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New One-Pot Synthesis of (*E*)-*β*-Aryl Vinyl Halides from Styrenes

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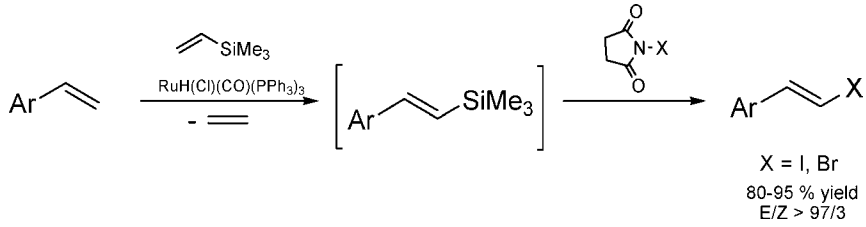
ABSTRACT



A new, efficient protocol for the highly stereoselective one-pot synthesis of (*E*)-*β*-aryl vinyl iodides and (*E*)-*β*-aryl vinyl bromides from styrenes based on sequential ruthenium-catalyzed silylative coupling-*N*-halosuccinimide-mediated halodesilylation reactions is reported.

Stereodefined *β*-aryl vinyl halides have been widely applied as extremely useful building blocks in transition-metal-catalyzed organic transformations and natural product synthesis.[1]

Classical methods for preparation of (*E*)-*β*-aryl vinyl halides are based on the Takai olefination of aromatic aldehydes[2] or the Hunsdiecker reaction involving the halodecarboxylation of cinnamic acid derivatives.[3] Alternatively, (*E*)-*β*-aryl vinyl halides may be formed by the stereoselective reduction of 1,1-dihaloalkenes[4] or homologation of benzyl bromides with dihalomethanes.[5]

Terminal alkynes can often serve as convenient starting materials for the preparation of (*E*)-haloalkenes via a hydrometalation/halogenation reaction sequence. Sterochemically pure (*E*)-*β*-aryl vinyl halides are obtained by two-step procedures starting from aryl-substituted alkynes and involving vinylboranes,[6] vinylsilanes,[7] vinylstannanes,[8] or vinylzirconium species[9] as intermediates.

Since the number of commercially available substituted styrenes far exceeds that of phenylacetylenes, and the former are much cheaper than their ethynyl analogues,[10] the development of new and straightforward synthetic methods

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for their direct conversion to stereodefined (*E*)-*β*-aryl vinyl halides is of great significance.

However, the stereoselective, direct transformations of terminal alkenes into (*E*)-vinyl halides are strongly limited, and to the best of our knowledge, there is no precedent for the one-pot (*E*)-selective iodination of terminal alkenes. Grubbs and co-workers reported a two-step synthesis of (*Z*)-vinyl bromides and (*E*)-vinyl iodides from alkenes via their sequential cross-metathesis with vinyl- or 1-propenyl boronates followed by halogenation of the resulting alkenylboronate intermediates.[11] However, iodination, in contrast to bromination, cannot be carried out in one pot with a cross-metathesis reaction. Very recently, the first example of cross-metathesis of 4-methoxystyrene with (*E*)-1,2-dichloroethene to yield (*Z*)-4-methoxystyryl chloride as predominant product has been reported.[12] (*E*)-Vinyl iodides can be also formed by the two-step oxidative cleavage of the terminal olefins with ozone or $OsO_4/NaIO_4$ followed by a Takai iodoolefination.[13]

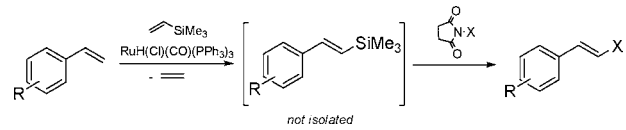
The silylative coupling of olefins with vinyl-substituted organosilicon compounds, which we have developed in the last two decades as a new effective catalytic activation of the C−H bond of olefins and C−Si bond of organosilicon compounds (generally occurring in the presence of complexes containing initially or generating in situ M−H and M−Si bonds), appears to be a valuable synthetic tool in the preparation of vinyl-substituted organosilicon reagents and polymers.[14] Recently, the ruthenium-catalyzed silylative coupling reaction followed by Hiyama coupling has been also successfully applied to the stereoselective synthesis of organic products such as (*E*)-stilbenes[15a] and (*E*)-*N*-styrylcarbazoles.[15b,c]

As we have previously reported, the silylative coupling of substituted styrenes with vinylsilanes catalyzed by ruthenium−hydride or ruthenium−silyl complexes occurred stereoselectively to give (*E*)-*β*-silylstyrenes in high yields.[16] Since alkyl-substituted vinylsilanes appear to be inactive in the ruthenium-catalyzed cross-metathesis,[17] the silylative coupling offers an attractive alternative to the selective synthesis of *β*-silyl-substituted vinylarenes.

