JOC Article

Highly Regio- and Chemoselective [2 + 2 + 2] Cycloaddition of Electron-Deficient Diynes with Allenes Catalyzed by Nickel Complexes: A Novel Entry to Polysubstituted Benzene Derivatives

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Diynes **1a**−**c** [$X(CH_2C{\equiv}CCO_2Me)_2$: X = $(CH_2)_2$, **1a**, X = CH_2, **1b** and X = O, **1c**] undergo [2 + 2 + 2] ene−diyne cycloaddition reactions with a variety of allenes (*n*-butylallene **2a**, phenylallene **2b**, (4-chlorophenyl)allene **2c**, (4-bromophenyl)allene **2d**, (3-methoxyphenyl)allene **2e**, 1-naphthylallene **2f**, cyclohexylallene **2g** and cyclopentylallene **2h**) in the presence of Ni(dppe)Br_2 and Zn powder in CH_3CN at 80 °C for 8 h to give the corresponding polysubstituted benzene derivatives **4a**−**l** in good to excellent yields. Under similar reaction conditions, unsymmetrical diynes **5a**−**c** ($HC{\equiv}CCH_2$-$XCH_2C{\equiv}CCO_2Me$) react with allenes **2** to afford exclusively the corresponding meta-isomers **6a**−**g** in 73−86% yields. The catalytic reaction is highly regioselective and completely chemoselective. This synthetic method is compatible with many functional groups such as Cl, Br, and OMe on the phenyl group of the allene moiety and an ether linkage in a diyne moiety. In this catalytic reaction, allenes are synthetically equivalent to terminal alkynes. Interestingly, unsymmetrical diyne **7** ($MeC{\equiv}C(CH_2)_4C{\equiv}CCO_2Me$) undergoes 2:1 cocyclotrimerization with allenes **2a** and **2g** to afford the corresponding polysubstituted benzene derivatives **9a,b** in 87% and 82% yields, respectively. A plausible mechanism involving a nickelacycloheptadiene intermediate is proposed to account for this nickel-catalyzed reaction.

Introduction

Polysubstituted benzene derivatives form an important class of organic compounds with numerous applications in industry as well as in academic laboratories. The transition-metal-catalyzed [2 + 2 + 2] cycloaddition is an attractive tool to construct polysubstituted benzene derivatives.[1] Although this cycloaddition has been known for more than 50 years, the control of both regio- and chemoselectivity remains a challenging problem to organic chemists.[2] Metal-catalyzed intermolecular cyclotrimerization of three monoalkynes generally gives poor regio- and chemoselectivity. Vollhardt reported an efficient regio- and chemoselective intramolecular triyne cyclization using $CpCo(CO)_2$ as the catalyst.[3] A partially intermolecular [2 + 2 + 2] cycloaddition is often more advantageous in the control of the substitution pattern on an arene ring than the cyclotrimerization of two or three different alkyne components. Recently, we have demonstrated a nickel-catalyzed highly regio- and chemoselective [2 + 2 + 2] cycloaddition of nonconjugated diynes with 1,3-diynes.[4] Although considerable attention has been paid to the intermolecular reaction of diynes with alkynes,[5] less work has been reported on intermolecular reaction of diynes with alkenes.[6] In particular, Ikeda[7] and our group[8] have reported the nickel-catalyzed selective

(1) For reviews, see: (a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (b) Trost, B. M. *Science* **1991**, *254*, 1471. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (d) Grotjahn, D. B. Transition Metal Alkyne Complexes: Transition Metal-Catalyzed Cyclotrimerization. In Comprehensive Organometallic Chemistry II.; Wilkinson, Stone, Abel, Eds.; Pergamon: Oxford, 1995; Vol.12, p 741. (e) Gevorgyan, V.; Yamamoto, Y. *J. Organomet. Chem.* **1999**, *576*, 232. (f) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.

(2) For the first transition-metal-catalyzed trimerization of alkynes, see: Reepe, W.; Schlitchting, O.; Klager, K.; Toepel, T. *Justus Liebigs Ann. Chem.* **1948**, *560*, 1.

(3) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.

(4) Jeevanandam, A., Korivi, R. P.; Huang, W.-I.; Cheng, C.-H. *Org. Lett.* **2002,** *4*, 807.

(5) (a) Müller, E. *Synthesis* **1974**, 761. (b) Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1357. (c) Bahataran, P.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2603. (d) Bahataran, P.; Smith, E. H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2163. (e) Duckworth, D. M.; Lee-Wong, S.; Slawin, A. M. Z.; Smith, E. H.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 815. (f) McDonald, F. E.; Zhu, H. Y. H.; Holmquist, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 6605. (g) Sato, Y.; Nishimata, T.; Mori, M. *Heterocycles* **1997**, *44*, 443. (h) Kotha, S.; Brahmachary, E. *Tetrahedron Lett.* **1997**, *38*, 3561. (i) Bradley, A.; Motherwell, W. B.; Ujjainwalla, F. *Chem. Commun.* **1999**, 917. (j) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426.

(6) (a) Chalk, A. J. *J. Am. Chem. Soc.* **1972**, *94*, 5928. (b) Suzuki, H.; Itoh, K.; Ishii, Y.; Simon, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 8494. (c) Sternberg, E. D.; Volhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 1574. (d) Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc.* **1993**, *115*, 1581. (e) Slowinski, F.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1999**, *40*, 707.

