



Nickel-catalyzed [4 + 2] Cycloaddition of Styrenes with Arynes via 1:1 Cross-coupling : Synthesis of 9,10-Dihydrophenanthrenes

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Nickel-Catalyzed [4 + 2] Cycloaddition of Styrenes with Arynes via 1:1 Cross-Coupling: Synthesis of 9,10-Dihydrophenanthrenes

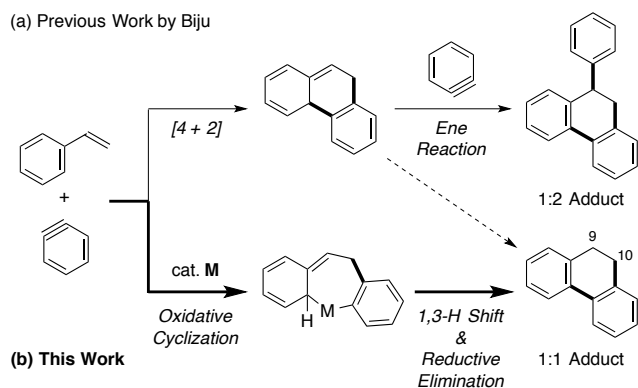
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The [4 + 2] cycloaddition of styrenes with arynes was achieved via 1:1 cross-coupling by a nickel catalyst. This protocol applies to a variety of styrenes and arynes generated *in situ* from *o*-(trimethylsilyl)aryl triflates to afford 9,10-dihydrophenanthrenes involving substituted aromatic rings. By using this method, a naturally occurring stilbenoid is easily synthesized.

Arynes are attractive intermediates in synthetic organic chemistry.¹ The strength of their application to organic synthesis is providing efficient routes for diverse and complex molecules, because their reactions enable forming two adjacent bonds in a one-pot operation, creating benzene-fused structures. Since Kobayashi and Sonoda developed a mild and convenient method for aryne generation using fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates,² aryne chemistry has drastically evolved. However, the high reactivities of arynes often cause introduction of multiple arynes.^{3,4} Recently, Biju and co-workers reported synthesis of 9-aryl-9,10-dihydrophenanthrenes via Diels–Alder [4 + 2] cycloaddition of styrenes with arynes, inevitably accompanied by the ene reaction with a second molecule of aryne (Scheme 1a).^{4b} In this reaction, only styrenes bearing an electron-withdrawing group (e.g., cyano, trifluoromethyl, and ester) at the 4-position provide the 1:1 cycloadducts, 9,10-dihydrophenanthrenes bearing no substituent at the 9 and 10-positions.^{5,6}



Scheme 1. Cycloaddition of styrenes and arynes.

To suppress multiple reactions, we assumed that transition metal catalysts can control the reactivity of arynes. When transition metal complexes are present, metal-mediated oxidative cyclization of styrenes with arynes proceeds as the initial step (Scheme 1b) instead of the Diels–Alder [4 + 2] cycloaddition.^{4–6} Subsequent 1,3-hydrogen shift followed by reductive elimination may afford 1:1 cycloadducts selectively. Based on this working hypothesis, we achieved an efficient nickel-catalyzed formal [4 + 2] cycloaddition of styrenes with arynes,⁷ enabling the synthesis

of 9,10-dihydrophenanthrenes involving unsubstituted 9- and 10-positions. The reactivity of arynes was adequately controlled using nickel, facilitating the one-to-one coupling of styrenes with arynes.

First, we investigated suitable conditions for nickel-catalyzed [4 + 2] cycloaddition using styrene (**1a**) and benzyne precursor **2a** as model compounds in 1,4-dioxane (Table 1). When **1a** was treated with **2a** and CsF as a fluoride source for generating benzyne without any metal catalysts, the [4 + 2] cycloadduct, 9,10-dihydrophenanthrene **3aa** was obtained in only 3% yield (Entry 1). Under these conditions, the addition of a catalytic amount of NiCl₂ afforded **3aa** in 34% yield along with the [2 + 2] cycloadduct **4aa**, whereas the 1:2 adduct, 9-phenyl-9,10-dihydrophenanthrene was completely absent (Entry 2). To improve the yield of **3aa**, ligands used for NiCl₂ were screened (Entries 3–7). Among the ligands examined, PCy₃ dramatically increased the yield of **3aa** (Entry 6). Due to screening of Ni sources, NiCl₂ was revealed as most efficient and selective (Entries 6, 8–12). Employing NiCl₂(PCy₃)₂ instead of NiCl₂ and PCy₃ separately, improved the yield of **3aa** up to 65% (Entry 13). Finally, increasing the amount of **2a** (1.5 equiv) afforded **3aa** in 76% yield (Entries 14).

