

Nickel-Catalyzed System for the Cross-Coupling of Alkenyl Methyl Ethers with Grignard Reagents under Mild Conditions

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Supporting Information

ABSTRACT: A nickel-catalyzed cross-coupling of alkenyl methyl ethers with Grignard reagents, under mild conditions, is described. These conditions allowed access to various stilbenes and heterocyclic stilbenic derivatives as well as to a potential anticancer agent DMU-212.



ransition-metal-catalyzed cross-couplings are important reactions to synthesize molecules in modern chemistry. Since 1970, these coupling reactions have been widely used to construct C-C and C-heteroatom bonds.¹ In this context, Grignard reagents are often used and coupled with halides and pseudohalides involving metal catalysts, such as palladium, copper, manganese, silver, iron, and nickel.² Since the pioneering work of Kumada et al.^{2f,3} and Corriu and Masse,⁴ nickel-catalyzed cross-coupling of Grignard reagents with halides has demonstrated its synthetic value to form C-C bonds, and many examples have been reported.⁵ The choice of Grignard reagents as organometallic partners is very popular due to their easy accessibility and advantages of not being toxic and for not generating toxic wastes.⁶ Recently, replacement of halides by methyl ethers as cross-coupling partners has gained importance to form C-C bonds using Grignard reagents. In particular, crosscoupling of aryl methyl ethers with alkyl,⁸ alkynyl,⁹ and aryl Grignard reagents¹⁰ has been widely studied. Although a few examples have been reported for the coupling of alkenyl methyl ethers with Grignard reagents,¹¹⁻¹³ either harsh conditions or complex, expensive, and/or nonstable catalysts are used (Scheme 1, eqs 1-3). Herein, we report a nickel-catalyzed cross-coupling of alkenyl methyl ethers with Grignard reagents, mostly aryl Grignard, under mild conditions using a stable nickel catalyst (Scheme 1, eq 4). Different nickel catalysts are available, but the less expensive one is $Ni(OAc)_{2}$, and we chose to test this latter catalyst.1

When the coupling reaction of 1a with *p*-tolylmagnesium bromide 2 was achieved with Ni(OAc)₂ at 40 °C,¹⁵ 3a was obtained in 39% yield for a conversion of 1a of 58% (Table 1, entry 2). Note that when the reaction was performed without Ni(OAc)₂ at 40 °C, only traces of 3a were detected (Table 1, entry 1). To increase the conversion of 1a and the yield of 3a, a screening of ligands was realized. Among the ligands tested, amines (Table 1, entries 3 and 4), phosphines (Table 1, entries 5–8), and phosphine oxides (Table 1, entries 9 and 10), triphenylphosphine oxide was the best one,¹⁶ as 1a was totally converted to 3a, and the latter was obtained in 70% yield with an E/Z ratio of 60:40 (Table 1, entry 10). In all cases, homocoupling product 4 was present as traces and up to 26%, and by using (O)PPh₃, 4 was isolated in 20%

Scheme 1. Nickel-Catalyzed Cross-Coupling of Alkenyl Methyl Ethers with Grignard Reagents

Previous work

• Wenkert et al. (1979–1984)



• Wang *et al.* (2011)



yield. When the reaction was performed only with $(O)PPh_3$, no reaction occurred (Table 1, entry 11).

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 Table 1. Optimization of the Ligand in the Nickel-Catalyzed