(7) (a) Ikeda, S.; Watanabe, H.; Sato, Y. *J. Org. Chem.* **1998**, *63*, 7026. (b) Mori, N.; Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1999**, *121*, 2722.

(8) (a) Huang, D.-J.; Sambaiah, T.; Cheng, C.-H. *New J. Chem.* **1998**, *22*, 1147. (b) Hsiao, T.-Y.; Santhosh, K. C.; Liou, K. F. J.; Cheng, C.-H. *J. Am. Chem. Soc.* **1998**, *120*, 12232. (c) Sambaiah, T.; Li, L.-P.; Huang, D.-J.; Lin, C.-H.; Rayabarapu, D. K.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3663. (d) Sambaiah, T.; Huang, D.-J.; Cheng, C.-H. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 195.

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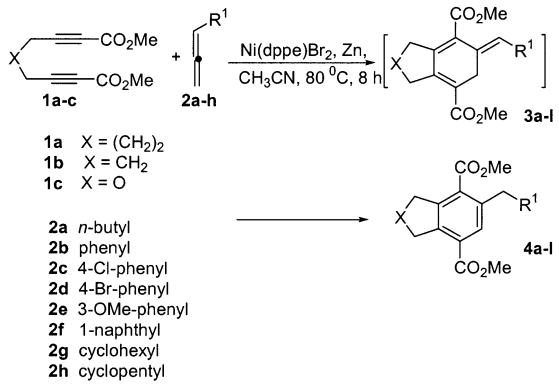
SCHEME 1



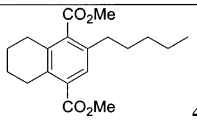
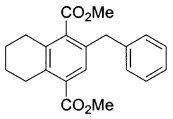
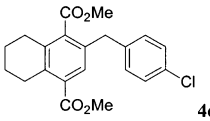
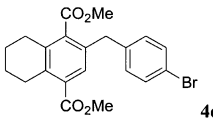
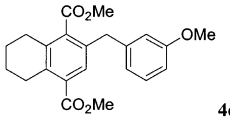
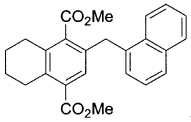
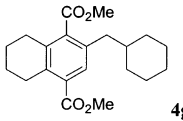
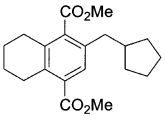
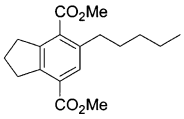
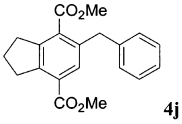
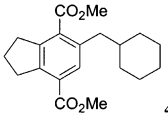
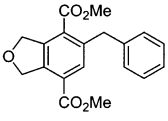
intermolecular reactions of diynes with alkenes. The alkenes used were limited to α,β-unsaturated ketones, 7-oxabenzonorbornadienes, and fullerenes. In many instances, this nickel-catalyzed reaction was promoted by the presence of other metal species such as aluminum phenoxide or zinc halide. Additionally, a high ratio of alkene to diyne was employed to suppress the competing dimerization and trimerization of diynes.[9]

The metal-mediated allene chemistry has been a subject of great interest in organic synthesis for the past few decades.[10] We have reported recently that Ni(dppe)Br_2 and Zn effectively catalyzed the cocyclotrimerization of propiolates with allenes to provide benzene derivatives in a highly regio- and chemoselective fashion.[11] Our continuous interest in metal-mediated allene chemistry[12] led us to examine the reaction of diynes with allenes. In this paper, we report the first example of a highly regio- and chemoselective [2 + 2 + 2] cycloaddition of electron-deficient diynes with allenes catalyzed by nickel complexes to afford polysubstituted benzene derivatives in good to excellent yields.

Results and Discussion

Treatment of dimethyl 2,8-decadiynedioate (**1a**) with *n*-butylallene (**2a**) in the presence of Ni(dppe)Br_2 (5 mol %) and zinc powder in CH_3CN at 80 °C for 8 h gave a 5,6,7,8-tetrahydronaphthalene derivative **4a** in 88% yield (Scheme 1, Table 1, entry 1). Control experiments revealed that in the absence of either Ni(dppe)Br_2 or zinc powder, no reaction occurred. The structure of **4a** was thoroughly characterized by spectroscopic data. Com-

TABLE 1. Nickel-Catalyzed [2 + 2 + 2] Cycloaddition of Diyne 1a−c with Allenes

Entry	Diyne	Allene	Product	Yield (%)[a]
1	**1a**	**2a**	 **4a**	88
2	**1a**	**2b**	 **4b**	90
3	**1a**	**2c**	 **4c**	81
4	**1a**	**2d**	 **4d**	84
5	**1a**	**2e**	 **4e**	82
6	**1a**	**2f**	 **4f**	75
7	**1a**	**2g**	 **4g**	77
8	**1a**	**2h**	 **4h**	76
9	**1b**	**2a**	 **4i**	75
10	**1b**	**2b**	 **4j**	90
11	**1b**	**2g**	 **4k**	82
12	**1c**	**2b**	 **4l**	63

[a] Isolated yield of product.

