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Note

Palladium-catalyzed reaction of aryl iodides with *tertiary* propargylic amides. Highly substituted allenes through a regioselective carbopalladation/β-N–Pd elimination reaction

Antonio Arcadi [a], Sandro Cacchi [b,*], Giancarlo Fabrizi [b], Fabio Marinelli [a], Luca M. Parisi [b]

[a] *Dipartimento di Chimica Ingegneria Chimica e Materiali della Facoltà di Scienze, Università di L'Aquila, Via Vetoio, Coppito Due, I-67100 L'Aquila, Italy*

[b] *Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi "La Sapienza", P.le A. Moro 5, 00185 Rome, Italy*

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Dedicated to Professor Jean Pierre Genêt on the occasion of his 60th birthday

Abstract

The palladium-catalyzed reaction of aryl iodides with *tertiary* propargylic amides affords highly substituted allenes. Best results have been obtained by using $Pd(OAc)_2$, $^nBu_3N$, HCOOH, and $^nBu_4NCl$ or LiCl in DME at 100 °C. The reaction is highly regioselective and the carbopalladation step is controlled by the strong directing effect of the *tertiary* amide group.

Keywords: Palladium; Allenes; Hydroarylation; Alkynes

1. Introduction

The palladium-catalyzed hydroarylations and hydrovinylations developed in our laboratories have provided a versatile route for the functionalization of alkynes [1]. The reaction is considered to proceed via formation of carbopalladation intermediates, their conversion into the corresponding formate derivatives via trapping with formate anions, subsequent decarboxylation and reductive elimination to give olefin compound, usually with high stereoselectivity, and regenerate the catalyst (Scheme 1).

We and others have successfully applied this chemistry to symmetrical alkynes [2] and to unsymmetrical alkynes such as arylethynylsilanes [3], alkyl arylpropynoates [4], arylpropargyl alcohols [5], 3,3-dialkoxy-1-aryl-1-propynes [6], and arylpropiolamides [7]. When the starting alkynes bear suitable nucleophilic and electrophilic centers close to the carbon–carbon triple bond, a cyclization reaction can follow the addition step and the whole process provides a valuable straightforward methodology for the preparation of cyclic compounds. This strategy has been successfully employed to develop new routes to quinolines [5], coumarins [4], chromenols [4], chromenes [8], and α-vinyl- [9] and α-arylbutenolides [10]. Intramolecular versions of the reaction have also been described [11]. As an extension of our studies on this chemistry, we decided to investigate the hydroarylation of *tertiary* propargylic amides. Hereafter, we report the preliminary results of this study.

2. Results and discussion

Our initial attempt explored the reaction of the propargylic amine **1a** (E = H)—prepared through the

* Corresponding author. Fax: +390-6-4991-2780.
E-mail address: sandro.cacchi@uniroma1.it (S. Cacchi).

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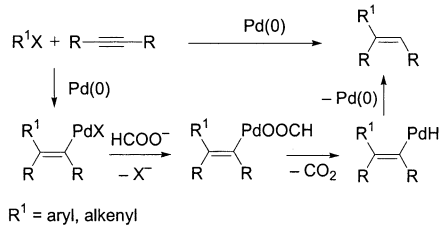
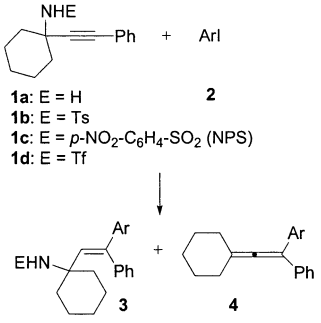


Scheme 1.

Sonogashira coupling of 1-ethynylcyclohexylamine with iodobenzene [12]—with *p*-iodoanisole in the presence of $Pd(OAc)_2$, $^nBu_3N$, and HCOOH in DMF at 40 °C (Scheme 2). However, no hydroarylation product was observed after 24 h and the starting material was recovered almost unchanged. Increasing the temperature to 60 °C led to the regioselective formation of the allylamine derivative **3a** in only 19% yield after 48 h. The starting alkyne was recovered in 60% yield. Employing the corresponding *N*-tosyl derivative **1b** as the starting alkyne under the same conditions did not provide any beneficial effect. Surprisingly, with the less polar THF as the solvent, **1b** was found to react with *p*-iodoanisole even at 40 °C producing 25% of the expected hydroarylation product **3b** and 36% of the allene derivative **4a**.

