Cross-Coupling

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Nickel-Catalyzed Kumada Reaction of Tosylalkanes with Grignard Reagents to Produce Alkenes and Modified Arylketones[**]

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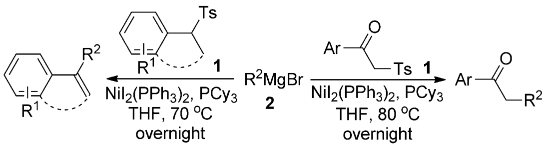
The cross-coupling of an organic electrophile with a nucleophilic organometallic reagent is one of the most important and common methods for the construction of carbon–carbon bonds.[1,2] Despite considerable progress in the field, examples of the transition-metal-catalyzed Kumada cross-coupling of an alkyl electrophile with a Grignard reagent are much less abundant and are more limited.[1–3] The products are generally modified alkanes, a carbonyl group in the substrates can often not be tolerated, and the alkyl electrophiles are focused on alkyl halides and pseudohalides (often tosylates).

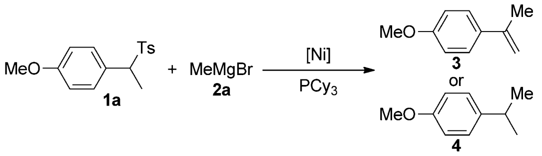
Sulfonylalkanes (often tosylalkanes) are an important class of organic compounds that are found in various agrochemicals, pharmaceuticals, and polymers.[4] They also serve as versatile synthetic building blocks in organic synthesis.[5] However, to our knowledge, the Kumada reaction of sulfonylalkanes with Grignard reagents remains an unexploited area. Herein, we report a mild selective synthesis of alkenes and modified arylketones through the $NiI_2(PPh_3)_2/PCy_3$ catalyzed Kumada coupling of tosylalkanes with Grignard reagents (Scheme 1). This is the first example of alkene synthesis from alkyl electrophiles with Grignard reagents using the Kumada reaction strategy. Furthermore, the carbonyl groups in tosylalkyl ketones are well-tolerated under the $NiI_2(PPh_3)_2$ and PCy_3 conditions.[3m] The products, alkenes and arylketones, are valuable synthetic intermediates and important structural units found in numerous natural products, pharmaceutical molecules, and functional materials.[6]



Scheme 1. Ni-Catalyzed Kumada reaction of tosylalkanes.

Our investigation began with the reaction of 1-methoxy-4-(1-tosylethyl)benzene (**1a**) with MeMgBr (**2a**) and 5 mol% $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) in THF at 70°C under argon atmosphere (Table 1, entry 1): the desired 1-methoxy-4-(prop-1-en-2-yl)benzene (**3**) was isolated in 53% yield. The yield was enhanced to 68% when PCy_3 was used (entry 2; the ligand effect is summarized in Table S1 of Supporting Information). The effects of varying the amount of $Ni(cod)_2$ were examined, and 10 mol% $Ni(cod)_2$ produced identical results to 5 mol% $Ni(cod)_2$ (entry 3). Subsequently, a number of Ni catalysts, including $NiI_2(PPh_3)_2$, $NiCl_2(dppe)_2$ (dppe = 1,2-bis(diphenylphosphino)ethane) and $NiCl_2$, were tested (entries 4–6). Gratifyingly, $NiI_2(PPh_3)_2$ was more effective than $Ni(cod)_2$ (entry 4 vs. entry 2) and the yield was increased to 74% in the presence of 5 mol% $NiI_2(PPh_3)_2$. However, the other catalysts displayed less catalytic reactivity than $Ni(cod)_2$ (entries 5 and 6). Screening revealed that the amount MeMgBr (**2a**) used affected the reaction in the presence of

Table 1: Condition screening.[a]



