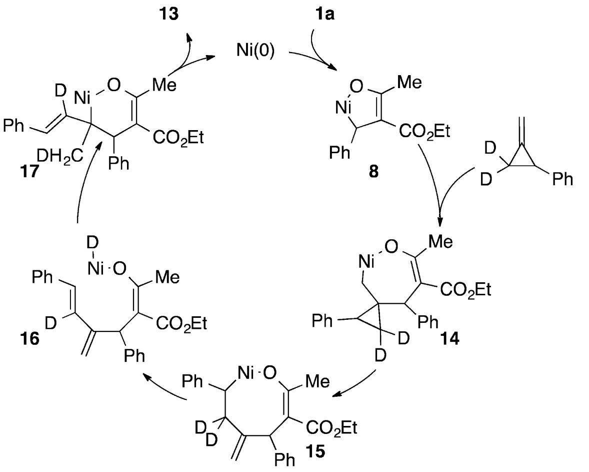
Decarbonylative Formation of Azanickelacycles from Phthalimides

Instead of phthalic anhydrides, the use of phthalimides also afforded cycloadducts with alkynes in the presence of a nickel catalyst.[19] As shown in Scheme 15, various N-substituted phthalimides were treated with a catalytic amount of Ni(0)/PMe$_3$ in the presence of alkyne. The process can be considered to proceed analogously to the reaction of phthalic anhydride.[17b] In the case of phthalic anhydride, the addition of a Lewis acid dramatically facilitated the reaction pathway by tuning the electron density of the nickelacycle. In the case of phthalimides, the group on nitrogen can tune the electron density of the crucial intermediate and can substitute for the use of Lewis acids. In fact, the electron-withdrawing group on nitrogen gave better yields.

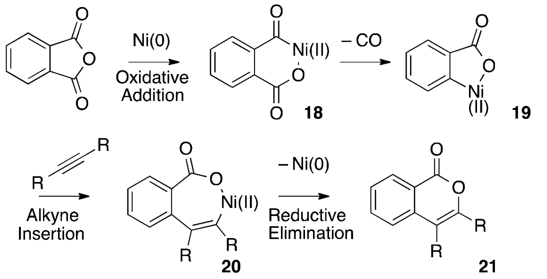
Instead of alkynes, 1,3-dienes were treated with the azanickelacycle from phthalimide to afford dihydroisoquinolones **25**, as shown in Scheme 16.[20] A comparison of these two transformations in Schemes 15 and 16 reveals that different solvents were used. For the insertion of dienes into the azanickelacycle, the polar intermediate π-allylnickel was formed; a polar solvent such as 1,4-dioxane was suitable for the reaction.

When 1-trimethylsilyloctyne was treated with the azanickelacycle derived from phthalimide, the expected isoquilonones (**24**) were obtained in only 15% yield as a mixture of regioisomers. Thus, we tried to improve the yield by adding a Lewis acid and found that the addition of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide (MAD))[21] afforded 5-membered isoindolinone **26** (Scheme 17).[22] With the assistance of a Lewis acid, Ni tends to be electron deficient and can strongly coordinate to 1-trimethylsilylalkyne. In this

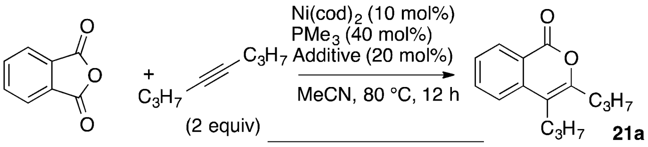
Scheme 9. Plausible Reaction Mechanism for 13



Scheme 10. Plausible Route for the Nickel-Catalyzed Decarbonylative Addition of Phthalic Anhydrides to Alkynes



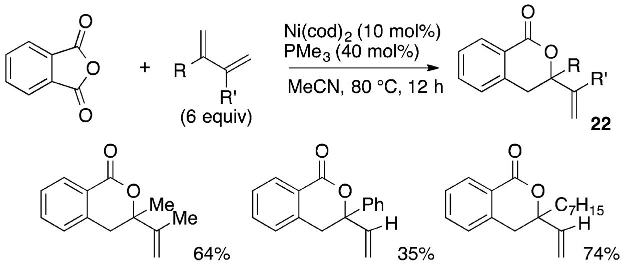
Scheme 11. Effect of the Lewis Acid



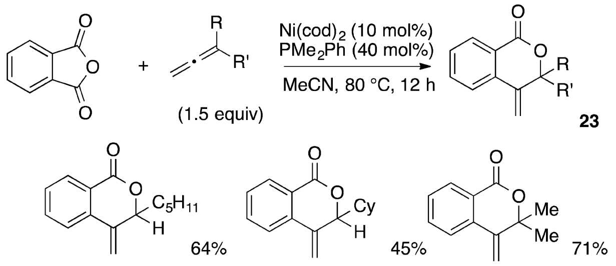
Additive	21a
none	12%
$ZnCl_2$	96
BPh_3	92
LiCl	76

step, the alkyne complex isomerized to a vinylidene complex by silyl group migration.[23] The vinylidene complex rearranged to a 6-membered azanickelacycle, which finally furnished the 5-membered product via reductive elimination. The configuration of the olefinic bond may be determined by the steric bulk of trimethylsilyl group during the formation of the 6-membered nickelacycle.

