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A Strictly “Pair”-Selective Synthesis of Conjugated Diynes via Pd-Catalyzed Cross Coupling of 1,3-Diynylzincs: A Superior Alternative to the Cadiot–Chodkiewicz Reaction

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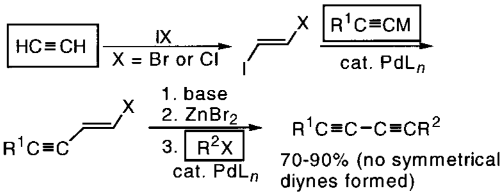
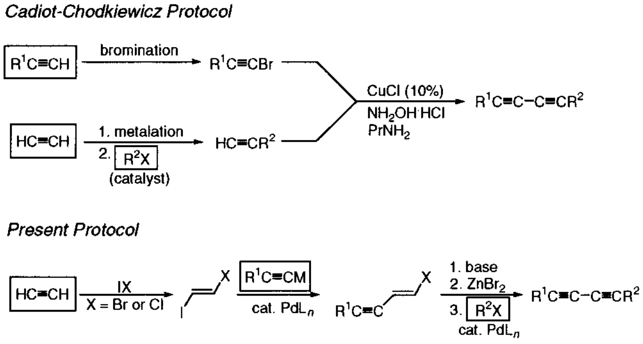
ABSTRACT



A strictly “pair”-selective synthesis of conjugated diynes via Pd-catalyzed cross coupling of 1,3-diynylzincs is described. This method, like the Cadiot–Chodkiewicz reaction, requires three steps for the synthesis of $R^1C{\equiv}CC{\equiv}CR^2$ from $R^1C{\equiv}CH$, R^2X, and $HC{\equiv}CH$. However, the high “pair”-selectivity permitting high-yield production of the desired conjugated diynes without separation of symmetrical diynes promises to make the present protocol superior to the Cadiot–Chodkiewicz reaction in many cases.

The Cadiot−Chodkiewicz reaction[1,2] represents the current benchmark for the synthesis of conjugated diynes. However, it is known that the reaction is plagued with the formation of one or both of the undesired homocoupling diynes, often leading to low yields of the desired products and technical difficulties associated with the delicate product separation. We report herein a strictly “pair”-selective synthesis of conjugated diynes containing one or two aryl, alkenyl, and/or alkyl groups via Pd-catalyzed cross coupling of 1,3-diynylzincs. Both the Cadiot−Chodkiewicz protocol and that reported herein require three steps for the synthesis of $R^1C{\equiv}CC{\equiv}CR^2$ from one alkyne ($R^1C{\equiv}CH$), one organyl halide or related electrophile (R^2X), and ethyne (Scheme 1). However, the high “pair”-selectivity permitting high-yield production of the desired conjugated diynes without oft

Scheme 1



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[1] (a) Chodkiewicz, W. *Ann. Chim. Paris* **1957**, *2*, 819. (b) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 597−647. (c) Brandsma L.; Vasilevski, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer-Verlag: Berlin, Heidelberg, 1999; pp 49−105.

[2] For other syntheses of conjugated diynes via stoichiometric or catalytic alkynyl-alkynyl coupling, see: (a) Sinclair, J. A.; Brown, H. C. *J. Org. Chem.* **1976**, *41*, 1078. (b) Pelter, A.; Hughes, R.; Smith, K.; Tabata, M. *Tetrahedron Lett.* **1976**, 4385. (c) Zweifel, G.; Stracker, E. C. *Tetrahedron Lett.* **1990**, *31*, 6815. (d) Wityak, J.; Chan, J. B. *Synth. Commun.* **1991**, *21*, 977. (e) Cai, C.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 2053. (f) Alami, M.; Ferri, F. *Tetrahedron Lett.* **1996**, *37*, 2763.