Entry	[Ni] (mol%)	PCy_3 [mol%]	Solvent	*T* [°C]	Yield [%][b] (product)
1	$Ni(cod)_2$ (5)	0	THF	70	53 (**3**)
2	$Ni(cod)_2$ (5)	10	THF	70	68 (**3**)
3	$Ni(cod)_2$ (10)	20	THF	70	66 (**3**)
4	$NiI_2(PPh_3)_2$ (5)	10	THF	70	74 (**3**)
5	$NiCl_2(dppe)_2$ (5)	10	THF	70	57 (**3**)
6	$NiCl_2$ (5)	10	THF	70	54 (**3**)
7[c]	$NiI_2(PPh_3)_2$ (5)	10	THF	70	64 (**3**)
8[d]	$NiI_2(PPh_3)_2$ (5)	10	THF	70	76 (**3**)
9	$NiI_2(PPh_3)_2$ (5)	10	diethylether	30	30 (**3**)
10	$NiI_2(PPh_3)_2$ (5)	10	toluene	120	58 (**4**)
11	$NiI_2(PPh_3)_2$ (5)	10	cyclohexane	80	91 (**4**)
12[e]	$NiI_2(PPh_3)_2$ (5)	10	THF	70	86 (**3**)
13[e]	$NiI_2(PCy_3)_2$ (5)	0	THF	70	84 (**3**)

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (5 equiv), [Ni] (see table), PCy_3 (see table), and anhydrous solvent (2 mL) overnight under argon atmosphere. [b] Yield of isolated product. [c] **2a** (2 equiv). [d] **2a** (10 equiv). [e] Undried THF was used. cod = 1,5-cyclooctadiene, Cy = cyclohexyl, dppe = 1,2-bis(diphenylphosphino)ethane.

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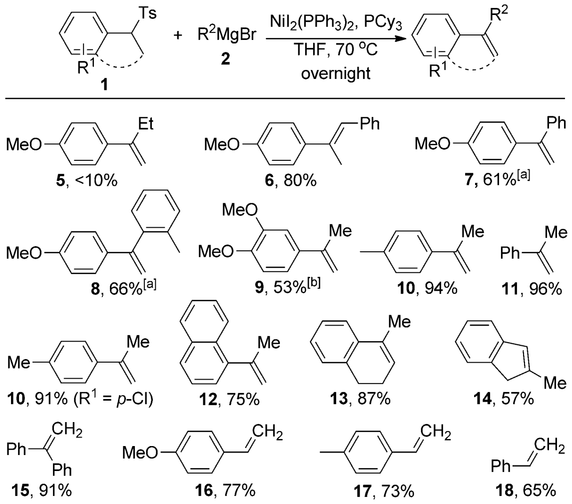
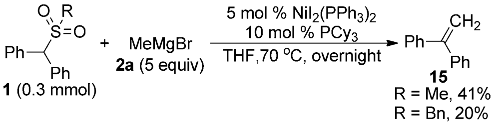
NiI$_2$(PPh$_3$)$_2$. Whereas the yield was lowered to 64 % when the loading of MeMgBr (**2a**) was decreased to 2 equiv (entry 7), the reaction with 10 equiv MeMgBr (**2a**) gave the same results as 5 equiv MeMgBr (**2a**) (entry 8). It was found that diethylether was less effective for the reaction (entry 9). Surprisingly, the chemoselectivity was shifted completely toward the traditional cross-coupled product **4**, 1-isopropyl-4-methoxybenzene, using either toluene or cyclohexane as the solvent (entries 10 and 11). The reaction in cyclohexane, for example, furnished product **4** in 91 % yield (entry 11). Interestingly, the yield of **3** is enhanced to 86 % yield using undried THF solvent (entry 12). Also, NiI$_2$(PCy$_3$)$_2$ gave the same effect as the NiI$_2$(PPh$_3$)$_2$/PCy$_3$ system (entry 13).

