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Palladium-catalyzed cross-coupling reaction of alkynylzincs with benzylic electrophiles

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This paper is dedicated to Professor Iwao Ojima of State University of New York at Stony Brook on the occasion of his 60th birthday

Abstract—The reaction of alkynylzinc bromides with benzyl bromides or chlorides in the presence of a catalytic amount of Pd(DPE-phos)Cl₂ in THF at 23 °C cleanly produces the corresponding benzylated alkynes in 73–97% yields. With 10^{-3} mol% of Pd(DPE-phos)Cl₂, the maximum turnover number of 7.1×10^4 has been observed for the formation of PhC=CCH₂Ph. © 2005 Published by Elsevier Ltd.

1. Introduction

Despite the well-known facts that benzyl halides readily undergo oxidative addition to Pd¹ and that the resultant benzylpalladium derivatives participate in cross-coupling reactions with aryl- $^{2-5}$ and alkenylmetals^{2,6,7} containing various metals, such as Zn,³ B,⁴ Sn,^{5,6} and Al,⁷ the corresponding reaction of alkynylmetals with benzylic electrophiles had remained virtually unknown until Sarandeses and his co-workers⁸ reported the reaction of (PhC=C)₃In and (TMSC=C)₃In with PhCH₂Br producing the corresponding benzylated alkynes in excellent yields in the presence of 1 mol% of Pd(dppf)Cl₂.⁹ Earlier attempts in the authors' group to achieve crosscoupling of PhC=CZnBr with PhCH₂Br in THF in the presence 5 mol% of Pd(PPh₃)₂Cl₂ or Pd(PPh₃)₄ led only to very low yields of 1,3-diphenylpropyne. Reinvestigation of the reaction in light of the favorable results reported by Sarandeses and co-workers⁸ improved the product yield to 43% by refluxing the reaction mixture at ca. 70 °C. However, bibenzyl was also produced in up to 47% yield. A more systematic optimization including ligand screening was thus conducted.

2. Results and discussion

As the results summarized in Table 1 indicate, the use of $Pd(DPEphos)Cl_2^{10}$ and $Pd(dppf)Cl_2$ has led to the formation of PhC=CCH_2Ph in excellent yields (entries 9,10,15,16). In particular, the reaction in the presence of 5 mol% of Pd(DPEphos)Cl_2 was complete in 4 h at 23 °C to produce PhC=CCH_2Ph in 97% yield (entry 9). The reaction in the presence of 5 mol% of Pd(dppf)Cl_2 hardly proceeded (<1%) within 4 h at 23 °C (entry 14). In refluxing THF, however, PhC=CCH_2Ph was obtained in 96% yield in 10 h (entry 15).

The superiority of Pd(DPEphos)Cl₂ as compared with Pd(dppf)Cl₂ was magnified, when the turnover numbers (TONs) of the reaction run in the presence of these two catalysts were compared. The maximum TON of 7.1×10^4 accompanied by a $\geq 70\%$ yield of PhC CCH_2Ph was observed with 10^{-3} mol% of Pd(DPEphos) Cl_2 (entry 12), whereas the use of Pd(dppf) Cl_2 at the same 10^{-3} mol% catalyst loading level yielded PhC≡CCH₂Ph only in 17% yield (entry 17). Since none of the catalysts containing monodentate phosphines, that is, PPh₃, (2-furyl)₃P, and ^tBu₃P, was satisfactory (entries 1-8), the use of bidentate ligands may be considered to be critically important under the conditions used. A couple of Ni catalysts, that is, $Ni(PPh_3)_2Cl_2$ and Ni(dppf)Cl₂, were also tested. However, neither proved to be satisfactory, the yield of PhC=CCH₂Ph being ca. 30%.

Keywords: Palladium-catalyzed cross-coupling; Alkynylzincs; Benzylic electrophiles; Benzylated alkynes; Pd(DPEphos)Cl₂.

