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Practical Iron-Catalyzed Allylations of Aryl Grignard Reagents

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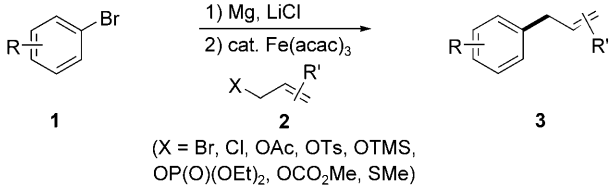
Abstract: An operationally simple iron-catalyzed reductive cross-coupling reaction between aryl halides and allyl electrophiles has been developed. The underlying domino process exhibits high versatility with respect to the allylic leaving group (acetate, tosylate, diethyl phosphate, methyl carbonate, trimethylsilanolate, methanethiolate, chloride, bromide) and high economic and environmental sustainability with respect to the catalyst system (0.2–5 mol% tris(acetylacetonato)iron(III), ligand-free) and reaction conditions (tetrahydrofuran, 0 °C, 45 min).

Keywords: allylic substitution; aryl halides; cross-coupling; Grignard reaction; iron

Allylbenzenes constitute one of the most prominent compound classes in nature with wide-spread occurrence in plant leafs, fruits, and roots (e.g., vine, tarragon, mint, basil, clove, sassafras, nutmeg, cinnamon, tea). They act as natural pesticides, attractants, signalling chemicals, and intermediates in the biosynthesis of pheromones.[1] Many derivatives exhibit a "candy shop" aroma and are being used as commercial odorants,[2] food flavorings,[3] essential oils,[4] pharmaceuticals,[5] and as precursors for the clandestine synthesis of psychoactive amphetamines[6]. Substituted allylbenzenes can be prepared by Friedel–Crafts-type reactions with allyl chloride in the presence of Lewis acids, albeit the control of regioselectivity is difficult.[7] Metal-catalyzed allylic substitution reactions with nucleophilic aryl species have matured over the past years and permit a facile synthetic access to various substituted allylbenzenes.[8] The range of suitable catalyst systems is dominated by copper, palladium, iridium, and nickel which also engage in asymmetric reactions.[9]

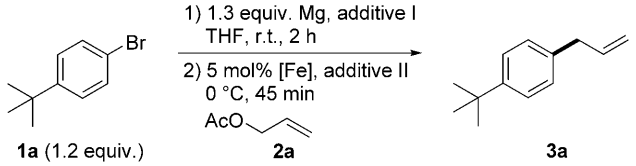
The emerging field of new cross-coupling methodologies under economically and environmentally attractive iron catalysis[10] has so far largely neglected allyl-aryl bond-forming reactions. Some effort has been directed at the development of iron-catalyzed allylations of heteroatomic[11] and CH-acidic nucleophiles[12]. An early mention of a carbon-carbon bond-forming allylation of a trimethylferrate dates from 1970.[13] Recently, Vogel et al. reported on desulfinylative allylations of Grignard reagents.[14] Nakamura et al. developed a carbometallation of oxabicyclic olefins as formal arylation of a strained allyl ether.[15] Fürstner and co-workers disclosed the catalytic activity of a tetrakis(ethylene)ferrate in allylations and propargylations of arylmagnesium halides.[16] However, the protocols reported to date exhibit either a limited substrate scope or require special reaction conditions.[17] We wish to report on a highly practical procedure for the rapid arylation of a wide range of allyl electrophiles with aromatic Grignard species in the presence of a ligand-free iron catalyst (Scheme 1).

We initiated our studies with the optimization of a model system: 4-*tert*-butylbromobenzene and allyl acetate in the presence of stoichiometric magnesium and catalytic ferric salts (Table 1). Unlike protocols utilizing pre-formed aryl-Grignard compounds without a discrete mentioning of preparative details, we directed our attention at the development of a wholistic procedure starting from commercially available aryl bromides with reported yields over two steps.[18] The addition of LiCl[19] for the Grignard formation and a slight excess of the aryl halide proved beneficial. Generally, reactions with catalytic $FeCl_3$ were accompanied by isomerization of the allyl moiety to give minor amounts of the corresponding 1-propenyl-



Scheme 1. Iron-catalyzed reductive aryl-allyl coupling.

