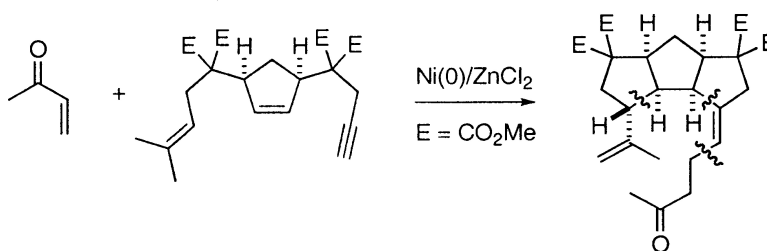


Ni-Catalyzed, ZnCl₂-Assisted Domino Coupling of Enones, Alkynes, and Alkenes

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Ni-Catalyzed, ZnCl₂-Assisted Domino Coupling of Enones, Alkynes, and Alkenes

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Abstract: A Ni(0)/ZnCl₂ system effectively promotes the coupling of enones and alkene-tethered alkynes. In the reaction with 1,6-enynes, the oxidative cyclization of Ni(0) species on enones across the alkyne part followed by ZnCl₂-promoted cleavage generates alkenylnickel intermediates. Subsequent migratory insertion of the tethered alkene occurs with 5-*exo*-cyclization. When the resulting σ -alkylnickel intermediates have β -hydrogen atoms, the reaction terminates by β -hydrogen elimination to provide cyclopentane derivatives. On the other hand, a σ -alkylnickel intermediate that does not have β -hydrogen atoms undergoes the insertion of a second alkene unit to cause a domino effect via a three-fold C–C bond formation process with and without the cleavage of one C–C bond.

Introduction

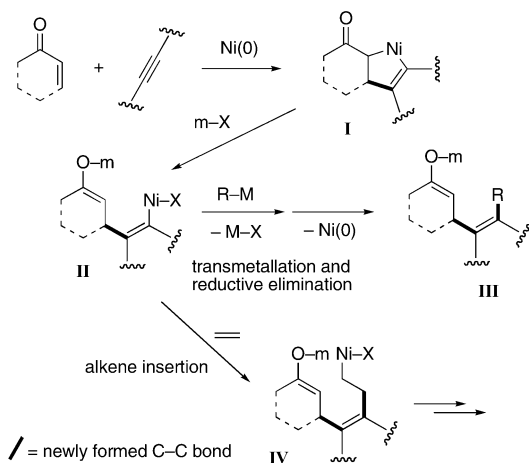
There is great interest in organometallic chemistry due to the wide variety of reactions in organic syntheses in which they can play a part. Among these reactions, the palladium-catalyzed arylation and alkenylation of alkenes, known as the Mizoroki–Heck reaction, have been established as useful synthetic procedures.^{1,2} Recently, sequential multicomponent reactions that include a palladium-catalyzed reaction have provided various elegant methods for constructing complex polycyclic compounds from simple acyclic precursors.³ In particular, sequential reactions that occur without adding another reagent or changing the reaction conditions are called domino reactions.⁴

In our research on the development of new organonickel chemistry, we have found that a nickel complex catalyzed the domino coupling of enones, alkynes, and organometallics to provide coupling products with high regio- and stereoselectivity (Scheme 1).⁵ The key to success in this reaction is the formation of a nickellacycle intermediate **I** caused by oxidative cyclization of a Ni(0) complex on an enone across an alkyne.^{6,7} The metallacycle **I** is cleaved by metal halides (m–X) to generate an alkenylnickel intermediate **II**. The reaction of **II** with organometallics (i.e., transmetalation) followed by reductive elimination furnishes the coupling product **III** along with release of nickel metal from the organic fragment.^{5a–d} We next envisaged a new domino process that involved the interception of **II** by an alkene unit.⁸ The resulting σ -alkylnickel intermediate **IV** should undergo β -hydrogen elimination or the insertion of a second alkene. We describe here in detail our studies on the Ni-catalyzed, ZnCl₂-assisted coupling of enones, alkynes, and alkenes and present a new methodology for a domino reaction.⁹

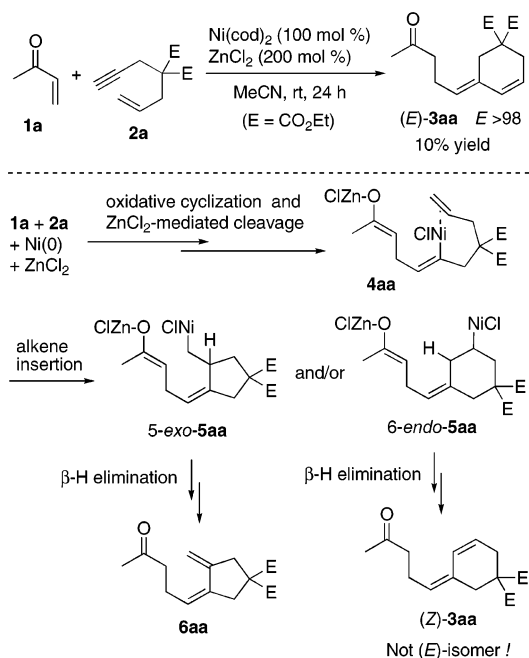
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- (2) Reviews: (a) Heck, R. F. In *Organic Reactions*; Dauben, W. G., Ed.; Wiley: New York, 1982; Vol. 27, p 345. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985. (c) Söderberg, B. C. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, p 241. (d) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423. (e) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. Reviews for the asymmetric version: (f) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371. (g) Loiseleur, M.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 1. (h) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 16.
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- (6) For the C-bound nickel enolate, see: (a) Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. *Organometallics* **1990**, *9*, 30. For related works of the nickel-promoted domino reaction, Montgomery recently reported generation and characterization of the O-bound nickel enolate. See: (b) Amarasinghe, K. K. D.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370. (c) Mahandru, G. M.; Skauge, A. R. L.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 13481. The O-enolate, which is generated by the oxidative cyclization of an enal and alkyne with Ni(0) species, contains a *cis* double bond in a seven-membered ring. However, a metallacycle generated by a cyclic enone such as 2-cyclopenten-1-one and alkyne with Ni(0) would not be the corresponding O-enolate, because the enolate contains a strained *trans* double bond in the seven-membered ring.
- (7) García-Gómez, G.; Moretó, J. M. *Chem.–Eur. J.* **2001**, *7*, 1503.
- (8) For an example of the [2 + 2 + 2] cycloaddition of alkynyl enones with activated alkenes via nickellacycle, see: Seo, J.; Chui, H. M. P.; Heeg, M. J.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 476.

