

# Ni-Catalyzed Highly Regio- and Chemoselective Cocycloaddition of Nonconjugated Diynes with 1,3-Diynes: A Novel Method for Polysubstituted Arylalkynes

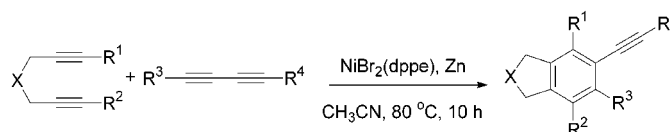
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## ABSTRACT



Effective nickel-catalyzed cocycloaddition of nonconjugated diynes with conjugated diynes yields polysubstituted arylalkynes in good to excellent yields with high regio- and chemoselectivity.

Transition-metal-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes is one of the most general methods for the construction of substituted benzene rings.<sup>1</sup> A partially intramolecular cyclotrimerization approach<sup>2</sup> is more successful and applicable to control the substitution pattern on an arene ring than the cyclotrimerization of two or three alkyne components. One of the straightforward methods for the preparation of arylalkynes is the palladium-mediated coupling of terminal alkynes with aryl halides, which was described<sup>3</sup> for the first time by Sonogashira et al. in 1975.

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Numerous applications of this method have been reported. However, regioselective construction of polysubstituted haloaromatics was achieved by stepwise introduction of the substituents and is not always practical. Under the conditions of Sonogashira coupling, an oxidative homo coupling of terminal alkyne to give the corresponding symmetrical diyne also occurs if oxygen is not excluded completely. Therefore, a large excess of the alkyne is usually employed. These difficulties<sup>4</sup> limit the application of Sonogashira coupling to the preparation of polysubstituted arylalkynes with the required regiochemistry. Palladium-catalyzed benzannulation of unsymmetrical 1,3-diynes yielded<sup>5</sup> a mixture of regioisomers (arylalkynes) with various regioselectivity. Cobalt-catalyzed cycloaddition of 1,3-diynes with cyanoalkynes has also resulted<sup>6</sup> in a mixture of bipyridine derivatives. The only report<sup>7a</sup> available to date involving nickel-catalyzed cocycloaddition of 1,3-diyne and an alkyne (propargyl ether

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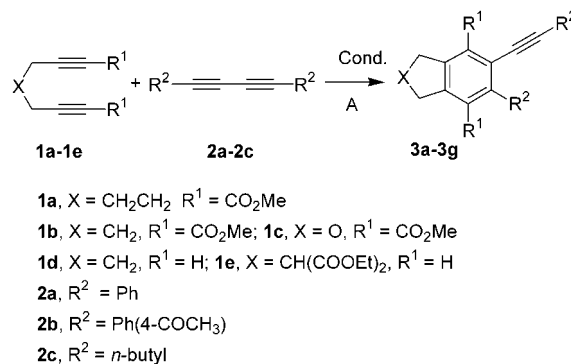
(6) (a) Varela, J. A.; Castedo, L.; Saa, C. *J. Am. Chem. Soc.* **1998**, 120, 12147. (b) Varela, J. A.; Castedo, L.; Saa, C. *Org. Lett.* **1999**, 1, 2141.

analogue) has been limited to a 1,3-diyne having a hydroxyl methyl group, and moreover it has resulted in poor regioselectivity. Recently, a transmetalation reaction of zircona-cyclopentadienes to other organometallic compounds (Ni or Cu) and subsequent insertion of a symmetrical 1,3-diyne has been reported<sup>7b</sup> for the regioselective synthesis of arylalkyne. Yet, this method requires the use of a stoichiometric amount of two transition metals. In our continued interest<sup>8</sup> in the nickel-mediated cycloaddition reactions for the construction of carbocycles, we observed a nickel-catalyzed chemo- and regioselective intermolecular cyclization of nonconjugated diyne **1** with conjugated diyne **2**. The catalytic reaction has been proven to be an efficient and widely applicable method for the synthesis of polysubstituted arylalkynes in a single transformation that does not rely upon aryl halide derivatives as starting material.

