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Nickel-Catalyzed Ring-Opening Alkylative Coupling of Enone with Methylenecyclopropane in the Presence of Triethylborane

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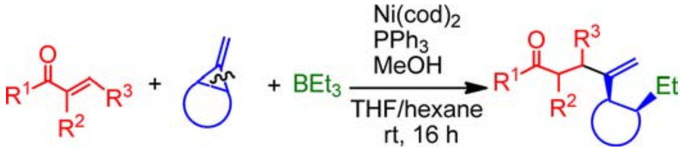
ABSTRACT



Nickel-catalyzed alkylative coupling of an enone or enal with methylenecyclopropane in the presence of triethylborane was achieved via stereospecific proximal C−C bond cleavage of methylenecyclopropane. With the use of methylenecyclopropane possessing an acyclic alkyl substituent, this reaction was also accompanied by the *β*-hydrogen elimination.

The nickel-catalyzed reductive and alkylative coupling reaction of a carbonyl compound with a C−C unsaturated compound is an effective means of synthesizing new unsaturated compounds via C−C bond formation. Although alkynes are used as the C−C unsaturated compounds[1] in the majority of earlier studies, reactions involving alkene compounds such as α-olefins,[2] 1,3-dienes,[3] allenes,[4] and norbornenes[5] have also been reported. Within this class of reactions, our research group has recently reported the unique reductive coupling reaction of methylenecyclopropane with aldehydes involving ring-opening or retention of the three-membered ring in the presence of a reducing agent using the nickel(0) catalyst system.[6] The ring-opening coupling reaction of methylenecyclopropane with an aldehyde using silane as the reducing agent proceeded in the presence of the Ni(cod)$_2$/*N*-heterocyclic carbene catalyst to generate a silylated allylic alcohol.[6a] In contrast, in the presence of the Ni(cod)$_2$/PCy$_3$ catalyst, the ring-retaining reaction of methylenecyclopropane with the aldehyde proceeded using triethylborane as a reductant.[6b]

In certain instances, the aldehyde has been replaced by α,*β*-unsaturated carbonyl compounds (as a reaction partner for the C−C unsaturated compound), where a unit of the C−C double bond participates in the coupling reaction.[7] Montgomery et al. reported the nickel-catalyzed

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(1) (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (b) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098. (c) Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950. (d) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221. (e) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442. (f) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, *126*, 3698. (g) Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 14030. (h) Sa-ei, K.; Montgomery, J. *Org. Lett.* **2006**, *8*, 4441. (i) Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 9568. (j) Baxer, R. D.; Montgomery, J. *J. Am. Chem. Soc.* **2008**, *130*, 9662. (k) Saito, N.; Katayama, T.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829. (l) Malik, H. A.; Chaulagain, M. R.; Montgomery, J. *Org. Lett.* **2009**, *11*, 5734. (m) Malik, H. A.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2010**, *132*, 6304.

(2) (a) Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 14194. (b) Ho, C.-Y.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 782. (c) Yang, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L-.X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 2248.

(3) (a) Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8559. (b) Sawaki, R.; Sato, Y.; Mori, M. *Org. Lett.* **2004**, *6*, 1131. (c) Sato, Y.; Hinata, Y.; Seki, R.; Oonishi, Y.; Saito, N. *Org. Lett.* **2007**, *9*, 5597.

(4) Ng, S.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 7320.

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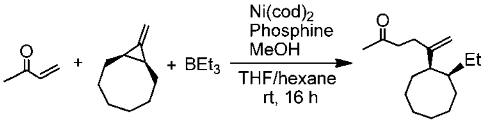
(6) (a) Ogata, K.; Atsuumi, Y.; Fukuzawa, S.-i. *Org. Lett.* **2010**, *12*, 4536. (b) Ogata, K.; Shimada, D.; Fukuzawa, S.-i. *Chem.—Eur. J.* **2012**, *18*, 6142.

