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Nickel-Catalyzed Regio- and Stereoselective Reductive Coupling between Methylenecyclopropanes, Aldehydes, and Triethylborane with Retention of the Cyclopropane Ring

Kenichi Ogata,* Daisuke Shimada, and Shin-ichi Fukuzawa*[a]

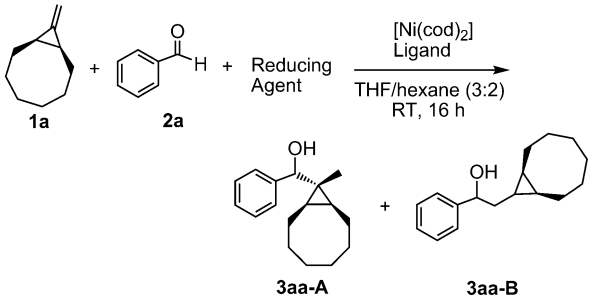
Transition-metal-catalyzed reductive coupling is one of the most effective synthetic methods for C–C bond formation using simple unsaturated compounds.[1] Noteworthy among these is the nickel-catalyzed reductive coupling between an aldehyde, alkyne, and reducing agent leading to an allylic alcohol.[2] Although the majority of the reports on nickel-catalyzed reductive couplings use alkynes, reactions involving some alkene compounds such as alpha olefins,[3] 1,3-dienes,[4] allenes,[5] and norbornene[6] have also been reported. Our research group has recently reported the first example of a reductive coupling of methylenecyclopropane with aryl aldehydes in the presence of silane leading to allylic alcohols through cleavage of the proximal C–C bond in the methylenecyclopropane ring using the $[Ni(cod)_2]$/N-heterocyclic carbene catalyst system.[7]

Recently, research has focused on the highly strained methylenecyclopropane as a versatile reactant in the field of organic synthesis using transition-metal catalysts.[8] Notably, these transformation reactions proceed almost exclusively through ring-opening of the cyclopropane moiety by cleavage of either the distal or proximal C–C bond.[9] Although the majority of reports within this category are reactions involving ring-opening of methylenecyclopropane, some examples of ring-retaining reactions have also been reported.[10] Within this category, ring-retaining reactions that construct new stereo-defined cyclopropane compounds are especially desirable to develop methods for stereoselective synthesis of cyclopropane skeletons, important subunits in a variety of natural products.[11] However, ring-retained coupling reactions of methylenecyclopropane that construct cyclopropane rings with formation of a quaternary stereogenic carbon center have scarcely been studied.[10e,f]

In this report, we describe the first example of a regio- and stereoselective reductive coupling reaction between methylenecyclopropanes, aldehydes and triethylborane with retention of the cyclopropane ring using a nickel/phosphine catalyst.

First, ligands and reducing agents were screened in the nickel-catalyzed reductive coupling reaction between methylenecyclopropane **1a**, benzaldehyde **2a**, and reducing agent, as shown in Table 1. In the presence of a $[Ni(cod)_2]$/PCy_3 catalyst, reductive coupling proceeded smoothly at room temperature to afford **3aa** in high yield with complete regio- and stereoselectivity using triethylborane in hexane solution as a reducing agent (Table 1, entry 1).[12] However, replacement of the triethylborane with diethyl zinc as the reducing agent resulted in a lower yield of **3aa** (entry 2) and other reductive coupling products involving ethylation by diethyl zinc were also isolated.[13] The reductive coupling reaction was not observed when triethylsilane was used for the reducing agent (Table 1, entry 3). In contrast to PCy_3, when $P(n\mathrm{Bu})_3$ is used as the ligand compound **3aa** was obtained

Table 1. Screening of ligands and reducing agents.[a]



Entry	Ligand	Reducing agent	Yield [%][b]	A/B
1	PCy_3	BEt_3	98	99:<1
2	PCy_3	Et_2Zn	33[c]	99:<1
3	PCy_3	Et_3SiH	0	–
4	$P(n\mathrm{Bu})_3$	BEt_3	64	89:11
5	PEt_3	BEt_3	98	85:15
6	PPh_3	BEt_3	0	–
7	$P(OMe)_3$	BEt_3	0	–
8	dppe	BEt_3	0	–

[a] $[Ni(cod)_2]$ (0.10 mmol), ligand (0.20 mmol), **1a** (2.0 mmol), **2a** (1.0 mmol), reducing agent (2.0 mmol), and THF/hexane (3 mL/2 mL) were employed. [b] Isolated product yield. [c] Reductive coupling product involving ethylation also formed in this reaction. See ref. [12]. cod = cycloocta-1,5-diene, Cy = cyclohexyl, dppe = bis(1,2-diphenylphosphino)-ethane, THF = tetrahydrofuran.

