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Regio- and Stereoselective Synthesis of Tri- and Tetrasubstituted Alkenes by Introduction of CO_2 and Alkylzinc Reagents into Alkynes

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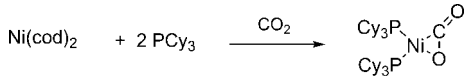
Keywords: Carbon dioxide / Oxanickelacyclopentene / Transmetalation / Alkynes / Alkenes / Heterocycles / Erythrocarine / Tamoxifen

Carbon dioxide (CO_2) is a useful C-1 unit resource in synthetic organic chemistry. It was known that a low-valent nickel complex could coordinate to CO_2 to form an oxanickelacyclopropane, which reacts with a terminal alkyne to form an oxanickelacyclopentene. Transmetalation of the oxanickelacyclopentene with an alkylzinc reagent gives a trisubstituted alkene in high yield after hydrolysis. A novel synthetic method for heterocycles from terminal alkynes containing suitably positioned heteroatoms was developed, using this alkylative carboxylation followed by a hetero-Michael reaction. Using this procedure, the synthesis of erythrocarine, one of the erthrina alkaloids, the total synthesis of which had not previously been achieved, was developed. Additionally, a regioselective synthesis of tetrasubstituted alkenes from disubstituted alkynes was also examined. A silylated alkyne was used and a tetrasubstituted alkene was obtained regioselectively. This reaction was further developed into a nickel-catalyzed reaction, and the effects of substituents on the alkyne were also examined. It was found that an alkyne containing a *tert*-butyl or a phenyl group predominantly gave one tetrasubstituted alkene. The results indicated that conjugation of the carboxyl group with the substituent in the oxanickelacyclopentene is important for the formation of oxanickelacycles, and that the thermodynamically more stable oxanickelacycle should be formed. Thus, thermodynamically more stable alkenes are formed; that is, an electron-donating group on the alkene would conjugate with the carboxyl group. Using this procedure, it was possible to synthesize tamoxifen, which is effective for the treatment of metastatic breast cancer and contains a tetrasubstituted alkene in its skeleton.

Introduction

Carbon dioxide (CO_2) is a useful resource in synthetic organic chemistry. There is abundant CO_2 in air, but utilization of CO_2 is difficult because it is thermodynamically stable. The conventional method for using CO_2 is in a Grignard reaction: an aryl or alkyl halide can react with Mg to form a Grignard reagent, which then reacts with CO_2 to produce the corresponding carboxylic acid. On the other hand, it is known that CO_2 can also react with low-valent transition metal complexes. Transition metal mediated or catalyzed carboxylation is a promising reaction because carbon–carbon bond formation is induced between the carbon–oxygen double bond of carbon dioxide and multiple bonds by the transition metals.[1] In 1975, Aresta and Nobile reported the formation of oxanickelacyclopropane **1**, generated from a nickel complex[2] [Equation (1)].



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Pyranone derivatives **2** were then synthesized from CO_2 and two alkynes by treatment with a nickel complex and a phosphane ligand.[3] These reactions were further developed

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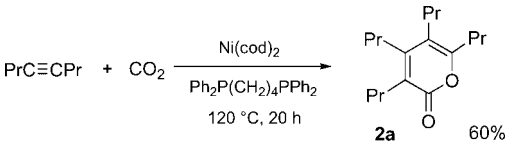
into an intramolecular reaction under higher pressures of CO_2, and fused pyranone derivatives were synthesized[4] [Equations (2), (3), and (4)].



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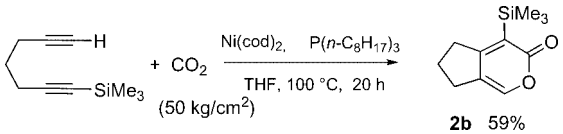

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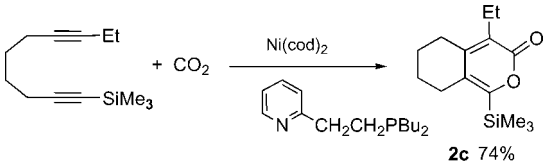
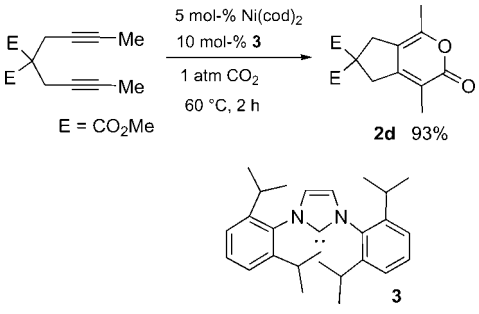


(4)

Recently, Louie improved this reaction using a heterocyclic carbene **3** as a ligand [Equation (5)]. The reaction proceeded under CO_2, and it was reported that oxanickelacyclopentene **4** was probably an intermediate[5] (Figure 1).



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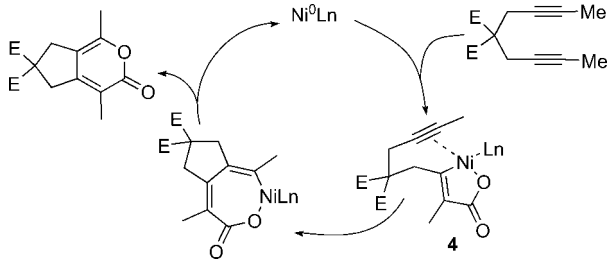
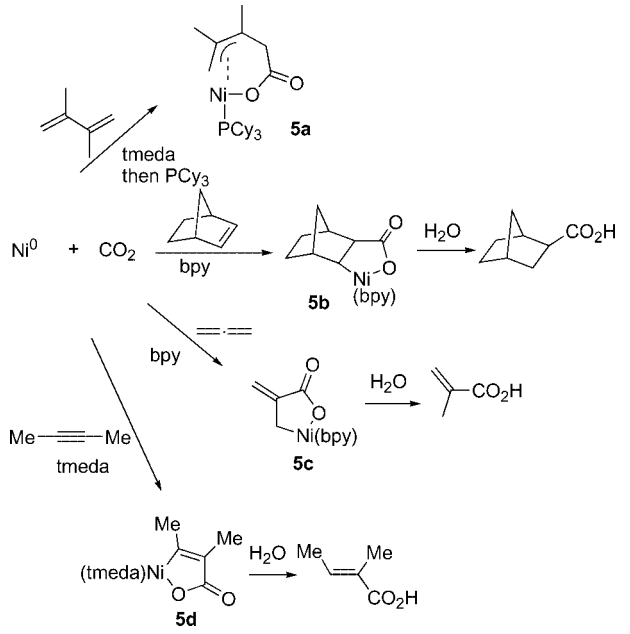


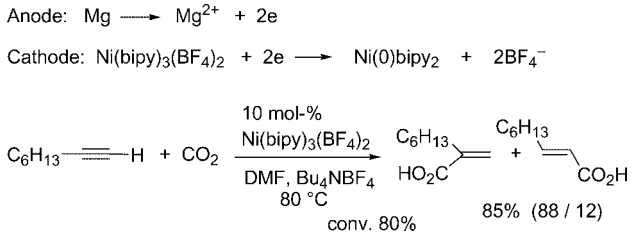
Figure 1. Reaction course for formation of α-pyranones.

On the other hand, Hoberg reported that the reactions of CO_2 and various multiple bond systems such as dienes,[6] alkenes,[7] allenes,[8] and alkynes[9] afforded the corresponding oxanickelacycles **5**. In each case a base such as tetramethylethylenediamine (tmeda) or bipyridyl (bpy) was used as ligand (Scheme 1).



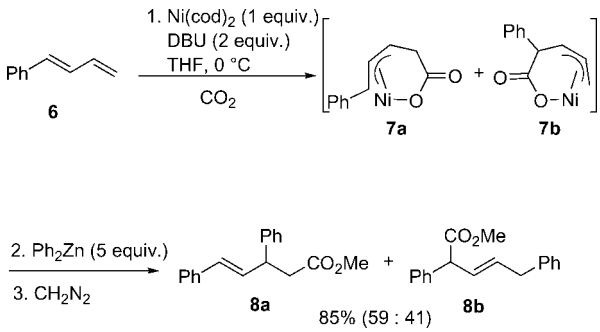
Scheme 1. Synthesis of oxanickelacycles from CO_2, Ni^0, and various multiple bond systems.

