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TRANSITION METAL-CATALYZED SYNTHESIS OF π -CONJUGATED CYCLIC ESTERS AND AMIDES FROM ALKYNES AND CARBONYL REAGENTS

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Abstract – The transition metal-catalyzed intermolecular reaction of carbonyl reagents with alkynes is one of the efficient methods for synthesizing carbonyl-containing valuable products. This review summarizes the syntheses of π -conjugated cyclic carbonyl compounds by the reaction of alkynes with suitable carbonyl reagents in the presence of transition metal catalysts, to afford isocoumarins, chromones, 2-quinolones, 4-quinolones, and isoquinolones.

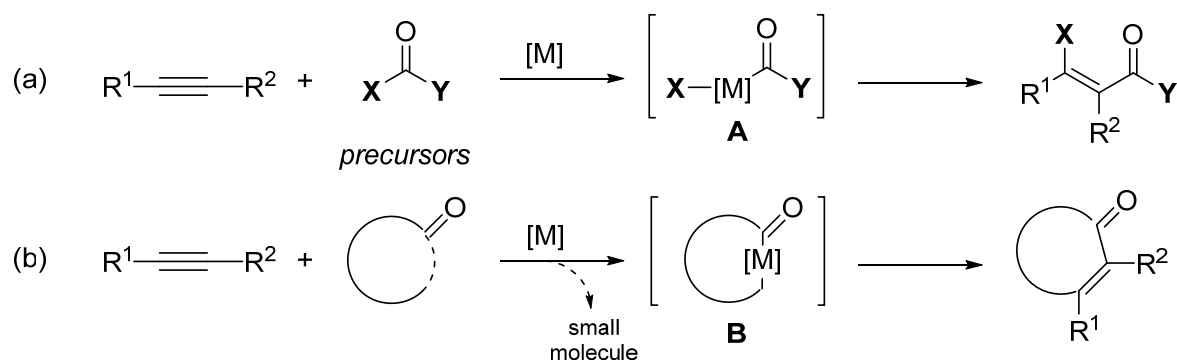
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1. INTRODUCTION

The synthesis and functionalization of carbonyl-containing heterocycles have been extensively studied because they are common in biologically active molecules.¹ Among them, π -conjugated cyclic esters such

as isocoumarins can be synthesized by the reaction of 2-halophenols with an alkyne and carbon monoxide in the presence of a palladium catalyst.² When 2-haloaniline derivatives instead of 2-halophenols are used, π -conjugated cyclic amides such as quinolones can be obtained.² Although these methods afford the desired products in good to high yields, the use of highly toxic carbon monoxide is a disadvantage. Thus, transformations avoiding carbon monoxide gas are highly desirable.³ Meanwhile, the transition metal-catalyzed transformations of carbonyl reagents with carbon-carbon multiple bonds, such as alkynes and alkenes, are particularly important.⁴ The addition of aldehydes (hydroacylation),⁵ formamides (hydrocarbamoylation),⁶ formates (hydroesterification),⁷ and acid chlorides (chloroacylation)⁸ has been reported to date (Scheme 1a). These transformations are attractive because all the atoms in the substrates are retained in the product.⁹ An important step of the transformation is the activation of the carbonyl reagents with transition metal complexes via oxidative addition, to afford an intermediate with a metal-carbon(CO) bond (**A**), as shown in Scheme 1a. Cyclic carbonyl compounds can be obtained by activating a suitable carbonyl reagent, to afford a metallacycle intermediate containing a metal-carbon(CO) bond (**B**) followed by the insertion of carbon-carbon unsaturated compounds (Scheme 1b).



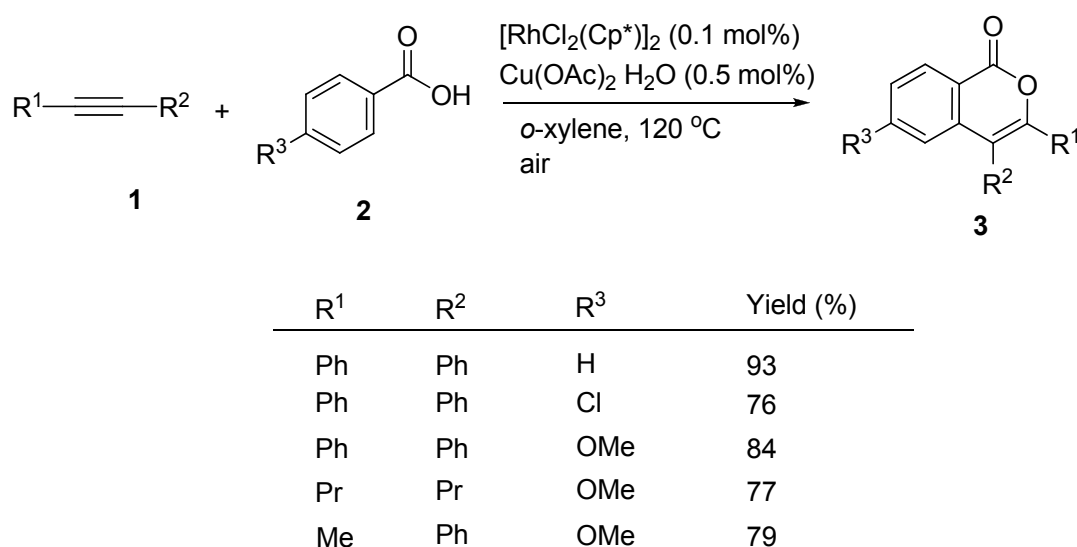
Scheme 1. Synthesis of π -conjugated carbonyl compounds from alkynes and suitable carbonyl reagents. (a) Addition of carbonyl reagents to alkynes and (b) synthesis of cyclic carbonyl compounds from carbonyl reagents and alkynes.

This review focuses on the transition metal-catalyzed synthesis of π -conjugated cyclic esters and amides from alkynes and carbonyl reagents. The elimination of a gaseous molecule such as carbon monoxide, carbon dioxide (CO₂), or molecular nitrogen, from a carbonyl reagent is one of the important processes to afford the metallacycle species, which is an indispensable intermediate in the transformation. The activation of the C-H bond also gave the metallacycle intermediate. Isocoumarins, chromones, 2-quinolones, 4-quinolones, and isoquinolones can be obtained by these methods. The substrate scope and reaction mechanism of these reactions are discussed.

2. π -CONJUGATED CYCLIC ESTERS

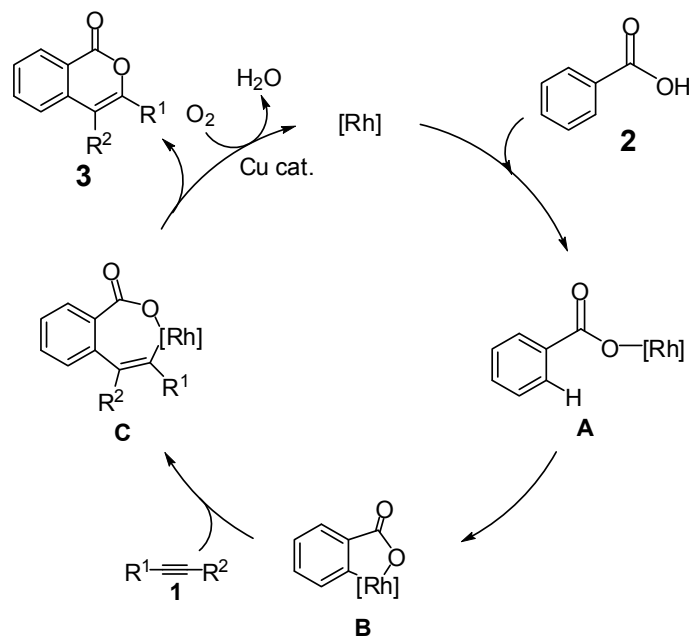
2-1. Synthesis of isocoumarins

Sato and Miura found that rhodium complexes catalyzed the reaction of benzoic acids with alkynes via C-H bond activation, to afford isocoumarin derivatives (**3**) (Scheme 2).¹⁰ The reaction of alkynes (**1**) and benzoic acids (**2**) in the presence of a catalytic amount of $[\text{RhCl}_2(\text{Cp}^*)]_2$ (Cp^* = cyclopentadienyl) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ under air atmosphere afforded **3** in a high yield. The electron-withdrawing and electron-donating substituents on the aromatic rings of the carboxylic acids did not affect the yield. Internal alkynes, such as 4-octyne, participated in the reaction, to afford the corresponding products in high yields. The reactions of unsymmetrical internal alkynes such as 1-phenyl-1-octyne proceeded in a regioselective manner.



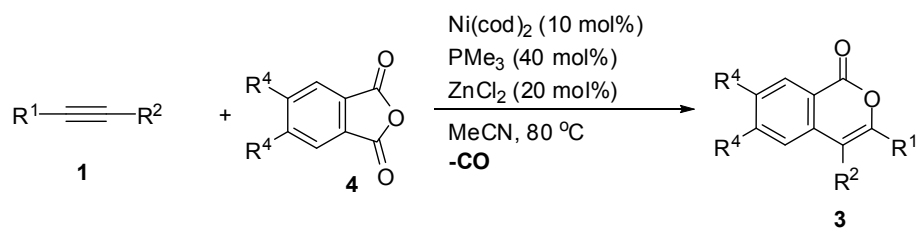
Scheme 2. Synthesis of isocoumarins (**3**) from benzoic acids (**2**) and alkynes (**1**).

A plausible catalytic cycle is shown in Scheme 3. First, the coordination of the carboxylate oxygen atom to rhodium(III) gives rhodium benzoate **A**. Subsequent *ortho*-rhodation gives a rhodacycle intermediate **B**. The insertion of the alkyne to the rhodium-carbon bond followed by the reductive elimination affords **3**. The rhodium(I) species is oxidized in the presence of the copper co-catalyst under air atmosphere to generate the rhodium(III) species, thus completing the catalytic cycle.



Scheme 3. A plausible catalytic cycle for the rhodium-catalyzed reaction of carboxylic acids with alkynes.

