

Efficient Metal-Catalyzed Hydroarylation of Styrenes

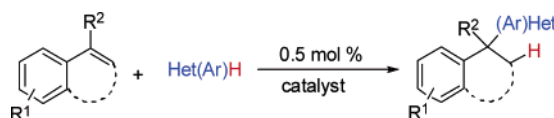
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ABSTRACT



A highly efficient metal-catalyzed hydroarylation of various styrenes has been developed. This new bismuth-catalyzed C–H functionalization provides straightforward access to a series of valuable 1,1-diaryltalkane products.

The functionalization of arenes and heteroarenes is of great importance in the synthesis of pharmaceuticals, agro-, and fine chemicals, and various procedures for their acylation and alkylation have been reported. Traditionally, these transformations are performed by Friedel–Crafts reactions with acyl or alkyl halides in combination with at least equimolar quantities of Lewis acids. Typically, drastic reaction conditions are employed resulting in low selectivities and overalkylation. Additionally, the need of electrophile preformation, coproduction of hydrogen halides, and a large amount of salt byproducts can be a significant drawback. Therefore, in view of the demand for efficient, economic, and environmentally friendly processes, the development of direct catalytic carbon–carbon bond-forming reactions of arenes with prior unmodified substrates is an important task. Recently, promising transition-metal- and acid-catalyzed C–H transformations of arenes and heteroarenes have been reported.¹ Examples include the addition of olefins to

acetophenones² and aromatic imines³ or the inter- and intramolecular arylation of alkynes, alkenes,^{4,5} benzyl, and propargyl alcohols.^{6,7} In this context, we recently demonstrated that Bi(OTf)₃⁸ is a highly reactive catalyst for the addition of benzyl alcohol and its derivatives to arenes and heteroarenes.⁹ The resulting products obtained from the latter

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reaction contain a diarylmethane motif which is of great interest as it is part of various valuable biologically active compounds and pharmaceuticals, such as papaverine, beclorate, dimetindene, phenprocoumon, avrainvilleol trimethoprim, haplopappin, or nafenopin (Figure 1).

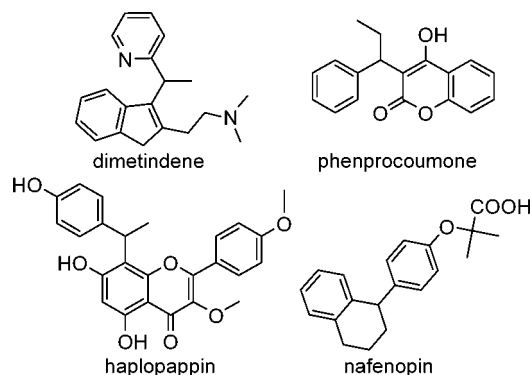


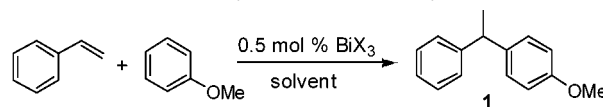
Figure 1. Examples of natural products or biologically active diarylalkanes.

Hence, the development of an even more practical route to this important class of products would be desirable. Therefore, we wondered whether it would be possible to replace the benzylic alcohol derivatives in our bismuth-catalyzed reaction⁹ with readily available styrene derivatives. This hydroarylation procedure would then result in the synthesis of 1,1-diarylalkanes and 1-aryl-1-heteroalkanes, as was just elegantly demonstrated by Beller et al. using 10 mol % of an FeCl_3 catalyst.¹⁰ Herein, we report the application of yet another highly efficient catalyst, a bismuth salt, for this important carbon–carbon bond-forming reaction.

Attracted by the direct addition of arenes to styrenes and by the fact that certain bismuth salts are highly efficient and mild Lewis acid catalysts for the arylation of benzyl alcohols, we decided to examine the bismuth-catalyzed hydroarylation of styrene. Hence, initial experiments focused on finding the appropriate bismuth catalyst, solvent, and temperature for the reaction of styrene with anisole to the corresponding 1-methoxy-4-(1-phenylethyl)benzene **1** (Table 1).

From these experiments, a considerable solvent dependence was revealed (Table 1, entries 6–10). No product formation was observed in acetonitrile or tetrahydrofuran, and unlike the arylation of benzyl alcohols, rapid exothermic decomposition and polymerization of styrene occurred in

Table 1. Bismuth-Catalyzed Reaction of Styrene with Anisole



entry	bismuth salt	solvent	time (h)	temp (°C)	yield (%) ^a
1	BiCl_3	cyclohexane	4	100	0
2	BiBr_3	cyclohexane	4	100	0
3	$\text{Bi}(\text{NO}_3)_3(\text{H}_2\text{O})_5$	cyclohexane	4	100	0
4	$\text{Bi}(\text{OTf})_3(\text{H}_2\text{O})$	cyclohexane	3	100	84
5	$\text{Bi}(\text{OTf})_3(\text{H}_2\text{O})$	cyclohexane	8	60	0
6	$\text{Bi}(\text{OTf})_3(\text{H}_2\text{O})$	cyclohexane	8	25	0
7	$\text{Bi}(\text{OTf})_3(\text{H}_2\text{O})$	CH_3NO_2	4	100	86
8	$\text{Bi}(\text{OTf})_3(\text{H}_2\text{O})$	THF	4	90	0
9	$\text{Bi}(\text{OTf})_3(\text{H}_2\text{O})$	CH_2Cl_2	4	40	0 ^b
10	$\text{Bi}(\text{OTf})_3(\text{H}_2\text{O})$	CH_3CN	4	80	0

