

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

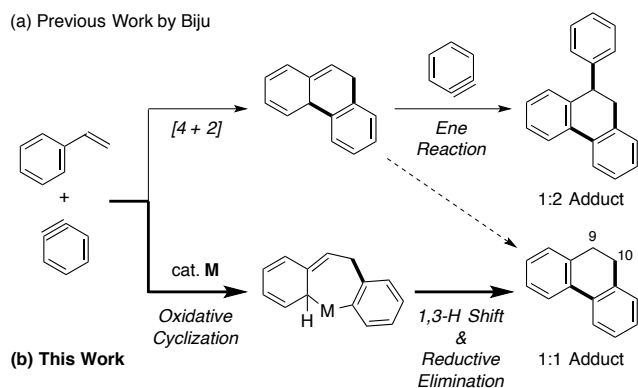
Teruhiko Kubo, Takeshi Fujita, and Junji Ichikawa*

Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8571

(Received <Month> <Date>, <Year>; CL-<No>; E-mail: <insert corresponding e-mail address>)

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 arynes generation using fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates,² arynes 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 arynes (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**

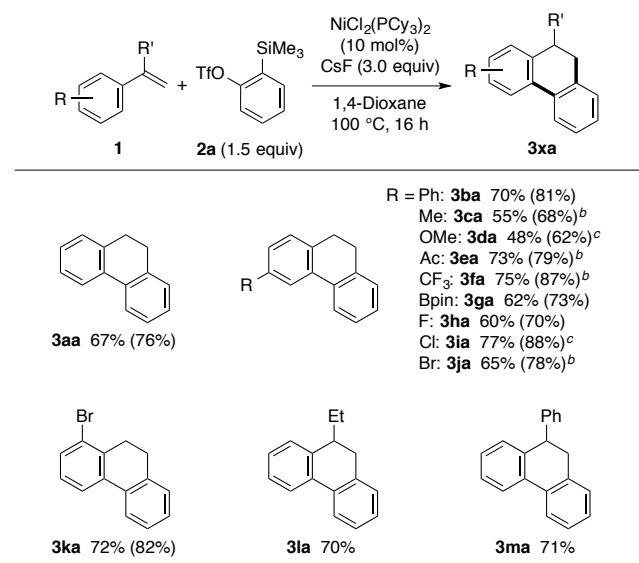
Entry	[Ni]	Ligand	3aa (%) ^a	4aa (%) ^a
1	–	–	3	N.D. ^b
2	NiCl ₂	–	34	3
3	NiCl ₂	PPh ₃	N.D. ^b	N.D. ^b
4	NiCl ₂	PMe ₃	46	7
5	NiCl ₂	P(<i>t</i> -Bu) ₃	56	8
6	NiCl ₂	PCy ₃	59	10
7 ^c	NiCl ₂	IPr·HCl	52	9
8	NiF ₂	PCy ₃	47	8
9	NiBr ₂	PCy ₃	55	9
10	Ni(OAc) ₂	PCy ₃	47	7
11	Ni(acac) ₂	PCy ₃	17	3
12	Ni(cod) ₂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

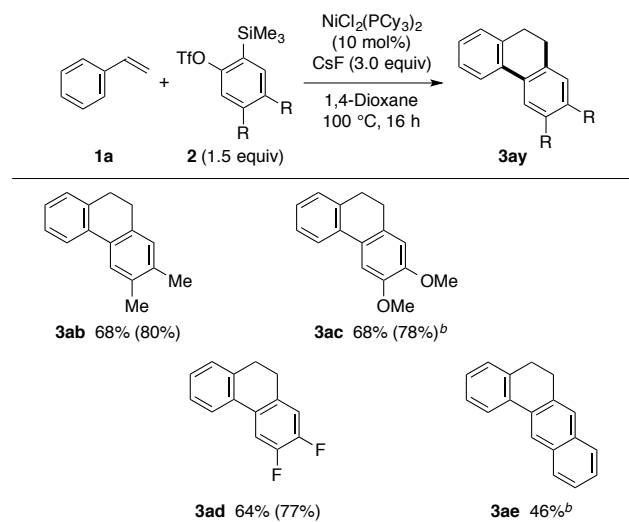
Table 2. Nickel-catalyzed [4 + 2] cycloaddition of substituted styrenes **1** with aryne precursor **2a**^a



^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.