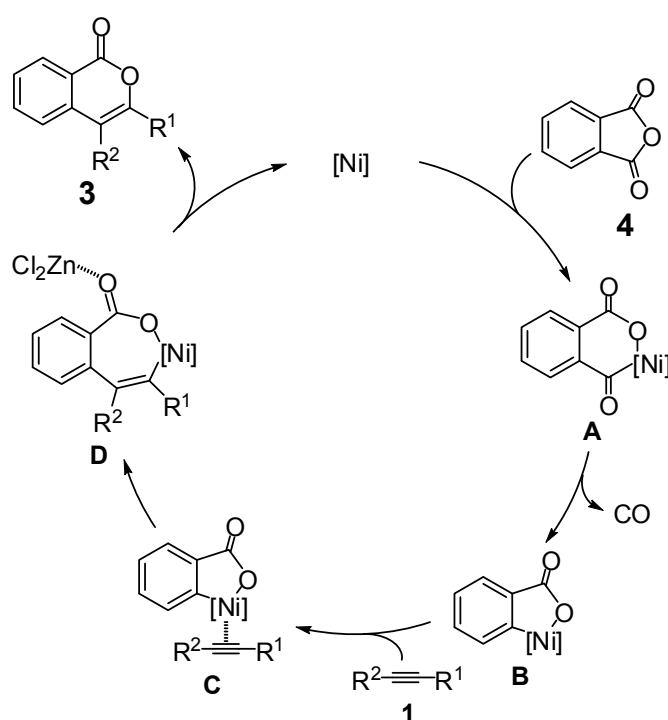
Kurahashi and Matsubara reported that the nickel-catalyzed decarbonylative addition of phthalic anhydride (4) to alkynes (1) gave **3** (Scheme 4).¹¹ The reaction of phthalic anhydride and 4-octyne with the Ni-PMe₃ (PMe₃: trimethylphosphine) system in acetonitrile at 80 °C afforded the corresponding product in only 12% yield. The addition of ZnCl₂ dramatically improved the yield to 96%. The diphenylacetylene produced a yield of 87%. Although a mixture of regioisomers was obtained for the unsymmetrical internal alkynes such as 2-octyne, the reaction of 1-trimethylsilyl-1-propyne afforded a single regioisomer. Substituted phthalic anhydride derivatives also gave the corresponding products in good yields.



R ¹	R ²	R ⁴	Yield (%)
Pr	Pr	H	96
Ph	Ph	H	87
C ₅ H ₁₁	Me	H	91 (1:1)
TMS	Me	H	93
Pr	Pr	Me	94
Pr	Pr	-(CH ₂) ₄ -	87
Pr	Pr	Ph	23

Scheme 4. Synthesis of isocoumarins (**3**) from phthalic anhydrides (**4**) and alkynes (**1**).

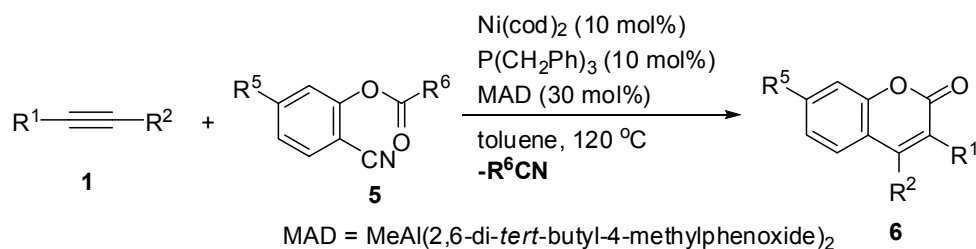
A plausible catalytic cycle is shown in Scheme 5. First, the oxidative addition of the O-CO bond of anhydride **4** to the Ni(0) complex with electron-rich phosphine ligands affords a nickelacycle intermediate **A**. Next, the intermediate is decarbonylated, to give **B**. Then, an alkyne is inserted into the nickel-carbon bond to afford a nickelacycle **D**. The reductive elimination of **D** gives **3** and regenerates the starting Ni(0) complex, thus completing the catalytic cycle. The coordination of ZnCl₂ to the carbonyl group on intermediate **D** may have assisted the reductive elimination.



Scheme 5. A plausible catalytic cycle for the nickel-catalyzed reaction of phthalic anhydride and alkynes.

2.2. Synthesis of coumarins

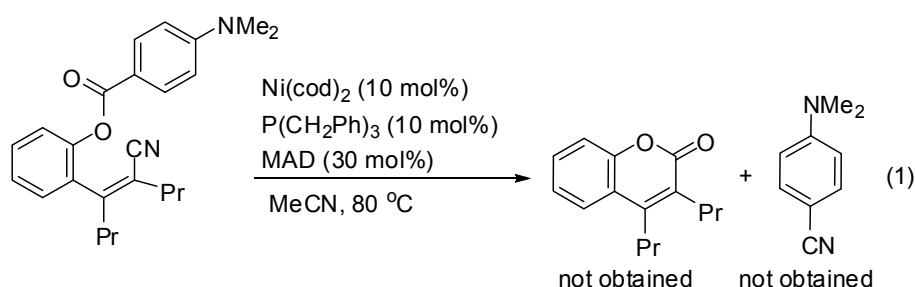
A method for synthesizing coumarin derivatives (**6**) from *o*-arylcarbonyloxybenzonitriles (**5**) and alkynes (**1**) via the elimination of benzonitriles has been developed (Scheme 6).¹² The reaction of *o*-benzoyloxybenzonitrile with 4-octyne in the presence of Ni(cod)₂ (cod = cyclooctadiene) and P(CH₂Ph)₃ with methylaluminum bis(2,6-di-*tert*-butyl-4-methoxyphenoxide) (MAD)¹³ as the co-catalyst, in toluene at 120 °C, afforded the desired product in 65% yield. In the absence of MAD, the reaction did not proceed. The benzonitriles containing *o*-arylcarbonyloxy moiety with electron-donating substituents such as dimethylamino, methoxy, and methyl groups, gave the corresponding products in high yields. However, the reaction of *o*-acetoxybenzonitrile failed.



R ¹	R ²	R ⁵	R ⁶	Yield (%)
Pr	Pr	H	C ₆ H ₅	65
Pr	Pr	H	4-Me ₂ NC ₆ H ₄	99
Pr	Pr	H	4-MeOC ₆ H ₄	80
Pr	Pr	H	4-MeC ₆ H ₄	81
Pr	Pr	H	Me	<1
Pr	Pr	MeO	4-Me ₂ NC ₆ H ₄	93
Pr	Ph	F	4-Me ₂ NC ₆ H ₄	95
Me	C ₅ H ₁₁	H	4-Me ₂ NC ₆ H ₄	75 (3:1)
Pr	Ph	H	4-Me ₂ NC ₆ H ₄	90 (2:1)
Me	SiMe ₃	H	4-MeC ₆ H ₄	75

Scheme 6. Synthesis of coumarins (**6**) from *o*-arylcarbonyloxybenzonitriles (**5**) and alkynes (**1**) via elimination of benzonitriles.

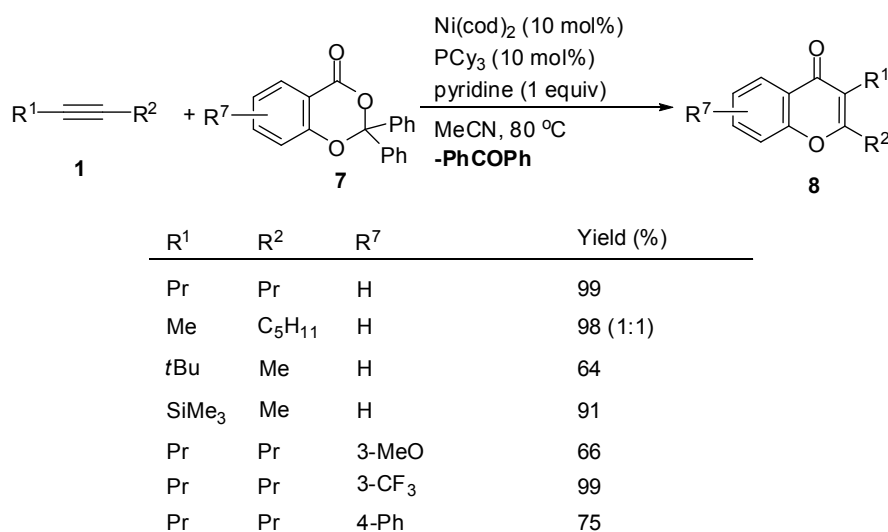
Although the reaction mechanism was not clear, a control reaction was carried out (eq. 1). When the product formed by the reaction of **5** with an alkyne via C-CN bond activation was treated with the nickel catalyst, **6** and the corresponding benzonitrile derivative were not obtained, indicating that the cycloaddition proceeded via the initial elimination of the benzonitrile derivative followed by the reaction with the alkyne.



2.3. Synthesis of chromones

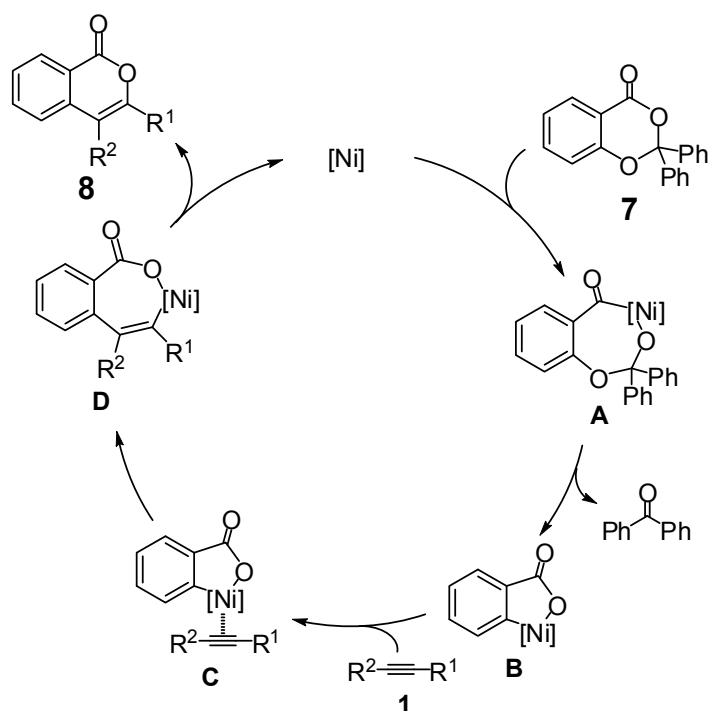
Kurahashi and Matsubara reported a unique method for the synthesis of chromone derivatives (**8**) from acid ketals (**7**) and alkynes (**1**) via the elimination of ketones (Scheme 7).¹⁴ The reaction of salicylic acid acetal with 4-octyne catalyzed by Ni(cod)₂ and tricyclohexylphosphine (PCy₃) in the presence of pyridine (1 equiv) afforded the corresponding product in 99% yield. The reaction did not proceed in the absence of

pyridine, and other additives such as DMAP and DABCO were not effective. The reaction of various internal alkynes afforded the corresponding products in good to high yields.