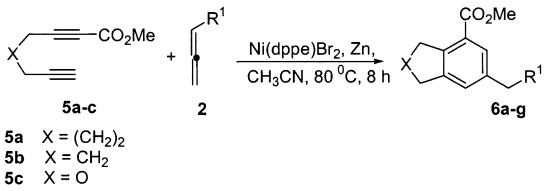
(9) Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1365. (b) Zhou, Z.; Battaglia, L. P.; Chiusoli, G. P.; Costa, M.; Nardeli, M.; Pelizzi, C.; Predieri, G. *J. Chem. Soc. Chem. Commun.* **1990**, 1632. (c) Zhou, Z.; Costa, M.; Chiusoli, G. P. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1399. (d) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Itoh, K. *J. Org. Chem.* **1998**, *63*, 9610.

(10) For reviews, see: (a) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (b) Yamamoto, Y.; Radhakrishnanan, U. *Chem. Soc. Rev.* **1999**, *28*, 199. (c) Zimmer, R.; Dinesh, C. U.; Nandanam, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (c) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (d) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590.

(11) Shanmugasundaram, M.; Wu, M.-S.; Cheng, C.-H. *Org. Lett.* **2001**, *3*, 4233.

(12) (a) Wu, M.-Y.; Yang, F.-Y.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 2471. (b) Chang, H.-M.; Cheng, C.-H. *J. Org. Chem.* **2000**, *65*, 1767. (c) Chang, H.-M.; Cheng, C.-H. *Org. Lett.* **2000**, *2*, 3439. (d) Yang, F.-Y.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2000**, *122*, 7122. (e) Yang, F.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2001**, *123*, 761. (f) Huang, T. −H, Chang, H.-M.; Wu, M.-Y.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 99.

SCHEME 2



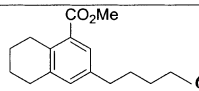
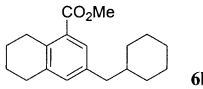
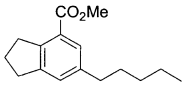
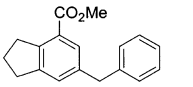
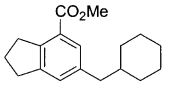
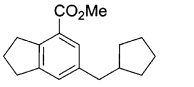
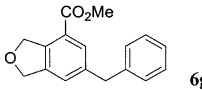
pound **4a** is presumably formed via a [2 + 2 + 2] cycloaddition of **1a** with **2a** to give a cyclohexadiene intermediate **3a**, followed by isomerization of the intermediate. The undesired competitive dimerization of diyne **1a** was suppressed very effectively and only a trace amount of the dimerization product of diyne was detected in the crude reaction mixture by ^{1}H NMR spectroscopy. To the best of our knowledge, this is the first example of a nickel-catalyzed [2 + 2 + 2] cycloaddition of diynes with allenes.

As shown in Table 1, diyne **1a** undergoes [2 + 2 + 2] cycloaddition with a variety of allenes. The reaction of **1a** with phenylallene **2b** in the presence of Ni(dppe)Br_2 and Zn powder affords product **4b** in 90% yield (entry 2). The presence of chloro or bromo groups in the reactants can be tolerated under the reaction conditions. Thus, treating diyne **1a** with allenes **2c** and **2d** afforded the corresponding cycloadducts **4c** and **4d** in 81% and 84% yields, respectively (entries 3 and 4). Similarly, 3-methoxyphenylallene **2e**, 1-naphthylallene **2f**, cyclohexylallene **2g**, and cyclopentylallene **2h** reacted efficiently with **1a** to give **4e**−**h** in 75−82% yields (entries 5−8).

In a similar manner, diyne **1b** reacts smoothly with allenes **2a**, **2b**, and **2g** in the presence of the Ni(dppe)-Br_2/Zn system to furnish the corresponding indane derivatives **4i**−**k** in 75%, 90%, and 82% yields, respectively (entries 9−11). Under similar conditions, oxygen-containing diyne **1c** also reacts with phenylallene **2b** to afford 1,3-dihydroisobenzofuran derivative **4l** in 63% yield (entry 12).

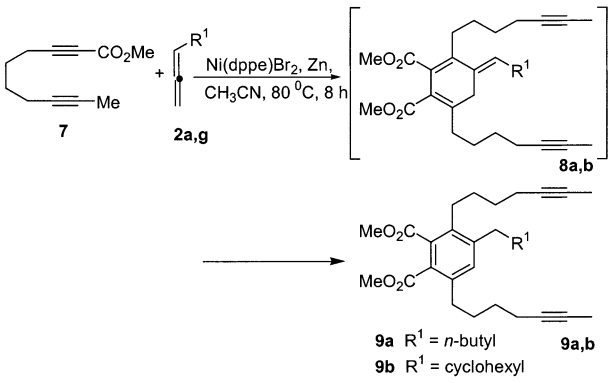
The present reaction is successfully extended to unsymmetrical diynes **5a**−**c** (Scheme 2). The Ni(dppe)Br_2/Zn catalyzed reaction of unsymmetrical diyne **5a** with *n*-butylallene **2a** is highly regio- and chemoselective, affording **6a** as the sole product in 79% yield (Table 2, entry 1). No other isomer was detected in the ^{1}H NMR spectrum of the crude reaction mixture. The regiochemical assignment is based on the ^{1}H NMR pattern of the aromatic protons. There are two aromatic protons in **6a** appearing as two sharp singlets at δ 7.01 and 7.45, suggesting that the ester and the *n*-pentyl groups are meta to each other. Similarly, the reaction of **5a** with cyclohexylallene **2g** afforded product **6b** having the same regiochemistry as **6a** in 82% yield (entry 2). Unsymmetrical diyne **5b** also reacts efficiently with various allenes **2** to afford the corresponding indane derivatives in a perfect regioselective manner. For example, treatment of **5b** with *n*-butylallene **2a** gave the cycloadduct **6c** in 73% yield (entry 3), and with phenylallene, **2b** furnished the desired product **6d** in 85% yield (entry 4). In a similar manner, cyclohexylallene **2g** and cyclopentylallene **2h** afforded the corresponding indane derivatives **6e** and **6f** in 86% and 84% yields, respectively (entries 5 and 6). Unsymmetrical diyne **5c** having an ether linkage also shows similar reactivity under the