Scheme 13. Decarbonylative Cycloadditions of Phthalic Anhydride with 1,3-Dienes



Scheme 14. Decarbonylative Cycloadditions of Phthalic Anhydride with 1,2-Dienes

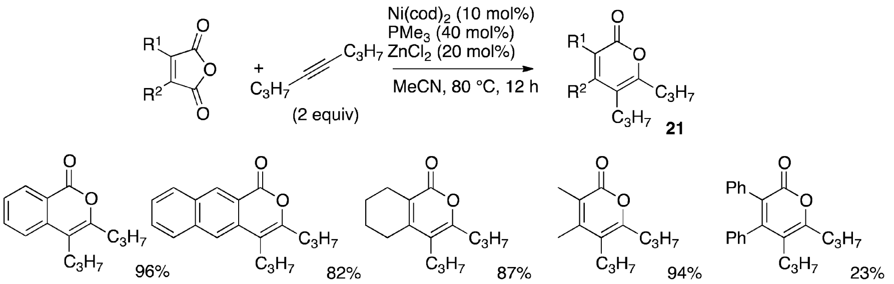


Decarbonylative Formation of Thionickelacycles from Cyclic Thiophtalic Anhydrides and Thiostatins

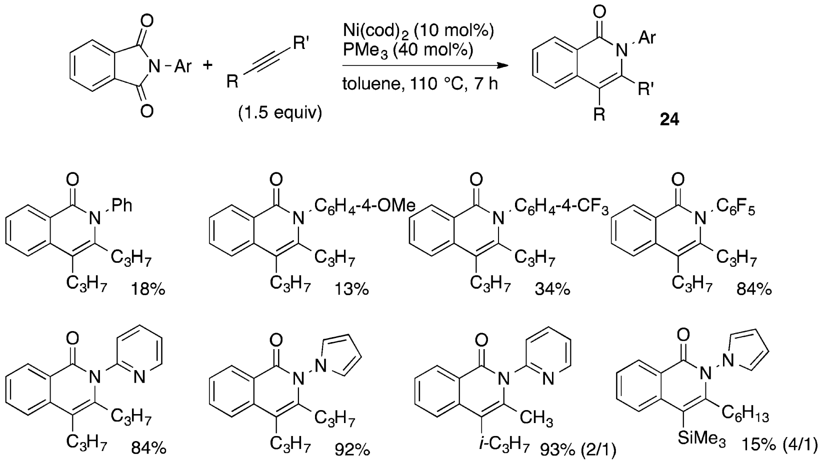
Thiophthalic anhydride exhibited characteristic reactivity with alkynes under nickel-catalyzed decarbonylation conditions. As shown in Scheme 18, three types of cycloaddition products were obtained. The treatment of thiophthalic anhydride with 4-octyne in the presence of a Ni(0) catalyst afforded a mixture of thioisocoumarin **27**, benzothiophene **28**, and thiochromone **29**. However, by carefully tuning the reaction conditions, the selective formation of **27**–**29** was possible.[24]

The formation of sulfur-containing cycloadducts **27**–**29** can be explained as shown in Scheme 19. The oxidative insertion of thiophthalic anhydride to Ni(0) afforded the 6-membered nickelacycle **30**, which formed the 5-membered nickelacycle **31** by decarbonylation, similar to the reactions observed for phthalic anhydride and phthalimide. The insertion of alkynes to **31** formed **27**. Conversely, the less strain energy of the sulfur-containing 7-membered ring, because of the longer C–S bond, permitted the formation of **32**, which in turn afforded **29** by a second nickel-catalyzed decarbonylation. To selectively form thiocoumarin **27** or **28**, the first decarbonylation from **30** should occur to form **31** before the insertion of an alkyne to afford 7-membered **32**. As bulky electron-rich tricyclohexylphosphine is advantageous to both oxidative insertion and decarbonylation, the Ni(0)/Cy_3P catalyst decides the route to

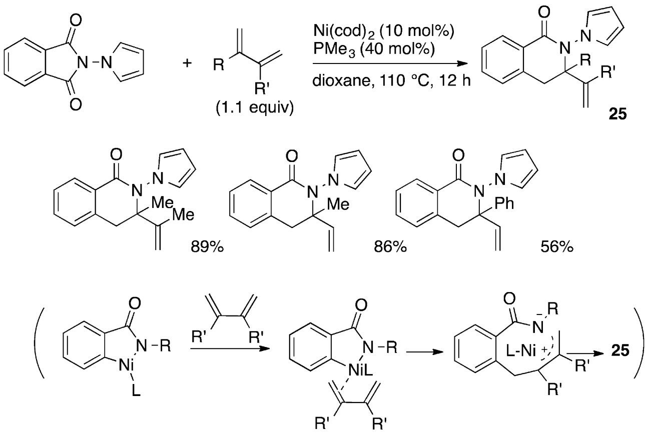
Scheme 12. Decarbonylative Cycloaddition of Cyclic Anhydrides to Alkynes



Scheme 15. Decarbonylative Cycloadditions of Phthalimide with Alkynes (Ratio of Regioisomers in Parentheses)



Scheme 16. Decarbonylative Cycloadditions of Phthalimide with 1,3-Dienes



27 and 28 from 30. The addition of MAD shortened the reaction period to afford 27. The additional reaction period led to the formation of 28 by the nickel-catalyzed decarbonylation of 27. The use of the less bulky and electron-rich PMe_3 as a ligand enhances oxidative insertion and alkyne insertion; however, it exhibits no steric merit for decarbonylation. As a result, it afforded 32, which led to the formation of thiochromone 29.

Starting from thiostatins (33), the nickel-catalyzed reaction with alkynes selectively formed thiochromones 29 (Scheme 20).[25] The oxidative insertion of the S−C (carbonyl) bond to Ni(0) followed by decarbonylation formed nickelacycle 34, which lead to corresponding thiochromone 29. The transformation from thiostatins to thiochromones 29 proceeded under milder conditions starting from thiophthalic anhydride and did not accompany the formation of thioisocoumarin 27 or benzothiophene 28.

As shown in Scheme 21, the reaction of thiophthalic anhydride with methylenecyclopropanes instead of alkynes formed the corresponding [4 + 1] adduct (i.e., benzothiolactones 35).[26] The reaction mechanism is explained in Scheme 22, which explains the same synthetic route as that of dihydrofurans 13 (Scheme 9).

