Synthetic Methods

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Nickel-Catalyzed Three-Component Coupling between Aryl Aldehydes, Norbornenes, and Silanes Leading to Indanols through Aromatic C–H Bond Activation of Aryl Aldehydes**

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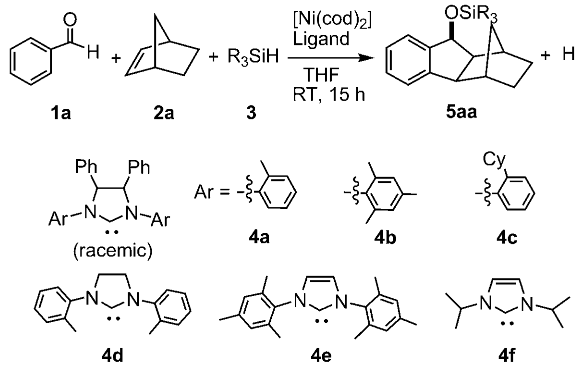
Transition-metal-catalyzed multi-component reactions that produce complex molecules from three or more simple compounds in one operation have become an increasingly important method for C–C bond formation in organic syntheses.[1] Noteworthy among these is the nickel-catalyzed reductive three-component coupling between an aldehyde, alkyne, and silane (or Lewis acid) leading to an allylic alcohol.[2] Although the majority of the reports on nickel-catalyzed three-component couplings use alkynes, reactions involving some alkene compounds such as alpha olefins,[3] 1,3-dienes,[4] and allenes[5] have also been reported.

Our research group has recently reported a reductive three-component coupling involving aryl aldehydes, methylenecyclopropane, and triisopropylsilane leading to allylic alcohols through cleavage of the proximal C–C bond in the methylenecyclopropane ring using the [Ni(cod)$_2$]/N-heterocyclic carbene (NHC) catalyst system.[6] This report was the first example of a nickel-catalyzed reductive three-component coupling by C–C bond activation. Herein, we describe an unprecedented diasteroselective three-component coupling, using a nickel/NHC catalyst, through aromatic C–H bond activation of an aryl aldehyde at the *ortho* position by combination with norbornene and silane, leading to a silylated indanol.[7] Although many examples for nickel-catalyzed reductive three-component couplings using aryl aldehydes have been reported, there are no examples of the present transformation through aromatic C–H bond activation of an aryl aldehyde.[8]

Table 1: Screening of ligands and silanes.[a]



Entry	Ligand	Silane	Yield [%][b]
1	**4a**	(iPr)$_3$SiH	92 (82)[c]
2[d]	**4a**	(iPr)$_3$SiH	54
3	**4a**	(tBu)Me$_2$SiH	79
4	**4a**	Et$_3$SiH	69
5	**4b**	(iPr)$_3$SiH	28
6	**4c**	(iPr)$_3$SiH	trace
7	**4d**	(iPr)$_3$SiH	5
8	**4e**	(iPr)$_3$SiH	9
9	**4f**	(iPr)$_3$SiH	trace

[a] Reaction conditions: [Ni(cod)$_2$] (0.10 mmol), **1a** (1.0 mmol), **2a** (2.0 mmol), **3** (2.0 mmol), **4** (0.10 mmol) and THF (3 mL) were employed. [b] Yield determined by GC analysis. [c] Yield of isolated product. [d] **2a** (1.0 mmol). cod = cycloocta-l,5-diene, cy = cyclohexyl, THF = tetrahydrofuran.

First, ligands and silanes were screened in the three-component reaction of benzaldehyde **1a**, norbornene **2a** (2.0 equiv), and silane **3** (2.0 equiv), as shown in Table 1. In the presence of a catalyst derived from [Ni(cod)$_2$] and NHC **4a**, the diastereoselective three-component coupling using triisopropylsilane proceeded smoothly at room temperature to afford **5aa** in high yield through aromatic C–H activation of benzaldehyde at the *ortho* position (Table 1, entry 1). The structure of the compound was confirmed by X-ray analysis of the desilylated product, which was produced in 88 % yield by the reaction of **5aa** with TBAF (see the Supporting Information).[9] When 1 equivalent of **2a** was used, the reaction resulted in a lower yield of **5aa** (Table 1, entry 2). Using other silanes such as *tert*-butyldimethylsilane and triethylsilane resulted in a slightly lower yield than that obtained with triisopropylsilane (Table 1, entries 3 and 4). In contrast to the NHC ligand **4a**, other saturated NHC ligands, which possessed 2,4,6-trimethylphenyl (**4b**) and *o*-cyclohexyl (**4c**) groups, were not effective in this reaction (Table 1, entries 5 and 6). With **4b** (Table 1, entry 5), another three-component product that did not involve aromatic C–H bond activation of benzaldehyde was also produced.[10] The reaction using NHC ligand **4d**, which does not contain phenyl substituents at the 4 and 5 positions, and unsaturated NHC ligands **4e** and **4f** also

