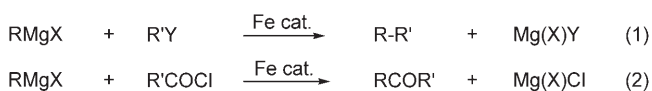


Iron-Catalyzed Desulfinylative C–C Cross-Coupling Reactions of Sulfonyl Chlorides with Grignard Reagents**

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Dedicated to Professor Horst Prinzbach on the occasion of his birthday

Carbon–carbon cross-coupling reactions are very important in the areas of material science and medicinal chemistry. Most current methods require expensive transition-metal catalysts (for example, based on Cu, Pd, Co, Ni, Pt, Ru, and Rh) and ligands (for example, phosphines). Early reports by Kharasch and Reinmuth^[1] in 1954 and then by Tamura and Kochi^[2] in 1971 suggested that inexpensive Grignard reagents and alkyl halides can be coupled in the presence of iron catalysts [Scheme 1, Equation (1)].



Scheme 1. Fe-catalyzed cross-coupling reaction of Grignard reagents with alkyl halides and the Fe-catalyzed acylation of Grignard reagents.

Apart from a few exceptions, this discovery remained dormant until 1992, when studies by Cahiez et al.^[3] and more recently by the research groups of Fürstner,^[4] Knochel,^[5] Nakamura,^[6] Bedford,^[7] and Cossy.^[8,9] However, in 1982 Julia and co-workers^[10] reported the Fe-catalyzed C–C cross-coupling reaction of Grignard reagents with vinylic sulfones, while in 1983 Molander et al. reported the Fe-catalyzed cross-coupling of aryl Grignard reagents with alkenyl halides,^[11] and in 1984 Marchese and co-workers^[12] developed the Fe-catalyzed acylation of Grignard reagents [Scheme 1, Equation (2)].

Our research group has demonstrated that sulfonyl chlorides can be used as electrophilic partners in desulfinylative C–C cross-coupling reactions catalyzed by palladium complexes^[13] or palladium nanoparticles in ionic liquids.^[14] However, when we attempted to carry out desulfinylative Corriu–Kumada C–C cross-coupling reactions^[15] between Grignard reagents and arenesulfonyl chlorides in the pres-

ence of Pd- or Ni-based catalysts, only products of aryl–aryl homocoupling were formed.^[16] Alkanesulfonyl chlorides are not suitable reagents in Pd-catalyzed desulfinylative C–C cross-coupling reactions as they undergo concurrent β elimination with the formation of the corresponding alkenes. Herein we report for the first time that alkane- and alkenesulfonyl chlorides undergo smooth desulfinylative C–C cross-coupling reactions with Grignard reagents in the presence of catalytic amounts of [Fe(acac)₃] (acetylacetonate) without the need for any extra ligands.

Treatment of *n*-octanesulfonyl chloride with PhMgBr in THF at 80 °C in the presence of [Fe(acac)₃] (5 mol %) afforded the coupling product *n*-octylbenzene in 28% yield, together with 5% of the corresponding sulfone (*n*-octylphenylsulfone; Table 1, entry 2). In the absence of any catalyst

Table 1: Optimization of the reaction conditions for the Fe-catalyzed desulfinylative C–C cross-coupling reaction of *n*OctSO₂Cl with PhMgBr.

<i>n</i> OctSO ₂ Cl + PhMgBr		Conditions		<i>n</i> OctPh + <i>n</i> OctSO ₂ Ph	
Entry	Conditions iron catalyst (equiv)	<i>n</i> OctPh [%] ^[a]	<i>n</i> OctSO ₂ Ph [%] ^[a]		
1	no catalyst, 0 °C to RT	–	76		
2	[Fe(acac) ₃] (5 %), THF, 80 °C ^[b]	28	5		
3	FeCl ₃ (10 %), TMEDA (2 equiv), THF, 80 °C ^[c]	decomp	–		
4	[Fe(acac) ₃] (5 %), THF, 80 °C ^[d]	16	48		
5	[Fe(acac) ₃] (5 %), TMEDA (10 %), THF, 80 °C ^[e]	58	–		
6	[Fe(acac) ₃] (5 %), HMTA (10 %), THF, 80 °C ^[e]	65	–		
7	[Fe(acac) ₃] (5 %), THF/NMP, 80 °C ^[e]	72	–		

[a] Yield determined after flash chromatography. [b] Grignard reagent was added immediately. [c] Starting materials were decomposed and no cross-coupled product or sulfone was observed. [d] Reaction was done in a microwave reactor, Grignard reagent was added to the reaction at –78 °C, and was heated for 1.5 h at 80 °C. [e] Grignard reagent in THF was added slowly (2 mL h^{–1}). TMEDA = *N,N,N',N'*-tetramethylethylenediamine, HMTA = hexamethylenetetramine.

