

Multicomponent Reactions

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

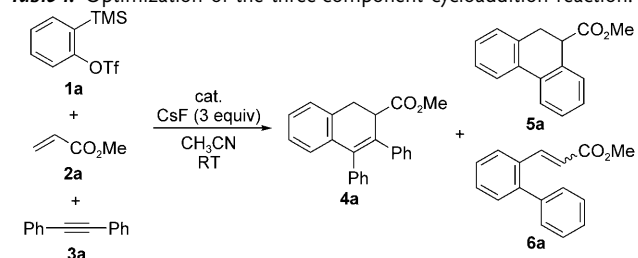
Zaozao Qiu and Zuowei Xie*

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.

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 CH₃CN 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 PPh₃ or adding PPh₃ 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-

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) ₃]	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 CH₃CN (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.

bis(diphenylphosphino)ethane) further decreased the yield of isolated **4a** to 21 % (Table 1, entry 10). No detectable amount of **4a** was observed when [NiCl₂(PnBu₃)₂]/Zn or [NiCl₂(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)₃] (dba = dibenzylideneacetone), [PdCl₂(PPh₃)₂]/Zn, and [Pd(PPh₃)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-propenoate **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

[*] Z. Qiu, Prof. Dr. Z. Xie
Department of Chemistry and
Center of Novel Functional Molecules
The Chinese University of Hong Kong
Shatin, N.T., Hong Kong (China)
Fax: (+852) 2603-5057
E-mail: zxie@cuhk.edu.hk

[**] This work was supported by grants from the Research Grants Council of the Hong Kong Special Administration Region (Project No. 404108) and the Chinese University of Hong Kong.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.200902006>.

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

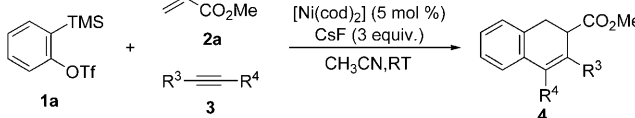
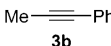
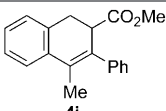
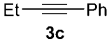
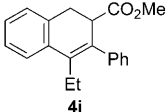
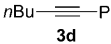
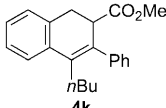
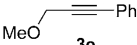
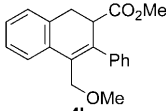
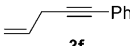
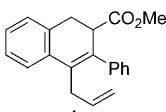
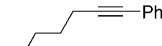
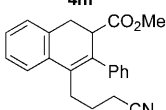
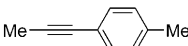
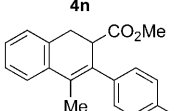
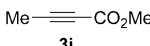
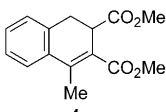
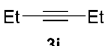
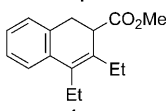
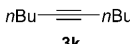
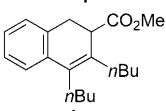
Table 2: Nickel-catalyzed three-component cycloaddition of arynes with activated alkenes and diphenylacetylene.^[a]

Entry	1	2	4	Yield [%] ^[b]
1				76
2	1a			72
3	1a			74
4	1a			3
5	1a			15
6		2a	—	—
7		2a		29 ^[c]
8		2a		46 ^[c]
9		2a	 	57 ^[c,d]

[a] Conditions: **1** (0.3 mmol), **2** (0.6 mmol), **3a** (0.6 mmol), CsF (0.9 mmol) in CH₃CN (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.

2a,b,c gave very high yields (72–76 %) of the corresponding isolated cycloaddition 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 cycloaddition products **4d** (3 %) and **4e** (15 %), respectively (Table 2,

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

				
Entry	3	4	Yield [%] ^[b]	
1			71	
2			78	
3			71	
4			75	
5			68	
6			32	
7			66	
8			19	
9			63 ^[c]	
10			47 ^[c]	

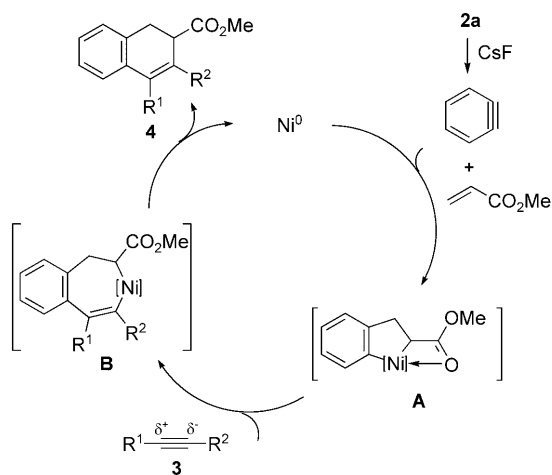
[a] Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), **3** (0.6 mmol), and CsF (0.9 mmol) in CH₃CN (1 mL) at room temperature for 5 h. [b] Yields of isolated products. [c] 3 mmol of alkyne was used.

