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Highly substituted enynes via a palladium-catalyzed tandem three carbon–carbon bonds forming reaction procedure from benzyl halides and alkynyl tributyltin reagents

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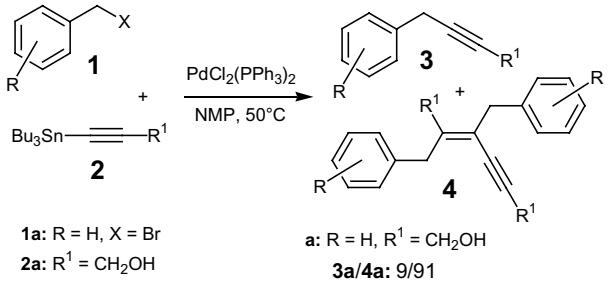
Abstract—The first report of the palladium-catalyzed cross coupling reaction of benzyl halides with alkynyl tributyltin reagents is described. This unprecedented coupling, which involves in a single reaction a tandem Stille–carbopalladation–Stille sequence allows the formation of three carbon–carbon bonds chemo-, regio- and stereoselectively and provides an efficient synthesis of highly substituted enynes.

The palladium-catalyzed cross-coupling of organostannanes with organic electrophiles, known as the Stille reaction, has become an extremely powerful tool for the construction of carbon–carbon bonds.[1] Moreover, the reaction tolerates a wide range of functionality in either or both of the coupling partners so that tedious protection-deprotection reactions of the functional groups carried into the coupling product are not necessary.

Among various organic electrophiles used, aryl, heteroaryl, alkenyl and allyl halides are well known to readily participate in the cross-coupling with organostannanes. Few studies on the palladium-catalyzed coupling with benzyl halides have been reported because good non-catalyzed reaction protocols exist. Benzyl bromide has been shown to couple under palladium catalysis with tetramethylstannane, phenyl- and alkenyltributylstannanes in good yields.[2] Reaction with hexaalkyldistannanes yields benzylic stannanes in fair to good yields.[3] However, to our knowledge, Pd-catalyzed alkynylation[4] of benzyl halides with alkynyltin derivatives[5] is not known. We sought to utilize this Stille coupling reaction for rapid synthesis of functionalized skipped arylalkynes **3** from various functionalized benzyl halides. Contrary to expectations, the major product from the reaction of **1a** with **2a** under standard conditions, summarized in Scheme 1, was found to be conjugated enyne **4a**, while the Stille product **3a** was only formed in small amounts (**3a**/**4a**: 9/91). On the basis of this result, we have explored this unprecedented tandem Stille–carbopalladation–Stille sequence for the preparation of highly substituted enynes **4** from functionalized benzyl halides **1** and alkynyltributyltin reagents **2**. This new four-component procedure allows in a single reaction the tandem formation of three carbon–carbon bonds in a stereo- and regioselective manner. A proposal for this reaction mechanism is presented in this paper.

In order to determine the optimum reaction conditions, we examined the influence of the palladium catalyst, ligand, additive and solvent towards the reaction of



Scheme 1.

Keywords: Stille coupling; Benzyl halides; Alkynylstannanes; Palladium; Enynes; Four-component coupling.
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Table 1. Optimization of the palladium-catalyzed four-component coupling of **2a** with benzyl bromide **1a**

Entry	PdLn	Additive	Solvent	Yield (%)[a]	
				3a	**4a**
1	$PdCl_2(PPh_3)_2$	—	NMP	4	43
2	$Pd(PPh_3)_4$	—	NMP	20	17
3	$Pd(dba)_2 + AsPh_3$	—	NMP	9	32
4	$Pd(dba)_2$ + TFP	—	NMP	—	68
5	$Pd(dba)_2$ + TFP	CuI	NMP	22	30
6	$Pd(dba)_2$ + TFP	—	MeCN	—	41
7	$Pd(dba)_2$ + TFP	—	THF	—	45
8	$Pd(dba)_2$ + TFP	—	Toluene	<3	75
9	$Pd(dba)_2$ + TFP	—	Dioxane	<3	75
10	$Pd(dba)_2$ + TFP	Bu_4NF	Dioxane	—	53

[a] Isolated yield based on benzyl bromide **1a**.

benzyl bromide **1a** with 3-tributylstannyl-prop-2-yn-1-ol **2a**. Table 1 summarizes the results of these studies.