TABLE 2. Nickel-Catalyzed [2 + 2 + 2] Cycloaddition of Unsymmetrical Diyne 5a−c with Allenes 2

Entry	Diyne	Allene	Product	Yield (%)[a]
1	**5a**	**2a**	 **6a**	79
2	**5a**	**2g**	 **6b**	82
3	**5b**	**2a**	 **6c**	73
4	**5b**	**2b**	 **6d**	85
5	**5b**	**2g**	 **6e**	86
6	**5b**	**2h**	 **6f**	84
7	**5c**	**2b**	 **6g**	73

[a] Isolated yield of product.

SCHEME 3



standard reaction conditions. Thus, **5c** reacts with phenylallene **2b**, affording 1,3-dihydroisobenzofuran derivative **6g** in 73% yield. (entry 7). In all cases, the [2 + 2 + 2] cycloaddition of **5** with allenes **2** is highly regioselective and completely chemoselective, affording only the corresponding meta-isomers **6a**−**g** in good to excellent yields (Table 2).

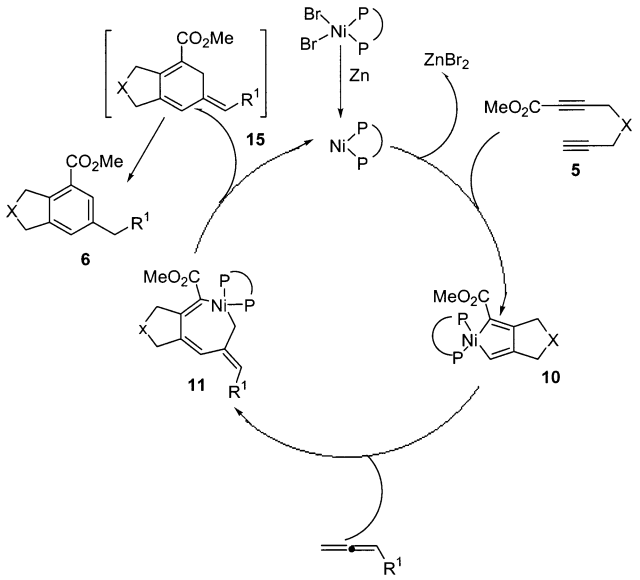
To further understand the regio- and chemoselectivity of the present [2 + 2 + 2] cycloaddition, the reaction with unsymmetrical diyne **7** bearing an ester group −CO_2Me on one side and a methyl group on the other side was investigated. Unlike diynes **1** and **5**, **7** undergoes 2:1 cocyclotrimerization with *n*-butylallene **2a** to give **9a** in 87% yield, instead of the expected [2 + 2 + 2] ene−diyne cycloaddition (Scheme 3). The structure of **9a** was confirmed by its ^{1}H and ^{13}C NMR and mass spectral data.

No other regioisomer and partially intermolecular [2 + 2 + 2] cycloaddition product was observed in the ^{1}H NMR spectrum of the crude reaction mixture. The regiochemical assignment is based on the diagnostic chemical shift of the aromatic proton as a singlet at δ 7.06 and also by the results of NOE experiments. Selective irradiation of the aromatic proton at δ 7.06 caused 3.06% and 2.8% increase of the intensity of methylene protons at δ 2.65 and 2.59 attached directly to the benzene rings.

Similarly, treatment of **7** with cyclohexylallene **2g** in the presence of the Ni(dppe)Br_2/Zn system gave **9b** in 82% yield. The ^{1}H NMR spectrum of **9b** also shows a characteristic singlet at δ 7.01 for the only proton on the benzene ring. The regiochemistry of this product is again established on the basis of the NOE data. Irradiation of the aromatic proton at δ 7.01 caused 2.76% enhancement of the signal for the methylene protons next to the cyclohexyl group at δ 2.47 and 2.79% enhancement of the methylene protons attached directly to the aromatic ring at δ 2.67. Irradiation of the methylene proton at δ 2.47 led to 4.1% enhancement of the methylene protons at δ 2.60 and also 3.84% enhancement of the aromatic proton at δ 7.01. The above NOE data strongly suggest that the two ester groups are ortho to each other and the two substituents of the propiolates are para to each other and ortho to the allene moiety. The regiochemistry of the above products **9a,b** is consistent with our previous reported reaction of alkyl propiolates with allenes that give rise to 1,4-dialkyl-substituted benzene derivatives.[11]