Scheme 7. Synthesis of coumarins (**8**) from ketals (**7**) and alkynes (**1**) via the elimination of ketones.

A plausible catalytic cycle is shown in Scheme 8. The oxidative addition of the O-CO bond of acid ketal **7** to Ni(0) complex with electron-rich phosphine ligands affords nickelacycle intermediate **A**. The subsequent elimination of benzophenone gives an intermediate **B**. Next, the alkyne is inserted into the nickel-carbon bond to afford a nickelacycle **D**. The reductive elimination of **D** gives **8** and regenerates the starting Ni(0) complex, thus completing the catalytic cycle.

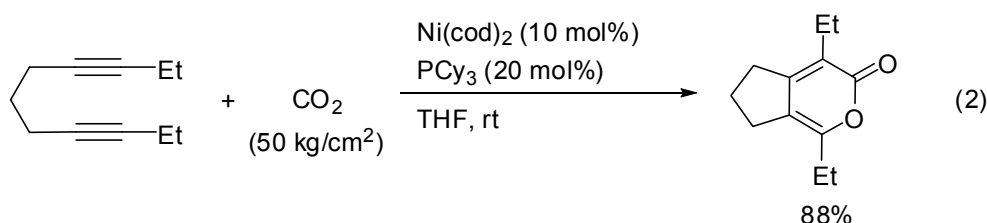


Scheme 8. A plausible catalytic cycle for the nickel-catalyzed reaction of acid ketals with alkynes.

2.4 Synthesis of pyrones from carbon dioxide

Carbon dioxide (CO₂) is a readily available, nontoxic, and renewable carbon source.¹⁵ The use of this environment-friendly raw material in the carbon-carbon bond-forming reactions is an important challenge in homogeneous transition metal catalysis.¹⁶ Useful transformations of CO₂, such as the hydrocarboxylation of carbon-carbon multiple bonds and the carboxylation of organozinc or boron compounds and aryl halides, have been reported. Furthermore, the cycloaddition via metallacycles using CO₂ and carbon-carbon multiple bonds is also a promising approach.

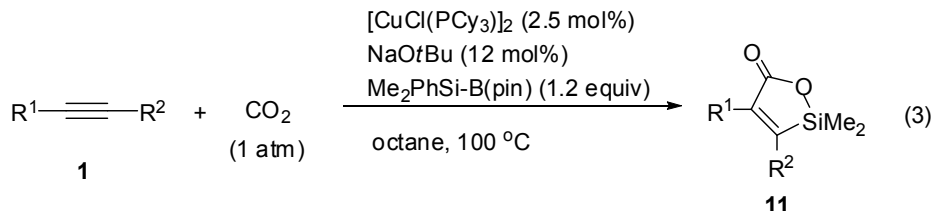
Tsuda and Saegusa reported that the Ni(0) complexes bearing bulky and basic phosphine ligands catalyzed the [2 + 2 + 2] cycloaddition of a diyne with CO₂ to afford the corresponding pyrone derivatives.¹⁷ The reaction of the diyne in tetrahydrofuran (THF) in the presence of a nickel catalyst with PCy₃ ligands under a high pressure of CO₂ (50 kg/cm²) gave the corresponding pyrone (eq. 2).



Recently, a nickel catalyst bearing an *N*-heterocyclic carbene ligand was found to be effective for the synthesis of pyrons from diynes (**9**) and CO₂ (Scheme 9).¹⁸ The reaction proceeded under atmospheric pressure of CO₂ with diverse diynes as the substrates. Furthermore, the synthesis of pyrones from two equiv of alkyne and CO₂ was also reported. However, the reaction required a high CO₂ pressure (20-120 atm).¹⁹

A plausible catalytic cycle is shown in Scheme 10. First, the oxidative cyclization of one of the carbon-carbon triple bonds in the diyne (**9**) with CO₂ catalyzed by a Ni(0) complex affords a nickelacycle intermediate **A**. The subsequent insertion of the second alkyne moiety into the nickel-carbon bond gives a seven-membered nickelacycle **B**. The reductive elimination of **B** affords the pyrone (**10**) and regenerates the starting Ni(0) complex.

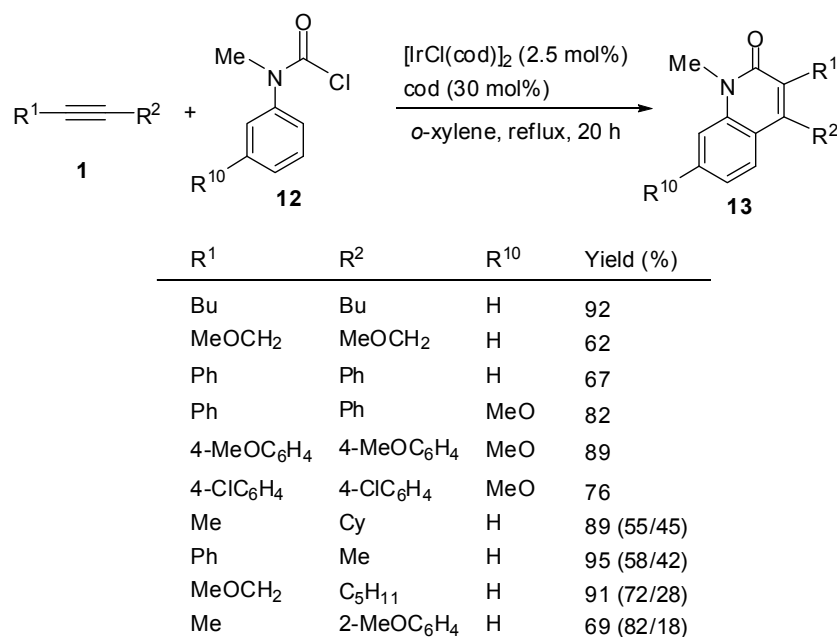
Recently, we reported the copper complex-catalyzed silacarboxylation of alkynes. The reaction of internal alkynes with a silylborane, as a silicon source, in the presence of a copper catalyst under CO₂ atmosphere afforded the corresponding silalactones (**11**) in good to high yields (eq. 3).²⁰



3. π -CONJUGATED CYCLIC AMIDES

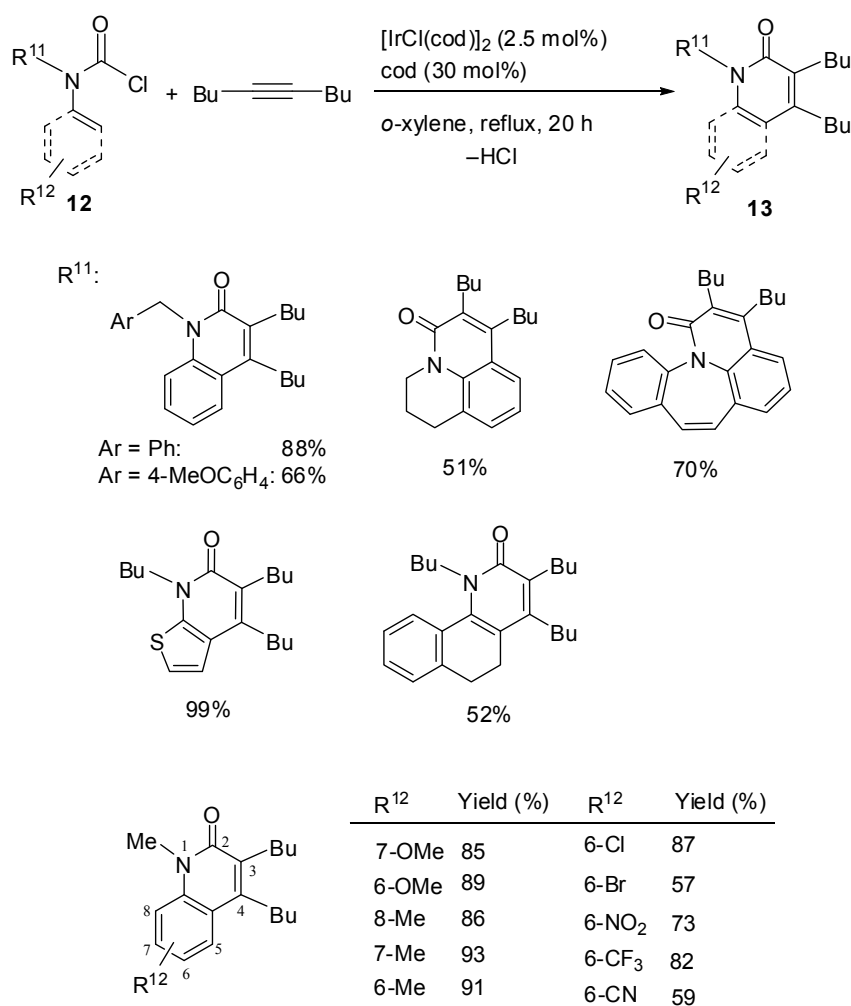
3.1. Synthesis of 2-quinolones

We have developed the efficient annulation of *N*-arylcarbamoyl chlorides (**12**) with internal alkynes (**1**) in the presence of an iridium catalyst to give 2-quinolones (**13**) (Scheme 11).²¹ The reaction of *N*-methyl-*N*-phenylcarbamoyl chloride with 5-decyne in the presence of a catalytic amount (2.5 mol%) of [IrCl(cod)]₂ and cod (30 mol%) in refluxing *o*-xylene afforded 3,4-dibutyl-1-methyl-2-quinolone in 92% yield. Various aliphatic and aromatic internal alkynes were converted to the corresponding 2-quinolones. The reaction of diarylalkynes with *N*-(3-methoxyphenyl)-*N*-methylcarbamoyl chloride gave the corresponding product in high yields as the single regioisomers. Unsymmetrical alkynes afforded the corresponding products in high yields, albeit with low regioselectivity. The use of unsymmetrical alkynes bearing an ether group improved the regioselectivity of the products, possibly because of the directing effect of the oxygen atom.



