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## Synthesis of 1,3-Diynes via Palladium-Catalyzed Reaction of 1,1-Dibromo-1-alkenes

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Both symmetric and unsymmetric 1,3-diynes were prepared from the palladium-catalyzed reaction of 1,1-dibromo-1-alkenes. The formation of symmetric 1,3-diynes 2 (homocoupling) was catalyzed by a weak ligand, tris(2-furyl)phosphine (TFP), and the addition of catalytic amount of Cul accelerated the reaction. The synthesis of unsymmetric 1,3-diynes 4 (the Sonogashira reaction) required a highly electron rich tris(4-methoxyphenyl)phosphine as the ligand, and Cul promotes the formation of byproduct 1,1-diynyl-1-alkenes 5.

1,1-Dibromo-1-alkenes<sup>1</sup> are versatile in palladium chemistry. They can form (*Z*)-1-aryl(alkenyl)-1-bromo-1-alkenes, stereospecifically trisubstituted alkenes, and disubstituted *cis*-1-bromo-1-alkenes through coupling with organoboronic acids (Suzuki reaction),<sup>2</sup> organostannanes (Stille reaction),<sup>3</sup> organozinc and Grignard reagents,<sup>4</sup> organozirconium reagents<sup>5</sup> and tributyltin hydride.<sup>6</sup> 1,1-Dibromo-1-alkenes can also be used as equivalents of 1-bromo-1-alkynes in palladium catalyzed reactions. This reaction was first reported by Zapta<sup>7</sup> and was recently investigated in detail by us.<sup>3a</sup> In this letter, we wish to report an extension of this methodology to the synthesis of both symmetric<sup>8,9</sup> and unsymmetric 1,3diynes.<sup>8e,10</sup>

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The homocoupling of methyl 4-(2',2'-dibromovinyl)benzoate (1a) is summarized in Table 1. With tris(dibenz-

Table 1.	Optimization	of the Homoc	oupling of <b>1a</b> <sup>a</sup>
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MeO <sub>2</sub> C´	la la	Br Br Ar = 4-(CC	► Ar—≡ 9 <sub>2</sub> Me)Ph	 2a	-Ar + Ar 3a - Ar
entry	CuI (%)	base	<i>T</i> (°C)	<i>t</i> (h)	products <sup>b</sup> (yield, %)
1	0	TEA	80	36	<b>2a</b> (73)
2	0	TEA	100	12	<b>2a</b> (61) <sup>c</sup>
3	20	TEA	80	4	2a (83), 3a (5.6)
4	100	TEA	80	1	<b>2a</b> (57), <b>3a</b> (28)
5	20	$K_2CO_3$	80	48	<b>2a</b> (15) <sup>d</sup>

<sup>*a*</sup> Reaction conditions: **1a** (1.0 mmol),  $Pd_2dba_3$  (2.5%), TFP (15%), and base (2.5 equiv) in DMF. <sup>*b*</sup> Yields are isolated. <sup>*c*</sup> **1a** was recovered (2%). <sup>*d*</sup> **1a** was recovered (9%).

ylideneacetone)dipalladium(0) ( $Pd_2dba_3$ ) as the palladium source, tris(2-furyl)phosphine (TFP) is found to be the most effective ligand for the homocoupling reaction. Though reducing agents were shown to facilitate the homocoupling of aryl halides,<sup>11</sup> they either had no effect on the reaction (2-propanol<sup>11a</sup>), resulted in partial reduction of diyne 2a (Zn<sup>11b,c</sup> and HCO<sub>2</sub>Na<sup>11d</sup>), or complicated the reaction (hydroquinone<sup>11e</sup> and  $Me_6Sn_2^{11f}$ ). The best results were obtained with triethylamine (TEA),<sup>12</sup> without using another reducing reagent (entry 1, Table 1). The reductant in this reaction is believed to be the tertiary amine, which was proposed previously in other palladium-mediated reactions.<sup>11a,13</sup> A controlled experiment also showed that the reaction required TEA, as the reaction proceeded very poorly with  $K_2CO_3$  (entry 5, Table 1). The addition of CuI greatly accelerates the reaction, though it also introduces byproduct 3a. The ratio of byproduct 3a to product 2a increases with increased amount of CuI used, while the reaction time decreases (entries 3 and 4. Table 1).