 Cross-Coupling of Alkenyl Methyl Ether 1a with *p*-TolMgBr

Ph 1a (<i>E/Z</i> = 55)	SOMe + BrMg 2 45) (1.5 equi	Me Ni(OAc) ₂ (x mol 0 L (y mol %) PhMe/THF (2:1 40 °C, 24 h v)	%)) Ph	3a Me + Ph	Ph 4
entry	$\frac{\text{Ni}(\text{OAc})_2}{(x \text{ mol } \%)}$	ligand L (y mol %)	τ_{c}^{a} (%)	yield ^a (%) of 3a (4)	E/Z ^a 3a
1				traces	
2	2.5		58	39 (18)	68:32
3	2.5	NMM (10)	95	61 (18)	63:37
4	2.5	TMEDA (5)	88	58 (26)	64:36
5	2.5	dppe (5)	36	14 (traces)	72:28
6	2.5	dppf (5)	19	7 (traces)	73:27
7	2.5	XantPhos (5)	47	25 (7)	60:40
8	2.5	$PPh_3(10)$	73	61 (5)	62:38
9	2.5	$(O)PCy_{3}(10)$	100	64 (22)	59:41
10	2.5	$(O)PPh_{3}(10)$	100	70 (20)	60:40
11		$(O)PPh_{3}(10)$			

^{*a*}Conversion, yield, and E/Z were obtained by analysis of the ¹H NMR spectra of the crude sample with CH₂Br₂. NMM = *N*-methylmorpholine, TMEDA = tetramethylethylene diamine.

To study the scope and limitation of the reaction, different alkenyl methyl ethers were coupled with the p-tolyl Grignard reagent 2 (Table 2). When the aromatic ring in 1 is substituted by an electron-donating group at the para-, meta-, or ortho-position, the yields in the coupling products were good and, in most cases, the E/Z ratios were close to those of the starting materials. The reaction is chemoselective as, with the substrates incorporating an aryl methyl ether, only the methoxy vinylic group reacts (Table 2, entries 2-5). Furthermore, basic groups are tolerated as the catalytic system is not deactivated by the presence of an amino group (Table 2, entries 6 and 7). On the contrary, when an electron-withdrawing group was present on the aromatic ring, as a nitro group at the para-position, no coupling product was observed. Alkenyl methyl ethers, substituted with heteroaromatics, can also be involved in the coupling reaction. The results are reported in Table 3.

Coupling products **3** were obtained in decent yields (50–64%) when amino heterocycles were present in **1** (pyridine, indole, pyrrole) (Table 3, entries 1–3). The reaction also took place when a furan or a thiophene was present (Table 3, entries 4 and 5). In these cases, the product was obtained as a mixture of stereoisomers enriched in the *E*-isomer compared to the starting material (e.g., E/Z = 36:64 for **1j** and E/Z = 71:29 for **3j**) (Table 3, entry 2).

Alkenyl methyl ether 1n could be involved in a coupling reaction with Grignard 2 to produce 3n in 59% yield, with a good retention of the configuration of the alkene (Scheme 2).

Different Grignard reagents, such as aryl, vinyl, alkyl, and heteroaromatic Grignard reagents, can be involved in the process. Aryl Grignard reagents gave the desired products in high yields (Table 4, entries 1–3). However, in the case of anilines, the yield was higher when the amino group was at the *ortho*-position rather than at the *meta*-position (Table 4, entries 4 and 5). When activated alkyl Grignard reagents were used, the coupling products were obtained in 62–69% yields (Table 4, entries 7 and 8). In most examples, the *E*/*Z* ratio was modified, compared to the starting material (e.g., *E*/*Z* = 55:45 for 1a and *E*/*Z* = 82:18 for 6g) (Table 4, entries 1 and 3–9).

Table 2. Scope of the Nickel-Catalyzed Cross-Coupling of	E
Various Alkenyl Methyl Ethers with <i>p</i> -TolMgBr	

Ar Ar	DMe + Tol—MgBr 2 (1.5 equiv)	Ni(OAc) ₂ (2.5 (O)PPh ₃ (10 r PhMe/THF 40 °C, 24	mol %) nol %) (2:1) ▲ A	r ع
entry	1 (E/Z)	3	yieldª (%)	E/Z^{b}
1	BnO 1b (49:51)	ОМе 3b	69	39:61
2	MeO 1c (48:52)	OMe 3c	71	56:44
3	OMe 1d (52:48)	1e 3d	62°	56:44
4	OMe 1e (55:45)	1e 3e	62°	61:39
5	MeO MeO 1f (50:50)	OMe 3f	72°	57:43
6	Me ₂ N 1g (40:60)	ОМе Зg	70	52:48
7	Et_2N OMe 1h (43:57)	OMe 3h	63	57:43

^aYield of isolated product. ${}^{b}E/Z$ ratio determined by ¹H NMR. ^cHomocoupling product of 1 was observed.