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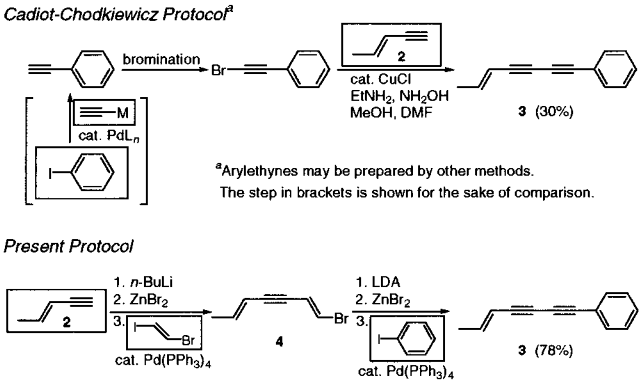
tedious separation of symmetrical diynes promises to make the present protocol vastly superior to the Cadiot−Chodkiewicz reaction in many cases.

We earlier reported a convenient and strictly "pair"-selective synthesis of conjugated diynes with the use of (*E*)-chloroiodoethylene.[3,4] However, the feasibility of incorporating unsaturated organic groups, such as aryl and alkenyl, via Pd-catalyzed cross coupling of 1,3-diynylmetals was not investigated. We recently required such a method in the synthesis of various natural products, such as xerulin[5] and found that the reaction of (*E*)-5-hepten-1,3-diynylzinc bromide with (*E*)-bromoiodoethylene in the presence of 2 mol % of Pd(PPh$_3$)$_4$ provided (1*E*,7*E*)-1-bromo-1,7-nonadiene-3,5-diyne[1] in 65% yield.[6]

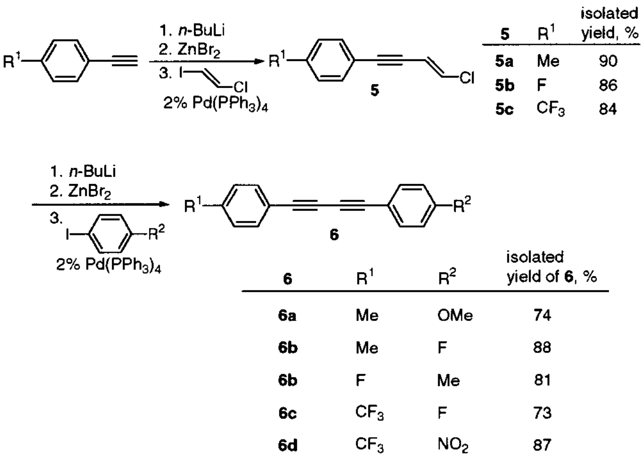
The favorable results mentioned above prompted us to further explore the scope of the conjugated diyne synthesis based on the Pd-catalyzed cross coupling vis-à-vis the Cadiot−Chodkiewicz reaction.[1] Typically, the reaction of (*E*)-3-penten-1-yne (**2**) with 2-bromo-1-phenylethyne under the Cadiot−Chodkiewicz conditions was reported to give (*E*)-1-phenyl-5-heptene-1,3-diyne (**3**) in 30% yield after repeated chromatography.[7,8] In contrast, the reaction of (*E*)-5-hepten-1,3-diynylzinc bromide, generated in situ by the treatment of (1*E*,5*E*)-1-bromo-1,5-heptadien-3-yne (**4**) with LDA and then ZnBr$_2$, with iodobenzene in the presence of 2 mol % of Pd(PPh$_3$)$_4$, cleanly produced **3** in 78% yield after simple short-path chromatography (Scheme 2).

Scheme 2



To see if the vastly different product yields observed with the two protocols shown in Scheme 2 represent a general trend or an exception, three *p*-substituted arylethynes containing Me, F, and CF$_3$ in the *p*-position were converted to arylenyne derivatives (**5**) in excellent yields by the Pd-catalyzed yne−ene coupling of the corresponding arylethynylzinc bromides with (*E*)-chloroiodoethylene. After in situ generation of conjugated diynylzinc derivatives by successive treatment of **5** with *n*-BuLi and ZnBr$_2$, their Pd-catalyzed cross-coupling with four *p*-substituted aryl iodides containing Me, OMe, F, and NO$_2$ in the *p*-position was carried out by using 2 mol % of Pd(PPh$_3$)$_4$ as a catalyst. As indicated by the results shown in Scheme 3, the yields of the desired products were uniformly high (73−88%) regardless of the *p*-substituents in either organozinc reagents or

Scheme 3



5	R^1	isolated yield, %
5a	Me	90
5b	F	86
5c	CF$_3$	84

6	R^1	R^2	isolated yield of **6**, %
6a	Me	OMe	74
6b	Me	F	88
6b	F	Me	81
6c	CF$_3$	F	73
6d	CF$_3$	NO$_2$	87

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(3) Negishi, E.; Okukado, N.; Lovich, S. F.; Luo, F. T. *J. Org. Chem.* **1984**, *49*, 2629.