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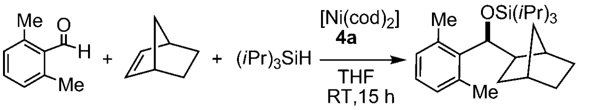
resulted in extremely low yields (Table 1, entries 7–9). When using phosphine ligands such as PPh$_3$, P(nPr)$_3$, and PCy$_3$ the three-component coupling was not observed. On the basis of this screening of ligands, the highest yield for the formation of **5aa** was achieved with NHC ligand **4a**.

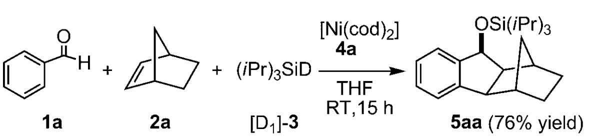
Next, the complex-catalyzed diasteroselective three-component coupling through aromatic C–H bond activation was examined using various aryl aldehydes as shown in Table 2. The use of *p*-substituted aryl aldehydes bearing electron-donating (methyl and methoxy) or electron-withdrawing (chloro, fluoro, and ester) substituents also afforded product **5** in good to high yields (Table 2, entries 2–6). In the case of *m*-substituted aryl aldehydes such as *m*-tolualdehyde **1g** and *m*-fluorobenzaldehyde **1h**, the corresponding products **5ga** and **5ha** were each obtained as a mixture of two regioisomers (Table 2, entries 7 and 8). The reaction with *o*-fluorobenzaldehyde **1i** also proceeded and gave the corresponding product **5ia**, albeit in low yield (Table 2, entry 9).[11] 3,5-Dimethylphenylaldehyde also participated in this reaction and gave the corresponding product **5ja** as a single product (Table 2, entry 10). However, upon replacement of the aryl groups with heteroaromatic groups such as 2-pyridyl and 2-thiophenyl groups, the corresponding three-component coupling did not proceed. The three-component reaction involving 2,6-dimethylphenyl aldehyde **1k**, for which aromatic C–H bond activation at the *ortho* position is not possible, proceeded and gave compound **6ka** [Eq. (1)], which is similar to the side product observed in entry 5 of Table 1 (see Ref. [10]). In contrast, alkyl aldehydes such as cyclohexanecarboxaldehyde did not participate in the reaction.[12]



1k **2a** **3** **6ka** (56% yield) (1)

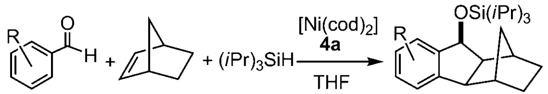
After demonstrating the scope of substitution patterns of the aryl aldehydes, we next examined the scope for the norbornene partner (Scheme 1). The *exo*,*exo*- and *endo*,*endo*-5,6-bis(methoxymethyl)-substituted norbornenes **2b** and **2c**, and benzonorbornadiene derivatives **2d** and **2e** were shown to successfully undergo the reaction to afford products **5ab**, **5ac**, **5ad**, and **5ae**, respectively, with good to high yields. Norbornadiene **2f** also participated in the reaction and gave the corresponding product **5af**, with retention of the double bond in the bicyclic ring. In contrast, an unstrained cyclic alkene such as cyclohexene could not participate in this reaction.

