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Nickel-Catalyzed Alkenylative Cross-Coupling Reaction of Alkyl Sulfides

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Abstract: A novel cross-coupling reaction of alkyl aryl sulfides with aryl Grignard reagents has been achieved to produce the alkenyl-aryl coupling products in high yields by using catalytic Ni(cod)$_2$ and a bulky *N*-heterocyclic carbene ligand, SIPr.

Transition-metal-catalyzed cross-coupling reactions are powerful tools in organic synthesis. While various electrophilic substrates have been utilized in the cross-coupling reactions, organosulfur compounds[1] have received far less attention among them in spite of the long history since the independent publications by Wenkert[2] and Takei[3] in 1979. The current status of underutilization of organosulfur compounds is partly due to their malodorous smell[4] and also due to our perception of them as a mere substitute for the other electrophiles. In fact, it has been shown that their reactivity is virtually the same as those of the widely used organic halides and pseudohalides,[5] and thus, there does not seem to be a significant advantage in pursuing their utility in modern cross-coupling technology. In light of the ample supply of sulfur sources,[6] especially as byproducts of refinery, in industrial chemistry, we have explored the reactivity of organosulfur compounds in the cross-coupling reaction and found that alkyl aryl sulfides act as *alkenyl* electrophiles to give the arylation products with the simultaneous installation of an olefinic part in the products (Scheme 1).[7] Herein, we report a novel Ni-catalyzed "alkenylative" cross-coupling reaction of alkyl sulfides with aryl Grignard reagents, which provides a new access to olefinic compounds of various substitution patterns.

Scheme 1. Alkenylative Cross-Coupling of Alkyl Aryl Sulfide

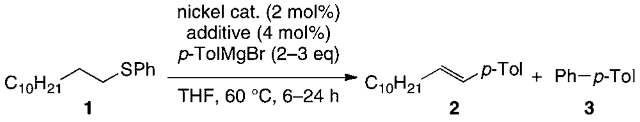

Table 1 summarizes the results of catalyst screening. In the presence of Ni(cod)$_2$, the highest yield (92%) of the desired alkenylative coupling product **2** was obtained after 6 h at 60 °C when a saturated-type *N*-heterocyclic carbene (NHC) ligand precursor, 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (SIPr·HCl), was used (entry 1). The reaction with the NHC ligand itself (SIPr) showed similar selectivity but gave a slightly lower yield (entry 2). Other NHC ligand precursors, IPr·HCl and SIMes·HCl, gave lower yields (entries 3 and 4). Ni(acac)$_2$ and NiCl$_2$ showed lower catalytic activity and required a higher reaction temperature, 80 °C, for complete conversion (entries 5 and 6). While phosphine ligands improved the yield of the biaryl coupling product **3**, the desired alkenylative coupling product **2** was not obtained (entries 7−10). In the absence of a nickel catalyst, the coupling reactions did not proceed at all (entry 11).

Table 1. Nickel Catalyst and Additive Screening on the Cross-Coupling of Dodecyl Phenyl Sulfide with *p*-TolMgBr

			yield (%)		RSM (%)[d]
entry[a]	nickel cat.	additive	**2** (*E*/*Z*)[b]	**3**[c]	**1**[c]
1	Ni(cod)$_2$	SIPr·HCl	92 (94/6)	3	0
2	Ni(cod)$_2$	SIPr	84 (95/5)	4	<1
3	Ni(cod)$_2$	IPr·HCl	76 (95/5)	4	0
4	Ni(cod)$_2$	SIMes·HCl	19 (92/8)	59	10
5[e]	Ni(acac)$_2$	SIPr·HCl	70 (95/5)	8	0
6[e]	NiCl$_2$	SIPr·HCl	75 (95/5)	5	0
7	NiCl$_2$	P^{t}Bu$_3$	0	67	19
8	NiCl$_2$(dppe)	none	0	57	23
9	NiCl$_2$(PPh$_3$)$_2$	none	0	75	17
10	NiCl$_2$	none	0	19	64
11	none	SIPr·HCl	0	0	>95

[a] Reactions were carried out on a 0.5 mmol scale. [b] The yield and *E*/*Z* selectivity were determined by ^{1}H NMR analysis using pyrazine as an internal standard. [c] The yield was determined by GC analysis using undecane as an internal standard. [d] Recovery of the starting material **1**. [e] Reactions were carried out at 80 °C.

Scope of the present nickel-catalyzed alkenylative cross-coupling reaction is shown in Table 2. The reactions of dodecyl sulfides possessing an electron-rich, electron-poor, or bulky aryl group all gave the alkenylative coupling products in high yields with excellent *E*/*Z* selectivities, and the parent dodecyl phenyl sulfide was found to give the optimum yield (entries 1−5). Secondary alkyl aryl sulfides also participate in the alkenlylative coupling reaction: cyclohexyl (or cycloheptyl) phenyl sulfide reacted with a variety of aryl Grignard reagents bearing dimethylamino, methoxy, methyl, and fluoro substituents to give the corresponding arylated cycloalkenes in good to excellent yields (entries 6−9, 13). The reaction was found to be rather sensitive to the steric demands of the aryl nucleophile, and thus, the coupling products with *o*-tolyl and mesityl Grignard reagents were obtained in poor yields (entries 10 and 11). A 2-naphthyl Grignard reagent took part in the reaction (entry 12).

