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Convenient One-Pot Synthesis of (*E*)-β-Aryl Vinyl Halides from Benzyl Bromides and Dihalomethanes

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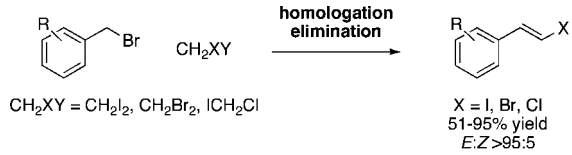
ABSTRACT



(*E*)-β-Aryl vinyl iodides are synthesized in high yield with excellent stereoselectivity from benzyl bromides by a one-pot homologation/stereoselective elimination procedure. Convenient conditions involving the anion of diiodomethane and an excess of base provide complete consumption of the benzyl bromide and elimination from a diiodoalkane intermediate. Similar conditions provide (*E*)-β-aryl vinyl chlorides and bromides by employing the anions of ICH_2Cl or CH_2Br_2. The functional group tolerance and facile purification allows rapid access to a wide range of functionalized vinyl halides.

The advent of transition-metal-catalyzed cross-coupling reactions has revolutionized the construction of C−C bonds over the past three decades.[1] As a result, aryl and vinyl halides have become increasingly important reactants. Although aryl halides are widely commercially available, stereochemically pure vinyl halides are much less so and are often more costly. Consequently, there has been much interest in facile, efficient means of preparing such compounds.

(*E*)-β-Aryl vinyl halides are often attractive substrates for the synthesis of compounds of biological/medicinal relevance,[2] and several methods have been developed for their preparation.[3−9] These methods often involve multiple steps: formation of a suitable alkene precursor followed by the installation of the halide. Commonly, (*E*)-β-aryl vinyl halides may be formed by a Hunsdiecker reaction involving the decarboxylation of cinnamic acid derivatives.[3] Another approach is the trapping of a vinyl metal species with an

(1) For a general overview, see: (a) Negishi, E.-i. *Acc. Chem. Res.* **1982**, *15*, 340–348. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (c) Luh, T.-Y.; Leung, M.-k.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187–3204. (d) Andersen, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997–1030. (e) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470. (f) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979–2018. (g) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Wiley: London, 2004.

(2) For recent relevant examples, see: (a) Kabir, M. S.; Van Linn, M. L.; Monte, A.; Cook, J. M. *Org. Lett.* **2008**, *10*, 3363–3366. (b) Besselièvre, F.; Piguel, S.; Mahuteau-Betzer, F.; Grierson, D. S. *Org. Lett.* **2008**, *10*, 4029–4032.

(3) For recent examples, see: (a) Kuang, C.; Yang, Q.; Senboku, H.; Tokuda, M. *Synthesis* **2005**, *131*, 9–1325. (b) You, H.-W.; Lee, K.-J. *Synlett* **2001**, 105–107. (c) Das, J. P.; Roy, S. *J. Org. Chem.* **2002**, *67*, 7861–7864. (d) Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron* **2005**, *61*, 637–642.

(4) (a) Brown, H. C.; Hamaoka, T.; Ravindran, N.; Subrahmanyam, C.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6075–6079. (b) Masuda, Y.; Hoshi, M.; Arase, A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2725–2726.

(5) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031.

(6) For I−Si exchange from (*E*)-vinyl silanes, see: Barluenga, J.; Alvarez-García, L. J.; González, J. M. *Tetrahedron Lett.* **1995**, *36*, 2153–2156.

(7) (a) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1981**, *46*, 3745–3747. (b) Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron* **2002**, *58*, 1491–1496. (c) Wang, L.; Li, P.; Xie, Y.; Ding, Y. *Synlett* **2003**, 1137–1140. (d) Horibe, H.; Kondo, K.; Okuno, H.; Aoyama, T. *Synthesis* **2004**, 986–988.

(8) (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173–2174. (b) Miyano, S.; Izumi, Y.; Fujii, K.; Ohno, Y.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1197–1202.

(9) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410. (b) Takai, K.; Ichiguchi, T.; Hikasa, S. *Synlett* **1999**, 1268–1270.