To obtain insight into the mechanism of the reaction, reactions with deuterium-labeled silane and aldehydes were carried out. The reaction between benzaldehyde **1a**, norbornene **2a**, and [D$_1$]-triisopropylsilane ([D$_1$]-**3**) catalyzed by [Ni(cod)$_2$]/**4a** afforded the product **5aa** [Eq. (2)]. In this reaction, deuterium was not incorporated in the product. Using [D$_5$]-benzaldehyde ([D$_5$]-**1a**) in the three-component coupling resulted in the formation of [D$_4$]-**5aa** [Eq. (3)]. These results indicate that the released hydrogen atoms in the reaction are derived from Si–H and the *o*-hydrogen atom of the aryl aldehyde.

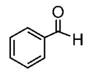
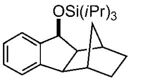
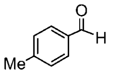
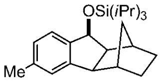
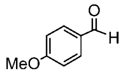
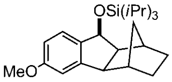
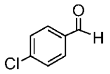
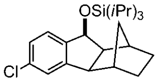
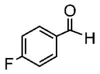
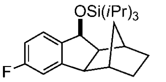
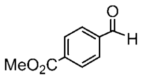
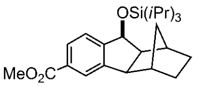
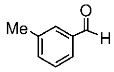
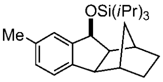
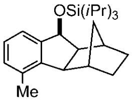
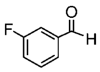
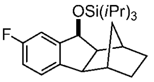
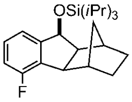
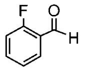
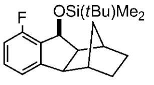
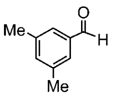
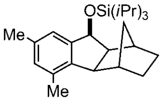


1a **2a** [D$_1$]-**3** **5aa** (76% yield) (2)

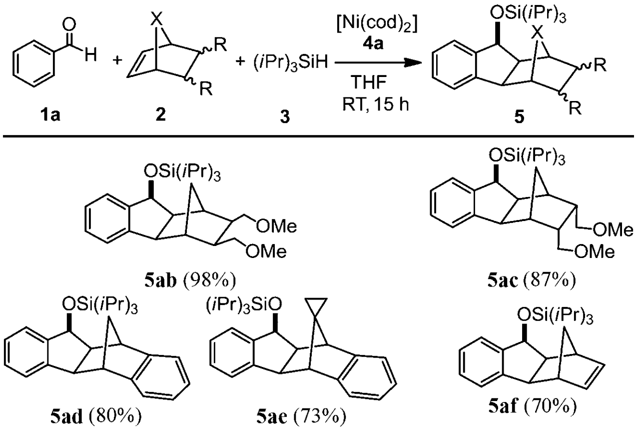
Table 2: Nickel-catalyzed three-component coupling between **1a–j**, **2a**, and **3**.[a]



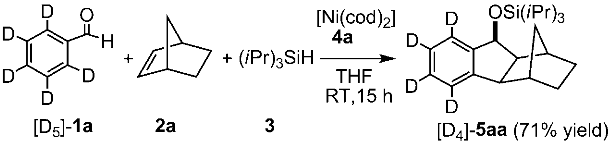
1 **2a** **3** **5**

Entry	Aldehyde		Product		Yield [%][b]
1	**1a**		**5aa**		82
2	**1b**		**5ba**		84
3[c]	**1c**		**5ca**		99
4[c]	**1d**		**5da**		51
5	**1e**		**5ea**		94
6	**1f**		**5fa**		73
7	**1g**		**5ga-A**		87[d]
			5ga-B		
8	**1h**		**5ha-A**		55[e]
			5ha-B		
9[f]	**1i**		**5ia**		33[g]
10[c]	**1j**		**5ja**		77