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 Ni⁰ (Table 3, entry 8).^[1a,16]

Compounds **4** were fully characterized by ¹H and ¹³C NMR spectroscopy as well as high-resolution mass spectrometry. The regioisomers were assigned by using NOESY analyses.^[17] The molecular structures of **4e** and **4i** 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



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

is likely initiated by oxidative coupling of benzyne and alkene on Ni⁰ 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.

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

Experimental Section

General procedure: CH₃CN (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 Na₂SO₄ 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]

Received: April 15, 2009

Published online: June 25, 2009

Keywords: alkynes · cyclization · homogeneous catalysis · nickel · three-component reactions

- [1] For reviews, see: a) N. E. Schore, *Chem. Rev.* **1988**, *88*, 1081–1119; b) B. M. Trost, *Science* **1991**, *254*, 1471–1477; c) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49–92; d) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901–2915.
- [2] a) D. Peña, S. Escudero, D. Pérez, E. Guitián, L. Castedo, *Angew. Chem.* **1998**, *110*, 2804–2806; *Angew. Chem. Int. Ed.* **1998**, *37*, 2659–2661; b) D. Peña, D. Pérez, E. Guitián, L. Castedo, *Org. Lett.* **1999**, *1*, 1555–1557; c) C. Romero, D. Peña, D. Pérez, E. Guitián, *Chem. Eur. J.* **2006**, *12*, 5677–5684.
- [3] a) D. Peña, D. Pérez, E. Guitián, L. Castedo, *J. Am. Chem. Soc.* **1999**, *121*, 5827–5828; b) K. V. Radhakrishnan, E. Yoshikawa, Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 7533–7535; c) D. Peña, D. Pérez, E. Guitián, L. Castedo, *J. Org. Chem.* **2000**, *65*, 6944–6950; d) Y. Sato, T. Tamura, M. Mori, *Angew. Chem.* **2004**, *116*, 2490–2494; *Angew. Chem. Int. Ed.* **2004**, *43*, 2436–2440; e) C. Romero, D. Peña, D. Pérez, E. Guitián, *J. Org. Chem.* **2008**, *73*, 7996–8000.
- [4] a) E. Yoshikawa, K. V. Radhakrishnan, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 7280–7286; b) E. Yoshikawa, Y. Yamamoto, *Angew. Chem.* **2000**, *112*, 185–187; *Angew. Chem. Int. Ed.* **2000**, *39*, 173–175.
- [5] I. Quintana, A. J. Boersma, D. Peña, D. Pérez, E. Guitián, *Org. Lett.* **2006**, *8*, 3347–3349.
- [6] a) M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2004**, *6*, 2821–2824; b) T. T. Jayanth, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2005**, *7*, 2921–2924; c) J. L. Henderson, A. S. Edwards, M. F. Greaney, *J. Am. Chem. Soc.* **2006**, *128*, 7426–7427; d) S. Bhuvaneshwari, M. Jeganmohan, M.-C. Yang, C.-H. Cheng, *Chem. Commun.* **2008**, 2158–2160; e) C. Xie, L. Liu, Y. Zhang, P. Xu, *Org. Lett.* **2008**, *10*, 2393–2396; f) S. Bhuvaneshwari, M. Jeganmohan, C.-H. Cheng, *Chem. Commun.* **2008**, 5013–5015.
- [7] M. Jeganmohan, S. Bhuvaneshwari, C.-H. Cheng, *Angew. Chem.* **2009**, *121*, 397–400; *Angew. Chem. Int. Ed.* **2009**, *48*, 391–394.
- [8] J. L. Henderson, A. S. Edwards, M. F. Greaney, *Org. Lett.* **2007**, *9*, 5589–5592.
- [9] a) Z. Liu, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2005**, *127*, 15716–15717; b) Z. Liu, R. C. Larock, *Angew. Chem.* **2007**, *119*, 2587–2590; *Angew. Chem. Int. Ed.* **2007**, *46*, 2535–2538.
- [10] S. Bhuvaneshwari, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2006**, *8*, 5581–5584.
- [11] a) J.-C. Hsieh, C.-H. Cheng, *Chem. Commun.* **2005**, 2459–2461; b) T. T. Jayanth, C.-H. Cheng, *Angew. Chem.* **2007**, *119*, 6025–6028; *Angew. Chem. Int. Ed.* **2007**, *46*, 5921–5924.
- [12] Z. Qiu, Z. Xie, *J. Am. Chem. Soc.* **2009**, *131*, 2084–2085.
- [13] a) H. L. Gingrich, T. Ghosh, Q. Huang, M. Jones, Jr., *J. Am. Chem. Soc.* **1990**, *112*, 4082–4083; b) T. Ghosh, H. L. Gingrich, C. K. Kam, E. C. Mobraaten, M. Jones, Jr., *J. Am. Chem. Soc.* **1991**, *113*, 1313–1318; c) Q. Huang, H. L. Gingrich, M.