With the optimized reaction conditions in hand, the above method was applied to the synthesis of various alkenes from tosylalkanes **1** and Grignard reagents **2** (Scheme 2). Initially, 1-methoxy-4-(1-tosylethyl)benzene (**1a**) was reacted with four different Grignard reagents, EtMgBr, BnMgBr, PhMgBr, and *o*-MeC$_6$H$_4$MgBr, in the presence of NiI$_2$(PPh$_3$)$_2$ and PCy$_3$ (Products **5**–**8**). Unfortunately, the reaction of substrate **1a** with EtMgBr gave a mixture of products (determined by GC-MS analysis), including (*Z*/*E*)-1-(but-2-en-2-yl)-4-methoxybenzene and 1-sec-butyl-4-methoxybenzene (**5**), the desired product. Gratifyingly, the internal alkene **6** was obtained in 80 % yield from the reaction of substrate **1a** with BnMgBr. Moderate yields were still obtained using two aryl Grignard reagents when they were conducted in dried THF (Scheme 2, products **7** and **8**). Subsequently, substituents on the aryl ring of 1-tosylaryl-alkanes, such as dimethoxy, Me, and Cl, were examined in the presence of MeMgBr (**2a**), NiI$_2$(PPh$_3$)$_2$, and PCy$_3$ (Products **9** and **10**). The results demonstrated that both dimethoxy and Me substituents were well-tolerated, but the Cl group was cross-coupled with MeMgBr (**2a**) during the alkene formation process (91 % yield; Scheme 2, product **10**). Screening showed that both 1-(1-tosylethyl)benzene and 1-(1-tosylethyl)naphthalene were suitable for the reaction, furnishing the corresponding products **11** and **12** in good to excellent yields. Notably, substrates with a six-membered ring or a five-membered ring successfully underwent the reaction with MeMgBr (**2a**), NiI$_2$(PPh$_3$)$_2$, and PCy$_3$, leading to the corresponding endocyclic double-bond-containing products **13** and **14** in good yields. Surprisingly, the substrate with a five-membered ring gave 2-methylation product **14** instead of the desired 1-methylation product. Using (tosylmethylene)dibenzene, ethene-1,1-diyldibenzene (**15**) was obtained in 91 % yield under the optimized conditions. The common alkenes, including 1-methoxy-4-vinylbenzene (**16**), 1-methyl-4-vinylbenzene (**17**), and styrene (**18**), could also be synthesized in good yields, which makes this method more useful for organic synthesis.



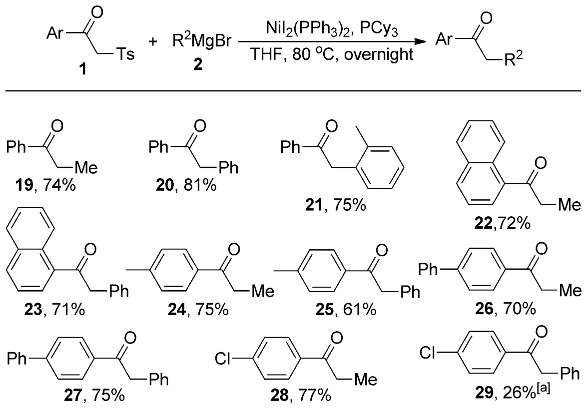
Scheme 2. NiI$_2$(PPh)$_2$/PCy$_3$ catalyzed synthesis of alkenes. Reaction conditions: **1** (0.3 mmol), **2** (5 equiv), NiI$_2$(PPh$_3$)$_2$ (5 mol %), PCy$_3$ (10 mol %), and THF (undried, 2 mL) at 70 °C overnight under argon atmosphere. [a] THF was dried at 80 °C. [b] A by-product, 4-(*tert*-butyl)-1,2-dimethoxybenzene (**9'**), was obtained in 11 % yield. Ts = *p*-toluene-sulfonyl.

As shown in Equation (1), two other sulfonyl-containing compounds were investigated in the presence of MeMgBr (**2a**), NiI$_2$(PPh$_3$)$_2$ and PCy$_3$. However, they were inferior to tosyl-containing substrates (Scheme 2, product **15**).