Scheme 1



Scheme 2

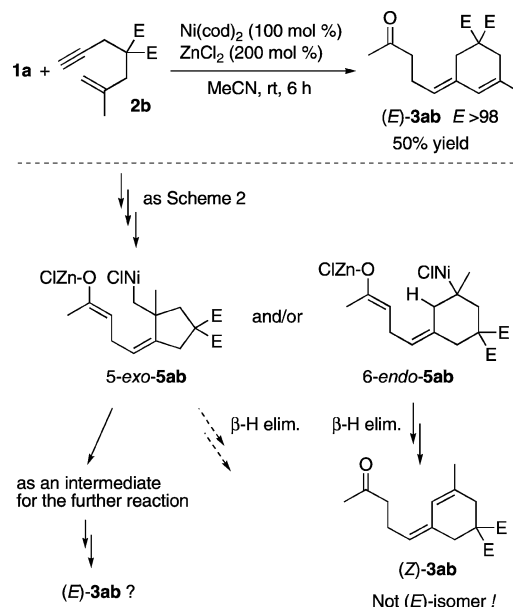


Results and Discussion

The reaction was accomplished in a partial intramolecular mode, i.e., with enones **1** and enynes **2**. First, we investigated the reaction of **2a** with methyl vinyl ketone (**1a**, 2 equiv) in the presence of Ni(cod)_2 (100 mol %) and ZnCl_2 (200 mol %) in MeCN at room temperature. Although most of the **2a** used might be consumed in oligomerization, a small amount of **3aa** was obtained (Scheme 2). The stereochemistry of **3aa** was determined to be E on the basis of the NOE experiment.

As depicted in Scheme 1, this reaction should occur with the formation of an alkenylnickel intermediate **4aa** caused by the oxidative cyclization of Ni(0) species on **1a** across the alkyne part of **2a** followed by ZnCl_2 -mediated cleavage. The subsequent migratory insertion enables us to produce two possible σ -alkenylnickel intermediates, i.e., 5-*exo*- and 6-*endo*-**5aa**. If each intermediate caused β -elimination of a C–H bond at the allylic

Scheme 3

Table 1. Nickel-Catalyzed, ZnCl_2 -Assisted Reaction of **1a** with **2b**^a

run	Ni cat.	conditions	yield of 3ab , ^b %	$E:Z$ ^c
1 ^d	Ni(cod)_2	rt, 48 h	trace	
2 ^d	Ni(cod)_2	reflux, 48 h	trace	
3	Ni(cod)_2	rt, 24 h	54	96:4
4 ^e	Ni(cod)_2	rt, 24 h	25	96:4
5	Ni(cod)_2	reflux, 2 h	56	88:12
6 ^f	Ni(cod)_2	rt, 24 h	43	89:11
7	Ni(acac)_2	rt, 24 h	52	95:5
8	Ni(acac)_2	reflux, 2 h	49	91:9
9	$\text{NiCl}_2(\text{PPh}_3)_2$	rt, 24 h	45	94:6
10	$\text{NiCl}_2(\text{PPh}_3)_2$	reflux, 2 h	49	88:12

^a Unless stated otherwise, the reaction was carried out in MeCN; molar ratio: $[\mathbf{1a}]/[\mathbf{2b}]/[\text{Ni cat.}]/[\text{ZnCl}_2]/[\text{Zn}] = 2.0:1.0:0.05:2.0:1.5$. ^b Isolated yield after purification by silica gel column chromatography. ^c Determined by ^1H NMR spectra. ^d The reaction was carried out in the absence of Zn dust. ^e ZnCl_2 (50 mol %) was used. ^f Et_3N (150 mol %) was added.

position, **6aa** and (Z)-**3aa** would be obtained, respectively. However, the actual reaction gives only (E)-**3aa**.

A similar reaction with **2b** tethered to a *gem*-disubstituted alkene part gave (E)-**3ab** in 50% yield (Scheme 3). The stereoisomer (Z)-**3ab** that would result from β -hydrogen elimination of 6-*endo*-**5ab** was not obtained. In this reaction, 5-*exo*-**5ab** that does not have β -hydrogen atoms is a σ -alkenylnickel species, and it is expected to undergo further reaction to furnish (E)-**3ab**.

For the reaction to progress to a nickel catalytic mode, the addition of zinc dust (150 mol %) was essential because of regeneration of the Ni(0) species (run 3 vs runs 1 and 2 in Table 1).¹⁰ When the reaction was performed in the presence of a catalytic amount (50 mol %) of ZnCl_2 , the yield of **3ab** decreased (run 4). Interestingly, the stereoselectivity of **3ab** was dependent on the reaction conditions. When the reaction was carried out at room temperature, the ratio of (E)-**3ab**/(Z)-**3ab** was determined to be 96:4 on the basis of the ^1H NMR spectra (run 3). However, under reflux conditions, the ratio decreased

(9) A portion of this work has been previously communicated. See: Ikeda, S.; Miyashita, H.; Taniguchi, M.; Kondo, H.; Okano, M.; Sato, Y.; Odashima, K. *J. Am. Chem. Soc.* **2002**, *124*, 12060.