Scheme 11. Synthesis of 2-quinolones (**13**) from *N*-arylcarbamoyl chlorides (**12**) and alkynes (**1**).

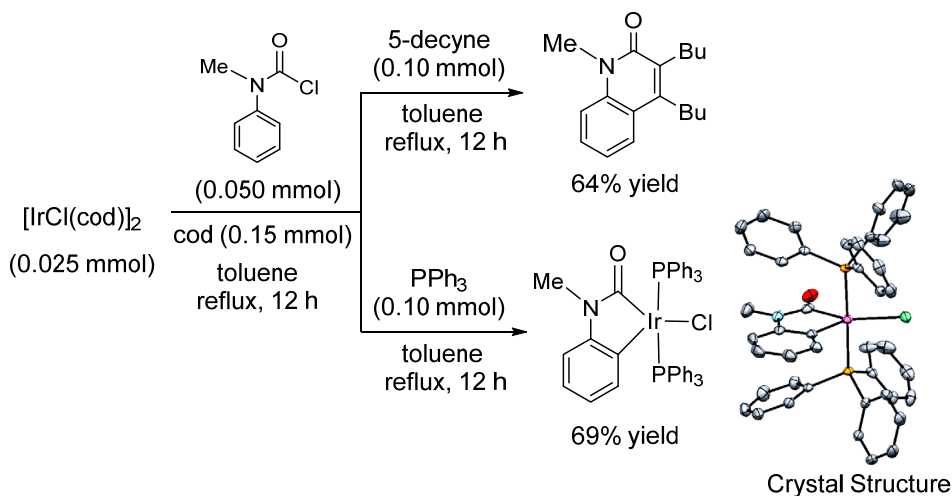
The substrates with electron-rich and electron-poor phenyl moieties on the nitrogen participated in the cyclization to afford the corresponding products in good to high yields (Scheme 12). The reactions with a carbamoyl chloride bearing a *meta*-substituted aryl ring produced a single isomer. The substrate with 4-methoxyphenylmethyl substituent on the nitrogen atom afforded the corresponding 2-quinolones in good to excellent yields. The 4-methoxyphenylmethyl group was removed by treating trifluoroacetic acid to afford 3,4-dibutyl-2-quinolone in 91% yield. The condensed ring systems could be constructed. The reaction was effectively used for *N*-aryl and *N*-alkenyl carbamoyl chlorides as the substrate.



Scheme 12. Substrate scope for the synthesis of 2-quinolones (**13**) from *N*-arylcaramoyl chlorides (**12**) and 5-decyne.

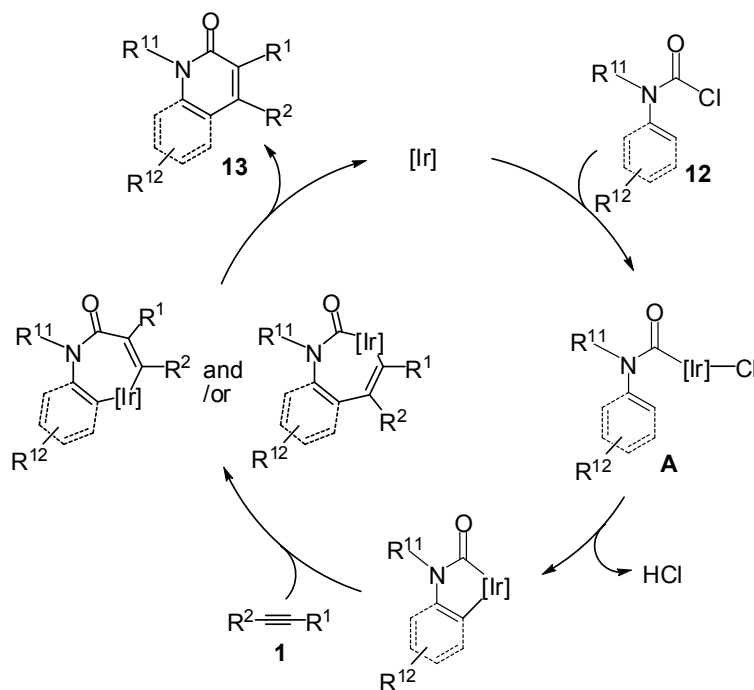
To gain further insight into the catalytic reaction mechanisms, the stoichiometric reaction of $[\text{IrCl}(\text{cod})]_2$ with *N*-methyl-*N*-phenylcarbamoyl chloride was carried out in the presence of additional amount of cod. The reaction of *N*-methyl-*N*-phenylcarbamoyl chloride was completed in refluxing toluene after 12 h. Then, the addition of 5-decyne to the reaction mixture under reflux afforded the corresponding product in 64% yield (Scheme 13). When PPh₃ (P/Ir = 2/1) was added to the reaction mixture instead of 5-decyne,

an iridium(III) metallacycle complex was isolated in 69% yield and its structure was confirmed by X-ray crystallographic analysis.



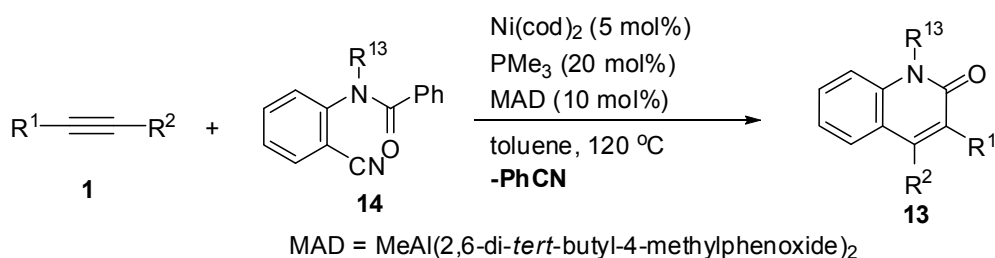
Scheme 13. Stoichiometric reactions of $[\text{IrCl}(\text{cod})]_2$ and *N*-methyl-*N*-phenylcarbamoyl chloride.

A plausible catalytic cycle is shown in Scheme 14. The oxidative addition of carbamoyl chloride **12** to iridium(I) affords a carbamoyl-chloro-iridium(III) complex **A**. The intramolecular cyclization of **A** gives a five-membered iridacycle that may play a crucial role in suppressing the decarbonylation. The subsequent insertion of the alkyne (**1**) followed by the reductive elimination affords 2-quinolone **13** and regenerates the iridium(I) species, thus completing the catalytic cycle.



Scheme 14. A plausible catalytic cycle for the iridium-catalyzed reaction of carbamoyl chlorides with alkynes.

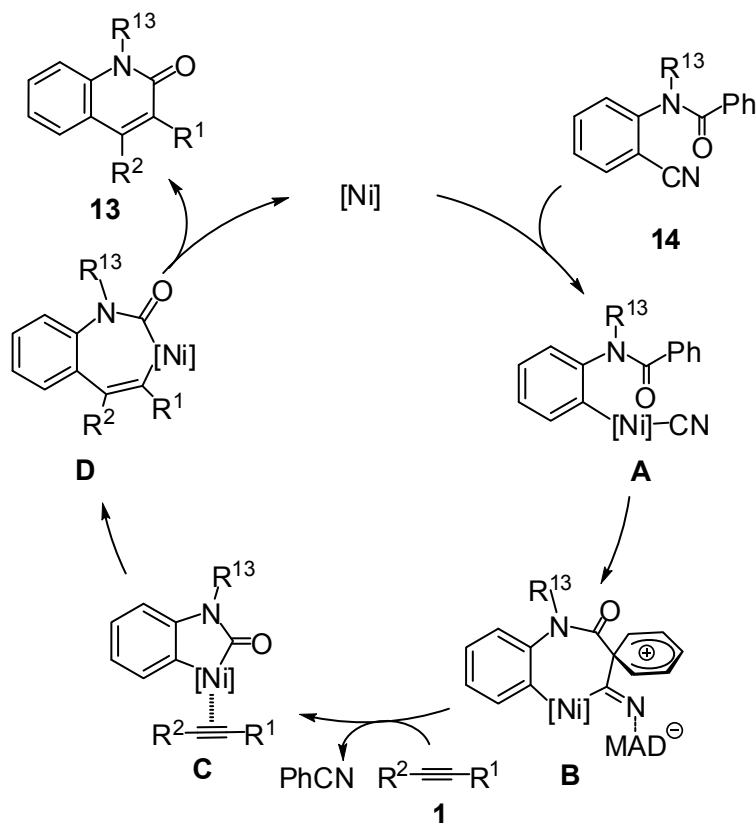
Kurahashi, Matsubara, and co-workers reported the nickel-catalyzed synthesis of 2-quinolones from *o*-cyanobenzamides (**14**) and alkynes via elimination of benzonitrile (Scheme 15).²² The reaction of *o*-cyanobenzamide with 4-octyne in the presence of MAD, as the co-catalyst, and Ni(cod)₂ and PMe₃, as the catalysts, in toluene at 120 °C afforded the desired product in 80% yield. When P(CH₂Ph)₃, an efficient ligand for the related reaction as shown in Scheme 6,¹² was used as the ligand, the yield of the product decreased to 36%. The amide substituents on the nitrogen atom affected the yield, and the phenyl group was the best substituent.



R ¹	R ²	R ¹³	Yield (%)
Pr	Pr	Me	80
Pr	Pr	Ph	99
Pr	Pr	4-MeOC ₆ H ₄	94
Pr	Pr	4-CF ₃ C ₆ H ₄	63
Pr	Pr	CH ₂ Ph	80
Ph	Ph	Ph	86 (PMe ₂ Ph as ligand)
Me	C ₅ H ₁₁	Ph	95 (1:1)
Me	<i>t</i> Bu	Ph	71 (2:1)
Me	SiMe ₃	Ph	71 (20/1)

Scheme 15. Synthesis of 2-quinolones (**13**) from *o*-cyanobenzamides (**14**) and alkynes (**1**).