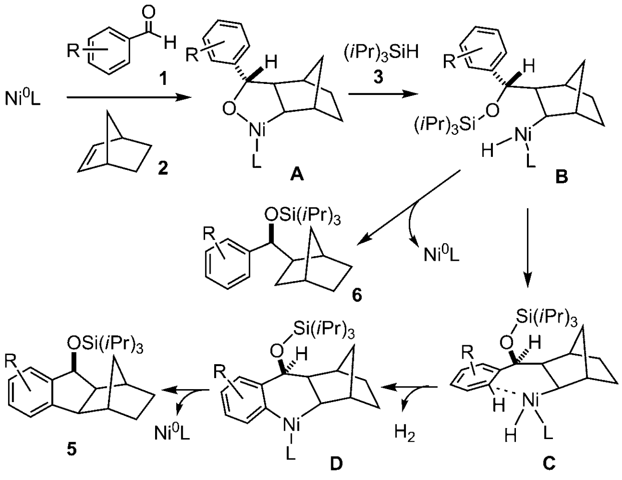
[a] Reaction conditions: [Ni(cod)$_2$] (0.10 mmol), **1** (1.0 mmol), **2a** (2.0 mmol), **3** (2.0 mmol), **4a** (1.0 mmol) and THF (3 mL) were employed. [b] Yield of isolated product. [c] [Ni(cod)$_2$] (0.20 mmol), **4a** (0.20 mmol). [d] **5ga-A**/**5ga-B** = 67:33 as determined by GC analysis. [e] **5ha-A**/**5ha-B** = 50:50 as determined by GC analysis. [f] (tBu)Me$_2$SiH was used in place of (iPr)$_3$SiH. [g] Yield determined by ^{1}H NMR spectroscopy.



Scheme 1. Nickel-catalyzed three-component coupling between **1a**, **2b–f**, and **3**. Reaction conditions: $[Ni(cod)_2]$ (0.10 mmol), **1a** (1.0 mmol), **2** (2.0 mmol), **3** (2.0 mmol), **4a** (0.10 mmol), and THF (3 mL) were employed. Yield of isolated product are in parentheses.

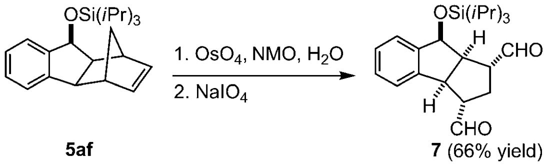
 (3)

A possible pathway for the three-component reaction is shown in Scheme 2. First, nickelacycle intermediate **A** is formed by the reaction of nickel(0) complex with aldehyde **1** and norbornene **2**. In this step, the phenyl group of the aldehyde may prefer to be located far from the methylene group of the norbornene unit to avoid steric hindrance. This is followed by σ-bond metathesis with silane, which proceeds to give intermediate **B**. When reductive elimination from **B** occurs, the normal reductive coupling product **6** is formed, as previously proposed in the reaction with alkynes.[2] Alternatively, σ-bond metathesis (C–H bond activation) can occur to generate H_2 and form intermediate **D**.[13] This C–H bond activation is probably assisted by the rigid cycloalkane structure around the *exo* position of the norbornane unit, and the orientation of the metal center close to an aromatic C–H bond.[14] Finally, reductive elimination from **D** occurs to afford the silylated indanol derivative **5**.



Scheme 2. Possible pathway for the three-component couplings.

As an example of a synthetic application, **5af** (which was produced by the reaction with norbornadiene) was subjected to oxidative cleavage of the carbon–carbon double bond [Eq. (4)]. The reaction with catalytic amounts of osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide (NMO), and subsequent treatment with $NaIO_4$, furnished diquinane compound **7**. The stereodefined diquinane compound is an important subunit of a variety of biologically interesting natural products.[15]

 (4)

In summary, we have demonstrated a diastereoselective three-component coupling reaction between aryl aldehydes, norbornenes (norobornadiene), and silanes leading to silylated indanol derivatives using a $[Ni(cod)_2]$/N-heterocyclic carbene catalyst system. This is the first example of a nickel-catalyzed reductive three-component reaction involving aromatic C–H bond activation of aryl aldehydes.