Scheme 2. Nickel-Catalyzed Cross-Coupling Reaction of an Aliphatic Alkenyl Methyl Ether with *p*-TolMgBr

OMe .	+ Me	Ni(OAc) ₂ (2.5 mol %) (O)PPh ₃ (10 mol %)	Me
8	BrMg 🔨	PhMe/THF (2:1)	He was
1n	2	40 °C, 24 h	3n
(<i>E/Z</i> = 51:49)	(1.5 equiv)	59%	(E/Z = 53:47)

When 10 was treated with isopropylmagnesium chloride 5j, the yield in the coupling product was only 18% with an E/Z ratio greater than 95:5 (Scheme 3).¹⁷

According to previous results, the coupling reaction seems to be stereoselective. Indeed, for each example, a partial inversion of the configuration of the double bond of the starting material was observed in favor of the *E*-isomer. To emphasize this phenomenon, which was already observed by Chatani et al.,¹⁸ the coupling reactions were performed from pure (*E*)-1a and (*Z*)-1a (Scheme 4). Complete conversion of (*Z*)-1a was observed after 20 min when the latter was involved in a coupling reaction with Grignard 2 to afford 3a in 80% yield in an *E*/*Z* ratio of 23:77. We can assume that the formation of (*E*)-3a from (*Z*)-1a could be explained by two distinct processes: (1) partial isomerization of

 Table 3. Scope of the Nickel-Catalyzed Cross-Coupling of

 Heteroaromatic-Containing Alkenyl Methyl Ethers with p-TolMgBr

🐟 OMe		Ni(OAc) ₂ (2.5 mol %) (O)PPh ₃ (10 mol %) PhMe/THF (2:1) 40 °C, 24 h		ol %) ol %)	in the second	
HetAr 7	2 (1.5 equiv)			Het. ⊔:1) Het.	3	
entry	$1\left(E/Z ight)$		3	yieldª (%)	$E/Z^{\rm b}$	
1	\bigcup_{N}^{n}		3 i	51	75:25	
2	Li (61:67)		3j	64	71:29	
3	(N Me 1k (38:62)		3k	51	45:55	
4	ریت 11 (62:38)		31	43°	89:11	
5	ر ج 1m (61:39)		3m	49°	87:13	

^{*a*}Yield of isolated product. ^{*b*}E/Z ratio determined by ¹H NMR. ^{*c*}Yield was obtained by analyzing the ¹H NMR spectra of the crude sample with 1,3,5-trimethoxybenzene.





intermediate (*Z*)-**C** into intermediate (*E*)-**C**; (2) partial isomerization of (*Z*)-**3a** to (*E*)-**3a** under catalytic conditions. In the case of (*E*)-**1a**, the reaction was slower than for (*Z*)-**1a** as a complete conversion was observed for (*E*)-**1a** after 12 h and **3a** was obtained in 65% yield as a single stereoisomer (E/Z = 100:0). With these results in hand, we hypothesize that for (*Z*)-**1a** and (*E*)-**1a**, the oxidative addition/ligand exchange produces intermediates (*Z*)-**C** and (*E*)-**C**, respectively. In the case of (*Z*)-**C**, the reductive elimination step is much faster than for (*E*)-**C**, probably due to steric hindrance. We have verified that, for a complete conversion of (*Z*)-**1a**, the percentage of (*Z*)-**3a** decreased in favor of (*E*)-**3a** over time under our catalytic conditions (see Supporting Information).