Table 1. Screening of conditions for cycloaddition of **1a** with **2a**

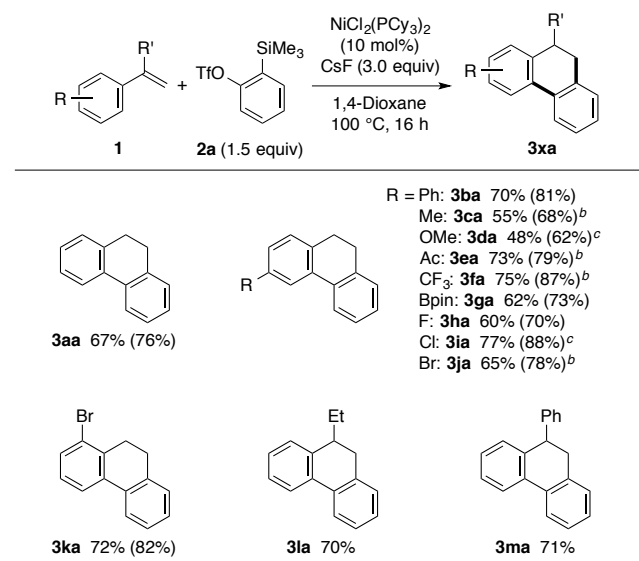
Entry	[Ni]	Ligand	3aa (%) ^a	4aa (%) ^a
1	–	–	3	N.D. ^b
2	NiCl ₂	–	34	3
3	NiCl ₂	PPh ₃	N.D. ^b	N.D. ^b
4	NiCl ₂	PMe ₃	46	7
5	NiCl ₂	P(<i>t</i> -Bu) ₃	56	8
6	NiCl ₂	PCy ₃	59	10
7 ^c	NiCl ₂	IPr·HCl	52	9
8	NiF ₂	PCy ₃	47	8
9	NiBr ₂	PCy ₃	55	9
10	Ni(OAc) ₂	PCy ₃	47	7
11	Ni(acac) ₂	PCy ₃	17	3
12	Ni(cod) ₂	PCy ₃	56	15
13	NiCl ₂ (PCy ₃) ₂	–	65	5
14 ^d	NiCl ₂ (PCy ₃) ₂	–	76	10

^a Yield was determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. ^b N.D. = Not detected. ^c IPr·HCl

(20 mol%) and K_2CO_3 (20 mol%) were used. ^d **2a** (1.5 equiv) and CsF (3.0 equiv) were used.

The scope of the reaction related to substituted styrenes **1** was explored under optimal conditions using **2a** (Table 2). Non-substituted and 4'-phenylated styrenes **1a** and **1b** underwent nickel-catalyzed [4 + 2] cycloaddition with **2a** to afford the corresponding 9,10-dihydrophenanthrenes **3aa** and **3ba** in isolated 67% and 70% yields, respectively, after purification by gel permeation chromatography (GPC). Reactions of styrenes **1c** and **1d** bearing electron-donating methyl and methoxy groups at the para positions proceeded fairly, whereas utilizing electron-withdrawing acetyl- and trifluoromethyl-bearing styrenes **1e** and **1f** produced rather high yields. Since boryl and halogen substituents like pinacolboryl, fluorine, chlorine, and bromine were tolerated under the reaction conditions, dihydrophenanthrenes **3ga–3ka** bearing boryl and halogen substituents on the benzene rings were synthesized in high yields. A sterically demanding bromine substituent at the ortho position caused no negative effect on the reaction. Cycloaddition of α -substituted styrenes were also investigated under the same conditions. The α -alkylated and α -arylated styrenes **1l** and **1m** were applicable to the reaction to afford dihydrophenanthrenes **3la** and **3ma**, respectively.

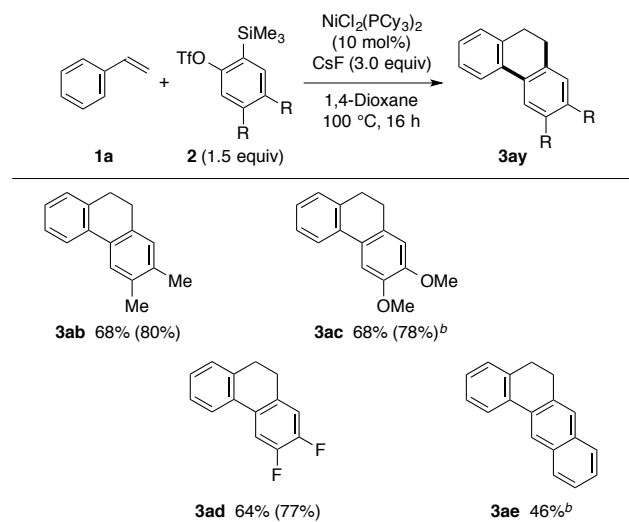
Table 2. Nickel-catalyzed [4 + 2] cycloaddition of substituted styrenes **1** with aryne precursor **2a**^a



^a Isolated yield after purification by preparative GPC. Yield determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard is given in parentheses. ^b **2a** (2.0 equiv) and CsF (4.0 equiv) were used. ^c $\text{NiCl}_2(\text{PCy}_3)_2$ (15 mol%) was used.