^a Isolated yield after column chromatography. ^b After catalyst addition, rapid decomposition and polymerization of styrene occurred.

dichloromethane. Other bismuth(III) salts tested did not show conversion to the desired products (Table 1, entries 1–3). However, in solvents such as cyclohexane or nitromethane, the reaction could be performed well with 0.5 mol % of $\text{Bi}(\text{OTf})_3$ and the corresponding product **1** could be isolated in >80% yield after column chromatography (Table 1, entries 4 and 7). Using these optimal conditions, we first explored the scope of the bismuth-catalyzed hydroarylation by varying the arene component (Table 2). In general, different arenes and heteroarenes can be employed and the corresponding 1,1-diarylethanes could be isolated in good yields after short reaction times (2–4 h). In all cases, the para-substituted product was obtained as the major product, except in the case of phenol (Table 2, entry 6). Surprisingly, despite the high affinity of bismuth to sulfur, even thiophene and 2-methylthiophene resulted in product formation (Table 2, entries 8 and 9).¹¹

Following the successful bismuth-catalyzed arylation of styrenes using various arenes and heteroarenes, we decided to examine a series of differently substituted styrene derivatives in the reaction with anisole (Table 3). With 0.5 mol % of $\text{Bi}(\text{OTf})_3$, differently halo-substituted styrenes reacted well in the hydroarylation, and the diarylalkane products were obtained in 70–90% yield (Table 3, entries 2–5). A better yield (92%) was achieved by using the more electron-donating 4-methyl-substituted styrene (entry 9). Additionally, the α -methyl- and α -phenyl styrene derivatives could be transformed to the corresponding products containing a quaternary carbon center, although in the latter case a larger amount of bismuth catalyst (5 mol %) had to be employed (Table 3, entries 7 and 8). Using indene and dihydronaphthalene in the hydroarylation resulted in the aryl-dihydronaphthalene and tetrahydronaphthalene derivatives which are useful intermediates in the synthesis of several agrochemicals,

(11) Trifluoromethanesulfonic acid can also be used as a catalyst in this transformation; however, yields are considerably lower due to styrene polymerization.

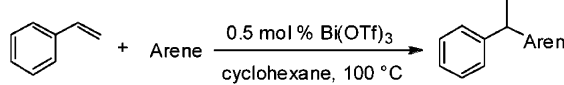
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Table 2. Reaction of Arenes and Heteroarenes with Styrene

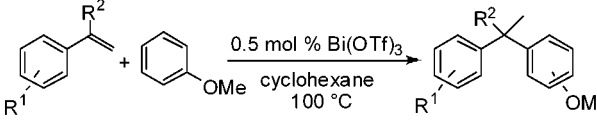
					
entry	arene	main product	time [h]	selectivity ^a	yield [%] ^b
1 ^c			3	5:1:1 ^d	72
2 ^c			4	1.2:1 ^d	50
3 ^c			4	10:1	71
4			2	7:1 ^d	71
5			3	5:1	84
6			3	3:1	78
7			2	5:1	72
8			2	3.3:1	65
9			2	10:3:1	66

^a Determined by ¹H NMR of the purified products. ^b Isolated yields after column chromatography. ^c 4 mL of the arene was used as solvent. ^d 1,3-Diphenylbut-1-ene.

fungicides, and compounds, such as nafenopin, a peroxisome proliferator.

In summary, we have developed an efficient bismuth-catalyzed hydroarylation of various styrenes. Compared to previous reactions using the Friedel–Crafts conditions, this method requires remarkably small amounts of reactive, inexpensive, and nontoxic Bi(OTf)₃ catalyst (0.5 mol %). Furthermore, the mild reaction conditions, operational simplicity, and practicability, as well as the applicability to differently substituted substrates, render this transformation an attractive approach to the valuable 1,1-diarylethanes. Further investigations are directed toward the application of this procedure in the synthesis of interesting biologically active compounds and its extension to the possible bismuth-catalyzed hydroalkylation of styrenes.

Table 3. Reaction of Various Styrene Derivatives with Anisole

					
entry	styrene	major product	time [h]	selectivity ^a	yield [%] ^b
1			3	5:1	84
2			8	20:1	89
3			24	6:1	81
4			20	20:1	73
5			24	10:1	76
6			16	10:1	67
7			8	99:1	42
8			24	99:1	78 ^c
9			3	11:1	92
10			3	20:1	62

^a Determined by ¹H NMR of the purified products. ^b Isolated yield after column chromatography. ^c With 5 mol % of catalyst.

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Supporting Information Available: A general experimental procedure and spectroscopic data of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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