[a] Dr. K. Ogata, D. Shimada, Prof. Dr. S.-i. Fukuzawa
Department of Applied Chemistry
Institute of Science and Engineering
Chuo University, 1-13-27 Kasuga, Bunkyo-ku
Tokyo 112-8551 (Japan)
Fax: (+81) 3-3817-1916
E-mail: orgsynth@kc.chuo-u.ac.jp

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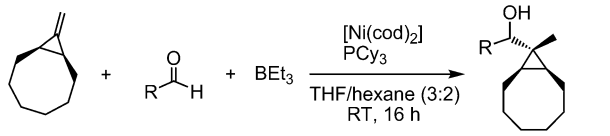
in a lower yield and regioselectivity (Table 1, entry 4). Although an effective reductive coupling reaction also occurred using PEt_3, the product was lower in regioselectivity than that obtained using the PCy_3 ligand (Table 1, entry 5). Triarylphosphine, trialkylphosphite, and diphosphine such as PPh_3, $P(OMe)_3$, and dppe did not participate in this reaction (Table 1, entries 6–8). On the basis of this screen of phosphine ligands, the highest yield and complete regio- and stereoselectivities for the formation of reductive coupling product **3aa** was achieved using the PCy_3 ligand in the presence of BEt_3 as the reducing agent.

Next, the nickel-catalyzed regio- and stereoselective reductive coupling reaction using methylenecyclopropane with retention of the cyclopropane ring was examined using various aldehydes as shown in Table 2. The use of electron-donating *p*-, *o*-methyl- or *p*-methoxy-substituted aryl aldehydes

Table 2. Ni-catalyzed reductive coupling between **1** and **2a–l** in the presence of BEt_3.[a]



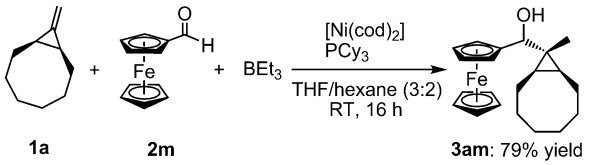
1a 2 3

Entry	2	R	Yield [%][b]
1	**2a**	Ph	**3aa** (98)
2	**2b**	*p*-MeC_6H_4	**3ab** (90)
3	**2c**	*o*-MeC_6H_4	**3ac** (81)[d]
4	**2d**	*p*-$MeOC_6H_4$	**3ad** (89)
5	**2e**	*p*-FC_6H_4	**3ae** (95)
6	**2f**	*p*-ClC_6H_4	**3af** (86)
7	**2g**	*p*-$MeO_2CC_6H_4$	**3ag** (98)
8	**2h**	2-furyl	**3ah** (80)
9	**2i**	2-thienyl	**3ai** (95)
10[c]	**2j**	3-pyridyl	**3aj** (64)
11	**2k**	*n*-C_5H_{11}	**3ak** (49)
12	**2l**	Cy	**3al** (51)

[a] $[Ni(cod)_2]$ (0.10 mmol), PCy_3 (0.20 mmol), **1a** (2.0 mmol), **2** (1.0 mmol), BEt_3 (2.0 mmol) and and THF/hexane (3 mL/2 mL) were employed. [b] Isolated product yield. [c] BEt_3 (3.0 mmol). [d] 14% regioisomer **3ac-B** was also contained.

also afforded product **3** in good to high yields (Table 2, entries 2–4). In the case of sterically hindered *o*-tolualdehyde (Table 2, entry 3), reductive coupling products were formed as a mixture of regioisomers (regioselectivity: 86%). Other substituted aryl aldehydes bearing electron-withdrawing groups (fluoro, chloro, and ester) also participated in this reaction to give the corresponding product **3** (Table 2, entries 5–7). In spite of the use of a Lewis acid (triethylborane), heteroaryl aldehydes such as 2-furyl, 2-thienyl, and 3-pyridyl aldehydes reacted to afford the reductive coupling products **3** selectively (Table 2, entries 8–10).[14] In addition to the aryl aldehydes, alkyl aldehydes such as 1-hexanal and cyclohexanecarbaldehyde also participated in this reaction to afford the corresponding coupling products with complete regio- and stereoselectivities (Table 2, entries 11 and 12). In contrast to aldehydes, ketones such as acetophenone did not participate in this reaction.