(0 °C to 25 °C), the sulfone was the sole product, and was obtained in 76% yield (Table 1, entry 1). Importantly, when the Grignard reagent was added slowly through a syringe pump, the formation of the sulfone was completely suppressed. Only decomposition products were observed under the conditions developed by Nakamura et al.^[6] for the cross-coupling reaction between aromatic Grignard reagents and alkyl halides (Table 1, entry 3).

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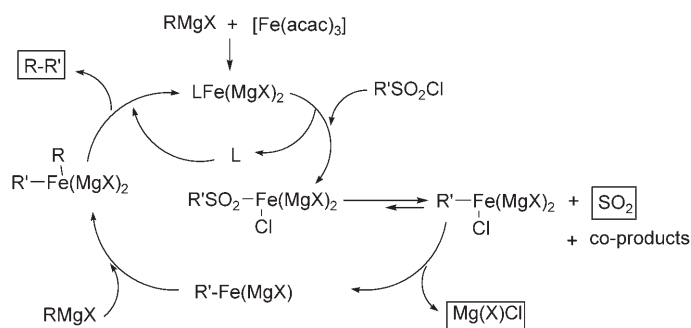
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When the reaction was carried out in refluxing diethyl ether or 1,2-dimethoxyethane (DME), the yields were low because of the competitive homocoupling of the Grignard reagents. If carried out at 25 °C, the reaction gives a larger proportion of the sulfone, as expected for all our desulfinylative C–C cross-coupling reactions.^[13,14,16] Additives such as TMEDA and HMTA^[3] were beneficial to the reaction (Table 1, entries 5 and 6). The best yield of *n*-octylbenzene was obtained in the absence of any ligand and using a mixture of THF and *N*-methylpyrrolidone (NMP) as the solvent at 80 °C (Table 1, entry 7).^[3] We found that the yield of the C–C cross-coupling reaction depends on the quality of the Grignard reagent. Interestingly, no C–C cross-coupling product was observed in the reaction of PhMgBr or PhMgCl with *n*-octyl chloride in the presence of [Fe(acac)₃]. This result shows that sulfonyl chlorides are better electrophilic partners than the corresponding chlorides in these reactions. Our optimized conditions were then applied to a wide range of sulfonyl chlorides and Grignard reagents (Table 2).

Unlike alkyl halides, which were found to react sluggishly with alkenyl Grignard reagents under the conditions developed by Nakamura et al.,^[6] alkanesulfonyl chlorides undergo the desulfinylative C–C cross-coupling reaction with alkenyl Grignard reagents. Unexpectedly, allyl- and benzylmagnesium bromides failed to give C–C cross-coupling products; only decomposition of *n*-octanesulfonyl chloride into 1-chlorooctane was observed. No 1-chlorooctane was observed when *n*-octanesulfonyl chloride was heated either alone in deuterated THF or in the presence of [Fe(acac)₃] in THF. This experiment demonstrates that [Fe(acac)₃] alone is not capable of catalyzing the desulfinylation of sulfonyl chlorides. The required catalyst must be a reduced form of Fe resulting from the reaction of [Fe(acac)₃] with the Grignard reagents.^[4,9]

Interestingly, (*E*)-styrenesulfonyl chloride reacted with phenyl-, *n*-hexyl-, and *n*-octylmagnesium bromide to give exclusively *E* alkenes (¹H NMR analysis of the crude reaction mixture). Unknown camphor derivatives were obtained by applying the methodology to camphor-sulfonyl chloride and various Grignard reagents. These compounds might be useful as chiral auxiliaries and ligands.



Scheme 2. Hypothetical mechanism for the desulfinylative C–C cross-coupling reaction of sulfonyl chlorides and Grignard reagents catalyzed by [Fe(acac)₃]. L = THF or NMP.

Table 2: Scope of the Fe-catalyzed desulfinylative C–C cross-coupling reaction of sulfonyl chlorides with Grignard reagents.

