

Pd-catalysed cross coupling of terminal alkynes to diynes in the absence of a stoichiometric additive

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An efficient, room temperature procedure for the cross-coupling of a range of terminal alkynes, using standard Sonogashira cross-coupling conditions (Pd/Cu) is presented. At higher reaction temperatures, head-to-tail or head-to-head dimerisation affords 1,3- and 1,4-disubstituted enynes, respectively as minor products.

The Sonogashira Pd-catalysed cross-coupling reaction¹ has proven to be a powerful method for the formation of arylalkynyl derivatives (**1**→**2**, Scheme 1). However, peculiarities in this cross-coupling reaction have been noted by us² and other workers in this field.³ Indeed, Pd-catalysed cross coupling of **3** to give **4** in the presence of CuI in a CH₃CN/Et₃N solvent mixture at 80 °C is low yielding. It is complicated by dehalogenation of **3**, accompanied by the formation of diynes **5** and trace quantities of enynes **6–8**. Given this result, in the absence of **3**, we envisaged access to an extremely efficient method for the synthesis of diynes. However, such a proposal assumes that the presence of **3** is not a prerequisite for diyne formation.

Diyne may be synthesised in a number of ways.⁴ The Glaser coupling (oxidative dimerisation) of terminal alkynes in the presence of CuCl₂ and O₂ is without question the best-known reaction, although difficulties are sometimes encountered.⁵ There are several Pd(0)-Cu(I) catalysed cross coupling reactions: (1) dimerisation of terminal alkynyl halides with terminal alkynes;⁶ (2) dimerisation of terminal alkynes using chloroacetone in benzene;⁷ (3) ethyl bromoacetate in THF;⁸ (4) allyl bromide under phase transfer conditions;⁹ (5) and reactions employing stoichiometric I₂ (using a Pd(II) pre-catalyst). These synthetic methods are in the main good, however with the exception of (1), all require the addition of a stoichiometric reagent to reoxidise Pd(0) to Pd(II).

Herein we report a new method for the formation of diynes, in the absence of an obvious oxidant, which can be performed under anhydrous conditions. The latter point is important as the procedure avoids side reactions associated with the Glaser reactions, where O₂ is used as the oxidant. Furthermore, it avoids the formation of alkynyl halides, as in the Sonogashira–Hagihara coupling reaction, and does not require the addition of

stoichiometric reagents (e.g. BrCH₂CO₂Et, ClCH₂COCH₃, I₂ etc.).

To investigate the dimerisation of terminal alkynes, we initially focused on the standard conditions taken from the Sonogashira coupling of **3** with phenyl acetylene **1a** ([PdCl₂(PPh₃)₂] (3 mol%), CuI (3 mol%), triethylamine/CH₃CN solvent mixture (1.6:1 v/v)) at reflux under an argon

Table 1 Effect of Pd-catalyst on the dimerization of 1-heptyne **1b**^a

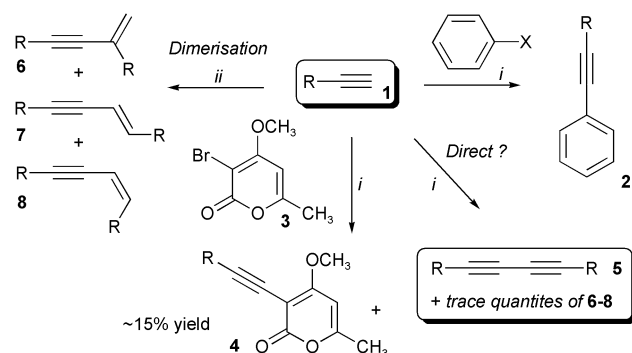
$\text{H}_3\text{C}(\text{H}_2\text{C})_4\text{—}\equiv\equiv\text{1b} \xrightarrow{\text{conditions}} \text{H}_3\text{C}(\text{H}_2\text{C})_4\text{—}\equiv\equiv\equiv\equiv\text{—}(\text{CH}_2)_4\text{CH}_3 \text{5b}$				
Entry	Temp. (°C)	Catalyst ^b	Diyne/enyne ^c	Yield (%) ^d
1	80	Pd(OAc) ₂ /PPh ₃ (2 h)	4.37:1	>97
2	80	Pd(PPh ₃) ₄ (2 h)	2.52:1	>97
3	80	Pd(dba) ₂ /PPh ₃ (2 h)	3.81:1	92
4	80	PdCl ₂ (PPh ₃) ₂ (2 h)	2.80:1	>97
5	25	PdCl ₂ (PPh ₃) ₂ (24 h)	11.34:1	>97
6	25	PdCl ₂ (PPh ₃) ₂ /PPh ₃ (24 h)	Diyne only ^e	97