(7) (a) Herath, A.; Thompson, B. B.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 8712. (b) Li, W.; Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2009**, *131*, 17024. (c) Herath, A.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 14030. (d) Li, W.; Chen, N.; Montogomery, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 8712.

10.1021/ol303548x

Table 1. Effect of Phosphine Ligands[a]



1a **2a** **2aa**

entry	phosphine	yield[b] (%)
1	PPh_3	84 (81)[c]
2[d]	PPh_3	35
3[e]	PPh_3	0
4[f]	PPh_3	0
5	$P(p\text{-}CF_3C_6H_4)_3$	79
6	$P(p\text{-}MeOC_6H_4)_3$	78
7	PEt_3	65
8	P^nBu_3	56
9	PCy_3	65

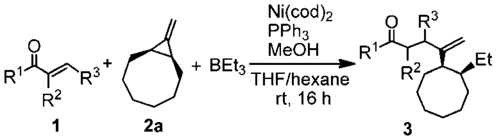
[a] Reaction conditions: $Ni(cod)_2$ (0.10 mmol), **1a** (2.0 mmol), **2a** (1.0 mmol), MeOH (2.0 mmol), THF (3 mL), and BEt_3 (1.0 M hexane solution, 2 mL, 2.0 mmol) were employed. [b] GC yield. [c] Isolated yield. [d] Reaction was conducted in the absence of MeOH. [e] $ZnEt_2$ was used instead of BEt_3. [f] Et_3SiH was used instead of BEt_3.

reductive coupling reaction of an enone with an alkyne in the presence of triethylborane, leading to γ,δ-unsaturated carbonyl compounds.[7a,b] The replacement of the enone with an enal, also reported by Montgomery et al., favored the reductive cyclization reaction.[7c] Concerning the reaction of enone with alkene compound in the presence of borane or silane, successful example using allene as alkene molecule have been reported by Montgomery et al.[7d] However, the coupling partner for the reductive or alkylative coupling reaction of α,β-unsaturated ketones with alkene compounds has scarcely been studied.[8]

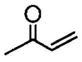
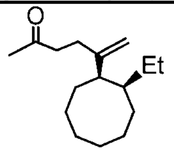
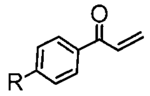
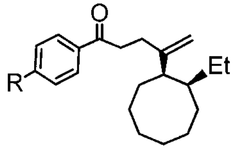
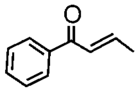
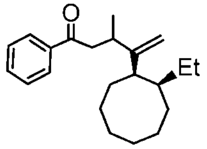
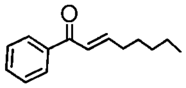
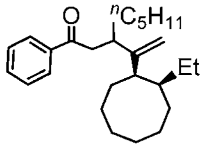
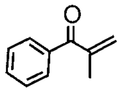
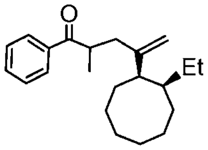
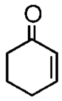
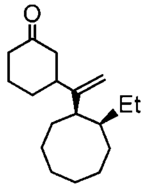
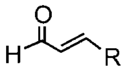
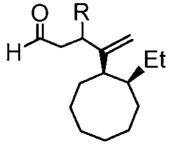
In this paper, we demonstrate the first example of an alkylative coupling reaction of an α,β-unsaturated carbonyl compound with methylenecyclopropane via stereospecific cleavage of the three-membered ring in the presence of triethylborane and a nickel catalyst.