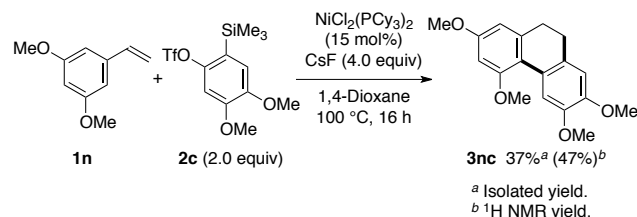
Substituted aryne precursors **2** were also examined in reactions using styrene (**1a**) under the optimal conditions (Table 3). Reactions of **1a** with aryne precursors **2b–2d** bearing two methyl, methoxy, and fluorine substituents proceeded to afford corresponding 2,3-disubstituted 9,10-dihydrophenanthrenes **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



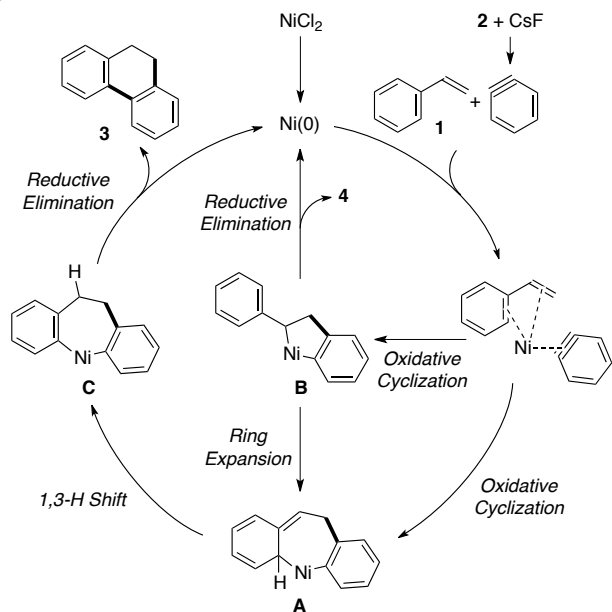
^a Isolated yield after purification by preparative GPC. Yield determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard is given in parentheses. ^b **2** (2.0 equiv) and CsF (4.0 equiv) were used.

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 arynes in a 1:1 ratio was accomplished. Consequently, we controlled the reactivity of arynes 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.

This work was financially supported by JSPS KAKENHI Grant Number JP19H02707 (J.I.) in Grant-in-Aid for Scientific Research (B), JSPS KAKENHI Grant Number JP18H04234 (J.I.) in Precisely Designed Catalysts with Customized Scaffolding, and JSPS KAKENHI Grant Number JP18K05116 (T.F.) in Grant-in-Aid for Scientific Research (C).

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

References and Notes

- For recent reviews on arynes, see: a) S. Yoshida, T. Hosoya, *Chem. Lett.* **2015**, *44*, 1450–1460. b) R. Karmakar, D. Lee, *Chem. Soc. Rev.* **2016**, *45*, 4459–4470. c) Y. Zeng, J. Hu, *Synthesis* **2016**, *48*, 2137–2150. d) S. S. Bhojgude, A. Bhunia, A. T. Biju, *Acc. Chem. Res.* **2016**, *49*, 1658–1670. e) J.-A. Garcia-López, M. F. Greaney, *Chem. Soc. Rev.* **2016**, *45*, 6766–6798. f) J. Shi, Y. Li, Y. Li, *Chem. Soc. Rev.* **2017**, *46*, 1707–1719. g) F. I. M. Idiris, C. R. Jones, *Org. Biomol. Chem.* **2017**, *15*, 9044. h) R. A. Dhokale, S. B. Mhaske, *Synthesis* **2018**, *50*, 1–16. i) T. Roy, A. T. Biju, *Chem. Commun.* **2018**, *54*, 2580–2594. j) A. Yoshimura, A. Saito, V. V. Zhdankin, *Chem. Eur. J.* **2018**, *24*, 15156–15166. k) H. Takikawa, A. Nishii, T. Sakai, K. Suzuki, *Chem. Soc. Rev.* **2018**, *47*, 8030–8056.
- Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.* **1983**, *12*, 1211–1214.
- a) J. M. Brinkley, L. Friedman, *Tetrahedron Lett.* **1972**, *13*, 4141. b) I. Tabushi, H. Yamada, Z. Yoshida, R. Oda, *Bull. Chem. Soc. Jpn.* **1977**, *50*, 285–290. c) J.-C. Hsieh, D. K. Rayabarapu, C.-H. Cheng, *Chem. Commun.* **2004**, 532–533. d) I. Quintana, A. J.