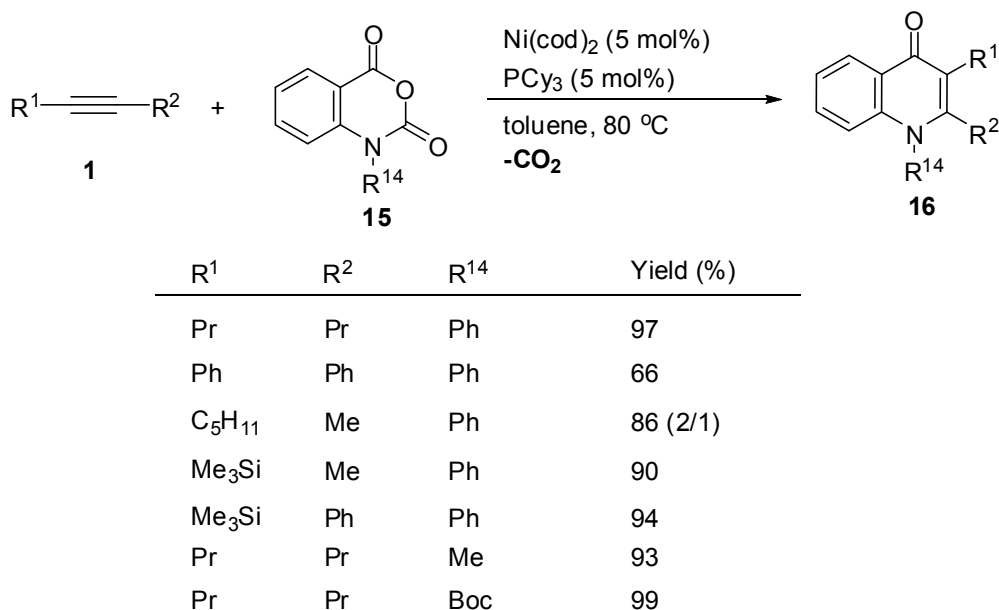
Scheme 16 shows a plausible catalytic cycle. First, the oxidative addition of the C-CN bond²³ in **14** to the Ni(0) complex gives aryl nickel species **A**. The electrophilic *ipso*-attack of the leaving aryl group affords seven-membered intermediate **B**. The subsequent elimination of the benzonitrile and coordination of the alkyne affords nickelacycle **C**. Finally, the insertion of the alkyne gives a seven-membered nickelacycle cycle **D**, and the reductive elimination affords **13** and regenerates the starting Ni(0) complex.



Scheme 16. A plausible catalytic cycle for the nickel-catalyzed reaction of *o*-cyanobenzamide and alkynes.

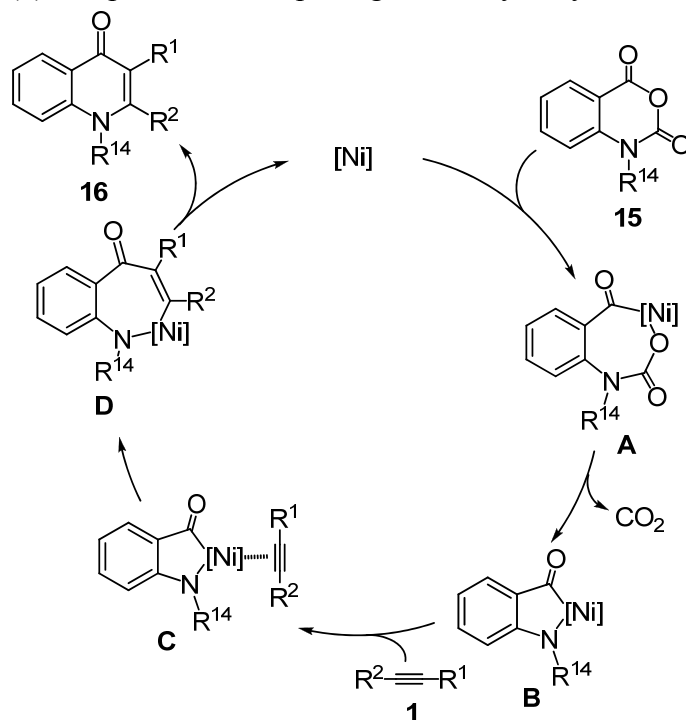
3-2. Synthesis of 4-quinolones

It has been reported that the nickel-catalyzed decarboxylative addition of isatoic anhydrides (**15**) to alkynes (**1**) afforded 4-quinolones (**16**).²⁴ The reaction of *N*-phenylisatoic anhydride with 4-octyne, Ni(cod)₂ and PCy₃ in toluene at 80 °C for 24 h gave the corresponding 4-quinolone in 97% yield. Various internal alkynes were converted to the corresponding 4-quinolones in good to high yields. The regioselectivity of the reaction can be explained by the direction of the alkyne insertion, where the repulsive steric interaction is minimal between the bulkier substituents on the alkyne and ligand. The reaction with 4-methyl-2-pentyne afforded a 6:1 mixture of regioisomers when PCy₃ was used as the ligands. In contrast, a less bulky ligand, PMe₃, reduced the regioselectivity of the reaction and resulted in a 3:2 mixture of regioisomers.



Scheme 17. Synthesis of 4-quinolones (**16**) from isatoic anhydrides (**15**) and alkynes (**1**) via elimination of CO₂.

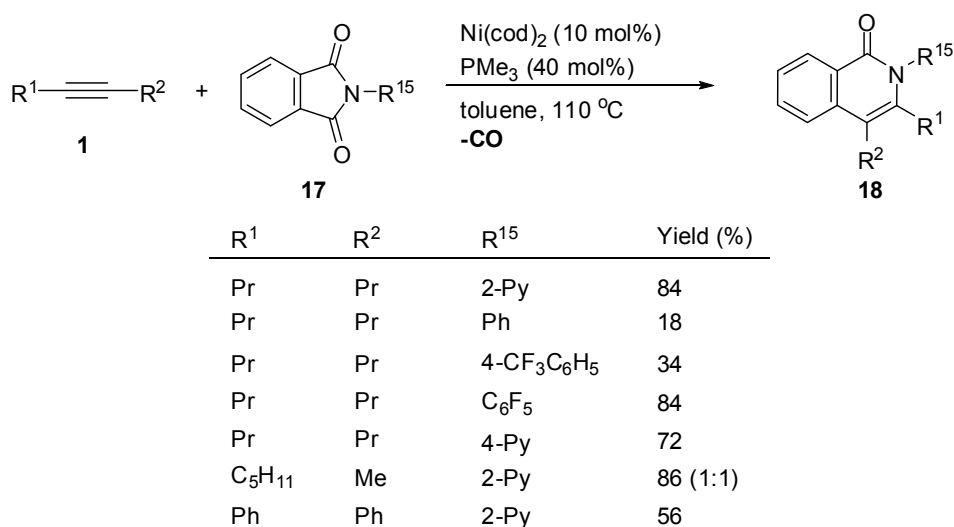
A plausible catalytic cycle is shown in Scheme 18. First, the oxidative addition of the C-CO bond of the isatoic anhydride (**15**) to the Ni(0) complex affords a seven-membered nickelacycle intermediate **A**. The subsequent decarboxylation of **A**, and coordination of alkyne affords an intermediate **C**. The insertion of the alkyne into the nickel-carbon bond gives nickelacycle **D**. The reductive elimination affords **16** and regenerates the starting Ni(0) complex, thus completing the catalytic cycle.



Scheme 18. A plausible catalytic cycle for the nickel-catalyzed reaction of isatoic anhydrides and alkynes.

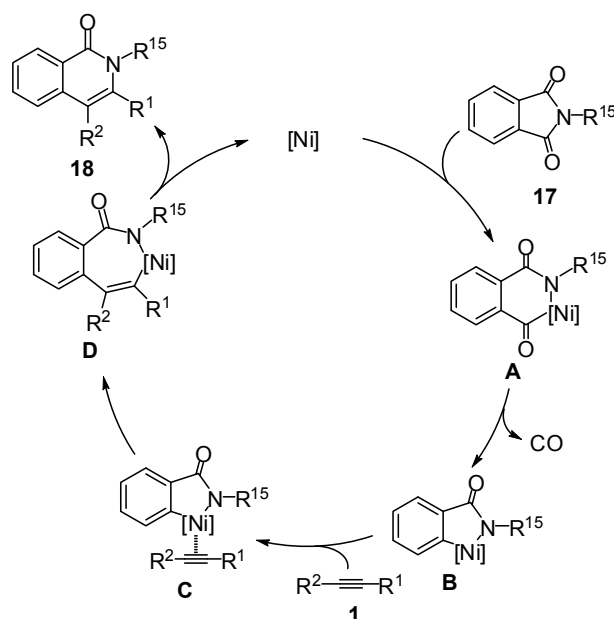
3.3. Synthesis of isoquinolones

The nickel-catalyzed decarbonylative addition of phthalimides (**17**) to alkynes (**1**) to give isoquinolones (**18**) has been reported (Scheme 19).²⁵ The reaction of *N*-(2-pyridyl)phthalimide with 4-octyne in the presence of Ni(cod)₂ and PMe₃ in toluene at 110 °C afforded the corresponding product in 84% isolated yield. Under the reaction conditions, *N*-phenylphthalimide was converted to the product only 18% yield, whereas an electron-withdrawing aromatic substituent on the phthalimide nitrogen atom favored the reaction. The reaction of aliphatic internal alkynes gave the corresponding products in high yields, even though the yield for diphenylacetylene was moderate.



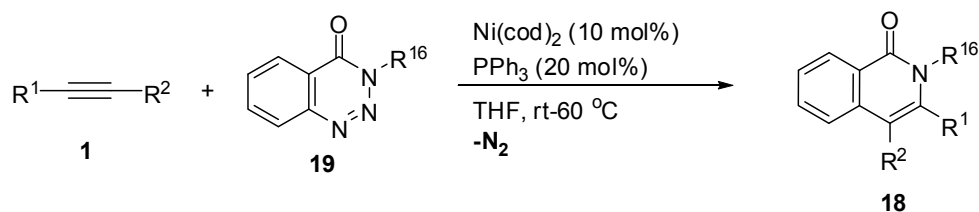
Scheme 19. Synthesis of isoquinolones (**18**) from phthalimides (**17**) and alkynes (**1**).