On the other hand, it was found that electrophilic bromination (or iodination)[18] of substituted styrylsilanes proceeded stereoselectively with molecular halogens[7,19] or *N*-halosuccinimides[20] to give the corresponding styryl halides with retention of configuration.

We have envisaged that the ruthenium-catalyzed (*E*)-selective silylative coupling of styrenes with trimethylvinylsilane followed by *N*-halosuccinimide-mediated halodesilylation can be a valuable synthetic method for one-pot conversion of styrenes into (*E*)-*β*-aryl vinyl halides (Scheme 1). Therefore, in this paper, we report a facile one-pot preparation of (*E*)-*β*-aryl vinyl iodides and (*E*)-*β*-aryl vinyl bromides from styrenes via the corresponding (*E*)-styrylsilane intermediates.

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



Initially, we focused on the synthesis of (*E*)-aryl vinyl iodides, as they generally display higher activity in cross-coupling reactions.

The reaction conditions were optimized with use of styrene and trimethylvinylsilane as substrates. For preliminary results on the silylative coupling reaction, equimolar amounts of the comercially available styrene and trimethylvinylsilane were used, and the reaction was conducted following the original procedure ($RuHCl(CO)(PPh_3)_3$ catalyst (1 mol %) toluene, 6 h, 100 °C, sealed ampule)[16a] to give exclusively (*E*)-styryltrimethylsilane (GC yield >99%). Treatment of (*E*)-styryltrimethylsilane with 2 equiv of *N*-iodosuccinimide (NIS) in acetonitrile at room temperature according to the method described by Kishi and co-workers[20c] allowed isolation of stereochemically pure (*E*)-*β*-iodostyrene in 90% yield. Thus, by sequencing the highly (*E*)-selective silylative coupling of styrene with a stereospecific iododesilylation, the stereochemical fidelity of the product is preserved. After several attempts, we found that iododesilylation of (*E*)-styrylsilane occurs efficiently also when the 4:1 mixture of acetonitrile and toluene is employed as the solvent without affecting either the reaction yield or the stereoselectivity. Additionally, we have managed to decrease the necessary amount of the iodinating agent to 1.2 equiv, making the reaction more economical.

This result prompted us to attempt the iododesilylation step in one pot with silylative coupling without further purification of the (*E*)-styryltrimethylsilane intermediate. In

(10) A recent comparison of euros/mol prices of substituted styrenes and phenylacetylenes reveals that the former are usually two to ten times cheaper than the latter. Styrene and 4-chlorostyrene are even 34th and 68th of the price of their ethynyl analogues (Aldrich catalog, 2008).

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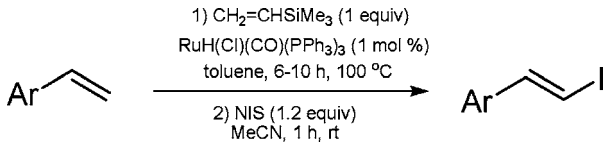
a typical procedure, the styrene, trimethylvinylsilane (1:1 ratio), and $RuHCl(CO)(PPh_3)_3$ catalyst (1 mol %) were dissolved in toluene (0.5 M concentration) and heated in Schlenk bomb flask fitted with a plug valve at 100 °C for 6 h. Next, after the reaction was cooled to room temperature, a 4-fold excess of acetonitrile and 1.2 equiv of solid *N*-iodosuccinimide were added. Treatement of the silylative coupling product with NIS caused iododesilylation in a stereospecific manner, giving (*E*)-*β*-iodostyrene in high geometrical purity (99%) within 1 h. The reaction was quenched with aqueous $Na_2S_2O_3$, extracted with hexane, and concentrated to dryness. Column chromathography of the resulting product (silica gel, eluent: hexane/ethyl acetate 50:2) afforded pure (*E*)-*β*-iodostyrene **1a** in 95% overall yield (entry 1 in Table 1). Both reactions are not air-sensitive and can be performed with commercially available reagents and solvents without further purification.