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Table 1.	Screening	of cataly	ysts for	the reaction	n of PhC≡CZnBr	with PhCH ₂ Br in THF

			3	1	2		
Entry	PdL_n	Mol%	Temp (°C)	Time (h)	1 (%)	2 (%)	3 (%)
1	Pd(PPh ₃) ₄	5	23	4	2	<1	96
2	$Pd(PPh_3)_4$	5	Reflux	10	43	47	<1
3	Pd(PPh ₃) ₂ Cl ₂	5	23	4	1	<1	96
4	Pd(PPh ₃) ₂ Cl ₂	5	Reflux	10	38	41	<1
5	Pd(TFP) ₂ Cl ₂ ^a	5	23	4	5	3	76
6	$Pd(TFP)_2Cl_2$	5	Reflux	10	18	8	<1
7	$Pd(^{t}Bu_{3}P)_{2}$	5	23	4	40	18	30
8	$Pd(^{t}Bu_{3}P)_{2}$	5	Reflux	10	46	21	13
9	Pd(DPEphos)Cl2 ^a	5	23	4	97	1	<1
10	Pd(DPEphos)Cl ₂	10^{-1}	23	8	98 ^b	<1	<1
11	Pd(DPEphos)Cl ₂	10^{-3}	23	10	17	<1	82
12	Pd(DPEphos)Cl ₂	10^{-3}	Reflux	24	71°	<1	24
13	Pd(DPEphos)Cl ₂	10^{-4}	Reflux	24	53	<1	40
14	Pd(dppf)Cl ₂ ^a	5	23	4	<1	<1	97
15	Pd(dppf)Cl ₂	5	Reflux	10	96	<1	<1
16	Pd(dppf)Cl ₂	10^{-1}	Reflux	24	80^{d}	<1	14
17	Pd(dppf)Cl ₂	10^{-3}	Reflux	24	17	<1	80

$BhC = C7nBr + BrCH_{2}Ph$	cat. PdLn		
	тиг		FIICH2/2
3	INF	1	2

^a TFP = tris(2-furyl)phosphine. DPEphos = bis(o-diphenylphosphinophenyl) ether, dppf = 1, 1'-bis(diphenylphosphino)ferrocene.

^b TON = 9.8×10^2 .

 $^{\rm c}$ TON = 7.1 × 10⁴.

 $^{\rm d}$ TON = 8.0 × 10².

In order to find the optimal countercations for the Pdcatalyzed alkynyl-benzylic coupling, several metals, that is, Mg, Zn, In, and Sn as well as Cu used in a catalytic amount (Sonogashira alkynylation)^{11b} were screened for the reaction of phenylethynylmetals with benzyl bromide in the presence of Pd(DPEphos)Cl₂ in THF.¹¹ The results with PhC=CZnBr are summarized in Table 1 (entries 9–13). In addition to Zn, two other metals, that is, B and In, can also serve as satisfactory metal countercations (Table 2, entries 1–3, 5, and 6). On the other hand, the product yields observed with Mg (42%), Sn (57%), and Cu (32%) were low, as indicated in parentheses. While the maximum TON observed with (PhC=C)₃In and accompanied by a ≥65–70% yield was 6.9×10^4 (entry 3), which is comparable with 7.1×10^4 observed with PhC=CZnBr (Table 1, entry 12), that observed with the corresponding borate under the conditions employed was less than 3.2×10^4 , the maximum TON accompanied by a ≥65–70% product yield being 8.3×10^2 .

As zinc salts are significantly less expensive than the corresponding indium salts on either per mole or equivalent basis,¹² zinc was chosen for exploring the scope of the Pd-catalyzed alkynyl–benzyl coupling. As the results summarized in Table 3 indicate, various alkynylzinc

Table 2. Effect of metal countercations on the reaction of $PhC \equiv CML_n$ with $PhCH_2Br$ in the presence of $Pd(DPEphos)Cl_2$ in THF^a

	Pd(DPEphos)Cla	`
$PhC \equiv CML_n + BrCH_2Ph$	<u> </u>	$PhC \equiv CCH_{2}Ph + PhCH_{3}$
"	THE	