Electrochemical reduction of $Ni(bipy)_3(BF_4)_2$ yielded an active catalyst for reactions of terminal alkynes and CO_2. A novel electrochemical carboxylation allowed transformation of terminal alkynes into α-substituted acrylic acids with selectivities of 65–90% and relatively good overall yields (Scheme 2).[10] The regioselectivity of the insertion of CO_2 into the alkyne is different from that observed by Hoberg.



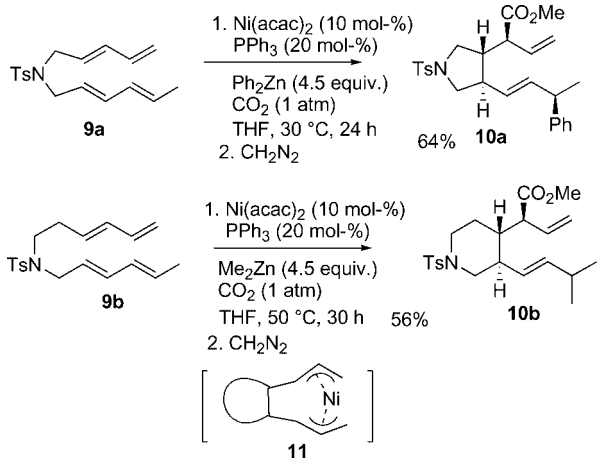
Scheme 2. Electrochemical carboxylation.

Transmetalation of π-allylnickel complexes **7a** and **7b**, generated from diene **6**, CO_2, and a nickel complex, with a phenylzinc reagent afforded phenylated carboxylic acids **8a** and **8b** in high yields in a 1:1 ratio [Equation (6)].[11]



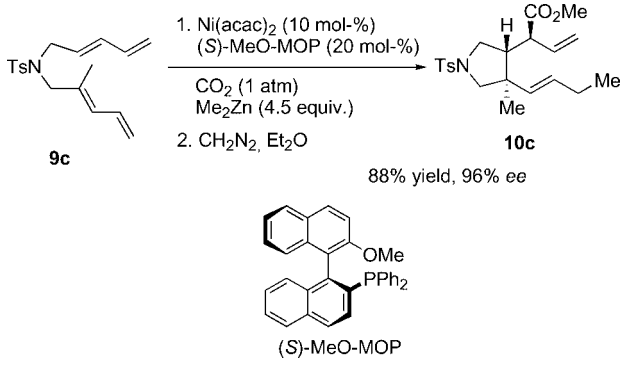
(6)

Furthermore, nickel-catalyzed ring-closing carboxylation using a nickel complex and a phosphane ligand was developed, and the reaction proceeded in a highly regio- and stereoselective manner to afford pyrrolidine and piperidine derivatives **10a** and **10b**. The bis(π-allyl)nickel complex **11** was presumably an intermediate (Scheme 3).[12]



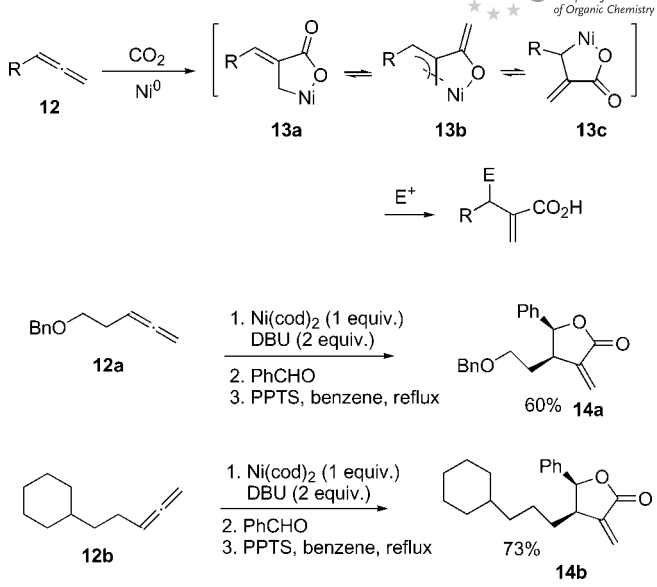
Scheme 3. Nickel-catalyzed ring-closing carboxylation.

This reaction was further developed into an asymmetric reaction by using (*S*)-MeO-MOP as a ligand, and pyrrolidine derivative **10c** was obtained in high yield and with high enantioselectivity (Scheme 4).[13]



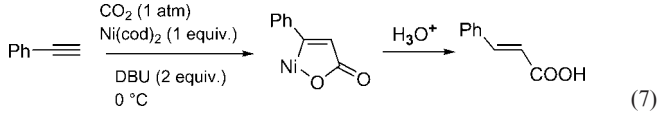
Scheme 4. Nickel-catalyzed asymmetric carboxylative cyclization.

On the other hand, allene **12** reacted with CO_2 in the presence of $Ni(cod)_2$ and DBU to afford oxanickelacycle **13a**, which exists in a state of equilibrium with π-allylnickel complex **13b**, and nucleophilic substitution of π-allylnickel complex to aldehyde should give the condensation product. Allene **12a** was treated with a nickel complex under CO_2 at 0 °C, and then benzaldehyde was added. The benzene solution of the crude product was heated at reflux in the presence of PPTS to give α-methylene-γ-lactone **14a** in good yield and in a stereoselective manner. In a similar treatment of **12b**, α-methylene-γ-lactone **14b** was produced (Scheme 5).[14]



Scheme 5. Synthesis of α-methylene-γ-lactones.

Oxanickelacyclopentene **5d** was prepared from an alkyne, CO_2, and a nickel complex in the presence of tmeda as a ligand. Hydrolysis of oxanickelacyclopentene **5d** gave an α,β-unsaturated carboxylic acid (Scheme 1).[9a] Using this procedure, Yamamoto and Saito reported the synthesis of an α,β-unsaturated carboxylic acid from a terminal alkyne and CO_2, in this case using diazabicycloundecene (DBU) as a ligand [Equation (7)].[15]

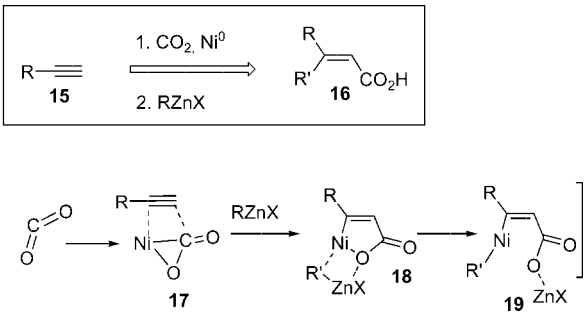


(7)

In this report, syntheses of tri- and tetrasubstituted alkenes via oxanickelacyclopentenes, generated from alkynes, CO_2, and low-valent nickel complexes, are discussed.

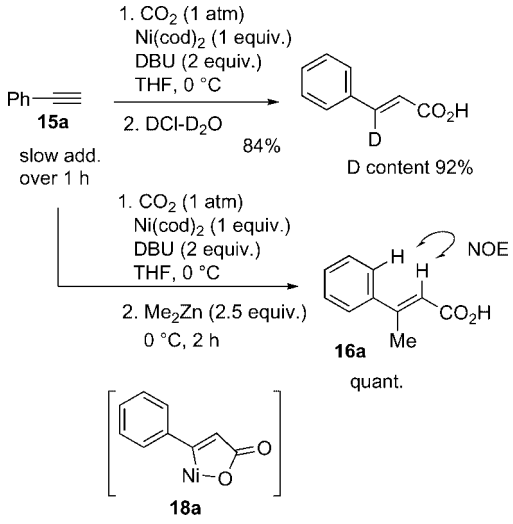
Synthesis of Trisubstituted Alkenes from Terminal Alkynes, CO_2, and Alkylzinc Reagents Using Nickel Complexes

The synthesis of trisubstituted alkenes **16** using oxanickelacyclopentenes generated from terminal alkynes **15**, CO_2, and nickel complexes was planned. It was interesting that CO_2 reacted with Ni^0 to afford oxanickelacyclopropane **17**.[2] Insertion of an alkyne into the oxanickelacyclopropane afforded an oxanickelacyclopentene **18**.[9] If transmetalation of oxanickelacyclopentene **18** with an alkylzinc reagent were to occur,[16] alkylnickel complex **19** would be formed (Scheme 6), and reductive elimination from **19** would give a trisubstituted alkene **16**. In this reaction, the regioselectivity for insertion of alkyne **15** into oxanickelacyclopropane **17** is important. Presumably, the nickel atom would be connected to the internal carbon atom of alkyne **15**, as was found in a study by Yamamoto.[15]



Scheme 6. Plan for synthesis of tetrasubstituted alkenes.