When these optimized homocoupling conditions were applied to the Sonogashira reaction,<sup>14</sup> a mixture of products (entry 1, Table 2) was obtained, with the major product being

Table 2 Ph 1a TE Pd	2. Opti — (2 A (3 eq.), <sub>2</sub> dba <sub>3</sub> (1.0	mization of the s eq.) DMF Ar $-(=)_2$ F $\overline{200}, 4a$	Sonogas Ph + Ar	shira Reaction of <b>1a</b> Ph + Ar $(=)_2$ Ar <b>5a</b> Ph <b>2a</b>
L (· entry	4.0%), 80 	ligand	2Me)Ph 	products <sup>a</sup> (yield, %)
1	20%	TFP	2	<b>4a</b> (26), <b>5a</b> (58), <b>2a</b> (13)
2	0	TFP	4	<b>4a</b> (39), <b>5a</b> (51), <b>2a</b> (9)
3	20%	(4-MeOPh) <sub>3</sub> P	4	<b>4a</b> (29), <b>5a</b> (26), <b>2a</b> (25)
4	0	(4-MeOPh) <sub>3</sub> P	4	<b>4a</b> (78), <b>5a</b> (18)

1,1-divnyl-1-alkene 5a. However, when the very electronrich tris(4-methoxyphenyl)phosphine was used as the ligand,

(9) 1,1-Dibromo-1-alkenes formed 1,3-symmetric diynes (a) under "CO" atmosphere with a strong base (5 N NaOH): Galamb, V.; Gopal, M.; Alper, H. Organometallics 1983, 2, 801. (b) As byproducts in the Suzuki reaction: Soderquist, J. A.; Leon, G.; Colberg, J. C.; Martinez, I. Tetrahedron Lett. 1995, 36, 3119.

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(12) Tertiary amines were also used in homocoupling of aryl halides without the addition of other reductants: (a) Clark, F. R. S.; Norman, R. O. C.; Thomas, C. B. J. Chem. Soc., Perkin Trans. 1 1975, 121. (b) Boger, D. L.; Goldberg, J.; Andersson, C.-M. J. Org. Chem. 1999, 64, 2422. (c) Boger, D. L.; Jiang, W.; Goldberg, J. J. Org. Chem. 1999, 64, 7094. (d) Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. Tetrahedron Lett. 1999, 40, 857.

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a good yield of the desired unsymmetric divne 4a was obtained without CuI (entry 4, Table 2).

These optimized conditions for the preparation of both symmetric (entry 3, Table 1) and unsymmetric 1,3-diynes (entry 4, Table 2) were used to synthesize a wide variety of 1,3-diynes, as summarized in Tables 3 and 4.15 Moderate to

Table 3. Homocoupling of 1,1-Dibromo-1-alkenes

R Br Br	Pd <sub>2</sub> dba <sub>3</sub> (2.5%), TFP (15%) Cul (20%), TEA (2.5 eq.) DMF, 80 °C, 4-8 h	R
entry	dibromoalkenes (1)	products (yield, %)
1	Br lb	<b>2b</b> (71)
2	MeO Br Ic	<b>2c</b> (87), <b>3c</b> (11)
3	MeO Br Br	<b>2d</b> (86)
4	OMe Br Br 1e	$2e (39),$ $\underbrace{\bigcirc}_{0} \underbrace{\longrightarrow}_{0} \underbrace{\frown}_{0} \underbrace{\bullet}_{0} \underbrace{\bullet}_{0} \underbrace{\bullet}_{0} \underbrace{\bullet}_{0} \underbrace{\bullet}_{0} \underbrace{\bullet}_{0}$

R 11

Br 1h

1f

2f (77)

2g (82)

2h (50)\*

2i (73), 3i (18)

5

6

7

8

<sup>a</sup> Pd(OAc)<sub>2</sub> (5 mol %) was used in place of Pd<sub>2</sub>dba<sub>3</sub>.<sup>38</sup>

good yields of the homocoupling products 2 were obtained with both 2-aryl- and 2-alkyl-1,1-dibromoethenes (Table 3). Para or meta substitutions (1a, 1c, 1d) on the aromatic rings do not affect the homo-coupling. However, ortho substituents might participate in the reaction.<sup>3b</sup> When 2-(o-methoxyphenyl)-1,1-dibromoethene (1e) was subjected to the homocoupling reactions, byproduct 6 was isolated along with the desired divne 2e.