Table 1. Synthesis of (*E*)-*β*-Aryl Vinyl Iodides[d]



Entry	Ar	Product structure	Yield (%)[a]	E/Z[c]
1	Ph	**1a**	95	99:1
2	4-MeC_6H_4	**1b**	94	> 99:1
3	3-MeC_6H_4	**1c**	90	> 99:1
4	3,5-$Me_2C_6H_3$	**1d**	82[b]	97:3
5	4-$MeOC_6H_4$	**1e**	91	99:1
6	3-$MeOC_6H_4$	**1f**	87	> 99:1
7	4-FC_6H_4	**1g**	86	> 99:1
8	4-ClC_6H_4	**1h**	92	99:1
9	4-BrC_6H_4	**1i**	85	> 99:1
10	4-PhC_6H_4	**1j**	80[b]	98:2

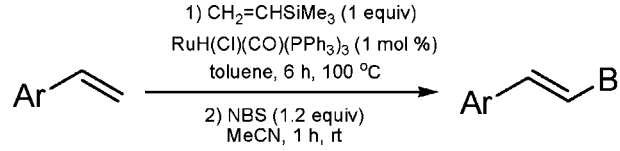
[a] Yield of isolated products. [b] silylative coupling performed for 10 h. [c] *E*/*Z* ratio determined by ^1H NMR. [d] Reactions were performed on a 5.0 mmol scale.

Given our optimized conditions, we investigated the scope of this one-pot reaction sequence using various substituted styrenes and 4-vinylbiphenyl (Table 1). Since the synthetic procedure requires the absence of byproducts of the homo-coupling of trimethylvinylsilane (which could form diiodinated side products), all the silylative coupling reactions were performed with a 1:1 ratio of substrates. Moreover, the silylative coupling reactions were carried out in 0.5 M solution of toluene to minimize polymerization of styrenes. Under these conditions, substituted styrenes bearing functional groups such as −Me, −Ph, −OMe, −Cl, −Br, and −F reacted successfully to give the corresponding (*E*)-*β*-aryl vinyl iodides in high yields, irrespective of the substituent electronic character and position on the aromatic ring (Table 1). However, the silylative coupling of 3,5-dimethylstyrene and 4-vinylbiphenyl with vinyltrimethylsilane (Table 1, entry 4 and 10) required a longer time (10 h).

The stereoselectivity of the overall transformation is excellent. In all cases, the (*E*)-double bond geometry was strongly favored, with an approximately 99:1 *E*/*Z* ratio as measured by ^1H NMR. Moreover, the (*E*)-configuration of the double bond of the compounds **1h**, **1i**, and **1j** was further confirmed by single-crystal X-ray diffraction analysis.[21]

Next, we successfully applied our one-pot strategy to the synthesis of selected (*E*)-*β*-aryl vinyl bromides using the $RuHCl(CO)(PPh_3)_3$-catalyzed silylative coupling/*N*-bromosuccinimide-mediated bromo-desilylation sequence. Extension to form (*E*)-*β*-aryl vinyl bromides via the succesive silylative coupling−bromodesilylation required no further modification to be successful. As with the aryl vinyl iodides, the use of a solvent mixture (1:5 toluene/acetonitrile) in the bromodesilylation step was a key to perform reaction sequence in one pot (Schlenk bomb flask fitted with a plug valve). Thus, a toluene solution of the selected silylative coupling products ((*E*)-styryltrimethylsilanes) was treated with a small excess of *N*-bromosuccinimide (NBS, 1.2 equiv) in acetonitrile (5-fold excess with respect to the toluene) at room temperature for 1 h to give the respective (*E*)-*β*-aryl vinyl bromides without loss of geometrical purity (Table 2).

Table 2. Synthesis of (*E*)-*β*-Aryl Vinyl Bromides[c]



Entry	Ar	Product structure	Yield (%)[a]	E/Z[b]
1	Ph	**2a**	92	99:1
2	4-BrC_6H_4	**2b**	94	99:1
3	4-ClC_6H_4	**2c**	93	99:1
4	3-$MeOC_6H_4$	**2d**	89	98:2

[a] Yield of isolated products. [b] *E*/*Z* ratio determined by ^1H NMR. [c] Reactions were performed on a 5.0 mmol scale.

Using this procedure, representative (*E*)-β-aryl vinyl bromides (**2a**−**d**) were prepared from styrenes containing both electron-donating and electron-withdrawing groups in over 98% (*E*)-selectivity and high yield (Table 2). It is worth noting that, contrary to the previously reported conditions,[20b] only a small excess of NBS is essential for effective bromodesilylation of β-silylstyrenes.

In summary, we have devised a versatile, one-pot protocol for stereoselective preparation of (*E*)-β-aryl vinyl iodides and (*E*)-β-aryl vinyl bromides from easily accessible styrenes via a highly selective catalytic silylative coupling/halodesilylation sequence. For both the vinyl iodides and bromides we were able to demonstrate functional group tolerance. Since the presented method avoids the use of large quantities of harmful metals or highly reactive organometallic compounds it provides an attractive alternative to the traditional synthetic routes employing alkynes or aldehydes as starting materials.

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

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