ORGANIC
LETTERS

2001
Vol. 3, No. 20
3111−3113

Highly Satisfactory Procedures for the Pd-Catalyzed Cross Coupling of Aryl Electrophiles with in Situ Generated Alkynylzinc Derivatives†

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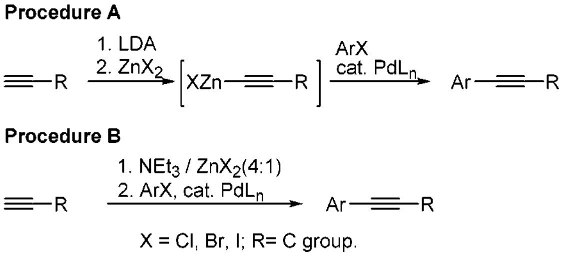
Received June 29, 2001

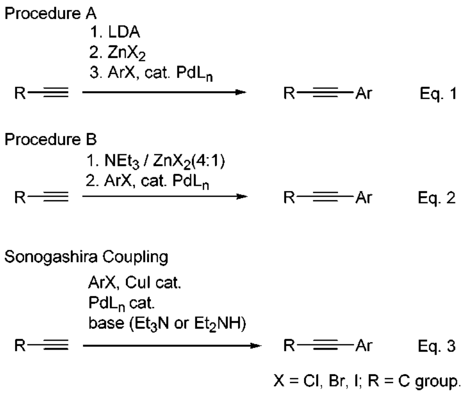
ABSTRACT



Two new and very efficient procedures (Procedures A and B) are reported for the Pd-catalyzed cross coupling of aryl electrophiles with terminal alkynes via their in situ conversion into alkynylzinc derivatives. Procedure A is particularly valuable in cases where electron-deficient alkynes are used, while Procedure B is operationally simple and very satisfactory in less demanding cases.

We report herein that in situ treatment of terminal alkynes with LDA or its equivalent followed by addition of $ZnBr_2$ or $ZnCl_2$ (Procedure A, eq 1 in Scheme 1) serves as a superior procedure in many cases for generating alkynylzinc reagents used in the Pd-catalyzed alkynylation. This procedure alleviates various difficulties associated with the widely used Pd-catalyzed alkynylation procedures such as the Sonogashira[1] and related reactions, as detailed below. We further report that the reaction of free alkynes with organic halides in the presence of premixed Et_3N, $ZnBr_2$ or $ZnCl_2$, and a suitable Pd catalyst (Procedure B, eq 2 in Scheme 1) provides in some cases a convenient alternative to the use of discrete alkynylzinc derivatives requiring rigorous exclusion of moisture. These two new procedures together with the previously reported Pd-catalyzed alkynylation with alkynylzincs[2] promise to provide a significantly more general

Scheme 1



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† Dedicated to Prof. Mario Anastasia on the occasion of his 58th birthday.

[1] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Sonogashira, K.; Yatake, T.; Tohda, Y.; Takahashi, S.; Hagihara, N. *J. Chem. Soc., Chem. Commun.* **1977**, 291. (c) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777. (d) Takahashi, S.; Kuriyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

10.1021/ol010145q CCC: $20.00

and satisfactory method for the Pd-catalyzed alkynylation than the other known methods.

Currently, the method most widely used by far is a hybrid of the Cu-promoted Castro−Stevens reaction[3] and the alkyne version of the Heck reaction,[4] commonly known as the Sonogashira reaction[1] (eq 3 in Scheme 1). Despite its overall excellence, however, various difficulties have also been noted. One widely reported is that, under the standard conditions, electron-deficient alkynes, such as $HC\equiv CCOOR$,[5] where R is Me, Et, and so on, 1-propyn-3-ones,[5h] and $HC\equiv CCF_3$,[6] tend to give their arylated and alkenylated derivatives in unacceptably low yields. Various modifications have been devised to overcome this difficulty. They include the use of (a) propynoic acid readily convertible in situ to electron-rich propynoate anion,[5a,b] (b) 3,3,3-tris(ethoxy)-1-propyne in place of ethyl propynoate, and (c) K_2CO_3[5d,e,g,h] or Na_2CO_3[5f] as a base in place of amines. These modifications are, however, indirect[5a,b,7] and hence somewhat cumbersome and/or of unpredictable and limited applicability.[5d−f] The most recent modification[5h] published during the course of this investigation does appear to represent an exception, but the use of preformed iodonium salts requiring both aryl iodides and sulfonates[8] adds an extra step and poses a question of how to attain the aryl/alkyne ratio of 1:1.