Excellent *E*/*Z* selectivity was achieved in the formation of disubstituted acyclic olefin, exemplified by the stereoselective synthesis of the *E*-stilbene derivative (entry 14). In contrast, low selectivity was observed in the formation of trisubstituted olefin (entry 15). This may be accounted for by nonstereoselective formation of enthiolate intermediates (see the mechanistic discussion below). When a nonsymmetrical secondary alkyl sulfide was subjected to the reaction conditions, the corresponding internal olefin **4** and terminal olefin **5** were obtained in a ratio of 46:54. Note that the stereoselectivity of this trisubstituted olefin **4** is acceptably high (entry 16). The olefin moiety in the sulfide substrate did not interfere with the coupling reaction (entry 17). As in entry 18, 8-phenylthio-1,4-dioxaspiro[4,5]decane gave a double arylation product, 8,8-diphenyl-1,4-dioxaspiro-[4,5]decane, in 37% yield along with the

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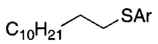
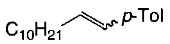
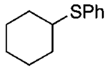
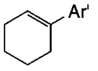
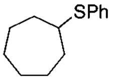
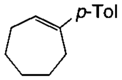
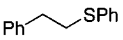
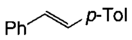
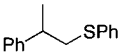
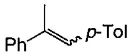
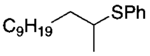
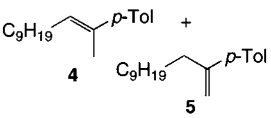
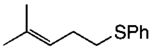
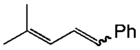
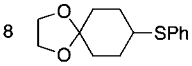
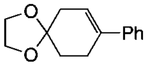
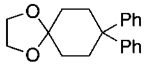
Table 2. Substrate Scope of Alkenylative Cross-Coupling

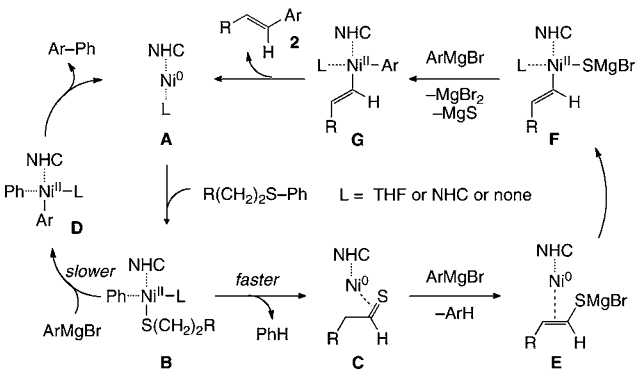
entry[a]	sulfide	conditions[b] temp, time	alkene product (isolated %yield)
			
1	Ar = 4-Me_2N-C_6H_4	60°C, 6 h	85%[c] E:Z = 95:5
2	Ar = 4-MeO-C_6H_4	60°C, 6 h	90%[c] E:Z = 95:5
3	Ar = Ph	60°C, 6 h	93%[d] E:Z = 94:6
4	Ar = 4-F-C_6H_4	60°C, 6 h	80%[c] E:Z = 94:6
5	Ar = mesityl	60°C, 30 h	84%[c] E:Z = 96:4
			
6		60°C, 3 h	Ar' = 4-Me_2N-C_6H_4 85%
7		60°C, 3 h	Ar' = 4-MeO-C_6H_4 89%
8		60°C, 6 h	Ar' = 4-Me-C_6H_4 86%
9		60°C, 6 h	Ar' = 4-F-C_6H_4 72%[c]
10		80°C, 6 h	Ar' = 2-Me-C_6H_4 34%
11		60°C, 32 h	Ar' = mesityl < 5%[e]
12		60°C, 6 h	Ar' = 2-naphthyl 82%
13		60°C, 6 h	 96%[c]
14		60°C, 6 h	 85%[c] only E isomer
15		80°C, 6 h	 86%[c] E:Z = 43:57
16		60°C, 12 h	 93% **4**:**5** = 46:54 **4*E***:**4*Z*** = > 95:5
17		60°C, 6 h	 75% E:Z = 98:2
18		60°C, 6 h	 43%  37%

[a] Reactions were carried out on a 0.5−1.0 mmol scale following the procedure in entry 1 in Table 1 unless otherwise noted. [b] $Ni(cod)_2$ (5 mol %) and SIPr·HCl (10 mol %) were used in the case of secondary alkyl sulfides. [c] NMR yields using pyrazine as an internal standard. [d] The reaction was carried out on a 10 mmol scale. [e] GC yield.

formation of the expected alkenylative coupling product (43% yield). The geminal diarylation products were also found as a minor byproduct (1−3% yields) in all the other entries, and the mechanism of the formation is discussed below.