(4) For a subsequent related study, see: Kende, A. S.; Smith, C. A. *J. Org. Chem.* **1988**, *53*, 2655.

(5) Kuhnt, D.; Anke, T.; Besl, H.; Bross, M.; Herrmann, R.; Mocek, U.; Steffan, B.; Steglich, W. *J. Antibiot.* **1990**, *43*, 1413.

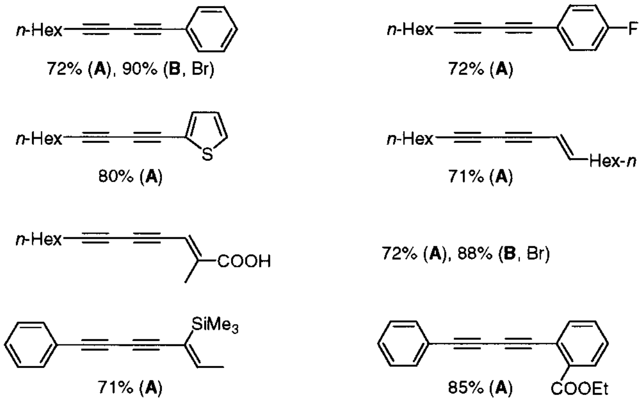
(6) Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65.

(7) Fairbrother, J. R. F.; Jones, E. R. H.; Thaller, V. *J. Chem. Soc. C* **1967**, 1035.

(8) Although no information about the two possible symmetrical diynes was given in the paper, the results and the experimental description suggest their formation to significant extents.

(9) **1-Phenyl-1, 3-decadiyne. Representative Procedure Using (*E*)-Chloroiodoethylene (Procedure A). (a) (*E*)-1-Chloro-1-decen-3-yne.** To a solution of 1-octyne (1.1 g, 10 mmol) in THF (15 mL) was added *n*-BuLi (4.0 mL of a 2.5 M hexane solution, 10 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and treated with a solution of anhydrous ZnBr$_2$ (3.0 g, 13 mmol) in THF (10 mL). (*E*)-Chloroiodoethylene [Van de Walle, H.; Henne, A. *Bull. Cl. Sci., Acad. R. Belg.* **1925**, *11*, 360] (1.9 g, 10 mmol) and Pd(PPh$_3$)$_4$ (231 mg, 2 mol %) were added to the reaction mixture at 0 °C, which was then stirred at 25 °C for 1 h. The reaction mixture was quenched with aqueous NH$_4$Cl, extracted with ether, dried over MgSO$_4$, and concentrated. Purification by column chromatography (silica gel, pentane) afforded 1.46 g (86%) of the title product [Kodaira, K.; Okuhara, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1625] as a colorless liquid. **(b) Conversion of (*E*)-1-Chloro-1-decen-3-yne into 1-Phenyl-1,3-decadiyne.** To a solution of (*E*)-1-chloro-1-decen-3-yne (171 mg, 1.0 mmol) in THF (3 mL) was added *n*-BuLi (0.8 mL of a 2.5 M hexane solution, 2.0 mmol) at −78 °C. The reaction mixture was stirred first at −78 °C for 30 min and then at −30 °C for 30 min and treated with anhydrous ZnBr$_2$ (270 mg, 1.2 mmol) in THF (1 mL). Iodobenzene (204 mg, 1.0 mmol) and Pd(PPh$_3$)$_4$ (23 mg, 2 mol %) were added to the reaction mixture at 0 °C. After 3 h of stirring at 25 °C, analysis of the reaction mixture indicated the formation of the title compound in 93% yield. The reaction mixture was quenched with aqueous NH$_4$Cl, extracted with ether, dried over MgSO$_4$, and concentrated. Purification by column chromatography (silica gel, pentane) afforded 152 mg (72%) of the title product [Ziegler, C. B.; Harris, S. M.; Baldwin, J. E. *J. Org. Chem.* **1987**, *52*, 443]. **Representative Procedure Using (*E*)-Bromoiodoethylene (Procedure B). (a) (*E*)-1-Bromo-1-decen-3-yne.** This compound [Andreini, B. P.; Benetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **1987**, *43*, 4591] was obtained in 74% yield in a manner similar to the preparation of (*E*)-1-chloro-1-decen-3-yne except that (*E*)-bromoiodoethylene was used. **(b) Conversion of (*E*)-1-Bromo-1-decen-3-yne into 1-Phenyl-1,3-decadiyne.** To a solution of (*E*)-1-bromo-1-decen-3-yne (215 mg, 1.0 mmol) in THF (3 mL) was added LDA (1.1 mL of a 2.0 M heptane/ethylbenzene solution, 2.2 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min, treated with anhydrous ZnBr$_2$ (270 mg, 1.2 mmol) in THF (1 mL), and warmed to 0 °C. The reaction of 1,3-decadiynylzinc bromide thus generated with iodobenzene (1.0 mmol) was performed as described in Procedure **A** to give 189 mg (90%) of the title compound.