(10) Although a base such as Et_3N was added in the absence of zinc dust, the Ni -catalyzed reaction did not proceed. In contrast, in the Pd -catalyzed Mizoroki–Heck reaction, it is well-known that a variety of bases promote the regeneration of Pd(0) from H-Pd-X species generated by β -hydrogen elimination. See refs 1–3.

Table 2. Nickel-Catalyzed, ZnCl₂-Assisted Reactions of **1** with **2**^a

entry	1	2	major 3	Ni cat. and conditions	yield, ^b % (<i>E</i> : <i>Z</i>) ^c
1		2b		Ni(acac) ₂ , rt, 24 h	47 (92:8)
				Ni(cod) ₂ , reflux, 2 h	44 (80:20)
2		2b		Ni(acac) ₂ , rt, 48 h	25 (>98:<2)
				NiCl ₂ (PPh ₃) ₂ , rt, 48 h	23 (>98:<2)
				Ni(cod) ₂ , reflux, 24 h	27 (97:3)
3		2b		Ni(cod) ₂ , rt, 48 h	trace
				Ni(cod) ₂ , reflux, 20 h	13 (88:12)
				Ni(cod) ₂ , ^d rt, 24 h	46 (>98:<2)
4	1a			Ni(cod) ₂ , rt, 24 h	40 (<2:>98)
				Ni(cod) ₂ , reflux, 2 h	31 (4:96)
5	1a			Ni(acac) ₂ , rt, 48 h	0
				Ni(acac) ₂ , reflux, 4 h	trace
				NiCl ₂ (PPh ₃) ₂ , reflux, 2 h	trace
				Ni(cod) ₂ , ^d rt, 48 h	trace

^a Unless stated otherwise, the reaction was carried out in MeCN; molar ratio: [1]/[2]/[Ni cat.]/[ZnCl₂]/[Zn] = 2.0:1.0:0.05:2.0:1.5. ^b Isolated yield after purification by silica gel column chromatography. ^c Determined by ¹H NMR spectra. ^d Ni(cod)₂ (100 mol %) was used without zinc dust.

to 88:12 (run 5). The addition of Et₃N also reduced the stereoselectivity (run 6). Similar results were observed in the reaction using Ni(acac)₂ and NiCl₂(PPh₃)₂ (runs 7–10).

The results of the Ni(0)/ZnCl₂-promoted coupling of various **1** and **2** are summarized in Table 2. Both β-substituted acyclic **1b** and cyclic **1c** reacted with **2b** to give the coupling products **3bb** and **3cb**, respectively (entries 1 and 2). The reaction with croton aldehyde (**1d**) gave **3db** in moderate yield with the use of a stoichiometric amount of Ni(cod)₂ without zinc dust (entry 3). *N*-Tosyl amide **2c** was also useful in the coupling reaction and selectively gave **3ac** (entry 4). These stereoselectivities were lower when the reactions were carried out under reflux conditions. Whereas the reaction with 1,6-enynes such as **2b** and **2c** was successful, attempts to obtain a seven-membered cyclic product **3ad** failed in the reaction with a 1,7-enyne **2d**, most of which would be consumed in oligomerization (entry 5).

The reaction of **1a** with **2e**, which has a tethered internal alkyne unit, gave (*E*)-**3ae** selectively (runs 1–3 in Table 3). In this reaction, not only the reaction temperature but also the quantity of PPh₃ affected the stereoselectivity of **3ae**. When the reactions were carried out in the presence of PPh₃, the ratio of (*E*)-**3ae**/*Z*-**3ae** decreased (runs 4 and 5), compared with those in the absence of PPh₃ (runs 1–3). The addition of excess PPh₃ or Et₃N remarkably reduced the selectivity (runs 6 and 7).

To address the possibility of product isomerization under these reaction conditions, we next investigated two further reactions:

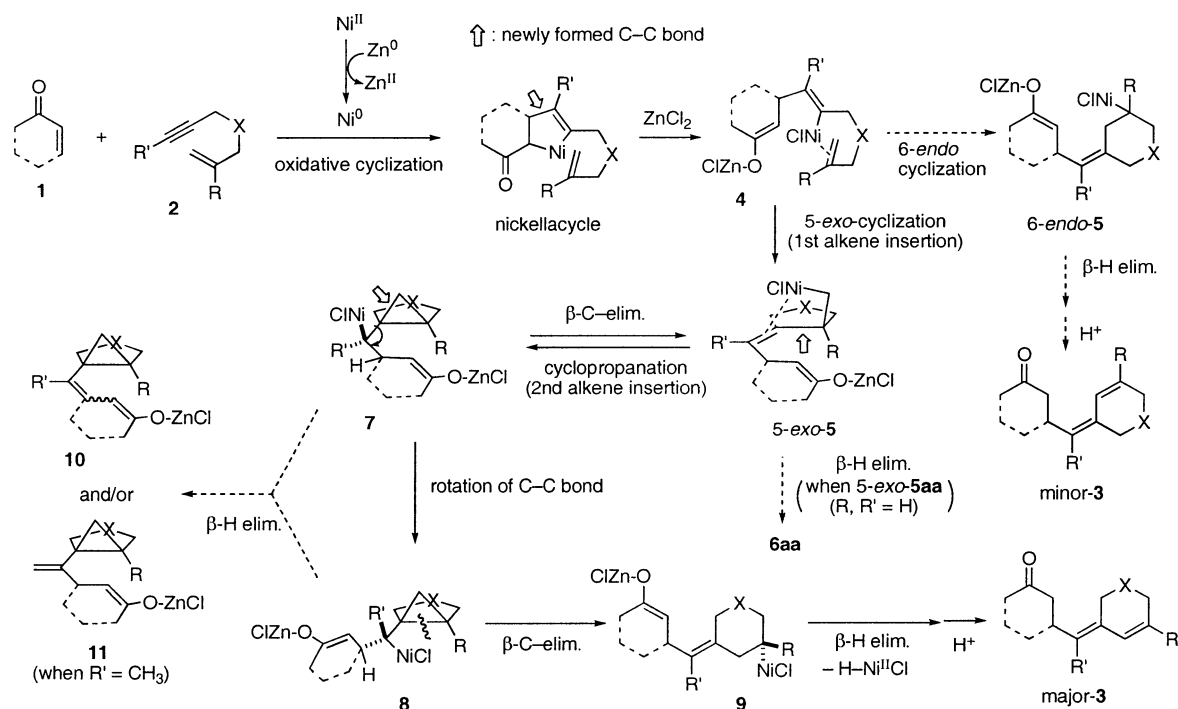
Table 3. Nickel-Catalyzed, ZnCl₂-Assisted Reaction of **1a** with **2e**^a

