Multicomponent Reactions

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# Nickel-Catalyzed Three-Component [2+2+2] Cycloaddition Reaction of Arynes, Alkenes, and Alkynes**

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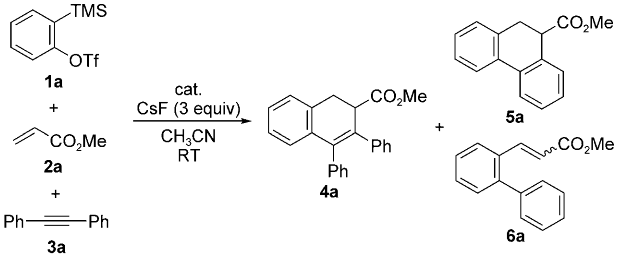
Transition-metal-mediated cycloadditions of alkynes and alkenes serve as a powerful strategy to construct a wide range of compounds, since complexation of the metal center to an olefin or alkyne significantly modifies the reactivity of this moiety.[1] Arynes, a class of very reactive analogues of alkynes, have recently been reported to undergo metal-catalyzed conversion.[2–11] For example, the cyclotrimerization of arynes[2] and the cocyclization of arynes with alkynes,[3] allylic halides,[4] or activated alkenes[5] can all be catalyzed by palladium. Palladium can also catalyze three-component cross-coupling reactions of arynes, allylic halides[6] (allylic epoxides[7] and aromatic halides[8]), and alkynyl stannanes[6a] (boronic acids[6b]) to form substituted benzenes, and three-component cyclization of arynes, aryl halides, and alkynes[9] or alkenes[10] to produce phenanthrene derivatives. In contrast, nickel-catalyzed transformations of arynes are much less explored.[11]

Very recently, we reported the nickel-mediated three-component [2+2+2] cycloaddition of carboryne with activated alkenes and alkynes to give dihydrobenzocarboranes.[12] In view of the similar reactivity pattern between carboryne and benzyne,[13] we extended our research to include arynes and found that nickel can efficiently catalyze three-component [2+2+2] cyclization of arynes, alkenes, and alkynes to afford a series of substituted dihydronaphthalenes that cannot be prepared from readily available starting materials.[14] These new findings are reported herein.

*Table 1:* Optimization of the three-component cycloaddition reaction.[a]



| Entry | Catalyst | Loading [mol %] | Yield of **4a** [%][b] (**4a**:**5a**:**6a**)[c] |
|---|---|---|---|
| 1 | $[Ni(PPh_3)_4]$ | 10 | 50 (55:<2:43) |
| 2 | $[NiCl_2(PPh_3)_2]/Zn$ (1:3) | 10 | 52 (67:8:25) |
| 3 | $[NiCl_2(PnBu_3)_2]/Zn$ (1:3) | 10 | 0 (<2:51:47) |
| 4 | $[NiCl_2(dppe)]/Zn$ (1:3) | 10 | 11 (17:32:51) |
| 5 | $[NiCl_2(dppp)]/Zn$ (1:3) | 10 | 0 (<1:27:72) |
| 6 | $[Ni(cod)_2]$ | 10 | 72 (90:<5:<5) |
| 7 | $[Ni(cod)_2]$ | 10 | 73[d] (90:<5:<5) |
| 8 | $[Ni(cod)_2]$ | 5 | 72 (90:<5:<5) |
| 9 | $[Ni(cod)_2]/PPh_3$ (1:2) | 10 | 51 (55:<2:43) |
| 10 | $[Ni(cod)_2]/dppe$ (1:1) | 10 | 21 (23:16:61) |
| 11 | $[Pd(dba)_2]$ | 10 | 0 (<2:37:61) |
| 12 | $[PdCl_2(PPh_3)_2]/Zn$ (1:3) | 10 | 0 (<2:52:46) |
| 13 | $[Pd(PPh_3)_4]$ | 10 | 0 (<1:88:11) |

[a] Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), **3a** (0.36 mmol), and CsF (0.9 mmol) in $CH_3CN$ (1 mL) at room temperature for 5 h. [b] Yields of isolated **4a**. [c] Ratio determined by $^1H$ NMR spectroscopy on the crude product mixture. [d] The reaction was carried out at 50 °C.