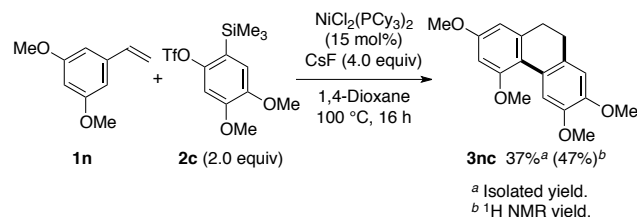
Substituted aryne precursors **2** were also examined in reactions using styrene (**1a**) under the optimal conditions (Table 3). Reactions of **1a** with aryne precursors **2b–2d** bearing two methyl, methoxy, and fluorine substituents proceeded to afford corresponding 2,3-disubstituted 9,10-dihydrophenanthrenes **3ab–3ad** in high yields. Aryne precursor **2e** with a naphthalene ring formed tetracyclic dihydrotetraphene **3ae** in 46% isolated yield.

Table 3. Nickel-catalyzed [4 + 2] cycloaddition of styrene (**1a**) with substituted aryne precursors **2**^a



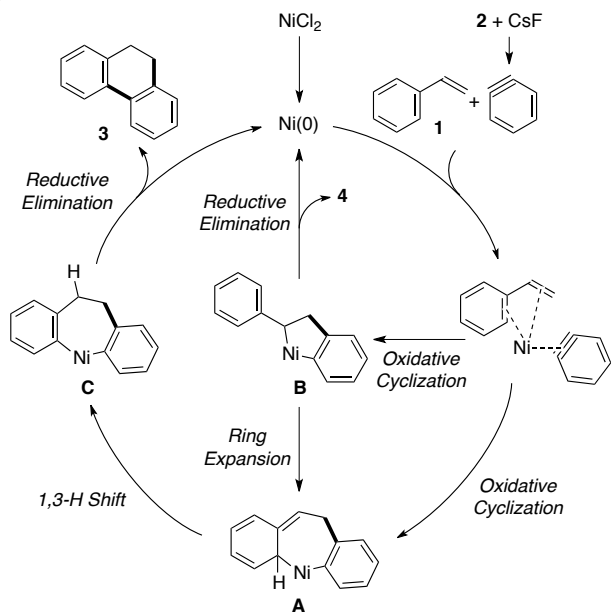
^a Isolated yield after purification by preparative GPC. Yield determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard is given in parentheses. ^b **2** (2.0 equiv) and CsF (4.0 equiv) were used.

This protocol was applied for the synthesis of a natural product. Callosumin (**3nc**),^{8,9} a naturally occurring stilbenoid¹⁰ was synthesized in 37% isolated yield via the nickel-catalyzed [4 + 2] cycloaddition using 3,5-dimethoxystyrene (**1n**) and aryne precursor **2c** (Scheme 2).



Scheme 2. Synthesis of callosumin (**3nc**).

Due to the formation of the [2 + 2] cycloadducts **4** and 9,10-dihydrophenanthrenes **3**, we propose the reaction mechanism in Scheme 3. The reaction begins with coordination of styrenes **1** and arynes generated from **2** to *in-situ* generated Ni(0) species.¹¹ Two ways exist for subsequent nickel-mediated oxidative cyclization between **1** and arynes to produce: (i) seven-membered nickelacycles **A** and (ii) five-membered nickelacycles **B**. Styrenes **1** react as 1,3-dienes via dearomatization to form **A**, whereas the vinylic moieties of **1** only are involved in the formation of **B**. We speculate that by-products **4** are formed via reductive elimination from **B**. In addition, nickelacycles **A** are formed even from **B** via ring expansion. Rearomatizing 1,3-hydrogen shift in **A** followed by reductive elimination affords 9,10-dihydrophenanthrenes **3** along with catalytically active Ni(0) species.



Scheme 3. Plausible reaction mechanism.

In summary, nickel-catalyzed [4 + 2] cycloaddition of styrenes with aryne in a 1:1 ratio was accomplished. Consequently, we controlled the reactivity of aryne using a nickel catalyst. Although 9,10-dihydrophenanthrenes with no substituent at the 9- or 10-positions are vital as naturally occurring stilbenoids in pharmaceutical and agrochemical sciences, conventional approaches for their production often exhibit poor efficiency/selectivity¹² or narrow substrate scope.¹³ These limitations were eliminated in this study by introducing an efficient method for the synthesis of 9,10-dihydrophenanthrenes.

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Supporting Information is also available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.

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