run	Ni cat. and additive	conditions	yield, ^b %	<i>E</i> : <i>Z</i> ^c
1	Ni(acac) ₂	rt, 24 h	54	89:11
2	Ni(cod) ₂ ^d	rt, 6 h	83	90:10
3	Ni(acac) ₂	reflux, 2 h	51	82:18
4	NiCl ₂ (PPh ₃) ₂	rt, 24 h	53	77:23
5	NiCl ₂ (PPh ₃) ₂	reflux, 2 h	58	71:29
6	NiCl ₂ (PPh ₃) ₂ + PPh ₃ ^e	reflux, 24 h	43	64:36
7	NiCl ₂ (PPh ₃) ₂ ^d + Et ₃ N ^f	rt, 5 h	88	53:47

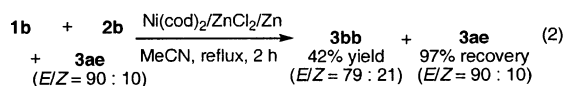
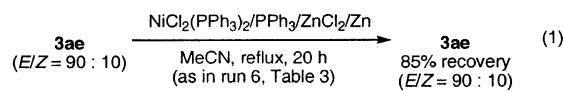
^a Unless stated otherwise, the reaction was carried out in MeCN; molar ratio: [1a]/[2e]/[Ni cat.]/[ZnCl₂]/[Zn] = 2.0:1.0:0.05:2.0:1.5. ^b Isolated yield. ^c Determined by ¹H NMR spectra. ^d Ni cat. (10 mol %) was used. ^e PPh₃ (20 mol %) was added. ^f Et₃N (150 mol %) was added.

(1) **3ae** (*E*/*Z* = 90:10) was added to a NiCl₂(PPh₃)₂/excess PPh₃/ZnCl₂/Zn system under reflux conditions (eq 1), and (2) **3ae** (*E*/*Z* = 90:10) was added to a reaction of **1b** with **2b**, which gave **3bb**, in the presence of Ni(cod)₂/ZnCl₂/Zn under reflux conditions (eq 2). In both reactions, **3ae** was recovered with no

Scheme 4



change in the *E/Z* ratio. These results suggest that the loss of stereoselectivity is not a simple result of product isomerization by some species generated in the catalytic reaction.



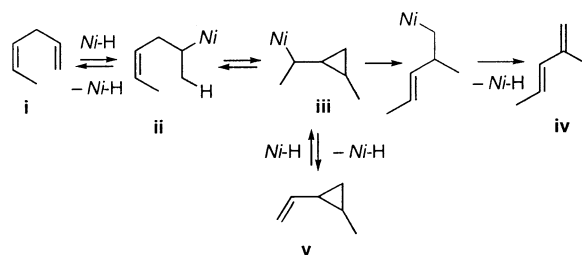
A plausible reaction pathway is shown in Scheme 4. As mentioned above, the nickellacycle would be cleaved by ZnCl_2 to generate an alkenylnickel species **4**. In the migratory insertion of the tethered alkene part of **4** into the C–Ni bond, straightforward 6-*endo*-cyclization is negligible. The resulting 6-*endo*-**5** causes the formation of minor-**3** (see Schemes 2 and 3). Inversion of the exocyclic alkene configuration can be reasonably explained by a process of two-fold migratory insertion and sequential β -C–C bond cleavage, i.e., β -carbon elimination.^{3g,11} Thus, the 5-*exo*-cyclization of **4** and the subsequent cyclopropanation of 5-*exo*-**5** generate a cyclopropylcarbinylnickel species **7**. β -Carbon elimination would effectively occur when the C–Ni and C–C bonds can be aligned to optimize the orbital overlap, i.e., the dihedral angle between the C–Ni bond and the β -C–C bond is as close to 0° as possible. While the β -carbon elimination of **7** merely gives 5-*exo*-**5**, that of the conformer **8** produces a new intermediate **9** in which the exocyclic alkene configuration is inverted. The β -hydrogen elimination of **9** finally provides the major-**3**. Although both **7** and **8** have β -hydrogen atoms, neither **10** nor **11** due to β -H elimination was observed.¹² The

(11) Negishi and co-workers reported the similar processes in the Pd-catalyzed arylation and alkenylation of enynes. See: Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091.

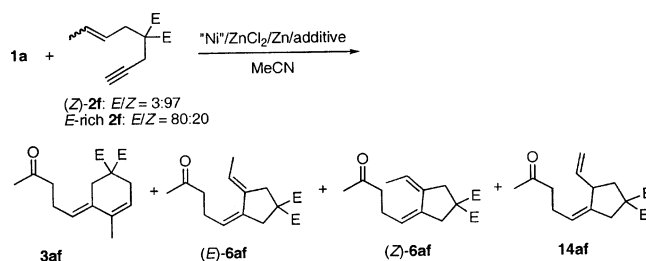
β -carbon elimination of **8** is more favorable than β -hydrogen elimination. It has been suggested that the conversion to **9** with a relief of ring strain in the cyclopropane part is a very low-energy process.¹³