Intrigued by the formation of the latter compound and by the possibility of developing this new reaction into a convenient tool for the synthesis of functionalized allenes, we turned our attention to optimizing that particular process. The following variables were examined: the solvent, the reaction temperature, the nature of the amide group, the presence or absence of formic acid and added salts. All reactions were run on a 0.283-mmol scale, using 5 mol% of $Pd(OAc)_2$, one equivalent of propargylic amide, 1.5 equivalents of aryl iodide, 5.5 equivalents of $^nBu_3N$, four equivalents of HCOOH, and one equivalent of $^nBu_4NCl$ or five equivalents of LiCl.

Some of the results of this study are summarized in Table 1. The addition of one equivalent of $^nBu_4NCl$ increased the yield of **4a** to 50% (Table 1, entry 3). Increasing the reaction temperature improved further the yield (Table 1, entries 4 and 6) and when the reaction was carried out at 100 °C in DME, the allene **4a** was isolated in 78% yield (Table 1, entry 7). Interestingly, only traces, if any, of the hydroarylation product were observed by increasing the reaction temperature.



Scheme 2.

The presence of formic acid proved necessary for the success of the reaction. Omitting formic acid led to the isolation of **4a** in only 13% yield (Table 1, entry 5).

A similar increase in the yield with increasing the reaction temperature was observed with other propargylic amides that we have investigated: the *N*-*p*-nitrophenylsulfonamide **1c** (compare entry 8 with entry 10) and the *N*-trifluoromethanesulfonamide **1d** (compare entry 9 with entry 11). The latter gave the highest yield and the allene **4a** was isolated in 87% yield (Table 1, entry 11).

When the reaction was performed with ethyl *p*-iodobenzoate as a model for electron-poor aryl iodides, however, no allene product was obtained at 80 °C in THF with the propargylic amides **1b**–**1d** (Table 1, entries 12–14), the biaryl derivative generated through the palladium-catalyzed homocoupling of ethyl *p*-iodobenzoate being the main reaction product. The starting propargylic amides were recovered almost unchanged. Since we have previously reported that LiCl tends to limit the formation of biaryl byproducts and that it is more effective than $^nBu_4NCl$ in this role [13], LiCl was substituted for $^nBu_4NCl$. Pleasingly, under these conditions the allene **4b** was isolated in satisfactory yields at 80 °C (Table 1, entries 15–17). As with *p*-iodoanisole, the best result was obtained with the propargylic amide **1d** at 100 °C (Table 1, entry 20).

As for the reaction mechanism, a possible working hypothesis accounting for the observed results is outlined in Scheme 3a and considers the following basic steps: (a) regioselective (and, most probably, stereoselective) [1] addition of the σ-arylpalladium complex formed in situ to the carbon–carbon triple bond to give the carbopalladation adduct **5**, (b) β-heteroatom elimination that produces the allene derivative **4** and Pd(II) species, and (c) regeneration of the catalytic Pd(0) through reduction.

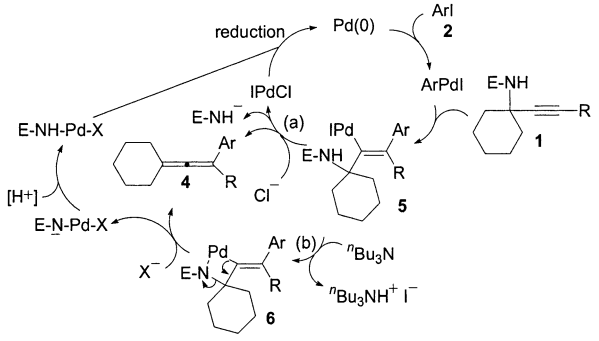
The high regioselectivity observed in the carbopalladation of the carbon–carbon triple bond parallels the results observed in our previous work on the hydroarylation and hydrovinylation of *tertiary* propargyl alcohols [5,8–10] and related reactions [14] involving a carbopalladation step. Most probably, steric effects as well as coordination of nitrogen to the incoming palladium during the carbopalladation step can account for the strong directing effect of the *tertiary* amide group.