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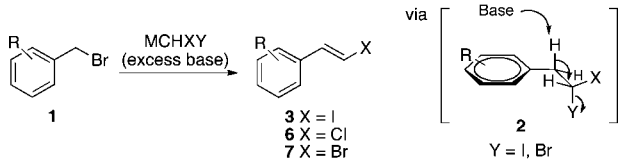
electrophilic halide source, where the *E*-stereochemistry can be installed by hydrometalation of an alkyne[4] or cross-metathesis with a vinyl boronate.[5,6] Alternatively, (*E*)-vinyl halides may be formed by the stereoselective reductive removal of one halide from a 1,1-dihaloalkene.[7]

Homologative methods that both form the olefinic C−C bond and install the appropriate stereochemistry are limited to the Wittig and Takai olefination reactions. The Wittig reaction using a halomethyl phosphonium salt is more appropriate for (*Z*)-vinyl iodides or leads to low *E*-selectivity.[8] The Takai−Utimoto olefination, involving the addition of a trihalomethane to an aldehyde followed by a stereoselective chromium-mediated reduction, often affords high *E*/*Z* ratios under mild conditions.[9] However, the requirement for large quantities of toxic metals detracts from the appeal of this method.

We recently reported improved conditions to synthesize *gem*-diiodoalkanes by alkylation of diiodomethane with alkyl iodides or benzyl/allyl bromides.[10,11] We demonstrated that $LiCHI_2$ and $NaCHI_2$ could be formed and used at a reaction temperature of −78 °C and in excess to provide high yields of the *gem*-diiodides.[10] We envisaged that this methodology could be applied to the synthesis of (*E*)-*β*-aryl vinyl halides; using "MCHXY" for the homologation of benzyl bromides followed by an in situ stereoselective *elimination* of HY from the *gem*-dihalide intermediate (**2**) (Scheme 1). This novel

Scheme 1. Proposed Synthesis of (*E*)-*β*-Aryl Vinyl Halides



disconnection could address some of the limitations of existing methodology. Furthermore, the wide range of commercially available benzyl bromides would allow direct access to a wide range of vinyl halides.

Here we report procedures for the synthesis of (*E*)-*β*-aryl vinyl iodides achieving high yields and excellent stereoselectivity. Furthermore, this method was extended to allow the synthesis of (*E*)-*β*-aryl vinyl chlorides and bromides in high yields and excellent *E*/*Z* stereoselectivity using the anions of ICH_2Cl and CH_2Br_2, respectively.

Initially, we focused on the synthesis of vinyl iodides, as they generally display higher reactivity in cross-coupling reactions. Our previously reported conditions for the synthesis of *gem*-diiodoalkanes from benzyl bromides employed 2 equiv of both LiHMDS and diiodomethane and led to minimal elimination from the diiodide (Table 1, entry 1).[10] We anticipated that the use of the more reactive sodium anion

Table 1. Selected Optimization Conditions for the Preparation of (*E*)-(2-Iodovinyl)benzene (**3a**) from Benzyl Bromide

entry[a]	equiv (NaHMDS/ CH_2I_2)	conditions	concn[b] (M)	convn[c] (%)	elimination[d] (%)
1	2.0[e]/2.0 (LiHMDS)	−78 °C to rt over 16 h	0.05	100	5
2	2.0/2.0	−78 °C to rt over 16 h	0.05	97	16
3	2.0/1.0	−78 °C to rt over 16 h	0.05	91	71
4	3/1.5	−78 °C to rt over 16 h	0.05	100	73
5	3/1.5	−78 °C to rt over 16 h then DBU 1 h	0.05	100	100
6	3/1.5	−78 °C to rt over 16 h	0.1	100	94
7	3/1.5	−78 °C to rt over 16 h	0.2	100	99
8	3/1.5	−78 °C to rt over 16 h	0.3	100	100
9	3/1.5	−78 °C 1 h, to rt 1 h	0.2	100	87
10[f]	3/1.5	−78 °C 1.5 h, to rt 30 min then DBU 1 h	0.2	100	100
11[g]	2.0[e]/2.0 (LiHMDS)	−78 °C to rt over 16 h then DBU 1 h	0.2	100	100

[a] Reaction performed on a 1 mmol scale. [b] Concentration of BnBr in reaction mixture. [c] Conversion as measured by ^{1}H NMR of crude reaction mixture. [d] Percentage of the *gem*-diiodide formed that underwent elimination to the vinyl iodide. Approx 99:1 *E*/*Z* selectivity observed in all cases by ^{1}H NMR. [e] Using LiHMDS in place of NaHMDS. [f] Method A. Uses 1 equiv of DBU. [g] Method B. Uses 2 equiv of DBU.