		" 3	THF	1	2		
Entry	$PhC \equiv CML_n$	Mol%	Temp (°C)	Time (h)	1 (%)	2 (%)	3 (%)
1	(PhC≡C) ₃ ln	5	23	4	96	<1	<1
2	(PhC=C) ₃ ln	10^{-1}	23	16	95	<1	<1
3	(PhC≡C) ₃ ln	10^{-3}	Reflux	24	69	<1	27
4	(PhC=C) ₃ ln	10^{-4}	Reflux	24	49	<1	50
5	$PhC \equiv CBL_n^b$	5	23	10	90	2	3
6	$PhC \equiv CBL_n$	10^{-1}	Reflux	16	83	<1	9
7	$PhC \equiv CBL_n$	10^{-3}	Reflux	24	31	<1	62
8	PhC=CMgBr	5	23	4	20	6	69
	PhC=CMgBr	5	Reflux	24	42	23	27
9	PhC=CMgBr	0	Reflux	24	2	35	39
10	PhC=CSnBu ₃	5	23	4	<1	<1	94
	PhC=CSnBu ₃	5	Reflux	24	57	<1	<1
11	PhC=CH+Cul ^e	5	23	4	2	1	90
	PhC=CH+Cul ^c	5	Reflux	24	32	14	18

^a All reactions were run with 1.2 equiv of alkynylmetals.

^b $BL_n = B$ -MeO-9-BBN.

^c K₂CO₃ used as an additive.

Table 3. Scope of benzylation of alkynylzinc bromides in the presence of 1 mol% of Pd(DPEphos)Cl₂ in THF^a

1% Pd(DPEphos)Cl₂

 $R^{1}C \equiv CZnBr + ArCH_{2}Br(or CI) \xrightarrow{THF, 23 \ ^{o}C, 10 \ h} R^{1}C \equiv CCH_{2}Ar$

Entry	R^1	ArCH ₂ Br(or Cl)	Yield ^b (%) of R ¹ C≡CCH ₂ Ar
1	Ph	PhCH ₂ Br	96 (91)
2	Ph	PhCH ₂ Cl	89
3	<i>p</i> -Tol	PhCH ₂ Br	94 (89)
4	p-FC ₆ H ₄	PhCH ₂ Br	97 (92)
5	"Hex	p-TolCH ₂ Br	81 (77) ^c
6	"Hex	<i>m</i> -PyCH ₂ Br ^d	80 (76)
7	HOCH ₂ CH ₂	PhCH ₂ Br	73 (70) ^e
8	\bigcirc	PhCH ₂ Br	94 (90)
9	PhC=C	PhCH ₂ Br	96 (93)
10	"HexC=C	PhCH ₂ Br	95 (89)
11	Н	PhCH ₂ Br	95 (91)
12	Me ₃ Si	PhCH ₂ Br	92 (88)

^a All reactions were run with 1.2 equiv of alkynylzinc derivatives generated in situ by treating alkynyllithiums with 1.2 equiv of dry ZnBr₂.
^b By GLC. The numbers in parentheses are isolated yields.

^cp-TolCH₂)₂ was produced in 14% yield.

 d Py = pyridyl.

^e 10% of PhCH₂Br remained.

bromides containing aryl (entries 1–4), alkyl (entries 5– 7), alkenyl (entry 8), alkynyl (entries 9 and 10), H (entry 11), and Me₃Si (entry 12) can produce the corresponding benzylated alkynes in \geq 70% isolated yields. Although the survey of scope with respect to benzyl halides has been limited, the use of PhCH₂Cl (entry 2) indicates that benzyl chloride may be satisfactory, while entry 6 represents a successful use of a heteroaryl-containing benzylic halide.

In principle, the synthesis of benzylated alkynes via Pdcatalyzed cross-coupling can be achieved in several different manners, as shown in Scheme 1.

The results presented above pertain to the Pd-catalyzed alkynyl-benzyl coupling route (Eq. 1). The synthesis of 3-phenylpropyne (entry 11 in Table 3) has also made the alkynylation route shown in Eq. 5 attractive and eminently feasible. On the other hand, the benzyl-alkynyl route (Eq. 2) and that via 1-halo-3-arylpropyne (Eq. 6) requiring in each case the preparation of 1-halo-alkynes do not appear to be attractive. In the view of recent studies on the reaction of a regioisomeric mixture



Scheme 1. Various cross-coupling routes to benzylated alkynes.