Scheme 2 shows a plausible mechanism based on the experimental results,[8,9] computational studies[10] (Figure 1), and related literature.[10−13] The catalytic cycle starts with the oxidative addition of an alkyl phenyl sulfide to a Ni(0) species **A** to afford a phenylnickel(II) intermediate **B**. β-Hydride elimination and subsequent reductive elimination of benzene give a Ni(0)-thioaldehyde complex **C**. A bulky NHC ligand would suppress the conventional biaryl coupling pathway (**A**−**B**−**D**). The thioaldehyde undergoes deprotonation by ArMgBr to give a Ni(0)-enethiolate complex **E**,[11,12] and the following C−S bond cleavage gave an alkenyl nickel(II) **F**.[13] Transmetalation between **F** and ArMgBr gives a diorganonickel **G** with production of byproducts $MgBr_2$ and MgS.[14] Reductive elimination gives the alkenylative coupling product, such as **2**, with regeneration of the active species **A**. The diarylation could take place via addition of an aryl Grignard reagent to a thiocarbonyl intermediate **C**,[15] followed by a nickel-catalyzed arylation of the resulting benzylthiolate.[16]

Scheme 2. A Plausible Mechanism



DFT calculations provide deeper insights into the alkenylative coupling reaction as shown in Figure 1: An unprecedented transition structure model was obtained for the transformation from **B** to **C**. The phenylnickel(II) **B** (R = H, L = none in Scheme 2) isomerizes to **B′**, in which an agostic Ni−H interaction is present. A concerted β-hydride-reductive elimination of benzene takes place via a five-centered transition structure $\mathbf{TS_{B-C}}$ to form a Ni(0)-thioaldehyde complex **C**. On the other hand, the transmetalation from **B** to **D** takes place via a transition structure resembling σ-bond methathesis, $\mathbf{TS_{B\text{-}D}}$. Relative Gibbs free energy of $\mathbf{TS_{B\text{-}D}}$ is 3.0 kcal/mol higher than that of $\mathbf{TS_{B-C}}$ probably owing to the steric demand of a bulky SIPr at $\mathbf{TS_{B\text{-}D}}$. These results are in good accordance with the experimental results, the selective formation of alkenylative coupling products in the presence of SIPr.

In summary, we have developed a nickel-catalyzed alkenylative cross-coupling reaction of alkyl aryl sulfides with aryl Grignard reagents. The key to success is the use of a bulky NHC ligand, SIPr, which suppresses the conventional biaryl coupling reaction. The theoretical calculation suggests a concerted mechanism for the β-hydride elimination and reductive elimination process from nickel(II) thiolate species, which accounts for the new reactivity of the organosulfur electrophile in the present alkenylative cross-coupling.

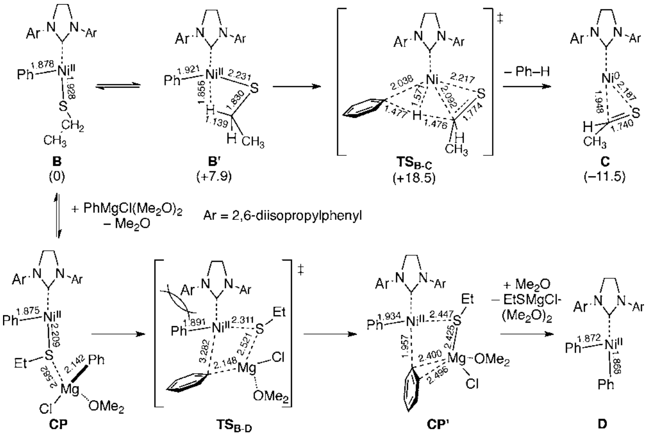


Figure 1. Reaction pathways for the reductive β-hydride elimination process (**B** to **C**) and the transmetalation process (**B** to **D**). Relative Gibbs free energies (ΔG, calculated at the B3LYP/6-311+G(d,p)-SDD//B3LYP/6-31G(d)-LANL2DZ level) relative to **B** are given in kcal/mol.

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Supporting Information Available: For details of the experimental procedure, computational studies, characterization, and physical data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The use of dodecanethiol instead of dodecyl phenyl sulfide did not give the alkenylative coupling product **2** but the conventional coupling product, 1-dodecyl-4-methylbenzene (7%), dodecane (24%), and 1-dodecene (27%), respectively.

(9) The reaction of 2,2,4,4,6,6-hexamethyl-1,3,5-trithiane, a trimer form of propane-2-thione, with 4-(*N*,*N*-dimethylamino)phenyl Grignard reagent gave the corresponding alkenylative coupling product, *N*,*N*-dimethyl-4-(prop-1-en-2-yl)aniline (17%) with recovery of the trithiane (51%), which indicates an intermediacy of thioketone in the present alkenylative coupling reaction.

(10) See the Supporting Information for details.

(11) For the deprotonation of thiocarbonyl compounds, see: (a) Nocher, A.-M. L.; Metzner, P. *Tetrahedron Lett.* **1992**, *33*, 6151. (b) Murase, M.; Yoshida, S.; Hosaka, T.; Tobinaga, S. *Chem. Pharm. Bull.* **1991**, *39*, 489.

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