The β-heteroatom elimination process in Pd(II)-catalyzed reactions (typically using $PdCl_2$ and $Pd(OAc)_2$) has been extensively investigated by Lu and coworkers [15]. Our process is the first example in which the β-heteroatom elimination occurs in a Pd(0)-catalyzed process. The β-heteroatom elimination has been sug-

Table 1
Palladium-catalyzed reaction of propargylic amides **1b**–**1d** with *p*-iodoanisole and ethyl *p*-iodobenzoate [a]

Entry	Propargylic amide **1**	Aryl iodide **2**	HCOOH	$^{n}Bu_3N$	Salt	Solvent	T (°C)	t (h)	Yield (%) [b]	
	E								**3**	**4**
1	Ts **1b**	*p*-MeO-C_6H_4-I **2a**	+	+	–	DMF	60	24	–	– [c]
2	Ts **1b**	**2a**	+	+	–	THF	40	72	25 **3b**	36 **4a**
3	Ts **1b**	**2a**	+	+	$^{n}Bu_4NCl$	THF	40	72	21 **3b**	50 **4a**
4	Ts **1b**	**2a**	+	+	$^{n}Bu_4NCl$	THF	60	48	20 **3b**	63 **4a**
5	Ts **1b**	**2a**	−	+	$^{n}Bu_4NCl$	THF	60	20	–	13 [d] **4a**
6	Ts **1b**	**2a**	+	+	$^{n}Bu_4NCl$	THF	80	48	10 3b	70 **4a**
7	Ts **1b**	**2a**	+	+	$^{n}Bu_4NCl$	DME	100	4	–	78 **4a**
8	NPS **1c**	**2a**	+	+	$^{n}Bu_4NCl$	THF	80	48	–	73 **4a**
9	Tf **1d**	**2a**	+	+	$^{n}Bu_4NCl$	THF	80	36	–	79 **4a**
10	NPS **1c**	**2a**	+	+	$^{n}Bu_4NCl$	DME	100	8	–	78 **4a**
11	Tf **1d**	**2a**	+	+	$^{n}Bu_4NCl$	DME	100	6	–	87 **4a**
12	Ts **1b**	*p*-EtOOC-C_6H_4-I **2b**	+	+	$^{n}Bu_4NCl$	THF	80	8	–	–
13	NPS **1c**	**2b**	+	+	$^{n}Bu_4NCl$	THF	80	8	–	–
14	Tf **1d**	**2b**	+	+	$^{n}Bu_4NCl$	THF	80	8	–	–
15	Ts **1b**	**2b**	+	+	LiCl	THF	80	48	–	45 **4b**
16	NPS **1c**	**2b**	+	+	LiCl	THF	80	60	–	45 **4b**
17	Tf **1d**	**2b**	+	+	LiCl	THF	80	72	–	51 **4b**
18	Ts **1b**	**2b**	+	+	LiCl	DME	100	24	–	50 **4b**
19	NPS **1c**	**2b**	+	+	LiCl	DME	100	24	–	46 **4b**
20	Tf **1d**	**2b**	+	+	LiCl	DME	100	27	–	62 **4b**

[a] Reactions were run by using 5 mol% of $Pd(OAc)_2$, one equivalent of propargylic amide **1**, 1.5 equivalents of aryl iodide **2**, 5.5 equivalents of $^{n}Bu_3N$, four equivalents of HCOOH, one equivalent of $^{n}Bu_4NCl$ or five equivalents of LiCl in 2.5 ml of solvent at the temperatures indicated.
[b] Yields are given for isolated products.
[c] **1b** was recovered in 80% yield along with a small amount of other products we have not further investigated.
[d] **1b** was recovered in 70% yield.



Scheme 3.

gested to proceed through an E2-like mechanism [15d] which involves simultaneous C–Pd bond cleavage and elimination of the leaving group. The fact that the highest yields have been obtained with **1d** (E = Tf) is in agreement with this view. Chloride anions should play a key role in the process. Their coordination to Pd should generate a highly electron-rich pentacoordinated Pd center [15d] (not represented in Scheme 2 for the sake of simplicity) and this should favor the β-heteroatom elimination path in a twofold manner: weakening the C–Pd bond and preventing formate anions from entering the coordination sphere of palladium (thus hampering the hydroarylation path).