First, various phosphine ligand of the nickel catalyst were screened in alkylative coupling reaction between methyl vinyl ketone **1a** and methylenecyclopropane **2a** in the presence of triethylborane and MeOH, as shown in Table 1. Using $Ni(cod)_2/PPh_3$ catalyst, the alkylative coupling reaction proceeded smoothly at room temperature via stereospecific cleavage of the proximal C−C bond of **2a** to give **3aa** in high yield (entry 1).[9] However, conducting the reaction in the absence of MeOH resulted in a lower yield of **3aa** (entry 2).[10] The use of diethyl zinc or

Table 2. Nickel-Catalyzed Reductive Coupling between **1a**−**k** and **2a** in the Presence of Triethylborane[a]



1 **2a** **3**

entry	1	product (% yield)[b]
1	 **1a**	 **3aa** (88)
		
2	**1b** (R = H)	**3ba** (82)
3	**1c** (R = Me)	**3ca** (85)
4	**1d** (R = OMe)	**3da** (87)
5	**1e** (R = Cl)	**3ea** (92)
	 **1f**	 **3fa** (84) (dr = 69:31)[c]
6	 **1g**	 **3ga** (82) (70:30)[c]
7	 **1h**	 **3ha** (88) (81:19)[c]
8	 **1i**	 **3ia** (37) (dr = 55:45)[c]
		
9	**1j** (R = Me)	**3ja** (64) (dr = 92:8)[c]
10	**1k** (R = Ph)	**3ka** (80) (dr = 91:9)[c]

[a] Reaction conditions: $Ni(cod)_2$ (0.10 mmol), **1** (2.0 mmol), **2a** (1.0 mmol), MeOH (2.0 mmol), THF (3 mL), and BEt_3 (1.0 M hexane solution, 2 mL, 2.0 mmol) were employed. [b] Isolated yield. [c] Diastereomeric ratio.

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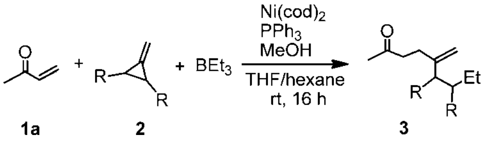
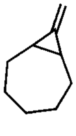
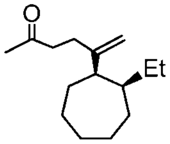
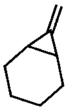
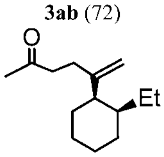
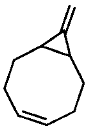
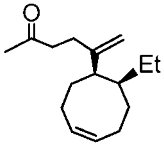
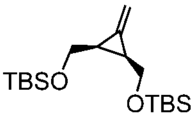
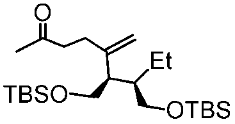
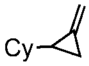
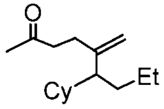
(8) Nickel-catalyzed direct conjugate addition of alkene compound and enone has been reported: (a) Ho, C.-Y.; Ohmiya, H.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 1893. (b) Ogoshi, S.; Haba, T.; Ohashi, M. *J. Am. Chem. Soc.* **2009**, *131*, 10350.

(9) The selective formation of **3** and its syn structure was determined by X-ray analysis. Compound **3ka** was converted to the corresponding carboxylic acid **5ka** in 85% yield by Pinnick oxidation using $NaClO_2$, NaH_2PO_4, and 2-methyl-2-butene, and the crystal structure of the product **5ka** was obtained. See the Supporting Information. CCDC no. 915409.

(10) MeOH probably acts as an activation reagent of triethylborane in the reaction pathway. See ref 7.

Table 3. Nickel-Catalyzed Reductive Coupling between **1a** and **2a**–**f** in the Presence of Triethylborane[a]



entry	2	product (% yield)[b]
1	 **2b**	 **3ab** (72)
2	 **2c**	 **3ac** (67)
3	 **2d**	 **3ad** (61) (92:8)[c]
4	 **2e**	 **3ae** (59)
5	 **2f**	 **3af** (56)

[a] Reaction conditions: Ni(cod)$_2$ (0.10 mmol), **1a** (2.0 mmol), **2** (1.0 mmol), MeOH (2.0 mmol), THF (3 mL), and BEt$_3$ (1.0 M hexane solution, 2 mL, 2.0 mmol) were employed. [b] Isolated yield. [c] Diastereomeric ratio.