^a Reaction conditions: 2.0 mmol of 1-heptyne, Et₃N (2.5 mL), CH₃CN (1.5 mL), CuI (3 mol%) at appropriate temp. [Pd] = 3 mol%. Additional ligand (9 mol%). ^b Numbers in parenthesis are reaction times. ^c The enyne fraction accounts for the total amount of enynes **6–8** formed. ^d Isolated yields of tetradeca-6,8-diyne **5b**. ^e Enynes **6–8** not detected by ¹H NMR spectroscopy (270 MHz).

Table 2 Effect of reaction temperature and additional ligand on PdCl₂(PPh₃)₂ catalyzed dimerization of 1-heptyne **1b**^a

$\text{H}_3\text{C}(\text{H}_2\text{C})_4\text{—}\equiv\equiv\text{1b} \xrightarrow{\text{conditions}} \text{H}_3\text{C}(\text{H}_2\text{C})_4\text{—}\equiv\equiv\equiv\equiv\text{—}(\text{CH}_2)_4\text{CH}_3 \text{5b}$				
Entry	Temp. (°C) ^b	Ligand ^c	Product purity (%) ^d	Conv. (%) ^e
1	80 (2)	Ph ₃ P	90	>95
2	80 (2)	dppp	92	>90
3	80 (2)	dppf	82	>90
4	80 (2)	(<i>o</i> -tol) ₃ P	95	>90
5	60 (3.5)	Ph ₃ P	>99	>90
6	60 (3.5)	dppp	92	>90
7	60 (3.5)	dppf	95	>90
8	60 (3.5)	(<i>o</i> -tol) ₃ P	98	>90
9	40 (5)	Ph ₃ P	>99	>97
10	40 (5)	dppp	95	>90
11	40 (5)	dppf	94	>90
12	40 (5)	(<i>o</i> -tol) ₃ P	>99	>90
13	25 (24)	Ph ₃ P	>99	>99
14	25 (24)	dppp	94	>90
15	25 (24)	dppf	>99	>90
16	25 (24)	(<i>o</i> -tol) ₃ P	>99	>90

^a Reaction conditions: 2.0 mmol of 1-heptyne, Et₃N (2.5 mL), CH₃CN (1.5 mL), CuI (3 mol%), (PPh₃)₂PdCl₂ (3 mol%) at appropriate temperature. ^b Number in parenthesis is the reaction time in hours. ^c Additional ligand: For Ph₃P and (*o*-tol)₃P (9 mol%). For [1,3]-bis(diphenylphosphino)propane (dppp) and [1,1']-bis(diphenylphosphino)ferrocene (dppf) (4.5 mol%). ^d Purity determined by ¹H NMR data of the crude reaction mixture. ^e Based on conversion and loss of 1-heptyne **1b** by ¹H NMR data of the crude reaction mixture.



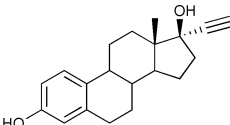


Scheme 1 Reagents and conditions: *i*, [Pd] (Cat.), ligand, CuI (Cat.), Et₃N, solvent, 80 °C; *ii*, Pd(OAc)₂, ligand, benzene, 80 °C.

atmosphere, 3 h). Thus, in the absence of **3**, phenyl acetylene **1a** was dimerised to give the diyne **5a** in 75% yield. Further addition of PPh₃ (9 mol%) enhances the yield of the diyne to 98%. We turned our attention to the alkyl substituted acetylenes and found that the enyne side products **6–8** were much more prominent. Four general Pd-catalysts were screened, employing 1-heptyne **1b** as our benchmark substrate (Table 1). The production of enyne side products varies according to choice of catalyst. Decreasing the reaction temperature to room temperature substantially reduces the formation of enynes **6–8** (compare entries 4 & 5, Table 1). To our delight carrying out the reaction at 25 °C with additional PPh₃ resulted in suppression of the enynes (entry 6, Table 1). It should be noted that these reactions do not proceed in the absence of triethylamine.

