

Nickel-catalyzed [2 + 2 + 2] cycloaddition of arynes and an unactivated alkene: synthesis of 9,10-dihydrophenanthrene derivatives†

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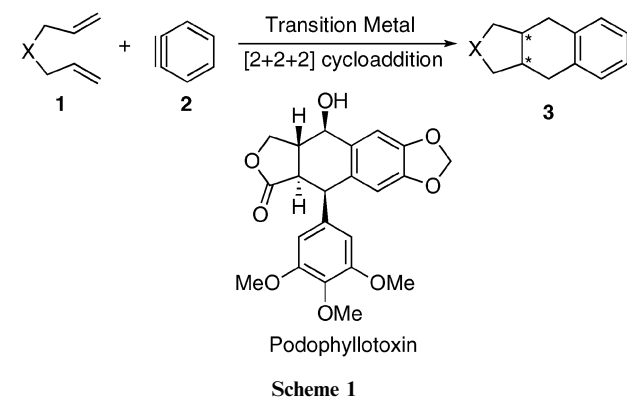
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A nickel-catalyzed [2 + 2 + 2] cycloaddition of two molecules of aryne and an alkene moiety in a α,ω -diene afforded 9,10-dihydrophenanthrene derivatives in good yields.

A transition metal-catalyzed [2 + 2 + 2] cycloaddition of multiple bonds has been an atom-economical and useful methodology for the synthesis of polycyclic compounds.¹ Since the first report on triphenylene synthesis *via* palladium-catalyzed [2 + 2 + 2] cyclotrimerization of benzyne in 1998,^{2a} arynes have been utilized in transition-metal catalyzed [2 + 2 + 2] cycloadditions as coupling partners.^{2–5} Recently, we have reported a palladium-catalyzed [2 + 2 + 2] cycloaddition of α,ω -diyne and arynes and its application to the synthesis of aryl naphthalene lignans, Taiwanins C and E, and dehydrodesoxypodophyllotoxin.⁶

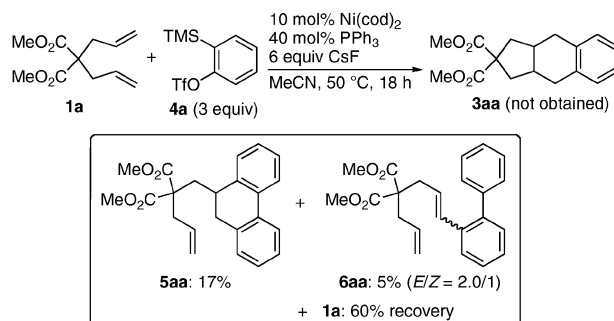
In this context, we envisaged that if a transition metal-catalyzed [2 + 2 + 2] cycloaddition of an α,ω -diene and aryne could proceed, a 1,2,3,4-tetrahydronaphthalene skeleton, which is one of the important frameworks found in a variety of biologically active natural products such as podophyllotoxin, could be efficiently constructed (Scheme 1).⁷

To examine the feasibility of the above plan, the reaction of a diene **1a** and benzyne, which was generated from the precursor **4a** and CsF,⁸ in the presence of 10 mol% of Ni(cod)₂ and 40 mol% of PPh₃ was carried out in MeCN at 50 °C (Scheme 2). The expected product **3aa** was not obtained, but a 9,10-dihydrophenanthrene derivative **5aa** was produced in 17% yield along with a diene having a biphenyl moiety **6aa** in 5% yield. The results suggested that **5aa** is formed by [2 + 2 + 2] cycloaddition of two molecules of benzyne and an alkene part in the diene **1a**.



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Scheme 2

To date, there have been only two examples in the literature of [2 + 2 + 2] cycloaddition of two arynes and one alkene catalyzed by a nickel or palladium complex.⁹ It was stated in both reports that only activated alkenes such as strained bicyclic alkenes^{9a} or alkenes having an electron-withdrawing group on the sp² carbon^{9b} are suitable for the cycloaddition with an aryne. Thus, the [2 + 2 + 2] cycloaddition of arynes and an unactivated alkene as shown in Scheme 2 has not been demonstrated previously. This unprecedented result prompted us to investigate the nickel-catalyzed [2 + 2 + 2] cycloaddition of unactivated alkenes and arynes.

