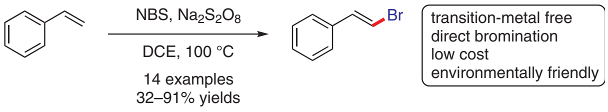
Facile Synthesis of β-Bromostyrenes by Direct Bromination of Styrenes with *N*-Bromosuccinimide and Sodium Persulfate

Yi Jing[a]
Yan Gao[a]
Qianyi Zhao[a]
Xuenian Chen*[a,b]
Yan-Na Ma*[a]



[a] School of Chemistry and Chemical Engineering, Henan Key Laboratory of Boron Chemistry and Advanced Energy Materials, Henan Normal University, Xinxiang, Henan 453007, P. R. of China
xnchen@htu.edu.cn
mayanna@htu.edu.cn
[b] College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou, Henan 450001, P. R. of China

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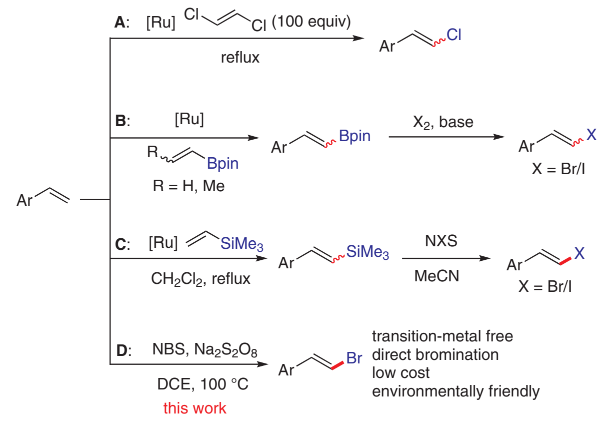
Abstract A new, direct, efficient, and transition-metal-free method is reported for the synthesis of β-bromostyrenes from styrenes by using *N*-bromosuccinimide as the brominating reagent and sodium persulfate ($Na_2S_2O_8$) as the oxidant. This convenient and concise reaction is practical, operationally simple, and can be adapted for large-scale syntheses.

Key words bromination, styrenes, bromosuccinimide, green chemistry, sodium persulfate, bromostyrenes

β-Halostyrenes are important building blocks for such transition-metal-catalyzed cross-coupling reactions as the Heck, Suzuki, Hiyama, Stille, or Ullmann processes, which are among the most commonly used methods in organic transformations and natural product syntheses.[1] In recent decades, several methods for the synthesis of alkenyl halides have been developed.[2] The classical methods are based on the Hunsdiecker decarboxylative bromination of α,β-unsaturated carboxylic acids,[3] the hydroxybromination of styrenes accompanied by dehydration,[4] or olefination of aromatic aldehydes.[5] Hydrometallation of alkynes followed by halogenation is another effective protocol for the synthesis of β-halostyrenes. The addition of an H–E bond (E = Si, B, Sn, Zr) to an alkyne leads to the corresponding vinyl derivative, which can be further substituted by a halogen atom by using various halogenating agents.[6]

Because commercially available substituted styrenes are much more abundant and less expensive than the corresponding phenylacetylene analogues, the use of substituted styrenes in the synthesis of β-halostyrenes has attracted much attention. In 2008, Grela's group reported the synthesis of β-chlorostyrenes through an olefin cross-metathesis reaction between terminal alkenes and (*E*)-1,2-dichloroethene with a Ru complex as the catalyst (Scheme 1A).[7] In 2003, Morrill and Grubbs synthesized a series of vinylboronates through ruthenium-catalyzed olefin cross-metathesis; these products can be further transformed into vinyl halides (Scheme 1B).[8] In 2009, Pawluć, Marciniec, and their co-workers synthesized β-bromo- and β-iodostyrenes through silylative coupling of vinylsilanes with substituted styrenes in the presence of $Ru(CO)Cl(H)(PPh_3)_3$, followed by halogenation with the appropriate *N*-halosuccinimide (Scheme 1C).[9] In 2017, Walkowiak and co-workers replaced the vinylboronates by vinylsilanes, and also realized this transformation.[10]