Furthermore, ferrocenecarboxyaldehyde was also shown to generate **3am** as a red solid in high yield with high regio- and stereoselectivities (Scheme 1). Red single crystals of



1a 2m **3am**: 79% yield

Scheme 1. Ni-catalyzed reductive coupling between **1a** and **2m** in the presence of BEt_3.

3am suitable for X-ray diffraction were grown from hexane solution. The ORTEP drawing of **3am** is shown in Figure 1, revealing the stereochemistry of the reductive coupling product.[15] The methyl group and cyclooctane moiety of the cyclopropane ring are located *cis* to each other.

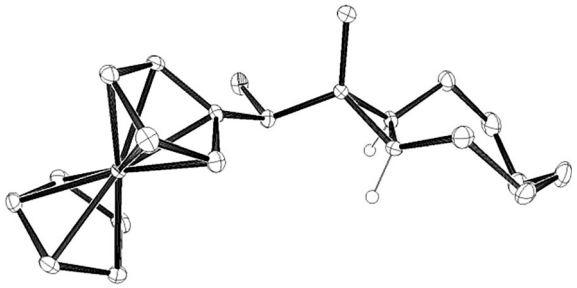
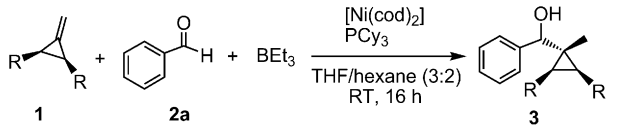
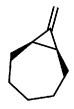
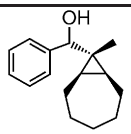
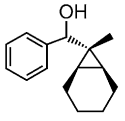
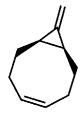
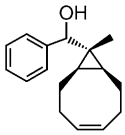
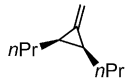
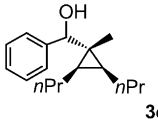
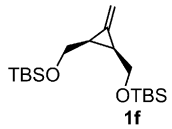
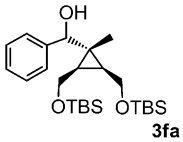
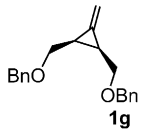
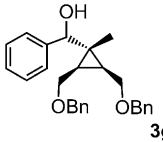
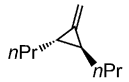


Figure 1. ORTEP drawing of **3am** with thermal ellipsoids drawn at the 50% probability level.

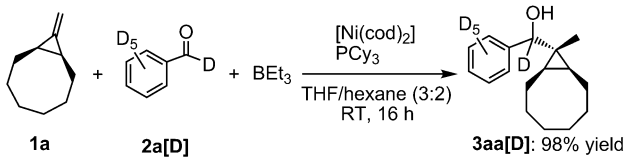
After demonstrating the scope of substitution patterns of the aldehydes, we next examined the scope for the methylenecyclopropane partner (Table 3). Cycloheptane-fused methylenecyclopropane **1b** provided the corresponding product **3ba** in good yield with complete regio- and stereoselectivities (Table 3, entry 1). Although cyclohexane-fused methylenecyclopropane **1c** also participated in this reaction, the product **3ca** was obtained as a mixture with the ring-opened reductive coupling product (Table 3, entry 2).[16] The corresponding silylated ring-opened product was obtained in our report by the reaction between methylenecyclopropane and aldehyde using nickel-NHC catalyst in the presence of silane.[6] Cyclooctene-fused methylenecyclopropane **1d** also participated in the reaction and gave the corresponding product **3da**, with retention of the double bond in the cyclooctene ring (Table 3, entry 3). The *cis*-dialkyl chain-substituted methylenecyclopropane **1e** afforded **3ea** in high yield (Table 3, entry 4). Methylenecyclopropanes bearing *cis*-alkyl chains with ether functionalities such as silyl ether and benzyl ether provided the corresponding products **3fa** and **3ga** in good yields (Table 3, entries 5 and 6). It should be