There are several interesting features that are noteworthy from this study. First, the chemoselectivity of the allenes used in the reaction is quite interesting. Only the internal carbon and the unsubstituted carbon of the allene moiety alone are involved in the cycloaddition, and no trace of other chemoisomer was detected in all of these reactions studied. It is notably that Takahashi et al.[13] reported the reaction of zirconacyclopentadienes with allenes in the presence of Ni(II) complexes, resulting in a mixture of chemoisomers. Second, the allenes employed in the present catalytic reaction are synthetically equivalent to the corresponding monosubstituted alkynes, but are more effective than the alkynes. To compare both the reactivity and selectivity of an alkyne with the corresponding allene, the reactions of **1a** and **5b** with 1-heptyne were examined. It should be mentioned that 1-heptyne is considered here synthetically equivalent to *n*-butylallene. Under our standard conditions, the reaction resulted only in the dimerization product of diynes and a trace amount of the corresponding [2 + 2 + 2] products **4a** and **6c**, as revealed by the ^{1}H NMR spectra of the crude reaction mixture. However, the reaction of **1a** and **5b** with *n*-butylallene under similar conditions afforded **4a** and **6c** in 88 and 73% yields, respectively (Table 1, entry 1 and Table 2, entry 3). These two experiments strongly suggest that the allenes are complementary to the monosubstituted alkynes in terms of reactivity and selectivity. Third, under our standard conditions, the ratio of diynes to allenes employed is almost 1:1. The competitive dimerization and trimerization of diynes were effectively suppressed; the dimerization product of diynes was observed in less than 5% yield in each reaction. This is in marked contrast to other cycloadditions that require excess alkenes to suppress the competing dimerization and trimerization of diynes.[9] Finally, under our standard conditions, 1,7-octadiyne and 1,6-heptadiyne failed to undergo cycloaddition with *n*-butylallene, affording only the dimerization of the corresponding diyne. The presence of an electron-withdrawing $-CO_2Me$ group in the diyne moiety plays an important role in promoting the present [2 + 2 + 2] cycloaddition in a highly regio- and chemoselective manner.

SCHEME 4



On the basis of the known organometallic chemistry of nickel and the observed regio- and chemoselectivity of [2 + 2 + 2] products **6**, a probable mechanism for the nickel-catalyzed reaction of diyne **5** with allene **2** is depicted in Scheme 4. The reduction of Ni(II) species to Ni(0) species by zinc metal likely initiates the catalytic reaction. Coordination of diyne **5** to the nickel center followed by cyclometalation gives the nickelacyclopentadiene intermediate **10**.[14,15] Coordination of allene and insertion into a Ni(II)−carbon bond produces nickelacycloheptadiene intermediate **11**. Subsequent reductive elimination of **11** and isomerization of **15** affords product **6** and regenerates the Ni(0) catalyst.

The mechanism for the formation of products **9** is proposed in Scheme 5. Coordination of two molecules of diyne **7** followed by regioselective head-to-head oxidative cyclometalation produces nickelacyclopentadiene intermediate **16**. Further coordination of allene and insertion of this molecule into a Ni(II)−carbon bond gives nickelacycloheptadiene intermediate **17**. Subsequent reductive elimination and isomerization furnishes product **9** and regenerates the Ni(0) catalyst.

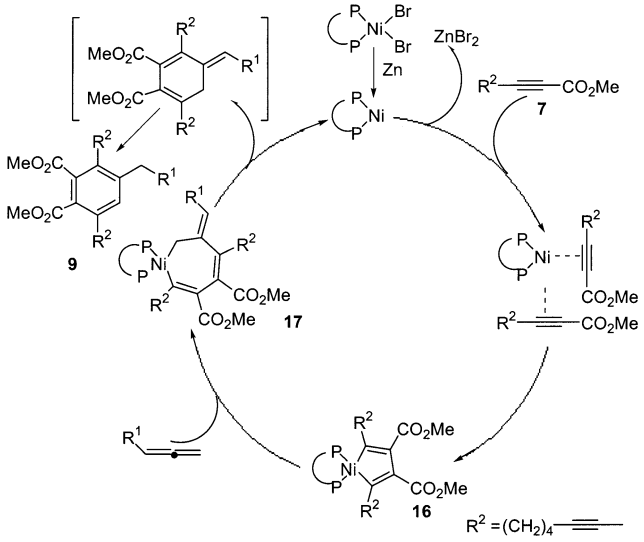
An alternative mechanism involves coordination of one molecule of allene and one molecule of diyne **7** to produce

(13) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1999**, *121*, 11093.

(14) (a) Eisch, J. J.; Gile, J. E. *J. Organomet. Chem.* **1975**, *96*, C23. (b) McAlister, D. R.; Bercaw, J. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 1666. (c) Eisch, J. J.; Piotrowski, A. M.; Han, K. I.; Kruger, C.; Tsay, Y. H. *Organometallics* **1985**, *4*, 224.