A plausible catalytic cycle is shown in Scheme 20. First, the nucleophilic attack of the Ni(0) complex on the electron-rich phosphine ligands on the amide (**17**) gives a nickelacycle intermediate **A**. The subsequent decarbonylation affords a nickelacycle **B**. Next, the insertion of the alkyne into the nickel-carbon bond affords **D**. The reductive elimination of **D** gives **18** and regenerates the starting Ni(0) complex.



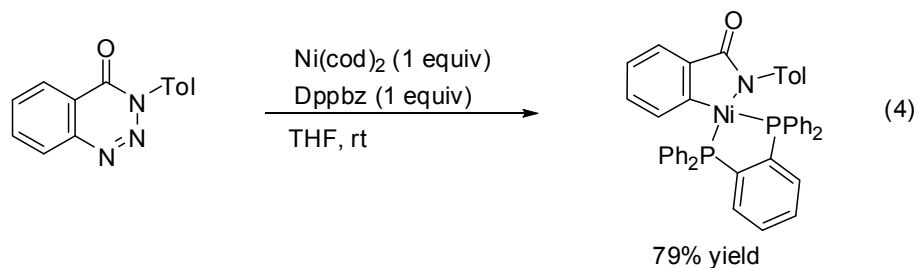
Scheme 20. A plausible catalytic cycle for the nickel-catalyzed reaction of phthalimides and alkynes.

Murakami and co-workers reported the synthesis of isoquinolones by the nickel-catalyzed denitrogenative alkyne insertion into 1,2,3-benzotriazin-4-ones (**19**) (Scheme 21).²⁶ The catalytic cycle starts with the insertion of the $Ni(0)$ species into the N-N bond of 1,2,3-benzotriazin-4-ones followed by the elimination of molecular nitrogen to afford a nickelacycle **B** (Scheme 19). The stoichiometric reaction of a 1,2,3-benzotriazin-4-one with $Ni(cod)_2$ and diphenylphosphinobenzene in THF at room temperature afforded an azanickelacycle species in 79% yield, and the molecular structure of the complex was determined by X-ray crystallographic analysis (eq. 4).²⁷ The enantioselective synthesis of 3,4-dihydroisoquinolone from 1,2,3-benzotriazin-4-ones and allenes using nickel catalysts with chiral phosphine ligands has also been reported.²⁶

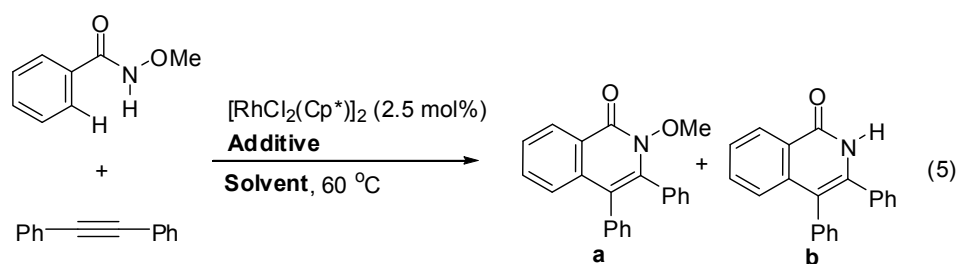


R^1	R^2	R^{16}	Yield (%)
Bu	Bu	Ph	91
Ph	Ph	Ph	98
Me	Ph	Ph	99 (86:14)
Pr	COOEt	4-MeC ₆ H ₄	99 (92:8)
Bu	Bu	4-MeOC ₆ H ₄	95
Pr	Pr	Bn	96

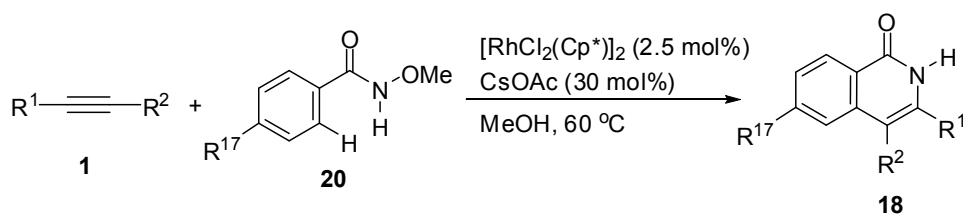
Scheme 21. Synthesis of isoquinolones (**18**) from 1,2,3-benzotriazin-4-ones (**19**) and alkynes (**1**) via elimination of nitrogen.



Guimond and co-workers reported the rhodium-catalyzed synthesis of isoquinolones (**18**) from *N*-substituted hydroxamic acids and alkynes via C-H bond activation (Scheme 22).²⁸ The reaction of benzohydroxamic acid with diphenylacetylene in the presence of $[\text{RhCl}_2(\text{Cp}^*)]_2$ and two equiv of $\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$, as the oxidant, in DMF at 60 °C afforded a mixture of isoquinolones (eq. 5). Interestingly, in the absence of the oxidant, the reaction proceeded to afford **18** in a high yield. The reaction of diverse alkynes gave the corresponding products in good to high yields.



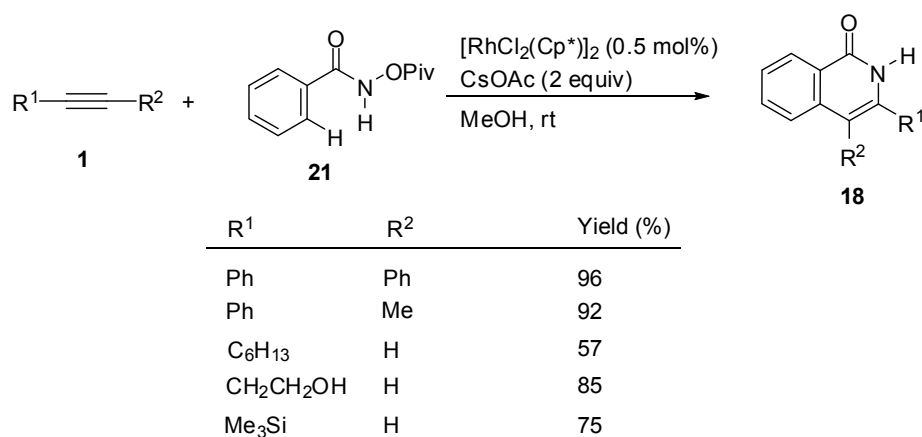
Solvent/Additive	Yield (a/b)
DMF/ $\text{Cu}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (2 eq)	89% (1/1.1)
DMF/ CsOAc (2 eq)	38% (1/20)
MeOH/ CsOAc (2 eq)	97% (1/20)
MeOH/ CsOAc (0.3 eq)	97% (1/20)



R^1	R^2	R^{17}	Yield (%)
Ph	Ph	H	90
Me	Ph	H	61
2-Py	Me	H	57
Ph	Ph	OMe	88
Bu	Bu	Br	85
Pr	Pr	NO_2	96

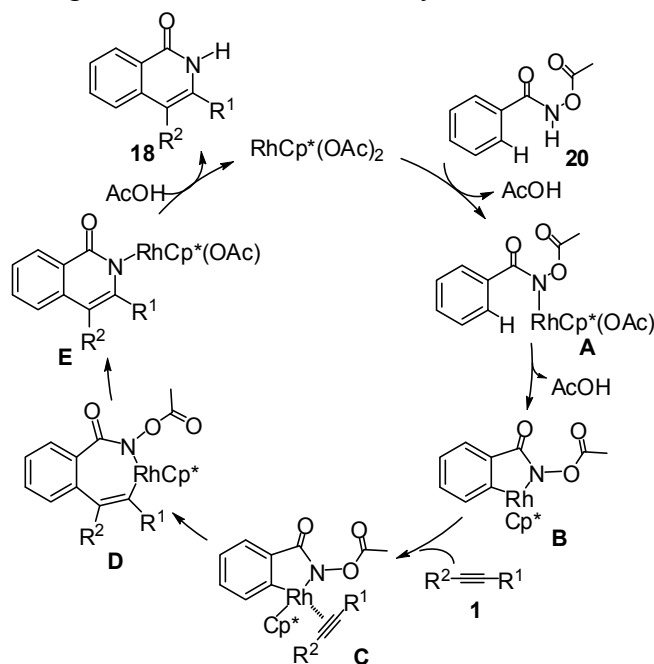
Scheme 22. Synthesis of isoquinolones (**18**) from *N*-substituted hydroxamic acids (**20**) and alkynes (**1**) via C-H bond activation.

Recently, Guimond and co-workers reported that substituents on the nitrogen atom affected the reactivity.²⁹ The pivaloyl group was the best substituent for the rhodium-catalyzed synthesis of isoquinolones. The reaction proceeded with a low catalyst loading at room temperature in the presence of 2 equiv of CsOAc (Scheme 23). Importantly, terminal alkynes participated in the reaction, and afforded the corresponding products in good to high yields and high regioselectivity.



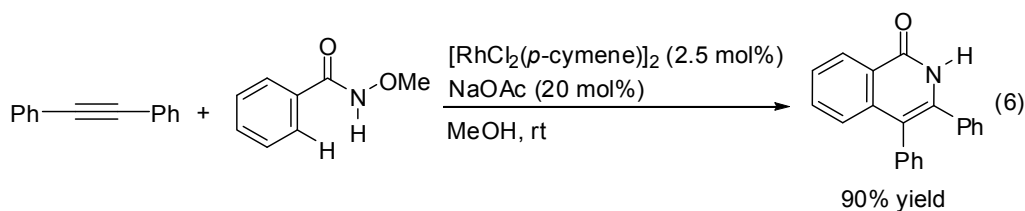
Scheme 23. Synthesis of isoquinolones (**18**) from *N*-substituted hydroxamic acids (**21**) and alkynes (**1**) via the C-H bond activation.

A plausible catalytic cycle is shown in Scheme 24. The reaction of the rhodium species with **21** gives rhodacycle intermediate **B** via the C-H bond cleavage. The alkyne is inserted into the Rh-C bond of the intermediate **B** to afford **D**. The concerted or stepwise C-N bond formation and N-O bond cleavage provided the product (**18**) and regenerates the rhodium catalyst.