The intermediate 5-*exo*-**5aa**, which is derived from the reaction with **2a**, did not undergo a β -hydrogen elimination to give **6aa**, even though it possesses a β -hydrogen atom. Instead, cyclopropanation followed by β -carbon elimination provides (*E*)-**3aa** (Scheme 2). β -Hydrogen elimination requires a vacant coordination site on the nickel metal and a dihedral angle as close to 0° as possible. At this time, the geometry of 5-*exo*-**5aa** (*R* and *R'* = *H* in Scheme 4) would be inaccessible for

(12) For the β -carbon vs β -hydrogen elimination of **7** and **8**, Miller and co-workers reported that the nickel-catalyzed skeletal rearrangement of **i** to **iv** was consistent with a mechanism that involved the β -carbon elimination of a complex **iii** induced by the cyclopropanation of **ii**.^{12a} However, product **v** derived from the β -hydrogen elimination of **iii** was not obtained. On the other hand, they also reported that the same nickel complex catalyzed the rearrangement of **v** to **iv**.^{12b} This result suggests that a rapid equilibrium is present between **iii** and **v**. In a similar manner, the presence of rapid equilibrium between **7** (or **8**) and **10** (and/or **11**) cannot be ruled out. (a) Pinke, P. A.; Miller, R. G. *J. Am. Chem. Soc.* **1974**, *96*, 4221. (b) Pinke, P. A.; Stauffer, R. D.; Miller, R. G. *J. Am. Chem. Soc.* **1974**, *96*, 4229.

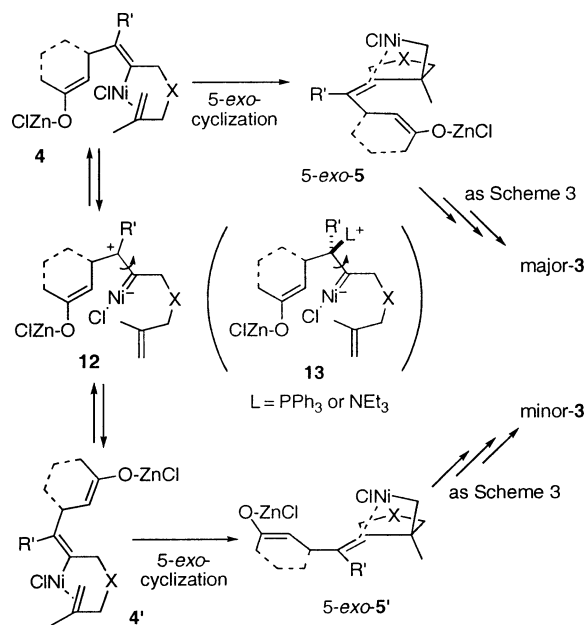


(13) Whereas a half-life of 30 h at 27 °C and an activation energy of ca. 26 kcal/mol were characteristic of the equilibration of homoallyl Grignard reagent,^{13a} the half-life for the nickel-catalyzed conversion of **i** to isomeric products such as **iv** was <2 min at 25 °C.^{13b} (a) Howden, M. E. H.; Maerker, A.; Burdon, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 1732. (b) Miller, R. G.; Pinke, P. A.; Stauffer, R. D.; Golden, H. J.; Baker, D. J. *J. Am. Chem. Soc.* **1974**, *96*, 4211.

Table 4. Nickel-Catalyzed, ZnCl₂-Assisted Reaction of **1a** with **2f**^a

run	2f	Ni cat. and additive	conditions	yield, ^b %	3af /(E - 6af)/(Z - 6af)/ 14af ^c
1	(Z)- 2f	Ni(cod) ₂	rt, 4 h	(22)	100:0:0:0
2		NiCl ₂ (PPh ₃) ₂	rt, 2 h	(20)	100:0:0:0
3		Ni(cod) ₂ + Et ₃ N ^d	rt, 4 h	(34)	87:0:0:13
4		NiCl ₂ (PPh ₃) ₂ + Et ₃ N ^d	rt, 2 h	60	34:0:12:54
5	E-rich 2f	Ni(cod) ₂ ^e	rt, 2 h	(3)	100:0:0:0
6		NiCl ₂ (PPh ₃) ₂	rt, 4 h	(3)	100:0:0:0
7		Ni(cod) ₂ + Et ₃ N ^d	rt, 4 h	(5)	~50:0:0:~50
8		NiCl ₂ (PPh ₃) ₂ + Et ₃ N ^d	rt, 2 h	58	7:57:4:32
9		NiCl ₂ (PPh ₃) ₂ + Et ₃ N ^d	reflux, 2 h	52	6:58:4:32

^a Unless stated otherwise, the reaction was carried out in MeCN; molar ratio: [**1a**]/[**2f**]/[Ni cat.]/[ZnCl₂]/[Zn] = 2.0:1.0:0.1:4.0:4.0. ^b Combined yield after purification by silica gel column chromatography. GC yield is in parentheses. ^c Determined by ¹H NMR spectra. ^d Et₃N (300 mol %) was added. ^e Ni(cod)₂ (100 mol %) was used.

Scheme 5

β -elimination of the C–H bond (the dihedral angle between the C–Ni bond and the β -C–H bond is greater than 0°) because of coordination of the exocyclic alkene part of 5-*exo*-**5aa** to the nickel metal.

The loss of stereoselectivity of **3** in reactions under reflux conditions is attributed to the equilibrium between **4** and **4'** via a zwitterionic carbene intermediate **12** (Scheme 5).¹⁴ The intermediate 5-*exo*-**5'** causes the formation of minor-**3**. In the reaction with **2e**, the electron-donating methyl group (R' = Me) stabilizes **12** and further promotes isomerization between **4** and **4'**. Moreover, in the presence of an excess amount of additive such as PPh₃ or Et₃N, **13** generated by the reversible addition of free PPh₃ or Et₃N to the β -vinyl carbon atom of **12** would more strongly contribute to isomerization.

