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A Convenient $FeCl_3$-Catalyzed Hydroarylation of Styrenes

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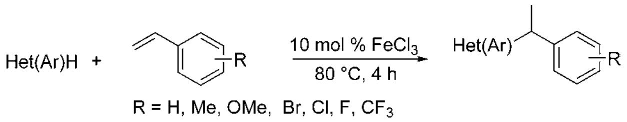
ABSTRACT



1,1-Diarylalkanes are easily synthesized by CH-functionalization reactions of electron-rich arenes and heteroarenes with styrenes in the presence of $FeCl_3$ as catalyst.

Arenes and heteroarenes are of outstanding importance for the chemical industry as pharmaceuticals, agrochemicals, and fine and bulk chemicals. Typically, well-known “classic” transformations such as Friedel−Crafts alkylations, Friedel−Crafts acylations, nitrations, and halogenations are used for their functionalization. Although these methods work reliably on large scale, they have significant drawbacks such as the necessity of drastic reaction conditions (high temperature, strong acidic conditions), regioselectivity problems, and large amounts of (salt) byproducts. Often the incorporation of a certain defined C−C-bond onto the aromatic core requires several steps including introduction of activating groups or protection and deprotection steps. Thus, the development of direct C−C coupling reactions of arenes is an important and ongoing task in organic synthesis.

Recently, organometallic chemistry and catalysis have become efficient tools for the development of more environmentally benign C−H transformations of arenes.[1] The addition of olefins to acetophenones (Murai reaction)[2] and aromatic imines,[3] novel additions of olefins to arenes[4,5] and heterocycles,[6] the addition of aromatics to alkynes[7] or alcohols,[8] and the cyclization of arene-alkyne substrates[9] are elegant examples of this.

In this respect we demonstrated that various late transition metal catalysts such as $IrCl_3$, $RhCl_3$, and H_2PtCl_6 catalyze the addition of benzylic acetates, alcohols, and carbonates to arenes and heteroarenes.[10] Most of the reactions gave high

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[2] (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatami, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529−531. (b) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatami, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 62−83. (c) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826−834. (d) Kakiuchi, F.; Uetsuhara, T.; Tanaka, Y.; Chatani, N.; Murai, S.; *J. Mol. Catal. A: Chem.* **2002**, *182*, 511−514. (e) Guari, Y.; Castellanos, A.; Sabo-Etienne, S.; Chaudret, B. *J. Mol. Catal. A: Chem.* **2004**, *212*, 77−82.

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[5] (a) Shimizu, I.; Meng Khien, K.; Nakajima, M.; Yamamoto, A. *Chem. Lett.* **1997**, 851−852. (b) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *Organometallics* **2004**, *23*, 4169−4171. (c) Bhalla, G.; Oxgaard, J.; Goddard, W. A.; Periana, R. A. *Organometallics* **2005**, *24*, 3229−3232.

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10.1021/ol0523143 CCC: $33.50

yields and selectivities under mild conditions. More recently, we presented the successful employment of $FeCl_3$ as an alternative, cheap catalyst for such reactions.[11]

The resulting diarylalkane motif[12] is an integral part of a number of biologically active compounds and pharmaceuticals. Typical examples include papaverine, beclobrate, dimetindene, and the warfarin derivative phenprocoumone (Figure 1).

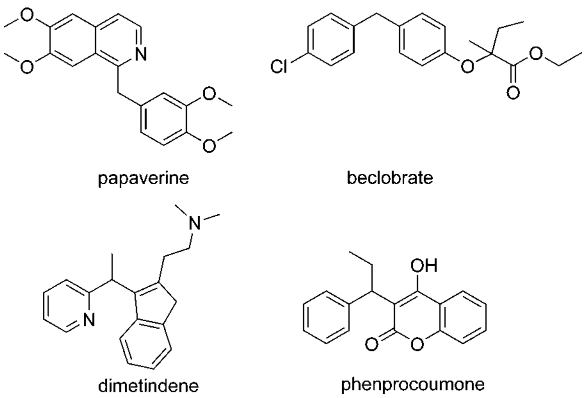


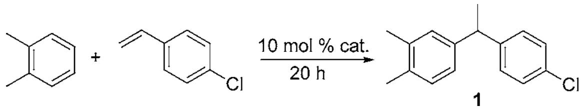
Figure 1. Biologically active compounds.

Instead of using benzylic alcohol derivatives, we thought that the direct addition of aromatic olefins to arenes should offer an easier and practically useful preparation of similar building blocks. Here, we present a general method for the synthesis of substituted 1,1-diarylalkanes and 1-aryl-1-heteroarylalkanes using $FeCl_3$ as catalyst.