Attempted coupling of **1a** with **2a** in N-methyl-pyrrolidinone (NMP), which has been shown to be the best solvent for Stille reaction[6] in the presence of $PdCl_2(PPh_3)_2$, gave no product at room temperature. However, heating the reaction at 50 °C for 3 h provided the conjugated enyne **4a** in 43% isolated yield together with a small amount of the Stille coupling product **3a** (4%) (entry 1); no reaction occurs in the absence of a palladium catalyst. It is noteworthy that the selectivity of this reaction markedly in favour of the enyne **4a** was dependant on the palladium catalysts. Changing the catalyst to $Pd(PPh_3)_4$ resulted in a mixture of both product **3a**/**4a** in a 54/46 ratio (entry 2). This selectivity was enhanced when using $Pd(dba)_2$ as catalyst associated with Farina ligands[6] such as triphenylarsine but side product **3a** is still produced in substantial amount (entry 3). Interestingly, replacing the triphenylarsine ligand by tri-2-furylphosphine (TFP) gave the enyne **4a** as the only product in a 68% isolated yield (entry 4). It should be noted that the addition of CuI as co-catalyst, which may facilitate the rate-determining transmetallation step[7] dramatically decreased both the yield and the selectivity of the reaction (entry 5). Finally, the influence of solvent was also examined and has a positive effect since the yield of **4a** was improved to 75% when the coupling reaction was performed in toluene or dioxane (entries 8 and 9). Under these optimum conditions, the use of TBAF as nucleophilic activator of organostannanes[8] resulted in a noticeable lowering of the yield (entry 10).

In order to demonstrate the efficiency of this new four-component procedure, a variety of functionalized benzyl bromides or chlorides were reacted with alkynyltributyltin derivatives **2** (Table 2). In most cases the reactions

Table 2. Synthesis of highly substituted enynes **4** by palladium-catalyzed coupling of alkynylstannanes with benzyl halides[a]

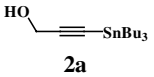
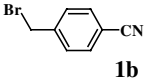
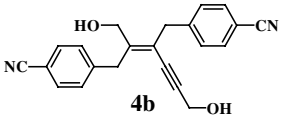
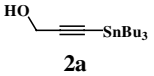
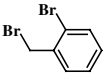
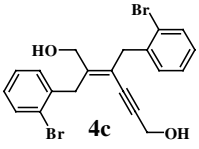
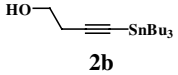
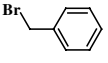
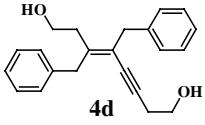
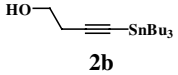
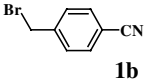
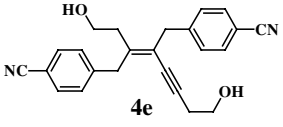
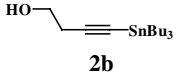
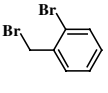
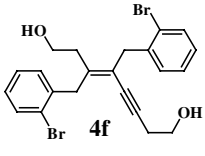
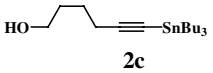
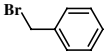
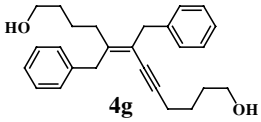
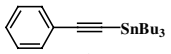
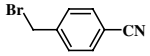
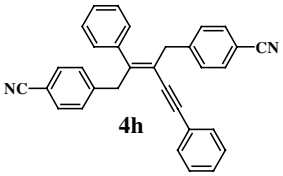
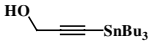
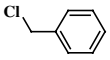
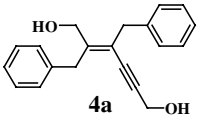
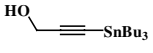
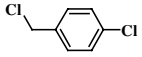
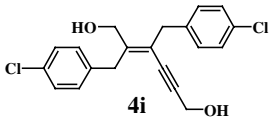
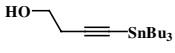
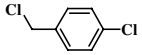
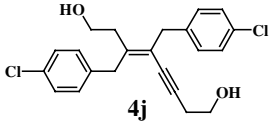
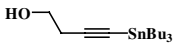
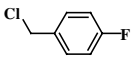
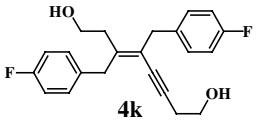
Entry	$RSnBu_3$ **2**	Benzyl halide **1**	Enyne **4**[b]	Yield (%)[c]
1	 **2a**	 **1b**	 **4b**	45
2	 **2a**	 **1c**	 **4c**	33
3	 **2b**	 **1a**	 **4d**	84
4	 **2b**	 **1b**	 **4e**	53
5	 **2b**	 **1c**	 **4f**	42