Table 3. catalyzed reductive coupling between **1b–h** and **2a** in the presence of BEt_3.[a]



	1	3	Yield [%][b]
1	 1b	 3ba	89
2	 1c	 3ca	60[c]
3	 1d	 3da	73
4	 1e	 3ea	94
5	 1f	 3fa	62
6	 1g	 3ga	64
7	 1h	–	0[d]

[a] $[Ni(cod)_2]$ (0.10 mmol), PCy_3 (0.20 mmol), **1** (2.0 mmol), **2a** (1.0 mmol), BEt_3 (2.0 mmol) and and THF/hexane (3 mL/2 mL) were employed. [b] Isolated product yield. [c] Yield obtained using ^1H NMR spectroscopy. Ring-opening product was also formed as mixture. See ref. [14]. [d] Hydroacylation product was formed in 50% yield. See ref. [9f]. Bn = benzyl. TBS = *tert*-butyldimethylsilyl.

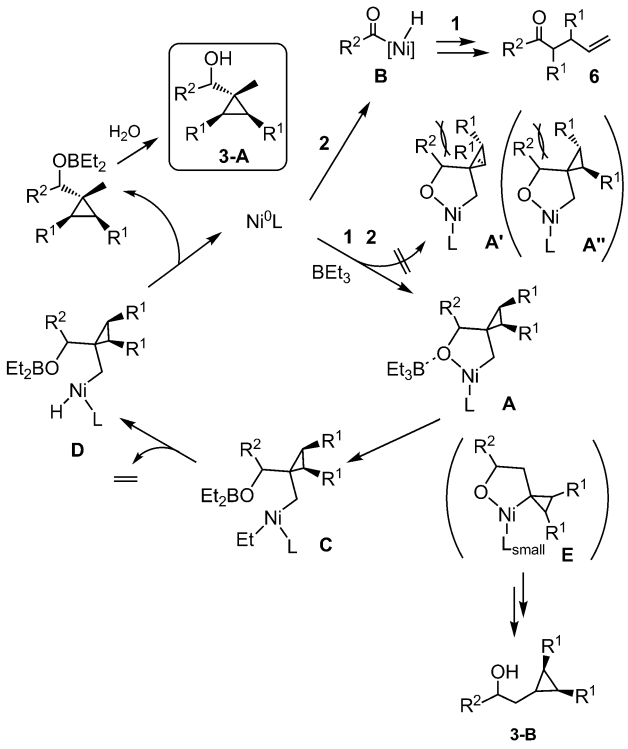


Scheme 2. Ni-catalyzed reductive coupling using $[D_6]$benzaldehyde (**2a[D]**).

noted, however, that the corresponding *trans*-dialkyl chain-substituted substrate **1h** did not give the product at all, and the ring-opened hydroacylation product of methylenecyclopropane (γ,δ-unsaturated ketone), which was reported by Suginome et al.,[9f] was formed (Table 3, entry 7). The formation of ring-opened hydroacylation product was also confirmed using monosubstituted methylenecyclopropane bearing cyclohexyl group.

To obtain insight into the mechanism of the reaction, the reaction was carried out using deuterium-labeled aldehyde. The nickel-catalyzed reaction between **1a** and $[D_6]$benzaldehyde (**2a[D]**) in the presence of triethylborane afforded compound **3aa[D]** (Scheme 2). In compound **3aa[D]**, the position of the deuterium incorporation showed that oxidative addition of the aldehydic C–H bond did not occur in the reaction.

A possible pathway for the regio- and stereoselective reductive coupling reaction is shown in Scheme 3. The most probable route involves the formation of a nickelacycle intermediate, whose formation has been postulated in previous nickel-catalyzed reductive coupling reactions.[2] First, nickelacycle intermediate **A** is formed by the reaction of a nickel(0) complex with methylenecyclopropane **1** and aldehyde **2**. In this step, the stereoselective formation of the metallacycle is likely due to steric hindrance. The R^1 substituents of the methylenecyclopropane moiety prefer to be located far from the R^2 substituent of the aldehyde unit to avoid steric hindrance of intermediate **A′**. In the case of *trans*-dialkyl chain-substituted methylenecyclopropane, steric hindrance would probably prevent the formation of nickelacycle intermediate **A″**, and oxidative addition of the C–H bond of the formyl group (formation of intermediate



Scheme 3. Possible pathway for the reductive coupling reaction.