Table 1. Selected optimization experiments.[a]

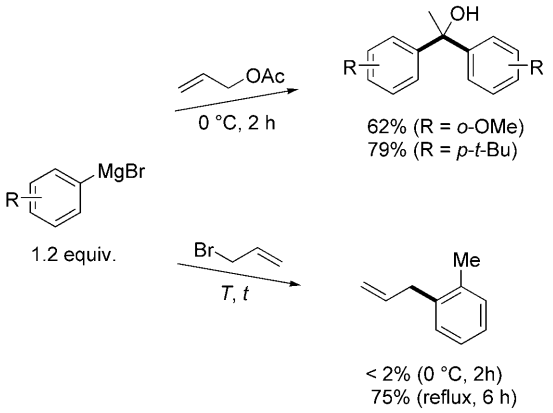


Entry	Additive I	Additive II	[Fe]	**3a** [%][b]
1			$FeCl_3$	45[c]
2	LiCl		$FeCl_3$	48[c]
3	TMEDA		$FeCl_3$	42[c]
4			$Fe(acac)_3$	49
5	LiCl		$Fe(acac)_3$	63
6	**LiCl[d]**		**$Fe(acac)_3$**	**69**
7	LiCl	pyridine	$Fe(acac)_3$	46
8	LiCl	TMEDA	$Fe(acac)_3$	49
9	LiCl	NMP	$Fe(acac)_3$	47

[a] 1.2 equiv. additives were used; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, NMP = *N*-methyl-2-pyrrolidinone.
[b] GC yields.
[c] Minor amounts of 1-propenyl isomer formed (10–15%).
[d] 1.5 equiv LiCl.

arene (10–15%). The addition of amine additives exhibited no beneficial effect. The set of optimized conditions involved Grignard formation with Mg turnings and LiCl in THF at room temperature and $Fe(acac)_3$-catalyzed coupling with allyl acetate at 0 °C for 45 min (acac = acetylacetonate). Extended reaction times (> 1 h) increased the occurrence of olefin migration (> 15%, see also Figure 2).[20] A similar effect was observed when a larger excess of the aryl-Grignard species was employed (> 1.2 equiv.). In the absence of catalyst, rapid double arylation of the carbonyl function was observed. Reactions of aryl-Grignard species with allyl bromide in refluxing THF have been reported,[21] while no conversion was observed after 2 h at 0 °C (Scheme 2).

Substrates with electron-donating, electron-withdrawing, and *ortho*-substituents were reacted with allyl acetate in good yields (Table 2). A reaction with highly pure $FeCl_3$ (> 99.9%, from Sigma–Aldrich) exhibited nearly identical yields as with the standard catalyst of 98% purity containing trace amounts of Mn, Zn, and Cu (entry 5).[22] Best yields were obtained with bromoarenes bearing oxygen substituents in the *ortho*-position (entries 6, 7, 8, 17), whereas 2-bromobenzonitrile showed poor reactivity. Employment of 3-bromopyridine required an elevated temperature for the coupling step (entry 18), possibly due to the lower nucleophilicity of the intermediate



Scheme 2. Catalyst-free reactions: Double arylation of allyl acetate (*top*); substitution with allyl bromide (*bottom*).

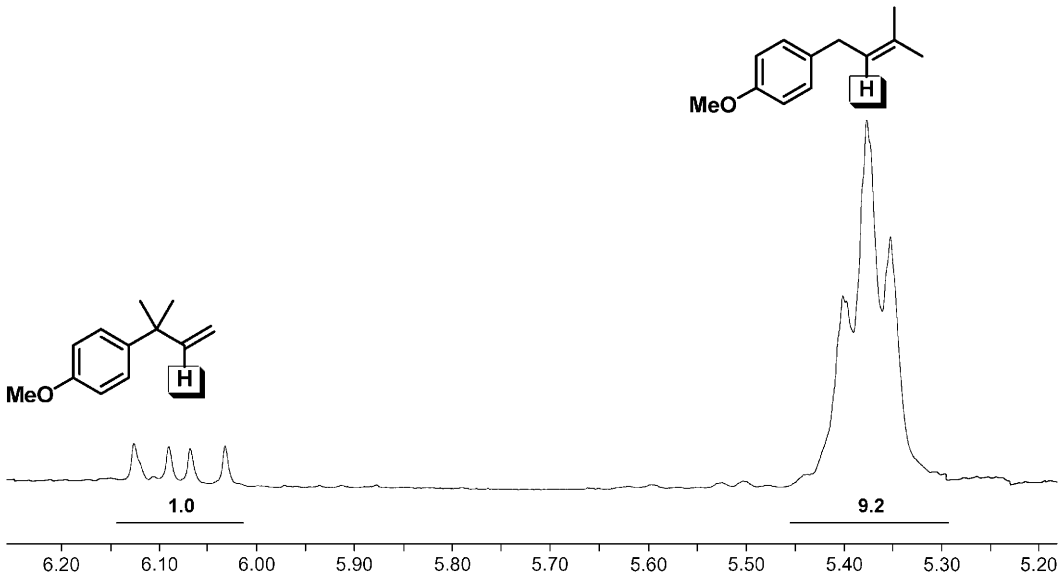
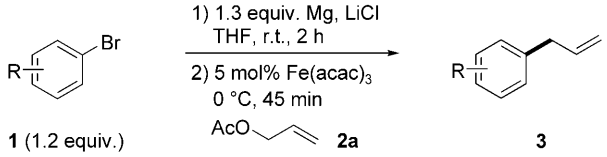