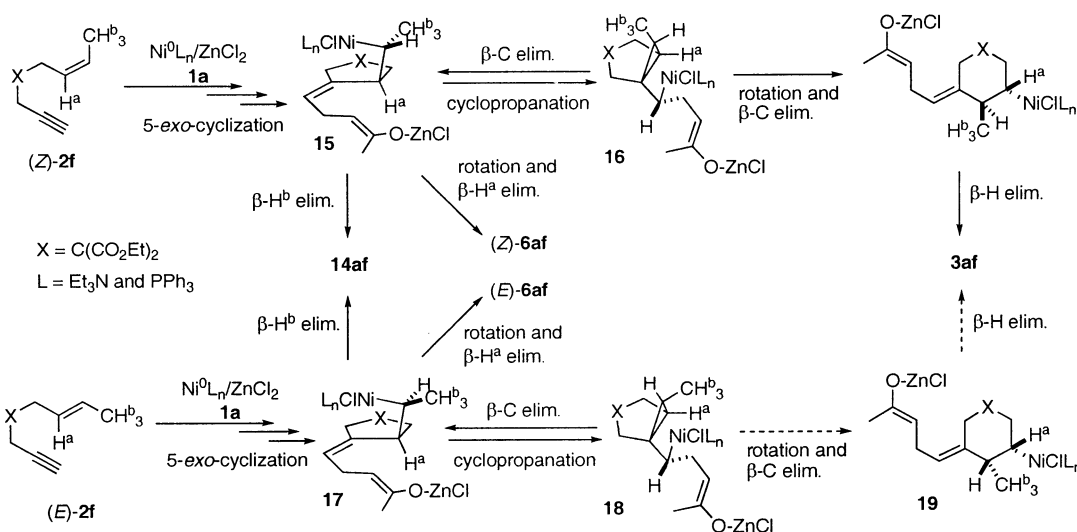
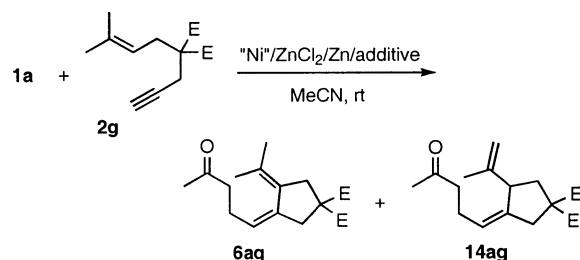
While the reaction with (Z)-**2f**, which has a methyl group at the terminal carbon atom of the alkene part, in the presence of Ni(cod)₂/ZnCl₂/Zn gave small amounts of **3af** (runs 1 and 2 in Table 4), the reaction using Et₃N provided **14af** as a byproduct (run 3). Interestingly, the NiCl₂(PPh₃)₂/ZnCl₂/Zn/Et₃N system effectively promoted the reaction to give a mixture of three isomers **3af**, (Z)-**6af**, and **14af** in a total yield of 60%. The ratio of **3af**/(Z)-**6af**/**14af** was determined to be 34:12:54 from the ¹H NMR spectra (run 4). In contrast, in the reaction with E-rich **2f** (E/Z = 80:20), (E)-**6af** was obtained as a major product (run 8). The production ratio of **3af**, (E)- and (Z)-**6af**, and **14af** did not change even under reflux conditions (run 9).

In these reactions, the geometry of the starting **2f** affects not only the product ratio of **3af**, **6af**, and **14af** but also the alkene geometry of **6af**. Cyclopropanation of **15** (derived from (Z)-**2f** in Scheme 6) or **17** (derived from (E)-**2f**) would produce intermediates **16** and **18**, respectively. However, **18** should revert to **17**. The conformational rotation of **18** followed by β -carbon elimination leading to **19** would be difficult because of the steric hindrance. Even if the path is possible, **19** does not have *cis*- β -hydrogen atoms at the allylic position to give **3af**. Thus, **3af** is derived not from (E)-**2f** but from (Z)-**2f**. In the reaction with E-rich **2f**, (Z)-**2f** that is present as the minor isomer undergoes the reaction leading to **3af**.

The addition of both PPh₃ and Et₃N to the reaction medium would accelerate β -hydrogen elimination of a C–H^a or C–H^b bond of **15** and **17**. These conformations are appropriate for β -H^b elimination leading to **14af**, since the dihedral angle of the C–Ni bond and C–H^b bond is close to 0°. In contrast, despite a lower C–H^a bond energy due to its allylic nature, the alignment for β -H^a elimination leading to **6af** is not ideal (the dihedral angle is greater than 0°). Therefore, it is necessary to take into account the conformational rotation of **15** and **17**, respectively. In the reaction with (Z)-**2f**, **15** underwent the conformational rotation followed by the β -H^a elimination to give (Z)-**6af**. Similarly, the β -H^a elimination of **17** derived from (E)-**2f** caused the formation of (E)-**6af**.

(14) Huggins, J. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 3002.

Scheme 6

Table 5. Nickel-Catalyzed, ZnCl₂-Assisted Reaction of **1a** with **2g**^a

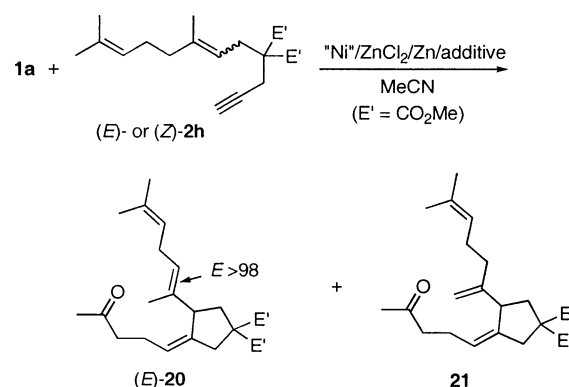
run	Ni cat. and additive	time, h	combined yield, ^b %	6ag/14ag ^c
1	Ni(cod) ₂	10	(23)	5:95
2	NiCl ₂ (PPh ₃) ₂	4	(21)	4:96
3	Ni(cod) ₂ + Et ₃ N ^d	6	61	5:95
4	NiCl ₂ (PPh ₃) ₂ + Et ₃ N ^d	4	68	8:92

^a Unless stated otherwise, the reaction was carried out in MeCN at room temperature; molar ratio: [**1a**]/[**2g**]/[Ni cat.]/[ZnCl₂]/[Zn] = 2.0:1.0:0.1:4.0:4.0. ^b Isolated yield after purification by silica gel column chromatography. GC yield is in parentheses. ^c Determined by ¹H NMR spectra. ^d Et₃N (300 mol %) was added.