(1)

We next planed to synthesize some other functional-group-containing alkene products using the NiI$_2$(PPh$_3$)$_2$/PCy$_3$ catalytic system. Although our plan failed after a series of trials, the carbonyl groups in 1-aryl-2-tosylethanones **1** were found to be well-tolerated in the presence of Grignard reagents **2** under the optimized conditions (Scheme 3). A variety of modified arylketones were prepared from the reaction of 1-aryl-2-tosylketones **1** with Grignard reagents **2**, NiI$_2$(PPh$_3$)$_2$ and PCy$_3$. For example, the treatment of 1-phenyl-2-tosylethanone with three Grignard reagents,

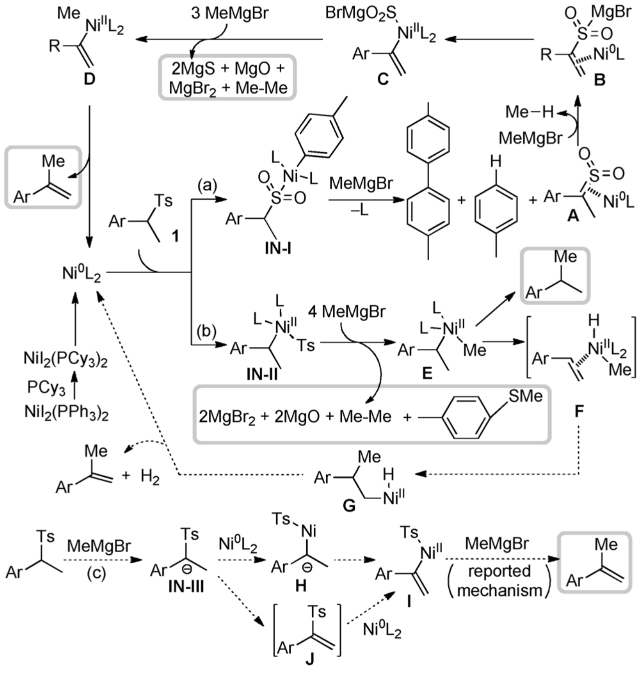


Scheme 3. NiI$_2$(PPh$_3$)$_2$/PCy$_3$ catalyzed Kumada cross-coupling of 1-aryl-2-tosylethanones (**1**) with Grignard reagents (**2**). Reaction conditions: **1** (0.3 mmol), **2** (5 equiv), NiI$_2$(PPh$_3$)$_2$ (5 mol %), PCy$_3$ (10 mol %), and THF (dried, 2 mL) at 80 °C overnight under argon atmosphere. [a] A Cl-coupled product, **27**, was isolated in 38 % yield.

MeMgBr (**2a**), PhMgBr, and *o*-MeC_6H_4MgBr, afforded the corresponding new arylketones **19–21** in good yields. The substrate 1-(naphthalen-1-yl)-2-tosylethanone was also suitable for reaction with either alkyl or aryl Grignard reagents (Product **22** and **23**). It was noted that substrates with Me, Ph, or Cl substituents on the aryl ring were compatible with the optimized conditions (Scheme 3, products **24–29**). The Cl group is perfectly tolerated in the reaction with MeMgBr (Scheme 3, product **28**). However, there was some coupling with PhMgBr when it was used to treat a Cl-substituted substrate (Scheme 3, products **29** and **27**).

The results demonstrated that $NiI_2(PCy_3)_2$ gave the same catalytic activity as the $NiI_2(PPh_3)_2/PCy_3$ system (Table 1, entry 21), suggesting that the ligand exchange of PPh_3 with PCy_3 takes place in the present procedure, and $NiI_2(PCy_3)_2$ is superior to $NiI_2(PPh_3)_2$ alone. To our surprise, 1,2-dimethoxy-4-(1-tosylethyl)benzene was found to yield a by-product, 4-(*tert*-butyl)-1,2-dimethoxybenzene (**9′**; a dimethyl-addition product; Scheme 2). These results imply that Ni carbenes may be involved in this process. However, the corresponding carbene product was not trapped by ethyl 2-diazoacetate during a control experiment (see the Supporting Information, Eq. (S5) of Scheme S1).