B) would proceed to give the ring-opening hydroacylation compound **6**.[9f] In the reductive coupling reaction, this is followed by transmetallation of the ethyl group involving triethylborane through its coordination with the oxygen of nickelacycle (**A**), which proceeds to give the nickel-ethyl intermediate **C**. After the formation of **C**, β-hydrogen elimination generates the nickel-hydride intermediate **D**. Reductive coupling from intermediate **D**, followed by hydrolysis to produce the reductive coupling product **3A**, occurs with complete stereoselectivity at the quaternary carbon center. Stoichiometric reaction between **1c** and **2a** in the absence of triethylborane resulted in the formation of ring-opened hydroacylation product **6ca**.[17] In the absence of triethylborane, the oxidative addition of the aldehyde C–H bond (formation of intermediate **B**) is faster than formation of nickelacycle. This result indicates that triethylborane probably assists in the formation of nickelacycle intermediate **A**.[18] When tri-*n*-alkylphosphine ligands such as $P(n\mathrm{Bu})_3$ and PEt_3 are used (Table 1, entries 4 and 5), regioisomer **3-B** is also produced as a by-product. The formation of regioisomer **3-B** is derived from the smaller steric hindrance of these alkyl phosphine ligands than that of PCy_3, and the reaction probably proceeds through intermediate **E**. In addition to the difference in phosphine ligands, small amounts of regioisomer **3-B** also form when sterically hindered aldehyde *o*-tolualdehyde is used (Table 2, entry 3). This regioisomer avoids steric hindrance between the *o*-tolyl group of the aldehyde and the R^1 substituent of the methylenecyclopropane.

In summary, the first regio- and stereoselective reductive coupling between methylenecyclopropanes, aldehydes, and triethylborane with retention of the cyclopropane ring was achieved using a nickel–phosphine catalyst. The reductive coupling reaction constructed a stereo-defined cyclopropane ring with formation of a quaternary stereogenic carbon center.

Experimental Section

Representative procedure (Table 2, entry 1): PCy_3 (56 mg, 0.20 mmol), THF (2 mL), BEt_3 (1.0 M hexane solution, 2.0 mL, 2.0 mmol), benzaldehyde **1a** (0.10 mL, 1.0 mmol), and methylenecyclopropane **2a** (272 mg, 2.0 mmol) were added to a mixture of $[Ni(cod)_2]$ (28 mg, 0.10 mmol) in a THF solution (1.0 mL). After stirring for 16 h at room temperature, saturated aq. NH_4Cl was added to the solution. The resulting mixture was extracted with diethyl ether, dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. The residue was purified by silica gel preparative TLC (ether/hexane = 1:5). Product **3aa** (239 mg, 0.98 mmol, 98%) was obtained as a colorless oil.

Acknowledgements

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Keywords: alkenes · cyclic compound · methylenecyclopropane · nickel · synthetic methods

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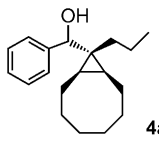
[12] The corresponding reductive coupling reaction did not proceed when using triphenylborane instead of triethylborane as the reducing agent.

[13] Ethylation product **4aa** was also isolated in 26% yield.

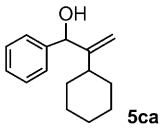
[14] When the reaction using 3-pyridyl aldehyde in the presence of two equiv of triethylborane, yield of product **3aj** (43% yield) was



4aa

lower than that of the reaction in the presence of 3 equiv of triethylborane.

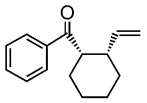
[15] CCDC-840836 (**3am**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



5ca

[16] In addition to the formation of **3ca**, ring-opening product **5ca** also formed in 16% yield. The corresponding silylated compound has been reported in our previous work (ref. [7]).

[17] Stoichiometric reaction between **1c** and **2a** in the absence of triethylborane resulted in the formation of ring-opened hydroacylation product **6ca** (ref. [9f]) in 69% yield.



6ca

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

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