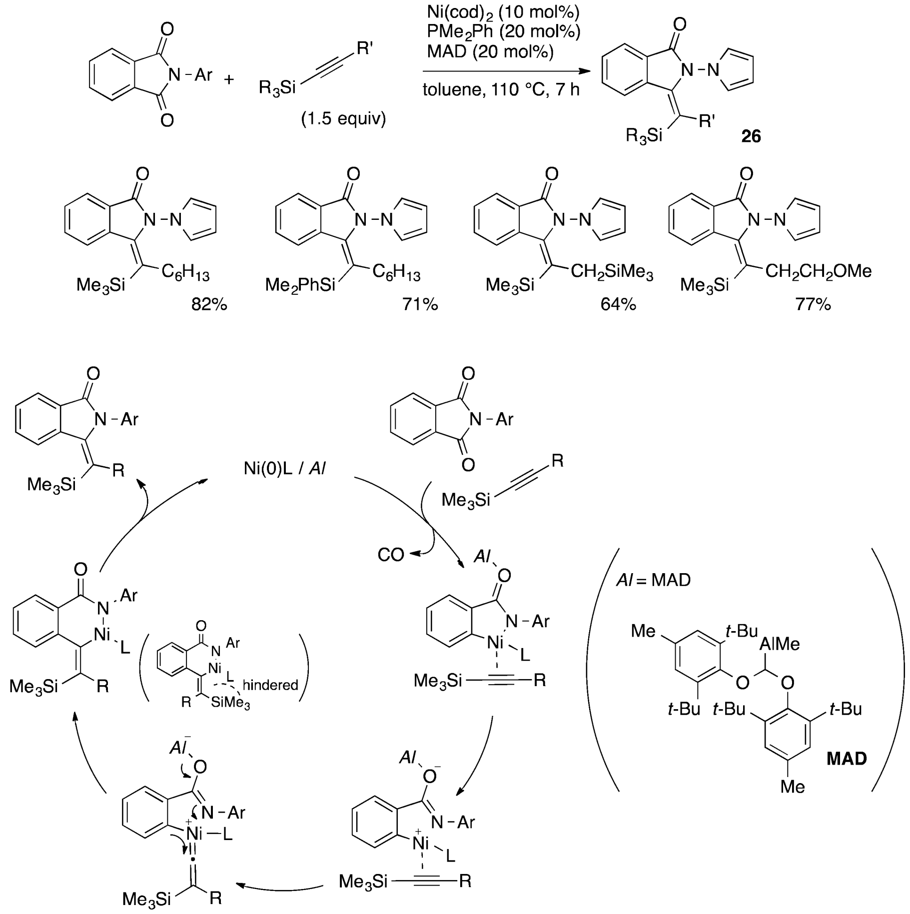
Formation of Indoles from Benzo-1,3-oxazinones via Nickel-Catalyzed Decarbonylation and Rearrangement

Treatment of benzo-1,3-oxazinones 36 with alkynes in the presence of the nickel catalyst prepared from $Ni(cod)_2$ and PPr_3 afforded indoles 40.[27] The reaction pathway can be explained as shown in Scheme 23. Decarbonylation of benzo-1,3-oxazinones 36 by nickel catalyst gave nickelacycle 37, which forms 8-membered nickelacycle 38 via an insertion of alkyne. Because of the unfavorable medium-ring strain, 6-membered nickelacycle was formed via 1,3-acyl migration to give 39. The following reductive elimination gave *N*-acylindoles 40. Treatment of 40 with sodium methanethiolate afforded deprotected indoles 41 (Scheme 23).

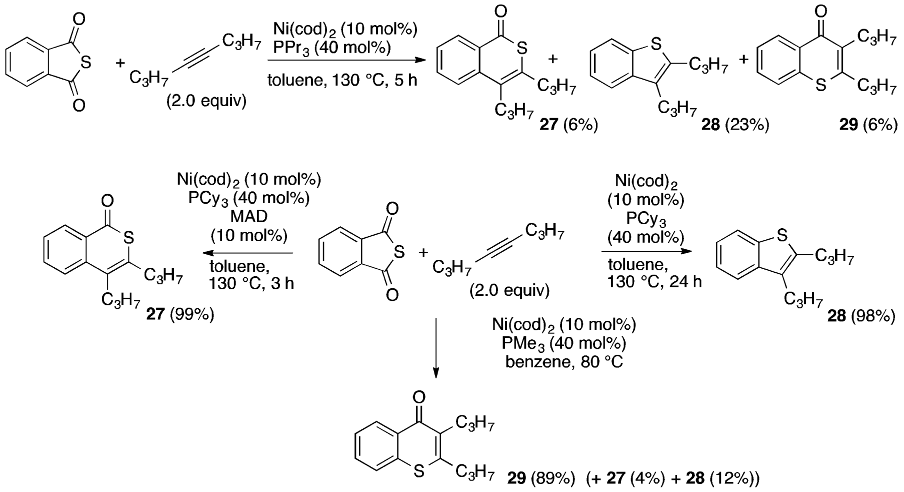
Decarboxylative Formation of Azanickelacycles from Isatoic Anhydrides

