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Ni(0)/ZnCl$_2$-Promoted Coupling of Enones and Enynes. Domino Process via Formation of Three C−C Bonds and Cleavage of One C−C Bond

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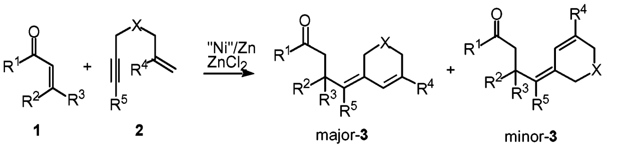
Transition-metal-promoted domino reactions are fascinating, because multiple carbon−carbon bond formation can be achieved in a single operation fairly simply.[1,2] In particular, some elegant domino processes that include the Pd-catalyzed arylation and alkenylation of unsaturated carbon molecules, known as the Mizoroki−Heck reaction, have been reported, for example, the construction of polycyclic molecules from acyclic precursors.[3]

Recently, we studied nickel-promoted domino reactions and showed the usefulness of domino coupling using enones **1** and alkynes.[4] The key to success in these reactions is the formation of a nickellacycle intermediate caused by the oxidative cyclization of a Ni(0) species with **1** and an alkyne part.[5,6] The intermediate reacts with organometallics as carbon nucleophiles to form multiple-component coupling products. We next envisaged a new strategy that involved the insertion of an alkene unit into the nickellacycle.[7] In this paper, we report a Ni(0)/ZnCl$_2$-promoted domino reaction using **1** and enynes **2** (eq 1).



(1)

1a: R^1 = Me, R^2 = R^3 = H
1b: R^1 = Et, R^2 = H, R^3 = Me
1c: R^1–R^2 = -(CH$_2$)$_2$-, R^3 = H
1d: R^1 = R^2 = H, R^3 = Me

2a: R^4 = Me, R^5 = H, X = C(CO$_2$Et)$_2$
2b: R^4 = Me, R^5 = H, X = NSO$_2$C$_6$H$_4$Me-*p*
2c: R^4 = R^5 = H, X = C(CO$_2$Et)$_2$
2d: R^4 = R^5 = Me, X = C(CO$_2$Et)$_2$

When **2a** was treated with **1a** (2 equiv) in the presence of Ni(cod)$_2$ (100 mol %) and ZnCl$_2$ (150 mmol %) in MeCN at 25 °C for 6 h, **3aa** was obtained in 50% isolated yield. The major isomer (96% selectivity) of **3aa** was determined to have a *E*-geometry by a NOE experiment. The reaction did not occur in the absence of ZnCl$_2$. Neither THF nor toluene was effective as a solvent. For the reaction to progress to a Ni-catalytic mode, the addition of Zn dust was essential, due to the regeneration of Ni(0) species (Table 1, runs 3 and 4 versus runs 1 and 2). The reaction did not proceed when a base such as Et$_3$N was used in place of Zn dust.[8]

Interestingly, the stereoselectivity of **3aa** was dependent on the reaction temperature. Thus, when the reaction of **1a** with **2a** was carried out at 25 °C, the ratio of (*E*)-**3aa**/(*Z*)-**3aa** was 96:4 (run 3). In contrast, under reflux conditions, this ratio was reduced to 90: 10 (run 4). A similar result was seen in reactions using other Ni catalysts such as NiCl$_2$, NiCl$_2$(PPh$_3$)$_2$, and Ni(acac)$_2$.

The reaction with β-substituted **1b** (runs 5 and 6), cyclic **1c** (runs 7 and 8), and an enal **1d** (run 9) selectively gave (*E*)-**3ba**, (*E*)-**3ca**, and (*E*)-**3da**, respectively. The stereoselectivities of **3ba** and **3da** were lower when the reactions were carried out under reflux conditions. *N*-Tosyl amide **2b** was also used in the reaction (run 10). On the other hand, the reaction with **2c**, which lacks a methyl group at the vinyl position (R^4 = H), gave **3ac** in low yield, even in the stoichiometric reaction using Ni(cod)$_2$ (run 11).

