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Metal catalyzed cross-coupling of aryl and benzyl methyl sulfides: nickel catalyzed $C_{\text{aryl}}-C_{\text{sp}^3}$ and $C_{\text{sp}^3}-C_{\text{sp}^3}$ bond formations†

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The functionalization of $C_{\text{Ar}}-\text{SMe}$ and $C_{\text{sp}^3}-\text{SMe}$ bonds by direct exchange of the sulfur atom with an activated sp^3 -carbon has been developed. Reactions with $\text{LiCH}_2\text{SiMe}_3$ in the presence of a Nickel catalyst proceed with good yields and allow the conversion of aryl and benzyl methyl sulfides to trimethylsilylated products which are valuable precursors for the synthesis of olefins, various alcohols and amines, diols and aromatic carboxylic acids.

Cross-coupling opens the door for a wide variety of molecular transformations due to the ability of transition metal catalysts to activate otherwise inactive bonds and to assist carbon-carbon and carbon-heteroatom bond formation.¹ However, there are limitations for both, the applicable substrates and the accessible products and many potentially useful transformations cannot be achieved with our current chemical knowledge. Anisole derivatives are a good example for such a limitation: although they are naturally available in a wide variety and thereby ecologically and economically interesting electrophiles for cross-coupling reactions, the dealkoxylation C–C bond forming cross-coupling of anisoles is limited to few transformations.^{2–5} In context of a recent natural product synthesis we envisioned a two-step process and developed a synthetic concept to enable diversification of unreactive anisole derivatives.⁵ During those studies the functionalization of unreactive aryl methyl sulfides (Scheme 1) caught our interest, since the replacement of the SMe group with an activated carbon atom would give access to a variety of products including olefins,⁶ various alcohols,⁷ and amines,⁸ diols,⁹ and aromatic carboxylic acids¹⁰ among others.⁵

Scheme 1 Nickel catalyzed replacement of the SMe group in aryl and benzyl methyl sulfides with a TMS-activated sp^3 carbon nucleophile.

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Due to the versatile appearance of sulfur in various oxidation states in thiols, thioethers, thioesters, sulfoxides, sulfones and sulfoximines, a number of C–S bond cleaving protocols are known.¹¹

The coupling of aryl methyl thioethers as the simplest analogs of thiophenols *via* cleavage of the inactive $C_{\text{sp}^2}-\text{SMe}$ bond is challenging, but at the same time interesting due to its atom economy and naturally unreactive character. $C_{\text{sp}^2}-\text{SMe}$ bond cleaving coupling reactions were first explored by Wenkert *et al.*, who used Grignard reagents in the presence of a Ni^{II} catalyst for the direct arylation and methylation of aryl methyl sulfides.¹² The addition of bridged phosphine ligands later led to a significant improvement of this method and enabled the coupling with β -hydrogen containing alkyl Grignard reagents.¹³

Cross-coupling of aryl methyl sulfides in the *ortho*-position of nitrogen containing heterocycles proceeds especially well and a series of elegant and valuable transformations has been developed by Knochel and others.¹⁴ The groups of Willis and Weller reported an elegant $\text{Rh}(\text{I})$ -catalyzed carbosulfonation of alkynes with aryl methyl sulfides.¹⁵ In addition, a very interesting amination reaction applying aniline derivatives as the nucleophiles in the presence of a palladium catalyst with NHC ligands was recently reported by Murakami and Yorimitsu *et al.*¹⁶ A first nickel catalyzed reductive cleavage of aryl methyl sulfides was reported by Martin and proceeds without additional ligand with high yields.¹⁷

We started the development of the aryl methyl sulfide functionalization with a reaction of 4-(methylthio)biphenyl (**1i**) with $\text{LiCH}_2\text{SiMe}_3$ (**2**) in the presence of $\text{Ni}(\text{COD})_2$ as the catalyst.