First, we examined the reaction of **1a** and **4a** using various ligands in the presence of Ni(cod)₂ and CsF in MeCN (Table 1). When 40 mol% of P(*p*-tol)₃ was used instead of

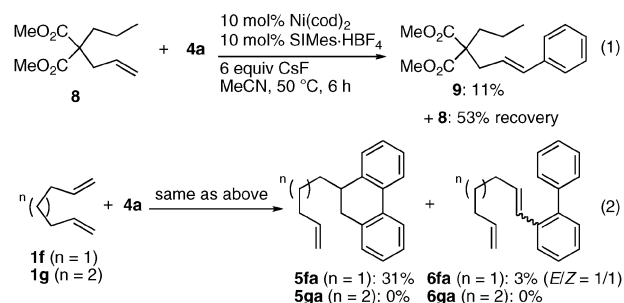
Table 1 Optimization of reaction conditions of [2 + 2 + 2] cycloaddition of diene **1a** and benzyne

Entry	Ligand (x mol%)	Time/h	Yield (%) ^a		
			5aa	E-6aa	Z-6aa
1	P(<i>p</i> -tol) ₃ (40)	24	24	7	2
2	P(<i>o</i> -tol) ₃ (40)	18	54	13	5
3	P(<i>o</i> -tol) ₃ (20)	4	70	11	5
4	IMes-HCl (10)	4	67	9	6
5	SIMes-HBF ₄ (10)	2	77 (71) ^b	11 (9) ^{bc}	5 (4) ^{bc}

^a Yields were determined by ¹H NMR analysis of the mixture of **5aa** and **6aa**. ^b Yields in parentheses are isolated yields. ^c The yields of *E*- and *Z*-**6aa** were determined by ¹H NMR analysis of the mixture of *E*- and *Z*-**6aa**.

PPh₃, the phenanthrene derivative **5aa** and diene (*E/Z*)-**6aa** were obtained in 24% yield and 9% yield, respectively (entry 1). On the other hand, the cycloaddition in the presence of P(*o*-tol)₃ as a ligand improved the yield of **5aa** to 54%, and diene (*E/Z*)-**6aa** was also obtained in 18% yield (entry 2). Interestingly, decreasing the loading of P(*o*-tol)₃ to 20 mol% accelerated the cycloaddition, and the starting diene **1a** was consumed within 4 h, giving **5aa** and (*E/Z*)-**6aa** in 70% yield and 16% yield, respectively (entry 3). From these results, it was thought that a bulky and electron-sufficient ligand is suitable for the cycloaddition. After screening such ligands, *N*-heterocyclic carbene (NHC) was found to be good ligand for the [2 + 2 + 2] cycloaddition (entries 4 and 5). The reaction using SIMes as a ligand gave dihydrophenanthrene derivative **5aa** in 77% yield (isolated yield of 71%) and 16% yield (isolated yield of 13%), respectively (entry 5).

Next, the [2 + 2 + 2] cycloaddition of various dienes and arynes under optimal conditions was investigated (Table 2). The reaction of **1b**, having a cyclic acetal moiety, and **4a** gave **5ba** and (*E/Z*)-**6ba** in 36% yield and 12% yield, respectively (entry 1). Dienes having a heteroatom in a chain **1c** and **1d** were also applicable to the cycloaddition, and the corresponding **5ca** or **5da** and **6ca** or **6da** were produced in slightly moderate yields (entries 2 and 3, respectively). Interestingly, when an unsymmetrical diene **1e** was used as a coupling partner of **4a**, the cycloaddition proceeded chemoselectively to give the phenanthrene derivative **5ea** and diene **6ea**, which were obtained by the reaction of a less-hindered allyl group and benzyne (entry 4). The reaction of **1a** and substituted arynes precursors **4b** and **4c** also proceeded smoothly to afford the



Scheme 3

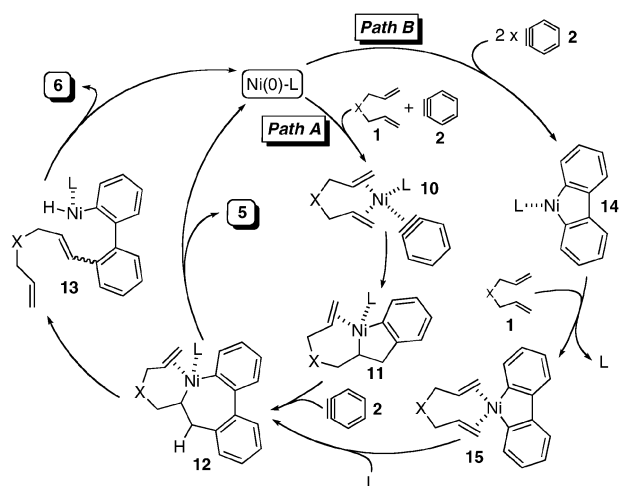
phenanthrene derivatives **5ab** or **5ac** and dienes **6ab** or **6ac**, respectively (entries 5 and 6).

