Diastereoselective Coupling of 1,3-Diene, Ketone, and Organometallic Reagents by Nickel Catalyst: Stereoselective Construction of Tetrasubstituted Carbon Centers

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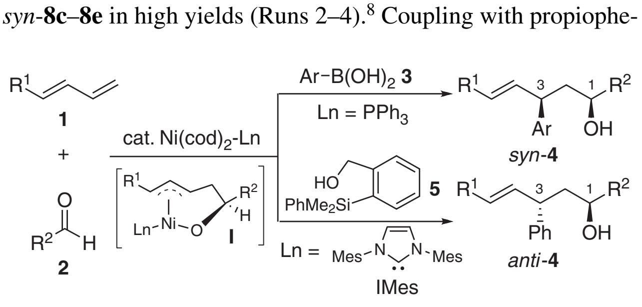
A nickel-catalyzed three-component coupling of 1,3-diene, ketone, and organoboron or organosilicon reagents was investigated. While the coupling reaction using $PhB(OH)_2$ afforded a 1,3-syn-substituted 4-penten-1-ol derivative as a single diastereomer, the reaction in the presence of tetraorganosilicon reagent under similar conditions exclusively produced the corresponding 1,3-anti isomer. In both reactions, a tetrasubstituted carbon center was constructed in a highly diastereoselective manner.

Multicomponent coupling reactions have attracted much attention as an efficient methodology in recent organic synthesis.[1] We have demonstrated a nickel-catalyzed multicomponent coupling of 1,3-dienes, aldehydes, and silane.[2–4] Recently, we also reported a diastereoselective coupling of 1,3-dienes, aldehydes, and organoboron or organosilicon reagents (Scheme 1).[5,6] That is, the coupling of **1** and **2** using organoboronic acid **3** gave *syn*-**4** diastereoselectively. On the other hand, the diastereoselectivity was changed in the reaction using organosilicon reagent **5** under similar conditions, producing the corresponding stereoisomer *anti*-**4**. In this context, we envisaged that if a ketone was used instead of aldehyde in this reaction, a coupling product having a tetrasubstituted carbon should be obtained. Furthermore, the stereochemistry at C1 and C3 positions would be controlled by the class of organometallic reagent.

According to previously optimized conditions,[5] diene **6** and acetophenone (**7a**) reacted with $PhB(OH)_2$ (**3**) in the presence of $Ni(cod)_2$ and PPh_3 in CPME (cyclopentyl methyl ether) at 50 °C for 75 h, giving the coupling product **8a** in 73% yield as a single diastereomer (Table 1, Run 1). As expected, the relative configurations of the hydroxy group at the C1 position and the phenyl group at the C3 position were determined to be 1,3-syn from a NOESY experiment of **9** derived from **8a**.[7] After screening ligands, it was found that $P(p\text{-tolyl})_3$ is suitable in this reaction, giving *syn*-**8a** in good yield (Run 4).



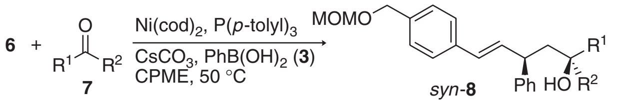
Scheme 1.

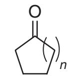
Table 1. Coupling reactions of **6**, **7a**, and **3** using various ligands[a]

Run	Ligand	Time/h	Yield of *syn*-**8a**/%
1	PPh_3	75	73
2	PPh_2Me	17	29
3	PCy_3	10	40
4	$P(p\text{-tolyl})_3$	20	79
5	$P(p\text{-MeOC}_6H_4)_3$	9	71

[a]Reaction conditions: **6** (1 equiv), **7a** (2 equiv), $Ni(cod)_2$ (10 mol %), ligand (10 mol %), $PhB(OH)_2$ (5 equiv), Cs_2CO_3 (3 equiv), CPME, 50 °C. [b]The ratio of syn isomer to anti isomer was >50 to 1.

Table 2. Coupling reactions of 1,3-diene **6** and various ketones **7**[a]



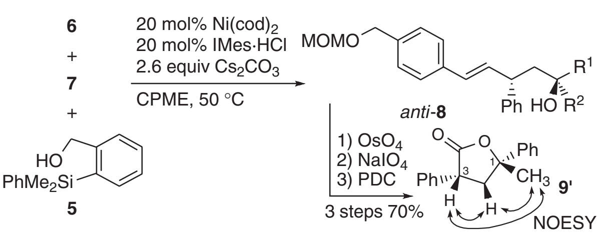
Run	Ketone **7**			Time/h	Yield of *syn*-**8**/%
		R^1 =	R^2 =		
1	**7b**	4-MeOC_6H_4	Me	15	**8b**: 25
2	**7c**	$4\text{-MeO}_2CC_6H_4$	Me	13	**8c**: 92
3	**7d**	F	Me	14	**8d**: 85
4	**7e**	CF_3	Me	13	**8e**: 89
5	**7f**	CF_3	Et	11	**8f**: 77
6	**7g**	*i*-Pr	Me	13	**8g**: 29
7	**7h**	*t*-Bu	Me	15	**8h**: 24
8	**7i**		$n = 1$	12	**8i**: 32
9	**7j**		$n = 2$	13	**8j**: 66
10	**7k**		$n = 3$	12	**8k**: 29

[a]Reaction conditions: diene **6** (1 equiv), ketone **7** (2 equiv), $Ni(cod)_2$ (10 mol %), $P(p\text{-tolyl})_3$ (10 mol %), $PhB(OH)_2$ (5 equiv), Cs_2CO_3 (3 equiv), CPME, 50 °C. [b]The ratio of syn isomer to anti isomer was >50 to 1.