In an initial attempt, a solution of benzyne precursor **1a** (1 equiv, 2-(trimethylsilyl)phenyltriflate), methyl acrylate **2a** (2 equiv), and diphenylacetylene **3a** (1.2 equiv) in $CH_3CN$ in the presence of $[Ni(cod)_2]$ (cod = 1,5-cyclooctadiene; 10 mol %) and CsF (3 equiv) was stirred at room temperature for 5 h to give the cyclization product **4a** in 72 % yield (Table 1, entry 6). Subsequent work focused on optimization of this reaction (Table 1). Changing the ligand from cod to $PPh_3$ or adding $PPh_3$ to $[Ni(cod)_2]$ led to a large decrease in the yield of isolated **4a** from 72 % to 50 % (Table 1, entries 1 and 9). Addition of bidentate ligand dppe (dppe = 1,2-bis(diphenylphosphino)ethane) further decreased the yield of isolated **4a** to 21 % (Table 1, entry 10). No detectable amount of **4a** was observed when $[NiCl_2(PnBu_3)_2]/Zn$ or $[NiCl_2(dppp)]/Zn$ (dppp = 1,3-bis(diphenylphosphino)propane) was used as catalyst (Table 1, entries 3 and 5). In contrast, palladium complexes such as $[Pd(dba)_2]$ (dba = dibenzylideneacetone), $[PdCl_2(PPh_3)_2]/Zn$, and $[Pd(PPh_3)_4]$ did not mediate three-component benzyne–alkene–alkyne cyclization; rather, they catalyzed two-component benzyne–alkene–benzyne cycloaddition and cross-coupling[15] to afford 9,10-dihydrophenanthrene **5a** and methyl 3-(1,1′-biphenyl-2-yl)-2-propenate **6a** (Table 1, entries 11–13). These results showed that 1) both the metal and ligand have a significant effect on the reactions; 2) activated alkene is more reactive than alkyne, otherwise two-component benzyne–alkyne–benzyne cycloaddition products should be observed; and 3) $[Ni(cod)_2]$ exhibited the highest catalytic activity in three-component [2+2+2] cyclization. The same results were observed when the catalyst loading was decreased from 10 mol % to 5 mol % (Table 1, entry 8) or the reaction

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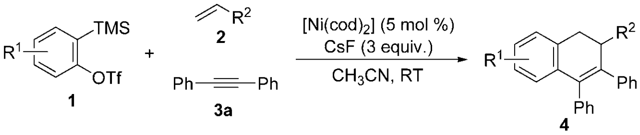
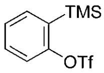
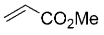
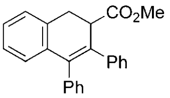
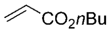
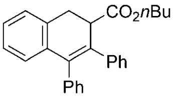
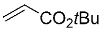
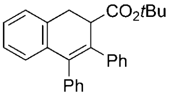
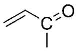
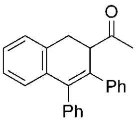
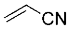
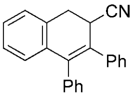
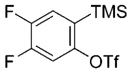
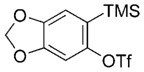
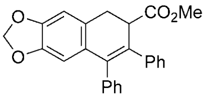
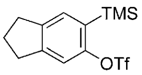
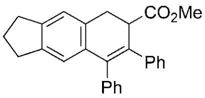
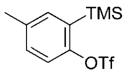
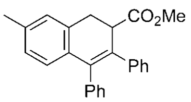
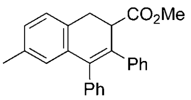
temperature was increased from room temperature (20 °C) to 50 °C (Table 1, entry 7).

