ORGANIC
LETTERS

2001
Vol. 3, No. 26
4233−4236

Nickel-Catalyzed Highly Regio- and Chemoselective Cocyclotrimerization of Propiolates with Allenes: A Novel Route to Polysubstituted Benzene Derivatives

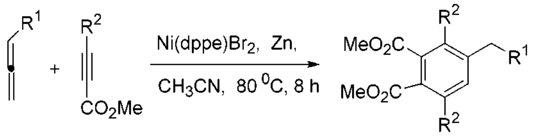
Muthian Shanmugasundaram, Ming-Si Wu, and Chien-Hong Cheng*

Department of Chemistry, Tsing Hua University, Hsinchu, Taiwan 300

chcheng@mx.nthu.edu.tw

Received October 16, 2001

ABSTRACT



The Ni(dppe)Br$_2$/Zn system effectively catalyzes the cocyclotrimerization of propiolates with allenes. The reaction is highly regio- and chemoselective to afford polysubstituted benzene derivatives in good to excellent yields.

The transition metal-catalyzed [2 + 2 + 2] cycloaddition is a powerful method for the construction of polysubstituted benzene derivatives.[1] Though a plethora of reports have appeared for the past few decades,[2] the intermolecular version of this cycloaddition still suffers poor regio- and chemoselectivity, severely limiting the synthetic application of this method. The nickel-catalyzed cocyclotrimerization of two alkynes and an alkene has been reported, but the alkenes used were limited to α,β-unsaturated ketones and 7-oxabenzonorbornadienes.[3,4] In addition, excess alkene was required to suppress the competing alkyne trimerization.[5] Our interest in metal-mediated allene chemistry[6] prompted us to explore the possibility of using allenes in the cocyclization with alkynes. In this Letter, we disclose the first example of nickel-catalyzed cocyclotrimerization of two propiolates with an allene, providing an efficient method for the synthesis of polysubstituted benzene derivatives in a highly regio- and chemoselective fashion.

The reaction of *n*-butylallene (**1a**) with DMAD (**2a**) was initially conducted at 80 °C for 8 h in CH$_3$CN in the presence of 5 mol % of Ni(dppe)Br$_2$ (dppe = bis(diphenylphosphino)ethane) and zinc metal powder. The reaction gave **4a** in 87% yield and the homo cyclotrimerization product of **2a** in less than 5% yield. The structure of **4a** was confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. Control experiments verified that in the absence of either Ni(dppe)Br$_2$ or zinc powder no reaction occurred. To the best of our knowledge, this is the first intermolecular alkyne−allene

---

(1) Reviews: (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, 23, 539. (b) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (c) Trost, B. M. *Science* **1991**, *254*, 1471. (d) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (e) 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. (f) Gevorgyan, V.; Yamamoto, Y. *J. Organomet. Chem.* **1999**, 576, 232. (g) 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) (a) Ikeda, S.; Mori, N.; Sato, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4779. (b) Ikeda, S.; Watanabe, H.; Sato, Y. *J. Org. Chem.* **1998**, *63*, 7026.

(4) (a) Hsiao, T.-Y.; Santhosh, K. C.; Liou, K.-F.; Cheng, C.-H. *J. Am. Chem. Soc.* **1998**, *120*, 1232. (b) Huang, D.-J.; Sambaiah, T.; Cheng, C.-H. *New. J. Chem.* **1998**, *22*, 1147. (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. *Perkin Trans. 1* **2000**, 195.

(5) 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.

(6) (a) Chang, H.-M.; Cheng, C.-H. *J. Org. Chem.* **2000**, *65*, 1767. (b) Chang, H.-M.; Cheng. C.-H. *Org. Lett.* **2000**, *2*, 3349. (c) Yang, F.-Y.; Wu, M.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2000**, *122*, 7122. (d) Yang, F.-Y.; Cheng, C.-H. *J. Am. Chem. Soc.* **2001**, *123*, 761.

10.1021/ol0169168 CCC: $20.00

cocyclotrimerization ever reported. Presumably, the formation of **4a** is via a [2 + 2 + 2] cocyclotrimerization of DMAD and *n*-butylallene to give intermediate **3a**, followed by isomerization to yield the final highly substituted benzene derivative **4a**. The other possible cocyclotrimerization product resulting from two *n*-butylallene and a DMAD molecules was not observed even when the reaction was carried out in a large excess of the allene.