Figure 1. NMR spectrum of prenylation regioisomers from competing S_N and S_N' attacks (see entry 1 in Table 3).

Table 2. Reactions with allyl acetate (**2a**).[a]



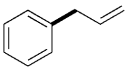
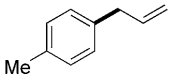
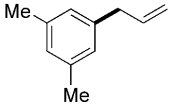
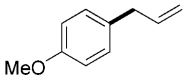
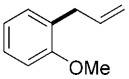
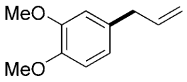
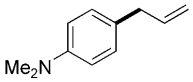
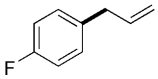
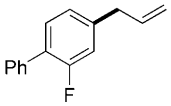
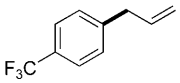
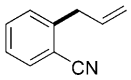
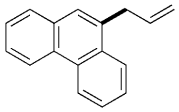
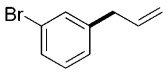
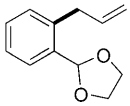
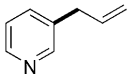
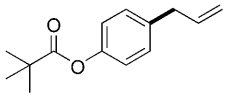
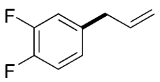
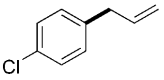
Entry	Product (**3**)	Yield of **3** [%][b]
1		(70)
2		(75)[c]
3		73
4		75 (83)
5		(80)[d]
6		91 (95)
7		89 (95)[e]
8		(86)[f]
9		70 (71)
10		65 (68)
11		65 (77)[g]
12		58 (63)
13		56
14		26[h]
15		70 (75)
16		59 (71)
17		87 (92)[e]
18		49 (55)[i]
19		60 (70)
20		75 (90)[e]

Table 2. (Continued)

Entry	Product (**3**)	Yield of **3** [%][b]
21		81 (92)[e]

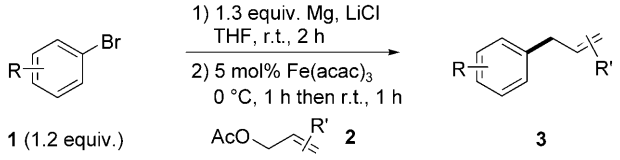
[a] For standard conditions, see Experimental Section.
[b] Isolated yields (GC yields in brackets).
[c] 16% 1-methyl-4-(prop-1-enyl)benzene.
[d] >99.9% $FeCl_3$ from Aldrich.
[e] 1 mol% $Fe(acac)_3$, 1.05 equiv. ArBr.
[f] 0.2 mol% $Fe(acac)_3$, 1.05 equiv. ArBr.
[g] 18% 1-fluoro-4-(prop-1-enyl)-benzene.
[h] Grignard formation with *i*-PrMgCl at −10 °C, ~20% 2-(*i*-Pr)-C_6H_4CN formed.
[i] 1 h at 40 °C.

Grignard species. Reactions with reduced catalyst loading (0.2–1 mol%) showed excellent selectivities (entries 7, 8, 17, 20, 21). A turnover number of 430 and a turnover frequency of 860 h^{-1} was observed with 0.2 mol% $Fe(acac)_3$ after 0.5 h (entry 8).

Allyl acetates bearing distal substituents in the 3-position (crotyl, prenyl, cinnamyl) were also competent electrophiles (Table 3). Prenyl acetate and crotyl acetate gave moderate yields of two regioisomers from competing S_N and S_N' pathways (linear *vs.* branched products). The linear allylarenes resulting from an S_N attack were the major products formed with selectivities of >9/1 from prenyl acetate (entries 1, 2, see also Figure 1). The regioselectivity of analogous crotylations was significantly lower (entries 3, 4, 5). Cinnamyl acetate exclusively gave linear products (formal S_N). The synthesis of 1,3-diphenyl-1-propene (entries 14, 15) displayed nearly identical yields from cinnamyl acetate (α-substitution) and (1-acetoxyallyl)benzene (γ-substitution), most likely as a consequence of an intermediate (π-allyl)iron complex. *p*-Tolylallene was prepared from propargyl acetate (entry 16).