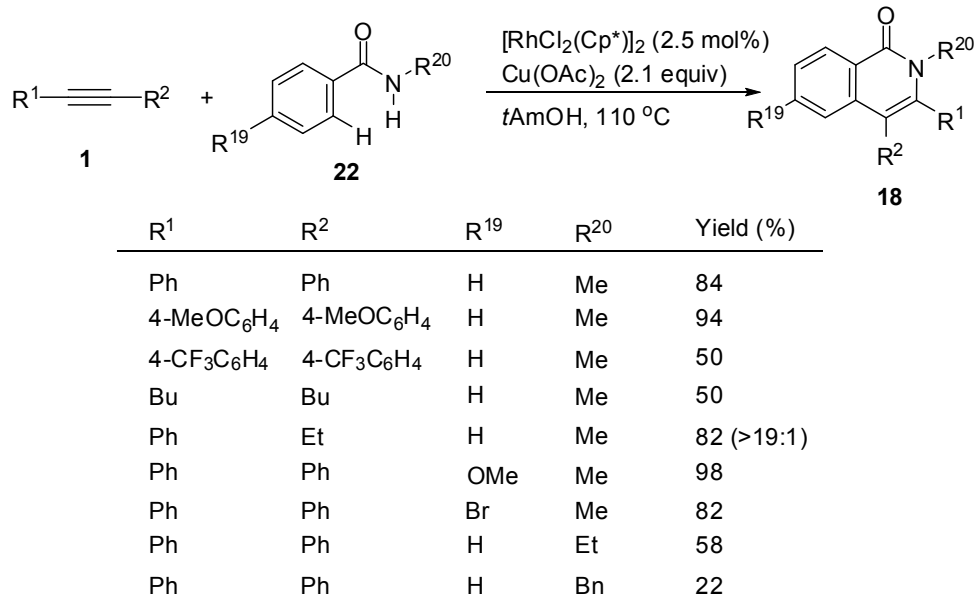


Scheme 24. A plausible catalytic cycle for the rhodium-catalyzed reaction of *N*-substituted hydroxamic acids and alkynes.

Li and Wang also reported the ruthenium-catalyzed isoquinolone synthesis via the C-H activation in the absence of oxidant (eq. 6).³⁰ The method was similar to Guimond's system that used rhodium catalysts.



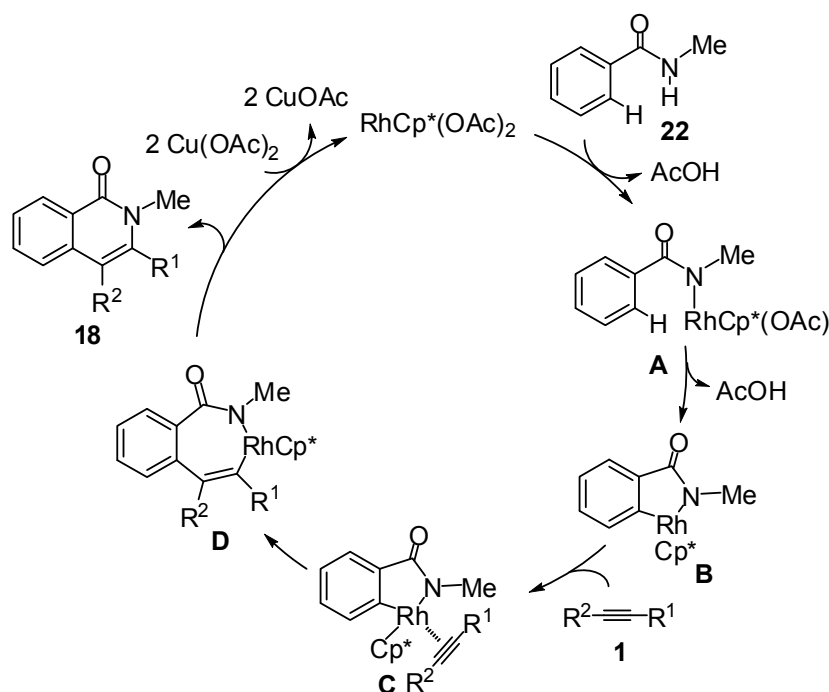
Rovis and co-workers reported the rhodium-catalyzed the oxidative cyclization of benzamide with alkynes via C-H/N-H bond activation (Scheme 25).³¹ The reaction of *N*-methylbenzamide with diphenylacetylene in the presence of $[\text{RhCl}_2(\text{Cp}^*)]_2$ and $\text{Cu}(\text{OAc})_2$, as the oxidant, in *t*AmOH afforded the corresponding product in 82% yield. The reactions of electron-rich aromatic internal alkynes gave the corresponding products in high yields, whereas electron-withdrawing substituents on the aromatic ring resulted in lower yields. The reaction of 5-decyne afforded the corresponding product in a moderate yield. The substituents on the nitrogen atom affected the yield strongly; methyl substituent gave the product in high yield, even though the reaction of *N*-benzyl substituted benzamide resulted in a lower yield.



Scheme 25. Rhodium-catalyzed synthesis of isoquinolones (**18**) from benzamides (**22**) and alkynes (**1**) via the C-H bond activation.

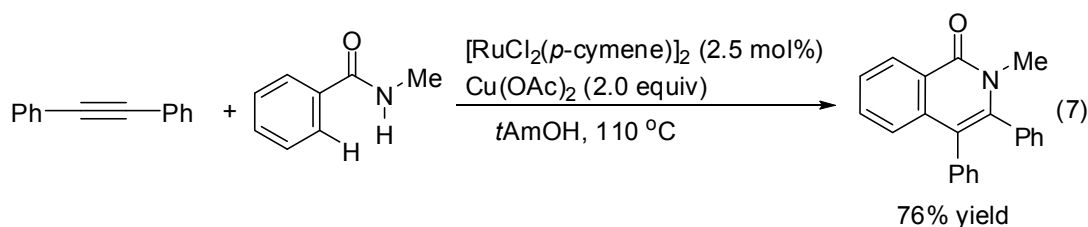
A plausible reaction mechanism is shown in Scheme 26. The reaction of the rhodium complex bearing acetate ligands with benzamide gives a five-membered rhodacycle intermediate (**B**) and acetic acid. The

subsequent insertion of the alkyne into the rhodium-carbon bond affords a seven-membered intermediate (**D**). The reductive elimination of **D** affords **18** and the rhodium complex is regenerated, thus completing the catalytic cycle.



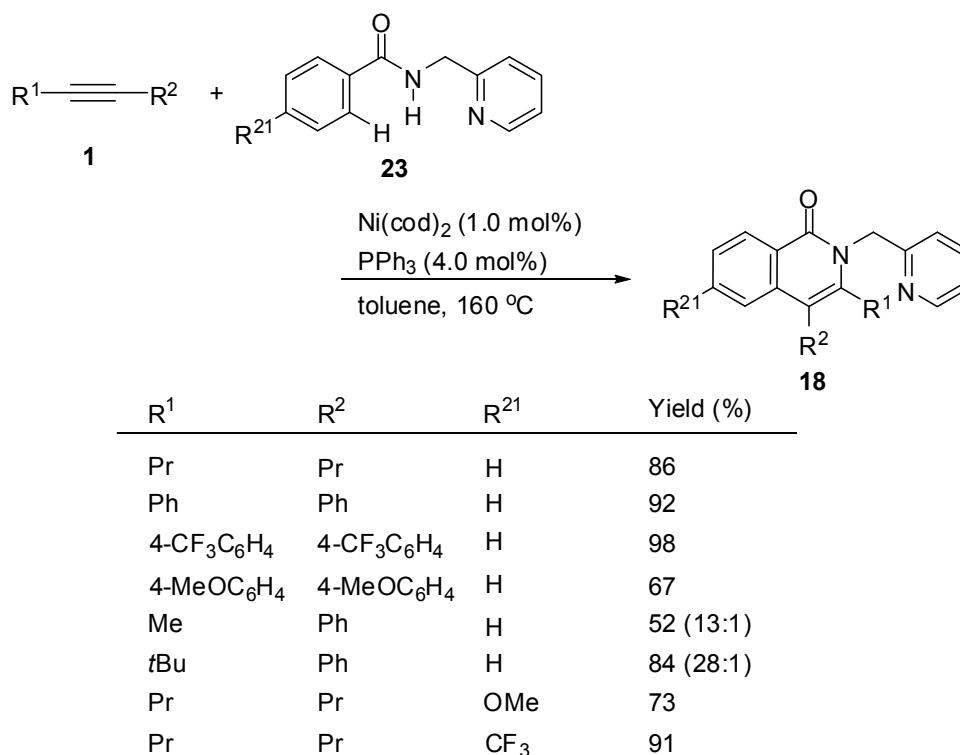
Scheme 26. A plausible catalytic cycle for the rhodium-catalyzed synthesis of isoquinolones from benzamides (**22**) and alkynes (**1**) via the C-H bond activation.

