Nickel-Catalyzed Addition of Grignard Reagents to Oxabicyclic Compounds. Ring-Opening Reactions with Previously Unreactive Substrates and Nucleophiles

Mark Lautens* and Shihong Ma

Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 3H6

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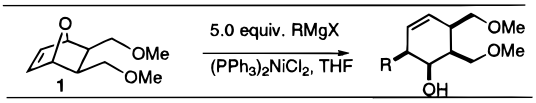
The transition metal-catalyzed carbometalation of alkenes is an attractive synthetic transformation since the resulting organometallic species are useful reagents in organic synthesis.[1] We now report a nickel-catalyzed Felkin-type coupling reaction between oxabicyclic compounds and organomagnesium halides leading to synthetically valuable six- and seven-membered rings.[2−5] The presence of nickel allows for the use of nucleophiles such as Me^- and Ph^- that were previously unreactive in the ring-opening reaction. In addition, several novel aspects related to the stereochemistry and regiochemistry of the coupling reaction were discovered during the study.

A catalytic amount of $(PPh_3)_2NiCl_2$ was found to promote the reaction of oxabicyclic[2.2.1] compound **1** with 5.0 equiv of MeMgBr after 23 h in THF to afford ring-opened product **2** in 70% yield as a single isomer (Table 1, entry 1). *Importantly, no reaction occurs in the absence of the catalyst* (Table 1, entry 2). Similar results are also observed in the coupling reaction of **1** with PhMgBr and $PhCH_2MgCl$, although the latter occurs in low yield (Table 1, entries 3 and 4). The reaction is highly regioselective, forming a product equivalent to clean S_N2' attack, and highly stereoselective in which the nucleophile attacks on the same side of the ring as the bridging oxygen (*syn* attack). Previous work has shown that alkylation reactions of allylic ethers with Grignard reagents using nickel catalysts typically proceed with *net inversion* of configuration.[5] Therefore, to the best of our knowledge, this is the first example of the coupling reaction between an allylic substrate and Grignard reagents that proceeds with exclusive net *retention*.

In order to learn more about the scope of the reaction, we carried out a set of experiments with **1** and MeMgBr using different catalysts and solvents, Table 2. Of the catalysts surveyed, $Ni(COD)_2$ gave **2** selectively regardless of the solvent (Table 2, entries 1−3). A higher yield of the ring-opened product was realized by conducting the reaction in THF rather than Et_2O, and less catalyst and lower temperatures were possible. In contrast to

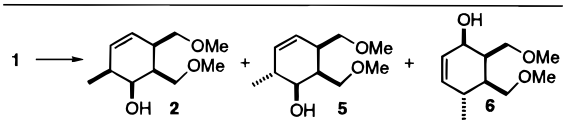
Table 1. $(PPh_3)_2NiCl_2$-Catalyzed Ring Opening of 1



Entry	RMgX	Catalyst (mol%)	Product	Temperature	Time	Yield[a] (%)
1	MeMgBr	2.6	**2**	r.t.	23 h	70
2	MeMgBr	0	**2**	reflux	48 h	<5
3	PhMgBr	2.5	**3**	r.t.	5 h	67
4	$PhCH_2MgCl$	6.0	**4**	reflux	3 h	18

[a] Isolated yield of analytically pure material.

Table 2. Catalyst and Solvent Effect in the Reaction of MeMgBr with 1



Entry	Catalyst[a]	Solvent	Yield of **2**[b]	Yield of **5**+**6**[b, c]
1		THF	70%	
2	$Ni(COD)_2$	Et_2O	48%[d]	
3		Et_2O/HMPA[e]	30%[f]	
4		THF	70%	
5	$(PPh_3)_2NiCl_2$	THF/HMPA[e]	68%	
6		Et_2O/HMPA[e]		5%[f]
7		THF	64%	
8	$(dppp)NiCl_2$	Et_2O/HMPA[e]		95%
9		*t*-butyl methyl ether /HMPA[e]		84%
10		toluene/HMPA[e]		80%