We discovered and developed in the 1977−1978 period the Pd-catalyzed alkynylation with alkynylmetals containing Zn,[2] B,[2c] Sn,[2c] Mg,[2c] and Al[2c] à la that with alkynylsodium of limited applicability reported by Cassar.[9] Of these metals, Zn has repeatedly been shown to be generally of superior reactivity leading to higher selectivity and product yields.[2c,10] Thus, the Pd-catalyzed alkynylation with alkynylzincs has been successfully applied to (a) direct ethynylation[2a,b,10,11] that cannot be achieved by the Sonogashira reaction, (b) synthesis of internal alkynes via (i) arylation and heteroarylation,[2b,c,10a,b,11a,b,12] (ii) alkenylation,[2a,10a,c,11b,c,12c,13,14] and (iii) acylation,[15] as well as (c) selective synthesis of conjugated diynes.[11c,12c,13a] Along with these favorable results, however, some unsatisfactory results, both understandable and inexplicable, have also been reported.[5b,11a,16] For example, we recently reported the synthesis of 3-aryl-2-propynoic esters by the Pd-catalyzed reaction of 3-zinco derivatives of ethyl propynoate with aryl iodides only in modest yields.[11a] The corresponding reaction of 2-propynone derivatives was even less satisfactory. We judged that the difficulty observed with these alkynes must be associated with the use of highly nucleophilic bases, such as *n*-BuLi, routinely used by us and others.[2, 9−16]

Accordingly, “non-nucleophilic” bases, LDA[17] in particular, were used to generate alkynyllithiums to be converted to the Zn derivatives (eq 1 in Scheme 1).[18]

As the results summarized in Table 1 indicate, the yields obtained with $HC\equiv CCOOMe$ are uniformly excellent, while the use of *n*-BuLi in place of LDA led only to traces of the desired cross-coupling products. Furthermore, LDA also permits the use of intrinsically more sensitive 1-propyn-3-ones without noticeable difficulties. We believe that this method (Procedure A) is generally more satisfactory than any of the known methods, including the most recently reported reaction of iodonium salts[5h] for the Pd-catalyzed alkynylation.

As the requirement for rigorous exclusion of moisture by flame drying or other forms of heating at reduced pressures (3 mmHg) has been considered to be an inconvenience in the Pd-catalyzed alkynylzinc coupling as compared with the Sonogashira reaction, we sought an operationally simpler procedure by the use of amines as bases for the Pd-catalyzed alkynylation (Procedure B, eq 2 in Scheme 1),[19] and the following new, simple, and efficient procedure was developed. To premixed $ZnBr_2$ and Et_3N (1:4 ratio) in THF were

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(11) (a) Kotora, M.; Negishi, E. *Synthesis* **1997**, 121. (b) Liu, F.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8591. (c) Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65.

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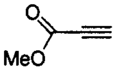
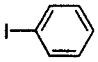
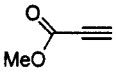
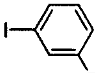
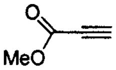
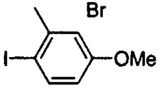
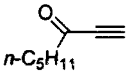
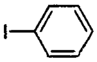
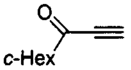
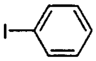
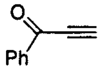
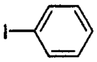
(17) We have previously used LDA to effect both elimination of haloalkenes and generation of alkynyllithiums in the synthesis of conjugated diynes (ref 11c, 12c).

(18) **Procedure A. Methyl 3-(4-Methoxyphenyl)propiolate. Representative Example.** To a solution of *N*,*N*-diisopropylamine (0.57 g, 5.6 mmol) in 5 mL of THF was added *n*-BuLi (2.5 M solution in hexanes, 2.2 mL) at 0 °C in a flame-dried flask under Ar atmosphere. After 10 min, the reaction mixture was successively treated with methyl propiolate (0.5 mL, 5.6 mmol) in 2 mL of THF (−78 °C, 10 min), dry $ZnBr_2$ (1.26 g, 5.61 mmol) in 3 mL of THF (−78 °C, 10 min), 4-iodoanisole (1.09 g. 4.67 mmol), and $Pd(PPh_3)_4$ (0.25 g, 0.23 mmol). The temperature was raised to 23 °C. After 3 h, the reaction mixture was diluted with Et_2O, washed with aqueous NH_4Cl and then with aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Chromatography on silica gel (95/5 hexane/EtOAc, v/v) gave methyl 3-(4-methoxyphenyl)propiolate as light yellow crystals (0.77 g, 87%), mp 41−42 °C.