To optimize the present catalytic reaction, the catalytic activities of various nickel phosphine complexes for the cocyclotrimerization of *n*-butylallene with DMAD were tested. The results are shown in Table 1. Monodentate phosphine complexes $Ni(PPh_3)_2Br_2$ and $Ni(PPh_2Me)_2Br_2$ exhibited low catalytic activity, affording **4a** in 22% and 5% yields, respectively (entries 1 and 2). The presence of excess PPh_3 strongly retarded the reaction (entry 3). Simple nickel complexes $NiBr_2$ and $Ni(COD)_2$ also catalyzed the reaction but in low product yield (entries 4 and 5). Nickel complexes with bidentate phosphine ligands dppm, dppp and dppb, were also examined and were shown to give low yields of **4a** (entries 6−8). The best yield of **4a** in 87% was obtained using $Ni(dppe)Br_2$ as the catalyst (entry 9). Studies on the effect of solvent revealed that acetonitrile was the solvent of choice. No reaction occurred in THF, toluene, and DMF (entries 10−12).

Table 1. Effect of Nickel Complex and Solvent on the [2 + 2 + 2] Cocyclotrimerization of DMAD with *n*-Butylallene[a]

entry	catalyst	solvent	yield, %[b]
1	$Ni(PPh_3)_2Br_2$	CH_3CN	22
2	$Ni(PPh_2Me)_2Br_2$	CH_3CN	5
3	$Ni(PPh_3)_2Br_2/PPh_3$[c]	CH_3CN	0
4	$NiBr_2$	CH_3CN	32
5	$Ni(COD)_2$[d]	CH_3CN	9
6	$Ni(dppm)Br_2$	CH_3CN	9
7	$Ni(dppp)Br_2$	CH_3CN	28
8	$Ni(dppb)Br_2$	CH_3CN	11
9	$Ni(dppe)Br_2$	CH_3CN	87
10	$Ni(dppe)Br_2$	THF	0
11	$Ni(dppe)Br_2$	toluene	0
12	$Ni(dppe)Br_2$	DMF	0
13		CH_3CN	0
14[e]	$Ni(dppe)Br_2$	CH_3CN	85

[a] Reactions of *n*-butylallene (1.10 mmol) with DMAD (2.00 mmol) were carried out at 80 °C for 8 h in 2 mL of solvent by using 5 mol % of Ni-catalyst and Zn (2.75 mmol). [b] Yields were measured from crude products by the ^1H NMR integration method using mesitylene as an internal standard. [c] 1.00 mmol of PPh_3 was used. [d] No zinc was used. [e] 10.0 mmol of *n*-butylallene was used.

Similarly, cyclohexylallene (**1b**), cyclopentylallene (**1c**), and phenylallene (**1d**) undergo cocyclotrimerization with DMAD in the presence of $Ni(dppe)Br_2$ and zinc powder to afford the corresponding products **4b−d** in 72%, 69%, and 71% yields, respectively (Table 2, entries 2−4). These products were fully characterized by their spectroscopic data.

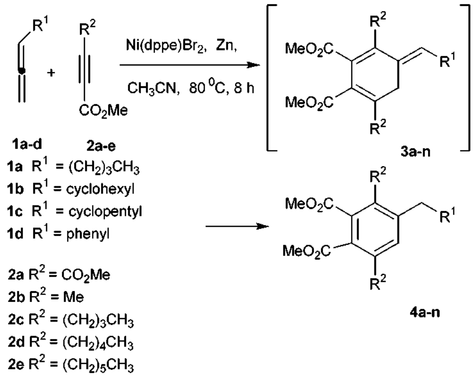
The present $Ni(dppe)Br_2/Zn$ system also effectively catalyzes the cocyclotrimerization of allenes with various substituted propiolates. The reaction of **1a** with methyl 2-butynoate (**2b**) is highly regio- and chemoselective, affording **4e** as the sole product in 84% isolated yield. No other isomer was seen in the ^1H NMR of the crude reaction mixture. The regiochemical assignment is based on the diagnostic chemical shift of the aromatic proton that appears as a singlet at δ 7.04 and on the results of difference NOE studies. Selective irradiation of the aromatic proton at δ 7.04 led to an enhancement of the signals at δ 2.56 by 2.06% and at δ 2.37 by 2.37% for the methylene and methyl protons, respectively, attached directly to the aromatic ring, whereas irradiation of the methylene protons at δ 2.56 caused an enhancement of the signals at δ 7.04 by 1.32% and δ 2.23 by 1.86% for the aromatic and the methyl protons, respectively. These NOE data strongly support the proposed structure for product **4e** shown in Scheme 1 and exclude other possible regioisomers.

