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Nickel-Catalyzed Ring-Opening Three-Component Coupling of Methylenecyclopropane with Aldehydes and Silanes

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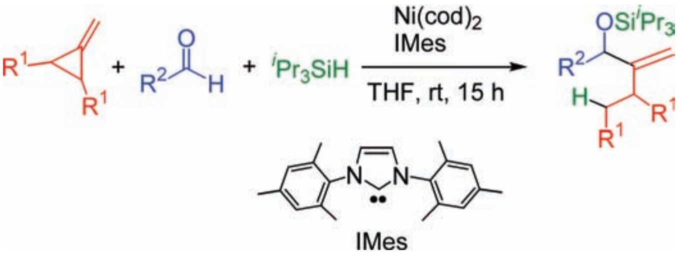
ABSTRACT



A nickel-catalyzed three-component coupling between methylenecyclopropane, aldehydes, and silanes afforded silylated allylic alcohols that possess an alkyl substituent at the 2-position via cleavage of the proximal C−C bond of methylenecyclopropane.

Transition metal-catalyzed multicomponent reactions that produce complex molecules from more than three parts of a simple compound in one operation have become increasingly important in recent organic syntheses.[1] Noteworthy among these is the convenient synthetic approach to allylic alcohols by the nickel-catalyzed reductive three-component reaction between an alkyne, aldehyde, and silane (or Lewis acid), which has been reported by several research groups.[2] Although many examples for the synthesis of allylic alcohols possessing mono- and disubstituted alkenes by this method have been reported, there are only a few examples of the selective synthesis of allylic alcohols which possess a monosubstituent at the 2-position. For example, Montgomery reported highly regioselective access to a mono-2-position-substituted silylated allylic alcohol by the reaction between a terminal alkyne, aldehyde, and silane in the presence of a nickel/*N*-heterocyclic carbene (NHC) catalyst.[2m] Jamison also reported the synthesis of an allylic alcohol that possessed an alkyl substituent in the 2-position by the nickel-catalyzed reaction between an α-olefin, aldehyde, and silyl triflate.[3]

Recently, methylenecyclopropanes have been used as versatile building blocks for nickel-catalyzed reactions because of their unique reactivities.[4] However, reductive multicomponent couplings with methylenecyclopropane have not been reported. In this report, we describe the first nickel/NHC-catalyzed three-component coupling between methyl-

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(1) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117.

(2) (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.

(3) (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.

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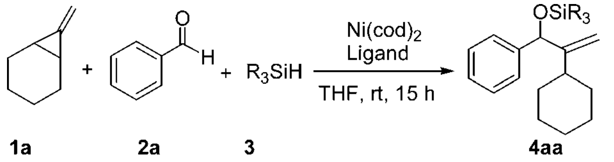
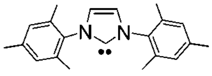
enecyclopropane, aldehydes, and silanes leading to silylated allylic alcohols which possess an alkyl substituent in the 2-position with *complete* regioselectivity.

First, ligands and silanes were screened in the three-component coupling of methylenecyclopropane **1a**, benzaldehyde **2a**, and silane **3**, as shown in Table 1. In the presence of a catalyst derived from Ni(cod)$_2$ and NHC bearing a mesityl substituent (IMes) (1:1),[5] the three-component coupling using triisopropylsilane proceeded smoothly at room temparature to afford **4aa** in high yield (entry 1). The use of triethylsilane resulted in a slightly lower yield than that of triisopropylsilane (entry 2). In comparison, *tert*-butyldimethylsilane was not effective, and this reaction resulted in a complex mixture (entry 3). The reaction with triisopropylsilane in the presence of Ni(cod)$_2$/PCy$_3$ catalyst resulted in an extremely low yield (entry 4). In this case, the ring-opening hydroacylation product of methylenecyclopropane (γ,δ-unsaturated ketone), which was reported by Suginome et al.,[4e] was also detected as a byproduct by GC-MS. P^{n}Bu$_3$ and PPh$_3$ were also ineffective for the reaction (entries 5 and 6). Using other NHC ligands bearing 2,6-diisopropylphenyl and isopropyl substituents, the three-component coupling reaction was not observed. On the basis of this screening of NHC and phosphine ligands, the highest yield for the formation of **4** was achieved with IMes.