A similar reaction was also reported by Ackermann and co-workers using ruthenium catalysts in the presence of $\text{Cu}(\text{OAc})_2$ as the oxidant (eq. 7).³²



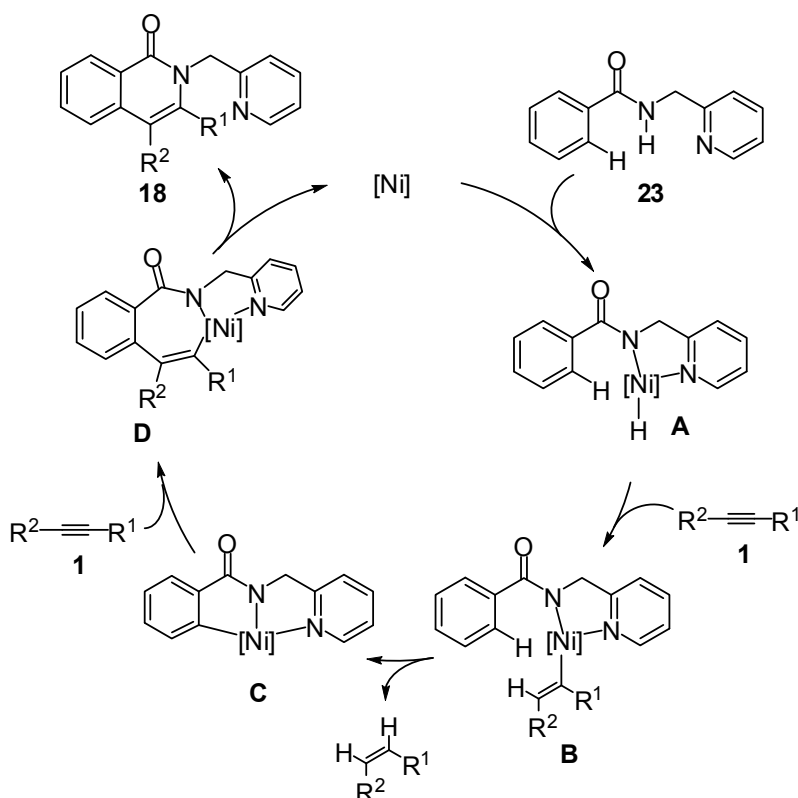
Chatani and co-workers reported the nickel-catalyzed synthesis of isoquinolones from alkynes and benzamides bearing a 2-pyridylmethyl group on the nitrogen atom (Scheme 27).³³ The reaction of the amide with 4-octyne in the presence of $\text{Ni}(\text{cod})_2/\text{PPh}_3$ catalyst system in toluene at $130\text{ }^\circ\text{C}$ for 18 h afforded the product in 28% yield. The yield increased to 86% on increasing the reaction temperature. The reaction of diphenylacetylene and aromatic internal alkynes bearing electron-withdrawing

substituents gave the products in high yields, whereas those with electron-donating aromatic alkyne substrates resulted in lower yields. The benzamide substituents also affected the yield.



Scheme 27. Synthesis of isoquinolones (**18**) from *N*-(2-pyridylmethyl)benzamides (**23**) and alkynes (**1**) via the C-H bond activation.

A plausible mechanism is displayed in Scheme 28. The coordination of the amide (**23**) to the nickel center as the *N,N*-donor followed by the activation of the N-H bond gives nickel hydride complex **A**. The insertion of the alkyne into the N-Ni bond of **A** affords vinylnickel intermediate **B**. The cleavage of the C-H bond and the concomitant formation of the alkene give an intermediate **C**. The insertion of the additional alkyne molecule into the nickel-carbon bond of **C** followed by the reductive elimination affords the isoquinolone (**18**) and regenerates the starting nickel catalyst.



Scheme 28. A plausible catalytic cycle for the nickel-catalyzed reaction of isoquinolones from *N*-(2-pyridylmethyl)benzamides and alkynes.

4. CONCLUSION

This review summarizes the recent developments in the methods for synthesizing π -conjugated cyclic esters and amides from alkynes and carbonyl reagents. The key to the successful methods is the formation of the metallacycle in the reaction of carbonyl reagents with transition metal complexes. The elimination of gases such as carbon monoxide, carbon dioxide, and nitrogen is one of the important methods, to afford the metallacycle. In addition, the C-H bond activation also afforded the metallacycle intermediates. Isocoumarins, chromones, 2-quinolones, 4-quinolones, and isoquinolones, which are common motifs in biologically active compounds, could be obtained by employing these methods.

REFERENCES AND NOTES

1. A. Katritzky, C. Ramsden, J. Joule, and V. Zhdankin, *Handbook of Heterocyclic Chemistry*, Elsevier, 2010; *Modern Carbonylation Methods*, ed. by L. Kollár, Wiley-VCH, Weinheim, 2008.
2. D. V. Kadnikov and R. C. Larock, *J. Org. Chem.*, 2004, **69**, 6772; D. V. Kadnikov and R. C. Larock, *J. Organomet. Chem.*, 2003, **687**, 425.
3. T. Morimoto and K. Kakiuchi, *Angew. Chem. Int. Ed.*, 2004, **43**, 5580; T. Fujihara, T. Hosoki, Y.

- Katafuchi, T. Iwai, J. Terao, and Y. Tsuji, *Chem. Commun.*, 2012, **48**, 8012; T. Ueda, H. Konishi, and K. Manabe, *Org. Lett.*, 2012, **14**, 3100; T. Ueda, H. Konishi, and K. Manabe, *Angew. Chem. Int. Ed.*, 2013, **52**, 8611; P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp, and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133**, 6061; S. T. Friis, R. H. Taaning, A. T. Lindhart, and T. Skrydstrup, *J. Am. Chem. Soc.*, 2011, **133**, 18114.
4. T. Fujihara, T. Iwai, J. Terao, and Y. Tsuji, *Synlett*, 2010, 2537.
 5. M. C. Willis, *Chem. Rev.*, 2010, **110**, 725; Y. J. Park, J.-W. Park, and C.-H. Jun, *Acc. Chem. Res.*, 2008, **41**, 222.
 6. T. Fujihara, Y. Katafuchi, T. Iwai, J. Terao, and Y. Tsuji, *J. Am. Chem. Soc.*, 2010, **130**, 2094; Y. Nakao, H. Idei, K. S. Kanyiva, and T. Hiyama, *J. Am. Chem. Soc.*, 2009, **131**, 5070; Y. Tsuji, S. Yoshii, T. Ohsumi, T. Kondo, and Y. Watanabe, *J. Organomet. Chem.*, 1987, **331**, 379; T. Kondo, T. Okada, and T. Mitsudo, *Organometallics*, 1999, **18**, 4123.
 7. S. Ko, Y. Na, and S. Chang, *J. Am. Chem. Soc.*, 2002, **124**, 750; E. J. Park, J. M. Lee, H. Han, and S. Chang, *Org. Lett.*, 2006, **8**, 4355; S. Fabre, P. Kalck, and G. Lavigne, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1092; I. J. B. Lin and H. Alper, *J. Chem. Soc., Chem. Commun.*, 1989, 248.
 8. T. Iwai, T. Fujihara, J. Terao, and Y. Tsuji, *J. Am. Chem. Soc.*, 2012, **134**, 1268; T. Iwai, T. Fujihara, J. Terao, and Y. Tsuji, *J. Am. Chem. Soc.*, 2009, **131**, 6668.
 9. R. A. Sheldon, *Pure Appl. Chem.*, 2000, **72**, 1233; B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695.
 10. K. Ueura, T. Sato, and M. Miura, *Org. Lett.*, 2007, **9**, 1407; Y. Unoh, K. Hirano, T. Satoh, and M. Miura, *Tetrahedron*, 2013, **69**, 4454.
 11. Y. Kajita, T. Kurahashi, and S. Matsubara, *J. Am. Chem. Soc.*, 2008, **130**, 17226.
 12. K. Nakai, T. Kurahashi, and S. Matsubara, *J. Am. Chem. Soc.*, 2011, **133**, 11066.
 13. S. Saito and H. Yamamoto, *Chem. Commun.*, 1997, 1585.
 14. A. Ooguri, K. Nakai, T. Kurahashi, and S. Matsubara, *J. Am. Chem. Soc.*, 2009, **131**, 13194.
 15. Carbon Dioxide as Chemical Feedstock; ed. by M. Aresta, Wiley-VCH, Weinheim, 2010; T. Sakakura, J.-C. Choi, and H. Yasuda, *Chem. Rev.*, 2007, **107**, 2365.
 16. Y. Tsuji and T. Fujihara, *Chem. Commun.*, 2012, **48**, 9956; L. Zang and Z. Hou, *Chem. Sci.*, 2013, **4**, 3395; K. Huang, C.-L. Sun, and Z.-J. Shi, *Chem. Soc. Rev.*, 2011, **40**, 2435; M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann, and F. E. Kühn, *Angew. Chem. Int. Ed.*, 2011, **50**, 8510.
 17. T. Tsuda, S. Morikawa, R. Sumiya, and T. Saegusa, *J. Org. Chem.*, 1988, **53**, 3140.
 18. J. Louie, J. E. Gibby, M. V. Farnworth, and T. N. Tekavec, *J. Am. Chem. Soc.*, 2002, **124**, 15188.
 19. Y. Kishimoto and I. Mitani, *Synlett*, 2005, 2141.
 20. T. Fujihara, Y. Tani, K. Semba, J. Terao, and Y. Tsuji, *Angew. Chem. Int. Ed.*, 2012, **51**, 11487.
 21. T. Iwai, T. Fujihara, J. Terao, and Y. Tsuji, *J. Am. Chem. Soc.*, 2010, **132**, 9602.

22. K. Nakai, T. Kurahashi, and S. Matsubara, *Org. Lett.*, 2013, **15**, 856.
 23. Y. Nakao, S. Oda, and T. Hiyama, *J. Am. Chem. Soc.*, 2004, **126**, 13904; Y. Nakao, A. Yada, S. Ebata, and T. Hiyama, *J. Am. Chem. Soc.*, 2007, **129**, 2428; N. M. Brunkan, D. M. Brestensky, and W. D. Jones, *J. Am. Chem. Soc.*, 2004, **126**, 3627.
 24. Y. Yoshino, T. Kurahashi, and S. Matsubara, *J. Am. Chem. Soc.*, 2009, **131**, 7494.
 25. Y. Kajita, T. Kurahashi, and S. Matsubara, *J. Am. Chem. Soc.*, 2008, **130**, 6058.
 26. T. Miura, M. Yamauchi, and M. Murakami, *Org. Lett.*, 2008, **10**, 3085.
 27. M. Yamauchi, M. Morimoto, T. Miura, and M. Murakami, *J. Am. Chem. Soc.*, 2010, **132**, 54.
 28. N. Guimond, C. Gouliaras, and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6908.
 29. N. Guimond, S. I. Gorelsky, and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449.
 30. B. Li, H. Feng, S. Xu, and B. Wang, *Chem. Eur. J.*, 2011, **17**, 12573.
 31. T. K. Hyster and T. Rovis, *J. Am. Chem. Soc.*, 2010, **132**, 10565.
 32. L. Ackermann, A. Lygin, and N. Hofmann, *Angew. Chem. Int. Ed.*, 2011, **50**, 6379.
 33. H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto, and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 14952.
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