The scope and limitations of this Ni-catalyzed cyclization process were then examined with various alkenes and aryne precursors. The results were summarized in Table 2. Acrylates **2a**,**b**,**c** gave very high yields (72–76 %) of the corresponding isolated cocyclization products **4a**,**b**,**c** (Table 2, entries 1–3). Methyl vinyl ketone (**2d**) and acrylonitrile (**2e**) offered very low yields of the desired aryne–alkene–alkyne cocyclization products **4d** (3 %) and **4e** (15 %), respectively (Table 2,

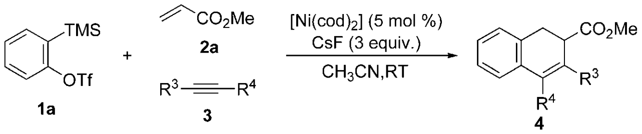
***Table 2:*** Nickel-catalyzed three-component cycloaddition of arynes with activated alkenes and diphenylacetylene.[a]

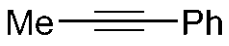
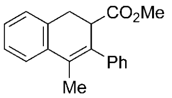
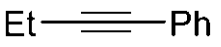
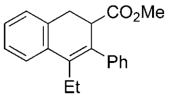
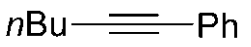
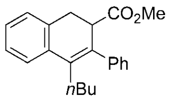
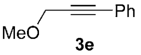
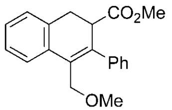
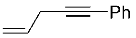
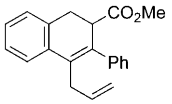
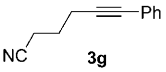
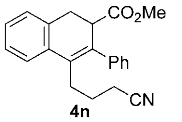
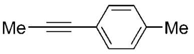
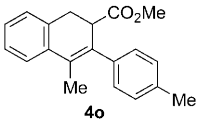
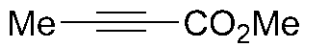
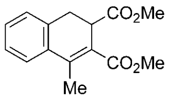
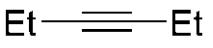
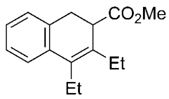
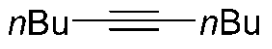
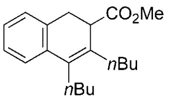


| Entry | 1 | 2 | 4 | Yield [%][b] |
|---|---|---|---|---|
| 1 | <br>**1a** | <br>**2a** | <br>**4a** | 76 |
| 2 | **1a** | <br>**2b** | <br>**4b** | 72 |
| 3 | **1a** | <br>**2c** | <br>**4c** | 74 |
| 4 | **1a** | <br>**2d** | <br>**4d** | 3 |
| 5 | **1a** | <br>**2e** | <br>**4e** | 15 |
| 6 | <br>**1b** | **2a** | – | – |
| 7 | <br>**1c** | **2a** | <br>**4f** | 29[c] |
| 8 | <br>**1d** | **2a** | <br>**4g** | 46[c] |
| 9 | <br>**1e** | **2a** | <br>**4h**<br><br>**4h'** | 57[c,d] |

[a] Conditions: **1** (0.3 mmol), **2** (0.6 mmol), **3a** (0.6 mmol), CsF (0.9 mmol) in $CH_3CN$ (1 mL) at room temperature for 5 h. [b] Yields of isolated products. [c] The reaction was carried out at room temperature overnight. [d] **4h**:**4h'** = 1.3:1. The ratio was estimated by $^1H$ NMR spectroscopy.

***Table 3:*** Nickel-catalyzed three-component cycloaddition of benzyne with methyl acrylate and various alkynes.[a]



| Entry | 3 | 4 | Yield [%][b] |
|---|---|---|---|
| 1 | <br>**3b** | <br>**4i** | 71 |
| 2 | <br>**3c** | <br>**4j** | 78 |
| 3 | <br>**3d** | <br>**4k** | 71 |
| 4 | <br>**3e** | <br>**4l** | 75 |
| 5 | <br>**3f** | <br>**4m** | 68 |
| 6 | <br>**3g** | <br>**4n** | 32 |
| 7 | <br>**3h** | <br>**4o** | 66 |
| 8 | <br>**3i** | <br>**4p** | 19 |
| 9 | <br>**3j** | <br>**4q** | 63[c] |
| 10 | <br>**3k** | <br>**4r** | 47[c] |