$\text{RMgX} + \text{R}'\text{SO}_2\text{Cl} \xrightarrow[\text{THF/NMP, 80 } ^\circ\text{C}]{[\text{Fe}(\text{acac})_3] \text{ (5 mol\%)}} \text{R-R}' + \text{SO}_2 \uparrow + \text{Mg}(\text{X})\text{Cl}$				
Entry	R	R'	Product	Yield [%] ^[a]
1	Ph	<i>n</i> Bu	BuPh	61
2	Ph	<i>n</i> -C ₈ H ₁₇	<i>n</i> OctPh	72 ^[b]
3	Ph	<i>n</i> -C ₁₀ H ₂₁	C ₁₀ H ₂₁ Ph	54
4	Ph	<i>n</i> -C ₁₆ H ₃₃	C ₁₆ H ₃₃ Ph	47
5	CH ₂ =CH	<i>n</i> -C ₈ H ₁₇	dec-1-ene	23
6	CH ₂ =C(Me)	<i>n</i> -C ₈ H ₁₇	2-methyldec-1-ene	46
7	Me ₂ C=CH	<i>n</i> -C ₈ H ₁₇	2-methylundec-2-ene	35
8	4-MeC ₆ H ₄	<i>n</i> -C ₈ H ₁₇	1-methyl-4-octylbenzene	68
9	4-MeOC ₆ H ₄	<i>n</i> -C ₈ H ₁₇	1-methoxy-4-octylbenzene	82 ^[c]
10	allyl	<i>n</i> -C ₈ H ₁₇	—	— ^[d]
11	Ph	Bn	diphenylmethane	55
12	4-MeC ₆ H ₄	Bn	4-methylC ₆ H ₄ Bn	58
13	PhCH ₂ CH ₂ MgCl	<i>n</i> -C ₈ H ₁₇	C ₁₀ H ₂₁ Ph	6
14	Ph	EtOCOCH ₂	—	— ^[d]
15	Ph	1-ethyl-naphthyl	α-(PhCH ₂ CH ₂)naphthalene	78
16	α-naphthyl	<i>n</i> -C ₈ H ₁₇	α-(<i>n</i> -octyl)naphthalene	traces
17	Ph	<i>i</i> Pr	cumene	24
18	4-MeC ₆ H ₄	<i>i</i> Pr	<i>p</i> -cymene	29
19	4-MeC ₆ H ₄	<i>s</i> Bu	2-(4-methylphenyl)butane	64
20	Ph	<i>s</i> Bu	2-phenylbutane	57
21	Ph	cyclopentyl	phenylcyclopentane	63
22	4-MeOC ₆ H ₄	cyclopentyl	4-cyclopentylanisole	71
23	Ph	cyclohexyl	phenylcyclohexane	68
24	CH ₂ =C(Me)	cyclohexyl	2-cyclohexylpropene	48
25	<i>n</i> -C ₆ H ₁₃	Ph-CH=CH-	Ph-CH=CH-C ₆ H ₁₃	68 ^[e]
26	<i>n</i> -C ₈ H ₁₇	Ph-CH=CH-	Ph-CH=CH-C ₈ H ₁₇	61 ^[e]
27	Ph	Ph-CH=CH-	(<i>E</i>)-stilbene	55 ^[e]
28	Ph		R = Ph	34
29	4-MeC ₆ H ₄		R = 4-MeC ₆ H ₄	32
30	4-MeOC ₆ H ₄		R = 4-MeOC ₆ H ₄	42

[a] Yields of isolated products after flash chromatography. [b] 56% yield using PhMgCl instead of PhMgBr. [c] 61% yield for the reaction at 25 °C, concurrent formation of the corresponding sulfone. [d] No C–C cross-coupling product observed. [e] *E* alkene is formed exclusively. Bn = benzyl.

A possible mechanism for our desulfinylative C–C cross-coupling reaction of sulfonyl chlorides with Grignard reagents is shown in Scheme 2. As proposed by Fürstner and co-workers,^[4] low-valent iron species probably react in a similar fashion as Pd⁰ catalysts. At this stage we cannot exclude a multiple-step process that involves radical intermediates^[7,17,18] during the formal oxidative additions and reductive eliminations of the metallic catalytical species.

For the first time, conditions have been uncovered that allow the desulfinylative C–C cross-coupling of inexpensive sulfonyl chlorides and Grignard reagents. These conditions rely on environmentally friendly iron catalysts and do not require expensive and/or toxic ligands.

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