Synthesis of Stereodefined Enynes by the Nickel-Catalyzed Coupling Reaction of Alkynyltins, Alkynes, and Enones

Shin-ichi Ikeda and Yoshiro Sato*

Faculty of Pharmaceutical Sciences
Nagoya City University, Tanabe-dori
Mizuho-ku, Nagoya 467, Japan

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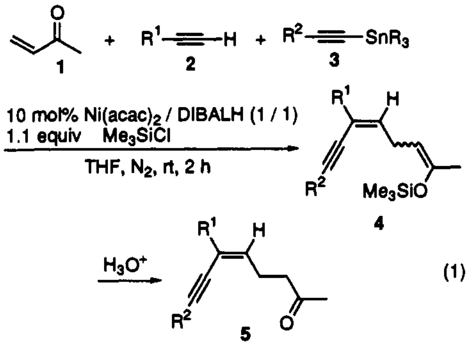
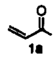
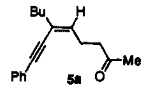
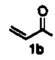
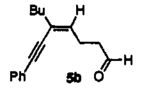
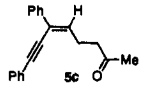
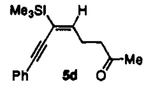
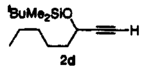
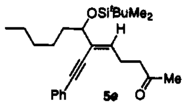
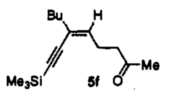
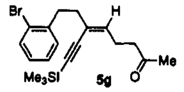
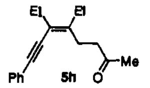
We report a nickel-catalyzed reaction with organotin reagents. Palladium-catalyzed coupling reaction of organotin reagents with organic electrophiles has been applied in organic synthesis as a versatile method for the formation of carbon-carbon bonds. Although comprehensive and intensive studies of the reaction have been reported,[1,2] it would seem that other transition-metal complexes have not been fully investigated for their catalytic activities. We have searched for another transition-metal-catalyzed reaction with the organotin reagents and have found that nickel complex catalyzed the reaction of alkynyltins with enones and alkynes, leading to stereodefined conjugated enynes (eq 1).[3]



(1)

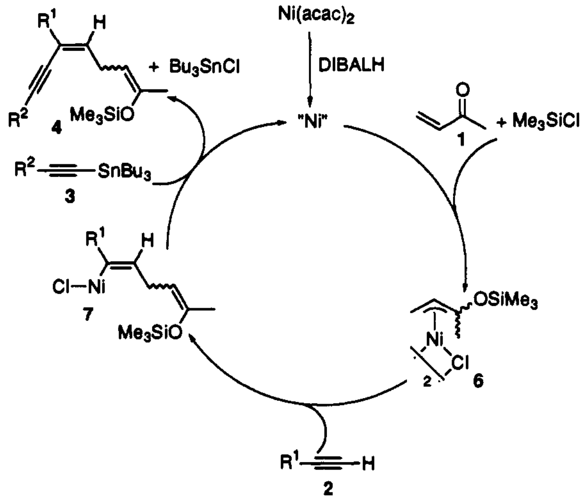
A typical procedure is as follows. To a THF solution of nickel catalyst prepared from 10 mol % Ni(acac)$_2$/DIBALH (1/1) were added 3-buten-2-one (**1a**) (1 equiv), 1-hexyne (**2a**) (1.2 equiv), (phenylethynyl)triethyltin (**3a**) (1.1 equiv), and Me$_3$SiCl (1.1 equiv). The reaction mixture was stirred at room temperature for 2 h under N$_2$ and then hydrolyzed by aqueous acid.[4] After removal of Et$_3$SnCl, which was formed through the coupling reaction, by aqueous NH$_4$F, the product **5a** was afforded in 80% yield by column chromatgraphy (silica gel).[5] The use of DMF or toluene solvent was less efficient than use of THF. When Me$_3$SiOTf or ^{t}BuMe$_2$SiCl instead of Me$_3$SiCl was added, the reaction hardly took place. The catalytic activities of some nickel complexes were investigated. Ni(acac)$_2$ in the absence of DIBALH and Ni(PPh$_3$)$_4$[6] led to lower yields of **5a** than did the Ni(acac)$_2$/DIBALH system (14% and 47% yields, respectively). Interestingly, the coupling reaction did not occur wwhen Pd(PPh$_3$)$_4$ or Pd$_2$(dba)$_3$ was used.

Table 1. Nickel-Catalyzed Coupling Reaction of Enones with Alkynes and Alkynyltins[a]

entry	enone	alkyne	alkynyltin	product[b]	yield, %[c]
1	 **1a**	Bu—≡—H **2a**	Ph—≡—SnEt$_3$ **3a**	 **5a**	80 (95)
2	**1a**	**2a**	Ph—≡—SnBu$_3$ **3b**		64 (95)
3	 **1b**	**2a**	**3a**	 **5b**	74 (95)
4	**1a**	Ph—≡—H **2b**	**3a**	 **5c**	52 (>98)
5	**1a**	Me$_3$Si—≡—H **2c**	**3a**	 **5d**	71 (>98)
6	**1a**	 **2d**	**3b**	 **5e**	31 (>98)
7	**1a**	**2a**	Me$_3$Si—≡—SnBu$_3$ **3c**	 **5f**	74 (96)
8	**1a**	o-BrC$_6$H$_4$CH$_2$CH$_2$—≡—H **2e**	**3c**	 **5g**	63 (92)
9	**1a**	Et—≡—Et **2f**	**3b**	 **5h**	58 (>98)

[a] Reaction conditions: enone (1 mmol), alkyne (1.2 mmol), alkynyltin (1.1 mmol), Me$_3$SiCl (1.1 mmol), Ni(acac)$_2$ (0.1 mmol), DIBALH (0.1 mmol), and THF (5 mL) at room temperature for 2 h under N$_2$. [b] Hydrolyzed product by aqueous acid. [c] Isolated yield. Isomeric purity is in parentheses.