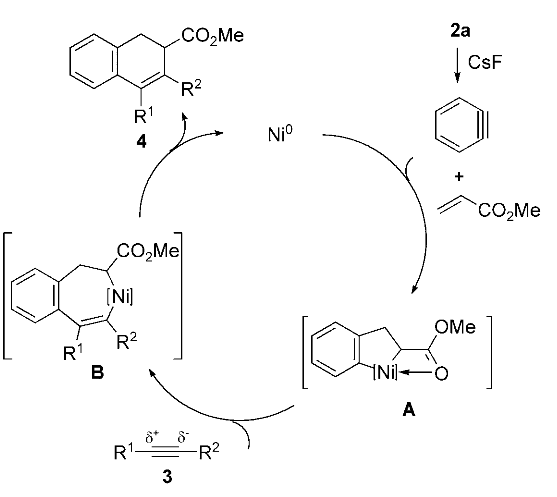
[a] Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), **3** (0.6 mmol), and CsF (0.9 mmol) in $CH_3CN$ (1 mL) at room temperature for 5 h. [b] Yields of isolated products. [c] 3 mmol of alkyne was used.

entries 4 and 5). In these reactions, the major products were aryne–alkene–aryne cyclization species. If unactivated alkenes were used, no desired products **4** were detected. Functionalized aryne precursors with electron-donating groups (**1c**,**d**,**e**) were less effective, producing dihydronaphthalene derivatives **4f**,**g**,**h/h′** in moderate yields (Table 2, entries 7–9). The electron-poor benzyne precursor **1b** afforded a complex inseparable mixture (Table 2, entry 6).

Various alkynes were compatible with this nickel-catalyzed cocyclization reaction and gave the desired products **4** in very good yields (Table 3). Excellent regioselectivity was observed for all unsymmetrical alkynes because of the polarity of these molecules (Table 3, entries 1–8). It is noteworthy that no C=C or C≡N insertion product was observed when **3f** or **3g** was used as the starting material (Table 3, entries 5 and 6). In case of methyl 2-butynoate (**3i**), the low yield was due to the trimerization of **3i** catalyzed by $Ni^0$ (Table 3, entry 8).[1a,16]

Compounds **4** were fully characterized by $^1H$ and $^{13}C$ NMR spectroscopy as well as high-resolution mass spectrometry. The regioisomers were assigned by using NOESY analyses.[17] The molecular structures of **4e** and **4l** were further confirmed by single-crystal X-ray analyses.[18]

A plausible mechanism for the nickel-catalyzed three-component cocyclization is shown in Scheme 1. The catalysis is likely initiated by oxidative coupling of benzyne and alkene on $Ni^0$ to form a nickelacycle **A**, which is probably stabilized by an intramolecular coordination of the heteroatom.[12] Subsequent insertion of alkyne into the nickel-C(aryl) bond gives the seven-membered intermediate **B**.[19] The regioselectivity observed in the reactions can be rationalized by the polarity of alkynes.[19a] Reductive elimination of **B** yields the final product **4** and regenerates the catalyst.



***Scheme 1.*** Proposed mechanism of nickel-catalyzed [2+2+2] cyclization reaction.

In summary, we have developed a novel nickel-catalyzed three-component [2+2+2] carboannulation reaction of arynes, activated alkenes, and alkynes. This work offers an exceptionally efficient route to 1,2-dihydronaphthlenes from readily available starting materials.

## Experimental Section

General procedure: $CH_3CN$ (1 mL), alkyne (0.6 mmol), alkene (0.6 mmol), and aryne precursor (0.3 mmol) were added to a flask containing $[Ni(cod)_2]$ (0.015 mmol) and CsF (0.9 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 5 h. The mixture was extracted with diethyl ether, and the resulting solution was dried over $Na_2SO_4$ and concentrated to dryness in vacuo. The residue was subjected to column chromatography on silica gel (40–230 mesh) using hexane/ethyl acetate as eluent to give the product.[17]

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**Keywords:** arynes · cyclization · homogeneous catalysis · nickel · three-component reactions

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[17] Experimental details and complete characterization data are provided in the Supporting Information.

[18] CCDC 727034 (**4e**) and 727035 (**4l**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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