An initial catalyst screening was performed for the model reaction of *o*-xylene and 4-chlorostyrene to give 4-[1-(4-chlorophenyl)-ethyl]-1,2-dimethylbenzene (**1**) as the target product. In this study the performance of different Brønsted acids and metal salts was compared using the arene as solvent at room temperature to 120 °C. Best results for the model coupling reaction were observed in the presence of $FeCl_3$ catalysts (Table 1).[13,14]

Here, **1** is obtained in high yield (87%) and excellent regioselectivity (>99:1) (Table 1, entry 5) at fairly mild conditions (80 °C; no strong acidic or basic medium). Interestingly, hydrated $FeCl_3$ gave comparable results (Table 1, entry 6). Hence, it is not necessary to exclude air or moisture in this reaction.

Table 1. Reaction of *o*-Xylene with 4-Chlorostyrene[a]



1

entry	catalyst	*T* [°C]	conv [%][b]	yield [%][c]	sel[d]
1	HCl	80	8	0	
2	TFA	80	10	0	
3	pTSA	80	20	11	93:7
4	HOAc	80	24	0	
5	$FeCl_3$	80	100	87	>99:1
6	$FeCl_3\cdot 6H_2O$	80	100	87	>99:1
7[e]	$FeCl_3\cdot 6H_2O$	80	93	84	98:2
8	$ZnCl_2$	80	2	0	
9	$CuCl_2\cdot 2H_2O$	80	6	0	
10	$NiCl_2$	80	1	0	
11	$Co(OAc)_2\cdot 4H_2O$	80	16	0	
12	$PdCl_2$	80	5	0	
13	$MesW(CO)_3$	80	3	0	
14	$RhCl_3$	80	2	0	
15	$IrCl_3$	80	19	9	96:4
16	H_2PtCl_6	80	80	57	>99:1
17	$CeCl_3$	80	5	0	
18	$La(OTf)_3$	80	3	0	
19	$Sc(OTf)_3$	80	40	30	94:6
20	AgOTf	80	4	0	
21	$Y(OTf)_3$	80	7	0	
22	$Yb(OTf)_3$	80	11	0	
23	$FeCl_3\cdot 6H_2O$	rt	6	1	
24	$FeCl_3\cdot 6H_2O$	50	31	23	96:4
25	$FeCl_3\cdot 6H_2O$	100	99	93	98:2
26	$FeCl_3\cdot 6H_2O$	120	100	93	98:2
27[f]	$FeCl_3\cdot 6H_2O$	80	100	36	>99:1
28[g]	$FeCl_3\cdot 6H_2O$	80	100	34	94:6

[a] Reaction conditions: 0.5 mmol of 4-chlorostyrene, 5 mL of *o*-xylene, 20 h. [b] GC conversion of 4-chlorostyrene. [c] GC yield of arylated products with 4-[1-(4-chlorophenyl)-ethyl]-1,2-dimethylbenzene as main product. [d] 4-/3-substitution. [e] 1 h. [f] 2.0 mmol of *o*-xylene, 5 mL of CH_2Cl_2. [g] 2.0 mmol of *o*-xylene, 5 mL of $MeNO_2$.

In general, the reactions were run for 20 h. However, after 1 h 4-[1-(4-chlorophenyl)-ethyl]-1,2-dimethyl-benzene was already formed in 84% yield (Table 1, entry 7). Unlike $FeCl_3$, catalytic amounts (10 mol %) of various Brønsted acids gave no or only low product yields (Table 1, entries 1−4). Likewise, most of the tested rare earth metal triflates were not catalytically active in this reaction. However, $Sc(OTf)_3$ gave **1** in 30% yield (Table 1, entry 19). Testing of late transition metal salts showed that H_2PtCl_6 was a productive

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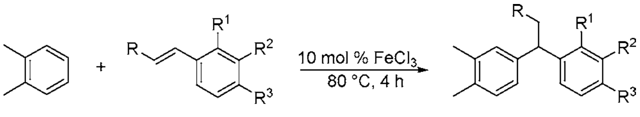
(11) Jovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem.* **2005**, *117*, 3981−3985; *Angew. Chem., Int. Ed.* **2005**, *44*, 3913−3917.