- Boersma, D. Peña, D. Pérez, E. Guitián, *Org. Lett.* **2006**, *8*, 3347–3349. e) H. Yoshida, T. Morishita, H. Nakata, J. Ohshita, *Org. Lett.* **2009**, *11*, 373–376. f) N. Saito, K. Shiotani, A. Kimbara, Y. Sato, *Chem. Commun.* **2009**, 4284–4286. g) T. Morishita, H. Yoshida, J. Ohshita, *Chem. Commun.* **2010**, *46*, 640–642. h) M.-J. Oliva-Madrid, I. Saura-Llamas, D. Bautista, J. Vicente, *Chem. Commun.* **2013**, *49*, 7997–7999. i) K. Neog, D. Dutta, B. Das, P. Gogoi, *Org. Lett.* **2017**, *19*, 730–733.
- a) W. L. Dilling, *Tetrahedron Lett.* **1966**, *9*, 939–941. b) S. S. Bhojgude, A. Bhunia, R. G. Gonnade, A. T. Biju, *Org. Lett.* **2014**, *16*, 676–679. c) Z. Chen, X. Han, J.-H. Liang, J. Yin, G.-A. Yu, S.-H. Liu, *Chin. Chem. Lett.* **2014**, *25*, 1535–1539.
- For an intramolecular reaction, see: J. C. Estévez, R. J. Estévez, L. Castedo, *Tetrahedron Lett.* **1992**, *33*, 6883–6884.
- An intermolecular reaction with a 1,4-benzodiyne precursor in a 1:1 manner was achieved albeit with low efficiency. See: I. Pozo, Z. Majzik, N. Pavlicek, M. Melle-Franco, E. Guitián, D. Peña, L. Gross, D. Pérez, *J. Am. Chem. Soc.* **2019**, *141*, 15488–15493.
- For selected reports on nickel-catalyzed cyclization with arynes, see: a) J.-C. Hsieh, C.-H. Cheng, *Chem. Commun.* **2005**, 2459–2461. b) J.-C. Hsieh, C.-H. Cheng, *Chem. Commun.* **2008**, 2992–2994. c) N. Saito, K. Shiotani, A. Kimbara, Y. Sato, *Chem. Commun.* **2009**, 4284–4286. d) Z. Qiu, Z. Xie, *Angew. Chem. Int. Ed.* **2009**, *48*, 5729–5732. e) D. A. Candito, M. Lautens, *Synlett* **2011**, 1987–1992. f) V. H. Thorat, N. S. Upadhyay, M. Murakami, C.-H. Cheng, *Adv. Synth. Catal.* **2018**, *360*, 284–289.
- For the synthesis of callosumin, see: R. M. Letcher, L. R. M. Nhamo, *J. Chem. Soc. C* **1971**, 3070–3076.
- For the isolation of callosumin from plants, see: a) P. L. Majumder, S. Banerjee, S. Sen, *Phytochemistry* **1996**, *42*, 847–852. b) H. Anton, L. Kraut, R. Mues, M. I. Morales Z. *Phytochemistry* **1997**, *46*, 1069–1075. c) P. L. Majumder, S. Majumder, S. Sen, *Phytochemistry* **2003**, *62*, 591–596.
- For selected reviews on stilbenoids, see: a) I. J. Flores-Sanchez, R. Verpoorte, *Phytochem. Rev.* **2008**, *7*, 615–639. b) T. Shen, X.-N. Wang, H.-X. Lou, *Nat. Prod. Rep.* **2009**, *26*, 916–935. c) C. Rivière, A. D. Pawlus, J.-M. Mérillon, *Nat. Prod. Rep.* **2012**, *29*, 1317–1333. d) M. Dvorakova, P. Landa, *Pharmacol. Res.* **2017**, *124*, 126–145. e) B. C. Akinwumi, K.-A. M. Bordun, H. D. Anderson, *Int. J. Mol. Sci.* **2018**, *19*, 792.
- A similar method for aryne generation can generate low-valent active Pd species from high-valent complexes even under reductant-free conditions. See: M. Feng, B. Tang, N. Wang, H.-X. Xu, X. Jiang, *Angew. Chem. Int. Ed.* **2015**, *54*, 14960–14964.
- For recent reports via reduction, see: a) E. Schachtl, J. S. Yoo, O. Y. Gutiérrez, F. Studt, J. A. Lercher, *J. Catal.* **2017**, *352*, 171–181. b) A. J. Smith, A. Young, S. Rohrbach, E. F. O'Connor, M. Allison, H.-S. Wang, D. L. Poole, T. Tuttle, J. A. Murphy, *Angew. Chem. Int. Ed.* **2017**, *56*, 13747–13751. c) W. Luo, H. Shi, E. Schachtl, O. Y. Gutiérrez, J. A. Lercher, *Angew. Chem. Int. Ed.* **2018**, *57*, 14555–14559.
- For recent reports via dimerization, see: a) D. Toummini, F. Ouazzani, M. Taillefer, *Org. Lett.* **2013**, *15*, 4690–4693. b) G. Revol, T. McCallum, M. Morin, F. Gagosz, L. Barriault, *Angew. Chem. Int. Ed.* **2013**, *52*, 13342–13345. c) Y. Liu, J. Bergès, Y. Zaid, F. O. Chahdi, A. Van Der Lee, D. Harakat, E. Clot, F. Jaroschik, M. Taillefer, *J. Org. Chem.* **2019**, *84*, 4413–4420

NOTE The diagram is acceptable in a colored form. Publication of the colored G.A. is free of charge. For publication, electronic data of the colored G.A. should be submitted. Preferred data format is EPS, PS, CDX, PPT, and TIFF. If the data of your G.A. is "bit-mapped image" data (not "vector data"), note that its print-resolution should be 300 dpi.