To optimize the reaction conditions for this process, the effects of ligand and solvent were examined. Symmetrical diynes **1a** and **2a** were used in these studies. The reaction using Ni(dppe)Br<sub>2</sub> (dppe = bis(diphenylphosphino)ethane) and zinc metal powder at 80 °C for 10 h in CH<sub>3</sub>CN gave arylalkyne **3a** in 82% yield in addition to a homo cyclotrimerization product of **2a** in <5% yield. In the absence of either Ni(dppe)Br<sub>2</sub> or zinc metal power, no product was observed. Monodentate phosphine complexes Ni(PPh<sub>3</sub>)<sub>2</sub>Br<sub>2</sub> and Ni(PPh<sub>2</sub>Me)<sub>2</sub>Br<sub>2</sub> also show catalytic activity for the reaction, but the yields of **3a** are only 20 and 15%, respectively. Addition of extra phosphine ligands strongly retarded the reaction. Simple nickel complexes NiBr<sub>2</sub> and Ni(COD)<sub>2</sub> are less effective and give **3a** in very low yields. Nickel complexes with bidentate phosphine ligands dpmp, dppp, and dppb were shown to afford **3a** in 10, 35 and 38% yields, respectively. In these studies, the yields were measured from the crude product mixtures by the <sup>1</sup>H NMR integration method using mesitylene as an internal standard. On the basis of the results of these studies, Ni(dppe)Br<sub>2</sub> appears to be the choice of nickel complex for the present catalytic reaction. Solvent also plays an important role for the catalytic reaction, and acetonitrile was found to be the most effective solvent. The yield was considerably lower (67%) in DMF, and the reaction did not proceed in THF and toluene.

Other 1,3-diynes **2b** and **2c** also underwent cycloaddition (Scheme 1) reactions with **1a** to afford the corresponding products **3b** and **3c** in 88 and 72% yields, respectively, as summarized in Table 1. In general, alkynes in the absence of electron-withdrawing groups are known<sup>9</sup> to exhibit low reactivity in [2 + 2 + 2] cycloaddition reactions. However,

Scheme 1



**2c** (entry 3) gave the desired product **3c** in 72% yield. The generality of the present catalytic reaction was further examined with respect to the nonconjugated diynes **1**. Methyl nona-2,7-diyne-1,9-dioate **1b** and propargyl ether diester **1c** reacted with **2a** to afford the expected arenes **3d** and **3e** in 88% and 70% yields (entries 4 and 5). On the basis of a

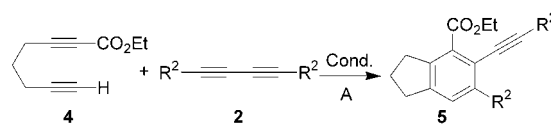
Table 1. Nickel-Catalyzed Intermolecular Coupling of 1,3-Diyne **2** with Nonconjugated Diyne **1**<sup>a</sup>

entry	1	2	X	R <sup>1</sup>	R <sup>2</sup>	3	yield (%)
1	<b>1a</b>	<b>2a</b>	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> Me	Ph	<b>3a</b>	82
2	<b>1a</b>	<b>2b</b>	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> Me	Ph(4-Ac)	<b>3b</b>	88
3	<b>1a</b>	<b>2c</b>	(CH <sub>2</sub> ) <sub>2</sub>	CO <sub>2</sub> Me	<i>n</i> -butyl	<b>3c</b>	72
4	<b>1b</b>	<b>2a</b>	CH <sub>2</sub>	CO <sub>2</sub> Me	Ph	<b>3d</b>	88
5	<b>1c</b>	<b>2a</b>	O	CO <sub>2</sub> Me	Ph	<b>3e</b>	70
6	<b>1d</b>	<b>2a</b>	CH <sub>2</sub>	H	Ph	<b>3f</b>	53
7	<b>1e</b>	<b>2a</b>	CH(COOEt) <sub>2</sub>	H	Ph	<b>3g</b>	62

<sup>a</sup> Reaction conditions A: 1,3-diyne **2a** (1.00 mmol), dimethyl deca-2,8-diyne-1,9-dioate **1a** (1.10 mmol), Ni catalyst (5 mmol %), and Zn (2.75 mmol) in CH<sub>3</sub>CN (2.5 mL) at 80 °C for 10 h.