To confirm the formation of oxanickelacyclopentene **18**, a THF solution of phenylacetylene (**15a**) was added to a THF solution of an equimolar amount of $Ni(cod)_2$ and 2 equiv. of DBU under CO_2, and the solution was stirred at 0 °C for 3 h. After addition of D_2O to this solution, β-deuterated cinnamic acid was obtained in 86% yield and the D content was 92% (Scheme 7). This result indicated that oxanickelacyclopentene **18a** had been formed and that it had remained unchanged until deuteriolysis.



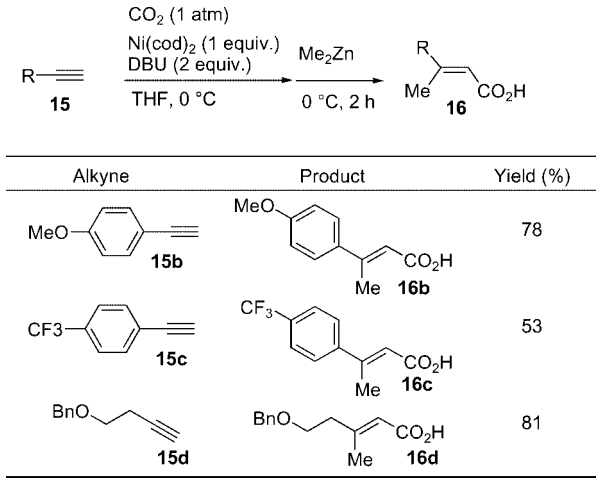
Scheme 7. Nickel-mediated carboxylation of alkynes.

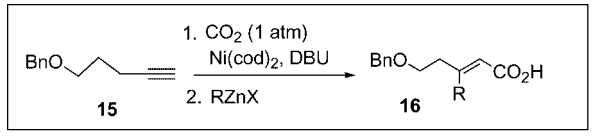
Subsequently, dimethylzinc reagent was added to a THF solution of oxanickelacyclopentene **18a** prepared in a similar manner and the solution was stirred at 0 °C for 2 h. After hydrolysis, β-methylcinnamic acid (**16a**) was obtained in quantitative yield. The result of an NOE experiment indicated that the nickel atom was connected to the internal carbon atom of alkyne **15a** and that the reaction proceeded in a highly regio- and stereoselective manner.

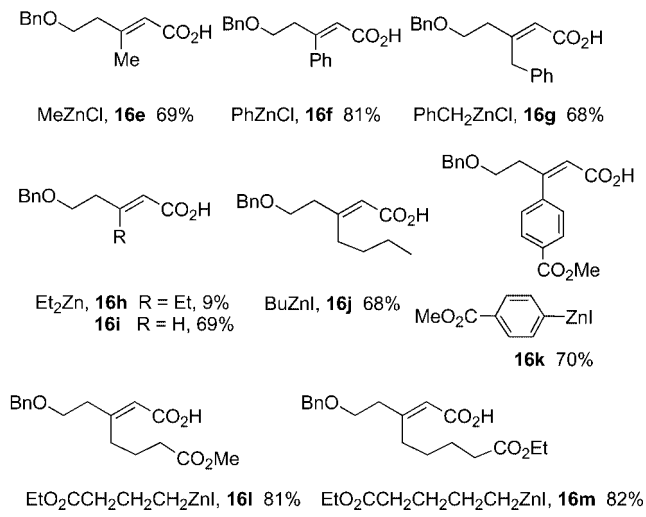
Various alkynes **15b–d** were examined in this reaction, and the corresponding trisubstituted alkenes **16b–d** were obtained in good yields (Table 1).

Various zinc reagents could be used for this reaction and a variety of trisubstituted alkenes were obtained in high yields. An alkylzinc reagent containing an ester group could also be used in this reaction (Scheme 8).[17]

Table 1. Synthesis of trisubstituted alkenes.



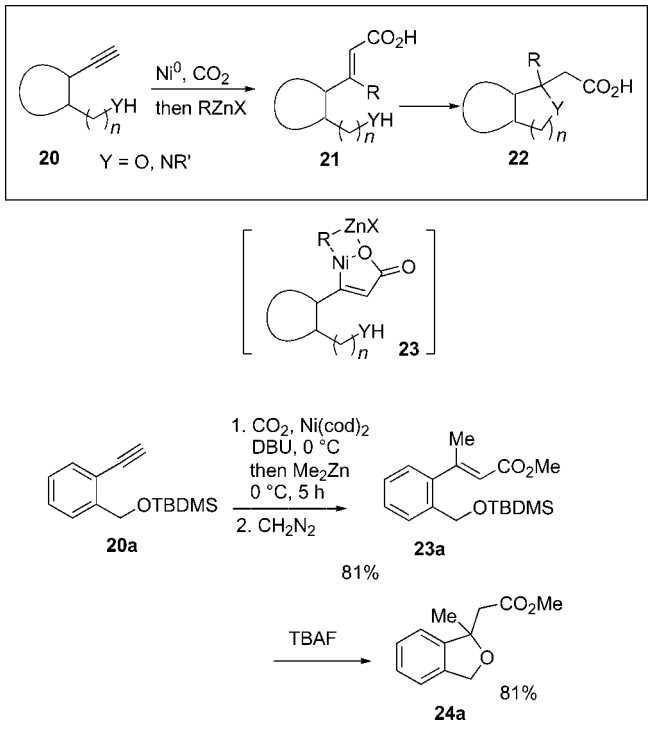




Scheme 8. Alkylative carboxylation of alkynes using various alkylzinc reagents.

Synthesis of Heterocycles by Alkylative Carboxylation of Alkynes

As an application of the method for the synthesis of trisubstituted alkenes, the synthesis of heterocycles was planned; the idea is shown in Scheme 9. When a terminal alkyne **20** containing a heteroatom at an appropriate position is treated with the nickel complex under CO_2 and an alkylzinc reagent is then added, the α,β-unsaturated carboxylic acid **21** should be formed via oxanickelacyclopentene **23**. If a Michael addition of the heteroatom onto the α,β-unsaturated alkene **21** were to occur, the heterocyclic compound **22** containing a tetrasubstituted carbon center should be obtained.



Scheme 9. Synthesis of heterocycles using alkylative carboxylation.

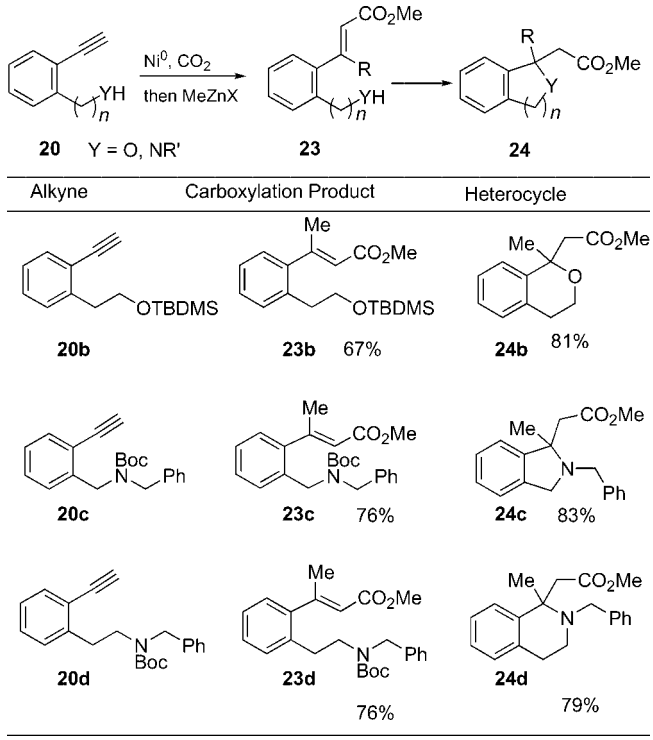
Compound **20a** was thus treated with CO_2 in the presence of Ni^0, and Me_2Zn was then added. After treatment of the resultant crude product with CH_2N_2, the α,β-unsaturated ester **23a** was obtained in 81% yield. Removal of the silyl group of compound **23a** with TBAF afforded isobenzofuran **24a** in high yield.