The use of Et₃N promotes the reaction with **2g**, which has two (*cis* and *trans*) methyl groups at the terminal carbon atom on the alkene part, to selectively give **14ag** (runs 3 and 4 vs runs 1 and 2 in Table 5). The use of NiCl₂(PPh₃)₂ catalyst slightly reduced the ratio of **14ag** to **6ag** (run 4).

Similar to the reaction with **2g**, the reaction with **2h**, which contains a trisubstituted alkene such as a geranyl (*E*-isomer) or neryl (*Z*-isomer) group, is effectively promoted by the addition of Et₃N to give a mixture of two possible 1,4-diene-type products **20** and **21** (Table 6). Interestingly, the stereochemistry of **20** was determined to be *E*-geometry from the ¹H NMR spectra. Although the ratio of (*E*)-**20**/**21** was dependent on the geometry of **2h**, the reaction in the presence of a NiCl₂(PPh₃)₂/ZnCl₂/Zn/Et₃N system tended to selectively produce (*E*)-**20**. In the reaction with (*E*)-**2h**, the presence of PPh₃ strongly influenced the production ratio (run 3 vs run 2). The result suggests that the geometry of **2h** affects coordination of the remote double bond to the nickel center in the reaction.

Cycloalkene-tethered enynes **2i–k** reacted with **1a** to give the corresponding coupling products **22ai**, **22aj**, and **22ak**,

Table 6. Nickel-Catalyzed, ZnCl₂-Assisted Reaction of **1a** with **2h**^a

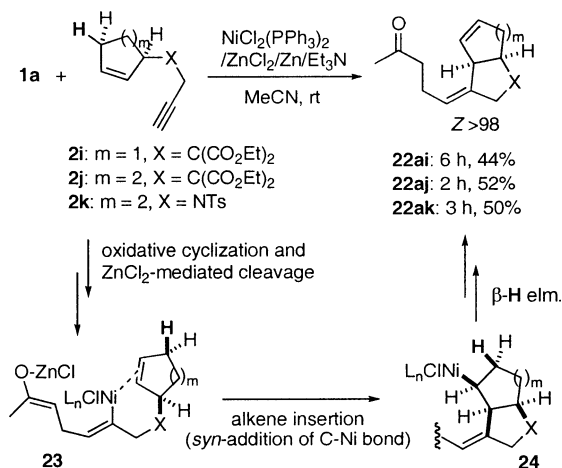
run	2h	Ni cat. and additive	time, h	combined yield, ^b %	(<i>E</i>)- 20 / 21 ^c
1	(<i>E</i>)- 2h	Ni(cod) ₂	20	(5)	
2		Ni(cod) ₂ + Et ₃ N ^d	20	51	42:0:58
3		NiCl ₂ (PPh ₃) ₂ + Et ₃ N ^d	4	57	62:0:38
4	(<i>Z</i>)- 2h	Ni(cod) ₂ + Et ₃ N ^d	20	57	72:0:28
5		NiCl ₂ (PPh ₃) ₂ + Et ₃ N ^d	4	54	77:0:23

^a Unless stated otherwise, the reaction was carried out in MeCN at room temperature; molar ratio: [**1a**]/[**2h**]/[Ni cat.]/[ZnCl₂]/[Zn] = 2.0:1.0:0.1:4.0:4.0. ^b ¹H NMR yield based on benzophenone. ^c Determined by ¹H NMR spectra. ^d Et₃N (300 mol %) was added.

respectively (Scheme 7). The intermediate **23** undergoes a *syn* addition of the C–Ni bond to the tethered cyclic alkene to produce **24**, which has a *cis* relationship between two hydrogen atoms attached to the bridge-head carbons. The reaction terminates by β -elimination of a *cis*-H (depicted in boldface) atom of **24** to furnish **22**.

