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Palladium-catalyzed desulfinylative Negishi C–C bond forming cross-couplings of sulfonyl and organozinc chlorides

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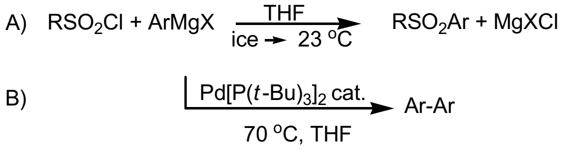
Abstract—Arene-, phenylmethane- and alkenesulfonyl chlorides are suitable electrophilic reagents in desulfinylative carbon–carbon bond formation cross-coupling reactions with organozinc reagents.

The search of efficient methods for the construction of carbon–carbon bonds represents an ongoing, central theme of research of organic synthesis.[1] Transition metal catalyzed cross-coupling of organometallic reagents with halides or triflates constitute today one of the most powerful methods to generate carbon–carbon bonds.[2] Arene- and alkanesulfonyl chlorides are inexpensive and readily available compounds. They have been used for more than a century in material sciences and medicinal chemistry.[3a–f] Recently, we have shown that Stille, carbonylative Stille,[4] Suzuki–Miyaura,[5] Sonogashira–Hagihara[6] type cross-couplings and Mizoroki–Heck[7] type arylations can be carried out using sulfonyl chlorides as electrophilic partners under desulfinylation conditions.[8] Although, the palladium-catalyzed Stille condensation has proved to be a highly versatile method for the C–C bond formation it suffers from the fact that it requires toxic organostannanes as nucleophilic carbon reagents. The alternative Suzuki–Miyaura cross-coupling reaction does not suffer from this inconvenience as it uses nontoxic organoboron reagents, but it requires costly copper salts as activators. Among the earliest and most useful organometallic nucleophilic reagents are the Grignard reagents which can be coupled with all kinds of electrophilic partners, as for the transition-metal catalyzed Kumada reactions.[9] The latter have never been applied to sulfonyl chlorides. Since 1929 it is known that Grignard reagents displace sulfonyl chlorides to generate the corresponding sulfones (Scheme 1A).[10a] We have now found reaction conditions under which desulfinylation occurs and generate products of C–C cross-couplings (Table 1).

As we have reported that most transition-metal desulfinylative C–C bond forming reactions[4–8] occur above 60 °C, we envisioned that heating sulfonyl chlorides with Grignard reagents under similar conditions might also lead to products of C–C cross-coupling. In fact, when we heated a 1:1 mixture of 2-methylbenzenemagnesium chloride and 4-methylbenzenesulfonyl chloride in boiling THF in the presence of 1–20 mol % Pd[P-(t-Bu)$_3$]$_2$,[11a] only products of Grignard reagent homocoupling (Ar–Ar:(2-MeC$_6$H$_4$)$_2$) were formed (Scheme 1B) together with small amounts of the expected sulfone 4-MeC$_6$H$_4$SO$_2$–C$_6$H$_4$–2-Me.[12] The same result was obtained using other palladium catalysts such as Pd$_2$(dba)$_3$ with carbenes or bulky ligands.[11b]

As the desulfinylative Kumada cross-coupling reaction is not a reality yet with the case studied above, we explored metal/metal exchange with the arylmagnesium



Scheme 1. Sulfones synthesis[13,14] and Grignard reagents C–C homocoupling.[15]

Keywords: Couplings; Negishi reaction; Organomagnesium reagents; Organozinc reagents; Palladium; Sulfones; Sulfonyl chlorides.

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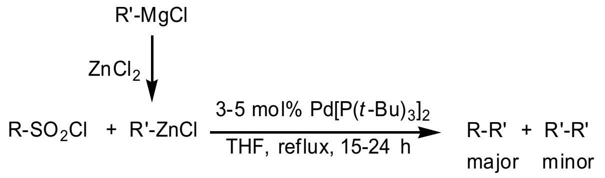
Table 1. Palladium-catalyzed desulfinylative Negishi cross-couplings of sulfonyl chlorides and organozinc halides



Entry	R	R′	Yield[a,b]
1	1-Naphthyl	Phenyl	58
2	1-Naphthyl	Phenyl	32[c]
3	1-Naphthyl	2-Methylphenyl	20[d]
4	1-Naphthyl	2-Methylphenyl	64
5	1-Naphthyl	3-Methylphenyl	61
6	1-Naphthyl	4-Methylphenyl	60
7	4-Methylphenyl	Phenyl	58
8	4-Methylphenyl	2-Methylphenyl	62
9	4-Methylphenyl	3-Methylphenyl	64
10	4-Methylphenyl	1-Naphthyl	70
11	4-Biphenyl	Phenyl	38
12	4-Biphenyl	4-Methylphenyl	68
13	(*E*)-PhCH=CH	Phenyl	32[e,f]
14	1-Naphthyl	Benzyl	21[e,f]
15	Benzyl	Phenyl	20[e,f]
16	Methallyl	2-Methylphenyl	20[e,f]
17	1-Hexyl	2-Methylphenyl	0

[a] Yields of cross-coupling products, determined after flash chromatography.

