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

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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] cyclotrimeration of benzenes in 1998,2a arynes have been utilized in transition-metal catalyzed [2+2+2] cycloadditions as coupling partners.2b-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 arynaphthalene lignans, Taiwanins C and E, and dehydrodesoxypodophyllotoxin.6 In this context, we envisaged that if a transition metal-catalyzed [2+2+2] cycloaddition of arynes and an alkene moiety 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, 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 alkenes8a or alkenes having an electron-withdrawing group on the sp2 carbon9b 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 arynes and alkenes.

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(o-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).

Scheme 1.

Scheme 2.
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 benzylene (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).

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.

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

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand (xmol%)</th>
<th>time (h)</th>
<th>5aa yield (%)</th>
<th>6aa E-Z-6aa yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(o-tol) (40)</td>
<td>24</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>P(o-tol) (40)</td>
<td>18</td>
<td>54</td>
<td>13 (5)</td>
</tr>
<tr>
<td>3</td>
<td>P(o-tol) (20)</td>
<td>4</td>
<td>70</td>
<td>11 (5)</td>
</tr>
<tr>
<td>4</td>
<td>IMes-HCl (10)</td>
<td>4</td>
<td>67</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>SIMes-HBF4 (10)</td>
<td>2</td>
<td>77 (71)</td>
<td>11 (9)</td>
</tr>
</tbody>
</table>

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

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**Table 2.** Reactions of various dienes and arynes.

<table>
<thead>
<tr>
<th>entry</th>
<th>diene</th>
<th>aryne precursor 4</th>
<th>yields*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>X = NTs</td>
<td>5ba: 36%</td>
</tr>
<tr>
<td>2</td>
<td>1c</td>
<td>X = O</td>
<td>5ca: 25%</td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>X = O</td>
<td>5da: 25%</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>X = CO2Me</td>
<td>5ea: 46%</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>R = -OCH2O-</td>
<td>5eb: 25%</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>R = -OMe</td>
<td>5ec: 57%</td>
</tr>
</tbody>
</table>

*Reaction conditions: diene (1 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) *Yields were determined by 1H NMR analysis of the mixture of E- and Z-6.

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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, \(\beta\)-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 benzynes 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.\(^{10}\)

\[ \text{Path A} \]

\[ \text{Path B} \]

\[ \text{Path C} \]

\[ \text{Path D} \]

In summary, during the course of study on \([2+2+2]\) cycloaddition of \(\alpha,\alpha\)-diene and arynes, we found a novel nickel-catalyzed \([2+2+2]\) cycloaddition of one unactivated alkene and two arynes, giving 9,10-dihydrophanthenetrine 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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Notes and references


10 For a similar mechanism of \([2+2+2]\) cycloaddition of acrylate and arylene proposed by Peña and Pérez et al., see, Ref 9b.