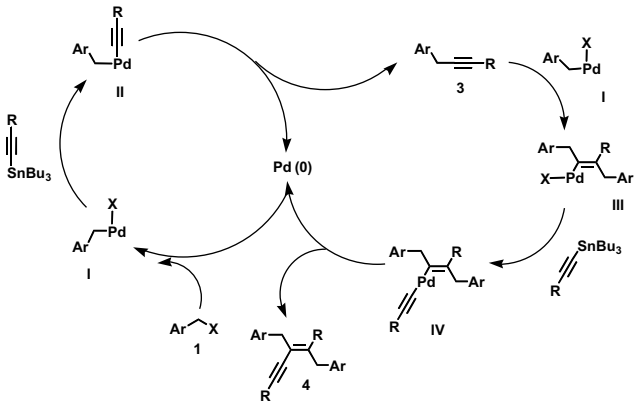
Table 2 (*continued*)

Entry	$RSnBu_3$ **2**	Benzyl halide **1**	Enyne **4**[b]	Yield (%)[c]
6	 **2c**	 **1a**	 **4g**	30
7	 **2d**	 **1b**	 **4h**	24
8	 **2a**	 **1d**	 **4a**	70[d,e,f]
9	 **2a**	 **1e**	 **4i**	36[d]
10	 **2b**	 **1e**	 **4j**	30[d]
11	 **2b**	 **1f**	 **4k**	29[d]

[a] For a general procedure see Ref. 9.
[b] The structures of enynes **4** were established by HMBC, NOESY and HSQC 2D NMR spectroscopy. All new compounds exhibited satisfactory spectral properties and isomeric purity (>95%).
[c] All reactions were carried out under unoptimized conditions. Isolated yield based on benzyl halide.
[d] Performed in the presence of a 1 M THF solution of TBAF (1 equiv).
[e] A 25% yield of skipped arylalkyne **3a** were isolated.
[f] Without TBAF, 13% yield of enyne **4a** and 43% yield of skipped arylalkyne **3a** were obtained.

produced the corresponding highly substituted enynes **4** in fair to good yields starting from benzyl bromides bearing different substituents in *ortho* or *para* position. The selectivity of this tandem Stille–carbopalladation–Stille sequence from the *ortho* bromobenzyl bromide **1c** must be especially underlined since no product arising from the coupling at the Csp^2–Br bond could be isolated (entries 2 and 5). On the other hand, this process is also effective from benzyl chlorides; the reaction required the use of TBAF as activator to promote the reactivity of **2** and afforded the enyne products in fair yields (entries 8–11). While the overall yield of this process is in some cases lower, it represents in a single reaction the formation of three carbon–carbon bonds.

On the basis of the known palladium chemistry, we propose a plausible reaction mechanism as shown in Scheme 2 to account for the present tandem Stille–carbopalladation–Stille sequence. The catalytic reaction is initiated by oxidative addition of benzyl halide **1** to palladium(0) followed by transmetallation of the resulting electrophilic Pd(II) complex **I** with alkynyltin and reductive elimination of **II** regenerate the palladium(0) complex and provide the Stille cross coupling



Scheme 2. Proposed mechanism for the Pd-catalyzed enyne synthesis (ligands on the scheme are omitted).

product **3**. This latter, undergoes then regio- and stereoselective benzylpalladation reaction of benzylpalladium intermediate **I** to give the vinylpalladium adduct **III**. Subsequent transmetallation of **III** with a second molecule of alkynyltin and reductive elimination of palladium from **IV** gives raise to the enyne derivative and regenerates the palladium(0) catalyst.

In conclusion, the tandem Stille–carbopalladation–Stille process developed here for the synthesis of enynes **4** allows in a single reaction to construct three carbon–carbon bonds chemo-, regio- and stereoselectively under mild conditions. This reaction represents the first examples of Pd-catalyzed cross coupling of benzyl halides with alkynylstannanes. Extension of this process to other alkynyl metal including alkynyl copper (Sonogashira–Linstrumelle reaction) is currently under investigations.