Based on our experiments, we propose the mechanisms shown in Scheme 4.[1–3,7–11] Initially, the ligand exchange of $NiI_2(PPh_3)_2$ with PCy_3 gives more reactive $NiI_2(PCy_3)_2$, followed by conversion of $NiI_2(PCy_3)_2$ into the active Ni^0L_2 species with the aid of Grignard reagent **2**. The active Ni^0 species subsequently undergoes oxidative addition of tosylalkane **1** at two possible positions: a) to the C(aryl)−S bond, or b) to the C(alkyl)−S bond. Pathway (a) results in intermediate **IN-I** by oxidative addition of the active Ni^0 species to the C_{Ar}−S bond.[7] Reductive elimination of intermediate **IN-I** with MeMgBr offers sulfene intermediate **A** (supported by in situ FTIR analysis),[9,10] 4,4′-dimethylbiphenyl, and toluene.[1] Intermediate **B** is readily formed from intermediate **A** with MeMgBr base, followed by oxidative addition of the active Ni^0 species to the C_{vinyl}−S bond affords intermediate **C**.[8] Transmetalation of intermediate **C** with MeMgBr (**2a**) furnishes intermediate **D**.[8a,b] Finally, reductive elimination of intermediate **E** affords the desired alkenes and the active Ni^0 species.



Scheme 4. Possible mechanisms. L = PCy_3.

Pathway (b), which involves intermediate **IN-II**, produces intermediate **E** by oxidative addition of the active Ni^0 species to the C_{alkyl}−S bond followed by transmetalation with MeMgBr. Intermediate **E** undergoes β-hydrogen elimination leading to a nickel–hydride complex intermediate **F**.[2,3,7] An addition reaction takes place on intermediate **F** to furnish intermediate **G**. Finally, β-hydrogen elimination and reductive elimination of intermediate **G** generates the desired alkenes, H_2, and the active Ni^0 species.

Pathway (c) is also proposed to generate intermediate **I** from tosylalkane **1** through α-deprotonation, oxidative addition, and β-deprotonation.[8]

As shown in Table 2 and Equation (2), some experiments were conducted to trap the proposed intermediates. Initially, we rechecked the GC-MS data from the reaction between substrate **1a** and MeMgBr (Table 2, entry 1 and Table 1, entry 20). The data shows an 88 % yield of **3** and a 27 % yield of 4,4′-dimethylbiphenyl (**32**), together with a 4 % yield of product **33** and a trace of products **4**, **34**, and others, all of which suggests that there is a competition between pathway (a) (supported by **32**) and pathway (b) (supported by **4** and **33**). This is also supported by DFT calculations.[11] If

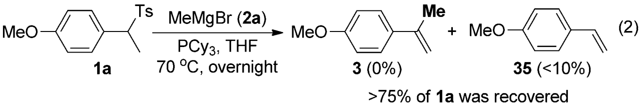
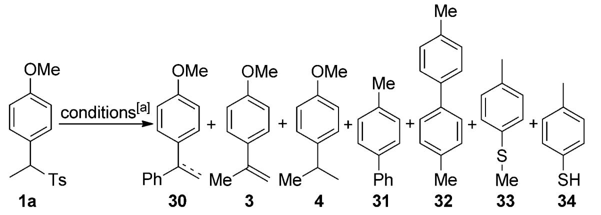


Table 2: Trapping experiments.