Various alkynes **20** containing heteroatoms were treated in a similar manner, and the desired heterocycles **24** containing tetrasubstituted carbon centers were obtained in high yields (Table 2). Nitrogen heterocycles such as isoindoline and isoquinoline derivatives **24c** and **24d** could be synthesized using this method. Development of the synthetic method for these nitrogen heterocycles provided a useful tool for the synthesis of natural products and related biologically active substances.[18]

Encouraged by these results, we planned a synthesis of erythrina alkaloids,[19] a widely distributed family of structurally interesting and biologically active natural products (Figure 2). An erythrina alkaloid has a tetracyclic framework that contains an isoquinoline skeleton with a tetrasubstituted carbon center at the benzylic position. Thus, for the synthesis of erythrina alkaloids, it is important to construct this tetrasubstituted carbon center. The erythrina alkaloids include many compounds; our target molecule was erythrocarine, which was isolated by Jackson in 1985.[20] The total synthesis of this alkaloid had not previously been achieved.

A retrosynthetic analysis of erythrocarine is shown in Scheme 10. This skeleton would be synthesized using dienyne metathesis[21] of **25**. Dienyne **25** would in turn be synthesized from isoquinoline derivative **26** containing a tetrasubstituted carbon center, which would be synthesized from the terminal alkyne **27** containing a suitably positioned heteroatom by treatment with CO_2, Ni^0, and an alkynylzinc reagent, while compound **27** should be synthesized from *o*-bromopiperonal (**28**).

Table 2. Synthesis of heterocycles using alkylative carboxylation followed by a hetero-Michael reaction.



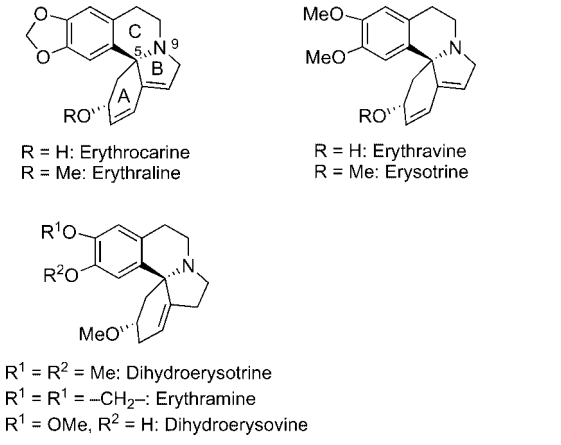
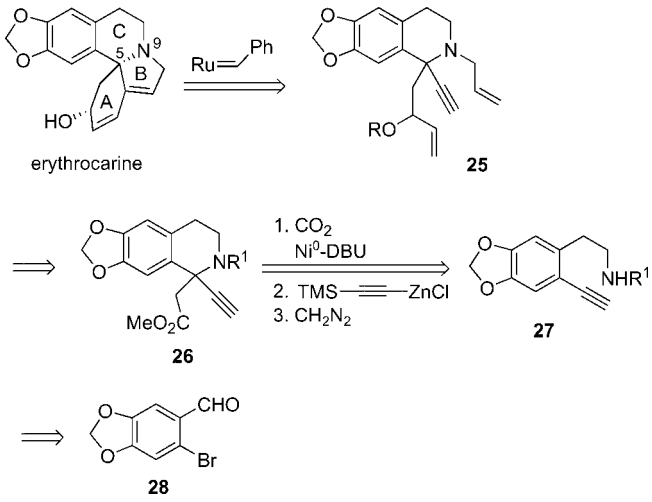


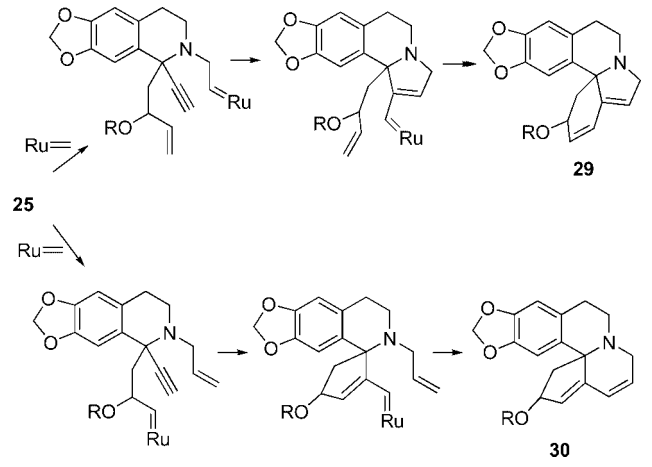
Figure 2. Erythrina alkaloids.

In this retrosynthetic analysis, there are two problems. It was not clear which compound, **29** or **30**, would be obtained in the dienyne metathesis (Scheme 11). If the (methylidene)ruthenium carbene complex were to react first with the alkene in allylamine, a fused 6,5,6-membered ring system connected with a benzene ring would be constructed; that is, compound **29** would be produced. However, if it were to react with the alkene in the allyl alcohol, compound **30** with a fused 6,6,5-membered ring system would be



Scheme 10. Retrosynthetic analysis of erythrocarine.

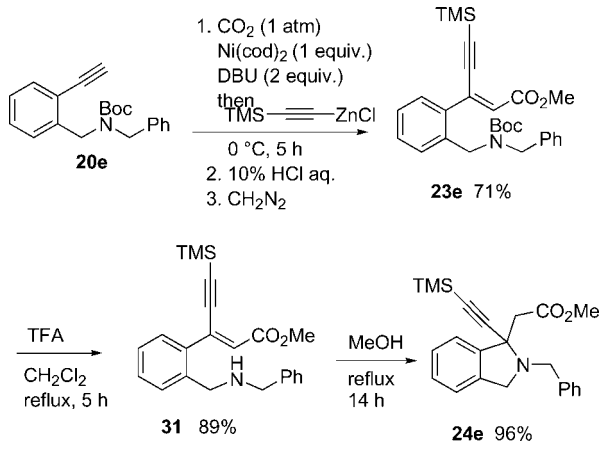
formed. The other problem was whether an alkynylzinc reagent could be used for the synthesis of the isoquinoline derivative **26**.



Scheme 11. Possible reaction course for dienyne metathesis.

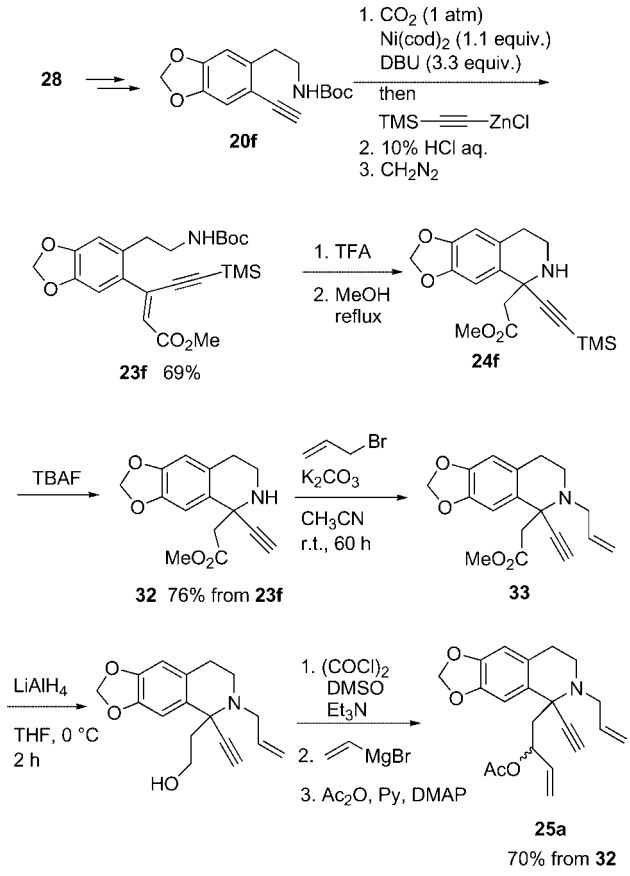
Firstly, it was examined whether the isoindoline derivative **24e** could be synthesized when an alkynylzinc reagent was used as a zinc reagent (Scheme 12). Terminal alkyne **20e** with a nitrogen atom attached to the benzylic position was treated with CO_2 in the presence of a nickel complex, and then an alkynylzinc reagent was added. After the usual workup, the desired α,β-unsaturated ester **23e** was obtained. Removal of the Boc group gave the secondary amine **31**, an MeOH solution of which was heated at reflux overnight to give isoindoline **24e** containing a tetrasubstituted carbon center at the benzylic position in high yield.