However, only 22% of the corresponding $\text{ArCH}_2\text{SiMe}_3$ product **3i** (Table 1, entries 1 and 2) was obtained. Increasing the temperature to 80 °C led to a significantly higher yield of 75% (entry 3), which could be further improved by the addition

Table 1 Reaction optimization for the Ar-SMe functionalization

$\text{Ar-SMe} \xrightarrow[\text{Ni(COD)}_2, \text{ligand, toluene, T, 16 h}]{\text{Li}^+ \text{ 2 SiMe}_3 \text{ (1.3 equiv)}} \text{Ar-SiMe}_3$					
Entry	Ar	Ni(COD) ₂ [mol%]	Ligand [mol%]	Temp. [°C]	Yield ^a [%]
1	4-Biphenyl	2.5	—	r. t.	22
2	4-Biphenyl	2.5	PCy ₃ (5)	r. t.	22
3	4-Biphenyl	2.5	—	80	75
4	4-Biphenyl	2.5	PCy ₃ (5)	80	88
5	4-Biphenyl	2.5	SiPr-HCl (5)	80	79
6	4-Biphenyl	—	—	80	— ^b
7	2-Naphthyl	1	—	r. t.	94
8	2-Naphthyl	1	—	80	99
9	2-Naphthyl	1	PCy ₃ (2)	r. t.	79

^a Yield of isolated product. ^b Control experiment without Ni catalyst.

of 5 mol% PCy₃ or SiPr ligands (entries 4 and 5). Interestingly, the opposite trend concerning PCy₃ addition was observed for 2-(methylthio)naphthalene (**1a**): whereas reactions without ligand yielded 94% at room temperature and 99% at 80 °C, the addition of PCy₃ (2 mol%) led to a reduced yield of 79% at 80 °C (entries 7–9). A control reaction without Ni catalyst did not lead to conversion of starting material (entry 6).

With acceptable reaction conditions in hand we explored the scope of the reaction. The reaction can be applied to a variety of substrates and the products **3a–p** were isolated in good yields (Table 2). Different substitution patterns as well as functional groups were tolerated. The selective C_{Ar}-S-cleavage in substrate **1k** that contains a methylthioether as well as a methoxy group could also be achieved indicating that the C-SMe bond cleaves faster than the C-OMe bond. In this case only 1 equivalent of the nucleophile was applied. In addition, aliphatic, aromatic and benzylic alcohols **1l–n** are suitable substrates for our transformation and also nitrogen containing heterocycles **1j**, **o**, **p** could be converted with good yields.

In order to expand the scope we examined the nickel catalyzed C_{sp}³-C_{sp}³ cross coupling using benzyl methyl sulfides. However, with the above optimized conditions, the cleavage of benzylic C-SMe bonds in the synthesis of phenethyl trimethylsilane derivative **5a** from benzyl methyl sulfide **4a** appeared to be difficult and only traces of the 4-biphenyl product **5a** were detected (Table 3, entries 1–3). Since different phosphine ligands (entries 4–9) did not lead to higher conversion, we increased the electron density at the Ni center by addition of the N-heterocyclic carbene (NHC) ligand 1,3-bis(2,6-diisopropylphenyl)imidazolidinium chloride (SiPr-HCl, 5 mol%). Using this catalyst 87% yield were obtained (entry 10).

A control experiment showed that no conversion was obtained in the absence of a Ni catalyst (entry 11). Interestingly, whereas the 4-biphenyl substrate **4a** could not be converted sufficiently when PCy₃ was employed as ligand, the transformation of naphthyl derivative **4i** proceeded well under these conditions (Table 3, entries 12–15).