Scheme 1



The results of the coupling reaction are summarized in Table 1.[7] It was noteworthy that the coupling reaction with a variety

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[1] Kosugi, M.; Migita, T. *J. Synth. Org. Chem. Jpn.* **1980**, *38*, 1142. Beletskaya, I. P. *J. Organomet. Chem.* **1983**, *250*, 551. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. Mitchell, T. N. *Synthesis* **1992**, 803.

[2] Recent papers: Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556. Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434. Ye, J.; Bhatt, R. K.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 1.

[3] Mackenzie and colleagues reported that Ni(cod)$_2$ catalyzed a conjugate addition of alkenyltins to enals, see: Grisso, B. A.; Johnson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160.

[4] The coupling product **4**, having enol silyl ether function, was moisture sensitive, so **4** was hydrolyzed by aqueous acid in the workup leading to the corresponding carbonyl compound **5**.

[5] The Ni-catalyzed reaction of **1a** (1 equiv) with **3a** (1.1 equiv) and Me$_3$SiCl (1.1 equiv) in the absence of **2a** gave **4c** (**5c**, 26% yield based on **1a** after hydrolysis), along with a trace amount of **2b**.

[6] For the preparation of Ni(PPh$_3$)$_4$ *in situ*, see: Negishi, E.; Baba, S. *J. Chem. Soc., Chem. Commun.* **1976**, 596.

[7] All new compounds were characterized by NMR, IR, and mass spectral data and by elemental analyses or high-resolution mass spectra. See supplementary material.

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of terminal alkynes **2a–e** proceeded regio- and stereoselectively to yield **5a–g** (entries 1–8). For example, the product **5d** (entry 5) was assigned to 8-phenyl-6-(trimethylsilyl)-5-octen-7-yn-2-one, not its regioisomer (i.e., 8-phenyl-5-(trimethylsilyl)-5-octen-7-yn-2-one), by the ^{1}H NMR spectral data. The double bond in **5d** was assigned *E* geometry by NOE experiment. The regio- and stereoselectivity of **5** are shown as isomeric purity. The *tert*-butyldimethylsiloxy group in **2d** (entry 6) and the bromine atom in **2e** (entry 8) remained intact in the reaction. The internal alkyne **2f** was applied to the coupling reaction (entry 9). The allyl- and vinyltins used in place of **3** did not react even under more forceful reaction conditions.[3]

The proposed reaction mechanism is shown in Scheme 1. In the catalytic events, [1-[(trimethylsilyl)oxy]allyl]nickel complex **6** would be generated from the reaction of nickel complex with **1** and Me_3SiCl.[8] Insertion of **2** into **6**, which would be the regio- and stereodetermining step, yields a vinylnickel complex **7**.[9] Transmetalation of **3** with **7** followed by reductive elimination gives the coupling product **4**, regenerating the nickel complex.[10,11]

In summary, we have described here an example of a new nickel-catalyzed reaction with organotin reagents.[3,12] The catalyst is easily prepared from inexpensive $Ni(acac)_2$ *in situ*. The present reaction provides a new synthetic method for the stereodefining conjugated enynes, which are important in the synthesis of a wide range of natural products, by multi-component coupling.[13] More detailed studies on the scope of the reaction are in progress.

Supplementary Material Available: Listing of experimental details and spectral and analytical data for the obtained products (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(8) Johnson, J. R.; Tully, P. S.; Mackenzie, P. B.; Sabat, M. *J. Am. Chem. Soc.* **1991**, *113*, 6172.

(9) Chiusoli, G. P.; Cassar, L. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 124. Chiusoli, G. P. *Pure Appl. Chem.* **1971**, *6*, 169. Chiusoli, G. P. *Acc. Chem. Res.* **1973**, *6*, 422. Casser, L.; Chiusoli, G. P.; Guerrieri, F. *Synthesis* **1973**, 509.

(10) Both Ni(I)/Ni(III) and Ni(0)/Ni(II) active catalyst systems have been proposed for related processes. For examples of Ni(I)/Ni(III) systems, see: Kochi, J. K. *Pure Appl. Chem.* **1980**, *52*, 571. Dayrit, F. M.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4466. Hegedus, L. S.; Thompson, D. H. P. *J. Am. Chem. Soc.* **1985**, *107*, 5663. For an example of Ni(0)/Ni(II) systems, see ref 3.

(11) The possibility that an alkynylstannylation of **3** to **2** is involved in the first step of the catalytic reaction was eliminated. Thus, no reaction of **2a** with **3b** in the presence of nickel catalyst occurred under the same reaction conditions.

(12) Ni-catalyzed coupling reaction of organic halides with tetramethyltin and carbon monoxide was reported, see: Tanaka, M. *Synthesis* **1981**, 47.

(13) For recent papers on the synthesis of conjugated enynes, see: Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1992**, *33*, 5363. Luo, F.-T.; Fwu, S.-L.; Huang, W.-S. *Tetrahedron Lett.* **1992**, *33*, 6839. Torii, S.; Okumoto, H.; Tadokoro, T.; Nishimura, A.; Rashid, M. A. *Tetrahedron Lett.* **1993**, *34*, 2139. Nuss, J. M.; Rennels, R. A.; Levine, B. H. *J. Am. Chem. Soc.* **1993**, *115*, 6991.