From *o*-bromopiperonal (**28**), the terminal alkyne **20f** was prepared (Scheme 13). Compound **20f** was then added under CO_2 to a THF solution of $Ni(cod)_2$ and DBU, and then the alkynylzinc reagent was added. After the usual workup, α,β-unsaturated ester **23f** was obtained and was treated with TFA to give the primary amine, an MeOH solution of which was heated at reflux overnight to give



Scheme 12. Synthesis of isoindoline using alkylative carboxylation followed by hetero-Michael reaction.

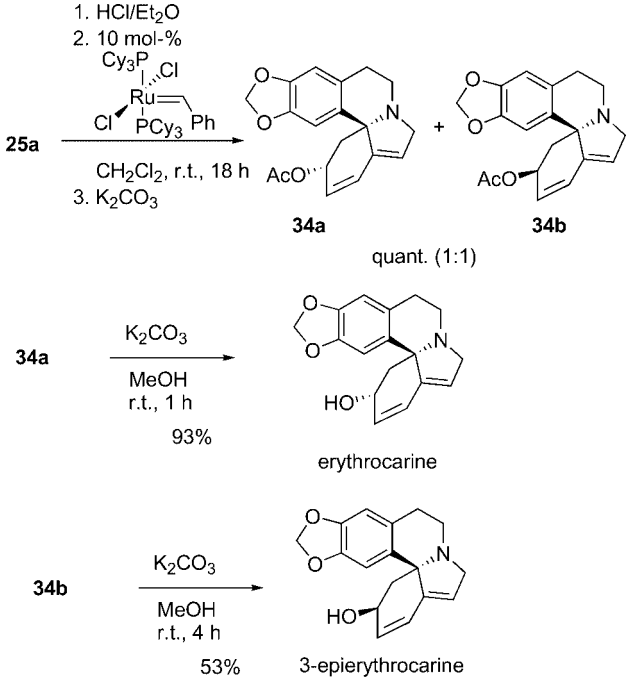
the desired isoquinoline derivative **24f**. Removal of the silyl group, followed by allylation, afforded compound **33**. Conversion of an ester group of **33** into the hydroxy group and subsequent Swern oxidation afforded the aldehyde, which was treated with vinylmagnesium bromide and then with acetic anhydride to give the desired dienyne **25a** as a mixture of diastereomeric isomers.



Scheme 13. Synthesis of dienynes.

Dienyne metathesis was carried out. Since compound **25a** has a tertiary amino group, **25a** was treated with HCl/

Et_2O to give **25a**·HCl,[22] because an amino nitrogen atom would coordinate to the ruthenium catalyst and the catalytic activity of the ruthenium catalyst would decrease. When a CH_2Cl_2 solution of dienyne **25a** was stirred in the presence of ruthenium carbene complex[23] at room temperature for 18 h, a mixture of cyclic compounds **34a** and **34b**, each containing a fused 6,5,6-membered ring system, was obtained in a 1:1 ratio in quantitative yield (Scheme 14). No product **30** with a fused 6,6,5-membered ring system was formed in this reaction. Compounds **34a** and **34b** represent a diastereomeric mixture (at the acetoxy group) and they were separable by column chromatography. From the result of an NOE experiment with each isomer, it was clear that the stereochemistry of compound **34a**, which appeared at a higher position in the TLC, was the same as that of erythrocarine (Figure 3). Deacetylation of this compound **34a** afforded erythrocarine, the spectroscopic data of which agreed with those reported in the literature. The other isomer **34b** was hydrolyzed to give epierythrocarine. Thus, the total synthesis of erythrocarine was achieved.[18b]



Scheme 14. Dienyne metathesis.

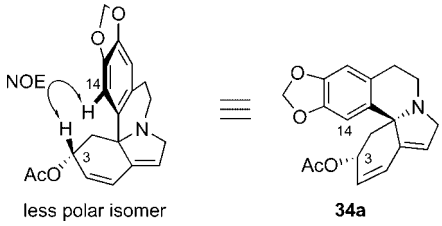
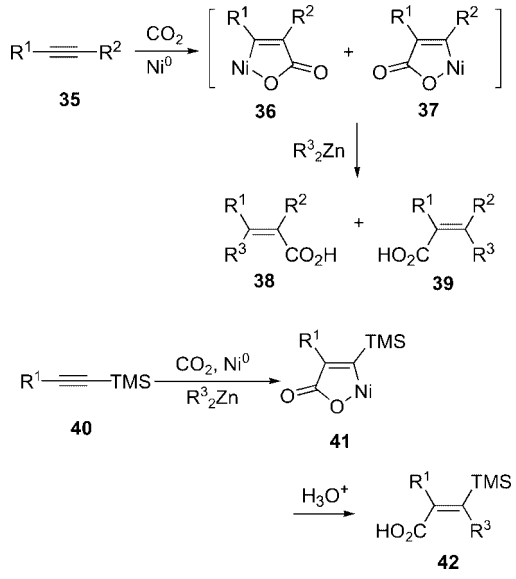


Figure 3. Determination of stereochemistry.

Highly Regio- and Stereoselective Syntheses of Tetrasubstituted Alkenes by Nickel-Mediated Carboxylation

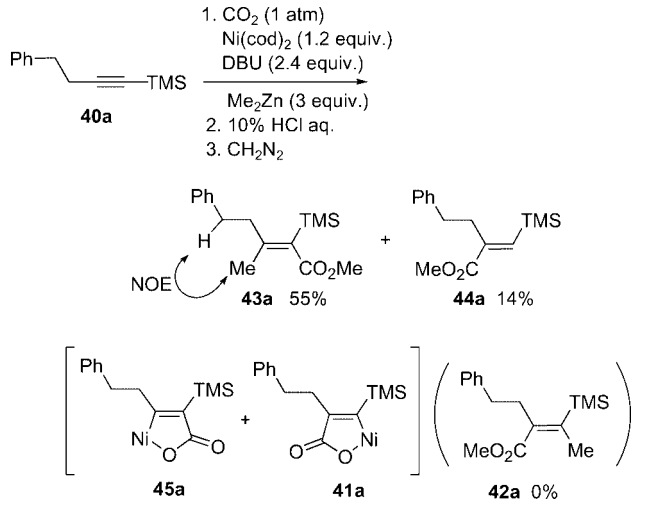
On the basis of the above results, the synthesis of tetrasubstituted alkenes from disubstituted alkynes was examined. If disubstituted alkyne **35** were to be treated with CO_2 in the presence of Ni^0 and an alkylzinc reagent were then added, two tetrasubstituted alkenes **38** and **39** should be formed via oxanickelacyclopentenes **36** and **37** (Scheme 15). The silylated alkyne **40** was used for the regioselective synthesis of tetrasubstituted alkenes, because the nickel atom should be connected with an alkyne carbon atom bearing a silyl group to form the oxanickelacycle **41**, due to the stabilizing effect of the silyl group to the metal atom.[24]



Scheme 15. Plan for synthesis of tetrasubstituted alkenes.

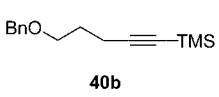
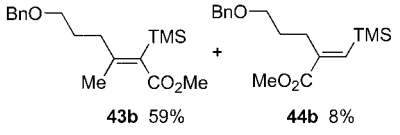
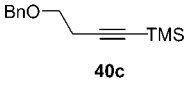
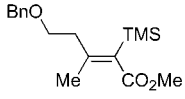
When the silylated alkyne **40a** was treated with an equimolar amount of $Ni(cod)_2$ and 2 equiv. of DBU under CO_2, and Me_2Zn was then added to this solution, the tetrasubstituted alkene **43a** was obtained in 55% yield along with the trisubstituted alkene **44a** in 14% yield after treatment of the crude product with CH_2N_2 (Scheme 16). From NOE experiments with these compounds, the stereochemistry of the former compound was determined to be that of **43a**, which was derived from the unexpected oxanickelacyclopentene **45a**. The other product was the trisubstituted alkene **44a**, derived from oxanickelacycle **41a** in 14% yield, while the tetrasubstituted alkene **42a** was not obtained.

Although the reason for the formation of **43a** is not clear at this stage, the result that one isomer (**43a**) was obtained predominantly was interesting. Thus, various silylated alkynes **40b–c** were treated in a similar manner and in each case the tetrasubstituted alkenes **43b–c**, which were derived from oxanickelacycle **36** (R^2 = TMS), were formed as the major products (Table 3).