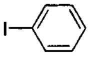
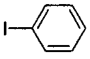
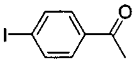
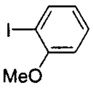
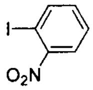
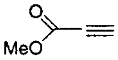
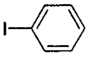
Table 1. Pd-Catalyzed Cross Coupling of Electron-Deficient Alkynes with Aryl Iodides: A Comparative Study

			product yield (%)[a]		
entry	alkyne	I-Ar	procedure A[b]	observed under Sonogashira conditions[c]	observed by others under modified Sonogashira conditions
1			99 (95)	< 1	(98)[d, e]
2			94 (91)	< 1	(33)[d]
3			89 (87)	< 1	(3)[d]
4			98 (95)	< 1	[f]
5			85 (82)	< 1	(65)[g]
6			95 (94)	< 1	(70)[g]

[a] GC yields with isolated yields in parentheses. [b] With 3 mol % of Pd(PPh_3)$_4$ at 23 °C. [c] Performed according to ref 1. [d] With K_2CO_3 as base (ref 5e). [e] In our hands, under the same literature conditions, the reaction gave a very poor yield (<15%). [f] Experiment not performed. [g] With diaryliodonium salts and K_2CO_3 as base (ref 5h).

added an organic halide, a terminal alkyne, and a suitable Pd catalyst.[20] Some other bases, solvents, and reagent ratios were examined for this reaction, but the procedure mentioned above was found to be superior to the other combinations. The reaction did not proceed without $ZnBr_2$ or the Pd catalyst. As the results summarized in Table 2 indicate, Procedure B is very satisfactory in less demanding cases. This procedure is also applicable to the synthesis of methyl 3-phenylpropiolate (entry 6), even though the results are less favorable than those obtained by using Procedure A.

Table 2. Pd-Catalyzed Alkynyl-Aryl Cross Coupling Using Procedure B[a]

entry	alkyne	I-Ar	product yield (%)[b]
1	n-C_6H_{13}—≡		96 (95)
2	TMS—≡		99 (97)
3	n-C_6H_{13}—≡		98 (95)
4	n-C_6H_{13}—≡		89 (87)
5	n-C_6H_{13}—≡		93 (89)
6			78 (75)[c]

[a] Performed with 3 mol % of Pd(PPh_3)$_4$ at 23 °C. [b] GC yields with isolated yields in parentheses. [c] With 3 mol % of $Cl_2Pd(PPh_3)_2$ at 60 °C.

Further extension of the scope of both Procedures A and B by the use of aryl bromides, and chlorides, as well as alkenyl halides is currently underway.

Acknowledgment. We thank the National Institutes of Health (GM 36792) as well as Herbert C. Brown Professorship Fund and other funds provided through Purdue University for support of this research. Johnson-Matthey is also acknowledged for its generous loan of palladium compounds.

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

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(19) **Procedure B. 1-Phenyl-1-octyne. Representative Example.** To a solution of $ZnBr_2$ (0.54 g, 2.4 mmol) in 5 mL of THF was added Et_3N (1.3 mL, 9.6 mmol). The reaction mixture turned red after stirring for 1−3 min at 23 °C. The reaction mixture was then successively treated with iodobenzene (0.48 g, 2 mmol), 1-octyne (0.26 g, 2.4 mmol), and Pd(PPh_3)$_4$ (0.11 g, 0.1 mmol). The reaction was monitored by GC using mesitylene as an internal standard. After 5 h, the reaction mixture was diluted with Et_2O, washed with aqueous NH_4Cl and then with aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. Chromatography on silica gel (hexane) gave 1-phenyl-1-octyne (0.36 g, 95%).

(20) These new conditions do not require anhydrous solvents and $ZnBr_2$, and no inert gas atmosphere is necessary.