Table 2. Results of Cocyclotrimerization of Allenes **1a−d** with Propiolates **2a−e**

entry	R^1	R^2	product	yield, %[a]
1	$-(CH_2)_3CH_3$	$-CO_2Me$	**4a**	80
2	-cyclohexyl	$-CO_2Me$	**4b**	72
3	-cyclopentyl	$-CO_2Me$	**4c**	69
4	-phenyl	$-CO_2Me$	**4d**	71
5	$-(CH_2)_3CH_3$	-Me	**4e**	84
6	$-(CH_2)_3CH_3$	$-(CH_2)_3CH_3$	**4f**	79
7	$-(CH_2)_3CH_3$	$-(CH_2)_4CH_3$	**4g**	82
8	$-(CH_2)_3CH_3$	$-(CH_2)_5CH_3$	**4h**	71
9	-cyclohexyl	-Me	**4i**	86
10	-cyclohexyl	$-(CH_2)_3CH_3$	**4j**	79
11	-cyclohexyl	$-(CH_2)_4CH_3$	**4k**	84
12	-cyclopentyl	-Me	**4l**	80
13	-cyclopentyl	$-(CH_2)_3CH_3$	**4m**	78
14	-phenyl	-Me	**4n**	75

[a] Isolated yields.

Scheme 1

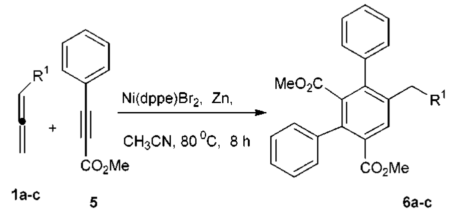


In a similar manner, alkyl-substituted propiolates **2b−e** react smoothly with **1a−d** catalyzed by the $Ni(dppe)Br_2/Zn$ system to yield products **4f−n** in good to excellent yields

(Table 2, entries 6−14). The [2 + 2 + 2] cocyclotrimerization is completely regioselective and highly chemoselective. In all of these reactions (Scheme 1 and Table 2), only one regioisomer of cocyclotrimerization was observed for each reaction. For methyl 2-butynoate (**2b**), a trace of homo cyclotrimerization product was also detected. For the long chain alkyl propiolates **2c**−**e**, no homo cyclotrimerization product was found in the ^{1}H NMR spectra of the crude products. Again, these cocyclotrimerization products **4f**−**n** show a characteristic singlet at ~7 ppm and the NOE studies of these products are consistent with the proposed structure that the two ester groups are ortho to each other and the two substituents R^2 of the propiolates are para to each other and ortho to the allene moiety.

Unlike alkyl-substituted propiolates **2b**−**e**, methyl phenylpropiolate (**5**) undergoes cocyclotrimerization with allenes to give products with different regiochemistry (Scheme 2). Thus, the reaction of **5** with *n*-butylallene (**1a**) under our standard reaction conditions afforded **6a** in 69% yield. This product shows a characteristic singlet at δ 7.37 for the proton on the benzene ring. The regiochemistry of this product is established unambiguously by the results of NOE experiments. Similarly, the reaction of **5** with cyclohexylallene **(1b)** and cyclopentylallene (**1c**) afforded **6b** and **6c** in 70% and 65% yields, respectively. The regiochemistry of **6b** and **6c** is the same as that of **6a** based on the NMR data and NOE experiments.