Table 1. Screening of Ligands and Silanes for the Three-Component Coupling between **1a**, **2a**, and **3**[a]



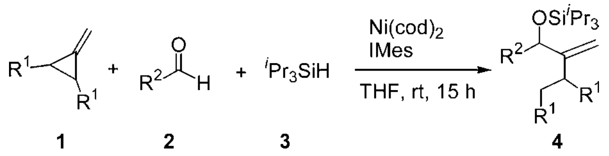
1a **2a** **3** **4aa**

entry	ligand	Silane (**3**)	yield [%][b]
1	 IMes	^{i}Pr$_3$SiH	98 (88)[c]
2	IMes	Et$_3$SiH	68[c]
3	IMes	^{t}BuMe$_2$SiH	trace
4	PCy$_3$	^{i}Pr$_3$SiH	6
5	P^{n}Bu$_3$	^{i}Pr$_3$SiH	0
6	PPh$_3$	^{i}Pr$_3$SiH	0

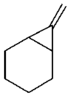
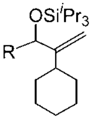
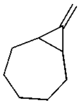
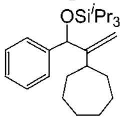
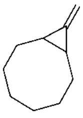
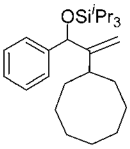
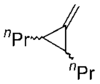
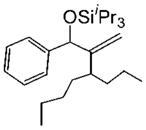
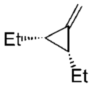
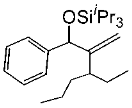
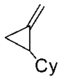
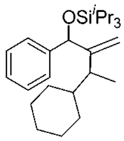
[a] Ni(cod)$_2$ (0.10 mmol), ligand (0.10 mmol), **1a** (1.0 mmol), **2a** (1.0 mmol), **3** (2.0 mmol), and THF (4 mL) were employed. [b] GC yield. [c] Isolated yield.

Next, the Ni(cod)$_2$/IMes-catalyzed three-component coupling reaction was examined with use of various methylenecyclopropanes and aldehydes as shown in Table 2.[6] The use of electron-donating (*p*-methyl and *p*-methoxy-substituted) or electron-withdrawing (*p*- and *m*- fluoro-substituted)

Table 2. Nickel-Catalyzed Three-Component Coupling between **1a**−**f**, **2a**−**g**, and **3**[a]



1 **2** **3** **4**

entry	1	2 (R^2)	product	yield [%][b]
1	 **1a**	**2a** (Ph)	 **4aa**	88%
2	**1a**	**2b** (*p*-MeC$_6$H$_4$)	**4ab**	51%
3	**1a**	**2c** (*p*-MeOC$_6$H$_4$)	**4ac**	53%
4	**1a**	**2d** (*p*-FC$_6$H$_4$)	**4ad**	91%
5	**1a**	**2e** (*m*-FC$_6$H$_4$)	**4ae**	60%
6	**1a**	**2f** (furyl)	**4af**	57%
7	**1a**	**2g** (thienyl)	**4ag**	61%
8	 **1b**	**2a** (Ph)	 **4ba**	73%
9	 **1c**	**2a**	 **4ca**	90%
10	 **1d-cis**	**2a**	 **4da**	90%
11	**1d-trans**	**2a**		48%
12	 **1e**	**2a**	 **4ea**	90%
13	 **1f**	**2a**	 **4fa**	29%

[a] Ni(cod)$_2$ (0.10 mmol), IMes (0.10 mmol), **1** (1.0 mmol), **2** (1.0 mmol), **3** (2.0 mmol), and THF (4 mL) were employed. [b] Isolated yield.