(12) Diarylmethanes are employed for the preparation of electroactive and photoactive oligomers and polymers; see: (a) Skabara, P. J.; Serebryako, I. M.; Perepichka, I. F. *Synth. Met.* **1999**, *102*, 1336−1337. (b) Khan, M. S.; Al-Mandhary, M. R. A.; Al-Suti, M. K.; Ahrens, B.; Mahon, M. F.; Male, L.; Raithby, P. R.; Boothby, C. E.; Kohler, A. *J. Chem. Soc., Dalton Trans. 1* **2003**, 74−84. (c) Jacob, J.; Oldridge, L.; Zhang, J. Y.; Gaal, M.; List, E. J. W.; Grimsdale, A. C.; Mullen, K. *Curr. Appl. Phys.* **2004**, *4*, 339−342.

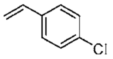
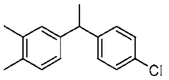
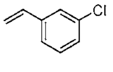
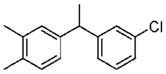
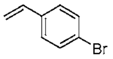
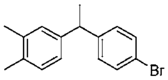
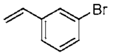
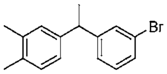
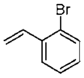
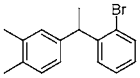
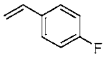
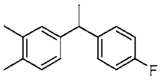
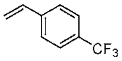
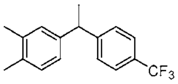
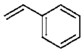
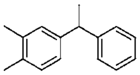
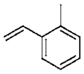
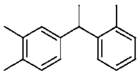
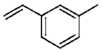
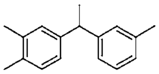
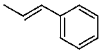
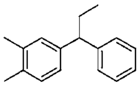
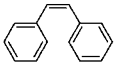
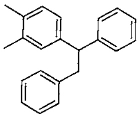
(13) Fe catalysts have been used previously for reactions of benzyl chloride with nonfunctionalized arenes. Here, stoichiometric amounts of unwanted hydrogen chloride are formed. For examples, see: (a) Pozdnyakovich, Y. V.; Savyak, R. P.; Shein, S. M. *J. Org. Chem. USSR (Engl. Transl.)* **1983**, *19*, 1484−1490; *Zh. Org. Khim.* **1983**, *19*, 1674−1681. (b) Pozdnyakovich, Y. V.; Savyak, R. P.; Shein, S. M. *Zh. Org. Khim.* **1986**, *22*, 584−589. (c) Pai, S. G.; Bajpai, A. R.; Deshpande, A. B.; Samant, S. D. *Synth. Commun.* **1997**, *27*, 2267−2273. (d) Choudhary, V. R.; Jana, S. K.; Kiran, B. P. *Catal. Lett.* **1999**, *59*, 217−219. (e) Pai, S. G.; Bajpai, A. R.; Deshpande, A. B.; Samant, S. D.; *J. Mol. Catal. A: Chem.* **2000**, *156*, 233−243. (f) Choudhary, V. R.; Jana, S. K.; Mamman, A. S. *Microporous Mesoporous Mater.* **2002**, *56*, 65−71; (g) Choudhary, V. R.; Jana, S. K. *Appl. Catal.* **2002**, *224*, 51−62; (h) Choudhary, V. R.; Jana, S. K. *J. Mol. Catal. A: Chem.* **2002**, *180*, 267−276.

(14) For an actual and excellent review on the use of Fe-catalysts in organic synthesis see: Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217−6254.

Table 2. Reaction of *o*-Xylene with Different Styrenes[a]

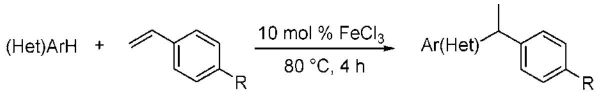


R = H, Me, Ph; R^1 = H, Me, Br; R^2 = H, Me, Br, Cl; R^3 = H, Br, Cl, CF_3, F

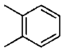
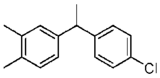
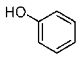
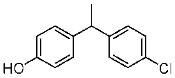
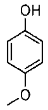
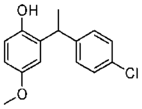
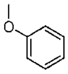
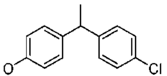
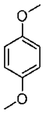
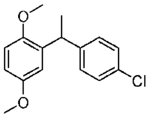
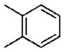
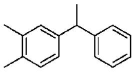
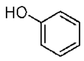
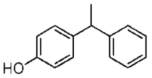
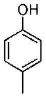
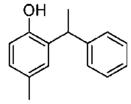
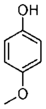
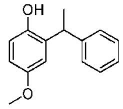
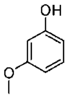
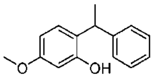
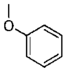
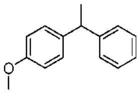
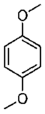
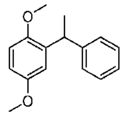
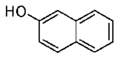
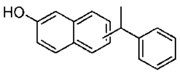
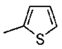
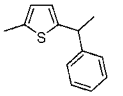
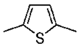
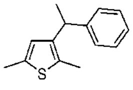
Entry	Styrene	Product[b]	Conv. [%][c]	Yield [%][d]	Sel.[e]
1			100	89	> 99:1
2			100	97	85:15
3			100	98	90:10
4			100	70	83:17
5			100	87	92:8
6			100	85	86:14
7			100	99	84:16
8			100	> 99	90:10
9			100	48	95:5
10			100	77	96:4
11[f]			100	95	72:28
12[f]			69	67	>99:1