As described above, preparation of the intermediary heteroatom-containing nickelacycle by decarbonylation gave the various heterocycles via addition with unsaturated C−C bonds. Carbon monoxide as a leaving group, however, may strongly coordinate with and deactivate the nickel catalyst. Thus, higher temperature or the strongly donative trialkylphosphine was used to perform the decarbonylative process as a nickel-catalyzed reaction. In addition, carbon monoxide is also toxic. From this viewpoint, the elimination of the neutral molecule instead of carbon monoxide is favorable.[28] The binding energy of $Ni(CO_2)$ is estimated to be 18 kcal/mol, whereas that of Ni(CO) is estimated to be 30 kcal/mol.[29] As shown in Scheme 24, treatment of *N*-phenylisatoic anhydride (42) with alkynes in the presence of Ni(0) gave quinolones 44 via the nickelacycle 43 under mild reaction conditions; nickelacycle 43 was formed by decarboxylation.[30] In this transformation, tricyclohexylphosphine was used as a ligand for the nickel catalyst under mild reaction conditions. The use of this bulky phosphine ligand resulted in the regioselective insertion of unsymmetrical alkynes to 43. We also performed DFT calculations for this decarboxylation protocol.[31] It rationalized the route via the 5-membered azanickelacycle as an intermediate for the cycloaddition and also showed the clear merit of the formation of Ni−phosphine−alkyne complex, which undergoes the key oxidative insertion and the following decarboxylation much easier than that of the Ni−phosphine complexes. Both of the transition states and the intermediates were stabilized by the coordination of an alkyne.

Scheme 17. Nickel-Catalyzed Decarbonylative Alkylidenation and its Plausible Reaction Mechanism



Scheme 18. Selective Cycloadditions of Thiophthalic Anhydride with Alkynes

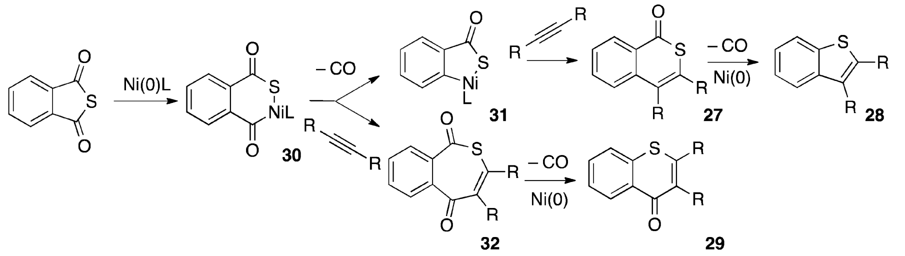


In the presence of MAD as a cocatalyst, treatment of *N*-phenylisatoic anhydride (**42**) with alkynes and Ni(0) catalyst gave indole **48** without forming quinolone **44** (Scheme 25).[32] The bulky Lewis acid MAD may coordinate carbonyl group selectively and form zwitterionic intermediate **45** via an insertion of Ni(0) instead of the formation of nickelacycle **43**. The route to indoles **48** can be explained by the formation of **46** and **47**.

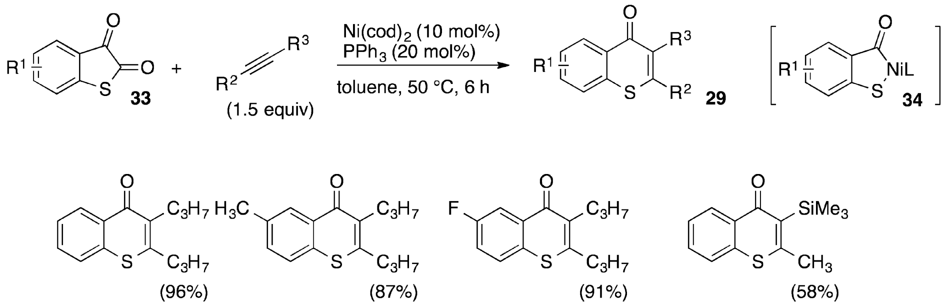
Formation of Oxanickelacycles by the Elimination of Ketone with Ni(0)

The decarboxylation protocol to prepare azanickelacycle **43** (Scheme 24) prompted us to prepare the corresponding oxanickelacycle (**51** in Scheme 26). First, we tried to prepare 4*H*-benzo[*d*][1,3]dioxine-2,4-dione (**42′**), but its preparation requires the use of phosgene or its equivalent. To avoid them, we decided to start from **49**. Even ketones can be used to eliminate a small molecule for the formation of nickelacycles. Acetal-type substrate **49**, whose strain was increased by the two

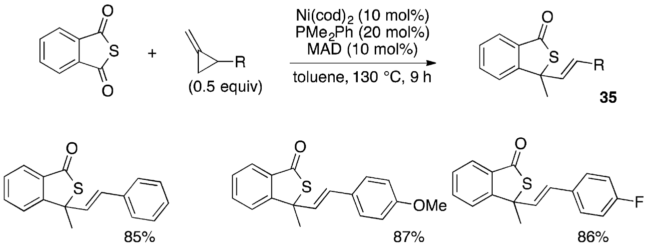
Scheme 19. Explanation for the Formation of 27−29



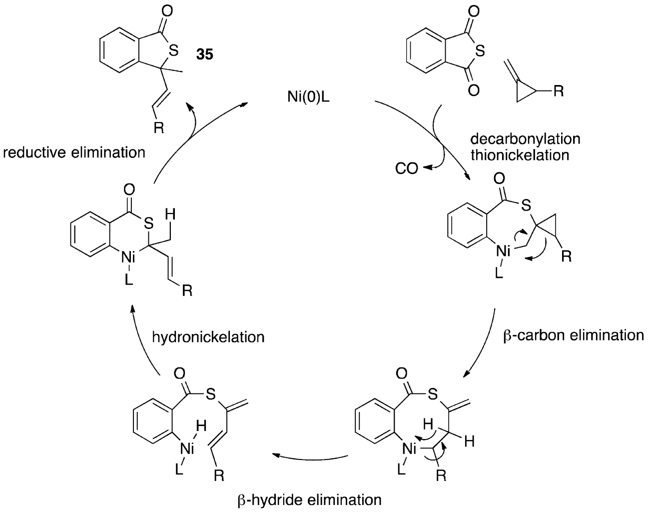
Scheme 20. Nickel-Catalyzed Reaction of Thioisatins and Alkynes