The general protocol could also be applied to allyl electrophiles bearing alternative leaving groups resulting in good yields with allyl bromide, chloride, methyl carbonate, tosylate, diethyl phosphate, trimethylsilyl ether, and methyl thioether,[23] respectively (Table 4). All employed allyl electrophiles showed comparable reactivities under the standard conditions. On the other hand, the degree of subsequent double bond migration was found to be highly dependent on the nature of the leaving group and was maximal (up to 20% after 1 h) for Br, Cl, OTs, and $OP(O)(OEt)_2$. We also observed enhanced isomerization to the propenyl derivatives when using a larger excess of the Grignard reagent (> 1.2 equiv.). Allyl methyl thioether and allyl methyl carbonate gave no isomerization but clean formation of the allylbenzenes.

Table 3. Reactions with substituted allyl acetates.[a]



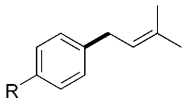
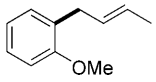
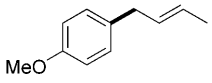
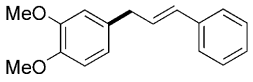
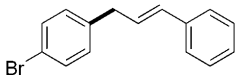
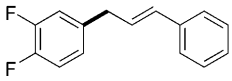
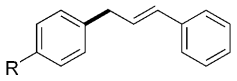
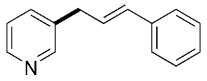
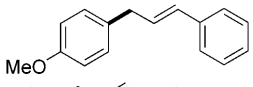
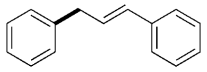
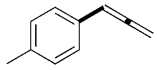
Entry	Product (**3**)	R =	Yield of **3** [%][b]
1		OMe	39 (9:1)
2		Me	36 (17:1)
3			54 (4:1)
4			56 (4:1)
5			62 (2:1)[c]
6			59
7			54
8			82

Table 3. (Continued)

Entry	Product (**3**)	R =	Yield of **3** [%][b]
9		Cl	90
10		F	90
11			65[d]
12			50
13			51[e]
14			48
15			50[e]
16			38[f]

[a] For standard conditions, see Experimental Section.
[b] Isolated yields (linear/branched regioisomer ratios in brackets).
[c] From 3-acetoxy-1-butene.
[d] 1.5 equiv. 3-pyridyl-MgBr, 1 h at 40 °C.
[e] From (1-acetoxyallyl)benzene.
[f] From propargyl acetate.

The crude reaction products engage in follow-up reactions without preceding purification or isolation. When applying an atmosphere of hydrogen to the reaction, iron-catalyzed double bond hydrogenation could be effected. Two examples of a magnesiation–allylation–hydrogenation reaction sequence resulting in the formation of *ortho*-alkylated anisoles are shown in Scheme 3. The terminal iron-catalyzed hydrogenation can be viewed as a non-toxic alternative to protocols employing Raney nickel catalysts.[24] Hydrogenation of both allylbenzene derivatives was complete within 4 h at 1 bar H_2 and room temperature; conversion of the minor 2-(1-propenyl)anisole components was somewhat slower (20 h). Further results toward this end will be communicated in due course. Figure 2 illustrates the isomerization of allylbenzenes when exposed to the reaction conditions for extended periods of time. It becomes obvious that the double bond migration is a downstream process subsequent to the iron-catalyzed allylation step which likely involves intermediate hydridoiron species.

In summary, we have developed a practical protocol for the allylation of aryl bromides. The reaction conditions are operationally simple and highly sustainable. The reaction sequence involves magnesiation of aryl bromides with Mg/LiCl and facile iron-cata-