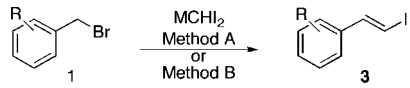
in the presence of excess base should induce a stereoselective elimination and reduce the reaction time. Screening equivalents of base and of diiodomethane (entries 2−4) led to full conversion with high levels of elimination, up to 73%, using 3 equiv of NaHMDS and 1.5 equiv of CH_2I_2 (entry 4). Furthermore, there was no residual diiodomethane in the crude product, facilitating purification. In all cases, the *E*-double bond geometry was strongly favored, with approximately 99:1 *E*/*Z* as measured by ^{1}H NMR. This is due to the minimization of unfavorable steric interactions in the transition state during the elimination of HI from intermediate **2** (Scheme 1).

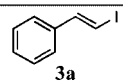
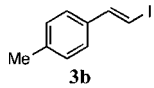
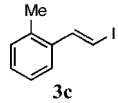
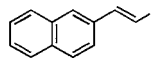
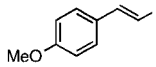
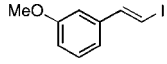
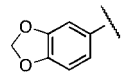
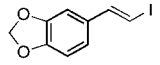
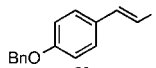
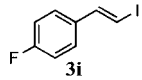
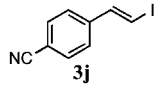
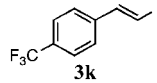
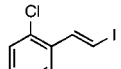
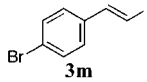
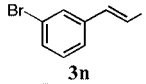
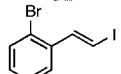
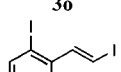
The addition of DBU (1 equiv) prior to workup led to the remaining *gem*-diiodide being eliminated rapidly, providing the vinyl iodide exclusively (entry 5).[12,13] Performing the reaction at increased concentration gave higher levels of elimination, providing 100% elimination from the diiodide at 0.3 M. The reaction time could be reduced to 1 h followed by 1 h to warm to rt (entry 9). Again, by allowing the reaction to warm to rt before workup the residual CH_2I_2 anion decomposed, meaning diiodomethane was not present in the crude product.

For reproducibility across substrates and reaction scales we chose to run the reactions at 0.2 M concentration and include the addition of DBU to ensure complete elimination of any remaining diiodide (entry 10, method A). These optimal conditions afforded the desired product in high yield following a simple workup and purification (Table 2, entry 1). We also developed a second set of reaction conditions, method B, using $LiCHI_2$ followed by the addition of DBU (Table 1, entry 11). These less basic conditions proved to be more suitable for some sensitive substrates.

(10) Bull, J. A.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 8097–8100.
(11) (a) Seyferth, D.; Lambert, R. L., Jr. *J. Organomet. Chem.* **1973**, *54*, 123–130. (b) Charreau, P.; Julia, M.; Verpeaux, J. N. *Bull. Soc. Chim. Fr.* **1990**, *127*, 275–282.
(12) García Martínez, A.; Martínez Alvarez, R.; Martínez González, S.; Subramanian, L. R.; Conrad, M. *Tetrahedron Lett.* **1992**, *33*, 2043–2044.
(13) The *E*/*Z* ratio remained excellent with elimination by DBU. Treatment of the isolated diiodide (see ref 10) with DBU alone at rt provided a 98:2 *E*/*Z* ratio of products.