Scheme 21. Decarbonylative Cycloaddition of Thiophthalic Anhydride with Methylenecyclopropanes



Scheme 22. Plausible Reaction Mechanism of 35

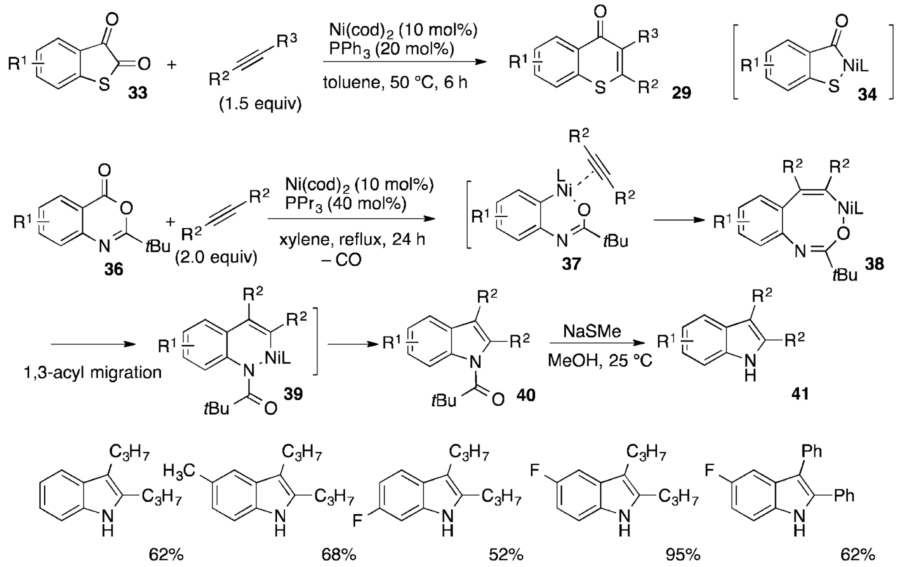


phenyl substituents on the quaternary carbon, was transformed to nickelaoxacycle **51** by the Ni(0) catalyst. The following insertion of alkynes and reductive elimination gave corresponding chromones **53**.[33] The characteristic point of the reaction condition is the addition of pyridine. In the reaction with 4-octyne in Scheme 26 without pyridine, the chromone **53a** (R^1=H, R^2=C_3H_7, R^3=C_3H_7) was obtained in only 38% yield. Pyridine may act as a donating ligand, which can facilitate the formation of oxanickelacycle **51**.

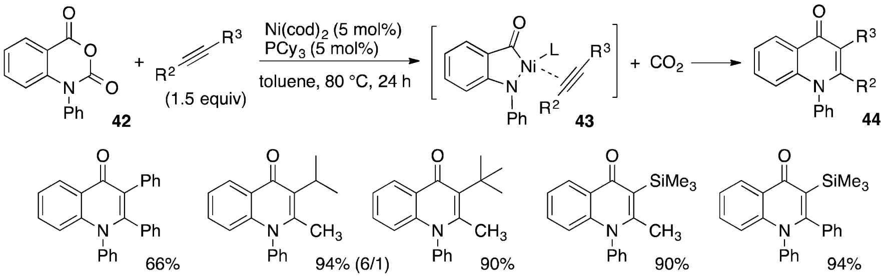
4. NICKEL-CATALYZED CYCLOADDITION VIA ELIMINATION OF ARENECARBONITRILE VIA TWO C−C σ-BOND ACTIVATION

Treatment of 2-cyanophenyl 4-(dimethylamino)benzoate with 4-octyne in the presence of Ni(cod)$_2$/P(CH$_2$Ph)$_3$ and MAD gave cycloadduct **55a** (81%) along with 4-(dimethylamino)-benzonitrile (40%) and (*Z*)-3-(4-(dimethylamino)phenyl)-2-propylhex-2-enenitrile (38%) as shown in Scheme 27.[34] As the alkenyl nitrile was the arylcyanation product of 4-(dimethylamino)benzonitrile with 4-octyne,[35] cycloadduct **55** should be formed accompanying the elimination of an equimolar amount of the nitrile. During this transformation, two C−C σ-bonds ("a" and "b") in **54a** should be cleaved. It was already reported that the oxidative insertion of aryl cyanide affords arylnickel cyanide at equilibrium.[36] This activation of the C−C bond had already been used for the addition to C−C unsaturated bonds.[35] For this reason, the "a" σ-bond in **54a** can be reasonably activated under the Ni(0)-catalyzed reaction conditions. The activation of the "b" σ-bond after a fission of bond "a" to construct the nickelacycle is hard to explain by an oxidative insertion, as the process requires the formation of unstable Ni(IV). DFT calculations also showed a negative result for the direct formation of an intermediary 5-membered nickelacycle by cleavage of two C−C σ-bonds ("a" and "b").[37] Instead, as shown in Scheme 28, it suggested that this reaction occurs via the oxidative addition of the C−CN σ-bond of *o*-arylcarboxybenzonitrile to the Ni(0) center (**54** to **56**) and alkyne insertion into the Ni(II)−aryl bond (**56** to **57**). The process is followed by isomerization of **57** to **58** and undergoes C−C coupling between the vinyl and acyl carbon atoms to afford nickel(II) complex **59**, *β*-aryl elimination (the second C−C σ-bond cleavage) and reductive elimination affords **55** and Ni(0) via **60**. The rate-determining step is *β*-aryl elimination. The role of MAD as a Lewis acid was also