As shown in Table 4, the reactions of 1,1-dibromo-1alkenes 1 with both aryl and alkyl terminal alkynes afforded moderate to good yields of the desired unsymmetric 1,3-

<sup>(8)</sup> Representative syntheses of symmetric 1,3-diynes: (a) Liu, Q.; Burton, D. J. Tetrahedron Lett. 1997, 38, 4371. (b) Sarkar, A.; Okada, S.; Nakanishi, H.; Matsuda, H. Helv. Chem. Acta 1999, 82, 138. (c) Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nazuki, H. Tetrahedron Lett. 1985, 26, 5585. (d) Haley, M. M.; Bell, M. L.; Brand, S. C.; Kimball, D. B.; Pak, J. J.; Wan, W. B. Tetrahedron Lett. 1997, 38, 7483. (e) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama, T. J. Org. Chem. 2000, 65, 1780.

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<sup>(15)</sup> All the 1,3-diynes (2, 4), 1,1-diynyl-1-alkenes (3, 5) and compound 6 gave satisfactory mass (DCI) and <sup>1</sup>H and <sup>13</sup>C NMR spectra.

Table 4	Br TEA (3 eq.) D	Unsymmetric q.)	1,3-Di	ynes
н ү В <sup>г</sup>	Pd <sub>2</sub> dba <sub>3</sub> (1%), (4-MeOPh) <sub>3</sub> P ( 80 °C	⊷ R <del> (==)</del> 2R <sup>1</sup> 4%) <b>4</b>	+ /== R	+ 2
entry	dibromide	R <sup>1</sup> ==	<i>t</i> (h)	products (yield, %)
1	1a	TIPS-==	4	<b>4b</b> (79), <b>2a</b> (13)
2		n-C <sub>5</sub> H <sub>11</sub>	4	4c (88), 2a (9)
3		4-(MeO)Ph-=	3	4d (63), 5d (23),
				<b>2a</b> (12)
4		HO	4	<b>4e</b> (71), <b>2a</b> (7)
5		2-Py-==	15	<b>4f</b> (46), <sup>a</sup> <b>2a</b> (6)
6		EtO₂C	12	<b>4g</b> (0), <sup>b</sup> <b>2a</b> (16)
7	1e	Ph-===	4	<b>4h</b> (73), <b>2e</b> (22)
8		TIPS-===	4	<b>4i</b> (68), <b>2e</b> (26)
9	1h	Ph	4	<b>4j</b> (47), <b>5j</b> (6.8),
				<b>2h</b> (21)
10		TIPS-	4	<b>4k</b> (53), <b>2h</b> (23)
11	o∕ → Br	Ph=	6	<b>4l</b> (62)
12	+° <sup>Br</sup> 1j	TIPS-=	4	<b>4m</b> (67), <b>2m</b> (10)

<sup>a</sup> Yield after recovered 1a (13%). <sup>b</sup> 1a (8%) was recovered.

diynes **4**. The homocoupling products **2** were usually isolated in minor amounts, and the bis-coupled products **5** were observed in a few cases (entries 3 and 9, Table 4). The electronic characteristics and the substitution patterns of 1,1dibromo-1-alkenes **1** do not affect the Sonogashira reaction, as both **1a** and **1e** afforded good yields of unsymmetric 1,3diynes **4**. However, the reaction is much slower with electron deficient alkynes, as the coupling of **1a** with 2-pyridylethyne gave low yield of **4f** after long reaction time (entry 5, Table 4), and no desired unsymmetric 1,3-diyne was found in the coupling of **1a** with ethyl propiolate (entry 6).