[a] Reaction conditions: 0.5 mmol (substituted) styrene, 10 mol % $FeCl_3$, 5 mL of *o*-xylene, 80 °C, 4 h. [b] Main product. [c] GC conversion of styrene. [d] GC yield of arylated products. [e] 4-/3-substitution. [f] 20 h.

Table 3. Reaction of Styrene or 4-Chlorostyrene with Various (Hetero) Aromatics[a]



R = H, Cl

Entry	Arene	Product[b]	Conv. [%][c]	Yield [%][d]	Sel.[e]
1[f]			100	89	> 99:1
2[f]			100	91	56:44
3[f]			100	82	69:31
4[f]			100	80	76:24
5[f]			100	92	-
6			100	> 99	90:10
7[g]			94	88	55:45
8[g]			100	99	> 99:1
9[g]			100	97	76:24
10			100	> 99	70:30
11			100	> 99	81:19
12[f]			100	95	-
13[f]			100	45	10:12:9:69
14[h]			76	51	15:75:10
15[h]			46	36	-

[a] Reaction conditions: 0.5 mmol of 4-chlorostyrene or styrene, 10 mol % $FeCl_3$, 5 mL of (hetero) arene, 80 °C, 4 h. [b] Main product. [c] GC conversion of styrene/4-chlorostyrene. [d] GC yield of arylated products. [e] Main product:other isomers. [f] 2 mmol of arene, 5 mL of CH_2Cl_2. [g] 2 mmol of arene, 5 mL of cyclohexane, 20 h. [h] 2 mL of arene, 32 h.

catalyst, generating 57% of **1** (Table 1, entry 16). When alternative solvents were used in this reaction the yield of **1** drastically decreased to 34−36% (Table 1, entries 27 and 28).

Following optimization of the conditions for our model reaction we became interested in the scope and limitation of this arylation reaction of styrenes catalyzed by $FeCl_3$. First a series of differently substituted styrenes was examined in the reaction with *o*-xylene (Table 2). In the presence of $FeCl_3$, all tested vinyl-substituted haloarenes (Br, Cl, F) reacted well as benzylation reagents to give the corresponding 1,1-diarylethanes with yields ≥70% (Table 2, entries 1−6). An excellent yield (99%) was obtained with 4-(trifluoromethyl)-styrene (Table 2, entry 7). Similarly, simple styrene reacts smoothly to give 1,2-dimethyl-4-(1-phenylethyl)benzene (> 99%) (Table 2, entry 8). 3-Methylstyrene yielded the corresponding product in 77%, whereas 2-methylstyrene gave only 48% of the arylated product (Table 2, entries 9 and 10). Generally, electron-rich styrenes react worse than electron-poor ones. Here, oligomerization and polymerization occur as unwanted side reactions.

Table 3 presents the range of possible 1,1-diaryl- and 1-aryl-1-heteroarylalkanes accessible by reacting different arenes with 4-chlorostyrene or styrene. The employed electron-rich arenes reacted with full conversion of the styrenes and gave high yields of the corresponding arylated products (≥80%) (Table 3, entries 1−12). The applied methylthiophenes reacted more slowly with moderate yields (Table 3, entries 14 and 15).

With regard to the mechanism, these reactions clearly operate via an electrophilic aromatic substitution process. Thus, different regioisomers can be formed; however, in a number of cases (see Tables 2 and 3) the arylation proceeded regioselectively to produce only one product.

In summary, we have developed a novel arylation reaction of styrenes with electron-rich arenes and heteroarenes (thiophene derivatives) in the presence of $FeCl_3$. The procedure allows for an easy and practical synthesis for a wide variety of 1,1-diarylalkanes and is especially attractive because of its cheap and easy to handle catalyst (no sensitivity toward air or moisture).

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Supporting Information Available: Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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