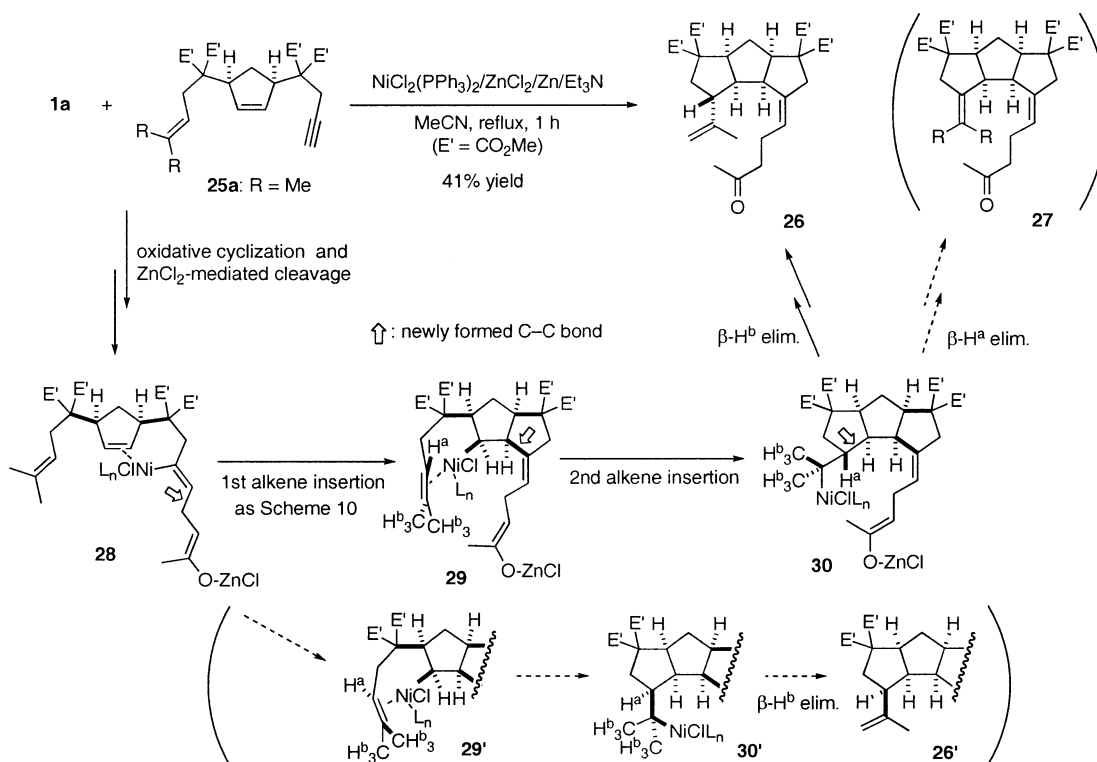
Finally, we investigated the construction of a polycyclic compound using domino coupling. It is important to inhibit premature β -hydrogen elimination to achieve the domino process. We sought to prepare **25** in which another alkene part displaces the *cis*-H (depicted in boldface) atom at the allylic position of **2i**. The intermediate **28** undergoes insertion of the adjacent cyclopentene part into the C–Ni bond to produce a σ -alkylnickel species **29** or **29'** that lacks any *cis*- β -hydrogen atoms. We expected that a second alkene was inserted into **29**

Scheme 7



or **29'**. When **25a** ($R = \text{Me}$) was treated with **1a** in the presence of the $\text{NiCl}_2(\text{PPh}_3)_2/\text{ZnCl}_2/\text{Zn}/\text{Et}_3\text{N}$ system under reflux conditions for 1 h, a triquinane derivative was obtained in moderate yield (Scheme 8).¹⁵ The structure was determined to be **26**, not **26'** or **27** ($R = \text{Me}$), on the basis of ¹H NMR spectra and NOE experiments. The choice of the tethered alkene part of **25** for domino coupling proved to be important, since a similar reaction with **25b** ($R = \text{H}$)¹⁶ did not give the corresponding **27** ($R = \text{H}$). The result indicates that **30** arising from the insertion of a second alkene in **29** underwent β-H^b elimination to furnish **26**, rather than β-H^a elimination leading to **27** ($R = \text{Me}$). The exocyclic alkylidene part of **27** is so close to another alkylidene part that the β-H^a elimination of **30** would be unfavorable. Similarly, because of the steric hindrance of **30'** arising from the insertion of **29'**, **26'** is also not obtained.

Scheme 8



Conclusion

We have demonstrated that the Ni-catalyzed, ZnCl₂-assisted coupling of enones and alkene-tethered alkynes is a new domino reaction. This reaction is a new Ni-promoted Mizoroki–Heck-type alkenylation of alkenes. Generally, the reaction starts with the oxidative addition of alkenyl halides and pseudohalides to a low-valent metal (e.g., Pd(0), Ni(0), etc.) complex to generate alkenylmetal intermediates.^{1–3,17} However, the present reaction differs in that an alkenyl halide or pseudohalide is not required. At the initial stage of the reaction with 1,6-enynes, oxidative cyclization of the Ni(0) species on enones across the alkyne part followed by ZnCl₂-promoted cleavage generates alkenylnickel intermediates. Subsequent migratory insertion of the tethered alkene part occurs with 5-*exo*-cyclization. When the resulting σ-alkylnickel intermediates have β-hydrogen atoms, the reaction terminates by β-elimination of the C–H bond to give the corresponding cyclopentane derivatives. The product should depend on the geometry of the intermediates at the termination stage. The geometry is governed not only by the structure of the starting enynes but also by the reaction medium, with or without Et₃N and/or PPh₃. On the other hand, the σ-alkylnickel intermediate that does not have β-hydrogen atoms undergoes the further insertion of another alkene unit. In the reaction with enynes with a *gem*-disubstituted alkene part, cyclopropanation of the intermediates 5-*exo*-5 ($R = \text{Me}$ in Scheme 4) gives **8**, which undergoes β-carbon elimination followed by β-hydrogen elimination to provide **3**. The reaction proceeds via a domino process with a three-fold C–C bond formation and one C–C bond cleavage. A cyclopentene bearing an alkynyl and alkenyl is tethered at two allylic positions, e.g., **25a** reacts with **1a** to give a triquinane-type product **26**. The domino reaction proceeds via a three-fold C–C bond formation, including the insertion of a second alkene in the intermediate

29. The further application of the present reaction to organic synthesis is under further investigation.

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Supporting Information Available: Experimental details and analytical and spectral characterization data of all new com-

(15) The reaction took place at room temperature for 3 days and gave **26** in 12% yield along with some unidentified products.

(16) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421.

pounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA047580A

(17) For the Ni-catalyzed “Mizoroki–Heck”-type reaction, see: (a) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1976**, 1803. (b) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1976**, 1810. (c) Mori, M.; Kudo, S.; Ban, Y. *J. Chem. Soc., Perkin Trans. 1* **1979**, 771. (d) Lebedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem.* **1988**, *344*, 253. For Ni-mediated reactions, see: (e) Bonjoch, J.; Solé, D.; Bosch, J. *J. Am. Chem. Soc.* **1995**, *117*, 11017. Also see: (f) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133. (g) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895. (h) Cancho, Y.; Martínez, M.; Llebaria, A.; Moretó, J. M.; Delgado, A. *Tetrahedron* **1998**, *54*, 1221.