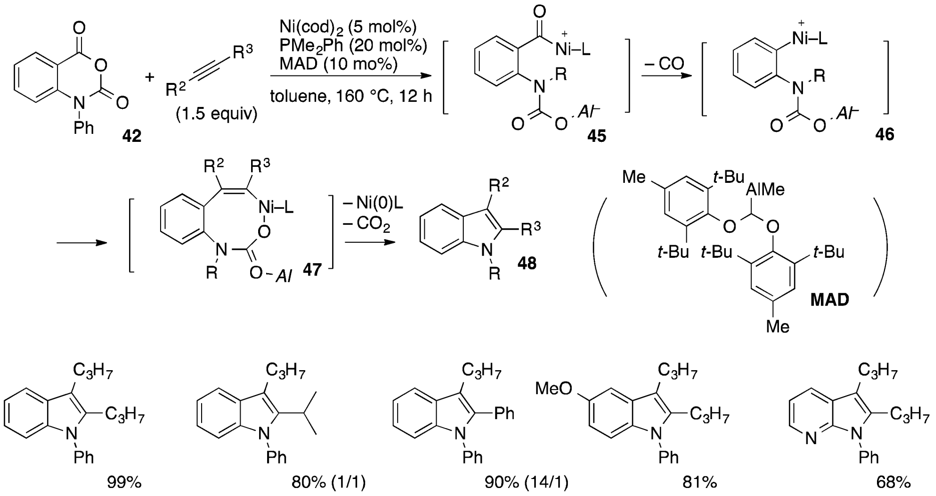
Scheme 23. Indole Formation via Decarbonylation and 1,3-Acyl Migration



Scheme 24. Decarboxylative Cycloaddition of Isatoic Anhydrides with Alkynes



Scheme 25. Decarbonylative and Decarboxylative Formation of Indoles



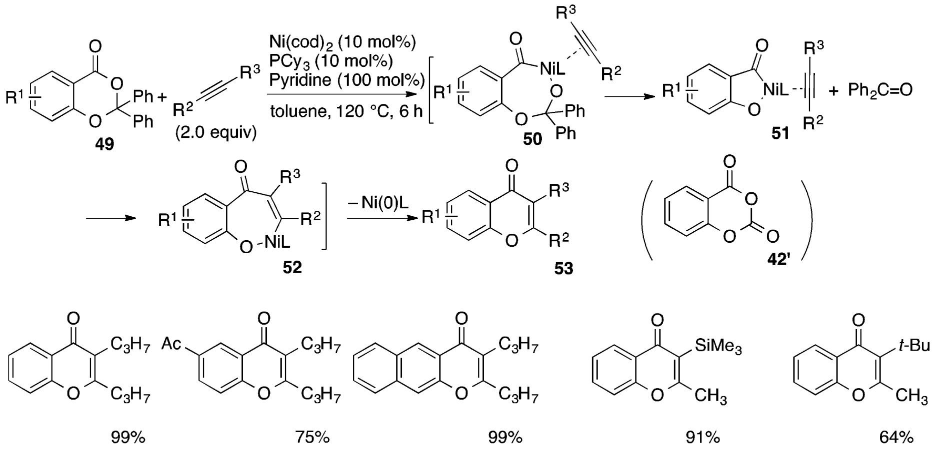
featured. One MAD interacts with the cyano nitrogen atom to accelerate the oxidative addition by stabilizing the unoccupied $\sigma^* + \pi^*$ C−CN antibonding orbital. One more MAD interacts with the carbonyl oxygen. The latter enhances the electrophilic nature of the carbonyl carbon to accelerate the C−C coupling because this step occurs through the nucleophilic attack of the vinyl carbon at the carbonyl carbon atom. Moreover, the second C−C σ-bond activation occurs via β-aryl elimination, the transition state of which is stabilized by the interaction between MAD and the carbonyl oxygen atom.

General examples are shown in Scheme 29. Although only the slight regioselectivities were observed in the reaction with unsymmetrical alkynes, the transformation efficiently gave coumarins **55**.

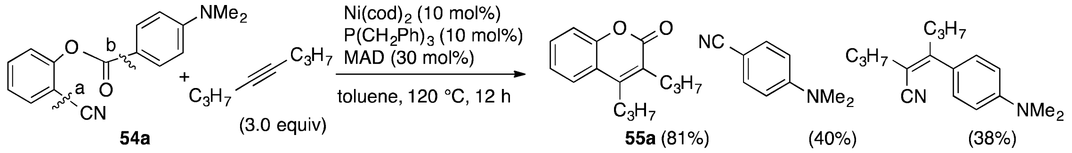
The nickel-catalyzed ring formation via two C−C σ-bond activations was found to be applicable for amide derivative **61** (Scheme 29).[38] Starting from **61**, various quinolones (**62**) were also obtained in good yields.

Ketone **63** was also a possible substrate for this cyclization with two C−C σ-bond activations (Scheme 31).[38b] The

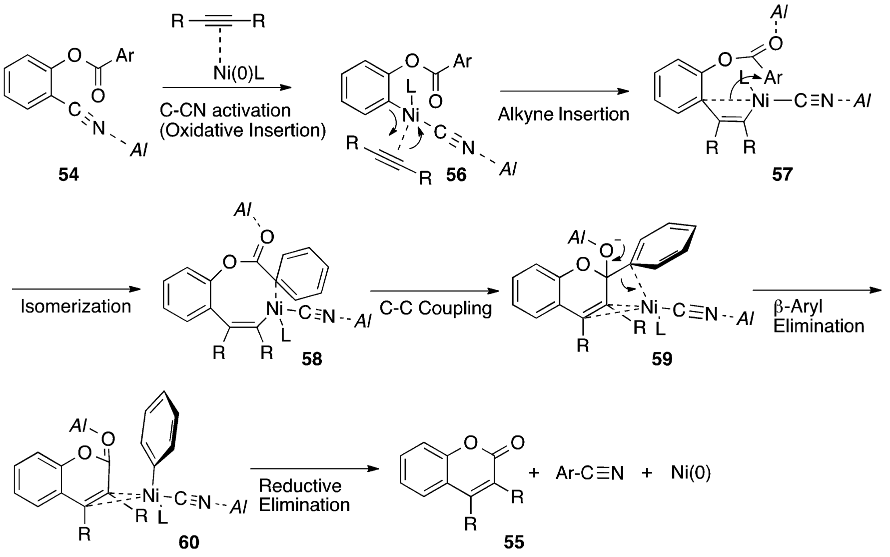
Scheme 26. Cycloaddition of Salicylic Acid Ketals with Alkynes via Elimination of Acetophenone