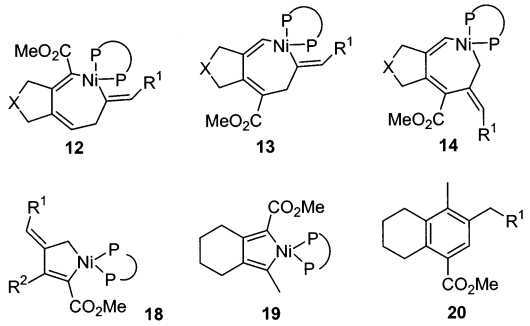
(15) For production of a cobaltacyclopentadiene complex, see: Wakatsuki, Y.; Nomura, O.; Kitaura, K.; Morokuma, K.; Yamzaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 1907.

SCHEME 5



five-membered nickelacyclopentene intermediate **18**,[16] followed by insertion of another diyne **7** into the Ni(II)−carbon bond to yield the seven-membered ring intermediate **17**. Subsequent reductive elimination of **17** gives the final product **9**. This mechanism cannot be totally ruled out, but it is less likely based on the partially intermolecular reaction of diynes **1** and **5** with allenes **2**.

The remarkable meta-selectivity can be explained by the ready regioselective formation of nickelacycloheptadiene intermediate **11**. The terminal carbon−carbon double bond of the coordinated allene is regioselectively inserted into the unsubstituted Ni−C single bond of **10** with the central carbon of the allene attaching to the unsubstituted carbon and the terminal carbon of the allene moiety connecting to the nickel center. Such regioselectivity for allene insertion was frequently observed in the metal-mediated addition of organic substrates to allenes.[12a,d,f] In addition, it has been proposed that insertion of an unsaturated carbon−carbon bond to a metalacyclopentadiene occurs preferably at the unsubstituted Ni−C bond of the metalacyclopentadiene moiety.[4,17] Other insertion modes leading to intermediates such as **12**−**14** are less likely due to electronic effect and/or steric repulsion. Intermediate **11** is supported by the nickel-catalyzed reaction of monosubstituted allenes reported by Pasto et al.,[18] in which the allene inserts into the five-membered nickelacycle with the unsubstituted carbon α to the metal.



The facile highly regioselective formation of metalacycle **16** from diyne **7** is the most characteristic feature of the cocyclotrimerization of diyne **7** with allenes. The formation of 1,4-dialkylmetalacycle **16** is more favorable than that of the corresponding 1,3-or 2,3-intermediates, presumably due to electronic effects.[11] The same regioselectivity was observed in the cocyclotrimerization of alkyl propiolates with allenes.[11] There is no partially intermolecular [2 + 2 + 2] cycloaddition product **20** from diyne **7** and allene. Although the exact reason is not clear, it appears that both electronic and steric effects make the formation of metalacycle **19** from diyne **7** less favorable. Consequently, no product **20** was observed.

To conclude, we have demonstrated the first nickel-catalyzed [2 + 2 + 2] cycloaddition of diynes with allenes. The catalytic reaction is highly regioselective and chemoselective, furnishing polysubstituted benzene derivatives in good to excellent yields. This methodology is compatible with several functional groups tested. The allenes are synthetically equivalent to monosubstituted alkynes, but they are superior to them in terms of the reactivity and selectivity. Although, this protocol holds good only for electron-deficient diynes, it offers a solution to the ongoing regio- and chemoselective problem affording exclusively the corresponding meta-isomers.

Experimental Section

All reactions were conducted under nitrogen atmosphere on a dual-manifold Schlenk line, unless otherwise mentioned, and in oven-dried glassware. The solvent CH_3CN was dried according to known methods and distilled prior to use.[19] Reagents and chemicals were used as purchased without further purification. Starting materials diynes[20] and allenes[21] were synthesized according to literature procedures. The catalyst Ni(dppe)Br_2 was prepared by following the literature procedures.[22] The purity of each product was checked by NMR analysis.

General Procedure for the Preparation of Polysubstituted Benzene Derivatives 4a−l and 6a−g. Ni(dppe)Br_2 (31 mg, 0.05 mmol) and Zn (180 mg, 2.75 mmol) were placed in a screw-capped vessel. The vial was sealed with a septum and flushed several times with nitrogen. Diynes **1a**−**c** and **5a**−**c** (1.00 mmol), respectively, allenes (1.2 mmol), and CH_3CN (2 mL) were injected into the reaction mixture via a syringe. The septum was removed, and the vial was sealed with a screw cap quickly under nitrogen. The reaction mixture was stirred at 80 °C for 8 h. The crude reaction mixture was diluted with CH_2Cl_2, filtered through a thin Celite pad, and washed several times with CH_2Cl_2. The solution was concentrated in vacuo. The residue was chromatographed on a silica gel column (hexane/EtOAc = 9/1) to give pure product.

General Procedure for the Preparation of Polysubstituted Benzene Derivatives 9a,b. Ni(dppe)Br_2 (31 mg, 0.05 mmol) and Zn (180 mg, 2.75 mmol) were placed in a screw-capped vessel. The vial was sealed with a septum and flushed several times with nitrogen. Diyne **7** (2.00 mmol), allenes (1.2

(16) For production of a cobaltacyclopentene complex, see: (a) Wakatsuki, Y.; Aoki, K.; Yamazuki, H. *J. Am. Chem. Soc.* **1974**, *96*, 5284. (b) Wakatsuki, Y.; Aoki, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1979**, *101*, 1123.

(17) Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 549.

(18) Pasto, D. J.; Huang, N.-Z.; Eigenbrot, C. W. *J. Am. Chem. Soc.* **1985**, *107*, 3160.