After the versatility of the coupling on E/Z mixtures was studied, the reactivity of (*E*)-alkenyl methyl ethers was examined (Table 5). When alkenyl methyl ethers (*E*)-1c, (*E*)-1f, and (*E*)-1g were coupled with aryl Grignard 2, the desired products were isolated in 60–64% yields (Table 5, entries 1–3). Good yields of (*E*)-6a and (*E*)-6b were obtained for the coupling of (*E*)-1a with aryl Grignard 5a and 5b (Table 5, entries 4 and 5). However, (*E*)-

MO COM	le + R -MaX	Ni(OAc) ₂ (2.5 (O)PPh ₃ (10 r	mol %) nol %)	R
1a (<i>E/Z</i> = 55:45)	5 (1.5 equiv)	PhMe/THF (40 °C, 24	(2:1) h	6
entry	Grignard reage 5	nts 6	yieldª (%)	$E/Z^{\rm b}$
1	Mg	Br 6a	81	63:37
2	MeO Sh	gBr 6b	85°	59:41
3	Sb () Mg	Br 6c	62	72:28
4	Sc Me ₂ N Mg	_{gBr} 6d	53 ^d	70:30
5	Su MgBr NMe ₂	6e	71 ^d	70:30
6	MgBr 5f	6f	72	75:25
7	MgB 5g	r 6g	69	82:18
8	Sg ├──MgBr 5h	6h	62	62:38
9	N Me 5i	Br 6i	46 ^d	99:1

 Table 4. Scope of the Nickel-Catalyzed Cross-Coupling of

 Alkenyl Methyl Ether 1a with Various Grignard Reagents

^{*a*}Yield of isolated product. ^{*b*}E/Z ratio determined by ¹H NMR. ^{*c*}Yield was obtained by analyzing the ¹H NMR spectra of the crude sample with 1,3,5-trimethoxybenzene. ^{*d*}Yield was obtained using 5 mol % of Ni(OAc)₂, 20 mol % of (O)PPh₃, and 2.0–2.6 equiv of RMgBr.

6k was isolated in lower yield when aryl Grignard **5k** was involved in the process (Table 5, entry 6). Encouraged by these results, we decided to apply the coupling conditions to the synthesis of DMU-212, which shows anticancer properties.¹⁹ Cross-coupling between (*E*)-**1p** and **5b** gave DMU-212 in 67% yield (Scheme 5).

In summary, we demonstrated that alkenyl methyl ethers and Grignard reagents can be cross-coupled stereoselectively under mild conditions using a simple and robust catalytic system, $Ni(OAc)_2/(O)PPh_3$. Cross-coupling can be performed on diversely substituted alkenyl methyl ethers with a variety of Grignard reagents. This nickel-catalyzed cross-coupling method can give access to stilbene derivatives with potential anticancer properties, such as DMU-212. Mechanistic studies are in progress to determine the intermediates involved in the coupling reaction and will be reported in due course.

Scheme 4. Stereoselectivity of the Nickel-Catalyzed Cross-Coupling





	Ar OMe (E)-1	+ Ar' —MgBr (3 equiv)	Ni(OAc) ₂ (2.3 (O)PPh ₃ (10 PhMe/THF 40 °C, 5-	5 mol %)) <u>mol %)</u> = (2:1) -30 h	Ar (E)- 3 or	∕ Ar' (<i>E</i>)-6
entry	(E)-1	Ar'M	gBr	(E)- 3 or	: (E)- 6	yield ^{a} (%)
1	(E)-1c	2		(E)-	3c	63 ^b
2	$(E)-\mathbf{1f}$	2		(E)-	3f	64
3	(E)- 1g	2		(E)-	3g	60
4	(E)-1a	5a		(E)-	6a	80
5	(E)-1a	5b		(E)-	6b	57 ^b
6	(E)- 1a	p-NMe ₂ C ₆ H	₄ MgBr, 5k	(E)-	6k	49 ^b

"Yield of isolated product. ^bYield was determined by analyzing the ¹H NMR spectra of the isolated fraction.

Scheme 5. Synthesis of DMU-212



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00313.

Experimental procedures, characterization, and ¹H and ¹³C NMR spectra of isolated compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(15) When the coupling reaction was performed at 100 °C with Ni(OAc)₂, **3a** was obtained in 54% yield (E/Z = 69:31) for a conversion of **1a** of 82%. Even without a nickel catalyst at 100 °C, **3a** was also obtained in 40% yield (E/Z = 76:24) for a conversion of **1a** of 60%.

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