Table 2. Synthesis of (*E*)-*β*-Aryl Vinyl Iodides



entry[a]	RC_6H_4	method[b]	product	yield (%)[c]	*E*/*Z*[d]
1	Ph (**1a**)	A	 **3a**	92	98:2
2		B		82	97:3
3	4-MeC_6H_4 (**1b**)	A	 **3b**	93	99:1
4	2-MeC_6H_4 (**1c**)	A	 **3c**	90	99:1
5	2-napthyl (**1d**)	A	 **3d**	70	98:2
7[e]	(4-OMe)C_6H_4 (**1e**)	A[f]	 **3e**	92	97:3
8	(3-OMe)C_6H_4 (**1f**)	A[f]	 **3f**	95	99:1
9	 (**1g**)	A[f]	 **3g**	93	99:1
10	(4-OBn)C_6H_4 (**1h**)	B[g]	 **3h**	76	99:1
11	4-FC_6H_4 (**1i**)	A	 **3i**	85	98:2
12	(4-CN)C_6H_4 (**1j**)	B	 **3j**	51	99:1
13	(4-CF_3)C_6H_4 (**1k**)	B	 **3k**	63	99:1
14	2-ClC_6H_4 (**1l**)	A	 **3l**	78	98:2
15	4-BrC_6H_4 (**1m**)	A	 **3m**	43	99:1
16		B		87	99:1
17	3-BrC_6H_4 (**1n**)	A	 **3n**	62	99:1
18		B		87	98:2
19	2-BrC_6H_4 (**1o**)	A	 **3o**	47	99:1
20		B		88	98:2
21[e]	2-IC_6H_4 (**1p**)	B	 **3p**	73	99:1

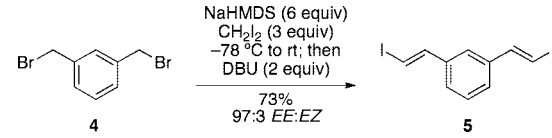
[a] Reactions performed on a 4.0 mmol scale. [b] Method A: CH_2I_2 (1.5 equiv), NaHMDS (3 equiv), 0.2 M, −78 °C (1 h 30 min) to rt (30 min) then DBU (1 equiv) for 1 h. Method B: CH_2I_2 (2 equiv), LiHMDS (2 equiv), 0.2 M, −78 °C to rt (16 h) then DBU (2 equiv) for 1 h. [c] Yield of isolated product. [d] *E*/*Z* ratio determined by ^{1}H NMR. [e] Performed on a 1.0 mmol scale. [f] Used 1.5 equiv of DBU. [g] Used 3.0 equiv of DBU.

With two sets of optimized conditions available, both providing complete conversion and elimination, the scope of the reaction was explored. Alkyl-substituted phenyl and napthyl substrates gave high yields and excellent *E*/*Z* ratios (entries 1−5). Method A was generally more convenient and provided higher yields on simple substrates than method B. Also, although excellent in all cases, the *E*/*Z* ratio was marginally improved by the use of the sodium base.

Benzyl bromides containing electron-donating groups gave the corresponding vinyl iodides in excellent yields and stereoselectivity (entries 7−10). However, excess DBU was required in these cases to effect complete elimination from the diiodide. Electron-withdrawing groups were also tolerated (entries 11−13) but generally required the milder reaction conditions of method B and gave marginally lower yields. Other more powerful electron-withdrawing groups, such as the nitro functionality, gave lower yields and some cases inseparable byproducts.

We were particularly interested in examples leading to products that would provide potential "lynchpin" fragments, i.e., that could be used as cross-coupling partners to couple different groups selectively at either site.[14] As such, (*E*)-*β*-aryl vinyl iodides in which the aryl group contained chloride, bromide, and iodide functionalities were synthesized in good yields (entries 14−21). In most cases, these examples benefited from the milder conditions of method B which resulted in significantly improved isolated yields. Furthermore, bis-vinyl iodide **5** could be prepared in high yield from α,α′-dibromo-*m*-xylene **4** (Scheme 2).

Scheme 2. Synthesis of 1,3-Bis((*E*)-2-iodovinyl)benzene **5**



Next, we applied this strategy to the synthesis of other vinyl halides. Gratifyingly, vinyl chlorides could be formed in high yield by the deprotonation of ICH_2Cl (Table 3). This required an extended reaction time to achieve complete consumption of the benzyl bromide. However, the addition of a second base was not required as complete elimination to the vinyl chloride was achieved in all cases. Importantly, when using NaHMDS only the vinyl chloride product was observed and in excellent *E*-selectivity; i.e., elimination of HCl from the 1,1-chloroiodoalkane intermediate was not observed.