Scheme 1 Synthesis of β-arylvinyl halides from styrenes

All the above reactions using styrenes as starting materials require expensive Ru complexes as catalysts, and in most cases require the use of expensive vinylboronates or vinylsilanes to form (β-arylvinyl)boronate or (β-arylvinyl)silane intermediates, which greatly increases their cost and makes it difficult to achieve large-scale syntheses. Therefore, the search for a direct method for synthesizing β-

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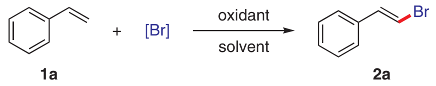
halostyrenes from styrenes under transition-metal-free conditions is of great significance. In the past decade, the direct borylation,[11] fluorination,[12] sulfonylation,[13] phosphorylation,[14] nitration,[15] and fluoroalkylation[16] of styrenes have all been reported, whereas the direct halogenation of styrenes has been less well studied. We have achieved a direct synthesis of β-bromostyrenes from styrenes by using NBS as the brominating reagent[17] and $Na_2S_2O_8$ as the oxidant in DCE in a sealed tube (Scheme 1D). Compared with previous ruthenium-catalyzed methods, our reaction conditions were simpler and operationally more convenient.

We started our investigation by using styrene as a model substrate with NBS as the bromine source in DCE to screen various oxidants (Table 1, entries 1–9). To our delight, the desired β-bromostyrene (**2a**) was obtained in 56% yield and a 10:1 *E*/*Z* ratio when $Na_2S_2O_8$ was used (entry 2). With $Na_2S_2O_8$ as the oxidant, we then investigated other bromine sources and found that 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), tribromoisocyanuric acid (TBCA), and dibromoisocyanuric acid (DBCA) also promoted this transformation, but NBS was still the best choice (entries 10–15). We next examined alternative solvents but, unfortunately, the reaction failed in all cases (entries 16–21). The yields of **2a** decreased at both higher or lower reaction temperatures (entries 22 and 23). However, when the concentration was increased, the yield improved to 63% (entry 24).[18] Encouraged by these results, we attempted to synthesize β-iodostyrene and β-chlorostyrene by using *N*-iodosuccinimide (NIS) and *N*-chlorosuccinimide (NCS), respectively, as halogenated reagents, but these reactions failed (entries 25 and 26).

With the optimized reaction conditions in hand, we examined the substrate scope of styrenes with various substituents (Table 2). First, styrenes bearing various groups at the *para*-position were explored. This showed that Me, F, Cl, Br, I, and CH_2Cl groups were all suitable substituents for this transformation, and the best yield of 72% was obtained when 4-fluorostyrene was used (Table 2, entries 2–7). 1-(2-Bromovinyl)-3-chlorobenzene (**2h**) was obtained in 42% yield with an *E*/*Z* ratio of 6.4:1 (entry 8). 2-Halostyrenes also reacted well to provide the desired products in moderate yields (entries 9–11). Note that the substrates with halogen atom in the *ortho*, *meta*, or *para* positions could be used this transformation, although the yield decreased slightly when a *meta*-halostyrene was used (entries 4, 8, and 10). A polysubstituted styrene also gave the corresponding product **2l** in 42% yield (entry 12). Finally, when 1,1-diphenylethylene was used as a reactant, the desired product **2m** was obtained in 66% yield (Table 2, entry 13); however, the corresponding iodo compound **2n** was obtained in 91% yield when NBS was replaced by NIS in this reaction (entry 14). We therefore believe that our reaction might proceed by a radical mechanism.