Next, we investigated the reaction of a mono-alkene **8** with **4a** instead of diene **1** (Scheme 3, eqn (1)). The [2 + 2 + 2] cycloaddition of **8** did not proceed, and only **9** was obtained in 11% yield along with recovered **8** in 53% yield. This result strongly suggested that the unreacted alkene part in the diene **1** is necessary for the [2 + 2 + 2] cycloaddition. Thus, we examined the chain length between two alkene parts in the diene (eqn (2)). When 1,6-heptadiene (**1f**) was used as a coupling partner, the [2 + 2 + 2] cycloaddition proceeded to give the phenanthrene derivative **5fa** in 31% yield along with diene having a biphenyl part **6fa** in 3% yield. On the other hand, no significant products were obtained when 1,7-octadiene (**1g**) was used as a substrate. From these results, it was thought that the positional relationship of the two alkene parts in the diene also affects the co-trimerization of alkene and two arynes.

Table 2 Reactions of various dienes and arynes^a

Entry	Diene 1	Aryne precursor 4	Yields ^b	
			5	6 (<i>E/Z</i>) ^c
1		4a		5ba : 36% 6ba : 12% (1/99)
2	1c (X = NTs)	4a	5ca : 25%	6ca : 12% (1.5/1)
3	1d (X = O)	4a	5da : 25%	6da : 9% (1.3/1)
4		4a		5ea : 46% 6ea : 7% (3.0/1)
5	1a	4b (R = OMe)		5ab : 68% 6ab : 14% (2.5/1)
6	1a	4c (R = -OCH ₂ O-)		5ac : 57% 6ac : 21% (2.6/1)

^a Reaction conditions: diene **1** (1 equiv.), **4** (3 equiv.), Ni(cod)₂ (10 mol%), SIMes-HBF₄ (10 mol%), CsF (6 equiv.), MeCN, 50 °C. Reaction time: 4 h (entries 1–5) or 2 h (entry 6). ^b Isolated yield. ^c The ratio of *E*- and *Z*-**6** was determined by ¹H NMR analysis of the mixture of *E*- and *Z*-**6**.



Scheme 4

Based on the above results, we propose a possible mechanism of the $[2 + 2 + 2]$ cycloaddition of alkene and benzyne as shown in Scheme 4. First, coordination of two alkene parts of **1** and a triple bond of benzyne (**2**) to nickel(0) complex gave π -complex **10**, from which oxidative cycloaddition of one alkene part and benzyne would proceed to afford nickelacycle **11** (Path A). It was thought that stabilization of complex **11** by coordination of tethered alkene to the nickel(II) center is the driving force for progress of oxidative cycloaddition from **10**. Then insertion of another benzyne into the nickel-carbon bond of **11** would afford seven-membered nickelacycle **12**. Finally, reductive elimination of the nickel complex from **12** would proceed to give the phenanthrene derivative **5**. On the other hand, β -elimination from **12** (depicted as **13**) followed by reductive elimination would produce diene having a biphenyl part **6**. Because a small amount of triphenylene formed by co-trimerization of three molecules of benzyne (**2**) was obtained in some cases (data not shown), an alternative pathway that involves the formation of nickelacycle **14** by oxidative cycloaddition of two benzyne to nickel(0) is also possible (Path B). In this pathway, the intermediate **15** would be formed from the coordinately unsaturated nickelacycle **14** and diene **1** accompanied by ligand (L) dissociation. Then insertion of alkene into the nickel-carbon bond and re-coordination of the ligand would occur to produce the seven-membered nickelacycle **12**. Although the detailed mechanism is still not clear, the $[2 + 2 + 2]$ cycloaddition might proceed through both reaction pathways.¹⁰

In summary, during the course of our study on the $[2 + 2 + 2]$ cycloaddition of α,ω -dienes and arynes, we found a novel nickel-catalyzed $[2 + 2 + 2]$ cycloaddition of one unactivated alkene and two arynes, giving 9,10-dihydrophenanthrene derivatives in good yields. Moreover, it was suggested that the unreacted tethered alkene played an important role in the progress of the co-trimerization of substrates.¹¹ Further studies along this line are in progress.

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