literature precedent,<sup>10</sup> parent diynes **1d** and **1e** were expected to be less efficient in the cyclotrimerization reaction due to the absence of electron-withdrawing groups. Under our reaction conditions, these diynes offered moderate yields of the expected products (entries 6 and 7). The parent diynes **1d** and **1e** were recovered from the reaction mixture in 18–20% yields, and the homo cyclotrimerization product of **2a** was also isolated in 8–10% yield. The observed high chemoselectivity in these reactions encouraged us to investigate the regioselective cycloaddition of unsymmetrical

Scheme 2



nonconjugated diynes (Scheme 2), and the results are given in Table 2.



(7) (a) Sato, Y.; Ohashi, K.; Mori, M. *Tetrahedron Lett.* **1999**, 40, 5231. (b) Takahashi, T.; Tsai, F. Y.; Li, Y.; Nakajima, K.; Kotori, M. *J. Am. Chem. Soc.* **1999**, 121, 11093.

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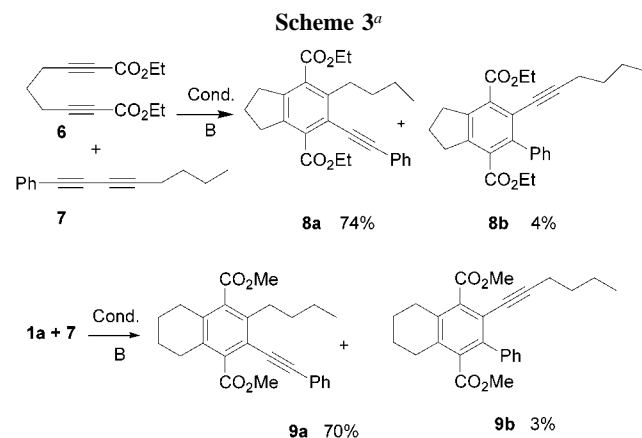
**Table 2.** Regioselective Synthesis of Arylalkynes from 1,3-Diynes **2** and Diynoate **4**

entry	<b>2</b>	<b>5</b>	R <sup>2</sup>	yield (%)
1	<b>2a</b>	<b>5a</b>	Ph	79
2	<b>2b</b>	<b>5b</b>		78
3	<b>2c</b>	<b>5c</b>	<i>n</i> -butyl	66
4	<b>2d</b>	<b>5d</b>		72
5	<b>2e</b>	<b>5e</b>	-SiMe <sub>3</sub>	58

The cyclization reaction of unsymmetrical 2,6-diyne **4** with **2a** under the optimized reaction conditions proceeded smoothly to afford product **5**. It is interesting to note that the cyclization is perfectly regioselective with respect to 1,3-diyne **2a**. The remaining carbon–carbon triple bond in the product is ortho to the ester group. The other regioisomer of **5** was not observed as indicated in the <sup>1</sup>H NMR spectrum of the crude reaction mixture. Similarly, other 1,3-diynes **2b–e** react with **4** to afford products **5b–e** with complete chemo- and regioselectivity. Of these diynes used, **2e** afforded **5e** in the lowest yield (58%) and **2e** was also recovered in 20% yield. The bulky trimethylsilyl group of **2e** appears to hinder the coordination of a triple bond to the nickel center and reduce the reactivity of **2e**.

The structure of **5** was confirmed by <sup>1</sup>H and <sup>13</sup>C NMR and mass spectral data, while the regiochemical assignment is based on the results of difference NOE studies of **5c**. In addition, the crystal structure of **5b** was determined by single-crystal X-ray diffraction and the structures of **5a**, **5d**, and **5e** were assigned by comparing their NMR data with those of **5b** and **5c**.