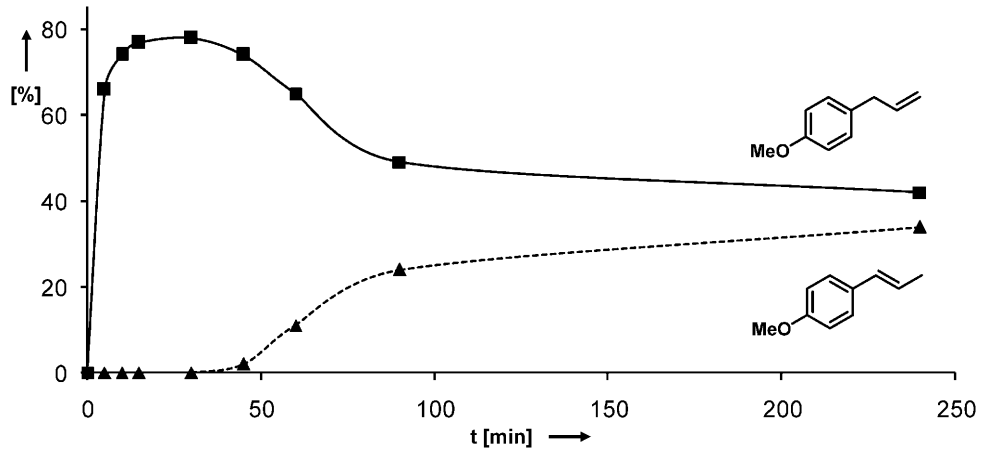
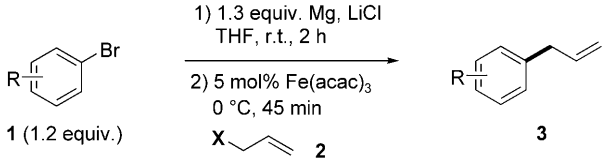


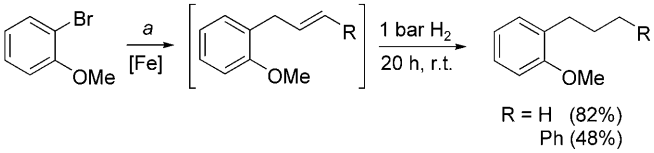
Figure 2. Iron-catalyzed isomerization of 4-allylanisole at 0 °C (for conditions, see entry 4 in Table 2).

Table 4. Reactions with different allyl electrophiles.[a]



Entry	Allyl–**X** (**2**)	Product (**3**)	Yield of **3** [%][b]
1	$-OCO_2Me$		71
2	–Cl		63[c]
3	–Br		73[c]
4	–OTs		73[c]
5	$-OP(O)(OEt)_2$		55[c]
6	–OTMS		71[c]
7	$-OCO_2Me$		65
8	–Cl		70[c]
9	–Br		85[c]
10	–SMe		65
11	$-OCO_2Me$		51
12	–Br		70[c]
13	$-OP(O)(OEt)_2$		59[c]
14	–SMe		71
15	–Br		68[c]
16	–OTs		62[c]
17	–SMe		64

[a] For standard conditions, see Experimental Section.
[b] GC yields.
[c] 10–20% propenyl isomer formed.



Scheme 3. Sequential one-pot reactions with terminal iron-catalyzed hydrogenation. Yields over three steps. *a*: standard conditions with allyl or cinnamyl acetate.

lyzed reaction of the intermediate aryl-Grignard species with a broad range of allyl electrophiles [halides, OTs, $OP(O)(OEt)_2$, OCO_2Me, SMe, OTMS, OAc]. The reaction conditions tolerate various electron-withdrawing, electron-donating, and *ortho*-positioned functional groups such as esters, acetals, F, Cl, amines, and pyridines. Allyl and cinnamyl acetates have been shown to be converted under especially mild conditions to selectively give the allylbenzene derivatives while subsequent olefin migration is suppressed. The reaction conditions favor the major formation of linear products. The crude reaction mixtures can be exploited in iron-catalyzed hydrogenation reactions. Investigations into the nature of the catalyst species and further studies of their ability to mediate asymmetric allylation, olefin isomerization, and hydrogenation reactions are currently being pursued.

Experimental Section

Standard Conditions

A 10-mL flask was charged with magnesium ribbon (63 mg, 2.6 mmol), dry LiCl (127 mg, 3.0 mmol), fitted with a rubber septum, and purged with argon (1 min). Freshly distilled THF (4 mL) and the aryl bromide (2.4 mmol) were added *via* a syringe. The mixture was stirred at room temperature for 2 h, then cooled to 0 °C in an ice bath. A solution of $Fe(acac)_3$ (35.3 mg, 0.1 mmol, 5 mol%) in dry THF (2 mL) was added, the solution stirred for 5 min, and the allyl acetate (2 mmol) added. After 45 min at 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated in vacuum, and subjected to SiO_2 flash chromatography (cyclohexene/ethyl acetate).

For more details on special procedures, compound characterization, and spectra, see the Supporting Information.

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