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Citation	Chemical Communications, 2009(28), 4284-4286 https://doi.org/10.1039/b907476g
Issue Date	2009-07-28
Doc URL	https://hdl.handle.net/2115/43287
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Type	journal article
File Information	CC28_4284-4286.pdf



Nickel-Catalyzed [2+2+2] Cycloaddition of Aryne and Unactivated Alkene: Synthesis of 9,10-Dihydrophenanthrene Derivatives

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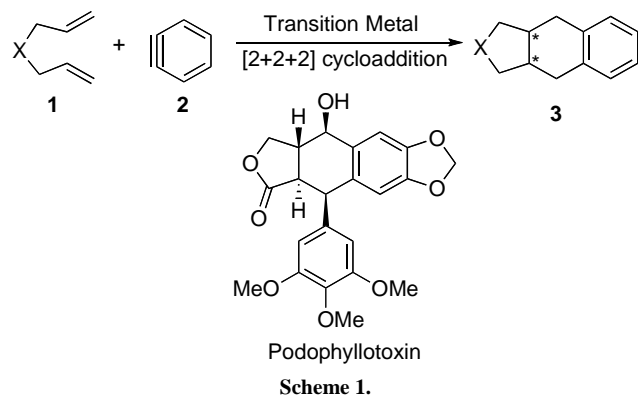
Received (in XXX, XXX) 1st January 2007, Accepted 1st January 2007

First published on the web 1st January 2007

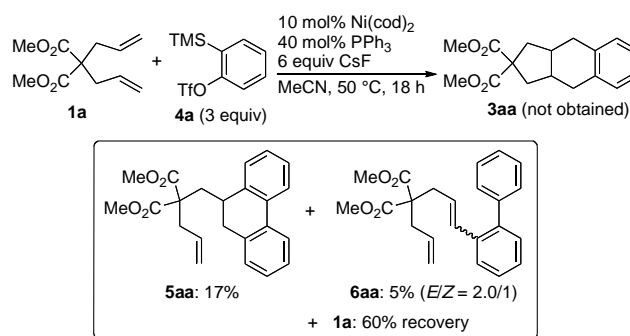
DOI: 10.1039/b000000x

A nickel-catalyzed [2+2+2] cycloaddition of two molecules of aryne and an alkene moiety in 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] cyclootrimerization 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 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



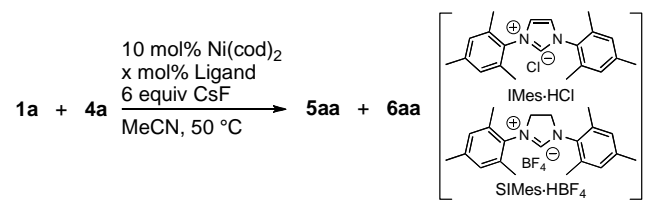
To examine the feasibility of the above plan, the reaction of a diene **1a** and benzyne, which was generated from the precursor **4a** and CsF,⁸ in the presence of 10 mol% of Ni(cod)₂ and 40 mol% of PPh₃ was carried out in MeCN at 50 °C (Scheme 2). The expected product **3aa** was not obtained, but 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**.



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 *sp*² carbon^{9b} are applicable to the cycloaddition with aryne. Thus, the [2+2+2] cycloaddition of arynes and an unactivated alkene as shown in Scheme 2 has not been demonstrated so far. 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*-tolyl)₃ was used instead of 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*-tolyl)₃ as a ligand improved the yield of **5aa** to 53%, and diene (*E/Z*)-**6aa** was also obtained in 18% yield (entry 2). Interestingly, decreasing the loading of P(*o*-tolyl)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).

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



entry	ligand (xmol%)	time (h)	yield (%) ^a		
			5aa	<i>E</i> - 6aa	<i>Z</i> - 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) ^{b,c}	5 (4) ^{b,c}

^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**.

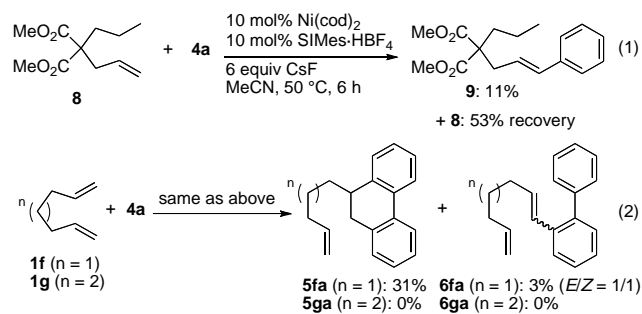
Next, the [2+2+2] cycloadditions of various dienes and arynes under optimal conditions were investigated (Table 2). The reaction of **1b** having a cyclic acetal moiety and **4a** gave **5ba** and (*E/Z*)-**6ba** in 36% yield and 12% yield, respectively (entry 1). Dienes having a heteroatom in a chain **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, respectively (entries 2 and 3). 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 aryne precursors **4b** and **4c** also proceeded smoothly to afford the phenanthrene derivatives **5ab** or **5ac** and dienes **6ab** or **6ac**, respectively (entries 5 and 6).

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	1b (X =)	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	1e (E = CO ₂ Me)	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)

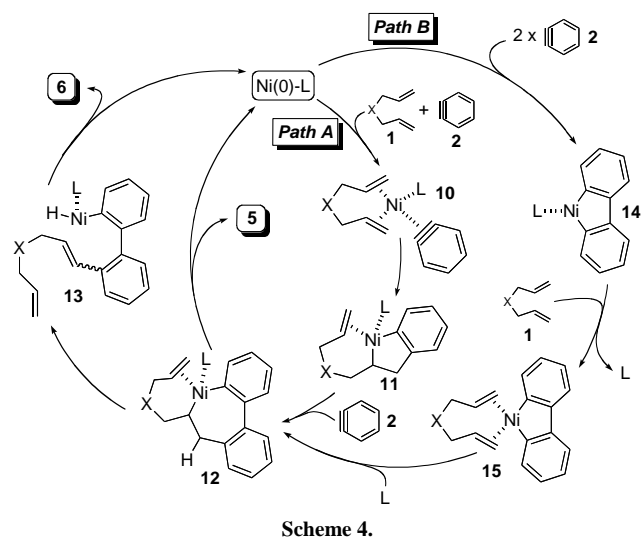
^a Reaction conditions: diene (1 equiv), **4** (3 equiv), Ni(cod)₂ (10 mol%), SIMes·HBF₄ (10 mol%), CsF (6 equiv), MeCN, 50 °C. Reaction time: 4 h (entries 1-5) or 2 h (entry 6). ^b Isolated yield. ^c The ratio of *E*- and *Z*-**6** was determined by ¹H NMR analysis of the mixture of *E*- and *Z*-**6**.

Next, we investigated the reaction of a mono-alkene **8** with **4** instead of diene **1** (Scheme 3, eq. 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 (eq. 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 two alkene parts in the diene also affects the co-trimerization of alkene and two arynes.



Scheme 3.

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 the 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 study on [2+2+2] cycloaddition of α,ω -diene 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.

Acknowledgement. Part of this work was supported by a

Grant-in-Aid for Scientific Research (B) (No. 19390001) from JSPS and by The Novartis Foundation (Japan) for the Promotion of Science, The Uehara Memorial Foundation, and Akiyama Foundation, which are gratefully acknowledged.

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† Electronic Supplementary Information (ESI) available: [detail experimental procedure and spectral data]. See DOI: 10.1039/b000000x/

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