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(4) Recently, much research for nickel(0)-catalyzed reaction using methylenecyclopropane has been reported, for example: (a) Kamikawa, K.; Shimizu, Y.; Takemoto, S.; Matsuzawa, H. *Org. Lett.* **2006**, *8*, 4011. (b) Komagawa, S.; Saito, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2446. (c) Saito, S.; Komagawa, S.; Azumaya, I.; Masuda, M. *J. Org. Chem.* **2007**, *72*, 9114. (d) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 5060. (e) Taniguchi, H.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 11298. (f) Komagawa, S.; Takeuchi, K.; Sotome, I.; Azumaya, I.; Masu, H.; Yamasaki, R.; Saito, S. *J. Org. Chem.* **2009**, *74*, 3323. (g) Yamasaki, R.; Terashima, N.; Sotome, I.; Komagawa, S.; Saito, S. *J. Org. Chem.* **2010**, *75*, 480. (h) Saito, S.; Maeda, K.; Yamasaki, R.; Kitamura, T.; Nakagawa, M.; Kato, K.; Azumaya, I.; Masu, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 1830.

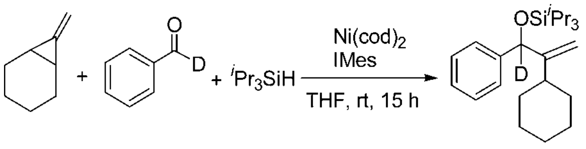
(5) The *N*-heterocyclic carbene was prepared in situ by the reaction of the corresponding imidazolium salt with ^{n}BuLi.

arylaldehydes afforded product **4** in good to high yields (entries 2−5). Reactions of **2f** and **2g**, which possess heteroaryl groups, also proceeded to form the products **4af** and **4ag** in good yields (entries 6 and 7). In contrast, alkylaldehydes such as 1-pentanal and cyclohexylaldehyde did not participate in the reaction.[7]

Various methylenecyclopropanes were then reacted with benzaldehyde **2a** and triisopropylsilane **3** (Table 2, entries 8−13). The use of seven- and eight-memberd bicyclic methylenecyclopropanes also afforded the corresponding products **4ba** and **4ca** in high yields (entries 8 and 9). The *cis*-dialkyl-chain-substituted methylenecyclopropane **1d-*cis*** also participated in the reaction in high yield (entry 10), but the reaction with the corresponding *trans* compound **1d-*trans*** resulted in a lower yield of **4da** (entry 11). The *cis*-ethyl-substituted methylenecyclopropane **1e** also participated in this reaction in high yield (entry 12). The reaction with cyclohexyl-substituted methylenecyclopropane **1f**, which has two nonequivalent proximal C−C bonds, proceeded with selective cleavage of the less hindered bond to give the corresponding product **4fa**, albeit with low yield (entry 13).

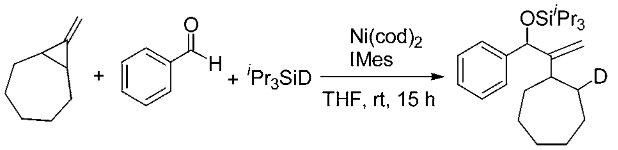
To obtain insight into the mechanism of the reaction, reactions with deuterium-labeled aldehydes and silanes were carried out. The reaction between **1a**, benzaldehyde-d_1 (**2a-D**), and triisopropylsilane **3** in the presence of Ni(cod)$_2$/IMes catalyst afforded compound **5** (Scheme 1). In compound **5**, the position of the deuterium incorporation[8] showed that oxidative addition of the aldehydic C−H bond did not occur in the reaction. Reaction of **1b**, **2a**, and triisopropylsilane-d_1 (**3-D**) by Ni(cod)$_2$/IMes catalyst afforded the product **6**, which incorporated deuterium in the cycloalkyl group (Scheme 2).[9]