[a] Conditions: 2 mol % to 10 mol % catalyst, 5.0 equiv of MeMgBr, 22 °C. [b] Isolated yield. [c] Ratio of 5:6, see ref 6a. [d] 28 mol % $Ni(COD)_2$, at reflux temperature. [e] Solvent/HMPA is 15:1. [f] Starting material recovered.

reactions with $Ni(COD)_2$, the regio- and stereoselectivity of reactions using $(PPh_3)_2NiCl_2$ and $(dppp)NiCl_2$ as catalysts were solvent dependent. For example, whereas reactions in THF and THF/HMPA gave **2**, the product of net retention (Table 2, entries 4, 5, and 7), use of Et_2O/HMPA, *tert*-butyl methyl ether/HMPA, and toluene/HMPA afforded a mixture of **5** and **6** wherein the newly formed C−C bond is *trans* to the hydroxyl group (Table 2, entries 6 and 8−10)![6a] The solvent system is totally governed the stereochemistry of the reaction since the ratio of **2** to **5** + **6** was <1:100 in entries 6 and 8−10 and the reverse under other conditions.[7] HMPA is an essential component in the formation of **5** and **6**, and reactions in Et_2O fail to give the ring-opened products.[8] $(dppp)NiCl_2$ in Et_2O/HMPA is much more reactive than $(PPh_3)_2NiCl_2$ and affords the ring-opened products **5** and **6** in excellent yield (Table 2, entries 8 and 6), respectively.

In addition to MeMgBr, we also studied the reactivity of substrate **1** with PhMgBr and $PhCH_2MgCl$ in the presence of $Ni(dppp)Cl_2$. The selectivity of the ring opening using phenylmagnesium bromide is low, giving three products in 66% yield. Product **3** is the major

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(6) (a) The ratio of **5** to **6** varied from 1.4:1 to 1:2.8 even when the same reaction was repeated several times, possibly due to the heterogeneous reaction conditions. (b) Some variation in the ratio of products was also observed for this reaction; see ref 6a.

(7) The ratio was determined by analysis of the crude mixture using GC and 400 MHz ^1H NMR spectra.

(8) HMPA was shown to be an important solvent in the coupling reaction between π-allylnickel complexes with alkyl halides, see: Corey, E. J.; Semmelhack, M. F. *J. Am. Chem. Soc.* **1967**, *89*, 2755.

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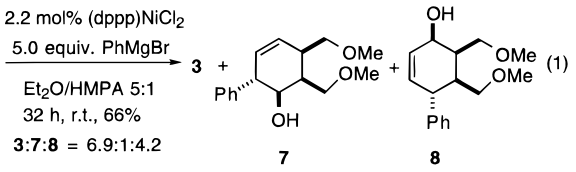
Table 3. Coupling Reactions of Oxabicyclic Compounds with MeMgBr

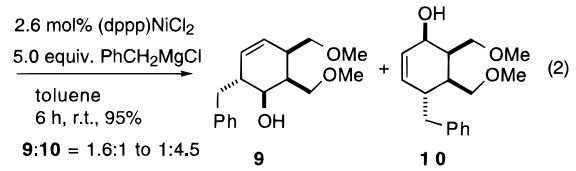
Entry	Substrate		$Ni(COD)_2$[a] (mol%)	Product		Yield[b] (%)
1	**11**	R^1=H, R^2=Me	3.0	**12**		56
2	**13**	$R^1 = R^2$=H	18	Mixture		
3	**14**	R^1=R^2=CH_3	6.1	N.R.		0
4	**15**	R^1=CH_2OH, R^2=Me	9.6	**16**		41 (69)[c]
5	**15**		0	N.R.		
6	**17**		8.0	**18**		74

[a] Conditions: 5.0 equiv of MeMgBr and the substrate were refluxed in Et_2O for 16 h. [b] Isolated yield. [c] 6.0 equiv of MeMgBr, yield based on recovered starting material.

product accompanied by significant amounts of **7** and **8**, the products of net inversion (eq 1).[6b]



No reaction occurred between **1** and $PhCH_2MgCl$ with Et_2O/HMPA in the presence of $Ni(dppp)Cl_2$. Switching the solvent to toluene led to two products, **9** and **10**, which are regioisomeric, in 95% yield in a ratio ranging from 1.6:1 to 1:4.5.[9] The product of net retention, **4**, could not be detected (eq 2). In contrast to the moderate regioselectivity observed, the stereoselectivity of the reaction was excellent.