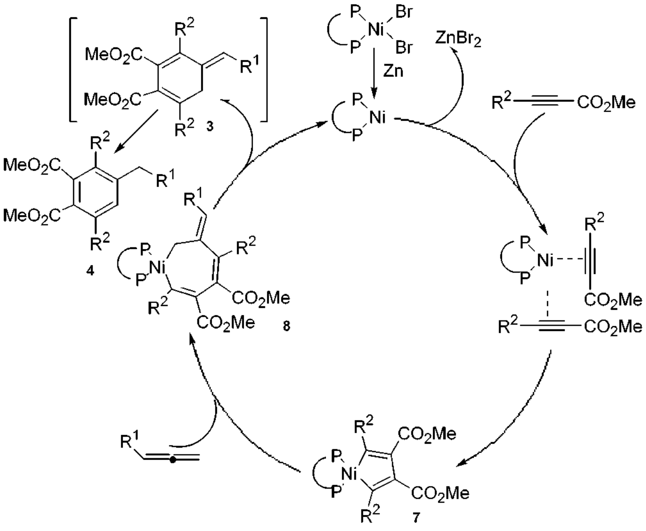
Scheme 2



In addition to the inherent interest of the present reaction that forms polysubstituted benzene derivatives in a completely regioselective fashion from propiolates and allenes, several intriguing features deserve comment. First, the reaction exhibits great chemoselectivity with the allenes used. Only the unsubstituted terminal carbon−carbon double bonds of allenes are involved in the cycloaddition. Second, the cycloaddition selectively reacts with two alkyne molecules and an allene molecule to afford the present cocyclotrimerization product. Under our standard conditions, the ratios of alkynes to allenes are kept nearly 2:1. The competing homo cyclotrimerization of propiolate is almost completely suppressed, and only a trace of homo trimerization products was seen in a few reactions. This is in striking contrast to other cycloadditions that require excess alkene to suppress the competing cyclotrimerization of an alkyne.[5] Third, in the present reaction, allene is synthetically equivalent to a terminal alkyne. However, it should be noted that the reaction of methyl 2-butynoate with 1-heptyne under our standard conditions resulted in a mixture of products with **4e** in ca. only 30% yield based on the ^{1}H NMR analysis. This result strongly suggests that allenes are much more selective than terminal alkynes in the cocyclotrimeriztion. Finally, no desired [2 + 2 + 2] product was obtained for the reaction of 1-hexyne and phenylacetylene with *n*-butylallene under similar conditions. Therefore, the presence of an electron withdrawing -CO$_2$Me group in the alkyne moiety is essential for the success of the present [2 + 2 + 2] cocyclotrimerization.

On the basis of the organometallic chemistry of nickel and the observed regio- and chemoselectivity of the cocyclotrimerization products, a plausible mechanism is proposed in Scheme 3. The reduction of Ni(II) species by zinc metal initiates the catalytic reaction. Coordination of two molecules of propiolates **2b**−**e** to the nickel center followed by regioselective head-to-head oxidative cyclometalation produces the nickelacyclopentadiene intermediate **7**.[7,8] Coordination of allene and subsequent insertion of this molecule into a Ni(II)−carbon bond gives nickelacycloheptadiene intermediate **8**. Subsequent reductive elimination and isomerization affords product **4** and regenerates the Ni(0) catalyst. For the reaction of methyl phenylpropiolate (**5**), a head-to-tail oxidative cyclometalation of methyl phenylpropiolate with the nickel center to produce nickelacyclopentadiene intermediate **9** and subsequent insertion of allene to give **10** is clearly involved.

Scheme 3



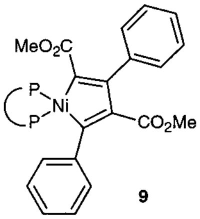
The results in Table 1 showing that Ni(dppe)Br$_2$/Zn is the most active catalytic system for the present cocyclotrimerization may be understood in terms of the ready formation

---

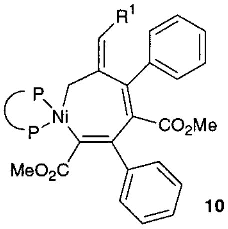
[7] (a) Eisch, J. J.; Glle, J. E. *J. Organomet. Chem.* **1975**, *96*, C23. (b) Eisch, J. J.; Piotrowski, A. M.; Han, K. I.; Kruger, C.; Tsay, Y. H. *Organometallics* **1985**, *4*, 224. For production of a cobaltacyclopentadiene complex, see: (c) Wakatsuki, Y.; Nomura, O.; Kitaura, K.; Morokuma, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 1907.

[8] McAlister, D. R.; Bercaw, J. E.; Bergman, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 1666.

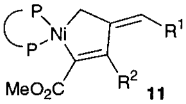
of nickelacycloheptadiene intermediate **8**. The chelating nature and the electron donating ability of the dppe ligand are likely responsible for the easy oxidative cyclometalation. Other bidentate phosphine ligands are less effective, probably due to the larger chelating ring causing greater steric conjecture. Recently, we observed a nickel-catalyzed reaction involving nickelacyclopentene as an intermediate that also shows Ni(dppe)Br_2 is the most effective catalytic system among the nickel complexes used.[9] The observed high regioselectivity of the reaction can be explained in terms of the regioselective formation of metalacycles. For propiolates with a linear alkyl group, the formation of 1,4-dialkylmetalacycle **7** is more favorable than that for the 1,3-intermediate probably because of an electronic effect. On the other hand, for phenylpropiolate **5**, 1,3-diphenylmetalacycle **9** is favored over the corresponding 1,4-substituted one due to steric congestion arising from these bulky substituents with the nickel moiety.



9



10



11

An alternative mechanism involves the coordination of an allene and propiolate to the nickel center to produce the five-membered nickelacyclopentene intermediate[10] **11** followed by insertion of another propiolate into the Ni(II)−carbon bond to yield the seven-membered ring intermediate **8**. This intermediate undergoes reductive elimination to give the final product. This mechanism cannot be totally ruled out.

In summary, we have successfully demonstrated a new nickel-catalyzed [2 + 2 + 2] cocyclotrimerization of propiolates with allenes. The reaction is highly regioselective and chemoselective, affording polysubstituted benzene derivatives in good to excellent yields. Further extension of this work into a partially intramolecular version and a detailed reaction mechanism is currently underway.

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: Experimental procedures, spectral data for all compounds, and NOE data for **4e**, **4i**, **4n**, **6a**, and **6c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0169168

---

[9] Rayabarapu, D. K.; Sambaiah, T.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1286.

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