Table 1. Ni(0)/ZnCl$_2$-Promoted Domino Coupling of **1** and **2**[a]

run	**1**	**2**	Ni catalyst	conditions	**3**	yield,[b] %	*E*:*Z*[c]
1[d]	**1a**	**2a**	Ni(cod)$_2$	25 °C, 48 h	**3aa**	trace	
2[d]	**1a**	**2a**	Ni(cod)$_2$	reflux, 48 h	**3aa**	trace	
3	**1a**	**2a**	Ni(cod)$_2$	25 °C, 24 h	**3aa**	53	96:4
4	**1a**	**2a**	Ni(cod)$_2$	reflux, 2 h	**3aa**	56	88:12
5	**1b**	**2a**	Ni(acac)$_2$	25 °C, 24 h	**3ba**	47	92:8
6	**1b**	**2a**	Ni(cod)$_2$	reflux, 2 h	**3ba**	42	82:18
7	**1c**	**2a**	Ni(acac)$_2$	25 °C, 24 h	**3ca**	25	>98:<2
8	**1c**	**2a**	Ni(cod)$_2$	reflux, 2 h	**3ca**	27	97:3
9	**1d**	**2a**	Ni(cod)$_2$[e]	25 °C, 24 h	**3da**	46	>98:<2
10	**1a**	**2b**	Ni(cod)$_2$	25 °C, 24 h	**3ab**	40	<2:>98
11	**1a**	**2c**	Ni(cod)$_2$[e]	25 °C, 24 h	**3ac**	10	>98<2

[a] Reaction conditions: **1** (2.0 mmol), **2** (1.0 mmol), Ni catalyst (0.05 mmol), Zn dust (1.5 mmol), and ZnCl$_2$ (1.5 mmol) in MeCN (5 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR spectra. [d] The reaction was carried out in the absence of Zn dust. [e] Ni(cod)$_2$ (1.0 mmol) was used without Zn dust.

The reaction with **2d**, which has a tethered internal alkyne unit (R^5 = Me), also gave (*E*)-**3ad** selectively (Table 2, run 1). In this reaction, not only the reaction temperature but also the quantity of PPh$_3$ affected the stereoselectivity of **3ad**. When the reaction was performed in the presence of PPh$_3$, the *E*/*Z* ratio decreased (runs 3 and 4), as compared to that in the absence of PPh$_3$ (runs 1 and 2). The addition of excess PPh$_3$ ligand (versus Ni metal) remarkably reduced the selectivity (run 5).

The possibility of product isomerization under the reaction conditions would be negligible. In both experiments of eqs 2 and 3, **3ad** was recovered in unchanged *E*/*Z* ratio.

$$\underset{(E/Z = 90{:}10)}{\textbf{3ad}} \xrightarrow[\text{MeCN, reflux, 20 h}]{\text{NiCl}_2(\text{PPh}_3)_2/\text{PPh}_3/\text{Zn}/\text{ZnCl}_2} \underset{\substack{\text{85\% recovery} \\ (E/Z = 90{:}10)}}{\textbf{3ad}} \qquad (2)$$

$$\textbf{1b} + \textbf{2a} + \underset{(E/Z = 90{:}10)}{\textbf{3ad}} \xrightarrow[\text{MeCN, reflux, 2 h}]{\text{Ni(cod)}_2/\text{Zn}/\text{ZnCl}_2} \underset{\substack{\text{42\% yield} \\ (E/Z = 79{:}21)}}{\textbf{3ba}} + \underset{\substack{\text{97\% recovery} \\ (E/Z = 90{:}10)}}{\textbf{3ad}} \qquad (3)$$

The domino reaction proceeded with inversion of the alkene configuration. The result indicates that we can rule out a pathway via the straightforward *endo*-cyclization of **4** to give minor-**3**. A more reasonable pathway is depicted in Scheme 1, that is, a domino process via (i) formation of nickellacycle (the first C−C bond formation), (ii) *exo*-mode cyclization of **4** (the second C−C bond

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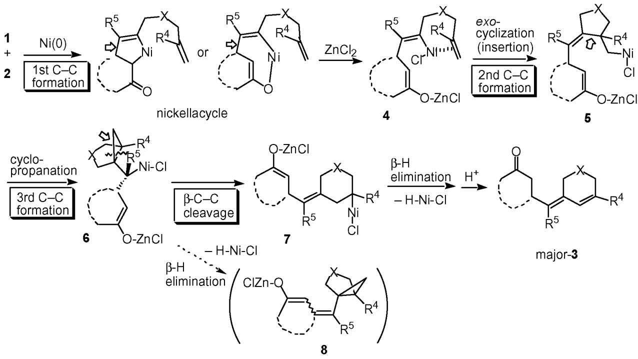
Table 2. Ni(0)/ZnCl$_2$-Promoted Domino Coupling of **1a** and **2d**[a]