Scheme 1



1a **2a-D** **3** **5** 81% yield

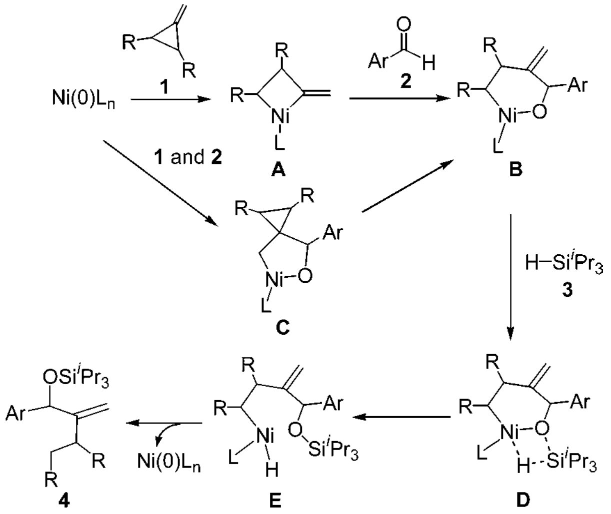
Scheme 2



1b **2a** **3-D** **6** 77% yield

A possible pathway for the three-component coupling is shown in Scheme 3. First, oxidative addition of the proximal C−C bond of methylenecyclopropane **1** to nickel(0) affords 2-alkylidene-1-nickelacyclobutane intermediate **A**. The formation of a 2-alkylidene-1-nickelacyclobutane complex from the nickel(0) complex system by reaction with methylenecyclopropane has been proposed previously.[4a,10,11] Next, the Ni−C bond of intermediate **A** undergoes insertion into aldehyde **2** to give intermediate **B**. In addition to this mechanism, the formation of metallacycle **C**, followed by ring-opening is also possible.[12] This is followed by cleavage of the nickel−oxygen bond by σ-bond metathesis of the nickelacycle with triisopropylsilane (**D**) to afford hydride- nickel intermediate **E**.[2] Finally, reductive elimination from **E** occurs to afford the silylated allylic alcohol derivative **4**.

Scheme 3



In summary, we have demonstrated the first three-component coupling between methylenecyclopropane, an aldehyde, and a silane leading to a silylated allylic alcohol that possesses an alkyl substituent in the 2-position using Ni(cod)$_2$/*N*-heterocyclic carbene as the catalyst. The reactions

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(6) In these reactions, almost all methylenecyclopropane molecules were consumed.

(7) In this reaction, complex mixtures were formed.

(8) In the ^{1}H NMR of **5**, the signal of the proton (5.19 ppm), which was observed in the mesearment of **4aa**, disappeared, and in ^{13}C NMR, the triplet signal (J_{CD} = 21.6 Hz) assignable to the silylated alcohol attached carbon was also detected at 77.5 ppm.

(9) The triplet signal (J_{CD} = 19.2 Hz) assignable to deuterium attached alkyl carbon was detected at 36.1 ppm in ^{13}C NMR.

(10) (a) Noyori, R.; Odagai, T.; Talaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780. (b) Noyori, R.; Kumagai, Y.; Umeda, I.; Takaya, H. *J. Am. Chem. Soc.* **1972**, *94*, 4018.

(11) (a) Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 4911. (b) Ohashi, M.; Taniguchi, T.; Ogoshi, S. *Organometallics* **2010**, *29*, 2386.

(12) We could not rule out the possibility of mechanism via intermediate **C**. In nickel-catalyzed dimerization of methylenecyclopropane, the formation of a nickelacycle intermediate containing a cyclopropane ring, followed by cyclopropropenyl−butenyl rearrangement was also proposed. See: Binger, P.; Doyle, M. J.; Benn, R. *Chem. Ber* **1983**, *116*, 1, and ref 11.

proceeded selectively via the cleavage of the proximal C−C bond of methylenecyclopropane.

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

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