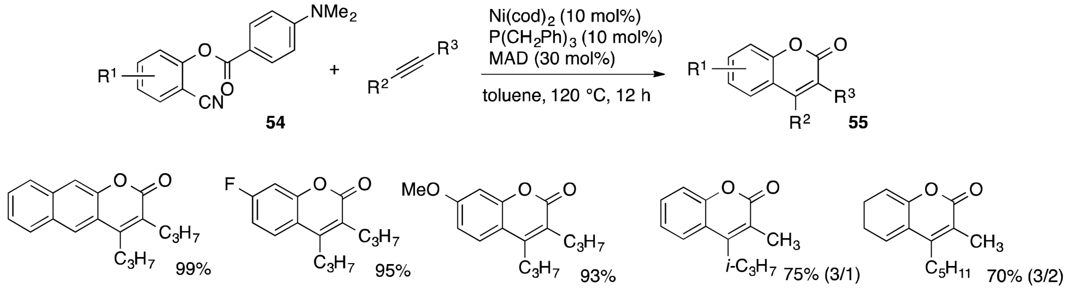
Scheme 27. Cycloaddition of *o*-Phenylcarboxybenzonitrile and 4-Octyne



Scheme 28. Reaction Mechanism of the Cleavage of Two C−C *σ*-Bonds

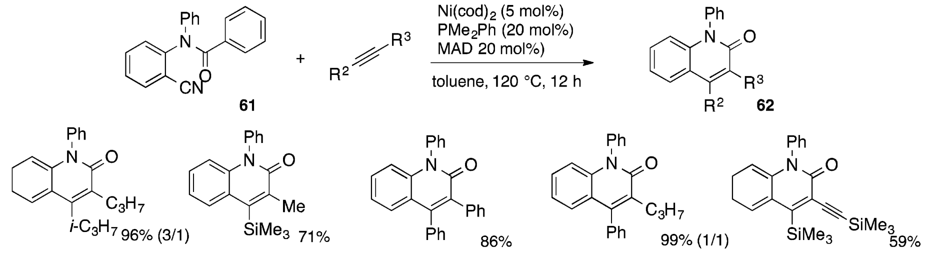


Scheme 29. Cycloaddition of *o*-Phenylcarboxybenzonitrile 54 and Alkynes

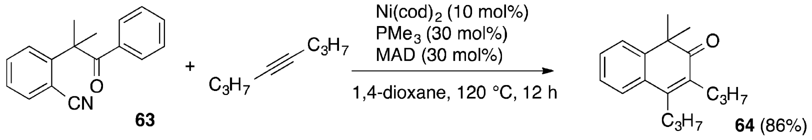


reaction would proceed via a nucleophlic attack from the vinyl nickel to the carbonyl as shown in Scheme 28, and in this case, the benzylic carbon in **63** should be quaternary to prevent enolization, which makes the nucleophilic attack difficult.

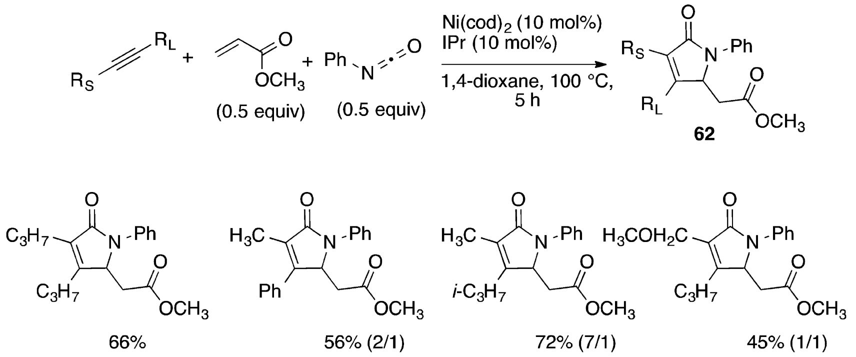
Scheme 30. Cycloaddition of *o*-Cyanophenylbenzamide 61 and Alkynes



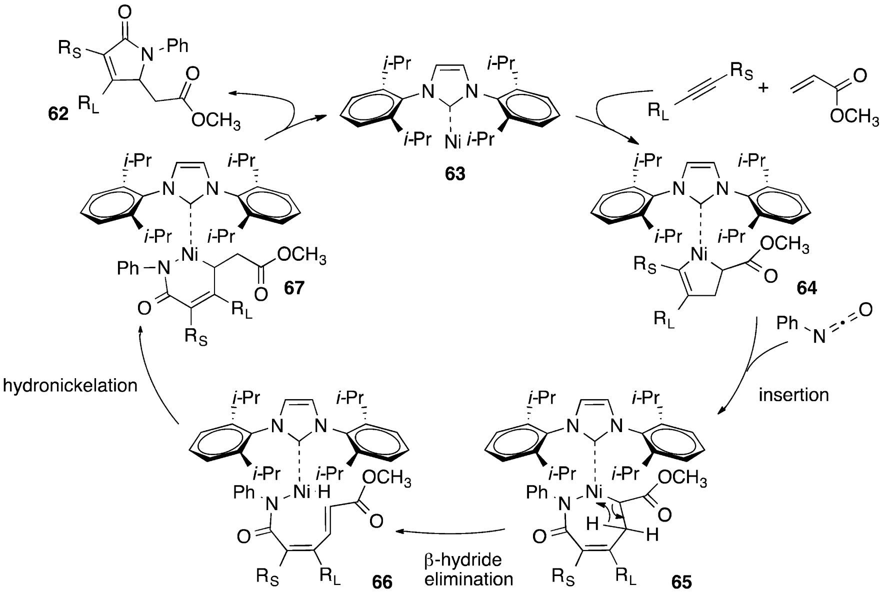
Scheme 31. Cycloaddition of α-(*o*-Cyanophenyl)acetophenone 63 and Alkynes