- Jones, Jr., *Inorg. Chem.* **1991**, *30*, 3254–3257; d) R. J. Cunningham, N. Bian, M. Jones, Jr., *Inorg. Chem.* **1994**, *33*, 4811–4812; e) D. M. Ho, R. J. Cunningham, J. A. Brewer, N. Bian, M. Jones, Jr., *Inorg. Chem.* **1995**, *34*, 5274–5278; f) L. Barnett-Thamattoor, G. Zheng, D. M. Ho, M. Jones, Jr., J. E. Jackson, *Inorg. Chem.* **1996**, *35*, 7311–7315; g) J. Jeon, T. Kitamura, B.-W. Yoo, S. O. Kang, J. Ko, *Chem. Commun.* **2001**, 2110–2111; h) T. Lee, J. Jeon, K. H. Song, I. Jung, C. Baik, K.-M. Park, S. S. Lee, S. O. Kang, J. Ko, *Dalton Trans.* **2004**, 933–937; i) L. Deng, H.-S. Chan, Z. Xie, *J. Am. Chem. Soc.* **2005**, *127*, 13774–13775; j) L. Deng, H.-S. Chan, Z. Xie, *J. Am. Chem. Soc.* **2006**, *128*, 7728–7729; k) Z. Qiu, Z. Xie, *Angew. Chem.* **2008**, *120*, 6674–6677; *Angew. Chem. Int. Ed.* **2008**, *47*, 6572–6575; l) S. Ren, H.-S. Chan, Z. Xie, *J. Am. Chem. Soc.* **2009**, *131*, 3862–3863.
- [14] a) J. Wennerberg, F. Ek, A. Hansson, T. Frejd, *J. Org. Chem.* **1999**, *64*, 54–59; b) T. Hamura, M. Miyamoto, K. Imura, T. Matsumoto, K. Suzuki, *Org. Lett.* **2002**, *4*, 1675–1678; c) H. Inoue, N. Chatani, S. Murai, *J. Org. Chem.* **2002**, *67*, 1414–1417; d) N. Asao, T. Kasahara, Y. Yamamoto, *Angew. Chem.* **2003**, *115*, 3628–3630; *Angew. Chem. Int. Ed.* **2003**, *42*, 3504–3506; e) H. Zhou, X. Huang, W. Chen, *J. Org. Chem.* **2004**, *69*, 5471–5472; f) M. Lautens, G. A. Schmid, A. Chau, *J. Org. Chem.* **2002**, *67*, 8043–8053; g) D. K. Rayabarapu, C.-F. Chiou, C.-H. Cheng, *Org. Lett.* **2002**, *4*, 1679–1682; h) M.-S. Wu, D. K. Rayabarapu, C.-H. Cheng, *J. Org. Chem.* **2004**, *69*, 8407–8412; i) M.-S. Wu, M. Jegannathan, C.-H. Cheng, *J. Org. Chem.* **2005**, *70*, 9545–9550, and references therein.
- [15] It is documented that Pd can catalyze two-component benzyne–alkene–benzyne cycloaddition and cross-coupling reactions; see Ref. [5].
- [16] A. K. Jhingan, W. F. Maier, *J. Org. Chem.* **1987**, *52*, 1161–1165.
- [17] Experimental details and complete characterization data are provided in the Supporting Information.
- [18] CCDC 727034 (**4e**) and 727035 (**4i**) 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.
- [19] a) M. A. Bennett, S. A. Macgregor, E. Wenger, *Helv. Chim. Acta* **2001**, *84*, 3084–3104; b) M. A. Bennett, M. Glewis, D. C. R. Hockless, E. Wenger, *J. Chem. Soc. Dalton Trans.* **1997**, 3105–3114.