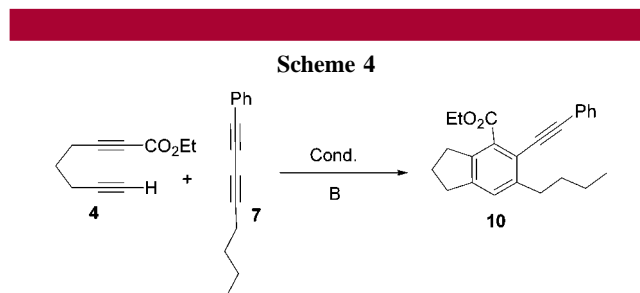
To further understand the regio- and chemoselectivity of the present [2 + 2 + 2] cycloaddition, we investigated the reaction of unsymmetrical 1,3-diyne **7** with symmetrical 1,6-diyne **6** (Scheme 3) in the presence of Ni(dppe)Br<sub>2</sub> and zinc powder at 80 °C. A mixture of isomers **8a** and **8b** was formed



<sup>a</sup> Reaction conditions B: the same as conditions A except the reaction was carried out at room temperature for 24 h.

in a 3:1 ratio (total yield 76%). Interestingly, the same reaction at room temperature afforded **8a** in 74% and **8b** in only 4% yield. The triple bond adjacent to the *n*-butyl group of **7** was involved in the cycloaddition reaction predominantly. These two isomers were separated, and the regiochemistry was determined on the basis of diagnostic signals in <sup>1</sup>H NMR spectrum. The methylene protons of the *n*-butyl group attached to the aromatic ring appear at  $\delta$  2.85 for product **8a**, whereas the methylene protons adjacent to the triple bond in **8b** appear at  $\delta$  2.25. Similarly, when **1a** was treated with **7** at room temperature, excellent regioselectivity was observed. Products **9a** and **9b** in a 19:1 ratio with a total yield of 78% were obtained in the crude reaction mixture. However, we could isolate only **9a** in pure form in 70% yield.

The regio- and chemoselectivity of the present catalytic reaction was best demonstrated by the reaction of unsymmetrical diynes **4** with **7** (Scheme 4) at room temperature.

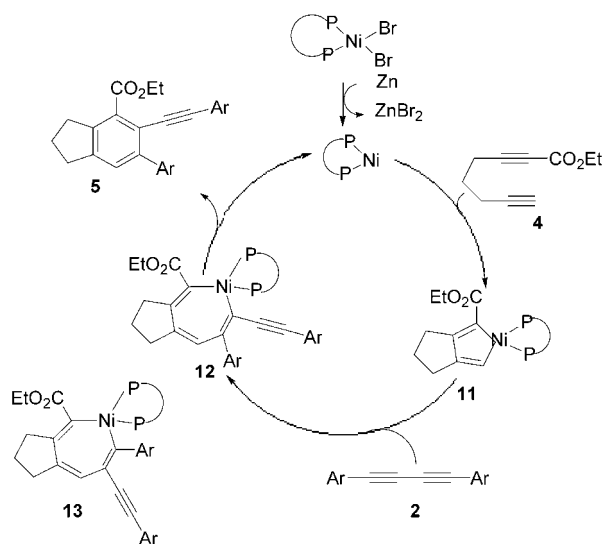


Statistically, four isomers can be formed from the reaction. Analysis of the crude reaction mixture by NMR showed that only two isomers in a 20:2 ratio (82%) were formed. The major isomer was isolated in 72% yield. NOE studies confirmed the structure of this major isomer as shown in **10** to arise from the reaction of the triple bonds adjacent to the *n*-butyl group of **7** with **4**. This result is in good agreement with those observed from the reactions shown in Schemes 2 and 3.

On the basis of the observed chemo- and regioselectivity and the known nickel chemistry, a plausible mechanism for the catalytic cocycloaddition of 1,6-diyne **4** with 1,3-diyne **2** is proposed as shown in Scheme 5. The reduction of Ni(II) to Ni(0) by zinc metal likely initiates the catalytic reaction. Coordination of both carbon–carbon triple bonds in **4** to the nickel center followed by oxidative cyclometallation produces nickelacyclopentadiene intermediate **11**.<sup>7,8</sup> Further coordination of **2** and subsequent insertion of this molecule into a Ni(II)–carbon bond gives nickelacycloheptatriene intermediate **12**. Subsequent reductive elimination affords product **5** and regenerates the Ni(0) catalyst.