The reaction was also successful using LiHMDS as the base, and in some cases, a higher yield was obtained (entries 2 and 7 vs 1 and 6). However, further reactions used NaHMDS as the base of choice due to poorer *E*/*Z* ratios and

(14) For examples of this approach, see: (a) Zeng, F.; Negishi, E.-i. *Org. Lett.* **2001**, *3*, 719–722. (b) Barluenga, J.; Moriel, P.; Aznar, F.; Valdés, C. *Adv. Synth. Catal.* **2006**, *348*, 347–353. (c) Organ, M. G.; Ghasemi, H.; Valente, C. *Tetrahedron* **2004**, 9453–9461.

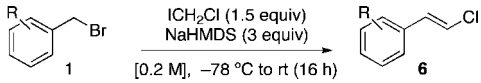
the presence of small quantities of the vinyl iodide being observed in some cases with the lithium base (entry 7).

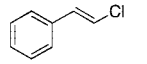
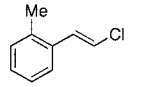
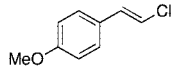
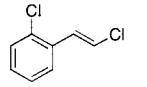
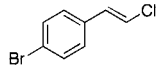
Extension to form vinyl bromides via the deprotonation of CH_2Br_2 required further modification to be successful. Although the *E*-selectivity was outstanding in many cases, byproducts from the reaction were observed, including the alkyne resulting from double elimination. These byproducts were minimized by extending the reaction time at −78 °C and by increasing the number of equivalents of dibromomethane to 4 (Table 4). This reduced the basicity of the reaction mixture and provided good isolated yields. The use of NaHMDS as base was essential for high conversions to the bromide. As with the chlorides, the addition of a second base was not required and the *gem*-dibromide intermediate was not observed.

For both the vinyl chlorides and bromides we were able to demonstrate functional group tolerance (Tables 3 and 4). As with the vinyl iodides, we were also able to generate potential lynchpin units, where the halide can be varied on either side of the unit (Table 3, entries 5 and 6; Table 4, entry 5).

In summary, we have established a facile one-pot route to (*E*)-*β*-aryl vinyl halides in high yields and excellent stereoselectivity. This method avoids the use of phosphines or heavy metals, which combined with complete conversion enables facile purification of these valuable structures. Additionally, a wide range of commercially available benzyl bromides allows access to a wide scope.

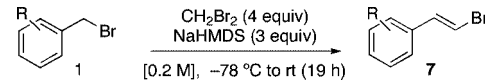
Table 3. Synthesis of (*E*)-*β*-Aryl Vinyl Chlorides

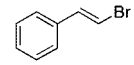
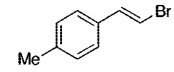
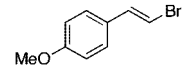
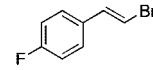
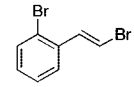


entry[a]	bromide	product		yield (%)[b]	*E*/*Z*[c]
1	**1a**		**6a**	89	97:3
2[d]	**1a**		**6a**	90	97:3
3	**1c**		**6c**	85	97:3
4	**1e**		**6e**	88	96:4
5	**1l**		**6l**	55	>99:1
6	**1m**		**6m**	69	>99:1
7[d]	**1m**		**6m**	80	94:6[e]

[a] Reactions performed on a 1.0 mmol scale. [b] Yield of isolated product. [c] *E*/*Z* ratio determined by ^{1}H NMR. [d] Used LiHMDS under otherwise identical conditions. [e] 2% vinyl iodide.

Table 4. Synthesis of (*E*)-*β*-Aryl Vinyl Bromides



entry[a]	bromide	product		yield (%)[b]	*E*/*Z*[c]
1	**1a**		**7a**	69	99:1
2	**1b**		**7b**	91	>99:1
3	**1e**		**7e**	72	>99:1
4	**1i**		**7i**	79	>99:1
5	**1o**		**7o**	67	>99:1

[a] Reactions performed on a 1.0 mmol scale. [b] Yield of isolated product. [c] *E*/*Z* ratio determined by ^{1}H NMR.

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Supporting Information Available: Experimental procedures, NMR spectra, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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