(19) Perrin, D. D.; Armarego, W. L. F. In *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: New York, 1988.

(20) Piers, E.; Skerlj, R. T. *Can. J. Chem.* **1994**, *72*, 2468.

(21) Brandsma, L.; Verkruijisse, H. D. *Synthesis of Acetylene, Allenes and Cumulenes;* Elsevier: New York, 1981.

(22) Colquhoun, H. M.; Holton, J.; Thompson, D. J.; Twigg, M. V. *New Pathways for Organic Synthesis—Practical Applications of Transition Metals;* Plenum Press: New York, 1988.

mmol), and CH_3CN (2 mL) were injected into the reaction mixture via a syringe. The septum was removed, and the vial was sealed with a screw cap quickly under nitrogen. The reaction mixture was stirred at 80 °C for 8 h. The crude reaction mixture was diluted with CH_2Cl_2, filtered through a thin Celite pad, and concentrated in vacuo. The residue was chromatographed on a silica gel column (hexane/EtOAc = 9/1) to give pure product.

Product yields of these reactions are listed in Tables 1 and 2, while important spectral data of these polysubstituted benzene derivatives are shown below or listed in the Supporting Information.

Dimethyl 2-pentyl-5,6,7,8-tetrahydro-1,4-naphthalenedicarboxylate (4a): colorless oil; R_f = 0.86 (hexane/EtOAc = 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.98 (bs, 2H), 2.68 (bs, 2H), 2.48 (t, J = 8.0 Hz, 2H), 1.73 (m, 4H), 1.55 (m, 2H), 1.27 (m, 4H), 0.86 (t, J = 6.5 Hz, 3H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 170.23, 168.26, 137.21, 136.17, 136.08, 134.55, 131.24, 128.36, 51.91, 33.26, 31.65, 30.83, 27.67, 27.39, 22.52, 22.38, 22.14, 13.92; HRMS calcd for $C_{19}H_{26}O_4$ 318.1831, found 318.1832.

Dimethyl 2-benzyl-5,6,7,8-tetrahydro-1,4-naphthalenedicarboxylate (4b): colorless oil; R_f = 0.55 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.29−7.13 (m, 5H), 3.93 (s, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 3.02 (bs, 2H), 2.72 (bs, 2H), 1.76 (m, 4H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 169.94, 168.09, 139.77, 137.42, 136.85, 135.02, 134.46, 131.50, 129.24, 128.91, 128.40, 126.26, 51.91, 39.00, 27.68, 27.45, 22.44, 22.08; HRMS calcd for $C_{21}H_{22}O_4$ 338.1518, found 338.1524.

Dimethyl 2-(4-chlorobenzyl)-5,6,7,8-tetrahydro-1,4-naphthalenedicarboxylate (4c): colorless oil; R_f = 0.82 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.21 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 3.87 (s, 2H), 3.83 (s, 3H), 3.75 (s, 3H), 3.00 (bs, 2H), 2.69 (bs, 2H), 1.74 (m, 4H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 169.85, 167.97, 138.26, 137.34, 137.13, 135.17, 133.86, 132.08, 131.56, 130.21, 129.11, 128.49, 51.99, 38.29, 27.71, 27.47, 22.38, 22.02; HRMS calcd for $C_{21}H_{21}ClO_4$ 372.1128, found 372.1131.

Dimethyl 2-(cyclopentylmethyl)-5,6,7,8-tetrahydro-1,4-naphthalenedicarboxylate (4h): colorless oil; R_f = 0.84 (hexane/EtOAc = 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.98 (bs, 2H), 2.68 (bs, 2H), 2.50 (d, J = 7.5 Hz, 2H), 2.05 (m, 1H), 1.72 (m, 4H), 1.68−1.16 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.32, 168.29, 137.38, 136.15, 135.54, 134.45, 131.02, 128.74, 52.00, 41.27, 38.94, 32.47, 27.70, 27.42, 24.81, 22.51, 22.12; HRMS calcd for $C_{20}H_{26}O_4$ 330.1831, found 330.1834.

Dimethyl 5-(cyclohexylmethyl)-4,7-indanedicarboxylate (4k): colorless oil; R_f = 0.72 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.21 (t, J = 7.6 Hz, 2H), 2.92 (t, J = 7.6 Hz, 2H), 2.58 (d, J = 7.2 Hz, 2H), 2.04 (m, 2H), 1.64−0.84 (m, 11H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 169.35, 167.16, 144.73, 144.56, 137.51, 133.01, 130.38, 127.19, 51.83, 41.00, 39.77, 33.55, 33.10, 32.22, 26.41, 26.23, 24.77; HRMS calcd for $C_{20}H_{26}O_4$ 330.1831, found 330.1834.

Dimethyl 5-benzyl-1,3-dihydro-4,7-isobenzofurandicarboxylate (4l): colorless oil; R_f = 0.34 (hexane/EtOAc = 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.26−7.08 (m, 5H), 5.35 (s, 2H), 5.21 (s, 2H), 4.33 (s, 2H), 3.89 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.92, 165.75, 142.84, 141.25, 140.86, 140.34, 132.37, 128.64, 128.57, 128.43, 126.35, 126.21, 74.47, 74.02, 52.35, 52.11, 39.38; HRMS calcd for $C_{19}H_{18}O_5$ 326.1154, found 326.1157.