The observation that the Ni(dppe)Br<sub>2</sub>/Zn system is most effective for the present cocyclotrimerization may be explained in terms of the chelating nature of the dppe ligand. The bidentate ligand occupies two cis coordination sites of the nickel catalyst and directs the coordination of two alkyne moieties to the nickel center at the other side of the dppe ligand leading to an easy oxidative cyclometallation of the two alkyne moieties to yield nickelacyclopentadiene **11**.

Scheme 5



Other bidentate phosphine ligands are less effective, probably because of the larger chelating ring causing greater steric conjecture. Recently, we observed nickel-catalyzed regio- and chemoselective cocyclotrimerization of alkyne<sup>11a</sup> and allene.<sup>11b</sup> These reactions also show that Ni(dppe)Br<sub>2</sub> is the most effective catalyst among the nickel complexes used. Nickelapentacycles were also proposed as intermediates for these catalytic reactions.

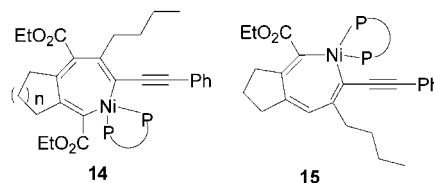
The origin of the observed high regioselectivity of the reaction of **4** with 1,3-diyne **2** can be explained by the insertion pathway depicted in Scheme 5. To reduce the steric interaction between nickel intermediate **11** and 1,3-diyne **2**, a selective insertion of **2** into the less substituted Ni–C bond to form nickelacycloheptatriene **12** or **13** is expected. The regiochemistry of final product **5** is determined by regioselective insertion of **2** to the Ni–C bond. Clearly, the insertion proceeds with complete regioselectivity with the terminal and internal carbons of the 1,3-diyne connected to the unsubstituted carbon and the nickel center, respectively, of intermediate **11**. In other words, nickelacycloheptatriene **12** is formed instead of **13** from **11**. It is known<sup>12</sup> that an alkyne moiety enters the metallacycle with the biggest lobe of its LUMO  $\beta$  to the metal. 1,3-Diynes reportedly<sup>6a</sup> have their biggest LUMO at the terminal carbons. This is expected

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to be  $\beta$  to the nickel center and accounts for the observed regiochemistry.

The chemo- and regioselectivity of 1,3-diyne **7** in the cocycloaddition with symmetrical diynes **6** and **1a** and unsymmetrical diynes **4** is intriguing and can be understood in terms of the formation of nickelacycles **14** and **15**. In all



of these reactions, the insertion of the triple bond adjacent to *n*-butyl group of **7** into the nickelacyclopentadiene intermediate occurs predominantly (Schemes 3 and 4). This result is surprising in view of the result from the competition reaction of diphenyl-1,3-diyne (**2a**, 1 mmol) and di-*n*-butyl-1,3-diyne (**2c**, 1 mmol) with **1a** (0.5 mmol) in acetonitrile in the presence of Ni(dppe)Br<sub>2</sub> and Zn metal powder at ambient temperature. The cycloaddition product from this competition is exclusively **3a** derived from **1a** and **2a**, and there is no product from **1a** and **2c**. The reason for the observed reactivity difference of 1,3-diynes **2a**, **2d**, and **7** is still unclear. Further studies to unravel the detailed mechanistic pathways are necessary to understand the observed unusual regioselectivity of these cocycloaddition reactions.

In conclusion, to the best of our knowledge, this is the first example of chemo- and regioselectively controlled nickel-catalyzed intermolecular cycloaddition between non-conjugated diynes and conjugated diynes leading to potential synthetic intermediate arylalkynes. Further mechanistic studies, the extension of this protocol to 1,3,5-triynes, and the synthesis of natural and unnatural products containing biaryls from suitable 1,3-diynes are in progress.

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**Supporting Information Available:** Experimental procedures, spectral data for all compounds, NOE data for **5c** and **10**, X-ray structure of **5b**, and <sup>1</sup>H NMR spectra of compounds **3a–g**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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