A possible mechanism for the reactions is proposed in Scheme 1. 1,1-Diboromo-1-alkene 1 undergoes normal palladium insertion to give intermediate 7. In a highly dipolar



solvent such as DMF and in the presence of a base, intermediate **7** transforms into alkynylpalladium **8**.<sup>3a</sup> In the absence of CuI and a terminal alkyne, intermediate **8** would yield homocoupling product **2**, with a mechanism similar to the homocoupling of aryl halides. In the presence of CuI, the palladium in intermediate **8** may interchange with copper-(I) to give alkynylcopper **9**, which couples with **8** at a much faster rate to give product **2**. This may explain the catalytic role of CuI. Because alkynylcopper **9** couples fast with organopalladium species, formation of monobromide **10** from the coupling of **7** and **9** becomes competitive to the transformation of **7** to **8**. Further coupling of **10** with **9** results in product **3**. The homocoupling also produces Pd(II) species, which is reduced by triethylamine to Pd(0) species to complete the palladium cycle.<sup>13</sup>

A parallel mechanism could be derived for the formation of unsymmetric 1,3-diynes **4**, and the byproducts **5**, as also shown in Scheme 1. The palladium cycle in these reactions ends with Pd(0) species, so that no reduction of Pd(II) species is necessary.

Further proof of the mechanism is obtained with the reaction of alkynyl bromide **11**,<sup>16</sup> as illustrated in Scheme 2. Under the homocoupling conditions developed for 1,1-



dibromo-1-alkenes, a comparable yield of **2a** was obtained from **11** in 0.5 h. Similarly, unsymmetric 1,3-diyne **4a** was obtained in good yield from **11** under the optimal conditions developed for the Sonogashira reaction of 1,1-dibromo-1alkenes **1**, though the byproduct is **2a** instead of **5a**.

In summary, we have developed convenient methods for the preparation of both symmetric<sup>17</sup> and unsymmetric<sup>18</sup> 1,3diynes from easily accessible 1,1-dibromo-1-alkenes **1**. Both

(18) **Typical Procedure for Preparation of Unsymmetric 1,3-Diynes 4.** A solution of **1a** (320 mg, 1.0 mmol), phenylacetylene (153 mg, 2.0 mmol),  $Pd_2dba_3$  (9.0 mg, 0.010 mmol), tris(4-methoxyphenyl)phosphine (14 mg, 0.040 mmol), and triethylamine (0.41 mL, 3.0 mmol) in anhydrous DMF (3.0 mL) was flushed with nitrogen and heated at 80 °C for 4 h. Usual aqueous work up was followed by column chromatography purification with hexanes/dichloromethane/ethyl acetate (70:25:5) to give **4a** as the first fraction (204 mg, 78%) and **5a** as the second fraction (65 mg, 18%).

<sup>(16)</sup> Compound **11** was prepared in quantitative yield according to the protocol in: Ratovelomanana, V.; Rollin, Y.; Gebehenne, C.; Gosmini, C.; Perichon, J. *Tetrahedron Lett.* **1994**, *35*, 4777.

<sup>(17)</sup> **Typical Procedure for Preparation of Symmetric 1,3-Diynes 2.** A mixture of **1a** (320 mg, 1.0 mmol),  $Pd_2(dba)_3$  (23 mg, 0.025 mmol), TFP (35 mg, 0.15 mmol), CuI (38 mg, 0.20 mmol), and triethylamine (0.42 mL, 3.0 mmol) in DMF (3 mL) was flushed with nitrogen and heated at 80 °C for 4 h. The reaction mixture was cooled, filtered through Celite and rinsed with ethyl acetate. The filtrate was partitioned between ethyl acetate (50 mL) and water (10 mL), and the organic layer was washed with water (10 mL, twice), dried over MgSO<sub>4</sub>, filtered, and concentrated. The residue was purified by flash chromatography, eluting with 0–5% ethyl acetate in hexanes/dichloromethane (1: 1) to give **2a** (132 mg), followed by **3a** (8.8 mg).

methods are relatively mild and appear to be broadly applicable. These reactions again demonstrate the utility of 1,1-dibromo-1-alkenes as synthons for alkynyl bromides and the importance of ligands, additives, and solvents in palladium catalyzed reactions of 1,1-dibromo-1-alkenes.

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<sup>(19)</sup> A comparable yield (43%) of **2h** was obtained with Pd<sub>2</sub>dba<sub>3</sub> as the palladium source, after purification with silica gel column twice (dba and **2h** have similar Rf values). As a comparison, **2a** (79%) and **3a** (6.1%) were resulted from the homocoupling of **1a** with Pd(OAc)<sub>2</sub> in place of Pd<sub>2</sub>-dba<sub>3</sub>.