Scheme 32. Nickel-Catalyzed [2 + 2 + 1] Cycloaddition of Alkynes, Acrylates, and Isocyanates



Scheme 33. Plausible Mechanism for Nickel-Catalyzed [2 + 2 + 1] Cycloaddition



5. PREPARATION OF HETEROCYCLES BY ASSEMBLING π-LIGANDS

As one of the most frequently used methods for the preparation of 6-membered cyclic molecules, transition-metal-catalyzed [2 + 2 + 2] reactions have been developed.[39] For this method, intermediary nickelacycles are formed by the oxidative addition of Ni(0) to two π-ligands and should react with the third π-ligand. Although the method still has room for improvement to prevent duplicate participation of the π ligand to sufficiently exploit divergency, several excellent examples have been reported since the pioneering study by Hoeberg and Tsuda.[40] The assembling method was also used for the synthesis of heteroatom-containing cyclopentanes by [2 + 2 + 1]-type cycloaddition. For example, the hetero-Pauson–Khand reaction, in which an alkyne, an aldehyde, and CO are assembled to form γ-butyrolactones, has been examined using several transition metal catalysts, including nickel.[41] Although this reaction entails some difficulty with the use of CO, it is useful because it exhibits divergency. During our synthetic studies for nickelacycle-mediated heterocycles, we also discovered the synthesis of γ-butyrolactames by [2 + 2 + 1]-type cycloaddition, in which alkynes, acrylates, and isocyanates were used as the assembly pieces (Scheme 32).[42]

The products were assembled using alkynes and isocyanates as a two-atom component; acrylate participated as a one-atom component. A plausible mechanism can be explained as shown in Scheme 33.[43] IPr-coordinated Ni(0) complex **63** would form nickelacycle **64** from an alkyne and an acrylate, in which alkyne regioselectivity was controlled by the steric factor of the alkyne carbon substituents. The bigger one (R_L) should choose the less hindered site from the bulky IPr ligand. The insertion of isocyanate afforded 7-membered nickelacycle **65**, which rearranges to **67** by β-hydride elimination and hydronickelation. Reductive elimination afforded product **62** with the regeneration of the initial catalyst **63**. The beneficial properties of bulky and electron-rich IPr leads to the selective formation of metalacycle **64**, which often suffers from the dimerization of alkynes. Despite the bulkiness of IPr as a ligand, its inner sphere is a cave, and the space around the Ni atom is quite beneficial for β-hydride elimination. The process entails oxidative cyclization (**63** to **64**), insertion (**64** to **65**), and β-hydride elimination (**65** to **66**). For such reactions, the IPr ligand is apt at each step.

6. CONCLUSION

Heterocycles are essential components in pharmaceuticals, agricultural chemicals, and other materials, and their synthesis has often been performed by employing classic condensation. Although quite reliable, classic condensation is slightly disadvantageous from the viewpoints of selectivity, availability, and diversity. In this regard, a significant breakthrough has been the use of metalacycles as intermediates for the synthesis of heterocyclic compounds. However, their use requires some improvement for the availability and reactivity of heteroatom-containing metalacycles. We have described herein novel methods for the synthesis of heteronickelacycles. The use of Ni as a key metal, which possesses a sufficiently high redox potential and affinity for heteroatoms, provides a novel route to obtaining heteronickelacycles that can react with π-donors, such as alkynes, allene, 1,3-diene, and enone, under catalytic conditions to form various heterocycles. This approach provides a wide scope for the synthesis of heterocycles, which may be further applied for various useful compound syntheses.

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Funding

The authors thank the following for financial support: Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (S.M.) and ACT-C (JST, T.K.).

Notes

The authors declare no competing financial interest.

Biographies

Prof. Seijiro Matsubara completed his Ph.D. in 1986 under Prof. Hitosi Nozaki, Prof. Manfred Schlosser, and Prof. Kiitiro Utimoto (Kyoto University, Université de Lausanne). He joined Kyoto University as an assistant professor in 1986. After postdoctoral research with Prof. Barry M. Trost in 1988–1989 at Stanford University, he became associate professor of Kyoto University in 1995. In 2006, he became a full professor of Kyoto University. He received the Inoue Research Award for Young Scientists in 1986 and the Incentive Award in Synthetic Organic Chemistry in Japan in 1998.

Dr. Takuya Kurahashi received his Ph.D. in 2003 under Prof. Tamejiro Hiyama (Kyoto University). After he worked as a postdoctoral researcher at Georg-August-Universität, Göttingen (Prof. Armin de Meijer), and at Kyoto University (Profs. Atsuhiro Osuka and Hiroshi Shinokubo). He became an assistant professor at Kyoto University in 2006, where he was promoted to associate professor in 2012. He has been honored with The Chemical Society of Japan Award for Young Chemists (2012) and the Thieme Journal Award (2014).

■ ACKNOWLEDGMENTS

We are grateful to Dr. Wei Guan and Prof. Shigeyuki Sakaki (Fukui Institute for Fundamental Chemistry, Kyoto University) who studied the DFT calculations for our nickel-catalyzed reactions. We are also grateful to the many talented students who contributed to this research over the years.

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