Entry	$PhB(OH)_2$ [equiv]	**30** [%][b]	**3** [%][b]	**4** [%][b]	**31** [%][b]	**32** [%][b]	**33** [%][b]	**34** [%][b]
1	none	0	88	trace	0	27	4	trace
2	0.8	0	78	10	31	11	12	7
3	1.0	0	56	5	40	11	trace	trace
4	2.0	0	37	9	52	6	trace	trace
5	2.0[c]	0	71	23	29	4	14	trace

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (5 equiv), [Ni] (5 mol %), PCy_3 (10 mol %), $PhB(OH)_2$ (see table), and anhydrous THF (2 mL) at 70 °C overnight under argon atmosphere. [b] Yield determined by GC-MS analysis using nitrobenzene as an internal standard. [c] 8 equiv of **2a** was used.

intermediates **IN-I** or **IN-II** are actually present, they should be transmetalated with other organometallic electrophiles, such as boronic acids.[1] Interestingly, a 53 % total yield of the tolyl group was trapped on the basis of yields of products **31** (coupled with $PhB(OH)_2$) and **32** at 0.8 equiv $PhB(OH)_2$, but the yield of product **3** was decreased to 78 % along with 10 % yield of **4**, 12 % yield of **33** and 7 % yield of **34** (Table 2, entry 2). Using 1 equiv $PhB(OH)_2$, the total yield of the tolyl group (62 %) is nearly consistent with the yield of product **3** (56 %). However, little yield of products **4** and **33** was generated (entry 3). Screening revealed that the yield of product **31** from substrate **1a** coupled with 2 equiv $PhB(OH)_2$ was enhanced to 52 %, whereas the yield of **3** was lowered (entry 4). The reason may be that some MeMgBr is consumed in the coupling of intermediate **IN-I** with $PhB(OH)_2$. As expected, the yield of **3** was enhanced to 71 % by increasing MeMgBr to 8 equiv (entry 5). Notably, in none of the experiments was $PhB(OH)_2$-coupled product **30** observed. The results in (Table 2) clearly support pathway (a).[11] Intermediate **IN-II** in pathway (b) can also be generated simultaneously, which results in product **4**, not product **3**. Generally, α-tosyl elimination is faster than α-hydrogen elimination when using strong bases. Indeed, only the α-tosyl/β-hydrogen elimination product (**35**) was observed when using MeMgBr alone, which does not support pathway (c) [Eq. (2)].

In summary, we have developed a new route to alkenes and modified arylketones through the Ni-catalyzed Kumada cross-coupling reaction. Alkenes can be prepared from the reaction of tosylalkanes with Grignard reagents, and the carbonyl group of the tosylalkane is well-tolerated using the $NiI_2(PPh_3)_2/PCy_3/THF$ system. Furthermore, the mechanism was evaluated based on in situ FTIR analysis, DFT calculations, and experimental results. Applications of this Ni-catalyzed Kumada cross-coupling transformation in organic synthesis are currently underway in our laboratory.

Experimental Section

Typical Experimental Procedure: Sulfonylalkane **1** (0.3 mmol), Grignard reagent **2** (1.5 mmol), $NiI_2(PPh_3)_2$ (5 mol %), PCy_3 (10 mol %), and THF (2 mL) were added to a Schlenk tube. The tube was then charged with argon, and stirred at 70 °C overnight until the starting material was completely consumed, as indicated by TLC and GC-MS analysis. After the reaction was finished, the reaction mixture was washed with brine, and the aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 200:1) to afford the desired product.

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Keywords: arylketones · cross-coupling · Kumada reaction · nickel · tosylalkanes

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[10] The in situ FTIR analysis of the results of the reaction between substrate **1a** and MeMgBr indicate that the sulfene intermediate **A** is produced, based on the S=O symmetric stretching vibration, and that the step from intermediate **IN-I** to intermediate **A** is rate-limiting (see the Supporting Information, Figure S1); a) *Structure Determination of Organic Compounds, Tables of Spectral Data*, 4th ed. (Eds.: E. Pretsch, P. Bühlmannn, C. Affolter), Springer, Berlin, **2009**, p. 305; b) Y. Hu, J. Liu, Z. Lü, X. Luo, H. Zhang, Y. Lan, A. Lei, *J. Am. Chem. Soc.* **2010**, *132*, 3153; c) Q. Liu, Y. Lan, J. Liu, G. Li, Y.-D. Wu, A. Lei, *J. Am. Chem. Soc.* **2009**, *131*, 10201.

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