We were intrigued by the effect of additional ligand and thus carried out investigations with other chelating phosphines, in the presence of [PdCl₂(PPh₃)₂] as the catalyst, at a variety of

Table 3 Dimerization of various terminal alkynes using optimised conditions^a

Entry	Alkyne	Diyne (%) ^b
1	Ph—C≡C— 1a	>97 (98) 5a
2	H ₃ C—C≡C— 1b	>99 (96) 5b
3	H ₃ C—C≡C— 1c	>99 (96) 5c
4	H ₃ C—C≡C— 1d	>99 (94) 5d
5	H ₃ C—C≡C— 1e	>97 (98) 5e
6	Me ₃ Si—C≡C— 1f	(80) 5f
7	HO—C≡C— 1g	(80) 5g
8	EtO ₂ C—C≡C— 1h	(80) 5h
9	HO—C≡C— 1i	>97 (98) 5i
10	AcO—C≡C— 1j	0 5j
11	PhO ₂ S—C≡C— 1k	0 5k
12	 1l	(95) 5l
13	 1m	(95) 5m
14	 1n	(82) 5n

^a Reaction conditions: 2.0 mmol of alkyne, Et₃N (2.5 mL), CH₃CN (1.5 mL), CuI (3 mol%), (PPh₃)₂PdCl₂ (3 mol%), PPh₃ (9 mol%), at 25 °C for 24 h. ^b Determined by GC analysis (hexadecane standard) (values in parenthesis are isolated yields after flash chromatography).

different temperatures (Table 2). On close inspection of Table 2 one can see quite clearly that the presence of either unidentate (Ph₃P and *o*-tol₃P) or bidentate ligands (dppp and dppf) serves to reduce the formation of the enyne side products. The employment of unidentate ligands results in generally higher selectivity for the diyne product, a trend which is observed at each temperature. Overall, it was found that additional Ph₃P provided reproducibly higher yields of the diyne products.

On mechanistic grounds an oxidant should not be required. To address whether O₂ acts as an oxidant, the reaction was conducted under strictly anhydrous conditions (solvents were degassed using freeze–pump–thaw cycles) under an argon atmosphere using our standard conditions at 25 °C [PdCl₂(PPh₃)₂] (3 mol%), CuI (3 mol%), PPh₃ (9 mol%) in dry Et₃N/CH₃CN (2.5 : 1.5, v/v). The reaction gave the diyne **5b** in >92% yield. Thus the reaction does not require the presence of O₂. Using these standard conditions, a range of terminal alkynes were evaluated for homocoupling (Table 3). The yields for the other alkyl acetylenes **1c–1e** were essentially quantitative (entries 2–5, Table 3). Dimerisation of trimethylsilyl acetylene **1f**, pent-5-yn-1-ol **1g**, ethyl but-4-yne carboxylate **1h** and propargyl alcohol **1i** all resulted in homocoupling to give the diynes **5f–i** in good yields (entries 6–9, Table 3). Enynes **6–8** were not observed in these reactions. Switching to propargyl acetate **1j** and propargyl phenylsulfone **1k** resulted in no reaction (entries 10, 11, Table 3). It is plausible that **1j** and **1k** oxidatively adds to palladium, possibly resulting in allene formation/decomposition. The cyclic alkynols **1l**, **1m** and **1n** couple efficiently using our reaction conditions (entries 12–14, Table 3). The latter example demonstrates that structurally complex terminal alkynes can be dimerised in good yield.

In summary, our method for the dimerisation of alkynes is efficient for the synthesis of a variety of diynes at room temperature. The method is tolerant to a range of functional groups and does not require the addition of stoichiometric reagents, such as I₂, chloroacetone, allyl bromide or ethyl bromoacetate. Our reactions show that terminal alkynes readily dimerise under seemingly standard conditions (Et₃N, CH₃CN, cat. CuI and cat. [PdCl₂(PPh₃)₂] at reflux) for the Sonogashira cross-coupling reaction. Detailed mechanistic studies are currently being pursued to understand this process more fully. Future studies will address cross-dimerisation possibilities.¹⁰

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