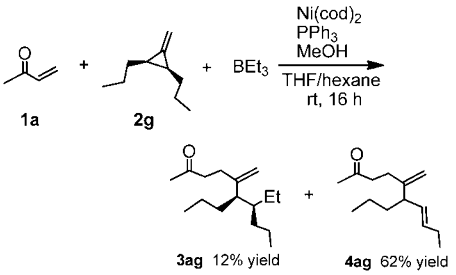
triethylsilane instead of triethylborane inhibited the production of **2aa** (entries 3 and 4). The reaction also proceeded effectively in the presence of *p*-substituted aryl phosphines such as P(*p*-CF$_3$C$_6$H$_4$)$_3$ and P(*p*-MeOC$_6$H$_4$)$_3$ (entries 5 and 6). The reaction using trialkylphosphines such as PEt$_3$, P^{n}Bu$_3$, and PCy$_3$ resulted in lower yields than that obtained using PPh$_3$ (entries 7–9). From the result of screening of phosphine ligands, the highest yield of the ring-opening alkylative coupling product **2aa** was achieved using the PPh$_3$ ligand in the presence of BEt$_3$ and MeOH.

Using the optimized catalytic system, the scope of the nickel-catalyzed alkylative coupling reaction was examined using various types of enones or enals as shown in Table 2. Enones bearing phenyl- or *para*-substituted aryl groups such as electron-donating (methyl and methoxy) or electron-withdrawing (chloro) substituents also afforded product **3** in good to high yields (entries 2–5). The use of enones bearing alkyl substituents (such as methyl and *n*-hexyl groups) in the 1-position yielded the corresponding alkylative coupling products (entries 5 and 6). Enones with methyl substituents in the 2-position also participated in this reaction to afford the product **3ha** in 88% yield (entry 7). The reaction using the cyclic enone **1i** proceeded to give the corresponding product **3ia**, albeit in moderate yield (entry 8). The alkylative coupling reaction also proceeded upon replacement of the enone with an enal (entries 9 and 10).

After screening the enones, the scope of the reaction was further examined with various methylenecyclopropane partners (Table 3). Seven- and six-membered bicyclic methylenecyclopropanes also afforded the corresponding products **3ab** and **3ac** in high yields (entries 1 and 2). Cyclooctene-fused methylenecyclopropane **2d** also participated in the reaction to give the product **3ad** bearing a double bond in the cyclic structure (entry 3). Methylenecyclopropanes bearing *cis*-alkyl silyl ether provided the corresponding products **3ae** in good yield (entry 4). The reaction of methylenecyclopropane **2f** bearing cyclohexyl group proceeded with the selective cleavage of the less hindered proximal C–C bond to give the product **3af** (entry 5).

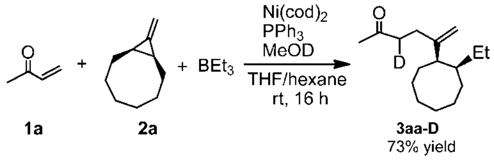
As shown in Scheme 1, in the case of the reaction with *n*-propyl-substituted methylenecyclopropane **2g**, the product **4ag**, which involves sp^3 C–H bond cleavage of the propyl chain, was formed in addition to the product **3ag**. The product **4ag** was obtained only as the *E*-type stereoproduct on the C–C double bond, which was generated during the coupling reaction.