Scheme 16. Nickel-mediated synthesis of tetrasubstituted alkynes.

Table 3. Synthesis of tetrasubstituted alkenes by nickel-mediated carboxylation.

Substrate	Products
 **40b**	 **43b** 59% **44b** 8%
 **40c**	 **43c** 61%

Development of Nickel-Catalyzed Arylative and Alkylative Carboxylation

The regioselective synthesis of tetrasubstituted alkene **43** from silylated alkyne **40** was achieved using a stoichiometric amount of Ni^0 and DBU. A possible reaction course for this is shown in Figure 4. In this reaction, $Ni(cod)_2$ should be converted into $Ni(dbu)_2$, which would react with alkyne **40** and CO_2 to afford oxanickelacyclopentene **45**. Transmetalation of this with an alkylzinc reagent would afford alkylnickel complex **46**, and reductive elimination from **46** would give tetrasubstituted alkene **43** (after treatment with CH_2N_2). If this reaction proceeds according to this scheme, Ni^0 would be regenerated. That is, this reaction should proceed with a catalytic amounts of Ni^0.

When, however, a THF solution of the silylated alkyne **40a**, 20 mol-% of $Ni(cod)_2$, 40 mol-% of DBU, and 3 equiv. of Me_2Zn was stirred at room temperature for 96 h, the desired tetrasubstituted alkene **43a** was not formed and the starting material **40a** was recovered unchanged in 96% yield (Scheme 17).

In this reaction, 20 mol-% of $Ni(cod)_2$ and 40 mol-% of DBU were used, along with 3 equiv. of Me_2Zn as a transmetalation reagent. Although DBU was used as a ligand for the nickel complex, it should also coordinate to the zinc reagent [Equation (8)].

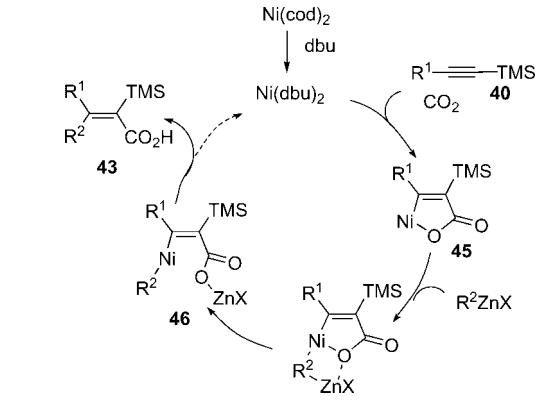
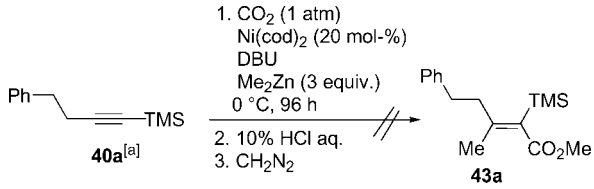


Figure 4. Possible reaction course.



Scheme 17. Investigation of the catalytic reaction. [a] Compound **40a** was recovered in 96% yield.

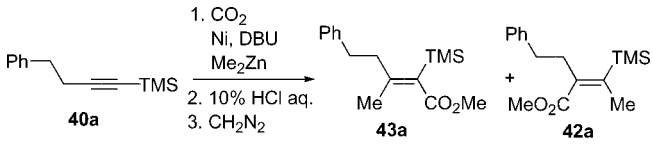
$$Me_2Zn + DBU \longrightarrow Me_2Zn(DBU)_2 \quad (8)$$

To achieve a nickel-catalyzed reaction, an excess amount of DBU would be required to coordinate to the zinc reagent. Thus, 20 mol-% of $Ni(cod)_2$, 6.5 equiv. of DBU, and 3 equiv. of the zinc reagent were used for this reaction, and we were pleased to find that tetrasubstituted alkenes **43a** and **42a** were produced in 33% and 8% yields, respectively (Table 4, Entry 1). This means that the catalytic cycle was established. The reactions were carried out under various conditions to improve the yield of **43a**, and the results are shown in Table 4. An increased amount of DBU slightly increased the yield of the desired compound **43a** (Entry 2), and a higher reaction temperature gave a good yield (Entry 3). Toluene could be used as a solvent (Entry 4) and even the use of 10 mol-% of $Ni(cod)_2$ gave a similar result (Entry 5). It is interesting that the use of divalent nickel complex $Ni(acac)_2$ afforded almost the same results (Entry 6).

Various silylated alkynes **40** were treated with Me_2Zn under CO_2 in the presence of a catalytic amount of $Ni(cod)_2$ to afford a variety of tetrasubstituted alkenes **43** via oxanickelacyclopentenes **45** in good yields (Table 5).[25]

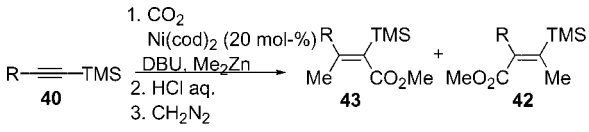
In the stoichiometric reaction, the tetrasubstituted alkene **43a** was obtained along with trisubstituted alkene **44a**, but in the catalytic reaction, the tetrasubstituted alkene **42a** was produced as a byproduct instead (Scheme 18). Each byproduct was derived from oxanickelacyclopentene **41a**. It

Table 4. Nickel-catalyzed carboxylation under various conditions.



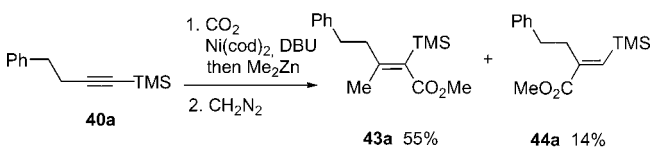
Entry	Ni (mol-%)	DBU (equiv.)	Solvent	Temp. (°C)	Time (h)	Yields (%) 43a	42a
1	$Ni(cod)_2$ (20)	6.5	THF	0	29	33	8
2	$Ni(cod)_2$ (20)	10	THF	0	19	38	10
3	$Ni(cod)_2$ (20)	10	THF	r.t.	20	68	23
4	$Ni(cod)_2$ (20)	10	toluene	40	18	64	21
5	$Ni(cod)_2$ (10)	10	THF	40	19	64	22
6	$Ni(acac)_2$ (20)	10	THF	40	21	59	20

Table 5. Synthesis of tetrasubstituted alkynes by nickel-catalyzed carboxylation.

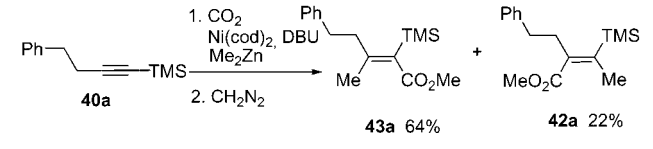


Entry	Substrate		Yields (%) 43	42
1	Ph, TMS	40a	68	23
2	BnO, TMS	40b	76	0
3	BnO, TMS	40c	67	18
4	BnO, TMS	40d	56	14
5	TMS	40e	68	10
6	Ph, MeO, TMS	40f	71	11

Stoichiometric Reaction



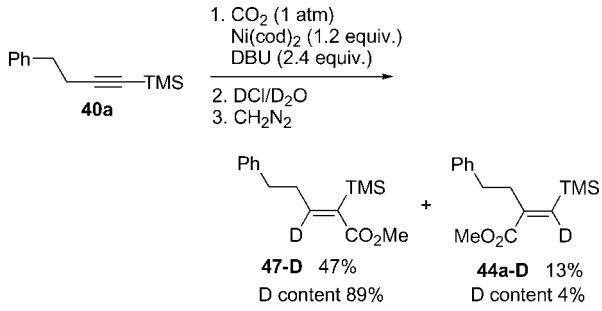
Catalytic Reaction



Scheme 18. Difference in products between a stoichiometric reaction and a catalytic reaction.