Table 1 Reaction Conditions Screening[a]

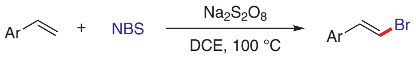


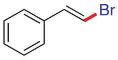
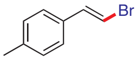
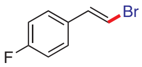
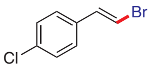
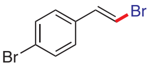
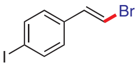
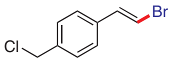
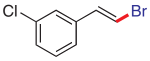
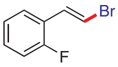
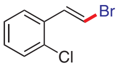
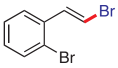
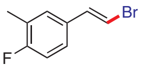
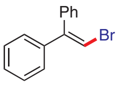
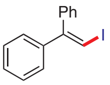
Entry	[X]	Oxidant	Solvent	Yield[b] (%)	*E*/*Z*[c]
1	NBS	$K_2S_2O_8$	DCE	trace	–
2	NBS	$Na_2S_2O_8$	DCE	56	10:1
3	NBS	$(NH_4)_2S_2O_8$	DCE	trace	–
4	NBS	Oxone	DCE	trace	–
5	NBS	$PhI(OAc)_2$	DCE	ND	–
6	NBS	*m*CPBA	DCE	ND	–
7	NBS	AgOAc	DCE	trace	–
8	NBS	$Cu(OAc)_2$	DCE	ND	–
9	NBS	TBHP	DCE	ND	–
10	DBDMH[d]	$Na_2S_2O_8$	DCE	32	8:1
11	TBCA[e]	$Na_2S_2O_8$	DCE	18	8:1
12	DBCA[d]	$Na_2S_2O_8$	DCE	12	8:1
13	NaBr	$Na_2S_2O_8$	DCE	ND	–
14	NH_4Br	$Na_2S_2O_8$	DCE	ND	–
15	Bu_4NBr	$Na_2S_2O_8$	DCE	ND	–
16	NBS	$Na_2S_2O_8$	toluene	trace	–
17	NBS	$Na_2S_2O_8$	MeCN	ND	–
18	NBS	$Na_2S_2O_8$	THF	ND	–
19	NBS	$Na_2S_2O_8$	DMF	trace	–
20	NBS	$Na_2S_2O_8$	DMSO	ND	–
21	NBS	$Na_2S_2O_8$	MeOH	ND	–
22[f]	NBS	$Na_2S_2O_8$	DCE	48	10:1
23[g]	NBS	$Na_2S_2O_8$	DCE	32	8:1
24[h]	**NBS**	**$Na_2S_2O_8$**	**DCE**	**63**	**10:1**
25	NIS	$Na_2S_2O_8$	DCE	trace	–
26	NCS	$Na_2S_2O_8$	DCE	ND	–

[a] Reaction conditions: styrene (1.0 mmol), halogen source [X] (1.05 mmol), oxidant (2.0 mmol) solvent (2 mL), 100 °C, under air, 3 h (unless otherwise noted).
[b] Isolated yield; ND = not detected.
[c] Determined by ^1H NMR.
[d] 0.6 mmol.
[e] 0.35 mmol.
[f] 80 °C.
[g] 120 °C.
[h] DCE (1.5 mL).

To verify our hypothesis, we performed several control experiments (Scheme 2). When 2.0 equivalents of a free-radical scavenger such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or butylated hydroxytoluene (BHT) were added to the reaction mixture of styrene (**1a**), none of the desired product **2a** was detected (Schemes 2A and 2B). When a 1:1 mixture of styrene (**1a**) and 1,1-diphenyle-

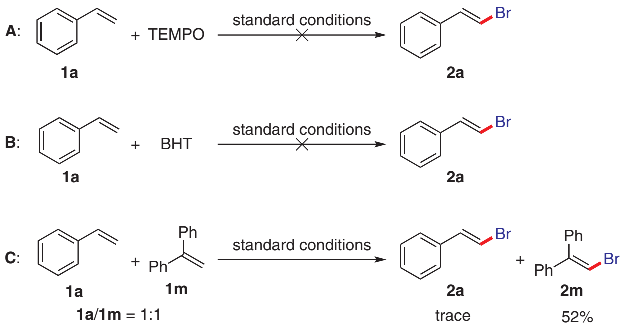
Table 2 Substrate Scope[a]