Table 2 Scope of the Ar-SMe functionalization^a

$\text{R-SMe} \xrightarrow[\text{Ni(COD)}_2 \text{ (2.5 mol\%)}, \text{ligand (5 mol\%)}, \text{toluene, 80 °C, 16 h}]{\text{Li}^+ \text{ 2 SiMe}_3 \text{ (1.3 equiv)}} \text{R-SiMe}_3$
3a , 99% ^b 94% ^c
3b , 99% ^b
3c , 86% ^b
3d , 98% ^b
3e , 96% ^b
3f , 47% ^b
3g , 88% ^d 75% ^b
3h , 98% ^d
3i , 88% ^d 75% ^b
3j , 97% ^b
3k , 75% ^{d,e}
3l , 81% ^f
3m , 57% ^f
3n , 47% ^g
3o , 84% ^d
3p , 61% ^b

^a Yields of isolated products. ^b No additional ligand. ^c Room temperature, no additional ligand. ^d PCy₃ (5 mol%). ^e PCy₃ (5 mol%), LiCH₂TMS (1 equiv.). ^f LiCH₂TMS (3 equiv.), Ni(COD)₂ (10 mol%). ^g LiCH₂TMS (3 equiv.), Ni(COD)₂ (5 mol%), PCy₃ (10 mol%).

In general, these reactions proceed with good yields for various benzyl methyl sulfides **5a–j** (Table 4). Similar to the transformation of thioanisole derivatives, benzyl methyl sulfide

Table 3 Reaction optimization for the Ar-CH₂-SMe functionalization

Entry	Ar	Ligand [mol%]	Temp. [°C]	Yield ^a [%]
1	4-Biphenyl	—	r. t.	Traces
2	4-Biphenyl	—	80	Traces
3	4-Biphenyl	PCy ₃ (5)	80	Traces
4	4-Biphenyl	PPh ₃ (5)	80	Traces
5	4-Biphenyl	Dcype (5)	80	Traces
6	4-Biphenyl	Dcypb (5)	80	Traces
7	4-Biphenyl	Dcypb (5)	80	Traces
8	4-Biphenyl	Dppm (5)	80	Traces
9	4-Biphenyl	Dppp (5)	80	Traces
10	4-Biphenyl	SiPr-HCl (5)	80	87
11	4-Biphenyl	—	80	— ^b
12	2-Naphthyl	PCy ₃ (5)	80	93
13	2-Naphthyl	SiPr-HCl (5)	80	86
14	2-Naphthyl	—	r. t.	Traces
15	2-Naphthyl	—	80	9

^a Yield of isolated product. ^b Control experiment without Ni catalyst.

derivatives with aryl substitution in *ortho*-, *meta*-, and *para*-position could be applied with good yields. In addition, 92% yield was obtained for the transformation of the morpholine derivative **4j** into the corresponding phenethyl trimethylsilane.

Conclusions

In summary, we have developed a metal catalyzed cross-coupling of aryl and benzyl methyl sulfides leading to selective C_{aryl}-C_{sp³} and C_{sp³}-C_{sp³} bond formations. The direct functionalization of C_{Ar}-SMe and C_{sp³}-SMe bonds by exchange of the sulfur atom with an activated sp³-carbon could be achieved for several thioethers using the nickel catalyzed cross coupling and an organolithium nucleophile. The reactions proceed with good yields and allow the conversion to the trimethylsilylated products which are valuable precursors for various products including olefins, alcohols, amines, diols and aromatic carboxylic acids.

Experimental

In a typical experiment an oven-dried, argon-flushed Schlenk tube was charged with the aryl or benzyl methyl sulfide (if solid; 0.25 mmol), the ligand and yellow Ni(COD)₂. The tube was immediately sealed and again flushed with argon. Subsequently, freshly distilled toluene (1.5 mL), the aryl or benzyl methyl sulfide (if liquid) and a LiCH₂SiMe₃ solution in pentane (1.0 M) were added and the mixture was stirred overnight at the appointed temperature. Upon purification *via* column chromatography (elution with *n*-hexane-EtOAc = 40 : 1) the pure product was obtained after solvent removal.

Table 4 Scope of the Ar-CH₂-SMe functionalization^a

 5a, 87%	 5b, 68%
 5c, 78%	 5d, 76%
 5e, 82%	 5f, 93%
 5g, 98%	 5h, 96%
 5i, 86% 93% ^b	 5j, 92%

^a Yields of isolates products. ^b PCy₃ (5 mol%) instead of SiPr-HCl was added as the ligand.

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