[b] The products are known, the characterizations are described in our previous letters.[4a,5]

[c] PhZnCl solution was not degassed.

[d] In situ prepared organocopper was engaged as the coupling partner.[23]

[e] ^{1}H NMR analysis of the crude.

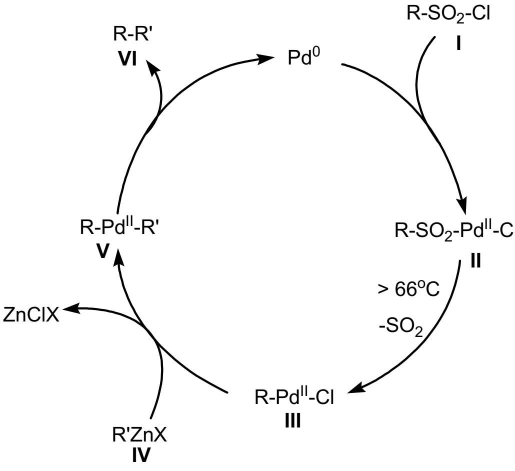
[f] Lower yield due to the self-coupling of the organozinc reagent.

chlorides[16] and first we generated the corresponding organozinc reagents with the hope that they will undergo the desulfinylative Negishi C–C cross-coupling reactions with sulfonyl chlorides. There are numerous palladium[11,17] and nickel-catalyzed[18] cross-coupling reactions between aryl and heteroaryl halides or sulfonates, and arylzinc reagents to form carbon–carbon bonds.[19]

Allylzinc compounds have been reported to displace arenesulfonyl chlorides to give the corresponding sulfones[20] (reaction analogous to that of Scheme 1A). With organozinc chlorides (R′ZnCl) and the sulfonyl chlorides (RSO_2Cl) of Table 1, no reaction was observed at 20 °C in THF and in the absence of catalyst. Upon heating in THF under reflux, slow decomposition was observed. However, in the presence of 1–5 mol % of Pd(0) catalyst such as $Pd[P(t\text{-}Bu)_3]_2$, smooth reactions occurred with elimination of SO_2 and formation of products (R–R′) of C–C cross-coupling (Table 1). The reaction was optimized for 1-naphthalenesulfonyl chlorides and 2-methylbenzenezinc chloride (generated in situ from the corresponding Grignard reagent) using 3–5 mol % $Pd[P(t\text{-}Bu)_3]_2$[11a] as catalyst in boiling THF. These conditions were then applied to the other reaction mixtures shown in Table 1. The best yields were obtained when the organozinc chloride solutions (control of the completion of the Mg/Zn exchange) were degassed by freeze–thaw cycles under vacuum (three times) followed by addition of degassed (He bubbling) of THF solutions of the sulfonyl chloride (RSO_2Cl) and the palladium catalyst. The latter solutions are better prepared in a glove box.[21]

As seen (Table 1), the yield of the C–C cross-coupled products depends on the nature of reagents. They are better for arenesulfonyl chlorides than for other sulfonyl chlorides (entries 13–16). With benzylzinc chloride (entry 14) the yield is poor, suggesting that arylzinc reagents are better behaved than alkylzinc reagents. In the case of 1-hexanesulfonyl chloride (entry 17), no product of C–C coupling was observed. This is probably due to the β-elimination of the 1-hexylpalladium intermediate that is expected to be fast in boiling THF. All reactions were accompanied with the concurrent formation of homocoupling product R′-R′ of organozinc chloride.[22] With the hope to reduce this undesired reaction we examined whether Mg/Cu exchange would be a better option than Mg/Zn metal/metal exchange. Thus 2-methylbenzenemagnesium chloride (entry 3) was treated with CuCN·2LiCl[23] in THF within 3 h at −78 to 0 °C before mixing with a THF solution of 1-naphthalenesulfonyl chloride and 4 mol % $Pd[P(t\text{-}Bu)_3]_2$. After heating under reflux overnight (until disappearance of 1-naphthalenesulfonyl chloride) analysis of the crude reaction mixture (^{1}H NMR) showed less product of C–C cross-coupling than for the reaction using the organozinc analogue.

The postulated mechanism of the reaction is shown in Scheme 2. The reactive unsaturated Pd(0)[24] catalyst undergoes oxidative addition of the SO_2–Cl bond of the sulfonyl chloride to give first a chloro palladium(II) sulfinate of type **II**. At temperature >66 °C desulfinylation occurs rapidly and an R–Pd–Cl complex of type **III** forms, which then undergoes the cross-coupling reaction with the organozinc halides **IV**, in a way similar to that of aryl halides or triflates in Negishi condensations.[19]



Scheme 2. Probable catalytic cycle for desulfinylative cross-coupling of sulfonyl and organozinc chlorides.

This work discloses the first examples of desulfinylative Negishi cross-coupling reactions that combine arene-, phenylmethane- and alkenesulfonyl chlorides with organozinc chlorides obtained in situ from the corresponding Grignard reagents.[25]

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