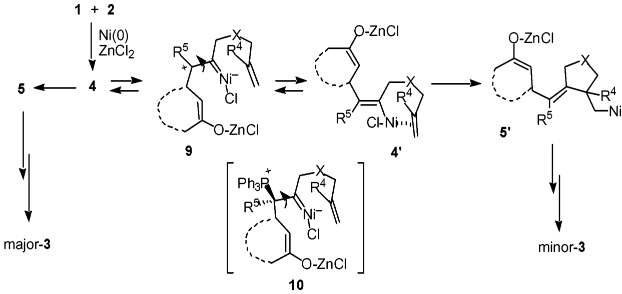
run	Ni catalyst	conditions	yield of **3ad**,[b] %	*E*:*Z*[c]
1	Ni(acac)$_2$	25 °C, 24 h	54	89:11
2	Ni(acac)$_2$	reflux, 2 h	51	82:18
3	NiCl$_2$(PPh$_3$)$_2$	25 °C, 24 h	53	77:23
4	NiCl$_2$(PPh$_3$)$_2$	reflux, 2 h	58	71:29
5	NiCl$_2$(PPh$_3$)$_2$ + PPh$_3$[d]	reflux, 4 h	43	64:36

[a] Reaction conditions: **1a** (2.0 mmol), **2d** (1.0 mmol), Ni catalyst (0.05 mmol), Zn dust (1.2 mmol), and ZnCl$_2$ (1.5 mmol) in MeCN (5 mL). [b] Isolated yield. [c] Determined by ^{1}H NMR spectra. [d] PPh$_3$ (0.2 mmol) was added.

Scheme 1



Scheme 2



formation), (iii) cyclopropanation of **5** (the third C−C bond formation), and (iv) *β*-carbon−carbon bond cleavage of **6** followed by *β*-hydrogen elimination of **7** to give major-**3**.[3e,9,10] Although **6** has *β*-hydrogens, the *β*-hydrogen elimination product **8** was not detected in the reaction.[11] It is expected to favor the *β*-carbon elimination of **6** by the relief of the ring strain of the cyclopropane part.[12]

The isomerization can be explained by route via **9** (Scheme 2). In the formation of the second C−C bond, that is, insertion of the alkenyl part of **4** into the Ni−C bond, equilibrium would be present between **4** and **4′** via **9**. The intermediate **4′** leads to the minor isomer of **3**. In the reaction with **2d** (R^5 = Me) in the presence of PPh$_3$, **10** generated from the reversible addition of free PPh$_3$ to the *β*-vinyl carbon of **4** would strongly contribute to the isomerization to **4′**.[13]

In summary, we have demonstrated that the Ni(0)/ZnCl$_2$-promoted reaction of enones and enynes represents a new domino coupling. The reaction would proceed via the formation of three carbon−carbon bonds and the cleavage of one carbon−carbon bond.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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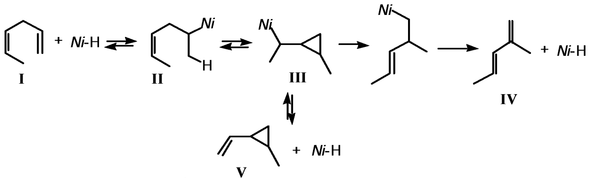
(11) Miller and co-workers reported that the nickel-catalyzed **I** to **IV** rearrangement was consistent with a mechanism involving the intervention of a complex **III** derived from cyclopropanation of **II**.[11a] In the reaction, *β*-H-elimination product **V** derived from **III** was not detected. On the other hand, they also found that the same nickel catalyst, which accomplished the rearrangement of **I**, caused the isomerization of **V**.[11b] These results suggest that the rapid addition−elimination of the nickel hydride species between **III** and **V** is present. In a similar manner as above, the presence of the rapid equilibrium between **6** and **8** is not rule 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.



I **II** **III** **IV** **V**

(12) The interconversion of **II** via **III** mentioned above would be a very low energy process relative to the allylcarbinylmagnesium analogue of the reaction. Thus, whereas half-life of 30 h at 27 °C and an activation energy of ca. 26 kcal/mol were characteristic of the equilibration of allylcarbinyl Grignard reagents,[12a] the half-life for the Ni-catalyzed conversion of **I** to isomeric products such as **IV** was <2 min at 25 °C.[12b] (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.
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