Scheme 4



aryl iodides. Equally important is the essential absence of any byproducts that might interfere with isolation of the products as pure compounds.

Under the Cadiot−Chodkiewicz conditions employing CuCl (0.1 equiv), $NH_2OH \cdot HCl$ (0.8 equiv), $PrNH_2$ (1.8 equiv), and EtOH, the yields of **6a**−**c** obtained by the reaction of R^1-containing arylethynes with R^2-containing arylethynyl bromides were 34% (**6a**, $R^1 = F$, $R^2 = OMe$), 34% (**6b**, $R^1 = Me$, $R^2 = F$), 48% (**6b**, $R^1 = F$, $R^2 = Me$), and 38% (**6c**, $R^1 = CF_3$, $R^2 = F$). In each case, at least one of the two symmetrical diynes was formed in the range of (20 ± 5)%.

The generality and uniform dependability of the protocol reported herein are further reinforced by the additional results shown in Scheme 4.[9] In most cases, the use of chloroiodoethylene and *n*-BuLi (as a base) may be recommended as a convenient procedure (procedure **A**), but bromoiodoethylene used in conjunction with LDA as a base (procedure **B**) is also satisfactory. It appears that a wide variety of carbon groups can be the substituents in haloenynes, although only some alkyl, aryl, and alkenyl groups are used in this study. (*E*)-1-Chloro-1-decen-3-yne and its bromo analogue were prepared in 86% and 74% yields from 1-octyne by using chloroiodoethylene and bromoiodoethylene, respectively. In each structure shown in Scheme 4, the substituent on the right is introduced last as part of a halide. In cases where an organic bromide is used, it is indicated by Br in parentheses, and **A** and **B** represent procedures **A** and **B**, respectively.

The apparent general applicability, the uniformly high product yields, and the strict “pair”-selectivity discussed above appear to be totally unprecedented in the synthesis of conjugated diynes containing two aryl and/or alkenyl groups,[10] and these favorable features combine to make the present method a superior alternative to the Cadiot−Chodkiewicz[1] and other related reactions[2,10] in many cases.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For other syntheses of conjugated diynes via 1,3-diynes and their derivatives, see: (a) Adams, S.; Potts, K. T. *Synthesis* **1988**, 375. (b) De Graaf, W.; Smits, A.; Boersma, J.; Van Koten, G.; Hoekstra, W. P. M. *Tetrahedron* **1988**, *44*, 6699. (c) Löffler, A.; Himbert, G. *Synthesis* **1991**, 232. (d) Alami, M.; Crousse, B.; Linstrumelle, G. *Tetrahedron Lett.* **1995**, *36*, 3687.