The products of either net retention or net inversion could be selectively obtained in the coupling reaction of oxabicyclic[2.2.1] compound **1** and MeMgBr as a function of the nickel catalyst and solvent system. However, only $Ni(COD)_2$ in ether at reflux worked well in the ring opening of other oxabicyclic compounds (Table 3). Thus, treatment of the less strained oxabicyclic[3.2.1] **11** with 3.0 mol % $Ni(COD)_2$ and 5.0 equiv of MeMgBr afforded **12**, the product of net retention, in 56% yield (Table 3, entry 1). Surprisingly, the corresponding alcohol **13**, gave a complex mixture of products (Table 3, entry 2), which illustrates the reversal of the reactivity in metal- and nonmetal-catalyzed reactions. Previous studies showed that **13** was successfully ring-opened with MeLi in TMEDA but **11** failed to react.[10]

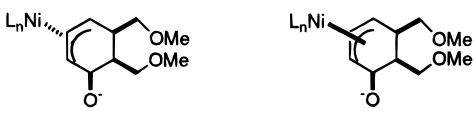


Figure 1.

No reaction was observed with the unsymmetrical oxabicyclic[3.2.1] substrate **14** bearing a methyl substituent at the bridgehead and MeMgBr (Table 3, entry 3), whereas **15**, which bears a hydroxymethyl group, gave the ring-opened product **16** in 41% yield! Although the yield was modest in this case, reaction with MeLi/TMEDA or MeMgBr in the absence of the catalyst (Table 3, entry 5) failed to provide any ring-opened products. When the [2.2.1] substrate **17** was treated with 5.0 equiv of MeMgBr in Et_2O at reflux with a catalytic amount of $Ni(COD)_2$, a 74% yield of a single regio- and stereoisomer **18** was obtained (Table 3, entry 6). We have devoted significant effort to the discovery of suitable conditions to ring open a variety of unsymmetrical oxabicyclic compounds with a methyl nucleophile and all have failed prior to the conditions reported above.[11] MeLi in TMEDA, MeLi in DME, MeLi/Me_3Al, and MeLi/12-crown-4 gave either no reaction or led to the formation of many products.

It is plausible that the nickel-catalyzed coupling reaction proceeds *via* a metal−π-allyl complex that undergoes reductive elimination of the dialkylmetal.[12,13] Oxidative addition of Ni(0) to oxabicyclic compounds to give π-allyl complexes could proceed with inversion or retention of configuration. Previous studies using nickel have indicated that attack at the metal usually occurs with "hard" nucleophiles.[2,5] If this scenario holds in our substrates, then both π-allyl complexes **19** and **20** must be formed depending on the solvent and ligand (Figure 1).

These studies demonstrate that nickel catalysts promote the coupling of alkylmagnesium halides and oxabicyclic compounds. The methodology is complementary to the organolithium and organocuprate ring opening of oxabicyclic compounds and extends the range of nucleophiles and reaction conditions that induce ring opening.

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Supporting Information Available: Experimental procedures and compound characterization data (17 pages).

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(9) The stereochemistry of **9** and **10** was established by X-ray crystallography of the 3,5-dinitrobenzoic acid and 3-chlorobenzoic acid derivatives, respectively; the stereochemistry of **6** was established using NOE studies following a hydroxyl-directed cyclopropanation; the stereochemistry of **12** and **16** was established by chemical means. See the supporting information for details. The author has deposited atomic coordinates for the derivatives of **9** and **10** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Cyrstallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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