Scheme 1

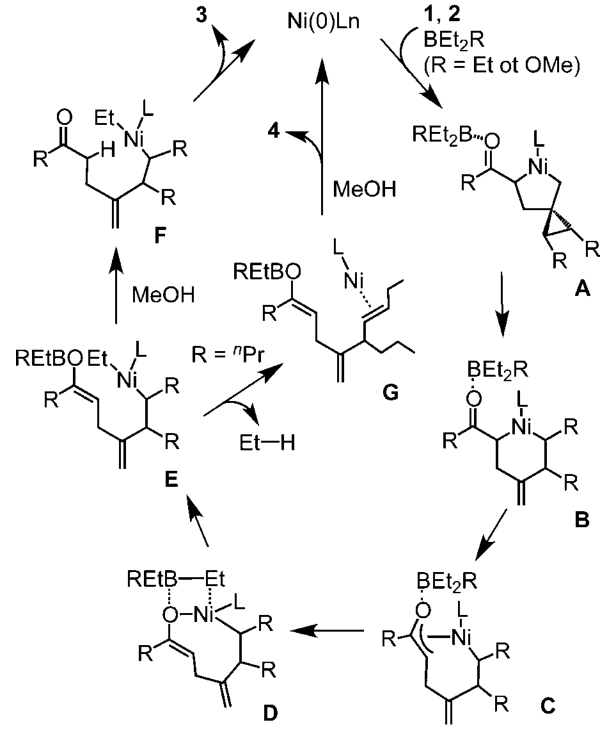


To obtain insight into the reaction mechanism, further reactions were carried out using methanol-*d*$_1$. The Ni(cod)$_2$/PPh$_3$-catalyzed reaction between **1a** and **2a** in the presence of triethylborane and methanol-*d*$_1$ afforded compound **3aa-D** (97% deuterium incorporation) (Scheme 2). Deuterium is incorporated solely into the α-position of

Scheme 2



Scheme 3



this product. It is thus deduced that the proton incorporated into the α-position of product **3** is derived from MeOH.[11]

A possible pathway for the coupling reaction is shown in Scheme 3. First, the nickelacyclopentane intermediate **A**, involving coordination of the borane moiety to the carbonyl carbon, is formed by the reaction of a nickel phosphine complex with enone **1** and methylenecyclopropane **2** and borane.[12,13] Next, the intermediate **A** undergoes β-carbon elimination to generate intermediate **B**.[14] Intermediate **B** then undergoes transmetalation of the ethyl group from the borane moiety to the nickel metal (intermediate **D**) via the oxa-π-allyl intermediate **C** to produce the nickel—ethyl intermediate **E**. The borane enolate of **E** reacts with methanol to give the intermediate **F**. Finally, reductive elimination from **F** affords the stereodefined product **3**. When di-*n*-propyl-substituted methylenecyclopropane **2g** was used (Scheme 2), product **4ag** was also produced. The formation of **4ag** probably resulted from β-hydrogen elimination from intermediate **E** through the formation of intermediate **G,** involving π-coordination of the *E*-alkene unit, given that the interaction of nickel metal with the β-hydrogen of flexible *n*-alkyl groups is more probable than the interaction with cycloalkyl groups.

In summary, we have demonstrated the first examples of the alkylative coupling reaction between enones (enals), methylenecyclopropane, and triethylborane leading to γ,δ-unsaturated carbonyl compounds via cleavage of the proximal C—C bond of methylenecyclopropane.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Innovation Areas Molecular Activation Directed toward Straightforward Synthesis from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We are grateful to Prof. Makoto Yamashita (Chuo University) for assistance with X-ray analyses.

Supporting Information Available. Standard experimental procedure, characterization data for new compounds, and ORTEP drawing. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] In the case of reaction between **1a** and **2a** in the presence of triethylborane and MeOH, followed by quench with D_2O, deuterium was not incorporated into product and **3aa** was obtained 74% isolated yield.

[12] The report for the formation of Et_2BOMe and $EtB(OMe)_2$ from BEt_3 in the presence of MeOH: Chem, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923In nickel-catalyzed reductive coupling reaction, it is also reported that these alkoxy borane species act as reducing agents; see ref 7.

[13] In the reductive coupling reaction in the presence of borane compound, borane coordination probably accelerates the oxidative cyclization of alkyne and aldehyde; see: McCarren, P. R.; Liu, P.; Cheong, P. H.-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2009**, *131*, 6654.

[14] In nickel-catalyzed dimerization of methylenecyclopropane, cyclopropropenyl—butenyl rearrangement was proposed. See: Binger, P.; Doyle, M. J.; Benn, R. *Chem. Ber.* **1983**, *116*, 1.

The authors declare no competing financial interest.