Experimental Section

Representative procedure (Table 2, entry 1): The mixture of $[Ni(cod)_2]$ (28 mg, 0.10 mmol), THF (3 mL), **4a** (49 mg, 0.10 mmol) was cooled to −78 °C, and *n*BuLi (1.67 M *n*-hexane solution, 60 μL, 0.10 mmol) was added dropwise before the cool bath was removed. After stirring for 10 min, triisopropylsilane **3** (0.41 mL, 2.0 mmol), benzaldehyde **1a** (0.10 mL, 1.0 mmol), and norbornene **2a** (188 mg, 2.0 mmol) were added. After stirring for 15 h at RT, the solution was filtered through small amounts of silica gel using ethyl acetate, and the solvent was removed using a rotary evaporator. The residue was purified by silica gel preparative TLC (eluent: *n*-hexane). Silylated indanol **5aa** (292 mg, 0.82 mmol, 82 %) was obtained as colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 0.89$ (d, $J = 8.2$ Hz, 1H, ethylene), 1.05 (m, 1H, ethylene), 1.1–1.4 (m, 24H, Si*i*Pr_3, ethylene), 1.5–1.6 (m, 2H, methylene), 2.24 (brs, 1H, bridgehead methine), 2.39 (t, $J = 7.9$ Hz, 1H, *endo* methine), 2.57 (brs, 1H, bridgehead methine), 3.05 (d, $J = 7.0$ Hz, 1H, *endo* methine), 5.55 (d, $J = 8.8$ Hz, 1H, CH-O), 7.2–7.3 (m, 3H, Ph), 7.34 ppm (m, 1H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 12.8$, (s, Si*i*Pr_3-CH), 18.3 (s, Si*i*Pr_3-CH_3), 28.4, 29.1, 33.6, 36.7, 42.5, 50.6, 53.7 (s, bicycle ring), 77.8 (s, CH-O), 124.2, 126.6, 127.9, 144.7, 146.7 ppm (s, Ph); HRMS (ESI) calcd for $C_{23}H_{36}OSi$ $[M+Na]^+$: 379.2428; found: 379.2430.

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Keywords: C–H activation · cycloalkenes · indanols · nickel · synthetic methods

[1] M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117.

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

[3] a) S.-S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2005**, *127*, 14194; b) C.-Y. Ho, T. F. Jamison, *Angew. Chem.* **2007**, *119*, 796; *Angew. Chem. Int. Ed.* **2007**, *46*, 782.

[4] a) R. Sawaki, Y. Sato, M. Mori, *Org. Lett.* **2004**, *6*, 1131; b) Y. Sato, Y. Hinata, R. Seki, Y. Oonishi, N. Saito, *Org. Lett.* **2007**, *9*, 5597.

[5] S.-S. Ng, T. F. Jamison, *J. Am. Chem. Soc.* **2005**, *127*, 7320.

[6] K. Ogata, Y. Atsuumi, S.-i. Fukuzawa, *Org. Lett.* **2010**, *12*, 4536.

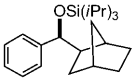
[7] Example of the catalytic synthesis of similar compounds bearing norbornane ring by the reaction using norbornene: a) R. C. Larock, Q. Tian, A. A. Pletnev, *J. Am. Chem. Soc.* **1999**, *121*, 3238; b) M. Lautens, J. Mancuso, *Org. Lett.* **2002**, *4*, 2105; c) T. Sugihara, T. Satoh, M. Miura, M. Nomura, *Adv. Synth. Catal.* **2004**, *346*, 1765; d) P. Shukla, C. H. Cheng, *Org. Lett.* **2006**, *8*, 2867; e) C. D. Smith, J. I. Gavrilyuk, A. J. Lough, R. A. Batey, *J. Org. Chem.* **2010**, *75*, 702.

[8] Transition-metal-catalyzed aromatic C–H bond activation and C–C bond formation reaction have become increasingly important in organic synthesis: a) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826; b) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731; c) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077; d) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013.

[9] CCDC 808019 (desilylated compound of **5aa**) 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.

[10] In this case, product **6aa** was also formed in 25% yield.

[11] In addition to the formation of **5ia**, small amounts of a **6aa**-type compound as shown in Ref. [10] were also formed in this reaction (**6ia**, 6% yield). Yields of these two compounds was determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard because it is difficult to separate these two compounds. Using triisopropylsilane resulted in lower yield of the corresponding three-component products (**5ia-TIPS**: 22% yield, **6ia-TIPS**: 5% yield).



6aa

[12] In this reaction, complex mixtures were formed.

[13] The production of H_2 gas was confirmed in this reaction, and in case of the reaction using **2b–e**, small amounts of hydrogenated norbornene derivatives were also confirmed in crude mixture by GC-MS analysis.

[14] We could not rule out the possibility of an *ortho* metalation mechanism through an nickel-oxygen atom coordinated intermediate. For an example of *ortho* C–H bond activation of a carbonyl compound through *ortho* metalation, see: Ref. [8].

[15] G. Mehta, A. Srikrishna, *Chem. Rev.* **1997**, *97*, 671.