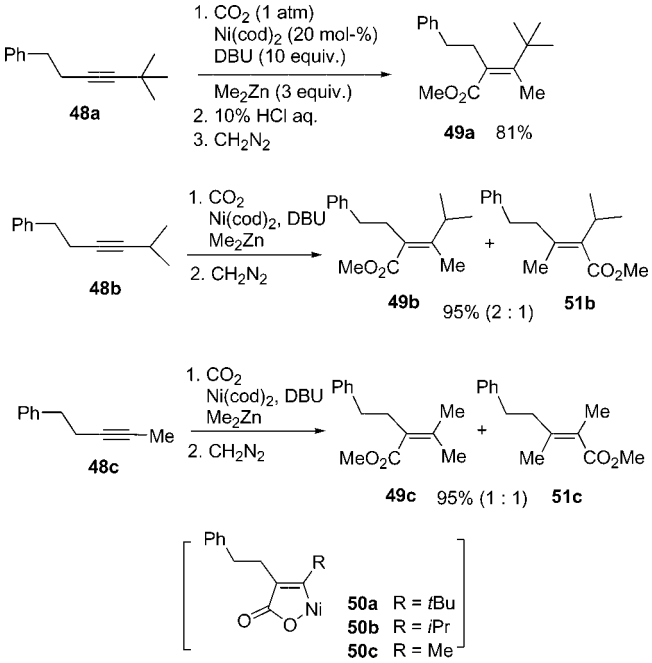
would be interesting to know the reason for the difference between the byproduct obtained in a stoichiometric reaction and that in a catalytic reaction.

To clarify these results, oxanickelacyclopentenes **45a** and **41a**, generated from **40a**, Ni^0, and CO_2, were synthesized in a stoichiometric reaction, DCl/D_2O was added to this solution and the crude product was treated with CH_2N_2. As a result, deuterated trisubstituted alkene **47-D** was obtained as a major product and the D content was 89% (Scheme 19). However, the D content of the minor trisubstituted alkene **44a-D** (13% yield) was only 4%. This means that oxanickelacyclopentene **41a** was probably hydrolyzed under these reaction conditions by a trace amount of H_2O. Thus, in the stoichiometric reaction, hydrolyzed trisubstituted alkyne **44a** should be formed during the reaction, while in the catalytic reaction, oxanickelacyclopentene **41a** formed from alkyne **40a**, CO_2, and Ni^0 would immediately be transmetalated with Me_2Zn in the reaction solution to produce the tetrasubstituted alkene **42a**.



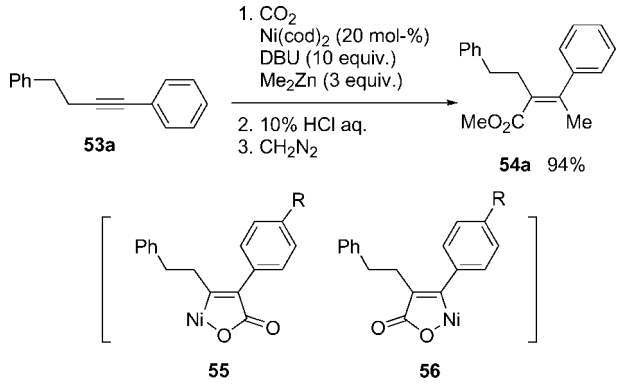
Scheme 19. Stoichiometric reaction followed by deuterium quenching.

Next, the substituent effect on the alkynes for the synthesis of tetrasubstituted alkenes was examined. When a THF solution of alkyne **48a**, bearing a *tert*-butyl group, and Me_2Zn was stirred in the presence of a catalytic amount of $Ni(cod)_2$ and DBU under CO_2, surprisingly, only tetrasubstituted alkene **49a** was formed, in 81% yield (Scheme 20). This compound **49a** was derived from oxanickelacycle **50a**. It is interesting that alkyne **48a**, containing a *tert*-butyl group, gave only tetrasubstituted alkene **49a**, which was derived from **50a**, but the silylated alkyne **40a** gave **43a**, which was derived from **45a**, as a major product. To confirm the substituent effect of the alkyl group, alkyne **48b**, bearing an isopropyl group, was treated in a similar manner. As a result, two tetrasubstituted alkenes, **49b** and **51b**, were obtained in 95% yield in a ratio of 2:1. Furthermore, alkyne **48c**, containing a methyl group, was treated in a similar manner to afford the two alkenes **49c** and **51c** in 95% yield in a ratio of 1:1. These results indicated that the methyl group derived from Me_2Zn was introduced preferentially onto the carbon atom of the disubstituted alkyne bearing a more substituted alkyl group, that is, in intermediate **50**, the nickel atom is connected to the same carbon atom, and the double bond that replaces the triple bond of the reactant alkyne is conjugated with the carboxyl group coming from CO_2.



Scheme 20. Reactions of alkynes containing alkyl groups.

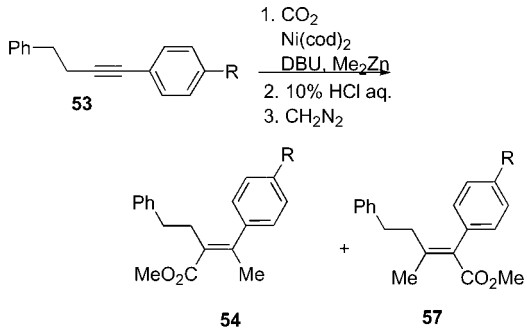
Next, an alkyne containing a phenyl group was examined. When alkyne **53a** was treated with Me_2Zn in the presence of Ni(cod)$_2$ and DBU under CO_2, only the tetrasubstituted alkene **54a**, which was derived from oxanickelacyclopentene **56a** (R = H), was obtained; that is, the nickel atom was connected to the carbon atom bearing the phenyl group in the oxanickelacyclopentene **56** (Scheme 21).



Scheme 21. Reaction of an alkyne containing phenyl groups.

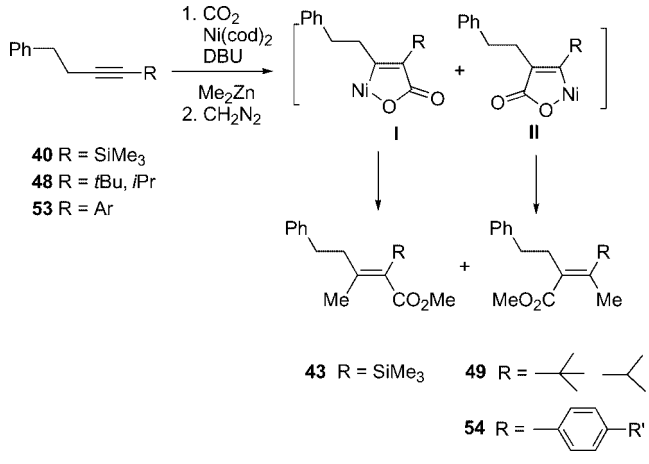
Since alkyne **53a**, containing a phenyl group, gave a single isomer in high yield, the electronic effect of the substituent on the aromatic ring was examined (Table 6). Alkyne **53b**, with a 4-methoxyphenyl group, was treated in a similar manner to afford only **54b**, in quantitative yield. However, in the case of alkyne **53c**, with a 4-methoxycarbonyl group, the major product was **54c**, but a relatively large amount of **57c** was obtained. These results indicated that the thermodynamically more stable alkene arises from the thermodynamically more stable oxanickelacycle.

Table 6. Effect of aromatic ring substituents.



R		54	57
H	**53a**	94%	0%
OMe	**53b**	quant.	0%
CO_2Me	**53c**	72%	23%

The effects of these substituents are summarized in Scheme 22. In the case of silylated alkyne **40**, the tetrasubstituted alkyne **43** (R = TMS) was obtained as the major product via oxanickelacycle **I**. However, the alkynes **48** and **53**, with the alkyl and aryl groups, predominantly afforded tetrasubstituted alkenes **49** and **54** in high yields via oxanickelacycle **II**. Presumably, for the formation of oxanickelacycles, conjugation of the carboxyl group with the substituent (R) in the oxanickelacyclopentene is important, and the thermodynamically more stable oxanickelacycle should be formed in this reaction. Thus, the thermodynamically more stable alkene would be formed; that is, the electron-donating group on the alkene would conjugate with the carboxyl group.

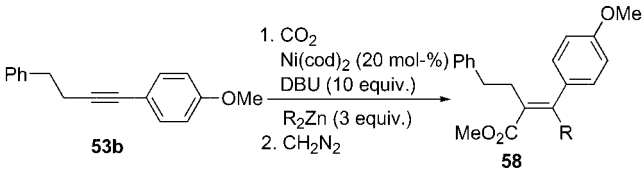


Scheme 22. Summary of the effects of substituents.