Acknowledgements

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References and notes

1. For an excellent review see: (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–652; (b) Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524.
2. (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992–4998; (b) Crisp, G. T.; Glink, P. T. *Tetrahedron* **1994**, *50*, 3213–3234; (c) Kamlage, S.; Sefkow, M.; Peter, M. G. *J. Org. Chem.* **1999**, *64*, 2938–2940; (d) Rayner, C. M.; Astles, P. C.; Paquette, L. *J. Am. Chem. Soc.* **1992**, *114*, 3926–3936; (e) Crawforth, C. M.; Burling, S.; Fairlamb, I. J. S.; Taylor, R. J. K.; Whitwood, A. C. *Chem. Commun.* **2003**, 2194–2195; (f) Crawforth, C. M.; Fairlamb, I. J. S.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 461–465.
3. Azizian, H.; Eaborn, C.; Pidcock, A. *J. Organomet. Chem.* **1981**, *215*, 49–58.
4. An excellent overview of palladium catalyzed alkynylation of organic halides appeared recently, see: Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979–2017.
5. For a recent report of palladium-catalyzed benzylation of tris(alkynyl)indiums, see: (a) Perez, I.; Perez Sestelo, J.; Sarandeses, L. *J. Am. Chem. Soc.* **2001**, *123*, 4155–4160; For noncatalyzed benzylation of alkynyllithium see: (b) Sun, H.; Mahadevan, A.; Razdan, R. K. *Tetrahedron Lett.* **2004**, *45*, 615–617.
6. Farina, V.; Krishman, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
7. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905–5911.
8. Fouquet, E.; Rodriguez, A. L. *Synlett* **1998**, 1323–1324.
9. To a solution of $Pd(dba)_2$ (5 mol%), TFP (10 mol%) and benzyl bromide (1 equiv) in dioxane ($c = 0.2$ M) was added under N_2 freshly prepared alkynyltin derivative (2 equiv). The reaction mixture was warmed at 50 °C, monitored by TLC until complete consumption of the benzyl halide (3–5 h) before to be treated at room temperature by potassium fluoride aqueous solution. After stirring for 2 h, the resulting white precipitate of tributyltin fluoride was removed by filtration and the filtrate was extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Silica gel chromatography of the residue afforded pure enyne **4**.
(*E*) 3,4-Dibenzyloct-3-en-5-yne-1,8-diol **4d**: ^{1}H NMR (400 MHz, DMSO-*d*-6, δ ppm) 7.29–7.16 (m, 10H), 4.72 (t, $1H_{OH}$, $J = 5.1$ Hz), 4.56 (t, $1H_{OH}$, $J = 5.1$ Hz), 3.69 (s, 2H), 3.52 (s, 2H), 3.41 (q, 2H, $J = 6.3$ Hz), 3.35 (q, 2H, $J = 6.7$ Hz), 2.33 (t, 2H, $J = 7.0$ Hz), 2.23 (t, 2H, $J = 7.1$ Hz). ^{13}C NMR (50 MHz, DMSO-*d*-6, δ ppm) 142.4, 139.7, 139.6, 128.5, 128.4, 128.2, 126.2, 120.5, 89.7, 83.1, 61.0, 60.8, 41.2, 38.1, 34.3, 23.7.
(*E*) 2,3-bis(4-cyanobenzyl)hex-2-en-4-yne-1,6-diol **4b**: ^{1}H NMR (400 MHz, DMSO-*d*-6, δ ppm) 7.74 (d, 2H, $J = 8.0$ Hz), 7.73 (d, 2H, $J = 8.0$ Hz), 7.43 (d, 2H, $J = 8.0$ Hz), 7.39 (d, 2H, $J = 8.0$ Hz), 4.13 (s, 2H), 4.01 (s, 2H), 3.81 (s, 2H), 3.64 (s, 2H). ^{13}C NMR (50 MHz, DMSO-*d*-6, δ ppm) 146.3, 145.7, 145.2, 132.2, 129.6, 129.5, 119.0, 118.9, 118.5, 109.1, 108.9, 93.3, 83.8, 58.2, 49.4, 38.0, 37.2.