Entry	Product		Yield (%)	*E*/*Z*[b]
1		**2a**	63	10:1
2		**2b**	32	5.9:1
3		**2c**	72	5.4:1
4		**2d**	62	7.0:1
5		**2e**	58	5.9:1
6		**2f**	38	>20:1
7		**2g**	56	6.7:1
8		**2h**	42	6.4:1
9		**2i**	68	7.6:1
10		**2j**	56	5.6:1
11		**2k**	38	4.3:1
12		**2l**	42	6.2:1
13		**2m**	66	–
14[c]		**2n**	91	–

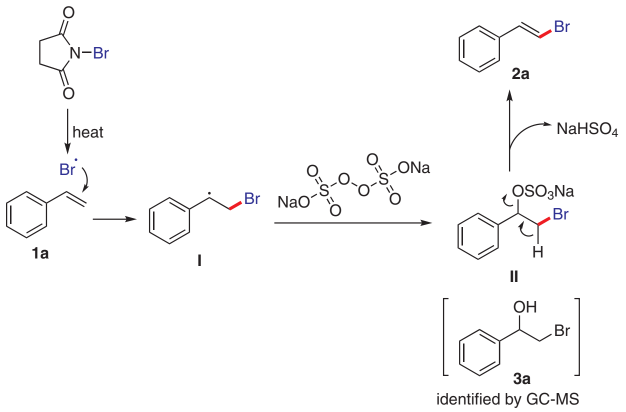
[a] Reaction conditions: styrene (2.0 mmol), NBS (2.1 mmol), $Na_2S_2O_8$ (4.0 mmol), DCE (3 mL), 100 °C, under air, 3 h.
[b] Determined by ^1H NMR.
[c] NIS (2.1 mmol) was used instead of NBS.

thene (**1m**) was subjected to the reaction system, a significant preference for bromination of **1m** over **1a** was found (Scheme 2C).



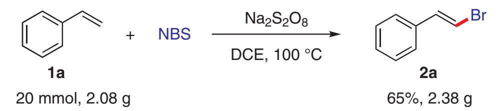
Scheme 2 Control experiments

Based on the above reactions and previous reports,[19] a plausible mechanism is proposed (Scheme 3). Initially, a bromine radical Br· is produced from NBS by heating. After a radical-addition step, the radical intermediate **I** is formed from styrene (**1a**). Subsequently, intermediate **II** is generated by the reaction of radical intermediate **I** and $Na_2S_2O_8$. Intermediate **II** undergoes elimination of $NaHSO_4$ to give the desired β-bromostyrene (**2a**). 2-Bromo-1-phenylethanol (**3a**) was detected by GC/MS after the reaction was completed, proving the formation of intermediate **II**.



Scheme 3 Proposed mechanism

To investigate the practicality of this transformation, a scaled-up reaction was carried out with styrene as the model substrate. The reaction proceeded well, and the desired product β-bromostyrene (**2a**) was obtained with no decrease in yield compared with the small-scale reaction (Scheme 4).



Scheme 4 Gram-scale reaction for the synthesis of β-bromostyrene

In summary, a direct bromination of styrenes was developed for the efficient and convenient synthesis of β-bromostyrenes under transition-metal-free conditions. The present method is applicable to a variety of substituted styrene derivatives and is a useful alternative to the Hunsdiecker decarboxylative bromination of α,β-unsaturated carboxylic acids.

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Supporting Information

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Primary Data

for this article are available online at https://doi.org/10.1055/s-0040-1707199 and can be cited using the following DOI: 10.4125/pd0119th.

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(18) **(2-Bromovinyl)benzene (2a); Typical Procedure**
Styrene (**1a**; 2.0 mmol, 1.0 equiv) was added to a solution of NBS (2.1 mmol, 1.05 equiv) and $Na_2S_2O_8$ (4.0 mmol, 2.0 equiv) in DCE (3 mL) in a sealed tube. The mixture was warmed to 100 °C and stirred for 3 h. When the reaction was complete, the mixture was purified directly by flash chromatography (silica gel, petroleum ether) to give a white oil; yield: 230.5 mg (63%, *E*/*Z* = 10:1).
^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.31–7.27$ (m, 5 H), 7.09 (d, $J = 14.0$ Hz, 1 H), 6.75 (d, $J = 14.0$ Hz, 1 H).

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