Scheme 2. Effects of Pd-phosphine catalysts on the propargyl-aryl coupling.

of organozincs with "BuLi and ZnBr2 with PhI, which produced 1,1-diphenylallene,¹³ it became interesting to see if the cross-coupling regiochemistry could be switched from allene formation to benzylated alkyne formation. The reaction of γ -phenylpropargylzinc bromide with PhI in the presence of $Pd(PPh_3)_4$ produced 1,1-diphenylallene and 1,3-diphenylpropyne in 81% and 5% yields, respectively, confirming in the main the previously reported results.¹³ On the other hand, the use of Pd(DPEphos)Cl₂ led to a mixture containing 36-39% of 1,3-diphenylpropyne and only 3% of 1,1diphenylallene (Scheme 2). Although significant amounts of the starting materials appeared to remain unreacted, the product yields could not be further improved at temperatures varying from 23 to 150 °C. The use of $Pd(dppf)Cl_2$ also produced predominantly 1,3-diphenylpropyne, but its yield was $\leq 16\%$, the yield of 1,1-diphenylallene being 1-2%. Unless further developed, the Pd-catalyzed propargyl-aryl coupling does not appear promising as a route to benzylated alkynes. The Pd-catalyzed reaction of PhZnBr with 3-bromo-1phenylpropyne was not investigated.

3. Summary

In summary, this investigation, following a seminal but very brief investigation by Sarandeses and co-workers,⁸ has established that the Pd-catalyzed alkynyl–benzyl coupling provides a long-sought, highly satisfactory, and widely applicable method for the synthesis of benzylated alkynes, the use of Zn and In as the countercations in alkynylmetals and Pd(DPEphos)Cl₂ as a catalyst has been demonstrated to be advantageous. Several other alternative Pd-catalyzed cross-coupling routes either appear to be unattractive or remain undeveloped, except that the Pd-catalyzed cross-coupling of 3-aryl-1-propynylmetals (Eq. 5 of Scheme 1) promises to provide a general and satisfactory route to benzylated alkynes.

4. Representative procedures

Representative procedure A. 1,3-Diphenylpropyne: To phenylacetylene (123 mg, 1.2 mmol) in THF (3 mL)

cooled to -78 ° C was added n-BuLi (0.48 mL, 2.5 M in hexane, 1.2 mmol). The resultant solution was stirred for 30 min at -78 °C, followed by addition of a solution of dry ZnBr₂ (270 mg, 1.2 mmol) in THF (1 mL). After the mixture thus obtained had been stirred for 5 min at -78 °C and warmed to 0 °C over 25 min, benzyl bromide (171 mg, 1.0 mmol) and Pd(DPEphos)Cl₂ (7.2 mg, 0.01 mmol) were added at 23 °C. The resultant mixture was stirred at 23 °C and monitored by GLC analysis. After 4 h, GLC analysis indicated that the starting material had been completely consumed and that the title compound was formed in 97% GLC yield. The reaction mixture was quenched with 1 M HCl, extracted with ether, washed with aqueous NaHCO₃, dried over MgSO₄, filtered, and concentrated. Flash chromatography (silica gel, hexane) afforded 175 mg (91%) of the title compound.

Representative procedure B. 1,5-Diphenyl-1,3-pentadiyne: To a solution of N,N-diisopropylamine (243 mg, 2.4 mmol) in 4 mL of THF was added n-BuLi (0.96 mL of 2.5 M solution in hexane, 2.4 mmol) at 0 °C in a flame-dried flask under Ar atmosphere. After 2-chloro-4-phenyl-1-buten-3-yne¹⁴ 30 min, (195 mg, 1.2 mmol) in 1 mL THF was added to the LDA solution prepared above by cannula 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 a solution of anhydrous ZnBr₂ (270 mg, 1.2 mmol) in THF (1 mL), and warmed to 0 °C over 30 min. Benzyl bromide (171 mg, 1.0 mmol) and Pd(DPEphos)Cl₂ (7.2 mg, 0.01 mmol) were added to the reaction mixture at 0 °C, which was then stirred at 23 °C for 3 h. The reaction mixture was diluted with Et₂O, washed with aqueous NH₄Cl and then with aqueous NaHCO₃, dried over MgSO₄, filtered, and concentrated. Chromatography on silica gel (hexane) gave 191 mg (93%) of the title compound as a light yellow oil.

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