Methyl 3-pentyl-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (6a): colorless oil; R_f = 0.91 (hexane/EtOAc = 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.01 (s, 1H), 3.84 (s, 3H), 2.98 (bs, 2H), 2.76 (bs, 2H), 2.50 (t, J = 8.0 Hz, 2H), 1.74 (m, 4H), 1.56 (m, 2H), 1.29 (m, 4H), 0.86 (t, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.79, 139.51, 138.14, 135.68, 133.12, 130.01, 127.82, 51.72, 35.23, 31.49, 31.11, 30.20, 27.47, 23.22, 22.52, 22.40, 14.01; HRMS calcd for $C_{17}H_{24}O_2$ 260.1776, found 260.1779.

Methyl 3-(cyclohexylmethyl)-5,6,7,8-tetrahydro-1-naphthalenecarboxylate (6b): colorless oil; R_f = 0.91 (hexane/EtOAc = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 6.97 (s, 1H), 3.84 (s, 3H), 2.98 (bs, 1H), 2.76 (bs, 1H), 2.39 (d, J = 6.8 Hz, 2H), 1.74 (m, 4H), 1.66−0.85 (m, 11H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 168.81, 137.92, 135.68, 133.88, 133.79, 129.85, 128.56, 51.72, 43.37, 39.64, 33.10, 30.22, 27.47, 26.52, 26.26, 23.24, 22.55; HRMS calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1937.

Methyl 6-benzyl-4-indanecarboxylate (6d): colorless oil; R_f = 0.68 (hexane/EtOAc = 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.27−7.17 (m, 6H), 3.96 (s, 2H), 3.85 (s, 3H), 3.21 (t, J = 7.5 Hz, 2H), 2.85 (t, J = 7.5 Hz, 2H), 2.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.67, 146.29, 144.58, 141.02, 139.21, 129.22, 128.80, 128.49, 127.85, 126.29, 126.11, 51.65, 41.53, 33.55, 32.48, 25.01; HRMS calcd for $C_{18}H_{18}O_2$ 266.1307, found 266.1309.

Methyl 6-(cyclopentylmethyl)-4-indanecarboxylate (6f): colorless oil; R_f = 0.92 (hexane/EtOAc = 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.19 (s, 1H), 3.86 (s, 3H), 3.20 (t, J = 7.5 Hz, 2H), 2.87 (t, J = 7.5 H, 2H), 2.57 (d, J = 7.5 Hz, 2H), 2.06 (m, 3H), 1.67−1.14 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.83, 145.78, 143.92, 140.44, 129.16, 128.27, 125.94, 51.59, 41.99, 41.59, 33.54, 32.48, 32.37, 25.00, 24.87; HRMS calcd for $C_{17}H_{22}O_2$ 258.1620, found 258.1621.

Methyl 6-benzyl-1,3-dihydro-4-isobenzofurancarboxylate (6g): colorless oil; R_f = 0.39 (hexane/EtOAc = 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.30−7.10 (m, 6H), 5.33 (s, 2H), 5.06 (s, 2H), 4.02 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.50, 141.12, 140.42, 139.61, 129.40, 128.81, 128.64, 128.24, 126.38, 125.86, 124.34, 74.74, 72.89, 52.07, 41.48; HRMS calcd for $C_{17}H_{16}O_3$ 268.1099, found 268.1098.

Dimethyl 3,6-di(5-heptynyl)-4-pentylphthalate (9a): colorless oil; R_f = 0.57 (hexane/EtOAc = 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.65 (t, J = 8 Hz, 2H), 2.59 (m, 4H), 2.11 (m, 4H), 1.75 (s, 6H), 1.61−1.21 (m, 14H), 0.88 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.72, 168.73, 144.19, 138.98, 136.14, 133.32, 132.73, 128.59, 78.96, 78.89, 75.61, 75.56, 52.22, 52.17, 33.06, 32.68, 31.82, 30.94, 30.64, 30.42, 29.30, 29.23, 28.78, 22.50, 18.50, 18.37, 14.00; HRMS calcd for $C_{29}H_{40}O_4$ 452.2927, found 452.2932.

Dimethyl 4-(cyclohexylmethyl)-3,6-di(5-heptynyl)phthalate (9b): colorless oil; R_f = 0.54 (hexane/EtOAc = 9/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.67 (t, J = 7.5 Hz, 2H), 2.60 (t, J = 6.5 Hz, 2H), 2.47 (d, J = 7.5 Hz, 2H), 2.10 (m, 4H), 1.75 (s, 6H), 1.66−0.89 (m, 19H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.76, 168.77, 142.54, 138.50, 136.64, 133.78, 133.30, 128.67, 78.97, 75.65, 52.23, 52.18, 40.68, 39.45, 33.36, 33.01, 30.63, 30.41, 29.35, 29.27, 26.44, 26.31, 18.51, 18.36; HRMS calcd for $C_{31}H_{42}O_4$ 478.3083, found 478.3084.

Acknowledgment. We thank the National Science Council of the Republic of China (NSC 90-2811-M-007-034) for support of this research.

Supporting Information Available: Spectral data for compounds **4d**−**g**, **4i**, **4j**, **6c**, and **6e**; ^{1}H NMR spectra of all compounds and NOE data for compounds **9a,b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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