Next, various zinc reagents were examined for the synthesis of tetrasubstituted alkenes. The results are shown in Table 7. Various zinc reagents such as Ph_2Zn, Bn_2Zn, and nBu$_2$Zn gave the corresponding tetrasubstituted alkenes **58**

(Figure 5) in high yields (Entries 1–3). However, in the case of nBu$_2$Zn, the desired compound **58c** was obtained in 79% yield along with trisubstituted alkene **58d** in 19% yield (Entry 4). This compound (**58d**) should be formed by β-hydrogen elimination from the butylnickel complex followed by reductive elimination.

Table 7. Reactions of alkynes with various zinc reagents.



Entry	R_2Zn	Temp.	Time (h)	Product	Yield (%)
1	Ph_2Zn	40 °C	15	**58a**	97
2	Bn_2Zn	40 °C	12	**58b**	90
3	nBu$_2$Zn	r.t.	18	**58c**	79[a]

[a] Compound **58d** was obtained in 19% yield.

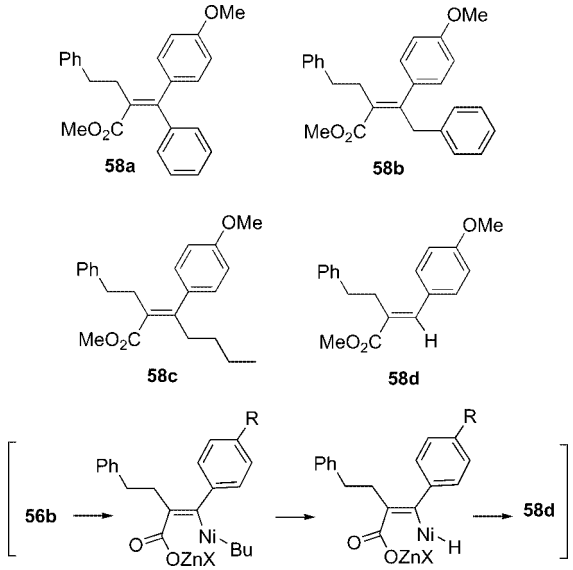
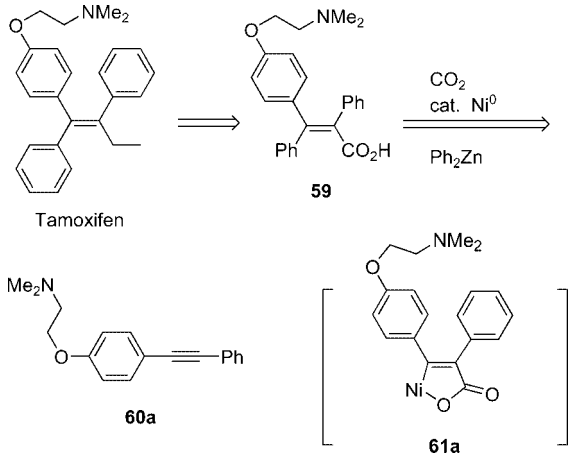
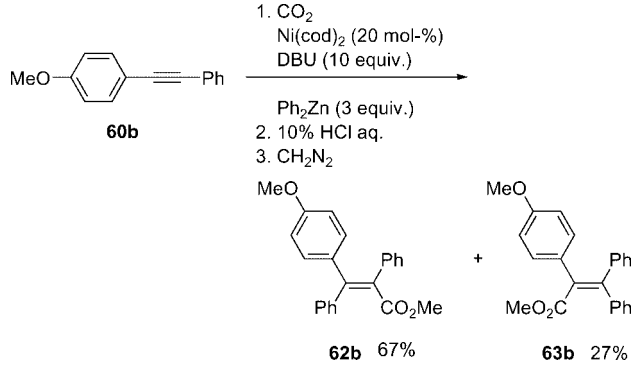


Figure 5. Structures of tetrasubstituted alkynes.

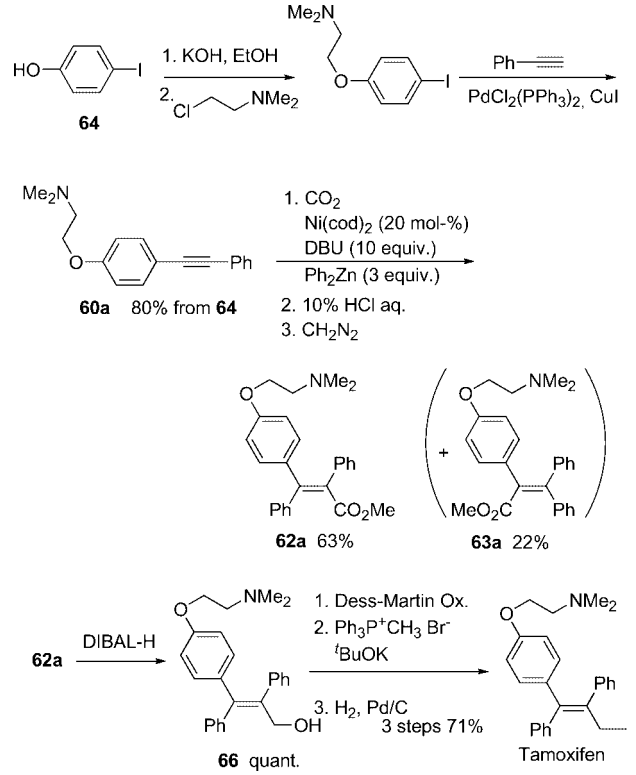


Scheme 23. Retrosynthetic analysis of tamoxifen.

Using regio- and stereoselective synthesis of tetrasubstituted alkenes, the synthesis of tamoxifen, which has a tetrasubstituted alkene in its skeleton, was planned. Tamoxifen is an anti-estrogenic anticancer drug that is effective for the treatment of metastatic breast cancer.[26] A retrosynthetic analysis of tamoxifen[27] is shown in Scheme 23. Tamoxifen would be synthesized from carboxylic acid **59**, which would be obtained from disubstituted alkyne **60a** by nickel-catalyzed arylative carboxylation. In this synthesis, the oxanickelacycle **61a** should be formed predominantly, because of the electron-donating group located at the 4-position of the aryl group.



Scheme 24. Synthesis of tetrasubstituted alkenes.



Scheme 25. Synthesis of tamoxifen.

To confirm this, 1-(4-methoxyphenyl)-2-phenylacetylene was used as a model compound. A THF solution of **60b** and Ph_2Zn was stirred in the presence of 20 mol-% of $Ni(cod)_2$ and DBU under CO_2 at 40 °C for 24 h. After the usual workup, the expected tetrasubstituted alkene **62b** was obtained as the major product (Scheme 24).

The desired alkyne **60a** was synthesized from 4-iodophenol by alkylation followed by condensation with phenylacetylene using a palladium catalyst (Scheme 25). Arylative carboxylation to give the disubstituted alkyne **60a** was carried out using Ph_2Zn to give tetrasubstituted alkene **62a** in 63% yield along with **63a** in 22% yield. Treatment of **62a** with DIBAL-H afforded alcohol **65**, which has already been converted to tamoxifen by Fallis.[27o] According to the procedure of Fallis, Dess–Martin oxidation followed by Wittig reaction and then hydrogenation afforded tamoxifen. Thus, the synthesis of tamoxifen was achieved.[28]

Conclusions

Utilization of CO_2 is a very important and challenging subject in synthetic organic chemistry because carbon dioxide is a useful C-1 unit resource and the abundant carbon dioxide in air can be used. Since it is known that CO_2 can coordinate to transition metals, metal complexes coordinated by carbon dioxide should be useful intermediates. In addition, regioselective syntheses of tri- and tetrasubstituted alkenes are important, so attempts were made to use CO_2 for the syntheses of tri- and tetrasubstituted alkenes. For that purpose, transmetalation of oxanickelacycles with zinc reagents was a key step. As a result, these compounds could be synthesized from terminal and disubstituted alkynes. The remarkable features of these reactions are that low-valent nickel complexes were used, CO_2 could be used, the reaction conditions were very mild, the reactions proceeded through transmetalation of intermediary oxanickelacyclopentenes with the zinc reagents to give tri- and tetrasubstituted alkenes, thermodynamically more stable alkenes were formed, and the yields were good. Various tri- and tetrasubstituted alkenes could be synthesized in a highly regio- and stereoselective manner. In the syntheses of tetrasubstituted alkenes, the reaction proceeded by use of catalytic amounts of divalent or low-valent nickel complex in the presence of excess amounts of DBU.

These procedures should provide a useful tool for the utilization of CO_2 in synthetic organic chemistry. Further utilization of CO_2 using transition metal complexes should be developed in the future.

Acknowledgments

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