Alternatively, the reaction might proceed through the mechanism outlined in Scheme 3b. It involves the intermediacy of the four-membered ring, nitrogen-containing palladacycle **6** [16] generated from **5** by halide displacement and formation of the allene **4** through a β-elimination of N–Pd species. According to this view, the acidity of the NH bond might influence the nucleophilic attack of the nitrogen atom to palladium by favoring the formation of an anionic nitrogen nucleophile or proton removal in the transition state leading to the palladacycle intermediate. In addition, the presence of an electron-withdrawing group linked to the nitrogen atom could favor the cleavage of the C–N bond in the conversion of **6** into **4**.

In both reaction mechanisms, the presence of formic acid is required for the efficient reduction of Pd(II) species. Accordingly, the allene product was obtained in very low yield when **1b** was treated with *p*-iodoanisole omitting formic acid (Table 1, entry 5).

The formation of the allene product through a base-catalyzed elimination of **3** is ruled out by the following experiment: **1b** was recovered in 93% yield and no evidence of **4a** was attained when **1b** was subjected to conditions described in Table 1, entry 7.

In conclusion, we have discovered that the palladium-catalyzed reaction of *tertiary* propargylic amides with aryl iodides provides an interesting new approach to

highly substituted allenes through a regioselective carbopalladation/β-N–Pd elimination reaction. Work along this line is in progress.

3. Experimental

3.1. General

Melting points were determined with a Büchi apparatus and are uncorrected. All the starting materials such as $Pd(OAc)_2$, salts, solvents, 1-ethynylcyclohexylamine, and aryl iodides are commercially available and were used as purchased, without further purification. Propargylic amide **1a** was prepared by the Sonogashira coupling of 1-ethynylcyclohexylamine with iodobenzene [12]. Propargylic amides **1b** and **1c** were prepared from **1a** using standard methods. Reaction products were purified on axially compressed columns, packed with SiO_2 25–40 μm (Macherey Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and eluting with *n*-hexane/ethyl acetate mixtures. ^{1}H-NMR (200 MHz) and ^{13}C-NMR (50.3 MHz) spectra were recorded with a Bruker Avance 200 spectrometer. IR spectra were recorded with a Jasco FT-IR 430 spectrometer.

3.2. Typical procedure for the preparation of allene (*4a*)

In Carusel Tube Reactor (Radleys Discovery Technologies), to a solution of *N*-tosyl-1-phenylethynylcyclohexylamide (0.100 g, 0.283 mmol) and *p*-iodoanisole (0.0993 g, 0.425 mmol) in 2.5 ml of DME, $Pd(OAc)_2$ (0.0031 g, 0.014 mmol), tetrabutylammonium chloride (0.078 g, 0.283 mmol), formic acid (43 l, 1.558 mmol) and tributylamine (371 l, 1.133 mmol) were added. The mixture was stirred for 4 h at 100 °C under an argon atmosphere. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; *n*-hexane/EtOAc, 99/1, v/v) to give 0.064 g of the allene product **4a** (78% yield). m.p.: wax; IR (neat): 2932, 2864, 1385 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.37–7.25 (m, 7H), 6.90 (d, $J = 6.7$ Hz, 2H), 3.84 (s, 3H), 2.35–2.29 (m, 4H), 1.73–1.62 (m, 6H) ppm; ^{13}C-NMR ($CDCl_3$): δ 200.1, 158.6, 138.3, 130.6, 129.7, 128.5, 128.3, 126.7, 113.8, 107.1, 105.5, 55.4, 31.7, 27.8, 26.3 ppm. Anal. Calcd. for $C_{21}H_{22}O$: C, 86.85; H, 7.64. Found: C, 86.96; H, 7.61%.

(**4b**): m.p.: wax; IR (neat): 2929, 2853, 1715, 1102 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.01 (d, $J = 8.4$ Hz, 2H), 7.44–7.17 (m, 7H), 4.39 (q, $J = 7.1$ Hz, 2H), 2.34–2.29 (m, 2H), 1.73–1.27 (m, 8H), 0.90 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C-NMR ($CDCl_3$): δ 201.3, 166.7, 143.3, 137.7, 129.6, 128.7, 128.6, 128.4, 128.2, 127.0, 107.2, 106.3, 60.9, 31.4, 27.7, 26.1, 14.5 ppm. Anal. Calcd. for $C_{23}H_{24}O_2$: C, 83.10; H, 7.28. Found: C, 83.19; H, 7.26%.

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