Coupling reactions of **6** and various ketones **7** under optimal conditions were investigated (Table 2). While the reaction of **6** and **7b** with a methoxy group on the aromatic ring gave *syn*-**8b** in low yield, the reaction of **7c**–**7e** bearing an electron-withdrawing group on the aromatic ring afforded the corresponding *syn*-**8c**–**8e** in high yields (Runs 2–4).[8] Coupling with propiophenone derivative **7f** also proceeded diaseteoselectively to give the product **8f** in 77% yield (Run 5). Although aliphatic ketones **7g**–**7h** and cycloalkanones **7i**–**7k** were also applicable to this reaction, the yields of products **8g**–**8k** were moderate to low (Runs 6–10). On the other hand, the reaction of an internal diene (e.g. 1,4-diphenylbuta-1,3-diene) and acetophenone (**7a**) gave no coupling product and only starting diene was recovered, probably due to the steric repulsion.

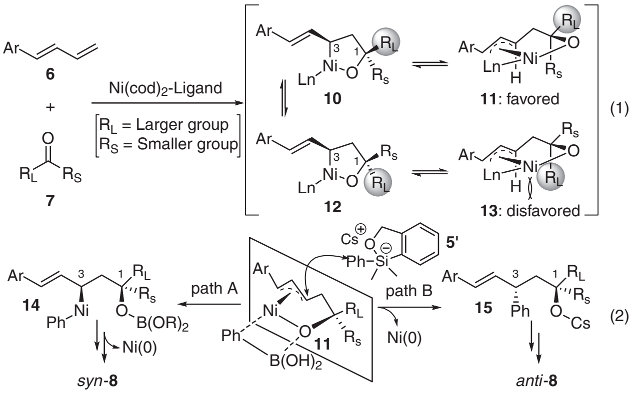
Next, we turned our attention to multicomponent coupling of 1,3-diene, ketone, and organosilicon reagent **5**[9] (Table 3). According to our previous protocol,[5] the reaction of **6**, **7**, and **5** was carried out in the presence of $Ni(cod)_2$, IMes•HCl, and Cs_2CO_3 in CPME at 50 °C. As a result, the coupling product *anti*-**8a** was obtained in 32% yield as a single diastereomer (Run 1), whose stereochemistry was determined from a NOESY experiment of

Table 3. Coupling reactions of 1,3-diene, ketone, and silicon reagent **5**[a]



Run	Ketone **7**	Time/h	Yield of *anti*-**8**/%[b]
1	**7a**	13	**8a** ($R^1 = C_6H_5$, R^2 = Me): 32
2	**7c**	24	**8c** (R^1 = 4-$MeO_2CC_6H_4$, R^2 = Me): 52
3	**7d**	48	**8d** (R^1 = 4-FC_6H_4, R^2 = Me): 26
4	**7j**	48	**8j** (R^1, R^2 = –$(CH_2)_5$–): 46

[a]Reaction conditions: diene **6** (1 equiv), ketone **7** (2 equiv), $Ni(cod)_2$ (20 mol %), IMes•HCl (10 mol %), **5** (1.1 equiv), Cs_2CO_3 (2.6 equiv), CPME, 50 °C. [b]The ratio of anti isomer to syn isomer was >50 to 1.



Scheme 2.

9′ in the same way as that of *syn*-**8a**. Reactions of **6** with ketones bearing an ester group (**8c**) or a fluoro group (**8d**) on the aromatic ring gave the corresponding products *anti*-**8c** and *anti*-**8d**, respectively (Runs 2 and 3). Cyclohexanone (**7j**) was applicable to coupling reaction using **5**, giving **8j** in 46% yield (Run 4).

A possible reaction mechanism is shown in Scheme 2. First, oxidative cycloaddition of diene **6** and ketone **7** to a Ni^0 complex occurs to give a nickelacycle **10** or **12**, and two diastereomers of π-allylnickel intermediate **11** and **13** would be formed through **10** and **12**, respectively.[10] It was thought that the complex **11** might be more stable than **13** because 1,3-diaxial interaction between a pseudo-axially oriented larger substituent (R_L) at C1 and a hydrogen atom at C3 in **13** is greater than that between a smaller substituent (R_s) and hydrogen atom in **11**. Therefore, the equilibrium between **11** and **13** would lie toward the intermediate **11**. In the reaction using $PhB(OH)_2$ (**3**), transmetallation between **3** and **11** proceeded to give intermediate **14**, and finally *syn*-**8** was obtained as a single diastereomer (eq 2, path A). On the other hand, when organosilicon reagent **5** was used, nucleophilic backside attack of the phenyl group of silicate **5′** generated from **5** and Cs_2CO_3[9] to **11** would occur, producing *anti*-**8** in a diastereoselective manner (path B).

In summary, we have demonstrated a diastereoselective three-component coupling of 1,3-diene, ketone, and organometallic reagent. The reaction using organoboronic acid provided 1,3-syn products exclusively. On the other hand, the use of a tetraorganosilicon reagent as a coupling partner provided the corresponding 1,3-anti isomers under similar conditions. In both reactions, a tetrasubstituted carbon center was constructed in a highly diastereoselective manner.

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